

Real-Time Vaccine Safety Surveillance  
for the Early Detection of Adverse  
Events

CDCs Vaccine Safety Datalink Project

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# Vaccine Safety Data Link

## **Collaborators – partial list**

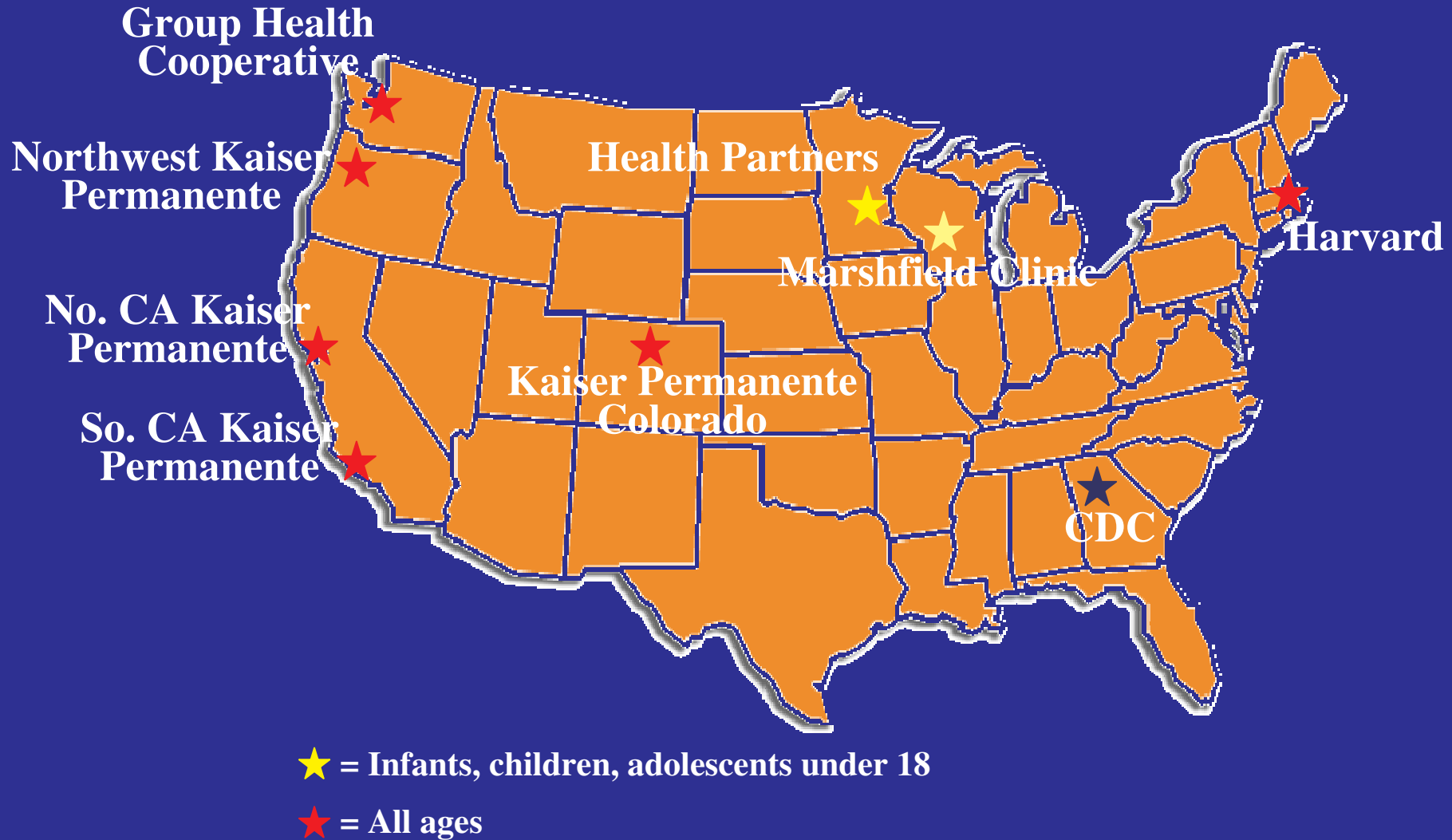
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GHC, Group Health Cooperative; HAR, Harvard; KPC, Kaiser Permanente Colorado; NCK, Northern California Kaiser

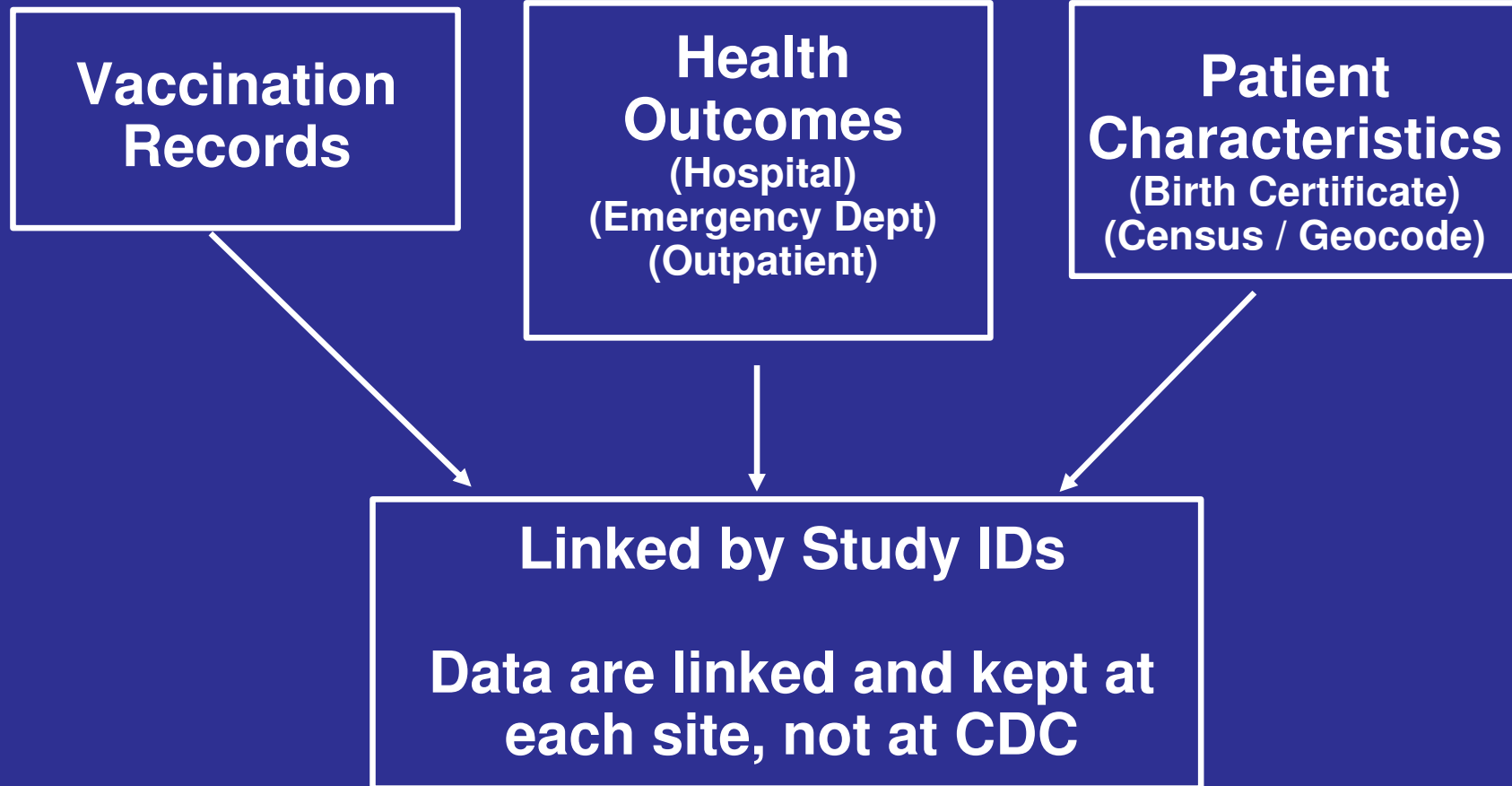
# Vaccine Safety Datalink (VSD) Project

- Rapid Cycle Analysis for Early Detection of Vaccine Adverse Events
- Sponsored by the Centers for Disease Control and Prevention (CDC)
- Collaborative effort of CDC and 8 Health Insurance Plans
- Data on >5.5 million persons annually, ~ 1.9% of U.S. population
- At the end of 2005: 2.3 million children, 3.2 million adults

# Vaccine Safety Datalink Sites



# VSD Data



# Rapid Cycle Analysis / Sequential Analysis

- A new approach to surveillance that takes advantage of VSD's strengths
- VSD now updates data on all vaccines and all outcomes every week
- We conduct updated analyses every week

# Surveillance via Rapid Cycle Analysis of VSD Data

- Menactra – for Guillain-Barre syndrome and other outcomes
- Rotateq – for intussusception, gastrointestinal bleeding and other outcomes
- MMRV and Tdap – for seizures and other outcomes
- HPV and influenza – being implemented

# Basics of Rapid Cycle Analysis

- For each vaccine, choose specific outcomes to monitor
- Hypothesis testing, not data mining
- Each week, evaluate the number of outcomes in vaccinated persons
- Compare it to the expected number of outcomes based on a comparison group

# Sequential Analysis Methods

- Each week, our analysis includes data from all previous weeks
- Problem: Repeated testing of the same data increases the chance of false-positive results
- Need to adjust for this statistically
- Solution: Maximized sequential probability ratio test

# Maximized Sequential Probability Ratio Test (MaxSPRT)

- $H_0: RR=1$
- $H_A: RR>1$  (composite alternative)
- $\alpha=0.05$

# MaxSPRT

Log likelihood ratio test statistic at time t:

$$\text{LLR}(t) = \max_{RR > 1} \ln \left( \prod_{i=1}^t \frac{P(c_i | H_A(RR))}{P(c_i | H_0)} \right)$$

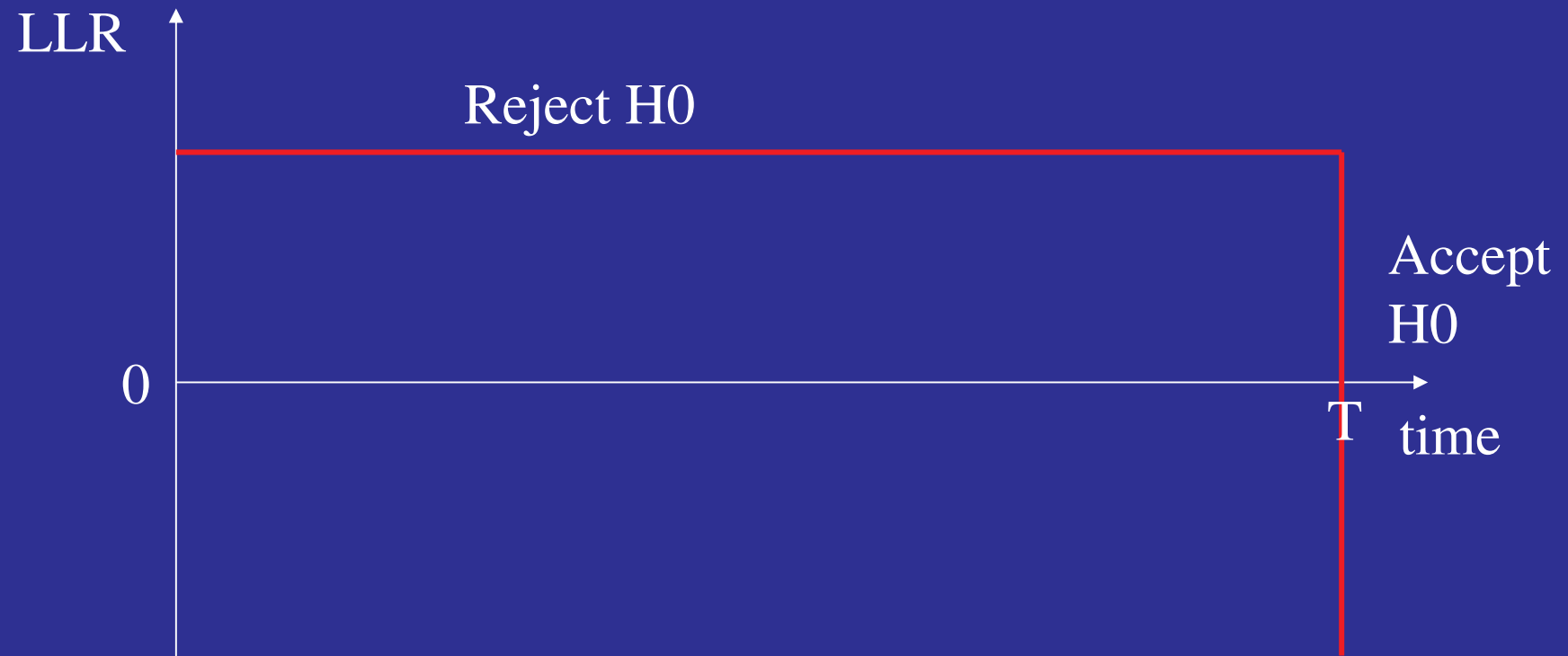
where  $c_i$  = the observed number of events at time i.

Reject  $H_0$  when  $\text{LLR}(t) > B$

Reject  $H_A$  when  $t > T$

Specify  $\alpha$  and  $T$  in advance, calculate  $B$ .

# Critical Bounds



# Maximum Length of Surveillance

The maximum length of surveillance,  $T$ , is defined in terms of expected events under the null, which is approximately equal to the number of vaccine doses.

# Expected Counts

Expected counts may be based on for example

- Historical Data
- Estimates from the Literature
- Concurrent Matched Controls

> KEY ISSUE

# Setting Up A Rapid Cycle Analysis

- Choose outcomes to monitor
- Choose comparison method(s) – e.g., historical, concurrent
- Set the upper limit for when to stop

# Choosing Outcomes

Select outcomes based on:

- Pre-licensure data
- Known biologic properties of the vaccine
- Adverse events for similar vaccines
- Clearly defined, e.g., Guillain-Barre syndrome rather than “neurologic problems”
- Acute-onset
- Relatively uncommon and serious

# Historical Comparison Method

- Uses incidence rates from historical data
  - Advantage: Knowing the historical rate of rare events allows earlier recognition that a small number of cases is unusual
  - Example: 4 cases of Guillain-Barre syndrome in vaccinees, 0 expected
  - Limitation: Background rates may vary over time (secular trends)

# Comparison Groups

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Menactra <sup>®</sup>	Teens making preventive visits
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Rotateq <sup>®</sup>	Infants who received any other vaccine
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MMRV	Toddlers who received MMR or MMR+V
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Tdap	Teens who received Td
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HPV	Female teens and 18-26 yr old females with preventive visits
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# Results: Menactra

- No MaxSPRT signals to date
- That's good!
- Surveillance terminated for most outcomes
- Still monitoring for Guillain-Barre syndrome

# When a Signal Occurs

- In a surveillance setting for multiple vaccines and outcomes, it is not possible to adjust for all possible confounders
- Not all signals represent a true increase in risk
- When a signal occurs, we conduct a series of evaluations using traditional epidemiologic methods

# How We Evaluate Signals – 1

1. Check data quality
2. Check whether comparison groups are defined appropriately
3. Conduct the analysis using a different control group (e.g., concurrent vs. historical) or different vaccine

## How We Evaluate Signals – 2

4. Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window
5. Conduct a definitive study using logistic regression analysis
6. Review charts to confirm or exclude cases as true cases

# Example of Signal Evaluation: Rotateq<sup>®</sup> and GI bleeding

- Nov 2006 – 6 GI bleeding diagnoses had occurred among 3,400 vaccine recipients, vs. 1.3 expected from the historical incidence rate
- RR 4.7, LLR 4.6 → Signal
- Problem – Historical incidence rate hadn't been adjusted for age and secular trend
- Resolution – signal disappeared

# Example of Signal Evaluation: Rotateq<sup>®</sup> and GI bleeding

- Feb 2007 – 36 GI bleeding diagnoses had occurred among 27,000 vaccine recipients, vs. 18 expected from the historical incidence rate
- RR 2.0, LLR 6.7 → Signal

# Example of Signal Evaluation: Rotateq<sup>®</sup> and GI bleeding

Definitive analysis – logistic regression comparing Rotateq<sup>®</sup> recipients with the concurrent comparison group – no signal

- Age, seasonality, and VSD site were associated with GI bleeding
- Rotateq<sup>®</sup> exposure was not

Conclusion – No true increase in risk

# **Vaccine Safety Datalink Project: Evaluation of MMRV and Febrile Seizures**

## **Northern California Kaiser Permanente**

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- **Bruce Fireman, MS**
- **Nicola Klein (PI), MD, PhD**
- **Paula Ray, MPH**
- **Liisa Lyons**
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- **Martin Kulldorff, PhD**

## **CDC**

- **Eric Weintraub**
- **James Baggs, PhD**
- **Julianne Gee, MPH**
- **John Iskander, MD, MPH**
- **Karen Broder, MD**

# **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.**
- **The Advisory Committee on Immunization Practices 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.**
- **In VSD, MMRV usage began in 2006, but analyses did not start until 2007**
- **Number of doses administered (01/08): >60,000**

# MaxSPRT Seizure Signal

- 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

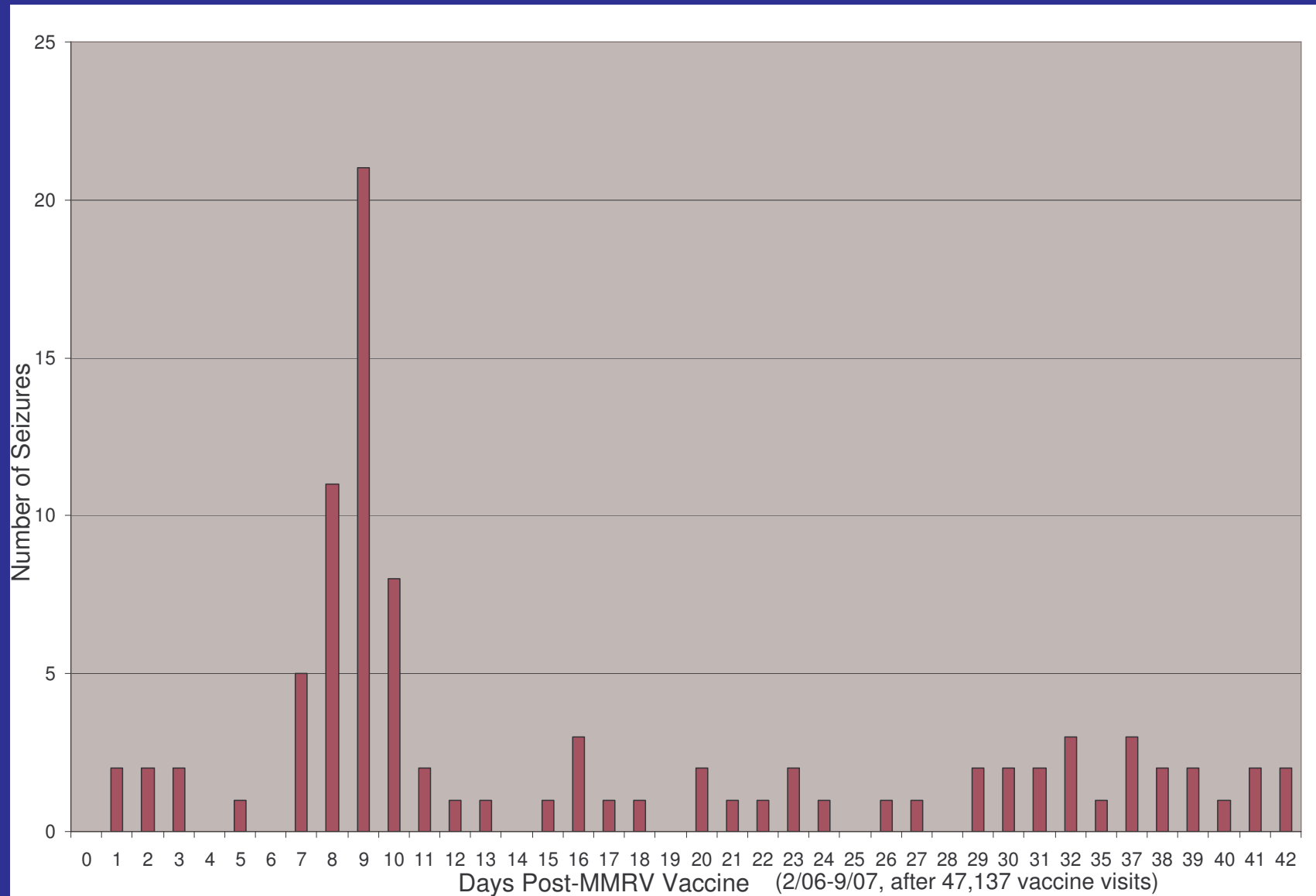
	Observed	Expected	Relative Risk	LLR (critical value)
Number Seizures	59	38	1.57	5.17 (4.12)

## Temporal Scan Statistics Results on Seizures in 42 Days after Vaccination

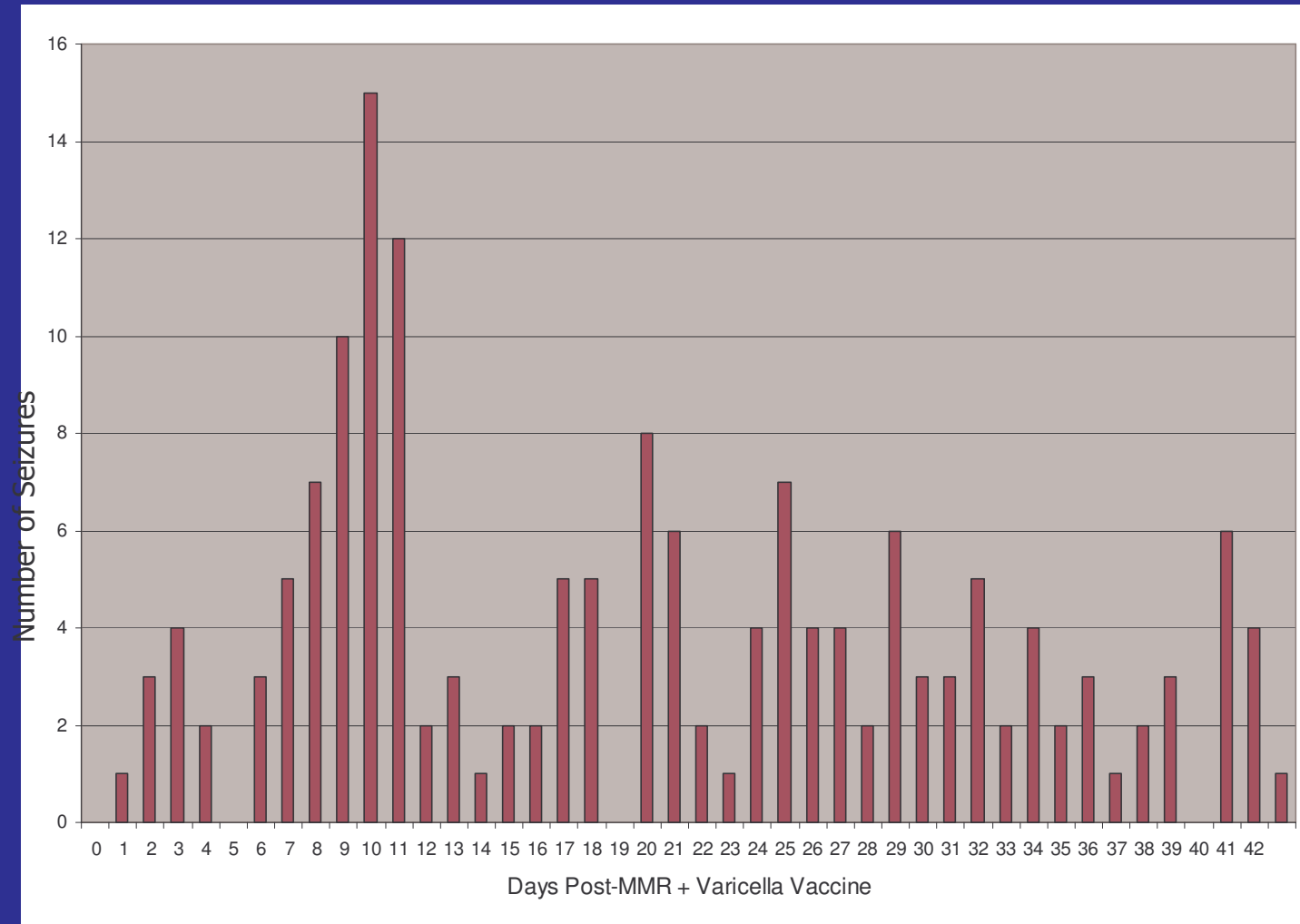
	MMRV	MMR+V*	MMR w/o V*	V* w/o MMR
<b>Total cases</b>	<b>93</b>	<b>164</b>	<b>32</b>	<b>101</b>
<b>Most likely cluster</b>	<b>Days 7-10</b>	<b>Days 7-10</b>	<b>Days 6-10</b>	<b>Days 21-24</b>
<b>Cases in cluster</b>	<b>45</b>	<b>44</b>	<b>11</b>	<b>21</b>
<b>RR</b>	<b>8.9</b>	<b>3.5</b>	<b>3.9</b>	<b>2.5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

\* V= varicella vaccine

# Temporal distribution of seizures after MMRV vaccination

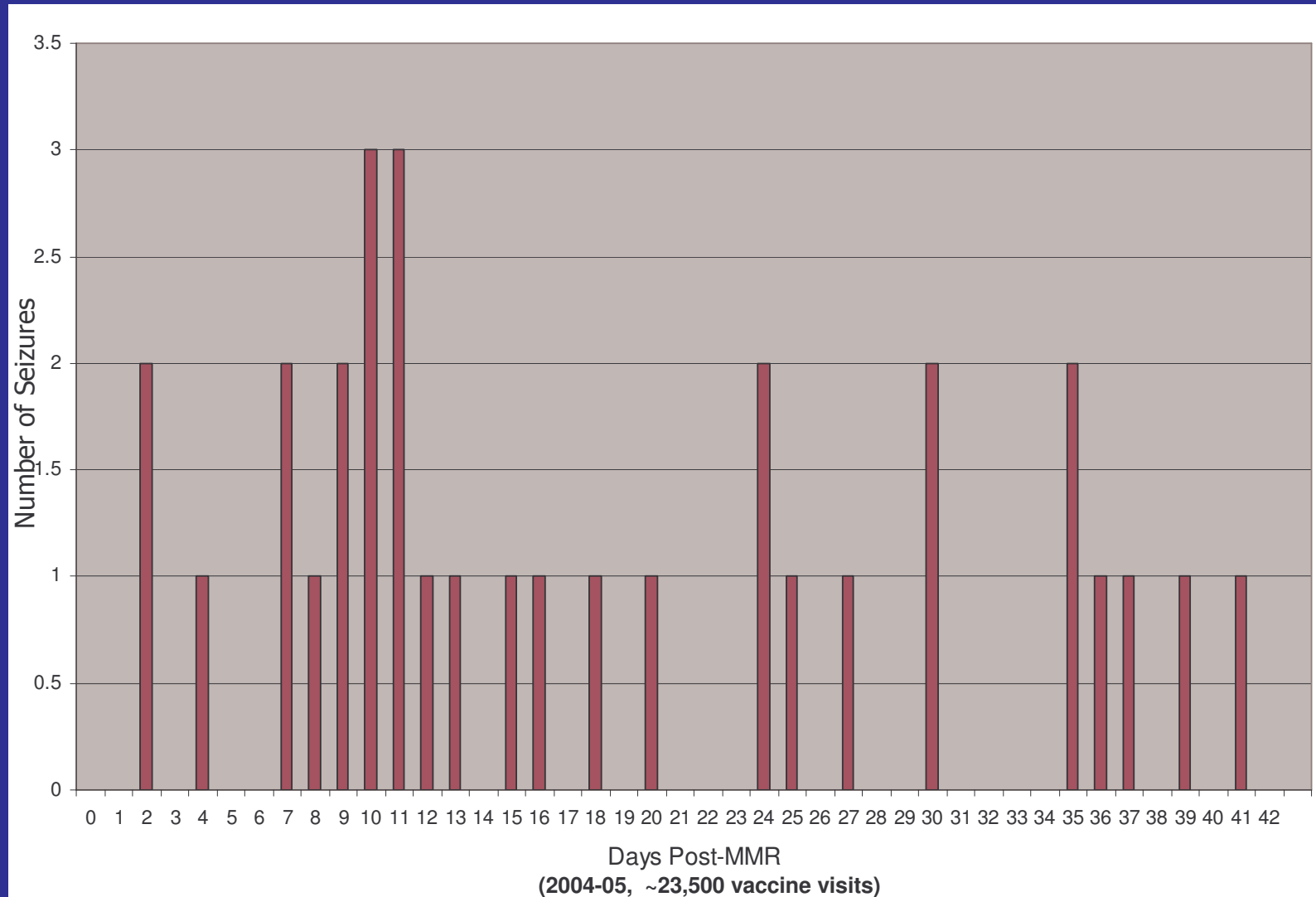


# Temporal distribution of seizures after simultaneous MMR and varicella vaccination

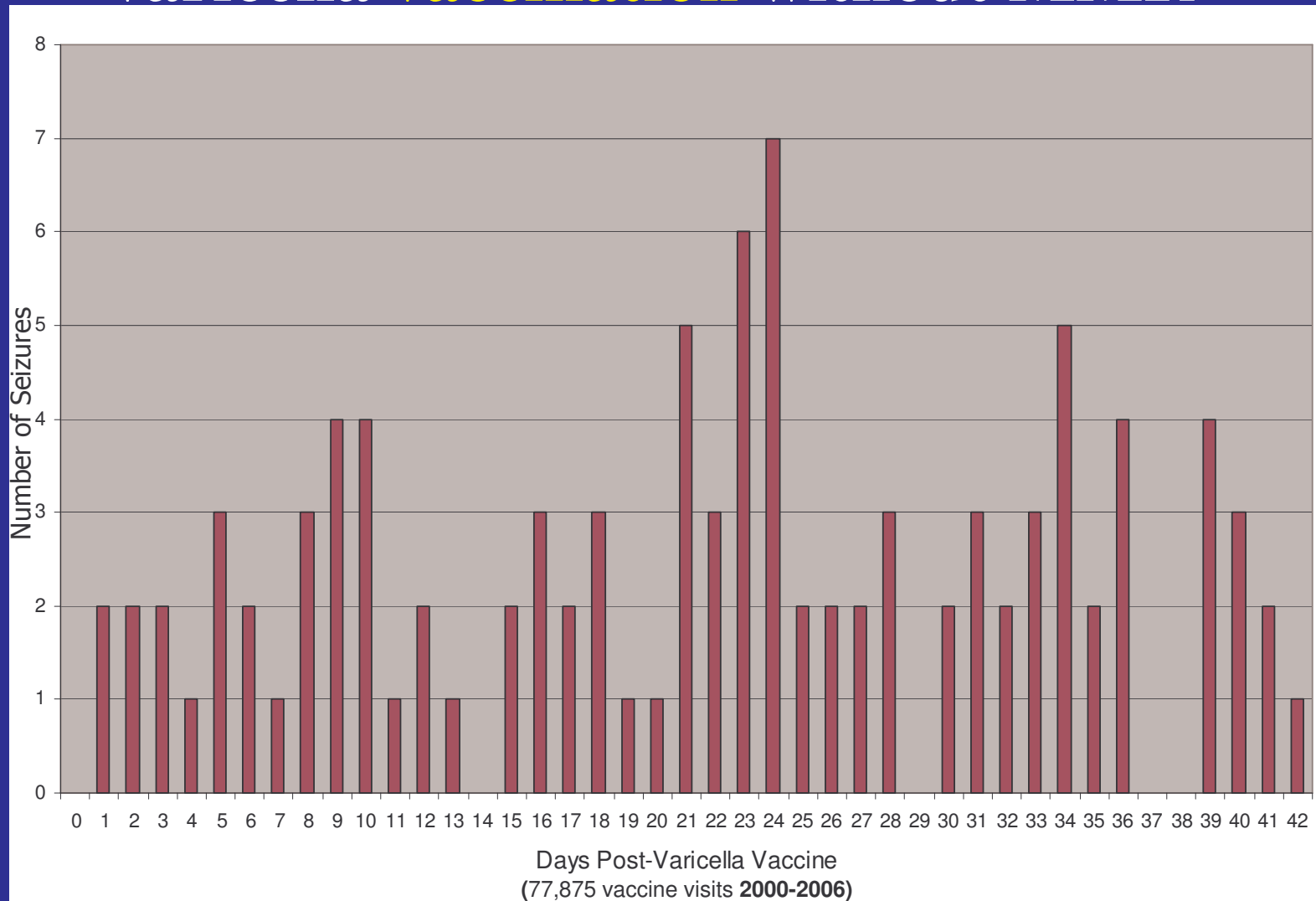


(2004-2005, ~90,000 vaccine visits)

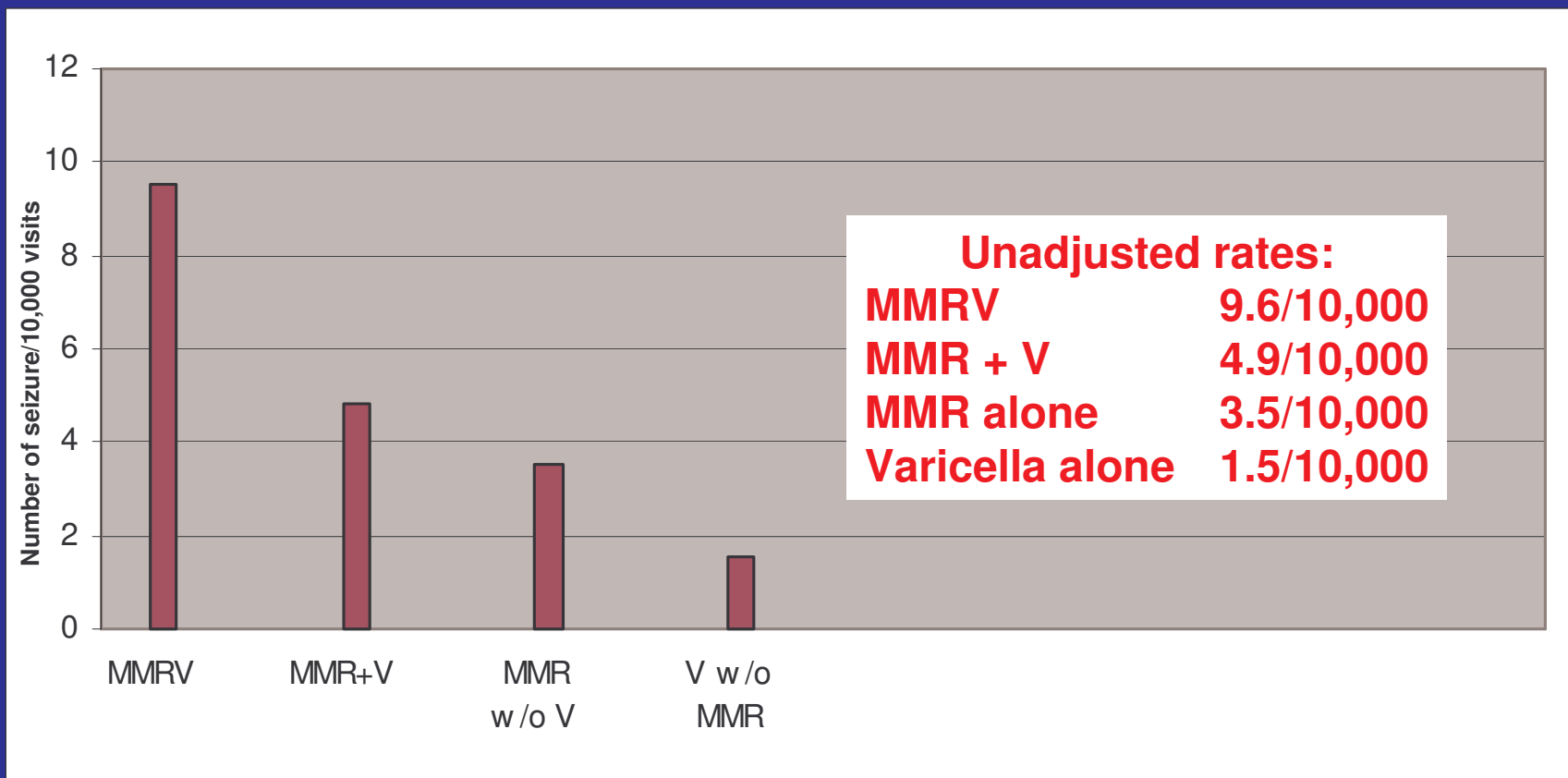
# Temporal distribution of seizures after MMR vaccination *without* varicella vaccination



# Temporal distribution of seizures after varicella vaccination without MMR



# 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**

	<b>Odds ratio*</b>	<b>95% Confidence Interval</b>	<b>P-value</b>
<b>MMRV versus MMR + V</b>	<b>2.0</b>	<b>1.4, 2.8</b>	<b>&lt;0.0001</b>

**\*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**

# 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**

	<b>Odds ratio*</b>	<b>95% Confidence Interval</b>	<b>P-value</b>
<b>MMRV versus MMR + V</b>	<b>2.3</b>	<b>1.6, 3.2</b>	<b>&lt;0.0001</b>

**\*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)**

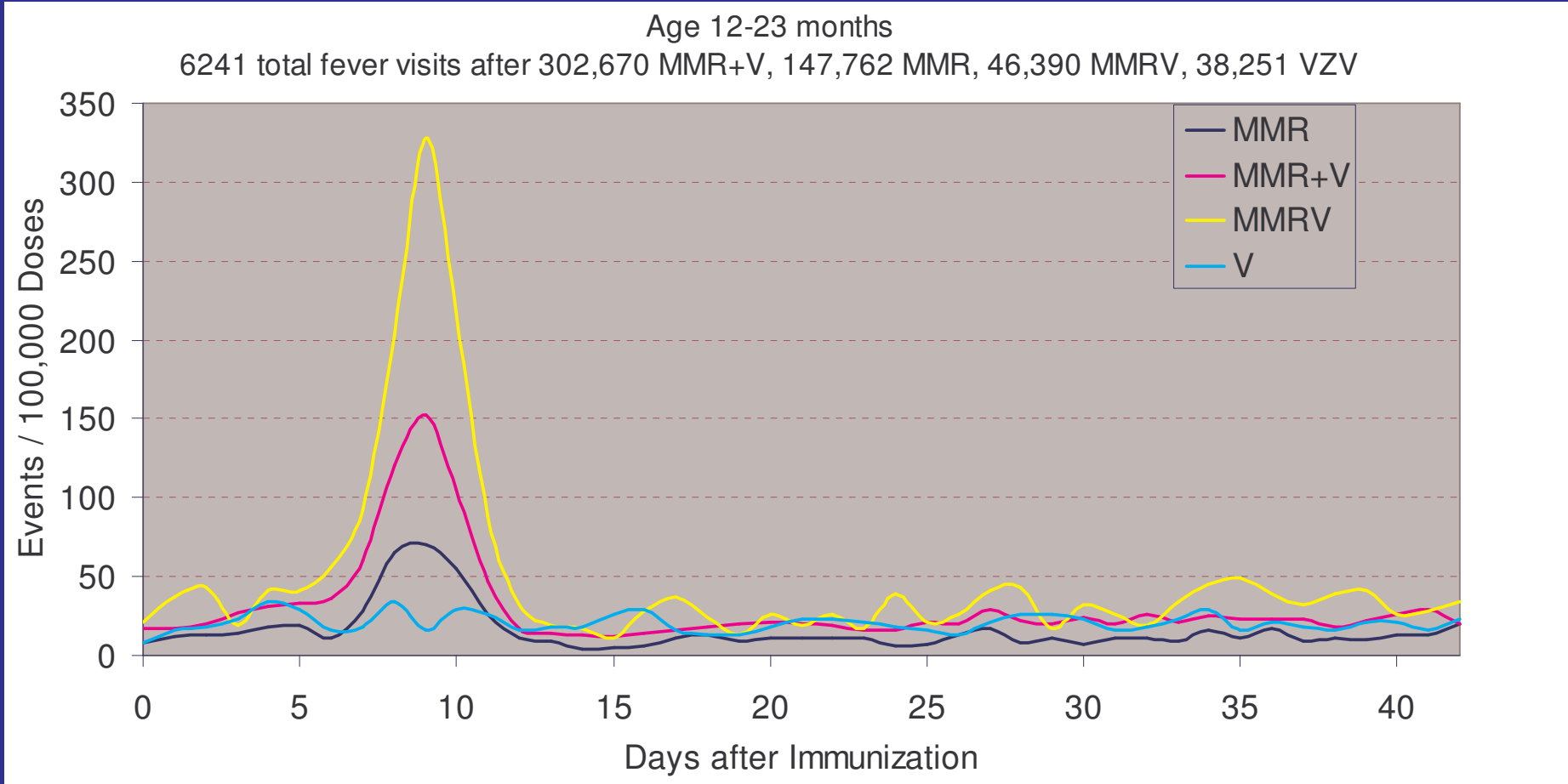
For every 10,000 children who receive MMRV instead of separate MMR + varicella vaccines, there will be approximately 5 additional seizures 7-10 days after vaccination.

- **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.

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



# 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.**
- **Attributable risk for seizures on days 7-10 after MMRV is 1 per 2000 doses when compared to separate MMR + varicella vaccines.**

# Conclusions

- On February 27, 2008, the Advisory Committee on Immunization Practices revised its recommendation by a vote of 10-2, no longer recommending the MMRV vaccine over separate MMR and Varicella vaccines
- On the same day, Merck and FDA revised the product label for MMRV, including information about the increased risk of seizures 7-10 days after vaccination.
- Additional follow-up studies are under way to evaluate the shift hypothesis

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.

# References

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