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# Recombinant hepatitis B vaccine and the risk of multiple sclerosis

## A prospective study

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**Abstract—Background:** A potential link between the recombinant hepatitis B vaccine and an increased risk of multiple sclerosis (MS) has been evaluated in several studies, but some of them have substantial methodologic limitations. **Methods:** The authors conducted a nested case-control study within the General Practice Research Database (GPRD) in the United Kingdom. The authors identified patients who had a first MS diagnosis recorded in the GPRD between January 1993 and December 2000. Cases were patients with a diagnosis of MS confirmed through examination of medical records, and with at least 3 years of continuous recording in the GPRD before their date of first symptoms (index date). Up to 10 controls per case were randomly selected, matched on age, sex, practice, and date of joining the practice. Information on receipt of immunizations was obtained from the computer records. **Results:** The analyses include 163 cases of MS and 1,604 controls. The OR of MS for vaccination within 3 years before the index date compared to no vaccination was 3.1 (95% CI 1.5, 6.3). No increased risk of MS was associated with tetanus and influenza vaccinations. **Conclusions:** These findings are consistent with the hypothesis that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS, and challenge the idea that the relation between hepatitis B vaccination and risk of MS is well understood.

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More than 350 million people worldwide are chronically infected with the hepatitis B virus. Of these, 65 million will die from cirrhosis or liver cancer.<sup>1</sup> The hepatitis B vaccine is over 95% effective in preventing chronic hepatitis B infection, and it is the first vaccine against a major human cancer.<sup>1</sup> It has also been considered one of the safest vaccines ever produced.<sup>2,3</sup> The World Health Organization recommends that hepatitis B vaccine be integrated into national immunization programs, and over 140 countries have done so.

In 1996, about 200 cases of CNS demyelinating disorders following hepatitis B vaccination were reported to the French pharmacovigilance system,<sup>4</sup> and two years later the French government suspended routine immunization of preadolescents in schools.<sup>2</sup>

The potential link between vaccination against hepatitis B and an increased risk of multiple sclerosis (MS) or demyelinating disease has since been evaluated in several studies.<sup>5–11</sup> Most studies were consistent with a null association between the vaccine and MS, but some of them had methodologic limitations that include retrospective ascertainment of vaccination status, use of date of diagnosis or an

imprecise date of first symptoms of MS, and small sample size. We adopted a nested case-control approach to evaluate the association between recombinant hepatitis B vaccination and risk of MS in a prospectively followed British population.

**Methods. Study population.** The General Practice Research Database (GPRD) includes over 3 million Britons who are enrolled with selected general practitioners (GPs).<sup>12</sup> These physicians have been trained to record their patients' medical and demographic information in a standard manner, and have agreed to supply it anonymously for research purposes. In addition, practices used in this study agree to collaborate in specific research projects by providing photocopies of their patients' paper medical records after personal identifiers have been removed. The information recorded in the GPRD includes drug prescriptions, which are computer-generated by the physicians (using the VAMP software) and automatically transcribed into the computer record (according to a coded drug dictionary based on the United Kingdom Prescription Pricing Authority), vaccines, medical diagnoses, which are entered using a classification compatible with the International Classification of Diseases (ICD), and demographic information. The information on drug exposure, vaccinations, and diagnoses recorded in the GPRD has been found to be of satisfactory quality for drug safety studies.<sup>13,14</sup>

**Case ascertainment.** Case ascertainment was conducted in two stages. In the first stage, we selected individuals of all ages with a first diagnosis of MS (ICD code 340.0) recorded in the database between January 1, 1993, and December 31, 2000. We

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then reviewed each computer record to assign a date of first symptoms to each individual. In the second stage, we contacted the GPs of these potential MS patients and requested photocopies of all MS-related paper records available in the GP's office, including all consultations, specialist referrals, test results, and hospital discharges. Paper records cover a longer period, often from birth or childhood, than computer records. Two physician investigators (M.A.H., M.J.O.) reviewed the paper medical records independently and blinded to the computerized exposure information, filled out a questionnaire including information on symptoms and diagnostic procedures, and classified the patients into MS, possible MS, or no MS diagnosis according to standardized research criteria.<sup>15,16</sup> To determine the onset of symptoms of MS we used the symptoms and criteria proposed by Poser.<sup>17</sup> Discrepancies were discussed until a consensus was reached. Our review of medical records confirmed 438 (61.4%) of the 713 first-stage cases as cases of MS with a first diagnosis on or after January 1, 1993. The remaining 275 subjects were not confirmed because 1) they had a diagnosis of possible MS (59) or prevalent MS (83 cases diagnosed before January 1, 1993) or 2) they did not have MS (52), or medical records could not be obtained because the patient had transferred out to another practice (71) or died (10). Ninety-eight percent of the confirmed cases had been seen and diagnosed by a neurologist in the United Kingdom, and 85% of the diagnoses were supported by a positive result on MRI. The date of first symptoms retrieved from the computer records was, on average, 24 months later than the date of first symptoms retrieved from the paper records. The earliest date of first symptoms was assigned to each case.

Of the 438 MS cases, 282 had their first symptoms after their first computer recorded medical information, and 163 had their first symptoms at least 3 years after their first computer recorded medical information.

**Study design.** We carried out a case-control study nested within the GPRD cohort. Cases were patients in the GPRD with a confirmed diagnosis of MS between January 1, 1993, and December 31, 2000, and with at least 3 years of continuous recording in the database before their date of first MS symptoms. Up to 10 controls per case were randomly selected, matched on age ( $\pm 1$  year), sex, practice, and date of joining the practice ( $\pm 1$  year). Controls had to be alive, be free of an MS diagnosis, be present in the database at the index date, and have at least 3 years of continuous recording in the database before the date of first symptoms of their corresponding case (the index date).

Because some previous studies used date of diagnosis of MS (as opposed to date of first symptoms of MS), for comparison purposes we conducted a second nested case-control study in which up to 10 controls per case were randomly selected as described in the previous paragraph, using the date of diagnosis as the index date.

**Vaccinations assessment.** Exposure to hepatitis B vaccine was determined from the computerized medical records. Subjects were classified as never or ever vaccinated during the 3 years before the index date. We also classified them by the time they received their last immunization (never, >0 to 1, >1 to 2, >2 to 3 years before index date) and by the number of immunizations received (0, 1 to 2, 3 or more) during the 3 years before the index date. We also extracted information on vaccination against tetanus and influenza, the two most common vaccinations in this population.

**Statistical methods.** We used conditional logistic regression to estimate OR and their 95% CI, adjusted for the matching factors. Under our design, the OR is a consistent estimator of the incidence rate ratio of MS in vaccinated vs unvaccinated subjects. Statements about statistical significance refer to the conventional (and arbitrary) 0.05 cutoff.

**Human subjects.** This research was approved by the Human Subjects Committee of the Harvard School of Public Health, and by the Scientific and Ethical Advisory Group of the GPRD.

**Results.** Our analyses included 163 MS cases and 1,604 matched controls (table 1). All vaccinated cases were over 18 years of age at first symptoms. One unvaccinated case was 16 years of age at first symptoms.

The proportion of cases that received at least one hepatitis B immunization during the 3 years before the date of first symptoms was 6.7%, compared with 2.4% of controls (table 2). The OR of MS for vaccination vs no vaccination

**Table 1** Characteristics of cases and controls

	MS cases	Controls
Women, %	68.7	69.5
Age, y		
Mean (SD)	36.2 (9.5)	36.3 (9.5)
<30, %	31.3	30.8
30–39, %	33.7	34.1
40–49, %	25.8	25.4
50 or more, %	9.2	9.7
Ever smokers, %	44.4	39.8
Mean (median) no. of health encounters before index date	26.2 (19)	26.5 (20)
Mean (median) no. of health encounters after index date	42.7 (35)	24.2 (17)
Course of the disease, %		
Relapsing-remitting	79.8	
Primary progressive	9.2	
Secondary progressive	11.0	
First symptoms,* %		
Optic neuritis/diplopia	25.8	
Sensory symptoms	49.1	
Motor deficit/weakness	17.2	
Ataxia/dysarthria/limb incoordination	20.2	

\* Total does not add to 100% because some subjects had more than one symptom at onset.

MS = multiple sclerosis.

was 3.1 (95% CI 1.5, 6.3). No increase in the risk of MS was observed for vaccination against influenza and tetanus (see table 2).

These results did not materially change after adjustment for smoking, and did not vary significantly by sex, age (<40, 40 or more years), calendar time (1988 to 1994, 1995 to 2000), clinical course of the disease (relapsing-remitting or progressive), and type of first symptoms (eye symptoms, sensory symptoms, other). The OR (95% CI) of MS for vaccination vs no vaccination was 2.4 (1.2, 4.8)

**Table 2** Association between vaccinations and risk of MS

Immunizations within 3 y before index date	MS cases (%)	Controls (%)	OR (95% CI)
<b>Hepatitis B (recombinant)</b>			
No	152 (93.3)	1565 (97.6)	1.0 (ref.)
Yes	11 (6.7)	39 (2.4)	3.1 (1.5, 6.3)
<b>Influenza</b>			
No	153 (93.9)	1508 (94.0)	1.0 (ref.)
Yes	10 (6.1)	153 (6.0)	1.0 (0.5, 2.0)
<b>Tetanus</b>			
No	144 (88.3)	1325 (82.6)	1.0 (ref.)
Yes	19 (11.7)	279 (17.4)	0.6 (0.4, 1.0)

MS = multiple sclerosis.

**Table 3** Timing and number of hepatitis B vaccinations in relation to the risk of MS

Hepatitis B vaccination within 3 y before index date	MS cases (%)	Controls (%)	OR (95% CI)
Unvaccinated	152 (93.3)	1,565 (97.6)	1.0 (ref.)
Years since last vaccination before index date			
>0–1	3 (1.8)	17 (1.0)	1.8 (0.5, 6.3)
>1–2	4 (2.5)	11 (0.7)	4.1 (1.3, 13.6)
>2–3	4 (2.5)	11 (0.7)	4.4 (1.3, 14.5)
No. of immunizations before index date			
1–2	5 (3.1)	19 (1.2)	2.8 (1.0, 7.8)
≥3	6 (3.7)	20 (1.2)	3.3 (1.3, 8.5)

MS = multiple sclerosis.

when the analysis included possible MS cases (188 cases and 1,838 controls), and 2.6 (1.2, 5.4) when the analysis was restricted to subjects without known indications for hepatitis B vaccination, i.e., occupational risk of hepatitis B infection, or history of alcoholism, drug abuse, or chronic renal failure/dialysis (159 cases and 1,576 controls).

The risk was greater, although not significantly, when the last immunization took place within the second or third years before first symptoms compared with the first year before first symptoms (table 3). Greater number of immunizations was not clearly associated with a greater risk. The age at the index date was similar by case-control and vaccination status. Specifically, the mean (SD) of age was 37.0 (10.0) years for vaccinated cases and 36.1 (9.7) years for unvaccinated cases ( $p$  value = 0.76). The mean (SD) of age was 34.9 (9.5) for vaccinated controls and 36.4 (9.7) for unvaccinated controls ( $p$  value = 0.35).

The proportion of cases that received hepatitis B immunization after the index date was 1.2% compared with 2.3% of controls. The OR of MS for vaccination vs no vaccination after first symptoms was 0.5 (95% CI: 0.1, 2.1). When we used the cases' date of diagnosis as the index date, the OR of MS for vaccination vs no vaccination within the 3 years before the matching date was 1.0 (95% CI: 0.5, 2.1). The mean (median) time between first symptoms and diagnosis was 5.0 (2.7) years.

**Discussion.** We estimated that immunization against hepatitis B was associated with a threefold increase in the incidence of MS within the 3 years following vaccination. Other common immunizations were not associated with an increased risk of MS.

Our study cannot distinguish whether the hepatitis B vaccine hastens the onset of MS in persons destined to develop the disease years later, or whether it causes new cases of MS in susceptible individuals. However, the similar age at first symptoms between vaccinated and unvaccinated cases does not support the former explanation.

Elucidating the reasons for the association be-

tween hepatitis B vaccine and MS may eventually contribute to a better understanding of the etiology of MS, but any decision concerning hepatitis B vaccination needs to take into account the large benefits derived from the prevention of a common and potentially lethal infection. It is also important to stress that 93% of the MS cases in our study had not been vaccinated.

The use of a nested case-control study minimized the bias due to inappropriate selection of controls, and the use of prospectively recorded computerized vaccination records prevented recall bias. Other types of differential misclassification of vaccination history are also unlikely because exposure information was gathered prospectively before the first symptoms of the disease. A certain degree of non-differential (random) misclassification of vaccination history is possible (e.g., a small proportion of persons might have been vaccinated without their GP's knowledge), but its practical consequence would be an attenuation of the association between vaccination and MS. As always in observational research, confounding is a theoretical explanation for the association. Our analyses are therefore matched on and adjusted for various known or suspected risk factors for MS.

The use of computerized medical records is an efficient strategy to identify individuals with a diagnosis of MS. However, our approach was to combine the use of computerized medical records to identify individuals with a diagnosis of MS with the retrieval and review of paper medical records to determine their date of first symptoms, since we found that the computer records did not provide sufficient information to determine the subjects' clinical history, including date of first MS symptoms. An accurate determination of the date of first symptoms is important because, as we observed, the probability of hepatitis B vaccination decreases after clinical onset of MS. Thus, the use of dates that are posterior to the true date of first symptoms may cause a downward bias of the OR for acute exposures such as vaccinations.

Several case-control studies have evaluated the association between hepatitis B vaccination and risk of MS or demyelination (table 4). Two French studies found about a 1.5-fold increase in the risk of a first episode of CNS demyelination during the 2 months following hepatitis B vaccination.<sup>5,6</sup> In both studies, the date of first symptoms was ascertained by review of medical records, and dates of vaccination were obtained retrospectively by questionnaire and phone interview of the participants. Concurrently with the first reporting of results from the French studies, a preliminary assessment of the association between hepatitis B vaccination and MS in the GPRD found a 1.6-fold increase (95% CI 0.6, 4.0) in the risk of MS or demyelination during the 12 months following hepatitis B vaccination.<sup>7</sup> MS diagnoses and dates of first symptoms were ascertained by review of computerized records only. More recently, a case-control study in three North American health maintenance



**Table 4** Previous case-control studies on hepatitis B vaccine and risk of onset of CNS demyelinating disorders

Reference no. of study	Determination of index date	Outcome	Period before index date	OR (95% CI)
5	Medical records	Demyelination	>0–2 mo	1.7 (0.5, 6.3)
			>2–6 mo	1.5 (0.5, 5.3)
6	Medical records	Demyelination	>0–2 mo	1.4 (0.4, 4.5)
			>2–12 mo	1.0 (0.6, 1.9)
			MS	1.6 (0.4, 5.6)
7*	Computerized medical records	MS or demyelination	1 y	1.6 (0.6, 4.0)
9	Questionnaire	MS	>0–2 y	0.6 (0.2, 1.5)
			Ever	0.7 (0.4, 1.3)
8	Medical records/phone interview	Demyelination	<1 y	0.8 (0.4, 1.8)
			1–5 y	1.6 (0.8, 3.0)
			>5 y	0.6 (0.2, 1.4)

\* Some cases of our General Practice Research Database (GPRD) study may have been included here.

MS = multiple sclerosis.

organizations (HMOs) found a nonsignificant increase in the risk of MS or optic neuritis 1 to 5 years after vaccination against hepatitis B, and no increase before 1 year or after 5 years.<sup>8</sup> The date of first symptoms was retrieved from medical records and telephone interviews, and vaccination histories included both vaccinations recorded in HMO records and those reported in telephone interviews.

A case-control study nested in the Nurses' Health Studies did not find an increased risk of MS associated with hepatitis B vaccination in women.<sup>9</sup> The vaccination status was obtained retrospectively and the analysis included only women who self-reported never having been vaccinated in a questionnaire, and those who self-reported having been vaccinated and for whom vaccination certificates were available. This design may cause selection bias leading to a downwardly biased OR.<sup>18–20</sup> Perhaps more important, the date of first symptoms of the disease was retrospectively assessed by questionnaires sent to each case and the current treating neurologist or internist.

Two other studies did not find an increased risk of MS after immunization against hepatitis B. A study conducted in a database consisting of integrated pharmacy and medical claims from six HMOs in the United States found no difference in the 3-year risk of diagnosis of demyelinating diseases between subjects vaccinated and non-vaccinated for hepatitis B.<sup>10</sup> This null finding is consistent with our null finding in the GPRD when we used date of diagnosis, rather than date of first symptoms, of MS to define the period of risk. An ecologic study compared the number of adolescents who developed MS before (1986 to 1992) and after (1992 to 1998) a school-based hepatitis B vaccination program was implemented in British Columbia, Canada.<sup>11</sup> Nine out of 288,657 unvaccinated teenagers and 5 out of 289,651 vaccinated teenagers had first symptoms of MS, but the

unvaccinated had up to 13 years of follow-up, while the vaccinated had only up to 7 years of follow-up and therefore less opportunity to be diagnosed with MS.

The recombinant hepatitis B vaccine is a non-infectious viral vaccine derived from hepatitis B surface antigen (HBsAg) produced in genetically engineered yeast (*Saccharomyces cerevisiae*) cells. Although several viruses (e.g., Epstein-Barr virus) have been postulated to cause MS, the hepatitis B virus has not been prominent in the discussions of viral triggers of MS.<sup>21</sup> It is therefore unclear how a recombinant vaccine that contains purified HbsAg, a portion of the hepatitis B virus, could trigger the immunologic processes that lead to MS. The vaccine also contains an adjuvant (aluminum hydroxyphosphate sulfate), a mercury-based preservative (thimerosal, eliminated from recent formulations), and yeast proteins (up to 5%), but these components have not been separately studied in relation to the risk of MS.

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