Original Article

Changing Epidemiological Patterns of Hepatitis A Infection in Singapore

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Abstract

Introduction: Singapore has experienced remarkable socioeconomic progress over the last few decades, with a corresponding rise in standards of sanitation and living conditions. We undertook a study to describe its epidemiological trends of hepatitis A over the last 2 decades. Materials and Methods: We analysed the epidemiological data on all laboratory-confirmed cases of hepatitis A from 1990 to 2009. We also described 3 outbreaks which occurred in 1991, 1992 and 2002. To determine the changing prevalence of hepatitis A virus (HAV) infection, we compared the findings from a seroepidemiological study conducted in 1993 with earlier surveys in 1975 and 1984/1985. Results: The incidence of indigenous hepatitis A cases per 100,000 population declined significantly from 1.8 in 1989 to 0.7 in 2009, and more than half were imported. While majority of the imported cases were Singapore residents, the proportion of imported cases among Singapore residents had decreased significantly. Most of the Singapore residents contracted the disease from Southeast Asia and the Indian subcontinent. The overall prevalence of HAV infection in the population declined from 31.8% in 1984/85 to 25.9% in 1993. Conclusion: The incidence and seroprevalence of hepatitis A in Singapore are comparable to other developed countries. As Singapore is situated in a region highly endemic for HAV, it is very vulnerable to the introduction of the disease because of the high volume of regional travel and import of food, especially shellfish. While we note that there have been no further shellfish-associated outbreaks since 2002, sustained vigilance, strict control of food import by the authorities and public health education on the risk of consuming shellfish, especially cockles, raw and half-cooked, should be maintained.

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Key words: Cockles, Imported cases, Outbreaks, Oysters, Shellfish, Seroprevalence

Introduction

Hepatitis A virus (HAV) is a ribonucleic acid (RNA) picornavirus transmitted by the faecal-oral route, either from person to person or through contaminated food or water. The clinical manifestations vary with age, and its severity and fatality increase with age.[1] HAV is usually silent or subclinical in children, and on a worldwide scale fewer than 5% of infections are recognised clinically.[2] Asymptomatic infection is much more common in children less than 6 years of age compared with older children and adults.[3] The mean incubation period is approximately 30 days, with a range of 2 to 6 weeks. The infection usually results in an acute self-limited illness and only rarely leads to fulminant hepatic failure. Approximately 85% of individuals infected with HAV have full recovery within 3 months, and nearly all have complete recovery by 6 months.[4]

HAV is endemic in Southeast Asia and many parts of the world. The epidemiological patterns vary, although the differences are linked more to socioeconomic conditions than actual geographical regions. In countries where a lack of adequate sanitation and poor hygiene practices facilitate the spread of infection, subclinical childhood infection is common and most children are immune by the age of 10 years. In developed countries with high standards of hygiene or sanitation, infection is uncommon in the young and it is usually acquired during travel to endemic areas.[5,6] The age-specific prevalence of antibodies to HAV (anti-HAV) in developed countries therefore tends to be a sigmoid curve, with a low prevalence among children and a high

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prevalence among the elderly.

Singapore has experienced remarkable socioeconomic progress over the last few decades, with a corresponding rise in standards of sanitation and living conditions. We undertook a study to review the epidemiological trends of acute hepatitis A, changing seroprevalence of HAV infection, and factors contributing to the occurrence of acute hepatitis A in Singapore over the last 20 years.

Materials and Methods

Hepatitis A is a legally notifiable infectious disease in Singapore, and the Ministry of Health (MOH) is responsible for its epidemiological surveillance, investigation, research, prevention and control. The Infectious Diseases Act (IDA) requires medical practitioners to notify all cases of, and deaths from, hepatitis A to MOH within 72 hours from the time of diagnosis. This can be done through fax, or via a dedicated website. The information required for each notification included demographic data such as name, unique identification number, date of birth, ethnic group, residential status, gender, residential and school or workplace addresses, dates of diagnosis and onset of illness, and whether the diagnosis was clinical or confirmed by laboratory tests. Upon receipt of notification of a case of acute hepatitis A, trained public health officers immediately conducted epidemiological investigations to determine the possible sources of infection. The patient or a family member was interviewed using a standard questionnaire, to obtain more details on food and travel history within 2 to 6 weeks prior to the onset of illness. Clinical and laboratory records for each case were also reviewed when necessary.

A case of hepatitis A was defined as a clinically compatible disease serologically confirmed with the presence of anti-HAV IgM.[7] Those who had a recent travel history outside Singapore within 2 to 6 weeks prior to onset of symptoms were classified as imported cases. An outbreak was defined as a cluster of 2 or more cases epidemiologically linked by time, place, and person. Case-control studies were conducted during outbreaks to determine the vehicle and mode of transmission.

To determine the changing seroprevalence of HAV infection in Singapore, we conducted a seroepidemiological study in 1993 and compared the findings with those of earlier surveys. In this study, the subjects were recruited through publicity in the mass media of a national survey on vaccine-preventable diseases. They were asked to report to one of the polyclinics near to their homes. Blood samples were collected from apparently healthy children and adults aged 6 months to over 40 years, after consent had been obtained. The subjects covered a cross section of the local population from various socioeconomic backgrounds. Sera were tested for anti-HAV IgG by enzyme-linked immunosorbent assay (ELISA) (HAVAB EIA; Abbott Laboratories, USA) at the Department of Pathology, Singapore General Hospital.

The epidemiological data of all laboratory-confirmed cases of hepatitis A maintained by the Communicable Diseases Division, MOH, for the period 1989 to 2009 were collated and analysed. Data on deaths from acute hepatitis A were also obtained from the Registry of Births and Deaths. For the calculation of age-specific and ethnic-specific incidence rates, the denominators used were the estimated mid-year population of the corresponding years obtained from the Department of Statistics, Ministry of

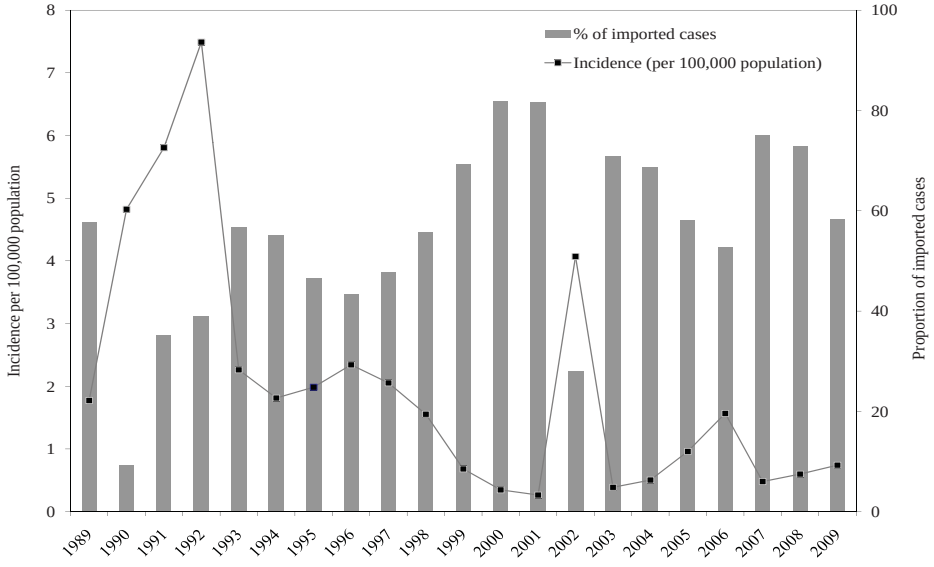

Fig. 1. Incidence (per 100,000 population) of indigenous cases and proportion (%) of imported cases of acute hepatitis A in Singapore, 1989 to 2009.

Trade and Industry, Singapore.

Statistical analyses of the data were carried out using SPSS 17.0 (SPSS Inc., Chicago, IL). For comparison of categorical variables between groups, Chi-square or Fisher's Exact test was used. To estimate the extent of risk, odd ratios (OR) and their 95% confidence intervals (CI) were computed. Linear patterns in classification (imported versus indigenous) of hepatitis A cases over the years were assessed using Chi-square test for trend. In all data analyses, a *P* value of less than 0.05 was considered statistically significant.

Results

Epidemiology

During the period 1989 to 2009, a total of 2955 cases of acute hepatitis A were reported. There was no death from acute fulminant hepatitis. Overall, 36% of the reported cases were classified as imported, and ranged from 9.3% in 1990 to 81.8% in 2000. The incidence of indigenous cases showed a declining trend over the last 2 decades, from 1.8 cases per 100,000 population in 1989 to 0.7 cases per 100,000 population in 2009. Two prominent spikes were observed in 1992 (7.5 cases per 100,000) and 2002 (4.1 cases per 100,000) (Fig. 1).

Excluding foreigners seeking medical treatment in Singapore and tourists, the mean annual age-specific incidence rate was highest in the 25 to 34 year age group with an overall male to female ratio of 2.4:1 (Table 1). Children below 5 years of age accounted for 1.0% of the reported cases.

Among the 3 major ethnic groups of Singapore residents, the mean annual incidence rate was the highest in Indians, followed by Chinese and Malays (Table 2). However, in 2002 and 2006, Chinese had the highest incidence rate.

Of the imported cases, the majority were Singapore residents who had contracted the disease overseas during vacation/business. They accounted for between 47% and 86% of all imported cases (Fig. 2). The other categories of imported cases were work permit holders (6% to 31%), foreigners seeking medical treatment in Singapore (7% to 33%) and tourists (0% to 5%). Between 1999 and 2009, the proportion of imported cases among Singapore residents decreased significantly while that of the other categories of foreigners combined increased correspondingly ($P < 0.05$). Most of the Singapore residents contracted the disease

Table 1. Age-Gender Distribution and Age-Specific Incidence (per 100,000 Population) of Reported Acute Cases of Hepatitis A*, 1999 to 2009

Age group (years)	Male	Female	Total	Mean incidence† per 100,000
0 – 4	5	5	10	0.42
5 – 14	62	29	91	1.58
15 – 24	128	50	178	2.58
25 – 34	219	80	299	3.22
35 – 44	154	60	214	2.58
45 – 54	72	37	109	1.69
55+	58	27	85	1.25
Total	698	288	986	2.15

* Exclude tourists and foreigners seeking medical treatment in Singapore.

† Based on estimated mid-year population, 2004.

Table 2. Ethnic-Gender Distribution and Ethnic-Specific Incidence (per 100,000 Population) of Reported Acute Cases of Hepatitis A*, 1999 to 2009

Ethnic group	Male	Female	Total	Mean incidence† per 100,000
Singapore residents				
Chinese	432	185	617	2.16
Malay	57	17	74	1.41
Indian	59	28	87	2.84
Others	35	16	51	7.77
Foreigners	115	42	157	1.89

* Exclude tourists and foreigners seeking medical treatment in Singapore.

† Based on estimated mid-year population, 2004

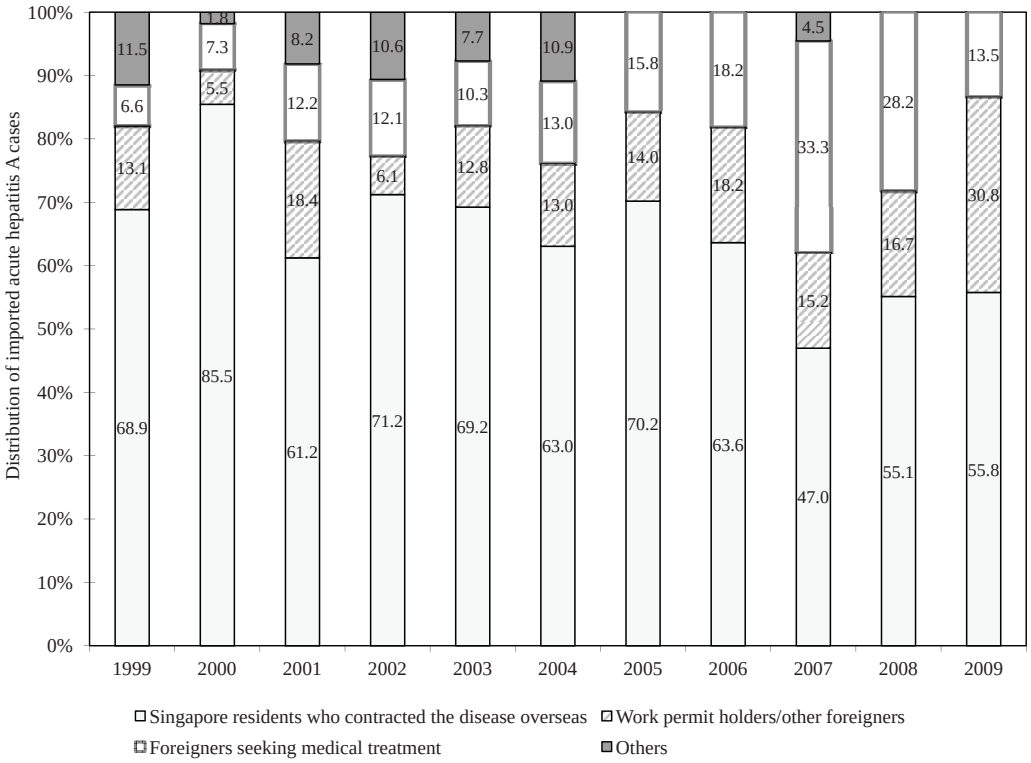

Fig. 2. Distribution (%) of imported acute hepatitis A cases by population group, 1999 to 2009.

Table 3. Distribution (%) of Imported Hepatitis A Cases Among Singapore Residents by Country Of Origin, 1999 to 2009

Country of Origin	1999 (n = 42)	2000 (n = 47)	2001 (n = 30)	2002 (n = 47)	2003 (n = 27)	2004 (n = 29)	2005 (n = 40)	2006 (n = 49)	2007 (n = 31)	2008 (n = 43)	2009 (n = 29)
Southeast Asia											
Brunei	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Indonesia	11.9	8.3	12.1	21.3	33.3	24.1	20.5	15.2	25.0	23.3	20.7
Malaysia	14.3	33.3	60.6	31.9	18.5	24.1	17.9	23.9	28.1	20.9	13.8
Myanmar	0.0	2.1	0.0	0.0	0.0	3.4	0.0	0.0	0.0	0.0	3.4
Philippines	2.4	8.3	0.0	0.0	0.0	3.4	2.6	6.5	3.1	4.7	3.4
Thailand	14.3	4.2	6.1	14.9	3.7	0.0	17.9	8.7	0.0	2.3	6.9
Vietnam	0.0	2.1	0.0	0.0	0.0	0.0	0.0	0.0	3.1	0.0	0.0
Indian Subcontinent											
Bangladesh	4.8	0.0	0.0	0.0	0.0	0.0	2.6	2.2	0.0	0.0	6.9
India	21.4	16.7	9.1	8.5	22.2	24.1	30.8	15.2	25.0	37.2	31.0
Nepal	4.8	0.0	0.0	0.0	3.7	0.0	0.0	4.4	6.3	2.3	3.4
Pakistan	0.0	2.1	3.0	0.0	11.1	0.0	0.0	6.5	0.0	2.3	0.0
Other Asian countries											
China	2.4	8.3	3.0	12.8	3.7	10.3	0.0	6.5	3.1	4.7	3.4
Hong Kong (SAR)	7.1	2.1	3.0	2.1	0.0	0.0	0.0	0.0	6.3	0.0	0.0
Japan	0.0	0.0	0.0	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
North Korea	0.0	0.0	3.0	0.0	0.0	0.0	2.6	0.0	0.0	0.0	0.0
South Korea	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0	0.0	0.0
Syria	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.4
Taiwan	2.4	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0	0.0	0.0
Uzbekistan	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.4
Other countries	11.9	12.5	0.0	6.4	3.7	10.3	5.1	6.5	0.0	2.3	0.0

from Southeast Asia and the Indian subcontinent (Table 3).

Outbreaks

Three outbreaks occurred during the period of review. In the first outbreak in 1991, the incidence of hepatitis A was noted to increase sharply from a weekly average of 4 to 16 cases in June. As soon as this increase was noted, epidemiological investigations were immediately carried out to determine the source of infection and mode of transmission. A total of 70 indigenous cases were notified between 18 June and 18 July. No icteric cases were detected through contact tracing. The attack rate was highest in the 15 to 24 (6.7 per 100,000) and 25 to 34 (4.9 per 100,000) year age groups with a male to female ratio of 2.1:1. Of the 3 major ethnic groups, Chinese had the highest attack rate (3 per 100,000), being significantly higher than that of Malays (0.3 per 100,000) (P <0.05). No significant difference was observed between the attack rates of Chinese and Indians (0.5 per 100,000) (P >0.05). Cases occurred sporadically and were not clustered in any specific geographical location by residential address or place of work. No particular food establishment was implicated. For the case-control study, the cases comprised those with no recent travel history and with a compatible clinical history, raised serum transaminases, and positive anti-HAV IgM. They were interviewed regarding frequency of consumption of a variety of food items such as shellfish, raw fish, raw vegetables, iced drinks, cut fruits and ice cream, between 2 weeks and 2 months prior to onset of jaundice. Controls, matched for age, sex, and ethnicity, were chosen from family members, colleagues or neighbours who had no history of jaundice or travel outside Singapore during the preceding 3 months. Statistical analyses of the case-control study showed that the consumption of raw or partially-cooked imported cockles (*Anadara granosa*) and oysters was significantly associated with the illness (OR = 4.1, P <0.001; OR = 6.5, P <0.01, respectively).[8]

In the second outbreak of 70 cases in September 1992, the epidemiological features were very similar to those of the 1991 outbreak with the highest attack rate among the ethnic Chinese in the 15 to 34 year age group and a male predominance. Case-control study showed that the vehicle of transmission was imported cockles (*Anadara granosa*) (P <0.001). No other types of shellfish such as oysters, crabs and prawns were implicated.[9]

In the last outbreak, a total of 159 indigenous cases were reported between 16 June and 16 November 2002. The epidemiological patterns were similar to those of the previous outbreaks with no clustering of cases in any locality by place of work or residence, and no specific food centre was implicated. Most of the cases (91.8%) were Chinese. The age-specific attack rate was highest in the 25 to 34 year age group with a male to female ratio of 1.5:1. Case-control study showed that consumption of cockles (*Anadara granosa*) and oysters was significantly associated with the illness. Further analysis showed that cases were more likely to have consumed raw or partially-cooked cockles than non-cases after controlling for oyster consumption (OR = 6.0; 95% CI: 2.8 to 13.2). No other types of shellfish and food items were implicated.[10]

Seroprevalence

In the seroprevalence survey in 1993, a total of 930 blood samples were collected and analysed between February and July. The overall prevalence of anti-HAV IgG was 25.9%. Only 2.5% of children and young adults below 25 years of age were seropositive. The age-specific antibody positivity rate increased from 31.1% in the 25 to 34 year age group to 77.0% in the over 45 year age group (Fig. 3). No statistical significant difference in seroprevalence by gender (males 21.2% and females 29.4%) was observed. Among the three major ethnic groups, the prevalence was highest among the Chinese (29.7%) followed by Indians (23.4%) and Malays (4.3%).[11]

Discussion

The incidence of indigenous acute hepatitis A cases had declined significantly from 1.8 cases per 100,000 population in 1989 to 0.7 cases per 100,000 population in 2009. Its incidence is comparable to that of other developed countries; e.g. it ranked between France (1.64 per 100,000 in 2007) and Italy (1.97 per 100,000 in 2007).[12] The majority (58% on average from 1999 to 2009) of the reported cases among Singapore residents were imported. This is similar to the situation in other industralised countries, where travel accounts for a significant proportion of hepatitis A cases.[13-15]

The 1993 seroepidemiological survey showed further decline in the age-specific HAV antibody prevalence when compared to previous studies conducted in 1975 and 1984/85. In 1975, 30% of children below 10 years of age were infected. The age-specific seroprevalence increased to 60% in the 10 to 19 year age group, and was higher than 80% in the 20 to 29 year age group. By the age of 30 years, virtually all were infected.[16] The overall prevalence of HAV infection in the population had declined from 31.8% in 1984/85 to 25.9% in 1993. This decline was seen in all age groups and was more marked in the younger age groups (<15 year olds and 15 to 24 year olds) than in the older age groups (25 to 34 year olds, 35 to 44 year olds, and >45 year olds) (Fig. 4).

The seroprevalence of HAV infection in Singapore with a very low level of transmission is similar to that of Japan (<1% in ages 0 to 19 years; 4% in ages 20 to 29 years),

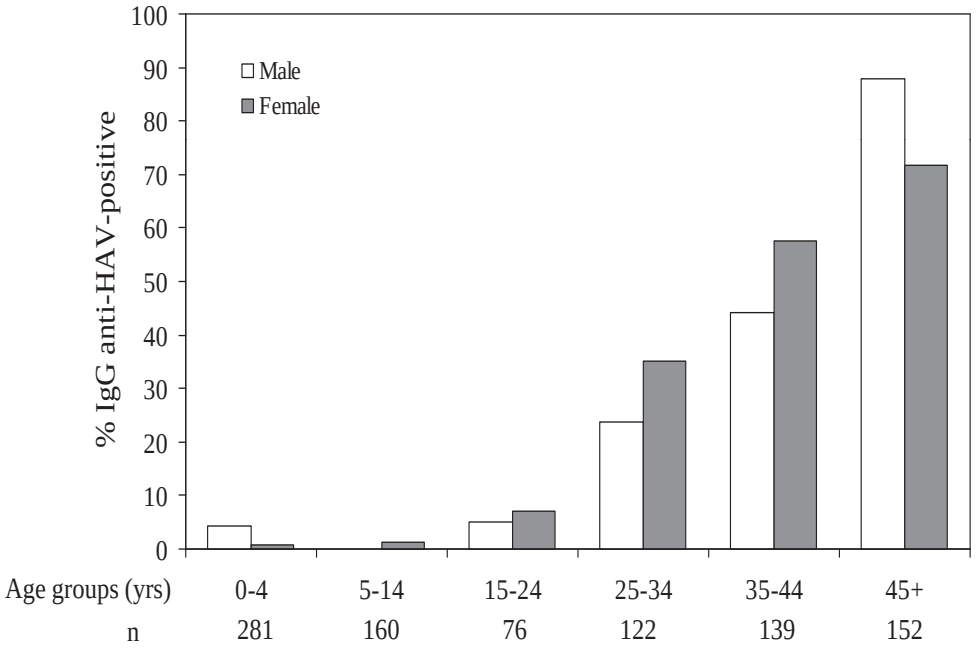

Fig. 3. Age-Gender distribution of IgG antibody to HAV in Singapore, 1993.

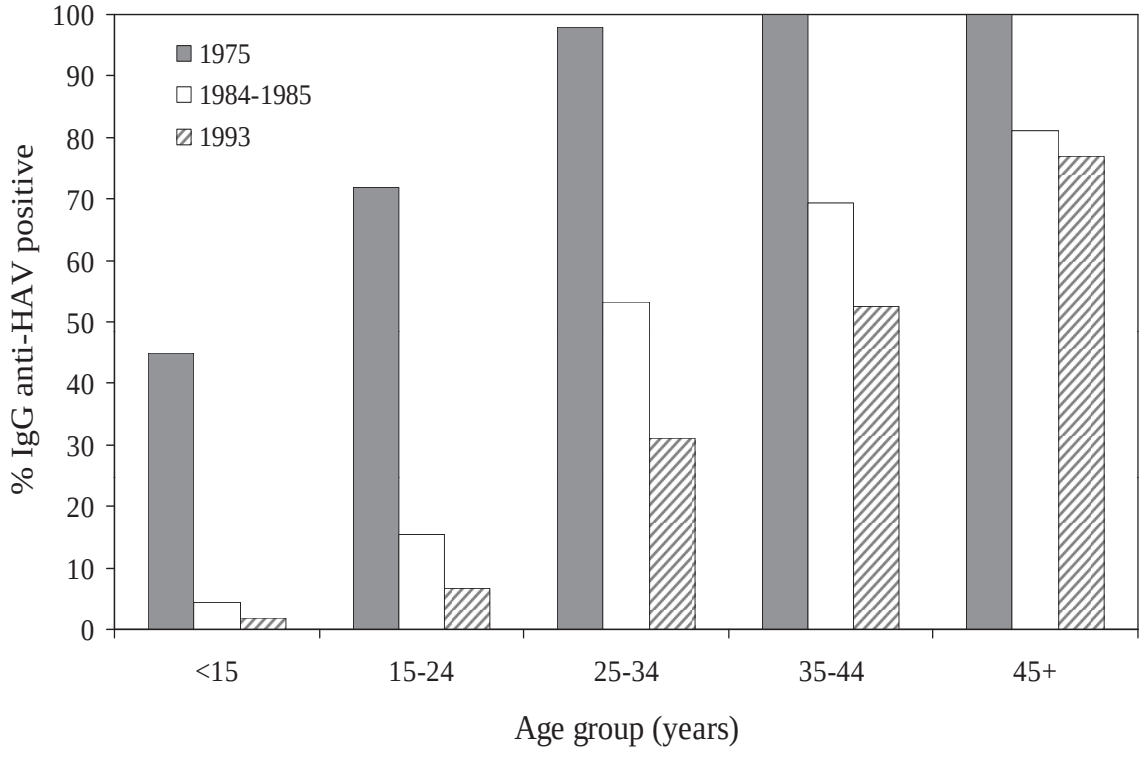

Fig. 4. Changing seroprevalence of HAV infection in Singapore, 1975, 1984/1985 and 1993.

Australia (40% overall), New Zealand (<20% in ages 30 to 55 years), Canada (<20% in children), the United States (30% overall), and United Kingdom (9% in ages 1 to 9 years).[17,18] The continuous decline in the age-specific seroprevalence over the last few decades reflects the marked improved standards of environmental hygiene and sanitation accompanying socioeconomic progress. The comprehensive disease surveillance system and measures taken against other food-borne diseases (typhoid and cholera) such as health education on personal and food hygiene had also contributed to the successful control of HAV.[19,20] The risk of acquiring hepatitis A in the community is very low, except for those occupationally exposed such as sewage workers[21] and a Gurkha community, which had a much higher seroprevalence than that of the general population in Singapore.[22]

As Singapore is situated in a region highly endemic for HAV infection, it is very vulnerable to the introduction of the disease because of the high volume of regional travel. Indeed, over the last 7 years (2003 to 2009), the proportion of imported cases remained consistently above 50%. Pre-travel health advisory should be issued to travellers reminding them to observe good personal and food hygiene when travelling to the endemic countries, in particular, to avoid raw or partially-cooked food, especially shellfish. Vaccination against HAV infection is an important measure. Several safe and effective vaccines against HAV have been available since the first approval of the products in Singapore in 1996, such as the formalin-inactivated vaccines, HAVRIX (GlaxoSmithKline) and VAQTA (Merck & Co., Inc). A combination hepatitis A/hepatitis B vaccine consisting of HAVRIX and Energix-B (Twinrix, GlaxoSmithKline) is also commercially available.[23] However, Asian travellers are generally less aware of the need for pre-travel consultation and vaccination compared to their Western counterparts and pre-travel hepatits A vaccination remains low among Singapore travellers.[24]

Besides the risk of travel-associated infection, sporadic and epidemic transmission of hepatitis A is also epidemiologically linked to the consumption of imported shellfish as demonstrated in the outbreaks described above. Cockles (*Anadara granosa*) and oysters are bivalve molluscan shellfish which are filter feeders and are able to accumulate and concentrate viruses and other human pathogens in an environment that is subject to chronic pollution from sewage.[25] They are cultivated along the muddy coastal regions in many countries in the region, where there is no sanitary control over their production and harvest. Cockles-associated outbreaks in Singapore were first reported in 1978 (57 cases), followed by other outbreaks in 1983 (161 cases between May and September),[26] 1985 (36 cases in October) and 1986 (37 cases in August/September). Chilled shucked oysters imported from the Philippines were associated with a massive outbreak of 312 cases in 1980,[27] as well as an outbreak of paratyphoid A in 1979.[28] Following these outbreaks, the import of chilled shucked oysters was prohibited.[27] Chilled shucked oysters smuggled from other countries had also been implicated in other hepatitis A outbreaks in 1987 (30 cases)[29] and 1989 (4 cases).[30]

The local population, especially the Chinese, prefers to consume shellfish raw or partially cooked, and this accounted for the highest attack rates in this ethnic group during outbreaks. For cockles, locally known as 'see-hum', one of the favourite methods of preparation is to pour boiling water over them till the shells are partially opened. The flesh and the gut are removed from the shell and usually eaten with chilli sauce and spices. Raw shucked cockles are also commonly added as an ingredient in food; e.g. curry noodle soup ('laksa') and fried noodles ('fried kway teow' and noodle with peanut sauce ('satay bee hoon'). In the case of oysters, they are served as oyster-omelet with the shucked shellfish added in to the fried eggs and flour just before the dish is served. These methods of food preparation are unlikely to inactivate the viruses that may be present in the core of the shellfish[31] as the virus may withstand boiling temperature for several minutes. Cockles commercially processed by 1 to 2 minutes of steaming to remove the shells, followed by 5 minutes boiling had been responsible for an extensive outbreak in the UK.[32]

The Agri-Food Veterinary Authority (AVA) is responsible for regulating the import of seafood including shellfish into Singapore. Live oysters can only be imported from countries where there is legislation for licensing of oyster farms and mandatory testing of the microbiological quality of the oysters and of the growing water in which oysters are cultured. Under AVA's regulations, every import shipment is to be accompanied by a health certificate issued by the competent authority of the exporting country. The import of chilled shucked oysters is prohibited, and frozen oysters can only be brought in from countries with national shellfish sanitation programme approved by AVA. Imported frozen oysters from these approved countries can only be released for sale if they satisfy the established microbiological standards. A high level of vigilance is maintained to prevent shucked oysters from being illegally brought into Singapore either directly by importers or indirectly by fishermen.

Unlike oysters, cockles are of relatively lower economic value. Cockles from countries in the region which are not part of the national shellfish sanitation programme are generally grown in estuarine waters. In addition, it is difficult to prevent pollution of these estuarine waters where cockles thrive best and to relay them in clean water before export. The live shellfish are generally packed in

60 to 65 kg gunnysacks and transported by lorries from the production areas. As such, the practical approach is to educate the public through public advisories against eating raw or uncooked cockles due to the risk of food poisoning from microbial pathogens. No health certificate is required for the importation of cockles into Singapore as unlike oysters, it would not be practical or meaningful to set an acceptable standard for the import of cockles.

In recent years, there has been an increase in demand for cockle meat instead of whole live cockles due to convenience in food preparation at retail food outlets. This trend has led to a proliferation of shucking activities which were carried out illegally under unhygienic conditions. Since 1 May 2007, AVA has implemented new regulations which only allow seafood importers with licensed cockle processing establishments to import live cockles. Previously, food service outlets (e.g. hawker stalls, restaurants) could buy live cockles and shuck these at their outlets for immediate consumption by the customers. AVA now requires that these imported cockle consignments be sent directly to the AVA-licensed processing premises upon importation and that these cockle-shucking establishments are allowed to distribute live cockles directly to retail or food service outlets only. AVA prohibits these shucking establishments from supplying the cockles to any distribution centres or wholesale markets.

About 8 to 10 tonnes are consumed by the population per day. Public health education on the risk of consuming raw and half-cooked cockles was stepped up during outbreaks and this had in some way moderated the consumption choice of this shellfish among the population. It is interesting to note that there have been no further cockle-associated outbreaks since 2002, although about 30% of the population continues to consume this shellfish in the traditional way. The reasons are not known. It is likely due to the availability of the hepatitis A vaccine and those who prefer to consume shellfish raw to partially-cooked could have been protected. However, we have no data to support this hypothesis. It could also be possible that farmers growing cockles are more aware of the risk of pollution and are growing their cockles in areas away from human settlements, thus reducing the risk of sewage contamination. Nevertheless, the public should continue to be reminded to refrain from consuming undercooked cockles, not only for the prevention of hepatitis A, but also other enteric diseases such as cholera and *Vibrio parahaemolyticus* food poisoning.[33]

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