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REVIEW

Hepatitis B vaccine boosters: Is there a clinical need in high endemicity populations?

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Abstract
The Steering Committee for the Prevention and Control of Infectious Diseases in Asia recently conducted a survey of primary-care physicians in Asia, which revealed that many physicians administer boosters in their clinical practice and that there is considerable variation and uncertainty among physicians regarding this practice. This paper serves as a response to physicians' uncertainties by reviewing the literature regarding the administration of hepatitis B vaccine boosters in high endemicity areas and presenting the Steering Committee's guidelines for booster administration. While there are few data to support a need for routine hepatitis B vaccine boosters as a public health measure, they help to provide reassurance of immunity against breakthrough infection in certain risk groups. In clinical practice, primary-care physicians must exercise their judgment regarding the need for booster vaccination on an individual basis. This paper examines the available literature on the administration and value of hepatitis B vaccine boosters, explores the differences between the public health approach and clinical practice, and provides guidelines for those who use boosters in high endemicity Asian populations. Relevant articles were identified through searches of MEDLINE (1975–2003) and the Cochrane Library, using 'hepatitis B' and 'booster' as primary search terms. Guidelines for those who decide to administer hepatitis B vaccine boosters include: boosting approximately 10–15 years after primary vaccination; boosting rather than not when monitoring of antibody levels is not feasible; boosting immunocompromised patients when the antibody to hepatitis B surface antigen titer falls below 10 mIU/mL; and boosting healthcare workers based on the endemicity of the particular country.

Key words: boosters, hepatitis B, immunization.

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INTRODUCTION

The Steering Committee for the Prevention and Control of Infectious Diseases in Asia meets biannually to discuss the latest research and clinical trends in infectious disease prevention and control. This review was written in response to a survey conducted by the Steering Committee of primary-care physicians in Asia, which showed considerable variation and uncertainty of opinion regarding the administration of hepatitis B vaccine boosters, despite many physicians administering boosters in their clinical practice.

The protective efficacy of a primary course of hepatitis B vaccine is well established. Long-term protection against clinically significant breakthrough hepatitis B virus (HBV) infection and chronic carriage depends on immunological memory, which appears to last at least 10–15 years in immunocompetent individuals who respond adequately to the primary vaccination.[1–3] Persisting antibodies to hepatitis B surface antigen (anti-HBs)[4] and/or *in vitro* B-cell stimulation response,[5] or an anamnestic response to a vaccine challenge,[2] provide evidence of adequate immunological memory in these individuals.

While there are few data to support a need for routine hepatitis B vaccine boosters in immunocompetent individuals who have responded to a primary course,[6,7] boosters are recommended and widely used to provide reassurance of protective immunity against breakthrough infection in certain risk groups. For example, advisory bodies in some countries state that healthcare workers should have their anti-HBs response measured following primary vaccination, and that their antibody levels should be monitored at regular intervals.[8–10] Booster immunization should be administered to any individual who is found to be inadequately protected (generally defined as an anti-HBs level <10 mIU/mL,[4]). Administration of these boosters will help to protect healthcare workers from the risk of infection when repeatedly exposed to HBV through contact with patients.

Other high-risk groups include persons with compromised immunity, such as hemodialysis and renal transplant patients,[11,12] leukemia patients,[13] and individuals with chronic hepatitis C.[14] Some populations are at increased risk as a result of high rates of at-risk behavior, such as adolescents,[15] homosexual men[4] and prison inmates.[16] Close contacts of HBV carriers are also at increased risk.[4] In immunocompromised individuals, monitoring of anti-HBs blood levels and hepatitis B vaccine boosters are currently recommended.[6] In other high-risk groups, primary vaccination is the main priority.[4,6]

In the general population, there is no apparent need for hepatitis B vaccine boosters in national immunization programs as a public health measure, particularly in the low endemicity areas of Europe, where the likelihood of exposure to HBV is low.[7,17] However, in high endemicity countries the risk of exposure is not only high, but also recurrent,[18] which is why we revisit the issue of the need for booster vaccination. It is here that physicians need to exercise their clinical judgment on an individual basis.

CURRENT PUBLIC HEALTH RECOMMENDATIONS

In 1991, the World Health Organization (WHO) recommended that the hepatitis B vaccine be integrated into all national immunization programs. As a result, many nations have implemented universal infant immunization with or without adolescent immunization.[19]

In Asia, the WHO recommendations have, to a large extent, been implemented, and effective vaccination programs have resulted in a shift in endemicity in some countries. While China continues to experience high HBV endemicity, countries with intermediate endemicity include India, Korea, the Philippines, Taiwan and Thailand.[18] Japan, Pakistan, Bangladesh, Singapore, Sri Lanka and Malaysia all have low endemicity.[18] In high endemicity areas primary vaccination remains the top priority public health measure against hepatitis B.

Most health advisory bodies are based in low endemicity regions such as Europe and North America. They currently stress the need for primary vaccination against hepatitis B, suggesting that routine boosting is not required, except in immunocompromised individuals, such as those with HIV infection or chronic renal disease (Table 1).[4,6,20,21] Booster doses may be needed in these individuals to avoid infection, disease, or the carrier status that may result from infection.[20] According to the Canadian National Advisory Committee on Immunization (NACI) guidelines, the optimal timing of booster doses in immunocompromised patients is unknown, so they recommend that the timing of boosters should be based on the severity of the compromised state and the results of regular monitoring.[20]

The European Consensus Group conclude that there is little available evidence to support the use of hepatitis B vaccine boosters in other high-risk groups, such as intravenous drug users, persons who engage in high-risk sexual behavior, residents of mental institutions, close contacts of hepatitis B surface antigen (HBsAg) carriers and immigrants to Europe.[6]

For low-risk individuals, the NACI and the US Immunization Practices Advisory Committee (ACIP) state that further investigation into the duration of the protective immunity in adolescents who were vaccinated against hepatitis B during infancy or childhood is necessary. The results of further research will determine future recommendations concerning booster doses for immunocompetent individuals.[4,20]

NON-RESPONDERS

Research in Europe and the USA has demonstrated that subjects who appear unresponsive or minimally responsive to the primary three-dose hepatitis B vaccination account for 5–15% of vaccinees.[22,23] However, these individuals are not necessarily absolute non-responders: the majority can develop protective levels of anti-HBs after additional hepatitis B vaccination, consisting of a fourth or fifth dose, or an additional complete course of vaccination.[21,24,25] Administration of these additional doses of vaccine to low-level or non-responders can, in most cases, result in adequate antibody response and

Table 1 Booster recommendations in North America and Europe

Advisory body	Recommendations
ACIP and CDC (USA)[4,20]	Boosters are not recommended for children or adults with normal immune status
	Post-vaccination testing should be considered for persons at occupational risk of hepatitis B virus infection (who may be exposed to the virus through needle-stick injury). Testing should take place 1–3 months after vaccination
	For hemodialysis patients, monitor antibody levels annually and administer a booster if levels fall below 10 mIU/mL
NACI (Canada)[20]	Boosters are not recommended for children or adults with normal immune status (including healthcare workers)
	For immunologically compromised patients, monitor antibody levels annually.
ECG (Europe)[6]	Boosters are not recommended for children or adults with normal immune status (including healthcare workers)
	Use boosters to maintain anti-HBs levels above 10 mIU/mL in immunocompromised individuals
	Post-vaccination testing every 6–12 months is advisable in immunocompromised patients.

ACIP, Immunization Practices Advisory Committee; CDC, Centers for Diseases Control and Prevention; ECG, European Consensus Group; NACI, National Advisory Committee on Immunization.

immunological priming.[6] This approach is therefore recommended for individuals who do not respond well to a primary course, to ensure that they eventually achieve antibody levels >10 mIU/mL.[6]

In a routine immunization program it is neither recommended nor feasible to test the postvaccination antibody response and titer. Therefore low-level and non-responders will not be identified. While 90–95% seroconversion may be acceptable in a national immunization program, 100% seroconversion may be the goal in clinical practice. Thus, variations from the vaccination schedule may need to be accommodated to achieve clinical goals.

LONG-TERM ANAMNESTIC ANTIBODY RESPONSE

In clinical studies conducted in Taiwan and Thailand, a primary course of hepatitis B vaccination has been shown to result in protective levels of antibody (>10 mIU/mL) in the great majority of vaccinees (83–99%).[1,26] However, the proportion of vaccinees with protective levels of antibody decreases to 75–87% after 5 years and to 50–70% after 10–12 years.[1,26]

Despite anti-HBs levels falling to <10 mIU/mL, data presented in a number of studies suggest that immunological memory continues to provide effective protection from hepatitis B disease (although not necessarily from infection).[1,2,27–31] This implies that, in the majority of individuals, booster vaccination is unnecessary at least until, or even beyond, 5–10 years following the primary vaccination series.

Huang *et al.* studied the children of hepatitis B e antigen-positive/HBsAg-carrier mothers in Taiwan, and found that the hepatitis B vaccine protected them to at least 10 years of age.[1] Immunologic memory was detected in all subjects, including those with anti-HBs titers <10 mIU/mL, when boosters were administered at 10 years of age.

Studies that have followed subjects for more than 10 years postvaccination have reported mixed results. In observational studies, protection against chronic carriage of hepatitis B has been reported to last up to 13–16 years postvaccination.[32–35] In randomized controlled trials, the rate of chronic carriage between 10 and 15 years postvaccination was found to be low (0.3% in one study and 0% in another),[36,37] and was significantly different from placebo in one study (0.3% *vs* 8.2%),[36] but not in another (0% *vs* 0%).[37]

West and Calandra reviewed studies on the persistence of immunological memory in vaccinated, healthy populations in Italy, Switzerland, the USA, New Zealand, Spain and Taiwan.[2] Few clinically significant breakthrough infections were found even in populations at high risk of exposure to HBV. They suggested that immunosuppressed patients may be the only subgroup in which it is necessary to maintain antibody levels >10 mIU/mL. In the case of healthy, immunocompetent vaccinees, the available choices are either not to boost and expect a small number of cases of infection to occur, to boost using a single lifetime booster, or to administer multiple boosters at intervals of 10 years.

Banatvala and Van Damme conducted a similar review looking at the European and worldwide literature on the persistence of immunity to hepatitis B.[7] They concluded that protection against HBV breakthrough infection is dependent on immune memory rather than anti-HBs levels. Therefore they agreed with the European Consensus recommendations that hepatitis B vaccine boosters appear to be unnecessary in immunocompetent individuals following completion of a primary course of vaccination. The authors point out, however, that long-term studies are needed to determine whether vaccinees develop breakthrough infection or the carrier state at a later stage.

In summary, for the vast majority of individuals receiving hepatitis B vaccine, protection from disease, but not necessarily infection, is present for more than 10 years. The absolute length of protection is yet to be determined.

NATURAL BOOSTING

There is some evidence that a natural boosting effect may occur from exposure to individuals with HBV, and that this is a mechanism for long-term protection against the disease in areas of high HBV endemicity.[38–40] Several studies have been conducted in high endemicity areas looking at children who were immunized at birth to see how many of these children have subsequently developed HBV infection.[39,41,42]

In Chinese[41] and Taiwanese[42] studies, the rate of acquisition of antibody to hepatitis B core antigen (anti-HBc) was approximately 1–2% per annum, but in no case did HBsAg develop and no clinical events occurred in any of these children. In a study of Senegalese infants immunized against hepatitis B at birth, 20% developed anti-HBc antibodies and serum HBsAg was detected in 2.2%.[39] No difference was observed in HBsAg detection between infants who received a booster dose at school age (one of 41 children) and those who did not (one of 51 children).

The significance of anti-HBc development is not clear. There is some concern that low level anti-HBs may make the individual more likely to develop vaccine escape variant viruses.[43] There is also some evidence that patients with hepatitis C and anti-HBc are at greater risk of development of occult hepatitis B infection,[44] which can contribute to the development of hepatocellular carcinoma (HCC); however, prospective studies are needed to allocate risks.

BOOSTER VACCINATIONS

Based on recommendations in Europe and the USA,[4,6,21] and taking into account the current state of knowledge, hepatitis B booster vaccination can only be firmly recommended for low-level and non-responders, particularly healthcare workers, those in other high-risk professions and the immunocompromised, living in Asia. However, key differences exist between conditions in Asia and those in North America and Europe. The higher endemicity of hepatitis B in Asia results in an increased likelihood of non-protected individuals being exposed to HBV at some stage in their life compared with the average risk of exposure for individuals in North America or Europe.

Hepatitis B virus infection in early childhood is the main cause of chronic HBV status in Asia, and universal vaccination of all infants is therefore the most effective method of control.[45] In high and intermediate endemicity countries, prevention of transmission of hepatitis B infection from HBsAg-positive mothers to infants is critical for decreasing both the hepatitis B carrier pool and the associated morbidity and mortality caused by chronic infection. However, implementation of such a universal primary vaccination program remains a major challenge in much of Asia.[45] Routine screening of all pregnant women is not feasible in many countries[43] and therefore vaccination of all newborns is necessary to prevent vertical transmission. However, this is problematic in areas where contact with immunization services may not be possible at the time of delivery.

Because of these differences between conditions in Asia and those in Europe and North America, a different approach to hepatitis B prevention and control may be warranted in each respective region, even in national immunization programs for public health. There are also a number of situations in which public health recommendations and the needs of the individual may not correspond (Table 2). In these situations, physicians should administer boosters at their own discretion. The Steering Committee for the Prevention and Control of Infectious Diseases in Asia have put forward guidelines for physicians in high endemicity areas who choose to administer hepatitis B vaccine boosters (Table 3).

CONCLUSIONS

The use of hepatitis B vaccine has been highly successful in preventing the development of chronic hepatitis B

Table 2 Occasions where public health recommendations and the needs of individuals may not correspond

Inadequate provision of primary immunization means that a small percentage of the population will miss out
Vaccine failure as a result of delivery problems or non-responders
Waning immunity with age or because of disease in immunocompromised patients
Occupational risk in healthcare workers
Viral factors (i.e. exposure to high viral titers)
Importance of low-level infection

Table 3 Hepatitis B vaccine booster guidelines, 2003

Widespread primary vaccination should be the top priority in Asia. Where there are concerns about a highly increased risk of infection, and immunity from primary vaccination is thought to be substandard, physicians should exercise their own clinical judgment on a case-by-case basis
Where administration of a booster vaccine is considered necessary, it should take place approximately 10–15 years after primary vaccination. For children vaccinated as infants this may be particularly important, as this is around the age when at-risk behaviour often begins
Where monitoring of antibody levels is not feasible, it is better to administer a booster than not. Again, physicians must use their own judgment in these cases
Boosting of immunocompromised persons should take place when antibody levels drop below 10 mIU/mL
Administering boosters to healthcare workers should be a selective decision, depending on the endemicity of the particular country in question. Despite the cost of boosting and the potential inconvenience, employers of healthcare workers have a responsibility to ensure staff are adequately protected. This may be done through routine anti-HBs assessment and boosters when necessary, or routine regular boosters without assessing antibody levels

and HCC in Asia and other areas of high hepatitis B endemicity.[18,19] Universal vaccination of infants is the top priority for hepatitis B control in Asia.

After successful vaccination against hepatitis B infection, immunity persists for at least 10 years in the majority of individuals, and routine booster administration is not currently recommended as a public health measure. However, there will always be circumstances in which the recommendations for an individual lie outside the recommendations for a population, and it is the role of the physician to offer his/her patient the best of care. In regions of Asia where hepatitis B is highly endemic, vaccine boosters may help to ensure immunity.

The Steering Committee for the Prevention and Control of Infectious Diseases in Asia have developed guidelines for physicians who choose to administer hepatitis B vaccine boosters in Asia, including: timing booster administration at approximately 10–15 years after primary vaccination; to boost rather than not when monitoring antibody levels is not feasible; to boost immunocompromised patients when the anti-HBs titer falls <10 mIU/mL; and to boost healthcare workers based on the endemicity of the particular country.

The question of whether widespread booster immunization against hepatitis B will be necessary at a later age, such as at 15 or 20 years, even in national immunization programs, requires further study,[4,6,7,20,32] and these studies are likely to be carried out in Asia.

Future research needs to concentrate on the following areas in order to learn more about the duration of immunological memory and thus help determine the best use of vaccine resources. Long-term data on the efficacy of the hepatitis B vaccine in non-responders need to be acquired.[21,24] The issue of postvaccination testing, and whether it should it be restricted to high-risk subjects, needs to be addressed, and more long-term monitoring is required to confirm the absence of clinically significant breakthrough infections in vaccinated groups up to the 10–15-year threshold.[1,4,6,7,20]

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