Recombinant hepatitis B vaccine and the risk of multiple sclerosis
A prospective study

Miguel A. Hernán, MD, DrPH; Susan S. Jick, DSc; Michael J. Olek, DO; and Hershel Jick, MD

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 vaccinations 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 5 years before the index date compared to no vaccination was 1.1 (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 vaccination 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. 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. It has also been considered one of the safest vaccines ever produced. 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, and two years later the French government suspended routine immunization of preadolescents in schools.

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. 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). 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 photocopied 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 Prescribing 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.

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 GPs' office, including all consultations, specialists referrals, test results, and hospital discharge. 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 blindly 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. To determine the onset of symptoms of MS we used the symptoms and criteria proposed by Poser. Disagreements were discussed until a consensus was reached. Our review of medical records confirmed 438 (61.4%) of the 715 first-stage cases as cases of MS with a first diagnosis on or after January 1, 1983. The remaining 277 cases confirmed because 1) they had a diagnosis of possible MS (56) or prevalent MS (26) (cases diagnosed before January 1, 1983) or 2) they did not have MS (52), or medical records could not be obtained because the patient had moved 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, 283 had their first symptoms after their first computer recorded medical information, and 155 had their first symptoms at least 8 years after their first computer recorded medical information.

Study design. We carried out a case-control study nested within the GPRD cohort. Case were patients in the GPRD with a confirmed diagnosis of MS between January 1, 1983, and December 31, 2000, and with at least 3 years of continuous recording in the database before their date of first symptoms. Up to 10 controls were selected, matched on age (±3 years), sex, practice, and date of joining the practice (±1 year). Controls had to be alive, to free of an MS diagnosis, present in the database at the index date, and have at least 8 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, 3 or more) during the 3 years before the 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 constant 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 15 years of age at first symptoms. One unvaccinated case was 15 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 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, 4.5).

### Table 1 Characteristics of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>MS cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>66.7</td>
<td>69.5</td>
</tr>
<tr>
<td>Age, y</td>
<td>36.2 (9.5)</td>
<td>36.3 (9.5)</td>
</tr>
<tr>
<td>&lt;20%,</td>
<td>31.3</td>
<td>30.8</td>
</tr>
<tr>
<td>30-39, %</td>
<td>33.7</td>
<td>34.1</td>
</tr>
<tr>
<td>40-49, %</td>
<td>25.8</td>
<td>25.4</td>
</tr>
<tr>
<td>50 or more, %</td>
<td>9.2</td>
<td>9.7</td>
</tr>
<tr>
<td>Ever smokers, %</td>
<td>44.4</td>
<td>39.8</td>
</tr>
<tr>
<td>Mean (median) no. of health encounters before index date</td>
<td>26.2 (19)</td>
<td>26.5 (20)</td>
</tr>
<tr>
<td>Mean (median) no. of health encounters after index date</td>
<td>42.7 (35)</td>
<td>42.1 (17)</td>
</tr>
<tr>
<td>Course of the disease, %</td>
<td>79.8</td>
<td>79.8</td>
</tr>
<tr>
<td>Relapsing-remitting</td>
<td>9.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>20.8</td>
<td>20.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>MS cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 y before index date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (recombinant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>152 (83.4)</td>
<td>1565 (79.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (6.7)</td>
<td>39 (2.4)</td>
</tr>
<tr>
<td>(OR 35 CI)</td>
<td>3.1 (1.5, 6.3)</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>153 (83.9)</td>
<td>1508 (94.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (6.1)</td>
<td>135 (5.4)</td>
</tr>
<tr>
<td>(OR 35 CI)</td>
<td>1.0 (0.5, 2.0)</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>144 (88.3)</td>
<td>1235 (62.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (11.7)</td>
<td>715 (37.4)</td>
</tr>
<tr>
<td>(OR 35 CI)</td>
<td>0.6 (0.4, 1.0)</td>
<td></td>
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</tbody>
</table>

MS = multiple sclerosis.
when the analysis included possible MS cases (185 cases and 1,835 controls), and 2.6 (1.2, 3.4) 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 (153 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 (3.7) 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-
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. 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. 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. 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. 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. Nine out of 288.557 unvaccinated teenagers and 5 out of 289.051 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 lost 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. 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 hydroxypophosphate 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.

Acknowledgment

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References


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VIDEO ALERT

This issue of Neurology has an online-only NeuroImage with a video:

- Syncope during EEG recording
  B. Schaefer, P. smear, P. Fuhr, and D. Leppert

Access www.neurology.org and search for the NeuroImage. Click on Video to view.
Does the hepatitis B vaccine cause multiple sclerosis?

Robert T. Naismith, MD; and Anne H. Cross, MD

The road to universal immunization against hepatitis B has been bumpy. The hepatitis B vaccine (HBV) has been anecdotally linked to multiple sclerosis (MS), systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, leukemia, and chronic fatigue syndrome. The possibility that the vaccine could induce MS prompted temporary halting of the universal HBV program in France in 1998 based on surveillance reports. In 2000, a French court awarded damages to three people with MS who had received the HBV, in a decision that was later highly criticized. Subsequently, numerous studies, commissions, and hearings have not corroborated the association. The report by Hernán et al. in this issue of Neurology has potential to reopen the debate.

The Hernán paper used the General Practice Research Database (GPRD) of the United Kingdom to ascertain 163 cases of confirmed MS, and performed a case-controlled analysis for the association of first MS symptoms with HBV. The authors identified 11 people who developed first symptoms of MS within 3 years of the vaccine, producing an odds ratio of 3.1 (95% confidence range 1.5 to 6.3) compared to matched controls. The current report is significant because the methods used were sound, and extensive measures were taken to confirm the diagnosis and reduce potential biases. Though it is hard to argue with the results, the question remains as to whether these 11 cases of MS can be generalized to the population at large.

The GPRD tracks many aspects of healthcare utilization, treatments, and adverse events in the U.K. It is an important epidemiologic tool specifically designed to uncover adverse reactions to treatments that might not be otherwise appreciated. The GPRD comprises 5% of the U.K. population, or 3 million Britons, and covers 35 million patient-years of data starting from 1997. It has been utilized in over 300 studies and has been subject to validation studies for various diagnoses. Data are entered by the general practitioner, the gatekeeper in the universal, government-sponsored U.K. healthcare system. Participating practitioners must undergo training before entering data, are compensated for each entry, and their entries are audited and can be voided if inconsistent.

In the present study, 163 cases of MS were culled from an original 713 cases with the diagnosis of MS recorded in the GPRD over an 8-year period. The 713 cases were initially pared to 438 after independent review of paper records established a definitive diagnosis. Seventy-one cases of MS were excluded because they transferred to another practice; 10 were excluded due to death. Patients for study were further limited to only those 163 patients who had their first symptoms at least 3 years after the first recorded database information was obtained. This led to the actual hazard data being derived from only 11 cases of MS. One must consider whether this selection process, which was deemed necessary to properly perform the study, might have led to some unrecognized bias.

The practice of vaccination against Hepatitis B in the U.K. at the time of this study was targeted toward high-risk individuals. These included healthcare and laboratory workers, travelers to endemic regions, those with liver disease, dialysis patients, prostitutes, and drug addicts. This might have biased the results. For example, healthcare workers, perhaps more cognizant of neurologic symptoms, might bring those to the attention of their physician earlier than people in other professions. Or perhaps this vaccinated high-risk cohort shares some other risk or exposure.

Of note, this study was not designed to evaluate whether HBV caused MS relapses or worsened disease in those already diagnosed. No data are presented to change the current Level C recommendation from the Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines, which was approved by the AAN. This committee determined that the HBV had not been found to be detrimental in those with established
MS, and recommended that patients follow the Centers for Disease Control immunization guidelines. It is curious to note that no associations of hepatitis B infection with MS onset or worsening have been reported. Thus, if the HBV is truly associated with MS onset, perhaps something about the vaccination itself, such as the adjuvants used, is the relevant factor. No associations of MS onset were observed with other vaccinations (influenza, tetanus) in the present study and others.

The present study stands in contrast to multiple studies and expert panels that have concluded that there is no link between HBV and MS. Although there may be methodological flaws or biases in some of the other studies, we must interpret the Hernán study in the context of these many negative studies. The authors of this study highlight the fact that 93.8% of those in the GPRD with MS had never received the HBV. Thus, this article should be viewed as another piece of the puzzle of MS causation, but the data presented do not provide proof of an association sufficient to implement policy changes with regard to immunization programs. The indisputable benefit that the HBV provides against an infection that kills 5,000 per year in the United States must be weighed against any uncommon risks that remain in dispute.

References