



## Comment on “Central Demyelinating Diseases After Vaccination Against Hepatitis B Virus: A Disproportionality Analysis Within the VAERS Database”

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Published online: 29 September 2018  
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We read with interest Mouchet and Bégaud’s recent analysis of the Vaccine Adverse Events Reporting System (VAERS) database [1]. They concluded that 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, and that the origin of the cases (United States [US] or non-US) did not influence their findings, before advocating further studies into this potential link. However, we disagree with their conclusions and highlight a fundamental flaw in their analysis.

In the 1990s, a suspected link between MS and HB vaccination received significant media coverage in France, which led to distrust in HB vaccines. Several litigation cases involving vaccinated healthcare professionals received financial compensation in France [2], which impacted the reporting of MS cases after HB vaccines versus other vaccines. For instance, MS cases that onset within 120 days after HB vaccination were reported to the VAERS after a time lag of several years (data not shown). In the early 2000s, after reviewing the evidence, several groups of experts concluded that there was an absence of evidence to support a causal association between HB vaccine and MS [3, 4]. Thus, the perception of risk changed over time, peaking in 1990s, and was particularly acute in France. Consistent with this, the authors found (see Table 1 in their article) that the geographical distribution of MS cases reported after HB vaccination differed significantly to that of MS cases reported after other

vaccines. They pooled both datasets in the main analyses and conclusions, and showed the impact of this pooling in their subgroup analysis (see Table 2 in their article). Table 1 in their article also shows an even larger heterogeneity according to the year of vaccination, with 52 MS cases reported after HB vaccination in 2001–2017 versus 128 MS cases in 1987–2000, while after other vaccines, 124 MS reported cases were vaccinated in 2001–2017 versus 52 MS cases in previous years. We were therefore surprised that despite this significant and expected temporal pattern, the authors did not account for it. Instead, they chose to pool all data over three decades in all analyses.

We also read with interest a systematic review and meta-analysis also published by Mouchet and Bégaud earlier this year [5]. This second article identified 13 studies on the risk of central demyelination after HB vaccination, and concluded that there is no evidence of an association. We find it curious that neither paper refers to the other or discusses their contradictory findings. To reduce bias due to confounding, disproportionality methods require subgroup analyses, e.g. by excluding litigation cases, and subgrouping by region or period. Ignoring diversity and potential confounding factors within a dataset may result in either signals being masked, or false associations being flagged as potential signals [6, 7]. In the VAERS, which is co-owned by the US Centers for Disease Control and Prevention (CDC) and US Food and Drug Administration (FDA), foreign adverse event reports are cases occurring abroad, and are mostly reported by vaccine manufacturers in compliance with FDA regulations. These reports are of variable data quality and completeness due to the different national reporting practices and surveillance system quality, and, consequently, US CDC analyses typically separate foreign reports from US cases [8].

We attempted to reproduce the authors’ data extraction (via Empirica software, Oracle) and found discrepancies with their data in the number of other events with onset

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This comment refers to the article available at <https://doi.org/10.1007/s40264-018-0652-4>.

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An author’s reply to this comment is available at <https://doi.org/10.1007/s40264-018-0734-3>

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**Table 1** Reporting ratios for multiple sclerosis per region and vaccination year considered: 1987–2000 and 2001–2017; 1987–2004 and 2005–2017

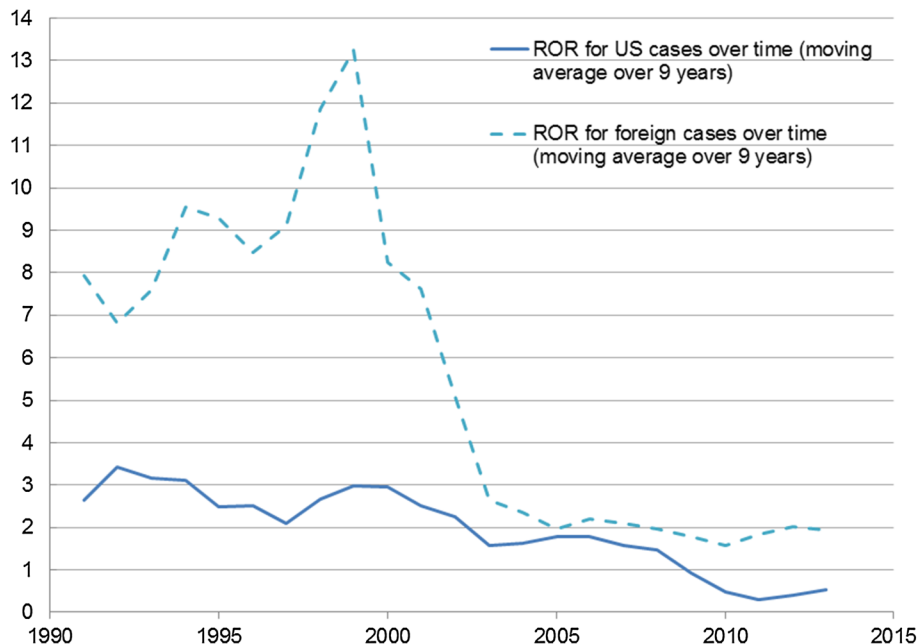
Location of cases	Vaccination year	Vaccines	MS cases	Other events	ROR (95% CI)	
USA	1987–2000	HB	48	8088	2.52	
		Other	41	17,385	(1.66–3.82)	
	2001–2017	HB	12	7338	1.86	
		Other	68	77,290	(1.01–3.44)	
	1987–2004	HB	55	9896	2.98	
		Other	52	27,849	(2.04–4.35)	
	2005–2017	HB	5	5530	1.06	
		Other	57	66,826	(0.42–2.65)	
	Foreign	1987–2000	HB	80	724	8.56
			Other	6	465	(3.71–19.79)
2001–2017		HB	46	1611	2.58	
		Other	52	4698	(1.73–3.85)	
1987–2004		HB	94	1092	10.03	
		Other	7	816	(4.63–21.74)	
2005–2017		HB	32	1243	2.19	
		Other	51	4347	(1.40–3.43)	

MS multiple sclerosis, ROR reporting odds ratio, CI confidence interval, HB hepatitis B

within 120 days after vaccination in 18- to 49-year-olds and in the number of MS cases. We calculated moving averages of the reporting odds ratio (ROR) by vaccination year (ROR for year  $N$  calculated over the years  $N - 4$  to  $N + 4$ ), which showed that foreign reporting rates of MS cases after HB vaccination in the 1990s were particularly high, before decreasing markedly in the early 2000s to levels more comparable with those in the US (Fig. 1, Table 1). This illustrates that pooling these data was inappropriate.

In conclusion, given the consistency between their data in Table 1 and the well-known history of the scientific and media perception of the potential association of MS with HB, we believe that Mouchet and Bégau’s decision to pool such heterogenous data over such a long period of time was fundamentally flawed and their conclusions unfounded. In 2002, the Global Advisory Committee on Vaccine Safety concluded that there is no association between administration of the HB vaccine and MS, consistent with the US Institute of Medicine, and their position has not changed since [9, 10].

**Fig. 1** Reporting ratios for multiple sclerosis per region considered: moving averages over 9-year periods of calendar time (i.e. ROR for vaccination year  $N$  is calculated over the years  $N - 4$  to  $N + 4$ ). ROR reporting odds ratio



**Acknowledgements** The authors wish to acknowledge Aumery Billon for his assistance in checking the data, and Grenville Marsh for his editorial assistance in preparing this letter.

## Compliance with Ethical Standards

**Conflicts of interest** Carine Cohen, Annick Houdeau and Alena Khromava are employed by Sanofi Pasteur.

**Funding** No sources of funding were used to assist in the preparation of this letter.

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