Original Article

Epidemiological Characteristics of Cholera in Singapore, 1992-2007

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Abstract

Introduction: We carried out an epidemiological review of cholera in Singapore to determine its trends and the factors contributing to its occurrence. Materials and Methods: Epidemiological data of all notified cases of cholera maintained by the Communicable Diseases Division, Ministry of Health, for the period 1992 to 2007 were collated and analysed. Case-control studies were carried out in outbreaks to determine the source of infection and mode of transmission. Linear patterns in age and ethnic distribution of cholera cases were assessed using $\chi 2$ test for trend. Results: There were a total of 210 cholera cases reported between 1992 and 2007. The incidence of cholera declined from 17 cases in 1992 to 7 cases in 2007. About a quarter of the cases were imported from endemic countries in the region. Between 76% and 95% of the reported cases were local residents. Four elderly patients with comorbidities and who sought medical treatment late died, giving a case-fatality rate of 1.9%. Vibrio cholerae 01, biotype El Tor, serotype Ogawa, accounted for 83.8% of the cases. The vehicles of transmission identified in outbreaks included raw fish, undercooked seafood and iced drinks cross-contaminated with raw seafood. Conclusion: With the high standard of environmental hygiene and sanitation, a comprehensive epidemiological surveillance system and licensing and control of food establishments, cholera could not gain a foothold in Singapore despite it being situated in an endemic region. However, health education of the public on the importance of personal and food hygiene is of paramount importance in preventing foodborne outbreaks. Physicians should also maintain a high level of suspicion of cholera in patients presenting with severe gastroenteritis, especially those with a recent travel history to endemic countries.

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Introduction

Cholera is an acute diarrhoeal disease that usually presents as abrupt massive watery diarrhoea and vomiting. The causative organism is *Vibrio cholerae* which is divided into serogroups based on the somatic O antigen. Only O1 and O139 serogroups are known to cause epidemic and pandemic disease. The O1 serogroup is further divided into two biotypes - El Tor and classical, and each of these biotypes can have serotypes of either Ogawa, Inaba and rarely, Hikojima.[1] The main reservoir of *V. cholerae* is humans[2] and there are also environmental reservoirs in brackish water where the bacteria multiply in association with copepods or other zooplankton.[3] The organism is transmitted mainly via the faecal-oral route through contaminated food and water.

The first cholera pandemic originated in India in 1817 and spread rapidly outwards to countries such as Burma and the Philippines. This and the subsequent five pandemics, were all believed to have started in the Ganges delta in Bengal.[4] We are currently in the midst of the seventh cholera pandemic which began in Sulawesi, Indonesia, in 1961[5] and the causative agent of this pandemic is *V. cholerae* O1 biotype El Tor. In October1992, a previously unknown strain of *V. cholerae*, designated O139 Bengal, caused outbreaks of cholera-like illness in India and Bangladesh.[6-8] Despite concerns that this new serogroup may herald the eighth cholera pandemic, O139 cholera is still largely confined to Asia.[2]

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Cholera was introduced into Singapore soon after it was founded as an entrepot port in 1819 during the first cholera pandemic (1819-1825).[9] Despite the implementation of stringent quarantine measures, several outbreaks of cholera were reported in Singapore during the nineteenth century in 1841, 1851, 1858, 1862 and 1864.[10,11] El Tor cholera was first reported in Singapore in 1944 in an outbreak at Loyang involving villagers who had consumed cabbages dumped into the sea from an infected Japanese ship.[12] It was re-introduced into the country in 1963 as an extension of the seventh cholera pandemic. Sporadic cases of El Tor cholera continued to be reported in subsequent years with islandwide outbreaks in 1972 (114 cases)[13] and 1978 (83 cases).[14] Well-defined localised outbreaks were reported among foreign construction workers in 1982,[15] inmates of an institution for the aged sick in 1987[16] and a psychiatric institution in 1990.[17]

We carried out an epidemiological review of the cholera situation in Singapore during the period 1992 to 2007 to determine its trends and the factors contributing to its occurrence.

Materials and Methods

Cholera is a legally notifiable disease in Singapore. Medical practitioners and directors of clinical laboratories are required to report all cholera cases within 24 hours of diagnosis to the Ministry of Health via fascimile or a dedicated website. The clinical and laboratory criteria for notification are based on a document disseminated to all medical practitioners.[18] Epidemiological data to be provided in the notification form include age, ethnic group, gender, nationality, addresses of residence and place of work/school and date of onset of illness. Upon receipt of notification of a cholera case, epidemiological investigations were immediately conducted by trained public health officers to search for other unreported cases in the family, place of work or school. Using a standardised questionnaire, the patient or a family member was interviewed to obtain more details on food and travel history within 5 days prior to onset of illness. The hospital records, laboratory findings and clinical outcome were also reviewed. Close contacts and implicated foodhandlers were referred to the Communicable Disease Centre, Tan Tock Seng Hospital, for screening of *V. cholerae* infection by stool and urine cultures. Environmental and food samples implicated were also collected for laboratory tests for the presence of *V. cholerae*. The laboratory protocols to confirm the presence of *V. cholerae* have been described elsewhere.[17]

During investigation of cholera outbreaks, case-control studies were conducted using standardised questionnaires to determine the source of infection and mode of transmission. Statistical analyses of data from the questionnaires were carried out on SPSS 14.0 (SPSS Inc., Chicago, IL). For comparison of categorical variables between groups, χ^2 test or Fisher's Exact test was used. To estimate the extent of risk, crude odds ratios and their 95% confidence intervals were also computed.

The epidemiological data of all laboratory confirmed cases of cholera maintained by the Communicable Diseases Division, Ministry of Health, for the period 1992 to 2007 were collated and analysed. We restricted our analysis to data from 1992 onwards as earlier data was not available in our electronic database. Data on deaths from cholera 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, Singapore. We stratified the incidence by age and ethnicity to determine whether or not the epidemiology of cholera is similar to that of other food-borne diseases such as salmonellosis and typhoid. Linear patterns in age and ethnic distribution of cholera cases over the years were assessed using χ^2 test for trend. A P value of less than 0.05 was considered statistically significant.

A case of cholera was defined as a clinically compatible case presenting with gastrointestinal illness from whom cholera-toxin producing *Vibrio cholerae* serogroups O1 or O139 was isolated from the stool, urine or bile. Imported cases were defined as those who had a recent travel history to a country with known cholera endemicity within 5 days prior to the onset of symptoms. An outbreak was defined as a cluster of 2 or more cholera cases epidemiologically linked by person, place and time.

Results

A total of 210 cases were reported over the 16-year period from 1992 to 2007, and the annual number ranged from 0 in 2006 to 42 in 1994. The incidence showed a downward trend from 17 cases in 1992 to 10 cases in 2000 and 7 cases in 2007 (Fig. 1). The incidence rate depicted some cyclical patterns with the peaks declining from 1.2 per 100,000 in 1994 to 0.8 per 100,000 in 1998 to 0.3 per 100,000 in 2006.

Cases were evenly distributed between the two genders. Adults had a higher incidence rate than children and those above the age of 55 years old had the highest age-specific incidence rate (Table 1). The mean annual proportion of cases in the age group of 15 to 24 years decreased significantly from 18.3% between 1992 and 1995 to 7.8% between 2004 and 2007 (P <0.05), while that in the age group of 55 years or older increased significantly from 29.7% between 1992 and 1995 to 61.0% between 2004 and 2007 (P <0.0005). The majority of the reported cases involved local residents. Foreigners constituted between 5% and 24% of the reported cases. Among the three major ethnic groups, the ethnic-

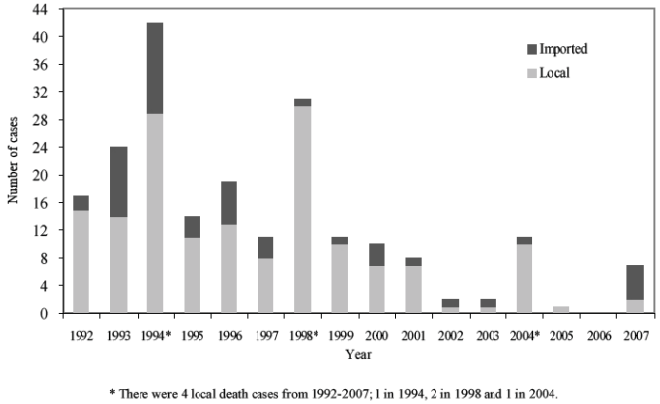

Fig. 1. Number of reported cholera cases by classification, 1992-2007.

Table 1. Mean Annual Age-Specific Incidence Rates (Per 100,000 Population) of Reported Cholera Cases, Singapore, 1992-2007

Age group (y)	1992-1995 (n = 97)	1996-1999 (n = 72)	2000-2003 (n = 22)	2004-2007 (n = 19)
0-14	0.1 (2.4)	0.1 (5.9)	0.0 (0.0)	0.0 (0.0)
15-24	0.8 (18.3)	0.3 (10.1)	0.1 (8.8)	0.1 (7.8)
25-34	0.7 (22.4)	0.4 (19.0)	0.1 (10.6)	0.1 (20.4)
35-44	0.6 (16.9)	0.4 (13.8)	0.2 (19.4)	0.1 (7.8)
45-54	0.8 (10.3)	0.6 (15.3)	0.1 (5.6)	0.04 (3.0)
55+	1.9 (29.7)	1.3 (35.9)	0.3 (55.6)	0.3 (61.0)
Total	0.7 (100.0)	0.5 (100.0)	0.1 (100.0)	0.1 (100.0)

Figures in brackets refer to percentage distribution

specific incidence rate of Malays was higher than that of Chinese and Indians during the period of 1996 to 2007 (Table 2). Among the resident cases, the mean annual proportion of Chinese increased significantly from 70.5% between 1992 and 1995 to 77.8% between 2004 and 2007 (P <0.05), while the distribution among Indians decreased significantly from 16.6% between 1992 and 1995 to 0% between 2004 and 2007 (P <0.0005).

Imported cholera accounted for 24.0% of all the reported cases (Table 3). Most of these cases acquired the disease from countries in the region such as Malaysia, Thailand, Indonesia, India and Pakistan.

There were 4 cholera-related deaths, 1 each in 1994 and 2004, and 2 in 1998, giving an overall case-fatality rate of 1.9 %. All the 4 deaths were local cases and their ages ranged from 67 to 89 years. They all had co-morbidities and were admitted to hospital in a state of severe dehydration.

Most of the cholera cases (83.8%) were caused by *V. cholerae* O1, biotype El Tor, serotype Ogawa (Table 3). All the cases due to the O139 serogroup were imported from India, Thailand, Indonesia and China.

Table 2. Mean Annual Ethnic-Specific Incidence Rates (Per 100,000 Population) of Reported Cholera Cases, Singapore, 1992-2007

Ethnic group	1992-1995 (n = 97)	1996-1999 (n = 72)	2000-2003 (n = 22)	2004-2007 (n = 19)
Residents				
Chinese	0.6 (57.5)	0.5 (55.8)	0.1 (61.9)	0.1 (70.6)
Malay	0.8 (10.4)	0.9 (28.1)	0.3 (13.7)	0.2 (9.1)
Indian	1.0 (7.9)	0.4 (5.7)	0.0 (0.0)	0.0 (0.0)
Others	0.8 (1.4)	3.0 (5.5)	0.0 (0.0)	0.5 (9.5)
Foreigners	1.2 (22.8)	0.1 (4.9)	0.2 (24.4)	0.1 (10.8)
Total	0.7 (100.0)	0.5 (100.0)	0.1 (100.0)	0.1 (100.0)

Figures in brackets refer to percentage distribution

Table 3. Local and Imported Cases of *Vibrio cholerae*, Serogroup O1 Biotype El Tor and Serogroup O139, 1992-2007

Serogroup	1992-1995 (n = 97)	1996-1999 (n = 72)	2000-2003 (n = 22)	2004-2007 (n = 19)
Local cases				
El Tor				
Ogawa	69	55	16	3
Inaba	0	6	0	10
O139	0	0	0	0
Imported cases				
El Tor				
Ogawa	20	9	1	3
Inaba	1	2	3	3
O139	7	0	2	0

Figures in brackets refer to percentage distribution

Based on available records of the Department of Pathology, Singapore General Hospital, both *V. cholerae* O1 and O139 were sensitive to ciprofloxacin and tetracycline. However, *V cholerae* O139 was resistant to cotrimoxazole, but that of O1 was sensitive.

Several outbreaks of cholera cases were reported. Three larger outbreaks are described below.

Outbreak at Pasir Ris, 1993

In November 1993, two Thai construction workers who were working in a public housing construction project at Pasir Ris were hospitalised for severe watery

diarrhoea and subsequently confirmed to be infected with *V. cholerae* O1. Their onset of illness was between 29 and 30 October. Initial investigations could not establish a common source of infection. When another Thai worker was admitted to hospital for cholera two weeks later, extensive epidemiological investigations, such as active case detection and mass rectal swabbing, were carried out. A total of 12 cases, including one of 431 foreign workers screened at the work site, with onset of illness between 15 November and 26 November, were confirmed to be infected with *V. cholerae* O1, biotype El Tor, serotype Ogawa. Further investigations revealed that many of the cases had consumed partially-cooked green mussels and other seafood caught in the rivers nearby. One of the rivers was the point of discharge of sewage effluent into the sea. *V. cholerae* O1 was isolated from one of 17 sea/river water tested, but none of the 8 samples of fish, green mussels, cockles and other shellfish was positive.[19]

Outbreak in Jurong, 1999

The setting of this outbreak was a Malay wedding function in a multi-purpose hall. About 1000 guests attended the event in October 1999. Food was prepared on site by an unlicensed food caterer with 6 assistants. A total of 8 cases of El Tor cholera, serotype Ogawa, was reported with 4 detected through contact tracing and 1 through screening of implicated foodhandlers. Based on the case-control study, the incriminated food item was an iced banana-flavoured drink ($P = 0.01$). Careful enquiries showed that the crushed ice for cooling the drink was probably cross-contaminated when it was stored in styrofoam boxes previously used for the storage and transport of raw fishes and other seafood. The foodhandler could not have been the source of infection as all the reported cases had the same date of onset of illness. The mean incubation period of this point source outbreak was 9.5 hours and ranged from 5.5 to 14 hours.[20]

Outbreak in Bedok/Tampines, 2004

In this outbreak, a total of 10 cases of El Tor cholera, serotype Ogawa, with onset of illness between 3 October and 10 October 2004 were reported. An elderly man with co-morbidities died. Seven of the cases lived in Bedok and Tampines and had taken their meals from various food establishments there. Extensive epidemiological investigations, including case-control study, could not implicate any specific food establishment. However, consumption of 4 seafood items (prawns in noodles, steamed prawns, cooked squid and fried fish) was significantly associated with illness. Of 350 implicated foodhandlers screened and 271 food samples and 22 environmental swabs tested, all were found negative for *V. cholerae* O1.It could not be established how the imported seafood was contaminated.[21]

Discussion

Despite Singapore being located in a cholera-endemic region, the disease incidence has been declining and the situation is currently very similar to that of other developed countries.[22-25] Factors contributing to the successful control of cholera include the high standard of environmental sanitation and hygiene,[26] the comprehensive disease surveillance system,[14] licensing and control of food factories and retail outlets, and health education and supervision of public foodhandlers.

The responsibility to ensure food safety and hygiene in Singapore lies in two governmental agencies. The Agri-Food and Veterinary Authority (AVA) is responsible for food safety issues from production up to the point just before retail. AVA inspects and accredits both local and overseas source farms, abattoirs and food processing establishments. It also inspects primary produce and processed food at the points of entry into Singapore. Laboratory testing is routinely carried out for a wide range of pathogens and chemical contaminants in livestock, frozen and chilled meat, live and chilled fish, vegetables, fruits, eggs and processed food.[27] Special emphasis is placed on the microbiological testings of imported shellfish such as cockles and oysters for *Vibrio cholerae* and other enteropathogens. On the other hand, the National Environment Agency (NEA) is in charge of hygiene practices in eating establishments to ensure that ready-to-eat food is prepared hygienically and is safe for consumption. All food retail establishments must be licensed by NEA and they are graded based on overall hygiene, cleanliness and housekeeping standards of the premises. In addition, all food handlers involved in food preparation and handling are required to register with NEA.[28]

The declining trend of cholera as well as other foodborne diseases such as typhoid and hepatitis A over the last 16 years could be attributed to further improvements in food hygiene practices. The NEA's grading system for eating establishments and food stalls, introduced in 1997, is a structured system of appraisal for food outlets that is intended to motivate licensees to improve and maintain good personal and food hygiene, and housekeeping of their premises. This regime has yielded significant improvements in food hygiene levels in Singapore. The proportion of grade 'A' and 'B' stalls increased from 46% in 2002 to 86% in 2008, while the remaining 14% of stalls were graded "C" and they met the hygiene requirements.[29] The NEA's hawker centres upgrading programme implemented in 2001 has also contributed to an improvement in overall hygiene standards at hawker centres. A total of 72 centres have since been upgraded with better facilities and toilets, amongst other improvements, while the remaining 30 centres will be upgraded by 2012.[30]

Cholera is predominantly an adult disease in Singapore,

especially among those above 55 years of age, unlike salmonellosis which affects mainly the young. The high incidence of cholera among the elderly could be contributed by the lower levels of gastric acid[31] and lower infective dose of *V. cholerae* needed to cause clinical disease in persons with hypochlorhydria.[32,33] The incidence of cholera has decreased in all ethnic groups. However, ethnic differences in incidence rates persist. This could not be attributed to environmental hygiene, as over the last two decades, there have been vast improvements in environmental sanitation, including universal potable water supply piped to every home in all communities. One possible reason for this could be differences in food preference and methods of food preparation among the ethnic groups. For example, the Chinese prefers to consume fish and shellfish such as cockles and oysters raw or partially cooked. Foreign workers are also not aware of the risk of contracting cholera by consuming wild shellfish indiscriminately picked up from sewage-contaminated areas, as shown in the outbreak at Pasir Ris in 1993.

Singapore remains highly vulnerable to the introduction of cholera through trade and travel. *V. cholerae* O139 was imported into the country in March 1993, just a few months after the epidemic of cholera-like illness started in Madras, India, in October 1992. Of the 5 imported cases reported, 1 was a Singapore resident who acquired the disease during a social visit to Madras, India, and the others were all Indian tourists from Madras.[34] Because of the high level of environmental hygiene, no secondary transmission occurred and *V. cholerae* O139 could not establish a foothold in Singapore.

However, sporadic cases of El Tor cholera continued to be reported with occasional localised outbreaks due to contaminated food, in particular seafood or articles cross-contaminated by it, as illustrated in the three outbreaks described above. Contaminated seafood eaten raw or inadequately cooked is a well-known vehicle of transmission.[35-40] Steamed prawns served in a cold dish was implicated in an outbreak in which 13 persons were infected (7 symptomatic and 6 asymptomatic) following a Mooncake Festival dinner in Chinatown in 1978.[14] 'Sambal sotong' (squid) was the vehicle of transmission in an outbreak in Marine Parade in 1981.[15] Consumption of raw sliced fish ('Yu-sheng') from imported fresh water carp ('Song-he') served with porridge in various outlets was responsible for 4 cases in 1995, 3 cases in 1996 and 12 cases in 1998.

So far, no large nationwide outbreaks of cholera due to imported food have been reported unlike other food-borne diseases such as hepatitis A traced to imported oysters from the Philippines[41] and imported cockles from Malaysia,[42] paratyphoid A due to imported oysters from the Philippines[43] and imported coconut from Malaysia,[44] and norovirus gastroenteritis due to imported oysters from China.[45]

However, there is no room for complacency. A high level of food safety and hygiene practices should be uniformly and consistently maintained at all times and the public should be discerning when consuming food, especially seafood which is served raw or undercooked. 'Yu-sheng' which is widely consumed during the Chinese New Year period is kept under close surveillance and samples routinely collected for testing of enteropathogens, including *V. cholerae*.

Unlike typhoid whose endemicity is maintained by chronic human carriers, cholera carriers are short-term execretors. While the source of infection of the sporadic cases of cholera with no travel history could not be determined, there is no reason to believe that they are infected by undetected carriers in the community. Occasionally, a few implicated public foodhandlers routinely referred for screening were incidentally found to be infected with *V. cholerae* O1. Since the infective dose of *V. cholerae* O1 is high (10^{8-11} organisms), secondary cases arising from person-person transmission in household settings are unlikely.[46]

About one quarter (24.0 %) of the cholera cases were imported. This reflects the significance of cholera as a travel-related disease. Singaporeans travelling to cholera-endemic countries should be educated on the importance of good food and water hygiene practices. Moreover, they should be reminded on the importance of prompt medical consultation should they develop symptoms of cholera during and after the trip. Healthcare professionals should also consider cholera as a differential diagnosis in severe diarrhoea cases, especially in those who give a recent travel history to a cholera-endemic country. They may also consider protecting travellers with an oral cholera vaccine consisting of inactivated vibrios plus B-subunit of the cholera toxin. The 4 cholera-related deaths which occurred during the study period were between 67 and 89 years of age, and they had other co-morbid conditions. They succumbed rapidly from severe dehydration as they sought medical treatment late. A high degree of clinical suspicion and early detection and treatment with rapid fluid and electrolyte replacement and antibiotic therapy[47,48] should lower the relatively high case-fatality rate (1.9% compared

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