Safety of Measles-Mumps-Rubella-Varicella Combination Vaccine in 1-2 Year old Children

Nicola P. Klein, MD, PhD[1], Edwin Lewis, MPH[1], Bruce Fireman, MA[1], Roger Baxter, MD[1], Simon J. Hambidge, MD, PhD[2], Allison Naleway, PhD[3], Jennifer Nelson, PhD[4], Edward Belongia, MD[5], Katherine Yih, PhD, MPH[6], James Nordin, MD, MPH[7] and Eric Weintraub, MPH[8]
(1)Kaiser Permanente Vaccine Study Center, Oakland, CA, (2)Kaiser Permanente Colorado, Denver, CO, (3)The Center for Health Research, Kaiser Permanente Northwest, Portland, OR, (4)Group Health Research Institute, Seattle, WA, (5)Epidemiology Research Center, Marshfield Clinic Research Foundation, Marshfield, WI, (6)Harvard Pilgrim Health Care Institute, Boston, MA, (7)HealthPartners Research Foundation, Minneapolis, MN, (8)Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA

Background

Among toddlers, measles-containing vaccines increase risk of seizure and fever during the 7-10 days after immunization.

Objective

To evaluate the risk of 7 outcomes, as well as seizure and fever, following combination measles-mumps-rubella-varicella (MMRV) and separately administered MMR and varicella (MMR+V) vaccines.

Methods

- 12-23 month old children at 8 sites in the Vaccine Safety Datalink 2000-2012.
- 9 pre-specified outcomes with varying post-vaccination risk intervals. Seizure and fever study period limited to 10/08-06/12. (**Table 1**)
- Primary analysis compared MMRV with MMR + V and estimated the relative risk of each outcome during outcome-specific risk intervals using stratified exact analyses. (**Table 2**)
- Secondary analyses compared risk during a risk interval post-MMRV or post-MMR+V with risk during a control interval (days 57-180) using case-centered logistic regressions. (**Table 3**)
  - First, we compared the risk interval with the control interval for each vaccine. (**Table 3 columns: "MMRV" and "MMR + V"**)
  - Second, we examined whether the difference between the risk interval and control interval differed between MMRV and MMR + V (i.e. examined the difference-in-differences). (**Table 3: "MMRV vs MMR + V" column**)
- Secondary analyses addressed potential unmeasured differences between MMRV and MMR + V vaccinees which could confound our primary comparison.

Case Definitions

Table 1. Pre-specified safety outcomes and outcome-specific risk intervals among 12-23 month olds following MMRV and MMR + V.

Outcome	Case Definition/ICD-9 Codes	Setting	Focal Risk Interval (post-vaccination days)	Broader Risk Interval (post-vaccination days)
Acute Disseminated Encephalomyelitis (ADEM)	323.61	All[a]	3-21	1-42
Anaphylaxis[b]	995.1 (angio-neurotic edema), 999.4 (anaphylactic shock due to serum)	All	0	Not applicable
Arthritis/Arthralgia[b]	714.9, 716.9, 056.71	All	1-42	1-42
Ataxia	052.7, 334.3, 781.2, 781.3	All	14-28	1-42
Immune Thrombocytopenia Purpura (ITP) I	Two platelet counts of <=50,000 within 7 days of each other	All	14-28	1-42
ITP II	Two platelet counts of <=150,000 within 7 days of each other	All	14-28	1-42
Kawasaki's Disease	446.1 (Acute febrile mucocutaneous lymph node syndrome)	All	1-28	1-56
Meningitis/Encephalitis/ Encephalopathy[b]	047.8, 047.9, 049.9, 321.2, 322*, 323.5, 323.9, and 348.3*	Inpatient only	3-21	1-42
Fever[c]	780.6	Outpatient	7-10	1-42
Seizures[c]	345*, 780.3*	Inpatient ED	7-10	1-42

[a] Includes inpatient, emergency department and outpatient clinic.
[b] Analyzed as a single group, not as separate analyses.
[c] Data limited to October 2008 through June 2012.

Results

Table 2. Risk of outcomes comparing MMRV with MMR + V among 12-23 month olds using stratified exact analyses, VSD population 2000-2012.

Outcomes	Post-Vaccination Risk Interval (Days)	MMRV Cases (N)	MMR + V Cases (N)	MMRV vs MMR + V Relative Risk (95% CI)
ADEM	3-21	0	0	NE
	1-42	0	0	NE
Anaphylaxis	0	0	0	NE
Arthritis/Arthralgia	1-42	1	1	12.12 (0.03-4443.16)
Ataxia	14-28	52	68	1.31 (0.78-2.17)
	1-42	134	215	0.98 (0.71-1.35)
ITP I[a]	14-28	4	6	0.79 (0.1-6.2)
	1-42	7	8	0.9 (0.18-4.77)
ITP II[a]	14-28	6	10	1.26 (0.26-5.37)
	1-42	10	25	0.9 (0.28-2.69)
Kawasaki Disease	1-28	0	2	NE (0-53.38)
	1-56	7	8	0.69 (0.17-2.98)
Meningitis/Encephalitis/ Encephalopathy	3-21	1	0	NE (0.01-NE)
	1-42	2	1	2.98 (0.04-627.05)
Fever[b]	7-10	155	807	1.16 (0.96-1.39)
	1-42	394	3487	0.91 (0.81-1.02)
Seizure[b]	7-10	18	53	**1.99 (1.08-3.53)**
	1-42	47	348	1.06 (0.75-1.46)

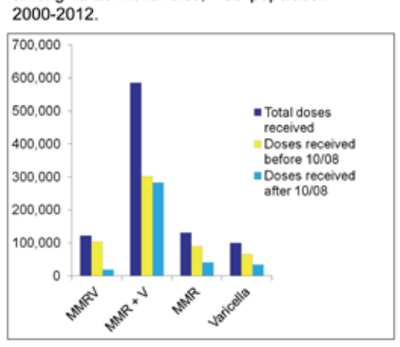
NE= Not estimable
[a] Immune thrombocytopenia purpura I and II as defined in Table 1.
[b] Data limited to October 2008 through June 2012.

Table 3. Risk of outcomes using case centered analyses following MMRV, following MMR+V, and comparing MMRV with MMR+V, VSD 2000-2012.

		MMRV		MMR + V		MMRV vs MMR + V
Outcome	**Post-Vaccination Risk Interval (Days)**	***Cases (N)***	***OR (95% CI)[a]***	***Cases (N)***	***OR (95% CI)[a]***	***OR (95% CI)***
ADEM	3-21	0	NE	0	NE	NE
	0-42	0	NE	1	NE	NE
Anaphylaxis	0	2	**15.34 (2.16-108.86)**	5	1.52 (0.31-7.37)	10.07 (0.81-124.64)
Arthritis/Arthralgia	1-42	1	0.05 (0-22.13)	3	0.24 (0.03-1.69)	0.22 (0-124.03)
Ataxia	14-28	55	0.61 (0.37-1.02)	212	**0.78 (0.62-0.99)**	0.78 (0.45-1.37)
	1-42	137	**0.7 (0.51-0.95)**	590	**0.81 (0.7-0.93)**	0.87 (0.62-1.22)
ITP I[a]	14-28	4	**11.28 (1.87-68.2)**	21	**10.04 (4.49-22.45)**	1.12 (0.16-8.07)
	1-42	7	3.75 (0.65-21.73)	33	**5.92 (2.98-11.75)**	0.63 (0.1-4.18)
ITP II[a]	14-28	6	2.86 (0.83-9.86)	35	**4.26 (2.33-7.77)**	0.67 (0.17-2.66)
	1-42	10	0.95 (0.28-3.17)	70	**2.81 (1.75-4.52)**	0.34 (0.09-1.23)
Kawasaki Disease	1-28	0	NE	12	NE	NE
	1-56	7	0.31 (0.06-1.69)	31	1.25 (0.69-2.28)	0.25 (0.04-1.49)
Meningitis/ Encephalitis/ Encephalopathy	3-21	2	4.88 (0.47-50.42)	5	1.59 (0.37-6.84)	3.08 (0.2-48.38)
	1-42	2	2.13 (0.21-22.02)	9	1.13 (0.38-3.43)	1.88 (0.14-24.89)
Fever[b]	7-10	157	**5.7 (4.05-8.01)**	2433	**3.84 (3.53-4.18)**	**1.48 (1.04-2.11)**
	1-42	394	1.19 (0.96-1.46)	7813	**1.05 (1.0-1.11)**	1.13 (0.91-1.4)
Seizures[b]	7-10	18	**17.26 (8.09-36.83)**	148	**4.43 (3.38-5.79)**	**3.9 (1.75-8.71)**
	1-42	47	**2.59 (1.52-4.42)**	626	**1.4 (1.21-1.61)**	**1.86 (1.07-3.22)**

NE= Not estimable
[a] Comparison interval is 57-180 days post-MMRV or MMR + V, as appropriate.
[b] Data limited to October 2008 through June 2012.

Figure. Number of vaccine doses administered among 12-23 month olds, VSD population 2000-2012.



Conclusions

- Comparing MMRV with MMR + V, there were no statistically significant differences in risk for any of the 7 additional outcomes.
- The elevated risk for ITP, similarly elevated after either vaccine, is consistent with previous studies.
- Using only previously unanalyzed data, this study confirmed:
  - Both MMRV and MMR + V are associated with fever and seizure 7-10 days after vaccination.
  - MMRV, compared with MMR + V, is associated with an increased risk of seizures 7-10 days after vaccination.

Implications

- The increased risk for anaphylaxis after MMRV and the reduced risk for ataxia after both MMRV and MMR + V require more investigation.
- Power was limited for outcomes other than fever and seizure. Ongoing monitoring of anaphylaxis and other outcomes is warranted.

vaccines.kaiser.org Nicola.klein@kp.org
Kaiser Permanente Vaccine Study Center
KAISER PERMANENTE

Contact Name: Nicky Klein
Contact Phone: 510-267-7540
Contact Email: nicola.klein@kp.org

SHOW NAME	IDWEEK 2013	MOVE IN:	SEPT 30	VENUE	MOSCONE

NeXtShow Exposition Services

FILE NAME:	WO Ref#
144_IDW_LAYOUT	

SIZE:	QTY:
91 X 45 ☑ S/S ☐ D/S	1

SIGN PLACEMENT

INSTALLATION DATE AND DISMANTLE DATE

SUBSTRATES:

☐ SINTRA ☐ 1MM ☐ 3MM

☐ FOAMCORE ☐ 1/8" ☐ 3/16" 1/2"

☐ ULTRABOARD ☐ 1/8" ☐ 3/16" ☐ 1/2"

☑ POSTER PAPER

☐ OTHER TRIM TO SIZE

☐ PLEXIE ☐ BACKLITE ☐ WHITE ☐ CLEAR

☐ OTHER

☐ COROPLAST ☐ 1/8" ☐ 3/16" ☐ 1/2"

☐ BLACK ☐ WHITE

☐ BANNER ☐ vinyl ☐ cloth ☐ other

☐ pole pockets ☐ grommets

☐ OTHER

ADDITIONAL REQUIREMENTS:

☐ DETACHABLE ARROWS ☐ OTHER

☐ EASEL BACKS ☐ D/F TAPE

☐ VELCRO

SPECIAL INSTRUCTIONS: