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static and *de novo* HCC. Our preliminary experiments suggest that a tumor-derived gene signature could be found to be predictive for HCC late-recurrence (Budhu et al., unpublished data). This is analogous to the recent findings that both tumor and non-tumor-derived gene signatures can predict HCC early-recurrence in multiple cohorts [4–9]. Thus, the jury is still out and further studies are needed.

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doi:10.1016/j.jhep.2009.05.007

A new French paradox: HBV vaccination

To the Editor:

In his recent article, DS Chen indicated that the hepatitis B vaccine was an innovation from France [1]. When listing the challenges that need to be overcome to extend hepatitis B mass vaccination he could have cited France again. The percentage of one-year-olds immunized with three doses of Hepatitis B in France was 29% in 2006 (vs. 86% in Germany, a comparable country), lower than most of the very poor countries in the world [2].

Recently, a paper by a French team published in a major journal concluded that “Engerix B vaccine appears to increase the risk of CNS inflammatory demyelination in childhood” [3]. A pre-publication release campaign worsened the message in the newspapers.

This research was conducted with public funding from several major national bodies. Evaluation could have helped avoiding: (a) subgroup analyses without *a priori* definition on the basis of known mechanisms or in response to previous findings; (b) absence of

declaration of the number of analyses performed; (c) lack of adjustment for multiple testing with tests for heterogeneity [4]. These pitfalls are easy to remember: Sleight showed, in a subgroup analysis of patients from the ISIS-2 trial, that aspirin therapy was significantly beneficial for all patients except those born under the astrological signs of Gemini or Libra [5]!

Guidelines were generated to improve quality of epidemiological studies (eg ‘STrengthening the Reporting of OBservational studies in Epidemiology’ (STROBE) [6]. Funding agencies, reviewers and journals editors must have actively endorsed these guidelines.

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doi:10.1016/j.jhep.2009.05.009

Hepatitis B vaccine and multiple sclerosis: A case of repeated déjà vu?

To the Editor:

I cannot agree more with Braillon [1] that in revealing the results of any study concerning the adverse reactions of treatment or prevention measures, everyone in the chain of releasing the information should be very prudent. This is especially true in relation to the hepatitis B vaccine.

The unusually low coverage of hepatitis B vaccination in France can be traced to the alleged concerns about the safety of the hepatitis B vaccine. The allegation started right after the country implemented an active hepatitis B vaccination program in 1994–1995 targeting at pre-adolescents in the first year of secondary schools as well as all infants [2]. Initially, the program was highly successful with a coverage rate of 76% in adolescents. During implementation of the program, reports of demyelinating disorders of the central nervous system (CNS) suspected to be associated with hepatitis B vaccination started to appear. Despite the lack of causal association, the issue caught the attention of mass media and, naturally, the general public then. The pressure cumulated became so great that it led the French health authority to suspend hepatitis B vaccination in a school-based program on October 1, 1998. The French government's decision was immediately condemned by the World Health Organization (WHO) and the French pediatricians [3], because it will very possibly result in a loss of public confidence in hepatitis B vaccination, and thus lead other countries to discontinue its use or decide not to introduce a hepatitis B vaccination program that is critical in the control of hepatitis B worldwide [4]. Indeed, the negative impact could be tremendous, if not handled appropriately. To avoid unnecessary negative impacts to our very successful mass hepatitis B vaccination program in Taiwan [5], right after the suspension of hepatitis B vaccine in France, Taiwan's Department of Health immediately issued a press release to assure the safety and necessity of hepatitis B vaccination in the country. Fortunately, the French issue did not ferment, and did not affect our program.

A premature or immature release of the results of any study concerning adverse reactions of the hepatitis B vaccines may be exploited by anti-vaccination groups, liability lawyers, and most importantly, the media. Even if the results are disproved finally, the media usually does not report them, because of the loss of news worthiness [6]. The public's initial wrong image remains, and becomes an obstacle in the implementation of the vaccination program. Unfortunately, despite the rejection of a causal relationship between hepatitis B vaccine and multiple sclerosis [7], reports suggesting a risk of multiple sclerosis associated with recombinant hepatitis B vaccine still appeared [8]. WHO responded quickly by denying the interpretation of the results of the study [WHO Global Advisory Committee on Vaccine Safety, September 2004; http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/sept_04/en/]. The issue recurred again recently, initiated after an article published by a French group in early October 2008 [9]. Based on subgroup analysis of children having followed the French vaccine recommendations, it was concluded that although hepatitis B vaccination does not increase the risk of CNS inflammatory demyelination in children, the Engerix hepatitis B vaccine appears to increase the risk, especially for the confirmed cases of multiple sclerosis. Although the authors conceded that their results require confirmation in future studies [9], the conclusions of the article very likely have had exerted another negative impact on hepatitis B vaccination, at least in France. The Global Advisory Committee on Vaccine Safety of WHO again responded immediately by concluding that the study did not provide convincing evidence that hepatitis B vaccine, or use of any brand of the vaccine, is associated with an increased risk of acute CNS inflammatory demyelination or multiple sclerosis [WHO Global Advisory Committee on Vaccine Safety, October 8, 2008; http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/oct_2008/en/]. In the meantime, the French health products safety agency (Afssaps) also responded promptly in refuting the association [[http://www.](http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/oct_2008/en/)