

Vaccine Safety Datalink Project: Review of MMRV and Febrile Seizures Study

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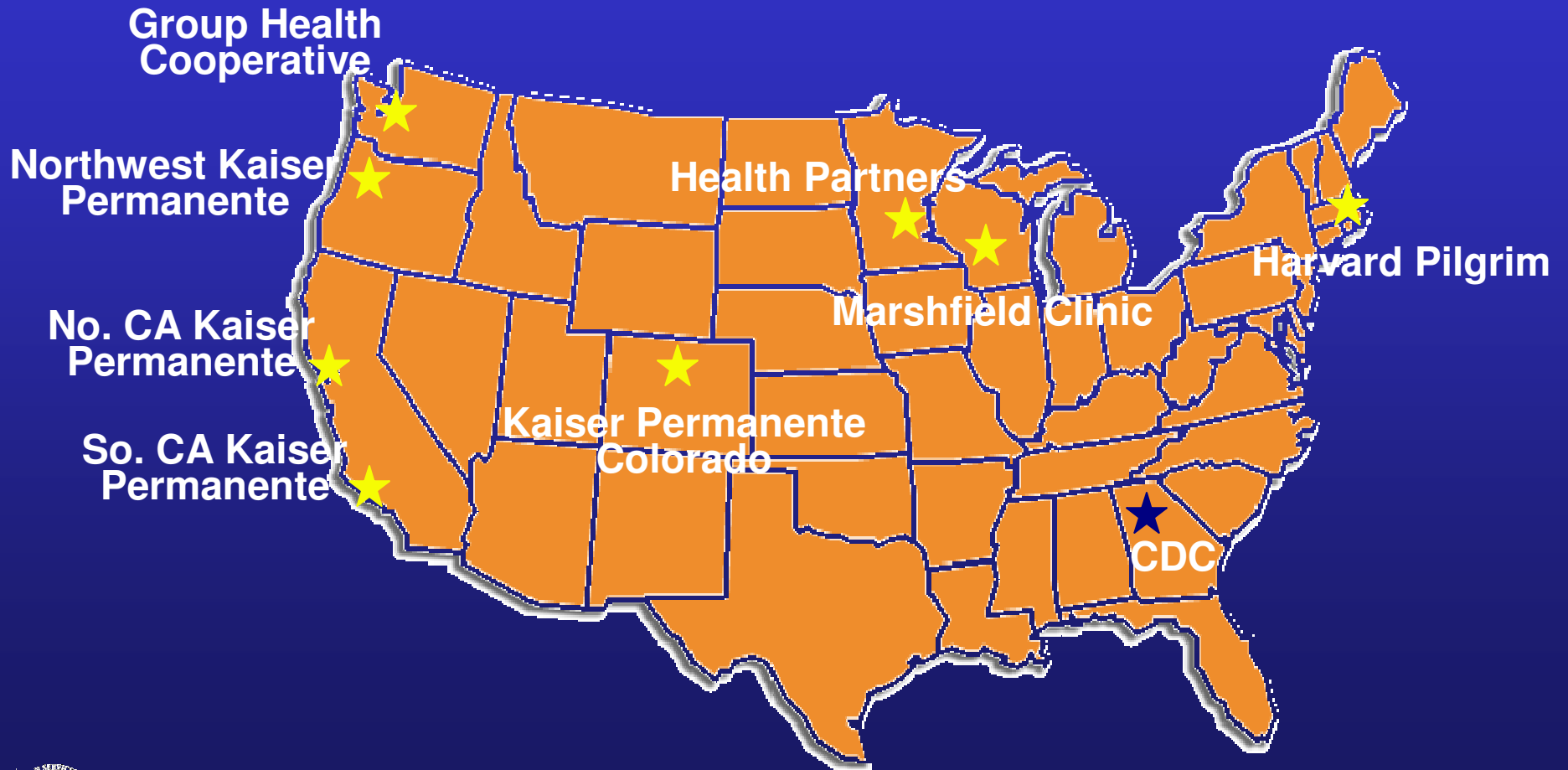
Outline

- Review preliminary results from the Vaccine Safety Datalink (VSD) study evaluating the risk for confirmed febrile seizures in children aged 12–23 months following receipt of MMRV dose 1
 - Data presented by Dr. Klein during February 28, 2008 ACIP meeting
- Summarize preliminary data on risk for seizures in children aged 4–6 years at one VSD site



Vaccine Safety Datalink

Collaboration between CDC and 8 managed care organizations
8.8 million members captured annually
(3% of US population)



Vaccine Safety Datalink Rapid Cycle Analysis (RCA)

- Conducted near real-time surveillance for specified outcomes during the 0–42 days following MMRV vaccine in 7 VSD sites (excluding SCK)
- Study population - children aged 12-23 months
 - 1st Seizure of any etiology in 42 day period
 - ICD-9 codes: 345.* (epilepsy), 780.3* (convulsions, febrile convulsions, other convulsions)
 - Limited to: emergency department or a hospitalization visit
 - Other outcomes monitored
 - Ataxia
 - Meningitis/ encephalitis
 - Thrombocytopenia
 - Arthritis
 - Allergic reaction



Vaccine Safety Datalink RCA (cont)

- A signal for seizures was detected in the 0–42 day period following MMRV compared with historical rates in MMR recipients
- Temporal scan statistics found significant clustering of seizure cases on days 7–10 after
 - MMRV vaccination
 - MMR and varicella vaccination (MMR+V) on the same day
- These two findings prompted an epidemiologic study in VSD to assess the risk for febrile seizures during days 7–10 after MMRV vaccination



VSD MMRV Follow Up Epidemiologic Study

- Study population: children aged 12–23 months who received MMRV or MMR+V
 - MMRV: contemporary cohort, 1/2006–8/2007
 - MMR+V: a largely historical cohort, 1/2000–8/2007
 - Dose 1 only
- Charts were reviewed for children with seizures during the 7–10 day post-vaccination period
 - For confirmation of febrile seizures
 - Diagnosis in the chart of a febrile seizure associated with an emergency department or a hospitalization visit



Risk for Confirmed Febrile Seizure During Days 7-10 After Vaccination: MMRV vs. MMR+V

- Unadjusted rate of febrile seizures 7–10 days following dose 1
 - 9 per 10,000 vaccinations among MMRV recipients
 - 4 per 10,000 vaccinations among MMR+V recipients

Logistic regression - adjusted for age and influenza season

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

- N=43,353 for MMRV (40 febrile seizures, days 7-10)
- N=314,599 for MMR + V (128 febrile seizures, days 7-10)



Attributable Risk for Confirmed Febrile Seizure During 7–10 Days After Vaccination: MMRV vs. MMR+V

- Attributable Risk for MMRV compared to MMR+V

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

For every 10,000 children who receive MMRV instead of separate MMR+V, there will be approximately 5 additional febrile seizures 7–10 days after vaccination

- Inverse of the above attributable risk for MMRV compared to MMR+V in the 7–10 day window (Number Needed to Harm)

1,923 (95% CI 1,235, 4,545)

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



Rates of Post-vaccination Unconfirmed Seizures Among Children Aged 4–6 Years

Post-vaccination Interval	MMRV Seizure Rate (frequency)	MMR+V Seizure Rate (frequency)
<u>7–10 days</u>	0.7 per 10,000 (4 per 56,535)	0 per 10,000 (0 per 44,836)
<u>0–42 days</u>	2.5 per 10,000 (14 per 56,535)	2.0 per 10,000 (9 per 44,836)

Data from the Northern California Kaiser Permanente VSD site (1995-2008); seizures identified from automated data without chart review



Summary

Children Aged 12-23 Months

- RCA surveillance detected a seizure signal following MMRV, clustering 7-10 days after vaccination
- Adjusted odds ratio is 2.3 for having a confirmed febrile seizure 7-10 days post-MMRV compared to MMR+V
- The increased risk with MMRV cannot be explained by other factors:
 - Simultaneous vaccination, temporal trends in seizures, VSD site, age or influenza season
- Attributable risk for febrile seizures on days 7–10 after MMRV is 1 per approximately 2000 doses when compared to separate MMR+V

Children Aged 4-6 Years

- Current VSD analysis conducted at one site using automated data
 - Seizure events were rare 7-10 days after MMRV
 - Current analysis has limited power to assess the risk of seizures after MMRV



MMRV RCA Team

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



Disclosure

- CDC, our planners, and the VSD investigators wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters except as noted below
 - Dr. Klein reports receiving research support from Merck



Additional Slides



Logistic Regression Analysis, Automated Data: Risk of Seizure 7–10 days after MMRV Compared with MMR+V, children aged 12–23 months

	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

