ProQuad® (MMRV) Post-licensure Observational Safety Study

Interim Results on Febrile Seizures

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ACIP 27 February 2008

Overview

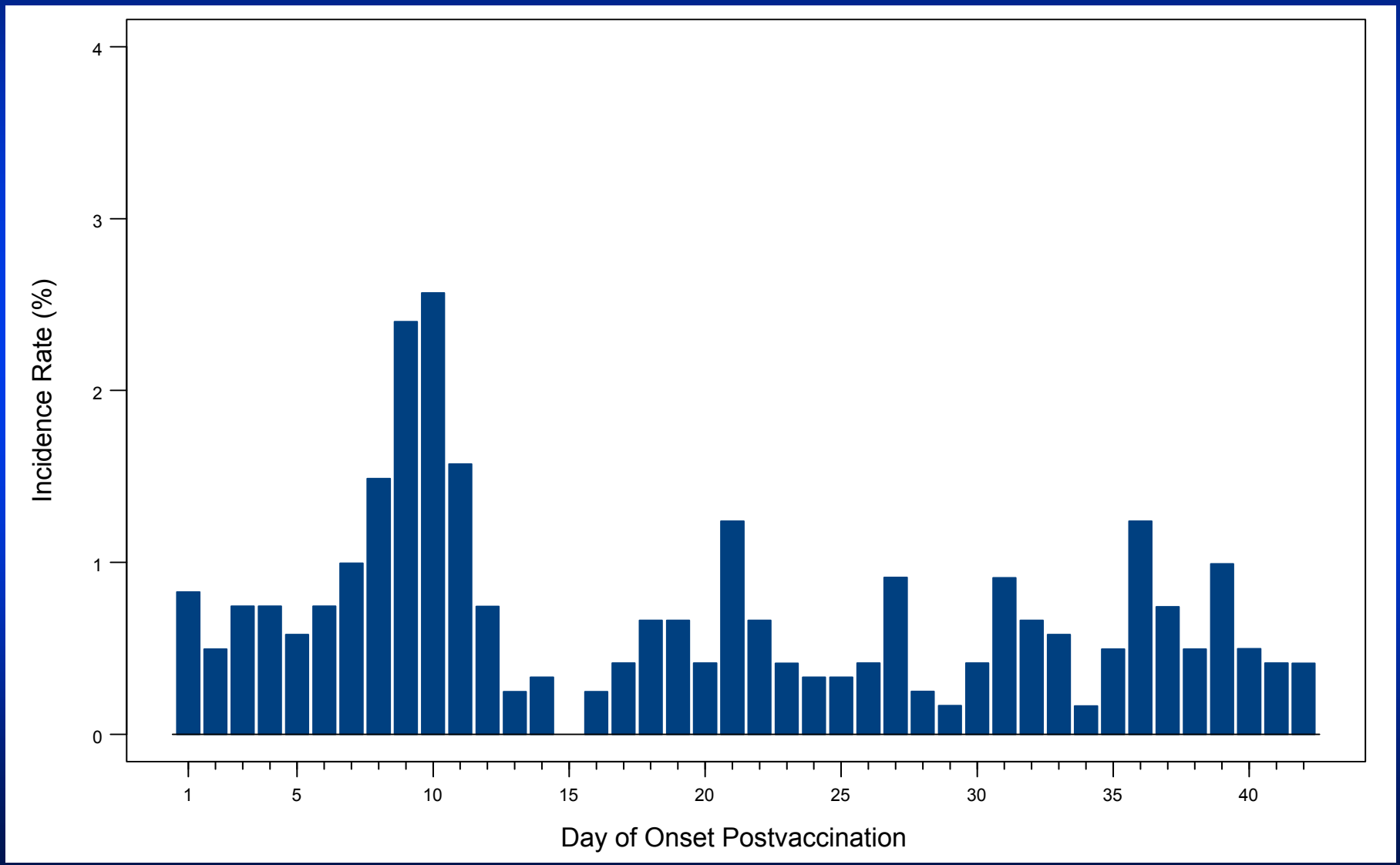
- Rationale for MMRV
- Postlicensure Safety Study
  - Background and Rationale
  - Study Design
  - Febrile Seizures - Interim Results
  - Strengths and Limitations of Interim Analysis
- Concluding Remarks

Why MMRV?

- Combination vaccines[1]:
  - Decrease number of injections
  - Increase vaccine compliance
  - Increase vaccine coverage rates
- MMRV identified by ACIP as key component to successful implementation of 2nd dose varicella recommendation
- ProQuad® (MMRV)
  - Introduced in the US Fall 2005
  - Limited supplies since June 2007
    - Due to manufacturing issues unrelated to vaccine safety or efficacy

1. Combination Vaccines for Childhood Immunization- MMWR 1999, 48, RR05: P1-15

M-M-R™ II – N= 1266 Subjects (Study Conducted 2001-2002) Fever Rate (%)



Clinical Trial Data

- Clinical trials of ProQuad® (MMRV), 12-23 month olds , 1st dose
  - Fever & measles-like rash: only systemic adverse events more frequent with MMRV than MMR+V
    - 45% of fever in 5-12 days post-vaccination
  - Small number of febrile seizures observed
- Lower fever rate after 2nd dose than after 1st dose

Febrile Seizures – MMRV vs MMR+V

Vaccine	N	Days 0-42		Days 5-12	
		Cases	Rate/1000	Cases	Rate/1000
MMRV	5,731	13	2.3	8	1.4
MMR + V	1,997	8	4.0	5	2.5

Post-licensure Study Rationale

- Higher rate of fever after MMRV than MMR+V in clinical trials
  - To assess incidence of febrile seizure following MMRV
- To better assess general safety of MMRV in routine practice

→ *Large-scale post-licensure observational study designed with FDA input*

Febrile Seizures (FS) - Background

- Associated with fever
- Observed during infectious diseases
  - Roseola, otitis, pneumonia, measles, varicella
- Observed after vaccines resulting in fever
  - DTaP, Pneumo conjugate, MMR
- Typically of short duration
  - Generally lasts < 15 minutes
  - Resolves without sequelae
- Incidence
  - Primarily 6 months - 5 years, peak ~18 months
  - By 5 years of age, 2-4% of children have had ≥ 1 FS
  - 1-2 /1000 children per month in 2nd year of life

Pre-specified Study Objectives

- Primary Objective - Febrile seizures
  - Incidence 5-12 days after first dose of MMRV
    - Children 12-60 months of age
  - Other protocol time windows include 0-4 and 0-30 days
    - FS in 0-4 day period considered not associated with MMR, MMRV, or V
- Secondary Objective - General safety evaluation
    - Children 12 months-12 years of age
    - MMRV as 1st or 2nd dose of MMR and/or V
    - On 0-30 day time period

→*General safety evaluation: No suggestion of a safety signal in interim results*

Study Design & Population

- Post-licensure observational cohort study
- Conducted at Kaiser Permanente Southern California (KPSC)
- Target of 25,000 children for primary objective on FS
  - 1st dose of ProQuad® between 12-60 months of age
  - MMR- and varicella disease/vaccination negative children
    - Continuous KPSC member from 6 months of age until 90 days post MMRV
- All study results reviewed and interpreted by external, independent study Safety Review Committee (SRC)
    - A vaccine specialist
    - A pediatric neurologist
    - A pharmacoepidemiologist

Comparison Groups

- Primary comparison group:
  - Historical controls vaccinated concomitantly with MMR+V prior to availability of ProQuad®
  - Matched on age, gender, date of vaccination, and dose sequence
- 2 other comparison groups primarily for general safety evaluation
  - Self-comparison periods (children as their own controls):
    - 60-90 days after MMRV (Post-vaccination self comparison)
    - 30-60 days before MMRV (Pre-vaccination self comparison)

Febrile Seizure (1)
Identification of Potential Cases

- From automated medical record database
  - Children with a health care contact in outpatient, ER, or hospital setting
  - Using a broad range of ICD-9 diagnosis codes
    - 345.X (epilepsy)
    - 780.3 (convulsion), 780.31 (febrile convulsion), 780.39 (other convulsion)
    - 779.0 (neonatal seizures)
    - 333.2 (myoclonus)
- These cases are referred to as "*unconfirmed seizures*"

Febrile Seizure (2)
Case Confirmation

- Group of seizure experts
  - Designed abstraction form
  - Established operational definition for FS (modeled after Brighton Collaboration's definition)
- Potential cases: Review and abstraction of medical record
- Adjudication Committee (distinct from study external Safety Review Committee)
  - 3 Kaiser Permanente physicians
  - Pre-specified procedure
  - No knowledge of vaccination status
  - To confirm diagnosis of FS
- The adjudication process identified "*confirmed FS*"

Time Periods of Interest for Assessing Febrile Seizures

Post-vaccination Days	Rationale for Evaluation
0-4	Likely unrelated to MMR, V, or MMRV Possibly related to concomitant vaccines
5-12	Main period of increased fever with MMRV Primary period of interest for FS
5-30 / 0-30	Period of viral replication for all 4 components Measles, Mumps, Rubella, Varicella

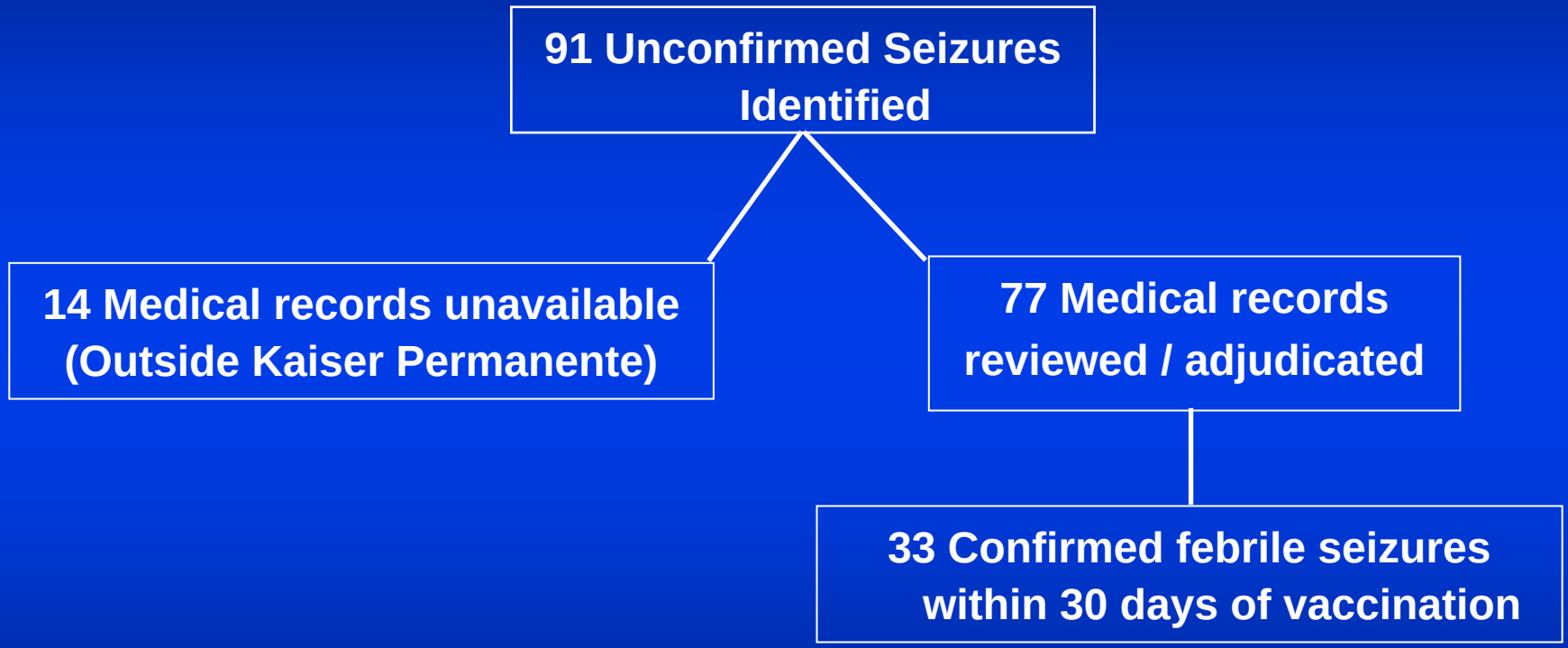
Study Progress

- Study accrual
  - Started when ProQuad® available at KPSC in Feb 2006
  - Completed 30-Jun-2007
- Follow-up period
  - Requires 6 months after 90-day post-vaccination observation period
- Interim report submitted to FDA, Dec 2007
  - Children vaccinated with MMRV until Sep 2006
- Final study report
  - Database cutoff for final analysis, 31-Mar-2008
  - On track for submission by Dec 2008

Study Population for Interim Analysis on FS

- MMRV recipients (1st dose)
  - N = 14,263 children, 2006
  - 99% 12-23 months of age (range 12-60 months)
  - Diverse ethnic background
  - 51% males
- Controls: Children vaccinated with MMR + V (1st dose)
  - N = 14,263 children, 2005
  - Matched on age, gender, date of vaccination

Review and Adjudication of Unconfirmed Seizure Cases



Unconfirmed Seizures and Confirmed FS First Dose - 12-60 Months of Age Interim Results

Outpatient, ER and Hospital

	MMRV (n=14,263)				MMR+V (n=14,263)			
	Unconf. Seizures		Confirmed FS		Unconf. Seizures		Confirmed FS	
Post-vaccination Period	n	Rate (/1000)	n	Rate (/1000)	n	Rate (/1000)	n	Rate (/1000)
0-4 days	16	1.1	4*	0.3	13	0.9	5*	0.4
5-12 days	17	1.2	7	0.5	11	0.8	3	0.2
13-30 days	10	0.7	3	0.2	24	1.7	11	0.8
0-30 days	43	3.0	14	1.0	48	3.4	19	1.3
5-30 days	27	1.9	10	0.7	35	2.5	14	1.0

*** Confirmed febrile seizures (FS) in day 0-4 possibly related to concomitant vaccines**
All FS in Days 0-4 had received Prevnar and / or DTaP

Relative Risk (RR) & Attributable Risk (AR)

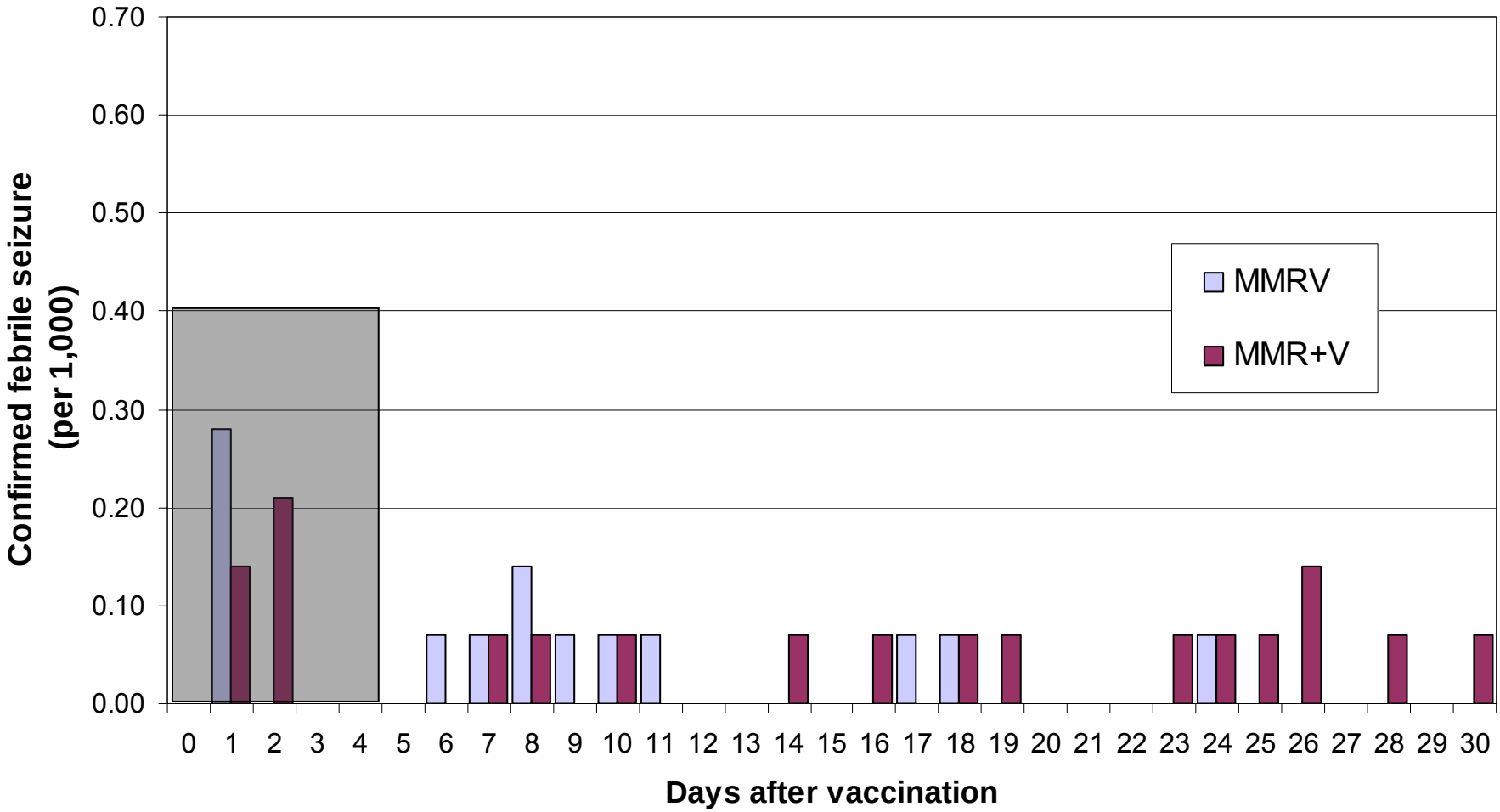
First Dose - 12-60 Months of Age

Interim Results

Confirmed Febrile Seizures

Days	MMRV (N = 14,263)		MMR + V (N =14,263)		RR (95% CI)	AR Rate/1000 (95% CI)
	Cases	Rate /1000	Cases	Rate /1000		
5-12	7	0.5	3	0.2	2.3 (0.6, 9.0)	0.3 (-0.2, 0.8)
5-30	10	0.7	14	1.0	0.7 (0.3, 1.6)	-0.3 (-1.0, 0.4)
0-30	14	1.0	19	1.3	0.7 (0.4, 1.5)	-0.4 (-1.2, 0.5)

Interim Results – N = 14,263 Children/Group
First Dose - 12-60 Months of Age
Confirmed Febrile Seizures by Day of Onset
Rate/1000 – MMRV and MMR+V



Strengths and Limitations of Interim Analysis

- Strengths
  - MMR+V controls closely matched to MMRV recipients
  - Cases adjudicated by independent Adjudication Committee
  - Utilized medically accepted febrile seizure criteria
    - 43% (33/77) with available medical records met case definition
  - Rigorous record review
    - Outpatient codes often represent past medical history, not new seizure event
- Limitations
  - Overall, case numbers small, precluding any firm conclusion
  - No adjustment for other factors (e.g., annual variability due to febrile infectious diseases, concomitant vaccines)
  - Medical records available for 85% of cases
    - Missing 6 MMRV, 8 MMR+V

Entire Study Population Preliminary Unvalidated, Unadjudicated Seizure Codes as of Feb 2008

- Additional data recently received
- Neither validated nor adjudicated data
- Outpatient, ER, & hospital data
- Validated, adjudicated results expected July-Aug 2008

Days	MMRV (N = 31,403)		MMR + V (N = 31,403)	
	Cases	Rate /1000	Cases	Rate /1000
5-12	47	1.5	28	0.9
5-30	86	2.7	73	2.3

Concluding Remarks (1)

- Febrile seizures
  - Included in labels for ProQuad®, M-M-R™II and VARIVAX®
  - ProQuad® label has been updated to include interim study results (5-12 and 0-30 days)
- Interim validated results available on ~14,000 of ~30,000 children vaccinated with ProQuad® and followed for 30 days
- Interim results on adjudicated confirmed cases of febrile seizures
  - Number of cases is low
  - Apparent increase in 5-12 day period
    - Attributable risk: 0.3/1000 [95%CI: -0.2, 0.8]
  - No difference in overall follow-up
    - 5-30 day period attributable risk: -0.3/1000 [95%CI: -1.0, 0.4]
    - 0-30 day period attributable risk: -0.4/1000 [95%CI: -1.2, 0.5]

Concluding Remarks (2)

- Final febrile seizure analysis expected July-Aug 2008
  - ~30,000 MMRV recipients and ~30,000 MMR+V recipients
  - Validated and adjudicated results
  - Shared with FDA, CDC, ACIP in timely fashion
- Final report including general safety analysis will be completed by 4Q2008, per CBER commitment
- Merck will continue to collaborate with Regulatory and Public Health Authorities, and with medical/scientific experts on the interpretation of the febrile seizure data