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Methods for addressing “innocent bystanders” when evaluating safety of concomitant vaccines

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Abstract

The need to develop methods for studying the safety of childhood immunization schedules has been recognized by the Institute of Medicine and Department of Health and Human Services. The recommended immunization schedule includes multiple vaccines in a visit. A key concern is safety of concomitant (same day) versus separate day vaccination. This paper addresses a methodological challenge for observational studies of the safety of concomitant vaccination. We propose a process for distinguishing which of several concomitantly administered vaccines is responsible for increased risk of an adverse event while adjusting for confounding due to relationships between effect modifying risk factors and concomitant vaccine combinations. We illustrate the approach by re-examining the known increase in risk of seizure 7–10 days after measles-mumps-rubella (MMR) vaccination and evaluating potential independent or modifying effects of other vaccines. Initial analyses suggested DTaP had an independent and potentiating effect on seizure. After accounting for the relationship between age and vaccine combination, there was no evidence for increased risk of seizure with same day administration; incidence rate ratio, 95% confidence interval 1.2 (0.9, 1.6), p-value = 0.226. We have shown that when investigating safety of concomitant vaccination, it can be critically important to adjust for relationships between effect modifying risk factors and vaccine combination.

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Keywords

Methods; Self-controlled; Vaccine safety; Immunization schedule; Seizure

Introduction

The childhood immunization schedule recommended by the Advisory Committee on Immunization Practices (ACIP) in the United States targets 14 preventable childhood diseases.¹ Although the majority of United States parents adhere to the recommended schedule, a vocal minority have concerns regarding the number of vaccinations. Surveys reported 10–30% of parents choose to vaccinate according to alternative schedules, either refusing or delaying vaccines.^{2–6} “Spacers” or “shot limiters” intend for their children to receive all recommended vaccines eventually, but believe it is safer if fewer vaccines are administered on the same day.⁷ Even among parents who adhere to the recommended vaccine schedule, 20% believe that delaying vaccines would be safer.^{3–6,8,9}

In light of the need for comprehensive studies addressing the safety of the recommended immunization schedule, the Institute of Medicine (IOM) and the Department of Health and Human Services (HHS) recommended that the Vaccine Safety Datalink (VSD) develop methods for studying safety of alternative immunization schedules. Currently, the vast majority of pre- and post-licensure evaluation of vaccine safety focuses on a specific vaccine and adverse event (AE) of interest; however, there is some recent literature on safety of concomitant vaccinations in both randomized trial evaluations^{10–12} and observational studies^{13,14}. Pre-licensure randomized trials are not of sufficient size to evaluate risk of uncommon adverse events following vaccination. Post-licensure studies, such as those conducted in the VSD have large observational samples, but characteristics of patients who follow the recommended schedule may differ from those who choose alternative schedules.

This paper addresses a methodological challenge for studies investigating safety of same versus separate day vaccination. In such studies, positive additive interaction would suggest it is safer for the vaccines to be spaced out and given at different visits whereas negative additive interaction would suggest that it is safer to give the vaccines on the same day rather than at separate visits (Table 1). Teasing out the effects of individual vaccines given on the same day poses significant methodological challenges. For example, MMR is recommended at 12–15 months, and DTaP is recommended at 15–18 months, therefore timing of vaccine combination is associated with age. Baseline risk of AE in young children, and the effect of MMR on AE can also change quickly with age.^{14–16} In this methodological paper, we show how this can cause bias and how to adjust for it. We re-examine the known increase in risk of seizure 7–10 days after MMR vaccination to illustrate a proposed process for discerning whether other vaccines in the schedule 1) independently increase the risk of AE or, 2) modify risk when administered concomitantly with MMR. The methods described can be applied for other vaccines and adverse outcomes.

Materials and Methods

We used vaccination and electronic medical record data from Kaiser Permanente Northern California and Colorado (1995–2015). We identified seizure using international classification of diseases 9th revision (ICD9) codes 780.3* or 345.* in inpatient, emergency room, and urgent care settings. To avoid contamination from effects of prior vaccination, we included vaccination dates that occurred after at least 56 days without vaccination. We restricted to vaccines administered in children 11–23 months. We included incident outcomes defined by ICD9 codes that occurred after at least 56 days of enrollment in the health system during which there were no recorded outcomes. We further restricted incident outcomes to those with incident vaccination dates within 56 days prior to each outcome. The 56 day threshold is similar to that used in prior studies investigating MMR and risk of seizure.^{14,16} All episodes with an incident outcome within 56 days following a valid vaccination date were included in the analysis (~2% of children contributed more than one episode). Every vaccine administered on a vaccination date was included as a same day vaccination. We categorized vaccines based on the Immunization Information Systems (IIS) HL7 standard CVX code set.¹⁷ The categories we evaluated included: diphtheria-tetanus-acellular pertussis (DTaP), inactivated influenza, Haemophilus influenza type B (HIB), hepatitis A, hepatitis B, measles-mumps-rubella (MMR), pneumococcal conjugate (PCV), varicella, and inactivated poliovirus. Because use of MMRV was low in our data and the risk of seizure and fever with MMRV is known to be twice as high as the risk for MMR, we excluded vaccination episodes that contained MMRV.¹⁶

Previous work has found the window for increased risk of seizure is 7–10 days post MMR vaccination.¹⁶ We re-evaluated the known findings using the self-controlled risk interval design¹⁸ while evaluating other vaccines for potential independent or modifying effects on risk of seizure. We included days 14–56 as the control window (Figure 1). There is a trade-off when determining the length of the control window. Longer windows can increase power and precision, however can also capture more changes within individual, such as changes in baseline risk by age. We used SAS 9.4 PROC LOGISTIC event/trials syntax to fit logistic regression models that accounted for the length of follow up in risk and control windows. We conditioned on the unique vaccination episode to make within episode comparisons (example code in the appendix). The stratified logistic model we used is equivalent to a conditional Poisson model that has an offset term equal to log(days).

Alternative approaches to evaluating safety of vaccinations given concomitantly with vaccine of interest

There are several approaches that could be taken to address our question of interest: are there vaccines other than MMR that increase the risk of seizure during the same risk interval? Univariate evaluation of all vaccines would be a naïve screening approach that ignores contamination from the known risk from MMR. Univariate evaluation of vaccination episodes during which only a single non-MMR vaccine was administered during the visit would relieve this concern. However, due to vaccine schedule recommendations that encourage multiple vaccines per visit, this approach would net small numbers of atypical individuals and low statistical power. Other ways to deal with the MMR vaccine's known

adverse reactions include restriction to vaccine episodes without MMR administration or multivariable analysis to adjust for MMR. However neither of these strategies would evaluate interactions between concomitant vaccinations. Inclusion of numerous interactions in multivariable analysis would at the extreme, stratify to the case of each unique combination of vaccines. Even if not parametrized to that extreme, models with numerous interactions can rapidly become highly stratified, with difficult to interpret coefficients. For example, when multiple interaction terms with MMR are in the same model, this implies that the effects of MMR vary according to unique combination of vaccines for which there is an interaction term. To reduce the number of combinations evaluated, variable selection approaches such as backward selection have been used in this context.¹⁴

Proposed process for evaluating safety of vaccinations given concomitantly with vaccine of interest

We went through the following seven step process to screen and evaluate concomitant vaccine combinations that may increase AE risk following MMR vaccination:

1. Univariate analyses
 - a. Naïve analyses – Do self-controlled analyses for each vaccine group separately.
 - b. Restrict - single vaccine - Repeat univariate analyses after restricting to vaccination episodes during which a single vaccine was administered (highly restricted).
 - c. Restrict - no MMR - Repeat univariate analyses after restricting to vaccination episodes during which MMR was not administered (moderately restricted).
2. Multivariable analyses
 - a. Conduct a multivariable analysis that includes every vaccine in the schedule, including MMR, as independent variables.
 - b. Conduct analyses for each vaccine where independent variables include only the vaccine of interest and MMR.
3. Evaluate whether risk is different for MMR with versus without a vaccine of interest

Do a simple logistic regression to evaluate whether there is a difference in proportion of children with AE in the risk window for children who received MMR with versus without the other vaccine of interest. This step involves a comparison between individuals, and is not a self-controlled risk interval analysis.
4. Evaluate departure from multiplicity after adjustment

Fit models with main terms plus interactions for vaccines of interest and MMR. Evaluate departure from multiplicity via the coefficient for the interaction term

between MMR and the vaccine of interest with and without adjustment for other same day vaccinations (as main terms).

5. Evaluate departure from additivity after adjustment

Estimated departure from additivity by using the coefficients from multiplicative interaction models in step 4 by applying formulas for Relative Excess Risk due to Interaction (RERI).¹⁹ Bootstrap for confidence intervals.

6. Repeat steps 3–5 with adjustment for relationship between age and concomitant vaccine combinations

Adjusted for the relationship between age at time of vaccination and the set of vaccines administered via interaction term with continuous age measured in months and/or stratification by age categories (11–13, 14–16, 17+).

7. Estimate attributable risk for same versus separate day vaccination with MMR

Estimate attributable risk (AR) for administration of MMR and vaccine of interest on the same day compared to separate days. AR was defined as the number of excess AEs divided by the total number of children vaccinated.

All eligible seizures were included in self-controlled analyses. To capture the denominators necessary to estimate AR, we identified all vaccination dates that met the inclusion criteria for the self-controlled analysis, but did not restrict to episodes with an outcome within 56 days of vaccination. We estimated the expected count of events during the risk window under the null hypothesis of no increase in risk by tallying the number of outcomes within the control window and multiplying by the ratio of person-time in the risk versus the control window. Because age is related to baseline risk of the outcome, we estimated the expected count within age categories (age in month at vaccination).

$$\text{Expected \# AE in risk window} = \# \text{ AE in control window} \left(\frac{\# \text{ days in risk window}}{\# \text{ days in control window}} \right)$$

We calculated the excess number of AE observed in the risk window as the difference between observed and expected number of AE for each age category and AR as the excess risk divided by the total number of eligible vaccines within that age category (Equation 1). We took a weighted sum of the age specific attributable risk where the weights standardized the age distribution to the observed age distribution for children who received MMR without the other vaccine of interest (Equation 2).

$$AR = \sum_{age=i}^n AR_i = \sum_{age=i}^n (\text{Observed}_i - \text{Expected}_i) / \# \text{ of eligible vaccinations}_i \quad \text{Equation 1}$$

$$AR_{age\ standardized} = \sum_{age=i}^n w_i (AR_i) \quad \text{Equation 2}$$

Results

We identified N = 2,610 vaccine episodes with seizure in the risk or control intervals.

1. Univariate analyses

Naïve univariate analyses resulted in strong positive associations between all vaccine groups (except H1N1) and seizure (Table 2A - 1a). These results reflect the lack of adjustment for same day administration of MMR, which has a known effect on risk of seizure. From this analysis we know that at least one vaccine causes seizure but not which one(s). If nothing had been found, we could have stopped here. Univariate analysis restricting to dates when only a single vaccine was administered resulted in very small numbers, some too small for self-controlled analyses to be feasible (Table 2A -1b). Similarly, the sample size for each vaccine group dropped considerably after restricting to vaccine episodes without MMR administration (Table 2A - 1c). From these analyses, we learn that MMR is associated with an increased risk of seizures, but the sample size is too small to draw inference regarding other vaccines.

2. Multivariable analyses

Other than MMR, DTaP had the strongest positive association with seizure after multivariable adjustment for all concomitantly administered vaccines; OR, 95% confidence interval: 1.4 (1.1, 1.7) (Table 2B - 2a), or adjusting only for MMR; IRR, 95% confidence interval: 1.3 (1.1, 1.6) with p-values = 0.002 (Table 2B - 2b). All other vaccines had estimated effect closer to 1.0 and p-values >0.10. From this analysis, there is little evidence to support an increase in risk of seizure in the 7–10 days post vaccination for vaccines other than MMR and possibly DTaP.

3. Evaluate whether risk is different for MMR with versus without a vaccine of interest

Children who were administered MMR and DTaP on the same day were 60% more likely to have seizure in the risk window than children who received MMR only, incidence rate ratio 1.6, 95% CI (1.2, 2.0) (Table 3).

4. Evaluate departure from multiplicity after adjustment

There was some evidence supporting divergence from multiplicity for risk of seizure with MMR and DTaP (coefficient for interaction term = 0.29, P = .124) but it was not statistically significant (Table 4). The incidence rate ratio (IRR) for same day MMR and DTaP was 4.6, whereas the multiplied incidence rate ratio for separate day MMR and DTaP was $2.9 \times 1.2 = 3.5$. Adjusting for other vaccines administered on the same day had little effect. From this analysis, there is a suggestion that risk of seizure in the 7–10 days following same day MMR

and DTaP vaccination may be greater than the risk expected from multiplying the risk from separate day MMR and DTaP vaccination.

5. Evaluate departure from additivity after adjustment

In this analysis we compared the risk from same day vaccination to the risk from the sum of separate day vaccination. The relative excess risk due to interaction (RERI) and 95% quantile intervals were 1.7 (0.6, 2.8), strongly suggesting that there is higher risk of seizure for same day MMR and DTaP vaccination than expected from adding the risk for separate day MMR and DTaP (Table 5).

6. Repeat analyses 3–5 with adjustment for relationship between age and concomitant vaccine combinations

After adjusting for the relationship between age at vaccination and the vaccine combination administered, children with same day administration of MMR and DTaP were no more likely to have seizure in the risk window than children who received MMR only, incidence rate ratio 1.2 95% CI (0.9, 1.6) (Table 3). There was strong evidence that age at time of vaccination modified MMR's effect on seizure but little evidence for departure from multiplicity of effects for MMR and DTaP. For example, incidence rate ratios for same day MMR and DTaP at 12, 15, and 18 months were 3.4, 4.9 and 7.3 respectively. The corresponding multiplied risks for separate day vaccinations at each age were $2.9 \times 1.2 = 3.4$, $4.3 \times 1.2 = 5.1$, $6.4 \times 1.2 = 7.7$ (coefficient for interaction term = 0.02, $P = 0.935$) (Table 4). Within age categories, the RERI across age categories ranged from -0.9 to 0.3. The 95% confidence intervals for each age category included 0.0, providing little support for departure from additivity within any age category, however confidence intervals were wide (Table 5).

7. Estimate attributable risk

The age standardized attributable risk of seizure in the risk window was <1 per 10,000 for DTaP without MMR. For MMR, the age standardized attributable risk was 3 per 10,000 vaccination events, regardless of whether DTaP was administered on the same day (Table 6).

Checking assumptions

In our self-controlled risk interval analyses, we assumed there were no meaningful trends in outcome incidence over the risk and control intervals (<56 days). For children between 12 and 22 months, the incidence rate for seizure was between 13 and 17 per 1,000 person-years (Figure 2). However, the incidence rate was lower at the tail ends of the age range included in our study. For children aged 11 months or 23 months the incidence rate was 9 to 11 seizures per 1,000 person-years. In our study sample, 95% of vaccinations occurred in children 12 to 22 months, where there was little variation in baseline risk of seizure. This suggests that our assumption of constant risk of seizure within 56 days of vaccination is reasonable. In situations where strong age related trends in seizure are observed, then age as a time-varying risk factor over the observed risk and control windows should be adjusted for.

Methods and results using fever as an outcome are available in the online appendix.

Discussion

This paper addressed a methodological challenge for evaluating the safety of concomitantly administered vaccines. We re-examined the known relationship between MMR and risk of seizure to illustrate an approach to evaluating whether other vaccines might independently increase or potentiate the risk of AE when administered on the same day as a vaccine with a known effect. Specific vaccine combinations are administered at different ages, and age can be a strong modifier of risk for vaccine associated adverse events. We showed how this can bias the results, and how to adjust for it. Initial analyses suggested DTaP had an independent effect of MMR on seizure. After accounting for the relationship between age and vaccine combination, there was no evidence for increased risk of seizure with same day administration ($p>0.3$). We found similar results for the outcome fever.

We proposed a systematic multi-step approach to investigate the safety of concomitant vaccination, starting with univariate and multivariable analysis to narrow the scope and target more focused investigation into vaccines with independent effects. The initial univariate and multivariable models to target vaccine groups for deeper investigation is both a strength as well as a limitation. For example, it is possible for a vaccine to have no effect on an AE, but still potentiate MMR's effect on the AE. This can be explored by proceeding to the next step of the proposed process even if nothing is found for that vaccine in the initial screen.

One issue to keep in mind is that same day exposure to a combination of vaccines could shift the true risk window for the AE. When using a uniformly specified risk and control window across vaccine combinations in a self-controlled design, this would lead to misclassification of whether the AE was in the true risk or control window. The direction of bias would depend on the direction that the true risk window shifts as well as the person days that are sampled for the control window.

Another issue is that unlike typical vaccine safety studies that use a self-controlled design to investigate the relationship between a vaccine and an adverse event, evaluation of same vs. separate day vaccination requires a between-person comparison in addition to the within-person comparison. This is because an individual child cannot receive both same and separate day vaccination. A typical self-controlled analysis is not biased by time-invariant characteristics and impact of confounding from changing risk due to age is minimal with short, proximal risk and control windows. However, the between-person component in evaluation of same versus separate day vaccination safety can be biased by time-invariant characteristics that are associated with vaccination combination and modify risk of outcome. Children who receive vaccinations at the recommended schedule may have different baseline risk factors than children whose parents choose alternative schedules. If these risk factors modify the effect of vaccines on an AE of interest, they can confound analyses that evaluate safety of same versus separate day vaccination. In our example, we demonstrated that age at vaccination was not only a modifier of the effect of MMR on AE, but also a confounder due to concomitant administration of MMR and DTaP being more common in older children and

the age related increase in risk of AE associated with MMR. When numerous risk factors are associated with vaccine combination, these could be summarized in a baseline disease risk score for adjustment of confounding.^{20–22}

In our example, we modeled a linear age interaction with MMR. However, it is possible that the modifying effect of age is non-linear. This can be explored in future work. We also imposed conservative criteria for defining incident vaccination that would exclude “spacers” whose children are vaccinated more than once within 56 days. While a washout to define incidence is necessary to distinguish the effects of vaccines administered on one day from proximal prior vaccinations, future studies could explore less restrictive requirements for defining incident exposure and outcome.

We have outlined a systematic approach to dissect which of several concomitantly administered vaccines is responsible for increased risk of an adverse event, while adjusting for confounding due to relationship between an effect modifying risk factor (age) and the vaccine combination recommended in immunization schedules. Immunization schedules recommend vaccines at specific ages. Vaccine associated risk of AE can change markedly in the first few years of life. We have shown that when investigating safety of concomitant vaccination, it is critically important to assess the potential for confounding by the relationship between age at vaccination and set of concomitant vaccines administered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Zhao Z, Smith PJ, Hill HA. Evaluation of potentially achievable vaccination coverage with simultaneous administration of vaccines among children in the United States. *Vaccine*. Jun 8; 2016 34(27):3030–3036. [PubMed: 27160040]
2. Institute of Medicine (IOM). The childhood immunization schedule and safety: Stakeholders concerns, scientific evidence, and future studies. Washington, DC: The National Academies Press; 2013.
3. Dempsey AF, Schaffer S, Singer D, Butchart A, Davis M, Freed GL. Alternative vaccination schedule preferences among parents of young children. *Pediatrics*. Nov; 2011 128(5):848–856. [PubMed: 21969290]
4. Gellin BG, Maibach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics*. Nov; 2000 106(5):1097–1102. [PubMed: 11061781]
5. Glanz JM, Kraus CR, Daley MF. Addressing Parental Vaccine Concerns: Engagement, Balance, and Timing. *PLoS biology*. Aug.2015 13(8):e1002227. [PubMed: 26252770]
6. Glanz JM, Newcomer SR, Jackson ML, et al. White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink. *Vaccine*. Feb 15; 2016 34(Suppl 1):A1–A29. [PubMed: 26830300]
7. Robison SG, Groom H, Young C. Frequency of Alternative Immunization Schedule Use in a Metropolitan Area. *Pediatrics*. 2012

8. Smith PJ, Humiston SG, Marcuse EK, et al. Parental delay or refusal of vaccine doses, childhood vaccination coverage at 24 months of age, and the Health Belief Model. *Public health reports* (Washington, DC : 1974). Jul-Aug;2011 126(Suppl 2):135–146.
9. Theeten H, Hens N, Aerts M, et al. Common attitudes about concomitant vaccine injections for infants and adolescents in Flanders, Belgium. *Vaccine*. Mar 18; 2009 27(13):1964–1969. [PubMed: 19368778]
10. Halperin SA, Tapiero B, Dionne M, et al. Safety and immunogenicity of a toddler dose following an infant series of a hexavalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus, Haemophilus influenzae type b, hepatitis B vaccine administered concurrently or at separate visits with a heptavalent pneumococcal conjugate vaccine. *The Pediatric infectious disease journal*. Jan; 2014 33(1):73–80. [PubMed: 24346596]
11. Hesley TM, Reisinger KS, Sullivan BJ, et al. Concomitant administration of a bivalent Haemophilus influenzae type b-hepatitis B vaccine, measles-mumps-rubella vaccine and varicella vaccine: safety, tolerability and immunogenicity. *The Pediatric infectious disease journal*. Mar; 2004 23(3):240–245. [PubMed: 15014300]
12. 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. *Human vaccines & immunotherapeutics*. Aug; 2013 9(8):1691–1697. [PubMed: 23744509]
13. Kawai AT, Martin D, Kulldorff M, et al. Febrile Seizures After 2010–2011 Trivalent Inactivated Influenza Vaccine. *Pediatrics*. 2015; 136(4):e848–e855. [PubMed: 26371192]
14. Duffy J, Weintraub E, Hambidge SJ, et al. Febrile Seizure Risk After Vaccination in Children 6 to 23 Months. *Pediatrics*. 2016
15. Hambidge SJ, Newcomer SR, Narwaney KJ, et al. Timely Versus Delayed Early Childhood Vaccination and Seizures. *Pediatrics*. 2014
16. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. Jul; 2010 126(1):e1–8. [PubMed: 20587679]
17. CDC. IIS: Current HL7 Standard Code Set CVX -- Vaccines Administered. 2016. <https://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?rpt=cvx>
18. Li R, Stewart B, Weintraub E. Evaluating efficiency and statistical power of self-controlled case series and self-controlled risk interval designs in vaccine safety. *Journal of biopharmaceutical statistics*. 2016; 26(4):686–693. [PubMed: 26098696]
19. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *European journal of epidemiology*. Jun; 2011 26(6):433–438. [PubMed: 21344323]
20. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. *Pharmacoepidemiology and drug safety*. 2012; 21(Suppl 2):138–147. [PubMed: 22552989]
21. Hansen BB. The prognostic analogue of the propensity score. *Biometrika*. Jun 1; 2008 95(2):481–488.
22. Sturmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Analytic strategies to adjust confounding using exposure propensity scores and disease risk scores: nonsteroidal antiinflammatory drugs and short-term mortality in the elderly. *American journal of epidemiology*. May 1; 2005 161(9):891–898. [PubMed: 15840622]

Key Points

When investigating safety of immunization schedules

- It is difficult to discern whether and which vaccines increase risk of adverse events
- Apparent modification due to confounding by true effect modifiers can suggest risk from vaccines that are actually “innocent bystanders”
- Including an interaction term between vaccines in a self-controlled risk interval design adds a between-person comparison, opening the door for confounding by time-invariant characteristics
- It is critically important to adjust for relationships between effect modifying risk factors and vaccine combination

Figure 1.
Risk and Control Intervals in Self-Controlled Design

Figure 2.
Incidence of seizure and frequency of vaccine combination by age

Table 1

Interpreting Additive Interaction in the Context of Same Versus Separate Day Vaccination

Additive interaction	Interpretation
+	Safer to administer vaccines on separate days
None	No difference in risk, recommend same day to reduce logistical burden of multiple doctor visits
-	Safer to administer vaccines on same day

Table 2 Univariate, Stratified and Multivariable Adjusted Risk of Seizure or Fever Following Standard Childhood Vaccination

A.

	1a. Naive ¹			Univariate				1c. Restrict - No MMR ³		
	N cases			N cases				N cases		
	Risk window	Control window	IRR (95% CI)	p-value	Risk window	Control window	IRR (95% CI)	p-value	Risk window	Control window
DTAP	223	945	2.5 (2.1, 2.9)	0.000	14	110	1.3 (0.8, 2.3)	0.307	65	581
FLU	77	549	1.5 (1.2, 1.9)	0.001	27	223	1.3 (0.9, 1.9)	0.239	41	431
HIN1flu	1	9	1.2 (0.1, 9.2)	0.884	0	5	-	-	0	8
HIB	192	794	2.5 (2.2, 3.0)	0.000	1	12	0.9 (0.1, 6.7)	0.898	42	355
HepA	114	659	1.8 (1.5, 2.2)	0.000	12	125	1.0 (0.6, 1.8)	0.979	42	401
HepB	17	105	1.7 (1.0, 2.8)	0.042	0	16	-	-	4	66
MMR	309	908	3.6 (3.1, 4.1)	0.000	6	18	3.5 (1.4, 8.8)	0.008	-	-
POLIO	53	218	2.6 (1.9, 3.4)	0.000	0	10	-	-	10	109
PCV13	49	248	2.1 (1.5, 2.8)	0.000	0	2	-	-	11	97
PCV7	127	483	2.8 (2.3, 3.4)	0.000	6	30	2.1 (0.9, 5.0)	0.097	24	217
VARICELLA	241	852	3.0 (2.6, 3.4)	0.000	5	27	1.9 (0.7, 5.0)	0.172	13	133

B.

2a. All concomitant vaccines ⁴			2b. Adjust for MMR ⁵		
N	IRR (95% CI)	p-value	N	IRR (95% CI)	p-value
DTAP	2,610	1.4 (1.1, 1.7)	0.002	1,168	1.3 (1.1, 1.6)
FLU	2,610	1.0 (0.7, 1.2)	0.716	626	1.0 (0.7, 1.2)
HIN1flu	2,610	0.8 (0.1, 6.7)	0.845	10	0.8 (0.1, 6.6)

B.	Multivariable				
	2a. All concomitant vaccines ⁴			2b. Adjust for MMR ⁵	
	N	IRR (95% CI)	p-value	N	IRR (95% CI) p-value
HIB	2,610	1.0 (0.8, 1.2)	0.757	986	1.1 (0.9, 1.3) 0.401
HepA	2,610	0.9 (0.7, 1.2)	0.644	773	0.9 (0.7, 1.1) 0.355
HepB	2,610	0.8 (0.4, 1.3)	0.346	122	0.9 (0.5, 1.4) 0.555
MMR	2,610	3.8 (2.9, 5.1)	0.000	n/a	
POLIO	2,610	1.0 (0.7, 1.4)	0.861	271	1.1 (0.8, 1.5) 0.491
PCV13	2,610	0.9 (0.6, 1.3)	0.462	297	0.8 (0.6, 1.1) 0.179
PCV7	2,610	1.2 (0.9, 1.5)	0.253	610	1.2 (0.9, 1.5) 0.134
VARICELLA	2,610	0.8 (0.6, 1.0)	0.097	1,093	0.8 (0.6, 1.0) 0.090

¹ Separate univariate models fit for each vaccine group, no adjustment for concomitant vaccinations

² Separate univariate models fit for each vaccine group, restricted to vaccination episodes with no concomitant vaccines

³ Separate univariate models fit for each vaccine group, restricted to vaccination episodes without MMR administration

⁴ Single model includes DTAP, FLU, H1N1 flu, HIB, Hep A, Hep B, MMR, POLIO, PCV13, PCV7, VARICELLA

⁵ Separate models fit for each vaccine group, each contains 2 independent variables - vaccine group of interest and MMR

- Sample size not sufficient

Seizure (risk window 7–10 days, control window days 14–56)

Table 3

Difference in Risk of Seizure for MMR with Concomitant Vaccine of Interest Versus MMR Without Concomitant Vaccine of Interest

	Incidence rate ratio, 95% CI	p-value
Same day MMR + DTaP versus MMR without DTaP	1.6 (1.2, 2.0)	0.007
+ age adjustment	1.2 (0.9, 1.6)	0.226

Age in months at time of vaccination included as continuous variable in logistic regression model

Table 4

Evaluate Departure from Multiplicity

Seizure		MMR (no DTaP)		DTaP (no MMR)		MMR and DTaP		Departure from multiplicity	
Terms in model									
n		695		646		522			
MMR + DTaP + MMR * DTaP		IRR (95% CI)		IRR (95% CI)		IRR (95% CI)		MMR*DTaP Interaction	
<i>No other adjustment</i>		2.9 (2.4, 3.5)		1.2 (0.9, 1.5)		4.6 (3.8, 5.5)		1.3 (0.9, 1.9)	
<i>Adjusted for concomitant vaccines¹</i>		3.5 (2.5, 4.8)		1.2 (0.9, 1.6)		5.3 (3.9, 7.3)		1.3 (0.9, 1.9)	
<i>Adjusted for concomitant vaccines¹ and age²</i>		12 mo		12 mo		12 mo			
		2.9 (2.1, 4.1)				3.4 (2.3, 5)			
		15mo				15mo			
		4.3 (3.2, 5.9)		1.2 (0.9, 1.6)		4.9 (3.6, 6.8)		1.0 (0.7, 1.5)	
		18mo				18mo			
		6.4 (4.4, 9.3)				7.3 (5.1, 10.3)			

¹ all other vaccine groups in the schedule² Age in months on date of vaccination included as interaction with MMR

Table 5

Evaluating Departure from Additivity (RERI)

Seizure	
MMR + DTaP	
All ages	1.7 (0.6, 2.8)
11–13	0.3 (–1.8, 2.2)
14–16	0.3 (–2.1, 2.6)
17+	–0.9 (–7.9, 3.0)

RERI - relative excess risk due to interaction

Age in months on date of vaccination included as interaction with MMR

Table 6

Attributable Risk (AR) for Same Versus Separate Day Vaccinations

Seizure				
	Excess events	Total Vaccinations	Crude AR	Age standardized AR
DTAP (no MMR)	9.7	397,271	0.00002	0.00001
MMR (no DTAP)	99.2	324,695	0.00031	0.00031
MMR and DTAP	123.3	225,352	0.00055	0.00033