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Hepatitis B vaccination and central demyelination – History, description and observed/expected analyses of 624 cases reported to the French pharmacovigilance over a 20-year period

Julie Mouchet *, Bernard Bégaud

Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, F-33000 Bordeaux, France

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ABSTRACT

Background: Confidence in vaccines is essential for achieving targeted immunization coverage. The current skepticism about vaccine safety feeds on controversies such as the suspicion about a link between hepatitis B (HB) vaccination and central demyelination (CD) after the massive HB immunization campaign in France in 1994–2000. This study assesses the robustness of this signal by analysing all validated cases reported in 1980–2000 and by conducting observed-to-expected (OE) comparisons.
Methods: After characterizing case profiles, reporting rates per 1,000,000 vaccine doses sold were computed for the period and per year. OE comparisons were conducted by using individual-based and person-year approaches and were stratified by gender.
Finding: A total of 624CD cases including 422 incident cases of multiple sclerosis (MS) were reported over 20 years. Women accounted for 73.2% (n = 457). Mean age was 29.8 years (SD = 11.1). Incidence of events peaked in 1995–1996 and 1997, these years accounting for 59.8% (n = 373) of cases. Events were mainly reported after booster doses (46.3%, n = 289). The overall reporting rate was 6.5 per 1,000,000 doses sold. The OE analyses produced inconclusive results, the number of observed cases remaining below the expected number.
Conclusions: The complete disjunction between target and joint populations in the 1990s French HB immunization campaign created an unpreceded situation with ~26 million of adults exposed at the age of MS onset. Two findings are noteworthy: the non-random distribution of reports according to the rank of vaccination or years of survey, and the fact that the number of reports sometimes approached the baseline incidence of MS, irrespective of underreporting. While the nature of the link remains unclear, our results are not consistent with a strong association between HB vaccine and MS. Current recommendations targeting newborns with a possible catch-up of at-risk adults should remain the preferred strategy in low-endemic countries.

1. Introduction

Confidence in vaccines is essential for achieving targeted immunization coverage. Recently, a large survey on confidence in immunization across 67 countries showed that Europe has the lowest confidence in vaccine safety, France being the worst [1]. The causes of this widespread skepticism are multiple and complex, but it is obvious that the debate which arose in the 90s about a putative link between hepatitis B (HB) vaccination and central demyelination played a major role. In July 1994, the French Health Ministry decided to launch a massive immunization campaign targeting newborns, children in the first year of secondary school and high-risk adults. By July 1996, i.e. less than two years later, 249 cases of central demyelinating disorders, including multiple sclerosis (MS), identified after injection of HB vaccine were reported to the French Medicines Agency [2]. In fact, a marked disjunction between the target and actually vaccinated population was observed: the immunization rate never exceeded 30% in newborns [3], whereas over 20 million adults, i.e. largely 10 times more than the high-risk population, were vaccinated at an age known to be at risk for MS and central demyelinating disorders [2,4]. The polemic was largely covered by the mass media. The French Medicine Agency conducted a nationwide investigation, and fourteen worldwide studies attempted to assess the putative association between central demyelination and HB vaccination [2,5–17]. Two previous

* Corresponding author.
E-mail address: julie.le-moal@u-bordeaux.fr (J. Mouchet).

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studies sought to estimate the strength of the French signal, but their aim was not to provide a history and extensive analysis of the campaign launched in France in 1994. Neither of them covered all the cases recorded by the national pharmacovigilance system during the critical period. Indeed, in both studies, the analysis was restricted to the first three years (1994–1996). Other limitations can be pointed out. For example, in the letter by Fourrier and Bégaud, 2001, the immunization schedule used for computations (3 injections at 1-month interval) did not represent the actual immunization practice at that time. Another point is that the authors derived the annual incidence of MS from prevalence data and the estimated duration of the disease, as no incidence rates were available at that time in France. Therefore, considering the much broader scope of our article, the historical perspective it provides, the methodological flaws of previous studies, and the importance of the polemic, which is still raging, it was of the utmost importance to re-assess the plausibility of this signal.

Among the pharmacoepidemiologic arsenal, observed-to-expected (OE) analyses aim at refining previously detected signals [18]. They cannot assess the degree of causality between an event and a medicinal product, but they help in interpreting the strength of a signal by putting suspected adverse reaction reports into context. For vaccines, large populations are usually exposed and potential rare events, related or not, may then be observed in the immunized population. The basic principle of OE analyses is to estimate the number of coincidental associations which would have been expected in any case under the null hypothesis of no association between the vaccine and the disease, and to compare it with the number of cases actually observed or reported. The latter is easily obtained by data from pharmacovigilance, i.e. spontaneous reporting, while the expected number can be derived from background incidence rates standardized according to the characteristics of the immunized population [18,19].

The objectives of this paper were to review and describe all cases of central demyelination, including multiple sclerosis (MS), reported in France after HB vaccination between 1980 and 2000, and to conduct several OE analyses in order to assess the robustness of the signal detected from which the polemic arose.

2. Methods

2.1. Study design

The present study reviewed all the cases of incident central demyelination occurring after HB vaccination reported to the French pharmacovigilance since the launch of the first HB vaccine in France (i.e., Hevac B® [Sanofi-Pasteur] in 1981) and 31 December 2000 (i.e., cut-off date of the pharmacovigilance report on the putative link between MS and HB vaccination, issued in France in 2001). OE analyses were restricted to cases of incident MS (i.e., first symptoms of MS, excluding relapses) and carried out by using two different approaches: an individual-based method and a population-time approach (considering person-years at risk).

2.2. Data sources

The complete reports issued by the French pharmacovigilance on the number and summaries of case reports of demyelination following HB vaccination were used to identify cases of interest. Relevant data were abstracted into an Excel standardized matrix including the identification number, the vaccine brand name or type, the vaccination date, the age and gender of the case, the rank of vaccination, the date of event, the event of interest, the vaccination and medical history of the case, the coadministration of other vaccines and additional comments in free text (if any). The level of data completion was dependent on the case report. At least two fields were required for case selection and data extraction: the event of interest and the date of either event occurrence or vaccination.

A high-level scientific and grey literature review was conducted in March 2018 to identify the background incidence rates of MS (overall and by gender) during the years covered by our study, as well as the number of HB vaccine doses sold during that period. Literature searches using a combination of keywords such as incidence, prevalence, multiple sclerosis, demyelination, vaccine, dose, France or French were performed in Medline via PubMed and were then complemented by pragmatic searches in Google and Google Scholar using similar keywords.

2.3. Events of interest

For the descriptive analysis, incident events of central demyelination including MS were considered, while the OE analysis was restricted to cases of incident MS only. At the time of the investigation in the early 2000s, these events were all reviewed and confirmed by a senior neurologist. Both adult and pediatric populations were investigated.

Relapses of MS, Guillain-Barré syndrome and peripheral demyelination (including Parsonage-Turner syndrome, chronic polyneuropathy and neuropathy) were excluded.

2.4. Statistical analysis

All case characteristics were summarized using descriptive techniques: summary statistics (mean, standard deviation (SD), median, minimum and maximum values) were computed for continuous variables while counts and percentages were calculated for categorical and binary variables.

Reporting rates (i.e., number of cases reported to the French pharmacovigilance system per 1,000,000 doses of HB vaccines sold) were computed for the whole study period and per year.

Time-to-onset was defined as the time interval between the last vaccine dose injection (regardless of the vaccine rank) and the occurrence of the event, while time-to-report refers to the interval between the event occurrence and the case reporting.

Two analytic approaches were used for OE analyses. The first (here referred to as "individual-based") was based on the number of subjects exposed to the HB vaccination, which was derived from the number of vaccine doses sold in France during the study period. To derive the number of exposed subjects, the total number of vaccines doses sold each year was divided by the number of injections recommended for a complete immunization schedule: four for years 1980–1994 and three thereafter, given that the vaccination schedule was revised in 1994 to reduce the immunization scheme to three doses at 0, 1 and 6 months. The booster dose at 12 months was therefore no longer recommended after 1994. The number of expected MS cases were derived from the MS background incidence rates for the French adult population per year of interest (from 1984 to 2000) and two-sided confidence intervals at 95% were computed by using the binomial distribution. The number of expected cases was then compared to the number of observed cases, i.e. case reports of the disease considered. OE analyses were then stratified by gender.

The second method was based on the total number of person-years "at risk" in the vaccinated population. Considering that (i) the HB vaccine induces specific humoral antibodies against HB surface antigens protective against the HB infection (i.e., anti-HBs titer >10 IU/l) within 1 month after injection and (ii) HB vaccine-induced antibody levels wane over time [20], we chose the month following the injection of one dose as the "at-risk" period. The risk of central neurological event was considered to be identical during

the month following each injection of one dose which generated the same time at risk and could be considered independently. Therefore, the total person-time at risk was computed by multiplying this one-month risk period by the number of doses administered and was then converted into exposed years. Under the null hypothesis of no association, the incidence of MS during "at-risk" time and non-exposed time are expected not to differ. As for the first approach, the numbers of expected MS cases were derived from the MS background incidence rates for the French adult population per year of interest (from 1984 to 2000), and confidence intervals at 95% were computed by using the binomial distribution. OE analyses were then stratified by gender.

Cases for which a time-to-onset was not completed were imputed according to the distribution of observed times between vaccination and the occurrence of events of interest.

2.5. Secondary analysis

In 1999, the French Institute for Public Health Surveillance (InVS) estimated that 5% of HB vaccine doses sold were not actually administered to subjects [4]. The OE analyses were therefore reproduced by using this revised number of vaccine doses.

3. Results

A total of 624 incident central demyelination cases were reported to the French Pharmacovigilance from the date of the first HB vaccine launched on the market (Hevac B® [Sanofi Pasteur] in 1981) until 31 December 2000. The first case of interest, not reported at this date, occurred in 1984 but the first case report was recorded in 1992 by the French pharmacovigilance. A total of 422 (67.6%) cases were confirmed as first episodes of MS by a senior neurologist. The ratio between events coded as a first episode of MS and those coded as incident central demyelination decreased over the study period. Indeed, all events which occurred between 1984 and 1990 were coded as a first episode of MS, *versus* less than a half (46.9%) for the most recent years (1998–2000). Women accounted for most cases (n = 457, 73.2%), corresponding to a female/male ratio of 2.7. This trend remained stable over the whole study period. Age of central demyelination cases ranged from 2 to 63.8 years (Q1-Q3: 21.6–38.5). Both mean and median age of cases converged with values of 29.8 years (SD = 11.1 years) and 29.0 years, respectively. Fig. 1 presents the age and gender distribution across the 618 case reports for which age and/or gender were available. Among confirmed cases of MS, mean age was 30.1 years (SD = 11.1 years) while median age was 29.0 years (Q1-Q3: 21.6–38.5).

A total of 86,622,362 doses of HB vaccines were sold over the study period for a total population of around 60 million at this period. Events of interest were mainly reported after the booster doses (46.3%, n = 289) (Fig. 2). The time-to-onset (i.e., time interval between the HB vaccination and the occurrence of event) for the whole series of cases ranged from 0 to 2982 days (i.e., 8 years and 2 months) (Fig. 3). The median time-to-onset was 74 days corresponding to 2 months and 14 days, while the mean (221.1 days; SD = 345.5) was distorted by outlier values. Overall, the median time-to-onset remained somewhat constant even for cases reported *a posteriori* after a long delay (Fig. 4).

In absolute values, incidence of events peaked in 1995, 1996, and 1997, these years accounting for 59.8% (n = 373) of all cases of interest. However, when looking at the reporting rates, the highest values were observed for years 1987, 1997 and 1998 with rates of 10.5, 12.5 and 14.7 per 1,000,000 doses sold, respectively, while the overall mean reporting rate was 6.51 per 1,000,000. The time-to-report ranged from 0 to 14 years with convergent mean and median values of 2 and 2.5 years, respectively. This time increased during the study period. Events were reported with a median time of 6 months in 1992, which increased to 3 years in 2000. Case reporting intensified dramatically after 1995 (Fig. 5).

Annual incidence rates for MS in France for the period corresponding to our study were provided by the National Health Insurance Fund for Employees (i.e., Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS)). Whatever the approach used, the number of observed cases never exceeded the expected number. With the individual-based approach, the estimated number of vaccinated people was 26,401,946 over the study period. The expected number of incident MS cases was 1200 [95% CI: 1132–1268], while the number of cases reported to the French pharmacovigilance was 422 during the whole study period, corresponding to an OE ratio of 35.2% (Table 1). Surprisingly, the highest OE ratio (105%) was observed for year 1987 with the number of reported events reaching the number of expected events, this being well before any mass media coverage of a potential link between MS and HB vaccination. By using the second approach, the number of person-years "at risk" within the month following immunization was 7,218,530. The expected number of events of interest was 325 [95%CI: 289–360] while the total number of reported cases was 100, representing an OE ratio of 30.8%, the latter being of the same magnitude as that produced by the first method, i.e. 35.2% (Table 2). However, the number of reported cases reached the number of expected events for years 1984 and 1987 without exceeding it.

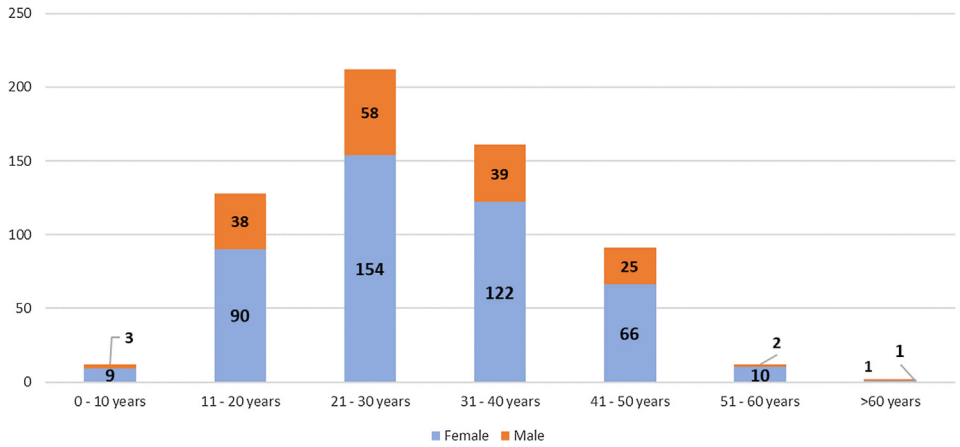

Fig. 1. Age and gender distribution of cases of interest.

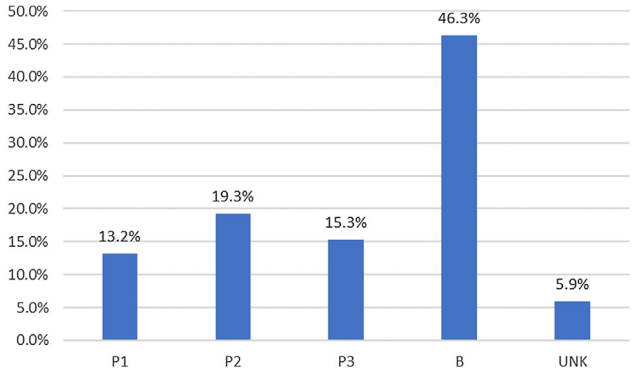

Fig. 2. Distribution of vaccination ranks for cases of interest (n = 624). Notes: P1: 1st vaccine dose of primovaccination; P2: 2nd vaccine dose of primovaccination; P3: 3rd vaccine dose of primovaccination; B: booster dose; UNK: unknown, information about vaccine dose after which an event occurred was missing (n = 37).

Nevertheless, these figures were based on too small numbers (1 and 2, respectively) to consider these estimates as reliable.

Stratifying OE analyses by gender led to similar conclusions, counts of observed cases remaining below the expected figures, except in women for whom the numbers of reported events equaled the number expected for years 1984, 1987, 1990 (person-years at risk approach) and year 1988 (individual-based approach). For men, this was observed for year 1985, only when using the person-years at risk approach. For both methods used, the OE ratios were consistently higher for women than for men (35.2 *versus* 26.1% and 30.0 *versus* 23.2%, respectively).

As expected, the secondary analysis led to slightly higher OE ratios (36.1 and 32.4%, respectively for individual-based and time-populational approaches) without changing the conclusions.

4. Discussion

Of the 624 incident central demyelination cases reported to the French Pharmacovigilance after HB immunization, our analysis identified 422 incident MS confirmed by a senior neurologist. The female/male ratio of 2.7 is fully in keeping with the data of the nationwide OFSEP registry in France (i.e., 2.5), which represents 61,022 MS adults in France in 2016 [21]. Overall, the mean age of cases with central demyelination and MS was 29.8 and 30.1 years respectively at the event occurrence, this being consistent but somewhat lower than the age of MS patients at disease onset (31.9 ± 10.5 years) as reported in the OFSEP registry [21].

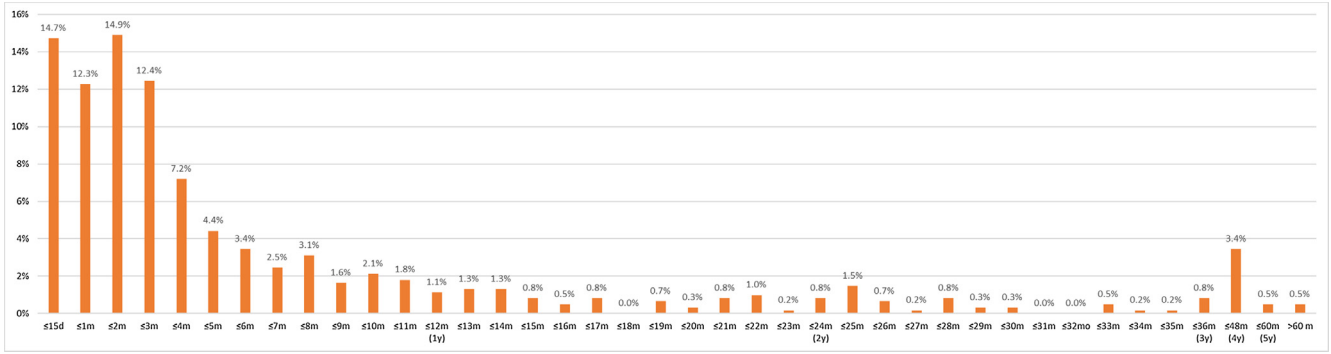

Fig. 3. Distribution of time-to-onset. Notes: 'Time-to-onset' refers to time interval between vaccination and occurrence of event. Information regarding time-to-onset was missing for 13 cases. Abbreviations: d: days; m: months; y: years.

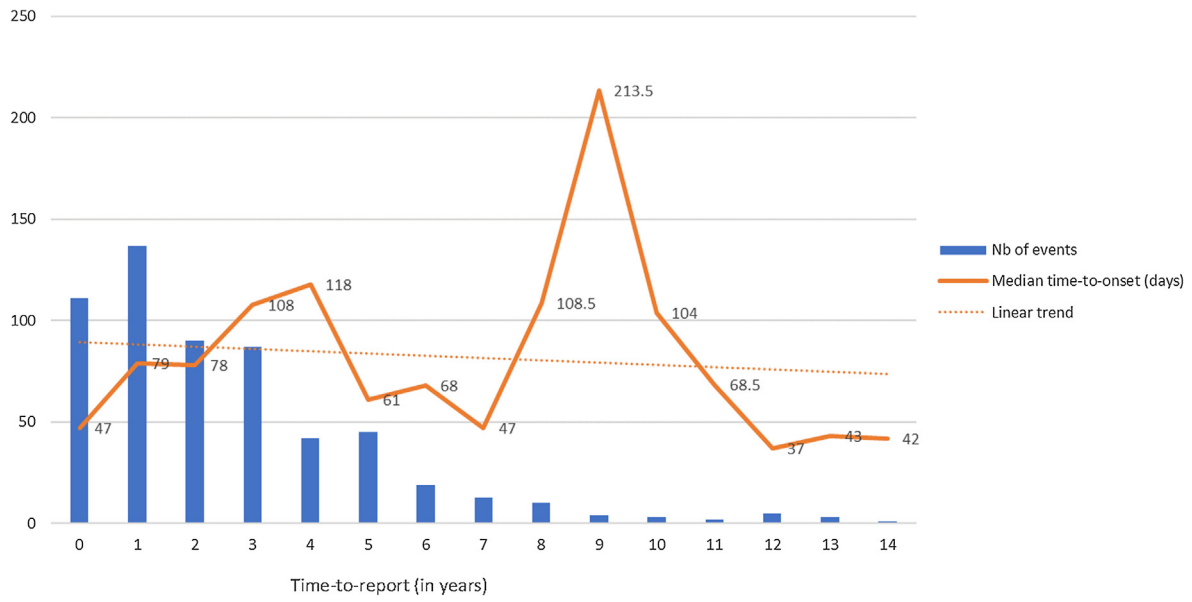

Fig. 4. Relationship between time-to-onset and time-to-report. Note: 'Time-to-onset' refers to time interval between vaccination and occurrence of event. 'Time-to-report' refers to time interval between occurrence of event and case reporting. Information regarding time-to-onset or time-to-report was missing for 52 cases.

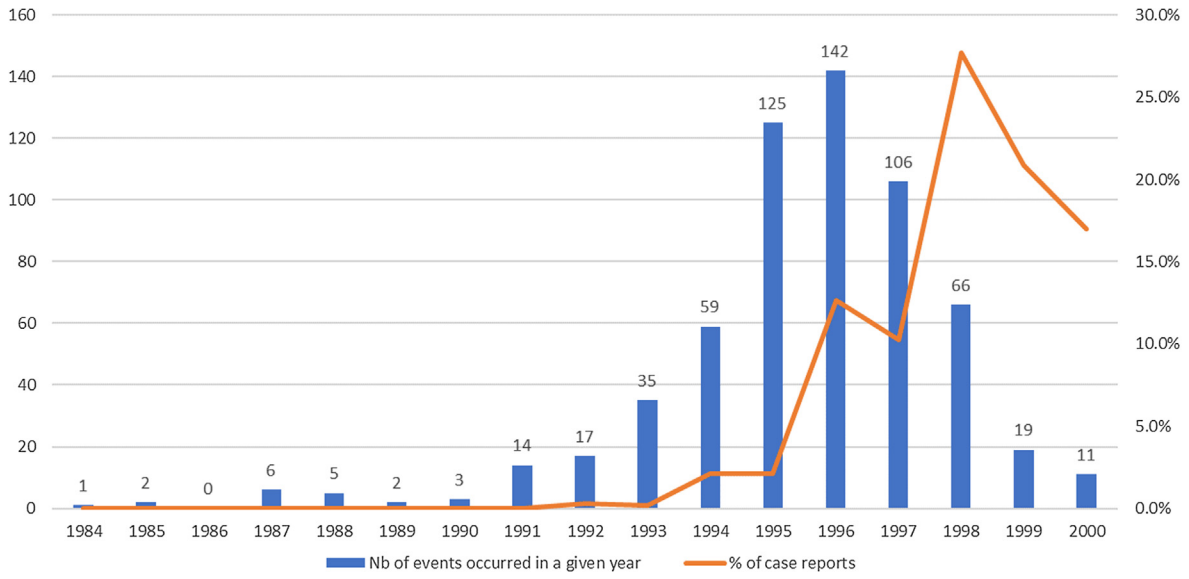

Fig. 5. Case reporting (%) and number of cases occurring in each year of study period.

Table 1
Observed-to-expected analysis by using individual-based approach.

Year	Annual incidence of MS (per 100,000)	Total number of vaccine doses sold	Estimated number of vaccinated people	Expected number of cases	[95%CI]		Number of 1st episodes of MS reported to French PV	OE ratio
1984	4	240,937	60,234	2	1.8	3.1	1	41.5%
1985	4	318,605	79,651	3	2.6	3.7	2	62.8%
1986	4	453,891	113,473	5	4.1	5.0	0	0.0%
1987	4	571,661	142,915	6	5.3	6.1	6	105.0%
1988	4	601,537	150,384	6	5.6	6.4	5	83.1%
1989	4	717,950	179,488	7	6.8	7.6	2	27.9%
1990	4	804,306	201,077	8	7.7	8.4	3	37.3%
1991	4	2,287,018	571,755	23	13.5	32.2	10	43.7%
1992	4	3,734,662	933,666	37	25.4	49.3	14	37.5%
1993	4	5,018,418	1,254,605	50	36.3	64.1	25	49.8%
1994	4	14,917,107	3,729,277	149	125.2	173.1	45	30.2%
1995	4	23,325,138	7,775,046	311	276.4	345.6	90	28.9%
1996	4.75	15,134,845	5,044,948	240	209.3	270.0	92	38.4%
1997	5.25	8,480,438	2,826,812	148	124.5	172.3	72	48.5%
1998	6	4,483,992	1,494,664	90	71.1	108.2	30	33.5%
1999	6.2	2,518,616	839,538	52	37.9	66.2	13	25.0%
2000	6.2	3,013,241	1,004,413	62	46.8	77.7	2	3.2%
TOTAL		86,622,362	26,401,946	1200	1131.8	1267.6	422	35.2%

Abbreviations: CI: Confidence interval; MS: Multiple sclerosis; Nb: Number; OE: Observed-to-expected.
Notes: Annual incidence rates of MS in France were provided by the 'Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés' (CNAMTS).

Our analysis showed that the onset of the event of interest was not homogeneously distributed across the rank of vaccine doses, most events (46.3%) occurring after the booster dose. During the study period, one booster dose was recommended one year after the initial injection of HB vaccines. After 1994, the vaccination schedule was reduced to the three doses of the primovaccination. This short time interval between the last two doses of the immunization schedule (i.e., 12 months) ruled out an age effect which would make vaccinated subjects at higher risk of declaring MS after a certain age. Spontaneous reporting is a mode of passive surveillance of adverse events considered as possibly related to drug use by the observer, mostly a physician in the present case. It relies on both the motivation of physicians to report and their conviction regarding the link between an event and a health product [22]. One hypothesis for this non-random distribution of cases according to the dose-rank could be a kind of selective reporting. A physician having observed several consecutive dose-event couples in a given person could have been more prone to reporting the case after the last one, since after the initial event he/she would have had less chance of suspecting a relationship.

Analysis of times-to-onset showed a wide dispersion with a median value of 2.5 that remained somewhat constant over the study period. Conversely, the time-to-report had clearly become longer by the end of the period. Again, this could partly be explained by an effect of the mass media coverage resulting in an extensive retrospective search for and identification of potential cases of interest. We also observed that reporting rates were doubled in 1987, 1997 and 1998. No clear explanation can be offered for this, even if the mass media coverage could also have played a role at least for years 1997 and 1998, but certainly not for 1987.

Regarding the OE analyses, the two methods produced congruent and inconclusive results, the number of observed cases being lower than or equaling the expected number. Stratification by gender led to similar findings. However, these figures are worthy of interest since a certain level of under-reporting is an expected and inescapable phenomenon with spontaneous reporting systems

Table 2
Observed-to-expected analysis by using 'person-years at risk' approach.

Year	Annual incidence of MS (per 100,000)	Total number of vaccine doses sold	Number of months at risk	Number of person-years at risk	Expected number of cases	[95%CI]		Nb of first episodes of MS reported to French PV within 1 month after vaccination*	OE ratio
1984	4	240,937	240,937	20,078	0.80	−0.31	1.92	1.0	124.5%
1985	4	318,605	318,605	26,550	1.06	0.09	2.03	1.0	94.2%
1986	4	453,891	453,891	37,824	1.51	0.70	2.33	0.0	0.0%
1987	4	571,661	571,661	47,638	1.91	1.18	2.63	2.0	105.0%
1988	4	601,537	601,537	50,128	2.01	1.30	2.71	1.0	49.9%
1989	4	717,950	717,950	59,829	2.39	1.75	3.04	0.0	0.0%
1990	4	804,306	804,306	67,025	2.68	2.07	3.29	2.0	74.6%
1991	4	2,287,018	2,287,018	190,584	7.62	7.26	7.99	1.0	13.1%
1992	4	3,734,662	3,734,662	311,221	12.45	12.17	12.73	4.0	32.1%
1993	4	5,018,418	5,018,418	418,201	16.73	16.48	16.97	9.0	53.8%
1994	4	14,917,107	14,917,107	1,243,092	49.72	35.90	63.54	14.0	28.2%
1995	4	23,325,138	23,325,138	1,943,761	77.75	60.47	95.03	24.0	30.9%
1996	4.75	15,134,845	15,134,845	1,261,237	59.91	44.74	75.08	16.0	26.7%
1997	5.25	8,480,438	8,480,438	706,703	37.10	25.16	37.27	14.0	37.7%
1998	6	4,483,992	4,483,992	373,666	22.42	13.14	22.63	8.0	35.7%
1999	6.2	2,518,616	2,518,616	209,884	13.01	5.94	13.29	0.0	0.0%
2000	6.2	3,013,241	3,013,241	251,103	15.57	7.83	15.82	3.0	19.3%
		Total	86,622,362	7,218,530	324.65	289.3	360.0	100.0	30.8%

Abbreviations: CI: Confidence interval; MS: Multiple sclerosis; Nb: Number; OE: Observed-to-expected. Notes: Annual incidence rates of MS in France were provided by the 'Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés' (CNAMTS).

* Including 4 imputed cases, estimated from total number of 13 cases without known time to occur and the distribution of time to occur (27.0% within 1 month).

[23]. Our overall OE ratios of 35.2 and 30.8% (for the individual-based and at person-years at risk approaches, respectively) correspond to under-reporting factors of 2.8 to 3.2. In other words, if reporting had been at least three times more intensive than it was, the number of observed events would have reached or exceeded the expected number.

In the present case, the reporting rates of incident central demyelination and first episodes of MS after HB vaccination were 6.5 and 4.8 per 1,000,000, respectively, while the mean population annual incidence rate of MS between 2000 and 2007, based on disease declarations to the French health insurance system, was 6.6 per 100,000, i.e. about 10 times higher.

It is important to note that the French vaccination campaign launched in the 1990s and initially targeting newborns and adolescents completely missed its target and led to the massive exposure of the adult population [2]. With a total of about 86 million doses of HB vaccine sold for a total population of 60 million inhabitants, no fewer than 20 million of adults were exposed to the HB vaccine [4]. This resulted in an unprecedented exposure of an adult population at an age prone to developing demyelinating diseases. Consequently, and based on the results of this study, it is difficult to ascertain whether the reported cases simply corresponded to fortuitous associations or if some of them were caused or anticipated by this massive off-target immunization campaign in predisposed people. In any case, our findings point to two conclusions: (i) if there is a link between the HB vaccine and central demyelination, it is weak since our results are not consistent with a strong association; and (ii) the current recommendations adopted in most low-endemic countries and targeting newborns with a possible catch-up of at-risk adults should remain the preferred strategy. If those recommendations had been followed, a major crisis would have been avoided and the acceptability of the HB vaccine would have been greater.

The present study has several strengths. First, it is based on comprehensive national reports and reliable data obtained from either French pharmacovigilance or nationwide data sources such as the CNAMTS, which covers 87% of the French population. Second, our OE analyses used two different approaches both based on a conservative hypothesis for estimating the size of the exposed population. Indeed, the total number of subjects receiving HB vaccination, which was estimated from the total number of vaccine doses sold divided by four or three depending upon the period was 26,401,946, while two previous publications provided similar estimates [2,4] and the French National Institute for Public Health communicated a compatible figure for a longer period with ~37 million people exposed to the vaccine between 1981 and 2010 [24]. Third, a secondary analysis was performed to test the robustness of the findings, with results converging with the main analyses. Nevertheless, the study has several limitations. First, our estimation of the exposed population was derived from the number of doses of vaccine sold, assuming that all people had completed the primo-immunization schedule with the four or three recommended injections. Therefore, we cannot exclude that the true exposed population was in fact larger than that considered in our computations, making, in any case, our estimations more conservative. Precise and robust data about the baseline annual incidence rates of MS over our study period are scarce, especially for the first part of the period (i.e., 1984–1993). Thus, for these 10 years, we had to extrapolate the annual incidence rates using both demographic growth and the linear increasing trend for MS observed between 1994 and 2000. Moreover, it has recently been estimated that, for various reasons including changes in diagnostic criteria, annual incidence rates for MS reported in the 1990s were likely underestimated by approximately 11–29%.[25] However, the impact of the two latter limitations on our conclusions is likely to be minimal, as both tended to reduce the value of the OE ratios. Finally, the time window chosen (i.e., 1 month) is debatable given that the median time-to-onset was found to be ~2.5 months. No clear consensus has been established so far on this point but most authors assessing the putative link between HB vaccination and central demyelination use a window comprised between 0 and 3 months. For practical reasons and given the vaccination schedule (0, 1, 6 and 12 months), we used a 1-month window. However, expanding this window to 2 or 3 months would have led to decreasing the OE ratios.

5. Conclusion

What happened in France in the 1990s was unprecedented with about 26 million adults exposed to the HB vaccine at an age at which MS could be diagnosed. In 20 years, at least 422 confirmed cases of MS were reported, including 100 cases occurring within

the month following the vaccine injection. Therefore, it is very difficult to define the exact role of the HB vaccine in their occurrence. A non-random distribution of rank of vaccination or years of report among cases should be noted. The O/E analyses did not allow us to draw any firm conclusions, even if the number of reported cases sometimes approached the expected number, while underreporting cannot be ruled out. Nevertheless, the following conclusions may be drawn: (i) if there is link between HB vaccine and MS, our results are not consistent with a strong association; (ii) the current recommendations adopted by most low-endemic countries with the targeted immunization of newborns and the possible catch-up of at-risk adults should remain the preferred strategy.

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