

Aseptic Meningitis after Childhood Immunization: A Case-Centered Analysis

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Background

Case reports of aseptic meningitis (AM) following vaccination in infants and young children have raised concerns that vaccines may rarely cause AM. We analyzed for an association between AM and childhood vaccines.

Study Population

Study period: 2007-2014

Age: 8 years of age and under

Data Sources: First diagnosis of AM in all Emergency Department (ED), Inpatient or Outpatient data in Kaiser Permanente Northern California (KPNC).

Vaccines: All vaccine types within 9 months prior to AM diagnosis.

Diagnostic Search Terms: Aseptic, Viral, or Unspecified Viral Meningitis

AM Case Confirmation: Medical records of all electronically identified AM cases who received a vaccine within the prior 4 weeks were reviewed to confirm AM diagnoses.

AM Onset Date: To determine the AM onset date, we used the earlier date of either the AM diagnosis or the start of symptoms (fever, headache, neck pain).

Exposure Intervals: Vaccination within 1-7 days and 1-28 days prior to AM onset date

Comparison Interval: Vaccination within 5 weeks - 9 months prior to AM onset date with same vaccine as the AM case

Methods

We identified cases in children aged 8 years and younger by searching KPNC databases from 2007 - 2014 for all first time AM diagnoses occurring within 9 months of any immunization. Exposure intervals of 1-7 and 1-28 days prior to AM diagnoses were selected based on case reports and biologic plausibility. We reviewed all potential cases within 4 weeks of any immunization to verify AM diagnosis and onset date.

Using a case-centered study design, we compared the proportion of cases recently vaccinated (1-7 days and 1-28 days prior) with an expected proportion derived from all age-sex matched KPNC members on the anchor onset date for each case (i.e., date AM case began). However, unlike a case control study, we did not sample controls. We included all matched KPNC members who were vaccinated in the 9 months prior to the anchoring onset date. We repeated the analysis for each vaccine type and for “Any Vaccine” separately using electronic data and using chart confirmed cases only. Here we report on chart confirmed analyses only.

Methods

We computed Mantel-Haenszel type risk difference estimates and corresponding 95% confidence intervals (CI) in order to account for the large number of immunizations given with relatively few aseptic meningitis cases within 9 months of a vaccine. The upper limit of the 95% CI of the risk difference estimate represents the maximal potential risk.

Results

During the study period >10 million vaccines were administered at KPNC within the study population (**Table 1**). We identified 28 potential AM cases which received vaccines during the prior 4 weeks. We chart-confirmed 25 (89%) as AM. We found no statistically significant increased risk of immunization compared with matched controls for any vaccine in either the 1-7 day or the 1-28 day exposure interval (**Tables 2-3**.)

Tables 2-3. Case Centered Analysis for chart confirmed Aseptic Meningitis from 2007-2014 in children 8 years of age and younger with vaccine exposure interval of 1-7 and 1-28 days prior to AM onset date and comparison interval within 5 weeks to 9 months of the same vaccine.

1-7 day exposure interval					
Vaccine	Odds Ratio	95% CI	Exact P-value	Cases in Exposure Interval	Cases in Comparison Interval
MMR	0	0.00,129.49	0.945	0	3
IPV	0	0.00,30.66	0.874	0	6
PNCV	3.549	0.09,50.64	0.441	1	3
Pediarix	4.14	0.36,33.33	0.234	2	6
RV5	0	0.00,47.12	0.898	0	4
DTaPIP	0	0.00,893.14	0.979	0	1
PNCV13	3.138	0.07,49.65	0.512	1	3
DTaP	0	0.00,20.33	0.826	0	7
VZV	8.634	0.33,72.92	0.147	1	5
MMR-V	0	0.00,93.19	0.941	0	4
H1N1	0	0.00,386.80	0.961	0	2
HepA	0	0.00,81.92	0.919	0	2
HepB	2.406	0.08,39.69	0.694	2	19
Hib	4.32	0.37,35.97	0.224	2	4
IIV	0.865	0.00,55.33	0.98	1	8
LAIV	0	0.00,37.65	0.838	0	2
Any	1.014	0.27,3.18	0.953	5	41

Table 1: Vaccinations administered to children 8 years of age and younger at KPNC from 2007 - 2014

Vaccination	Vaccines administered in the study period
H. influenzae type b (Hib)	1,314,379
Inactivated Influenza (IIV)	1,260,139
DTaP, Heb B, Polio (Pediarix)	893,295
Hepatitis A (HepA)	893,294
Pneumococcal conjugate, 13 valent (PCV13)	805,366
Pneumococcal conjugate, 9 valent (PNCV)	745,971
Diphtheria, tetanus, acellular pertussis (DTaP)	645,686
Varicella (VZV)	514,269
Measles, Mumps, Rubella (MMR)	510,519
Rotavirus - Rotateq (RV5)	472,467
Hepatitis B (HepB)	457,258
Inactivated Polio Virus (IPV)	322,893
Live-attenuated influenza vaccine (LAIV)	285,111
Measles, Mumps, Rubella, Varicella (MMR-V)	264,909
Rotavirus - Rotarix (RV1)	245,330
H1N1 Influenza (H1N1)	194,683
DTaP, IPV (DTaPIP)	192,732
DTaP, IPV, Hib (Pentacel)	103,405
Typhoid (ITyph)	36,246
Total	10,157,952

1-28 day exposure interval					
Vaccine	Odds Ratio	95% CI	Exact P-value	Cases in Exposure Interval	Cases in Comparison Interval
MMR	0	0.00,30.89	0.805	0	3
IPV	0	0.00,6.42	0.552	0	7
PNCV	2.382	0.27,18.32	0.408	4	3
Pediarix	2.206	0.44,11.16	0.337	7	6
RV5	3.411	0.45,22.58	0.212	4	4
RV1	-	0.06, -	0.671	2	0
DTaPIP	9.896	0.24,403.47	0.19	1	1
PNCV13	2.669	0.35,19.71	0.334	4	3
DTaP	1.279	0.05,8.71	0.766	1	7
VZV	1.87	0.07,15.40	0.584	1	5
MMR-V	1.773	0.05,23.32	0.679	1	4
H1N1	0	0.00,39.81	0.711	0	4
HepA	0	0.00,19.97	0.726	0	2
HepB	1.137	0.15,8.06	0.912	10	22
Hib	3.462	0.74,16.75	0.113	8	4
IIV	0.87	0.04,10.43	0.943	2	13
LAIV	0	0.00,16.70	0.684	0	2
Any	0.854	0.37,1.90	0.717	21	41

Results

The risk difference for “Any” childhood vaccine and AM in the 1-7 day exposure interval was calculated to be 0.014 per one million doses of vaccine (95% CI -0.93, 1.50; **Table 4**), and -0.444 (95% CI -2.38, 1.97; **Table 5**) in the 1-28 day exposure interval. Results for analyses using electronic data only were similar.

Tables 4-5. Risk Difference per million doses for chart confirmed Aseptic Meningitis from 2007-2014 in children 8 years of age and younger with vaccine exposure interval of 1-7 days and 1-28 days prior to AM onset date and comparison interval within exposure interval of the same vaccine

1-7 day exposure interval		
Vaccine	Risk Difference	95% CI
MMR	-0.162	-0.18,4.99
IPV	-0.943	-1.03,11.58
PNCV	1.847	-1.43,9.16
Pediarix	2.919	-1.19,8.94
RV5	-0.536	-1.32,3.76
DTaPIP	-0.123	-0.13,10.23
PNCV13	1.079	-0.96,5.77
DTaP	-0.483	-0.52,4.10
VZV	2.285	-0.90,10.22
MMR-V	-0.291	-0.33,8.07
H1N1	-0.435	-0.62,14.74
HepA	-0.13	-0.14,2.69
HepB	3.38	-4.37,19.05
Hib	1.77	-0.62,5.99
IIV	-0.031	-0.31,1.92
LAIV	-1.02	-1.93,5.59
Any	0.014	-0.93,1.50

1-28 day exposure interval		
Vaccine	Risk Difference	95% CI
MMR	-0.648	-0.86,4.15
IPV	-4.335	-5.64,8.09
PNCV	3.438	-3.24,14.03
Pediarix	4.788	-3.52,14.75
RV5	9.399	-5.46,26.35
RV1	6.291	-7.23,24.17
DTaPIP	5.319	-2.28,22.04
PNCV13	2.928	-1.84,10.47
DTaP	0.54	-2.97,8.10
VZV	1.189	-2.22,8.83
MMR-V	1.69	-3.23,13.93
H1N1	-3.734	-7.88,9.94
HepA	-0.512	-0.67,2.14
HepB	1.455	-10.93,24.56
Hib	4.33	-0.65,11.18
IIV	-0.164	-2.23,3.16
LAIV	-2.767	-6.67,5.23
Any	-0.444	-2.38,1.97

Conclusion

Our large-scale analysis applying a case-centered method did not detect any statistically significant association between cases of AM and receipt of Any Vaccine in the previous week. If a risk for AM following Any Vaccine does exist, the risk is less than 2 in 1 million doses.