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

Julie Mouchet [a,*], Francesco Salvo [a], Emanuel Raschi [b], Elisabetta Poluzzi [b], Ippazio Cosimo Antonazzo [b], Fabrizio De Ponti [b], Bernard Bégaud [a]

[a] Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, F-33000 Bordeaux, France
[b] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

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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

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

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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.