HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2019 August 25.

Published in final edited form as:

Clin Infect Dis. 2016 December 01; 63(11): 1456–1462. doi:10.1093/cid/ciw607.

Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis

Roger Baxter[1], **Edwin Lewis**[1], **Kristin Goddard**[1], **Bruce Fireman**[1], **Nandini Bakshi**[2], **Frank DeStefano**[3], **Julianne Gee**[3], **Hung Fu Tseng**[4], **Allison L. Naleway**[5], **Nicola P. Klein**[1]

[1]Northern California Kaiser Permanente Vaccine Study Center, Oakland [2]Permanente Medical Group, Antioch, California [3]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia [4]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena [5]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

Abstract

Background—Case reports have suggested that vaccines may trigger transverse myelitis (TM) or acute disseminated encephalomyelitis (ADEM), but the evidence for a causal association is inconclusive. We analyzed the association of immunization and subsequent development of TM or ADEM.

Methods—We identified all cases of TM and ADEM in the Vaccine Safety Datalink population. Using a case-centered method, we compared vaccination of each case to vaccination of all matched persons in the study population, who received the same type of vaccine, with respect to whether or not their vaccination occurred during a predetermined exposure interval. We calculated a risk difference (excess risk) of TM and ADEM for each vaccine.

Results—Following nearly 64 million vaccine doses, only 7 cases of TM and 8 cases of ADEM were vaccinated during the primary exposure window 5–28 days prior to onset. For TM, there was no statistically significant increased risk of immunization. For ADEM, there was no statistically significant increased risk following any vaccine except for Tdap (adolescent and adult tetanus, reduced diphtheria, acellular pertussis) vaccine. Based on 2 exposed cases, the odds ratio for Tdap exposure 5–28 days prior to ADEM onset was 15.8 (95% confidence interval [CI], 1.2–471.6; P = .04), and the estimated excess risk was 0.385 (95% CI, −.04 to 1.16) cases per million doses.

Conclusions—We found no association between TM and prior immunization. There was a possible association of ADEM with Tdap vaccine, but the excess risk is not likely to be more than 1.16 cases of ADEM per million vaccines administered.

Correspondence: R. Baxter, Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16th Flr, Oakland, CA 94612 (roger.baxter@kp.org).

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

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Keywords

vaccine; immunization; transverse myelitis; acute disseminated encephalomyelitis

Concerns that vaccines might trigger autoimmune demyelination have existed for many years [1–3]. Most publications on the subject are anecdotal case reports [4–7], with limited scientific evidence to support these concerns, and multiple studies have found no association [8–15]. The Institute of Medicine has judged the evidence to be inconclusive with respect to a causal association between specific acute demyelinating events (ADEs) and any vaccine [16]. However, many parents, patients, and providers consider the possibility of an association between vaccines and ADEs to be both plausible and worrisome [3, 17].

Studies of possible associations of ADEs with vaccinations have been problematic for multiple reasons [1, 2]; primarily, ADEs are rare and very large populations are needed to study them with adequate statistical power. Furthermore, for many ADEs, incidence rates peak during early and middle adulthood, times of life when fewer people are receiving vaccines of any kind, compared with young children and older adults. Evaluation for associations between previous immunizations and disease onset is therefore difficult because long periods of time have often elapsed since vaccination. In addition, it may not be possible to identify an unvaccinated comparison group similar to the vaccinees; for observational studies, many differences between vaccinated and unvaccinated groups may not be measured and thus cannot be controlled in an analysis [18, 19]. A significant challenge for earlier studies of ADEs in general is that there is limited understanding about the underlying pathophysiology or causes of these diseases. For example, seasonality may be an important confounder in studies of vaccine adverse events, particularly if the adverse event might also be precipitated by an infection, such as influenza.

Case-series, risk-interval, or case-centered analyses may be useful for addressing some of the challenges in evaluating possible associations between vaccinations and ADEs. Adverse events that are most amenable to study using these methodologies are events that are relatively abrupt in onset, clearly defined, occur relatively soon after vaccination, have a limited period of risk (termed the “risk interval” [20]), and are serious enough that people seek medical care for them. If an illness advances slowly over a long period of time prior to diagnosis, or has a long latency period, determining the time of actual symptom onset may be very challenging. This clinical complexity may make any determination of a possible relationship between disease development and timing of vaccination very difficult. In this study, we analyzed the association of immunization and subsequent development of TM and ADEM, 2 diseases which have a relatively acute onset and for which patients seek medical care in a timely fashion.

Acute transverse myelitis (TM) is a rare acquired demyelinating disorder that presents with sudden onset of neurologic deficits due to spinal cord lesions. Annual incidence in the general population is thought to be between 1 and 8 per million [7, 21, 22], with most studies showing a significant proportion with onset of symptoms preceded within a few weeks by an infectious disease.

Like TM, acute disseminated encephalomyelitis (ADEM) is a rare disease, often preceded by a respiratory or gastrointestinal illness. It has also been reported after a number of immunizations, mostly as case reports unable to support causality [23, 24]. Patients with ADEM present with fever and headache, and then progress rapidly to manifest symptoms due to brain or spinal cord inflammation, such as obtundation or motor deficits.

METHODS

The study used a case-centered design, which compares vaccination patterns during an exposure interval prior to the outcome in cases vs the entire study population, matched by age, sex, and site.

Study Population

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention's (CDC) Immunization Safety Office and several integrated healthcare systems across the United States. These health systems provide essentially all healthcare services and capture data from outpatient department visits, emergency department visits, and hospitalizations. The VSD has data on >9 million subjects annually, including 2.1 million children and 7.2 million adults. Participating VSD sites maintain automated databases of healthcare encounters, including immunization registries. All sites have the capability to access medical records and other data sources to provide detailed information on specific healthcare encounters. Our study population included all children and adults of any age enrolled in the health plans at 6 VSD sites who received 1 or more vaccines during the period from 1 January 2007 through 31 December 2012.

Case Selection

We utilized each VSD site's internal electronic medical record (EMR) diagnostic text codes to identify first-ever TM and ADEM diagnoses in any setting (hospital, emergency, or outpatient clinic), and required at least 1 diagnosis by a neurologist within 3 months of the initial diagnosis. These text codes are more specific than *International Classification of Diseases,* Ninth Revision codes, and are what the medical provider sees and chooses when making a diagnosis. We used case selection criteria for acute idiopathic TM and ADEM and excluded cases due to other causes, such as compression, multiple sclerosis, or neuromyelitis optica. We excluded individuals with either a prior or subsequent history of multiple sclerosis. Trained medical records analysts (MRAs) reviewed all identified cases to verify that a neurologist made the diagnosis within 3 months of the first electronic diagnosis, to validate the date of onset, to ensure the diagnosis did not change over time, and to abstract pertinent information. Following this, a neurologist with expertise in demyelinating illnesses reviewed each case. For ADEM, cases were confirmed using the Brighton Collaboration Criteria [25],and we accepted diagnostic levels of certainty 1, 2, and 3 as cases. For TM we used the Transverse Myelitis Consortium Working Group criteria [26], because Brighton Criteria were not available. The date of onset used for analysis was that determined by medical record review.

Vaccines

We evaluated all administered vaccines, both individually and combined. To increase power for the study, we combined all inactivated influenza vaccines together, including trivalent, quadrivalent, and high dose. We analyzed meningococcal conjugate vaccines (both Menactra and Menveo), and pneumococcal conjugate vaccines (7- and 13-valent) both separately and combined. We also looked at any vaccine (all vaccines combined).

Exposure Intervals

On the basis of prior studies and expert opinion, we used 2 exposure intervals: (1) 5–28 days as the most likely interval following immunization to result in a demyelination illness and (2) 2–42 days as reassurance that we are not missing an increased risk with the same type of vaccine, beyond the shorter 5- to 28- day exposure interval. All persons (cases and comparisons) in the study were immunized with at least 1 vaccine within 9 months prior to the cases' onsets. We used the period after the longer exposure interval, 43 days through 9 months, as the comparison interval. Nine months was chosen as the comparison interval to avoid duplicate influenza vaccines over 2 seasons.

Statistical Methods

We used a case-centered method, as has been previously described [18, 27–29]. We identified all cases in the vaccinated study population. We compared each case to all similar (by age, sex, and VSD site) vaccinees who were in the study population on the diagnosis date of the case. We compared the cases to the general population, with respect to whether or not their vaccination occurred during the exposure interval. Thus, the method is equivalent to a matched case-control study, except that it utilizes all available matched controls who received the same vaccine type, rather than just a sample of them. Risk sets consisting of cases and all matched controls were constructed at each site from presummarized immunization follow-up data on the entire VSD population, and matching was done by age and sex. All cases and comparison matches were vaccinated with the same vaccine in the 9 months prior to the onset of the case. We determined the proportion of each risk set that was vaccinated within the exposure interval prior to the date of illness onset for each matched TM or ADEM case. We examined whether or not each case was vaccinated in the exposure interval or the comparison interval prior to the date of illness onset in relation to the proportion of the entire risk set that was vaccinated in the exposure interval prior to the case onset date. We used a stratified exact binomial method to calculate the odds ratios (ORs) with confidence intervals (CIs) and *P* values. The OR directly estimates the relative risk of being diagnosed with ADEM or TM in the exposure interval compared to the rest of the 9 months after vaccination.

Risk Difference Calculation

To take advantage of the large number of immunizations given over the study period, when only relatively small numbers of TM and ADEM cases had their onset within even a year of a vaccine, we used a Mantel–Haenszel–type weighted average [30] to estimate the excess risk (also known as the risk difference) and 95% CIs [31] associated with immunization and TM and ADEM. Wald-type *P* values were calculated. The risk difference amounts to the risk

per day of the outcome diagnosis during the exposure interval minus the risk per day during the rest of the 9 months after vaccination. The results are scaled to the risk per dose of each vaccine. Unlike the OR, which is a relative measure where 1.0 indicates no association, the attributable risk is a difference measure in which zero indicates lack of association.

The study protocol was approved by institutional review boards at the CDC and each VSD site, and it was determined that informed consent was not required.

RESULTS

Over the study period, nearly 64 million vaccine doses were recorded and used in the analyses (Table 1).

Over all VSD sites, we identified 545 potential cases of TM in the EMRs. One hundred eighty-four of these were rejected by the MRA (132 had an old history of TM, 24 were ruled out, and 28 were miscoded). The remaining 361 cases were reviewed by a neurologist. One hundred ninety-three did not meet inclusion criteria, and 87 had alternative diagnoses. Eighty-one cases (14.9%) were accepted as new, acute-onset idiopathic TM using the TM Consortium Working Group definition. Of these 81 cases, 67 had received an immunization within 9 months prior to onset, and were included in the analysis. One case was vaccinated 29–42 days prior to TM diagnosis, and this case was included in the 2- to 42-day analysis, but not the 5- to 28-day analysis.

Of 118 cases of ADEM diagnosed in the EMR, 29 were rejected by the MRA (13 had a history of ADEM, 8 were ruled out, and 8 were miscoded). Of the remaining 89 cases reviewed by the neurologist, 17 were indeterminate and 16 were other diagnoses, so that 56 (47.5%) were accepted both by the MRA and by the neurologist as an acute new diagnosis (54 Brighton level 1, 1 level 2, and 1 level 3). Forty-seven of these had received an immunization within 9 months prior to the onset of ADEM.

Tables 2 and 3 show the results of the case-centered analyses results for TM and ADEM using the 5- to 28-day exposure interval. Results for the 2- to 42-day exposure interval are presented in Supplementary Tables 1 and 2. For TM, there was no statistically significant increased risk of immunization in either the 5- to 28-day or the 2- to 42-day risk interval prior to onset.

For ADEM, the Tdap (adolescent and adult tetanus, reduced diphtheria, acellular pertussis) vaccine was associated with a statistically significant increase in risk in the 5- to 28-day exposure interval (OR, 15.8 [95% CI, 1.2–471.6]; $P = .04$), but not the longer 2- to 42-day interval.

We calculated the excess risk (risk difference) for each vaccine and outcome in the 5- to 28-day exposure interval (Tables 4 and 5). The tables show the calculated attributable risk per 1 million doses of each vaccine. The excess risk for Tdap was calculated to be 0.385 (95% CI, −.04 to 1.16).

DISCUSSION

Our study examined the risk of TM and ADEM following vaccines of any kind. Our case-centered method used only cases and comparison individuals who had previously been vaccinated. This controlled for many of the differences between vaccinated and unvaccinated individuals. In addition, this method, by anchoring each case and comparison to a specific calendar date, controls exceedingly well for time-varying confounding, such as seasonality.

For TM, we found no evidence of a safety concern, or any association with subsequent illness. If there is any association, it is <1 per million doses for vaccines other than live zoster and live attenuated influenza vaccines, and <2 per million doses of these 2 vaccines. For ADEM, we found a possible association with the Tdap vaccine in the 5- to 28-day risk interval (OR, 15.8 [95% CI, 1.2–471.6]; $P = .04$). However, there are some caveats to this finding. First, the number of exposed cases (2) was very small. Of the 2 cases, 1 was a healthy adult who was routinely vaccinated 11 days prior to symptoms. The second case was vaccinated with both the meningococcal polysaccharide vaccine (not recommended for his age group at that time) and Tdap. The case vaccinated in the comparison period was immunized routinely with Tdap, quadrivalent human papillomavirus vaccine (HPV4), quadrivalent meningococcal conjugate vaccine (MCV4), and hepatitis A vaccine at the same time. Statistically, we would not have been surprised by 1 exposed case, and a second exposed case is what gives us a statistically significant result. The paucity of cases leads to a wide CI for the OR, the lower bound of which is close to 1.0. In addition, we performed a great number of statistical comparisons, and we did not adjust for multiple testing; therefore, this result could be due to chance alone. However, if we accept this finding at face value that Tdap does increase the risk of ADEM, we estimate that the attributable risk of ADEM with Tdap vaccination is only 0.4 cases per 1 million doses of vaccine. Because so many vaccines were given, the CI for the risk difference estimate is narrow, and from the upper bound of the 95% CI, we can be confident that the excess risk is not likely to exceed 1.16 cases of ADEM per million doses of Tdap. For other vaccines, the excess risk is even smaller or nonexistent.

These results are similar to what we have found previously in assessment of the association between immunization and other acute demyelinating diseases [29, 32] and are very reassuring.

Strengths and limitations of the study are as follows: Review of all TM and ADEM cases minimized misclassification. We did not analyze combinations of vaccines. The method depends on selection of an appropriate risk (exposure) interval, so if the interval is misspecified, an increased risk could have been missed. We purposely did not adjust for multiple observations in order to increase the sensitivity of our results; nonetheless, we identified only 1 statistically significant association.

In conclusion, TM and ADEM are rarely, if ever, associated with vaccines. If there is an association of ADEM with Tdap, the excess risk is not likely to exceed 1.16 cases of ADEM per million doses of Tdap administered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support. This work was supported by a task order from the CDC (contract number 200-2012-53581/0006).

Potential conflicts of interest. R. B. and N. P. K. report research grants for unrelated studies from GSK, Sanofi Pasteur, Merck, Pfizer, Protein Sciences, and MedImmune. A. L. N. Reports research grants for unrelated studies from Merck, Pfizer, and MedImmune. F. D. and J. G. are employees of the CDC. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Table 1.

Vaccines Given at Vaccine Safety Datalink Sites During the Study Period, 2007–2012

Vaccine Type	Vaccine Count
Trivalent and quadrivalent inactivated influenza (IIV)	18 926 060
Tetanus, reduced diphtheria, acellular pertussis (Tdap)	5 940 485
Any pneumococcal conjugate (7- or 13-valent) (PCV)	3 611 754
Hepatitis A (HAV)	3 459 116
Haemophilus influenzae type b (Hib)	2 911 711
Varicella	2 427 803
7-valent pneumococcal conjugate (PCV7)	2 272 002
Hepatitis B (HBV)	2 147 046
Quadrivalent human papillomavirus (HPV4) (Gardisil)	2 131 486
Diphtheria, tetanus, acellular pertussis (DTaP)	1 955 611
Monovalent H1N1 influenza	1 773 442
DTaP + inactivated polio (IPV) + HBV (Pediarix)	1 712 276
Any quadrivalent meningococcal conjugate (MCV4) (Menactra or Menveo)	1 581 856
Measles, mumps, rubella (MMR)	1 576 861
Quadrivalent meningococcal conjugate (MCV4) (Sanofi-Menactra)	1 525 239
23-valent pneumococcal polysaccharide (PPSV23)	1 509 189
Rotavirus 5	1 453 465
IPV	1 321 888
PCV13	1 318 310
Live attenuated influenza vaccine (LAIV)	905 363
Tetanus, diphtheria (Td)	806 054
Live zoster vaccine	670 492
MMR + Varicella	431 991
Injectable typhoid	317 895
DTaP + IPV + Hib (Pentacel)	302 904
DTaP + IPV (Kinrix)	246 986
Rotavirus 1	186 275
HAV + HBV (Twinrix)	122 231
Yellow fever	81 314
MCV4 Novartis (Menveo)	44 317
Quadrivalent meningococcal polysaccharide (MPSV4)	5228
Rabies	1846
Total number of vaccines given	63 678 496

Table 2.

Relative Risk[a] of Transverse Myelitis in the 5- to 28-Day Risk Interval Following Vaccines, Compared to Remainder of the 9 Months After Vaccination—Vaccine Safety Datalink, 2007–2013

	Vaccinated Cases		Comparison Risk Sets: Cases and Noncases[b]				
Vaccine Type	**No.**	**% in Exposure Interval**	**No.**	**% in Exposure Interval**	**Adjusted Odds Ratio**	**(95% CI)**	***P* Value**
MMR	1	0	188	12.8	0	(.0–129.8)	.87
DTaP/IPV/HBV	1	0	150	22.7	0	(.0–64.8)	.77
MCV4 (Sanofi)	3	33.3	10 221	7.2	5.2	(.2–70.9)	.27
Tdap	16	6.3	121 768	8.8	0.7	(.0–3.8)	.78
Rotavirus 5	1	0	151	20.5	0	(.0–73.5)	.79
Zoster	2	50	6079	11.1	7.7	(.2–301.4)	.23
PCV13	1	0	154	22.7	0	(.0–64.6)	.77
Varicella	4	0	4725	7.5	0	(.0–10.7)	.67
PPSV23	5	0	27 940	8.1	0	(.0–9.4)	.66
HPV4	3	0	7273	9.7	0	(.0–15.3)	.73
Any MCV4	3	33.3	10 221	7.2	5.2	(.2–70.9)	.27
Any PCV	2	0	218	21.6	0	(.0–12.0)	.6
HAV	4	0	3057	9	0	(.0–12.6)	.71
HBV	2	0	284	12	0	(.0–30.0)	.79
Hib	1	0	157	22.3	0	(.0–66.2)	.78
IIV	38	7.9	969 316	6.2	1	(.2–4.0)	.98
LAIV	1	100	2640	29.7	NE	(.1 to . . .)	.3
Td	2	0	3419	6.8	0	(.0–34.1)	.82
Any	66	10.6	1 692 825	10.3	1.1	(.4–2.4)	.87

Abbreviations: CI, confidence interval; DTaP, diphtheria, tetanus, acellular pertussis vaccine; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; HPV4, quadrivalent human papillomavirus vaccine; IIV, inactivated influenza vaccine; IPV, inactivated polio vaccine; LAIV, live attenuated influenza vaccine; MCV4, quadrivalent meningococcal conjugate vaccine; MMR, measles, mumps, rubella vaccine; NE, not evaluable; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria vaccine; Tdap, adolescent and adult tetanus, reduced diphtheria, acellular pertussis vaccine.

[a]This relative risk is estimated by the odds ratio, using the case-centered method, as described in the “Methods” section.

[b]Comparative risk sets: cases and noncases: All Vaccine Safety Datalink (VSD) members similar to cases (matched on age, sex, vaccine type, and VSD site) on the onset date of the case. No. represents the number of people in all the risk sets. If there were no cases within 9 months of a vaccine, we could not perform a case-centered analysis, so these are not included in the table.

Table 3.

Relative Risk[a] of Acute Disseminated Encephalomyelitis in the 5- to 28-Day Risk Interval Following Vaccines, Compared to Remainder of the 9 Months After Vaccination—Vaccine Safety Datalink, 2007–2013

	Cases		Comparison Risk Sets: Informative Cases and Noncases[b]				
Vaccine Type	**No.**	**% in Exposure Interval**	**No.**	**% in Exposure Interval**	**Adjusted Odds Ratio**	**(95% CI)**	***P* Value**
MMR	6	33.3	46 482	10.1	5	(.6–29.9)	.12
IPV	1	0	6025	6.6	0	(.0–270.1)	.93
PCV7	3	0	39 788	4.5	0	(.0–48.1)	.87
MCV4 (Sanofi)	3	0	14 731	9	0	(.0–18.0)	.76
Tdap	3	66.7	9972	11.5	15.8	(1.2–471.6)	.04
DTaP/IP/Hib	2	0	5387	7.9	0	(.0–40.7)	.85
Zoster	1	0	3226	9.9	0	(.0–173.1)	.9
DTaP/IP	4	25	29 751	8.9	4.1	(.1–44.0)	.32
PCV13	3	33.3	7047	22.8	3.6	(.1–95.4)	.49
DTaP	1	0	6153	6.6	0	(.0–270.4)	.93
Varicella	6	33.3	44 953	10.5	4.3	(.5–25.4)	.14
MPSV4	1	100	3	33.3	NE	(.1 to . . .)	.33
PPSV23	3	0	13 359	10.3	0	(.0–14.5)	.71
HPV4	6	16.7	56 846	12.1	1.5	(.1–10.7)	.7
MMR-Varicella	1	0	2046	6.1	0	(.0–292.0)	.94
Any MCV4	3	0	16 157	9.1	0	(.0–17.5)	.75
Any PCV	6	16.7	46 862	7.3	2.8	(.1–21.2)	.4
H1N1	6	0	56 953	1.3	0	(.0–102.7)	.95
HAV	8	12.5	60 878	7.5	1.9	(.1–13.0)	.54
HBV	2	0	2112	2.4	0	(.0–128.7)	.95
Hib	3	0	18 285	6.8	0	(.0–25.3)	.8
IIV	21	19	281 468	7	1.5	(.4–5.0)	.53
LAIV	4	0	2650	12.6	0	(.0–4.9)	.34
Td	1	0	155	1.9	0	(.0–962.7)	.98
Any	47	17	813 498	8.8	1.7	(.7–3.8)	.19

Abbreviations: CI, confidence interval; DTaP, diphtheria, tetanus, acellular pertussis vaccine; DTaP/IP, diphtheria, tetanus, acellular pertussis, inactivated polio; DTaP/IP/Hib, diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenza type B; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; HPV4, quadrivalent human papillomavirus vaccine; IIV, inactivated influenza vaccine; IPV, inactivated polio vaccine; LAIV, live attenuated influenza vaccine; MCV4, quadrivalent meningococcal conjugate vaccine; MMR, measles, mumps, rubella vaccine; MPSV4, quadrivalent meningococcal polysaccharide vaccine; NE, not evaluable; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria vaccine; Tdap, adolescent and adult tetanus, reduced diphtheria, acellular pertussis vaccine.

[a] This relative risk is estimated by the odds ratio, using the case-centered method, as described in the “Methods” section.

[b] Comparison risk sets: cases and noncases: All Vaccine Safety Datalink (VSD) members similar to cases (matched on age, sex, vaccine type, and VSD site) on the onset date of the case. No. represents the number of people in all the risk sets. If there were no cases within 9 months of a vaccine, we could not perform a case-centered analysis, so these are not included in the table.

Table 4.

Mantel–Haenszel Estimate of Risk Difference (Excess Risk) of Transverse Myelitis in the 5–28 Days After Immunization, per 1 Million Doses of Each Vaccine—Vaccine Safety Datalink, 2007–2013

Vaccine	Risk Difference per Million Doses	(95% CI)	*P* Value	Total Risk Cases
MMR	−0.161	(−.21 to 1.76)	.693	0
DTaP/HBV/IP	−0.393	(−.97 to 1.19)	.750	0
MCV4 (Sanofi)	0.709	(−.41 to 3.25)	.152	1
Tdap	−0.107	(−.41 to .55)	.667	1
Rotavirus 5	−0.459	(−1.33 to 1.33)	.739	0
Zoster	1.446	(−.72 to 6.39)	.137	1
PCV13	−0.356	(−.61 to 1.54)	.750	0
Varicella	−0.268	(−.34 to .85)	.810	0
PPSV23	−0.369	(−.46 to 1.12)	.815	0
HPV4	−0.210	(−.29 to .81)	.782	0
Any MCV4	0.682	(−.39 to 3.11)	.152	1
Any PCV	−0.364	(−.61 to .66)	.836	0
HepA	−0.173	(−.22 to .66)	.793	0
HepB	−0.334	(−.48 to 1.81)	.745	0
Hib	−0.218	(−.38 to .94)	.748	0
IIV	−0.004	(−.39 to .49)	.507	3
LAIV	1.725	(−.87 to 5.91)	.118	1
Td	−0.542	(−.66 to 3.63)	.741	0
Any	0.014	(−.20 to .28)	.454	7

Comparison is within 9 months of the same vaccine. This analysis requires at least 1 case in the exposure or comparison interval.

Abbreviations: CI, confidence interval; DTaP/HBV/IP, diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; HPV4, quadrivalent human papillomavirus vaccine; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; MCV4, quadrivalent meningococcal conjugate vaccine; MMR, measles, mumps, rubella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria vaccine; Tdap, adolescent and adult tetanus, reduced diphtheria, acellular pertussis vaccine.

Table 5.

Mantel–Haenszel Estimate of Risk Difference (Excess Risk) of Acute Disseminated Encephalomyelitis in the 5–28 Days After Immunization, per 1 Million Doses of Each Vaccine—Vaccine Safety Datalink, 2007–2013

Vaccine	Risk Difference per Million Doses	(95% CI)	*P* Value	Total Risk Cases
MMR	1.807	(−.55 to 6.05)	.084	2
IPV	−0.148	(−.19 to 3.23)	.642	0
PCV7	−0.201	(−.37 to 1.47)	.698	0
MCV4 (Sanofi)	−0.255	(−.33 to 1.24)	.766	0
Tdap	0.385	(−.04 to 1.16)	.042	2
DTaP/IPV/Hib	−1.751	(−3.72 to 9.26)	.712	0
Zoster	−0.185	(−.24 to 2.65)	.672	0
DTaP/IP	3.616	(−2.45 to 17.12)	.17	1
PCV13	0.797	(−.69 to 3.93)	.196	1
DTaP	−0.079	(−.10 to 1.75)	.641	0
Varicella	0.95	(−.35 to 3.30)	.097	2
MPSV4	470.628	(−214.74 to 1940.23)	.124	1
PPSV23	−0.295	(−.37 to 1.17)	.789	0
HPV4	0.189	(−.68 to 2.00)	.377	1
MMR-Varicella	−0.226	(−.31 to 5.10)	.637	0
Any MCV4	−0.245	(−.32 to 1.19)	.766	0
Any PCV	0.285	(−.47 to 1.83)	.282	1
H1N1	−0.071	(−.16 to 1.11)	.627	0
HAV	0.233	(−.38 to 1.64)	.289	1
HBV	−0.081	(−.12 to 1.96)	.627	0
Hib	−0.207	(−.37 to 0.95)	.742	0
IIV	0.137	(−.26 to .63)	.263	4
LAIV	−2.018	(−3.86 to 1.41)	0.9	0
Any	0.141	(−.07 to .41)	.107	8

Comparison is within 9 months of same vaccine. This analysis requires at least 1 case in the exposure or comparison interval.

Abbreviations: CI, confidence interval; DTaP, diphtheria, tetanus, acellular pertussis vaccine; DTaP/IP, diphtheria, tetanus, acellular pertussis, inactivated polio; DTaP/IP/Hib, diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenza type B; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; HPV4, quadrivalent human papillomavirus vaccine; IIV, inactivated influenza vaccine; IPV, inactivated polio vaccine; LAIV, live attenuated influenza vaccine; MCV4, quadrivalent meningococcal conjugate vaccine; MMR, measles, mumps, rubella vaccine; MPSV4, quadrivalent meningococcal polysaccharide vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Tdap, adolescent and adult tetanus, reduced diphtheria, acellular pertussis vaccine.