ORIGINAL CONTRIBUTION

Vaccinations and Risk of Central Nervous System Demyelinating Diseases in Adults

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Background: Several case reports of the onset or exacerbation of multiple sclerosis or other demyelinating conditions shortly after vaccination have suggested that vaccines may increase the risk of demyelinating diseases.

Objective: To evaluate the association between vaccination and onset of multiple sclerosis or optic neuritis.

Design: Case-control study involving cases of multiple sclerosis or optic neuritis among adults 18 to 49 years of age. Data on vaccinations and other risk factors were obtained from computerized and paper medical records and from telephone interviews.

Setting: Three health maintenance organizations.

Participants: Four hundred forty case subjects and 950 control subjects matched on health maintenance organization, sex, and date of birth.

Interventions: None.

Main Outcome Measures: Onset of first symptoms of demyelinating disease at any time after vaccination and during specified intervals after vaccination (<1 year, 1-5 years, and >5 years).

Results: Cases and controls had similar vaccination histories. The odds ratios (95% confidence intervals), adjusted for potential confounding variables, of the associations between ever having been vaccinated and risk of demyelinating disease (multiple sclerosis and optic neuritis combined) were 0.9 (0.6-1.5) for hepatitis B vaccine; 0.6 (0.4-0.8) for tetanus vaccination; 0.8 (0.6-1.2) for influenza vaccine; 0.8 (0.5-1.5) for measles, mumps, rubella vaccine; 0.9 (0.5-1.4) for measles vaccine; and 0.7 (0.4-1.0) for rubella vaccine. The results were similar when multiple sclerosis and optic neuritis were analyzed separately. There was no increased risk according to timing of vaccination.

Conclusion: Vaccination against hepatitis B, influenza, tetanus, measles, or rubella is not associated with an increased risk of multiple sclerosis or optic neuritis.

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SEVERAL CASE reports of onset or recurrence of symptoms of demyelination after vaccination have raised concerns that vaccines may cause or exacerbate multiple sclerosis (MS) or other central nervous system (CNS) demyelinating disorders. Although the greatest concern has been with hepatitis B vaccine,[1-11] there also have been several reports after influenza vaccination[12-22] and other vaccines.[23-31] It is difficult, however, to infer causality from individual case reports. The reported cases may simply represent coincidental temporal associations with vaccination.

Multiple sclerosis is generally believed to be an autoimmune disease that occurs in genetically susceptible people.[32] Unknown environmental factors, including certain infections,[33] are also suspected to be involved in its pathogenesis. Environmental factors, such as vaccines, could be involved in actually causing the disease, resulting in an overall excess of MS in the population, or as possible triggers for the clinical expression of MS in individuals with subclinical disease. For patients who already have MS, there may be theoretical reasons to be concerned that the immunologic stimulation from vaccination could trigger an exacerbation, as occurs after certain infections.[34,35]

Except for hepatitis B vaccine,[36-38] there has been little published research on vaccines as risk factors for CNS demyelinating diseases. To more fully evaluate the association between hepatitis B and other vaccines and risk of CNS demyelinating diseases, we conducted a case-control study in 3 large health maintenance organizations (HMOs).

METHODS

Cases and controls were selected from the membership of 3 HMOs that participate in the Centers for Disease Control and Prevention's Vaccine Safety Datalink project.[39] The study was reviewed and approved by the institutional review board of each participating organization.

IDENTIFICATION OF CASES

We identified potential cases by searching inpatient and outpatient computerized databases for diagnoses of MS (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 340) or optic neuritis (ON; code 377.3). Individuals who had diagnoses of both ON and MS were categorized as MS cases. We were not able to include patients with transverse myelitis as potential cases of demyelinating diseases because there is not a specific code for transverse myelitis. Cases were restricted to adults 18 to 49 years of age with a first diagnosis of MS or ON from January 1, 1995, through December 31, 1999, at 1 HMO or from January 1, 1996, through December 31, 1999, at the 2 other HMOs. Cases had to have been HMO members for at least 1 year before their first identified demyelinating disease diagnosis in the automated database. We reviewed the paper medical records to confirm case status and determine dates of clinical events.

CASE DEFINITION

For the main analyses, cases were defined as those that had a physician's diagnosis in the paper medical record of *multiple sclerosis* or *optic neuritis* (including *retrobulbar neuritis*). In secondary analyses, we also evaluated 2 alternative case definitions: (1) diagnosis of MS by a neurologist or of ON by a neurologist, ophthalmologist, or optometrist; and (2) the standard diagnostic criteria for clinically definite MS[40,41]—2 clinical demyelinating events separated in space and time (as documented in the medical record or reported in the telephone interview).

To determine the onset of symptoms of MS, we used the symptoms and criteria proposed by Poser.[42] Symptoms were ascertained in both the chart abstraction and telephone interviews and must have lasted at least 24 hours.

CONTROL SUBJECTS

Up to 3 controls were matched to each case. Controls had the same eligibility criteria as cases and were individually matched on date of birth (within 1 year) and sex. Controls had to have been members of the HMO for at least 1 year before the date of the first demyelinating disease diagnosis in the automated record of the matched case.

EXPOSURE

Information on vaccinations was ascertained from computerized vaccination records, review of paper medical records, and telephone interviews. We relied primarily on vaccination data recorded in the medical records or computer databases to define exposure. However, we accepted self-reported vaccination information if a vaccination was reported in the telephone interview to have been received outside the HMO or from an unspecified provider and the vaccination had not been already captured in the HMO records. From the medical records, we collected information on all vaccinations received from 10 years of age to the date of chart abstraction. In the telephone interview, for most vaccines we obtained dates of first and last vaccination; for tetanus vaccine we asked only about the date of most recent vaccination. For hepatitis B vaccine and influenza vaccine, we asked more detailed questions on source of vaccination that allowed us to compare self-reported vaccinations against vaccination records.

ANALYSIS

We used conditional logistic regression to estimate odds ratios (ORs). We defined the index date for demyelinating disease onset as the earliest reported date in the telephone interview or medical record of a demyelinating disease symptom. Matched controls were assigned a corresponding index date. In the main analysis, we evaluated vaccine exposure as ever or never before the index date. We also performed analyses of timing of vaccination relative to the index date.

We used matching and statistical adjustment to control for potential confounding. We matched for age, sex, and HMO. Variables that we evaluated for potential confounding included race and ethnicity, ancestry (northern European or Scandinavian), family history of demyelinating or other autoimmune diseases, education, marital status, occupation, residence history, cigarette smoking, pet ownership, and certain groups at high risk for hepatitis B infection (eg, health care workers and patients undergoing dialysis). We evaluated each variable individually for its association with case status, and all variables with a P value less than .20 were included in the regression model.[43] We also evaluated interactions by sex. We defined a P value less than .05 as statistically significant. We present 95% confidence intervals (CIs) for the ORs. In general, if the CI does not overlap 1.0, the result is statistically significant.

RESULTS

Beginning with the computerized diagnoses files, we identified 1159 potential cases of MS or ON. On medical record review, 556 of the potential cases had a first diagnosis of MS or ON during 1995 through 1999 and were eligible for the study. Of the eligible cases, 106 were excluded for the following reasons: deceased (2), not able to locate or arrange interview (55), refused interview (46), and language or hearing impairment (3). Ten interviewed cases were excluded because we could not identify a suitable control or because subsequent chart review showed that the subject did not meet the eligibility criteria. Thus, 440 cases were included in the analysis.

We initially selected 2047 potential controls, but 162 were excluded because their matched cases did not meet study eligibility criteria or had incomplete data. Of the remaining controls, 935 were excluded for the following reasons: deceased (1), not able to locate or arrange interview (550, of whom 324 were from one HMO that oversampled controls and did not pursue the additional controls once 3 controls had been interviewed for a case), refused (360) or did not complete (2) interview, language or hearing impairment (19), and too ill to be interviewed (3). Thus, 950 controls were included in the analysis.

Of the 440 demyelinating diseases cases, 332 had MS and 108 had ON only. Because of matching, cases and controls had similar distributions of sex and age (**Table 1**). Cases and controls also had similar levels of education. Compared with controls, cases were more likely to be African American and less likely to be Hispanic, Asian, or Pacific Islander; less likely to have been born in the western region of the United States or a foreign country and more likely to have been born in another region of the United States; less likely to be widowed, separated, or divorced; slightly more likely to have ancestors from Scandinavia; more likely

Table 1. Characteristics of Cases and Control Subjects*

Characteristic	Cases, No. (%) (n = 440)	Controls, No. (%) (n = 950)
Sex		
Female	336 (76.4)	729 (76.7)
Male	104 (23.6)	221 (23.3)
Age (at index date), y		
<18	26 (5.9)	50 (5.3)
18-30	154 (35.0)	323 (34.0)
31-40	161 (36.6)	366 (38.5)
>40	99 (22.5)	211 (22.2)
Race and ethnicity		
White, not Hispanic	314 (71.4)	673 (70.8)
African American	54 (12.3)	78 (8.2)
Hispanic	38 (8.6)	107 (11.3)
Asian, Pacific Islander	13 (3.0)	45 (4.7)
Other	21 (4.8)	46 (4.8)
Place of birth		
West	300 (68.2)	720 (75.8)
Midwest	44 (10.0)	72 (7.6)
South	28 (6.4)	37 (3.9)
Northeast	33 (7.5)	43 (4.5)
Foreign country	31 (7.0)	78 (8.2)
Education		
<12 y	14 (3.2)	34 (3.6)
High school graduate	271 (61.6)	583 (61.4)
College graduate	153 (34.8)	333 (35.1)
Marital status		
Married	314 (71.4)	653 (68.7)
Widow/separated/divorced	57 (13.0)	154 (16.2)
Never married	69 (15.7)	143 (15.0)
Scandinavian ancestry	67 (15.2)	138 (14.5)
Family history		
Demyelinating diseases	36 (8.2)	26 (2.7)
Autoimmune diseases	24 (5.5)	31 (3.3)
Occupation (ever worked)		
Health care	117 (26.6)	236 (24.8)
Other high risk	181 (41.1)	398 (41.9)
Hepatitis infection	23 (5.2)	38 (4.0)
Ever smoker	243 (55.2)	424 (44.6)

*Totals for some characteristics do not equal the total number of cases or controls because of missing data.

to have a family history of demyelinating diseases or other autoimmune diseases; equally likely to have worked in health care or some other potentially high-risk occupation for hepatitis B infection; and more likely to have ever smoked cigarettes. Only a few cases and controls had a history of hepatitis infection.

Vaccination against tetanus, which included tetanus toxoid and combined tetanus and diphtheria toxoids vaccines, was the most common vaccination among both cases and controls (**Table 2**). Tetanus also was the vaccination with the largest difference between cases and controls, with just more than one third of cases having been vaccinated before their index date compared with nearly one half of controls. Cases also tended to be somewhat less likely to have received rubella vaccine. For the other vaccines, cases and controls had similar vaccination histories. Few cases or controls had received hepatitis A or pneumococcal vaccines, and we were not able to include these 2 vaccines in any further analyses.

As noted previously, the vaccination histories included both vaccinations recorded in HMO records and

Table 2. Vaccination Histories of Cases and Control Subjects

Vaccine	Ever Vaccinated (Before Index Date), No. (%)	
	Cases (n = 440)	Controls (n = 950)
Hepatitis B	34 (7.7)	77 (8.1)
Tetanus	155 (35.2)	449 (47.3)
Influenza	73 (16.6)	177 (18.6)
Measles, mumps, rubella	28 (6.4)	71 (7.5)
Measles	42 (9.6)	102 (10.7)
Rubella	45 (10.2)	124 (13.1)
Hepatitis A	5 (1.1)	5 (0.5)
Pneumococcal	5 (1.1)	9 (1.0)

those reported in the telephone interview. Among the vaccinated cases and controls, respectively, the proportion whose vaccinations were only from outside the HMO (and thus self-reported) were 0.51 and 0.50 for hepatitis B; 0.38 and 0.30 for tetanus; 0.32 and 0.39 for influenza; 0.64 and 0.65 for measles, mumps, and rubella (MMR); 0.51 and 0.50 for measles; and 0.53 and 0.44 for rubella. When we compared the reliability of the self-reported vaccinations against the HMO records, we found generally good agreement among both cases and controls. For example, hepatitis B vaccinations that were reported to have been received at an HMO facility could be verified in the HMO records for 76% reported by cases and 73% reported by controls. Reports of influenza vaccinations were verified for 83% of those reported by cases and 82% of control reports.

The results of the conditional logistic regression analyses indicated that ever having been vaccinated with any of the vaccines of interest did not increase the risk of MS or ON (**Table 3**). In these analyses, the case definition required a documented physician's diagnosis of MS or ON. For the 2 conditions combined, none of the ORs were greater than 1.0. When the 2 conditions were evaluated separately, the only OR greater than 1.0 was for the association between hepatitis B vaccine and ON, but the OR was only 1.2 and not statistically significant. The strongest association was found for tetanus vaccination, which had a consistently decreased OR of 0.6 for the 2 conditions individually and combined, and the 95% CI excluded 1.0 for the individual association with MS and the association with the combined demyelinating diseases category. Rubella vaccine also tended to have decreased ORs between 0.6 to 0.7, although none was statistically significant. There were no statistically significant interactions by sex for any of the associations between specific vaccines and demyelinating disease outcomes, indicating that the results were not different between men and women.

The 2 secondary analyses that we performed using different case definitions were consistent with the main analysis. In the analysis in which we required that MS or ON have been diagnosed by a specialist, there were 309 MS cases and 97 ON cases. The ORs using this more restrictive case definition were not materially different from those presented in Table 3. For example, the ORs (95% CIs) of the associations with the combined category of demyelinating diseases were 0.9 (0.6-1.5) for ever

Table 3. Odds Ratios of Associations Between Ever Vaccinated and Risk of Demyelinating Disease, by Vaccine and Demyelinating Condition

Vaccine	Odds Ratio (95% Confidence Interval)*		
	Multiple Sclerosis (332 Cases/722 Control Subjects)	Optic Neuritis (108 Cases/228 Control Subjects)	Either (440 Cases/950 Control Subjects)
Hepatitis B	0.8 (0.5-1.4)	1.2 (0.5-3.1)	0.9 (0.6-1.5)
Tetanus	0.6 (0.4-0.8)	0.6 (0.4-1.1)	0.6 (0.4-0.8)
Influenza	0.7 (0.5-1.1)	1.2 (0.6-2.3)	0.8 (0.6-1.2)
Measles, mumps, rubella	0.9 (0.4-1.8)	0.8 (0.3-2.2)	0.8 (0.5-1.5)
Measles	1.0 (0.5-1.7)	0.7 (0.3-1.8)	0.9 (0.5-1.4)
Rubella	0.7 (0.4-1.2)	0.6 (0.2-1.4)	0.7 (0.4-1.0)

*Odds ratio (95% confidence interval) from conditional logistic regression model stratified by matching variables (health maintenance organization, sex, date of birth) and adjusted for race, marital status, ever smoked, family history of a demyelinating disease, family history of autoimmune disease, place of birth, and Scandinavian ancestry.

Table 4. Odds Ratios of Associations Between Timing of Vaccination and Risk of Demyelinating Disease, by Vaccine

Vaccine	Time of Vaccination Before Index Date*		
	<1 y	1-5 y	>5 y
Hepatitis B	0.8 (0.4-1.8)	1.6 (0.8-3.0)	0.6 (0.2-1.4)
Tetanus	1.2 (0.7-2.0)	0.8 (0.6-1.1)	0.5 (0.4-0.7)
Influenza	0.8 (0.5-1.4)	1.1 (0.7-1.7)	0.6 (0.3-1.1)
Measles, mumps, rubella	. . .	0.9 (0.4-1.9)	0.8 (0.4-1.5)
Measles	. . .	0.9 (0.4-1.9)	0.8 (0.5-1.3)
Rubella	. . .	0.9 (0.5-2.0)	0.6 (0.4-0.9)

Abbreviation: Ellipses, not estimable.
*Odds ratio (95% confidence interval) from conditional logistic regression models stratified by matching variables (health maintenance organization, sex, date of birth) and adjusted for race, marital status, ever smoked, family history of a demyelinating disease, family history of autoimmune disease, place of birth, and Scandinavian ancestry.

having been vaccinated with hepatitis B vaccine, 0.5 (0.4-0.7) for tetanus vaccination, 0.9 (0.6-1.3) for influenza vaccine, 0.8 (0.5-1.5) for MMR vaccine, 0.8 (0.5-1.3) for measles vaccine, and 0.7 (0.4-1.0) for rubella vaccine. With the use of the recommended diagnostic criteria[40,41] to define MS cases, 276 cases met the case definition. The ORs (95% CIs) for the association with MS were 0.8 (0.4-1.4) for hepatitis B vaccine, 0.6 (0.4-0.8) for tetanus vaccination, 1.0 (0.6-1.4) for influenza vaccine, 0.8 (0.4-1.7) for MMR vaccine, 0.9 (0.5-1.7) for measles vaccine, and 0.7 (0.4-1.2) for rubella vaccine.

We repeated the analyses restricting vaccination exposures to those that had been documented in the HMOs' records. The results were consistent with the findings of the analyses that included self-reported vaccinations. The ORs (95% CIs) of the associations with any demyelinating disease were 0.9 (0.5-1.6) for hepatitis B vaccine, 0.6 (0.4-0.8) for tetanus vaccination, 0.9 (0.6-1.3) for influenza vaccine, 0.8 (0.5-1.5) for MMR vaccine, 0.9 (0.5-1.4) for measles vaccine, and 0.7 (0.4-1.0) for rubella vaccine.

In the analyses of timing of vaccination and risk of onset of demyelinating disease, we did not find any indications of an increased risk for any of the vaccines (**Table 4**). The only 2 statistically significant ORs were both less than 1.0: 0.5 for tetanus vaccination and 0.6 for rubella vaccination more than 5 years before the index date. The results were not materially different when we repeated the analyses of vaccination timing restricted to vaccinations that were documented in the HMOs' paper or electronic records (data not shown).

COMMENT

We found that hepatitis B vaccine and several other vaccines that are more commonly administered to adults are not associated with an increased risk of MS or ON. The only statistically significant finding was of a decreased risk associated with tetanus vaccination. Multiple sclerosis is a disease that can have a long subclinical phase. Environmental exposures that may be etiologically related could occur several months to years before initial clinical manifestations. On the other hand, exposures that occur shortly before initial clinical symptoms, as has been the situation in the case reports of demyelination after vaccination,[1-31] would be most likely acting as triggers of clinical disease expression in individuals who already have an underlying disease process. We did not find any increased relative risks regardless of the timing of vaccination, indicating that vaccinations do not cause CNS demyelination, nor do they trigger its clinical manifestation in those with subclinical disease.

Hepatitis B has been the vaccine about which there has been the greatest controversy regarding a possible association with demyelinating diseases. The suggestion of a possible association stemmed from case reports of onset or recurrence of symptoms of demyelination within a few days to a few months of vaccination.[1-11] Our results add to the accumulating evidence that hepatitis B vaccine is not causally associated with demyelinating diseases. A case-control study conducted within the US Nurses' Health Study did not find an association between hepatitis B vaccine and risk of MS.[36] An analysis of a US pharmacy benefits management database did not find a statistically significant association between claims for hepatitis B vaccination and subsequent claims for treatment of CNS demyelinating disorders.[37] A study of the occurrence of adolescent-onset cases of MS in British Columbia found no differences between periods before (1986-1992) and after (1992-1998) the initiation of an annual hepatitis B vaccination program of students in sixth grade (11 to 12 years of age).[38] Two European case-control studies[44,45] found relative risks around 1.5 that were not statistically significant for onset of demyelination within 2 months to 1 year of hepatitis B vaccination.

For the other adult vaccines, the only evidence of a possible association with demyelinating diseases is from individual case reports.[12-31] It is difficult to interpret these case reports, however, because it is not possible to distinguish whether an observed event that follows shortly after a vaccination is causal or coincidental. Ours is the

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first epidemiologic study, to our knowledge, to evaluate several of the adult vaccines, and our results indicate that the observations in the published case reports probably represent coincidental temporal associations rather than causal associations.

Studies of vaccinations in patients who have MS also provide evidence that vaccines do not cause or exacerbate demyelination. A recent European study involving 643 patients with relapses of MS[46] used a case-crossover design to compare the risk of relapse during the 2 months after vaccination with the risk during other time periods. No increased risk of relapse was found after tetanus, hepatitis B, or influenza vaccination. A randomized controlled trial of influenza vaccination of patients with MS did not find any statistically significant differences in attack rates or disease progression during 6 months between vaccinees and placebo recipients.[47]

Ours was a large population-based case-control study that included both men and women. It adds to existing knowledge by providing information on different types of demyelinating diseases and several adult vaccines that had not previously been studied. The results were stable and robust under different case definitions and exposure assumptions. The retrospective nature of the case-control design may be subject to recall bias, but we tried to minimize such bias by enrolling only recently diagnosed cases and relying on information documented in the medical records to the fullest extent possible. We did accept self-reported information on vaccines that were received outside of the HMO. Our comparisons of self-reports of vaccinations received in the HMO against HMO records indicated reasonably good agreement. Furthermore, when we restricted the analyses to vaccinations documented in the HMO records, the results were the same as the analyses in which we included self-reported vaccinations.

Another potential limitation of our study was the lower participation rate by controls compared with cases. Given that most of the ORs were less than 1.0, we have to consider the possibility that the controls who participated may have been more likely to have been vaccinated than the general population of HMO members. This concern would probably be greatest for tetanus toxoid, where we found significantly decreased risks of demyelinating diseases. We compared the self-reported tetanus vaccination histories of the controls in our study against similar self-reported vaccination data from a sample of US adults in the 1995 National Health Interview Survey.[48] In the National Health Interview Survey, 65% of adults 18 to 49 years of age reported having received tetanus toxoid vaccine in the previous 10 years. Among the similar-aged controls in our study, 48% reported having received tetanus toxoid vaccine in the 10 years before the study. Thus, it does not seem that controls who participated in our study were more likely to be vaccinated than the general population.

In conclusion, our study adds to the weight of epidemiologic evidence that hepatitis B vaccine is not causally associated with MS. Our results also indicate that previous case reports of onset of demyelinating diseases shortly after receipt of several other vaccines probably represent coincidental temporal associations and not true causal associations.

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