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REVIEW

Emerging hepatitis B virus infection in vaccinated populations: a rising concern?

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Hepatitis B infection, especially by perinatal transmission, is endemic in Asian countries. After the first successful universal hepatitis B virus (HBV) vaccination programme for newborns in Taiwan, it became feasible to prevent HBV transmission and the resultant hepatocellular carcinoma in endemic countries. However, a small subset of vaccinated people have a suboptimal immunological response to vaccination, and the immunity of some young adults who were vaccinated as infants seems to have waned over time. Despite this loss, recent studies suggest that anamnestic anti-HBs antibody responses rapidly resume and eliminate acute HBV infection acquired through sexual contact or blood transfusion, even though the anti-HBs antibody titre has decreased below a protective level. These observations indicate prolonged protection by the HBV vaccine. Therefore, for people with a low infection risk, a universal booster vaccination is not currently recommended, but it should be considered for high-risk groups. However, we still advocate close monitoring of acute hepatitis B among patients who lack a protective level of anti-HBs antibody and suggest a wait-and-see policy to determine the necessity for booster vaccines.
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INTRODUCTION

Chronic viral hepatitis is known to have many detrimental health outcomes. Hepatitis B virus (HBV) infection is the major cause of viral hepatitis and affects more than 350 million individuals worldwide. The consequences of chronic hepatitis B infection include liver cirrhosis, liver failure and hepatocellular carcinoma (HCC).[1] After researchers elucidated the infection route and the natural clinical course of hepatitis B, they found that perinatal transmission of HBV from carrier mothers to infants plays an important role in spreading the virus and leads to chronic infection beginning in childhood. Perinatal transmission is the major route of hepatitis B transmission in Asia, where the infection is endemic.

THE POLICY ON AND EFFICACY OF HBV VACCINATION

To prevent perinatal HBV transmission, HBV vaccination has been advocated since the 1980s, based upon reliable results from clinical trials. Beasley *et al.*[2] and Lo *et al.*[3] demonstrated the effectiveness of both passive and active immunisation to interrupt perinatal HBV transmission. The introduction of safe, effective and highly immunogenic HBV vaccines led to the recommendation for universal immunisation of all newborns in Taiwan from 1984. The first worldwide vaccination programme effectively prevented perinatal HBV transmission and the chronic carrier state, and approximately 85% of infant vaccinees had adequate levels of protective antibody at 18 months of age.[4] This programme is extremely successful in the control of HBV infection in Taiwan in several ways. Firstly, the HBsAg carrier rate in children gradually decreased from 11% in 1984 to 1% in 2004.[5–8] Secondly, after the implementation of universal vaccination of newborns, the infant mortality rate from fulminant hepatitis decreased from 5.36 per 100 000 to 1.71 per 100 000.[9] Fulminant hepatitis B almost disappeared in children older than 1 year of age.[10] Thirdly, the average annual incidence of HCC in children 6–14 years of age significantly declined from 0.70 per 100 000 children between 1981 and 1986 to 0.57 per 100 000 children between 1986 and 1990, and to 0.36 per 100 000 children between 1990 and 1994. The incidence of HCC in children 6–9 years of age also significantly declined from 0.52 per 100 000 children for those born between 1974 and 1984 to 0.13 per 100 000 children for those born between 1984 and 1986, after the universal vaccination programme was implemented.[11] This decline in HCC incidence extended to teenagers and young adults 2 decades post vaccination.[12,13] This was the first study demonstrating that a vaccine can prevent a human cancer and serve as a potential way to eliminate hepatitis B.[14]

POOR RESPONDERS AND FAILURE OF HBV VACCINATION

Although the current vaccines are highly effective, there are still some populations with suboptimal immunogenic responses, such as preterm infants, the elderly, smokers, obese individuals, and those with chronic liver or renal diseases, diabetes mellitus (DM) or human immunodeficiency virus (HIV) infection.[14] For newborns, HBV vaccination should be given within 24 h of delivery with or without hepatitis B immune globulin (HBIG); otherwise, the protective

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efficacy will be lower.[15] It is known that the hepatitis B vaccine has a lower immunogenicity in preterm infants than in infants born at term, especially those with gestational ages < 34 weeks[16] or birth weights < 1800 g.[17] For preterm infants of HBsAg-negative mothers, deferring the first vaccination dose by 1 month is recommended to improve the vaccine's immunogenicity and efficacy.[18]

Some newborns fail to complete their vaccination courses, and approximately 10% of children born to HBeAg-positive mothers with high viral loads become persistently infected with HBV owing to HBIG or vaccination failure.[19] These newborn HBV carriers, along with the existing adult chronic HBV carriers, are still at risk of developing HBV-related complications, such as cirrhosis and HCC, in the following 30 years.

DECLINING ANTI-HBV TITRES IN THE VACCINATED COHORTS DURING LONG-TERM FOLLOW-UP: RISK OF HBV INFECTION?

After the first dose of the hepatitis B vaccine, adequate protective anti-HBs antibody levels (> 10 IU/L) develop within 1 month in 48% of neonates. Anti-HBs antibody is detected in 91% of neonates 2 months after the second dose, and in 96% at 6 months.[20] However, the anti-HBs antibody titre declines rapidly in the first year and then gradually after 1 year.[21] The persistence of anti-HBs antibody depends on the initial postvaccination concentration.[22] The immunity gained from perinatal HBV vaccination further diminishes in adolescents, approximately 10–15 years after immunisation.[23,24] Approximately 62.4% of 15 year olds no longer have protective levels of anti-HBs antibody.[23]

At the same time, those adolescents are more likely to be exposed to HBV infection than children because of sexual activity, substance abuse, or medical interventions. Therefore, it is important to determine whether HBV infection can emerge in this population and cause clinical problems and whether a routine vaccine booster is required.

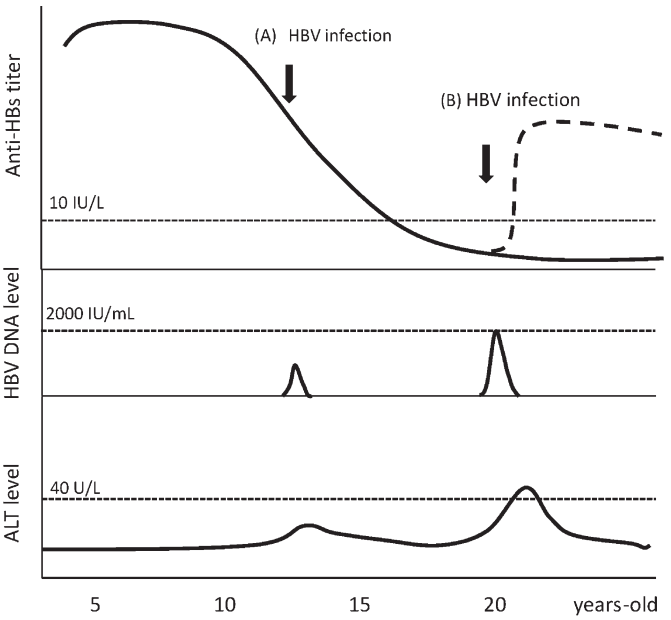

Figure 1 This diagram shows the dynamic change in the serum anti-HBs antibody titre, HBV DNA and ALT levels during acute HBV infection in an HBV vaccinee. (**A**) If the infection occurs in a subject with a protective level of anti-HBs antibody, then viraemia would be detected only transiently, and anti-HBc seroconversion would result. (**B**) If the infection occurs in a subject with an anti-HBs antibody titre below the protective level, then higher HBV viraemia would be detected and would sometimes be followed by an elevation of aminotransferase levels. The anti-HBs antibody titre immediately rises above the protective level; this increase is the so-called anamnestic effect of anti-HBs antibody. The dotted line indicates the protective level of anti-HBs antibody in the upper panel and the normal level of ALT in the lower panel.

HBV INFECTIONS IN PREVIOUSLY VACCINATED SUBJECTS: AN UNUSUAL CLINICAL COURSE

To better understand the HBV infections that occur in HBV-vaccinated subjects, it is important to follow prospectively individuals who might be exposed to HBV.[24] A large-scale longitudinal survey of 18 779 subjects showed that vaccination in infancy provides adequate long-term protection for up to 20 years. Despite occasional exposure to HBV (0.1%–4% anti-HBc seropositive rate), the risk of persistent HBV infection did not increase with age, before adulthood.[8]

Recently, after a mass screening of 3.7 million blood donations by nucleic acid testing, Stramer *et al.*[25] identified nine occult HBV donors harbouring low levels of HBV viraemia. Six had previously received the HBV vaccine and exhibited low or undetectable anti-HBs antibody titres (0–96 IU/L). Careful tracing indicated that these individuals probably acquired acute HBV infection from their sexual partners, who had high HBV loads ($> 10^6$ IU/ml). At follow-up visits, these newly infected individuals only presented with transient HBV viraemia (11–86 IU/ml) for a few months and did not show biochemical hepatitis. A rapid anamnestic escalation of anti-HBs antibody was also observed after HBV infection, which was attributed to the priming by the HBV vaccine about 7–27 years earlier.[25] In contrast, unvaccinated blood donors developed clinically significant acute hepatitis B after exposure to HBV via sexual transmission. From this study by Stramer *et al.*, it is clear that vaccinated subjects with anti-HBs antibody titres below the protective level are still susceptible to HBV infection, especially if they are exposed to a high viral load. Interestingly, only transient viraemia and subclinical hepatitis were observed, and none of the vaccinated subjects became HBsAg carriers. Similarly, Liu *et al.*[26] evaluated 327 HBV-naïve blood transfusion recipients and found that four vaccinated children developed transient HBV viraemia (3.4×10^4 – 3.3×10^5 HBV DNA copies/ml) within 1 month of receiving blood transfusions contaminated with HBV. These children exhibited only subclinical HBV infection, with minimal alanine aminotransferase (ALT) level elevation, after transfusion. Although their anti-HBs antibody titres were low or undetectable (0–150.4 IU/L) at the time of the blood transfusion, none became HBsAg carriers, and all cleared the HBV infection after 1 month. These two studies suggest that anamnestic anti-HBs antibody responses rapidly resume and eliminate acute HBV after infection resulting from sexual contact or blood transfusion, up to 27 years post vaccination. A dynamic change in the serum anti-HBs antibody titre, HBV DNA and ALT levels during acute HBV infection in an HBV vaccinee is illustrated in Figure 1. Recently, anti-HBc antibody levels have been shown to reflect an individual's immune activity to HBV. Whether there is also a dynamic change in anti-HBc antibody levels after acute HBV infection in vaccinated individuals remains to be elucidated.[27]

THE ANAMNESTIC EFFECT OF ANTI-HBS ANTIBODY

The anamnestic effect of anti-HBs antibody was observed in individuals who received an additional vaccine dose, who showed a rapid and immediate rise in antibody titre.[28] Several studies of health volunteers confirmed the immunological memory demonstrated by anti-HBs antibody escalation, with a titre > 10 IU/L in 73%–100% of vaccinees after a booster dose administered 5–12 years after the first dose.[29] This immunologic memory following booster vaccination was verified by *in vitro* assays, demonstrating that memory B lymphocytes were present

in vaccinated adults even though these adults exhibited low anti-HBs antibody titres. Such B lymphocytes would maintain the capacity to differentiate and produce anti-HBs IgG upon subsequent stimulation by HBsAg.[30] If this immunological memory still provides immunity despite an inadequate level of anti-HBs antibody, then a breakthrough persistent infection is unlikely to occur. From clinical observations, although many vaccinees fail to maintain 10 IU/L of anti-HBs antibody, there have been very few significant breakthrough infections despite HBV exposure.[29]

THE NECESSITY OF BOOSTER VACCINATION IN TARGET GROUPS

According to the aforementioned evidence, vaccinated individuals rapidly regain protection against HBV transmission through sexual exposure or blood transfusion even if their anti-HBs antibody titre falls below the detection limit. Therefore, for people with a low infection risk, a universal booster vaccination is not currently recommended.

However, there are special groups that require more attention. Zanetti *et al.*[31] studied 1212 children and 446 Air Force recruits in Italy with follow-up for 10 years, when they found a well-preserved immunological memory in 64% of children vaccinated at infancy and in 89% of young adults vaccinated at 12 years of age. HBV infection was rare over the 10 years of the study, and none of the individuals studied became HBsAg carriers, even though their anti-HBs antibody titres declined with time. Thus, the investigators concluded that vaccination protection persists for longer than 10 years after primary vaccination, and booster doses of hepatitis B vaccine may not be needed.[31] In a study of 60 children receiving a living-donor liver transplant, recipients with anti-HBs antibody levels $>$ 1000 IU/L after a booster vaccination were all protected from *de novo* hepatitis B even after transplantation with a liver from an anti-HBc-positive donor.[32] The booster for vaccine responders before their liver transplantation yielded good protection. A recent study enrolled 127 college students without protective anti-HBs antibody levels who were administered booster vaccinations. The percentages of individuals exhibiting seroprotective levels of anti-HBs antibody for 7–10 days, 1, 6 and 7 months post vaccination were 20.5%, 75.6%, 94.5%, and 99.2%, respectively. The early booster response predicts higher levels of protection at 1 and 6 months post vaccination. At least one quarter of these HBV vaccinees had lost their immune memory to the HBV vaccine by the time they enter college. A prompt immunological memory to revaccination was present in only 20% of the vaccinees studied. Therefore, at least 2 doses of booster vaccines are recommended for at-risk vaccinated adults without persistent protection.[33] However, postvaccination testing of anti-HBs antibody levels is not routinely needed because of the high response rate ($>$ 96%) to vaccination.[28]

In contrast, in several studies of immunocompromised adults with HIV infection, only 40%–53% of vaccinees developed anti-HBs antibody.[34] The hyporesponders to HBV vaccination were patients with chronic renal failure, alcoholism, type 1 DM, or cancer. The vaccine also has been shown to have low immunogenicity in older adults, smokers, males and obese individuals. The poor response to HBV vaccination may be rescued by shifting to intradermal injection, by increasing vaccine dosage and frequency or by improving adjuvants.[14] For the hyporesponder populations, a postvaccination test of anti-HBs antibody levels may be needed.[29] For populations at high risk of infection, a booster vaccination may be considered after adulthood.

In conclusion, HBV vaccination is an effective way to terminate perinatal and early horizontal transmission of hepatitis B. The antibody levels raised in response to vaccination decline with time, but the protection afforded by vaccination seems to persist for 2 decades or more because of the anamnestic effect of anti-HBs antibody. Therefore, although HBV infections might occur in vaccinated individuals as they reach adulthood, these infections do not seem to be a substantial threat to the population as a whole. However, we advocate close monitoring for acute hepatitis B among these individuals in the future and a wait-and-see policy to determine the necessity for booster vaccines.

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