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*
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Members of the Scientific Working Group on Viral Hepatitis Prevention

Dr SS LEE (Chairman)  Consultant, SPP, DH
Mr Anthony Chan  Chief Pharmacist, DH
Dr Sarah CHOI  SMO (EHRS), DH
Dr Teresa CHOI  SMO (SPP), DH
Prof CL LAI  Professor, Dept of Medicine, HKU
Dr SY Lee  PMO(4), DH
Dr Nancy LEUNG  Hepatologist, Dept of Medicine, CUHK
Dr NK LEUNG, JP  Hospital Chief Executive, PMH
Dr WL LIM, JP  Consultant Microbiologist, Virus Unit, DH
Dr CK LIN  Chief Executive, HKRCBTS
Dr HY LO  Consultant Physician, QEH
Dr KH Mak  Consultant (Community Medicine), DH
Prof John Tam  Professor, Dept of Microbiology, CUHK
Dr KT TSE  Consultant, O&G, QEH
Dr LY TSE  Consultant (Community Medicine), Student Health Service, DH
Dr Helen KY Yau  PMO (FHS), DH
Dr Betty YOUNG  Consultant Paediatrician, PYNEH
Dr Kenny CHAN (Secretary)  MO (SPP), DH
Mr John YIP (Secretary)  SEO (SPP), DH

The Scientific Working Group on Viral Hepatitis Prevention advises the Director of Health on all issues relating to viral hepatitis prevention

Correspondence to:

Secretariat
Scientific Working Group on Viral Hepatitis Prevention
5/F 145 Battery Street
Yaumatei, Kowloon
Hong Kong
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This paper presents the recommendations on the regimens for hepatitis B vaccination, its applications in different settings, and an examination of technological advances as they relate to the design of vaccination programmes in the future.

Hepatitis B Virus Infection

1. Hepatitis B virus (HBV) is a DNA-containing 42nm hepadnavirus. While acute infection is frequently asymptomatic, carrier state is associated with chronic hepatitis, cirrhotic changes and hepatocellular carcinoma. Risk of carriage development varies with 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 carriers. 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% are carriers. The number of carriers would reach 400 million by the year 2000.
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 safer in terms of infection risk resulting from human products. As an inactivated vaccine, multiple doses are required. The first dose essentially 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.

The Standard Hepatitis B Vaccination Regimen

4. A 3-dose schedule administered at 0, 1, 6 months is the standard regimen agreed by the international communities, through a variety of regimens studied. From the biological point of view, after the priming dose, a second dose at 1 month shall be able to elicit a satisfactory humoral response. The third dose, which is essentially serving 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.

5. In terms of documented efficacy, the regimen 0,1,6 months is, nonetheless,
among the most widely tested regimen, reporting consistent results of achieving above 95% seroconversion rates. (Table 1) Local studies since early eighties have demonstrated good response rate and technical feasibility both in health care workers and neonatal vaccination³. Boostering is not required for those who have satisfactorily completed a standard three-dose regimen.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age</th>
<th>Schedule (months)</th>
<th>Seroconversion rate with anti-HBs≥10mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyes and Milne⁴, 1988</td>
<td>81</td>
<td>0-10 years</td>
<td>0,1,6</td>
<td>99% at 7 months</td>
</tr>
<tr>
<td>*Poovorowan⁵, 1989</td>
<td>68</td>
<td>0-12 hours</td>
<td>0,1,2,12</td>
<td>95.7% at 2 months, 100% at 4 months</td>
</tr>
<tr>
<td>Poovorowan⁶, 1992</td>
<td>263</td>
<td>0-12 hours</td>
<td>0,1,6 vs 1,2,12</td>
<td>98.3% vs 100%</td>
</tr>
<tr>
<td>Lai CL⁷, 1993</td>
<td>Group 1=105 Group 2=106 Group 3=107</td>
<td>0.25-11.90 yr</td>
<td>0.1 (HB-Vax II) vs 0.1,6 (HB-Vax II) vs 0.1,6(plasma-derived vaccine)</td>
<td>92.9% vs 99% vs 99.1%, at 8 months</td>
</tr>
<tr>
<td>Wainwright⁸, 1997</td>
<td>1630</td>
<td>&gt;6 months</td>
<td>0,1,6</td>
<td>98% (age&lt;20), 95% (age 20-49), and 70% (age &gt;=50), at 12 months</td>
</tr>
</tbody>
</table>

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

**Scheduling the Regimens – the issue of flexibility**

6. Flexibility in the arrangement of the schedule for individuals should be carefully addressed, to enhance adherence and thus completion of the schedule on one hand, and not to jeopardize immunological response on the other. Some factors to be considered are as follows⁹¹⁰:

(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, although some believe response will still be good in these circumstances**
**Pre-vaccination Serological Testing**

7. The decision of determining 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 health care workers, in excluding those 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 also be safely excluded from vaccination consideration.

**Post-vaccination Serological Testing**

8. The consideration for post-vaccination screening could be used to determine the individual responses to vaccination. The decision also varies with the setting. Measurement, if indicated, 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\(^8\)\(^,11\) in healthy individuals, including infants, after a complete course of vaccination. An anamnestic response to the subsequent challenge of hepatitis B exists regardless of the titre of anti-HBs at that time\(^7\).
9. 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 setting like occupational injuries in health care professionals.

**Hypo-responders and non-responders**

10. 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 age\(^{12}\), immunocompromised status\(^{13}\) prior to vaccination. However, none has been used widely in making clinical decision of serological testing.

11. The current 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\(^{14}\)\(^{15}\). A repeat course of vaccination induces a moderate antibody response in 41%\(^{11}\).

**Interrupted Course of Vaccination**

12. 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.
**Between first and second dose**

A minimum of two doses is required before an immune response could be initiated. The maximally accepted interval between the first two doses has not been defined. Most regimens in clinical trials have dosed the first and second injections at an one to two months intervals, whereas trials on dosing interval greater than three months have not been reported. While the exact antibody responses towards the different dosing regimens have not been delineated clearly, a maximally acceptable interval between the first and second doses of 12 weeks is advised.

**Between second and third dose**

The third dose of vaccine is essentially to boost up the antibody response generated by the first two doses. Its timing is therefore not as critical as the second. As long as it is given more than 8 weeks after the second, it should be able to elicit an adequate response. Again, there is no adequate data on the maximally acceptable interval between the second and the third dose. Some regimens have been administering the third dose in one year’s time. A case-by-case evaluation is advised.

**Hepatitis B Vaccination in Post-Exposure Prophylaxis**

13. While hepatitis B vaccination is generally adopted for pre-exposure prophylaxis, it has been also 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%.\textsuperscript{16} The efficacy of protection could be increased, by adding a standard of regimen of vaccination, to 85 to 95%.\textsuperscript{17,18} 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 at separate sites.

14. Post-exposure prophylaxis also applies to health care workers. The main concern is the possibility of repeated exposure in health care workers and the hepatitis B status of source persons. 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

15. Hong Kong is among the very few places that has initiated universal neonatal vaccination as early as in 1988. There are two reasons. First, perinatally acquired hepatitis B infection has been regarded the most important cause of the high carrier rate in Hong Kong. Second, a successful universal neonatal vaccination shall 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 HBeAg, the HBsAg titer\(^9\) and maternal virus load\(^9\), but not the mode of delivery or breast-feeding\(^9\). In the absence of intervention, nearly 90% of the infants born to e-antigen positive carrier mothers become infected, and among
which, 90% will become chronic carriers.

16. To ensure good coverage of and adherence to neonatal vaccination, the regimens are modified to integrate into the existing childhood immunization programme. A regimen of 3 doses using half the adult dose administered at birth, one month after birth, and the third dose in 3-5 months is to facilitate operational convenience that the latter could be administered concurrently with the second dose of DTP vaccine. A lower dose\textsuperscript{22}, while achieving comparable seroconversion rates, has been reportedly associated with lower post-vaccination antibody levels, the significance of which in the long term is not exactly known. There has been, however, no additional immunological advantage to provide the third dose at 3-5 months compared to that provided at 6 months. As a public health programme, pre- and post-vaccination screening is generally not required although pregnant mothers shall be offered serological testing to decide if hepatitis B immunoglobulin shall be given, on top of the vaccination, at birth.

\textit{Pre-term infants}

17. Concerns of 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. To ensure coverage, however, the preterm babies shall be given the first dose prior to hospital discharge. A seroconversion rate of 90\% has been reported if the first dose of vaccine is given at hospital discharge. A controlled study in Hong Kong\textsuperscript{23} 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.

18. However, for preterm babies born to carrier mothers, the combined HBIg and hepatitis B vaccination shall be initiated as in term babies to achieve maximal individual protection. Some authorities recommend post-vaccination serological testing to determine if the response is adequate.

Children

19. 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. While the standard 3-dose regimen, using half the adult doses at 0,1,6 months is recommended, flexibility in scheduling may be allowed to ensure completion of vaccination. The half doses are used up to the age of 16 for those indicated for vaccination.

Adolescents and Adults

20. 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.

21. 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 providers and the clients to discuss on safer sex issues.

22. The standard hepatitis B vaccination regimen after a pre-vaccination evaluation, which should include both the chances of future exposures and the serological status prior to vaccination, is advisable.

Health care workers

23. 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: a percutaneous injury with a contaminated needle or sharp, and exposure through a broken epithelium or mucous membrane.

24. Active vaccination with post-vaccination serological testing is recommended for all susceptible health care workers. As for adult evaluation, pre-vaccination hepatitis B serology screening is advisable. These should preferably be provided in early phase of the career, for instance, during recruitment, 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 shall be clear about their own hepatitis B status and be reminded of the necessary actions to be taken in case of parenteral exposures.
People with compromised immune status

25. People with compromised immune status\textsuperscript{25} 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/ml\textsuperscript{26}.

Hepatitis B vaccination to prevent iatrogenic transmissions

26. 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 are advised to examine the potential risks of iatrogenic hepatitis B transmission and provide relevant advice in the course of evaluation for treatment initiation.

Technological Advancement and Hepatitis B Vaccination

27. 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

28. 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 component. Most have shown results comparable with the currently available monovalent vaccines. A number of these combined vaccines have actually been licensed in some countries, e.g. DTP-HB, Hib-HB and HEP AB. Both the issue of its efficacy in inducing adequate antibody responses and applicability in the local situation are examined.

Tetravalent DTP and Hepatitis B vaccine

Efficacy studies on this tetravalent vaccine has 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 could not be 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

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

29. 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 mutants\textsuperscript{29}. 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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General references:


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