

Vaccine Safety Datalink Project: Evaluation of MMRV and Febrile Seizures

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for the
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Combination Measles, Mumps, Rubella and Varicella Virus Vaccine (MMRV)

- **FDA licensed combined MMRV in 2005 for use in children 12 months to 12 years of age.**
- **ACIP recommended use of MMRV in 2006.**

Febrile Seizures and Measles-Containing Vaccines

- **MMR vaccine is associated with febrile seizures 8-14 days post-vaccination.**
- **MMR is associated with 1 additional febrile seizure for every 3,000 to 4,000 doses administered.**
- **Pre-licensure studies found higher rates of fever and measles-like rash 5–12 days after MMRV vaccination compared with separate, same-day MMR and varicella vaccination (children aged 12–23 months).***

* Shinefield, PIDJ 2005.

Overview of MMRV RCA study

- Age: 12-23 months
- Outcomes monitored:
 - Ataxia
 - Seizures
 - Meningitis and encephalitis
 - Thrombocytopenia
 - Arthritis
 - Allergic reactions
- Post vaccination observation for 42 days.
- Expected rates of seizures, ataxia, and allergic reactions were calculated based on historical rates among MMR recipients (with or without varicella vaccine).

Participating VSD sites: Group Health Cooperative, Kaiser Colorado, Kaiser Northwest, Harvard Pilgrim Health Care, Health Partners, Northern California Kaiser and Marshfield Clinic.

MMRV RCA Seizure Outcome

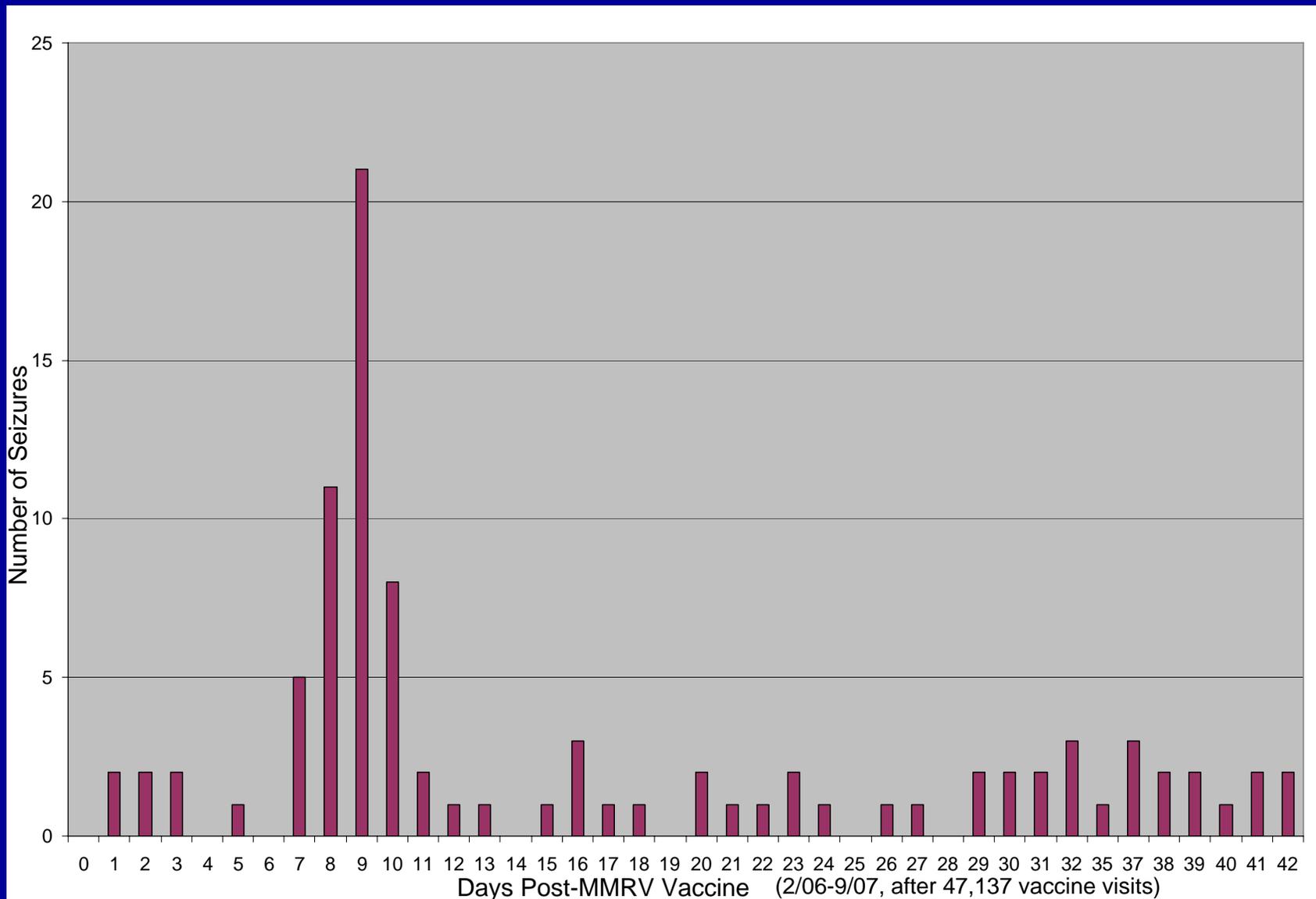
- **Seizure definition:**
 - **First instance coded for epilepsy or convulsion in the Emergency Department or in the inpatient setting in a 42 day period.**
- **MMRV usage began in VSD: January 2006**
- **Data analysis began: late June 2007**
- **Number of doses administered (01/08): >60,000**

RCA Seizure Signal 0-42 Days Post-MMRV Vaccine

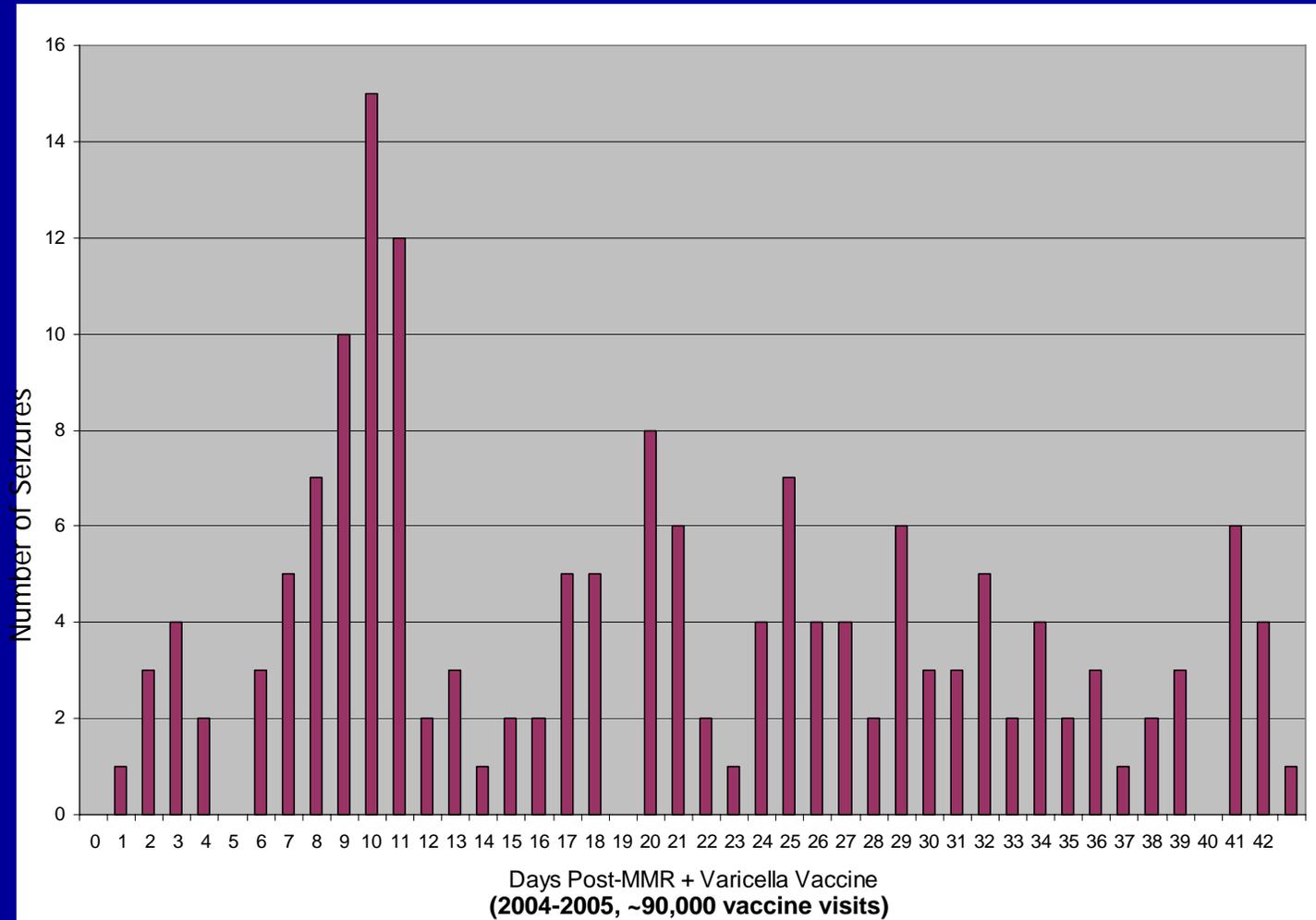
- The number of observed seizures in the 42 day post-vaccination time window first exceeded the number expected by enough to justify a signal in the week of 2/11/07.
- Cumulative doses at that time: 25,779

	Observed	Expected	Relative Risk	LLR (critical value)
Number Seizures	59	38	1.57	5.17 (4.12)

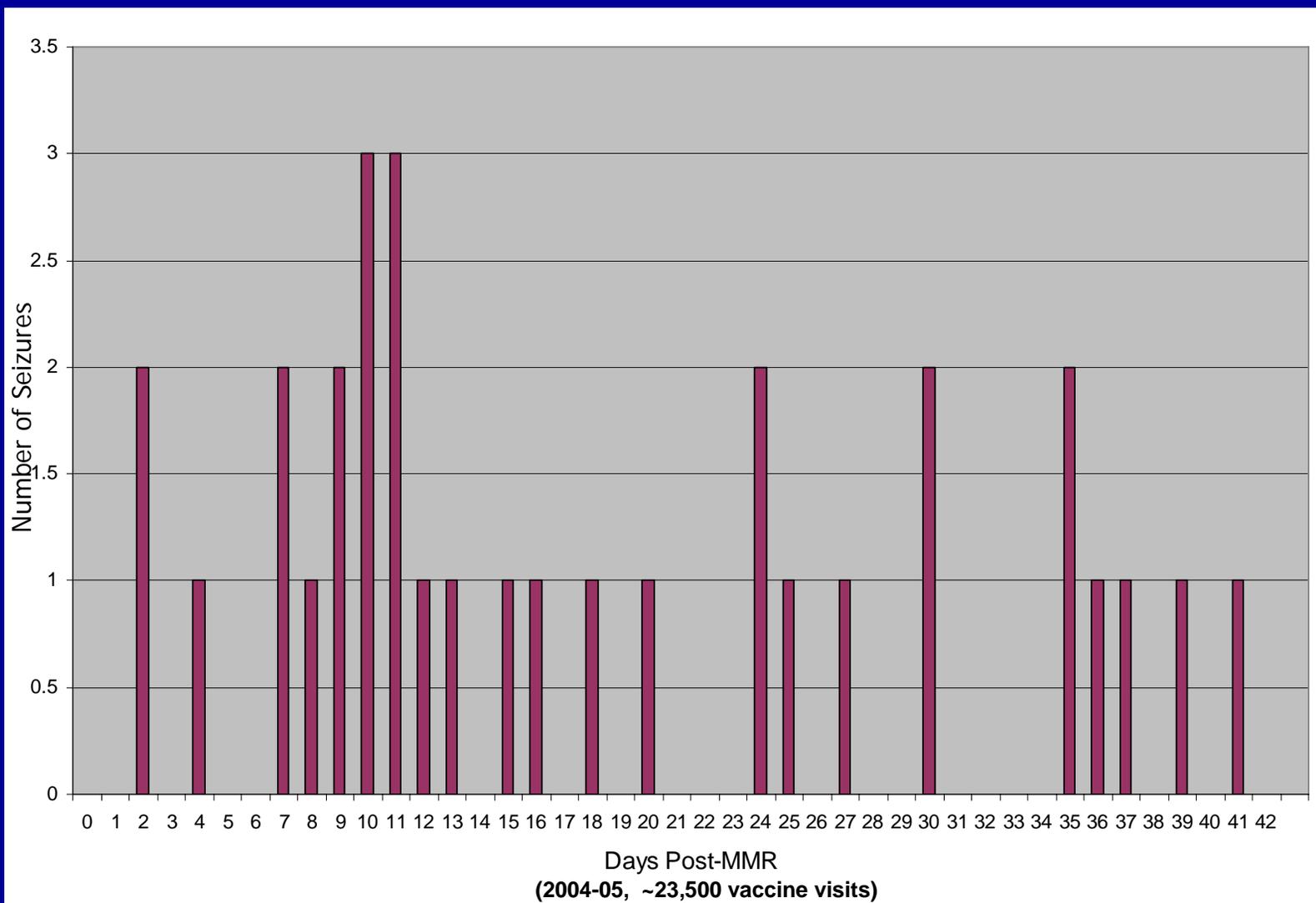
Temporal distribution of seizures after MMRV vaccination



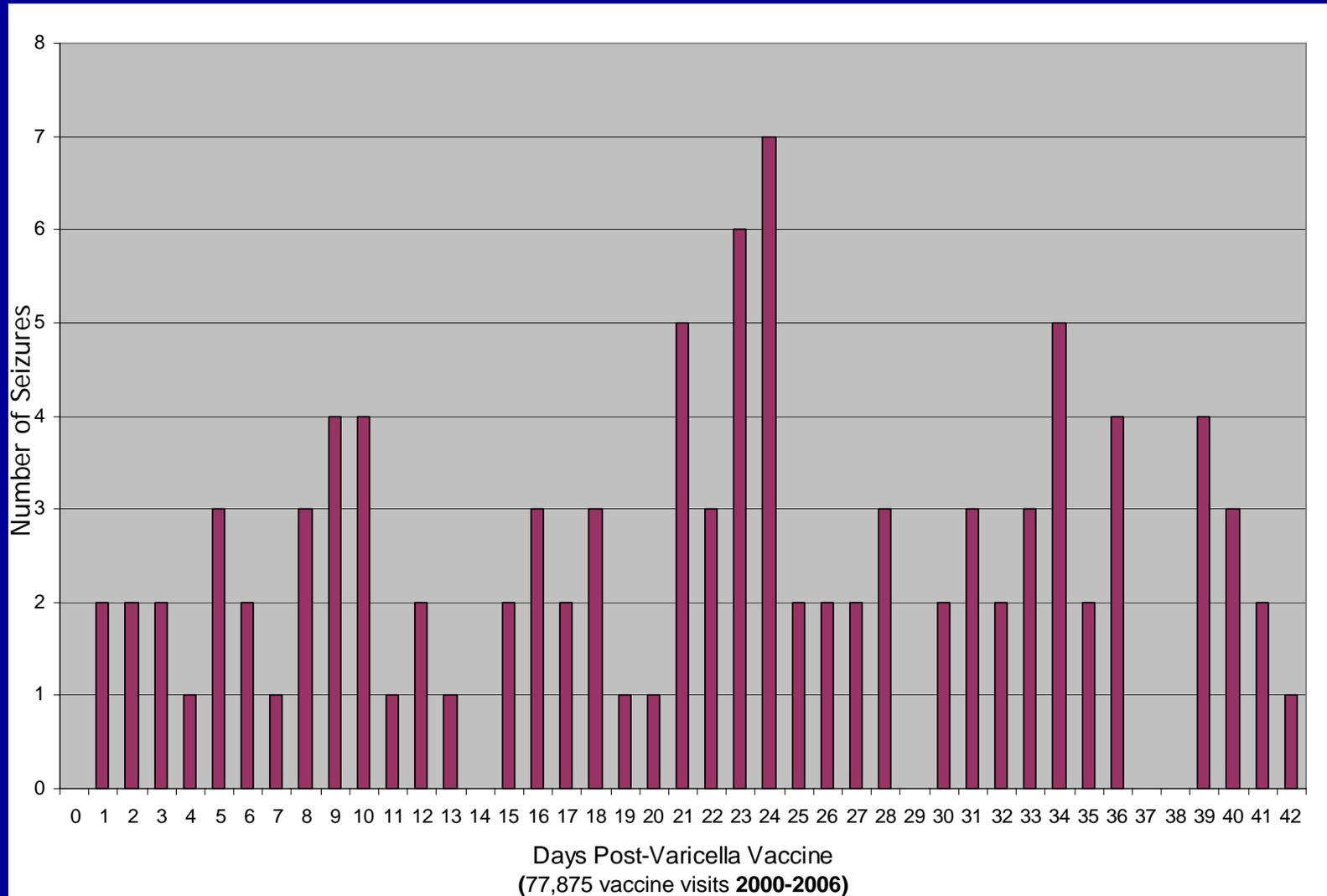
Temporal distribution of seizures after simultaneous MMR and varicella vaccination



Temporal distribution of seizures after MMR vaccination *without* varicella vaccination



Temporal distribution of seizures after varicella vaccination without MMR

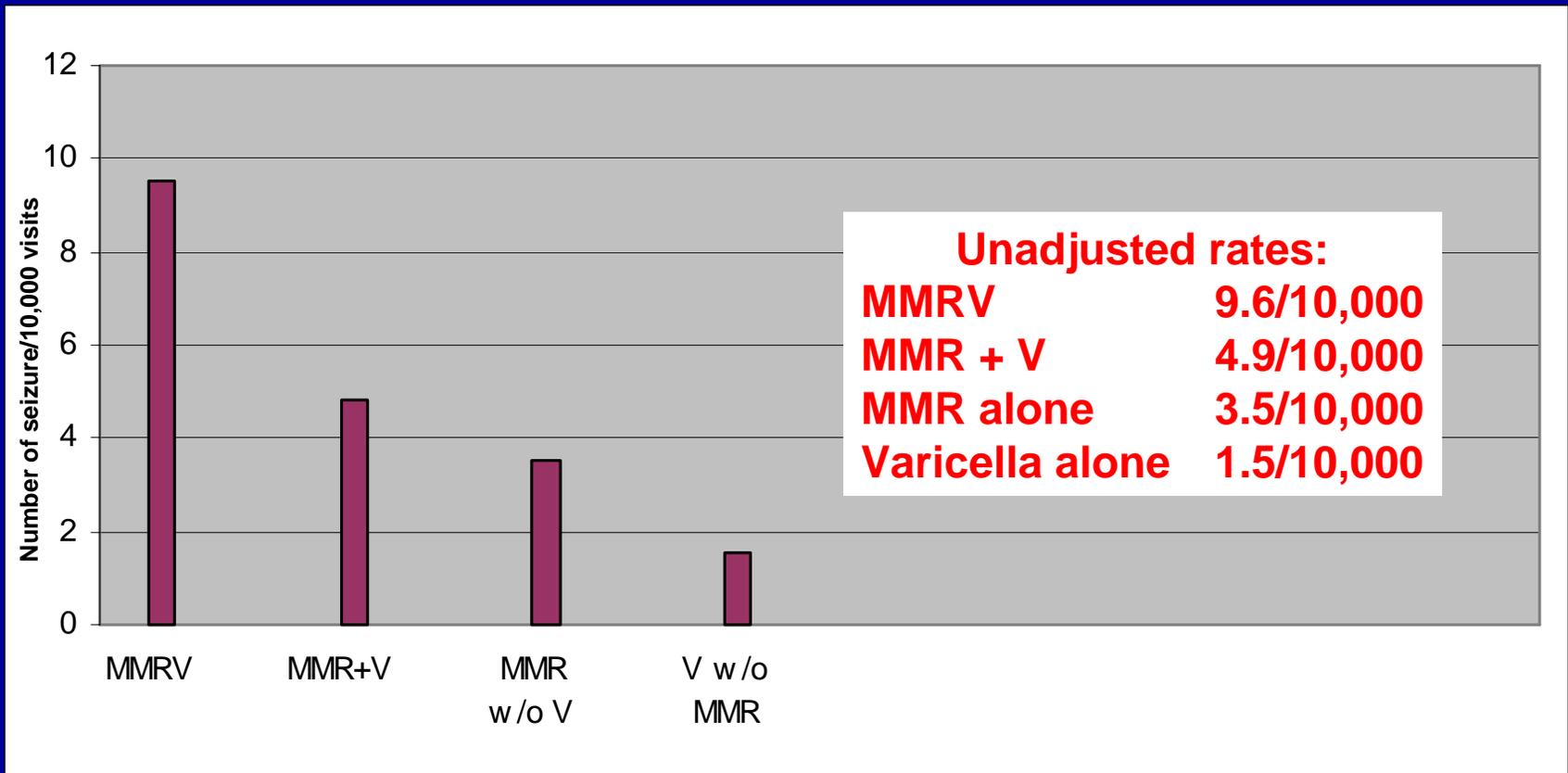


Temporal Scan Results on Seizures in 42 Days after Vaccination

	MMRV	MMR+V*	MMR w/o V*	V* w/o MMR
Total cases	93	164	32	101
Most likely cluster	Days 7-10	Days 7-10	Days 6-10	Days 21-24
Cases in cluster	45	44	11	21
RR	8.9	3.5	3.9	2.5
P-value	0.00001	0.00001	0.063	0.047

* V= varicella vaccine

Unadjusted Rates of Seizures 7-10 Days Post-Vaccination



* V= varicella vaccine

Logistic Regression Analysis: Risk of Seizure 7-10 days after MMRV Compared to MMR + Varicella Vaccines

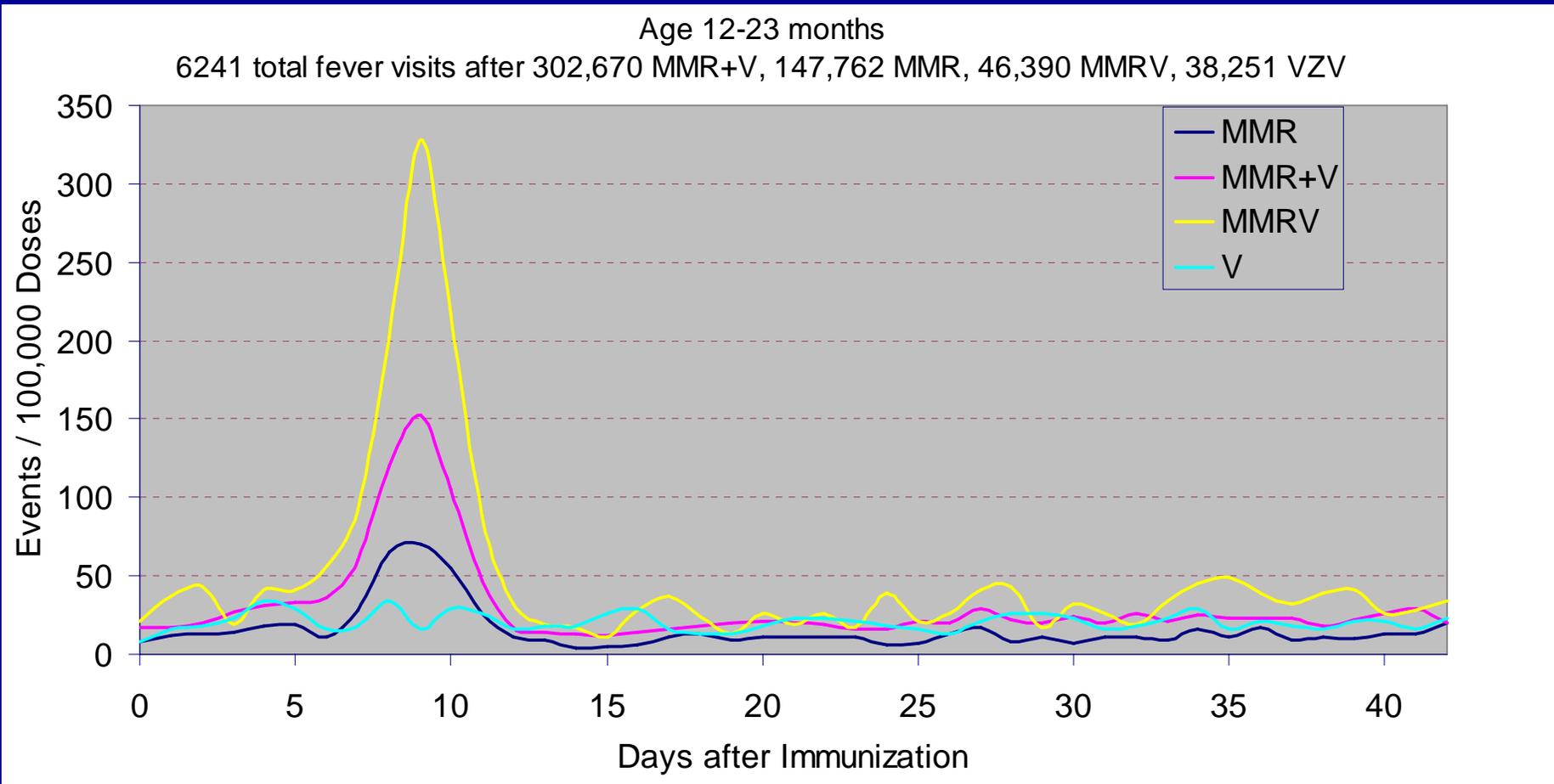
	Odds ratio*	95% Confidence Interval	P-value
MMRV versus MMR + V	2.0	1.4, 2.8	<0.0001

*Adjusted for age and influenza season.

None of the following influenced the association between MMRV and seizures:
Sex, VSD site, concomitant vaccines and seizure temporal trends.

N for MMRV = 43,356, MMR + V = 314,625

Outpatient Visits for Fever by Day after Vaccine at Northern California Kaiser Permanente: 1995-2008



Majority of Charts Confirmed Seizures as Febrile

	MMRV (n=45)	MMR + V* (n=132)
Febrile seizure	42 (93%)	124 (94%)
Afebrile	3 (7%)	3 (2%)
Unknown	0	5 (4%)

*varicella vaccine

Logistic Regression Analyses: Risk of seizure 7-10 days Post-Vaccination using Chart Verified Febrile Seizures

	Odds ratio*	95% Confidence Interval	P-value
MMRV versus MMR + V	2.3	1.6, 3.2	<0.0001

*Adjusted for age and influenza season.

N for MMRV = 43,353, MMR + V = 314,599

Risk Difference during 7-10 Day Post-Vaccination Window

- **Attributable Risk for MMRV compared to MMR + varicella vaccines.**

5.2/10,000 (95% CI 2.2, 8.1)

For every 10,000 children who receive MMRV instead of separate MMR + varicella vaccines, there will be approximately 5 additional seizures 7-10 days after vaccination.

- **Inverse of the above risk difference for MMRV compared to MMR + varicella vaccines in the 7-10 day window (Number Needed to Harm):**

1,939 (95% CI 1,234, 4,516)

There will be approximately 1 additional seizure 7-10 days post-vaccination for every 2000 children vaccinated with MMRV instead of MMR + varicella vaccine.

Chart Review Findings among Febrile Seizure Cases

	MMRV (n=42)	MMR + V (n=124)
Hospitalized	4 (10%)	22 (18%)
First seizure event	30 (71%)	86 (69%)
Family history	8 (19%)	14 (11%)

Risk of Seizure 0-42 Days after MMRV Vaccination Compared to MMR + Varicella Vaccine

	Odds ratio*	95% Confidence Interval	P-value
MMRV versus MMR + V	1.32	1.05, 1.64	0.015

*Adjusted for age and influenza season.

Attributable Risk for MMRV compared to MMR + varicella vaccines.

5.1/10,000 (95% CI 0.5, 9.7)

N for MMRV = 43,406; MMR + V = 314,985

Preliminary Results: Encephalitis/Meningitis

- **As of January 2008, 2 cases of encephalitis in >60,000 MMRV doses administered.**
- **Both cases were among those being investigated for seizures and both occurred 7-10 days after MMRV in late 2006.**

Preliminary Results: Encephalitis/Meningitis

- No etiology for encephalitis was identified for either case.
 - Case 1 (febrile): December 2006. Clinical workup was negative (CSF: 1 WBC, 0 RBC, glucose 103, protein 135, neg for bacteria, viruses, and HSV PCR).
 - Outcome as of February 2007: largely back to baseline, on anti-seizure medication, with possible mild developmental delay. No further information available.
 - Case 2 (afebrile): November 2006. Extensive clinical workup was negative, including laboratory investigation by the state. (CSF: 1 RBC, 1 WBC, glucose 53, protein 26, cultures neg)
 - Outcome as of late 2007: residual sequelae, including seizure disorder and language delays.
- We will continue to monitor via RCA.

Post-Vaccination Seizures Among 4-6 Year Olds at One VSD Site

	MMRV	MMR
0-42 days post-vaccination	9/35,185	19/68,915
7-10 days post-vaccination	2/35,185	3/68,915

Data from the Northern California Kaiser Permanente VSD site only (1/05-2/08).

Summary

- **RCA surveillance detected a seizure signal following MMRV, clustering 7-10 days after vaccination.**
- **Chart review data confirmed >90% seizures were febrile.**
- **Adjusted odds ratio is 2.3 for having a confirmed febrile seizure 7-10 days post-MMRV compared to MMR + varicella vaccine.**
 - **Increased risk with MMRV cannot be explained by concomitant vaccines, temporal trends in seizure, VSD site, age or influenza season.**
- **There was no difference in hospitalizations post-vaccination, personal or family history of seizures between MMRV and MMR + varicella vaccine recipients.**

Summary

- **Attributable risk for seizures on days 7-10 after MMRV is 1 per 2000 doses when compared to separate MMR + varicella vaccines.**
- **RCA will continue to monitor for encephalitis.**
- **VSD has limited power to assess risk of seizures after MMRV among older children.**

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

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Additional Slides

Risk Difference during 0-42 Day Post-Vaccination Window

**Inverse of the risk differences for MMRV
compared to MMR + varicella vaccines.**

1,958, (95% CI 1,033, 18,700)

Concomitant Vaccines

	Seizures Days 7-10	Seizures days 0-6 or 11-42	No seizures 0-42 days
Received MMRV with concomitant vaccines (%)	95.7	98.2	96.3

- Concomitant vaccines (hepatitis A, PCV1, Hib, influenza and DTaP) were not significant predictors for seizure, either for MMR + V compared to MMRV nor for MMRV recipients alone.
- The number of concomitant vaccines was not a significant predictor of seizures in the model.
- Frequencies of seizures by number of concomitant vaccines were similar between groups.