Questions and answers

1. Why is the issue of an association between vaccination hepatitis B vaccination and multiple sclerosis surfacing again?
The possible role of vaccination against hepatitis B in the occurrence of multiple sclerosis (MS) is being raised again as a result of the recent publication of a study (Hernan et al., Neurology 2004) which revives questions raised ten years ago.

2. What is the nature of this new study?
This retrospective study, which had been presented in September 2003, uses the General Practice Research Database of the United Kingdom (GPRD) to identify all adult patients with MS and to compare vaccination received during the previous years with those received by a group of control adult patients without MS. Among 713 patients with a suspicion of MS, 275 were eliminated because their diagnosis of MS was incorrect or uncertain, their files were incomplete, or their follow-up stopped due to death. The files of the 438 remaining patients were analyzed to determine the date of the first symptoms of MS. The authors then concentrated on 163 patients with at least 3 years of follow-up in the GPRD before the supposed date of their first symptoms. By analyzing these 163 files, the authors observed that the majority of the patients (141/152, 93.3%) had not been vaccinated against hepatitis B. The small proportion of patients who had been vaccinated against hepatitis B (11/152, 6.7%) was however 3 times higher (OR 3.1, IC95 1.5 - 6.3) than that of the controls (39/1565, 2.4%). If this observation could be generalized to the population this could indicate that hepatitis B vaccination plays a role in the occurrence of MS.

3. How does this study differ from previous studies?
All the studies have characteristics which could lead to different results. A characteristic of the study by Hernan et al. is to have used the medical files put together by general practitioners, whereas other studies relied on information provided by patients to identify vaccination history and the date of onset of MS symptoms. If some vaccinations were not recorded in the files of the general practitioners this would distort the results. Another limitation is that vaccination against hepatitis B is only recommended in England for certain high risk groups (health professionals, travellers to endemic regions, patients with hepatic or renal dysfunction, prostitutes and drug addicts), which could not be representative of the populations included in the other studies. The authors had to eliminate a substantial number of medical files which were either incomplete or unclear, which reduced the number of observations to a very small number patients (only 11 having been vaccinated against hepatitis B). An error in the vaccination dates or dates of onset of symptoms in only 1-2 patients would be enough for the Hernan study to conclude, as in the preceding studies, that there is no correlation between vaccination against hepatitis B and MS. Another difference is the fact that the Hernan study includes a longer risk period (3 years) that goes beyond that suggested by the French pharmacovigilance data.

4. Does this study suggest that vaccination against hepatitis B could accelerate the occurrence of SEP among certain predisposed patients?
No, the results of the study by Hernan do not suggest that vaccination can accelerate the occurrence of MS. Firstly, the average age at the time of the first symptom of MS was similar for subjects vaccinated and unvaccinated against hepatitis B. Secondly, the proportion of patients having developed MS in the 12 months after vaccination was close to that of controls (1.8% and 1.0%, respectively). The only apparent difference relates to the period between 12 and 36 months after vaccination. This study is thus in agreement with all the other studies not having identified an increased risk of developing MS in the year following vaccination against hepatitis B as had been suggested by French pharmacovigilance data.

5. Does this study suggest that vaccination against hepatitis B could cause MS?
The Hernan study presents limitations which prevent the extension of its results to the general population: it rests on the analysis of a very small number of vaccinated patients (11) with risk factors for hepatitis B. The present study contrasts with the conclusions of multiple other studies and review panels which concluded that there is no link between MS and hepatitis B vaccination. Although there may be methodological flaws in some of the other studies, we have to consider the Hernan study in the context of the other negative studies.

6. Are the results of this study in accordance with those of the other studies?
No. None the many preceding studies highlighted a significantly increased risk of MS after hepatitis B vaccination. The Hernan study must thus be regarded as an unexpected part of the puzzle in a set of data supporting the safety of hepatitis B vaccination.

7. Could the difference between this study and previous studies be due to the different methodology used?
In order to determine if the unexpected results of this study could be explained by the methodology used, the CDC applied the same methodology to a large American dataset (VSD), by using either the medical data, or the data provided by the patients (De Stefano F, 20th International Conference on Pharmacoepidemiology, Bordeaux, August 2004). Their observations confirm that the medical files often contain only part of the information available to the patients, in particular with regard to their vaccinations! This American study analyzed the files of 276 patients and 599 matched controls and failed to identify any correlation between hepatitis B vaccination and the occurrence of MS at any time in the 5 years following vaccination. These data reinforce the suspicion of the existence of confounding factors in the Hernan study, including the vaccination of subjects at risk, the analysis of possibly non-exhaustive medical data and the small number of patients selected.

8. What are the results of this study in relation to other vaccines?
Following the same approach as for hepatitis B vaccination, Hernan and colleagues found the same proportion of patients (6.1%) and controls (6.0%) vaccinated against influenza during the previous 3 years. This is in accordance with other studies which have shown that influenza vaccination has no influence on the occurrence of MS. The authors observed that the proportion of patients vaccinated against tetanus (11.7%) during the previous 3 years was significantly lower than that of the controls (17.4%). The limitations of the study do not make it possible however to suggest that vaccination against tetanus could have a protective effect on the occurrence of MS.

9. If the results of this study were representative, what would be the biological hypothesis?
If the results of this study were representative of the general population, it would be necessary to find a hypothesis compatible with an increase in the risk of MS between 12 and 36 months after vaccination of adult patients against hepatitis B. This time interval is not in line with a non-specific effect of the vaccines or their adjuvants, observed in the weeks after vaccination. It would thus be necessary to imagine a causal role of the HBsAg antigen, but this is made improbable by the absence of association between infection hepatitis B and MS. The potential role of aluminium and thiomersal contained in the hepatitis B vaccine is contradicted by the absence of influence of the tetanus and influenza vaccines in the same study. Thus, there is currently no biological hypothesis which could explain the observations of this study.

10. If the results of this study were generalizable, would this incriminate the adjuvants or additives contained in the vaccines against hepatitis B?
No. If the results of this study were generalizable to the general population and indicated an increased risk of MS between 12 and 36 months after vaccination, one could not imply that this risk is related to aluminium or thiomersal since these components are also present in the tetanus and influenza vaccines, which have not been associated with an increased risk of MS either in the Hernan study or any of the previous ones.

11. If the results of this study were representative, what would be the greatest possible risk for the population vaccinated against hepatitis B?
If the results of this study were representative of the general population, it should be expected that the risk of developing MS within 3 years of an hepatitis B immunization in adult patients could increase by 3.1 times, increasing for example from approximately 1 patient/100' 000 to 3 patients/100'000. But the limitations of this study and the vaccine safety data accumulated throughout the world indicate that this scenario is not likely.

12. Will the results of this study result in modifications of the recommendations concerning vaccination against hepatitis B?
Neither the authors of the study, nor its editorial, questions the importance of hepatitis B immunization. The preliminary results of this study were already presented publicly more than a year ago. Although it is too early for health authorities to have reached a conclusion on the matter, none have expressed the intention of modifying their recommendations concerning vaccination against hepatitis B for which the medical reality is of much greater significance than that of a theoretical risk which has not been proved. It is essential to highlight that regardless of the factors resulting into the observation of Hernan, his study only relates to the immunization of adult patients at risk of hepatitis B. Evidence has accumulated during the last 20 years to support the safety of hepatitis B immunization in neonates, infants, children and adolescents.