Commonly Found Variations/Mutations in the HBsAg of Hepatitis B Virus in the Context of Effective Immunization Programs: Questionable Clinical and Public Health Significance

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We read with interest the paper of Bian et al. entitled “Change in hepatitis B virus large surface antigen variant prevalence 13 years after implementation of a universal vaccination program in China,” published in the *Journal of Virology* (1), and the associated commentary subsequently appearing in *Microbe* (2). We wish to point out several incorrect virological and public health-related assumptions made by the authors of both reports. Specifically, they claim to show that hepatitis B virus (HBV) “breakthrough mutants capable of infecting vaccinated people are emerging, threatening the hepatitis B immunization programs’ long-term success.” From their data set, the authors are specifically referring to a number of HBV variants isolated 13 years after the introduction of the hepatitis B vaccination program (see Table 3 in their article). Of all these variants, only one, the sG145R variant, has been recognized as a vaccine escape variant (VEM) (3, 4). The others have the status of naturally occurring polymorphic variants of the HBV. The authors provide no evidence that these other isolates have the potential to act as VEMs.

To date, in all studies of this kind, emergence of sG145R is a rare, uncommon event, more typically associated with use of hepatitis B immune globulin, in the liver transplantation setting (5), rather than hepatitis B vaccination (6). To put this into perspective, the study of Bian and colleagues identified only three sG145R viruses from children in the 2005 survey. In 1992, of the 157 children who were found to be HBsAg positive, 118 were viremic (HBV DNA positive), and no sG145R was identified. By 2005, 116 children were found to be HBsAg positive, 101 of them were viremic, and three sG145R isolates were identified (2.9%). In the context of the vaccinated cohort, the prevalence of VEM was thus 3/4,596 children, or 0.065%. This does not, in our view, represent an “explosion of VEMs due to the hepatitis B immunization program.”

As a consequence of natural selection, the introduction of an effective control program will place positive selective pressures on the HBV, and not surprising then, the mutation rate will increase. As we have previously suggested (7), an international consensus definition of VEMs needs to be established as more hepatitis B immunization programs around the world are being evaluated for their effectiveness in reducing rates of hepatitis B infection. Achieving such a consensus will require the development of validated *in vitro* and *in vivo* assays for evaluating the infectivity, neutralizability, and clinical significance of particular variant/mutants identified as or claimed to be VEMs. This should be possible with

the recent discovery of the receptor for HBV (8) and subsequent development of antibody neutralization assays using international reference antibody preparations against wild-type and known VEMs such as sG145R. In the meantime, efforts must continue to increase vaccine coverage rates among newborns, ensuring that the birth dose and the overall 3-dose vaccine schedule (e.g., 0, 1, and 6 months) continue.

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