

The Need for new Hepatitis B Vaccines

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Hepatitis B virus (HBV) infection is a major public health problem on a global scale, with over 350 million chronically infected patients, the large majority of whom live in Asia¹. HBV is however potentially eradicable due to the long standing availability of effective vaccines. In areas of high endemicity like Asia, the major route of transmission is mother to infant or horizontal among children². WHO has therefore advocated the introduction of HBV vaccine into the Global Expanded Program of Immunization since 1995. The global effort against HBV has gained further momentum after the formation of the Global Alliance for Vaccination and Immunization (GAVI). Pakistan has been successful in gaining funding from GAVI HBV vaccine and this is currently being incorporated in the EPI in various parts of the country.

The surface of the HBV consists of pre-S¹, pre-S² and S proteins, the S being the predominant constituent of HBV vaccines and bearing the a determinants common to all HBV isolates³. Anti-antibodies protect against the majority of infections and develop in 94-95% of subjects vaccinated with vaccines containing the S protein. However HBV variants have emerged that contain amino acid changes between residues 39-147 of the S protein which is critical for binding to anti-antibodies⁴. Theoretically inclusion of the pre-S protein into the vaccine should be able to minimize the impact of such HBV surface variants. It is also important to minimize the vaccine failure rate in high-risk groups such as health care workers, patients on hemodialysis etc.

There are other biologically important arguments in favor of including the pre-S antigens in the HBV vaccine. The pre-S₁ domain carries the essential attachment elements of HBV, from amino acids 21-47g. This sequence induces neutralizing antibodies that could theoretically block viral attachment. Similarly the functions of the pre-S₂ that are recognized to be important include a proteolysis site which is important for viral assembly, a site for binding and activating protein kinase C that activates cellular proliferation, a site for binding human albumin and a permeabilization sequence that mediates transfer of viral particles through the cytosol⁶. All these sites are potential targets for neutralizing antibodies. Moreover both pre-S₁ and S₂ have been shown to be good T-cell antigens and could augment the B-cell mounted against HBV⁷.

The need for multiple doses spread over a 6-12 month period represents a further drawback associated with the use of the existing vaccines. A vaccine that is capable of inducing the same level of immunity as the current vaccines but uses fewer doses would be expected to enhance compliance and efficacy by omitting the dependence on the third dose.

Newer HBV vaccines containing the pre S₁/S₂ antigens along with the S antigen have been developed and tested in clinical trials in many cases⁸. In head to head comparisons between the standard vaccine containing S antigen alone and the triple antigen vaccines, the latter has been shown to consistently produce higher levels of protection and higher antibody levels. Moreover with the use of 2 doses of the triple vaccine, 91% individuals achieved protection while with the standard 3-dose regimen the protection rate increased to 98%⁹. In non-responders or poor responders (anti-HBs < 100 IU/L) to the single

antigen vaccine, a single dose of the triple antigen vaccine produced a response in 79% of individuals compared to 69% by a further dose of the single antigen vaccine.

In this issue of the journal, Qureshi et al report their results of a triple antigen vaccine in a Pakistani population and show an overall response of 96.2% and a 100% response in children up to the age of 14 years. The study suffers from a lack of a comparative group of the single antigen vaccine but uses previously published figures of response to the single antigen vaccine. It therefore only determines that the triple antigen vaccine that they tested was probably equal in efficacy to the standard vaccine. However it could be cheaper as it is produced in CHO cells, which would be an advantage in a country like Pakistan.

What then does the future hold for chronic HBV infection and its vaccines. Clearly HBV could be eradicated from the world if an effective campaign like the polio effort is mounted. Processes are underway to make that happen at a global level. The introduction of more effective vaccines would obviously aid this effort. The triple antigen HBV vaccine seems to be an advance in that it will take care of the HBV surface variant and will help some people who have not responded to the standard single antigen vaccine. However a greater impact is likely to occur if the newer vaccines can be shown to be just as effective with a two-dose regime, thus cutting down cost and improving compliance. Data on two dose regimens is still limited to make a definitive conclusion. In the meantime we will have to stick to the three-dose regimen of 0,1 and 6 months or better still, undertake our own studies on two dose regimens using the newer generation of HVB vaccines.

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