Case-centered Analysis of Optic Neuritis After Vaccines
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We evaluated the risk of optic neuritis (ON) after vaccines, using a case-centered analysis, comparing the time since vaccination for the patients with ON with that for all similar vaccinees in a large integrated health plan population. We did not detect any association between ON and receipt of any type of vaccine.

Keywords. vaccine; immunization; adverse event; optic neuritis; vaccine safety.

Acute optic neuritis (ON) is generally idiopathic and is characterized by the sudden onset of unilateral painful loss of vision due to demyelination [1]. ON can affect all ages, can result in permanent visual impairment, and is associated with a prior or subsequent diagnosis of multiple sclerosis. Many patients with ON report a viral illness in the month preceding the onset of visual loss [2].

Concerns that vaccines might trigger demyelinating diseases have existed for many years [3, 4], with case reports highlighting a possible association and sometimes making the faulty assumption that an illness that follows a vaccine is therefore due to a vaccine [5]. Other than case reports, there is limited scientific evidence to support these concerns, and multiple studies have shown no association [6, 7]. Observational studies investigating for an association between ON and vaccination have been limited by a lack of understanding about the underlying pathophysiological mechanisms or causes of disease, by the rareness of the condition, and by epidemiological issues inherent in a comparison between vaccinated and unvaccinated individuals [8]. The Institute of Medicine observed that there was not sufficient evidence to either accept or reject the notion that vaccines are causally related to ON [7].

The aim of the current study was to determine whether the observed rate of vaccination before onset of ON is higher than expected, by comparing vaccination rates in patients with ON to those in the matched general population. We estimated both the multiplicative effects (relative risk) and the additive effects (risk difference) of ON after vaccines in persons of all ages.

METHODS

Study Population
Kaiser Permanente Northern California (KPNC) is an integrated healthcare system providing medical care to approximately 3.5 million members, which owns and operates >40 medical clinics and 19 hospitals with pharmacies and laboratories. Patients receive essentially all care at KPNC facilities. KPNC databases capture vaccinations, laboratory tests, and inpatient, emergency department, and outpatient diagnoses from a completely electronic medical record. The study period was 1 January 2007 through 31 December 2012.

Case Selection
We used internal electronic medical record diagnostic terms to identify first-ever ON diagnoses in any setting (hospital, emergency, or outpatient clinic), excluding individuals with a history of multiple sclerosis. We required an ON diagnosis made by either an ophthalmologist or a neurologist within 3 months of the initial diagnosis. Trained medical records analysts reviewed all identified cases to verify the specialist diagnosis and that the diagnosis was new onset and symptoms began within the study period.

Exposure Intervals
Based on prior studies and expert opinion, we used 2 exposure intervals: (1) 2–42 days, as the most common interval used in prior studies of demyelinating illness, and (2) 5–28 days, as a narrower and biologically plausible alternative. Proportions of vaccinations were determined by the vaccines given during the exposure interval, compared with the rest of the 9 months (comparison interval) before onset of ON.

Statistical Methods
Case-centered analyses [9–11] look back from the case onset dates to determine whether vaccinations cluster in the exposure interval before the onset. The observed odds of exposure (immunization) during the exposure interval before the outcome are compared with the expected odds of exposure during the same exposure interval, based on vaccination times in the population of all similar persons vaccinated with the same vaccine of interest. The method is equivalent to a matched case-control study that uses all matched controls (no sampling) and is anchored to an index date for each case. Each case patient with ON was matched by age and sex to all KPNC members who, as of the onset date for the ON case, received the same vaccine in the 9 months before the onset date of the index case.
compared the proportion of case patients vaccinated within pre-determined exposure intervals, relative to the rest of the 9 months before vaccination (eg, 43 days through 9 months), with the proportion of all matched KPNC members vaccinated in the same exposure interval time period. A case-centered logistic regression model was applied to estimate the odds ratios (ORs) with confidence intervals (CIs) and P values. The OR estimates the relative risk of being in the exposure interval versus the rest of the 9 months.

**Risk Difference Calculation**

We pooled strata with 0 cases and used a Mantel-Haenszel type weighted average [12] to estimate the excess risk (also known as the risk difference) and 95% CIs associated with immunization and ON diagnosis.

This study was approved by the KPNC Institutional Review Board.

**RESULTS**

During the study period, we assessed >20 million vaccines administered in KPNC and identified 1033 potential cases of ON. A list of all vaccines monitored is available in Supplementary Table 1. After excluding patients with multiple sclerosis and prior history of ON, and applying membership criteria, we detected 179 potential ON cases with exposure to a vaccine in the prior 9 months, 91 (51%) of which were confirmed as ON after chart review.

Case-centered analyses demonstrated no significantly increased risk of vaccination in the 2–42 days (Table 1) or 5–28 days (Supplementary Table 2) before the onset of ON. For inactivated influenza vaccines (IIVs), the OR for the prior 2–42 days was 0.6 (95% CI, 1.1–2.6), and for any vaccine it was 1.1 (0.5–2.0). For meningococcal conjugate, tetanus, pneumococcal polysaccharide, and 4-valent human papillomavirus vaccines, OR point estimates were ≥2 or more, but very few cases occurred after these vaccines, so the CIs were wide and not statistically significant.

We calculated the risk difference per million doses for each vaccine (Table 1 and Supplementary Table 3). As examples, we can conclude that either inactivated influenza vaccine has no effect on ON or its effect amounts to ≤0.92 cases per 1 million doses in the 2–42 days after vaccination (upper bound of 95% CI). Similarly, for hepatitis B vaccines, we can rule out that hepatitis B vaccines could be associated with >3.47 excess cases of ON per million doses. If “any vaccines” (ie, all vaccines combined) were causally associated with ON, the effect would be less than about 1 case per million doses.

**DISCUSSION**

Our study found no evidence that vaccines are associated with development of ON in the 4 or 6 weeks after immunization. Using a large population, chart review of all cases, and a method that controls carefully for confounding variables, we found no

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**Table 1. Relative Risk and Risk Difference of Optic Neuritis in the 2–42-Day Risk Interval After Vaccines vs the Remainder of the 9 Months After Vaccination, Kaiser Permanente Northern California 2007–2013**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Vaccines Given, No.</th>
<th>% in Exposure Interval</th>
<th>% in Exposure Interval</th>
<th>Adjusted OR (95% CI)</th>
<th>Risk Difference per 1 Million Doses (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>493 229</td>
<td>1</td>
<td>0</td>
<td>253</td>
<td>0 (0.0–136.1)</td>
</tr>
<tr>
<td>Hepatitis A/B combination</td>
<td>94 188</td>
<td>1</td>
<td>100</td>
<td>104</td>
<td>23.1</td>
</tr>
<tr>
<td>MCV4</td>
<td>497 973</td>
<td>6</td>
<td>33</td>
<td>35 389</td>
<td>15.1</td>
</tr>
<tr>
<td>Tdap</td>
<td>2 036 282</td>
<td>33</td>
<td>24</td>
<td>348 107</td>
<td>15.7</td>
</tr>
<tr>
<td>VZV</td>
<td>754 954</td>
<td>4</td>
<td>25</td>
<td>96 989</td>
<td>16.6</td>
</tr>
<tr>
<td>PPSV23</td>
<td>474 448</td>
<td>5</td>
<td>40</td>
<td>89 707</td>
<td>17.7</td>
</tr>
<tr>
<td>Injectable typhoid</td>
<td>175 981</td>
<td>1</td>
<td>0</td>
<td>202</td>
<td>12.9</td>
</tr>
<tr>
<td>HPV4</td>
<td>556 643</td>
<td>5</td>
<td>60</td>
<td>42 063</td>
<td>23.8</td>
</tr>
<tr>
<td>H1N1</td>
<td>681 737</td>
<td>8</td>
<td>13</td>
<td>106 498</td>
<td>3.1</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1 154 486</td>
<td>4</td>
<td>0</td>
<td>62 229</td>
<td>15.2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>653 832</td>
<td>3</td>
<td>0</td>
<td>26 641</td>
<td>20.9</td>
</tr>
<tr>
<td>IIV</td>
<td>6 989 046</td>
<td>57</td>
<td>11</td>
<td>1 577 312</td>
<td>10.4</td>
</tr>
<tr>
<td>LAIV</td>
<td>490 432</td>
<td>2</td>
<td>0</td>
<td>64 903</td>
<td>27.6</td>
</tr>
<tr>
<td>Td</td>
<td>232 434</td>
<td>1</td>
<td>0</td>
<td>278 226</td>
<td>16.5</td>
</tr>
<tr>
<td>Any vaccine</td>
<td>20 393 108</td>
<td>91</td>
<td>18</td>
<td>2 930 191</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; H1N1, monovalent pandemic influenza; HPV4, 4-valent human papillomavirus; IIV, inactivated influenza vaccine; KPNC, Kaiser Permanente Northern California; LAIV, live attenuated influenza vaccine; MCV4, meningococcal conjugate vaccine; MMR, measles, mumps rubella; NE, not evaluable; ON, optic neuritis; OR, odds ratio; PPSV23, pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis; VZV, varicella-zoster virus.

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*The relative risk is estimated according to the OR, using the case-centered method, as described in “Methods” section. Risk difference indicates excess risk for ON per million doses of each vaccine.

b Comparison risk sets included case patients with ON and all KPNC members similar to those patients (matched for age, sex, and vaccine type) on the onset date of ON.
Many vaccine safety outcomes are rare, which means that even with very large numbers of vaccinees, it is hard to rule out small adverse effects, it is generally not possible to prove that a vaccine is never associated with a particular outcome. On the other hand, when a large number of vaccines are given and only a very small number of adverse events occur, estimation of the risk difference permits conclusions about how much reassurance can be provided. Based on the upper 95% confidence limit of the risk difference for all vaccines combined, we can conclude that the excess risk of ON is ≤1 per million doses. Possible excess risks associated with specific vaccines were also small. Our study showed no association of inactivated influenza vaccines with ON, but if a risk were to exist, it would be <0.92 case per million doses given. For vaccines given less often, such as pneumococcal polysaccharide and 4-valent human papillomavirus, no statistically significant associations were found, but larger studies would be needed to be able to confidently rule out ≤10 cases per million doses.

Among the strengths of our study, analyses restricted to vaccinees avoid the need to adjust for the differences between vaccinated and unvaccinated individuals. Anchoring to calendar time effectively controls for time-varying confounding, and review of all cases of ON kept misclassification to a minimum. The study also had limitations: We did not analyze concomitant vaccines, and our method depends on selecting an appropriate risk interval, so an increased risk could be missed if the interval is incorrectly specified.

In conclusion, we found no increased risk of ON after immunization. We had power to detect a small excess risk, and it is reassuring that we found no evidence of excess risk for ON after any vaccine.

**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.

**Notes**

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