Reduced Prevalence of HBsAg Variants following a Successful Immunization Program in China

Wolfgang Jilg,a Heléne Norder,b Mark Kane,c Pierre Van Damme,d Alex Vorsters,d on behalf of the Viral Hepatitis Prevention Board

Institute for Medical Microbiology and Hygiene, University of Regensburg, Regensburg, Germanya; Sahlgrenska Academy, University of Gothenburg, Gothenburg, Swedenb; 4816 W. Mercer Way, Mercer Island, Washington, USAc; Vaccine and Infectious Disease Institute, University of Antwerpen, Antwerp, Belgiumd

The content of the recent 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” (1), was discussed at our recent Viral Hepatitis Prevention Board meeting (Split, Croatia, November 2013). On behalf of this group of experts (a list of Viral Hepatitis Prevention Board advisors is available at www.vhpb.org), we would like to reply with some major comments on this article.

First, the paper of Bian et al. describes the frequency and nature of variants of the large envelope protein of hepatitis B virus (HBV) (LHBs or PreS1/PreS2/S protein) in Chinese children in 1992, when universal hepatitis B vaccination was introduced, and in 2005, 13 years after introduction. The findings shown in Tables 2 to 7 of the paper are interesting and merit publication; however, the presentation and the interpretation of the data are incomplete, sometimes incorrect, and misleading.

According to the data shown in Table 2, of 1,825 children tested in 1992, 157 (8.6%) were HBsAg positive. The sequence was available for 138 children: in 9 out of these (6.5%), variants were shown. In 2005, 4,596 children were examined; 116 (2.5%) tested HBsAg positive, with the sequence available in 101: 15 of these (14.8%) showed variants. Thus, from 1992 to 2005, the carrier rate in the children decreased from 8.6% to 2.5%, i.e., by 70.9%. The proportion of variants in the carriers increased during this period, from 6.5% to 14.8%. However, due to the dramatic decrease in the prevalence of HBsAg carriers, this relative increase in the frequency of variants in fact represents an overall decrease in the prevalence of variants in the population studied. The prevalence of HBsAg variants in the children fell from 0.49% (9/1,825) in 1992 to 0.33% (15/4,596) in 2005 (a decrease of 33%, i.e., about one-third). Thus, both HBsAg prevalence and the prevalence of the variants decreased, but the variant prevalence decreased at a somewhat lower rate.

Unfortunately, this outcome is neither mentioned nor discussed in the text of the publication. On the contrary, throughout the paper, the authors give the incorrect impression that the prevalence of variants in the population is increasing due to the universal hepatitis B vaccination program. In the abstract and Discussion, they write, “The prevalence of α-determinant mutants in the children increased from 6.5% in 1992 to 14.8% in 2005.” Readers could get the impression (as stated in the Microbe summary [2]) that universal vaccination programs are potentially dangerous, leading to a selection for mutant viruses able to escape vaccine-induced protection and to a dramatic increase of these viruses which would undermine the effect of the vaccination. In reality, quite the contrary is the case, as the overall prevalence of mutants decreases along with the (dramatically) decreasing HBsAg carrier rate in immunized populations.

These mutants may arise when HBV replicates in the presence of anti-HBs. This can happen when, in newborns of carrier mothers, neonatal postexposure prophylaxis is administered too late because infection has already taken place due to transplacental leakage or in the presence of a very high maternal viral load. Also, treatment with nucleoside analogues or immunologic selection pressures through the host or vaccine-induced immune responses (including hepatitis B immune globulin) can select mutants generated by the HBV polymerase lacking proofreading activity. After introduction of universal neonatal vaccination, such events may occur more often, and vaccine-induced mutants may be selected by this mechanism. As shown by Hsu et al., and in fact by this study as well, this leads to only a relative increase of such mutants and not to an absolute one (3, 4).

Second, in 2012, Lai and coworkers reported a “so-called” rise in the prevalence of HBV envelope mutants in adults immunized against HBV 18 to 21 years previously in Taiwan (5). An editorial by D. Shouval and S. Locarnini challenged the concept expressed in this article that some of these mutants are indeed confirmed vaccine escape mutants (VEM), emphasizing that not all HBsAg variants are VEMs (6). This caveat should also be applied to the analysis of the data in the paper by Bian et al. A differentiation between HBsAg variants and proven VEM should be provided. Most of the reported variants in this study do not classify as confirmed VEM. For example, sG145R is a confirmed VEM, but in variant sG145A, minimal conformational impact and anti-HBs binding have been described. In fact, to the best of our knowledge, only 3 of the 15 variants in the children’s cohort of 2005 are proven VEM. This would bring the prevalence of VEM in the vaccinated cohort to 3/4,596 children, i.e., 0.065%.

Third, the effect of the age of the studied children should be discussed in the paper. The children in the 2005 study were born between 1991 and 1994. The general vaccination program started in 1992 in China, but as we have understood, it had a slow start in many provinces and increased in coverage with the GAVI intervention starting in 2001-2002. These children were at that time 7 to 10 years old and may have been missed in the infant vaccination program. Also, the potential impact of the increased mean age of the children in the survey of 2005, compared to that in the survey of 1992, and the diversity between the regions should have been addressed. For the Guangxi province, the mean age of the children increased from 9.4 in 1992 to 14.3 in the 2005 survey. By 2005,
many Chinese mothers were being screened for HBsAg, and some infants of carrier mothers received hepatitis B immune globulin (HBIG) at birth (often late), and this could also have contributed to higher rates of mutants in the vaccine failures. Further information on these issues is required, as these are important elements in the understanding of the paper.

Fourth, the paper also lacks information on the vaccines that were used. China produced and used plasma-derived vaccines as well as recombinant vaccines. It has been reported that more α mutants emerged in children immunized with plasma-derived vaccines than in those immunized with recombinant vaccines (4). Information on which vaccines were used should be added for the 4 regions studied.

Fifth, if we look at Table 2, the increased proportion of mutants is driven by the increase of mutants in Guangxi province, i.e., from 8.3% in the 1992 survey to 36.8% in the 2005 survey. The change in prevalence of mutants in the three other provinces is very limited and not significant. The discussion does not address the major differences between the regions. Were coverage rates comparable? Was the replacement of plasma-derived vaccine by the recombinant vaccine done simultaneously? Was there a difference in HBIG administration to infants of carrier mothers? Could there be an effect of ethnicity?

Today, 181 nations successfully implement universal HBV vaccination of newborns, infants, and/or adolescents as recommended by the World Health Organization, and worldwide HBsAg carrier rates are falling dramatically in immunized cohorts of children (7, 8). There is no evidence that “vaccine escape mutants” have had a public health impact in any country. It would be unfortunate if incorrect data analysis and misleading conclusions (as in the Microbe summary) could potentially damage a highly successful global immunization program.

REFERENCES