Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood

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ABSTRACT

Background: The risk of CNS inflammatory demyelination associated with hepatitis B (HB) vaccine is debated, with studies reporting conflicting findings.

Methods: We conducted a population-based case-control study where the cases were children with a first episode of acute CNS inflammatory demyelination in France (1994–2003). Each case was matched on age, sex, and geographic location to up to 12 controls, randomly selected from the general population. Information on vaccinations was confirmed by a copy of the vaccination certificate. The odds ratios (ORs) of CNS inflammatory demyelination associated with HB vaccination were estimated using conditional logistic regression.

Results: The rates of HB vaccination in the 3 years before the index date were 24.4% for the 349 cases and 27.3% for their 2,941 matched controls. HB vaccination within this period was not associated with an increase in the rate of CNS inflammatory demyelination (adjusted OR, 0.74; 0.54–1.02), neither >3 years nor as a function of the number of injections or brand type. When the analysis was restricted to subjects compliant with vaccination, HB vaccine exposure >3 years before index date was associated with an increased trend (1.50; 0.93–2.43), essentially from the Engerix B vaccine (1.74; 1.03–2.95). The OR was particularly elevated for this brand in patients with confirmed multiple sclerosis (2.77; 1.23–6.24).

Conclusions: Hepatitis B vaccination does not generally increase the risk of CNS inflammatory demyelination in childhood. However, the Engerix B vaccine appears to increase this risk, particularly for confirmed multiple sclerosis, in the longer term. Our results require confirmation in future studies.
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GLOSSARY

ADEM = acute disseminated encephalomyelitis; **BCG** = Bacille Calmette–Guèrin; **HB** = hepatitis B; **MS** = multiple sclerosis; **OR** = odds ratio.

The first reports of an association between recombinant hepatitis B (HB) vaccine exposure and cases of CNS inflammatory demyelination involved not only multiple sclerosis (MS) but also clinically isolated syndromes such as acute disseminated encephalomyelitis (ADEM) or transverse myelitis.[1] The later conditions are in fact considered to be more likely than MS a consequence of acute exposure to viral or vaccine antigen stimulation.[2-4] However, most epidemiologic studies were performed in adult patients and evaluated the association between HB vaccine and an increase in confirmed MS. They demonstrated for most of them no increase in risk after immunization but methodologic limitations were raised by some authors.[5-9] Only one database nested case-control study reported a significant increase in the risk of adult-onset MS within the first 3 years of vaccination.[10] In a recent population-based case-control study,

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we found no increase in the risk of incident MS, even within prolonged risk periods after vaccination.[11] However, we observed a trend toward an increased risk over the long term and a slight difference between HB vaccine brand types.

We performed a population-based case-control study to investigate whether exposure to the HB vaccine in childhood increases the risk of a first ever episode of acute CNS inflammatory demyelination.

METHODS

This study is a part of a research program evaluating the impact of environmental risk factors on acute CNS inflammatory demyelinations in childhood. A first study assessed the risk of childhood-onset MS and found no association with HB vaccine exposure.[11] The present study addresses the risk of a first ever episode of acute CNS inflammatory demyelination in childhood, whatever the course of the disease after the first attack.

Cases definition and controls selection. The case series for this study was selected from patients enrolled in the French neuropediatric "KIDSEP" cohort.[12-15] Cases were all patients with a first episode of acute CNS inflammatory demyelination occurring between January 1, 1994, and December 31, 2003, before the age of 16 years, and born in France. Thus, the case definition includes patients with single episodes without relapse during the follow-up, as well as patients who went on to relapse and were diagnosed with MS. The last group of patients was included in the previous study with a similar design that tested specifically confirmed MS.[11]

The procedure of population-based selection of controls was previously described in detail.[11] In short, we aimed to individually match each case with up to 12 controls selected from the French general population on the basis of age (±6 months), sex, and current area of residence. Controls were selected by random telephone dialing in the geographic area of residence of each case. Households including an eligible subject were sent an information letter and questionnaire after consent. Each matched control was assigned the index date of the case (the date of onset of the symptoms of the first episode) for the evaluation of previous vaccinations.

Data collection and exposure confirmation. An information letter and a questionnaire were sent to all cases and controls, as previously described.[11] In summary, a copy of the child's vaccination certificate (carnet de santé), that includes all recordings of vaccinations and particularly for HB, was requested as well as information on familial autoimmune history (in siblings or parents) and parental smoking at home before index date.

Statistical analysis and ethical considerations. Conditional logistic regression for matched case-control data was used to estimate odds ratios (ORs) of first ever episodes of acute CNS inflammatory demyelination associated with HB vaccine exposure. Subjects not exposed to HB vaccine, between birth and the index date, were used as the reference group. In addition to the intrinsic confounder adjustment for the matching factors, the regression model was used to perform further adjustment for family history of MS or of other autoimmune diseases, occupation of the head of the family, and parental smoking at home.[16]

Various exposure time windows were used. Our primary hypothesis was the time window of effect within or more than the last 3 years before index date. The study was determined to have sufficient power to detect an OR of 1.5, with a minimal number of four controls per case, considering a frequency of exposure of 20% for 3 years in the controls. In addition, we studied ever use (defined by the entire exposure period spanned from birth to index date), the number of doses, and the major brand type of vaccine (last injection before index date).

Different sensitivity analyses were also realized. Analyses were restricted to cases without a family history of MS or another autoimmune disease, or with a low socioprofessional status of head of family, or with an age at index date ≥3 years (to eliminate possible biases from younger children not exposed for the full 3-year exposure period), or with an age at index date ≥10 years, or belonging to one or the other group of severity among MS cases. We also considered the year period just before the index date as an unexposed period to assess the theoretical possibility of a prescription bias in cases related to unrecognized symptoms during this period and performed another analysis excluding the controls recruited from the same household.

To control for a potential selection bias from subjects who agreed to participate in the study, we performed an analysis restricted to cases and controls compliant with vaccinations guidelines. We considered the distribution of vaccine coverage in children in France in the study period to develop the definition.[17] Compliant subjects were defined as receiving at least one Bacille Calmette–Guèrin (BCG) vaccine, one mumps-rubella-measles vaccine, and four diphtheria-tetanus-poliomyelitis vaccine during the first 2 years of life. BCG vaccine is an obligation to be accepted in community care structures (day-nursery, nursery school) in France but could also be realized voluntarily. Mumps-rubella-measles is recommended by Health Authorities but is not an obligation. Diphtheria-tetanus-poliomyelitis vaccine is an obligation (three injections at 2, 3, and 4 months of age and a booster before 18 months of age). Other less restricted definitions of compliance were also used: 1) four diphtheria-tetanus-poliomyelitis vaccine and one mumps-rubella-measles during the first 2 years of life, and 2) one mumps-rubella-measles during the first 2 years of life. These sensitivity analyses were not performed in our previous study[11] and, accordingly, we also reanalyzed cases with a relapsing course (confirmed MS).

The study was approved by the Comité National Informatique et Liberté (the French data protection agency). All patients gave informed consent for their inclusion in the study. The study was supported by the Société Française de Neuropédiatrie 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, conduct, analysis, interpretation, and publication of the study.

RESULTS

The initial case series amounted to 403 cases, of which 86.6% agreed to participate, including 349 cases who provided a copy of their vaccination certificate and who were retained for analysis. These were not significantly different baseline characteristics from the 54 patients who did not participate (data not shown). Among the 349 cases included in the study, the diagnosis confirmed by the course of disease was 1) single episodes without relapse for 198 cases including ADEM (n = 79,

Table 1 Characteristics of cases with a first episode of acute CNS inflammatory demyelination and matched population-based controls

Variable	All case patients (n = 349)	All matched controls* (n = 2,941)
Male	156 (44.7)	1,349 (45.9)
Age, y, mean ± SD	9.3 ± 4.6	9.0 ± 4.5
Residence in Paris or suburbs	109 (31.2)	898 (30.5)
Familial MS history	8† (2.3)	31 (1.1)
Other familial autoimmune disease history	18 (5.2)	210 (7.1)
Low socioprofessional status of head of family (unemployed people, laborers, and low-income employees)	166† (47.6)	1,606 (54.6)
Infection during the month before disease onset	149 (43)	
Symptoms at disease onset		
Multiple	219 (64)	
Transverse myelitis	49 (14)	
Optic neuritis	86 (25)	
Severe mental status change	121 (35)	
Brainstem dysfunction	127 (36)	
CSF		
Oligoclonal bands	89 (26)	
Cells ≥10/μL	157 (45)	
Proteins ≥0.5 g/dL	88 (25)	
MRI		
Child-MS MRI criteria‡	124 (36)	
Three Barkhof MRI criteria§	124 (36)	

*Matched on age (±6 months), sex, geographic location (place of residence).
†$p < 0.05$ (χ^2 test for comparison of proportions or t test for comparison of means).
‡Corpus callosum long axis perpendicular lesions or sole presence of well-defined lesions.[13]
§Three criteria among four: at least one gadolinium-enhancing T1 lesion or ≥9 T2 lesions, at least one infratentorial T2 lesion, at least one juxtacortical T2 lesion, ≥3 periventricular lesions.[31]

39.9%), isolated optic neuritis (n = 19, 9.6%), isolated transverse myelitis (n = 18, 9.1%), and brainstem dysfunction (n = 8, 4.0%), and other episodes (n = 74, 37.4%); 2) MS (confirmed by at least one other episode) for 151, including 90 (59.6%) with a higher initial index of early severity.[14]

A total of 371,996 households were contacted for the recruitment of controls. Among the 5,838 eligible households contacted, 1,666 refused to participate in the study at first contact. We identified 4,172 eligible controls who accepted and could be matched to the case on age, sex, and geographic location; 2,941 of them provided vaccination information (response rate 70.5%). The reasons for a lack of vaccination information for 1,231 recruited controls, despite initial consent, were no response despite a full recall procedure (n = 807, 65.6%), refusal at first recall (n = 208, 16.9%), lost vaccination certificate (n = 98, 8.0%), never reached by phone or incorrect telephone number or address given (n = 118, 9.5%).

Our analyses therefore included 349 cases of first episode of acute CNS inflammatory demyelination and 2,941 matched controls (n = 207, 7.0) were recruited from the same household) (table 1). Vaccination information was provided in the form of a copy of the vaccination records for 97.7% (n = 2,873) of controls; the others had a standardized telephone interview. However, all these data were used for analysis. The median number of controls per case was 9 (mean: 8.4): 60 (17.2%) had 11 to 12 controls, 232 (66.5%) had 7 to 10 controls, 50 (14.3%) had 4 to 6 controls, and only 7 cases (2.0%) had 1 to 3 controls. The frequency of family heads with a low socioprofessional status was lower for cases than for controls (table 1). The frequency of family history of MS was higher in cases, but the frequency of familial autoimmune diseases was similar in the two groups.

The rates of any HB vaccination in the 3 years before the index date were 24.4% for the 349 cases and 27.3% for their 2,941 matched controls. The adjusted OR of such episode occurrence associated with any HB vaccination during a risk period of 3 years was 0.74 (95% CI: 0.54–1.02). Other results of analyses in all study subjects are presented in table 2. Similar results were obtained for more detailed risk periods within 3 years, ever use, number of HB immunizations, and last brand type used. ORs were similarly not significantly different from 1 in analyses restricted to cases without a family history of MS or another autoimmune disease, or with a low socioprofessional status of head of family, or with an age at index date ≥3 years, or with an age at index date ≥10 years, or belonging to one or the other group of severity among MS cases. Similar results were found in considering the 1-year period just before the index date as an unexposed period or excluding the controls recruited from the same household.

When cases compliant with vaccination guidelines were compared with noncompliant according to variables of table 1, there were no significant differences except for location in Paris and suburbs for cases with a CNS inflammatory demyelination (42.9% in compliant vs 21% in noncompliant) and for the detection of oligoclonal bands in CSF (36.1% in compliant vs 58.2% in noncompliant) for confirmed MS. There was no differential compliance between cases and their matched controls because, before exclusions of cases without controls and of controls without cases required by the analysis method, 166/349 (47.6%) cases with a CNS inflammatory demyelination and 1,612/2,941 (54.8%) of their controls were compliant. It was the same for cases with confirmed MS: before exclusions required by the analysis method, 74/151 (49.0%) cases and 615/1,192 (51.6%) of their controls were compliant.

Table 2 Crude and adjusted OR of acute CNS inflammatory demyelination associated with timing, number, and brand of hepatitis B vaccine

Hepatitis B (HB) vaccine exposure	Case patients (n = 349), n (%)	Matched controls* (n = 2,941), n (%)	Crude OR†	Adjusted OR (95% CI)‡
No HB vaccination	195 (55.9)	1,543 (52.5)	1	Reference
HB vaccination before index date				
Ever use	154 (44.1)	1,398 (47.5)	0.80	0.81 (0.62–1.05)
0–1 y	30 (8.6)	317 (10.8)	0.64	0.65 (0.42–1.02)
>1–2 y	25 (7.2)	247 (8.4)	0.67	0.70 (0.43–1.16)
>2–3 y	30 (8.6)	239 (8.1)	0.93	0.94 (0.58–1.51)
>3 y	69 (19.8)	595 (20.2)	0.92	0.93 (0.65–1.31)
No. of HB immunizations before index date				
1–2	23 (6.6)	187 (6.4)	0.79	0.80 (0.48–1.32)
≥3	131 (37.5)	1,211 (41.2)	0.80	0.81 (0.62–1.06)
Last brand type used before index date				
Engerix B ever use	84 (24.1)	724 (24.6)	0.85	0.86 (0.63–1.16)
Engerix B 0–3 y	45 (12.9)	409 (13.9)	0.75	0.76 (0.52–1.12)
Engerix B >3 y	39 (11.2)	315 (10.7)	0.98	0.98 (0.65–1.48)
GenHevac B ever use	47 (13.5)	415 (14.1)	0.77	0.78 (0.52–1.16)
GenHevac B 0–3 y	24 (6.9)	229 (7.8)	0.65	0.68 (0.40–1.14)
GenHevac B >3 y	23 (6.6)	186 (6.3)	0.92	0.91 (0.54–1.54)
Other HB vaccine ever use§	23 (6.6)	259 (8.8)	0.70	0.71 (0.45–1.14)
Other HB vaccine 0–3 y	16 (4.6)	165 (5.6)	0.77	0.79 (0.46–1.38)
Other HB vaccine >3 y	7 (2.0)	94 (3.2)	0.58	0.59 (0.26–1.32)

*Matched on age (±6 months), sex, geographic location (current place of residence).
†No HB vaccine exposure is the reference group.
‡Adjusted on covariates: familial multiple sclerosis history, family history of another autoimmune disease, parental smoking at home before index date, socioprofessional status of the head of the family.
§HBVax, Hevac B, Twinrix, or Recombivax.

As shown in table 3, when the analysis was restricted to compliant cases and their matched compliant controls, HB vaccine exposure >3 years before index date was associated with an increased trend for acute CNS inflammatory demyelination, essentially from the Engerix B vaccine. The OR was particularly elevated for this major brand type in patients with confirmed MS (table 4). Similar results were found with other less restricted definition of compliance to vaccination (four diphtheria-tetanus-poliomyelitis vaccine and one mumps-rubella-measles during the first 2 years of life). Engerix B exposure >3 years before index date was associated with an adjusted OR of 1.50 (0.92–2.45) for CNS inflammatory demyelination and 2.40 (1.16–4.94) for confirmed MS. GenHevac B was associated with ORs of 1.36 (0.69–2.70) for CNS inflammatory demyelination and 1.21 (0.43–3.44) for confirmed MS. Similar results were also found with a third definition of compliance to vaccination (recommended but not obligated: one mumps-rubella-measles during the first 2 years of life). Engerix B exposure >3 years before index date was associated with an adjusted OR of 1.29 (0.82–2.03) for CNS inflammatory demyelination and 1.96 (1.00–3.82) for confirmed MS. GenHevac B was associated with ORs of 1.48 (0.80–2.71) for CNS inflammatory demyelination and 1.18 (0.46–3.06) for confirmed MS.

DISCUSSION This study is the second part of a research program evaluating the impact of vaccinations on acute CNS inflammatory demyelination in childhood. We evaluate the risk associated with HB vaccine exposure of any first episode of acute CNS inflammatory demyelination in childhood and report of a lack of increase in risk within a risk period of 3 years or more or considering the number of injections. However, in the subgroup analysis restricted to subjects compliant with vaccinations guidelines, Engerix B exposure >3 years before index date was associated with an increased risk that was significant in patients who went on to develop MS. Our new results suggesting a possible association of HB vaccine with pediatric MS (albeit HB vaccine of a specific manufacturer and only in vaccine-compliant

Table 3 Crude and adjusted OR of acute CNS inflammatory demyelination associated with timing, number, and brand of hepatitis B vaccine, restricted to subjects compliant with vaccination*

Hepatitis B (HB) vaccine exposure	Case patients (n = 163), n (%)	Matched controls† (n = 892), n (%)	Crude OR‡	Adjusted OR (95% CI)§
Unvaccinated	78 (47.9)	435 (48.8)	1	Reference
Vaccinated against HB before index date				
Ever use	85 (52.1)	457 (51.2)	0.96	1.03 (0.70–1.51)
0–1 y	13 (8.0)	78 (8.7)	0.78	0.81 (0.40–1.63)
>1–2 y	11 (6.7)	87 (9.8)	0.42	0.45 (0.20–1.01)
>2–3 y	14 (8.6)	79 (8.9)	0.82	0.89 (0.43–1.84)
>3 y	47 (28.8)	213 (23.8)	1.40	1.50 (0.93–2.43)
No. of HB immunizations before index date				
1–2	11 (6.7)	54 (6.1)	0.93	0.99 (0.46–2.15)
≥3	74 (45.4)	403 (45.2)	0.96	1.03 (0.70–1.53)
Last brand type used for vaccination before index date				
Engerix B ever use	51 (31.3)	236 (26.5)	1.11	1.17 (0.76–1.79)
Engerix B 0–3 y	20 (12.3)	121 (13.6)	0.68	0.71 (0.39–1.29)
Engerix B >3 y	31 (19.0)	115 (12.9)	1.63	1.74 (1.03–2.95)
GenHevac B ever use	22 (13.5)	121 (13.6)	0.91	1.03 (0.56–1.89)
GenHevac B 0–3 y	10 (6.1)	63 (7.1)	0.61	0.68 (0.28–1.65)
GenHevac B >3 y	12 (7.4)	58 (6.5)	1.34	1.50 (0.71–3.17)
Other HB vaccine ever use‖	12 (7.4)	100 (11.2)	0.65	0.70 (0.35–1.41)
Other HB vaccine 0–3 y	8 (4.9)	60 (6.7)	0.69	0.75 (0.32–1.77)
Other HB vaccine >3 y	2 (2.5)	40 (4.5)	0.59	0.63 (0.20–2.00)

*Defined as at least one BCG vaccine, one mumps-rubella-measles vaccine, and four diphtheria-tetanus-poliomyelitis vaccine during the first 2 years of life.
†Matched on age (±6 months), sex, geographic location (current place of residence).
‡No HB vaccine exposure is the reference group.
§Adjusted on covariates: familial multiple sclerosis history, family history of another autoimmune disease, parental smoking at home before index date, socioprofessional status of the head of the family.
‖HBVax, Hevac B, Twinrix, or Recombivax.

cases) are not in contradiction with prior results. Indeed, in this new study, we enlarged the analysis to all first episodes of CNS inflammatory demyelination and tried to address the potential selection bias from the partial answer of subjects who could participate, using different definitions of compliance to vaccination guidelines.

The first case reports in adults of a possible association between recombinant HB vaccine exposure and CNS inflammatory demyelination involved any first episodes of acute CNS inflammatory demyelination.[1,18-25] A French case-control study included 236 adult cases (193 with an initial episode of definite or probable MS according to follow-up data) and 355 matched controls recruited in hospital.[26] The adjusted ORs for CNS inflammatory demyelination within a 2-month risk period was 1.8 (95% CI: 0.7–4.6) in the whole group and 1.4 (95% CI: 0.4–4.5) in the subgroup of subjects referring to vaccination certificates during the phone interview. In a retrospective cohort study on 134,698 individuals (children and adults) enrolled in the US healthcare database (integrated pharmacy and medical claims from six health maintenance organizations plans) from 1988 to 1995, authors found no association between CNS inflammatory demyelination and HB vaccine (comparison to nonvaccinated individuals matched on age and sex) in the 3 years after vaccination and over.[27] However, the accuracy of validation of MS status was debated.[9]

Two case-control studies in adults focused on recombinant HB vaccine with a systematic validation procedure for case status and ascertainment of information on vaccinations from computerized records. The first, in three American health maintenance organizations, involved 108 cases of isolated optic neuritis and 332 of MS, matched to 950 controls, and found no increase in risk of both diseases combined or analyzed separately, associated with HB vaccine in the short or the long term (<1 year, 1–5 years, >5 years, and within 3 years after HB vaccination).[6,7] The second, a large database nested case-control study with patients issued from the General Practice Research Database in UK, involved 163 cases of MS,

Table 4 Crude and adjusted OR of confirmed multiple sclerosis associated with timing, number, and brand of hepatitis B vaccine, restricted to subjects compliant with vaccination*

Hepatitis B (HB) vaccine exposure	Case patients (n = 72), n (%)	Matched controls† (n = 347), n (%)	Crude OR‡	Adjusted OR (95% CI)§
Unvaccinated	27 (37.5)	153 (44.1)	1	Reference
Vaccinated against HB before index date				
Ever use	45 (62.5)	194 (55.9)	1.26	1.35 (0.72–2.56)
0–1 y	6 (8.3)	29 (8.4)	0.98	0.88 (0.28–2.79)
>1–2 y	6 (8.3)	41 (11.7)	0.42	0.45 (0.12–1.71)
>2–3 y	8 (11.1)	36 (10.4)	1.10	1.20 (0.38–3.74)
>3 y	25 (34.6)	88 (25.4)	1.86	2.12 (1.00–4.48)
No. of HB immunizations before index date				
1–2	5 (6.9)	27 (7.8)	0.78	0.75 (0.21–2.61)
≥3	40 (55.6)	167 (48.1)	1.34	1.48 (0.78–2.82)
Last brand type used for vaccination before index date				
Engerix B ever use	30 (41.7)	91 (26.2)	1.71	1.92 (0.96–3.85)
Engerix B 0–3 y	11 (15.3)	43 (12.4)	1.05	1.11 (0.43–2.90)
Engerix B >3 y	19 (26.4)	48 (13.8)	2.38	2.77 (1.23–6.24)
GenHevac B ever use	11 (15.3)	68 (19.6)	0.82	0.96 (0.38–2.46)
GenHevac B 0–3 y	6 (8.3)	35 (10.1)	0.69	0.82 (0.22–3.00)
GenHevac B >3 y	5 (6.8)	33 (9.5)	0.98	1.13 (0.36–3.55)
Other HB vaccine ever use‖	4 (5.6)	35 (10.1)	0.60	0.55 (0.14–2.07)
Other HB vaccine 0–3 y	3 (4.2)	28 (8.1)	0.51	0.45 (0.09–2.21)
Other HB vaccine >3 y	1 (1.4)	7 (2.0)	0.90	0.88 (0.07–10.54)

*Defined as at least one BCG vaccine, one mumps-rubella-measles vaccine, and four diphtheria-tetanus-poliomyelitis vaccine during the first 2 years of life.
†Matched on age (±6 months), sex, geographic location (current place of residence).
‡No HB vaccine exposure is the reference group.
§Adjusted on covariates: familial multiple sclerosis history, family history of another autoimmune disease, parental smoking at home before index date, socioprofessional status of the head of the family.
‖HBVax, Hevac B, Twinrix, or Recombivax.

matched to 1,604 controls, and reported a significant increase in the risk of adult-onset MS within the first 3 years of vaccination for adult MS (OR 3.1; 95% CI: 1.5–6.3).[10] The brand types used were not specified in all these studies.

The strengths of our study include the accurate ascertainment of the first episode of acute CNS inflammatory demyelination, the validation of the vaccination status by a copy of the vaccination certificates, and the inclusion of the vast majority of incident pediatric cases in France.[11] Another was the population-based nature of the selection of controls by random sampling for controls among the French population, with matching on age, sex, and geographic area of living of the corresponding case. It was tempered by the partial response rate of controls. Indeed, 1,666 eligible households contacted refused to participate in the study. Although these controls were replaced by others who were also individually matched with cases and agreed to participate at initial contact, this could have introduced a selection bias. However, it is a constant limitation of case-control studies on vaccine safety and the level of participation we obtained was satisfying compared to previous population-based case-control field studies, as discussed previously.[11,16,28,29] To address this bias, we restricted the analysis to subjects who were compliant with vaccinations guidelines. We deemed that the actual response rate to our requests among compliant subjects would be higher than in less compliant subjects. The rates of exposure to vaccines in controls were consistent with that previously described for the general childhood population in France, considering the study period.[17] In compliant subjects, the OR was particularly elevated for Engerix B vaccine, the major brand type, in patients with confirmed MS. This analysis was not performed in our previous study in patients with MS that already indicated a nonsignificant trend toward a higher risk in subjects having received Engerix B >3 years before the index date. Considering the relatively small number of exposed subjects, the results concerning GenHevac B vaccine should be considered inconclusive. A clinically relevant risk associated with this vaccine cannot

be ruled out by this study. Our significant results concerning Engerix B vaccine were obtained from subgroup analyses, and were thus subject to false significance from multiple comparisons. Nevertheless, the risk magnitude we observed in patients with MS for Engerix B vaccine exposure is close to the one using the General Practice Research Database in United Kingdom, for exposure to any HB vaccine within 3 years before index date.[10] However, this latter study did not present analysis according to the brand. Further studies would be needed to assess the brand influence among the UK population of adults in this study period and to confirm our results in children. Differences between children and adults in susceptibility to immune stimulation must be considered to interpret the results.[3,30] Two possible explanations for the differences between brands could be as follows: 1) each vaccine uses a different section of the HBs antigen and some protein fragments produced by yeasts may induce molecular mimicry while others do not; 2) the production process varies by brand and differences in yeast protein content may be crucial if yeast protein may trigger autoimmune reactions: it is stated in the description of Engerix B manufacturing process that the vaccine has no more than 5% of yeast proteins, whereas it is no more than 1% for GenHevac B.

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APPENDIX

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