

Recommendations on Hepatitis B Vaccination Regimens in Hong Kong

- **consensus of the Scientific Working Group on Viral Hepatitis Prevention**

Scientific Working Group on Viral Hepatitis Prevention

Department of Health

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Recommendations on Hepatitis B Vaccination Regimens in Hong Kong

Consensus of the Scientific Working Group on Viral Hepatitis Prevention

The Working Group has achieved consensus on the regimens of hepatitis B vaccination and their applications in various settings. This paper updates the previous recommendations with respect to mercury content in vaccine, newborn vaccination, two-dose vaccination schedule and management of interrupted vaccinations, as of Jan 2001

Hepatitis B Virus Infection

1. Hepatitis B virus (HBV) is a DNA-containing 42nm hepadnavirus. While acute infection is frequently asymptomatic, a carrier state may develop which is associated with chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. The risk of carriage varies with the age of infection. It occurs in 90-95% of infants affected by perinatal transmission, 30% of children aged 1 to 5 years, and 5-10% in older children, adolescents and adults. Routes of transmission, in terms of relative importance in Hong Kong, include: perinatal infection, horizontal transmission, parenteral and sexual contact.
2. Globally, there are 350 million hepatitis B carriers¹. China and Southeast Asia are among the high-prevalence areas with more than half the population being infected some time in their lives, and more than 8% being carriers.

Hepatitis B Vaccination

3. Development of the HB vaccine since the 70s has brought hope to ultimately eliminating the infection. Early on, hepatitis B surface antigen (HBsAg) harvested from the plasma of healthy carriers was found to be highly immunogenic. Its injection into vaccinees stimulates the production of hepatitis B surface antibody (anti-HBs) which could effectively ward off infection. The most widely used hepatitis B vaccines nowadays are manufactured using recombinant technology. Both types are equivalent in immunogenicity yet the latter is theoretically safer in terms of infection risk resulting from human products. As an inactivated vaccine, multiple doses are required. The first dose primes the immune system while subsequent doses elicit the humoral immune response. Hepatitis B vaccination effectively protects one from acute illness and chronic complications, while natural infection may still occur in some vaccinees.
4. In recent years, there has been concern over exposure to mercury as a result of thimerosal-containing vaccines², which may be particularly worrisome in neonates. In Hong Kong, current hepatitis B vaccine preparations contain thimerosal. It is therefore important that a coherent strategy be developed to address the role of various mercury-free or low mercury vaccines in the overall immunisation programme of Hong Kong. There remains no convincing evidence of harmful effects of small amount of thimerosal in vaccines. Until then, the Working Group does not advise any change in the regimen and formulation of hepatitis B vaccination.

The Standard Hepatitis B Vaccination Regimen

5. A 3-dose schedule of vaccines given at 0, 1, 6 month is the standard regimen agreed by international communities. From the biological point of view, after the priming first dose, a second dose at 1 month shall be able to elicit a satisfactory humoral response³. The third dose, which essentially serves a boosting effect, shall challenge the immune system not less than 2 months after the second dose. As a general rule, increasing the interval between doses of a multi-dose vaccine such as HB vaccine should not diminish its efficacy, but unduly decreasing these intervals might interfere with antibody response and protection.

6. In terms of documented efficacy, the regimen of 0,1,6 months is among the most widely tested regimen, reporting consistent results of achieving above 95% seroconversion rates (Table). Local studies since the early 80s have demonstrated good response rate and technical feasibility both in health care workers and neonatal vaccination⁴. Routine boosting is not required for those who have satisfactorily completed a standard three-dose regimen.

Table. Examples of trials on vaccine efficacy

Study	Population (n)	Age	Schedule (months)	Seroconversion rate with anti-HBs ≥ 10mIU/ml
Moyes and Milne ⁵ , 1988	81	0-10 years	0,1,6	99% at 7 months
*Poovorowan ⁶ , 1989	68	0-12 hours	0,1,2,12	95.7% at 2 months, 100% at 4 months
Poovorowan ⁷ , 1992	263	0-12 hours	0,1,6 vs 1,2,12	98.3% vs 100%
Lai CL ⁸ , 1993	Group 1=105 Group 2=106 group 3=107	0.25-11.90 yr	0,1 (HB-Vax II) 0,1,6 (HB-Vax II) 0,1,6(plasma-derived vaccine)	92.9% 99% 99.1%, at 8 months
Wainwright ⁹ , 1997	1630	>6 months	0,1,6	98% (age<20), 95% (age 20-49), and 70% (age ≥50), at 12 months

*Seroconversion rates quoted do not distinguish between anti-HBs levels above or below 10mIU/ml

Scheduling the Regimens – the issue of flexibility

7. Flexibility in the arrangement of the schedule for individuals should be carefully addressed, to enhance adherence and thus completion of the schedule on the one hand, but not to jeopardize immunological response on the other. Some factors to be considered are as follows^{10 11}:

- (a) *Response is poorer if the second dose is given less than 4 weeks after the first, or a third dose is given less than 8 weeks after the second*
- (b) *A more widely spaced schedule results in a better response rate*
- (c) *A more tightly packed schedule results in earlier protection*
- (d) *Data are sparse regarding a second dose given more than 8 weeks after the first; and a third dose given more than 10 months after the second, but most authorities believe response will still be good in these circumstances*

Pre-vaccination Serological Testing

8. The need to determine the pre-vaccination hepatitis B status varies with the settings. It is generally not required for newborns and children. To adequately reduce perinatal infection, however, all expectant mothers shall have their hepatitis B status determined; and babies of carrier mothers should be provided hepatitis B immunoglobulin within 24 hours of life for additional protection. Pre-vaccination serological screening may be useful in other settings, for example in excluding those health care workers who have already been exposed to natural hepatitis B infection. For those tested positive for HBsAg, health consequences related to the infection should be discussed, and the screening of family members (e.g. spouse) be advised. Those who have developed natural immunity to the infection, i.e. anti-HBs positive, could be safely excluded from vaccination consideration.

Post-vaccination Serological Testing

9. Post-vaccination screening could be used to determine individual responses to vaccination. The decision also varies with the setting. If indicated, measurement should be made at 1-4 months after the third dose to obtain the peak antibody levels. Though antibody levels fall gradually over time, those who have mounted an initial response following the 3-dose regimen could achieve effective protection upon challenge by the natural infection. Studies have also documented long-term protection^{9,12} in healthy individuals, including infants, after a complete course of vaccination. An anamnestic response to a subsequent challenge of hepatitis B exists regardless of the titre of anti-HBs at that time⁸.

10. In view of the high seroconversion rate of over 95% with the standard regimen, post-vaccination serological testing generally has little place in public health programmes. The post-vaccination serological status would, however, be important in guiding the subsequent post-exposure prophylaxis management in special settings like occupational injuries in health care professionals.

Hypo-responders and non-responders

11. Adequate response on post-vaccination serological testing refers to an anti-HBs titre of 10 mIU/ml or higher. While those who have no detectable anti-HBs are considered non-responders, hypo-responders refer to those whose anti-HBs titre is between 0 to 10 mIU/ml. Factors causing a suboptimal response include: obesity, the male sex, smoking, older age¹³, and immunocompromised status¹⁴ prior to vaccination.

12. The consensus is that non-responders and hypo-responders shall be given a second course of the 3-dose standard regimen. It was reported that 18 - 25% of hypo- and non-responders respond to an extra dose of vaccine^{15 16}. A repeat course of vaccination induces a moderate antibody response in 41%¹².

Interrupted Course of Vaccination

13. There are numerous reasons why one may fail to adhere to a schedule of vaccination. Management in these circumstances should aim at ensuring that vaccination is ultimately successful on the one hand, and minimizing

inconvenience and cost on the other.

14. A minimum of two doses is required for an adequate immune response. Most regimens in clinical trials have dosed the first and second injections at one to two months' intervals. Although trials with dosing intervals greater than three months have not been reported, it is generally advised that the second dose should be administered not more than 12 weeks after the first. The third dose of vaccine strives to boost the response generated by the first two doses. As long as it is given more than 8 weeks after the second dose, it should be able to elicit an adequate response. If, for some reason, there is interruption after completion of the first two doses, it is not necessary to restart a new course of vaccination.

Hepatitis B Vaccination in Post-Exposure Prophylaxis

15. While hepatitis B vaccination is generally adopted for pre-exposure prophylaxis, it has also been used for post-exposure prophylaxis in the setting of preventing perinatal transmission from carrier mothers. It has been demonstrated that the administration of HBIg alone could lower the infant carrier rate at 12 months from 92% to 54%¹⁷. The efficacy of protection could be increased to 85 to 95% by adding a standard regimen of vaccination^{18 19}. Hepatitis B vaccination generates continued protection as that provided by HBIg gradually wanes, obviating the need of further HBIg injections. Under this circumstance, the first dose of vaccine should be given within 7 days of birth, and HBIg within 24 hours of birth. They may be given concurrently but at separate sites.

16. Post-exposure prophylaxis also applies to health care workers. The main concern is the possibility of repeated exposure in health care workers. Susceptible individuals who lack both HBsAg and HBsAb should be given HBIG for immediate protection. A standard three-dose regimen shall be offered to those who have not received any hepatitis B vaccinations before. Moreover, in known hypo- or non-responders, follow-up HBIG is indicated, one month after the first dose.

Hepatitis B Vaccination in Specific Population Groups

Newborns

17. Hong Kong initiated universal neonatal vaccination as early as in 1988.

There were two reasons. First, perinatally acquired hepatitis B infection was regarded as the most important cause of the high carrier rate in Hong Kong. Second, a successful universal neonatal vaccination should minimise the susceptibility of the population and ultimately reduce the circulation of the virus in the community. For babies born to carrier mothers, the efficiency of transmission correlates with the presence of maternal HBeAg, HBsAg titer²⁰ and virus load²¹, but not the mode of delivery or breast-feeding²². In the absence of intervention, nearly 90% of the infants born to e-antigen positive carrier mothers become infected, among whom 90% will become chronic carriers.

18. A regimen of 3 doses using half the adult dose administered at birth, one

month after birth, and the third dose in 6 months is recommended for all newborns in Hong Kong. A lower dose²³, while achieving comparable seroconversion rates, has reportedly been associated with lower post-vaccination antibody levels, the significance of which in the long term is not exactly known. As a public health programme, pre- and post-vaccination screening is not required although pregnant mothers shall be offered serological testing to decide if hepatitis B immunoglobulin has to be given in addition to active vaccination at birth.

Pre-term infants

19. Concerns regarding the need for modifications of regimens in preterm infants originate from the observation of their poorer immunological responses towards vaccination. It is recommended that preterm babies shall have their vaccination initiated when body weight achieves 2 kg. A controlled study in Hong Kong²⁴ confirmed that 79% of pre-term infants vaccinated at less than 2 kg body weight responded, comparing with 91% in those vaccinated at 2 kg, and 100% in normal term infants. To ensure coverage, however, the preterm babies shall be given the first dose prior to hospital discharge.

20. Nevertheless, for preterm babies born to carrier mothers, hepatitis B vaccination combined with HBIG shall be initiated after birth as in term babies to achieve maximal individual protection. This dose of vaccine however should not be counted in the 3-dose course of vaccination²⁵. The first valid dose of vaccine is given when the baby reaches 2 kg of weight. Some

authorities recommend post-vaccination serological testing to determine if the response is adequate.

Children

21. Since Hong Kong started universal neonatal hepatitis B vaccination ten years ago, all children born after 1988 should have already been immunised. Among those who have not received a complete course of vaccination, such as in the case of defaulted series, or immigrants, an assessment to determine the need to provide a complete course of vaccination is advisable. This would protect the children from potential person-to-person (horizontal) transmission of the virus, especially in those with family members who are hepatitis B carriers. The standard 3-dose regimen, using half the adult doses at 0,1,6 months is recommended. The half doses are used up to the age of 16 for those indicated for vaccination.

Adolescents and Adults

22. Adolescents and adults who lack both HBsAg and HBsAb are susceptible to hepatitis B through routes like sexual contact, injecting drug use, or close contact of a chronically infected person.

23. Evaluation of an adolescent or adult who requests HB vaccination should be based on the risk of infection. Factors like multiple sexual partners, injecting drug use, frequent transfusion of blood/blood products and sexual contact with a known carrier add weight towards a decision of vaccination. The evaluation process opens the communication channel between the health

care provider and the client to discuss safer sex issues.

24. If a pre-vaccination evaluation that includes both the chances of future exposures and the serological status prior to vaccination indicates hepatitis B vaccination, the standard regimen should be employed as far as possible.
25. A 2-dose regimen with Recombivax HB[®] (Merck) has been approved by the US Food and Drug Administration for use in persons aged 11-15, based on relatively short term data of 2 years²⁶. According to this schedule, two 10ug doses are given 4-6 months apart. Pending long term data, this schedule should be considered as an alternative only when the standard regimen is not practicable, for reasons such as anticipated poor compliance.

Health care workers

26. As hepatitis B virus is primarily a blood-borne pathogen, health care workers are regarded as the main occupational group at risk of the infection. Conceivable occupational routes of transmission include percutaneous injury with a contaminated needle or sharp, and exposure through a broken epithelium or mucous membrane.
27. Active vaccination with post-vaccination serological testing is recommended for all susceptible health care workers²⁷. As is the case with adult evaluation, pre-vaccination hepatitis B serology screening is also advisable. These should preferably be provided in early phase of the career, for instance, during recruitment, or in schools of medicine, dentistry, nursing, laboratory

technology and other allied health professions. To facilitate future management decisions on post-exposure prophylaxis, all health care workers should be clear about their own hepatitis B status and be reminded of the necessary actions to be taken upon exposure.

People with compromised immune status

28. People with compromised immune status²⁸ may have a poorer response towards hepatitis B vaccination. There have been suggestions of larger vaccine doses and/or a higher number of doses. Post-vaccination serology testing is recommended to ascertain the status and booster may be indicated when anti-HBs falls below 10 mIU/ml²⁹.

Hepatitis B vaccination to prevent iatrogenic transmissions

29. People undergoing treatment procedures that may subject them to the risk of iatrogenic hepatitis B infection may be vaccinated against hepatitis B. Some examples are thalassaemia major and hemophilia patients and those on hemodialysis. The attending health care providers shall examine in their work environment the potential risks of iatrogenic hepatitis B transmission along with other blood borne diseases, review the practice of infection control and provide relevant advice to their clients.

Technological Advancement and Hepatitis B Vaccination

30. The application of recombinant technology to manufacture cheap and sterile

hepatitis B vaccines has already made significant contribution in the implementation of hepatitis B vaccination. In this section, areas relating to the scientific and technological advancement are examined. These would have implications on the design of vaccination programmes in future.

Combined Vaccines

31. With the continued expansion of the immunization programme, it is clear that combined vaccines may be useful in minimizing administrative costs on the one hand, and enhancing adherence on the other. Studies have been done on a variety of combined vaccines in which hepatitis B is a component³⁰. Most have shown results comparable with the currently available monovalent vaccines. A number of these combined vaccines have actually been licensed in some countries, eg DTP-HB, Hib-HB and HEP AB³¹. Their efficacy in inducing adequate antibody responses and applicability in the local situation should be examined.

Tetravalent DTP and Hepatitis B vaccine

32. Efficacy studies on this tetravalent vaccine have attracted much interest in the past few years. Immunogenicity and reactogenicity have been documented in newborns, children and preterm babies. The main application of this vaccine is to facilitate the design of a convenient childhood immunization programme. The full integration of DTP-HB in Hong Kong may not be substantiated as DTP is not given at birth. A possible modification would be to give a monovalent HB vaccine at birth, followed by the combined vaccine later in the schedule.

Combined Hepatitis A and B Vaccine

33. The application of the combined Hepatitis A and B vaccine is largely for the convenience of adults who wish to gain protection against the two infections. The role of hepatitis A vaccination, and thus the combined vaccine, in newborns has yet to be determined. As exposure to both infections is relatively common in adults in the local community, the use of this vaccine may be limited to individual use, especially in those who are at risk of both infections.

Vaccine with additional antigens

34. The inclusion of pre-S regions in hepatitis B vaccine carries the theoretical advantages of expanding the epitopes for T-cells. Potential implications are it may improve the long term immunity and protect against mutants³². The latter refers to the vaccine escape mutant described in the recent years, the commonest being one related to the 145 gly to arg mutation in the "a" epitope. One possible contributing factor is the use of hepatitis B immunoglobulin in babies born to carrier mothers. The mutant virus may also escape detection in tests based on monoclonal anti-HBs reagents. The application and the clinical importance of these have yet to be determined.

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ADDENDUM (March 2004)

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Vaccination to Pre-term infants under para 19 and 20 :

Evidence has accumulated in recent years to show that medically stable preterm babies vaccinated at the chronologic age of 1 month yield satisfactory response independent of body weight. For this reason, hepatitis B vaccine given at the time of hospital discharge or the chronologic age of 1 month (if medically stable) should also be counted as valid and counted toward the three-dose course of vaccination, regardless of the body weight at time of vaccination. Alternatively, one may employ the traditional approach of delaying vaccination until hospital discharge or a body weight above 2 kg, whichever occurs earlier. Either way, for babies born to carrier mothers, both vaccine and HBIg should be given at birth.