ProQuad® (MMRV) Post-licensure Observational Safety Study

Febrile Seizure Results

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Overview

- Background
- Postlicensure Safety Study
  - Design & Methods
  - Febrile Seizure Results
  - 2nd dose
  - Strengths & Limitations
- Concluding Remarks

Background

- Febrile seizures may occur after:
  - Febrile illnesses
  - Vaccines (e.g. MMR, DTaP, PCV)
- In clinical trials, fever reported after MMRV at a higher rate than MMR+V
- Regulatory commitment to conduct a postlicensure safety study to assess rate of febrile seizures
- Interim results presented at ACIP (Feb 2008)
  - ~50% of final sample size

MMRV Postlicensure Safety Study *Design & Methods*

Pre-specified Study Objectives

- Primary Objective - Febrile seizures (FS)
  - 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
- Secondary Objective - General safety
    - Children 12 months-12 years of age
    - MMRV as 1st or 2nd dose of MMR and/or V
    - 0-30 day time period

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

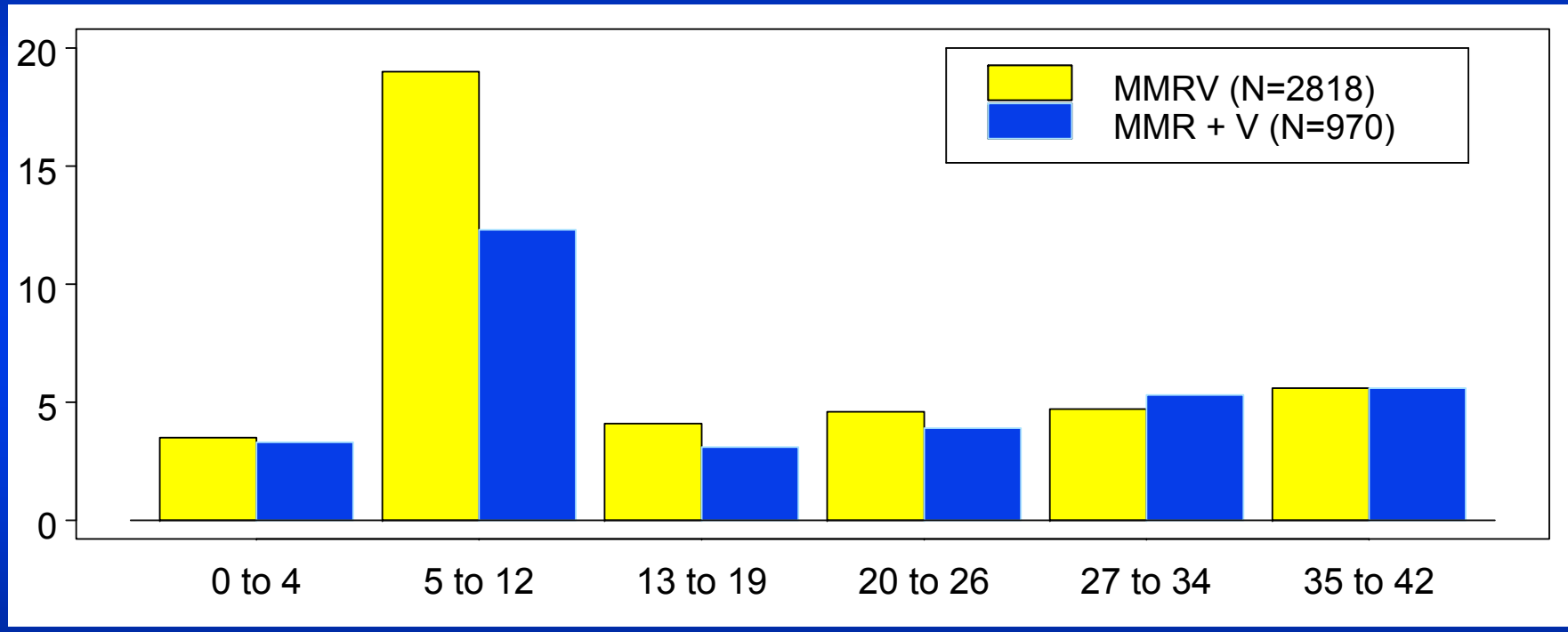
Rationale for 30 Day Follow-up

- Animal studies
  - Show viral replication for up to 4 weeks following inoculation for VZV/OKA and measles/Moraten strains [1,2]
- Clinical trials
  - Fever, measles & varicella-like rash reported throughout 42 days postvaccination *(next slides)*

→ Overall, suggestive of viral replication during 1st month following vaccination

1. Moffat *et al. J Virol* (1998) 72, 2: 965-74
2. Valsamakis *et al.* *J Infect Dis* (2001) 183: 498-502

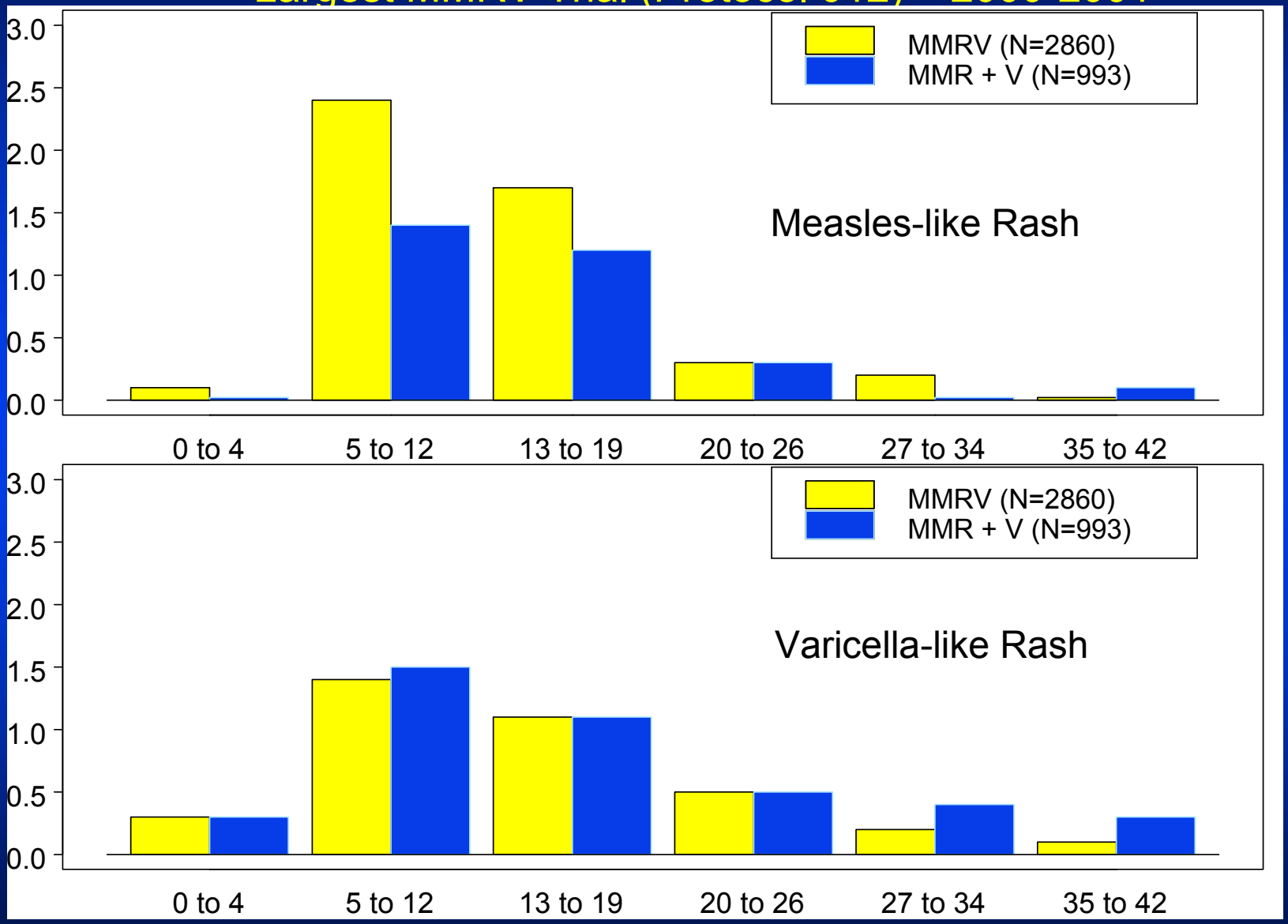
Incidence of Fever ≥102°F in 12-23 Month Olds
0-42 Days Postvaccination
Largest MMRV Trial (Protocol 012) – 2000-2001



N=Average number of subjects in each day range.

Incidence of Measles- and Varicella-like Rashes 0-42 Days Postvaccination in 12-23 Month Olds

Largest MMRV Trial (Protocol 012) – 2000-2001

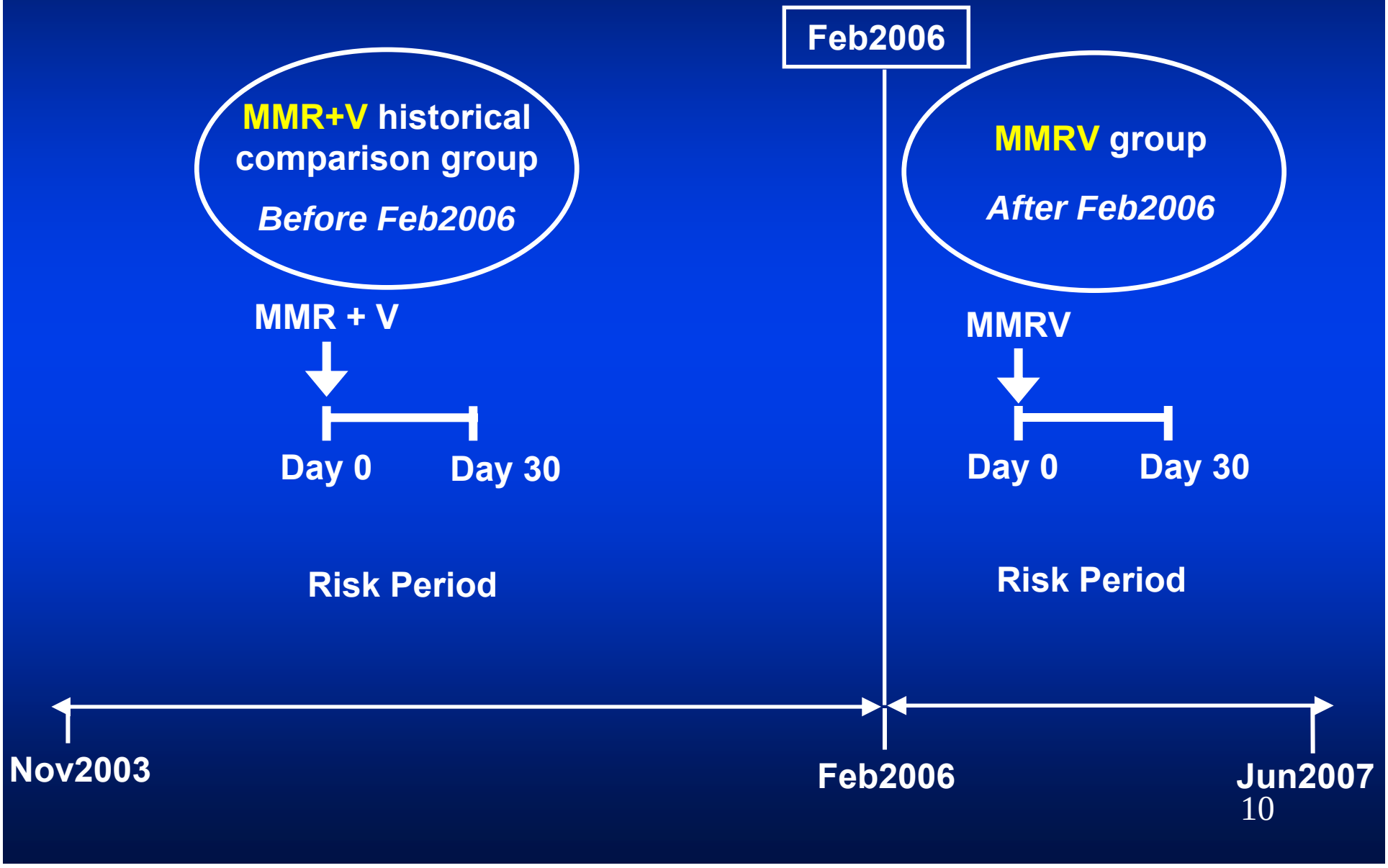


Postlicensure Study Design & Population

- Observational cohort study
- Study conducted & data analyzed 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 & varicella disease/vaccination negative children
- Actual study population
  - ~69,000 ProQuad® recipients (1st or 2nd dose) & ~69,000 matched controls (MMR+V)
    - ~31,000 in each group for FS objective (1st dose)
- All study results reviewed & interpreted by external, independent study Safety Review Committee (SRC)

Primary Comparison Group: MMR+V

Individually matched on age, gender, calendar date of vaccination



Febrile Seizure (FS) Adjudication

- Detection from automated medical record database
  - Children with health care contact in outpatient, ER, or hospital setting
  - All ICD-9 diagnosis codes for epilepsy or convulsions*
  - These cases are referred to as "*unconfirmed seizures*"
- Adjudication Committee (3 KPSC Physicians)
  - Reviewed medical records data
  - Used Brighton Collaboration definition
  - The adjudication process identified "*confirmed FS*"

* ICD-9 diagnosis codes used for detection of potential seizures: 345.X (epilepsy); 780.3X (convulsion, febrile convulsion, other convulsion); 779.0 (neonatal seizures); 333.2 (myoclonus)

MMRV Postlicensure Safety Study *Final Results*

Study Population for Analysis of Febrile Seizures

After 1st Dose

- MMRV recipients
  - N = 31,298 children, Feb 2006-Jun 2007
  - 99% 12-23 months of age (range 12-60 months)
  - Diverse ethnic background
- Historical comparison group: Children vaccinated with MMR+V
  - N = 31,298 children, Nov 2003-Jan 2006
  - Individually matched on age, gender, calendar date of vaccination

Risk of Confirmed FS Increased in 5-12 but Not 0-30 or 5-30 Days Postvaccination

1st Dose - 12-60 Months of Age

Outpatient, ER, and Hospital

Days	MMRV (N = 31,298)		MMR+V (N =31,298)		Relative Risk (95% CI)	Attributable Risk per 1000 (95% CI)
	Cases	Rate /1000	Cases	Rate /1000		
0-4	9†	0.3	7†	0.2	1.3 (0.5, 3.5)	0.1 (-0.2, 0.3)
5-12	22	0.7	10	0.3	2.2 (1.0, 4.7)*	0.4 (0.0, 0.7)*
13-30	13	0.4	23	0.7	0.6 (0.3, 1.1)	-0.3 (-0.7, 0.1)
0-30	44	1.4	40	1.3	1.1 (0.7, 1.7)	0.1 (-0.5, 0.7)
5-30	35	1.1	33	1.1	1.1 (0.7, 1.7)	0.1 (-0.5, 0.6)

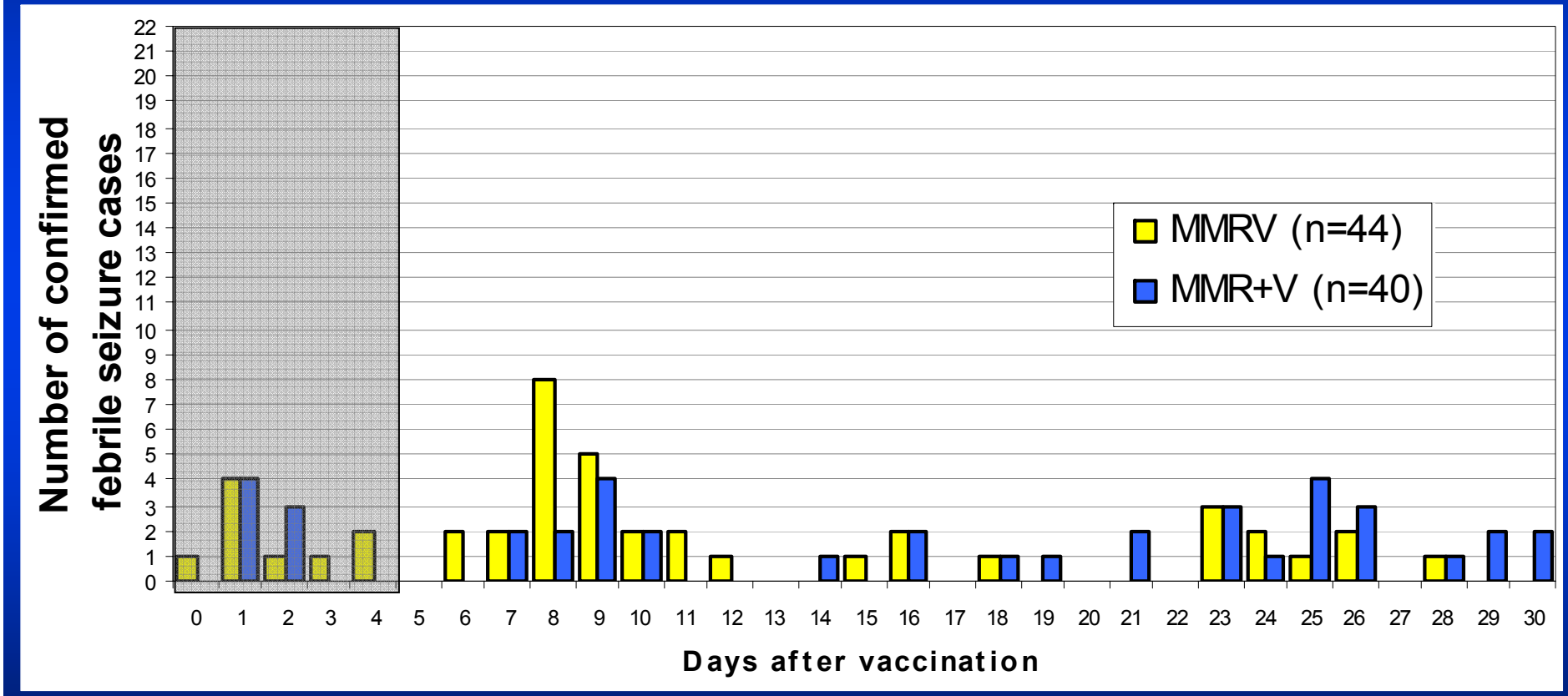
† Confirmed febrile seizures (FS) in day 0-4 possibly related to concomitant vaccines (all but 1 FS in each group had received Pneumo conjugate and/or DTaP)

* Statistically significant ($p<0.05$)

Confirmed Febrile Seizures by Day of Onset

N = 31,298 Children/Group

1st Dose - 12-60 Months of Age



Shaded area indicates time period when FS unlikely to be related to MMRV or MMR+V

Importance of Adjudication Procedure

- 2 coding practice changes at KPSC from 2004-2007
  - Transition from paper to electronic medical records
  - KPSC recommended improved coding in ER setting
- Coding changes resulted in documented increase in seizure code use over study period *(see next slide)*
  - More seizure codes used during MMRV period
    - Many codes corresponded to follow-up visit for prior seizure or history of seizure, not new seizure event
- Increased use of seizure codes without FS adjudication would introduce bias when comparing MMRV vs. MMR+V
- Adjudication likely removed most of this bias, improving validity of results

Use of Febrile Seizure Codes Increased from 2004-2007

All children ≤12 years old, KPSC

Hospitalizations

Year	2004	2005	2006	2007
# hospitalizations with FS dx	83	90	93	117
Total # hospitalizations	36,434	35,628	37,652	39,014
Rate per 1000 - hospitalizations with FS dx	**2.28**	**2.53**	**2.47**	**3.00**

ER Visits

Year	2004	2005	2006	2007
# ER visits with FS dx	159	301	347	426
Total # ER visits	77,311	77,093	70,138	72,329
Rate per 1000 – ER visits with FS dx	**2.06**	**3.90**	**4.95**	**5.89**

FS diagnosis based on ICD9 = 780.31 (simple febrile convulsion) or 780.32 (complex febrile convulsion)

MMRV Postlicensure Safety Study

2nd Dose Results

Limited Data Suggest No Increase in Unconfirmed Seizure Codes* Among "2nd Dose Recipients†"

General Safety Analysis – Postlicensure Study
1 to 12 Year Olds (>95% 4-6 Year Olds)

ER and Hospital

Postvaccination Period	MMRV† (n=25,212)		MMR+/-V† (n=24,788)		Relative Risk (95% CI)
	n	Rate (/1000)	n	Rate (/1000)	
5-12 days	1	0.04	1	0.04	1.0 (0.1, 15.7)
0-30 days	5	0.2	5	0.2	1.0 (0.3, 3.4)

* Including ICD-9 codes for epilepsy, febrile seizures, and other seizure disorders - Not adjudicated

† MMRV or MMR+/-V given to children who received MMR+V in the past

Strengths & Limitations

- Strengths
  - MMR+V controls closely matched to MMRV recipients
    - Control for potential seasonality effect
  - Cases adjudicated by Committee using medically accepted febrile seizure criteria
    - Many seizure codes in outpatient and ER setting did not meet case definition
      - Codes corresponded to previous seizure, not new seizure event
  - Study data reviewed by independent Safety Review Committee
- Limitations
  - No adjustment for year-to-year variation in febrile infectious diseases
  - Medical records unavailable for 9% of cases

Concluding Remarks

Viral Replication

- Occurs during 1st month after vaccination (based on animal & clinical data)

Febrile Seizures after 1st Dose

- Confirmed febrile seizures in 12-23 month olds are rare within 30 days postvaccination
  - Incidence*: MMRV 1.4/1000
    MMR+V 1.3/1000
- Rigorous adjudication of seizure codes likely corrected for most potential bias resulting from coding practice changes
- Comparison of adjudicated FS data for MMRV to MMR+V shows:
  - ~2-fold increase in FS in 5-12 day period
    - Attributable risk for MMRV: 0.4/1000 [95%CI: 0.0, 0.7]
  - No increased risk of FS in 30 day period
    - Attributable risk for MMRV: 0.1/1000 [95%CI: -0.5, 0.7]

* Includes ER, hospital, and outpatient visits

Concluding Remarks

Febrile Seizures after 2nd Dose

- Clinical trial data show lower rate of fever after MMRV administered 3 months after 1st Dose (in 2nd year of life)
- Limited data from postlicensure study suggest no increase in seizures following MMRV vs. MMR+/-V. Incidence in 1-12 year olds in each group:
  - 0.04/1000 in 5-12 day period
  - 0.2/1000 in 0-30 day period

Update and Next Steps

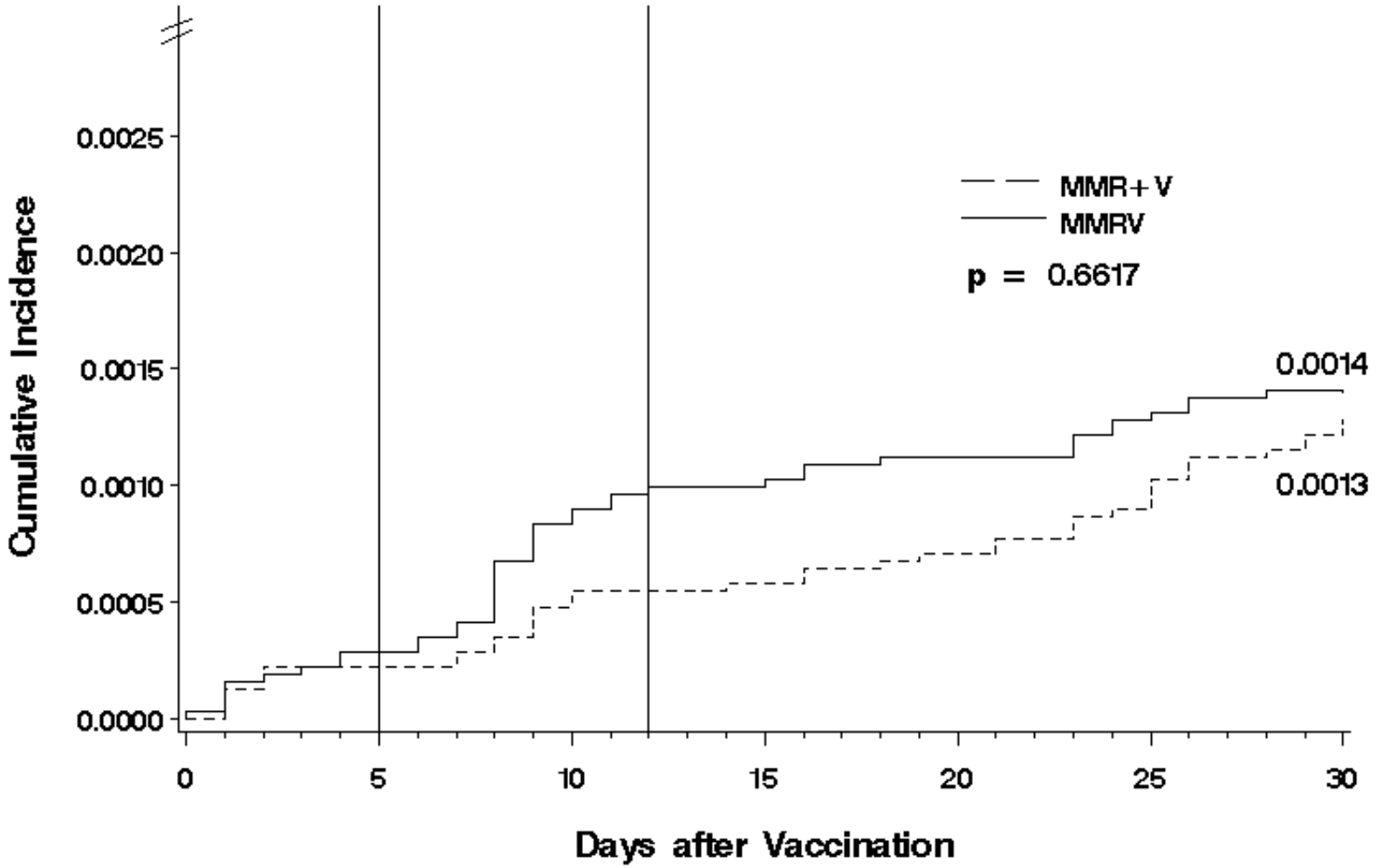
- Final study report with general safety results to CBER by Dec 2008
  - Final febrile seizure report sent to CBER (Aug 2008)
- ProQuad® label updated in Feb 2008 to include interim study results (5-12 and 0-30 days)
  - Label update with final results submitted to CBER
- ProQuad® not currently being distributed in the U.S.

Study Team

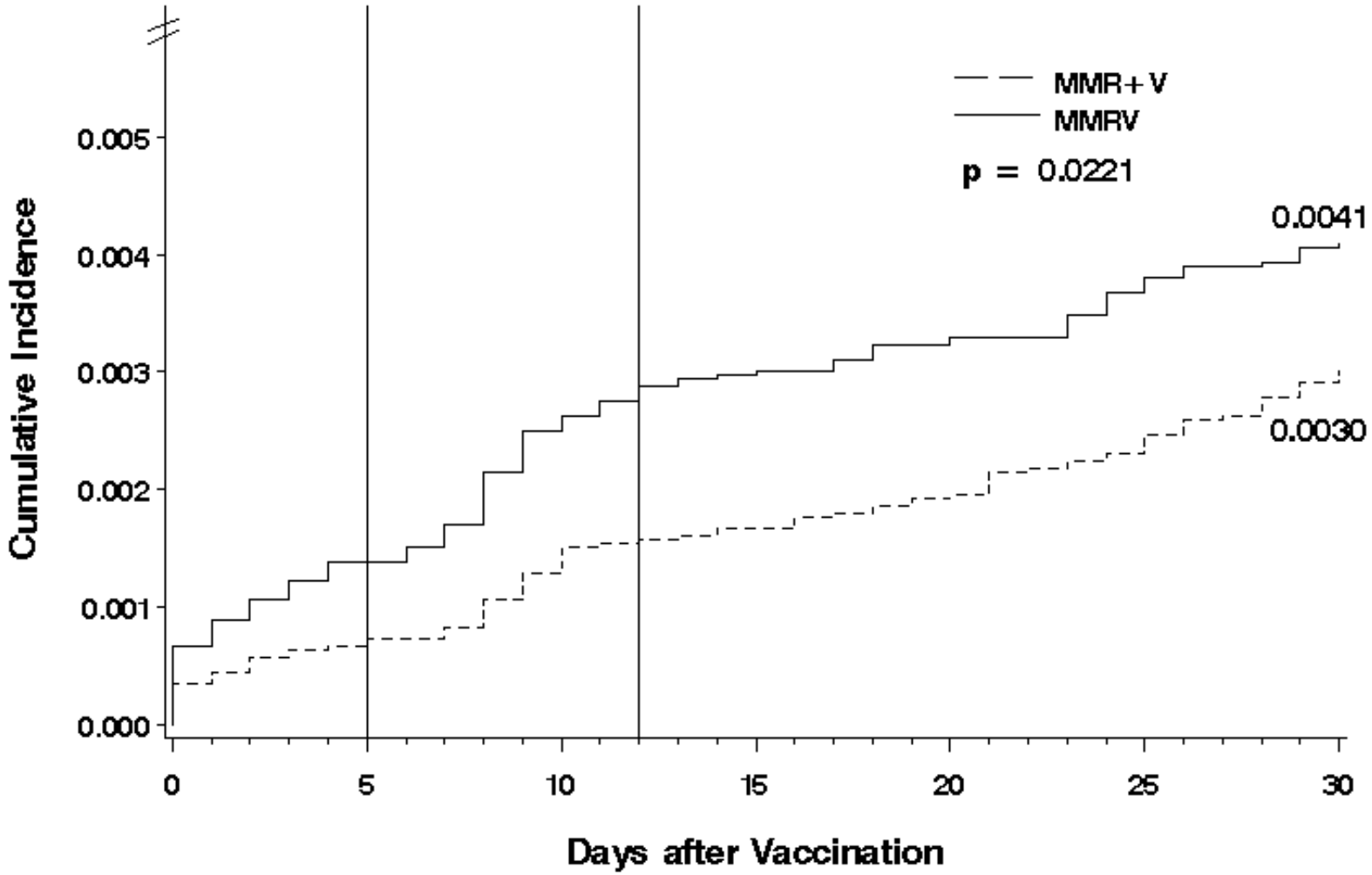
- Kaiser Permanente Southern California Research Team
  - Steven Jacobsen, PI
  - Bradley Ackerson, co-PI
  - Janis Yao, statistician
  - Lina Sy, study coordinator
  - Physician adjudicators
- Safety Review Committee (SRC)
  - Allen Hauser, pediatric neurologist, Columbia University, SRC chair
  - Neal Halsey, vaccine specialist, Johns Hopkins University
  - Samy Suissa, pharmacoepidemiologist, McGill University
- Merck Team
  - Trung Tran, Eric Maiese, Patricia Saddier, Epidemiology
  - Ouzama Nicholson, Luwy Musey, Clinical
  - Jonathan Hartzel, Biostatistics
  - Mike Dekleva, Donna Zacholski, Regulatory
  - Fabio Lievano, English Willis, Christina Budzynski, Clinical Risk Management
  - Chet Kitchen, Michelle Goveia, Dennis Brooks, Barbara Kuter, Medical Affairs

Additional Slides

Kaplan-Meier Curves - MMRV and MMR+V *Confirmed* Febrile Seizures



Kaplan-Meier Curves - MMRV and MMR+V
Unconfirmed Seizures



Unconfirmed Seizure Codes following "2nd Dose" MMRV or MMR+/-V

1-12 year olds who previously received MMR+V

Vaccine(s)	Days Postvaccination		
	0-4	5-12	13-30
MMRV (n=5)	2 FS	1 epilepsy	1 FS 1 epilepsy
MMR+/-V (n=5)	2 FS	1 FS	2 FS

FS- Febrile seizure code