VACCINATIONS AND THE RISK OF RELAPSE IN MULTIPLE SCLEROSIS

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ABSTRACT

Background   There has been some concern that vaccination may precipitate the onset of multiple sclerosis or lead to relapses. Since the recent hepatitis B vaccination program in France, there have been new reports of an increased risk of active multiple sclerosis after vaccination.

Methods   We conducted a case–crossover study to assess whether vaccinations increase the risk of relapse in multiple sclerosis. The subjects were patients included in the European Database for Multiple Sclerosis who had a relapse between 1993 and 1997. The index relapse was the first relapse confirmed by a visit to a neurologist and preceded by a relapse-free period of at least 12 months. Information on vaccinations was obtained in a standardized telephone interview and confirmed by means of medical records. Exposure to vaccination in the two-month risk period immediately preceding the relapse was compared with that in the four previous two-month control periods for the calculation of relative risks, which were estimated with the use of conditional logistic regression.

Results   Of 643 patients with relapses of multiple sclerosis, 15 percent reported having been vaccinated during the preceding 12 months. The reports of 94 percent of these vaccinations were confirmed. Of all the patients, 2.3 percent had been vaccinated during the preceding two-month risk period as compared with 2.8 to 4.0 percent who were vaccinated during one or more of the four control periods. The relative risk of relapse associated with exposure to any vaccination during the previous two months was 0.71 (95 percent confidence interval, 0.40 to 1.26). There was no increase in the specific risk of relapse associated with tetanus, hepatitis B, or influenza vaccination (range of relative risks, 0.22 to 1.08). Analyses based on risk periods of one and three months yielded similar results.

Conclusions   Vaccination does not appear to increase the short-term risk of relapse in multiple sclerosis. (N Engl J Med 2001;344:319-26.)

THE safety of vaccinations in patients with multiple sclerosis has been debated for decades.[1] Clinical onset and relapses of multiple sclerosis after vaccination have been reported.[2-20] The results of post-marketing surveillance studies[21-28] and small studies of the safety of influenza vaccination in patients with multiple sclerosis[29-36] have been reassuring. However, most clinicians are still reluctant to vaccinate patients with multiple sclerosis. Recently, there have been reports of onset or relapse of multiple sclerosis after the extensive immunization program in France against hepatitis B.[20,28,37-39]

To assess whether vaccination increases the short-term risk of relapse in patients with multiple sclerosis, we designed the Vaccines in Multiple Sclerosis (VACCIMUS) Study, an observational, multicenter, case–crossover study. The study was conducted in a network of multiple sclerosis clinics that have standardized, computerized patient records. In patients who had had a relapse of multiple sclerosis, exposure to vaccination in the period immediately preceding the relapse was compared with that during control periods, so that patients served as their own controls.

METHODS

Source Population

Study subjects were chosen from among patients with multiple sclerosis attending neurology centers affiliated with the European Database for Multiple Sclerosis (EDMUS) network.[40] The EDMUS software, introduced in 1990 and currently used in more than 180 clinics worldwide,[41] enables users to collect in a standardized fashion retrospective and prospective data on patients with multiple scle-

rosis. Among hospital-based medical centers with more than 500 patients enrolled in their data bases, six centers in France, Spain, and Switzerland successfully underwent a pilot phase and were selected for the study.

Definition of Cases

Eligible patients were initially identified from the EDMUS data base of each participating center by means of a computer algorithm. All patients with a definite or probable diagnosis of multiple sclerosis according to the diagnostic criteria of Poser et al.[42] and with at least one index relapse of the disease were considered for inclusion. A relapse was defined as an occurrence, reappearance, or worsening of symptoms of neurologic dysfunction that lasted more than 24 hours. Fatigue alone or a transient, fever-related worsening of symptoms was not considered to be a relapse. Symptoms that occurred within one month of each other were considered to be part of the same relapse.[40] The index relapse was defined as the first relapse that occurred between January 1, 1993, and December 31, 1997, was confirmed at an outpatient visit or during a hospitalization in the center within 2 months, and was preceded by a relapse-free period of at least 12 months. According to the design of the study, the initial manifestations of the disease could not be selected as the index relapse.

The fact that patients met the criteria for inclusion and the features of relapses were confirmed by a neurologist on the basis of medical files. The level of certainty of the index relapse was assessed as follows: definite, if the neurologist determined that highly suggestive symptoms were present and that there was objective confirmation on examination; probable, if highly suggestive symptoms were present but there was no objective confirmation on examination; and possible, if only atypical or minimal symptoms were present. Additional information regarding the history of the disease was also collected, including the course of disease,[43,44] the course of disability,[45] the occurrence of any relapses before the index relapse, and prescriptions for corticosteroids or immunosuppressive or immunomodulating treatments during the 18 months before the index relapse.

Assessment and Confirmation of Exposure to Vaccines

Eligible patients were invited by letter to seek information about their vaccinations between January 1, 1992, and December 31, 1997 — i.e., for a standard six-year period starting one year before the period of interest for index relapses. They were provided with a list of existing vaccines and conditions that might be related to vaccination.

Interested patients were then interviewed by the study administrator of their center, who used a standardized telephone questionnaire. For all patients, data were collected regarding vaccinations received during the entire six-year period (1992 through 1997). Patients were unaware of the specific hypothesis being tested and of the date of the relapse of interest. The interviewer was unaware of which relapse was of interest. The interview included systematic questions related to all vaccinations the patient might have received. Whenever a vaccination was reported, detailed information on the nature, name, and date of the vaccine was collected. A vaccination was defined as the administration of a commercial preparation of vaccine, regardless of whether it was monovalent or multivalent (i.e., specific for several infectious diseases), whether it was a single vaccination or part of a series, and whether it was for primary immunization or was a booster. Information about reported vaccinations was confirmed on the basis of written medical documentation, usually a copy of the vaccination record. When the copy could not be obtained from the patient, written confirmation was sought from the physician who had performed the vaccination; a high priority was placed on obtaining such confirmation for vaccinations reported to have been received during the 15 months before the index relapse. At the end of the study, an additional confirmation procedure was performed with the data from a random sample of 97 patients drawn from all centers who reported having received no vaccinations between 1992 and 1997: a copy of the patients' vaccination records was requested, and their general practitioners were contacted to verify the absence of vaccinations.

Study Design

The case–crossover design of this study is equivalent to a case–control approach in which patients serve as their own controls, with data used from different points in time.[46] The subjects were patients who had had a relapse of multiple sclerosis. We assessed the relative risk of relapse associated with vaccination by comparing the exposure to vaccination in the period immediately preceding the index relapse (the risk period) with that in control periods that preceded the risk period and were not followed by a relapse (Fig. 1).

On the basis of the literature,[1-39] analyses were performed under the assumption that a relapse due to vaccination would occur within two months after vaccination; we also performed analyses using one- and three-month periods. Patients who had received at least one vaccination during the two months before the index relapse were considered to have been exposed during the risk period. For each patient, the four two-month periods preceding the risk period were used as control periods. In the analyses based on a one-month risk period, we used the previous nine one-month periods as control periods, and in the analyses based on a three-month risk period, we used two three-month control periods.

Statistical Analysis

Each exposure to vaccine during the 10 months before the index relapse was allocated either to the risk period or to a control period, depending on when it occurred with respect to the date of the index relapse and on the duration of the risk period chosen for the analysis. We measured the association between exposure to vaccine and the occurrence of a relapse within two months after exposure by estimating the odds ratio for exposure during the risk period as compared with exposure during the control periods. Conditional logistic regression was used for these estimations, because there was a 1:4 ratio between the risk period and the control periods for each patient. The main analysis was performed with the inclusion of the data for all patients, regardless of the level of certainty about their index relapse, and all confirmed vaccinations. On the basis of the results of a pilot phase, the probability of exposure to vaccination during any two-month control period was estimated to be 2.8 percent. With four control periods per patient and a one-tailed α level of 0.05, the inclusion of 600 patients allowed the study to detect an odds ratio of 2.0 with a statistical power of more than 90 percent. Therefore, the protocol specified that enrollment would stop when this target number of patients was reached. To assess the robustness of the findings, sensitivity analyses were performed for one- and three-month periods of exposure, for all reported vaccinations even if they were not confirmed, and for only the patients with a definite index relapse. Additional analyses were performed according to the type of vaccine. All analyses were performed with the use of SAS software.[47]

To ensure the strict application of the protocol, a user's manual was provided to the study administrator at each center and the study was monitored by research assistants from a clinical research organization. All patients gave informed consent for their inclusion in the study; consent was oral in all cases and written in the majority of cases. The use of computerized files at the hospitals in France was authorized by the French Commission Nationale de l'Informatique et des Libertés. The study protocol was approved by the ethics committees of the hospitals in Basel, Switzerland, and Barcelona, Spain. The organization of the study was approved by the Société Française de Neurologie. The study was overseen by a scientific advisory board composed of independent experts who approved the protocol, conduct, analysis, and publication of the study.

RESULTS

Eligibility and Base-Line Characteristics of the Patients

At the six participating centers, a total of 1176 patients were found by the computer algorithm to be
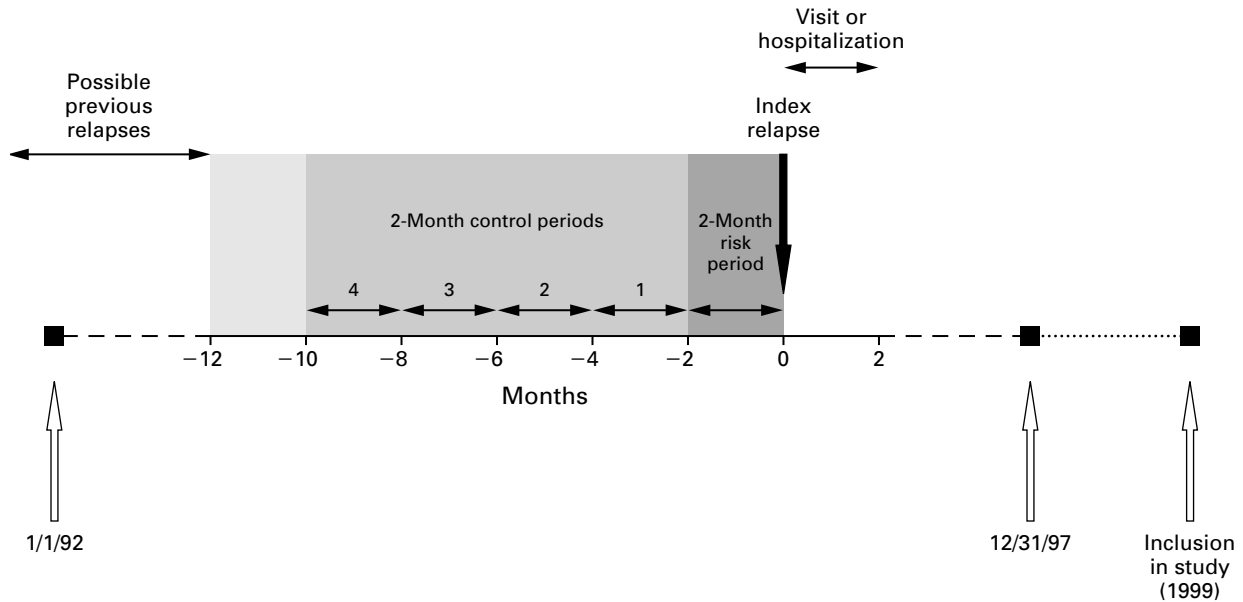
Figure 1. The Case–Crossover Design Used in the Study.
Previous relapses could have occurred at any time before 12 months before the index relapse.

eligible; 1037 of these patients were confirmed as eligible on the basis of medical records; 1009 were sent an informational letter; and 960 consented to be interviewed. Recruitment was stopped when the target number of patients was reached. At that point, 643 patients had been interviewed (Fig. 2). The base-line characteristics of the 216 patients who did not consent to be interviewed or who were excluded for the reasons listed in Figure 2 did not differ substantially from those of the patients who were included.

Index Relapse

The index relapse was considered by the neurologists at each center to be definite in 492 patients (77 percent), probable in 112 patients (17 percent), and possible in 39 patients (6 percent). By design, the interval between the index relapse and the previous relapse was at least 12 months. It was greater than 18 months in 468 patients (73 percent).

Vaccinations

The patients reported having received 960 vaccines during the period between 1992 and 1997; of these, 748 (78 percent) could be confirmed. Eighty percent of the confirmed vaccinations (596 of the 748) were confirmed by means of copies of vaccine certificates. During the confirmation procedure used for the 97 randomly sampled patients with no reported vaccinations, 3 patients could not be contacted, nonvaccinated status could be formally confirmed for 89 patients, and confirmation was not possible for 5. No vaccina-

tions were discovered in any patients during this procedure.

Of the 643 interviewed patients, 260 (40 percent) had received at least one confirmed vaccination between 1992 and 1997, 57 (9 percent) reported vaccinations that could not be confirmed, and 326 (51 percent) reported receiving no vaccination at all. The patients with confirmed vaccinations were younger, had had fewer relapses before the index relapse, and had a lower Kurtzke disability score[45] (range, 0 to 10, with higher scores indicating more severe disability) than the patients with no validated vaccinations (Table 1).

During the 12 months preceding the index relapse, 96 patients (15 percent) reported 144 vaccinations, 135 of which (94 percent) could be confirmed. Of these 135 vaccinations, 49 percent were against tetanus, either alone or in combination with poliovirus or diphtheria or both, and only 2 were live attenuated vaccines (Table 2). A total of 89 patients (14 percent) received these 135 confirmed vaccinations during that 12-month period, 60 receiving 1 vaccination only, 18 receiving 2, 8 receiving 3, and 3 receiving 4 or more. Their base-line characteristics are provided in Table 1. In 71 of these patients (80 percent) the index relapse was assessed as definite, in 15 patients (17 percent) as probable, and in 3 patients (3 percent) as possible.

Vaccination and Risk of Relapse

The proportion of patients vaccinated during any one of the four two-month control periods ranged
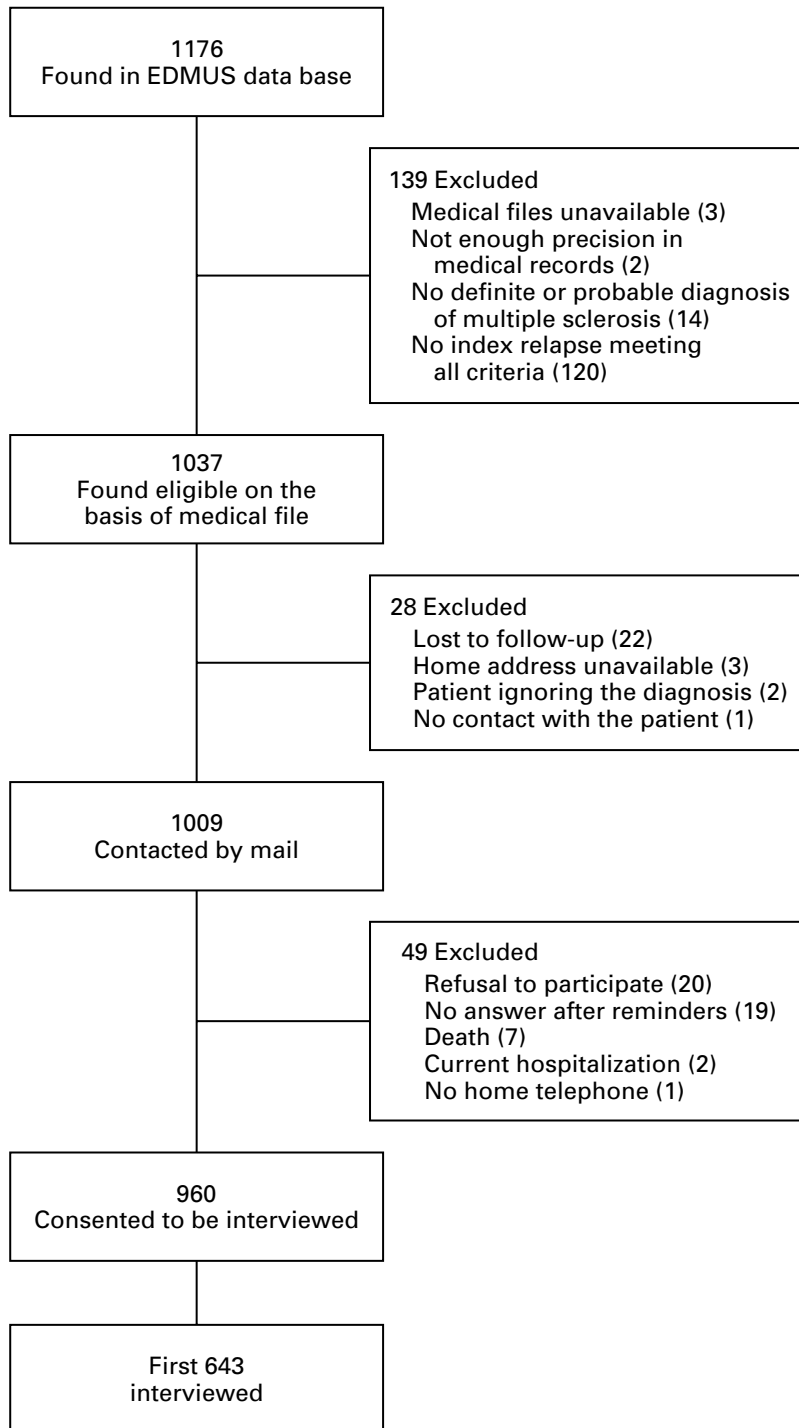
Figure 2. Numbers of Patients with Multiple Sclerosis Assessed and Enrolled in the Study.

TABLE 1. BASE-LINE CHARACTERISTICS OF 643 PATIENTS WITH A RELAPSE OF MULTIPLE SCLEROSIS, ACCORDING TO EXPOSURE TO VACCINATIONS.*

CHARACTERISTIC	NO VACCINATION OR ONLY UNCONFIRMED VACCINATIONS BETWEEN 1992 AND 1997 (N=383)	AT LEAST 1 CONFIRMED VACCINATION BETWEEN 1992 AND 1997 (N=260)	P VALUE	AT LEAST 1 CONFIRMED VACCINATION IN THE 12 MO PRECEDING THE INDEX RELAPSE (N=89)
Center — no. (%)			0.008	
Rennes, France	94 (25)	83 (32)		26 (29)
Lyons, France	91 (24)	79 (30)		26 (29)
Barcelona, Spain	76 (20)	31 (12)		13 (15)
Toulouse, France	53 (14)	29 (11)		13 (15)
Bordeaux, France	51 (13)	33 (13)		10 (11)
Basel, Switzerland	18 (5)	5 (2)		1 (1)
Female sex — no. (%)	260 (68)	188 (72)	0.23	69 (78)
Age at index relapse — yr	39±10	37±11	0.04	37±11
Last known Kurtzke disability score†	3.1±2.2	2.4±2.1	0.001	2.1±2.0
Median	3	2		1
Range	0–8	0–9		0–7
Diagnosis of multiple sclerosis — no. (%)‡			0.96	
Definite	370 (97)	251 (97)		86 (97)
Probable	13 (3)	9 (3)		3 (3)
Type of initial symptoms — no. (%)			0.81	
Optic neuritis only	83 (22)	63 (24)		22 (25)
Brain-stem symptoms only	59 (15)	34 (13)		11 (12)
Long tract symptoms only	178 (46)	116 (45)		40 (45)
Mixed symptoms	56 (15)	43 (17)		14 (16)
Other or unknown	7 (2)	4 (2)		2 (2)
Course of disease — no. (%)§			0.10	
Relapsing–remitting	280 (73)	209 (80)		73 (82)
Secondary progressive	92 (24)	45 (17)		14 (16)
Progressive relapsing	11 (3)	6 (2)		2 (2)
Duration of disease at index relapse — yr	9.5±7.6	8.6±7.4	0.13	8.6±7.9
Median	7	6		7
Range	1–43	1–43		1–43
No. of relapses before index relapse	3.9±3.5	3.3±3.0	0.02	3.0±2.7
Median	3	2		2
Range	1–25	1–23		1–13
Disease-modifying agent — no. (%)¶			0.10	
Any	88 (23)	45 (17)		11 (12)
Azathioprine	54 (14)	28 (11)		7 (8)
Methotrexate	9 (2)	4 (2)		2 (2)
Interferon beta	17 (4)	6 (2)		1 (1)

*Plus–minus values are means ±SD.

†The Kurtzke Disability Status Scale[45] is an ordinal scale based on data from neurologic examination and ambulatory ability. It ranges from 0 (no neurologic abnormality) to 10 (death related to multiple sclerosis).

‡The Poser criteria for diagnosis[42] are dissemination of lesions in time; dissemination of lesions in space, evidence of which may be clinical or paraclinical (from magnetic resonance imaging, computed tomography, or measurement of evoked potentials); and quantitative or qualitative abnormalities of immunoglobulins in the cerebrospinal fluid. Clinically definite cases are defined by dissemination in time and space, regardless of the results of cerebrospinal fluid analysis; laboratory-supported definite cases are defined by abnormalities in the cerebrospinal fluid and either dissemination in time or dissemination in space; clinically probable cases are defined by dissemination in time or space alone; laboratory-supported probable cases are defined by abnormalities in the cerebrospinal fluid alone.

§In the relapsing–remitting form of multiple sclerosis, relapses are separated by periods of remission with clinical stability, and there is no progression (continuous worsening of neurologic symptoms and signs for a minimum of six months) between relapses. In the progressive forms, there is a continuous worsening of neurologic symptoms and signs for a minimum of six months, with or without superimposed relapses. Clinical progression in multiple sclerosis can occur after an initial relapsing–remitting phase of the disease (secondary progressive form) or from the clinical onset of the disease (primary progressive form).[43,44]

¶The modifying agent was administered for a minimum of 3 months during the 18 months preceding the index relapse.

VARIABLE	NO. OF PATIENTS (%)
Type of vaccine*	
Monovalent	
Hepatitis B	39 (28.9)
Tetanus	25 (18.5)
Influenza	23 (17.0)
Hepatitis A	2 (1.5)
Typhoid	2 (1.5)
Yellow fever (live vaccine)	2 (1.5)
Total	93 (68.9)
Combined	
Combined tetanus with poliovirus, diphtheria, or both	41 (30.4)
Typhoid and paratyphoid	1 (0.7)
Total	42 (31.1)
Vaccination rates during the periods before the index relapse†	
1–2 mo (risk period)	15 (2.3)
3–4 mo (1st control period)	19 (3.0)
5–6 mo (2nd control period)	18 (2.8)
7–8 mo (3rd control period)	26 (4.0)
9–10 mo (4th control period)	19 (3.0)
11–12 mo	17 (2.6)

*Percentages are of the 135 patients with confirmed vaccinations during the 12-month period.

†Percentages are of the 643 patients with multiple sclerosis.

TABLE 3. RISK OF RELAPSE ASSOCIATED WITH EXPOSURE TO SPECIFIC VACCINES IN THE TWO MONTHS PRECEDING A RELAPSE IN 643 PATIENTS WITH MULTIPLE SCLEROSIS.*

TYPE OF VACCINE	PERCENT EXPOSED		RELATIVE RISK (95 PERCENT CONFIDENCE INTERVAL)
	RISK PERIOD	CONTROL PERIODS	
Any vaccine	2.3	3.2	0.71 (0.40–1.26)
Tetanus alone	0.6	0.8	0.75 (0.23–2.46)
Combined tetanus	0.3	1.2	0.22 (0.05–0.99)
Hepatitis B	0.6	0.9	0.67 (0.20–2.17)
Influenza	0.8	0.7	1.08 (0.37–3.10)
Monovalent vaccines	2.0	2.3	0.92 (0.49–1.74)
Combined vaccines	0.3	1.1	0.26 (0.06–1.12)

*For each patient there was one risk period and four control periods.

dex relapse (calendar year, month of onset, or time elapsed since the previous relapse).

DISCUSSION

This study suggests that commonly administered vaccinations (specifically, against tetanus, hepatitis B, and influenza) do not increase the risk of relapse in patients with multiple sclerosis. Most vaccinations, especially those against tetanus plus poliomyelitis or diphtheria, were actually associated with a lower risk of relapse, although the difference was not significant. Results remained stable when the length of the risk period was varied from one to three months and when all reported vaccinations were included, even if they were not confirmed. Interestingly, the proportion of patients who had been vaccinated during the 12 months preceding the relapse was relatively high (15 percent) and was extremely stable over that period. The study results are consistent with the lack of increase in disease activity observed on magnetic resonance imaging in patients with multiple sclerosis after influenza vaccination[33,34] or vaccination with bacille Calmette–Guérin.[48] Some studies[49,50] have also reported a lack of association between hepatitis B vaccination and the onset of multiple sclerosis, in contrast to others that have suggested some association.[37-39]

The case–crossover design of this study, equivalent to a case–control approach in which patients serve as their own controls, has numerous advantages for studies of acute events such as relapses of multiple sclerosis and transient exposures such as vaccinations. It is efficient, since it does not require control subjects, and in this case, it enabled us to account for confounding factors that could not be accounted for with a classic case–control design because of the large variability in the course of disease in patients with multiple sclerosis. However, the design does necessitate some assumptions. First, the risk of relapse after vaccination is as-

from 2.8 to 4.0 percent; the proportion vaccinated during the two-month risk period was 2.3 percent (Table 2). The relative risk of relapse associated with any vaccine exposure during a two-month period was 0.71 (95 percent confidence interval, 0.40 to 1.26), with specific relative risks for tetanus, hepatitis B, and influenza vaccines ranging from 0.22 to 1.08 (Table 3).

The overall relative risk of relapse associated with exposure to vaccination remained stable between 0.68 and 0.79 when one to five two-month control periods were used in the analysis. It did not change substantially when we performed sensitivity analyses using periods of varying lengths. The relative risk of relapse associated with any vaccine exposure during a three-month period was 0.58 (95 percent confidence interval, 0.35 to 0.99). With a one-month risk period and three to seven control periods, the relative risk varied from 0.97 to 1.18, with confidence intervals wider than 0.6 to 1.8. When all reported vaccinations were considered even if they were not confirmed, the relative risk was 0.76 (95 percent confidence interval, 0.44 to 1.31). The relative risk remained stable when the analysis was restricted to patients with a definite relapse (0.58; 95 percent confidence interval, 0.29 to 1.15). The relative risk was not substantially modified by consideration of a series of other characteristics of the in-

sumed to be the same after each vaccination. We repeated the analysis in patients who had had only one vaccination, and the risk was unchanged. Second, vaccination exposure is assumed to be constant over time during the control periods — an assumption that our study confirmed. Third, recall bias is a potential problem, since exposures at different times are compared.

A strength of our study is that data on vaccination exposures were collected for the entire study period, and the patients were unaware of the specific hypothesis being tested and the timing of the relapse of interest. Thus, recall bias is likely to have been minimal. In addition, 94 percent of the vaccinations were confirmed on the basis of medical documentation, and the lack of exposure to vaccines was confirmed in a sample of patients who reported receiving no vaccinations. We considered only relapses that were followed by a consultation with a neurologist within two months. The quality of the data in our study was ensured by on-site monitoring and confirmation on the basis of medical records. Finally, the study was designed to have 90 percent power to detect a doubling of the risk of relapse within two months after vaccination. The results are compatible with a relative risk of up to 1.26 with 5 percent error.

Selection bias is likely to have been minimal in this study. Patients were identified retrospectively through the use of a computerized algorithm in data bases of a European network already used for epidemiologic studies.[41,51] This method allowed us to identify all eligible patients in the data bases, using standardized definitions. To design a case–crossover study that allowed sufficient time for exposure during the control periods and a constant probability of exposure to vaccination, we restricted the study to patients with multiple sclerosis who had had a relapse preceded by a relapse-free period of 12 months. This criterion led to the exclusion of patients with very frequent relapses.

The choice of a two-month risk period in which vaccination might be considered to trigger a relapse was based on data from the literature and on expert opinion. The additional analyses performed with periods of one and three months yielded relative risks of 1.18 and 0.58, respectively, indicating that one month was probably the most relevant risk period in this population of patients with multiple sclerosis who had received inactivated vaccines, most of which were tetanus boosters likely to induce rapid immunologic stimulation. The relative risk seems to decrease when the length of the risk period is increased, possibly because of a dilution effect.

Our analyses consistently identified no increased risk of relapse after vaccination in patients with multiple sclerosis who were relapse-free for at least 12 months before the relapse of interest.

APPENDIX

The members of the VACCIMUS Study Group were as follows: *Design and Protocol Committee:* C. Confavreux, S. Vukusic, A. Biron, and M.H. Le Hir (EDMUS Coordinating Center, Lyons, France); C. Wolfson (Center for Clinical Epidemiology and Community Studies, Jewish General Hospital, Montreal); S. Suissa (McGill Pharmacoepidemiology Research Unit, Montreal); and P. Saddier, C. Vaillant, L. Hedreville, and S. Mitter (Aventis Pasteur, Lyons, France). *Final Steering Committee:* study coordination by C. Confavreux and V. Bourdès (EDMUS Coordinating Center, Lyons, France); epidemiology and statistics by S. Suissa and B. Rainville (McGill Pharmacoepidemiology Research Unit, Montreal). *Scientific Advisory Board:* A. Compston (Cambridge, United Kingdom); E. Miller (London); and R. Salmi (chairman, Bordeaux, France). *Investigators and study administrators:* T. Arbizu, O. Carmona, and A. Martinez-Yélamos (Barcelona, Spain); L. Kappos, D. Schoett, and M. Hoschi (Basel, Switzerland); B. Brochet, A. Gayou, and H. Brochet (Bordeaux, France); C. Confavreux, S. Vukusic, and A.C. Foray (Lyons, France); G. Edan, P. Brunet, and I. Brunet (Rennes, France); and M. Clanet, M. Mestassi, and F. Ory (Toulouse, France). *Clinical Research Organization:* MAPI Clinical Research, Lyons, France (X. Fournie, V. Oriol, and F. Poulenard).

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