# MMRV Vaccine Safety Working Group: Interim Synthesis of Evidence for Febrile Seizure Risk after MMRV Vaccination and Considerations for Future Activities

**Advisory Committee on Immunization Practices Meeting**
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# Outline: MMRV Vaccine (ProQuad®) and Risk for Febrile Seizures

- Background on Febrile Seizure
- Evidence Framework for Risk Assessment
- Interim Evidence Synthesis for Dose 1 MMRV
- Considerations for Future Activities

# Febrile Seizures*

- Seizures that occur in febrile children who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures[1,2]
  - Usually occur at ages 6–60 months
  - Peak age 14–18 months
- Affects 2%–5% of young children in the United States[1]
- Generally excellent prognosis[1,2]
  - Children with simple febrile seizures are not at greater risk for epilepsy than general population


**1. AAP. Pediatrics. 2008.**

**2. Johnston M. Nelson Textbook of Pediatrics. 2007.**


*Adapted from presentation to the MMRV WG by Dr. Brown, University of Pennsylvania

# Pathophysiology of Febrile Seizures*

- Age-related increased susceptibility to seizures induced by fever
- Peak temperature is a major determining factor[1]
- Certain infections (e.g. rosela [HHV6], salmonella, shigella) have higher likelihood of febrile seizure
- DTP and MMR vaccines are transiently associated with increased risk for febrile seizures[2]

1. Berg AT, et al. Epilepsia 36:334, 1995
2. Davis. Pediatric Drugs. 2003.

*Adapted from presentation to the MMRV WG by Dr. Brown, University of Pennsylvania

# Evidence Framework Used to Assess MMRV Vaccine and Febrile Seizure Risk*

| Evidence Line | Status/ Description |
|---|---|
| **Clinical Importance of Event** | To be assessed after October 2008 ACIP meeting: requires consideration of medical impact and perceived severity of adverse event following immunization (AEFI). |
| **Population-based Risk** | Assess the epidemiologic evidence regarding a possible causal relationship between the vaccine exposure and the AEFI. |
| **Biological Plausibility** | Assess the biological plausibility of the association between the immunization and the AEFI. The association should be explicable biologically according to known facts in the natural history and biology of the disease, antigen and/or host response. |

*Adapted from criteria used by the Institute of Medicine (IOM), World Health Organization (WHO), and draft guidance from the ACIP Evidence Based Recommendations Working Group (EB WG)

# MMRV Vaccine Safety Working Group (MMRV WG) Approach: Synthesis of Evidence Regarding Risk for Febrile Seizures after MMRV Vaccine

- Examined methods and results of two unpublished, postlicensure studies of dose 1 MMRV (ProQuad®) vaccine and risk for febrile seizures*
  - Vaccine Safety Datalink (VSD) Project: Preliminary results
  - Merck-sponsored study: Final results
- Addressed biological plausibility through
  - Review of prelicensure data for MMRV, MMR, and varicella vaccines and other relevant medical literature
  - Consultation with experts
- Conducted WG member survey and discussed input within the WG to rate quality of evidence

*** VSD study Principal Investigator (PI): Dr. Klein; Merck-sponsored study PI: Dr. Jacobson**

# Quality of Evidence Grading Definitions*

| Level | Definition |
|---|---|
| High | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | Moderate confidence that the evidence reflects the true effect. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low | Low confidence that the evidence reflects the true effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very Low | Any estimate of effect is very uncertain. |

***From draft ACIP Evidence Based Recommendation Working Group guidance**



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# Interim Synthesis of Evidence for Febrile Seizure Risk after Dose 1 MMRV Vaccine

# Summary Results from VSD and Merck-sponsored Studies for Confirmed Febrile Seizures Dose 1 MMRV vs. MMR and Varicella Vaccines

| Post-vaccination Interval | VSD<br>All aged 12–23 months | Merck-sponsored<br>99% aged 12–23 months* |
|---|---|---|
| Weeks 1–2 | **7–10 days†**<br>**OR: 2.3**<br>**(95% CI: 1.6, 3.2)**<br>**AR: 5.2 per 10,000**<br>**(95% CI: 2.2, 8.1)** | **5–12 days†**<br>**RR: 2.2**<br>**(95% CI: 1.0, 4.7)**<br>**AR: 3.8 per 10,000**<br>**(95% CI: 0.3, 7.4)** |
| Weeks 3–4 | No chart review done | 13–30 days<br>RR: 0.6 (95% CI: 0.3, 1.1)<br>AR: -3.2 per 10,000 (95% CI: -7.0, 0.6) |
| Weeks 1–4 | No chart review done | 0–30 days<br>RR: 1.1 (95% CI: 0.7, 1.7)<br>AR: 1.3 per 10,000 (95% CI: -4.5, 7.0) |

* Data provided with permission from Merck on 10/13/08

†Significant at p<0.05 OR= odds ratio; RR = relative risk; AR= attributable risk

# Quality of Evidence Grading Assessment: Risk of Febrile Seizures after Dose 1 MMRV vs. MMR and Varicella Vaccines

## MMRV WG Interim Assessment on 10-17-2008*

| Evidence Category | Weeks 1–2 post vaccination (7–10 and 5–12 days) ⇑ RELATIVE RISK after MMRV | Weeks 3–4 post vaccination (13–30 days) ⇓ RELATIVE RISK after MMRV |
|---|---|---|
| **Population-based Risk** | HIGH | LOW to MODERATE |
| **Biological Plausibility** | HIGH | LOW |

*Survey results from 25 of 26 WG members

# Evidence for Dose 1: Increased risk for febrile seizures 1 to 2 weeks after MMRV vaccination, compared with separate injections of MMR and varicella vaccines at the same visit?

# Population-based Assessment
## ⇑ Risk for Febrile Seizures (FS) after MMRV vs. MMR and Varicella Vaccines in Weeks 1– 2

| Domain* | Description: VSD and Merck-sponsored Studies |
|---|---|
| **Study design?** | • Observational cohort studies<br>• MMRV recipients compared with historical cohorts of children receiving MMR + varicella (V) vaccines (MMRV licensed in 2005).<br><br><u>VSD Study</u>:<br>MMRV: N= 43,353<br>MMR+V: N= 314,599<br><br><u>Merck-sponsored Study</u><br>MMRV: N=31,298<br>MMR+V: N=31,298 |
| **Strength of association?** | • **MMRV vs. MMR+V: ~ 2-fold increase risk in both studies**<br>  • Tight confidence intervals in the VSD study: OR: 2.3 (95% CI: 1.6, 3.2)<br>• MMRV vs. MMR+V: AR ~4 to 5 per 10,000 |



***Adapted from WHO criteria and draft EB WG guidance**

# Population-based Assessment (cont)
## ⇑ Risk for Febrile Seizures after MMRV vs. MMR and Varicella Vaccine in Weeks 1– 2

| Domain* | Description: VSD and Merck-sponsored Studies |
|---|---|
| **Consistency?** | **<u>Remarkable consistency</u>**:<br>• ~2 fold increase in FS risk **7–10/5–12 days** after MMRV vs. MMR+V in both studies<br>• Very similar point estimates<br>• Statistically significant findings<br>• Independent study populations<br>• Different methods |
| **Specificity of event?** | • Not specific<br>• FS occur in persons with fever; multiple etiologies, including after vaccination |
| **Temporal relation?** | • FS event onset clearly follows vaccination |

***Adapted from WHO criteria and draft EB WG guidance**

# Population-Based Risk Assessment: Study Strengths

## ⇑ Risk for Febrile Seizure after MMRV vs. MMR and Varicella Vaccines in Weeks 1–2

| VSD Study | Merck-sponsored Study |
|---|---|
| • Cohort study with logistic regression<br>• Access to a very large geographically diverse population<br>• Chart review performed by specially-trained staff who were blinded as to the nature of the study under review<br>• >99% of charts available for review (0.4% missing) | • Cohort study with MMR + V controls closely matched to MMRV recipients<br>• Rigorous record review using Brighton Collaboration case definition<br>• Cases confirmed by independent Adjudication Committee |

# Population-Based Risk Assessment: Study Limitations

## ⇑ Risk for Febrile Seizures after MMRV vs. MMR and Varicella Vaccine in Weeks 1–2

| Potential Limitation | VSD Study | Merck-sponsored Study |
|---|---|---|
| **Comparison group?** | • Largely historical | • All historical |
| **Year-to-year adjustment for variation in febrile infections?** | • Not done | • Not done |
| **Confirmation of febrile seizure?** | • No external adjudication process | • Adjudicators not blinded to year of vaccination |
| **Missing medical records for seizure cases?** | • Not a limitation (0.4% missing) | • 9% with missing records |

# US Postlicensure Experience: Febrile Seizures after MMR or Varicella Vaccination

- MMR: Study of ~137,000 children aged < 7 years vaccinated with MMR identified an increased risk for febrile seizure during 8–14 days after vaccination, compared with unvaccinated children[1]
  - 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 seizure during 0–30 days after vaccination, after controlling for co-administration of MMR vaccine[2]

1. Barlow, Davis et al. NEJM, 2001.
2. Black S et al. NEJM, Pediatric Infectious Diseases Journal, 1999.



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# Biological Plausibility Assessment: Increased Risk for Febrile Seizures in Children Receiving MMRV vs. MMR and Varicella (V) Vaccines

- **Strong biological plausibility for increased febrile seizure risk after MMRV vs. MMR+V during days 5 to 12 after vaccination**

| Factor | Description |
|---|---|
| **Vaccine properties** | • MMRV (Proquad®) has ~7 times more varicella antigen content than varicella vaccine (Varivax®)<br>• MMRV has the same measles antigen content as MMR |
| **Immunogenicity** | • MMRV induces similar antibody titers to varicella as MMR+V vaccine<br>• MMRV induced higher antibody titers to measles than MMR+V vaccine, suggesting higher levels of measles vaccine virus replication<br>– In natural measles infection, active viral replication throughout the body occurs 7 to 14 days after exposure |

**Sources: ProQuad® package insert, 2-2008; Long. Principles and Practices of Pediatric Infectious Diseases, Third Edition. 2008.**



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# Biological Plausibility Assessment: Increased Risk for Febrile Seizures in Children Receiving MMRV vs. MMR and Varicella Vaccines (cont)

- **Strong biological plausibility for increased febrile seizure risk after MMRV vs. MMR+V during days 5 to 12 after vaccination**

| Factor | Description |
|---|---|
| **Host febrile responses to vaccination** | • Significantly higher rates of fever and measles-like rash reported after MMRV compared with MMR+V[1]<br>– Fever and measles-like rash usually occurs during 5 to 12 days after vaccination in both groups<br>– Probability of reported fever increased with increasing measles antibody response in both groups[2] |
| **Clinical context** | • Febrile seizures occur in setting of fever |

1. ProQuad® Package insert, 2-2008.
2. Kuter B. et al. Human Vaccines. 2006.

# Prelicensure Studies: Vaccine-related Fever and Systemic Rash during Days 0–42 in Children Aged 12–23 Months Administered MMRV or MMR and Varicella Vaccine

| Dose 1 | MMRV N=4,497 | MMR+V N=2,038 |
|---|---|---|
| **Days 0–42** | | |
| Fever ≥ 102°F | 21.5%* | 14.9% |
| Measles-like rash | 3.0%* | 2.1% |
| Varicella-like rash | 2.1% | 2.2% |

* Rate significantly higher in MMRV group

- **Fever days 5–12: 45% for MMRV and 36% for MMR + V**
- **Measles-like rash days 5–12: 82% for MMRV and 81% for MMR+ V**

Source: Package insert 2-2008 and unpublished data from Merck on 10-20-08



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# Evidence for Dose 1: Decreased risk for febrile seizures 3 to 4 weeks after MMRV Vaccine, compared with separate injections of MMR and varicella vaccines at the same visit?

# Population-based Assessment

## ⇓Risk for Febrile Seizures after MMRV vs. MMR and Varicella Vaccine in Weeks 3– 4

| Domain* | Description: Merck-sponsored Study |
|---|---|
| **Strength of association?** | • RR: 0.6; 95% CI: 0.3, 1.1<br>• Finding not statistically significant |
| **Consistency?** | • Finding observed in Merck-sponsored study; chart review data not available from VSD study |
| **Specificity of adverse event?** | • Not specific<br>• FS occur in persons with fever; multiple etiologies, including after vaccination |
| **Temporal relation?** | • FS event onset clearly follows vaccination |

***Adapted from WHO criteria and draft EB WG guidance**



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# Population-based Assessment
## ⇓ Risk for Febrile Seizures after MMRV vs. MMR and Varicella Vaccine in Weeks 3–4

| Potential Limitation | Merck-sponsored Study |
|---|---|
| **Comparison group?** | • All historical |
| **Year-to-year adjustment for variation in febrile infections?** | • Not done |
| **Confirmation of febrile seizure?** | • Adjudicators not blinded to year of vaccination |
| **Missing medical records for seizure cases?** | • 9% with missing records |

# Potential Reasons for Observed Decrease Risk for FS 13–30 Days after MMRV, Compared with MMR and Varicella Vaccine Unrelated to Vaccine(s)

| Factor | WG Assessment |
|---|---|
| **Chance finding** | • Decreased risk not statistically significant |
| **Historical cohort bias for MMR and varicella vaccine recipients** | • Different patterns of co-infection may have been present across years, particularly for severe influenza<br>• If higher infection rates in historical cohort, effect would lead to increased rates of febrile seizures postvaccination in MMR+V recipients (affects estimates for all time windows) |

# US Postlicensure Experience: Febrile Seizures after MMR and Varicella Vaccination

- MMR: Study of ~137,000 children aged <7 years vaccinated with MMR identified similar risk for FS during 15–30 days after vaccination, compared with unvaccinated children[1]
  - RR 0.97 (95% CI: 0.49, 1.95)
- Varicella vaccine: Study of ~35,000 children aged 12–23 months vaccinated with varicella vaccine identified no increased risk for febrile seizure during 0–30 days after vaccination, controlling for co-administration of MMR vaccine[2]

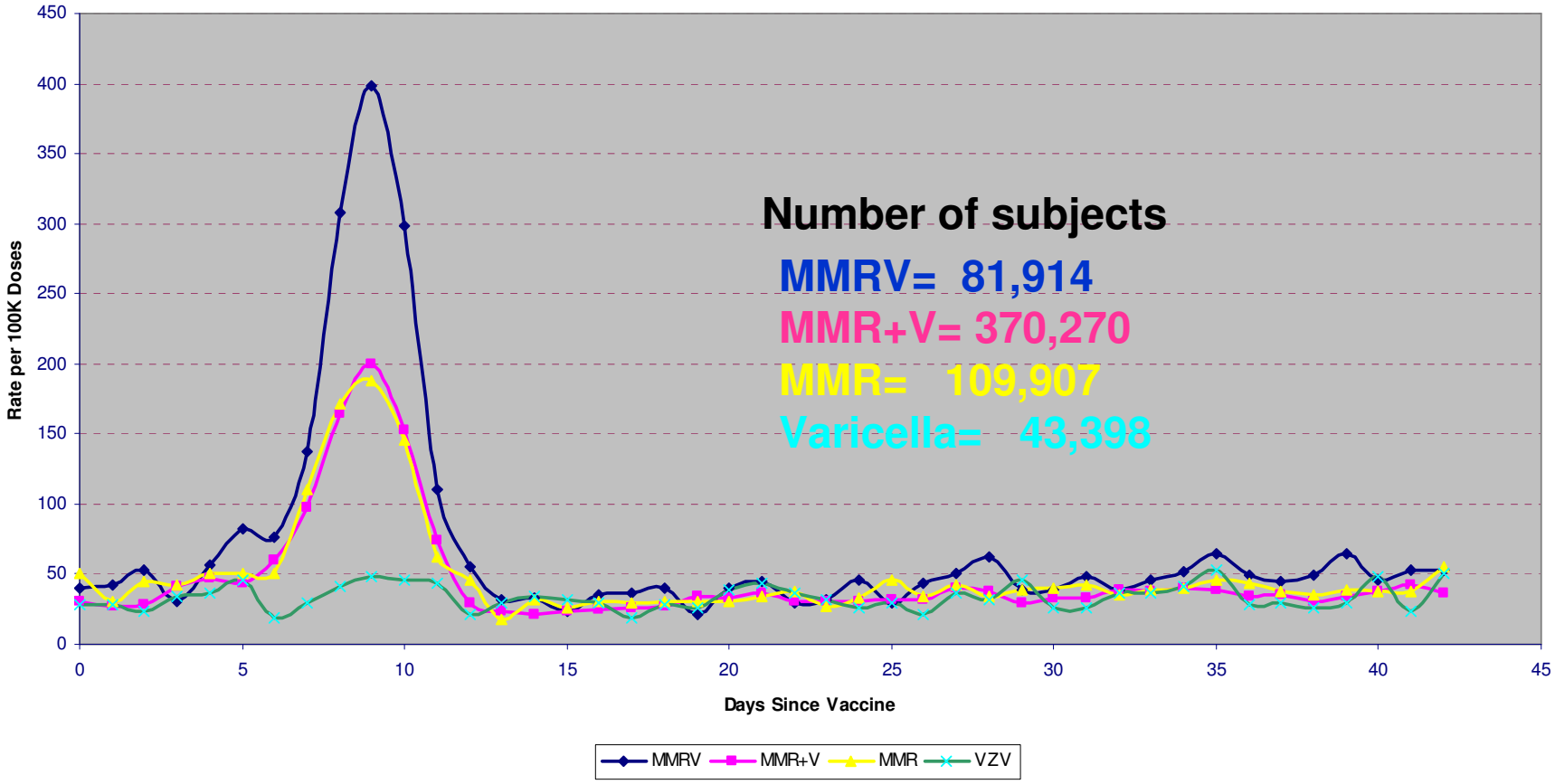
1. Barlow, Davis et al. NEJM, 2001.
2. Black S et al. NEJM, Pediatric Infectious Diseases Journal, 1999.

# Potential Reasons for Observed Decrease Risk for FS 13–30 Days after MMRV, Compared with MMR and Varicella Vaccine
## Biological Plausibility Assessment

- **No compelling biological reason to explain a decreased risk for febrile seizures after MMRV vs. MMR+V during days 13-30 after vaccination**

| Factor | Description |
|---|---|
| **Host responses patterns (related to different vaccine properties)** | • MMRV may induce more robust/ earlier immune earlier response; could offer short-term secondary protection from infectious illnesses and febrile seizure |
| **Social effect** | • MMRV associated with higher fever rates in 5–12 days than MMR+V; children with fever may have less exposure to other children with infectious diseases which might offer short-term protection from febrile seizure |

# Outpatient Visits for Fever by Day after Vaccine in 7 VSD Sites among Children Aged 12–23 Months: 2000-2008*




*Excluding SCK site

Courtesy of N. Klein, N. Lewis and the VSD investigators



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# Summary: Conclusion 1 of 2
# Interim Evidence for Febrile Seizure Risk after Dose 1 MMRV Vaccination

- Compared with separate dose 1 injections of MMR and varicella vaccines administered at the same visit
  - The evidence supports a causal relationship between receipt of dose 1 MMRV vaccine and increased risk for febrile seizures during the 5 to 12 days after vaccination; the magnitude of the risk is about 2-fold.
  - During the 5 to 12 days after MMRV vaccine, 1 additional febrile seizure is expected to occur per approximately 1,900 to 2,600 children vaccinated.

# Summary: Conclusion 2 of 2
# Interim Evidence for Febrile Seizure Risk after Dose 1 MMRV Vaccination

- Compared with separate dose 1 injections of MMR and varicella vaccines administered at the same visit
  - The evidence is insufficient to accept or reject a conclusion that dose 1 MMRV vaccine is associated with a decreased risk for febrile seizures during the 13 to 30 days after vaccination.
  - Therefore, the evidence is also insufficient to accept or reject a conclusion that children receiving dose 1 MMRV vaccine have no overall increased risk for febrile seizures during the 0 to 30 days after vaccination.

# Considerations for Future MMRV Vaccine Activities

# Additional Assessment for Dose 1 MMRV Vaccine and Febrile Seizure Risk

- WG proposed conducting an epidemiological study in the VSD population to assess confirmed febrile seizure risk after dose 1 MMRV vaccine in periods other than 7–10 days, including risk during 0–30 days after MMRV vaccine
  - VSD conducting additional analyses in the automated seizure data that includes more MMRV recipients
  - VSD and CDC to develop epidemiologic study plan
  - WG to assess new data as they become available
- WG to discuss potential additional analyses or studies that may be conducted in various research venues

# Assessment for Dose 2 MMRV and Febrile Seizure Risk

- Febrile seizures are less common in children aged 4–6 years, than those aged 12–23 months[1]
- VSD and Merck-sponsored febrile seizure studies were conducted for dose 1
- In light of dose 1 findings, the WG is reviewing dose 2 safety data from
  - Prelicensure studies
  - Postlicensure data on unconfirmed seizures after vaccination

1. Johnston M. Nelson Textbook of Pediatrics. 2007.

# Summary:
# Prelicensure Safety Experience during Days 0–42 after Dose 2 MMRV Vaccine

- Lower fever rates in children aged 15–26 months receiving dose 2 MMRV compared with dose 1 MMRV (N=1035)[1]
- Similar fever rates in children aged 4–6 years receiving MMRV (N=397) compared with MMR and varicella vaccines (N=193)[2]
  - Fever ≥102º F or warm to touch (10% both groups)
- No febrile seizures reported in study subjects receiving dose 2 MMRV vaccine[3]


1. ProQuad® Package Insert, February 2008.
2. Reisinger et al. Pediatrics, 2006
3. Personal communication with Dr. Kuter, Merck on 10-20-08.

# Summary: Postlicensure Safety Experience after Dose 2 MMRV Vaccine

- Data on unconfirmed seizures from automated data after vaccination
  - Charts not reviewed
- VSD one site
  - Dose 2 subjects = Children aged 4–6 years with no MMR or varicella vaccine dose in past 12 months
- Merck-sponsored study[2]
  - Dose 2 subjects = Children aged 1–12 years who received MMR + varicella vaccines in the past (for most children in MMR+V group, dose 2 is MMR only)
  - >95% of subjects aged 4-6 years

1. Personal communication with Dr. Kuter on 10-20-08

# Summary Results from VSD and Merck-sponsored Studies Unconfirmed Seizures from Automated Data Dose 2 MMRV vs. MMR and Varicella Vaccines

| Post-vaccination Interval | VSD* All aged 4–6 years | Merck** 1-12 years old (>95% aged 4–6 years) |
|---|---|---|
| Weeks 1–2 | 7–10 days<br>MMRV: 0.7 per 10,000<br>(4 per 56,535)<br>MMR+V: 0<br>(0 per 44,836) | 5–12 days<br>MMRV: 0.4 per 10,000<br>(1 per 25,212)<br>MMR+V: 0.4 per 10,000<br>(1 per 24,788) |
| Weeks 1–4 | 0-42 days<br>MMRV: 2.5 per 10,000<br>(14 per 56,535)<br>MMR+V: 2.0 per 10,000<br>(9 per 44,836) | 0-30 days<br>MMRV: 2.0 per 10,000<br>(5 per 25,212)<br>MMR+V: 2.0 per 10,000<br>(5 per 24,788) |

*Data from Northern California Kaiser Permanente only, 1995-2008
**Includes codes for seizure and epilepsy; Permission from Merck on 10/17/08



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# Additional Future MMRV WG Activities

- Assess evidence regarding clinical importance of febrile seizures
- Providers' survey about perceptions of febrile seizure severity and MMRV use underway*
- Conduct review of 2 encephalitis cases in VSD data presented 2-2008 ACIP meeting
- Develop policy options for use of MMRV for ACIP
  - Consider risks and benefits of dose 1 and dose 2 as routinely recommended by ACIP

*** Study is a collaboration between University of Colorado and CDC**

**We acknowledge the contributions of the ACIP MMRV Vaccine Safety Working Group members and expert consultants. The findings in this presentation represent the current views of the MMRV Vaccine Safety Working Group do not represent CDC or HHS policy.**



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# ACIP Recommendations for MMRV Use: Voted in February 2008

"Combination MMRV vaccine is approved for use among healthy children aged 12 months--12 years. MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella. ACIP does not express a preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine)."

[1]CDC. Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine. MMWR. 57(10);258-260