

# Hepatitis B Seroprevalence Study 1999

L James, C W Fong, B H Foong, M K Wee, A Chow, E Shum, S K Chew

## ABSTRACT

Hepatitis B is a disease of public health importance in Singapore. A study was conducted in 1999 to estimate the overall and gender-, age- and ethnic-specific prevalence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and antibody to hepatitis B surface antigen in the Singapore population. A cross-sectional sample of the Singapore population constituting 4,698 Singapore residents aged 18-69 years was surveyed. This was the first time a large-scale study has been conducted to assess the hepatitis B seroprevalence rates in the Singapore population. The overall prevalence of the HBsAg in the general population was estimated to be about 4%. About 13% of the HBsAg carriers were also HBeAg positive. Only about 40% of the population had immunity to hepatitis B virus either through immunisation or from previous exposure to the virus. There was still a large proportion (60%) of the population who had no immunity, especially the younger age group of 18-29 years where only 28% had immunity. There is a need to strengthen the hepatitis B immunisation programme to reach out to those who have no immunity, especially the young adults.

**Keywords:** Hepatitis B, Seroprevalence, Control, Immunisation, Singapore

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## INTRODUCTION

Hepatitis B is an important health problem in both developed and developing countries. In developed countries, where most of the major communicable diseases have been successfully controlled, hepatitis B continues to cause considerable morbidity and mortality, and therefore has become one of the priority public health problems in these countries. In developing countries the prevalence is much higher and its health impact even greater.

About 50-80% of persons with hepatitis B virus (HBV) infections are asymptomatic or may present

with mild flu-like symptoms. The majority of patients with HBV infection can expect full recovery. The hepatitis B surface antigen (HBsAg) is present during the acute phase and normally disappears during convalescence. In some patients, however, the antigen persists. The persistence of HBsAg in the serum for more than six months is an indicator of chronic carrier state. The carrier state in hepatitis B is established in about 5-10% of infected adults<sup>(1)</sup>. The carrier state is closely associated with subsequent development of chronic illness, such as chronic hepatitis, cirrhosis and sometimes primary liver cancer (e.g. 15 in 1,000 chronic infections)<sup>(2)</sup>.

Carriers appear to be the most dangerous source of infection. There is a large pool of chronic carriers in the world, the prevalence varying from 0.1% in developed countries (Europe, America, Australia) to 15% of the population in developing countries<sup>(3)</sup>. In the developed countries, HBsAg is most often found in the 20-40 years age group; in the developing countries, in children of the 4-8 years age group<sup>(3)</sup>. Carrier state among the young has been found to be more infectious than among adults<sup>(1)</sup>.

The hepatitis B e antigen (HBeAg) is detected in a relatively small proportion of HBsAg positive sera. Possession of the e antigen appears to be associated with a worse prognosis with regard to liver disease. It is a reliable indicator of infectivity and the presence of HBeAg is in fact the main determinate of HBV transmission. HBeAg is found more often in young than in adult carriers.

## HEPATITIS B VIRUS CONTROL PROGRAMME IN SINGAPORE

The public health importance of viral hepatitis in Singapore has been recognised and viral hepatitis was made a legally notifiable disease by the Ministry of Health under the Infectious Diseases Act on 1 June 1976<sup>(4)</sup>. Being of high public health and economic importance, effective control measures have been implemented.

The HBV Control Programme includes surveillance, hepatitis B immunisation, introduction of

**Communicable Diseases Branch  
Epidemiology and Disease Control Division  
Ministry of Health  
College of Medicine Building  
16 College Road  
Singapore 169854**

L James, MBBS,  
MMed (Public Health)  
Deputy Director

**Biostatistics and Research Branch  
Epidemiology and Disease Control Division  
Ministry of Health**

C W Fong, BSc (Hons)  
Manager, Health Statistics

B H Foong, BA  
Data Manager

**Epidemiology and Disease Control Division  
Ministry of Health**

M K Wee, MBBS,  
MMed (Public Health)  
Assistant Director

A Chow, MBBS,  
MMed (Public Health)  
Assistant Director

E Shum, MBBS  
Medical Officer

S K Chew, MBBS,  
MSc (Public Health),  
DLSHTM (UK), MSc  
Epidemiology,  
FAMS  
Director

**Correspondence to:**  
Dr L James  
Tel: (65) 325 9169  
Fax: (65) 325 9194  
Email: Lyn\_JAMES@moh.gov.sg

disposable needles and syringes in health care institutions, universal precautions, public education and routine screening of voluntary blood donors for HBsAg carriers.

#### HEPATITIS B IMMUNISATION PROGRAMME IN SINGAPORE

The key component in the HBV Control Programme is the Hepatitis B Immunisation Programme, which was first introduced in mid-1983 with the voluntary immunisation of high-risk groups such as health care workers. A mass immunisation programme against hepatitis B for babies born to HBsAg carrier mothers was incorporated into the National Childhood Immunisation Programme on 1 October 1985, when laboratory facilities for the routine screening of antenatal women for HBsAg became available<sup>(5)</sup>. Hepatitis B vaccination was subsequently extended on 1 September 1987 to cover all newborns<sup>(5)</sup>. Older children and adults were also encouraged to be immunised.

With the incorporation of the Hepatitis B vaccination into the National Childhood Immunisation Programme, good coverage of infants completing the full three-dose course of hepatitis B immunisation before one year of age has been achieved. The coverage for infants who have completed three doses before one year of age increased from 50% in 1988 to 91% in 1994<sup>(6)</sup>. From 1994 to 1999, the coverage has been maintained at above 90%<sup>(6)</sup>.

#### HBV INFECTIONS IN SINGAPORE

The comprehensive HBV Control Programme that has been put in place has contributed to the reduction of both horizontal and perinatal transmission of HBV in Singapore. The annual incidence of acute HBV infection has declined from 10.4 cases per 100,000 population in 1985<sup>(7)</sup> to 4.4 per 100,000 population in 1999<sup>(8)</sup>. A total of 140 cases of acute hepatitis B was reported during the year 1999<sup>(8)</sup>. The incidence of acute hepatitis B in children less than 15 years of age has declined from 1.44 per 100,000 in 1983-1985 to 0.14 per 100,000 in 1995-1997<sup>(9)</sup>.

The monitoring of rates for liver cancer constitutes an important part of the hepatitis B surveillance system. Overall, incidence rates showed a decline in both males and females. The age-standardised incidence rate of primary liver cancer among males has dropped from 27.8 per 100,000 per year during 1978 - 1982<sup>(10)</sup> to 18.9 per 100,000 per year during 1993-1997<sup>(11)</sup>, dropping in ranking from the third to the fourth commonest cancer for males in Singapore. The incidence rate of primary liver cancer during 1993-1997 was highest in Chinese males (21.6 per 100,000) followed by Malay males (15.5 per 100,000) and Indian males (7.0 per 100,000)<sup>(11)</sup>.

#### HEPATITIS B SEROPREVALENCE IN SINGAPORE HBsAg

Several seroprevalence surveys for HBV infection conducted locally on various population groups show that carrier rates vary in different population groups. For studies conducted between 1978 and 1992, the overall HBsAg prevalence in the general population was estimated to be about 5%<sup>(5)</sup>. Among the males, the hepatitis B carrier rate was 5.7% and among the females it was about 3.4%<sup>(5)</sup>. In another seroprevalence survey conducted in 1992, which had a high representation of young subjects (aged 0-14 years old), the hepatitis B carrier rate was estimated to be about 2.2%<sup>(12)</sup>.

Studies conducted between 1978 and 1992, showed that the HBsAg prevalence increased with age from 3.1% in children below five years of age to reach a peak of 6.3% in the 35 to 44 age group and thereafter declined<sup>(5)</sup>. For all age groups, males had a higher prevalence of HBsAg positivity than females<sup>(5)</sup>.

Ethnic difference exists in the frequency of HBsAg carrier rate in Singapore in the three major ethnic groups. Among all the three major ethnic groups, the HBsAg carrier rate was significantly higher among the Chinese than the non-Chinese<sup>(5)</sup>. In a 1982 study, they were highest among the Chinese (6.6%), followed by Malays (2.9%), then Indians (0.9%), being higher in males than in females within each ethnic group<sup>(13)</sup>.

The prevalence of HBsAg in selected population groups has been observed to be declining<sup>(14)</sup>. The hepatitis B carrier rate in primary school children has dropped from 5.7% in 1972<sup>(14)</sup> to 4% in 1987<sup>(14)</sup> and 0% in 1994<sup>(9)</sup>. In 1972, the prevalence was 5.7% in Chinese children 5-9 years of age and 8.5% in Chinese adults; the corresponding figures in 1987 were 3.4% and 6.2%, respectively<sup>(5)</sup>. Among antenatal women routinely tested for hepatitis B carrier state, the HBsAg prevalence was 4.4% in 1980-1981<sup>(14)</sup>, but it dropped to 2.8% in 1995<sup>(14)</sup> and 2.7% in 1999<sup>(15)</sup>.

#### HBeAg

For studies conducted between 1979 and 1992, about 39% of the HBsAg carriers in the general population were HBeAg positive<sup>(5)</sup>. The prevalence of HBeAg among HBsAg-positive persons remained consistently high in early childhood (88.3%) and persisted until early adolescence (73.3%)<sup>(5)</sup>. It subsequently declined to 47.7% in the late teens and 34.9% in young adulthood<sup>(5)</sup>. For those above 45 years of age, 11.5% were HBeAg positive<sup>(5)</sup>. This pattern has also been observed in other countries where a steadily increasing proportion of the HBsAg carriers clear HBeAg with age<sup>(5)</sup>.

No significant difference in the prevalence of HBeAg among HBsAg-positive persons was observed

between males and females and between Chinese and non-Chinese<sup>(5)</sup>. Studies also indicated that about one-third of the HBsAg carriers mothers in 1980-1981 were "e" antigen positive mothers<sup>(4)</sup>.

#### anti-HBs

Among the three major ethnic groups, studies conducted between 1979 and 1992 showed that 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%)<sup>(6)</sup>.

#### HEPATITIS B SEROPREVALENCE STUDY 1999

So far, estimates of the hepatitis B carrier rate in the general population have been based on seroprevalence studies conducted in various population groups. To obtain a more accurate estimate of the hepatitis B carrier rate in the general adult Singapore population, the Epidemiology and Disease Control Division, Ministry of Health, conducted a Hepatitis B Seroprevalence Study in late 1999 using stored blood samples from participants of the National Health Survey 1998 (NHS98), which included the National Nutrition Survey 1998. The NHS98 was a national cross-sectional survey conducted between September and November 1998 and representative of the Singapore population aged 18-69 years. The Ministry of Health and the National Medical Research Council in Singapore approved the study protocol and all subjects gave their written consent on the actual survey day.

#### SURVEY OBJECTIVES

The objectives of the survey were to:

- estimate the overall prevalence of HBsAg in the Singapore population (based on a representative sample);
- estimate the gender-specific, age-specific and ethnic-specific prevalence of HBsAg in the Singapore population;
- study the differences in prevalence of HBsAg and antibodies to HBsAg between the gender groups, age groups and ethnic groups; and
- assess the need to strengthen the hepatitis B immunisation programme.

#### SAMPLE SIZE DETERMINATION AND SAMPLE SELECTION

A baseline HBsAg prevalence of 3% was used as the premise to estimate the sample size required to detect changes in prevalence levels. It was calculated that a sample size of 3,460 would be required to detect 10% relative change from the baseline measurement with 95% confidence.

For logistical convenience, 4,698 eligible NHS98 participants who had given written consent for future research on their blood serum during the NHS98 were used for the Hepatitis B Seroprevalence Study. This sample was representative of the Singapore population aged 18-69 years and was selected by a combination of disproportionate stratified sampling and systematic sampling from the reference population of 2.16 million Singapore residents aged 18-69 years. Only Chinese, Malay and Indian residents in this age group were recruited for the NHS98.

#### SURVEY METHODOLOGY

Blood serum from all NHS98 subjects was stored in a freezer at the Department of Pathology, Singapore General Hospital. The stored blood sera of eligible NHS98 subjects were sent to the Virus Laboratory, Department of Pathology, Singapore General Hospital, for screening of HBV markers by enzyme immunoassay (EIA) using commercial reagents (Abbott Laboratories, North Chicago, USA).

The stored blood sera were first tested for HBsAg (by AUSZYME MONOCLONAL). Sera of subjects found to be HBsAg positive were further tested for HBeAg (by AxSYM HBe). Those found to be HBsAg negative were screened for anti-HBs (by AUSAB EIA). Those with antibody levels to HBsAg (anti-HBs) <10mIU/ml were considered non-immune to the HBV and those with levels  $\geq$ 10mIU/ml were considered to have immunity to HBV. The results were then sent to the Epidemiology and Disease Control Division, Ministry of Health, for analysis. Prior to data analysis, subjects' identifiers such as NRIC No. were de-linked from their blood serum results.

#### STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical software package, Statistical Analysis System Windows 6.12. The survey sample data was adjusted to the age, ethnic group and sex distribution of the 1998 Singapore resident population, to ensure that the characteristics of the sample conformed to that of the general population. Age-standardisation of prevalence rates was calculated by the direct method, using the 1990 Singapore resident population as the standard. The differences in the age-standardised rates between the sexes, ages and ethnic groups were computed and tested for statistical significance using the Z-test.

#### SURVEY FINDINGS

##### Overall

The overall prevalence of HBsAg among Singapore residents aged 18-69 years was 4.1% (192/4,698) (95% CI: 3.5-4.6). HBeAg was detected in 13.0% (25/192) of

those who were HBsAg positive. Immunity to HBV (anti-HBs $\geq$ 10mIU/ml) was present in 39.5% (1,855/4,698) of the population (Table I).

#### By Gender

The age-standardised prevalence of HBsAg in males was 4.5% (115/2,356) compared with 3.0% (77/2,342)

for females (0.001<p<0.005) (Table II). There was no significant difference in the age-standardised HBeAg positivity rate among carriers of the two sexes, 11.3% (13/115) in males and 15.6% (12/77) in females. With regards to immunity to HBV, there was no significant gender difference, 36.8% (908/2,356) in males and 38.8% (948/2,342) in females.

**Table I. Overall Results on HBV Markers.**

	Number	Percent
<b>HBsAg positive</b>	<b>192</b>	<b>4.1</b>
HBeAg positive	25	0.5
HBeAg negative	163	3.5
<b>Anti-HBs</b>		
Negative (<10 mIU/ml)	2649	56.4
<b>Positive (<math>\geq</math>10 mIU/ml)</b>	<b>1855</b>	<b>39.5</b>
Undetermined	2	0.0
<b>Total Screened</b>	<b>4698</b>	<b>100.0</b>

**Table II. Age-standardised Prevalence (%) of HBV Markers by Gender.**

	Male (n = 2,356)	Female (n = 2,342)	Both Genders (n = 4,698)
<b>HBsAg positive</b>	<b>4.5*</b>	<b>3.0*</b>	<b>3.8</b>
HBeAg positive	0.5	0.5	0.5
HBeAg negative	3.9	2.5	3.2
<b>Anti-HBs</b>			
Negative (<10 mIU/ml)	58.7	58.1	58.4
<b>Positive (<math>\geq</math>10 mIU/ml)</b>	<b>36.8</b>	<b>38.8</b>	<b>37.8</b>
Undetermined	0.0	0.1	0.0

\* Difference is statistically significant (0.001<p< 0.005).

**Table III. Age-standardised Prevalence (%) of HBV Markers by Ethnic Group.**

	Chinese (n = 3,753)	Malay (n = 597)	Indian (n = 348)	All Ethnic Groups (n = 4,698)
<b>HBsAg positive</b>	<b>4.3*</b>	<b>2.1*</b>	<b>0.4*</b>	<b>3.8</b>
HBeAg positive	0.6	0.4	0.0	0.5
HBeAg negative	3.6	1.5	0.4	3.2
<b>Anti-HBs</b>				
Negative (<10 mIU/ml)	53.2	79.3	78.6	58.4
<b>Positive (<math>\geq</math>10 mIU/ml)</b>	<b>42.6**</b>	<b>18.6**</b>	<b>21.0**</b>	<b>37.8</b>

\* Difference between Chinese and Malay is statistically significant (0.001<p< 0.005). Similarly for difference between Chinese and Indian (p<0.001).

\*\* Difference between Chinese and Malay is statistically significant (p< 0.001). Similarly for difference between Chinese and Indian (p<0.001).

#### By Ethnic Group

Among the three major ethnic groups, the age-standardised HBsAg prevalence was highest among Chinese (4.3%) (177/3,753), followed by Malays (2.1%) (13/597) and Indians (0.4%) (2/348) (Table III). The age-standardised prevalence of HBeAg among those who were HBsAg positive was highest among the Malays (15.4%) (2/13), followed by Chinese (13.0%) (23/177). There was no case with HBeAg positivity among the Indians (0/348). Among the Chinese there was also a higher proportion with immunity to HBV (42.6%) (1,660/3,753) compared to Indians (21.0%) (77/348) and Malays (18.6%) (118/597) (Table III).

#### By Age Group

The prevalence of HBsAg was lowest at 2.0% (24/1,230) among young adults in the age group 18-29 years and highest at 5.5% (63/1,140) in the age group 40-49 years (Table IV).

HBeAg positivity among those found to be HBsAg positive was highest in the age group 18-29 (20.8%) (5/24), followed by the age-groups 30-39 (17.2%) (10/58), 40-49 (11.1%) (7/63), 60-69 (6.3%) (1/16) and 50-59 (3.2%) (1/31).

The proportion with immunity to HBV was lowest among those in the age group 18-29 (27.9%) (343/1,230). Those in the age group 50-59 had the highest proportion with immunity (48.5%) (305/629) (Table IV).

## DISCUSSION

The overall prevalence of the HBsAg in the general population is about 4%, with males and Chinese having a higher prevalence than females and non-Chinese respectively. The prevalence increases with age, peaking in the 40-49 years age group.

**Table IV. Age-specific Prevalence (%) of HBV Markers by Age Group (Years).**

	18-29 (n = 1,230)	30-39 (n = 1,314)	40-49 (n = 1,140)	50-59 (n = 629)	60-69 (n = 385)	18-69 (n = 4,698)
<b>HBsAg positive</b>	<b>2.0</b>	<b>4.5</b>	<b>5.5</b>	<b>4.9</b>	<b>4.1</b>	<b>4.1</b>
HBeAg positive	0.4	0.8	0.6	0.2	0.2	0.5
HBeAg negative	1.5	3.7	4.7	4.7	3.4	3.5
<b>Anti-HBs</b>						
Negative (<10 mIU/ml)	70.0	55.6	50.2	46.5	50.0	56.4
<b>Positive (<math>\geq</math>10 mIU/ml)</b>	<b>27.9</b>	<b>39.9</b>	<b>44.3</b>	<b>48.7</b>	<b>45.9</b>	<b>39.5</b>
Undetermined	0.1	0.0	0.1	0.0	0.0	0.0

About 13% of the HBsAg carriers are also HBeAg positive, with the rate decreasing with age. There is no significant difference in the HBeAg positivity rate between males and females and between the three ethnic groups.

Only about 40% of the population have immunity to HBV either through immunisation or from previous exposure to the HBV. The higher immunity in the older age groups is probably attributed to previous exposure to the HBV. Chinese have a significantly higher level of immunity compared to non-Chinese. There is no significant gender difference.

The National Immunisation Programme for hepatitis B has been largely successful in reducing the hepatitis B carrier rate and increasing immunity levels in the population. This is especially so in the below 15 years age group where the immunity level to hepatitis B is as high as 90% and carrier rate is 0%<sup>(16)</sup>.

However, there is still a large proportion (60%) of the population who have no immunity, especially the younger age group of 18-29 years where only 28% have immunity. This group was not covered by the National Childhood Immunisation Programme, which was only implemented in 1987. Therefore, children born before 1987 (now 13 years or older) would not have been covered under the National Childhood Immunisation Programme, although all susceptible individuals have been encouraged to be immunised against HBV. A recent study conducted by the School Health Services, Ministry of Health, showed that overall only 33% of Secondary one to five students (aged 13-17 years) had received Hepatitis B immunisation<sup>(17)</sup>.

As adults between 18-29 years of age had the lowest seroprevalence for anti-HBs, they are therefore at the greatest risk of acquiring HBV infection. The relatively high level of susceptibility of HBV in this age group probably accounts for the high age-specific morbidity rate for acute hepatitis B in the 15-34 years age group; highest in the 25-34 years age group (8.3 per 100,000) followed by the 15-24 years age group (7.8 per 100,000)<sup>(8)</sup>.

The key to the prevention and control of HBV infection is vaccination, which is aimed at protecting susceptibles from being infected and hence helping to reduce the pool of carriers in the community.

As hepatitis B infection can be transmitted sexually and the age-specific morbidity rate is highest in the 15-34 age group<sup>(8)</sup>, hepatitis B vaccination is strongly recommended for all susceptible teenagers and young adults as well as other population groups whose behaviour may expose them to a high risk of acquiring HBV infection.

## CONCLUSION

There is a need therefore to strengthen the hepatitis B immunisation programme to reach out to those who have no immunity especially the young adults. Since February 2001, the School Health Service, Ministry of Health, has implemented a four-year hepatitis B immunisation programme for students in secondary schools, junior colleges, centralised institutes, institutes of technical education, polytechnics and universities who were born before 1987 and who were likely to have missed the hepatitis B immunisation. To complement the school immunisation programme, a mass media education programme was also launched in February 2001 to educate the public on the risks of hepatitis B infection and encourage members of the public who have not been immunised to be screened and immunised against HBV infection.

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