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Timely Versus Delayed Early Childhood Vaccination and Seizures

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WHAT'S KNOWN ON THIS SUBJECT: Reasons for childhood immunization delay include parental intent and barriers such as transportation. To date there has been 1 study of the association of delayed vaccination and seizures, which found measles-mumps-rubella and measles-mumps-rubella-varicella vaccines are both associated with a higher rate of seizures if received after 15 months of age.

WHAT THIS STUDY ADDS: Our study found no association between the timing of vaccination and occurrence of seizures in the first year of life. By using different methods, our results support the observation that delaying vaccination with measles-containing vaccines past 15 months of age increases the incidence of postvaccination seizures.

abstract

FREE

BACKGROUND: Little is known regarding the timing of childhood vaccination and postvaccination seizures.

METHODS: In a cohort of 323 247 US children from the Vaccine Safety Datalink born from 2004 to 2008, we analyzed the association between the timing of childhood vaccination and the first occurrence of seizure with a self-controlled case series analysis of the first doses of individual vaccines received in the first 2 years of life.

RESULTS: In infants, there was no association between the timing of infant vaccination and postvaccination seizures. In the second year of life, the incident rate ratio (IRR) for seizures after receipt of the first measles-mumps-rubella vaccine (MMR) dose at 12 to 15 months was 2.65 (95% confidence interval [CI] 1.99–3.55); the IRR after an MMR dose at 16 to 23 months was 6.53 (95% CI 3.15–13.53). The IRR for seizures after receipt of the first measles-mumps-rubella-varicella vaccine (MMRV) dose at 12 to 15 months was 4.95 (95% CI 3.68–6.66); the IRR after an MMRV dose at 16 to 23 months was 9.80 (95% CI 4.35 –22.06).

CONCLUSIONS: There is no increased risk of postvaccination seizure in infants regardless of timing of vaccination. In year 2, delaying MMR vaccine past 15 months of age results in a higher risk of seizures. The strength of the association is doubled with MMRV vaccine. These findings suggest that on-time vaccination is as safe with regard to seizures as delayed vaccination in the first year of life, and that delayed vaccination in the second year of life is associated with more postvaccination seizures than on-time vaccination. *Pediatrics* 2014;133:e1492–e1499

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KEY WORDS

vaccine safety, immunization, vaccine, seizures, vaccine delay

ABBREVIATIONS

ACIP—Advisory Committee on Immunization Practices
CL—confidence limit
DTaP—diphtheria, tetanus, and acellular pertussis vaccine
DTaP-IPV-HIB—diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenza type B combined vaccine
ED—emergency department
IRR—incident rate ratio
MCOs—managed care organizations
MMR—measles-mumps-rubella vaccine
MMRV—measles-mumps-rubella-varicella vaccine
PPV—positive predictive value
SCCS—self-control case series
VSD—Vaccine Safety Datalink

(Continued on last page)

Despite the evidence for the safety of childhood vaccines,[1–3] an increasing number of families are requesting delayed immunization schedules for their young children,[4] often out of concern that the schedule recommended by the Advisory Committee on Immunization Practices (ACIP)[5] may confer risks for their children. To date, although there are multiple studies detailing the risk of a variety of vaccine-preventable diseases in children who are undervaccinated,[6–8] there are few studies directly comparing vaccine safety in children on delayed versus recommended immunization schedules.[9] The Institute of Medicine has recently called for an assessment of studies related to the safety of the recommended versus nonstandard schedules.[2]

Children may be on delayed schedules because of parental intent, or because of barriers to immunization, such as lack of health insurance and transportation.[10–14] Regardless, there is no reason to think a priori that vaccine adverse events will differ based on the underlying reason for a child being on a delayed schedule. In fact, a recent large cohort study demonstrated that emergency department (ED) use was roughly equivalent in undervaccinated children compared with those vaccinated on time.[15] We used a previously defined large national cohort of children on both recommended and delayed immunization schedules[15] to examine risk for seizures after vaccination in young children. Specifically, we asked the following questions: Is there an association between seizures and receipt of the first dose of each vaccine administered in the first 2 years of life? Does the magnitude of any association differ in children who received vaccinations on time versus on a delayed schedule? These questions are particularly relevant for vaccines, such as measles-containing vaccines, that have known associations with postvaccination febrile seizures.[9,16–21]

METHODS

Setting and Population

We used a previously described cohort[15] from the pediatric population of the Vaccine Safety Datalink (VSD),[22] a collaborative project between the Centers for Disease Control and Prevention and several managed care organizations (MCOs) from across the United States that cover >3% of the US population. The MCOs offer similar preventive service packages and age-specific delivery of childhood vaccines. The study period was 2004 through 2010. The initial cohort (Fig 1) consisted of any child born between 2004 and 2008, continuously enrolled in 1 of 8 VSD MCOs from 2 to 12 months of age and up to 24 months of age, and who had at least 1 outpatient visit within the MCO. This study was approved by the institutional review boards at all participating sites and at the Centers for Disease Control and Prevention. Children older than 24 months were excluded, as very few vaccines are administered in the VSD cohort in the third and fourth years of life, resulting in very few vaccinated cases to analyze in this age group.

For this study, we first identified any child with an *International Classification of Diseases, Ninth Revision, Clinical Modification* code for seizure (345.x and 780.3x, based on previous published work[16]) in the ED or hospital between 38 days and 730 days (2 years) of life. We excluded time before 38 days, as we did not want to identify neonatal seizures that would have occurred before the earliest age that an infant should receive the recommended 2-month immunizations.[5] We next excluded any child who had a diagnosis for newborn convulsions or myoclonus, so as to exclude children with chronic seizure disorders. The final analytic cohort consisted of 5667 children, 1659 of whom had a first seizure in the first year of life, whereas 4008 had a first seizure in the second year of life. Of note, ~2% of children in the VSD population have a seizure in the first 2 years of life.

Defining Exposure Status: Immunization On Time Versus Delayed

We used a modification[15] of the method first described by Luman et al[23] to define the days underimmunized for each child in the cohort. For each vaccine received in the first 2 years of life, with the exception of influenza and hepatitis A vaccines, we defined on time versus delayed per the recommended ACIP schedule.[5] Any vaccine recommended at 2 months of life was considered on time if received before 93 days of life. Any vaccine recommended at 12 to 15 months of life was considered on time if received before 489 days of life (16 months of age). Hepatitis A vaccine was excluded because it was not universally recommended until 2007, and influenza vaccine was excluded because of the changing make-up of the vaccine on an annual basis and the seasonality of vaccine administration. We did not include the first dose of hepatitis B vaccine (recommended shortly after birth) in the analysis. We examined only the first dose of each vaccine because others have observed that the first dose of certain vaccines (diphtheria, tetanus, and acellular pertussis vaccine [DTaP][24] and measles-containing vaccines[16]) may be the most reactogenic. We did not analyze specific "catch-up" vaccination schedules.

Defining Outcome Status: Seizure

As described previously, a seizure was defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 345.x and 780.3x. In previous VSD work,[16] these codes have been shown to have a positive

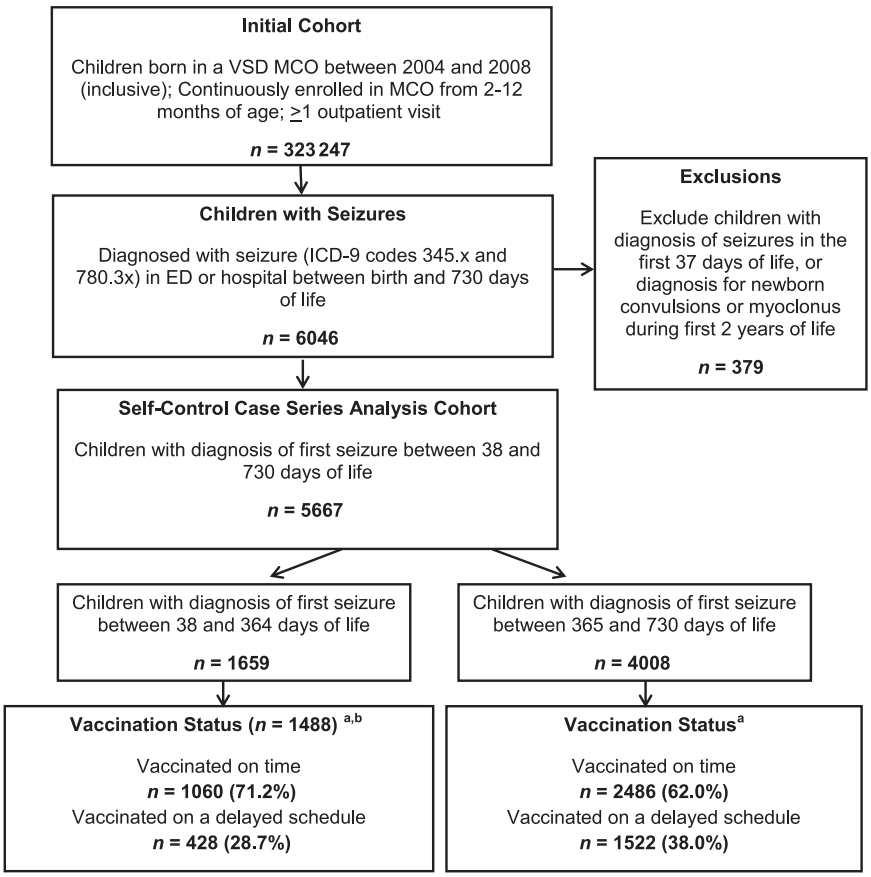

FIGURE 1

Cohort for self-controlled case series analysis. [a]Vaccination status was assessed until the time of the first seizure by using the average number of days undervaccinated metric.[15] Children vaccinated on time had average number of days undervaccinated = 0 and children on a delayed schedule had average number of days undervaccinated >0. [b]Excluded children ($n = 171$) who had a diagnosis of seizure before 93 days of life, making them ineligible for a delay.

predictive value (PPV) of 94% for seizures in the ED or hospital settings in children age 12 to 23 months; 92% of these were febrile seizures. Additional work in the VSD has shown that similar codes have a 92% PPV for seizures in the ED setting for infants from 6 weeks to 12 months of age, and 99% for children older than 1 year.[25] Based on these high PPVs, we did not conduct chart review on seizure cases. We limited our analysis to evaluation of first-ever seizure diagnosis for each child.

Study Design and Analysis

We used a self-controlled case series (SCCS) design[26] to examine the relationship between vaccination and incidence of seizures. In this case-only method, the incidence rate of events in a postvaccination risk window is compared with the incidence rate of events in an unexposed window composed of time periods before vaccination and after the risk window. Each case serves as its own control, thus implicitly controlling for confounders that do not change over time, such as gender or racial/ethnic background. We conducted the SCCS analysis for the first dose of each vaccine recommended at 2 months and 12 months of age, stratified by timing of vaccination (on time versus delayed). Each vaccine was evaluated separately, without regard to receipt of other concomitant vaccines. The risk window for each vaccine was based on biologic plausibility and evidence from the literature.[27] We used a 0- to 2-day risk window for all vaccines recommended at 2 months of age, except rotavirus, for which we used a 0- to 7-day risk window, as this is a time period of possible risk for intussusception[28] and a time when the live attenuated or reassortant virus vaccines would be expected to replicate; there are no data on seizures after rotavirus vaccination. For measles-mumps-rubella (MMR), varicella, and measles-mumps-rubella-varicella (MMRV) vaccines, we used a risk window of 7 to 10 days[16] after vaccination. The time period from 1 to 14 days before vaccination was excluded to reduce the potential "healthy vaccinee effect."[29] The control period was defined as the 14-day period directly after the postvaccination risk window, and the 14-day period directly before the healthy

vaccinee window; this earlier control period was truncated if any days included age 37 days or younger.

For each vaccine and exposure group (exposures were receipt of vaccine on time or late), we calculated the incidence rate ratio (IRR) of first-time seizures in a postvaccination window using conditional Poisson regression.[30] The IRR represents, among children with a first diagnosis of seizure, the incidence rate of seizure in an exposed time period (risk window) after vaccination versus the incidence rate of seizure in unexposed time periods (control window). Because we used an SCCS study design, in which cases serve as their own controls, we used conditional Poisson models to analyze the discrete outcome and account for the dependence of observations within a case. All analyses were conducted by using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

The initial cohort consisted of 323 247 children. After exclusions and limiting the analysis to vaccinated cases with seizures, the final analytic cohort contained 5667 children (Fig 1). Of these children, 49.7% were vaccinated on time in the first 2 years of life for all vaccines. Assessing vaccination status at the time of first seizure, 71.2% of children with a first seizure at age 38 to 364 days were vaccinated on time; for children with a first seizure at age 365 to 730 days, 62.0% were vaccinated on time.

For children who received their first infant vaccines at the ACIP-recommended age of 38 to 92 days, there was no association of vaccination with seizures (Table 1). Seizures were less common in this age group in general, but were no more likely to occur in a risk window after vaccination than in the control periods. For example, the IRR for seizure occurring within 2 days of DTaP vaccination compared with control periods was 1.26 (95% confidence interval [CI] of 0.65–2.45). For children who received their first vaccination on a delayed schedule between 93 and 730 days of life, the IRRs for seizures were generally elevated but not significant. For example, for DTaP, the IRR was 1.56 (95% CI 0.19–12.92).

TABLE 1 Timing of First Vaccination[a] and Occurrence of Seizure, Stratified by Vaccine: Vaccines Recommended at 2 Months of Age

Vaccine	Age at Receipt, d	Seizures		Days Patient Time		IRR[c]	95% Confidence Interval
		Exposed[b]	Unexposed	Exposed	Unexposed		
DTaP	38–92	10	73	249	2309	1.26	0.65–2.45
	93–730	1	6	21	196	1.56	0.19–12.92
PCV	38–92	9	74	249	2309	1.12	0.56–2.24
	93–730	1	7	24	224	1.33	0.16–10.84
HIB	38–92	8	71	237	2197	1.04	0.50–2.16
	93–730	1	6	21	196	1.56	0.19–12.92
IPV	38–92	10	73	249	2309	1.26	0.65–2.45
	93–730	1	6	21	196	1.56	0.19–12.92
Rotavirus	38–92	10	30	320	1120	1.17	0.57–2.39
	93–730	1	5	48	168	0.70	0.08–5.99

PCV, pneumococcal conjugated vaccine (either PCV-7 or PCV-13).

[a] Excluding Hepatitis B virus vaccine.

[b] Exposure window = postvaccination days 0 to 2 (DTaP, PCV, HIB, and IPV vaccines) and days 0 to 7 (rotavirus vaccine): 38–92 d = vaccine administered as recommended; 93–730 d = vaccine delayed.

[c] The IRR represents, among children with their first diagnosis of seizure, the incidence rate of seizure in an exposed time period (risk window) after vaccination versus the incidence rate of seizure in unexposed time periods (control window).

We next examined vaccines first recommended for administration after 1 year of age (Table 2). When the MMR vaccine was administered according to ACIP recommendations at 12 to 15 months of age (361–488 days), it was associated with an increased risk of seizures in the 7 to 10 days after vaccination: IRR 2.65, 95% CI 1.99–3.55. This association was greater if administration of the vaccine was delayed past 15 months: IRR 6.53, 95% CI 3.15–13.53. When we conducted a subgroup analysis to examine the timing of vaccination in more detail, we found the association of MMR vaccination with seizure at 16 to 18 months had an IRR of 5.09 (95% CI 2.05–12.66) and was most pronounced at 19 to 21 months of age, with an IRR of 8.75 (95% CI 2.35–32.58). Data were too sparse in children ages 22 to 23 months to permit analyses (n = 1 exposed case, no unexposed cases) because of the low number of children vaccinated at this age.

Varicella vaccine was associated with an increased risk for seizures 7 to 10 days postvaccination. When administered at 12 to 15 months, the IRR was 2.75 (95% CI 2.05–3.70); the IRR increased to 3.64 when administered at 16 to 23 months of age.

The association of vaccination with seizure was approximately twice as strong among recipients of MMRV vaccine than recipients of MMR vaccine, both among those who received vaccination on time and among those whose vaccinations were delayed (Table 2). Specifically, for on-time MMRV vaccine receipt, the IRR for seizure in the 7 to 10 days after vaccination was 4.95 (95% CI 3.68–6.66). For delayed receipt of MMRV, the IRR was 9.80 (95% CI 4.35–22.06). The vaccine-seizure association was most pronounced if MMRV vaccine was administered between 16 and 18 months of age (IRR 11.00, 95% CI 4.26–28.38).

DISCUSSION

We found no significant association between vaccination in the first year of

TABLE 2 Timing of First Vaccination and Occurrence of Seizure, Stratified by Vaccine: Vaccines Recommended After 12 Months of Age

Vaccine	Age at Receipt	Seizures		Days Patient Time		IRR[b]	95% Confidence Interval
		Exposed[a]	Unexposed	Exposed	Unexposed		
MMR	361–488	63	167	916	6420	2.65	1.99–3.55
	489–730	14	16	116	826	6.53	3.15–13.53
VAR	361–488	61	155	864	6042	2.75	2.05–3.70
	489–730	13	25	152	1064	3.64	1.86–7.12
MMRV	361–488	75	106	724	5068	4.95	3.68–6.66
	489–730	14	10	96	672	9.80	4.35–22.06

VAR, varicella.

[a] Exposure window = 7 to 10 d postvaccination for MMR, VAR, and MMRV vaccines: 361–488 d = vaccine administered as recommended; 489–730 d = vaccine delayed.

[b] The IRR represents, among children with their first diagnosis of seizure, the incidence rate of seizure in an exposed time period (risk window) after vaccination versus the incidence rate of seizure in unexposed time periods (control window).

life and acute seizure events regardless of vaccine type and regardless of whether the vaccine was received on time or delayed. However, in the second year of life, delay of the first MMR vaccine until 16 months of age or older resulted in an IRR for seizures in the 7 to 10 days after vaccination that was 3 times greater than if administration of MMR vaccine occurred on time. Receipt of MMRV compared with MMR doubled the IRR for postvaccination seizures, both at 12 to 15 months and at 16 to 23 months of age, as described recently.[9]

Historically, the whole-cell diphtheria-tetanus-pertussis vaccine was associated with an increased risk of postvaccination febrile seizures in infants.[17,18] There is no evidence that the acellular DTaP vaccines in use since the late 1990s are associated with seizures in the United States.[31] Other infant vaccines currently in use, for instance the DTaP, inactivated poliovirus, and Haemophilus influenza type B combined vaccine (DTaP-IPV-HIB), have not been associated with seizures in the United States,[32] although DTaP-IPV-HIB has been linked with increased febrile seizures in Denmark.[24] Other early childhood vaccines that have been associated with febrile seizures in the United States include inactivated influenza vaccine, but only in some influenza seasons, such as 2010–2011, and the 13-valent pneumococcal conjugate vaccine.[33] The risk for seizures after inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine was greatest if the vaccines were given the same day and in the second year of life.[33] It should be noted that early-childhood vaccines in the first year of life are given at a time of relatively low background rate of febrile seizures.[34,35]

The relationship between timing of vaccination and febrile seizures changes in the second year of life, when receipt of MMR and MMRV vaccines between 16 and 23 months is associated with a higher relative incidence of seizures than between 12 and 15 months. Regardless of vaccination, young children are at their greatest risk for febrile seizures at ~16 to 18 months of age.[34,35] In the VSD cohort, the incidence of febrile seizures increases from just >1 per 100 000 person-days at 7 months of age to a maximum of almost 5 per 100 000 person-days at 17 months of age before decreasing to 3 per 100 000 days by 24 months and to 1 per 100 000 days by age 45 months (data not shown). The stronger association of seizures with both MMR and MMRV vaccines administered after 15 months of age, compared with 12 to 15 months, is likely due to a complex interplay between the immunogenicity of the vaccines, the genetic and physiologic susceptibility of the child, and the age-based maturation of the child's immune system; as the immune system matures in the second year of life[36] it also becomes capable of greater febrile response to immune stimulants, such as vaccines. The relationship between the reactogenicity and the immunogenicity of vaccines was suggested in a recent study that demonstrated a greater risk of measles disease among school-aged children who had received 2 doses of MMR vaccine with the first dose at 12 to 13 months versus at least 15 months of age.[37] Thus, lower reactogenicity of vaccines earlier in the second year of life may also result in lower clinical effectiveness.

A twofold increased risk of febrile seizures in the 7 to 10 days after MMRV vaccine, compared with MMR and varicella vaccines administered as separate vaccines on the same day, was first reported by Klein et al in 2010.[16] They estimated that use of MMRV, compared with separate MMR and varicella vaccines, will result in 1 additional febrile seizure 7 to 10 days after vaccination for every 2300 MMRV doses administered in the second year of life. The more pyrogenic nature of MMRV compared with separate MMR and varicella vaccines may be because of the higher concentration of attenuated varicella virus in the MMRV formulation (>7 times the tissue culture infectious dose compared with varicella vaccine).[20] Alternatively, it may be because MMRV vaccine induces higher antibody titers to measles than does separate MMR plus varicella vaccines, suggesting higher levels of measles vaccine replication.[21]

Rowhani-Rahbar et al[9] recently examined the impact of age in the second year of life on febrile seizures after vaccination. Using a risk-interval cohort study design (as compared with

the SCCS design in this study) they found that the risk of a seizure in the 7 to 10 days after any measles-containing vaccine was doubled (from an incident rate ratio of 3.4 to 6.5) if the child was 16 to 23 months rather than 12 to 15 months at the time of vaccine receipt. The risk was doubled in both age groups if MMRV was used instead of separate MMR plus varicella vaccines.[9] Thus, our results, using a partially overlapping patient population and a different analytic approach, confirm these findings. Based on the findings of Klein et al,[16] Rowhani-Rahbar et al,[9] and our team, we estimate that vaccine type and age of the child both independently but additively increase the risk of seizure 7 to 10 days after receipt of measles-containing vaccine. Thus seizures are approximately twofold more likely to occur after MMRV versus MMR plus varicella vaccine, twofold more likely in 16- to 23-month-old children versus 12 to 15 months, and roughly fourfold more likely in older children who receive MMRV versus younger children who receive MMR plus varicella vaccine. Although our data from the second year of life have significant overlap with those published previously,[9] we felt it important to include these results because of the implications for vaccine delivery in the context of parental delay.

Our findings are subject to several limitations. First, despite the size of our cohort, there were sparse data on seizures in the first year of life (for example, for DTaP vaccine there were 7 exposed cases). Thus, we were not able to directly examine the seizure risk of deferring first vaccination until late in the first year of life, when the incidence of febrile seizures begins to increase. Second, we did not account for simultaneous administration of different vaccines on the same day, but instead conducted analyses on each vaccine individually. There are too few vaccines given in isolation in early childhood to conduct a meaningful analysis on nonsimultaneously administered vaccines. However, our approach results in, for example, an elevated risk for seizures in the 7 to 10 days after varicella vaccine, but this association is due to the elevated risk caused by MMR vaccine that is administered on the same day.[16] Other studies have not found concomitant administration of vaccines to be a risk for increased adverse events in the second year of life compared with nonconcomitant delivery.[38,39] Third, the SCCS design does not permit a direct statistical comparison of the IRRs between different vaccines. However, our finding that the IRR for seizures after MMRV vaccine is doubled compared with MMR vaccine mirrors that recently described in the literature.[9,16,40]

In summary, in our primary analysis, we found no association between vaccination in the first year of life and subsequent seizures, either among infants vaccinated on time or on a delayed schedule. In the second year of life, receipt of MMR and MMRV vaccines was associated with an increased risk of seizure, with stronger associations observed in children receiving vaccinations on a delayed schedule. It is known that the risk of seizure peaks at 16 to 18 months of life regardless of vaccination status; therefore delaying MMR or MMRV vaccine until this age may result in more febrile seizures. Given the overall low absolute risk of seizures after MMR and MMRV vaccines,[9,16] the lack of association of simple febrile seizures with long-term adverse consequences,[34,35] and the known benefits of on-time vaccination, our findings provide additional rationale for not delaying childhood vaccinations.

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REFERENCES

1. IOM (Institute of Medicine). *Adverse Effects of Vaccines: Evidence and Causality.* Washington, DC: The National Academies Press; 2011
2. IOM (Institute of Medicine). *The Childhood Immunization Schedule and Safety Stakeholder Concerns, Scientific Evidence, and Future Studies.* Washington, DC: The National Academies Press; 2013
3. DeStefano F. Vaccines and autism: evidence does not support a causal association. *Clin Pharmacol Ther.* 2007;82(6):756–759
4. Dempsey AF, Schaffer S, Singer D, Butchart A, Davis M, Freed GL. Alternative vaccination schedule preferences among parents of young children. *Pediatrics.* 2011;128(5):848–856
5. Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 years and Adults Aged 19 Years and Older—United States, 2013. *MMWR* 2013;62 (Suppl 1):1–19
6. Glanz JM, McClure DL, Magid DJ, et al. Parental refusal of pertussis vaccination is associated with an increased risk of pertussis infection in children. *Pediatrics.* 2009;123(6):1446–1451
7. Glanz JM, McClure DL, Magid DJ, Daley MF, France EK, Hambidge SJ. Parental refusal of varicella vaccination and the associated

risk of varicella infection in children. *Arch Pediatr Adolesc Med*. 2010;164(1):66–70

8. Glanz JM, McClure DL, O'Leary ST, et al. Parental decline of pneumococcal vaccination and risk of pneumococcal related disease in children. *Vaccine*. 2011;29(5):994–999
9. 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
10. Kennedy AM, Brown CJ, Gust DA. Vaccine beliefs of parents who oppose compulsory vaccination. *Public Health Rep*. 2005;120(3):252–258
11. Kennedy A, Basket M, Sheedy K. Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. *Pediatrics*. 2011;127(suppl 1):S92–S99
12. Salmon DA, Moulton LH, Omer SB, DeHart MP, Stokley S, Halsey NA. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. *Arch Pediatr Adolesc Med*. 2005;159(5):470–476
13. Mills E, Jadad AR, Ross C, Wilson K. Systematic review of qualitative studies exploring parental beliefs and attitudes toward childhood vaccination identifies common barriers to vaccination. *J Clin Epidemiol*. 2005;58(11):1081–1088
14. Niederhauser VP, Markowitz M. Barriers to immunizations: Multiethnic parents of under- and unimmunized children speak. *J Am Acad Nurse Pract*. 2007;19(1):15–23
15. Glanz JM, Newcomer SR, Narwaney KJ, et al. A population-based cohort study of undervaccination in 8 managed care organizations across the United States. *JAMA Pediatr*. 2013;167(3):274–281
16. 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
17. 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
18. Davis RL, Barlow W. Placing the risk of seizures with pediatric vaccines in a clinical context. *Paediatr Drugs*. 2003;5(11):717–722
19. 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
20. Measles, mumps, rubella, and varicella virus live lyophilized preparation for subcutaneous injection (package insert). Issued August 2011 by Merck & Co., Inc., Whitehouse Station, New Jersey. Available at: www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123796.pdf. Accessed April 6, 2014
21. Food and Drug Administration. CBER clinical review of studies submitted in support of licensure of Proquad™. 2005. Available at: www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm123800.pdf. Accessed June 4, 2013
22. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics*. 2011;127(suppl 1):S45–S53
23. Luman ET, Barker LE, Shaw KM, McCauley MM, Buehler JW, Pickering LK. Timeliness of childhood vaccinations in the United States: days undervaccinated and number of vaccines delayed. *JAMA*. 2005;293(10):1204–1211
24. Sun Y, Christensen J, Hviid A, et al. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. *JAMA*. 2012;307(8):823–831
25. Shui IM, Shi P, Dutta-Linn MM, et al; Vaccine Safety Datalink Research Team. Predictive value of seizure ICD-9 codes for vaccine safety research. *Vaccine*. 2009;27(39):5307–5312
26. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am J Epidemiol*. 1996;143(11):1165–1173
27. 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
28. Shui IM, Baggs J, Patel M, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA*. 2012;307(6):598–604
29. Virtanen M, Peltola H, Paunio M, Heinonen OP. Day-to-day reactogenicity and the healthy vaccinee effect of measles-mumps-rubella vaccination. *Pediatrics*. 2000;106(5). Available at: www.pediatrics.org/cgi/content/full/106/5/e62
30. Xu S, Gargiullo P, Mullooly J, McClure D, Hambidge S, Glanz J. Fitting parametric and semi-parametric conditional Poisson regression models with Cox's partial likelihood in self-controlled case series and matched cohort studies. *Journal of Data Science*. 2010;8:349–360
31. Huang WT, Gargiullo PM, Broder KR, et al; Vaccine Safety Datalink Team. Lack of association between acellular pertussis vaccine and seizures in early childhood. *Pediatrics*. 2010;126(2):263–269
32. Nelson JC, Yu O, Dominguez-Islas CP, et al. Adapting group sequential methods to observational postlicensure vaccine safety surveillance: results of a pentavalent combination DTaP-IPV-Hib vaccine safety study. *Am J Epidemiol*. 2013;177(2):131–141
33. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine*. 2012;30(11):2024–2031
34. Waruiru C, Appleton R. Febrile seizures: an update. *Arch Dis Child*. 2004;89(8):751–756
35. Jones T, Jacobsen SJ. Childhood febrile seizures: overview and implications. *Int J Med Sci*. 2007;4(2):110–114
36. Gasparoni A, Ciardelli L, Avanzini A, et al. Age-related changes in intracellular TH1/TH2 cytokine production, immunoproliferative T lymphocyte response and natural killer cell activity in newborns, children and adults. *Biol Neonate*. 2003;84(4):297–303
37. Defay F, De Serres G, Skowronski DM, et al. Measles in children vaccinated with 2 doses of MMR. *Pediatrics*. 2013;132(5). Available at: www.pediatrics.org/cgi/content/full/132/5/e1126
38. Yetman RJ, Shepard JS, Duke A, et al. Concomitant administration of hepatitis A vaccine with measles/mumps/rubella/varicella and pneumococcal vaccines in healthy 12- to 23-month-old children. *Hum Vaccin Immunother*. 2013;9(8):1691–1697

39. Halperin SA, Tapiéro B, Dionne M, et al. Safety and immunogenicity of a toddler dose following an infant series of a hexavalent diphtheria, tetanus, acellular pertussis, inactivated poliovisur, haemophilus influenza type b, hepatitis b vaccine administered concurrently or at separate visits with a heptavalent pneumococcal conjugate vaccine. *Pediatr Infect Dis J.* 2014;33(1):73–80

40. 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

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Dr Hambidge conceptualized and designed the study, reviewed and interpreted study data, and drafted the initial manuscript; Ms Newcomer contributed to study design, conducted analyses, reviewed and interpreted study data, and critically reviewed the manuscript; Dr Narwaney reviewed and interpreted study data, conducted analyses, and critically reviewed the manuscript; Drs Glanz, Daley, Rowhani-Rahbar, Klein, Lee, Nelson, Lugg, Naleway, Nordin, and DeStefano, and Ms Shoup and Mr Weintraub contributed to study design, reviewed and interpreted study data, and critically reviewed the manuscript; Dr Xu contributed to study design, supervised analyses, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

Dr Hambidge and Ms Newcomer had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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