

Prevention and Control of Hepatitis B Virus Infection in Singapore

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Abstract

Hepatitis B virus (HBV) accounted for 24% to 54% of the reported acute viral hepatitis cases in Singapore from 1982 to 1996. The prevalence of HBV infection, as indicated by the presence of markers of HBV, increased from 9.3% in children below 5 years of age to 54.6% in adults above 55 years. The overall hepatitis B surface antigen (HBsAg) prevalence was 5.7% for males and 3.4% for females, with the highest rate among the Chinese. About 39% of the HBsAg carriers were hepatitis B 'e' antigen positive. The main mode of transmission during the first year of life was perinatal, with 43% of the babies born to HBsAg-positive mothers developing the carrier state. Horizontal transmission within the infected household was significantly associated with sharing of personal and household articles. Based on the findings of seroprevalence surveys in various population groups and clinical trials on the safety, immunogenicity and efficacy of various doses and schedules with the plasma-based and yeast-derived hepatitis B vaccines in newborn babies, a national childhood hepatitis B vaccination programme was formulated and implemented in phases, starting with babies born to carrier mothers on 1 October 1985 and finally extending to all newborns on 1 September 1987. The hepatitis B prevention and control programme has been successful. During the period 1994 to 1996, more than 90% of children completed the full schedule of immunisation by below one year of age, and 85% had evidence of vaccination at school entry at age six. Follow-up of 2 cohorts of vaccinated children showed that perinatal transmission has been reduced by 80% to 100%. Horizontal transmission has also declined through other public health measures. The efficacy of the hepatitis B vaccine and the adequacy of reduced doses in the long-term protection of chronic carrier state have been shown in children and adults. The incidence of acute hepatitis B has declined from 10.4 per 100 000 in 1985 to 4.8 per 100 000 in 1996. There is a noticeable reduction in HBsAg prevalence in selected population (school children, national servicemen and antenatal women). The age-standardised incidence rate of primary liver cancer among males had also dropped from 27.8 per 100 000 per year during 1978 to 1982 to 19.0 per 100 000 per year during 1988 to 1992.

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Introduction

Hepatitis B virus (HBV) infection was a major public health problem in Singapore.* It was estimated that there were about 120 000 hepatitis B surface antigen (HBsAg) carriers.² The carrier state is closely associated with the subsequent development of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma.³ Cancer of the liver was the third commonest cancer for males in Singapore and its incidence was highest among Chinese males above 40 years of age.^{4,5} The incidence of liver cancer among carriers in this group was estimated to be 613 per 100 000 per year compared with 22.9 per 100 000 per year for non-carriers, giving a relative risk of 26.8.⁶ The direct cost of treating patients in government hospitals for acute viral hepatitis, chronic hepatitis, liver cirrhosis and primary liver cancer was \$3.1 million in 1984. This did not include cases treated by doctors in private hospitals, outpatient clinics or the intangible economic loss of workdays and premature deaths, and the emotional impact on patients and families. The large pool of carri-

ers has serious implications for the blood bank, as a relatively high proportion of the voluntary blood donors has to be rejected and additional cost is required in implementing the screening programme to prevent post-transfusion hepatitis B.

Before specific control measures could be formulated and implemented to reduce the hepatitis B problem, viral hepatitis was made a notifiable infectious disease by the Ministry of Health on 1 June 1976 and epidemiological investigations were routinely conducted for each notified case by the Quarantine & Epidemiology Department, Ministry of the Environment, to elucidate the mode of transmission and source of infection. A Scientific Committee on Hepatitis & Related Disorders and an Advisory Committee on Hepatitis & Related Disorders were appointed by the Ministry of Health to undertake research and to provide guidance on the hepatitis B prevention and control programme. Seroepidemiological surveys were planned and conducted to determine the actual extent of HBV infection in various population

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groups. Research on the modes of transmission of HBV infection was also carried out. When hepatitis B vaccine became commercially available, clinical trials were designed and conducted to determine the optimal schedule and dosage for the hepatitis B vaccination programme. Surveillance data collected, collated and analysed over the last two decades provided the basis for evaluating the efficacy of specific prevention and control programme against hepatitis B.

Epidemiology of Acute Hepatitis B

Hepatitis B, defined as a physician-diagnosed case of acute viral hepatitis with a compatible clinical history, raised serum transaminase levels and presence of HBsAg in the serum, constituted between 24% and 54% of the total viral hepatitis cases notified. The mean annual incidence rate for the period 1977 to 1985 was 8.2 per 100 000 population and the case-fatality rate, 2.2%.⁷ Of the reported cases, 11.2% were imported, mainly from Southeast Asia. The morbidity rate was highest in the 25 to 34 age group. There was a male predominance with a male to female ratio of 4.6:1. The case-fatality rate was high in children below 5 years of age and in adults above 55 years. The ethnic-specific morbidity rate of the Chinese and Indians was significantly higher than that of the Malays.

Acute hepatitis B was significantly associated with exposure to various parenteral procedures. Several small localised outbreaks with two or more cases traced to a common source had been identified. The vehicles of transmission included contaminated syringes and tattoo needles.⁸ However, more than two-thirds of the reported cases had no known history of exposure to any percutaneous procedure. They must have acquired the infection through close contact with the large pool of carriers via non-parenteral or inapparent parenteral routes.

Based on a study conducted on 71 acute cases, all confirmed by the presence of IgM antibody to hepatitis B core antigen (anti-HBc), admitted to the Communicable Disease Centre, it was found that 9.9% remained HBsAg positive when tested six months later. Although the finding cannot be conclusive, as anti-HBc IgM may also be seen in chronic active hepatitis, the rate is similar to the 5% to 10% carrier rate following an acute infection reported in other studies.⁹

Seroepidemiology of HBV Infection

The prevalence of HBsAg and HBV infection (any HBV marker positive) in various population groups is shown in Table I. The high-risk groups are family contacts of chronic hepatitis B carriers¹⁰ multiple-transfused patients,¹¹ male and female prostitutes,^{12,13} the mentally handicapped,^{14,15} drug addicts and prisoners. The prevalence of health care workers was similar to that of the

general population¹⁶ (comprising school children,^{17,18} children in welfare homes,¹⁹ national servicemen, pre-clinical medical and dental students, home contacts of acute hepatitis A cases and office workers). However, further analyses of the data showed that the age-specific prevalence of HBV infection of doctors and dentists was higher than that of other categories of health care personnel. In dental personnel, dentists had a significantly higher HBsAg and anti-HBc prevalence (11.4% and 45.6%, respectively) than other categories of dental personnel (3.1% and 25.7%, respectively). The higher anti-HBc prevalence in all age groups of dentists compared with other categories of dental personnel suggests that they had a greater occupational risk of acquiring HBV infection.²⁰

In the general population, the prevalence of HBV infection increased from 9.3% in children below 5 years of age to 10.9% in the 5 to 14 age group, 22.7% to 24.6% in the 15 to 34 age group, 40.5% to 44.6% in the 35 to 54 age group and 54.6% in the 55+ age group (Fig. 1). The overall prevalence of HBsAg among males and females was 5.7% and 3.4%, respectively, and the corresponding HBV prevalence, 26.7% and 17.3%, respectively. For all age groups, males had a higher prevalence of HBsAg positivity and HBV infection rate than females. The HBsAg prevalence increased with age from 3.1% in children below 5 years of age to reach a peak of 6.3% in the 35 to 44 age group and thereafter declined. The HBsAg positivity rate for healthy children was one-third of that reported in a survey on children admitted to a paediatric unit for non-liver conditions.^{21,22}

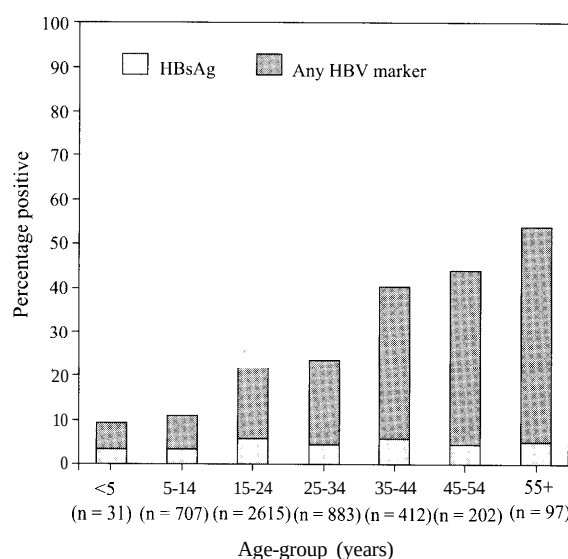


Fig. 1. Age-specific prevalence of HBsAg and HBV infection in the general population * in Singapore.

* Comprising school children, children in welfare homes, national servicemen, pre-clinical medical and dental students, home contacts of acute hepatitis A cases and office workers.

TABLE 1: SEROPREVALENCE OF HBV INFECTION IN VARIOUS POPULATION GROUPS IN SINGAPORE, 1978 TO 1992

Population group (Year of survey)	No. tested	Prevalence (%)	
		HBsAg	Any HBV marker
Babies born to carrier mothers followed up for one year (1980 to 1981)	56	42.9	46.4
Siblings of babies born to HBeAg+ve/HBeAg+ve carrier mothers (1983 to 1985)	192	74.4	92.7
Siblings of babies born to HBsAg+ve/HBeAg+ve carrier mothers (1983 to 1985)	195	6.7	22.1
Spouses of HBsAg+ve/HBeAg+ve carrier women (1983 to 1985)	51	15.7	58.8
Spouses of HBsAg+ve/HBeAg+ve carrier women (1983 to 1985)	51	7.8	37.3
Antenatal women (1983 to 1985)	32 375	4.1	
Family contacts of chronic hepatitis B carriers (1978 to 1983)	358	38.0	74.6
Family contacts of acute hepatitis B cases (1982 to 1983)	369	8.1	40.7
Family contacts of acute hepatitis A cases (1985)	88	6.8	43.2
First time blood donors (1985 to 1986)	3342	3.9	
Chinese men above 35 years of age ²⁷ (1979 to 1984)	8829	10.0	
Outpatients requesting for hepatitis B vaccination ⁸⁶ (1988 to 1989)	1600	4.8	17.3
Paediatric patients below 12 years of age ²¹ (1981)	458	10.9	27.3
Health care personnel (1983)	2536	4.3	28.3
Dental surgeons (1985)	114	11.4	45.6
Other categories of dental personnel (1985)	579	3.1	25.7
Pre-clinical medical and dental students (1985)	654	4.0	17.1
National servicemen (1984)	1172	7.9	26.9
Office workers (1987)	906	4.1	36.0
School children (1987)	642	3.3	12.6
Children in welfare homes (1983 to 1986)	583	5.0	19.4
Intellectually disabled school children (1992)	339	2.7	15.9
Mentally handicapped males (1987)	330	14.5	79.7
Male drug addicts (1984)	200	8.0	62.0
Male prisoners (1987)	207	7.2	54.1
Male juvenile delinquents (1985)	68	13.2	27.9
Male prostitutes ⁷ (1982)	121	14.9	88.4
Female prostitutes ^{7*} (1982)	239	6.3	64.0
Patients with sexually-transmitted disease (1990 to 1992)	497	6.2	41.2
HIV-infected persons (1990 to 1992)	47	8.5	61.7
Multiple-transfused patients ¹¹ (1984)	70	13.0	74.0
Patients with systemic lupus erythematosus ⁸⁷ (1992)	76	1.3	19.7

Sera were analysed for HBV markers by enzyme immunoassay or radioimmunoassay.

Among the three major ethnic groups, the frequencies of antibody to hepatitis B surface antigen (anti-HBs) were of the same order (Chinese 27.8%, Malays 22.3% and Indians 20.6%), but the prevalence of HBs antigenaemia was significantly higher among the Chinese (6.9%) than the non-Chinese (1.5%) ($P < 0.000001$). It has been suggested that this is due to differences in immunological responsiveness to HBsAg which is genetically determined.^{23,24} No sex and ethnic difference in HBsAg prevalence was observed among family contacts of chronic hepatitis B carriers as HBV infection was acquired at an early age when the probability of developing the carrier state is very high,²⁵ irrespective of sex and ethnic group.

Among different groups of the general population surveyed, the age-specific HBV prevalence varied considerably from 17.1% for pre-clinical medical and dental students to 26.9% for national service recruits. This is probably due to differences in socio-economic back-

ground of the various groups surveyed.²⁶ Most of the drug addicts and prisoners had low educational level and were probably exposed to HBV prior to incarceration. The HBsAg prevalence among Chinese male adults has been shown to be associated with socio-economic status with a lower rate among the professional, technical and administrative personnel compared with other occupational groups.²⁷

Familial clustering of HBsAg carriers²⁸⁻³¹ was marked among home contacts of patients with HBsAg-positive hepatocellular carcinoma and chronic hepatitis B. The prevalence of HBsAg of these family contacts (38%) was significantly higher than those of acute hepatitis B (8.1%) ($P < 0.000001$). It was particularly high in children of HBsAg-positive mothers (42.9%).³² Most of the infected family members were probably unable to eliminate HBsAg by mounting an immunological response with the production of anti-HBs, until after 25 years of age when the anti-HBs prevalence almost doubled from

17.1% to 23.5% in the 1 to 24 age group to 36.4% to 71.4% in the 25 to 55+ age group.

The main determinant for HBV transmission is the presence of HBeAg. It is a reliable indicator of infectivity as it is closely associated with the presence of Dane's particles and DNA polymerase activity.^{29,33} About 39% of the HBsAg carriers in the general population were HBeAg positive. The HBsAg prevalence rate in children of HBeAg-positive mothers was 74.4% compared to 6.7% when the mother was HBeAg negative. Moreover, HBeAg was detected in a significantly higher proportion of HBsAg-positive children whose mothers were HBeAg-positive (90.9%) compared to those of HBeAg-negative mothers (53.8%) ($P < 0.000001$). The prevalence of HBeAg among HBsAg-positive persons remained consistently high in early childhood (88.3%) and persisted until early adolescence (73.3%). It subsequently declined to 47.7% in the late teens and 34.9% in young adulthood. For those above 45 years of age, 11.5% were HBeAg positive (Fig. 2). This pattern has also been observed in other countries³⁴⁻³⁶ where a steadily increasing proportion of the HBsAg carriers clear HBeAg with the development of anti-HBe.³⁷ It has been estimated that the mean annual clearance rate of HBeAg was 9.6%.³⁸ No significant difference in the prevalence of HBeAg among HBsAg-positive persons was observed between males and females and between Chinese and non-Chinese.

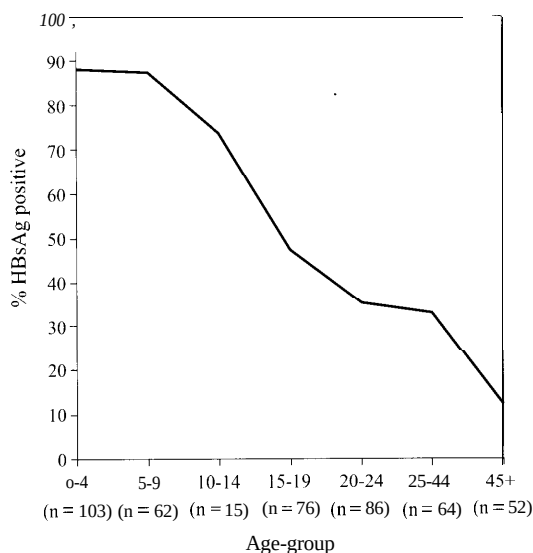


Fig. 2. Prevalence of HBeAg by age among HBsAg-positive persons in Singapore

Prolonged contact with highly infectious carriers either in a family or in an institution will result in a high proportion of the susceptibles becoming infected.³⁹ The annual rate of asymptomatic acquisition of HBV infection among the susceptible home contacts in the families of acute hepatitis B cases (where 60% of the HBsAg-

positive persons were HBeAg positive) was 9%.³⁹ It was 29.4% for inmates in an institution for male delinquents (where 66.7% of the carriers were HBeAg positive). This is considerably higher than the 5% annual seroconversion rate reported for prostitutes.¹²

Modes of Transmission

Maternal-infant Transmission

In a study on maternal-infant transmission, HBsAg was detected in 24 (42.9%) of 56 babies born to HBsAg carrier mothers and followed up for 12 months.³² The median interval between delivery and time of first appearance of antigenaemia was 64 days. HBV transmission occurred in 22 (88%) of 25 babies born to HBeAg-positive mothers and in 2 (7.4%) of 27 born to mothers positive for antibody to hepatitis B e antigen (anti-HBe). None of the 4 babies born to mothers who were negative for HBeAg and anti-HBe were infected. Intrauterine infection occurred in 2 (8.3%) of 24 HBV transmission as indicated by the presence of HBsAg in cord blood, day-old blood and subsequent follow-up blood samples. No significant difference in HBV transmission was demonstrated between Chinese and non-Chinese, probably because of the small number of carriers in the non-Chinese ethnic group. There was also no difference in the frequency of transmission between male and female and between breast-fed and non-breast-fed babies. Transmission of HBV from carrier mothers to infants resulted in the development of chronic carrier state in 18 (78.3%) of 23 babies followed up at one year. In the other 5, the infants were able to mount an immunological response to eliminate the virus with production of anti-HBs.

Maternal-infant transmission provides a continuous source of HBV carriers in the country. Taking into consideration a 4.1% carrier rate for mothers, a 42.9% transmission rate and an average annual live births of 50 000, it was estimated that about 880 newborns become infected per year. Of these, 690 would become chronic carriers. Therefore, in one generation, more than 21000 carriers would be added to the existing large pool of carriers in the country. The carrier status may last for several years or for the lifetime of an individual.

Intrafamilial Transmission

Perinatal transmission could only account for about half of the HBsAg prevalence in one-year-old children. The majority of the infection must have been acquired horizontally from carriers within the same household. An epidemiological enquiry was conducted to determine the route and vehicle of spread from person to person in 369 home contacts of 80 acute cases of hepatitis B.³⁹ It was found that sharing of various personal and household items between infected family members and acute cases was significantly associated with HBV trans-

mission. These items included toothbrush, towel, handkerchief, clothing, razor and comb. Sharing of bed and bedding was also a risk factor, but sleeping in the same bedroom, eating together at meals and sharing of eating and drinking utensils were not associated with an increased risk of transmission of infection. The prevalence of infection of the spouses (72.7%) was not significantly higher than that of the parents (61.7%) of acute cases.

Sexual Transmission

To determine the role of sexual transmission of HBV infection,⁴⁰⁻⁴³ a cross-sectional study of 497 male patients presenting with a new episode of sexually-transmitted diseases at a government outpatient clinic was undertaken. The overall seroprevalence of HBsAg and HBV infection was 6.2% and 41.2%, respectively, compared with 4.5% and 33.3%, respectively, for 418 healthy males aged 15 years and above (controls). Using stepwise logistic regression analysis, the adjusted seroprevalence of HBV infection was 2.4 times higher than in controls. Sex-related factors significantly associated with higher infection rates, independent of age and ethnic group, were reactive VDRL test (a routine blood test for syphilis), participation in anal intercourse and having 10 or more lifetime sexual partners. This study confirmed the importance of sexual transmission of HBV in Singapore.⁴⁴

Transmission by Mosquitoes

The risk of passive mechanical transmission of HBV via contaminated mouthparts of mosquitoes^{45,46} was of extremely low epidemiological significance. This was demonstrated in a study in which none of the 1540 adult female mosquitoes (including 720 recently fed with blood meals) comprising five genera; viz. *Aedes aegypti*, *Aedes albopictus*, *Culex quinquefasciatus*, *Culex tritaeniorhynchus* and *Culex gelidus*, caught in eight fixed *Aedes* monitoring stations in the urban and suburban areas, was found to be positive for HBsAg by radioimmunoassay at the WHO Immunology Research & Training Centre, Department of Microbiology, National University of Singapore.

Vaccine Trials

With the development of a safe and efficacious vaccine against hepatitis B,⁴⁷ an invaluable public health tool is available to break the chain of perinatal transmission by preventing the initial establishment of the carrier state^{48,49} and thus help to reduce the HBV reservoir in the country. However, when the plasma-based and the yeast-derived vaccines were first marketed, the cost was very high. Studies were therefore conducted to determine whether or not a dosage lower than that recommended by the manufacturer would be as immunogenic and efficacious as the standard dose.

In a clinical trial to assess the efficacy of plasma-based Merck Sharp & Dohme (MSD) vaccine in the prevention of perinatal transmission, babies born to 'e' Ag-positive or 'e' Ag-negative mothers were randomised into four subgroups to receive either the 5 µg reduced dose or the 10 µg standard dose administered by the intramuscular route at the anterolateral aspect of the thigh at birth, one month and two months.⁵⁰ Those born to 'e' Ag-positive mothers were also given hepatitis B immunoglobulin (HBIG) at birth. Venous blood was collected at 24 hours, 4 weeks, 8 weeks, 12 weeks, 6 months and 12 months. At the end of one-year follow-up, between 84% and 94% of the babies immunised developed anti-HBs, and there was no significant difference in the seroconversion rate and geometric mean titre (GMT) between the 5 µg and 10 µg dose. There was also no significant difference in the incidence of HBsAg between the 5 µg and 10 µg dose in babies born to 'e' Ag-positive carrier mothers. Based on the frequency of HBs antigenaemia in a historical control group, the vaccine efficacy for babies born to 'e' Ag-positive carrier mothers was 80% and ranged from 79.3% for the 10 µg dose to 80.9% for the 5 µg dose. However, if intra-uterine transmission were excluded, the efficacy was increased to 88% (89.9% for the 5 µg dose and 86.1% for the 10 µg dose). None of the babies born to 'e' Ag-negative carrier mothers developed HBsAg and the vaccine efficacy was 100%. The overall vaccine efficacy in the prevention of perinatal transmission was lower than the 91% to 94% protection reported in other clinical trials in which the 10 µg or 20 µg vaccine was used in the 0, 1, 6 schedule.^{48,51}

In an efficacy study with a reduced dosage (2.5 µg) of the MSD yeast-derived vaccine, 5 (13.2%) of 38 babies given the 2.5 µg dose at birth (together with HBIG), 1 month and 6 months became HBsAg positive at the end of one-year follow-up, including two who acquired the infection *in utero*. However, HBsAg was not detected in any of the babies vaccinated with the standard dose (5.0 µg). The vaccine efficacy was 83.7% for babies given the 2.5 µg dose and 100% for those immunised with the 5 µg dose. For babies born to HBeAg-negative carrier mothers, the 2.5 µg dose was as immunogenic and efficacious as the 5.0 µg dose in the prevention of perinatal transmission even without HBIG.⁵² None of them were positive for HBsAg.

In another clinical trial to evaluate the immunogenicity of four different dosages (0.6 µg, 1.25 µg, 2.5 µg and 5 µg) of MSD yeast-derived vaccine given at 0, 1 and 6 months to seronegative children 1 to 12 years of age, no significant difference in seroconversion rate and GMT was demonstrated.⁵³ Even the lowest dosage which is one-eighth of that recommended by the manufacturer, elicited excellent antibody response with peak GMT of >1000 mIU/ml recorded at 9 months. At 48-month follow-up, the GMT dropped to between 72.6 and 118.8

mIU/ml. All the vaccinees remained asymptomatic and free from HBV infection. Anti-HBc was not detected in any of the vaccinated children and there was no evidence of elevation of alanine amino transferase (ALT) levels.⁵⁴

In seronegative teenagers 12 to 18 years old, the sero-conversion rate and GMT of those given the 2.5 µg MSD yeast-derived vaccine were not significantly different from those given the 5.0 µg dose.⁵⁵ Similarly in seronegative adults, the 5 µg dose was as immunogenic as the 10 µg dose.^{56,57}

The findings of these clinical trials are of practical importance, since the use of a lower dosage without compromising its immunogenicity and efficacy would markedly reduce the cost of the vaccination programme.

Prevention and Control

Before the availability of hepatitis B vaccine, prevention and control were based entirely on sanitary precautions and personal health education to minimise horizontal transmission. These included routine screening of blood donors for HBsAg, sterilisation of medical and dental equipment, introduction of disposable needles and syringes in health care centres and surveillance of tattoo parlours and acupuncture clinics. Known cases and carriers were advised to practise good personal hygiene such as handwashing and proper handling or disposal of articles contaminated with blood and other body secretions. Household members of acute cases and carriers were educated to avoid the habits of sharing toothbrushes, towels, handkerchiefs, clothes, razors and combs.

The key to the prevention and control of HBV infection is vaccination, the aim of which is to protect an estimated 1.9 million susceptibles from being infected and thus help to reduce the large pool of carriers in the community.

The Hepatitis B Vaccination Programme

In the formulation of a hepatitis B vaccination programme, considerations were given to the findings of epidemiological studies on the modes of transmission of HBV infection, prevalence of HBV markers in various population groups and clinical trials on the safety, immunogenicity and efficacy of reduced dosages of the plasma-based and yeast-derived vaccines; adequacy of the existing laboratory services to undertake routine serological screening of HBV markers; cost-benefit analysis,⁵⁸ and existing health infrastructures in the implementation of the national childhood immunisation programmes.⁵⁹ As in other immunisation programmes, the main strategy of hepatitis B vaccination is to immunise 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 immunisation of all newborn infants. The reduction in incidence is less marked if immunisation is confined only to babies born to carrier mothers.^{60,61}

Because of the high cost of the vaccine, the programme was implemented in phases and targeted at the population groups with the greatest risk of acquiring hepatitis B. The programme started in mid-1983 with the immunisation of health care workers on a voluntary basis. Immunisation of babies born to carrier mothers was not started until 1 October 1985, when laboratory facilities for the routine screening of antenatal women for HBsAg became available. In order to break the perinatal and horizontal chain of transmission, on 1 September 1987, the programme was extended to include all newborns.⁶² The plasma-based vaccine was replaced by the yeast-derived vaccine. Routine screening of antenatal women is still necessary to enable HBIG to be administered to newborns of HBeAg carrier mothers.

A Hepatitis Control Unit was set up in the Quarantine & Epidemiology Department, Ministry of the Environment, to coordinate epidemiological surveillance and research, to evaluate the national immunisation programme and to monitor adverse post-immunisation reactions.

The coverage for infants who have completed three doses before one year of age increased from 49% in 1988 to 94% in 1995. Virtually all the babies born to carrier mothers were immunised.⁶³ Reported post-vaccination reactions were mild and included rash (67 per million doses), fever (18 per million doses) and abscess (9 per million doses).⁶⁴

Evaluation of Long-term Efficacy Of Hepatitis B Vaccination Programme in the Prevention Of Chronic HBsAg Carriage

To monitor the efficacy of the vaccination programme in the prevention of HBsAg carriage, two cohorts of children and two cohorts of seronegative adults were followed up for a duration of 6 to 12 years. In addition, two serological surveys were conducted to determine the prevalence of HBsAg among vaccinated and unvaccinated population groups.

Children Vaccinated with Plasma-based Vaccine

The cohort of children born to HBsAg carrier mothers and vaccinated with the plasma-based vaccine at birth (together with HBIG if maternal sera were HBeAg positive), 1 month and 2 months was followed up at 2 years, 4 years, 6 years and 8 years. Anti-HBs was detected in 170 (85.9%) of 198 children born to HBeAg carrier mothers at 1 year, 156 (82.5%) of 189 at 2 years, 143 (89.4%) of 160 at 4 years, 155 (73.5%) of 211 at 6 years, and 121 (56.5%) of 214 at 8 years. However, no carriers were detected at 4- and 8-year follow-up, even among those found to be anti-HBs negative. The GMT dropped from

between 129.4 and 168.4 mIU/ml at 1 year to between 58.0 and 78.8 mIU/ml at 4 years and to between 29.4 and 30.9 mIU/ml at 8 years. No significant difference in seroconversion rate and GMT was noted between the 5 µg and 10 µg dose. The frequency of HBsAg positivity in vaccinated and unvaccinated children born to 'e' Ag-positive carrier mothers is shown in Figure 3. Virtually all of these children acquired HBsAg during the first year of life. Molecular epidemiological studies showed that 16 (39%) of 41 breakthrough perinatal infections resulted from HBV vaccine variants, the most frequent was a virus in which a single amino acid substitution glycine to arginine occurred at amino acid position 145 of the outer protein coat of the virus.⁶⁵⁻⁶⁷

When the non-responders were revaccinated with a course of hepatitis B vaccine at 4-year follow-up, all of them seroconverted, the majority with an anamnestic reaction.⁶⁸ For the responders, whose anti-HBs levels had dropped to a low level, administering a booster dose also elicited a sharp secondary antibody response (GMT increased by 16 to 67 times).⁶⁹ For those given a booster for the first time at 8 years, there was again a sharp anamnestic reaction, with the GMT raised by 15 times.⁷⁰ These phenomena indicate that once an immune response has been induced, it can be restimulated by exposure to the wild virus with active increase in anti-HBs during the early phase of the incubation period of the disease, thereby protecting against clinical illness or development of the carrier state.⁷¹

Children Vaccinated with Yeast-derived Vaccine

The cohort of children born to HBsAg carrier mothers and vaccinated with the yeast-derived vaccine at birth (together with HBIG if maternal sera were positive), 1 month and 6 months was followed up at 2 years, 4 years and 6 years. All the babies born to HBeAg-negative carrier mothers and vaccinated with either 2.5 µg or 5.0 µg dose did not develop the persistent HBsAg carrier state, although transient HBs antigenaemia was detected in 5 babies given the 2.5 µg dose. In the HBeAg-positive group, 5 babies vaccinated with the 2.5 µg dose and one vaccinated with the 5.0 µg dose were found to be persistently HBsAg positive at the end of 6-year follow-up. Two were due to intrauterine infection as HBsAg was detected since birth. Molecular epidemiological studies confirmed that in two others, the infection was caused by antibody escape mutants of HBV. The potential variants of the remaining two HBsAg-positive children were not sequenced.⁶⁵ No significant difference in seroconversion rate, GMT and prevalence of anti-HBc was noted between the 2.5 µg and 5.0 µg groups throughout the duration of follow-up. The GMT dropped from a peak of between 165.3 and 352.7 mIU/ml at nine months to 32.5 and 66.6 mIU/ml at 6-year follow-up. A booster dose of vaccine given to children at 6 years of

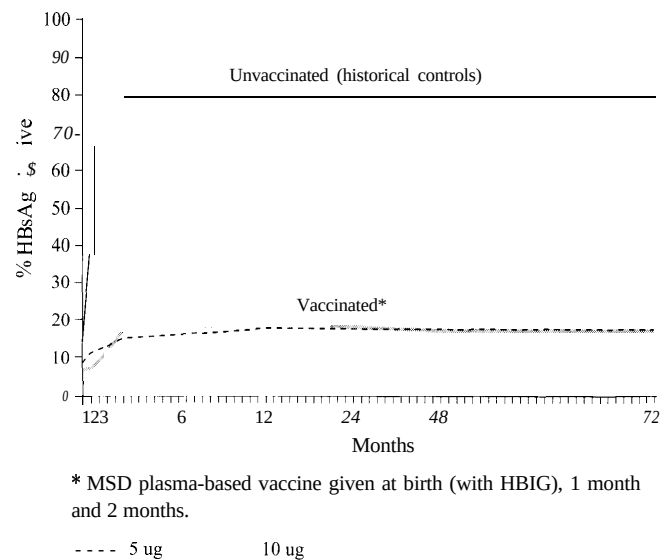


Fig. 3. Frequency of HBsAg positivity in vaccinated and unvaccinated babies born to HBsAg+/HBeAg+ carrier mothers and followed up for 72 months.

age, including those with no detectable anti-HBs, resulted in a sharp anamnestic response with titres as high as 23 000 mIU/ml. Anti-HBc was detected in 14.9% to 25% of the vaccinees in the HBeAg-positive group and in 3.7% to 7.5% of those in the HBeAg-negative group at the end of the follow-up period.⁷²

National Servicemen Vaccinated with Plasma-based Vaccine

To determine the duration of protection against HBsAg carrier state and the persistence of anti-HBs in adults, a cohort of 293 seronegative national servicemen vaccinated with a reduced dosage (10 µg) of MSD plasma-based vaccine at 0, 1 and 6 months were followed up for 12 years. At the end of the follow-up period, 76.3% still possessed anti-HBs; 55% with titres ≥ 10 mIU/ml. The GMT dropped from 80.7 mIU/ml at one year to 24.8 mIU/ml at 12 years. Anti-HBc was detected in 0.9%, 1.4%, 2.7%, 2.0% and 3.4% of the vaccinees at 1, 2, 4, 6 and 12 years, respectively. Transient HBs antigenaemia was noted in 2 vaccinees at 4-year follow-up. Another cohort of seronegative national servicemen who declined to be vaccinated was also screened for HBV markers at 6 years. Eight (4.2%) of 191 unvaccinated national servicemen became HBsAg positive compared with none of 196 vaccinees at 6-year follow-up. The vaccine efficacy in the prevention of HBsAg carriage was 100%.⁷³

Pre-clinical Medical and Dental Students Vaccinated with Plasma-based Vaccine

A cohort of 240 seronegative pre-clinical medical and dental students vaccinated with 10 µg MSD plasma-based vaccine at 0, 1 and 6 months were followed up for 5 years. The GMT dropped from 412.6 mIU/ml at one year to 174.9 mIU/ml at 5 years. However, all of them

continued to be negative for HBsAg throughout the duration of follow-up at 1 year, 2 years, 3 years and 5 years, even among those with no detectable anti-HBs. The prevalence of anti-HBs and anti-HBc was 93% and 1.0%, respectively, at 5-year follow-up.⁷³

Seroprevalence Surveys on HBV Markers in the General Population

In 1987, a sample of 285 children 1 to 2 years of age vaccinated with the full schedule of plasma-based vaccine at birth (together with HBIG if maternal sera were positive), 1 month and 2 months were tested for HBV markers. HBsAg, anti-HBs and anti-HBc were detected in 3%, 88% and 4%, respectively, of the vaccinees. HBsAg was only detected in children whose mothers were HBeAg positive. The immunogenicity and efficacy of the vaccine were similar to the findings of the clinical trial and comparable to the mass immunisation programme in Taiwan where an efficacy of 80% was reported 18 months after vaccination.⁷⁴

In a national serological survey conducted in 1993, based on blood samples collected from 878 healthy children and adults from six months to more than 45 years of age, HBsAg was detected in 17 (5.6%) of 303 unvaccinated persons and in 2 (0.3%) of 575 vaccinated persons, giving an overall efficacy of 76.8%. However, both HBsAg-positive vaccinees were over 45 years of age and not serologically tested prior to vaccination (Fig. 4).⁷⁵

These follow-up studies have conclusively demonstrated that both plasma-based and yeast-derived hepatitis B vaccines, even when administered with a reduced dosage, protected both children and adults against acute and chronic hepatitis.⁷⁶ The persistence of immunological memory was well demonstrated in children when a booster dose resulted in a sharp anamnestic response. Low or undetectable levels of circulating anti-HBs may not necessarily indicate loss of protection, as it has been shown that protection persists even when humoral antibody is no longer detectable.⁷⁷ Although HBV infection, as indicated by anti-HBc positivity and transient HBs antigenaemia, could occur with falling vaccine-induced antibody titre below 10 mIU/ml, the vaccinees were protected against clinical hepatitis and HBsAg carrier state. The maintenance of an immune response to HBsAg suggests that administering a booster dose may not normally be necessary for vaccinees who have responded to the full schedule of immunisation, for at least 12 years after vaccination.

Discussion

The hepatitis B surveillance programme in Singapore is now well established. Virtually all reported acute cases of hepatitis B are serologically confirmed by the presence of IgM anti-HBc and every notified case inves-

tigated. The annual incidence has been declining from 291 cases (10.8 per 100 000) in 1989 to 146 cases (4.8 per 100 000) in 1996. Various measures taken to prevent horizontal transmission appeared to be effective. Since routine screening of voluntary blood donors for HBsAg was implemented in 1973, the incidence of post-transfusion hepatitis B was reduced from 13 to 23 cases per year to fewer than one per year.⁷⁸ The introduction of disposable needles and syringes in health care institutions has brought about a significant decline in the transmission of acute hepatitis B associated with parenteral exposure, from 62.1% in 1977 to 21.9% in 1996 and tattoo-associated outbreaks have been virtually eliminated. However, surveillance into other less apparent parenteral modes of transmission has been stepped up, as recent epidemiological investigations showed that acute hepatitis B was also significantly associated with exposure to contaminated razors in barber shops and hairdressing salons.

The national childhood hepatitis B immunisation programme has been successfully implemented. The main thrust is universal immunisation of all newborns to prevent both perinatal and horizontal transmission. The success of the programme is attributed to its integration into the existing childhood immunisation programme, wide publicity on the importance of HBV infection⁷⁹ and use of Medisave funds for payment of hepatitis B vaccination. The cost of the vaccine is kept low through bulk purchase and whenever possible, use of a reduced dosage without compromising for its immunogenicity and efficacy. Despite the emergence of antibody escape variant of HBV, there was no evidence of horizontal transmission,⁸⁰ and current hepatitis B vaccines remain highly efficacious. The efficacy of hepatitis B vaccine in the prevention of HBsAg carriage among vaccinated children and adults was confirmed by the 1993 national serological survey.

There are indications that the prevalence of HBsAg in the general population has been declining. In 1972, the prevalence by counterimmuno-electrophoresis was 5.7% in Chinese children 5 to 9 years of age and 8.5% in Chinese adults; the corresponding figures (by enzyme immunoassay) in 1987 was 3.4% and 6.2%, respectively. The overall HBsAg positivity among voluntary blood donors in 1975 was 9.1% by the reverse passive haemagglutination method,⁸¹ with a prevalence of 13.6% for Chinese, 7.3% for Malays and 6.0% for Indians.⁸² The corresponding figures (by enzyme immunoassay) in 1986 were 3.9%, 4.6%, 1.6% and 0.9%, respectively. The prevalence in national servicemen has also declined from 8.1% in 1984 to 4.4% in 1988. Among antenatal women, the overall HBsAg prevalence was 4.4% in the period 1980 to 1981, 4.1% in the period 1983 to 1985, and 2.9% in 1996.

In primary school children, the HBsAg prevalence

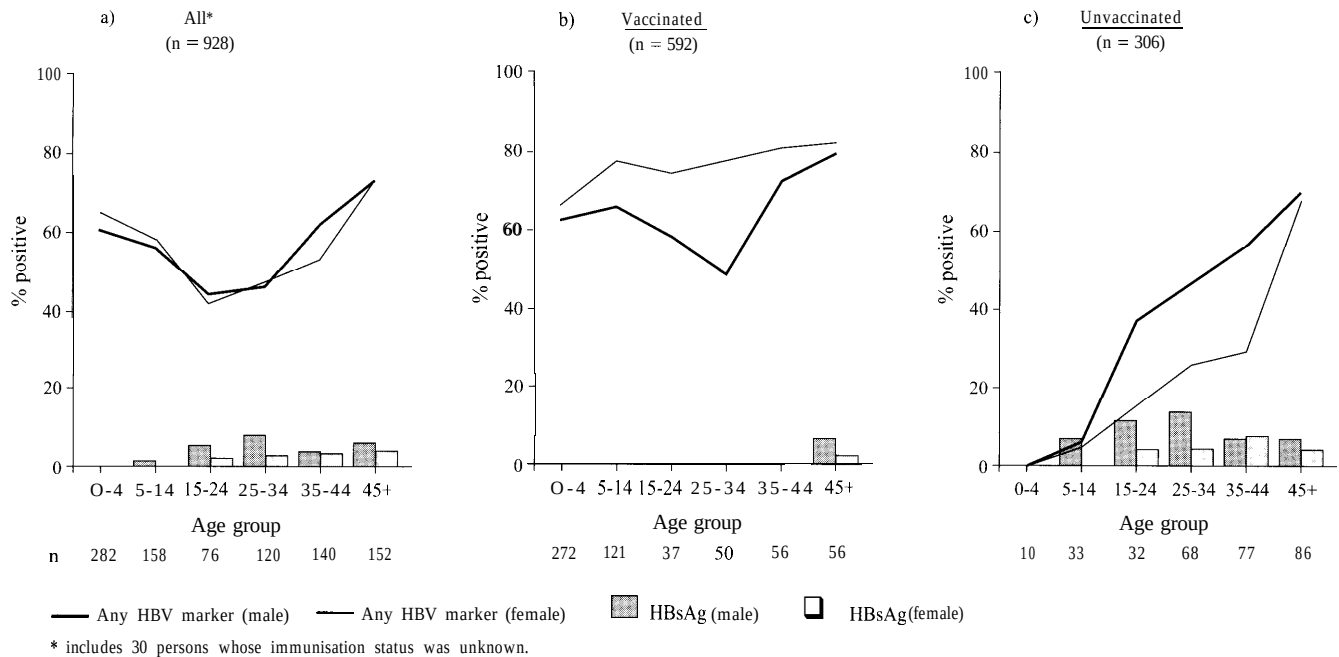


Fig. 4. Age-sex-specific seroprevalence of HBV infection in healthy children and adults in Singapore, 1993.

was 4% in 1987, but a cohort of 672 primary one school students followed up from 1994 to 1996 were found to be negative for HBsAg.⁸³ The age-standardised incidence rate of primary liver cancer among males had also dropped from 27.8 per 100 000 per year during the period 1978 to 1982 to 19.0 per 100 000 per year during the period 1988 to 1992.⁸⁴ However, it should be pointed out that the decline in HBsAg prevalence and primary liver cancer incidence in the adult population has already occurred prior to the implementation of the national childhood hepatitis B immunisation programme.

There are still gaps in the understanding of the epidemiology of HBV infection in Singapore. For example, although all the major ethnic groups were equally exposed to HBV (as indicated by anti-HBs positivity), the HBsAg prevalence of the Chinese was significantly higher than that of the non-Chinese. The ethnic-specific prevalence of HBeAg among HBsAg-positive antenatal women was similar, and there was no significant difference in the frequency of perinatal transmission between the Chinese and non-Chinese. The rate of development of the carrier state following an acute infection with HBV was also similar among the ethnic groups. It is also not known why the delta antigen is extremely uncommon among the carriers in Singapore,⁸⁵ including intravenous drug addicts and the sexually promiscuous.

The achievements that have been made in the prevention and control of HBV infection in Singapore should be consolidated and maintained. More cost-effective strategies for prevention and control should also be ex-

plored. As hepatitis B is a sexually-transmitted disease and the age-specific morbidity rate is highest in the 15 to 34 age group, the national childhood immunisation programme against hepatitis B should be extended to teenagers and young adults as well as other population groups whose lifestyles expose them to high risk of acquiring HBV infection. The molecular epidemiology of vaccine-induced escape mutants of HBV and its public health implications should be closely monitored and evaluated through periodic serological surveys.

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