

REVIEW



HBV vaccine and risk of developing multiple sclerosis: a systematic review and meta-analysis

Cristina Sestili^a, Inês Grazina ^b, and Giuseppe La Torre^a

^aDepartment of Public Health and Infectious Diseases, Sapienza University, Rome, Italy; ^bFaculty of Pharmacy, University of Lisbon, Portugal

ABSTRACT

Hepatitis B virus (HBV) infection is one the most common in the world. Aim of this study is to perform a systematic review on the relationship between HBV vaccination and multiple sclerosis. Research was conducted on Pubmed, ISI Web of Science, and Scopus. Terms “*hepatitis b vaccination*” and “*multiple sclerosis*” were used. Meta-analysis and metaregression were performed. 414 papers were found. Seven articles were selected. For the reported crude risk estimates for MS no statistically significant association was observed with pooled OR 1,19 (95%CI: 0,96–1,49). For the adjusted ORs, the pooled odds ratio (OR) was 0,965 (95%CI: 0,886– 1,051). Meta regression show that year of publication is negatively (β : $-0,019$; $P < 0,001$) and NOS score and publishing in Europe are positively associated with O.R. value. Funnel plot showed the presence of publication bias. Results showed that Hepatitis B vaccination is not associated with an increased risk of developing MS.

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Introduction

Hepatitis B virus (HBV) infection is one the most common in the world that results in substantial morbidity and mortality, mostly later the develop of chronic infection.¹ HBV chronic infection can lead to serious liver damage. The transmission is through exposure to infected blood and body fluids.² Vaccine against Hepatitis B was developed in 1976 and available since 1982.³ This represent one of the major event in preventive medicine and public health and immunization against hepatitis B is now a priority in all countries. hepatitis B vaccination was added into national immunization programs worldwide in 199.⁴ In early 90's in French population developed the rumors about a link by hepatitis B immunization and cases of Multiple Sclerosis or other demyelinating diseases. Cases of multiple sclerosis that developed in few weeks after the administration of the vaccine were reported in Paris.^{5,6} Based on the results of 2 case-control studies indicating a nonsignificant increase in the risk of multiple sclerosis among individuals who had undergone vaccination,^{7,8} the French government suspended the school-based program of hepatitis B vaccination. The etiology of MS is not fully understood, and the pathophysiology is said to be immune-mediated.

In literature some systematic review,^{9–11} two with metanalysis^{12,13} are present but some of low methodological quality. Some of this take into account a small number of study.¹³ In recent systematic review and metanalysis¹² authors include in the metanalysis for adjusted OR two studies that take into account the same population^{14,15} or study in wich not all data are available.⁸

Aim

So, the aim of the present study is to perform a systematic review on the existing evidence about the relationship between HBV vaccination and multiple sclerosis.

Results

The selection of articles is shown in the flowchart (Figure 1). Overall 414 papers were found 108 articles through Pubmed, 77 through Scopus and 228 through Web of Science. Successively, 139 duplicates and 164 articles that did not respect the inclusion criteria by title and abstract were excluded. The remaining 110 papers were analyzed, and from these, 104 articles were excluded because were not pertinent, or for inappropriate study design or because there wasn't outcome of interest. Furthermore, three studies^{14–16} were excluded because use data already used in another study included. Seven articles fulfill the inclusion criteria and selected for the meta-analysis.^{17–23} All work included intended to evaluate the link between HB vaccination and the occurrence of MS. No work was added by references.

Table 1 presents the main characteristics of the studies retained for the meta-analysis, which included a total of 15,389 cases and 11,856 controls. One was nested case-control studies,¹⁷ six were case-control studies. Except for one study,¹⁸ the quality of the studies evaluated by the Newcastle Ottawa Scale was good for all papers from six to eight points (Table 2).

From the seven studies having reported crude risk estimates for MS, using a random effect model, since heterogeneity was found ($p = 0,031$), no statistically significant

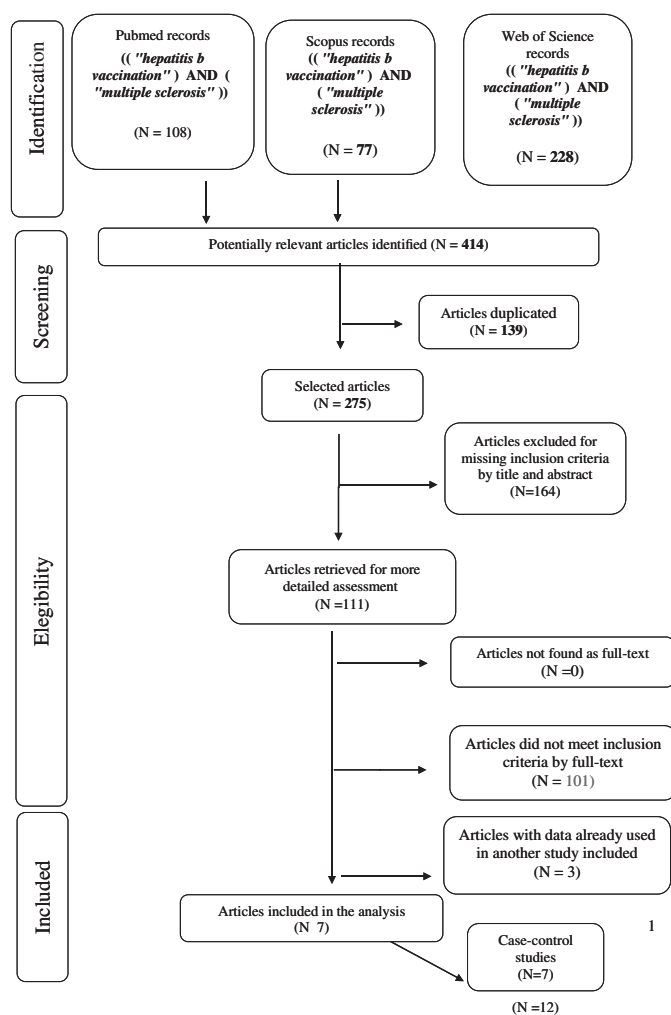


Figure 1. Flow-chart of search strategy.

association was observed (Figure 2), the pooled odds ratio (OR) being 1,19 (95%CI: 0,96–1,49).

Considering the adjusted ORs, we used the fixed effect model, since no heterogeneity was found ($p = 0.060$), and the pooled odds ratio (OR) was 0,965 (95%CI: 0,886– 1,051) (Figure 3). Because no adjusted O.R. was available it was excluded in this case work by Eftekarian¹⁸ which was also of low quality (Table 2). A meta regression was performed (Table 3) and results show that year of publication is nega-

tively associated with O.R. (beta: $-0,019$; $P < 0.001$), Newcastle Ottawa Score and Publishing in Europe are positively associated with O.R. value. Publication bias was assessed from funnel plots (Figure 4)

Discussion

In this work was found that for the seven studies included the pooled risk estimates not found statistically significant association between anti-hepatitis B vaccination and the occurrence of multiple sclerosis. The case-control study of Ascherio¹⁷ showed relative risk of 0.9 (95 percent confidence interval, 0.5 to 1.6) at any time before the onset of the disease. The relative risk associated with hepatitis B vaccination within two years before the onset of the disease was 0.7 (95 percent confidence interval, 0.3 to 1.8). The authors concluded with no association between hepatitis B vaccination and the development of multiple sclerosis.

Langer Gould et al in 2014²⁰ did not find an association of new-onset MS or in the 1 to 3 years after vaccination either adjusted or unadjusted models. The base population study of Mikaeloff²¹ conducted in French general population of children and adolescents younger than 16 years between January 1994 and December 2003 found no increase in the risk of a first episode of MS in childhood after vaccination against HB. Eftekharian et al (2018) reported that hepatitis B vaccination did not increase the risk of MS significantly ($p > 0.05$), although found trend toward more vaccination rate in the patients. Ramagoplan¹⁷ found no significant differences between cases and controls for the frequency of hepatitis B ($p = 0.69$). The multicentre case-control study of Touzè²³ found that the risk of a first CNS demyelinating event was not significantly increased within the 2 months after HB vaccination but considered “not implausible” an association between HB vaccine and MS. The only study that found an association between MS and Hepatitis B vaccination was that of Hernan et al.¹⁹ In this study after adjustment for smoking sex, age calendar time, clinical course of the disease and type of first symptoms (eye symptoms, sensory symptoms, other) The OR (95% CI) of MS for vaccination vs no vaccination was 2.4 (crude OR was 3.1. The review by Mouchet¹² use as crude O.R a value equal to 2.9 instead of 3.1

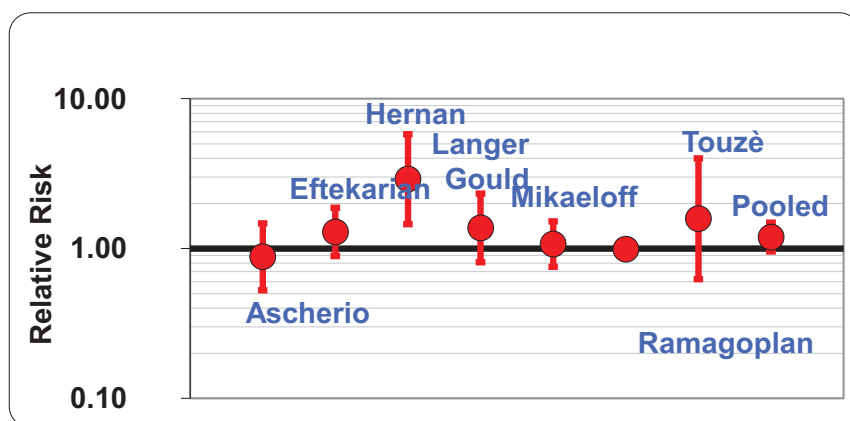
The investigation by Sturkenboom et al.⁸ included by Mouchet was excluded because of few details of this study are available,

Table 1. Characteristics of included studies.

First Author	Country	Year	Study design	Sample Size	Mean Age	Events	NOS(max 9)
Ascherio ¹⁷	France	2001	Nested Case control	192 cases and 645 controls	37.6 y	32 (cases) 84 (controls)	7
Eftekarian ¹⁸	Iran	2015	Case control	250 cases 250 controls	33 y	101 (cases) 149 (controls)	2
Hernan ¹⁹	Usa	2004	Case control	163 cases 1604 controls	NR	11 (cases) 152 (controls)	8
Langer Gould ²⁰	Usa	2014	Case control	43 cases 249 controls	39.3 y	18 (cases) 762 (controls)	7
Mikaeloff ²¹	France	2007	Case Control	143 cases 1122 controls	11 y	80 (cases) 63 (controls)	7
Ramagoplan ²²	Canada	2009	Case control	14,362 cases 7671 controls	49 y	12,330 (cases) 2032 (controls)	6
Touzè ²³	France	2002	Case control	236 cases 355 controls	NR	9 (cases) 118(controls)	8

Table 2. Newcastle Ottawa Scale for included studies.

	SELECTION					EXPOSURE			Total score (max 9 stars)
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	COMPARABILITY	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate	
Ascherio	1	1	1	1	2	0	1	0	7
Eftekarian	0	0	0	0	2	0	0	0	2
Hernan	1	1	1	1	2	0	1	1	8
Langer-Gould	1	1	1	0	2	0	1	1	7
Mikaeloff	1	1	1	1	2	0	1	0	7
Ramagoplan	1	0	1	1	2	0	1	0	6
Touze	1	1	1	1	2	1	1	0	8



Number of studies:	7	Model:	Random effects			
Study	RR	LL	UL	ln(RR)	V(ln(RR))	Relative weight
Ascherio	0,880	0,530	1,470			0,12
Eftekarian	1,290	0,890	1,870			0,17
Hernan	2,900	1,460	5,790			0,08
Langer Gould	1,370	0,810	2,320			0,11
Mikaeloff	1,070	0,750	1,520			0,18
Ramagoplan	0,990	0,910	1,070			0,30
Touzè	1,580	0,620	4,000			0,05
Pooled	1,192	0,956	1,486	0,17547	0,01263	1,00
P for homogeneity:	0,038					

Figure 2. Crude risk estimate following Hepatitis B vaccination.

since it was published only as an abstract, but the results appear compatible with a lack of association. To our knowledge few systematic review on argument exist in literature.^{9-12,24} The systematic review with metanalysis¹³ conducted in 2011 found not association between Ep. B vaccination and an increased risk of developing MS but this work was affected by a poor quality. An Umbrella review in 2015²⁵ wich aim was to summarize the environmental risk factors that have been studied in relation to onset of multiple confirms no association between the Hepatitis B vaccine and multiple sclerosis onset.

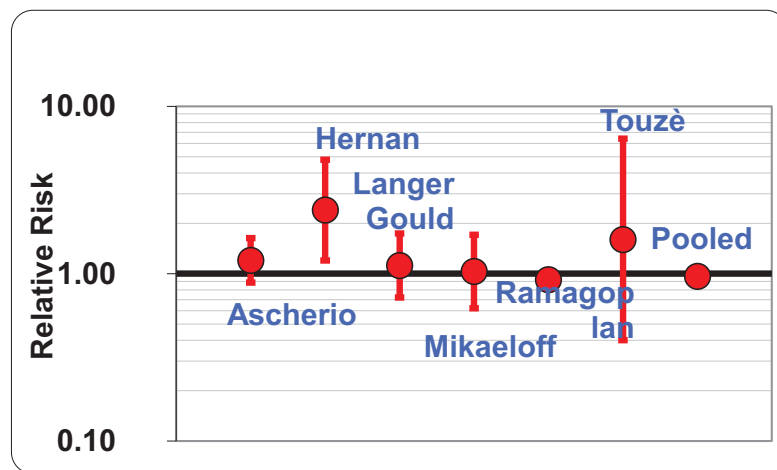
This meta-analysis has some strengths. It includes studies of good quality except for one. The scores based on the Newcastle Ottawa Scale raging from 6 point and over. It was limited the heterogeneity.

This review found results that failed to find conclusive evidence of the association between administration of HBV and MS.

Materials and methods

Identification of relevant studies

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁶ The research was conducted on the electronic databases Pubmed, ISI Web of Science, and Scopus to February 2018. The combination of terms “*hepatitis b vaccination*” and “*multiple sclerosis*” was used to retrieve studies. No restriction about language



Number of studies:	6	Model:	Fixed effects			
Study	RR	LL	UL	ln(RR)	V(ln(RR))	Relative weight
Ascherio	1,200	0,300	1,630			0,08
Hernan	2,400	1,200	4,800			0,02
Langer Gould	1,120	0,720	1,740			0,04
Mikaeloff	1,030	0,620	1,710			0,03
Ramagoplan	0,920	0,840	1,010			0,84
Touzè	1,600	0,400	6,400			0,00
Pooled	0,965	0,886	1,051	- 0,03547	0,00190	1,00
P for homogeneity:	0,060					

Figure 3. Adjusted risk estimates following HBV vaccination.

Table 3. Meta regression analysis.

Variables	O.R.
Year of publication	Beta (p)
NOS	-0,019 8(0.001)
Europe	1,211 (<0.001)
R² 0.974	0,063 (<0.001)

or time period was applied. Furthermore, the references of review, letters, comments, editorials and case reports, identified by the search strategy, were checked for retrieving further relevant literature.

Study selection

The first selection was performed filtering duplicate articles by JabRef 4.10 program and Mendeley for Windows. The articles identified were selected initially by title and abstract, independently by two researchers, and then each investigator evaluated the inclusion criteria by full-text. Disagreements between the two reviewers were resolved by a third one. Articles that take into account relationship between Hepatitis B vaccination and multiple sclerosis were included in the systematic review. Primary study case-control and cohort studies were included.

Data extraction and quality assessment

Data extraction was carried out with the same strategy of the selection of the studies: two researchers collected the data, and the disagreement was resolved by a third researcher.

A quality assessment was performed according to the Newcastle-Ottawa Scale (NOS) for cohort and case control study. The following characteristics were collected: first author, study design (cohort, case-control), year of publication, country of the first author, quality score, age of patients, O.R., sample size, main results.

Statistical analysis

The meta-analysis was realized in the case of the data were homogenous and available. The pooled prevalence with relative 95% confidence interval (95% CI) was calculated. The level of significance was set $p < 0.05$. The effect size heterogeneity was considered significant when heterogeneity probability values $p < 0.05$.

Analyses were performed using "Episheet," an Excel spreadsheet-based analytical package for meta-analyses²⁷ and IBM SPSS v.25. For meta-analysis, was estimated the summary effect size and its 95% CI with both fixed-effects and random effects models. A multivariate analysis was performed with a metaregression. Funnel plot was

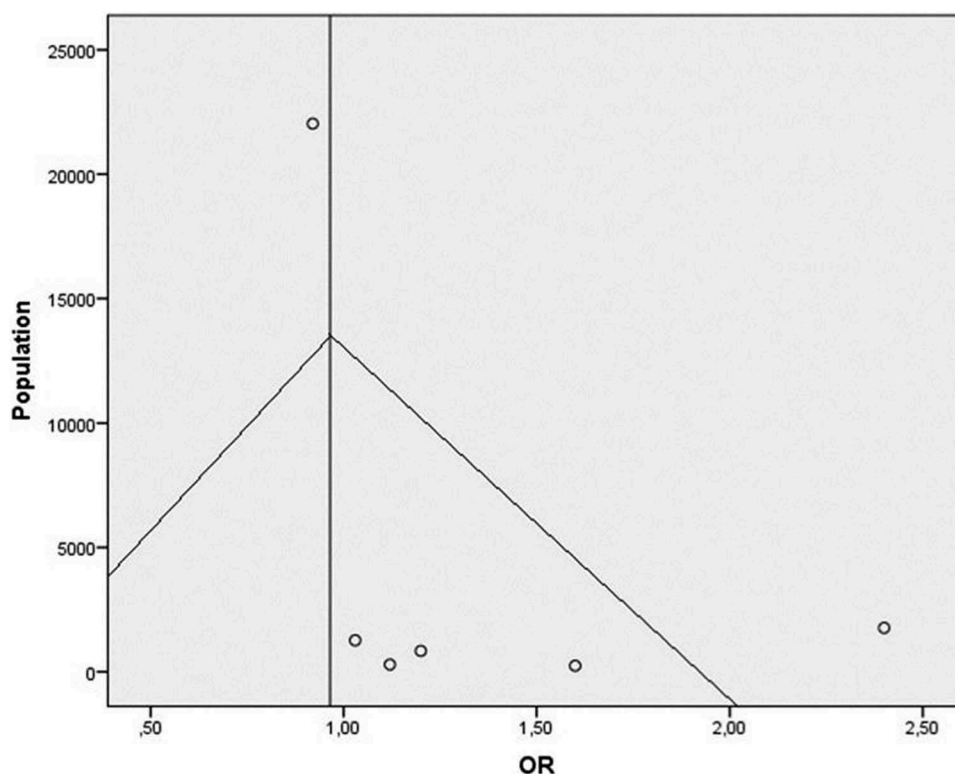


Figure 4. Funnel Plot.

constructed to evaluate publication bias. Statistical review of the study was performed by a biomedical statistician.

Conclusion

The present systematic review identified seven studies. Pooled estimates demonstrate a lack of association between multiple sclerosis and Hepatitis B vaccination. There is suggestive evidence that Hepatitis B immunization is not associated with an increased risk of developing MS.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was reported by the authors.

ORCID

Inês Grazina  <http://orcid.org/0000-0003-0372-5608>

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