Selected Summaries

A boost to hepatitis B vaccine: No need for boosters

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Long-term immunogenicity of hepatitis B vaccination and policy for booster: An Italian multicentre study. *Lancet* 2005;**366:** 1379–84.

SUMMARY

The duration of protection against hepatitis B virus (HBV) infection provided by vaccines remains somewhat uncertain, raising doubts about the need for boosters later in life. In this multicentre Italian study, the authors assessed the duration of immunity induced by hepatitis B vaccine when administered to infants and adolescents.

The study, sponsored by the Italian Ministry of Health, included 1212 children and 446 air force recruits, who had been vaccinated against hepatitis B more than 10 years ago, as infants and adolescents, respectively. For each study subject, concentrations of antibodies against hepatitis B surface antigen (anti-HBs; known to protect against hepatitis B infection) were measured, and the presence of antibodies to hepatitis B core antigen (anti-HBc; induced by HBV infection but not by vaccination, thus serving as a marker of breakthrough HBV infection) was looked for at enrolment. In line with standard criteria, those with anti-HBs concentration of ³10 IU/L were considered as protected against HBV infection. Individuals with anti-HBs levels <10 IU/L were given a booster dose of the vaccine and re-tested 2 weeks later for anamnestic response (anti-HBs ³10 IU/L). Those who failed to show such response received two additional doses of the vaccine and underwent re-testing one month after the last dose. Individuals with anti-HBc were tested for serum markers of chronic HBV infection (hepatitis B surface antigen [HBsAg] and HBV DNA).

A large proportion of the children (779 of 1212, 69%; 95% CI: 61.6–67.0) and air force recruits (398 of 446, 89%; 95% CI: 86.4–92.1) had anti-HBs in protective amounts. The concentration of antibody was higher in recruits than in children (geometric mean titre 234.8 IU/L *v*. 32.1 IU/L; p=0.0001). Of the 433 remaining children and 48 recruits, who lacked protective levels of anti-HBs, 342 and 48, respectively, received a booster; of those receiving the booster, most (332 of 342 children [97%] and 46 of 48 recruits [96%]) showed an anamnestic response. Of the 10 children and 2 recruits who did not show anamnestic response, 8 and 2, respectively, received two additional vaccine doses, with development of protective anti-HBs levels in all of them. One child and four recruits had evidence of prior HBV infection, but none of them had chronic HBV infection (positive anti-HBc, but negative HBsAg and HBV DNA).

In conclusion, most individuals who had received primary immunization against HBV during infancy and adolescence showed persistence of strong immunological memory more than 10 years later. Thus, the authors concluded that booster doses of the vaccine appear unnecessary for long term protection against HBV.

COMMENT

HBV infection is responsible for significant morbidity and mortality worldwide.[1] The clinical consequences of HBV infection are varied, ranging from asymptomatic infection, through acute viral hepatitis to fulminant hepatic failure. A proportion of those infected develop chronic infection, which is associated with an increased risk of development of chronic hepatitis, cirrhosis of the liver and hepatocellular carcinoma.[1] It is estimated that nearly 350 million people worldwide have chronic HBV infection, and that one million people die annually of HBV infection, mostly from the sequelae of chronic infection.[1] Thus, it is important to prevent HBV infection, especially chronic HBV infection. Since the risk of chronicity depends primarily on the age at which the infection is acquired, being nearly 90% among infants, around 60% in children aged 1–6 years and only about 5% in those infected during adolescence or adulthood, control measures need to be directed at prevention of infection during early life.

Fortunately, safe and highly effective vaccines are available for prevention against HBV infection. These subunit vaccines contain the viral surface protein (HBsAg), are usually administered as three intramuscular doses, and induce protective antibodies (anti-HBs) in amounts sufficient to protect against HBV (³10 IU/L) in >95% of healthy individuals. Further, these vaccines are easy and cheap to produce using recombinant technology, providing hope of significant control, if not eradication, of HBV infection and disease.

Several developing countries took a lead by introducing these vaccines in their childhood immunization programmes. These programmes have led to reduced rates of chronic HBV infection.[2] For example, the prevalence rates of HBsAg in Gambian children decreased from 10.3% to 0.6%;[3] similar results have been reported from other regions including Italy, Thailand, American Samoa, China, Taiwan, etc.[1,3,4] This has been accompanied by significant reduction in the rates of serious illnesses related to acute and chronic HBV infection, such as fulminant hepatic failure[5] and hepatocellular carcinoma.[6]

However, the level of antibodies induced in the vaccinees declined with time, becoming undetectable in a proportion of them after 5–10 years.[7] This raised a concern that the protection provided by the vaccine may not be lifelong, and that booster doses may be needed. However, detection of persistent anti-HBs antibodies, though easy, is not a particularly sensitive method of

measuring protection. For instance, *in vitro* specific lymphoproliferation studies showed persistence of immunological memory in those in whom anti-HBs antibodies have waned;[8] further, HBV-specific B cells could be detected in the blood of such individuals using elispot assays.[8] However, such *in vitro* evidence may not be adequate, and follow up studies of immunized individuals who have lost antibodies are necessary to demonstrate immunological memory *in vivo* and continuing protection against HBV infection and disease.

In the study under consideration, Zanetti *et al*. provide such evidence. They studied individuals who had been immunized against HBV more than 10 years ago, either as children or as adolescents, and assessed whether they were protected against HBV, either through detectable anti-HBs antibodies or through immunological memory that enabled them to quickly mount an immune response on exposure. They found that nearly one-third of those immunized as infants and a smaller proportion of those immunized in adolescence lacked protective antibody levels. However, these subjects mounted an anamnestic immune response on challenge with one dose of vaccine, with a quick boosting up of antibody response. Further, none of the vaccinees had chronic HBV infection, as would have been expected if protection had waned.

Are these findings new? Not really. Similar data have been reported from several other countries over the past few years. In a Taiwanese study, though only 37% of vaccinees had protective antibody levels 12 years after primary vaccination with no booster doses, only 2 of 258 had serological evidence of infection with HBV, despite residence in a high-endemicity area with frequent opportunities for exposure.[9] Similarly, in an Alaskan study, though anti-HBs levels declined with the passage of time over a 15-year period post-vaccination, only a few vaccinees had breakthrough HBV infection, always asymptomatic and mostly in vaccine non-responders.[10] In another study from Hong Kong,[11] among 318 Chinese subjects followed up for up to 18 years after 2 or 3 doses of vaccines, only 3 had breakthrough HBV infection; none of these infections was symptomatic or became chronic. These results clearly indicate that hepatitis B immunization induces protection for at least 15–18 years.

However, most of these studies have been from regions where HBV infection is highly endemic. In these regions, frequent exposure to HBV may have been responsible for an inapparent boosting of antibody levels or immunological memory. Thus, it is possible that persistence of immunological memory in non-endemic regions, where exposure to HBV may be infrequent, was not as good. There has only been one previous study in a non-endemic region.[12] In that study from the UK, though half the children who had been immunized about 12 years ago lacked anti-HBs antibodies, most of them showed a good anamnestic response with a booster dose.[12] In the study under consideration, Zanetti *et al*. provide a valuable confirmation of these results, setting at rest concerns about the long term efficacy of hepatitis B vaccine in non-endemic regions.

What do the results of this study mean for us in India? These results do not add much to the available evidence for HBV-endemic countries, which need this vaccine the most, since data on long term protection by the vaccine in these regions have been loud and clear. In fact, the duration of follow up in the current study was much shorter than the 15 to 18-year follow up previously available from HBV-endemic countries.[9–11] Thus, the current data are more important for countries in which HBV infection is infrequent. Further, these data should provide reassurance to HBV-endemic countries that the vaccine will continue to have long term efficacy even after they have successfully controlled this infection and the prevalence of HBV infection has decreased.

At the last count, of the 192 member states of the WHO, 138 had introduced infant hepatitis B immunization in the entire country and 9 had done so in parts of the country.[13] India is one of the few laggards in this area, despite clear evidence of the tremendous benefits that will accrue from the introduction of this vaccine.[14] The current study serves to draw our attention again to the subject and adds some more weight to the already overwhelming evidence in favour of this useful public health measure. Will we act even now?

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