HEPATITIS B VACCINATION AND THE RISK OF MULTIPLE SCLEROSIS

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ABSTRACT

Background Reports of multiple sclerosis developing after hepatitis B vaccination have led to the concern that this vaccine might be a cause of multiple sclerosis in previously healthy subjects.

Methods We conducted a nested case–control study in two large cohorts of nurses in the United States, those in the Nurses' Health Study (which has followed 121,700 women since 1976) and those in the Nurses' Health Study II (which has followed 116,671 women since 1989). For each woman with multiple sclerosis, we selected as controls five healthy women and one woman with breast cancer. Information about hepatitis B vaccination was obtained by means of a mailed questionnaire and was confirmed by means of vaccination certificates. The analyses included 192 women with multiple sclerosis and 645 matched controls (534 healthy controls and 111 with breast cancer) and were conducted with the use of conditional logistic regression.

Results The multivariate relative risk of multiple sclerosis associated with exposure to the hepatitis B vaccine at any time before the onset of the disease was 0.9 (95 percent confidence interval, 0.5 to 1.6). The relative risk associated with hepatitis B vaccination within two years before the onset of the disease was 0.7 (95 percent confidence interval, 0.3 to 1.8). The results were similar in analyses restricted to women with multiple sclerosis that began after the introduction of the recombinant hepatitis B vaccine. There was also no association between the number of doses of vaccine received and the risk of multiple sclerosis.

Conclusions These results indicate no association between hepatitis B vaccination and the development of multiple sclerosis. (N Engl J Med 2001;344:327-32.)

ACCORDING to the World Health Organization, more than 2 billion people in the world have serologic markers of hepatitis B infection, including 350 million chronic carriers of the virus,[1] of whom about 65 million will die from liver disease caused by the infection.[1] A vaccine against hepatitis B became available in 1982, and more than 1 billion doses have been administered, with documented reductions in the rate of childhood liver cancer.[1] This vaccine, considered one of the least reactogenic, has an excellent safety profile[2-4] and is part of routine immunization programs in many countries. Nevertheless, several cases of multiple sclerosis that developed within a few weeks after the administration of the vaccine were reported between 1995 and 1997, after a mass immunization campaign in France.[5,6] In October 1998, the French government decided to suspend temporarily the school-based hepatitis B vaccination program.[7] This decision was based in part on the preliminary results of one case–control study conducted in France[5] and one conducted in the United Kingdom,[8] both of which reported a nonsignificant increase in the risk of multiple sclerosis among vaccinated as compared with unvaccinated subjects.[7]

We report here the results of a case–control study whose subjects were drawn from two large cohorts of nurses in the United States. The purpose of the study was to determine whether hepatitis B vaccination increases the risk of multiple sclerosis. The strengths of the study include the high prevalence among nurses of immunization with the hepatitis B vaccine and the availability of confirmation in the form of vaccination records that are usually kept by the nurses' employers for insurance purposes.

METHODS

Study Population

The study population for this investigation comprised participants in the large cohorts involved in two ongoing studies — the Nurses' Health Study and the Nurses' Health Study II. The Nurses' Health Study began in 1976, when 121,700 female registered nurses from 11 states, between 30 and 55 years old, responded to a mailed questionnaire about their history of diseases and their lifestyles. The Nurses' Health Study II began in 1989, when 116,671 female registered nurses from 14 states, between 25 and 42 years old, responded to a similar questionnaire. Follow-up questionnaires are mailed to the participants in both studies every two years. A specific question on the lifetime occurrence of multiple sclerosis was first included in the 1992 questionnaire for the Nurses' Health Study and in the 1991 questionnaire for the Nurses' Health Study II. It asked, "Have you ever had a diagnosis of multiple sclerosis made by a physician?" A question about the diagnosis of multiple sclerosis within the previous two years was included in subsequent questionnaires. In the Nurses' Health Study, most cases of multiple sclerosis diagnosed before 1992 had already been reported through an open-ended question about "other major illnesses." Women who had received a diagnosis of multiple sclerosis before enrollment in the cohort (i.e., base line) were excluded from our study.

Ascertainment of Cases and Selection of Controls

Details of the follow-up of patients with multiple sclerosis in these cohorts have been reported previously.[9] Briefly, we wrote

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to the women who reported a new diagnosis of multiple sclerosis to obtain permission to contact their neurologists and review their medical records. After obtaining permission, we sent the neurologists a questionnaire regarding the certainty of the diagnosis (definite, probable, or possible multiple sclerosis or not multiple sclerosis), the date of onset of neurologic symptoms related to multiple sclerosis, other aspects of the clinical history, and results of relevant laboratory tests. If a neurologist had not been involved in the case or did not respond to the questionnaire, we mailed the questionnaire to the woman's internist. We confirmed the diagnoses made by these physicians by applying the criteria established by Poser et al. for the diagnosis of multiple sclerosis to the clinical and laboratory data provided in each questionnaire.[10] Since 93 percent of all definite and probable diagnoses were confirmed by the application of these criteria, we classified women who had a diagnosis of definite or probable multiple sclerosis according to their physicians as having the disease. The date of onset of the disease was determined by asking both the women and their physicians for the date of the first neurologic symptoms. The earlier of the two dates was used in the analyses. Women with multiple sclerosis that began during the follow-up period but remained undiagnosed by April 1998 would not have been included in our analyses as women with multiple sclerosis. However, this exclusion is likely to be independent of the history of vaccination and is therefore unlikely to have biased the results of our study. The age-specific incidence of multiple sclerosis in these cohorts has been reported previously[9]; on the basis of those rates, we estimated the lifetime risk of multiple sclerosis as 4.9 per 1000 — a risk similar to that reported in other prospective investigations.[9]

A total of 318 newly diagnosed cases of definite or probable multiple sclerosis were documented between the base-line questionnaire and April 1998 and were included in the study. For each woman with multiple sclerosis, we randomly selected as controls five women with no history of multiple sclerosis or breast cancer (healthy controls) and one woman with breast cancer, who were matched to the woman with multiple sclerosis according to year of birth, study cohort, and (for the controls with breast cancer) date of diagnosis. Women with breast cancer were included as controls so as to address the potential bias that may derive from differential recall among women with a serious disease. Two of the 1590 randomly selected healthy controls and 1 of the 318 controls with breast cancer were deemed ineligible because of self-reported but unconfirmed multiple sclerosis and were excluded from further consideration.

Assessment and Confirmation of Exposure to Hepatitis B Vaccine

History of immunization with the hepatitis B vaccine was initially assessed by means of a questionnaire. Women who reported that they had never been vaccinated against hepatitis B were considered unvaccinated. Women who reported having received the vaccine at any time in the past were asked for permission to obtain their vaccination records from their employers. The initial questionnaire included questions regarding childhood infections and vaccinations for measles and tetanus. The cover letter that was sent with the questionnaire did not make specific reference to the hepatitis B vaccine, since it was only one of several types of exposure addressed by the study. The questionnaire was returned by 301 of the 318 women with multiple sclerosis (95 percent), 1393 of the 1588 healthy controls (88 percent), and 280 of the 317 controls with breast cancer (88 percent). Among the respondents, all 301 women with multiple sclerosis had at least 1 matched healthy control (a total of 1317 matched healthy controls), and 263 had a matched control with breast cancer.

According to their own reports, 51.8 percent of the women with multiple sclerosis, 66.5 percent of the healthy controls, and 64.6 percent of the controls with breast cancer had been vaccinated against hepatitis B at some time in the past. After obtaining permission, we contacted the employers of these women to obtain a copy of their vaccination records. We sent up to three mailings and telephoned the nonrespondents. Vaccination records were obtained for 62 percent of the women with multiple sclerosis, 64 percent of the healthy controls, and 64 percent of the controls with breast cancer. The records obtained confirmed that the hepatitis B vaccine had been administered in more than 94 percent of the women with multiple sclerosis and the controls. However, the self-reported dates of vaccination were often inaccurate. For this reason, we excluded from the primary analyses women who reported having been vaccinated but for whom we could not obtain vaccination certificates. Those excluded for this reason included 106 of the 301 women with multiple sclerosis (35.2 percent), 466 of the 1317 healthy controls (35.4 percent), and 96 of the 263 controls with breast cancer (36.5 percent). Among the women with multiple sclerosis excluded were 94 of the 263 with a matched control with breast cancer (35.7 percent). As a last step, we excluded those who remained unmatched (5 women with multiple sclerosis and 317 controls for analyses using healthy women as controls; and 58 women with multiple sclerosis and 56 controls for analyses using women with breast cancer as controls). Thus, the final study population included 192 women with multiple sclerosis; 190 of these women were matched to 534 healthy controls, and 111 were matched to an equal number of controls with breast cancer. The diagnosis of multiple sclerosis was made by a neurologist in 93 percent of the 192 women with multiple sclerosis included in the analyses, and the diagnosis was supported by a positive result on magnetic resonance imaging in 86 percent. These proportions increased to 96 percent and 97 percent, respectively, for women with an onset of multiple sclerosis after 1987 (when a recombinant hepatitis B vaccine was introduced).

Covariates

Other data obtained from the women included age, latitude of birthplace, ancestry (Scandinavian, southern European, other white, or nonwhite), pack-years of smoking (none, <10, 10 to 24, or ≥ 25), and (for the Nurses' Health Study II only) type of nursing job (inpatient, outpatient, emergency room, nursing education, or other). The associations of birthplace latitude, ancestry, and smoking history with the risk of multiple sclerosis in these cohorts have been previously reported.[9,11] The type of job was included because of its potential relation to both hepatitis B vaccination and the risk of multiple sclerosis.

Statistical Analysis

The women with multiple sclerosis were classified as having been exposed or not exposed to the hepatitis B vaccine according to their vaccination status at the time of the onset of multiple sclerosis. For the controls, we used the time of the onset of multiple sclerosis in the woman with whom the control was matched. For both women with multiple sclerosis and controls, we refer to this date as the index date. Two categories of exposure were used in the main analyses: receipt of at least one dose of hepatitis B vaccine at any time before the index date, and receipt of the first dose of the vaccine within two years before the index date. All the analyses were conducted through comparisons of the women who had multiple sclerosis with their matched controls, unless otherwise indicated. The relative risk of multiple sclerosis for women who had been vaccinated against hepatitis B as compared with those who had not been vaccinated was estimated with the use of conditional logistic regression. We used a period of two years in categorizing exposure because analyses based on shorter periods of exposure would have been more sensitive to errors in the estimation of the date of the onset of multiple sclerosis. To assess the presence and magnitude of recall bias, we conducted further analyses using the self-reported dates of vaccination.

RESULTS

A summary of selected characteristics of the women with multiple sclerosis and the controls is presented in Table 1. The type of occupation at base line was available only for women in the Nurses' Health Study

II. The main analyses of the association between hepatitis B vaccination and the risk of multiple sclerosis are presented in Table 2. The age-adjusted relative risk of multiple sclerosis for vaccinated women as compared with unvaccinated women was 0.9 (95 percent confidence interval, 0.5 to 1.6) according to the analyses using healthy controls, and 1.2 (95 percent confidence interval, 0.5 to 2.9) according to the analyses using controls with breast cancer. The corresponding relative risks for women vaccinated within two years before the index date were 0.7 (95 percent confidence interval, 0.3 to 1.7) and 1.0 (95 percent confidence interval, 0.3 to 4.2). Adjustment for latitude of residence at birth, pack-years of smoking, and other covariates did not materially change these relative risks.

Because a recombinant vaccine against hepatitis B was introduced in 1987, we repeated the analyses excluding women with an onset of multiple sclerosis before 1987. The new analyses included data on 28 women with multiple sclerosis who had a documented history of vaccination before the onset of the disease. In eight of these women, the first dose was administered within two years before the onset of the disease. The corresponding relative risks ranged from 0.6 to 0.8 (Table 3). Similar results were obtained from an analysis that used information from the vaccination certificates regarding the type of vaccine administered.

For older women who might have retired several years before our study began, a report of no history of hepatitis B vaccination could be unreliable; we therefore conducted further analyses including only participants in the Nurses' Health Study II. Women in this cohort are younger, are more likely to have received hepatitis B vaccine, and were professionally active in 1989, when they were recruited into the study. Again, no significant associations were found between hepatitis B vaccination and the risk of multiple sclerosis.

When the controls were pooled, the age-adjusted relative risk for women vaccinated against hepatitis B as compared with unvaccinated women was 0.9 (95 percent confidence interval, 0.5 to 1.6), and that for women vaccinated within two years before the index date was 0.7 (95 percent confidence interval, 0.3 to 1.8). Further adjustment for the type of employment at base line and other covariates did not materially change the results.

The total number of doses of hepatitis B vaccine received by the women with multiple sclerosis and the controls who had been vaccinated before the in-

TABLE 1. SELECTED CHARACTERISTICS OF WOMEN WITH MULTIPLE SCLEROSIS AND CONTROLS.

CHARACTERISTIC	WOMEN WITH MULTIPLE SCLEROSIS (N=192)	HEALTHY CONTROLS (N=534)	CONTROLS WITH BREAST CANCER (N=111)
Mean age (yr)	37.6	38.1	38.1
Mean no. of siblings	3.6	3.6	3.3
Birth at >42°N latitude (%)	45	32	38
Scandinavian ancestry (%)	5	6	5
Southern European ancestry (%)	19	17	18
History of smoking, at base line (%)*	54	50	48
Parents' educational level (%)			
Father did not complete high school	30	43	38
Mother did not complete high school	30	34	30
Vaccination history (%)†			
Measles	18	19	17
Tetanus	89	92	90
Hepatitis B	43	60	59
History of infectious mononucleosis (%)†	22	13	14
Measles or mumps after age of 15 yr (%)	8	3	5
Type of nursing job at base line (%)‡			
Inpatient	36	33	35
Outpatient	11	14	12
Emergency room	5	6	8
Nursing education	5	3	6

*Base line was 1976 for the Nurses' Health Study and 1989 for the Nurses' Health Study II.

†Vaccination or mononucleosis could have occurred at any time in the past and was reported on the questionnaire sent to participants in June 1998.

‡Occupation data were available for Nurses' Health Study II only, and base line was 1989.

TABLE 2. RELATIVE RISK OF MULTIPLE SCLEROSIS ACCORDING TO VACCINATION STATUS, WHEN ANALYSIS INCLUDED ALL STUDY WOMEN.*

VACCINATION STATUS	WOMEN WITH MULTIPLE SCLEROSIS (N=190)	HEALTHY CONTROLS (N=534)	RELATIVE RISK (95% CI)		WOMEN WITH MULTIPLE SCLEROSIS (N=111)	CONTROLS WITH BREAST CANCER (N=111)	RELATIVE RISK (95% CI)		POOLED CONTROLS, RELATIVE RISK (95% CI)
			MATCHED	MULTIVARIATE			MATCHED	MULTIVARIATE	MULTIVARIATE
	no. (%)				no. (%)				
Not vaccinated or vaccinated after index date	158 (83.2)	450 (84.3)			94 (84.7)	96 (86.5)			
Vaccinated >2 yr before index date	23 (12.1)	54 (10.1)			12 (10.8)	10 (9.0)			
Vaccinated ≤2 yr before index date	9 (4.7)	30 (5.6)	0.7 (0.3–1.7)	0.7 (0.3–1.7)	5 (4.5)	5 (4.5)	1.0 (0.3–4.2)	1.3 (0.3–6.1)	0.7 (0.3–1.8)
Vaccinated at any time before index date	32 (16.8)	84 (15.7)	0.9 (0.5–1.6)	0.8 (0.5–1.5)	17 (15.3)	15 (13.5)	1.2 (0.5–2.9)	1.3 (0.5–3.7)	0.9 (0.5–1.6)

*Vaccination status was confirmed by employers' insurance records. Women with multiple sclerosis and controls were matched for year of birth, study cohort, and year of diagnosis (for controls with breast cancer). The multivariate analyses adjusted for pack-years of smoking at base line, latitude of residence at birth (north, middle, or south), history of infectious mononucleosis, history of measles or mumps after the age of 15, and ancestry (Scandinavian, southern European, other white, or nonwhite). CI denotes confidence interval.

TABLE 3. RELATIVE RISK OF MULTIPLE SCLEROSIS ACCORDING TO VACCINATION STATUS, WHEN ANALYSIS INCLUDED ONLY WOMEN WITH ONSET OF DISEASE AFTER 1986 AND THEIR MATCHED CONTROLS.*

VACCINATION STATUS	WOMEN WITH MULTIPLE SCLEROSIS (N=88)	HEALTHY CONTROLS (N=235)	RELATIVE RISK (95% CI)		WOMEN WITH MULTIPLE SCLEROSIS (N=48)	CONTROLS WITH BREAST CANCER (N=48)	RELATIVE RISK (95% CI)		POOLED CONTROLS, RELATIVE RISK (95% CI)
			MATCHED	MULTIVARIATE			MATCHED	MULTIVARIATE	MULTIVARIATE
	no. (%)				no. (%)				
Not vaccinated or vaccinated after index date	60 (68.2)	152 (64.7)			35 (72.9)	33 (68.8)			
Vaccinated >2 yr before index date	20 (22.7)	54 (23.0)			9 (18.8)	10 (20.8)			
Vaccinated ≤2 yr before index date	8 (9.1)	29 (12.3)	0.6 (0.2–1.5)	0.5 (0.2–1.5)	4 (8.3)	5 (10.4)	0.7 (0.2–3.3)	0.4 (0.1–2.9)	0.6 (0.2–1.5)
Vaccinated at any time before index date	28 (31.8)	83 (35.3)	0.8 (0.4–1.4)	0.7 (0.4–1.3)	13 (27.1)	15 (31.2)	0.8 (0.3–2.1)	0.5 (0.1–2.0)	0.7 (0.4–1.3)

*Vaccination status was confirmed by employers' insurance records. Women with multiple sclerosis and controls were matched for year of birth, study cohort, and year of diagnosis (for controls with breast cancer). The multivariate analyses adjusted for pack-years of smoking at base line, latitude of residence at birth (north, middle, or south), history of infectious mononucleosis, history of measles or mumps after the age of 15, and ancestry (Scandinavian, southern European, other white, or nonwhite). CI denotes confidence interval.

dex date was similar. Eighty-four percent of the women with multiple sclerosis and 87 percent of the controls had received three doses; only two of the women with multiple sclerosis and three of the controls had received four or more doses. Thirty-two women with multiple sclerosis were vaccinated against hepatitis B before the onset of multiple sclerosis. In only one woman did the onset of multiple sclerosis occur within two months after any dose of hepatitis B vaccine. The time between the administration of the vaccine and the onset of multiple sclerosis among these women is shown in Figure 1.

To address the possibility of bias due to the exclusion of women with missing vaccination records, we repeated the analyses of the association between hepatitis B vaccination and the risk of multiple sclerosis, using the self-reported dates of vaccination to estimate the exposure status of women with missing records. According to these analyses, the multivariate relative risks of multiple sclerosis when pooled controls were used for comparison were 1.0 (95 percent confidence interval, 0.7 to 1.5) for women who had been vaccinated at any time in the past and 1.0 (95 percent confidence interval, 0.6 to 1.9) for women who had

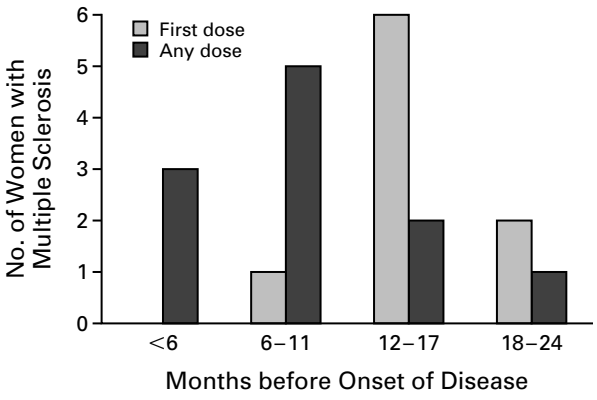

Figure 1. Time between the Administration of Hepatitis B Vaccine and the Onset of Multiple Sclerosis among Women Vaccinated within Two Years before the Onset of the Disease.

been vaccinated within two years before the onset of symptoms.

Finally, we examined what the association between hepatitis B vaccination and the risk of multiple sclerosis would be if we had relied only on the self-reported dates of vaccination for all women. When only the healthy controls were used for comparison, the multivariate relative risks of multiple sclerosis were 1.2 (95 percent confidence interval, 0.8 to 1.7) for women who had been vaccinated at any time and 1.9 (95 percent confidence interval, 1.1 to 3.3) for those who had been vaccinated within the two years before the onset of symptoms. The relative risks when controls with breast cancer were used for comparison were 0.9 (95 percent confidence interval, 0.5 to 1.5) and 1.3 (95 percent confidence interval, 0.6 to 3.0), confirming the expectation that recall bias would be reduced by using women with breast cancer as controls.

The existence of recall bias was also confirmed in analyses restricted to unvaccinated women and those with a valid vaccination certificate. In comparisons with the healthy controls, the multivariate relative risks in these analyses were 1.2 (95 percent confidence interval, 0.7 to 2.1) for women who recalled being vaccinated at any time and 2.3 (95 percent confidence interval, 1.0 to 5.3) for women who recalled being vaccinated within the two years before the onset of multiple sclerosis. In comparisons with the controls with breast cancer, the multivariate relative risks were 0.7 (95 percent confidence interval, 0.2 to 1.8) and 1.5 (95 percent confidence interval, 0.3 to 7.2), respectively.

DISCUSSION

In this nested case–control study, we found no evidence of an increased risk of multiple sclerosis among women who had been vaccinated against hepatitis B. The use of a nested case–control design reduced the bias due to inappropriate selection of controls, and the high rates of participation reduced the bias that may result from differential rates of response in case subjects and controls. Recall bias was avoided through the use of vaccination records. Recall bias would be likely to cause a spurious positive association, as was clearly shown in the analyses in which we used self-reported dates of vaccination. We were concerned about the effects of excluding women with missing vaccination records. However, the results of analyses in which we used self-reported dates of vaccination for women with missing records suggest that the extent of bias from this source was small. Finally, errors in determining the date of the onset of multiple sclerosis could have resulted in falsely low estimates of relative risk. This inaccuracy would be exacerbated in analyses in which we estimated the relative risk of multiple sclerosis in the few months after exposure to the hepatitis B vaccine. For this reason, we used a period of two years for our definition of recent exposure. The fact that in these analyses we found relative risks well below 1.0 suggests that any possible positive association between the vaccine and the risk of multiple sclerosis was small.

The null result that we found in this investigation is consistent with the recent observation that there was no increase in the number of cases of multiple sclerosis after the vaccination of more than 260,000 adolescents in Canada between 1992 and 1998.[12] There was also no increase in demyelinating disease after hepatitis B vaccination in a retrospective cohort study among subjects included in a U.S. health care data base.[13] These results and ours seem to contradict those of three previous case–control studies, including two in France, that reported nonsignificant increases in risk.

One of the French studies was a hospital-based pilot study[14] that included 121 women with multiple sclerosis and 121 controls; vaccination certificates were obtained in only a small proportion of cases, and recall bias remains a likely explanation for the small positive association reported (relative risk of onset of neurologic symptoms within the two months after exposure to vaccine, 1.7; 95 percent confidence interval, 0.5 to 6.3).

The second investigation included 152 patients in whom demyelinating disease of the central nervous system was diagnosed in 18 departments of neurology in 1994 and 1995, along with 253 controls chosen from patients with other diseases who were treated at the same hospitals. Study subjects were considered exposed if they had received a dose of the vaccine within the two months before the onset of symptoms, as compared with the two years we used in our study. This short period was chosen because, according to data from the passive surveillance of adverse drug effects in France, most cases of demyelination in the

central nervous system occur within two months of exposure.

The hypothesis was that the vaccine could cause an acute autoimmune reaction in susceptible persons soon after administration.[15] Although this hypothesis may appear plausible given what we know about adverse reactions to other drugs, its appropriateness to multiple sclerosis is questionable. In many patients with multiple sclerosis, demyelinating lesions in the central nervous system are likely to precede by weeks or months the onset of neurologic symptoms; this pattern is evident in the fact that when the diagnosis is first suspected, it is common to find multiple, clinically silent abnormalities on magnetic resonance imaging.[16] Thus, even if the vaccine had an adverse effect of short duration, the clinical consequences would most likely take several months to become apparent.

From a practical point of view, the shortening of the window of exposure to two months had the effect of dramatically reducing the power of the study, as indicated by the wide confidence interval reported in the French study (relative risk, 1.4; 95 percent confidence interval, 0.4 to 4.5). It would therefore be important to know whether the association found in the French investigation persisted when a longer period of exposure was considered.

The investigation by Sturkenboom et al. was conducted with the use of a computerized data base[8] and included 360 cases of multiple sclerosis, 140 cases of "demyelination," and 6 matched controls per case, all from the same practice in the United Kingdom. With the period of exposure set at 12 months, the reported relative risk was 1.6 (95 percent confidence interval, 0.6 to 4.0). The wide confidence interval reflects the rarity of exposure to the hepatitis B vaccine in this population. Few details of this study are available, since it was published only as an abstract, but the results appear compatible with a lack of association. Finally, there have been a few case reports of central nervous system demyelination occurring within a few weeks after the administration of hepatitis B vaccine,[15,17-19] but as their authors recognize, these studies cannot demonstrate a causal or triggering association.[15]

In summary, our results do not demonstrate an association between hepatitis B vaccination and multiple sclerosis in women. Considering the public health importance of preventing hepatitis B infection, concern about possible increases in the risk of multiple sclerosis does not appear to justify changes in vaccination policy that could compromise or delay the control of the infection.

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