ARTICLE

Hepatitis B Vaccination and the Risk of Childhood-Onset Multiple Sclerosis

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Objective: To investigate whether vaccination against hepatitis B (HB) increases the risk of incident multiple sclerosis (MS) in childhood in the short and long terms.

Design: Case-control study.

Setting: Population-based study conducted in France from January 1, 1994, to December 31, 2003.

Participants: The case patients had incident MS with onset before age 16 years. Each case was individually matched for age, sex, and geographic location (current place of residence) to 12 control participants randomly selected from the general population of France.

Exposure: Hepatitis B vaccine.

Main Outcome Measure: The risk of MS associated with HB vaccine exposure.

Results: One hundred forty-three case patients with MS were matched to 1122 control participants. The rate of HB vaccination in the 3 years before the index date was approximately 32% for both cases and controls. Vaccination against HB within the 3-year study period was not associated with an increased rate of a first episode of MS (adjusted odds ratio, 1.03; 95% confidence interval, 0.62-1.69). The rate was also not increased for HB vaccination within 6 months of the index date or at any time since birth or as a function of the number of injections or the brand of HB vaccine.

Conclusion: Vaccination against HB does not seem to increase the risk of a first episode of MS in childhood.

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SEVERAL STUDIES[1-8] HAVE evaluated the possibility of an association between recombinant hepatitis B vaccine (HBV) and an increase in incident multiple sclerosis (MS) in adults. Most found no significant increase in the risk of incident MS in the short term (primarily within 2 months) or long term (>1 year to any time) after immunization in cohort or case-control studies.[1-8] However, Hernán et al[9] reported a significant increase in the risk of MS within 3 years of vaccination, suggesting that prolonged risk periods should be carefully evaluated. Some of these epidemiologic studies have been criticized for methodological limitations, including the methods used for case ascertainment and control selection, the validation of vaccination status, and limited statistical power.[10]

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This controversy created public misgivings about HB vaccination. Hepatitis B vaccination in children remained low in several countries despite vaccination campaigns supporting early vaccination against hepatitis B (HB) in children as a means of inducing strong and long-lasting immunity and despite high levels of HBV-related morbidity and mortality worldwide.[11] In France, less than half of all children and adolescents had complete vaccine coverage, consisting of 3 injections, in 2002.[12]

Multiple sclerosis is rare in children, accounting for only 3% to 4% of all MS cases. We carried out a population-based case-control study based on an existing cohort of children with MS established for other purposes in France[13-15] to determine whether exposure to HBV in childhood increases the risk of a first episode of MS before age 16 years during prolonged risk periods.

METHODS

DESIGN AND STUDY POPULATION

The base population for this study was the French general population of children and adolescents younger than 16 years between January 1, 1994, and December 31, 2003. The case series consisted of patients from the French Kid

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Sclérose en Plaques (KIDSEP) neuropediatric MS cohort, which includes most incident cases of childhood-onset MS in France. The control participants were selected from the general population. All cases and controls supplied a vaccination certificate and completed a health questionnaire.

CASE ASCERTAINMENT

The French KIDSEP neuropediatric MS cohort has been described previously.[13-15] We included only patients with confirmed MS with a first episode occurring between January 1, 1994, and December 31, 2003, before the patients were 16 years of age. We excluded 1 patient of foreign origin with a different pattern of exposure to vaccination and 30 patients enrolled in the main study between January 1, 1990, and January 1, 1994, because levels of HB vaccination were low in France before that date.[12] The final study cohort comprised 164 patients with MS.

Case patients had to have had a first episode of MS (leading to their initial referral) followed by at least 1 additional episode during follow-up. The index date was the date of onset of the symptoms of the first episode of MS in case patients. A relapse was defined as a second episode of neurologic symptoms lasting more than 24 hours and followed by partial or complete stabilization or resolution, as previously described.[13-16] All episodes were recorded by a trained pediatric neurologist (Y.M. or M.T.), including a description of symptoms, and were identified on the basis of systematic follow-up to June 30, 2006, by means of routine clinic visits, telephone calls, and written questionnaires, as previously described.[13-15]

CONTROL SELECTION

We attempted to individually match each case patient with 12 control participants selected from the French general population on the basis of age (±6 months), sex, and current area of residence, to control for geographic variations in vaccination and incidence of MS. Each matched control was assigned the index date of the case patient for the evaluation of previous vaccinations. Controls were selected by a professional organization specializing in population-based opinion polls and case-control studies on health topics (CSA Institute, Paris, France). A 2-step, population-based, random-selection method was used. In the first step, random telephone numbers in the geographic area of residence of each case were selected at random from the telephone directory. If the selected number corresponded to a household, the polling organization then determined whether the household included an eligible child, adolescent, or young adult. If the household contained an eligible child, adolescent, or young adult and consent for participation was obtained, the name and address of the eligible household was noted so that the information letter and questionnaire could be sent. Failure to reach the randomly selected telephone number was defined as at least 10 unanswered calls to that number. Current area of residence was determined on the basis of postal code (each postal code being associated with a "commune," an administrative district generally corresponding to a town). Controls with the same postal code as the corresponding case were selected when possible. If too few individuals with the same postal code were available, current area of residence was defined as the "*département* of residence" (a *département* being a larger administrative district including a number of towns). We recruited no more than 2 controls per household.

DATA ACQUISITION

An information letter describing the study was sent to all cases and controls. This letter dealt with exposure to all vaccines to avoid focusing on the HBV alone. A questionnaire was also sent to all case patients and controls, requesting all vaccination certificates, information on family history of MS in siblings and parents, other family history of autoimmune diseases (thyroiditis, rheumatoid arthritis, lupus erythematosus, diabetes mellitus requiring insulin treatment, and other diseases described as autoimmune by family physicians in siblings or parents). Information about the profession of the head of the family, based on the categories defined by the French National Institute of Statistics and Economic Studies, was assessed using a standardized questionnaire.[17] Low socioprofessional status corresponded to unemployed persons, laborers, and low-income employees.

Families (if the case patient or control was younger than 18 years) or young adults who did not return the requested information within 2 weeks of receiving the information letter and questionnaire were contacted again. We sent a maximum of 2 letters, 4 weeks apart, and made 2 telephone calls, each 2 weeks after sending a letter, in an attempt to obtain the required information. A *recall* was defined as a letter followed by a telephone call.

ASSESSMENT OF EXPOSURE IN CASES AND CONTROLS

The exposure studied was HBV. However, we collected information for all vaccinations, including dates of injections, and requested a copy of the child's vaccination certificate (*carnet de santé*). Standardized telephone interviews were used to obtain vaccination information for a few controls after failure of the entire recall process to obtain information. These controls were included in the analysis. A *vaccination* was defined as the administration of a commercial preparation of vaccine, either as a single vaccination or as part of a series, whether for primary immunization or as a booster.

STATISTICAL ANALYSIS

Conditional logistic regression analysis for matched case-control data was used to estimate matched odds ratios (ORs) and 95% confidence intervals (CIs) for first episodes of MS associated with HBV exposure. Case patients and controls not exposed to HBV between birth and the date of onset of the symptoms of the first episode of MS (index date) composed the reference group. In addition to the inherent adjustment for the factors used for matching, we also adjusted the analysis for family history of MS (siblings or parents) or of other autoimmune diseases (siblings or parents) and for the profession of the head of the family.

The main exposure period for the analysis was 3 years to facilitate comparison with the study by Hernán et al,[9] for which the study was determined to have sufficient power to detect an OR of 2. In addition, exposure periods of 6 months and as long as the entire exposure period since birth to the index date were also analyzed. We also investigated the effect of the number of doses, comparing 1, 2, and 3 or more immunizations, and the brand of vaccine.

The study, including data input into a computerized system, was approved by the National Committee for Computerized Data and Liberty, the French data protection agency. All patients gave informed consent for inclusion in the study. The organization of the study was approved by the French Society of Neuropediatrics and the French Ministry of Health (Direction Générale de la Santé). The study was overseen by a scientific committee and advisory board composed of independent experts who approved the protocol, administration, analysis, and publication of the study.

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Table 1. Characteristics of the Study Subjects[a]

Characteristic	All Case Patients (n=143)	All Matched Controls[b] (n=1122)	Aged <10 y		Aged ≥10 y	
			Case Patients (n=42)	Matched Controls (n=357)	Case Patients (n=101)	Matched Controls (n=765)
Male sex	52 (36.4)	431 (38.4)	21 (50.0)	180 (50.4)	31 (30.7)	251 (32.8)
Age, mean±SD, y	11.5±3.8	11.3±3.8	NA	NA	NA	NA
Residence in Paris or suburbs (Ile de France)	42 (29.4)	307 (27.4)	9 (21.4)	70 (19.6)	33 (32.7)	237 (31.0)
History in siblings or parents						
MS	6 (4.2)	18 (1.6)[c]	3 (7.1)	4 (1.1)[c]	3 (3.0)	14 (1.8)
Other autoimmune disease	8 (5.6)	86 (7.7)	1 (2.4)	21 (5.9)	7 (6.9)	65 (8.5)
Low socioprofessional status of head of family	66 (46.2)	696 (62.0)[c]	18 (42.9)	212 (59.4)[c]	48 (47.5)	484 (63.3)[c]
Infection during month before disease onset	**39** (27.3)		17 (40.5)		22 (21.8)	
Symptoms at disease onset						
Multiple	**66** (46.2)		24 (57.1)		42 (41.6)	
Transverse myelitis	**12** (8.4)		6 (14.3)		6 (5.9)	
Optic neuritis	**51** (35.7)		13 (31.0)		38 (37.6)	
Severe mental status change	**19** (13.3)		12 (28.6)		7 (6.9)	
Brainstem dysfunction	**53** (37.1)		14 (33.3)		39 (38.6)	
Cerebrospinal fluid						
Oligoclonal bands in 123 patients studied	**69** (48.3)		12 (28.6)		57 (56.4)	
Cells ≥10/μL	**63** (44.1)		21 (50.0)		42 (41.6)	
Proteins ≥0.5 g/dL	**29** (20.3)		12 (28.6)		17 (16.8)	
Magnetic resonance imaging results						
Childhood MS criteria[d]	**78** (54.5)		16 (38.1)		62 (61.4)	
At least 3 Barkhof criteria[e]	**70** (49.0)		13 (31.0)		57 (56.4)	

Abbreviation: MS, multiple sclerosis; NA, data not available.
[a] Values are given as number (percentage) of patients unless otherwise indicated.
[b] Matched for age (± 6 months), sex, and geographic location (ie, place of residence).
[c] $P < .05$, χ^2 test for comparison of proportions or unpaired *t* test for comparison of means.
[d] Corpus callosum long axis perpendicular lesions or sole presence of well-defined lesions (Mikaeloff et al[14]).
[e] At least 1 gadolinium-enhanced T1 or 9 T2 lesions or more, at least 1 infratentorial T2 lesion, at least 1 juxtacortical T2 lesion, or 3 periventricular lesions or more (McDonald et al[16]).

RESULTS

No vaccination information was obtained for 21 of the 164 cases, and these patients were not retained for analysis (response rate, 87.2%). The baseline characteristics of the 143 patients retained for analysis, who provided a copy of their vaccination certificate, were not significantly different from those of the 21 patients not included because of missing information about vaccine exposure (data not shown). In particular, family history of MS did not differ between these 2 groups (6 of 143 [4.2%] in studied cases vs 1 of 21 [4.8%] in the excluded cases).

For the recruitment of controls, 200 351 households were contacted, all randomly selected within the current area of residence of the cases. There was no child living in the household or eligible child fitting the matching criteria for 98.7% of the numbers dialed, and 894 eligible households contacted refused to participate in the study. We thus identified 1705 eligible controls who could be matched to a case patient for age, sex, and current area of residence, of which 1122 provided vaccination information. The reasons for a lack of vaccination information for 583 of the recruited controls, despite initial consent, were as follows: no response despite a full recall procedure (62.1%), refusal at first recall (14.1%), lost vaccination certificate (10.9%), and incorrect telephone number or address given, making further contact impossible (12.9%). Vaccination information was provided in the form of a copy of the vaccination records for 97.3% (n=1092) of participants and through a standardized telephone interview for 2.7% (n=30); all of these data were used for analysis. Twenty-two of the 1705 controls recruited (1.3%) belonged to the same household as another control (maximum of 2 controls recruited per household). The mean number of controls per case was 8. Twenty-two cases (15.4%) had 11 or 12 controls, 81 (56.6%) had 7 to 10 controls, 34 (23.8%) had 4 to 6 controls, and 6 (4.2%) had 1 to 3 controls.

Our analyses, therefore, included 143 MS cases and 1122 matched controls (**Table 1**). The incidence of a family head with a low socioprofessional status was lower in cases ($P<.001$). The incidence of a family history of MS was slightly higher in cases ($P=.03$). The incidence of a family history of autoimmune diseases, as other characteristics, was similar. The incidence of exposure to HBV was similar in cases and controls (**Table 2**). The incidence of exposure (≥1 injection during the entire exposure period from birth to the index date) in controls, as a function of age at the index date, was as follows: 44 of 609 (7.2%) before age 5 years vs 5 of 80 (6.2%) in cases, 53 of 609 (8.7%) between 5 and 9 years of age vs 5 of 80 (6.2%) in cases, 155 of 609 (25.5%) between 10 and 13 years of

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Table 2. Timing and Number of HB Vaccinations in Relation to the Risk of MS[a]

HBV Exposure	Case Patients (n=143)	Matched Controls[b] (n=1122)	Crude OR	Adjusted OR (95% CI)[c]
Unvaccinated[d]	63 (44.1)	513 (45.7)	1 [Reference]	1 [Reference]
Vaccinated against HB at any time	80 (55.9)	609 (54.3)	1.09	1.10 (0.71-1.69)
Years since last HB vaccination before index date				
Analysis 1				
0-½	10 (7.0)	75 (6.7)	0.98	0.99 (0.44-2.21)
>½	70 (49.0)	534 (47.6)	1.11	1.12 (0.71-1.78)
Analysis 2				
0-1	14 (9.8)	118 (10.5)	0.86	0.85 (0.43-1.71)
>1	66 (46.2)	491 (43.8)	1.19	1.21 (0.75-1.94)
Analysis 3				
0-2	28 (19.6)	237 (21.1)	0.84	0.88 (0.50-1.54)
>2	52 (36.4)	372 (33.2)	1.34	1.30 (0.79-2.16)
Analysis 4				
0-3	46 (32.2)	356 (31.7)	1.00	1.03 (0.62-1.69)
>3	34 (23.8)	253 (22.5)	1.22	1.20 (0.70-2.05)
Analysis 5				
0-1	14 (9.8)	118 (10.5)	0.83	0.83 (0.41-1.67)
>1-2	14 (9.8)	119 (10.6)	0.87	0.96 (0.46-2.01)
>2-3	18 (12.6)	119 (10.6)	1.42	1.42 (0.70-2.90)
>3	34 (23.8)	253 (22.5)	1.30	1.27 (0.73-2.21)
Analysis 6				
0-4	62 (43.4)	476 (42.4)	1.04	1.05 (0.66-1.68)
>4	18 (12.6)	133 (11.9)	1.24	1.23 (0.64-2.37)
Analysis 7				
0-5	71 (49.7)	548 (48.8)	1.04	1.04 (0.66-1.64)
>5	9 (6.3)	61 (5.4)	1.38	1.47 (0.62-3.50)
Analysis 8				
0-6	74 (51.7)	578 (51.5)	1.03	1.04 (0.67-1.62)
>6	6 (4.2)	31 (2.8)	1.86	1.89 (0.66-5.38)
No. of immunizations with HBV at any time before index date				
Analysis 9				
1-2	7 (4.9)	85 (7.6)	0.66	0.68 (0.29-1.60)
≥3	73 (51.0)	524 (46.7)	1.18	1.19 (0.76-1.84)

Abbreviations: CI, confidence interval; HB, hepatitis B; HBV, HB vaccine; MS, multiple sclerosis; OR, odds ratio.
[a] Values are given as number (percentage) of patients unless otherwise indicated.
[b] Matched for age (±6 months), sex, and geographic location (ie, current place of residence).
[c] Adjusted on covariates: family history of MS, family history of another autoimmune disease, and socioprofessional status of the head of the family.
[d] The reference group includes those with no HBV exposure.

age vs 22 of 80 (27.5%) in cases, and 357 of 609 (58.5%) between 14 and 16 years of age vs 48 of 80 (60.0%) in cases.

Exposure to HBV was not associated with a significant increase in the risk of a first episode of MS (Table 2). After adjustment for family history of MS or another autoimmune disease and the socioprofessional status of the head of the family, the adjusted OR of a first episode of MS associated with HBV exposure during a risk period of 3 years was 1.03 (95% CI, 0.62-1.69), and for a risk period of 1 year was 0.85 (95% Cl, 0.43-1.71). Similar results were obtained for other risk periods (6 months; 2, 4, 5, and 6 years; and any time since onset of exposure) for stratified complementary analysis considering cases with an index date after December 31, 1997 (99 of 143 [69.2%]), those without a family history of MS or another autoimmune disease (129 of 143 [90.2%]), those with low socioprofessional status of the head of the family (66 of 143 [46.2%]), those at least 10 years old at the index date (101 of 143 [70.5%]), and in an analysis excluding the 22 controls recruited from the same household (data not shown). Moreover, the number of HB immunizations in the 3 years before the index date had no significant association with the risk of MS.

The OR for the 2 main brands used for the last injection before the index date was not significantly different from 1 (**Table 3**). For Engerix-B (GlaxoSmithKline, Brentford, England) administered more than 3 years before the index date, the adjusted OR was 1.68 (95% CI, 0.93-3.05). Taking into account the brand used for the first injection before the index date, ORs were 1.52 (95% CI, 0.94-2.47) for Engerix-B and 0.75 (95%CI, 0.40-1.40) for GenHevac B (Aventis Pasteur MSD, Maidenhead, England). All case patients and 1113 controls vaccinated before the index date received exclusively or almost exclusively either Engerix-B or GenHevac B.

COMMENT

To our knowledge, this is the first such study in children and the first to report no increase in the risk of a first episode of MS after HBV exposure in children, whether for a

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Table 3. Timing of HB Vaccinations According to Brand Used for the Last Injection Before Index Date in Relation to the Risk of MS[a]

HBV Exposure	Case Patients (n=143)	Matched Controls[b] (n=1122)	Crude OR	Adjusted OR (95% CI)[c]
Unvaccinated[d]	63 (44.1)	513 (45.7)	1 [Reference]	1 [Reference]
Vaccinated against HB at any time				
Engerix-B[e]	50 (62.5)	301 (49.4)	1.38	1.38 (0.86-2.23)
GenHevac B[f]	22 (27.5)	232 (38.1)	0.73	0.75 (0.41-1.37)
Other	8 (10.0)	76 (12.5)	0.91	0.93 (0.41-2.11)
Years since last HB vaccination before index date				
Engerix-B, 0-3	25 (17.5)	165 (14.7)	1.16	1.17 (0.65-2.13)
Engerix-B, >3	25 (17.5)	136 (12.1)	1.70	1.68 (0.92-3.04)
GenHevac-B, 0-3	15 (10.5)	136 (12.1)	0.83	0.88 (0.44-1.79)
GenHevac-B, >3	7 (4.9)	97 (8.6)	0.61	0.59 (0.24-1.45)
Other, 0-3	6 (4.2)	55 (4.9)	0.94	0.97 (0.38-2.50)
Other, >3	2 (1.4)	20 (1.8)	0.86	0.80 (0.17-3.71)

Abbreviations: CI, confidence interval; HB, hepatitis B; HBV, HB vaccine; MS, multiple sclerosis; OR, odds ratio.
[a] Values are given as number (percentage) of patients unless otherwise indicated.
[b] Matched for age (± 6 months), sex, and geographic location (ie, current place of residence).
[c] Adjusted for family history of MS, family history of another autoimmune disease, and socioprofessional status of the head of the family.
[d] The reference group includes those with no HBV exposure.
[e] GlaxoSmithKline, Brentford, Middlesex, England.
[f] Aventis Pasteur MSD, Maidenhead, England.

risk period of 3 years or other risk periods from 6 months to the entire exposure period from birth to the index date. The numbers of immunizations and vaccine brand also seemed to have no association with MS risk.

Previous field or database studies on the risk of incident MS in adults have provided conflicting results.[1-10] Five studies found no increased risk but could not exclude a relative risk less than 2.[2-4,7,8] Two French case-control studies estimated a 40% to 70% increase in MS risk in the 2 months after vaccination, including patients with encephalitis.[5,6] A study in the United Kingdom, based on the General Practitioner Research Database, reported a 60% increase in risk within 1 year of immunization.[1] A recent nested case-control study based on that same database reported an increase in MS risk in the first 3 years after vaccination.[9]

In our study, ascertainment of the first episode of MS was rendered more reliable by the pediatric context. Patients were recruited from the French KIDSEP neuropediatric MS cohort, which was constituted for other purposes.[13-15] Inclusion was exhaustive at participating centers. Moreover, the rarity of MS in children made it possible to collect most incident cases nationwide in France, making this study much more representative than any study in adults, in whom MS occurs more frequently. For each first episode, the precise date and a description of symptoms were recorded. Multiple sclerosis was diagnosed on the basis of the gold standard clinical criterion of relapse. The precise dates of the first and second episodes were known, averting the potential gap between date of onset of first symptoms and identification of MS onset or diagnosis of MS that may have generated selection bias in some previous studies in adults.[8,10,18] The underreporting of second episodes is unlikely because second episodes are often considered indicative of a chronic disease requiring advice from a reference pediatric neurology center. Bias may result from there being a long interval between the first and second episodes, precluding the inclusion of some patients in whom the diagnosis of MS would later be confirmed. However, we previously demonstrated that 80% of second episodes in children occur within the first 2 years and 90% within 3 years.[15] Therefore, the potential bias is likely small.

The selection of control participants is a major challenge in case-control studies because they must come from the same basic study population as the case patients.[19-22] Because the cases in our study were taken from the French population as a whole, we carried out random sampling for the selection of controls among the French population but selected participants who were of the same age and sex and came from the same geographic area as the corresponding case. The response rate of controls was satisfying compared with previous population-based case-control field studies.[21,22] The response rate was lowest for controls when the head of the family had low socioprofessional status, as reported in similar studies.[19] The low proportion of controls recruited from the same household, probably with a similar pattern of exposure, did not influence our results.

The validation of vaccination status was facilitated by the pediatric context because it was possible to obtain a copy of the vaccination certificate, which is considered a reliable indicator of exposure, for most subjects.[23] The incidence of exposure in recruited controls was consistent with that previously described for the general childhood population.[12] Indeed, 54.3% of children or adolescents recruited as controls had received at least 1 HBV injection, consistent with the incidence obtained by Denis[12] in 2002 in the general French population, which showed that 66% of adolescents and 36% of children aged 11 to 13 years received at least 1 HBV injection. During the study, a vaccination campaign conducted by the French Health Minister recommended vaccination of all infants during the first year of life and organized actively to reach older children and adolescents who had not been vaccinated. In September 1994, a general im-

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munization campaign was initiated by the French Health Minister for preadolescents and adolescents and, in December 1994, a free school-based vaccination program was instituted for adolescents. In October 1998, the French Health Minister decided to stop HB vaccination in schools. As illustrated by our results, preadolescents and adolescents were the primary target reached by the campaign. All vaccines must be listed on the vaccination certificate in France, making it unlikely that subjects had received injections that had not been noted. Moreover, the *carnet de santé* contains not only the vaccination certificate but also all information about primary visits and hospitalizations.

We controlled for potential confounding factors previously identified in pharmacoepidemiologic studies of vaccines.[23,24] We verified that the cases who did not respond had baseline characteristics similar to the cases retained in the analysis. Because the probability of exposure varies according to geographic location and the socioprofessional status of the parents, controls were matched to cases on the basis of geographic location (current area of residence) and the analysis was adjusted for the socioprofessional status of the head of the family. We also matched cases and controls for age and sex and adjusted for the main potential confounding factors of family history of MS and of other autoimmune diseases. The incidence of a family history of MS in cases and controls was similar to that in the entire MS population in France.[25] We obtained similar consistent results from stratified analyses of calendar time, age at the index date, and family history of MS or of other autoimmune diseases.

Analyses took into account different periods of exposure to vaccine to facilitate comparisons with the results of previous studies. The main risk period considered was 3 years to facilitate comparison with the study by Hernán et al.[9] We also investigated longer risk periods, including the entire period from birth to the index date, inasmuch as the duration of the true risk period is unknown, as is the time course of white matter and axonal destruction in MS after stimulation with external antigens such as vaccines.[26,27] We found no increase in the risk of MS associated with HBV exposure during childhood irrespective of the risk period studied and of the number of doses administered. The upper boundary of the 95% CI indicates that increase in risk by a factor of 1.7 or higher (for the 3-year period and for the indefinite period) could be excluded, with higher statistical power than in previous studies. However, statistical power was not high enough for the evaluation of short risk periods (<6 months), which was not our primary objective.

In conclusion, in this first (to our knowledge), large population-based case-control study in children, the main target population for vaccination campaigns, we found no increase in the risk of MS with exposure to HBV. We also recently reported that HBV exposure in children who had previously had a first episode of central nervous system inflammatory demyelination was not associated with an increase in the risk of conversion to MS in either short-term or long-term risk periods.[28] We plan to investigate whether the risk of monophasic episodes of central nervous system inflammatory demyelination (primarily, acute disseminated encephalomyelitis, which occurs more frequently in children than in adults)[13] is influenced by HBV exposure. This will also make it possible to evaluate further the possible influence of the brand of HBV (taking into account the other components used in the manufacturing process) on the induction of both monophasic and relapsing demyelination episodes.

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Author Contributions: Drs Mikaeloff, Suissa, and Tardieu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Mikaeloff, Suissa, and Tardieu. *Acquisition of data:* Mikaeloff, Caridade, Rossier, and Suissa. *Analysis and interpretation of data:* Mikaeloff, Caridade, Rossier, and Suissa. *Drafting of the manuscript:* Mikaeloff, Suissa, and Tardieu. *Critical revision of the manuscript for important intellectual content:* Mikaeloff, Caridade, Rossier, Suissa, and Tardieu. *Statistical analysis:* Mikaeloff and Suissa. *Obtained funding:* Suissa and Tardieu. *Administrative, technical, and material support:* Caridade and Tardieu. *Study supervision:* Suissa and Tardieu.
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REFERENCES

1. Sturkenboom M, Abenhaim L, Wolfson C, Roullet E, Heinzlef O, Gout O. Vaccinations, demyelination and multiple sclerosis study (VDAMS): a population-based study in the UK. *Pharmacoepidemiol Drug Saf.* 1999;8(suppl 2):S170-S171.
2. Zipp F, Weil JG, Einhaupl KM. No increase in demyelinating diseases after hepatitis B vaccination. *Nat Med.* 1999;5(9):964-965.
3. Sadovnick AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet.* 2000;355(9203):549-550.
4. Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med.* 2001;344(5):327-332.
5. Touzé E, Gout O, Verdier-Taillefer MH, Lyon-Caen O, Alpérovitch A. The first episode of central nervous system demyelinization and hepatitis B vaccination [in French]. *Rev Neurol (Paris).* 2000;156(3):242-246.
6. Touzé E, Fourrier A, Rue-Fenouche C, et al. Hepatitis B vaccination and first central nervous system demyelinating event: a case-control study. *Neuroepidemiology.* 2002;21(4):180-186.
7. DeStefano F, Verstraeten T, Jackson LA, et al; Vaccine Safety Datalink Research Group, National Immunization Program, Centers for Disease Control and Prevention. Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol.* 2003;60(4):504-509.
8. DeStefano F, Weintraub ES, Chen RT. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology.* 2005;64(7):1317.
9. Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology.* 2004;63(5):838-842.
10. Hernán MA, Jick SS. Hepatitis B vaccination and multiple sclerosis: the jury is still out. *Pharmacoepidemiol Drug Saf.* 2006;15(9):653-655.
11. Kane M, Clements J, Hu D. Hepatitis B. In: Jamison DT, Mosley WH, Measham AR, Bobadilla JL, eds. *Disease Control Priorities in Developing Countries.* New York, NY: Oxford University Press; 1993:321-330.
12. Denis F. Hepatitis B vaccination in France: vaccination coverage in 2002. *Bull Acad Natl Med.* 2004;188(1):115-123.
13. Mikaeloff Y, Suissa S, Vallee L, et al; KIDMUS Study Group. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. *J Pediatr.* 2004;144(2):246-252.
14. Mikaeloff Y, Adamsbaum C, Husson B, et al; KIDMUS Study Group on Radiation. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain.* 2004;127(pt 9):1942-1947.
15. Mikaeloff Y, Caridade G, Assi S, Suissa S, Tardieu M. Prognostic factors and early severity score in a cohort of childhood multiple sclerosis. *Pediatrics.* 2006;118(3):1133-1139.
16. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol.* 2001;50(1):121-127.
17. National Institute for Statistics and Economic Studies. *Nomenclature des professions et catégories professionnelles 2003.* Paris, France: National Institute for Statistics and Economic Studies; 2003.
18. Naismith RT, Cross AH. Does the hepatitis B vaccine cause multiple sclerosis? *Neurology.* 2004;63(5):772-773.
19. Rodrigues LC, Smith PG. Use of the case-control approach in vaccine evaluation: efficacy and adverse effects. *Epidemiol Rev.* 1999;21(1):56-72.
20. Grimes DA, Schulz KF. Compared to what? finding controls for case-control studies. *Lancet.* 2005;365(9468):1429-1433.
21. Bernstein L. Control recruitment in population-based case-control studies. *Epidemiology.* 2006;17(3):255-257.
22. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med.* 2000;343(25):1826-1832.
23. Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. *Pharmacoepidemiology.* 3rd ed. New York, NY: John Wiley & Sons Inc; 2000:707-732.
24. Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccine. *Am J Epidemiol.* 1992;136(2):121-135.
25. Alizadeh M, Genin E, Babron MC, et al; French Multiple Sclerosis Genetics Group. Genetic analysis of multiple sclerosis in Europeans: French data. *J Neuroimmunol.* 2003;143(1-2):74-78.
26. Piaggio E, Ben Younes A, Desbois S, et al. Hepatitis B vaccination and central nervous system demyelination: an immunological approach. *J Autoimmun.* 2005;24(1):33-37.
27. Schattner A. Consequence or coincidence? the occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine.* 2005;23(30):3876-3886.
28. Mikaeloff Y, Caridade G, Assi S, Tardieu M, Suissa S; KIDSEP Study Group of the French Neuropaediatric Society. Hepatitis B vaccine and risk of relapse after first childhood CNS inflammatory demyelination. *Brain.* 2007;130(pt 4):1105-1110.

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