The hepatitis B immunization programme in Singapore


A voluntary immunization programme to prevent perinatal transmission of hepatitis B virus (HBV) infection in Singapore was implemented on 1 October 1985 as an integral component of the national childhood immunization programme. Up to April 1988, a total of 68,845 mothers who attended government maternal and child health clinics were screened for the disease. Of these, 2432 (3.5%) were positive for hepatitis B surface antigen (HBsAg) and 904 (1.3%) for hepatitis B e antigen (HBeAg). Virtually all the babies born to carrier mothers completed the full immunization schedule; and in addition, those of HBeAg-positive mothers were given a dose of hepatitis B immunoglobulin at birth. The hepatitis B immunization programme was extended on 1 September 1987 to cover all newborns. About 90% of the 15,943 babies delivered in government institutions from September 1987 to April 1988 were immunized at birth, with the subsequent doses being administered at maternal and child health clinics at 4–6 weeks and 5 months later. More than 85% of the children given the full course of plasma-derived and yeast-derived hepatitis B vaccine from birth continued to have protective antibody to HBV two years after immunization. The programme is being closely monitored to assess the duration of immunity and the need for booster doses, while seronegative adults are also being encouraged to be vaccinated.

Introduction

Viral hepatitis B is a disease of major public health importance in Singapore, where the annual morbidity rate of reported acute cases is 10.4 per 100,000 and the case-fatality rate is 2.0% (1). The disease is responsible for 46% of acute viral hepatitis cases during non-epidemic periods.

In Singapore the majority of viral hepatitis B infections are subclinical. For example, sero-epidemiological surveys of the healthy population aged from 6 months to ≥55 years of age showed that the infection, as indicated by the presence of any hepatitis B virus (HBV) markers, is acquired continuously throughout life and that the prevalence increased gradually with age from 6.5% among 0–4-year olds to 54.6% among those aged ≥55 years. The age-specific prevalence of hepatitis B surface antigen (HBsAg) also increased with age from 1.6% for 1-year olds to 3.4% for 5–14-year olds and reached 6.3% for 35–44-year olds. About 6–8% of adult males and 4% of adult females in Singapore are HBV carriers (2, 3).

Based on the age-specific prevalence of HBsAg in various population groups, the number of carriers in the country is about 120,000, with 54.6% of these being highly infectious, as indicated by the presence of hepatitis B e antigen (HBeAg). An estimated 1.9 million persons had no immunity to HBV and were at risk of acquiring the infection from the large pool of carriers. HBsAg carrier status is strongly associated with chronic hepatitis, non-alcoholic cirrhosis, and primary liver cancer (4)—the third most common cancer among males in Singapore. There are about 500 hospital discharges for chronic hepatitis/cirrhosis and 550 for primary liver cancer per year, while the rate of primary liver cancer between 1968 and 1977 was 28.7 per 100,000 per year for males and 7.4 per 100,000 for females (5).

The direct cost per annum of treating patients admitted to government hospitals with hepatitis, chronic liver diseases, and liver cancer is about US $2 million. This does not include cases treated by doctors in private hospitals, outpatient clinics, or the intangible economic loss of work-days and
premature deaths, and the suffering of patients and families. Also each year, about 1600 potential blood donors have to be rejected because they are HBV carriers.

**Materials and methods**

**Strategies for prevention and control**

The key to the prevention and control of viral hepatitis B is immunization, the aim of which is to protect susceptibles from being infected and thus help to reduce the large pool of carriers in the community. Clinical and epidemiological research and health education to reduce transmission are other important components in the overall strategies for the prevention and control of the disease.

In the first year of life, the mode of transmission of HBV is predominantly perinatal and this mode forms the most important link in maintaining the endemicity of HBV in the country. About 48% of babies born to carrier mothers develop the carrier state, and estimates indicate that approximately 870 of the 40 000 babies born each year in Singapore are infected perinatally and that 630 of these continue to harbour the virus for the rest of their lives (6). However, horizontal spread of infection from the large carrier reservoir through various parenteral routes and by intimate contact continues throughout life (7-9). Children born to non-carrier mothers could also be subsequently infected by other carriers within and outside the family setting. As in other immunization programmes, the main strategy of hepatitis vaccination should be to immunize infants and young children in order to prevent acquisition of HBsAg as early in life as possible.

The results of mathematical modelling studies indicate that the most effective strategy to reduce the incidence of HBV infection is continuous immunization of all newborns. The reduction in incidence is less marked if immunization is confined only to babies born to carrier mothers. Mass immunization of the whole population (both children and adults) reduces the incidence of the disease even more markedly, but once the programme is stopped the incidence returns to its initial endemic level (10, 11). The cost of the vaccine is the key determinant in deciding the best strategy.

Clinical trials were planned and conducted to determine the best schedule and dosage for the programme. The results indicated that immunoprophylaxis could reduce perinatal transmission of HBV by 85% and that a 5-µg dose of Merck Sharp & Dohme plasma-based vaccine was as efficacious in this respect as the 10-µg dose recommended by the manufacturer (12). Similarly, trials with lower doses of Merck Sharp & Dohme yeast-derived vaccine for pre-exposure prophylaxis in children (using 0.6-µg, 1.25-µg, and 2.5-µg doses) demonstrate that the immune response is as good as that obtained with the recommended dose (5 µg) (13). These findings are of practical importance since the use of a lower dose of vaccine without compromising its efficacy and immunogenicity would markedly reduce the cost of the programme. No adverse post-immunization reactions have been reported in the clinical trials for both types of vaccine.

**The hepatitis B immunization programme**

Because of the high cost of the vaccine, the programme was implemented in phases and targeted at population groups with the greatest risk of acquiring viral hepatitis B. Priority was given to children, especially babies born to carrier mothers. Adults who were at risk of the infection, such as health care workers and contacts of acute hepatitis B cases and carriers, were also included. Since a programme that incorporates serological testing is expensive, no pre-immunization screening was recommended initially, except for pregnant women.

The programme was also made available to members of the public at nine selected polyclinics and five major government hospitals. Medical practi-

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>infants and preschool children</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>Hepatitis B and HB immunoglobulin</td>
</tr>
<tr>
<td>before discharge from hospital</td>
<td>if HBsAg-positive</td>
</tr>
<tr>
<td>4-6 weeks</td>
<td>BCG</td>
</tr>
<tr>
<td>(development assessment)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>DPT³/polio</td>
</tr>
<tr>
<td>4 months</td>
<td>DPT/polio</td>
</tr>
<tr>
<td>5 months</td>
<td>DPT/polio and hepatitis B</td>
</tr>
<tr>
<td>12 months</td>
<td>Measles</td>
</tr>
<tr>
<td>18 months</td>
<td>DPT/polio (1st booster dose)</td>
</tr>
</tbody>
</table>

**Schoolchildren**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>≥6 years⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT,⁵ polio (2nd booster dose) and BCG (if no immunization scar)</td>
<td></td>
</tr>
<tr>
<td>DT, polio (3rd booster dose), BCG (if no immunization scar) and rubella</td>
<td></td>
</tr>
<tr>
<td>BCG (if no immunization scar)</td>
<td></td>
</tr>
</tbody>
</table>

- ² Immunization against diphtheria and measles is compulsory.
- ³ DPT = diphtheria—pertussis—tetanus.
- ⁴ A booster dose of hepatitis B vaccine may be introduced at this stage.
- ⁵ DT = diphtheria—tetanus.
The hepatitis B immunization programme in Singapore

Table 2: Recommended schedule for hepatitis B (HB) immunization in Singapore

<table>
<thead>
<tr>
<th>Recipients</th>
<th>Vaccine dose</th>
<th>Site of injection</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns of HBsAg/HBeAg-positive mothers</td>
<td>Plasma-based 5 µg</td>
<td>Anterolateral aspect of thigh</td>
<td>Birth (vaccine + HB immunoglobulin) at 1 month and 5 months</td>
</tr>
<tr>
<td>Newborns of HBsAg/HBeAg-positive mothers</td>
<td>Yeast-derived 5 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other newborns and infants &lt;1 year of age</td>
<td>Plasma-based 5 µg</td>
<td>Anterolateral aspect of thigh</td>
<td>Birth, 1 month, and 5 months</td>
</tr>
<tr>
<td>Children aged 1–18 years</td>
<td>Yeast-derived 2.5 µg</td>
<td>Deltoid area</td>
<td>0, 1 month, and 6 months</td>
</tr>
<tr>
<td>Adults aged 18–40 years</td>
<td>Plasma-based 10 µg</td>
<td>Deltoid area</td>
<td>0, 1 month, and 6 months</td>
</tr>
<tr>
<td>Adults &gt;40 years</td>
<td>Yeast-derived 5 µg</td>
<td>Deltoid area</td>
<td>0, 1 month, and 6 months</td>
</tr>
<tr>
<td>Adults &gt;40 years</td>
<td>Yeast-derived 10 µg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dosages shown refer to vaccine manufactured by Merck Sharp & Dohme, USA. For vaccines manufactured by Pasteur Institute, Paris, France, and Smith, Kline Biologicals, Belgium, the doses and schedules are as recommended by the manufacturers.

*Given intramuscularly.

0.5 ml given to babies born to HBeAg-carrier mothers.

tectioners working in the private sector were also encouraged to participate in the programme.

The hepatitis B immunization schedule for infants has been fully integrated into the existing national childhood immunization programmes (14) (Table 1). The schedule and dosages for the plasma-based and yeast-derived vaccine are shown in Table 2.

In order to monitor the acceptance rate of the programme, all immunization procedures carried out

Fig. 1. Scheme for antenatal screening of mothers for HBsAg/HBeAg, immunization of newborns and infants against viral hepatitis B, and notification of immunization procedures in Singapore. DPT = diphtheria–pertussis–tetanus.

Antenatal clinic

- Blood for HBsAg/HBeAg testing
- HBsAg/HBeAg status indicated in referral letter to hospital
- Health education on hepatitis B immunization

Hospital

- HBsAg/HBeAg status stamped in all records
- Health education on hepatitis B immunization
- Consent for immunization
- Payment by Medisave fund
- Health booklet issued with immunization record
- First dose of hepatitis B vaccine (+ hepatitis B immunoglobulin if HBeAg-positive) at birth
- Instruction to complete full course of immunization

Maternal and child health well-baby clinic

- Second dose of hepatitis B vaccine at 4–6 weeks (development assessment)
- Third dose of hepatitis B vaccine at 5 months (together with DPT and Sabin)

Hepatitis control unit

- Return of antenatal screening results
- Notification of hepatitis B immunization and post-immunization adverse reactions

Maternal and child health well-baby clinic

- Second dose of hepatitis B vaccine at 4–6 weeks (development assessment)
- Third dose of hepatitis B vaccine at 5 months (together with DPT and Sabin)
were made notifiable. A hepatitis control unit was also set up to coordinate epidemiological surveillance and research, to evaluate the programme, and to monitor adverse post-immunization reactions. A quality assurance scheme for HBsAg and antibody to hepatitis B surface antigen (anti-HBs) was also introduced for all laboratories conducting these tests.

Implementation of the programme

The programme started in mid-1983 with the immunization of health care workers on a voluntary basis. Immunization of babies born to carrier mothers was not started until 1 October 1985, when laboratory facilities for the routine screening of pregnant women for HBsAg and HBeAg became available. The programme was implemented after an intensive health education campaign in the mass media to educate the public on the importance of HBV infection, its mode of transmission, and its prevention. Medical and nursing staff were also repeatedly instructed on the operational aspects of the programme.

In order to break the vertical as well as horizontal chain of transmission, on 1 September 1987 the programme was extended to include all newborns. However, since the necessary vaccine for immunizing the 30000 babies delivered annually to non-carrier mothers in government institutions would have increased the programme's costs about thirteenfold, it was decided that the programme should be effected through the use of parents' Medisave funds.* Health education of the public and of the medical and nursing staff was again intensified prior to the implementation of the extended programme. Routine antenatal screening of women is still necessary to enable hepatitis B immunoglobulin to be administered to newborns of HBeAg-carrier mothers. The scheme for antenatal screening of women for HBsAg/HBeAg, immunization of newborns and infants against HBV, and notification of hepatitis B immunization status is shown in Fig. 1.

As laboratory facilities in Singapore have expanded, and also for medico-legal and ethical reasons, pre-immunization serological testing for HBV markers has been carried out on children or adults who request immunization, and only those found to be seronegative are immunized.

Results

Immunization coverage

A total of 52191 women who attended government maternal and child health clinics were screened for HBsAg and HBeAg between October 1985 and August 1987. Of these, 1845 (3.5%) were HBsAg-positive and 720 (1.4%) HBeAg-positive. Virtually all the babies born to carrier mothers in government institutions had completed the full course of hepatitis B immunization, and, in addition, those born to HBeAg-carrier mothers received a dose of hepatitis B immunoglobulin at birth. Also, babies born to mothers of unknown carrier status were included in the immunization programme.

Between September 1987 and April 1988 when use of Medisave funds was permitted to pay for the immunizations, 16654 women who attended antenatal clinics were screened, 569 (3.4%) of whom were HBsAg-positive and 184 (1.1%) HBeAg-positive. A total of 14080 (88.3%) of 15943 babies born in four government institutions were immunized at birth. The coverage rate for the 474 babies born to carrier mothers was 99.6%. However, from September 1987 to March 1988, only 1761 babies, i.e., about 13% of the live births, born in six private hospitals received HBV vaccine. This arose because the majority of babies born to non-carrier mothers in those hospitals were immunized after discharge at government maternal and child health clinics where the cost of immunization was considerably cheaper.*

From mid-1983 to August 1987, more than 400000 doses of hepatitis B vaccine were administered by the Ministry of Health. General practitioners gave an additional 50000 doses to the general public over this period. Since 1 September 1987, when the use of Medisave was authorized for hepatitis B immunization, the response from the public has been overwhelming—about 90000 doses of hepatitis B vaccine were given between September and December 1987.

Monitoring the immune response of vaccinees

Three cohorts of children—one born to HBeAg-carrier mothers, one to HBsAg-positive but HBeAg-negative mothers, and one to non-carrier mothers—were followed up 1 year and 2 years after completing the full course of immunization with 5 μg Merck Sharp & Dohme plasma-derived vaccine. At the first year follow-up visit, 88.2% (82/93), 84.9%

* Medisave is a form of social security whereby employees make a compulsory monthly contribution of 3% of their income to the Central Provident Fund Board with a further 3% being contributed by employers until a total of US $7500 has been accumulated by individuals for hospitalization and selected medical procedures.

* The maximum amount that can be withdrawn from the Medisave fund for hepatitis B immunization is US $15 for children <1 year of age, US $22.50 for children <18 years of age, and US $45 for adults.
(73/86) and 95.8% (23/24) of the children in each of these respective cohorts exhibited protective antibodies (anti-HBs). The corresponding proportions at the 2-year follow-up visit were 87.9% (80/91), 84.4% (65/77), and 86.4% (19/22). A fourth cohort of children born to non-carrier mothers and given three 2.5-μg doses of Merck Sharp & Dohme yeast-derived vaccine was also followed up 1 year and 2 years after immunization. Protective levels of anti-HBs were detected in 100% (30/30) of the vaccinees at the 1-year and 92.6% (25/27) at the 2-year follow-up visit.

Three groups of seronegative adults aged < 40 years who had been immunized with three 10-μg doses of Merck Sharp & Dohme plasma-derived vaccine were also followed up for various periods. Protective levels of anti-HBs were detected in 96.3% (181/188) at the 1-year follow-up visit in the first group; in 81.2% (229/282) at the 2-year visit in the second group; and in 95.5% (21/22) at the 4-year visit in the third group.

**Discussion**

The comprehensive network of health care services, the integration of hepatitis B immunization into the existing childhood immunization programmes, the wide publicity on the disease, and the use of the Medisave fund all contributed to the successful implementation of the programme in Singapore. The main thrust of the programme was aimed at preventing perinatal and horizontal transmission of HBV during infancy; however, all other susceptible population groups were also encouraged to receive the vaccine. The cost of immunization was kept within the reach of the general population through bulk purchase of vaccine, and, whenever possible, a low dose was used, based on the results of local clinical trials (12, 13). The vaccine was very safe.

It is still too early to assess the efficacy of the programme, although there was an 18% reduction in the incidence of acute HBV infection in Singapore in 1987. Seroepidemiological surveys are being conducted periodically on various population groups to monitor the changing prevalence of HBV markers, and the immune response of immunized children and adults is continuing to be monitored to determine the duration of immunity. Clinical trials with a 2.5-μg dose of Merck Sharp & Dohme yeast-derived vaccine to prevent perinatal transmission of HBV have been initiated. Based on the results of these studies, modifications to the immunization programme may be made, if necessary. If the duration of protection could be conclusively shown to be at least 5 years, it would be purposeful to give a booster dose to primary school entrants at 6 years of age together with the vaccines in other childhood immunization programmes.

With the availability of other plasma-based and DNA-recombinant vaccines on the market and the recent revision to the WHO biological requirements for hepatitis B vaccines, it is expected that the price of a suitable vaccine will drop further (15). This would encourage its wider acceptance by the population. In order to assess the long-term impact of the immunization programme, relevant epidemiological data are being compiled and the particulars of hepatitis B carriers will be compared with data in the Singapore Cancer Registry to determine whether or not the programme might lead to a reduction in the incidence of hepatocellular carcinoma.

**Acknowledgements**

We thank the Advisory Committee on Hepatitis and Related Disorders, the Scientific Committee on Hepatitis and Related Disorders, and the Expert Committee of the Immunization Programme in Singapore for their guidance and support in formulating and implementing the hepatitis B immunization programme. We would also like to express our gratitude to the medical and nursing staff of the Ministry of Health and Ministry of the Environment and all the medical practitioners in Singapore for their assistance and cooperation.

**Résumé**

**Singapour: le programme de vaccination anti-hépatite B**

L'hépatite virale B, pose un important problème de santé publique à Singapour. Dans le pays, on estime à 140 000 le nombre de porteurs, dont environ un tiers sont très contagieux, et à 1,4 million le nombre de personnes sensibles à l'infection. L'état de porteur chronique est étroitement associé à l'hépatite chronique, à la cirrhose hépatique non alcoolique et au cancer primitif du foie, qui, à Singapour, vient au troisième rang des cancers les plus communs chez les hommes. Au cours de la première année de vie, la transmission du virus de l'hépatite B est essentiellement périnatale, mais l'infection peut être contractée tout au long de l'existence selon divers modes de transmission horizontale.

Un programme de vaccination volontaire a été mis en place à Singapour à partir du 1er octobre 1985, dans le cadre du programme national de vaccination infantile, afin de briser la chaîne de transmission de cette infection. Le prix du vaccin est resté abordable pour l'ensemble de la population grâce à une politique d'achat en grandes
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quantités et à l'utilisation, dans la mesure du possible, de doses faibles, basées sur les résultats des essais cliniques effectués localement. Bien que le principal groupe cible ait été constitué par les nouveau-nés et les jeunes enfants, on a également incité les adultes séronnégatifs à se faire vacciner.

Entre octobre 1985 et avril 1988, 68 845 femmes enceintes qui consultaient dans les dispensaires de santé maternelle et infantile de l'Etat ont été soumises au dépistage de l'HBV. Parmi elles, 2 432 (3,5%) étaient HBsAg-positives et 904 (1,3%) HBeAg-positives. Pratiquement tous les enfants nés de mères porteuses ont reçu l'ensemble des vaccinations prévues au calendrier. En outre, les enfants de femmes porteuses de l'HBeAg ont reçu à la naissance une dose d'immunoglobuline anti-hépatite B. Le programme a ensuite été élargi au 1er septembre 1987 pour couvrir tous les nouveau-nés par l'intermédiaire du Medisave fund, une sorte de sécurité sociale couvrant l'hospitalisation et certains traitements médicaux. Sur les 15 943 enfants nés dans les établissements nationaux entre septembre 1987 et avril 1988, environ 90% ont été vaccinés à la naissance contre l'hépatite B et ont reçu les doses ultérieures dans les dispensaires de santé maternelle et infantile.

On peut attribuer le succès de ce programme à l'importance du réseau des soins de santé, au fait que la vaccination anti-hépatite B s'est faite dans le cadre du programme de vaccination infantile, à la vaste campagne publicitaire lancée sur les dangers de cette maladie et la nécessité de la vaccination, ainsi qu'à l'utilisation des fonds du Medisave pour couvrir le coût de l'opération.

Plus de 85% des enfants vaccinés présentaient encore des anticorps protecteurs au bout de deux ans. On suit de très près ce programme de façon à pouvoir évaluer la durée de l'immunité, la nécessité d'administrer des doses de rappel, et on espère qu'il permettra un jour ou l'autre d'éradiquer le cancer primitif du foie à Singapour.

References


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