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Hepatitis B vaccination and the putative risk of central demyelinating diseases – A systematic review and meta-analysis

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ABSTRACT

Background: The anti-hepatitis B immunization campaigns launched in the early 1990s were a major public health breakthrough and targeted various populations (at-risk adults, newborns, adolescents). However, debate is still active about a possible link between this vaccine and central demyelination. This study provides a pooled estimate of this risk based on a comprehensive review and meta-analysis of all available epidemiologic studies.

Methods: A systematic review was conducted in Medline, Embase, ISI Web of Science and the Cochrane Library from database inception to 10 May 2017. Grey literature was searched and snowballing was also undertaken. Only observational studies including a control group were retained. Primary outcome was multiple sclerosis diagnosed by recognized criteria. Study selection was performed by two independent reviewers with disagreements solved through discussion. This meta-analysis based on crude, adjusted estimates, or risks limited to the 3 months following immunization was performed using a generic inverse variance random-effect model. Heterogeneity was investigated; sensitivity and subgroup analyses were performed when necessary. This study followed the PRISMA statement and the MOOSE reporting guideline (Study protocol registered in PROSPERO: CRD42015020808).

Findings: Of the 2804 references reviewed, 13 studies with a control group were analysed. None of the pooled risk estimates for either multiple sclerosis or central demyelination following HB immunization reached statistical significance. When considering adjusted risk ratios, the following non-significant figures were obtained: 1.19 (95%CI: 0.93 – 1.52) and 1.25 (95%CI: 0.97 – 1.62), for multiple sclerosis and central demyelination, respectively.

Conclusions: No evidence of an association between hepatitis B vaccination and central demyelination was found.

1. Introduction

Infection with the hepatitis B virus (HBV) can lead to serious lifelong liver damage such as acute, chronic and fulminant hepatitis or hepatocellular carcinoma, for which HBV is the established leading cause worldwide [1]. To fight this pandemic, vaccines have been developed since 1976 [2]. The first one was approved in the United States in 1981 [3] and ten years later, the World Health Organization (WHO) encouraged universal mass vaccination campaigns tailored according to the prevalence of HB antigen carriers in the geographical zone considered. Therefore, several vaccination strategies were proposed (targeting infants, children, adolescents, or high-risk adults), possibly combined for greater efficiency [4].

However, in numerous countries, the recommended population coverage has not been achieved. Among the reasons put forward is the persisting rumor about a possible link between this vaccination and the occurrence of cases of central demyelinating diseases, notably multiple sclerosis. This suspicion was raised less than two years after the launch of the French immunization campaign targeting newborns, children in the first year of secondary school and high-risk adults. Indeed, by July 1996, 249 cases of central demyelinating disorders, including multiple sclerosis (MS) after injection of HB vaccine had been reported to the French Medicines Agency; [5] thus raising concern about a potential causal association between anti-hepatitis B vaccine and central demyelinating

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disorders, with an intense debate on the global vaccination policy across Europe [7–9].

Notwithstanding the global interest in the topic, five systematic reviews [10–14] have been performed in the past, with different methodological issues. However, the acceptability of vaccines is still a burning issue for parents of young children, adults and even the medical community. At a time when several countries are about to increase the number of mandatory vaccinations, physicians need to have robust arguments about the not debatable benefit-risk balance of vaccines in order to be able convince refractory subjects or their family. In this context and considering that additional observational studies [15,16] have been recently published, the objective of this paper was to compile the results from the epidemiological studies conducted on both adults and children aiming to evaluate the risk of MS or central demyelination after anti-hepatitis B vaccination in order to provide the most actualized evidence to health professional and authorities.

2. Methods

2.1. Data sources and searches

A systematic review was carried out in Medline, Embase, ISI Web of Science, and The Cochrane Library from inception to 10 May 2017. A combination of terms related to *vaccination/vaccines* and *neurological events* (see Supplementary materials) were used to find pertinent studies. Pragmatic searches were conducted and bibliographies of reviews were also screened (i.e. snowballing). No restriction regarding the language or time period was applied. The present study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline [17,18].

2.2. Study selection

Eligibility criteria were defined according to the PICOS criteria [17]. As randomized controlled trials are a priori not ethically feasible and have a good chance to be underpowered for assessing rare outcomes following immunization, only observational studies with controls allowing matching and/or adjusting on subject characteristics at an individual level (i.e., studies considering aggregate data were excluded) and reporting a crude or adjusted relative estimate of risk (e.g. Odds Ratio, OR; Hazard Ratio, HR; Incidence Rate Ratio, IRR) of developing an acute central demyelinating disorder following vaccination against hepatitis B were selected. Uncontrolled studies (e.g., case reports, case series, expert opinions, ecological studies) as well as case/non-case studies were excluded. Both adults and children were considered for the present study. Publication type included peer-reviewed articles and abstracts. The latter were included when sufficient data was presented and no full article was available after contacting the authors.

Outcomes of interest were defined as an incident neurological adverse event including MS and central demyelinating disorders. MS had to be diagnosed by a neurologist using established diagnostic criteria, which include the occurrence of at least one central demyelination attack and the demonstration of dissemination of central nervous system lesions in space and time [19–21]. Relapses of MS, which rely on a different physiopathological mechanism, were not considered as an outcome for the present analysis.

Two authors (JM and ER) reviewed the titles and abstracts of all retrieved citations independently. Disagreements were solved through discussion. In the event of doubt, a third person (BB) was asked to confirm the selection of the study.

2.3. Data extraction and quality assessment

For all publications finally retained, data extraction concerned the following items: study design, population characteristics (number of subjects in each group, mean or median age, gender, risk factors for central demyelination or multiple sclerosis), medical event, study period, vaccine exposure, crude and adjusted risk estimates and statistical analysis. When necessary, authors of selected publications were contacted to obtain additional information. Individual quality of each selected study was assessed by using the Newcastle Ottawa Scale for cohort and case-control designs [25]. The strength of the evidence generated was evaluated with the GRADE framework [26,27].

2.4. Data synthesis and analysis

To conduct the meta-analysis, risk estimates and the corresponding 95% confidence intervals (95%CI) were extracted into Review Manager software [Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. In observational settings, authors generally provide several different risk estimates, so choosing the most relevant one for a meta-analysis is often problematic. Indeed, the strength of the association between exposure and outcome can vary according to the methodological options considered by the authors. For this reason, three different types of results were considered when provided by the authors: (i) crude risk estimate (i.e. possibly based on matched sets for case-control studies but without further adjustment aiming at controlling for putative confounding variables), (ii) adjusted risk estimate highlighted as the most relevant by the authors of the publication, and (iii) risk estimate computed, when feasible, within the three months following immunization. The latter was chosen for deriving a pooled estimate for a time-window making studies roughly comparable on that point and *a priori* relevant when exploring a risk putatively induced by an acute drug administration. Forest plots were drawn accordingly. Given the non-randomized nature of the included studies and the adjusted odds ratios they provided, a generic inverse variance random-effect model was used to assess the overall risk estimate [22].

Heterogeneity across the included studies was evaluated by the Q Cochran test, and p values < 0.10 were considered as statistically significant [23]. I^2 statistics were also measured to quantify inconsistencies across estimates [23]. When present, source of heterogeneity was investigated. The selected studies were removed one by one from the model, the meta-analysis being repeated without the excluded study in order to obtain less heterogeneity. Subgroup analyses were performed according to the type of population considered for the meta-analysis (child *versus* adult), study design, and to the studies' methodological quality score. In order to challenge the consistency of findings drawn from non-experimental designs, the analysis was repeated using 99% confidence intervals. Since publication bias is particularly to be feared for non-interventional studies for which preliminary registration in a trial repository is not yet required by the health authorities [24], we planned to test the funnel plot asymmetry provided that the number of studies retained for meta-analysis was larger than 10. Otherwise the test power is too low to distinguish chance from real asymmetry [22].

2.5. Role of the funding source

This meta-analysis was conducted according to the protocol recorded *a priori* in the PROSPERO database, with minor adjustments (CRD42015020808). The study was funded by the University of Bordeaux and INSERM.

Table 1
Studies selected for meta-analysis.

Reference	Country	Study design	Study period	Sample size	Outcome assessed	Population source	Time window considered at risk	Statistical methods used for bias control	Quality (Newcastle Ottawa Scale – max 9 stars)
Ascherio [28]	USA	Nested case-control	1976–1998	Cases: n = 192 Breast cancer controls: n = 111 Healthy controls: n = 534	MS	Nurses' Health Study and the Nurses' Health Study II	≤ 2 years Anytime	Matching on year of birth, study cohort, and year of diagnosis (for controls with breast cancer) Adjustment for pack-years of smoking at baseline, latitude of residence at birth (north, middle, or south), history of infectious mononucleosis, history of measles or mumps after the age of 15, and ancestry (Scandinavian, southern European, other white, or non-white)	7 stars
DeStefano [37]	USA	Case-control	1 January 1995 to 31 December 1999	Cases: n = 440 Controls: n = 950	MS	3 HMOs that participate in the Centers for Disease Control and Prevention's Vaccine Safety Datalink project	Anytime	Matching on age, sex and HMO Adjustment for race, ethnicity, ancestry (northern European or Scandinavian), family history of demyelinating or other autoimmune diseases, education, marital status, occupation, residency history, cigarette-smoking, pet ownership, and certain groups of high risk for hepatitis B (healthcare workers, dialyzed patients)	7 stars
Eftekharian [15]	Iran	Case-control	January to May 2014	Cases: n = 250 Controls: n = 250	MS	Population referring to Hamadan multiple sclerosis society in west of Iran	Anytime	Matching on age and sex No information about possible adjustment	2 stars
Hernan [30]	UK	Nested case-control	1 January 1993 to 31 December 2000.	Cases: n = 163 Controls: n = 1604	MS	GPRD database	≤3 years	Matching on age, sex, practice, and date of joining the practice Adjustment for age, sex, practice, and date of joining the practice, smoking, clinical course of disease, type of first symptoms	8 stars
Hocine [31]	France	Self-Controlled Case Series	31 August 1993 to 31 December 1995	Cases: n = 287	MS + CNS	18 departments of neurology	≤2 months	No matching as SCCS design (cases act as their own controls) Adjustment for age according to 4 models	8 stars
Langer-Gould [16]	USA	Nested case-control	1 January 2008 to 31 December 2011	Cases: n = 43 Controls: n = 249	MS + CNS	Kaiser Permanente Southern California	≤3 months ≤ 3 years	Matching on date of birth, sex, and zipcode (a surrogate measure for socio-economic status) Adjustment for race/ethnicity, hospitalizations, outpatient visits, emergency department visits, comorbid chronic diseases, and infections within 6 months before symptom onset/index date	7 stars
Mikaeloff [32]	France	Case-control	1 January 1994 to 31 December 2003	Cases: n = 143 Controls: n = 1122	MS	French Sclérose en Plaques neuropaediatric MS cohort	≤3 years	Matching on age, sex, and current area of residence Adjustment for age, sex, current area of residence, family history of MS (siblings or parents) and other autoimmune diseases (siblings or parents) and for profession of head of family	7 stars
Mikaeloff [33]	France	Case-control	1 January 1994 to 31 December 2003	Cases: n = 349 Controls: n = 2941	MS + CNS	French Sclerose en Plaques neuropaediatric MS cohort	≤3 years	Matching on age, sex, and current area of residence Adjustment for age, sex, current area of residence, familial multiple sclerosis history, family history of another autoimmune disease, parental smoking at home before index date, socio-professional status of head of family	6 stars
Ramagopalan [38]	Canada	Case-control	Unknown	Cases: n = 14,362 Controls: n = 7671	MS	Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS)	Anytime	Adjustment on age and sex	7 stars

(*continued on next page*)

Table 1 (*continued*)

Reference	Country	Study design	Study period	Sample size	Outcome assessed	Population source	Time window considered at risk	Statistical methods used for bias control	Quality (Newcastle Ottawa Scale – max 9 stars)
Sturkenboom [34] (abstract only)	UK	Case-control	Unknown	Cases: n = 500 Controls: n = unknown	MS	GPRD database	≤2 months	Matching on age, gender and practice No information about possible adjustment (authors contacted)	Not assessed as only abstract available
Touzé [5]	France	Case-control	1 January 1994 to 31 December 1995	Cases: n = 121 Controls: n = 121	CNS	Patients referred for first time to Fédération de Neurologie	≤2 months	Matching on age, sex and date of medical consultation or hospitalization Adjustment for age, marital status, birth country and urban/rural residence	8 stars
Touzé [6]	France	Case-control	1 January 1994 to 31 December 1995	Cases: n = 236 Controls: n = 355	MS + CNS	18 departments of neurology	≤2 months	Matching on gender, age and date of referral to neurology department Adjustment for age, exposure outside time window, marital status, number of children, education level, other vaccinations, health occupation, place of residence (urban/rural), country of birth	7 stars
Zipp [36]	USA	Retrospective cohort	1988–1995	Exposed: 27,229 Unexposed: 107,469	CNS	Healthcare database consisting of integrated pharmacy and medical claims from six Diversified Pharmaceutical Services affiliated HMO plans	≤2 months ≤3 years	Matching on age and sex No information about possible adjustment	7 stars

Abbreviation: CNS: Central Nervous System Demyelination, GPRD: General Practice Research Database, HMO: Health Maintenance Organization, MS: Multiple Sclerosis, SCCS: Self-Controlled Case Series, USA: United States of America.

3. Results

Of the 2804 references identified, thirteen articles describing epidemiological studies including a control group were selected for the meta-analysis (cf. Supplementary materials: PRISMA Flow chart) [6,15,16,28–38]. Seven intended to evaluate the link between HB vaccination and the occurrence of MS, [15,28,30,32,34,37,38] two considered central demyelination more broadly [35,36], and four investigated both outcomes [6,16,31,33].

Table 1 presents the main characteristics of the studies retained for the meta-analysis, which included a total of 16,799 cases and 15,908 controls for the case-control studies and 134,698 individuals for the retrospective cohort. Except for the study conducted by Eftekharian et al., the quality of the studies evaluated by the Newcastle Ottawa Scale was good and comparable for all papers included ranging from six to eight stars (cf. Supplementary materials).

From the seven studies having reported crude risk estimates for MS, no statistically significant association was observed (Fig. 1A), the pooled odds ratio (OR) being 1.19 [95%CI 0.95–1.46]. The same was true for the association between central demyelination and HB vaccination (evaluated in five studies) with a pooled OR of 1.06 [95%CI 0.88–1.28] (Fig. 1B). For the analysis based on adjusted risk estimates, the values obtained were similar for MS (i.e. 1.19 [95% CI: 0.93–1.52]) (Fig. 2A) and slightly higher, without reaching statistical significance, for central demyelination (i.e. 1.25 [95%CI: 0.97–1.62]) (Fig. 2B). Finally, restricting the analysis to risk estimates within the 3-month period after vaccine injection led to the highest figures but, again, without being statistically significant, either for MS or for central demyelinating events (cf. Supplementary materials), the pooled odds ratios being 1.39 (95%CI: 0.90–2.15) and 1.38 [95%CI: 0.82–2.34], respectively.

A moderate heterogeneity emerged when computing crude and adjusted pooled risks for multiple sclerosis (I^2 = 56 and 53%, respectively). Because the limited number of studies precluded the use of a meta-regression, the source of heterogeneity was assessed by removing studies one by one from the meta-analytic model. Only one study [30] was found to introduce heterogeneity. Nevertheless, when it was excluded from the meta-analysis, the results were not markedly affected, with the crude and adjusted pooled risks for MS decreasing to 1.01 [95%CI 0.94–1.08] and 1.00 [95%CI 0.86–1.16], respectively. When computing crude and adjusted pooled risks for demyelination, heterogeneity was low or even null (I^2 = 7 and 0%, respectively).

Results of the subgroup analyses are presented in Table 2. When considering the adult population only, crude risk pooled estimates were 1.25 [95%CI 0.94–1.66] and 1.29 [0.93–1.76] for MS and central demyelination; whereas adjusted estimates were 1.11 [0.88–1.41] and 1.29 [0.86–1.95], respectively. The main conclusion was therefore not altered as statistical significance was not reached. Similar findings were obtained when restricting the studies to those having the highest quality scores evaluated by the Newcastle Ottawa Scale (i.e. >seven stars) or when restricting the meta-analysis to case-control studies only. When increasing the confidence level at 99%, no change was observed for pooled risk estimates but the intervals became slightly wider, as expected (Table 2).

As mentioned in the Methods section, checking the plausibility of a publication bias by observing the symmetry of a funnel plot was not recommended owing to the limited number of studies, i.e. 10 or fewer, included in the present meta-analysis [22]. The strength of the evidence was considered as low owing to the observational nature of studies included and the imprecision of the individual studies according to the GRADE framework (cf. Supplementary materials).

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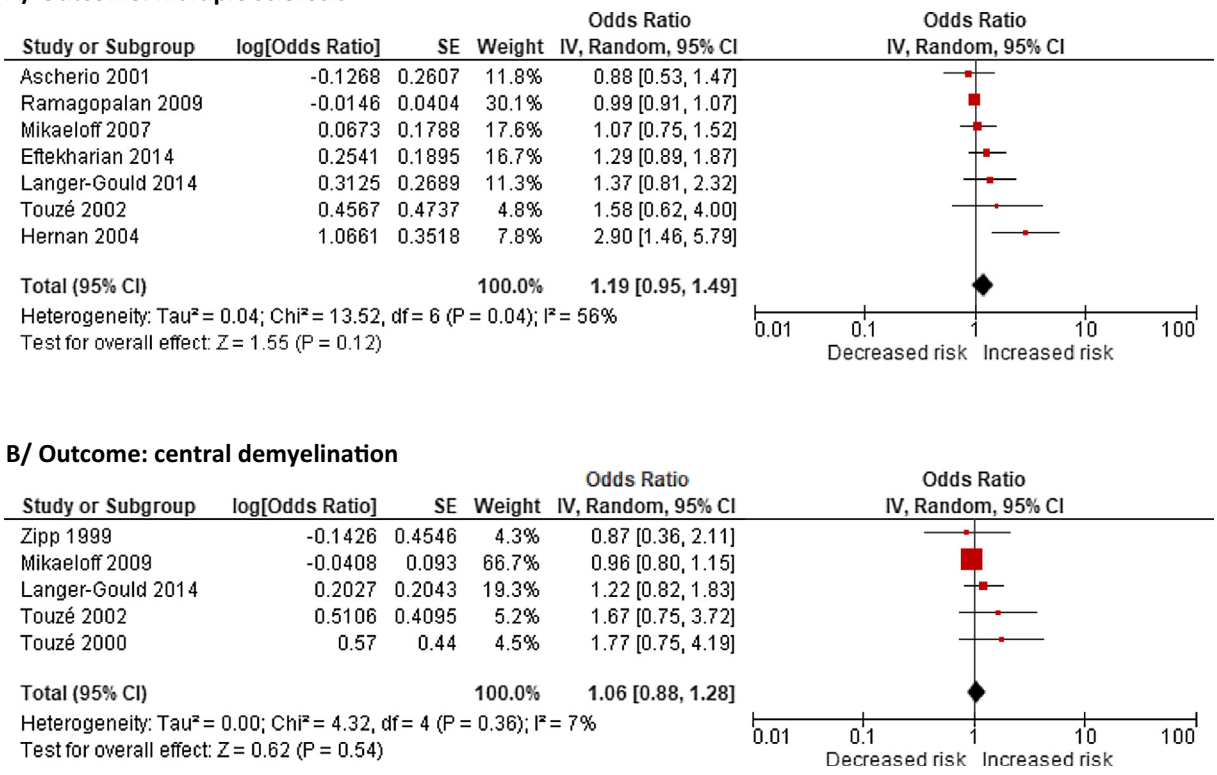

Fig. 1. Forest plots of comparison for crude risk estimates following HBV vaccination.

4. Discussion

The main finding of this meta-analysis is that, for the six situations studied, none of the pooled risk estimates found a statistically significant association between anti-hepatitis B vaccination and the occurrence of multiple sclerosis or central demyelination. However, all the studies included, except the one conducted by Hernan et al. in 2004, yielded inconclusive findings.

In this regard, two studies [28,30] came out as opposite outliers and deserve discussion. The case-control study by Ascherio et al. [28] was nested in two cohorts of American women (Nurses' Health Study and Nurses' Health Study II). The authors concluded in the absence of association between hepatitis B vaccination and the subsequent development of MS, the relative risk being 0.7 (95% CI: 0.3–1.8) two years after vaccination. This value, which seems to suggest a protective effect of the vaccine that is *a priori* not supported by any biological plausibility, is surprising. In this respect, one should note that the percentage of vaccination against hepatitis B was not high for a population of nurses and surprisingly lower in MS cases than in controls (51.8% *versus* 66.5%), as self-reported by the participants. Proof of vaccine exposure was sought only for women who had reported that they were vaccinated, and confirmation by vaccination records was ascertainable for only 96 out of 301 MS cases (i.e. 32%). Moreover, the very low number of cases (n = 9) vaccinated during the two years preceding the disease onset precluded computing a risk estimate for a short time-window, e.g. 2 months, which is more suitable for exploring an association with an acute neurological event.[39] It is worth noting, that this research, on the contrary of other studies retained in our meta-analysis, included only women. However, no evidence of a difference in risk according to gender has been observed so far [38].

By contrast, Hernan et al. [30] remains the only study that concluded in a significant association between anti-hepatitis B vaccination and MS. This nested case-control study, conducted within the General Practice Research Database (GPRD) in the United Kingdom (UK) from January, 1st 1993 to December 31, 2000, produced an odds ratio of 3.1 (95%CI: 1.5, 6.3) after adjustment on age, gender, general physician practice, and date of joining the practice, but not on several putative risk factors such as race or ethnic ancestry. Exposure ascertainment used prospectively recorded data to minimize recall bias. However, records covering the three years preceding the first symptoms were available for only 163 of the 438 MS cases identified. As a consequence of the low adult immunization rate in UK, only 11 of them were found to be vaccinated against hepatitis B. Interestingly, the authors did not find any association with the risk of MS for influenza and tetanus vaccines, which are *a priori* not suspect in that respect [11]. Geier et al. came to the same conclusion in 2005 with their study conducted in the VAERS database, the risk of developing MS after anti-hepatitis B vaccination being 5.2-fold higher than for anti-tetanus vaccination [40].

The most recent study evaluating the risk of central demyelination after hepatitis B vaccination was published in 2014 [16]. Despite being conducted within a large population-based electronic medical records database (i.e. Kaiser Permanente Southern California), the statistical power sufficient to conclude about such a risk was not achieved. Indeed, hepatitis B vaccination was uncommon in this population, with only 3.3% of controls and 4.0% of cases vaccinated in the 3 years before the index date or symptom onset.

This meta-analysis has several strengths. Firstly, it includes multiple analyses based on three different *scenarii* in order to increase both the robustness and the confidence in the results. Secondly, the great majority of studies were judged as being of good quality, i.e. having individual scores based on the Newcastle Ottawa Scale equal to 7 stars and over. Thirdly, heterogeneity was evaluated as moderate or even null, allowing the selected

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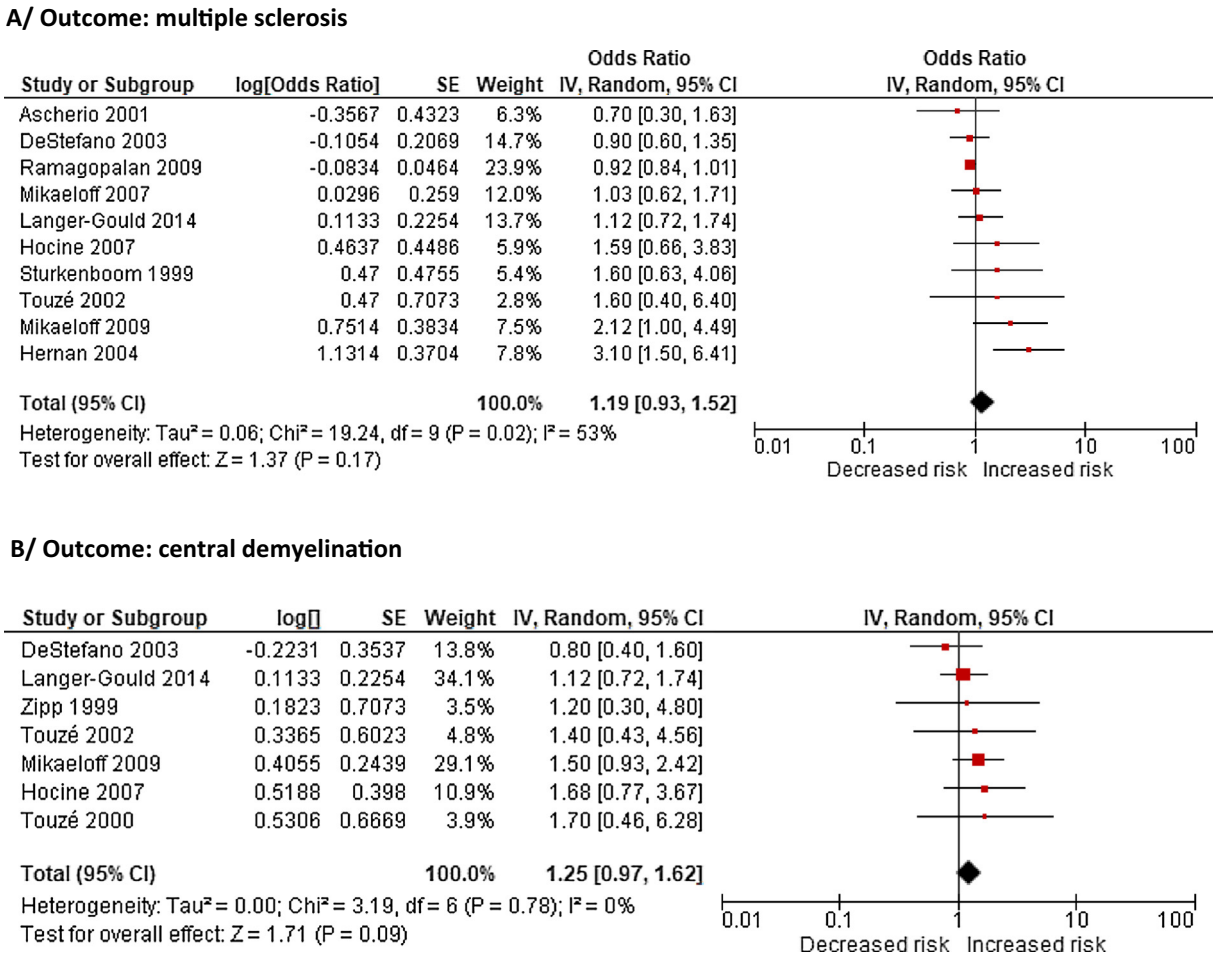

Fig. 2. Forest plots of comparison with adjusted risk estimates following HBV vaccination.

Table 2
Subgroup analyses.

Scenario considered	Outcome considered	Subgroup analyses			Wider Confidence Intervals (CI)	Reference
		Adult pop only[a]	Case controls only[b]	Quality score evaluated by Newcastle Ottawa scale >7[c]	99%CI	Pooled risk ratios [95%CI]
1/Crude risk estimates	Multiple Sclerosis	1.25 [0.94–1.66]	*No change*	1.19 (0.92–1.54]	1.19 [0.89–1.60]	1.19 [0.95–1.46]
	Central demyelination	1.29 [0.93–1.76]	1.13 [0.88–1.45]	1.29 (0.93–1.76]	1.06 [0.83 – 1.35]	1.06 [0.88–1.28]
2/Adjusted risk estimates	Multiple Sclerosis	1.11 [0.88 – 1.41]	1.17 [0.90–1.51]	1.09 [0.86–1.39]	1.19 [0.86 – 1.64]	1.19 [0.93–1.52]
	Central demyelination	1.29 [0.86 – 1.95]	1.10 [0.85–1.42]	1.28 [0.90–1.82]	1.25 [0.89–1.76]	1.25 [0.97–1.62]
3/Risk estimates within 3 months after vaccination	Multiple Sclerosis	*No change*	1.33 [0.81–2.19]	1.38 [0.70–2.73]	1.39 [0.79–2.46]	1.39 [0.90–2.15]
	Central demyelination	*No change*	1.25 [0.56–2.80]	*No change*	1.38 [0.69–2.77]	1.38 [0.82–2.34]

[a] Exclusion of 2 studies Mikaeloff et al., [32] and Mikaeloff et al., [33].
[b] Exclusion of 2 studies [Zipp et al., [36] and Hocine et al., 2007].
[c] Exclusion of 3 studies [Sturkenboom et al., [34] (not evaluated for quality) – Efthekarian et al., 2014 (NOS score = 2) and Mikaeloff et al., [33] (NOS score = 6)].

studies to be pooled. Fourthly, this paper presents a clear added value to the body of evidence drawn from the five articles having already investigated this issue. Two of them [10,14] were systematic reviews but are clearly outdated as they were published at least thirteen years ago. The meta-analysis performed by Farez et al. [11] included a limited number of studies available on the topic and some methodological points remain unclear such as the selection of an odds ratio equal to 1.0 for the study by Hernan et al. The most recent papers [12,13] retained respectively twelve and fifteen studies for a qualitative review but none of the authors performed a meta-analysis. The need for an updated systematic review and, overall, a meta-analysis, was thus more crucial than ever, especially as additional observational studies [15,16] have been published recently.

However, several limitations must be acknowledged. Firstly, the overall pooled estimates obtained in the present meta-analysis failed to reach statistical significance, so no definitive conclusion can be drawn about the possibility of a small excess in risk. Secondly, a potential for a diagnostic bias and more specifically the so-called unmasking phenomenon (i.e., vaccinations lead to

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diagnosing symptoms that would otherwise have gone unnoticed, resulting in a bias toward an association) [41] could be envisaged, even if most of the studies were of the case-control type and the majority of cases were ascertained by a neurologist taking into account the date of demyelinating disorder onset. Thirdly, several studies, including the most recent one [16], would have been underpowered if intending to demonstrate a potential risk after hepatitis B vaccination, the main reason being that the prevalence of vaccination was too low in their study samples. It should also be noted that the methodological choices made by authors (i.e. adjustment factors or selection of controls) appeared rather heterogeneous across the studies. For this reason, we chose to consider three *scenarii* in order to address this issue.

Another issue might be the statistical model used for this meta-analysis. In the present context, i.e., a meta-analysis based only on observational studies and focusing on a rare dichotomous outcome, an "exact" method would have *a priori* been the best option [42]. However, not only would this have been difficult to implement but it would also have required particular statistical expertise beyond the scope of the study [43,44]. Owing to the low incidence of the events considered [45], the Peto one-step odds ratio method was the next best option [46]. However, while it is perfectly suited for clinical trials, a prerequisite for using it is that the groups compared are more or less of the same size, which was definitely not the case for some of the studies meta-analysed [22,42]. Finally, and even if its use has been shown to be questionable for rare events [47], we chose to use a generic inverse variance model as it allowed us to compute adjusted odds ratios from non-randomized studies, for which contingency tables and counts were not appropriate. Otherwise, these studies would have been excluded, leading to a small number of eligible studies and thus hampering any calculation of pooled estimates. To test the robustness of our model for crude risk estimates, we also used the random-effect Mantel-Haenszel method, which is an option for rare and dichotomous outcomes [48]. The estimates it provided were fully consistent with those reported in this paper (see Supplementary materials).

5. Conclusion

The present systematic review identified thirteen studies having assessed the risk of central demyelination after immunization against hepatitis B. The pooled estimates failed to demonstrate a link other than coincidental between vaccine exposure and the outcomes of interest across a number of analyses.

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Not applicable.

Ethical approval, consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no competing interest for the submitted work.

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Contributors

JM wrote the protocol with input from FS, ER, EP, FDP and BB. ER, ICA and JM screened the references. JM extracted the data and conducted the statistical analyses with input from FS and BB. JM wrote the first version of the manuscript with input from FS, ER, EP, FDP and BB. All authors reviewed and approved the final version of the manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.02.036.

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