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Epidemiology of acute hepatitis E in Singapore

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KEYWORDS

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Summary Objectives: We undertook an epidemiological review to determine the trend and characteristics of acute hepatitis E in Singapore over the last 12 years.

Methods: We analysed the epidemiological records of all laboratory-confirmed cases of acute hepatitis E maintained at the Communicable Diseases Division, Ministry of Health, from 2000 to 2011.

Results: A total of 540 laboratory-confirmed cases of acute hepatitis E was reported with more than half imported, mainly from India and Bangladesh. Among the indigenous cases, the mean annual incidence per 100,000 population increased from 0.05 in 2000–2002 to 0.92 in 2009–2011. There was a male predominance and the median age was 46 years. Among the 3 major ethnic groups of Singapore residents, Chinese and Indians had higher mean annual incidence rate compared to Malays. All the indigenous cases occurred singly and sporadically and could not be epidemiologically linked to one another by person, place or time. No common food item was implicated.

Conclusions: Indigenous acute hepatitis E has emerged as a major cause of acute viral hepatitis in Singapore. While epidemiological investigations are ongoing to elucidate the risk factors and modes of transmission, travellers should be reminded to practise a high standard of personal and food hygiene when visiting endemic countries.

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Introduction

Hepatitis E was first recognized as a distinct human disease during a water-borne epidemic of enterically transmitted viral hepatitis which occurred in the Kashmir Valley in November 1978. Based on unique clinical and epidemiological features and the absence of serological evidence of acute hepatitis A and hepatitis B virus infection, the existence of another hepatitis virus distinct from the post-transfusion non-A, non-B type of human hepatitis was postulated.¹ This was soon followed by isolation and successful demonstration of transmission of the hepatitis E virus (HEV).² The virus was previously classified within the family of caliciviruses, but it is now recognised as the only member of the genus *Hepevirus* and is placed in the family *Hepeviridae*.³ The human HEV also infects several other mammals, in particular, pigs. In swine, HEV infection is very common, although the infection is largely asymptomatic.^{4,5} Seroprevalence surveys showed that HEV infection is present across both developed and developing countries, with two distinct epidemiological patterns linked to socio-economic conditions rather than actual geographical regions. In highly-endemic regions such as Southeast Asia and the Indian Sub-continent, numerous water-borne outbreaks have been documented.^{6–8}

In low-incidence industrialised countries, most of the reported acute hepatitis E cases were imported by travellers from highly-endemic countries. However, sporadic cases related to autochthonous transmission are increasingly being reported in recent years.^{9,10} The main mode of transmission appears to be zoonotic¹¹ and some studies have identified an association between acute HEV infection and consumption of raw or under-cooked pig liver^{12–19} and meat/offal from wild boar and deer.^{20,21} Shellfish have also been implicated^{22–24} and consumption of uncooked shellfish has been identified as a risk factor among passengers on a cruise ship.²⁵

The clinical presentations of HEV and hepatitis A virus (HAV) infection are quite similar.²⁶ However, with acute HEV infection, pregnancy, in particular, is associated with increased mortality, which may reach 20% in the third trimester.²⁷ Chronic HEV infection is not common with the exception of patients who are severely immune-compromised, such as kidney or liver transplant recipients in whom about two-thirds progress to chronic hepatitis E.^{28,29} There is no specific anti-viral therapy for acute HEV infection²⁶ but a safe and highly efficacious HEV vaccine has recently been marketed in China.^{30,31}

In Singapore, among tests for confirming the clinical diagnosis of acute viral hepatitis, commercial serological assays have been used to detect IgG and IgM antibodies against HEV (anti-HEV IgG and anti-HEV IgM) by the Virology Laboratory at Singapore General Hospital (SGH) since 1993 and 1995, respectively. This makes it possible to classify acute HEV infection as a separate entity from other types of acute viral hepatitis.

We undertook a 12-year review to determine the epidemiological characteristics of acute hepatitis E in Singapore from 2000 to 2011.

Materials and methods

Acute hepatitis E is a legally notifiable infectious disease in Singapore. The Virology Laboratory at SGH is the central laboratory for the processing of acute hepatitis E blood specimens in Singapore. The diagnosis of acute hepatitis E is based on ELISA tests for anti-HEV IgM. The anti-HEV IgM ELISA detection kit (MP Biomedicals, Singapore) was used by SGH until September 2008, after which a new test kit, anti-HEV IgM ELISA 3.0 (MP Biomedicals, Singapore), was introduced. Samples were tested once and if positive, were retested in duplicate as per manufacturer's instruction. Only ELISA was used; molecular tests were not performed.

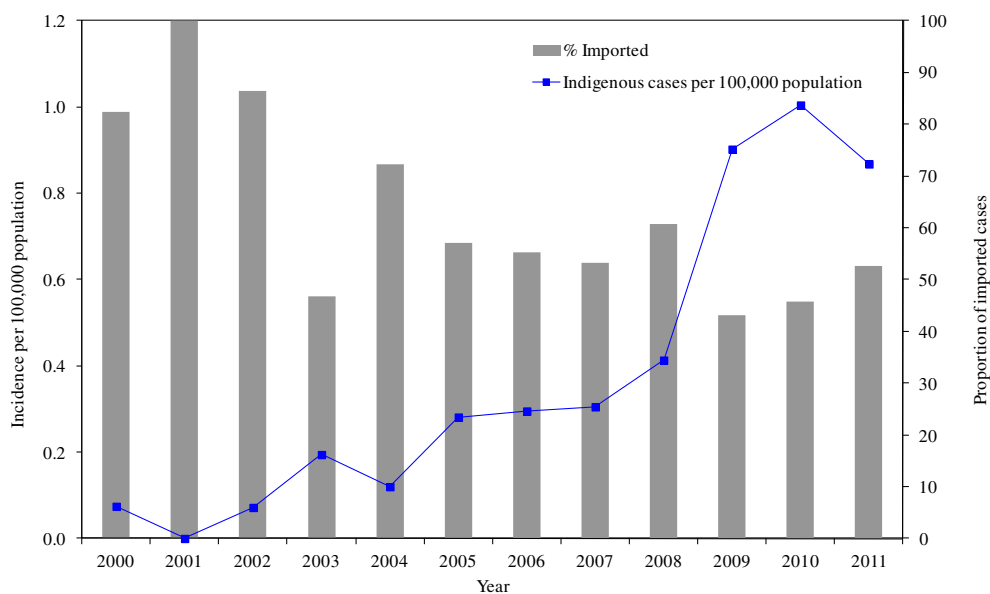


Figure 1 Incidence (per 100,000 population) of reported indigenous acute hepatitis E cases and proportion (%) of reported cases which were imported, 2000–2011*. *Excluded 59 foreigners and tourists seeking medical treatment in Singapore.

Table 1 Mean annual age-specific incidence rates (per 100,000 population) of reported indigenous acute hepatitis E cases in Singapore, 2000–2011.

Age group (years)	2000–2002 (<i>n</i> = 6)	2003–2005 (<i>n</i> = 25)	2006–2008 (<i>n</i> = 47)	2009–2011 (<i>n</i> = 141)
0–4	0	0	0	0
5–14	0	0	0.13	0.07
15–24	0.05	0.16	0.23	0.34
25–34	0.08	0.12	0.40	0.68
35–44	0	0.40	0.41	0.98
45–54	0.06	0.34	0.37	1.28
55–64	0.13	0.31	0.50	1.76
65+	0.12	0.12	0.49	2.66
Total	0.05	0.20	0.34	0.92

All cases and deaths are to be reported to the Communicable Diseases Division (CDD), Ministry of Health (MOH), within 72 h from the time of diagnosis.

For every reported case, investigations are routinely conducted by MOH to obtain relevant demographic and epidemiological information using a standard questionnaire form. These include date of onset of illness, food items consumed and travel history within 8 weeks prior to the onset of illness, and contact with a known clinical case of acute hepatitis within the same period. Contact tracing is initiated when there is a cluster involving two or more cases with epidemiological linkage, and clinical and laboratory records of the notified cases are also reviewed.

A case of acute hepatitis E was defined as a clinically compatible disease serologically confirmed by the presence of anti-HEV IgM. Those who had a recent travel history outside Singapore within 8 weeks prior to onset of symptoms were classified as imported cases.

The epidemiological records of all laboratory-confirmed cases of acute hepatitis E maintained by the CDD, MOH, for the period 2000 to 2011 were retrieved, collated and analysed. For deaths from acute hepatitis E, the Registry of Births and Deaths was also cross-referenced to ensure that no death was omitted. For the calculation of age- and ethnicity-specific incidence rates, the estimated mid-year population of the corresponding years was obtained from the Department of Statistics Singapore.³² Differences in proportions were tested by the Chi-square test. Significance of trends was tested by linear regression or by the Chi-square test for trend. The Mann–Whitney *U* test was used to compare the median age between the indigenous and imported cases. Statistical significance was taken as $P < 0.05$. Data were analysed using PASW Statistics (SPSS) version 18.0.

As collection and analysis of acute hepatitis E data by the Ministry of Health, Singapore, is performed under the powers of the Infectious Diseases Act, no permission from the ethics committee is required. Only aggregate data was used for this study and no unique person identifiers were presented in the results.

Results

During the period from 2000 to 2011, a total of 540 laboratory confirmed cases of acute hepatitis E was reported, including 59 tourists and foreigners seeking medical treatment in Singapore. However, we only included local residents and foreigners residing in Singapore in the analysis of epidemiological trends, and these 59 tourists and foreigners seeking medical treatment in Singapore were excluded. There was no recorded death from acute fulminant hepatitis. Imported cases constituted 54.5% of the 481 reported cases (Fig. 1). The mean annual incidence rate of indigenous cases per 100,000 population increased from 0.05 in 2000–2002 to 0.20 in 2003–2005, 0.34 in 2006–2008 and 0.92 in 2009–2011. The sharpest rise was noted in the last 3-year period (Fig. 1 and Table 1).

Indigenous cases

Of the 219 indigenous cases, more than three-quarters (79%) were Singapore residents, while the remaining 21% were foreigners residing in Singapore. They were considered to have acquired the infection locally as they had no recent travel history outside the country. No case was reported in children below 5 years of age (Table 1). The median age was 46 years (interquartile range [IQR], 33–59). In

Table 2 Mean annual ethnicity-specific incidence rates (per 100,000 population) of reported indigenous acute hepatitis E cases in Singapore, 2000–2011.

Age group (years)	2000–2002 (<i>n</i> = 6)	2003–2005 (<i>n</i> = 25)	2006–2008 (<i>n</i> = 47)	2009–2011 (<i>n</i> = 141)
<i>Singapore residents</i>				
Chinese	0.04	0.23	0.37	1.25
Malay	0.00	0.07	0	0.07
Indian	0.12	0.23	0	0.48
Others	0	0.48	1.46	0.81
<i>Foreigners</i>	0.09	0.13	0.38	0.69

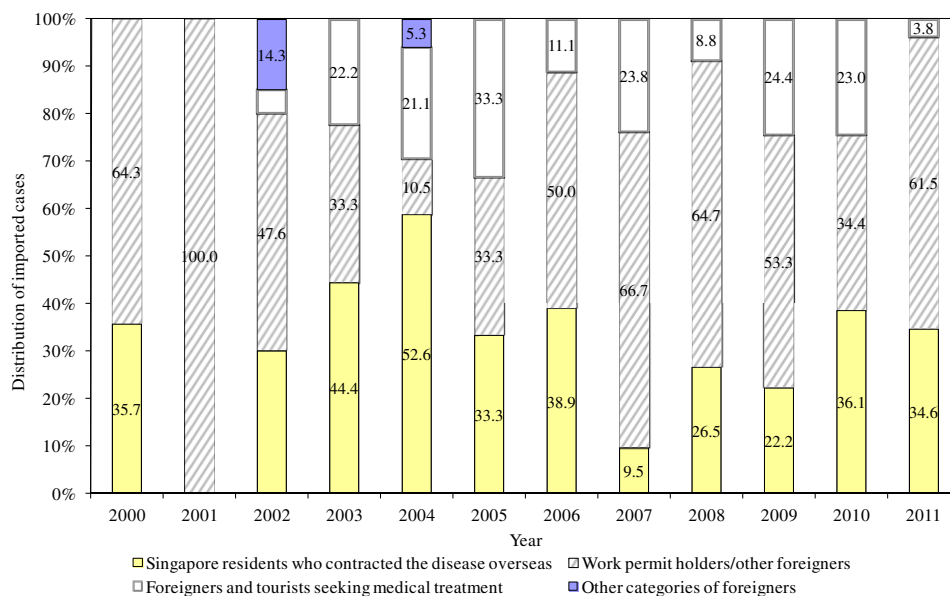


Figure 2 Distribution (%) of imported acute hepatitis E cases by population group, Singapore, 2000–2011.

comparison, the median age of the Singapore resident population in 2011 was 38 years.³³ The proportion of cases in the age group of 55 years and older increased significantly from 23.4% in 2006–2008 to 39.7% in 2009–2011 ($P = 0.043$). While the disease continued to affect males predominantly, there has also been a relatively sharper increase in the annual incidence rate per 100,000 population among females during the past 6 years from 0.14 in 2006 to 0.68 in 2011 ($P = 0.033$). During this period, the annual incidence per 100,000 population in the age group 55 years and older has also increased significantly from 0.6 in 2006

to 2.3 in 2011 ($P = 0.012$), in particular, the annual incidence per 100,000 population among those 65 years and older increased significantly from 0.6 in 2006 to 2.6 in 2011 ($P = 0.022$). Among the 3 major ethnic groups of Singapore residents, Chinese had the highest mean annual incidence rate (1.25 per 100,000 population) compared to Malays (0.07 per 100,000 population) and Indian (0.48 per 100,000 population) in 2009–2011 (Table 2).

None of the reported indigenous cases could be epidemiologically linked to one another by person, place or time. All the cases occurred singly and sporadically throughout

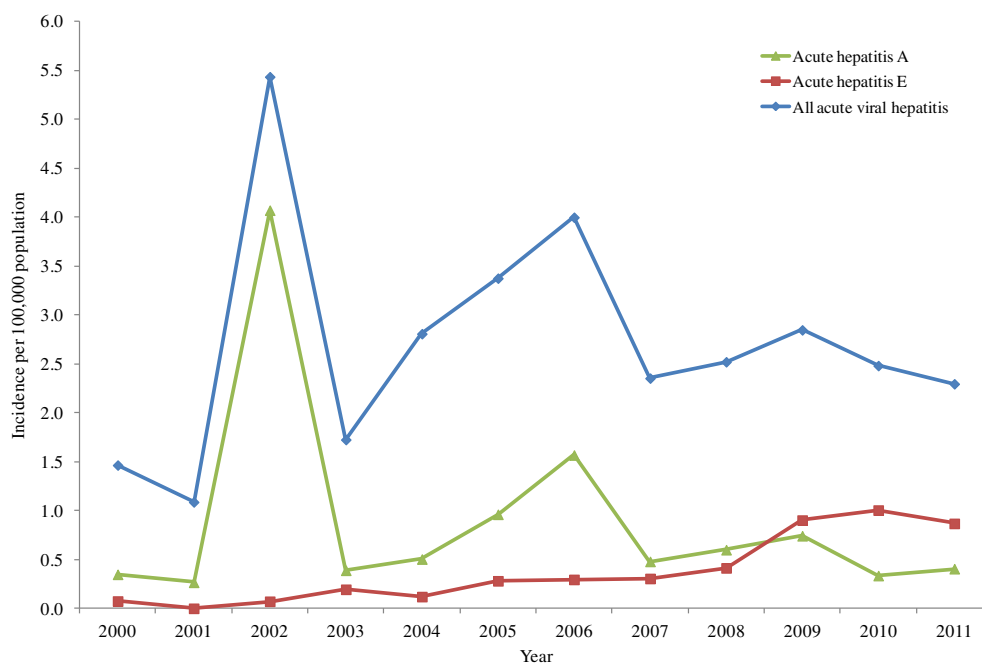


Figure 3 Incidence rates of indigenous cases of acute hepatitis A, acute hepatitis E and all acute viral hepatitis, Singapore, 2000–2011.

the island. No common source outbreak or secondary cases among close contacts was detected. No specific food item, including shellfish, has been implicated.

Imported cases

Among the 321 imported cases, Singapore residents who contracted the disease overseas comprised 31.3%; work permit holders, 48.2%; foreigners seeking medical treatment in Singapore, 16.9%; and foreign tourists diagnosed to have the disease on arrival in Singapore, 2.3% (Figs. 2 and 3). Most of the imported cases originated from Southeast Asia and the Indian subcontinent with Bangladesh and India topping the list (Table 3). The median age of the imported cases (32 years) (IQR, 25–45) was significantly lower than that of the indigenous cases ($P < 0.0005$). There was predominance among males (76.3%).

Discussion

The most notable observation of this epidemiological review was the sharp increase in both imported and indigenous

cases of acute hepatitis E in the last 3 years. For the imported cases, the increase could be attributed to the influx of immigrants and foreign workers from highly endemic countries in the region, in particular, India and Bangladesh. Between the period 2001 and 2010, the number of non-residents in Singapore increased by 73%, compared to the resident population which increased by 15%.³⁴

Locally acquired acute hepatitis E has now emerged to be more common than acute hepatitis A. The increasing trend of indigenous cases of acute hepatitis E is in sharp contrast to the continuing decline in the incidence of indigenous acute hepatitis A from 1.8 per 100,000 population in 1989 to 0.4 per 100,000 in 2011.³⁵ Our findings of the rising incidence of indigenous acute hepatitis E as well as the predominance in older males (mean age of 54 years or older) mirror those reported in other developed countries such as the United States, the United Kingdom, Japan, Hong Kong, New Zealand and Australia.¹¹

We believe that the increase in indigenous cases of acute hepatitis E is real as there had been no significant increase in the number of serological tests carried out by the Virology Laboratory at SGH, except for the year 2010 (Table 4). We do not know why the number of blood samples tested at

Table 3 Distribution (%) of imported acute hepatitis E cases by country of probable acquisition among Singapore residents and foreigners, Singapore, 2000–2011.^a

Country of probable acquisition	Singapore residents		Foreigners	
	<i>n</i> = 101	%	<i>n</i> = 161	%
<i>Southeast Asia</i>				
Cambodia	0	0.0	1	0.6
Indonesia	6	5.9	3	1.9
Malaysia	17	16.8	4	2.5
Philippines	1	1.0	8	5.0
Thailand	9	8.9	2	1.2
Vietnam	2	2.0	0	0.0
<i>The Indian subcontinent</i>				
Bangladesh	1	1.0	110	68.3
India	28	27.7	26	16.2
Maldives	1	1.0	0	0.0
Nepal	1	1.0	2	1.2
Pakistan	0	0.0	1	0.6
Sri Lanka			1	0.6
<i>Other Asian countries</i>				
China	16	15.8	1	0.6
Hong Kong	7	6.9	0	0.0
North Korea	1	1.0	0	0.0
Saudi Arabia	1	1.0	0	0.0
South Korea	2	2.0	0	0.0
Taiwan	1	1.0	0	0.0
<i>Other countries</i>				
Australia	2	2.0	0	0.0
Chile	1	1.0	0	0.0
United Arab Emirates	0	0.0	1	0.6
New Zealand	1	1.0	0	0.0
Seychelles	1	1.0	0	0.0
Spain	1	1.0	0	0.0
United States of America	1	1.0	0	0.0
Zambia	0	0.0	1	0.6

^a Excluded 59 foreigners and tourists seeking medical treatment in Singapore.

Table 4 Serological tests for clinical diagnosis of acute hepatitis E at Virology Laboratory, Department of Pathology, Singapore General Hospital, 2000–2011.

Year	No. positive ^a	No. tested	% positive
2000	15	475	3.2
2001	11	448	2.5
2002	23	464	5.0
2003	20	315	6.3
2004	32	393	8.1
2005	38	463	8.2
2006	34	367	9.3
2007	40	365	11.0
2008	70	411	17.0
2009	91	443	20.5
2010	130	830	15.7
2011	100	934	10.7

^a HEV IgM ELISA test kits (MP Biomedicals, Singapore) from 1999 to Sept 2008; HEV IgM ELISA 3.0 (MP Biomedicals, Singapore) from Oct 2008–2010.

SGH increased almost two-fold from 2009 to 2010. We also could not ascertain if it was due to a greater awareness among clinicians of the emerging problem of acute hepatitis E in Singapore.

The introduction of the new diagnostic test kit (HEV IgM ELISA 3.0) produced by the same manufacturer (MP Biomedicals, Singapore) since October 2008 could partly, but not entirely, account for the increase in the number of reported cases as its sensitivity (98.0%) in accordance to the manufacturer's data, is slightly higher than that of the previous diagnostic kit (93% sensitivity) which had been in use since 1995. Even after adjusting the number tested positive from 2009 to 2011 based on a lower sensitivity of 93%, we note that the trend in the proportion tested positive remained similar to that of the observed pattern. In fact, a significant increase in the incidence rate had already occurred from 1999 to 2007, before the new diagnostic kit was introduced ($P = 0.044$).

The exact mode of transmission of HEV infection in Singapore could not be determined despite careful epidemiological enquiries. No common food item could be identified. While consumption of undercooked shellfish had been associated with several outbreaks of hepatitis A,³⁵ it was not implicated as a vehicle of transmission for acute hepatitis E in Singapore. The proportion of reported acute hepatitis E cases who had consumed raw or undercooked shellfish within 6 months prior to onset of illness was not significantly different from that of acute hepatitis B, which is not a food-borne disease.³⁶

We also have no evidence to implicate consumption of inadequately cooked pig liver which has been identified as a possible source of HEV infection in Hong Kong.¹⁸ Nevertheless, there is indirect evidence to suggest that consumption of porcine products may play a role in the transmission of HEV in Singapore. During the period from 2009 to 2011, among the three major ethnic groups in Singapore, the mean annual incidence rates of Chinese and Indians were 17.9 and 6.9 times, respectively, higher than that of Malays (who are mostly Muslims). A serological survey conducted in

1994 also showed that the prevalence of HEV infection in Chinese (12.7%) was significantly higher than that in Malays (4.0%) ($P < 0.001$).³⁷

Epidemiological investigations are ongoing to elucidate the risk factors and modes of transmission of HEV infection in Singapore. As neither anti-viral therapy nor a vaccine is currently available, travellers should be reminded to practise a high standard of personal and food hygiene when visiting endemic countries.

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