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Multiple sclerosis and hepatitis B vaccination: Adding the credibility of molecular biology to an unusual level of clinical and epidemiological evidence

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Summary In spite of a huge number of reports of severe hazards after injection of hepatitis B vaccine (HBV), the issue is regularly raised that no mechanism is available for the development of central demyelinating disorders such as multiple sclerosis (MS). A number of convergent facts, however, suggests that the manufacturing process could introduce HBV polymerase as a contaminant, and then trigger an auto-immune process against myelin in some vaccinated subjects. Of great significance, this hypothesis is likely to give the missing link to account for the considerable body of clinical and epidemiological evidence documenting that, for a drug used with a preventive purpose, HBV has an unusual potential to induce central neurological disorders amongst others unwanted side-effects. © 2005 Elsevier Ltd. All rights reserved.

In a recent paper [1], we reviewed evidence showing that hepatitis B vaccine (HBV) has a marked potential to induce auto-immune hazards, neurological as well as non-neurological. We emphasized that for a drug used as a prevention, HBV was remarkable by the unusual *frequency*, *severity* and *variety* of its hazards. Clearly struck by the strength of the clinical and epidemiological evidence given, the authors of an accompanying editorial [2] rightly stressed that there was no precise data offered with respect to mechanism(s).

As indicated in our paper, the documented hazards of HBV pertain to two categories: (1) disorders reproducing almost the whole spectrum of non-hepatic manifestations of natural hepatitis B (including *peripheral* demyelinating disorders such as Guillain-Barré syndromes), generally within a quite evocative latency period (a few days or weeks); (2) central demyelinating disorders such as multiple sclerosis (MS), which may have their first clinical manifestations some years after vaccination. Potential mechanisms for the former complications are not too difficult to imagine and it is of interest to remind that the risk for a vaccine to reproduce the auto-immune disorders of hepatitis B was evoked quite early [3,4]. In fact, Selmi

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et al's objection mainly applies to the latter hazards since, pending further information, MS or related diseases are not known as potential complications of natural hepatitis B. Published some weeks after ours, the review by Faure [5] may be an important step on the way of identifying one credible mechanism for vaccine-induced MS.

In contrast with Selmi's et al. assertion that up till now, no obvious similarity was identified between the HBV genome and human proteins, Faure gives convincing evidence of significant similarities between viral genome and not only "human proteins" in general, but well and truly *myelin* basic protein in particular. In addition, making the quite credible hypothesis that the manufacturing process could leave minute amounts of HBV polymerase protein as a contaminant, he shows that this protein could be synthesised by alternative transcriptional or translational strategies and exposed on the outside of the virus particles, thereby becoming immunogenic and triggering an auto-immune process against the myelin of some vaccinated subjects.

Whereas, Faure's observations obviously reinforce the reach of our review in producing at least one credible amongst other potential mechanisms, they are themselves reinforced in a reciprocal manner. Indeed, expectedly unfamiliar with clinical and epidemiological research, Faure was more than cautious in his formulations, e.g., when he said that "causality between VHB and the onset of demyelinating syndrome has not been proved" – a major stance amongst manufacturers and their experts (which are often the same as those of regulatory bodies or the WHO...) Yet, for any expert in the field

of pharmacovigilance or pharmaco-epidemiology, the level of causality concerning HBV hazards is far higher than that usually considered as sufficient to take severe restriction measures, such as those leading to the withdrawal of the antiparkinsonian Tasmar after rare and problematic reports of hepatitis and in spite of a genuine interest in people ill enough to accept a significant level of risk in the hope of a clinical improvement. In addition, as we reminded in our review, the overall assessment of evidence has been significantly distorted by dissimulation of data, reports or studies of dubious validity and selective assessment of available results, as exemplified by the unusual criticism against the remarkable study by Hernan et al. [6] as compared to the astonishing leniency for investigations the methodological weaknesses of which are striking [7,8]. On the other hand, it should be reminded that, produced by one institution already involved in major French health scandals (contaminated blood, growth hormone), one of the vaccine extensively used in France was never registered in any developed country: this unusual situation raises important concerns about the overall quality of the application dossier for this product, esp. as regards the manufacturing process. The impact of these concerns on the risk of contamination by the viral polymerase, as described by Faure, is obvious. Overall, this alarming exception might significantly contribute to the fact that the health impact resulting from mass campaign could be truly more severe in France than elsewhere, as opposed to the extensive use of this apparent 'French paradox' by manufacturers and regulatory authorities to give credence to the lame argument that the

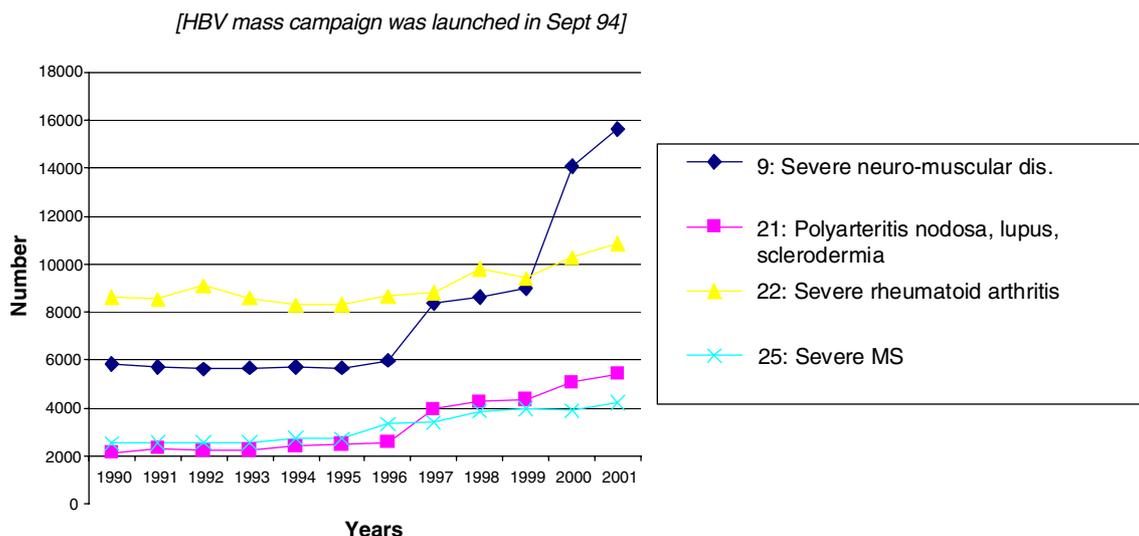


Figure 1 Data of the French health system (CNAM) on the evolution of diseases with a 100% coverage (1990–2001).

terrible situation now observed in our country (see Fig. 1) would be a simple artefact.

To conclude, putting together the strength of clinical and epidemiological evidence that we reviewed as well as the credibility of the mechanism suggested by Faure, we strongly support his view that the ‘‘principle of precaution’’ should urgently be applied having regard to the tiny benefit (if any) of large HBV vaccination in low-endemic countries. In addition, the benefit/ratio of this costly prophylaxis should be seriously re-assessed even in countries where the frequency of HBV is higher.

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