

Safety of Measles-Containing Vaccines in 1-Year-Old Children

Nicola P. Klein, MD, PhD^a, Edwin Lewis, MPH^a, Bruce Fireman, MA^a, Simon J. Hambidge, MD, PhD^b, Allison Naleway, PhD^c, Jennifer C. Nelson, PhD^d, Edward A. Belongia, MD^e, W. Katherine Yih, PhD, MPH^f, James D. Nordin, MD, MPH^g, Rulin C. Hechter, MD, PhD^h, Eric Weintraub, MPHⁱ, Roger Baxter, MD^a

abstract

BACKGROUND AND OBJECTIVES: All measles-containing vaccines are associated with several types of adverse events, including seizure, fever, and immune thrombocytopenia purpura (ITP). Because the measles-mumps-rubella-varicella (MMRV) vaccine compared with the separate measles-mumps-rubella (MMR) and varicella (MMR + V) vaccine increases a toddler's risk for febrile seizures, we investigated whether MMRV is riskier than MMR + V and whether either vaccine elevates the risk for additional safety outcomes.

METHODS: Study children were aged 12 to 23 months in the Vaccine Safety Datalink from 2000 to 2012. Nine study outcomes were investigated: 7 main outcomes (anaphylaxis, ITP, ataxia, arthritis, meningitis/encephalitis, acute disseminated encephalomyelitis, and Kawasaki disease), seizure, and fever. Comparing MMRV with MMR + V, relative risk was estimated by using stratified exact binomial tests. Secondary analyses examined post-MMRV or MMR + V risk versus comparison intervals; risk and comparison intervals were then contrasted for MMRV versus MMR+V.

RESULTS: We evaluated 123 200 MMRV and 584 987 MMR + V doses. Comparing MMRV with MMR + V, risks for the 7 main outcomes were not significantly different. Several outcomes had few or zero postvaccination events. Comparing risk versus comparison intervals, ITP risk was higher after MMRV (odds ratio [OR]: 11.3 [95% confidence interval (CI): 1.9 to 68.2]) and MMR + V (OR: 10 [95% CI: 4.5 to 22.5]) and ataxia risk was lower after both vaccines (MMRV OR: 0.8 [95% CI: 0.5 to 1]; MMR + V OR: 0.8 [95% CI: 0.7 to 0.9]). Compared with MMR + V, MMRV increased risk of seizure and fever 7 to 10 days after vaccination.

CONCLUSIONS: This study did not identify any new safety concerns comparing MMRV with MMR + V or after either the MMRV or the MMR + V vaccine. This study provides reassurance that these outcomes are unlikely after either vaccine.

^aKaiser Permanente Vaccine Study Center, Oakland, California; ^bKaiser Permanente Colorado Institute for Health Research, Denver and Department of Ambulatory Care Services, Denver Health, Denver, Colorado; ^cThe Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon; ^dGroup Health Cooperative and the University of Washington, Seattle, Washington; ^eCenter for Clinical Epidemiology & Population Health, Marshfield Clinic Research Foundation, Marshfield, Wisconsin; ^fHarvard Pilgrim Health Care Institute, Boston, Massachusetts; ^gHealthPartners Research Foundation, Minneapolis, Minnesota; ^hResearch and Evaluation, Kaiser Permanente Southern California, Pasadena, California; and ⁱImmunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia

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

Dr Klein led the design of the study, oversaw the data collection, interpreted the data, drafted the initial manuscript, and was the lead author of the manuscript; Mr Lewis collected the data, conducted the analysis, and contributed to critical revision of the manuscript for important intellectual content; Mr Fireman contributed to study design, assisted with the analysis, and contributed to critical revision of the manuscript for important intellectual content; Dr Baxter and Mr Weintraub assisted with the study design and contributed to its critical revision for important intellectual content; Drs Hambidge, Naleway, Nelson, Belongia, Yih, Nordin, and Hechter contributed to data collection, reviewed the manuscript, and made critical revisions of the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-1822

DOI: 10.1542/peds.2014-1822

WHAT'S KNOWN ON THIS SUBJECT: Measles-containing vaccines are associated with several types of adverse events. Because measles-mumps-rubella-varicella (MMRV) versus separate measles-mumps-rubella (MMR) and varicella (MMR + V) vaccine increases a toddler's risk for febrile seizures, we investigated whether MMRV is riskier than MMR + V and whether either vaccine elevates risk for additional safety outcomes.

WHAT THIS STUDY ADDS: Comparing MMRV with MMR + V, no increased risk of immune thrombocytopenia purpura, anaphylaxis, ataxia, arthritis, meningitis/encephalitis, acute disseminated encephalomyelitis, and Kawasaki disease was detected. No new safety concerns were identified after either vaccine, and most outcomes studied were unlikely after either vaccine.

The measles-mumps-rubella (MMR) vaccine has been associated with several safety outcomes, including febrile seizures,¹⁻⁴ fever,⁵⁻⁷ immune thrombocytopenia purpura (ITP),⁸⁻¹⁰ anaphylaxis,¹¹⁻¹³ and possibly arthritis/arthritis.¹⁴ After licensure of the combination measles-mumps-rubella-varicella vaccine (MMRV), the Advisory Committee on Immunization Practices recommended in 2006 that it preferred use of the MMRV over separate MMR and varicella (V) vaccines for the 2 recommended doses at 12 to 15 months and 4 to 6 years of age.¹⁵

Beginning in 2006, the Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink (VSD) conducted near real-time safety surveillance known as Rapid Cycle Analysis for several prespecified safety outcomes after MMRV.^{16,17} Rapid Cycle Analysis conducts routine vaccine safety surveillance by monitoring for prespecified postvaccination adverse events with the use of data accumulated weekly. In 2008, Rapid Cycle Analysis monitoring detected increased risk for seizures in 12- to 23-month-old children after MMRV,¹⁸ although not for other safety outcomes. Follow-up studies verified that MMRV is associated with an approximately twofold increased risk of fever and febrile seizures 7 to 10 days after vaccination compared with separate MMR + V.^{19,20} The CDC subsequently recommended that either MMRV or MMR + V could be administered to 1- to 2-year-olds receiving their first doses; however, families without a strong preference for MMRV should receive MMR + V.²¹ A subsequent study in 4- to 6-year-olds detected no association between MMRV or MMR + V and an increased risk of fever or febrile seizure.²²

Because it is clear that MMRV compared with MMR + V has a higher risk of febrile seizures, we hypothesized that MMRV may present

a higher risk for additional safety outcomes. Examining this question also provided us the opportunity to investigate MMRV and MMR + V for possible association with these safety outcomes. The present study therefore had 2 goals: (1) to evaluate 7 main outcomes in relation to MMRV and MMR + V vaccines from 2000 to 2012, comparing MMRV versus MMR + V and after either vaccine; and (2) to replicate and refine our previously reported findings regarding the association of measles-containing vaccines with fever and seizure using previously unexamined data from 2008 to 2012.

METHODS

Study Population

This was a cohort study that included children aged 12 to 23 months who were members of 8 VSD sites from January 2000 through June 2012 and who received MMRV (Merck & Co) or separately administered, same-day MMR (Merck & Co) + V (Merck & Co) vaccines. Seven main outcomes were prespecified: anaphylaxis, ITP, ataxia, arthritis, encephalitis/meningitis/encephalopathy, acute disseminated encephalomyelitis (ADEM), and Kawasaki disease. We chose these 7 outcomes based on being known adverse outcomes (ITP, anaphylaxis), theoretical/biologically plausible outcomes following MMR and/or varicella vaccines (ADEM, ataxia, arthritis, encephalitis/meningitis/encephalopathy), and CDC input (Kawasaki Disease). Because many of these outcomes are rare, data since 2000 were included to compute more accurate background rates and to better adjust for confounders. For fever and seizure, we had previously reported seizure and fever 7 to 10 days after vaccination from January 2000 until October 2008²⁰; for the present study, therefore, we included only previously unreported seizure and fever data 7 to 10 days after vaccination from October 2008 through June 2012. Seizure and fever

were identified as described previously^{20,22}; most seizures captured as described are febrile seizures.²⁰ Outcomes were identified by using specific *International Classification of Diseases, Ninth Revision*, codes during focal and broad risk intervals tailored for each outcome (Table 1). The risk intervals were chosen based on previous studies,^{8,20,23,24} CDC input, and expert opinion. Similar to previous vaccine safety studies that focused resources on statistically significant outcomes,^{16,25-28} charts were reviewed only for the anaphylaxis outcome.

The present study was powered to detect large safety signals. Given the observed outcomes after MMR + V and the number of MMRV doses available, we calculated post-hoc power to ascertain what incidence rate during MMRV's risk interval would have given 80% power to detect a difference between the 2 vaccines. These incidence rates were: 1 case of ADEM per 20 533 MMRV doses; 1 case of anaphylaxis per 17 734 MMRV doses; 1 case of arthritis per 19 346 MMRV doses; 1 case of ataxia per 5059 MMRV doses; 1 case of ITP I (2 platelet counts of <50 000 within a 1-week observation window) per 11 648 doses; 1 case of ITP II (2 platelet counts of <150 000 within a 1-week observation window) per 9755 MMRV doses; 1 case of Kawasaki disease per 11 824 MMRV doses; and 1 case of meningitis/encephalitis per 17 734 MMRV doses.

Participating VSD sites were as follows: Group Health Cooperative (Washington State), Harvard Vanguard Medical Associates and Harvard Pilgrim Health Care (Massachusetts), HealthPartners (Minnesota), Kaiser Permanente (Colorado, northern California, northwest [Oregon/Washington], southern California [only included data for the years 2007-2012]), and Marshfield Clinic (Wisconsin). The institutional review

TABLE 1 Prespecified Safety Outcomes and Outcome-Specific Postvaccination Risk Intervals Among 12- to 23-Month-Olds After Immunization With MMRV or MMR + V

Outcome	Case Definition/ICD-9 Codes	Exclusions	Setting	First Diagnosis in What Period?	Focal Risk Interval (Postvaccination Days)	Broader Risk Interval (Postvaccination Days)
ADEM	323.61	None	All ^a	First in 42 d	3–21	1–42
Anaphylaxis ^b	995.1 (angioneurotic edema), 999.4 (anaphylactic shock due to serum)	None	All ^a	First in 42 d	0	Not applicable
Arthritis/arthralgia ^b	714.9, 716.9, 056.71	None	All ^a	First in 42 d	Not applicable	1–42
Ataxia	052.7, 334.3, 781.2, 781.3	None	All ^a	First in 42 d	14–28	1–42
ITP definition 1 ^c	Two platelet counts of ≤50 000 within 7 d of each other	Exclude cases who have any of the following codes in the 6 mo prior to the first low platelet count: 140.0-208., ^d 228., ^d 279., ^d 283., ^d 284., ^d 286.6, 570, 571., ^d 742.59	All ^a	First in 6 mo	14–28	1–42
ITP definition 2 ^c	Two platelet counts of ≤150 000 within 7 d of each other	Same as for thrombocytopenia definition 1	All ^a	First in 6 mo	14–28	1–42
Kawasaki disease	446.1 (acute febrile mucocutaneous lymph node syndrome)	None	All ^a	First in 1 y	1–28	1–56
Meningitis/encephalitis/encephalopathy ^b	047.8, 047.9, 049.9, 321.2, 322, ^d 323.5, 323.9, and 348.3 ^d	047.0–047.1, 048, ^d 049.0–049.8, 053 ^d –056, ^d 320 ^d	Inpatient only	First ever since birth	3–21	1–42
Fever	780.6	None	Outpatient	First in 42 d	7–10	Not applicable
Seizures	345, ^d 780.3 ^d	None	Inpatient ED	First in 42 d	7–10	Not applicable

^a Includes inpatient, emergency department (ED), and outpatient clinic.

^b Analyzed as a single group (not as separate analyses).

^c ITP defined with 2 different platelet counts to include cases using both strict and more relaxed laboratory criteria.

^d Indicates that all *International Classification of Diseases, Ninth Revision (ICD-9)*, codes that began with these numbers were included.

boards of all participating sites approved the study.

Statistical Analyses

This study conducted 2 prespecified analyses (Fig 1). The primary analysis assessed whether MMRV versus MMR + V was associated with an increased outcome risk during outcome-specific risk intervals by using exact binomial tests, stratified according to age, gender, calendar week, and VSD site. To prevent confounding by VSD site, this analysis used data only during weeks in which a VSD site used both MMRV and MMR + V vaccines by requiring that concurrent follow-up time be available after both vaccines at the VSD site. Our goal was to minimize confounding by VSD site because diagnostic and coding practices, as well as decisions regarding which patient gets which vaccine, may be site-specific. However, from the outset, we suspected that this stringent concurrent follow-up time requirement might be problematic (eg, the MMRV

vaccine was unavailable during 2008–2010 due to shortage), and secondary analyses were planned to partially overcome this limitation.

Secondary analyses evaluated whether MMRV or MMR + V was independently associated with an increased outcome risk by examining

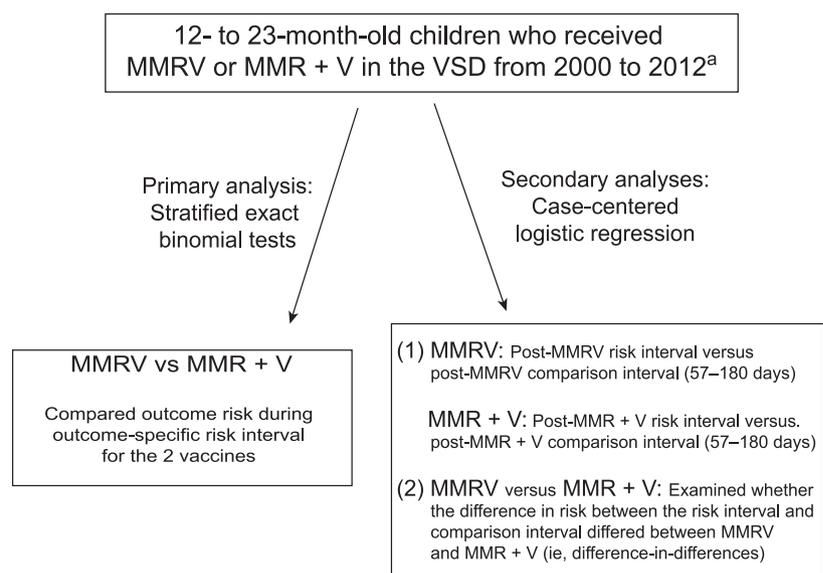


FIGURE 1

Analytic approach for primary and secondary analyses through June 2012 for seizure and fever outcomes. ^aStudy population limited to October 2008.

risk during a risk interval shortly after vaccination versus a comparison interval 57 to 180 days after vaccination (“case-centered analyses”)^{20,29–31}; MMRV vaccinees were examined separately from MMR + V vaccinees. For each vaccine–outcome pair, a simple logistic regression model was fit to a data set, including 1 record for each outcome event in either a risk or comparison interval. The dependent variable was whether the outcome occurred during the risk interval. The independent variable was based on the proportion of vaccinees in the risk interval on the calendar day of the case’s outcome event, among all vaccinees in the case’s age–gender stratum that were in either the risk or comparison interval on that date. The logit of this proportion was included as an offset in an intercept-only logistic regression model so that the fitted model yielded an estimate of the relative risk associated with being inside-versus-outside of the risk interval.

We next examined whether the difference between risk and comparison intervals differed between the vaccinees. The intercept-only model

was expanded by adding a binary variable indicating MMRV or MMR + V, which permits a test of the difference-in-differences: whether the risk versus comparison interval contrast is different among MMRV vaccinees than among MMR + V vaccinees. This analysis addressed potential unmeasured differences between MMRV and MMR + V vaccinees that could confound our primary comparison.

For each type of outcome event and risk interval, 2 types of risk difference were calculated (often referred to as attributable risk): (1) the difference in outcome risk comparing post-MMRV risk interval versus post-MMR + V risk interval; and (2) the difference between observed and expected outcome incidence during the risk interval after each vaccine in which the expected incidence was derived from the comparison interval. We derived 95% confidence intervals (CIs) for the risk difference by using a score method for differences in proportions appropriate for sparse data.^{32,33} The upper bound indicates how large of an attributable risk could be ruled out with 95% confidence.

RESULTS

A total of 123 200 MMRV doses and 584 987 MMR + V doses administered to children 12 to 23 months old from 2000 to 2012 were evaluated. Reflecting the MMRV shortage in 2008–2010 and the CDC’s 2010 recommendation that the use of MMRV be limited to those whose parents request it, only 19 180 (16%) of the MMRV doses were administered after October 2008, whereas almost one half of the MMR + V doses (282 765 [48%]) were administered after October 2008.

Overall, rates for the 7 main outcomes during postvaccination risk intervals were low, with several outcomes having few or zero events in the risk interval after either vaccine. Estimated risk differences between MMRV and MMR + V were not statistically significant for any of the 7 main outcomes, although it was for seizure. Comparing MMRV with MMR + V, the risk difference that can be ruled out with 95% confidence ranged from 0.5 case (Kawasaki disease, days 1–28) to 35 cases (ataxia, days 1–42) per 100 000 MMRV doses (Table 2).

TABLE 2 Cases and Unadjusted Outcome Rates During Focal and Broad Risk Intervals, VSD 2000–2012

Outcome	Risk Interval	MMRV		MMR + V		MMRV Versus MMR + V Unadjusted Risk Difference/100 000 Doses (95% CI)
		No. of Risk Cases/100 000 Doses	Rate/1000 PY (95% CI)	No. of Risk Cases/100 000 Doses	Rate/1000 PY (95% CI)	
ADEM	3–21	0 (0)	0.00 (0.00 to 0.48)	0 (0)	0.00 (0.00 to 0.10)	0.00 (NE to 3.69)
	1–42	0 (0)	0.00 (0.00 to 0.22)	0.17 (1)	0.02 (0.00 to 0.08)	–0.17 (–0.98 to 3.06)
Anaphylaxis	0	1.68 (2) ^a	6.13 (0.74 to 22.13)	0.85 (5)	3.12 (1.01 to 7.29)	0.82 (–0.85 to 5.29)
Arthritis/ arthralgia	1–42	0.84 (1)	0.07 (0.00 to 0.41)	0.52 (3)	0.05 (0.01 to 0.13)	0.32 (–0.91 to 4.26)
Ataxia	14–28	46.27 (55)	11.27 (8.49 to 14.66)	36.81 (212)	8.96 (7.80 to 10.26)	9.45 (–2.50 to 24.13)
	1–42	115.26 (137)	10.02 (8.42 to 11.85)	102.51 (590)	8.91 (8.21 to 9.66)	12.75 (–6.98 to 35.11)
ITP I	14–28	3.36 (4)	0.82 (0.22 to 2.10)	3.65 (21)	0.89 (0.55 to 1.36)	–0.28 (–3.10 to 5.15)
	1–42	5.89 (7)	0.51 (0.21 to 1.06)	5.73 (33)	0.50 (0.34 to 0.70)	0.16 (–3.66 to 6.64)
ITP II	14–28	5.05 (6)	1.23 (0.45 to 2.68)	6.08 (35)	1.48 (1.03 to 2.06)	–1.03 (–4.65 to 5.17)
	1–42	8.41 (10)	0.73 (0.35 to 1.35)	12.16 (70)	1.06 (0.82 to 1.34)	–3.75 (–8.75 to 3.77)
Kawasaki disease	1–28	0 (0)	0.00 (0.00 to 0.33)	2.93 (17)	0.38 (0.22 to 0.61)	–2.93 (–4.70 to 0.48)
	1–56	5.90 (7)	0.38 (0.15 to 0.79)	5.42 (31)	0.35 (0.24 to 0.50)	0.48 (–3.32 to 6.95)
Meningitis/encephalitis	3–21	1.68 (2)	0.32 (0.04 to 1.17)	0.86 (5)	0.17 (0.05 to 0.39)	0.82 (–0.86 to 5.29)
	1–42	1.68 (2)	0.15 (0.02 to 0.53)	1.56 (9)	0.14 (0.06 to 0.26)	0.12 (–1.75 to 4.63)
Fever ^b	7–10	881.00 (157)	804.46 (683.54 to 940.6)	860.99 (2433)	786.19 (755.26 to 818.07)	20 (–110.84 to 170.28)
Seizure ^b	7–10	101.01 (18)	92.23 (54.66 to 145.76)	52.37 (148)	47.82 (40.43 to 56.18)	48.63 (10.38 to 107.63)

NE, not estimable.

^a Chart review did not confirm anaphylaxis in either case.

^b Data limited to October 2008 through June 2012.

In the primary analysis, there was no statistically significant difference in risk between MMRV and MMR + V during either the focal or broad risk interval for the 7 main outcomes (Table 3). Analyses of seizures after October 2008 confirmed that MMRV, compared with MMR + V, was associated with a twofold increased risk 7 to 10 days after vaccination. Table 3 case counts differed from those in Table 2 because of the requirement for concurrent follow-up time after MMRV and MMR + V at each VSD site.

Secondary analyses comparing risk versus comparison intervals after MMRV or MMR + V revealed an increased risk of ITP and a decreased risk of ataxia after both vaccines (Table 4). Analyses also detected an increased risk for anaphylaxis after MMRV. This result was based on only 2 cases, neither of which was confirmed as acute anaphylaxis after chart review; both diagnoses were related to a history of allergic reactions. Similar to the primary analysis, there were no significant differences in risk for the 7 main outcomes during any risk interval comparing MMRV with MMR + V (Table 4).

Table 5 displays the differences in risk between risk and comparison intervals for the 7 main outcomes after each measles-containing vaccine. After MMR + V, the risk of ataxia was significantly lower during the risk interval. For the remaining outcomes, risk differences that can be ruled out with 95% confidence ranged from 0.08 case (arthritis) to 11 cases (ITP II, days 1–42) per 100 000 MMR + V doses. Similarly, ataxia risk was significantly lower after MMRV. For the remaining outcomes, we could rule out risk differences that ranged from 0.5 case (Kawasaki disease, days 1–28) to 10 cases (ITP I, days 1–42) per 100 000 MMRV doses.

Case-centered analyses demonstrated a significantly increased risk of seizure and fever 7 to 10 days after both MMRV and MMR + V and confirmed that MMRV, compared with MMR + V, was associated with a significantly higher risk for seizure and fever 7 to 10 days after vaccination (Table 4).

DISCUSSION

Comparing MMRV with MMR + V, the present study found no statistically

significant differences in risk for all 7 main outcomes and detected no new safety concerns comparing MMRV with MMR + V. We quantified the risk attributable to MMRV versus MMR + V that could be ruled out with 95% confidence and observed that at most, few cases could potentially be attributed to MMRV. These findings provide reassurance that these outcomes were unlikely after either vaccine.

The present study examined both measles-containing vaccines. No new safety concerns were found after either vaccine. We estimated how much risk we could rule out with 95% confidence for each of the 7 outcomes after either MMRV or MMR + V. These estimates indicate that even if an increased risk for these outcomes exists, the risk is low and rare after either measles-containing vaccine. This study further confirmed (by using previously unanalyzed data) that MMRV and MMR + V are both associated with fever and seizure 7 to 10 days after vaccination, and validated our previous findings and those of others that MMRV versus MMR + V is associated with an excess risk of seizures 7 to 10 days after vaccination.^{19,20,34–36} This study replicated previously reported safety findings, which provides additional reassurance that assessing the 7 main outcomes with this approach was reasonable.

The present study detected no difference in risk for ITP between recipients of MMRV compared with MMR + V. However, receipt of MMRV and MMR + V were individually associated with an elevated risk for ITP, highest during postvaccine days 14 to 28 but also during the 1- to 42-day risk interval. The similarly elevated risk for ITP after either vaccine is consistent with previous studies which found increased ITP risk after MMR in children.^{8–10} To our knowledge, the present study represents the first report that MMRV

TABLE 3 Risk of Outcomes Comparing MMRV With MMR + V Among 12- to 23-Month-Olds by Using Stratified Exact Binomial Tests, VSD Population 2000–2012

Outcome	Postvaccination Risk Interval (d)	No. of MMRV Risk Cases	No. of MMR + V Risk Cases	MMRV Versus MMR + V Relative Risk (95% CI)
ADEM	3–21	0	0	NE
	1–42	0	0	NE
Anaphylaxis	0	0	0	NE
Arthritis	1–42	1	1	12.12 (0.03 to 4443.16)
	14–28	52	68	1.31 (0.78 to 2.17)
Ataxia	1–42	134	215	0.98 (0.71 to 1.35)
	14–28	4	6	0.79 (0.1 to 6.2)
ITP I ^a	1–42	7	8	0.9 (0.18 to 4.77)
	14–28	6	10	1.26 (0.26 to 5.37)
ITP II ^b	1–42	10	25	0.9 (0.28 to 2.69)
	14–28	6	10	1.26 (0.26 to 5.37)
Kawasaki disease	1–28	0	2	0 (0 to 53.38)
	1–56	7	8	0.69 (0.17 to 2.98)
Meningitis/encephalitis	3–21	1	0	NE (0.01 to NE)
	1–42	2	1	2.98 (0.04 to 627.05)
Fever ^c	7–10	155	807	1.16 (0.96 to 1.39)
Seizure ^c	7–10	18	53	1.99 (1.08 to 3.53)

NE, not estimable.

^a Two platelet counts of <50 000 within a 1-week observation window.

^b Two platelet counts of <150 000 within a 1-week observation window.

^c Data limited to October 2008 through June 2012.

TABLE 4 Risk of Outcomes Using Case-Centered Analyses After MMRV or MMR + V Alone and Comparing MMRV With MMR + V, VSD 2000–2012

Outcome	Postvaccination Risk Interval (d)	MMRV			MMR + V			MMRV Versus MMR + V, OR (95% CI)
		No. of Risk Cases	No. of Comparison Cases ^a	OR (95% CI) ^a	No. of Risk Cases	No. of Comparison Cases ^a	OR (95% CI) ^a	
ADEM	3–21	0	1	NE	0	2	NE	NE
	1–42	0		NE	1		NE	NE
Anaphylaxis	0	2	37	15.34 (2.16 to 108.86)	5	158	1.52 (0.31 to 7.37)	10.07 (0.81 to 124.64)
Arthritis	1–42	1	6	0.05 (0 to 22.13)	3	25	0.24 (0.03 to 1.69)	0.22 (0 to 124.03)
Ataxia	14–28	55	527	0.61 (0.37 to 1.02)	212	2214	0.78 (0.62 to 0.99)	0.78 (0.45 to 1.37)
	1–42	137		0.7 (0.51 to 0.95)	590		0.81 (0.7 to 0.93)	0.87 (0.62 to 1.22)
ITP I ^b	14–28	4	7	11.28 (1.87 to 68.2)	21	22	10.04 (4.49 to 22.45)	1.12 (0.16 to 8.07)
	1–42	7		3.75 (0.65 to 21.73)	33		5.92 (2.98 to 11.75)	0.63 (0.1 to 4.18)
ITP II ^c	14–28	6	29	2.86 (0.83 to 9.86)	35	73	4.26 (2.33 to 7.77)	0.67 (0.17 to 2.66)
	1–42	10		0.95 (0.28 to 3.17)	70		2.81 (1.75 to 4.52)	0.34 (0.09 to 1.23)
Kawasaki disease	1–28	0	15	NE	17	60	NE	NE
	1–56	7		0.31 (0.06 to 1.69)	31		1.25 (0.69 to 2.28)	0.25 (0.04 to 1.49)
Meningitis/encephalitis	3–21	2	3	4.88 (0.47 to 50.42)	5	26	1.59 (0.37 to 6.84)	3.08 (0.2 to 48.38)
	1–42	2		2.13 (0.21 to 22.02)	9		1.13 (0.38 to 3.43)	1.88 (0.14 to 24.89)
Fever ^d	7–10	157	1148	5.7 (4.05 to 8.01)	2433	16 512	3.84 (3.53 to 4.18)	1.48 (1.04 to 2.11)
Seizure ^d	7–10	18	132	17.26 (8.09 to 36.83)	148	1534	4.43 (3.38 to 5.79)	3.9 (1.75 to 8.71)

NE, not estimable.

^a Comparison interval is 57 to 180 days' post-MMRV or MMR + V, as appropriate.

^b Two platelet counts of <50 000 within a 1-week observation window.

^c Two platelet counts of <150 000 within a 1-week observation window.

^d Data limited to October 2008 through June 2012.

is associated with a similar increased risk of ITP during the same postvaccination risk intervals as MMR.

A 2011 Institute of Medicine report concluded that the evidence supports a causal relationship between MMR vaccine and anaphylaxis.¹⁴ Previous studies have suggested that anaphylaxis after MMR is rare

(approximated at 1.5–1.8 events per 1 million doses).^{11–13} In our study, neither of the 2 cases identified via electronic data as having anaphylaxis after MMRV was ultimately confirmed as acute anaphylaxis according to chart review. Analyses comparing MMRV with MMR + V did not identify any statistical difference; however, given the low frequency of

anaphylaxis after administration of measles-containing vaccines, continued monitoring for anaphylaxis after these vaccines is warranted.

The present study found no difference in ataxia risk with MMRV versus MMR + V during either the 14- to 28-day period or the 1- to 42-day period after vaccination. Surprisingly, MMRV and MMR + V were both associated with decreased ataxia diagnoses after vaccination. Previous passive surveillance suggested a temporal relationship between MMR and increased ataxia,³⁷ whereas a more recent self-controlled case series analysis found no association between gait disturbances and MMR.³⁸ Overall, the Institute of Medicine concluded that the evidence was “insufficient or absent to assess an association between MMR vaccine and ataxia.”¹⁴ Although it is theoretically possible that both vaccines offer protection against ataxia, we instead favor the interpretation that this observation is more likely due to chance, outcome misclassification, or other unmeasured confounding. One potential explanation may be because

TABLE 5 Risk Difference Between Risk and Comparison Intervals for Each Type of Measles-Containing Vaccine

Outcome	Postvaccination Risk Interval (d)	Unadjusted Risk Difference/100 000 Doses (95% CI)	
		MMRV ^a	MMR + V ^b
ADEM	3–21	−0.13 (−0.74 to 3.10)	−0.06 (−0.21 to 0.61)
	1–42	−0.29 (−1.65 to 2.95)	0.05 (−0.31 to 0.86)
Anaphylaxis	0	1.42 (0.20 to 5.86)	0.62 (0.13 to 1.77)
Arthritis	1–42	−0.9 (−3.07 to 3.13)	−1.05 (−1.88 to 0.08)
Ataxia	14–28	−8.4 (−20.15 to 6.25)	−12.92 (−18.00 to −7.24)
	1–42	−37.80 (−60.05 to −13.32)	−36.75 (−46.55 to −26.36)
ITP I ^c	14–28	2.64 (0.44 to 7.94)	3.15 (1.87 to 5.09)
	1–42	3.86 (0.13 to 10.21)	4.35 (2.55 to 6.71)
ITP II ^d	14–28	2.04 (−0.99 to 8.07)	4.44 (2.68 to 6.84)
	1–42	−0.01 (−5.33 to 7.51)	7.51 (4.77 to 10.91)
Kawasaki disease	1–28	−2.90 (−4.79 to 0.52)	0.42 (−0.90 to 2.27)
	1–56	0.09 (−4.76 to 6.77)	0.39 (−1.77 to 2.93)
Meningitis/encephalitis	3–21	1.29 (−0.15 to 5.74)	0.12 (−0.48 to 1.30)
	1–42	0.81 (−1.27 to 5.30)	−0.07 (−1.13 to 1.43)

^a Risk difference between risk versus comparison intervals after MMRV as described in Methods.

^b Risk difference between risk versus comparison intervals after MMR + V as described in Methods.

^c Two platelet counts of <50 000 within a 1-week observation window.

^d Two platelet counts of <150 000 within a 1-week observation window.

children are just beginning to walk at the time of their MMRV/MMR+ V vaccines, if the child's gait is abnormal, providers may be reluctant to diagnose ataxia until the children have been walking long enough to stabilize their gait on their own.

Alternatively, ataxia diagnoses may have been due to misclassification of electronic data, which due to resource limitations, we were unable to subject to chart review. Varicella disease is associated with cerebellar ataxia,^{39,40} and these data support that varicella vaccine (given either with MMR or as MMRV) is not associated with increased risk of ataxia. Importantly, this study reassuringly found no difference in ataxia between recipients of MMRV and of MMR + V.

We observed some small differences between analyses for fever risk after vaccination. The risk of fever 7 to 10 days after vaccination comparing MMRV with MMR + V slightly missed statistical significance in the primary analysis, whereas the secondary analyses used more data and reached statistical significance. In general, both analyses were broadly consistent with each other, as well as with previous clinical trials^{5-7,41-43} and observational studies,^{20,44} supporting the idea that MMRV compared with MMR + V increases risk of fever 7 to 10 days after vaccination.

All 7 main outcomes (except arthritis) were assessed during a focal risk interval during which events would be most likely to occur if they were related to vaccination and all (except anaphylaxis) during a broad risk interval. Focal risk intervals were assessed to potentially increase detection of safety concerns during the postvaccination period most likely to be relevant, while we assessed broad risk intervals because

the precise postvaccination risk interval is not always known. In this manner, we sought to evaluate outcome risk as specifically as possible while ensuring that we did not inadvertently miss a safety finding by centering too narrowly on the focal risk interval.

Primary and secondary analyses comparing MMRV with MMR + V had advantages and disadvantages. We prespecified stratified exact binomial tests as primary because it was the most direct method to calculate an outcome risk difference between MMRV and MMR+V. By design, this method only analyzed data from each VSD site during weeks when both MMRV and MMR + V were in use, thereby preventing confounding by site; these stringent criteria resulted in a decreased number of available cases, particularly because this study overlapped with an MMRV shortage, and MMRV/MMR + V use varied at VSD sites. Furthermore, the 2010 CDC recommendations regarding MMR + V use in 1-year-old children likely influenced which vaccine type children received, and children who received MMRV may have differed from those who received MMR + V. We therefore prespecified secondary case-centered analyses that included more cases; however, case-centered comparisons between MMRV and MMR + V indirectly calculated outcome risk differences, yielding wider confidence intervals. In this study, it was reassuring that neither primary nor secondary analyses detected an increased risk for any of the 7 main outcomes when comparing MMRV with MMR + V.

Our study had limitations. Despite using all the data in the secondary analyses, power remained low for a number of outcomes. The primary

analysis had limited power for some outcomes other than fever and seizure. In addition, we did not conduct chart reviews other than for the 2 cases of anaphylaxis due to resource limitations, and some outcomes may have been misclassified.

For a relatively new vaccine, there is value in monitoring for safety and reporting results periodically even before all safety outcomes can be fully evaluated to potentially detect a large safety concern as early as possible. This monitoring provides the public with reassurance that surveillance is ongoing and that if a large safety problem exists, it would be detected. Our findings offer modest reassurance that there is no greatly elevated risk for any of the 7 main outcomes.

CONCLUSIONS

This study did not identify any new safety concerns associated with the MMRV or MMR + V vaccines. There was no statistically significant difference in risk for any of the 7 main outcomes evaluated comparing MMRV with MMR + V. Similarly, other than for previously known outcomes of seizure, fever, and ITP, there was no increased risk for new safety outcomes after either MMRV or MMR + V. This study confirmed that MMRV and MMR + V were associated with fever and seizure 7 to 10 days after vaccination, and that MMRV versus MMR + V is associated with an increased risk of seizures 7 to 10 days after vaccination. Power was limited for some outcomes, and ongoing monitoring is warranted. This study provides reassurance that most of these safety outcomes are extremely rare and unlikely after either vaccine.

Accepted for publication Nov 19, 2014

Address correspondence to Nicola P. Klein, MD, PhD, Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16th Floor, Oakland, CA 94612. E-mail: nicola.klein@kp.org

FINANCIAL DISCLOSURE: Drs Klein and Baxter report research support from Merck & Co, GlaxoSmithKline, Sanofi-Pasteur, Pfizer, Novartis, MedImmune, and Nuron Biotech; Dr Naleway reports research support from GlaxoSmithKline; and Dr Belongia reports research support from MedImmune. The other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a subcontract with America's Health Insurance Plans under contract 200-2002-00732 from the Centers for Disease Control and Prevention.

POTENTIAL CONFLICT OF INTEREST: Drs Klein, Naleway, and Baxter have received research support from Merck and GlaxoSmithKline. The other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Barlow WE, Davis RL, Glasser JW, et al; Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med*. 2001;345(9):656–661
2. Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet*. 1995;345(8949):567–569
3. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures after measles-mumps-rubella immunization. *Pediatrics*. 1991;88(5):881–885
4. Vestergaard M, Hviid A, Madsen KM, et al. MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. *JAMA*. 2004;292(3):351–357
5. Lieberman JM, Williams WR, Miller JM, et al; Consistency Lot Study Group for ProQuad. The safety and immunogenicity of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children: a study of manufacturing consistency and persistence of antibody. *Pediatr Infect Dis J*. 2006;25(7):615–622
6. Shinefield H, Black S, Digilio L, et al. Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. *Pediatr Infect Dis J*. 2005;24(8):665–669
7. Shinefield H, Black S, Thear M, et al; 013 Study Group for ProQuad. Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined Haemophilus influenzae type b conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J*. 2006;25(4):287–292
8. France EK, Glanz J, Xu S, et al; Vaccine Safety Datalink Team. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics*. 2008;121(3). Available at: www.pediatrics.org/cgi/content/full/121/3/e687
9. Bertuola F, Morando C, Menniti-Ippolito F, et al. Association between drug and vaccine use and acute immune thrombocytopenia in childhood: a case-control study in Italy. *Drug Saf*. 2010;33(1):65–72
10. O'Leary ST, Glanz JM, McClure DL, et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. *Pediatrics*. 2012;129(2):248–255
11. Bohlke K, Davis RL, Marcy SM, et al; Vaccine Safety Datalink Team. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003;112(4):815–820
12. Carapetis JR, Curtis N, Royle J. MMR immunisation. True anaphylaxis to MMR vaccine is extremely rare. *BMJ*. 2001;323(7317):869
13. Pool V, Braun MM, Kelso JM, et al; VAERS Team. US Vaccine Adverse Event Reporting System. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. *Pediatrics*. 2002;110(6). Available at: www.pediatrics.org/cgi/content/full/110/6/e71
14. Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academies Press; 2011
15. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and Reports*. 2006;55(RR-15):1–48
16. Belongia EA, Irving SA, Shui IM, et al; Vaccine Safety Datalink Investigation Group. Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. *Pediatr Infect Dis J*. 2010;29(1):1–5
17. Lieu TA, Kullidorff M, Davis RL, et al; Vaccine Safety Datalink Rapid Cycle Analysis Team. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care*. 2007;45(10 suppl 2):S89–S95
18. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP). Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. *MMWR Morb Mortal Wkly Rep*. 2008;57(10):258–260
19. Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine*. 2009;27(34):4656–4661
20. Klein NP, Fireman B, Yih WK, et al; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e1
21. Marin M, Broder KR, Temte JL, Snider DE, Seward JF; Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-3):1–12

22. Klein NP, Lewis E, Baxter R, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. *Pediatrics*. 2012;129(5):809–814
23. Rowhani-Rahbar A, Klein NP, Dekker CL, et al; Risk Interval Working Group of the Clinical Immunization Safety Assessment Network. Biologically plausible and evidence-based risk intervals in immunization safety research. *Vaccine*. 2012;31(1):271–277
24. Tseng HF, Sy LS, Liu IL, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. *Vaccine*. 2013;31(22):2578–2583
25. Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine*. 2011;29(46):8279–8284
26. Klein NP, Hansen J, Chao C, et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. *Arch Pediatr Adolesc Med*. 2012;166(12):1140–1148
27. Baxter R, Toback SL, Sifakis F, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in adults 18-49 years of age. *Vaccine*. 2012;30(20):3053–3060
28. Baxter R, Toback SL, Sifakis F, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age. *Vaccine*. 2012;30(19):2989–2998
29. Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. *Am J Epidemiol*. 2009;170(5):650–656
30. Rowhani-Rahbar A, Klein NP, Lewis N, et al. Immunization and Bell's palsy in children: a case-centered analysis. *Am J Epidemiol*. 2012;175(9):878–885
31. Baxter R, Bakshi N, Fireman B, Lewis E, Ray P, Vellozzi C, et al. Lack of association of Guillain-Barré syndrome with vaccinations. *Clin Infect Dis*. 2013;57(2):197–204
32. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927;22(158):209–212
33. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873–890
34. Schink T, Holstiege J, Kowalzik F, Zepp F, Garbe E. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. *Vaccine*. 2014;32(6):645–650
35. Hambidge SJ, Newcomer SR, Narwaney KJ, et al. Timely versus delayed early childhood vaccination and seizures. *Pediatrics*. 2014;133(6). Available at: www.pediatrics.org/cgi/content/full/133/6/e1492
36. MacDonald SE, Dover DC, Simmonds KA, Svenson LW. Risk of febrile seizures after first dose of measles-mumps-rubella-varicella vaccine: a population-based cohort study. *CMAJ*. 2014;186(11):824–829
37. Plesner AM, Hansen FJ, Taudorf K, Nielsen LH, Larsen CB, Pedersen E. Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study. *Acta Paediatr*. 2000;89(1):58–63
38. Miller E, Andrews N, Grant A, Stowe J, Taylor B. No evidence of an association between MMR vaccine and gait disturbance. *Arch Dis Child*. 2005;90(3):292–296
39. van der Maas NA, Bondt PE, de Melker H, Kemmeren JM. Acute cerebellar ataxia in the Netherlands: a study on the association with vaccinations and varicella zoster infection. *Vaccine*. 2009;27(13):1970–1973
40. Rack AL, Grote V, Streng A, et al. Neurologic varicella complications before routine immunization in Germany. *Pediatr Neurol*. 2010;42(1):40–48
41. Kuter BJ, Brown ML, Hartzel J, et al; Study Group for ProQuad. Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad). *Hum Vaccin*. 2006;2(5):205–214
42. Klein NP, Shepard J, Bedell L, Odrlijn T, Dull P. Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in healthy toddlers. *Vaccine*. 2012;30(26):3929–3936
43. Blatter MM, Klein NP, Shepard JS, et al. Immunogenicity and safety of two tetravalent (measles, mumps, rubella, varicella) vaccines coadministered with hepatitis a and pneumococcal conjugate vaccines to children twelve to fourteen months of age. *Pediatr Infect Dis J*. 2012;31(8):e133–e140
44. Rowhani-Rahbar A, Fireman B, Lewis E, et al. Effect of age on the risk of Fever and seizures following immunization with measles-containing vaccines in children. *JAMA Pediatr*. 2013;167(12):1111–1117

Safety of Measles-Containing Vaccines in 1-Year-Old Children

Nicola P. Klein, Edwin Lewis, Bruce Fireman, Simon J. Hambidge, Allison Naleway, Jennifer C. Nelson, Edward A. Belongia, W. Katherine Yih, James D. Nordin, Rulin C. Hechter, Eric Weintraub and Roger Baxter

Pediatrics 2015;135:e321

DOI: 10.1542/peds.2014-1822 originally published online January 5, 2015;

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/135/2/e321
References	This article cites 41 articles, 10 of which you can access for free at: http://pediatrics.aappublications.org/content/135/2/e321#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Administration/Practice Management http://www.aappublications.org/cgi/collection/administration:practice_management_sub Safety http://www.aappublications.org/cgi/collection/safety_sub Infectious Disease http://www.aappublications.org/cgi/collection/infectious_diseases_sub Vaccine/Immunization http://www.aappublications.org/cgi/collection/vaccine:immunization_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Safety of Measles-Containing Vaccines in 1-Year-Old Children

Nicola P. Klein, Edwin Lewis, Bruce Fireman, Simon J. Hambidge, Allison Naleway,
Jennifer C. Nelson, Edward A. Belongia, W. Katherine Yih, James D. Nordin, Rulin
C. Hechter, Eric Weintraub and Roger Baxter

Pediatrics 2015;135:e321

DOI: 10.1542/peds.2014-1822 originally published online January 5, 2015;

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/135/2/e321>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

