



VIRAL HEPATITIS

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ISSUES SURROUNDING VIRUS MUTANTS SHOULD NOT DETER PUSH FOR UNIVERSAL HB IMMUNIZATION WORLDWIDE

The VHPB tackled the subject of hepatitis B virus mutants at its June, 1998 meeting in St Petersburg. Hepatitis B virus (HBV) is like all other viruses in that mutations in the virus occur. With HBV, mutations have been found in most areas of the virus, although the majority of these have no significance for immunization or therapy.

The subject of virus mutants is a controversial one that has raised concerns among scientists and garnered considerable media attention. The concerns are that virus mutants - in this case HBV mutants - could possibly escape detection by available assays, that mutants could negatively impact vaccination or immunoglobulin therapy, and that virus mutants could have a selective advantage and eventually become the dominant virus strain. In addition, it is currently under discussion as to whether virus mutants have clinical significance and can affect the outcome of chronic hepatitis, although no definitive data confirm this.

Undoubtedly, it is necessary to continue the study of HBV mutants, to be vigilant in ensuring that assays can detect relevant variants and that mutants do not negatively impact immunization programmes or post-exposure therapy. However, we should not forget that current vaccines are 90%-95% effective and that immunization remains the most effective means of protecting against HBV infection.

What follows is a brief explanation of HBV mutants and variants, a discussion of the current situation, and recommendations from the VHPB on what is needed for a more complete understanding of virus mutants and their implications for HBV control programmes. Most important, the VHPB cannot stress strongly enough that available vaccines and the current recommended immunization strategies are effective in controlling HBV in the population. Where they are in place, these programmes should be continued. Furthermore, we should not abandon the push for universal immunization the world over as this is the most effective way to control and possibly eliminate the spread of HBV infection.

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VHPB CONSENSUS STATEMENT ON HBV MUTANTS AND VARIANTS

As with all viruses, mutations occur in hepatitis B virus. During evolution, stable forms of the virus emerged which were initially characterised serologically and called subtypes. Now, different forms of virus mutants or variants are classified by the analysis of their genomic sequences and called genotypes. Up to now, there are no strong data that genotypes and subtypes influence the course of HBV infection and its clinical sequelae. Genotypes and subtypes are, however, useful in understanding epidemiological phenomena such as the geographic spread of the virus or its transmission in the community.

Viruses undergoing additional changes in their amino acid sequences due to genomic mutations are named variants and mutants. Variants are then defined as viruses occurring naturally, while mutants are viruses selected by external influence such as immune pressure. This distinction is a valuable working hypothesis which is not yet fully supported by laboratory evidence.

The most clinically relevant mutations are located in the precore region, the X-protein and the S-region of the HBV genome. The most frequent precore mutant leads to a loss of HBeAg despite ongoing viral replication, and is frequently associated with progression to chronic liver disease. Certain other mutants and, in particular, combinations of them may be implicated in fulminant hepatitis. Mutations in the S-region can lead to conformational changes of the major epitopes (e.g. "a" determinant) which are the main target for neutralising antibodies. Thus, binding of the antibodies can be hampered with several possible consequences: first, mutant viruses of this type may escape detection by certain commercial HBsAg kits. Second, clones of these viruses may have a selective advantage in carriers treated with passive-active immunization (HBIG and/or HB vaccine), and become the dominant clone. This process of selection and "escape" has been described during passive therapy with HBIG in HBsAg positive liver transplant patients and in newborns of HBsAg and HBeAg positive mothers who have become HBV carriers despite treatment with HBIG and HB vaccine.

The most common mutation described in these children (at aa position 145) has also been found in HBsAg positive carrier mothers and in other adults who have never received active or passive prophylaxis, although it is often not the dominant clone. This mutant is stable over time, but

transmission to other humans has not been described. In chimpanzee experiments the virus is transmissible, but it has not been possible to infect fully immunized chimpanzees. Thus, this mutation may be a partial explanation for the 10% to 15% HBIg and/or HB vaccine failure in newborns of HBsAg positive carrier mothers; there is no evidence at present that this mutant has spread in immunized populations or that it poses a threat to national immunization programmes.

The following consensus was reached:

Present vaccines and vaccination strategies are 90% to 95% effective in reduction of the HBV carrier prevalence in immunized cohorts of children, and are highly effective in preventing transmission in other at-risk groups. These prevention strategies should be vigorously continued in the over 100 countries which have already introduced universal immunization, and should be implemented in all countries where they are not yet in place.

A much more complete understanding of the potential impact of “escape” mutants on the epidemiology and prevention of hepatitis B is needed. To reach this goal, the following activities should be encouraged and implemented:

- The tools to detect HBV mutants and variants should be optimized:
 - There is a need for the evaluation of existing HBsAg diagnostic assays to determine if they detect relevant HBsAg variants and mutants. This will require the development of a serum panel containing such mutated viruses/antigens, and validation by external quality control.
 - A true neutralization assay is necessary to evaluate the potential of mutants to escape passive or active immunization or natural immunity.
 - Methods to detect and classify mutants and variants should be standardized. A definition of a wild type virus is needed.
- There is a need for a surveillance network to detect HB mutants worldwide.

- Epidemiological studies are needed to determine:
 - the attributable risk of HBV infection from these mutants following post-exposure immunization;
 - the risk of person-to-person transmission of these mutants in susceptible and immunized persons.
- Research should be encouraged to understand better the mechanisms/pressures for naturally occurring variants and for mutants induced by passive or active immunization. For this reason, there is a need either to characterize further or to standardize hepatitis B immunoglobulin preparations, or to replace these with pools of monoclonal antibodies with defined properties known to neutralize “S” mutants, and to study further the vaccines which might prevent the occurrence of relevant immune escape mutants.

This *Viral Hepatitis* fact sheet is prepared from material presented at the VHPB meeting held 2-4 June, 1998 in St Petersburg, Russia. Participants:

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