



Febrile Seizures following Measles, Mumps, Rubella, and Varicella (MMRV) vaccine

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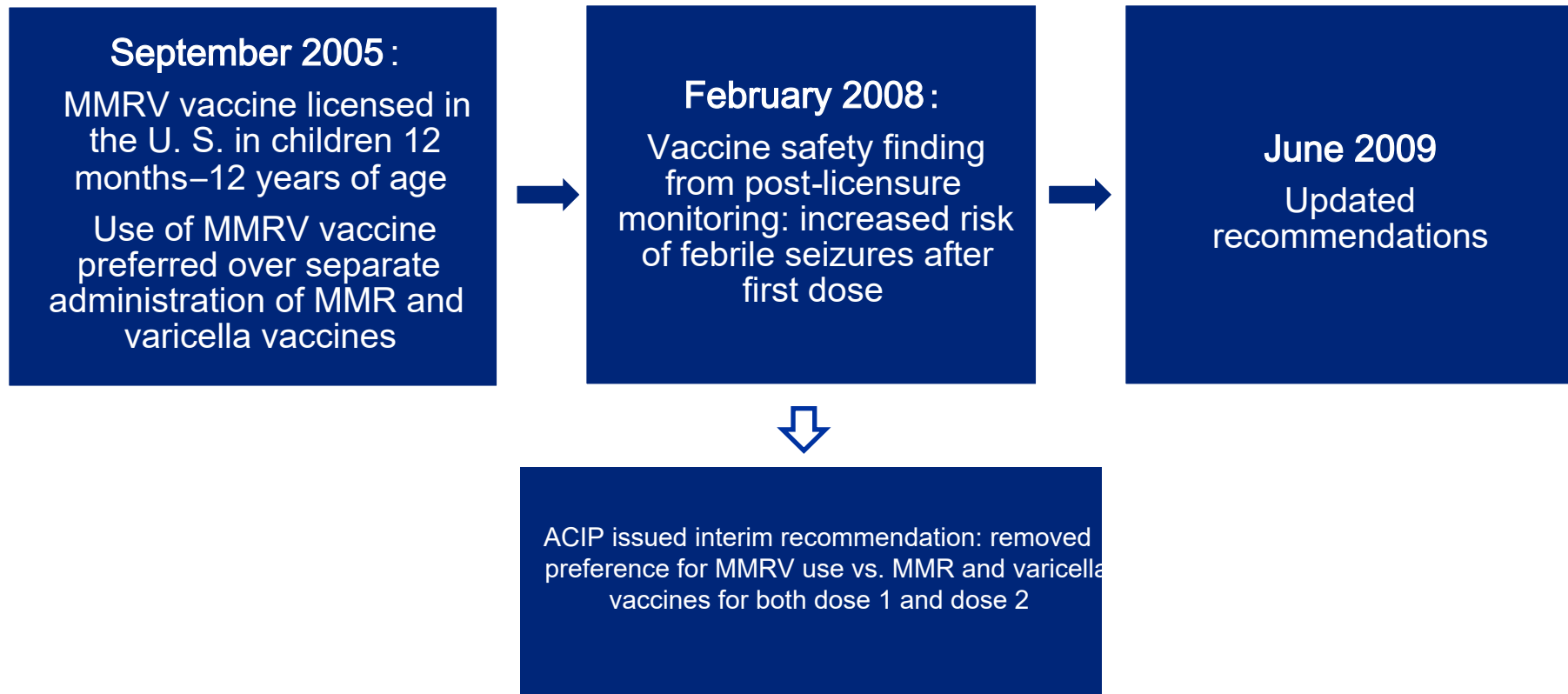
Centers for Disease Control and Prevention

September 18, 2025

September 2025: Request to CDC from ACIP Chair

Presentation on febrile seizures post administration of MMRV vs. simultaneous administration of separate MMR and Varicella vaccines, by two different age groups, 1–2 and 4–6-year-olds. Please use data both from randomized trials and from the Vaccine Safety Datalink (VSD), presented from the VSD project.

Timeline of recommendations for MMRV vaccine use in the United States

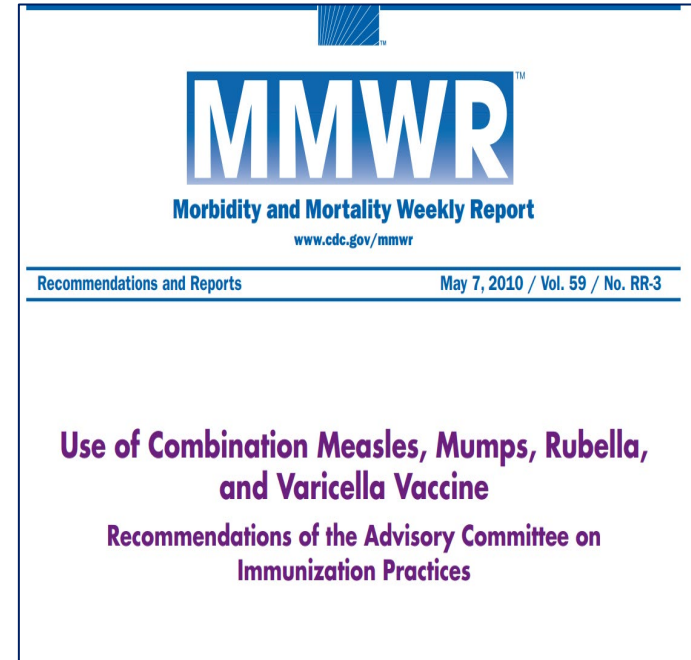


Presentation of preliminary safety findings to ACIP February 2008 to June 2009 that led to revised MMRV recommendations in June 2009

- **Multiple presentations to ACIP from Vaccine Safety Datalink and Merck**
- **Evidence review and synthesis of data to ACIP: MMRV ACIP Working Group assessed multiple sources of data**
 - Review of two post-licensure studies
 - Merck-sponsored study
 - Vaccine Safety Datalink study
 - Review of literature and other data sources (e.g., parent/provider focus groups data)
 - Consultation with experts
 - MMRV Vaccine Safety Working Group (WG) discussions
 - WG member surveys
 - October 2008 and June 2009

ACIP Updated Recommendations: June 2009

- For the first dose of measles, mumps, rubella, and varicella vaccination at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering the MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers.
 - CDC implementation guidance: unless the parent or caregiver expresses a preference for the MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine be administered for the first dose in this age group.
- For the first dose at age ≥ 48 months and for the second dose at any age (15 months–12 years), MMRV is generally preferred over separate injections of MMR vaccine and varicella vaccine



Background: MMRV vaccine

- **Combination vaccine***
 - Decreases the number of injections
 - Increases vaccine compliance
 - Increases vaccine coverage rates
- **MMRV licensed for children 12 months through 12 years of age**
 - Routinely recommended ages:
 - First dose: age 12 through 15 months
 - Second dose: age 4 through 6 years
 - In the United States, MMRV vaccine licensed is ProQuad (Merck & Co, Inc)

* <https://www.cdc.gov/vaccines/hcp/imz-best-practices/timing-spacing-immunobiologics.html>

Background: Febrile seizures

- **By 5 years of age, 2-4% of children have had ≥ 1 febrile seizure¹**
- **Occurs primarily 6 months – 5 years of age, peak age is 14-18 months**
- **Typically of short (<15 min) duration^{1,2}; majority resolve without sequelae**
- **Observed during early childhood infections and diseases^{1, 2}**
 - Middle ear infections, viral upper respiratory tract infections, roseola
 - Can be associated with any condition that results in fever
- **Observed following a fever associated with vaccination^{1,2}**
 - DTaP, pneumococcal conjugate, MMR
- **Family history of febrile seizures increases the risk of febrile seizures³**

¹ Marin, M, et al. Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR May 7, 2010/59(RR03);1-12

² <https://www.cdc.gov/vaccine-safety/about/febrile-seizures.html>

³ Sawires R, Buttery J, Fahey M. A Review of Febrile Seizures: Recent Advances in Understanding of Febrile Seizure Pathophysiology and Commonly Implicated Viral Triggers. Front Pediatr. 2022 Jan 13;9:801321.

Background: Pre-licensure MMRV studies

- **MMRV prelicensure studies conducted among children aged 12 to 23 months**
 - Fever and measles-like rash were reported at significantly greater rate among children receiving the first dose of MMRV vaccine than children receiving first doses of MMR vaccine and varicella vaccine (at the same visit)
 - Fever (reported as abnormal or elevated $\geq 102^{\circ}\text{F}$ [$\geq 39^{\circ}\text{C}$])
 - 21.5% of MMRV vaccine recipients compared with 14.9% of separate MMR vaccine and varicella vaccine recipients (risk difference [RD]: 6.6%; 95% confidence interval [CI] = 4.6-8.5)
 - Measles-like rash:
 - 3.0% of MMRV vaccine recipients compared with 2.1% of separate MMR vaccine and varicella vaccine recipients (RD: 1.0%; 95% CI = 0.1-1.8)
- **In light of these findings, CDC and Merck initiated separate post-licensure studies to evaluate if an increased risk for febrile seizures might be associated with the first dose of MMRV vaccine**

Febrile seizures following first dose of MMRV

Summary results from VSD and Merck-sponsored studies for chart confirmed febrile seizures after first dose of MMRV vs. MMR and varicella (MMR+V) vaccines

Post-vaccination Interval	VSD study* All aged 12-23 months	Merck-sponsored study † 99% aged 12-23 months
	MMRV: N= 83,107 MMR+V: N= 376,354	MMRV: N=31,298 MMR+V: N=31,298
Weeks 12	<u>7–10 days</u> RR: 2.0 (95% CI: 1.4, 2.9) AR: 4.3 per 10,000 (95% CI: 2.6, 5.6)	<u>5–12 days</u> RR: 2.2 (95% CI: 1.0, 4.7) AR: 3.8 per 10,000 (95% CI: 0.3, 7.4)
Weeks 14	<u>0-30 days</u> RR: 1.4 (95% CI: 1.1, 2.0) AR: 4.7 per 10,000 (95% CI: 0.7, 7.6)	<u>0-30 days</u> RR: 1.1 (95% CI: 0.7, 1.7) AR: 1.3 per 10,000 (95% CI: 4.5, 7.0)

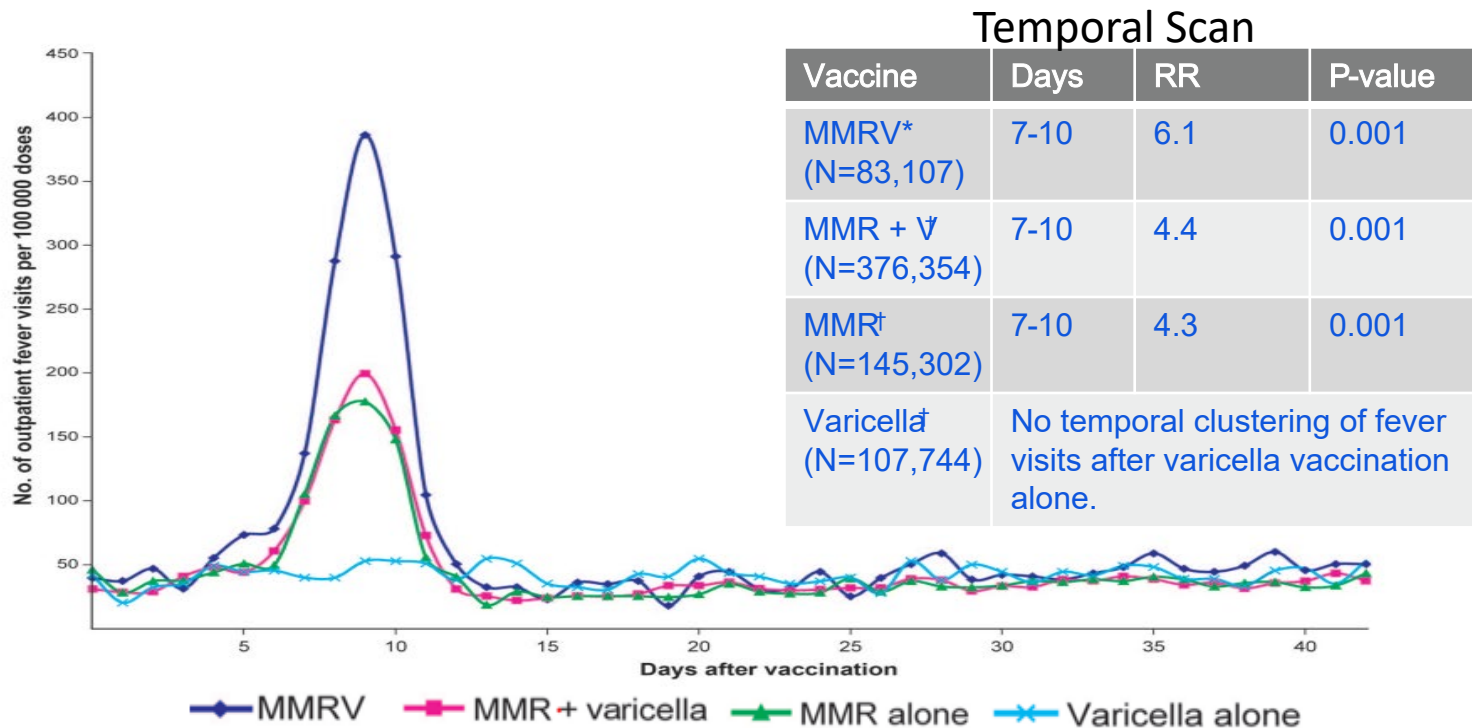
*Klein NP, et al. Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010 Jul;126(1):e1-8

†Jacobsen SJ et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine. 2009 Jul 23;27(34):4656-61.

§ Significant p <0.05

RR = relative risk; AR= attributable risk; CI: confidence interval

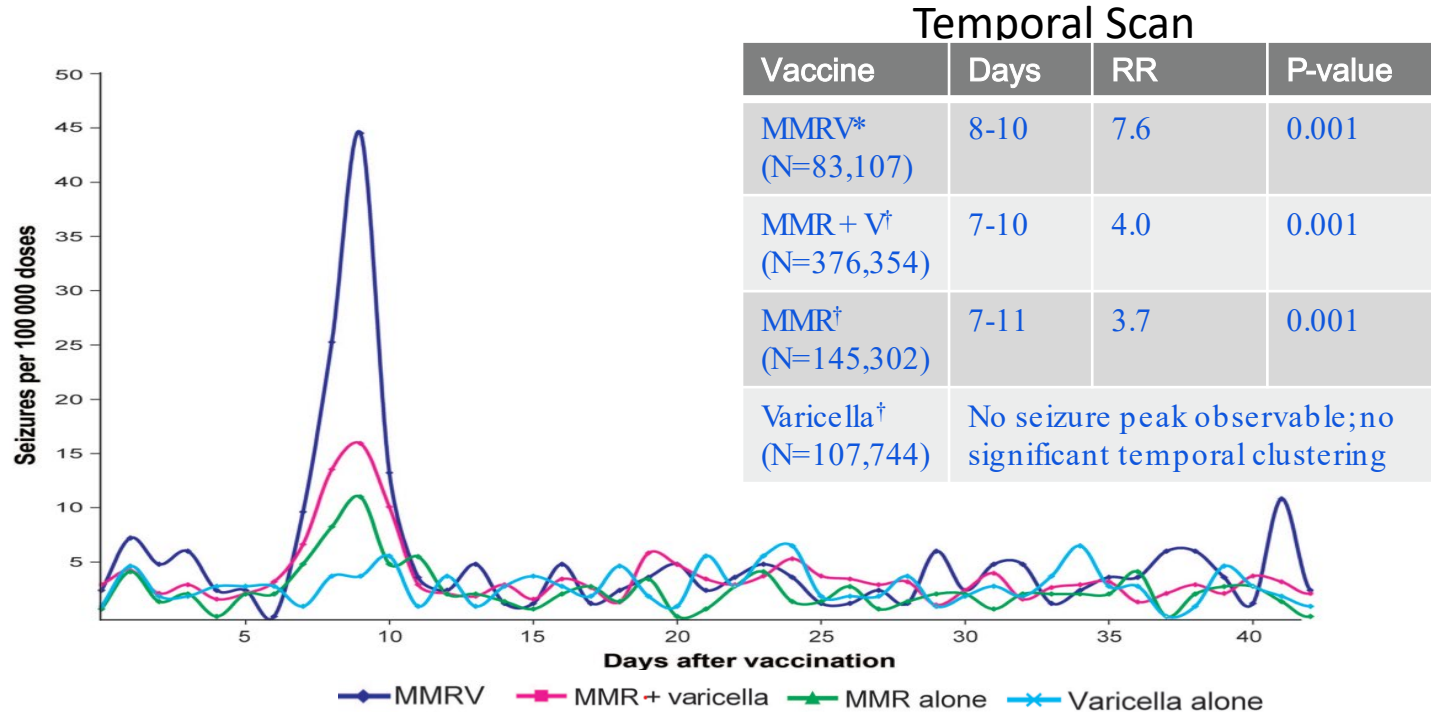
Post-vaccination outpatient fever visits among 12-23-month-olds according to vaccine received by vaccine type, VSD, 2000 –2008



* Vaccinated between January 2006 and October 2008; † Vaccinated between January 2000–October 2008

Klein NP, et al. Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010 Jul;126(1):e1-8

Post-vaccination febrile seizures among 12-23-month-olds by vaccine type, VSD, 2000-2008



* Vaccinated between January 2006 and October 2008; † Vaccinated between January 2000-October 2008

U.S. post-licensure experience: Febrile seizures after MMR or varicella vaccination

- MMR vaccine: Study of ~137,000 children aged <7 years vaccinated with MMR identified an increased risk for febrile seizures during 8–14 days after vaccination, compared with unvaccinated children¹
 - RR 2.83 (95% CI: 1.44, 5.55)
 - ~1 additional febrile seizure per 3,000–4,000 children vaccinated
- Varicella vaccine: Study of ~35,000 children aged 12–23 months vaccinated with varicella vaccine identified no increased risk for febrile seizures during 0–30 days after vaccination, after controlling for co-administration of MMR vaccine²

1. Barlow WE, Davis RL, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001 Aug 30;345(9):656-61.

2. Black S; Shinefield H, et al. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. The Pediatric Infectious Disease Journal 18(12):p 1041-1046, December 1999.

Risk of febrile seizure after MMRV vaccines: A systematic review and meta-analysis

- Included some studies that had subjects as young as 9 months of age
- Clinical trial review and analysis (31 published or unpublished studies involving about 40,000 subjects)
 - No evidence of significant differences in incidence of febrile seizure or vaccine-related febrile seizure between MMRV and MMR +/- V after any doses, in the risk windows of 0-28, 0-42, 0-56, and 7-10 days
 - Receipt of concomitant MMRV and other pediatric vaccines was not a significant predictor of febrile seizure
- Post-marketing review and analysis
 - Included data from 8 post-marketing studies, involving more than 3,200,000 children*
 - Approximately 2-fold increase in risk of seizure or febrile seizure during 7-10 days or 5-12 days after MMRV in children aged 10-24 months

* One study included children ages 4-6 years who received second dose MMRV: Study included both ProQuad (available in US) and Priorix-Tetra study (available internationally)
Ma SJ, Xiong YQ, Jiang LN, Chen Q. Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis. *Vaccine*. 2015;33(31):3636-3649.
doi:10.1016/j.vaccine.2015.06.009

Cochrane review: MMRV vs MMR + V in children

- **Febrile seizure review**

- Risk of febrile seizures after MMRV vaccination compared to MMR+V vaccination
 - Includes evidence from five cohort studies*
 - Overall estimates:
 - Within 42 days after vaccination: RR 1.31 (95% CI: 1.19 to 1.45)
 - Within 7 to 10 days after vaccination: RR 1.98 (95% CI: 1.69 to 2.33)
- Risk of febrile seizure after MMRV studies (grouped by brand) compared to MMR+V vaccination
 - Priorix-Tetra study:
 - Within 0 to 42 days after vaccination: RR 1.95 (95% CI: 0.85 to 4.48)
 - Within 7 to 10 days after vaccination: RR 1.69 (95% CI: 0.93 to 3.07)
 - ProQuad studies†:
 - Within 0 to 42 days after vaccination: RR 1.30 (95% CI: 1.17 to 1.44)
 - Within 7 to 10 days after vaccination: RR 2.01 (95% CI: 1.70 to 2.38)

* Four studies are dose 1; One study includes children ages 4-6 years who received dose 2; † Includes one study of children ages 4-6 years who received dose 2.

Summary of evidence for febrile seizure risk after first dose of MMRV vaccination

- Post-licensure studies assessed rates of febrile seizures in children aged 12-23 months who received dose 1 MMRV vaccine and compared these rates with children who received separate dose 1 injections of MMR and varicella vaccines at the same visit.
- The studies used different methods, populations of children, and different formulations of MMRV.
- Despite these differences, studies show remarkable consistency in findings

Conclusion: Evidence for febrile seizure risk after first dose MMRV vaccination

- During the 6 weeks after vaccination, an increased risk for febrile seizures after dose 1 MMRV compared with dose 1 MMR+V is only present during the 1-2 weeks after vaccination
- The risk of febrile seizures occurring during other periods after vaccination is similar between dose 1 MMRV and MMR+V

Febrile Seizures following second dose of MMRV

Risk of febrile seizures and fever following second dose of MMRV vaccine

- Risk for febrile seizures is lower among children aged 4-6 years than among children aged 12-15 months
- Prelicensure trials:
 - Lower fever rates in children aged 15-31 months receiving dose 2 MMRV compared with dose 1 MMRV (N=1035)¹
 - Similar fever rates in children aged 4-6 years receiving dose 2 MMRV (N=397) compared with dose 2 MMR + varicella vaccines (N=193)²

¹ Merck ProQuad package insert, 2024

² Reisinger KS, et al. Brown ML, Xu J, et al. A combination measles, mumps, rubella, and varicella vaccine (ProQuad) given to 4- to 6-year-old healthy children vaccinated previously with MM-RII and Varivax . Pediatrics. 2006;117(2):265-272.

Merck-sponsored study findings of febrile seizures following second dose of MMRV and MMR+V

- **Among children aged 4-6 years:**
 - No febrile seizures occurred during the 5-12 days post-vaccination
 - 22,212 children receiving second dose MMRV vaccine
 - 24,778 children receiving second dose of MMR + V vaccine at same visit

VSD findings for all seizures after second-dose of measles-containing vaccine identified from electronic medical records for children aged 4-6 years

- Very few seizures identified by ICD-9 codes in electronic data

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	Rate/10 000	Rate/10 000 Doses	Rate/10 000	Rate/10 000 Doses	Rate/10 000	Rate/10 000 Doses	Rate/10 000
	(Number Events)	PY (95% CI)	(Number Events)	PY (95% CI)	(Number Events)	PY (95% CI)	(Number Events)	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)

VSD findings of chart-confirmed febrile seizures 7 to 10 days after second dose of measles-containing vaccination for children aged 4–6 years, 2000–2008

- **Electronic medical record review of the 4 post-MMRV seizures:**
 - Febrile seizure: 1
 - Afebrile seizures: 2
 - Improbable seizure: 1

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)

Risk of febrile seizure after second dose of MMRV: Systematic review and meta-analysis

- Pre-licensure studies:**

Pool analyses of incidence of febrile seizure and vaccine related febrile seizure following vaccination in healthy children aged 9–24 months.

Dose	Comparison categories (risk window/group)		Febrile seizure			
			No. of studies	Pooled incidence (‰)	Pooled RD (‰, 95% CI)	Pooled RR (95% CI)
Second MMRV dose	MMRV vs. MMRV + others	0–28 d	1	3.10 (1/323)	0.07 (–8.41, 8.54)	1.02 (0.06, 16.26)
		MMRV + others		3.03 (1/330)		
	7–10 d	MMRV	1	0 (0/323)	0 (–5.98, 5.98)	1.02 (0.02, 51.33)
		MMRV + others		0 (0/1453)		
	MMRV + others vs. others	0–28 d	1	0 (0/347)	0 (–4.09, 4.09)	4.18 (0.08, 210.43)
		Others		0 (0/1453)		
	7–10 d	MMRV + others	1	0 (0/347)	0 (–4.09, 4.09)	4.18 (0.08, 210.43)
		Others		0 (0/1453)		

- Post-licensure study:**

- Only included one study of children 4–6 years; no evidence to suggest elevated risk of febrile seizure

Conclusion: No evidence for febrile seizure risk after dose 2 MMRV vaccination

- **Among children aged 4-6 years**
 - Data do not suggest that children who receive dose 2 MMRV have an increased risk of febrile seizures after vaccination compared with those who receive dose 2 as MMR + varicella vaccination at the same visit

Conclusion

- There is a small increased risk for febrile seizures after first dose of MMR and MMRV vaccines
- The risk is slightly higher with MMRV combination vaccine after the first dose
 - Studies have shown a small increased risk for febrile seizures during the 5- 12 days after a child has received their first vaccination with MMR vaccine
 - Studies have not shown an increased risk for febrile seizures after the varicella vaccine
- There is no increased risk of febrile seizures after vaccination with MMRV vaccine in children aged 4 through 6 years

Questions?

For more information, contact CDC

1-800-CDC-INFO (232-4636)

TTY: 1-888-232-6348 [cdc.gov](https://www.cdc.gov) [atsdr.cdc.gov](https://www.atsdr.cdc.gov)

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