Drug Saf (2018) 41:767–774
https://doi.org/10.1007/s40264-018-0652-4

ORIGINAL RESEARCH ARTICLE

Central Demyelinating Diseases after Vaccination Against Hepatitis B Virus: A Disproportionality Analysis within the VAERS Database

Julie Mouchet[1] · **Bernard Bégaud**[1]

Published online: 20 March 2018

Abstract

Introduction Hepatitis B (HB) vaccination programs were set up worldwide in the early 1990s. Despite their major focus on reducing the burden of HB infection, they have seldom achieved the targeted population coverage in most countries, including the USA, with around 24.5% of adults being vaccinated against HB. Among proposed reasons for this is the persisting doubt about a possible link between HB vaccination and the occurrence of cases of multiple sclerosis (MS).

Objective Our objective was to evaluate a potential safety signal between MS and HB vaccination. We conducted a disproportionality analysis (DPA) using the cases reported to the Vaccine Adverse Event Reporting System (VAERS).

Methods We calculated the proportional reporting rate (PRR) and reporting odds ratio (ROR) of MS having occurred within the 120 days following HB immunization in adults aged 19–49 years when compared with other vaccines using the reports recorded in the VAERS database. Both ratios were estimated globally and then according to the origin of reports (USA vs. non-USA). We then performed a sensitivity analysis using a broader category of demyelinating events.

Findings MS cases following HB vaccination were more likely to originate from outside the USA and to be reported before 2000 than those associated with other immunizations. All computed ratios were found to be statistically significant, with PRRs ranging from 3.48 to 5.56 and RORs ranging from 3.48 to 5.62. When considering the geographical origin, similar RORs were obtained for both US and non-US cases.

Conclusion In VAERS, MS cases were up to five times more likely to be reported after an HB vaccination than after any other vaccination. Since DPA is mainly suited for hypothesis generation, further studies evaluating the nature of the link between MS and HB vaccination would be of considerable importance.

Key Points

Multiple sclerosis (MS) cases were up to five times more likely to be reported after a hepatitis B (HB) vaccination than after any other vaccination.

Origin of the cases (USA or non-USA) did not influence these findings.

Further studies evaluating the nature of the link between MS and HB vaccination would be of considerable importance.

1 Introduction

Infection by the hepatitis B (HB) virus can lead to serious lifelong liver damage such as acute, chronic, and fulminant hepatitis or hepatocellular carcinoma, for which HB virus

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40264-018-0652-4) contains supplementary material, which is available to authorized users.

✉ Julie Mouchet
julie.le-moal@u-bordeaux.fr

[1] Inserm, Bordeaux Population Health Research Centre, Team Pharmacoepidemiology, UMR 1219, University Bordeaux, 33000 Bordeaux, France

is the established leading cause worldwide [1]. Vaccines to prevent HB virus infection have been developed since 1976 [2], with the first approved in the USA in 1981 [3]; 10 years later, the World Health Organization 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]. Despite their major focus on reducing the burden of HB infection and its complications, notably hepatocellular carcinoma, they have not achieved the targeted population coverage in most developed countries, including the USA, where the vaccination coverage has tended to stagnate at around 24.5% in adults [5]. Among the reasons proposed for this is the persisting doubt about a possible link between this vaccination and the occurrence of cases of central demyelinating diseases, notably multiple sclerosis (MS). MS is an autoimmune central demyelinating disease generally appearing after the age of 15 years with an incidence peak at 30 years. It is clearly more prevalent in women and in highly developed Northern European countries [6]. According to a report from the Multiple Sclerosis International Federation, the worldwide prevalence of MS is increasing and was estimated to be 33 per 1,00,000 inhabitants in 2013 [7], with large geographical variations (North America and Europe exceeding 100 per 100,000 inhabitants) [8]. The possibility of either a coincidental or causal association between HB vaccine and reports of MS was raised in the early 1990s, mainly after massive exposure of the French adult population to the vaccine [9]. A total of 53 million doses of HB vaccine were sold in France for a total population of 60 million inhabitants between 1994 and 1996, with 21.6 million to vaccinees aged 20–44 years. This unprecedented exposure of an adult population at an age prone to developing demyelinating diseases led to a pharmacovigilance alert, with 636 cases reported until 31 December 1999 [10]. In addition, cases of central and peripheral demyelination were reported worldwide in a close temporal relationship following the administration of HB vaccine [11–25]. In 2002, the US Immunization Safety Review Committee acknowledged there was weak evidence for biological mechanisms by which HB vaccination could possibly influence an individual's risk of the central or peripheral nervous system disorders of MS, first episode of central demyelinating diseases, acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, Guillain-Barré Syndrome (GBS), or brachial neuritis [26]. To our knowledge, 12 epidemiological studies have been conducted so far to evaluate the potential risk of central demyelination following immunization against HB [27–38]. Most were inconclusive, except one nested case–control study conducted within the General Practice Research Database (GPRD), which reported a significant odds ratio (OR) of 3.1 (95% confidence interval [CI] 1.5–6.3) for MS following anti-HB vaccination within 3 years preceding the index date compared with no vaccination [30]. In a recent nested case–control study using the Kaiser Permanente Southern California (KPSC) database [32], vaccination of any type (either HB vaccine or human papillomavirus vaccination) was associated with an increased risk of acquired central nervous system demyelinating syndromes within the first 30 days after vaccination only in individuals aged <50 years (OR 2.32; 95% CI 1.18–4.57). Unfortunately, this study was insufficiently powered to detect a potential risk with HB vaccination only. The exposure of adults to vaccination was rather infrequent, with only 3.3% of controls and 4.0% of cases receiving any HB-containing vaccine in the 3 years before the index date or symptom onset. To evaluate a potential safety signal between MS and HB vaccination, we conducted a disproportionality analysis (DPA) using the cases reported in the Vaccine Adverse Event Reporting System (VAERS) database.

2 Methods

2.1 Data Source

VAERS is a national vaccine safety surveillance program that collects information about adverse events having occurred after the administration of vaccines licensed for use in the USA. It provides a nationwide mechanism by which adverse events following immunization may be reported, analysed, and made available to the public. VAERS has demonstrated its public health importance by providing health scientists with signals about possible adverse events following immunization. For instance, VAERS enabled the detection of intussusception exceeding what would be expected to occur by chance alone after the launch of the first US licensed rotavirus vaccine (RotaShield; Wyeth Laboratories, Madison, NJ, USA) in 1998 [39]. Epidemiologic studies thereafter confirmed this increased risk [40, 41], and these data contributed to removal of the product from the US market. In another example, the analysis of VAERS data indicated there might be a small increase in the risk of GBS after the meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid 4 conjugate vaccine (Menactra; Sanofi Pasteur Inc., Swiftwater, PA, USA) [42]. Because of this finding, a history of GBS became a contraindication to the vaccine, and further controlled studies researching this issue are ongoing [43, 44]. VAERS receives around 30,000 reports annually, with 13% classified as serious (i.e., associated with disability, hospitalization, life-threatening

illness, or death). Since 1990, VAERS has received over 2,00,000 reports, most consisting of non-serious symptoms, such as fever [33]. For the present study, the period from VAERS inception (i.e., cases occurring before 1980) to 26 August 2017 (last date of data extraction) was considered for analysis.

2.2 Study Objectives

The primary objective of the present study was to estimate the proportional reporting rate (PRR) and reporting odds ratio (ROR) of MS having occurred within the 120 days following HB vaccination for adults aged 19–49 years when compared with other vaccines using the reports recorded in the VAERS database.

2.3 Study Population

Cases were defined as reports of MS following immunization with vaccines containing an HB antigen and registered in the VAERS database since the implementation of vaccination programs against HB.

Non-cases were defined as reports of any event other than MS following immunization with vaccines containing an HB antigen and registered in the VAERS database.

The reference group included "other vaccines cases" (i.e., reports of MS following immunization with any vaccine other than HB vaccine) and "other vaccines non-cases" (i.e. reports of any event different to MS following immunization with any vaccine other than HB vaccine).

Only cases and non-cases aged between 19 and 49 years at the date of the event occurrence were considered. This age category was retained as it represents the life period at risk for developing MS according to, among others, the US National MS Society [45].

2.4 Vaccine Exposure

Six different categories, including five multivalent vaccines, were found in VAERS for vaccines containing an HB antigen (see Table 1 in the Electronic Supplementary Material [ESM]). Only events occurring within 120 days after injection of one dose were considered. HB vaccines induce specific humoral antibodies against HB surface antigens protective against the HB infection (anti-HBs titer >10 IU/l) within 1 month after injection and then HB vaccine-induced antibody levels wane over time [46]. Focusing on this short period (0–120 days) allowed us to "maximize" the chance of observing a true pharmacovigilance signal by considering the period at the highest risk. In addition, considering events that occurred several years after vaccine administration makes the causal relationship questionable. As information contained in the VAERS database did not allow an extensive control for potential confounders (other vaccines or drug exposures, medical history, etc.), we decided to focus on events occurring within a short time window after vaccine exposure.

2.5 Outcomes of Interest

Primary outcomes included the following events: MS, progressive MS, progressive-relapsing MS, and relapsing-remitting MS. As diagnosis of MS requires at least one attack (often two considered) and one magnetic resonance imaging (MRI)-detectable clinical lesion [47], it requires a significant duration of observation to be valid. Consequently, a sensitivity analysis was performed by excluding cases diagnosed within 9 days after the injection. In addition, a sensitivity analysis was performed using a broader category of demyelinating diseases, including ADEM, demyelination, clinically isolated syndrome (CIS), MS, myelitis transverse, neuromyelitis optica (NMO), NMO spectrum disorder, progressive MS, progressive-relapsing MS, relapsing-remitting MS, nervous system disorder, neurological examination abnormal, and neurological symptom.

MS relapse was excluded from the events of interest, given that the present analysis focused on the occurrence of a first episode of MS or central demyelination. Corresponding codes used in VAERS are detailed in Table 2 in the ESM.

2.6 Data Analysis

We first conducted a descriptive analysis of MS cases per vaccination type (HB vs. any other vaccines) before calculating any ratios (PRR or ROR). The distribution of cases per the following age categories (18–29, 30–39, and 40–49 years) and per sex was documented. The geographical location of cases, either American, non-US, or unknown, was also described. VAERS also receives reports from US manufacturers that are transmitted by their foreign subsidiaries. Indeed, US FDA regulations require any manufacturer notified of a foreign case report related to an event that is both serious and unexpected to submit it to VAERS. Time to onset between immunization and the event of interest, in addition to the year of vaccination, were also detailed. To conduct such analyses, VAERS data extracts were obtained through the CDC WONDER (Wide-ranging Online Data for Epidemiologic Research), which is an easy-to-use, menu-driven system requiring no computer expertise or special software. 'N-1' Chi-squared tests were used to compare proportions for each descriptive variable per group (i.e., MS cases following HB vaccination vs. those following any other vaccination).

As DPA represents the primary class of analytic methods for analyzing data from spontaneous reporting systems (SRSs) from a drug safety surveillance perspective [48], we conducted such an analysis using a two-by-two contingency table. The latter was populated with the "HB cases" (i.e., reports of MS following immunization with any vaccine containing an HB antigen), the HB non-cases (i.e., reports of any event other than MS following immunization with any vaccine containing an HB antigen), the "other vaccines cases" (i.e., reports of MS following immunization with any vaccines other than HB vaccine), and the "other vaccines non-cases" (i.e., reports of any event different to MS following immunization with any vaccines other than HB vaccine). Results were expressed as PRR and ROR according to the following formulas:

$$\text{PRR} = a/e \times c/f \quad \text{and} \quad \text{ROR} = ad/bc,$$

where a is the number of MS cases following HB vaccination, b is the number of non-MS cases following HB vaccination, c is the number of MS cases following other vaccination (non-HB), d is the number of non-MS cases following other vaccination (non-HB), e is the total of cases (MS and non-MS) following HB vaccination, and f is the total of cases (MS and non-MS) following other vaccination (non-HB).

These ratios were provided with their 95% CIs. Both measures (PRR and ROR) have been shown to be important for assessing potential signals in SRSs [49]. Ratios were estimated globally and then by region (USA vs. non-USA). Events associated with an "unknown" vaccine were excluded from the present analysis. As recommended by Evans et al. [50], Chi-squared tests with Yates's correction were estimated for PRR. In addition, sensitivity analyses using a broader category of demyelinating events (e.g., ADEM, NMO, etc.) or excluding cases occuring within 0–9 days after vaccine injection were conducted. A sensitivity analysis per vaccine type (multivalent vs. single HB vaccine) was planned.

3 Results

3.1 Descriptive Overview of Cases

No significant difference was observed between MS cases following HB vaccination and those following another vaccination, except for the geographical origin and the years of vaccination. MS cases following HB vaccination were more likely to originate from outside of the USA and less likely to be American cases than MS cases following any other immunization. In addition, MS cases following HB vaccination were more likely to be reported before 2000, whereas MS cases following any other vaccination were more frequently reported after 2000. For further details, refer to Table 1.

3.2 Disproportionality Analysis

All computed ratios (both PRR and ROR) were above the classic cut-off value of 2 (routinely used to identify signals [50, 51]) and were found to be statistically significant. ROR ranged from 3.48 to 5.62, with 95% CIs not overlapping 1; PRR gave very similar estimates (ranging from 3.48 to 5.56), with Chi-squared tests >4. Both ratios were concordant. It should also be noted that ratios were similar regardless of their geographical origin (USA or non-USA) (Table 2). The sensitivity analysis that excluded the MS cases occurring within 9 days after injection of one dose led to higher ratios, with ROR 7.02 (95% CI 5.33–9.25) and PRR 7.01 ($p<0.05$) for all regions combined (USA, non-USA, and unknown).

Sensitivity analyses using a broader category of demyelinating events found different patterns (Table 3). When considering all regions (USA, non-USA, and unknown), lower but still statistically significant estimates were observed for both PRR and ROR. Moreover, both estimates remained above the threshold of 2 considered for a signal generation. However, when considering each region separately, PRR and ROR for cases of foreign origin were still above this cut-off of 2, whereas the ROR and PRR for US cases remained under this threshold. In other words, the frequency of the reports seemed lower for these less specific events than for MS after an anti-HB immunization, at least for cases originating from USA.

No sensitivity analysis per vaccine type (multivalent vs. single HB vaccine) was carried out as most cases ($n = 163$ [90.6%]) were reported after a monovalent HB vaccine.

4 Discussion

The main finding of this DPA in the VAERS database is that cases of MS were reported significantly more after HB vaccination than after any other vaccination. As recommended by the European Medicines Agency (EMA) in their guideline on statistical signal-detection methods [51], PRRs with more than three individual cases, being ≥ 2, and having a Chi-squared test ≥ 4 should be considered a potential signal. For ROR, a cut-off value of 2 with a lower bound of the CI at 95% CI >1 is routinely used to identify signals [50, 51]. Although DPA is mainly suited for hypothesis generation and not for causal inference, all our ratios met these requirements, and the sensitivity analysis did not alter the global conclusion. Surprisingly, the magnitude of ROR and PRR was congruent across US and non-US cases, at least for the primary analysis. This would

Table 1 Descriptive analysis of MS cases reported to VAERS per vaccination type (HB versus any other vaccine)

	MS cases following HB vaccination			MS cases following any vaccination (except HB)			*p* value
		N	%		*N*	%	
Symptoms	Multiple sclerosis	180	100.0%		180	99.4%	0.2986
	Relapsing-remitting multiple sclerosis	0	0.0%		1	0.6%	
Gender	Female	134	74.4%		125	69.1%	0.3442
	Male	45	25.0%		55	30.4%	0.5515
	Unknown	1	0.6%		1	0.6%	
Age	18–29	68	37.8%		79	43.6%	0.4773
	30–39	68	37.8%		71	39.2%	0.8658
	40–49	44	24.4%		31	17.1%	0.4507
Onset Interval	0–9 days	66	36.7%		90	49.7%	0.1074
	10–14 days	8	4.4%		15	8.3%	0.7318
	15–30 days	28	15.6%		23	12.7%	0.7706
	31–60 days	30	16.7%		27	14.9%	0.8539
	61–120 days	48	26.7%		26	14.4%	0.2287
Origin of cases	US	53	29.4%		97	53.6%	**0.0045**
	Unknown	6	3.3%		13	7.2%	0.7454
	Foreign	121	67.2%		71	39.2%	**0.0002**
Year of vaccination	Range		1987–2015	Range		1968–2016	
	1987–2000	128	71.1%	1968–2000	57	31.5%	**< 0.0001**
	2001–2017	52	28.9%	2001–2017	124	68.5%	**< 0.0001**
Vaccine Type	Hepatitis B	163	90.6%	Influenza vaccine	61	27.5%	**NA**
	Hepatitis A and B vaccine	17	0.4%				
				Human papillomavirus vaccine	38	17.1%	
				Anthrax vaccine	15	6.8%	
				Hepatitis a	13	5.9%	
				Typhoid vaccine	13	5.9%	
				Poliovirus vaccine	9	4.1%	
				Rabies virus vaccine	9	4.1%	
				Tetanus toxoid	6	2.7%	
				Meningococcal vaccine	5	2.3%	
				Pneumococcal vaccine	5	2.3%	
				Varivax-varicella virus live	5	2.3%	
				Yellow fever vaccine	3	1.4%	
				Lyme vaccine	2	0.9%	
				Bacillus Calmette-Guerin vaccine	1	0.5%	
				Cholera vaccine	1	0.5%	
				Mumps virus vaccine	1	0.5%	
				Plague vaccine	1	0.5%	
				Smallpox vaccine	1	0.5%	
				Tick-borne encephalitis vaccine	1	0.5%	
				Combined vaccines	32	14.4%	

HB Hepatitis B, *MS* multiple sclerosis, *VAERS* vaccine adverse event reporting system

mean that the disproportionality was still significant regardless of the geographic origin of cases, in conflict with the common belief that a putative link between HB and MS is solely a European, if not French, debate. As the safety profile of a vaccine may differ substantially within the target population, estimates of disproportionality in our

Table 2 Reporting ratios for multiple sclerosis per region considered

	MS*	Other events	ROR (95%CI)	PRR (Yates' chi-square; p value)
Global (US + non-US + unknown)				
HB vaccine	180	76,740	5.62	5.56
Other vaccines (except HB)	181	429,951	(4.57–6.91)	(335.16; <0.0001)
US only (+ unknown)				
HB vaccine	59	61,203	3.48	3.48
Other vaccines (except HB)	110	397,331	(2.54–4.78)	(66.03; <0.0001)
Non-US only				
HB vaccine	121	15,537	3.58	3.56
Other vaccines (except HB)	71	32,620	(2.67–4.80)	(81.22; <0.0001)

PRR proportional reporting ratio, *ROR* reporting odds ratio

*Symptoms included for MS: multiple sclerosis, progressive multiple sclerosis, progressive relapsing multiple sclerosis, relapsing-remitting multiple sclerosis

Table 3 Sensitivity analyses using a broader category of events

	Cases*	Other events	ROR (95%CI)	PRR (Yates' chi-square; p value)
Global (US + non-US + unknown)				
HB vaccine	342	76,578	2.88	2.88
Other vaccines (except HB)	665	429,467	(2.53–3.29)	(273.79; <0.0001)
US only (+ unknown)				
HB vaccine	102	61,160	1.52	1.52
Other vaccines (except HB)	436	397,005	(1.22–1.88)	(14.14; <0.0001)
Non-US only				
HB vaccine	240	15,418	2.21	2.19
Other vaccines (except HB)	229	32,462	(1.84–2.65)	(75.48; <0.0001)

PRR proportional reporting ratio, *ROR* reporting odds ratio

*Symptoms included for MS: acute disseminated encephalomyelitis (ADEM), demyelination, clinically isolated syndrome (CIS), multiple sclerosis, myelitis transverse, neuromyelitis optica (NMO), NMO spectrum disorder, progressive multiple sclerosis, progressive relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, nervous system disorder, neurological examination abnormal and neurological symptom

study were restricted to reports in the adult population (i.e., 18–49 years), allowing a comparison across groups that have a similar age-specific background risk for illness, as recommended by the EMA in the guideline on good pharmacovigilance practices [52].

To our knowledge, this DPA is the only up-to-date VAERS analysis for MS cases following HB vaccination. A paper published in 2005 reported concordant findings [53]. In that study, adults receiving HB vaccine had a significant increased OR for MS (5.2; 95% CI 1.9–20; $p < 0.0003$) unlike the tetanus-containing vaccine-exposed group. In addition, we chose to estimate two different ratios (PRR and ROR). The fact that both ratios provided very similar results reinforces the confidence regarding the robustness of our conclusions.

Nevertheless, several limitations should be acknowledged. First, VAERS is a SRS, allowing anyone (e.g., vaccine providers, other healthcare givers, vaccine recipients and relatives of recipients, vaccine manufacturers, attorneys, and other interested parties) to report adverse events [54]. However, as the virulent debate about this potential link was mainly publicized in Europe, a notorious bias seems rather unlikely in the USA. This is supported by the fact that reporting ratios found in this study were of the same order regardless of their geographical origin. Furthermore, the lack of standardization of diagnoses may hamper the validity of reported events. In 2002, Ball et al. [54] highlighted the limited information in many reports. Indeed, after an independent review of VAERS reports by three neurologists, 32% of reviewed cases of MS showed insufficient data to confirm the disease diagnosis. This pleads for the need for supplemental collection of follow-up data and indicates that VAERS reports should be interpreted

cautiously. However, we anticipate that this potential misclassification bias should not be differential between the HB vaccine-exposed group and the reference group.

5 Conclusion

The present study found a significant disproportionality of MS frequency in HB-exposed subjects, with MS cases being up to five times more likely to be reported after an HB vaccination than those exposed to any other vaccination. Geographical area (USA vs. non-USA) was not found to play a major role. Despite results being above the classic threshold of 2 for signal detection, DPA is not suitable for hypothesis validation, so a statistical association does not in any way establish a causal relationship between the administration of the vaccine and the occurrence of adverse events. In light of the present work, further study evaluating the potential link between MS and HB would be of considerable importance.

Compliance with Ethical Standards

Conflicts of interest Julie Mouchet and Bernard Bégaud have no conflicts of interest that are directly relevant to the content of this study.

Funding This study was funded by the University of Bordeaux, France, and the 'Institut national de la santé et de la recherche médicale' (Inserm). The funding source had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Cohen C, Caballero J, Martin M, Weerasinghe I, Ninde M, Block J. Eradication of hepatitis B: a nationwide community coalition approach to improving vaccination, screening, and linkage to care. J Community Health. 2013;38(5):799–804.
2. Buynak EB, Roehm RR, Tytell AA, Bertland AU 2nd, Lampson GP, Hilleman MR. Development and chimpanzee testing of a vaccine against human hepatitis B. Proc Soc Exp Biol Med. 1976;151(4):694–700.
3. Philadelphia TC. Hepatitis A and Hepatitis B [Available from: http://www.historyofvaccines.org/content/articles/hepatitis-and-hepatitis-B]
4. Zuckerman J, van Hattum J, Cafferkey M, Gjorup I, Hoel T, Rummukainen ML, et al. Should hepatitis B vaccination be introduced into childhood immunisation programmes in northern Europe? Lancet Infec Dis. 2007;7(6):410–9.
5. Williams WW, Lu PJ, O'Halloran A, Kim DK, Grohskopf LA, Pilishvili T, et al. Surveillance of vaccination coverage among adult populations—United States, 2014. MMWR Surveill Summ. 2016;65(1):1–36.
6. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010;9(5):520–32.
7. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. Lancet Neurol. 2015;14(3):263–73.
8. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. Rev Neurol. 2016;172(1):3–13.
9. Fourrier A, Bégaud B, Alpérovitch A, Verdier-Taillefer MH, Touzé E, Decker N, et al. Hepatitis B vaccine and first episodes of central nervous system demyelinating disorders: a comparison between reported and expected number of cases. Br J Clin Pharmacol. 2001;51(5):489–90.
10. Agence Française de Sécurité Sanitaire et des Produits de Santé. Vaccination anti hepatite b - mise a jour des donnees et des etudes de pharmacovigilance. Février 2000.
11. Agmon-Levin N, Kivity S, Szyper-Kravitz M, Shoenfeld Y. Transverse myelitis and vaccines: a multi-analysis. Lupus. 2009;18(13):1198–204.
12. Arhan E, Gücüyeter K, Aktürk A, Kasapkara Ç, Demir E, Serdaroğlu A. Guillain-Barre syndrome associated with hepatitis b vaccine and a review of the literature. Gazi Med J. 2009;20(2):83–5.
13. Cabrera-Gomez JA, Echazabal-Santana N, Garcia Gonzalez L, Ramos Cedeno AM, Rodriguez Roque MO, Lopez Hernandez O, et al. A severe episode in a patient with recurrent disseminated acute encephalitis due to vaccination against hepatitis B. For or against vaccination? Rev Neurol. 2002;34(4):358–63.
14. Erguven M, Guven S, Akyuz U, Bilgic O, Laloglu F. Optic neuritis following hepatitis B vaccination in a 9-year-old girl. J Chin Med Assoc. 2009;72(11):594–7.
15. Heekin R, Gandhy C, Robertson D. Seronegative Neuromyelitis Optica Spectrum Disorder following Exposure to Hepatitis B Vaccination. Case Rep Neurol. 2015;7(1):78–83.
16. Herroelen L, de Keyser J, Ebinger G. Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine. Lancet. 1991;338(8776):1174–5.
17. Iniguez C, Mauri JA, Larrode P, Lopez del Val J, Jerico I, Morales F. Acute transverse myelitis secondary to hepatitis B vaccination. Rev Neurol. 2000;31(5):430–2.
18. Karaali-Savrun F, Altintas A, Saip S, Siva A. Hepatitis B vaccine related-myelitis? Eur J Neurol. 2001;8(6):711–5.
19. Khamaisi M, Shoenfeld Y, Orbach H. Guillain-Barre syndrome following hepatitis B vaccination. Clin Exp Rheumatol. 2004;22(6):767–70.
20. Konstantinou D, Paschalis C, Maraziotis T, Dimopoulos P, Bassaris H, Skoutelis A. Two episodes of leukoencephalitis associated with recombinant hepatitis B vaccination in a single patient. Clin Infect Dis. 2001;33(10):1772–3.
21. Renard JL, Guillamo JS, Ramirez JM, Taillia H, Felten D, Buisson Y. Acute transverse cervical myelitis following hepatitis B vaccination. Evolution of anti-HBs antibodies. Presse Med. 1999;28(24):1290–2.
22. Tartaglino LM, Heiman-Patterson T, Friedman DP, Flanders AE. MR imaging in a case of postvaccination myelitis. AJNR Am J Neuroradiol. 1995;16(3):581–2.
23. Terney D, Beniczky S, Barsi P, Kondakor I, Perenyi J, Faludi B, et al. Multiple sclerosis after hepatitis B vaccination in a 16-year-old patient. Chin Med J. 2006;119(1):77–9.
24. Tourbah A, Gout O, Liblau R, Lyon-Caen O, Bougniot C, Iba-Zizen MT, et al. Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS? Neurol. 1999;53(2):396–401.
25. Zafrir Y, Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y. Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases. Lupus. 2012;21(2):146–52.

26. In: Stratton K, Almario D, McCormick MC, editors. Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders. Washington (DC)2002.
27. Ascherio A, Zhang SM, Hernan MA, Olek MJ, Coplan PM, Brodovicz K, et al. Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med. 2001;344(5):327–32.
28. DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol. 2003;60(4):504–9.
29. Eftekharian MM, Mousavi M, Hormoz MB, Roshanaei G, Mazdeh M. Multiple sclerosis and immunological-related risk factors: Results from a case-control study. Hum Antibodies. 2014;23(1, 2):31–6.
30. Hernan MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurol. 2004;63(5):838–42.
31. Hocine MN, Farrington CP, Touze E, Whitaker HJ, Fourrier A, Moreau T, et al. Hepatitis B vaccination and first central nervous system demyelinating events: reanalysis of a case-control study using the self-controlled case series method. Vaccine. 2007;25(31):5938–43.
32. Langer-Gould A, Qian L, Tartof SY, Brara SM, Jacobsen SJ, Beaber BE, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. JAMA Neurol. 2014;71(12):1506–13.
33. Mikaeloff Y, Caridade G, Rossier M, Suissa S, Tardieu M. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. Arch Pediatr Adolesc Med. 2007;161(12):1176–82.
34. Mikaeloff Y, Caridade G, Suissa S, Tardieu M. Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. Neurol. 2009;72(10):873–80.
35. Sturkenboom M, Abenhaim L, Wolfson C, Roullet E, Heinzlef O, Gout O. Vaccinations, demyelination and multiple sclerosis study (VDAMS): a population-based study in the UK. Pharmacoepidemiol Drug Saf. 1999;8(suppl 2):S170–1.
36. Touze E, Fourrier A, Rue-Fenouche C, Cile E, Ronde-Oustau V, Jeantaud I, et al. Hepatitis B vaccination and first central nervous system demyelinating event: a case-control study. Neuroepidemiology. 2002;21(4):180–6.
37. Touze E, Gout O, Verdier-Taillefer MH, Lyon-Caen O, Alperovitch A. First central nervous system demyelination and hepatitis B vaccination: A pilot case control study. Rev Neurol. 2000;156(3):242–6.
38. Zipp F, Weil JG, Einhäupl KM. No increase in demyelinating diseases after hepatitis B vaccination. Nature Med. 1999;5(9):964–5.
39. Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine–United States, 1998–1999. MMWR Morb Mortal Wkly Rep. 1999;48(27):577–81.
40. Kramarz P, France EK, Destefano F, Black SB, Shinefield H, Ward JI, et al. Population-based study of rotavirus vaccination and intussusception. Pediatr Infect Dis J. 2001;20(4):410–6.
41. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344(8):564–72.
42. Centers for Disease Control and Prevention (CDC). Guillain-Barre syndrome among recipients of Menactra meningococcal conjugate vaccine–United States, June-July 2005. MMWR Morb Mortal Wkly Rep. 2005;54(40):1023–5.
43. Centers for Disease Control and Prevention. (CDC). Update: Guillain-Barre syndrome among recipients of Menactra meningococcal conjugate vaccine–United States, June 2005-September 2006. MMWR Morb Mortal Wkly Rep. 2006;55(41):1120–4.
44. Velentgas P, Amato AA, Bohn RL, Chan KA, Cochrane T, Funch DP, et al. Risk of Guillain-Barre syndrome after meningococcal conjugate vaccination. Pharmacoepidemiol Drug Saf. 2012;21(12):1350–8.
45. Zorych I, Madigan D, Ryan P, Bate A. Disproportionality methods for pharmacovigilance in longitudinal observational databases. Stat Methods Med Res. 2013;22(1):39–56.
46. US National Multiple Sclerosis Society. Who gets MS? 2018 [Available from: https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS.
47. European Medicine Agency . Summary of Product Characteristics Engerix B 2000 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Engerix_B_30/WC500011088.pdf].
48. Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. J Autoimmun. 2014;48–49:134–42.
49. Waller P, van Puijenbroek E, Egberts A, Evans S. The reporting odds ratio versus the proportional reporting ratio: 'deuce'. Pharmacoepidemiol Drug Saf. 2004;13(8):525–6 **(discussion 7–8)**.
50. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483–6.
51. European Medicine Agency. Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system. 2006.
52. European Medicine Agency. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases. 9 December 2013.
53. Geier DA, Geier MR. A case-control study of serious autoimmune adverse events following hepatitis B immunization. Autoimmunity. 2005;38(4):295–301.
54. Ball R, Halsey N, Braun MM, Moulton LH, Gale AD, Rammohan K, et al. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the vaccine: adverse event reporting system. J Clin Epidemiol. 2002;55(8):819–24.