The Editor
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Sir,

As exemplified by an accompanying editorial[1], results of two studies[2,3] published in a recent issue of NEJM have been overwhelmingly interpreted as demonstrating that no link exists between hepatitis B (HB) vaccine and multiple sclerosis (MS). In France, although the paper of Ascherio et al was the first, to my knowledge, to discuss the results of previous case-control studies as suggesting "nonsignificant increases in risk" (the predominating thesis here being rather that lack of statistical significance demonstrated a lack of risk), it has become almost impossible to publish any fair discussion on these investigations, the results of which have been largely extrapolated as demonstrating the overall safety of HB vaccines and the justification of the French vaccination program: henceforth, as suggested by Gellin and Schaffner,[1] methodological objections on these issues cannot be more than limitations in "understanding of immunizations"... The first point, however, is that the products and immunization schedules may be quite different according to the country of reference (and indeed are not at all the same in the US as compared to France), which precludes any hasty extrapolation.

Concerning the study by Confavreux et al.[2], two points must be made. Firstly, there is no belief that *any* vaccination could have the same potential of exacerbating MS and due to lack of statistical power, the potential risk of *one* vaccination might easily be drowned in pooling. Secondly, as (justified or not) the contraindication of the vaccinations in people with MS was a quite classical one, one could expect that those patients immunized in spite of this should have been those *with the less severe* disease : this is exactly what appeared from Table 1, which showed that the baseline number of relapses was significantly lower ($p = 0.02$) in those subjects receiving vaccination.

Regarding the study by Asherio et al.[3], previous work of the same team suggests that the incidence of MS was quite heterogeneous in both cohorts[4], this marked heterogeneity being likely to mask a small increase in relative risk (e.g. 1.5) largely susceptible to account for a major health problem after exposure of 30 millions persons. But the main objection is that a cohort of nurses should have been the last one would have thought of in order to investigate the neurological risk of HB vaccine: indeed, as such immunization is more or less an occupational obligation, it was perfectly expectable than those with any neurological history or risk would be less likely to receive this vaccination (due to the classical contra-indication assessed by Confavreux et al[2]) and, once again, this was perfectly confirmed in Table 1, which showed that the percentage of HB vaccination history was only 43% in women with MS as compared to 60% in controls: in other words, there was a clear bias accounting for greater

exposure to the investigated risk factor *in the controls* as compared to the cases. Incidentally, the overall percentage (40-60%) of HB vaccination in this population with a high level of occupational risk seems fairly low, raising doubts about the accuracy of the assessment of exposure.

Although not echoed with the same intensity by medical or lay media, a paper[5] published within the same time showed a significant increase in adverse health outcomes (such as arthritis) in children less than 6 years of age after HB vaccine : this led the authors to discuss the benefit/risk ratio of this vaccination having regard to the "negligible" risk of HB "for most infants", in accordance with another recent paper reporting an unusually high number of reports with this vaccine from the Vaccine Adverse Events Reporting System (VAERS) in the US.[6] At least in part, statistical shortcomings of available studies could result from the fact that narrowing the focus of investigations on quite specific pathophysiological entities such as MS (but which may raise acute problems of recognition and differential diagnosis[7]) is likely to split increasing evidence that there could be a significant problem of *immune complications* with HB vaccination.

Sincerely.

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