Cholera Outbreaks in South-East Asia

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Abstract This chapter highlights the cholera situation in South Asia and the Bay of Bengal region, the original 'homeland' of cholera. A detailed discussion of cholera outbreaks in individual countries in South-East Asia follows. The countries of the World Health Organization (WHO) SEARO (South-East Asia Region) region are discussed first, followed by discussions about the other countries in South-East Asia that do not fall within the purview of the WHO SEARO classification of the member countries of the region. Therefore, the chapter attempts to provide a comprehensive yet precise outline of the major cholera outbreaks that have occurred in the region over the years.

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Current Topics in Microbiology and Immunology
DOI: 10.1007/82_2014_362

1 Introduction

Enteric diseases represent a leading cause of death by infectious diseases in the world just after respiratory diseases and HIV/AIDS. Among them cholera remains a major public health issue. Cholera, an acute waterborne diarrhoeal disease, continues to be a significant global health threat. The currently ongoing seventh pandemic of cholera, which started in 1961, has been reported in over 50 countries and has affected over 7 million individuals. It is affecting all ages and is primarily due to unhygienic living conditions, poverty and lack of clean drinking water. Importantly, the disease remains a threat in many tropical regions of the world, specifically in the coastal parts of South Asia, Africa and Latin America. The World Health Organization (WHO) estimates that 3–5 million cholera cases occur every year, leading to 100,000–120,000 deaths due to cholera every year with an average case fatality rate of 2.25 % (range 1–10 %) (WHO 2012). Its actual mortality and morbidity is underestimated due to gross under-reporting, growing risks due to climate change, increased bacterial virulence (new variants of O1 El Tor) and emergence of antibiotic resistance, etc.

In May 2011, the World Health Assembly (WHA) recognised the re-emergence of cholera as a significant global public health problem and adapted resolution WHA 64.15, calling for the implementation of an integrated comprehensive global approach to cholera control (WHO 2011). The dismal picture of cholera in recent years is reflected by a 130 % increase in the number of cases of cholera from 2000 to 2010 (WHO 2011). Importantly, in 2010, 48 countries reported the incidence of the disease. The situation is critical in Asia where the disease is both endemic and epidemic. Despite current national and international efforts, the morbidity and mortality rates remain high and represent a significant burden in the region, both economic as well as societal (WHO 2010).

2 Cholera: Global Scenario

Cholera is a widespread and serious disease, which is still endemic in approximately 50 countries that fall under the category of developing nations. Between 2006 and 2008 an average of 200,000 suspected cases and 5,000 deaths were reported to WHO (WHO 2010). Studies reviewing unreported epidemics actually found significant under-reporting because of various reasons including stigmatisation and fear of economic losses. Importantly, a review of the Indian notification

data between 1997 and 2006 showed that only 37,783 cases were reported to WHO, when 222,038 cases were actually identified (Kanungo et al. 2010). It should be noted that although 98 % of all cholera cases and 99 % of all deaths in 2009 were reported from 30 affected African countries, the disease is still endemic in most countries in South-East Asia and outbreaks are periodically reported although countries with high rates have not started reporting (Waldor et al. 2010).

The current pandemic is the seventh in line, which began in 1961 and is still ongoing. Unlike the first six, it originated in Indonesia. It devastated populations across Asia and the Middle East and eventually reached Africa in 1971. By 1973, the pandemic had spread to Italy. There were also small outbreaks of the same El Tor strain in Japan and the South Pacific in the late 1970s. In 1991, a century after cholera had been vanquished from South America, there was a fresh outbreak in Peru that spread throughout the continent, killing about 10,000 people in its wake. In 1994, there was a big outbreak among Rwandan refugee camps in the Democratic Republic of Congo that killed tens of thousands of people. In 2008, an outbreak in Zimbabwe involved almost 12,000 cases. The outbreak is believed to be the result of deteriorating infrastructure resulting from political unrest. In recent times, the Haiti outbreak is the largest outbreak to be recorded that devastated the country (Fig. 1). From the scientific front, the major discovery from this period has been the identification of the new serogroup of cholera bacteria (O139) in India (Ramamurthy et al. 1993) and Bangladesh in 1992 (Albert et al. 1993), which has since been detected in 11 countries. This discovery has raised concerns about the fear of an eighth pandemic. Recent studies using robust molecular techniques, however, place *Vibrio cholerae* O139 as a derivative of El Tor *V. cholerae* O1 (Mutreja et al. 2011).

3 Cholera in South Asia and Bay of Bengal Region

The coastal regions of South Asia, for example Bangladesh and Kolkata in the state of West Bengal in India, have a long history of cholera outbreaks and are collectively considered the native homeland of the cholera disease since the early nineteenth century. Cholera incidence data at the International Center for Diarrhoeal Disease Research in Bangladesh (ICDDR,B) is very well documented and is one of the longest and most detailed cholera datasets in the world.

Cholera seasonality in the Bengal delta region is unique in the sense that it shows two cholera outbreaks in a given annual cycle. It is believed that the spring outbreaks are the results of intrusion of coastal water in the Bay of Bengal aided through low river discharge, while the autumn cholera outbreaks are the result of flooding caused by high river discharge. Importantly, cholera incidence in this region has been historically linked to environmental and climate variables such as precipitation, floods, river level, sea surface temperature, coastal salinity, dissolved organic material and faecal contamination. Also, ponds known as *pukurs*

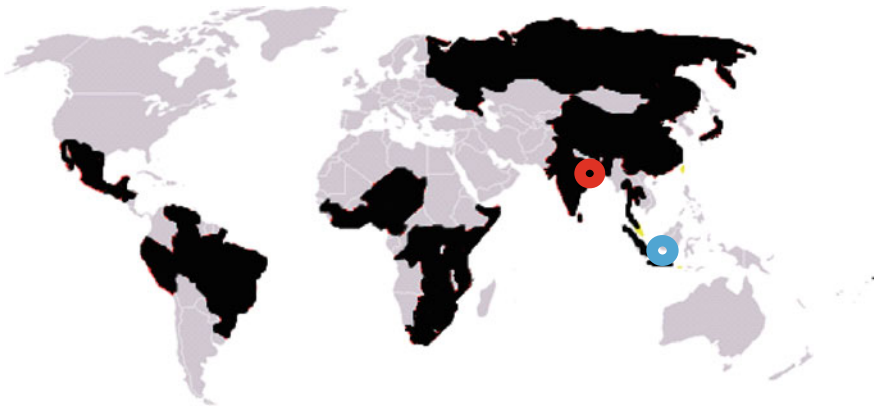

Fig. 1 Countries that have experienced cholera outbreaks during the seventh cholera pandemic. *Black shading* indicates areas where cholera outbreaks have occurred. The *red circle* (India) indicates the origin of the first six pandemics, while the *blue circle* (Indonesia) indicates the origin of the seventh pandemic (Data compiled from the WHO and CDC)

in common Bengali parlance are a source of *V. cholerae* for cholera outbreaks, as many country folk use the water not only for washing purposes but also for drinking purposes.

4 Cholera Outbreaks in Specific Countries of South-East Asia

As per the classification of the SEARO by WHO, this region is constituted by 11 countries. These include Bangladesh, India, Nepal, Sri Lanka, Bhutan, Thailand, Indonesia, Maldives, Myanmar, Timor-Leste and the Democratic People's Republic of Korea. Outbreak of cholera will be covered in these WHO Member States first before moving on to some other countries in the region, which although do not fall within the WHO classification, we feel should not be left out as some of these countries have also experienced cholera outbreaks from time to time. These include Malaysia, Singapore, Philippines, Vietnam and Laos.

4.1 Bangladesh

Bangladesh is a low-lying South Asian country with a population of over 164 million people that lies mainly within the broad delta of the Ganges and Brahmaputra rivers. Given its location, the country has often been the victim of devastating floods and cyclones. It is the most densely populated country in the

world, with an estimated 1,102 people /km^2. Although the country's population growth is declining rapidly, its population is still expected to reach more than 215 million by 2040 (World Bank 2011).

Bangladesh has a gross domestic product (GDP) per capita of USD 560 (in 2008)—placing it among the least developed countries in the world. Around 40 % of the population lives below the poverty line, with approximately 20 % being considered very poor. Around 20 % of the population does not have access to safe drinking water and 64 % do not have improved sanitation (United Nations 2008). An estimated 44 % of the population over the age of 15 is still illiterate. However, despite these statistics, Bangladesh has been making steady economic progress over the past two decades, achieving economic growth rates of 4–5 % per year since 2004. During this period, Bangladesh has made impressive improvements in the health status of its population, compared to other nations in South Asia. Life expectancy at birth has risen from 55 years in 1991 to 66 years by 2008 (World Bank 2013), with inappreciable differences between male and female populations.

The three top causes of death in Bangladesh for all ages are pneumonia (14 %), respiratory failure (7.5 %) and diarrhoea (6.26 %) (WHO 2005). Diarrhoeal disease was the number one cause of hospitalisation at public health facilities in 2008, which accounted for more than 15 % of all admissions. Importantly, diarrhoeal disease due to *V. cholerae* continues to be a major problem in Bangladesh (Sack et al. 2003).

Cholera in Bangladesh occurs both as endemic disease, with seasonal peaks before and after the monsoons, and in epidemics that often take place during or following the frequent floods, droughts and cyclones that occur in the country.

As in most developing countries, Bangladesh does not have a national surveillance system that can identify cholera through laboratory diagnosis. Most of the available information on cholera has been generated by the ICDDR,B, which has conducted cholera-related research since 1960 and treats cholera patients both in its hospital in Dhaka and at its field station hospital in Matlab. Based on the available disease surveillance data of ICDDR,B and disease outbreak data, the Institute of Epidemiology, Disease Control & Research (IEDCR) estimates annual 450,000 cholera cases each year in Bangladesh. The diarrhoeal hospital of ICDDR,B estimates about 300,000 severe cholera cases requiring hospitalisation each year in the country. Importantly, for each hospitalised case there are three more cases in the community. This gives around 1,200,000 infections due to *V. cholerae* each year.

Cholera is both a rural and an urban disease in Bangladesh. It is associated with poor sanitation, contaminated water supplies—including surface water and shallow tube wells that are the main sources of drinking water in rural areas—as well as crowded living conditions, such as those found in the country's urban slums. Tube wells, until recently were considered a safe source of drinking water particularly in rural areas are now contaminated with arsenic, forcing people to revert back to using untreated surface water from *pukurs* and rivers.

Few cholera outbreaks have been reported during the past few years. However, in September 1991, a major outbreak of cholera broke out in Bangladesh, which

Table 1 1991 cholera outbreak in Bangladesh: Epidemic investigation by ECPP

Regions	No. of cases with watery diarrhoea	No. of rectal swabs collected	*V. cholerae* 01	
			Positive	Rate per 1,000 swabs
North-West	1,265	266	137	515
North-East	1,598	507	299	589
Mid-West	162	56	36	642
Total	3,025	829	472	569[a]

[a] 95 % CI: 535–603

started in the North-Western region and spread throughout most of the northern part of the country. The government epidemic surveillance between September and November 1991, reported 214,856 cases of diarrhoea with 2,620 deaths (Siddique et al. 1992). In 1985, escalation of cholera epidemics prompted the Government of Bangladesh (GOB) and the ICDDR,B to develop an Epidemic Control Preparedness Programme (ECPP). The ECPP, between 1985 and 1991, collaborated with the GOB health services in the investigation of and intervention in diarrhoeal epidemics in nearly 400 rural *upazilas* (sub-districts). During the 1991 outbreak, the ECPP physicians saw 4,018 diarrhoea patients during their epidemic investigations; 3,025 (75 %) had acute watery diarrhoea from which 829 rectal swabs were collected (Table 1). Table 1 also shows the *V. cholerae* isolation rates from each of the regions. The overall *V. cholerae* 01 isolation was 569 cases per 1,000 rectal swabs (95 % CI: 535–603).

Besides the outbreak in 1991, there were a number of outbreaks in Bangladesh between 1985 and 1990. The GOB carried out epidemic surveillance, which was supplemented by the surveillance carried out by the ECPP. There were a large number of cases in 1987 and 1988. In those years, there were severe floods that affected most of the country, particularly the northern and the middle regions, perhaps increasing the number of cases during these periods (Table 2). Importantly, Table 2 also shows the number of cases treated by the ECPP physicians and the rate of *V. cholerae* 01 isolations.

The region-wise distribution of *V. cholerae* 01 by biotype is depicted in Table 3.

In 1992, *V. cholerae* 0139 Bengal emerged in Bangladesh, which is a derivative of the El Tor biotype that was responsible for an extensive epidemic. This new serogroup has now been detected in 11 countries and warrants close surveillance. While currently there is no evidence available to gauge the significance of these developments, the possibility of a new pandemic cannot be ruled out.

Several programmes and initiatives are in place to control cholera. Following research conducted on oral rehydration solution (ORS) by the ICDDR,B, the government has established a Control of Diarrhoeal Disease (CDD) Program throughout the country. Several initiatives, both by the government as well as non-governmental organisations (NGOs) to increase awareness about the benefits of ORS has led to a significant decrease in case fatality rates due to diarrhoeal diseases, including cholera.

Table 2 Diarrhoea epidemic surveillance of outbreaks in Bangladesh: 1985–1990

Government epidemic surveillance			ECPP epidemic investigation			
Year	No. of attacks	No. of deaths	No. of cases examined	No. of rectal swabs collected	*V. cholerae* 01	
					No. of positive	Per cent
1985	47,150	4,101	4,983	296	112	37.8
1986	53,046	3,997	3,432	211	78	36.9
1987[a]	303,391	4,726	3,692	312	141	45.1
1988[a]	988,391	3,676	13,879	1,967	764	38.8
1989	43,535	1,783	1,821[b]	419	226	53.9
1990	48,916	1,309	–[b]	–	–	–

[a] Years of heavy flooding
[b] ECPP non-operational from June 1989 to December 1990

Table 3 Distribution of *V. cholerae* 01 by biotype and region: Bangladesh (September 1988–May 1989)

Regions	No. of rectal swabs collected	*V. cholerae* 01 positive		
		Classical	El Tor	Rate per 1,000 swabs
North-Western	131	0	55	442
North-Eastern	702	2	272	359
Middle Belt	1,021	1	414	339
Southern	532	164	43	375
Total	2,386	167	784	

Regarding water and sanitation, a number of large donor-supported projects are being implemented to improve population access to safe water and adequate sanitation. These projects include the construction of piped water systems and water treatment facilities in urban areas, arsenic mitigation in rural areas and decentralised initiatives to build improved sanitation facilities. The Director General of Health Services (DGHS) has a diarrhoeal case-reporting system in place from all the districts and *upazila* (sub-district) hospitals in the country, but cholera surveillance is not routinely conducted by the Government, due to the lack of systematic laboratory testing in government facilities for the disease. This is why, in an effort to build an early warning system for infectious disease outbreaks, the IEDCR has developed a sentinel site, hospital-based Priority Communicable Disease Surveillance (PCDS) system, which tracks 13 priority diseases, including acute watery diarrhoea and others. In addition, IEDCR conducts laboratory-based surveillance during cholera outbreaks, often in collaboration with ICDDR,B. Several long-term, laboratory-confirmed surveillance studies of cholera and other diarrhoeal diseases are being conducted.

Overall, cholera is both endemic and causes epidemics in Bangladesh. Case fatality due to cholera is low, but mortality is still too high in the country.

Providing access to all Bangladeshis with adequate care for cholera and the prevention of severe dehydration requires increasing household use of ORS in rural areas and slums, and the use and access of public sector health facilities for the treatment of diarrhoeal diseases by the population. Improvement in the water and sanitation facilities for the whole population is likely to take many years, during which time cholera vaccination in the high risk population could provide a short- to medium-term solution to control the disease in Bangladesh. Moreover, it should be noted that cholera is not officially reported from Bangladesh. This could have political connotations or could arise from embargoes on trade and travel. However, this mindset needs to change in order to tackle the problem in a more holistic fashion.

4.2 India

India, which comprises 28 states and seven union territories, has a total population of 1.27 billion people and approximately two-thirds of the population lives in rural areas, where only 28 % use piped drinking water and 26 % access to good sanitation (MOHFW, Govt. of India 2013). Therefore, it is but natural that cholera continues to be an important public health problem in India. Cholera cases are severely under-reported mainly because disease surveillance is incomplete, laboratory capacity, especially in peripheral health centres, is inadequate. Importantly, the ground reality is that there is a breakdown in sanitation and safe water supply, which is often not acknowledged by the authorities for fear of societal repercussions.

Over the last decade or so, a large number of cholera outbreaks have occurred in India, with the highest frequency in West Bengal and Odisha (formerly Orissa). The other states which have reported cholera outbreaks include Tamil Nadu, Karnataka, Gujarat, Andhra Pradesh, Maharashtra, Punjab, Haryana and Delhi. These outbreaks are briefly described below.

4.2.1 West Bengal

In May 2010, a cluster of diarrhoeal disease cases were reported among the inmates of a shelter-home for mentally retarded females in Parbaksi village of Howrah district in West Bengal. Of the 101 inmates, 91 (90 %) developed diarrhoea, and three patients died (case fatality: 3 %). Four of the five stool specimens were positive for *V. cholerae* O1 Ogawa. Importantly, drinking of water from the pond-connected tube well (adjusted odds ratio: 25.7; 95 % CI: 2.7–236.4) was associated with the illness. Relocation of the pond-connected tube well away from the groundwater tube well, colour-coding of the tube wells meant for drinking purposes and regular disinfection of the tube wells were recommended (Datta et al. 2012).

In March 2010, an outbreak of diarrhoeal disease was reported among workers of a jute mill in Kolkata, West Bengal. Rectal swabs were collected from the hospitalised case-patients, and the local water supply system was assessed. In total, 197 case patients were identified among 5,910 residents of the workers' colony (attack rate: 3.33 %). Of 24 stool samples, 15 were positive for *V. cholerae* O1. The outbreak started on 7 March, peaked on 11 March and ended on 16 March 2010. Compared to 120 controls, 60 cases did not differ in terms of age and socioeconomic status. Drinking water from the reservoir within the mill premises was associated with the outbreak, which had been contaminated during a strike at which time the mill was closed. The outbreak occurred almost immediately after the strike was called off and the mill reopened (Mridha et al. 2011).

The year 2009 was marked by the occurrence of the super-cyclone *Aila* that passed through West Bengal and entered Bangladesh to wreak havoc. Three independent studies were carried out that centred around this cyclone. In one study, it was observed that following *Aila*, at the end of May, a block in the Sunderbans area of West Bengal reported increased cases of diarrhoea (Bhunia and Ghosh 2011). A matched case-control study was conducted and rectal swabs and water specimens were collected. In total, 1,076 probable case patients and 14 deaths (attack rate: 44/10,000) were identified. *V. cholerae* O1 El Tor Ogawa was isolated from two of the five probable case-patients' stool specimens. The outbreak started in the fourth week of May, with two peaks in the second and fourth weeks of June, and lasted until August 2009. Compared with controls, cases were more likely to drink non-chlorinated piped water [matched odds ratio (mOR): 16; 95 % CI: 4.9–51; population attributable fraction: 58 %] and were less likely to drink chlorine-treated water (mOR: 0.06; 95 % CI: 0.02–0.18). Villagers had broken the water pipelines near their houses for easy access to water, which subsequently led to faecal contamination. Importantly, there is a need for more education efforts at the ground level with regard to hygiene and sanitation. Another study examined two subdivisions in the district of Midnapore (East) in West Bengal, immediately following the aftermath of the tropical cyclone *Aila* (Panda et al. 2011). Significantly, increased occurrence of diarrhoea was observed in June 2009 in two subdivisions, namely Haldia and Egra (OR 1.6 and 1.3 respectively; 95 % CI: 1.52–1.65 and 1.21–1.32; $p < 0.001$) considering 2007 as baseline. *V. cholerae* grew from 54 % of the stool samples (21/39; 17 *V. cholerae* O1-Ogawa and four non-O1-non-139), confirming a community outbreak of cholera. Increased rate of admission in treatment centres due to diarrhoea in the whole district coincided with the formation of cyclone and showed over two-fold rise compared to the admission recorded 6 days prior. Haldia subdivision had the highest attack rate of nine per 1,000 in the month of June, 2009 whereas for the whole district it was five per 1,000 in the same month. It may be concluded from the study that pre-*Aila* changes in the environment, *Aila* and seasonality of diarrhoea in the study district interplayed towards increased occurrence of diarrhoea. The third study supported the other two studies as it investigated the environmental sources of *V. cholerae* associated with the cholera outbreak post-*Aila* (Palit and Batabyal 2010). A total of 33 water samples (from tap, tubewell and ponds) were analysed. From them, 11

(33.3 %) samples were found to be contaminated with *V. cholerae* among which 5 (45 %) isolates were *V. cholerae* O1 biotype Ogawa. Three (36 %) *V. cholerae* isolates were found to be *ctxB* positive (2 *ctxB* Classical).

The year 2006 saw another cholera outbreak in West Bengal (Bhunia et al. 2009). In April 2006, Garulia municipality reported a cluster of diarrhoea cases. A total of 298 cases of diarrhoea were reported to various healthcare facilities (attack rate: 3.5/1,000; no deaths). The attack rate was highest among children (6.4/1,000). *V. cholerae* El Tor O1 Inaba was isolated from two of seven rectal swabs. The outbreak started on 10 April, peaked on 26 April and lasted till 6 May. Importantly, cases clustered in an area distal to leaking water pipelines. Drinking municipal water exclusively was significantly associated with the illness (OR 13; 95 % CI: 6.5–27). Out of the 12 water specimens from the affected area, 8 had faecal contamination and poor chlorine content.

In rural West Bengal, outbreaks of cholera are often centred around ponds (*pukurs*) that is a feature of the environment. Five investigations of laboratory-confirmed, pond-centred outbreaks of cholera occurred between the years 2004 and 2008 (Mukherjee et al. 2011). Case–control odds ratios were approximated with relative risks (RRs) as the incidence was low. The environment was investigated to understand how the ponds could have become contaminated and could have infected villagers. These outbreaks led to 277 cases and three deaths (median attack rate: 51/1,000 people; case fatality: 1.1 %; median age of case-patients: 22 years; median duration: 13 days; range: 6–15 days). Factors significantly ($p < 0.05$) associated with cholera in the case-control ($n = 4$) and cohort investigations ($n = 1$) included washing utensils in ponds (four outbreaks; RR range: 6–12), bathing (three outbreaks; RR range: 3.5–9.3) and exposure to pond water, including drinking (two outbreaks; RR range: 2.1–3.2), mouth washing (one outbreak; RR: 4.8) and cooking (one outbreak; RR: 3.0). Initial case-patients contaminated ponds through washing soiled clothes ($n = 4$) or defecation ($n = 1$). This study reiterates the fact that ubiquitous ponds used for many purposes transmit cholera in West Bengal and there is a need for focused health education, hygiene and sanitation in order to protect the villagers.

4.2.2 Odisha

A large outbreak of cholera occurred during April–July 2009 in the Kendrapada district of Odisha (Pal et al. 2013). A total of 41 rectal swabs and 41 water samples, collected from diarrhoeal patients and from different villages were bacteriologically analysed for the isolation of bacterial enteropathogens, antibiogram profile and detection of various toxin genes. The bacteriological analyses of rectal swabs and environmental water samples revealed the presence of *V. cholerae* O1 Ogawa biotype El Tor. The multiplex polymerase chain reaction (PCR) assay on *V. cholerae* strains revealed the presence of *ctxA* and *tcpA* genes. The mismatch amplification of mutation assay (MAMA) PCR on clinical and environmental isolates of *V. cholerae* revealed that the strains were El Tor biotype, which

harboured the *ctx* gene of the classical strain. The random amplified polymorphic DNA (RAPD) PCR analysis and pulsed-field gel electrophoresis (PFGE) results indicated that the *V. cholerae* isolates belonged to the same clone. The investigation gives a warning that the El Tor variant of *V. cholerae* has spread to the coastal areas of Odisha that requires closer monitoring and surveillance.

An outbreak of cholera in Odisha in 2008 (Kumar et al. 2009) resulted in collection of 32 *V. cholerae* isolates. All the isolates belonged to serogroup O1, biotype El Tor, serotype Ogawa. Two multiplex PCR assays confirmed the presence of various toxigenic and pathogenic genes in all of the isolates, suggesting infection of isolates by classical CTXφ. The molecular diversity of *V. cholerae* isolates studied by enterobacterial repetitive intergenic consensus sequence PCR, BOX-PCR and RAPD analysis uniformly showed the clonal relationship among the outbreak *V. cholerae* O1 isolates. The results of this study suggest that cholera-causing *V. cholerae* strains are constantly evolving in epidemic areas, highlighting the potential of the emergence of more virulent strains.

An outbreak of cholera occurred in Kashipur and Dasmantpur blocks of Odisha during July–September 2007 (Pal et al. 2010). A total of 60 rectal swabs and 28 water samples collected from diarrhoea patients at different hospitals and villages were bacteriologically analysed for the identification, antibiogram and detection of toxic genes of *V. cholerae*. The outbreak was caused by *V. cholerae* O1 Ogawa biotype El Tor in both Kashipur and Dasmantpur blocks. The multiplex PCR assay revealed that all the clinical and environmental *V. cholerae* isolates were positive for the *ctxA* and *tcpA* genes, showing biotype El Tor. Interestingly, 88 % of the *ctxB* gene of the classical strain, as confirmed by MAMA-PCR assay. Importantly, this was the first report of the El Tor variant of *V. cholerae* O1 Ogawa having the *ctxB* gene of the classical strain with altered antibiogram causing epidemics of cholera in Odisha.

Two sequential outbreaks of severe diarrhoea were investigated in two neighbouring villages of Odisha in 2005 (Das et al. 2009a). The attack rates were 5.6 % (n = 62) and 5.2 % (n = 51), respectively. One death was reported in the second village (case fatality: 2 %). Consumption of milk products prepared in the household of the index case (mOR: 5.7; 95 % CI: 1.7–30] in the first village and drinking well water in the second village were associated with the illness (mOR: 4.7; 95 % CI: 1.6–19). *V. cholerae* El Tor O1 Ogawa was isolated from stool samples from both the villages. Mishandling of milk products led to the cholera outbreak in the first village, which led to sewerage contamination of a well and another outbreak in the second village. The study re-emphasises the need to prevent environmental contamination during cholera outbreaks.

In November 2003, an outbreak of severe diarrhoea was reported from Parbatia, a village in Odisha (Das et al. 2009b). There were 41 cases, with an attack rate of 4.3 %, and no deaths. Thirteen of these cases were hospitalised. A matched case-control study was conducted to identify the possible exposure variables. Descriptive epidemiology suggested clustering of cases around one public well. *V. cholerae* El Tor O1, serotype Ogawa was isolated from four of six rectal swabs. The water from the public well was associated with the outbreak (mOR: 12; 95 %

CI: 1.2–44.1). On the basis of these conclusions, access to the well was immediately barred. Importantly, the study highlights the broader use of field epidemiology methods to implement public health actions guided by epidemiologic data to control an epidemic of cholera.

4.2.3 Tamil Nadu

An outbreak of cholera occurred in Uthamapalayam village, Theni district of Tamil Nadu in May 2010 (Sekar et al. 2012). Stool and rectal swab specimens were collected from the randomly selected patients attending the Government Theni Medical College (GTMC) Hospital and various primary healthcare centres of Theni district for bacteriological investigation. Of the 66 faecal samples collected, *V. cholerae* O1 was isolated in 37 samples (56 %). All the isolates of *V. cholerae* were identified as El Tor biotype and Ogawa serotype. The samples collected from the village were found to be contaminated with El Tor *V. cholerae* O1, Ogawa serotype. During this outbreak, one death was recorded.

Cholera has been associated with rainfall and flooding events by contamination of potable water with environmental *V. cholerae*. The continuation of the epidemic in a region, however, is often due to secondary transmission of the initial outbreak strain through human excreta. A study from Chennai, Tamil Nadu reports, on the contrary, a rapid shift of genotype from one *V. cholerae* strain to another one in an epidemic region (Goel and Jiang 2011). The isolates were characterised by PCR, antibiogram and genomic fingerprinting analysis. The results showed that in spite of the similarity of toxin genes and antibiogram, the *Vibrio* isolates grouped into two different clusters based on the ERIC-PCR fingerprinting. Each cluster corresponded to a distinct peak of cholera outbreak, which occurred after separate heavy rainfall. The results suggested that the rainfall event can bring various genotypes of *V. cholerae* strains causing multiple outbreaks.

4.2.4 Karnataka

A cholera outbreak occurred in a village in Kolar district of Karnataka in early 2012 (Deepthi et al. 2013). A total of 73 cases were reported during the outbreak, with an attack rate of 17.5 %. Attack rates were similar among males and females and the highest rates were observed among the elderly (33.3 %), while the lowest rates were observed among adults (14.7 %). Importantly, most households (81 %) surveyed did not use any method of water purification, 79.7 % practiced open field defecation and 58.2 % practiced inadequate hand washing, indicating poor sanitary practices. Cases were most commonly observed in houses which did not practice any method of water purification ($p < 0.001$) and among people living below the poverty line ($p = 0.02$). Of importance, despite the high attack rate, no deaths were reported.

4.2.5 Gujarat

An outbreak of gastroenteritis broke out in Lalpur town, Jamnagar district of Gujarat on 19 December 2010 (Shah et al. 2012). Although initially 57 cases were reported, this number increased to 330 between 19 December 2010 and 2 January 2011. Nineteen patients were found to be positive for *V. cholerae* O1 (Ogawa) out of 117 stool samples. The outbreak had an attack rate of 1.88 % with no mortality. Investigations revealed that the epidemic was waterborne. Ten leakages were found in the pipelines of the affected areas of Lalpur town.

4.2.6 Andhra Pradesh

Thirty-four *V. cholerae* isolates collected from a cholera outbreak in Hyderabad, Andhra Pradesh in 2010 (Goel et al. 2011), were found to belong to serogroup O1 biotype El Tor serotype Ogawa. All the isolates were found to be PCR positive for *ctxAB*, *ompW*, *rflO1*, *rtxC* and *tcpA* genes. All the isolates but one harboured *rstR* (El Tor) allele. However, one isolate carried both *rstR* (El Tor) as well as *rstR* (Classical) alleles. Cholera toxin (*ctxB*) genotyping of the isolates confirmed the presence of altered CTB of classical biotype in all the isolates. The results of this study suggest that altered El Tor biotype *V. cholerae* with the classical cholera toxin gene are involved in cholera outbreaks in India.

4.2.7 Maharashtra

A cholera outbreak occurred in Solapur, Maharashtra in 2010 (Jain et al. 2011). A total of 41 *V. cholerae* isolates were found to belong to serogroup O1, biotype El Tor and serotype Ogawa. All the isolates harboured *rstR* (El Tor) allele indicating the presence of CTXΦ (El Tor). However, cholera toxin (*ctxB*) gene sequencing and a *ctxB* allele specific PCR of the isolates confirmed the presence of *ctxB* of classical biotype. All the isolates were PCR positive for class 1 integron and SXT elements also. Fingerprinting analysis revealed the clonal relationship among the outbreak isolates. The results suggested the involvement of multi-drug resistant *V. cholerae* El Tor biotype isolates having *ctxB* gene of classical biotype in the cholera outbreak.

4.2.8 Punjab and Haryana

In Punjab and Haryana states of northern India, during July–September 2007, six clusters of cholera outbreak were identified (Taneja et al. 2009). A total of 745 case-patients were admitted to local governmental hospitals; the attack rate was 183/1,000 population. Four deaths were reported (case-fatality rate: 0.5 %). The number of cases per cluster varied from 15 to 400, and adults were primarily

affected (74 %); 20 % of patients had severe dehydration. *V. cholerae* O1 Ogawa was confirmed from stool cultures by using standard techniques. Of 53 water samples tested during the 2007 outbreak, 4 grew *V. cholerae*. Three samples were confirmed to be non-O1, non-139 strains. Only one isolate was *V. cholerae* O1, which was positive for *tcp*, *ctxA* and *ctxB* of both Classical and El Tor types. The four deaths from cholera, along with adult preponderance, high attack rate, more severe illness and six different clusters, point towards a change in the disease's epidemiology. This change may be related to circulation of the hybrid vibrios in the region.

4.2.9 Chandigarh

An outbreak of cholera occurred in Chandigarh in 2002 (Taneja et al. 2009). In this outbreak one death was reported (case-fatality rate: <0.01 %); the attack rate was 20/1,000, 58.6 % were children and only 10 % had severe dehydration.

4.2.10 Delhi

There was a cholera outbreak in Delhi in 2005 (Rajeshwari et al. 2008). *V. cholerae* O1 El Tor serotype Ogawa has been responsible for most of the cholera outbreaks in India. The 2005 outbreak in Delhi documented the occurrence of *V. cholerae* O1 Inaba as a predominant causative organism of cholera in children. All strains isolated were sensitive to gentamicin and a high level of resistance towards nalidixic acid and amoxicillin was seen. No case fatality was reported.

4.3 Nepal

Nepal, officially known as the Democratic Republic of Nepal, is a landlocked sovereign state located in South Asia. It is located in the Himalayas and bordered to the north by China, and to the south, east and west by India. It has a population of approximately 27 million, with approximately 2 million absentee workers living abroad.

Documented cholera is fairly new to Nepal. The first report of cholera was officially published in the years 1958–1960 in Kathmandu by a medical doctor visiting Nepal (Dixit et al. 2011). In November 2011, there was a small outbreak of cholera in Saptari district of eastern Nepal, which was investigated by the B.P. Koirala Institute of Health Sciences. Importantly, two people from *Tilathi* village died in this outbreak. Clinical and water samples were collected from three wards with active cases of diarrhoeal illness. Five clinical samples from symptomatic individuals without any antibiotic administration and four water samples (pond and underground) were collected for investigation. The causative agent of

diarrhoeal illness was found to be *V. cholerae* O1, El Tor, Ogawa serotype, in three clinical and water samples each. Phenotypically, the isolates from the pond water samples were identical to the samples isolated from the patients. This finding suggests that the clinical isolates probably disseminated from the pond. In this context, the villagers had recently celebrated one of their important festivals, *Chhath*; the rituals for which are performed in ponds. Moreover, the habit of open defecation and use of pond water as a major source of water for drinking, cooking and bathing had a foremost role in the cholera outbreak. Importantly, the people seemed to be aware of the spread of diarrhoeal illnesses but were not motivated to use their toilets at home, thereby aggravating the problem.

There was an outbreak of diarrhoeal diseases in districts of far-western region of Nepal in early-2009 followed by a massive outbreak in Jajarkot district of mid-western region in late-2009 (Bhandari and Bhusal 2013). A descriptive study was conducted from three districts of the far-western region (Achham, Baitadi and Doti) from middle of April to September 2009 to observe the trend of morbidity. Similarly, 51 stool samples were taken from the patients for laboratory analysis. Out of the total 51 stool samples tested, 27 were diagnosed as *V. cholerae*. All the isolates were sensitive to commonly used antibiotics except Nalidixic acid and Cotrimoxazole. The highest number of cases were seen in the month of July–August.

A prospective study was carried out at Dhulikhel Hospital, Kathmandu University Teaching Hospital, Kavrepalanchok during 1 May 2004 to 31 October 2004 (Tamang et al. 2005). A total of 148 stool samples from patients with acute diarrhoea were collected for investigation. Out of the 148 stool samples, 46 cases (31 %) were found to be positive for *V. cholerae* serogroup O1, biotype El Tor and serotype Ogawa. Both sexes were equally affected. The young age group of less than 30 years was mostly affected. *Brahmin* was the most affected ethnic group. The isolates were sensitive to all the antibiotics tested except cotrimoxazole. Among the laboratory-confirmed cholera cases 30 % exhibited co-infection with other parasites among which *Giardia lamblia* and *Ascaris lumbricoides* were the most common.

Seasonal outbreaks of cholera have been reported from Kathmandu in 1995 (Ise et al. 1996). *V. cholerae*, O1 biotype El Tor Ogawa was the major causative agent of these outbreaks. The pattern of spread suggested a waterborne infection related to contaminated river water and this was confirmed by a field survey. Although the mortality rate was low, younger children were more susceptible. It has been suggested that in the Kathmandu Valley, a major problem is the old water supply infrastructure, which is prone to leakages leading to contamination of the drinking water (Sharma 2006).

A study was conducted from May 1995 to April 1996 to track cholera outbreaks (Pokhrel and Kubo 1996). One thousand one hundred seven children with acute diarrhoea receiving Oral Rehydration Therapy (ORT) at National Kanti Children's Hospital were included in the study. Stool samples were investigated, but none showed growth of *V. cholerae* 0139 synonym Bengal. In Nepal, *V. cholerae* could be isolated from June to November. From December to May, no cases of

V. cholerae were detected. Mixed infections along with *V. cholerae* were also seen in 29 % of cholera patients. *V. cholerae* O1, Hikojima types were the major isolates in the study followed by Ogawa type. *V. cholerae*, Hikojima and Ogawa serotypes were associated with mixed infection in 16.1 and 12.9 % of patients, respectively. These isolates were associated with *Shigella*, *Salmonella* and pathogenic *E. coli*.

During 1991, a substantial cholera outbreak occurred in Nepal (WHO 1992). It presented as one of the causes of a multicausal gastroenteritis epidemic which reportedly resulted in nearly 92,000 cases and 1,800 deaths. The 1991 epidemic appeared to have been more severe with a longer duration than the epidemic which occurred in 1990. The overall case-fatality rate was 2.0 %. Cholera was confirmed in 63 % of faecal specimens processed, compared with 46 % during the 1990 epidemic. Specimens from the first and last laboratory-confirmed cases were collected on 14 June and 26 September 1991, respectively. The presence of cholera was confirmed in all five developmental regions in the country and contaminated water was incriminated in sustaining the transmission.

4.4 Sri Lanka

Sri Lanka, officially the Democratic Socialist Republic of Sri Lanka, is an island country in the northern Indian Ocean off the southern coast of the Indian subcontinent in South Asia, known until 1972 as Ceylon. Sri Lanka has maritime borders with India to the north-west and the Maldives to the south-west.

In all, there has been three publications from Sri Lanka that documents the spread of El Tor in the country during the early and mid-1970s (Mendis et al. 1975, 1977; Sivagnanasundram et al. 1975). However, no abstracts are available for these. Other than these, there are no reports of any cholera outbreaks.

4.5 Thailand

Thailand, officially the Kingdom of Thailand, formerly known as Siam, is a country located at the centre of the Indochina peninsula in South-East Asia. It is bordered in the north by Myanmar and Laos, in the east by Laos and Cambodia, in the south by the Gulf of Thailand and Malaysia and in the west by the Andaman Sea and the southern extremity of Myanmar.

A study was undertaken to characterise *V. cholerae* O1 isolates from outbreaks in Thailand with special reference to genotypic variations over time (Okada et al. 2012). A total of 343 isolates of *V. cholerae* O1 from cholera outbreaks from 2007 to 2010 were investigated, and 99.4 % were found to carry the classical cholera toxin B subunit (*ctxB*) and El Tor *rstR* genes. Pulsed-field gel electrophoresis differentiated the isolates into 10 distinct pulsotypes, clustered into two major groups, A and B, with an overall similarity of 88 %. Ribotyping, multiple-locus

variable-number tandem-repeat analysis (MLVA), and PCR to detect Vibrio seventh pandemic island II (VSP-II) related genes of randomly selected isolates from each pulsotype corresponded to the results obtained by PFGE. Epidemiological investigations revealed that MLVA type 2 was strongly associated with a cholera outbreak in north-eastern Thailand in 2007, while MLVA type 7 dominated the outbreaks of the southern Gulf areas in 2009 and MLVA type 4 dominated the outbreaks of the central Gulf areas during 2009–2010. Only MLVA type 16 isolates were found in a Thai–Myanmar border area in 2010, whereas those of MLVA types 26, 39 and 41 predominated this border area in 2008. Type 39 then disappeared 1–2 years later as MLVA type 41 became prevalent. Type 41 was also found to infect an outbreak area. Importantly, in the present study, MLVA provided a high-throughput genetic typing tool for understanding the in-depth epidemiology of cholera outbreaks.

A number of outbreaks of food borne cholera have occurred in Thailand over the years. Two consecutive outbreaks involved the consumption of Hainanese chicken rice, a Chinese delicacy, in north-western Thailand in April 2010 (Swaddiwudhipong et al. 2012). The two outbreaks involved persons who attended two meetings. The first outbreak involved 17 cholera cases (35.4 %) among 48 attendants and 16 cases in the community. The onset of symptoms was between 19 and 23 April 2010. People who ate the chicken rice had a higher attack rate of infection than those who did not. All 12 food handlers at the implicated food shop were screened for cholera infection by rectal swab, culture; three were culture-positive. Although the food shop was closed temporarily following the outbreak, some chicken rice was produced and served at the second meeting and caused 11 more cases (23.4 %) among 47 meeting attendants. All cholera isolates obtained from patients and food handlers were *V. cholerae* O1, biotype El Tor and serotype Ogawa. Another foodborne cholera outbreak occurred among tourists in a cruise liner sailing in South-East Asia (Boyce et al. 1995). Serum samples were collected from all passengers reporting diarrhoea. A case was defined as diarrhoeal illness with onset between 8 and 28 February 1994 and a cholera antitoxic titer more than or equal to 800. Six passengers met the case definition. Illness was associated with eating yellow rice at a buffet restaurant in Bangkok. This international outbreak demonstrates foodborne transmission of *V. cholerae* O139 Bengal, an emerging cause of epidemic cholera in Asia, to tourists from Western countries. Another foodborne outbreak of cholera occurred in July 1988 with 71 culture-confirmed cases of biotype El Tor, serotype Ogawa, which occurred in a non-endemic area in Mae Sot district, Tak Province (Swaddiwudhipong et al. 1992). Fifty-two cases had diarrhoea and 19 had asymptomatic cholera infection. No deaths were recorded. Epidemiological investigation revealed a significant association between cholera infection and the consumption of uncooked beef. The beef was possibly contaminated with *V. cholerae* O1 from an infected butcher. In yet another outbreak of foodborne cholera, which occurred in a village near Chiangmai in October 1987, 264 attendants of a funeral were affected (Swaddiwudhipong et al. 1990). All the attendants were screened for infection by bacteriological examination of their rectal swabs and were kept under diarrhoeal surveillance. Of them, 20

patients and 40 matched controls were interviewed about the details of their eating foods served at the funeral. *V. cholerae* O1, Inaba, El Tor was detected from 24 persons (9.1 %), 15 of whom suffered from mild diarrhoea and the rest 9 had inapparent infections. There were no deaths. The only significant association ($p < 0.01$; OR = 15) was found between an attack of cholera and eating *laeb-moo*—an uncooked pork preparation with Thai spices and chilli. The transmission of cholera appeared to have occurred through eating the uncooked pork presumably due to its contamination with *V. cholerae* shed by the infected butcher. As outbreaks of foodborne diseases, including cholera, have been reported frequently after the consumption of raw food in many parts of Thailand, preventive educational efforts should be directed towards modifying the traditional behaviour patterns of consuming raw food among the Thai people.

A couple of nosocomial cholera outbreaks have been reported from Thailand over the years. One study reports nosocomial cholera outbreak in a general hospital located in a Thai–Myanmar border area (Swaddiwudhipong and Peanumlom 2010). Between May and October 2007, a community outbreak of cholera with 477 cases took place in Mae Sot District, Tak Province. A 71-year-old diabetic female who had undergone craniotomy following intracerebral haemorrhage contracted nosocomial cholera with mild diarrhoea on 6 August 2007, 37 days after admission in a female ward of the Mae Sot hospital. She received a nasogastric tube-fed diet four times a day. The investigation suggested that the tube-fed diet might have been contaminated with *V. cholerae* O1 directly from an infected caregiver. Importantly, the concerned caregiver was culture-positive for cholera of the same biotype, serotype and antibiograms. Another study reports that from 30 October to 7 December 1984, an outbreak of nosocomial cholera involving 11 cases of biotype El Tor, serotype Inaba, took place in a 755-bed hospital in southern Thailand (Swaddiwudhipong and Kunasol 1989). The outbreak occurred primarily among patients admitted with severe illness. Of the 11 cases, 7 were children and 4 were adults. Most cases had mild symptoms of cholera and no case died in the outbreak. The first two cases occurred sporadically with a subsequent cluster of cases showing an explosive pattern. A case–control study found that a history of receiving liquid tube-fed diet was significantly more common among cholera cases than their matched controls, but it could not be determined how the diet was contaminated with cholera.

Outbreaks of cholera occurred twice in the same institutional home for mentally retarded persons, once in 1987 (Swaddiwudhipong and Limpakarnjanarat 1991) and again in 1992 (Jiraphongsa et al. 1994). The first outbreak in June–July 1987 was caused by *V. cholerae* O1, biotype El Tor, serotype Inaba. Of the 447 retarded inmates, 74 were found to be infected and 1 died. The second outbreak occurred between 29 July and 9 August 1992, and was due to the Ogawa strain. The clinical attack rate was 8 % of 440 children; there were two deaths.

Cholera outbreaks occurred in Thailand in 2007 (Okada et al. 2010). Isolates from the north-eastern regions were analysed. Interestingly, the outbreak strain was identified as biotype El Tor; serotype Ogawa with cholera toxin B subunit gene (*ctxB*) of the classical type and CTX prophage repressor gene of the El Tor

type. The clone was genetically closely related to pulsotype H, which is predominantly found in India. It was probably subsequently introduced into Thailand quite recently.

There was a cholera outbreak in 2007 that involved mainly Myanmar migrants living in overcrowded conditions with poor sanitation in a Thai–Myanmar border district (Swaddiwudhipong et al. 2008). Both passive and active case surveillance were carried out in Mae Sot District, Tak Province since the beginning of the outbreak. Samples of various types of drinking and non-drinking water from the infected areas, communal waters and some selected foods were analysed for the presence of cholera contamination. A case–control study was conducted to determine the vehicle of cholera transmission among Myanmar migrants in one municipal community with a cluster of 72 cholera cases. Between May and October 2007, 477 cholera cases of biotype El Tor, serotype Inaba, were identified in the district. The majority of them (93.1 %) were detected by active case surveillance in the communities. None died in this outbreak. Most (84.9 %) were Myanmar migrants and the remainder were local Thai residents. Three samples of seafood illegally imported from Myanmar were positive for cholera of the same biotype and serotype. A total of 15 of 324 (4.6 %) food handlers in the district were found to carry *V. cholerae* O1. A case–control study in one municipal community revealed a significant association between infection and frequently having food purchased from one infected food handler.

An unusually high incidence of *V. cholerae* O1 infection was observed in southern Thailand between late December 1997 and March 1998. Fifty-seven *V. cholerae* O1 strains were isolated in five provinces during the outbreak and were examined (Kondo et al. 2001). They were El Tor Ogawa strains exhibiting similar antibiograms. All strains were resistant to tetracycline, which had not been reported in Thailand since 1993. All southern Thailand strains and the 1998 international traveller strain of Thai origin showed indistinguishable genetic fingerprinting patterns that were distinct from those of other test strains. The results suggest that a tetracycline-resistant clone newly emerged in late December 1997 caused the large outbreak in southern Thailand and that the variants with a slightly different antibiogram appeared during the course of the spreading epidemic.

An epidemic of a cholera-like disease occurred among Khmers in a camp in Aranyaprathet, Thailand, in May 1990 (Bagchi et al. 1993). Of 215 patients with diarrhoea, *V. cholerae* O1 was isolated from 25 (12 %) and *V. cholerae* non-O1 was isolated from 15 (7 %). Five of 15 (33 %) non-O1 *V. cholerae* isolates hybridised with two different oligonucleotide probes previously used to detect *V. cholerae* non-O1 that produces a heat-stable toxin. Importantly, this was the first description of an epidemic of diarrhoea caused by *V. cholerae* non-O1 that produces heat-stable toxin.

From September through October 1987, a cholera outbreak involving 59 cases of biotype El Tor, serotype Inaba occurred in Sunpathong district, Chiang Mai (Swaddiwudhipong et al. 1989). No cases died. A total of 27 cases were males and 32 were females. The age ranged between 4 months and 85 years, with a median of 36 years. The outbreak affected seven small communities, and showed different

vehicles of infection. Six housewives and one girl were infected with cholera in the first localised outbreak. The transmission of infection appeared due to the consumption of packed food contaminated by an infected food handler. In the second localised outbreak, six young males acquired cholera after eating uncooked fish harvested from a canal contaminated with *V. cholerae*. Another outbreak of cholera with 24 culture-confirmed cases occurred among guests at a funeral held in one rural village. The source of infection was traced to uncooked pork contaminated from an infected butcher.

4.6 Indonesia

Indonesia, officially the Republic of Indonesia, is a sovereign state in South-East Asia and Oceania. Indonesia is an archipelago comprising approximately 17,508 islands. It encompasses 34 provinces with over 238 million people, making it the world's fourth most populous country. The nation's capital city is Jakarta. The country shares land borders with Papua New Guinea, East Timor and Malaysia. Other neighbouring countries include Singapore, the Philippines, Australia, Palau and the Indian territory of the Andaman and Nicobar Islands.

Indonesia has been plagued by the consumption of street food as a major health risk, particularly in its capital, Jakarta. Importantly, edible ice used in the preparation of street food has been incriminated as a major source of *V. cholerae* contamination, as two recent papers testify (Waturangi et al. 2012, 2013).

Cholera-specific surveillance in Indonesia was initiated to identify the introduction of the newly recognised *V. cholerae* non-O1, O139 serotype (Simanjuntak et al. 2001). Findings from 7 years (1993–1999) of surveillance efforts yielded regional profiles of the importance of cholera in both epidemic and sporadic diarrhoeal disease occurrence throughout the archipelago. Outbreak findings showed that *V. cholerae* O1, Ogawa serotype, was the predominant aetiology in all 17 instances of investigated epidemic transmission. Importantly, there was no instance of non-O1, O139 serotype introduction in either epidemic or sporadic disease form.

An outbreak of El Tor biotype cholera occurring in a rural village in Irian Jaya, Indonesia was evaluated for risk factors associated with death from cholera (Korthuis et al. 1998). Among those dying in the village during the epidemic, a significant association between membership in one of the five tribal groups in the village complex was associated with an elevated risk of suffering a cholera death (OR: 5.9). Interviews with members of the decedents' families revealed a very strong association (OR: 11.6) between risk of cholera death and having attended the 2-day funeral of a woman who died of cholera-like illness a few days prior to an outbreak of cholera-like diarrhoeal disease in the village complex. Importantly, recent flooding may have contributed to the creation of an environment conducive to cholera transmission.

4.7 Other Countries Within the WHO SEARO Classification System

The other countries within the WHO SEARO classification system, namely Bhutan, Maldives, Myanmar, Timor Leste and the Democratic People's Republic of Korea have no documented reports of cholera outbreaks from within their borders.

4.8 South-East Asian Countries Where Cholera Outbreaks have been Reported but Which are Outside the WHO SEARO Classification System

Below, we describe a few countries where cholera outbreaks have been reported from time to time, and which are within the confines of South-East Asia, but which are excluded from the WHO SEARO Classification System.

4.8.1 Malaysia

Malaysia is a federal constitutional monarchy in South-East Asia. It consists of thirteen states and three federal territories. It is separated by the South China Sea into two similarly sized regions, Peninsular Malaysia and Malaysian Borneo. Land borders are shared with Thailand, Indonesia and Brunei, and maritime borders exist with Singapore, Vietnam and the Philippines. The capital is Kuala Lumpur, while Putrajaya is the seat of the federal government.

Malaysia is a country that has been associated with a number of cholera outbreaks. For example, in November 2009, a cholera outbreak in Terengganu, Malaysia was caused by two El Tor *V. cholerae* variants resistant to typical antimicrobial drugs (Teh et al. 2012). Importantly, evidence of replacement of treatable *V. cholerae* infection in the region with antimicrobial-resistant strains calls for increased surveillance and prevention measures.

A cholera outbreak occurred in Kelantan, Malaysia between November and December 2009, in which a total of 20 *V. cholerae* isolates were recovered for investigation (Ang et al. 2010). All isolates were biochemically characterised as *V. cholerae* serogroup O1 Ogawa of the El Tor biotype. The isolates were found to be resistant to multiple antibiotics. However, all isolates were sensitive to ciprofloxacin, norfloxacin, chloramphenicol, gentamicin and kanamycin. Multiplex PCR analysis confirmed the biochemical identification and revealed the presence of virulence genes, viz. *ace*, *zot* and *ctxA*, in all of the isolates. Interestingly, the sequencing of the *ctxB* gene showed that the outbreak strain harboured the classical cholera toxin gene and therefore belonged to the newly assigned El Tor variant biotype. Clonal analysis by PFGE demonstrated that a single clone of a

V. cholerae strain was responsible for the outbreak. Importantly, this was the first molecular evidence that the toxigenic *V. cholerae* O1 El Tor variant had invaded Malaysia.

There was an outbreak of cholera in Miri, Sarawak, Malaysia between November 1997 and April 1998 (Radu et al. 2002). The data on antimicrobial susceptibility patterns of *V. cholerae* O1 from patients during the outbreak period were found to be high but with variable rates of multi-drug resistance. Thirty-two of 33 *V. cholerae* isolates harboured the *tcp*, *ctx*, *zot* and *ace* genes, suggesting their possible roles in the outbreak cases. The molecular diversity of the isolates was analysed by RAPD. The 30 typable isolates could be separated into four major clusters containing 5, 17, 2 and 6 isolates, respectively. However, no particular RAPD pattern was predictive of a particular pattern of antibiotic susceptibility. The findings of the study indicated that multiple clones seemed to be responsible for the cases in the outbreak.

Forty-three clinical strains of *V. cholerae* O1 biotype El Tor were isolated between 3 May and 10 June 1998 during an outbreak in the metropolitan area of Kuala Lumpur and its suburbs (Vadivelu et al. 2000). With the exception of three Inaba strains that were restricted to three members of a family, all the others belonged to the Ogawa serotype. The strains were analysed for clonality using ribotyping and PFGE. Two ribotypes, V/B21a and B27, were identified among 40 Ogawa isolates using BgII restriction endonuclease. Ribotype V/B21a has been described previously from Taiwan and Colombia and several Asian countries, while B27 has been reported among isolates from Senegal. The three Inaba strains belonged to one ribotype, designated type A, not previously reported. Pulsed-field gel electrophoresis analysis using NotI revealed that all isolates within a ribotype had identical profiles demonstrating clonality amongst the strains. Dice coefficient analysis of the two Ogawa genotypes revealed 89 % similarity on ribotype patterns and 91.3 % on PFGE profiles. Ribotype V/B21a isolates were associated with cases from dispersed areas of Kuala Lumpur and its suburbs while ribotype B27 was restricted to cases from one particular area suggesting a common-source outbreak.

4.8.2 Singapore

Singapore, officially the Republic of Singapore, is a South-East Asian island city-state off the southern tip of the Malay Peninsula. An island country made up of 63 islands, it is separated from Malaysia by the Straits of Johor to its north and from Indonesia's Riau Islands by the Singapore Strait to its south.

An epidemiological investigation of cholera was carried out in Singapore between 1992–2007 in order to elucidate its characteristics as well as the factors contributing to its occurrence (Wong et al. 2010). Epidemiological data of all notified cases of cholera maintained by the Communicable Diseases Division, Ministry of Health, for the period 1992–2007 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 Square test for trend. There were a total of 210 cholera cases reported between 1992 and 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 %. *V. cholerae* O1, 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.

An outbreak of cholera caused by *V. cholerae* O1, biotype El Tor, serotype Inaba, phage type 4, occurred in an institution for the aged in Singapore in August and September 1984 (Goh et al. 1987). Ninety-six inmates were infected (21 symptomatic and 75 asymptomatic) and five died. The index case was a 72-year-old male inmate who continued to assist in food preparation in the kitchen from the time on onset of diarrhoea until he was seriously ill and hospitalised 4 days later. Another kitchen helper was found to have asymptomatic *V. cholerae* O1 infection. The infection rate for males was significantly higher than that for females ($p < 0.025$), associated with the use of unsanitary toilets. The main mode of transmission was through food contaminated by the two kitchen helpers who probably accounted for most of the infections, while poor personal hygiene of the inmates helped to sustain person-to-person spread.

An outbreak of cholera broke out in a group of foreign construction workers in Singapore between 3 and 11 November 1982 (Goh et al. 1984). The outbreak pathogen was *V. cholerae* O1, biotype El Tor, serotype Ogawa, phage type 1. Epidemiological investigations revealed that a total of 22 workers were confirmed to have cholera and another 15 had asymptomatic *V. cholerae* O1 infection. The source of infection was traced to contaminated seafood prepared at the construction site canteen where two food handlers were found to be infected with *V. cholerae* O1. The incubation period of cholera in this outbreak ranged from 4 to 203 h with a median of 38 h. Luckily, only two workers had moderate to severe dehydration and required intravenous therapy.

4.8.3 Philippines

The Philippines, officially known as the Republic of the Philippines, is a sovereign island country in South-East Asia in the western Pacific Ocean. To its north across the Luzon Strait lies Taiwan. West across the South China Sea sits Vietnam. The Sulu Sea to the southwest lies between the country and the island of Borneo, and to the south the Celebes Sea separates it from other islands of Indonesia. It is bounded on the east by the Philippine Sea. Its location on the Pacific Ring of Fire and its tropical climate make the Philippines prone to earthquakes and typhoons but have also endowed the country with natural resources and made it a mega-diverse country. Its capital city is Manila.

A cholera outbreak occurred in Pohnpei Island (Micronesia) in which vaccination was used as a control measure (Calain et al. 2004). Mass vaccination with the single-dose live-attenuated oral cholera vaccine CVD 103-HgR was carried out as a potential adjunct measure. Importantly, the outbreak provided a unique opportunity to evaluate the practicality of use and effectiveness of the vaccine. Under field conditions encountered in Pohnpei, crude vaccine efficacy was estimated at 79.2 % (95 % CI: 71.9–84.6 %) in the target population. Retrospective analysis suggests that mass vaccination with oral cholera vaccines can be a useful adjunct tool for controlling outbreaks, particularly if implemented early in association with other standard control measures.

During surveillance for cholera in the community of Can-Itom (Negros Occidental, Philippines) in which the disease is endemic, a limited outbreak of cholera occurred (WHO 1970). Although it was not possible to determine how the infection arose, the index case was detected and the spread of infection traced. The infection was found to be transmitted initially from person-to-person until the water of a dug well became contaminated, as a result of which a waterborne outbreak of a rather explosive nature occurred. Although 25 out of 288 individuals living in the community were infected with the El Tor biotype of *V. cholerae*, there was no manifest case of cholera; 13 persons had mild diarrhoea and 12 were asymptomatic. The outbreak subsided without any control measures having been adopted.

The introduction of cholera into many of the islands of the Philippines in 1961 often occurred in an explosive manner. The disease was introduced into Bacolod City and Talisay in Negros Occidental Province in such a manner in November 1961 (WHO 1965). The hospital and health department records in Bacolod City and Talisay and the results of interviews conducted with adult patients 10 months after the explosive outbreak were carefully analysed. The results suggest that infection during the initial explosive wave of cases in Bacolod City and Talisay in November 1961 was transmitted principally by consumption of raw shrimp.

4.8.4 Vietnam

Vietnam, officially the Socialist Republic of Vietnam, is the easternmost country on the Indochina Peninsula in South-east Asia. The country is bordered by China to the north, Laos to the north-west, Cambodia to the southwest and South China Sea to the east. Its capital city has been Hanoi since the reunification of North and South Vietnam in 1976.

Since 2007, there has been a re-emergence of cholera outbreaks in northern Vietnam. To understand the molecular epidemiological relatedness and determine the antibiotic susceptibility profiles of responsible *V. cholerae* O1 outbreak strains, a representative collection of 100 *V. cholerae* O1 strains was characterised (Tran et al. 2012). *V. cholerae* O1 strains isolated from diarrhoeal patients in northern Vietnam between 2007 and 2010 were investigated for antibiotic susceptibility and characterised by using phenotypic and genotypic tests, including PFGE analysis.

The results revealed that all isolates were resistant to cotrimoxazole and nalidixic acid, 29 % were resistant to tetracycline and 1 % were resistant to azithromycin. All strains were susceptible to ampicillin-sulbactam, doxycycline, chloramphenicol and ciprofloxacin and 95 % were susceptible to azithromycin. MIC values did show reduced susceptibility to fluoroquinolones and 63 % of the strains were intermediately resistant to tetracycline. The isolates expressed phenotypic traits of both serogroup O1 Ogawa and El Tor and harboured an *rstR* El Tor and *ctxB* classical biotype. Among the outbreak isolates, only a single PFGE pattern was observed throughout the study period. This study showed that multi-drug resistant *V. cholerae* altered El Tor producing classical CT strains had become predominant in northern Vietnam.

Vietnam is a place where the killed oral cholera vaccine (OCV) has been evaluated in an outbreak situation. In 2007–2008, unprecedented cholera outbreaks occurred in the capital, Hanoi, prompting immunisation in two districts (Anh et al. 2011). From 16 to 28 January 2008, vaccination campaigns with the Vietnamese killed OCV were held in two districts of Hanoi. No cholera cases were detected from 5 February to 4 March 2008, after which cases were again identified. Beginning 8 April 2008, residents of four districts of Hanoi admitted to one of five hospitals for acute diarrhoea with onset after 5 March 2008 were recruited for a matched, hospital-based, case–control outbreak investigation. Cases were matched by hospital, admission date, district, gender and age to controls admitted for non-diarrhoeal conditions. Subjects from the two vaccinated districts were evaluated to determine vaccine effectiveness. Fifty-four case–control pairs from the vaccinated districts were included in the analysis. There were 8 (15 %) and 16 (30 %) vaccine recipients among cases and controls, respectively. The vaccine was 76 % protective against cholera in this setting (95 % CI: 5–94 %; $p = 0.042$). Importantly, this was the first study to explore the effectiveness of the reactive use of killed OCVs during a cholera outbreak.

It has been reported from Vietnam that cholera outbreaks can be caused by an altered *V. cholerae* O1 El Tor biotype strain producing classical cholera toxin B (Nguyen et al. 2009). It was found that *V. cholerae* O1 isolates collected during cholera outbreaks occurring from late 2007 to early 2008 in northern Vietnam were revealed to represent an altered strain containing the RS1 element followed by a CTX prophage harbouring El Tor type *rstR* and classical *ctxB* on the large chromosome.

4.8.5 Laos

Laos, officially the Lao People's Democratic Republic, is a landlocked country in South-East Asia, bordered by Myanmar and China to the north-west, Vietnam to the east, Cambodia to the south and Thailand to the west. The capital city is Vientiane.

A cholera outbreak in Laos in July 2010 involved 237 cases, including four deaths (Sithivong et al. 2011). Molecular sub-typing indicated relatedness between

the *V. cholerae* isolates in this and in a 2007 outbreak, uncovering a clonal group of *V. cholerae* circulating in the Mekong basin. The study suggested that the subtyping methods would affect this relatedness.

Large-scale cholera outbreaks were reported in Laos in 1993 and 1994 and from 2000 to 2002 (Lenglet et al. 2010). On 23 December 2007, a drastic increase in acute watery diarrhoea patients at a health center in Sekong Province was reported to the provincial health office. An outbreak investigation was initiated to understand the magnitude of the outbreak, identify new cases, identify the suspected causal agent, implement control measures and prevent new cases. Through active village based surveillance, 370 cases and three deaths were reported from 31 villages between 15 December 2007 and 29 January 2008. Of these reported cases, 29 % were under the age of 5. From 28 fresh stool samples taken, 17 (58.6 %) were positive for *V. cholerae* O1 Ogawa strain. Two water sources close to affected villages were found to be contaminated with the same strain of *V. cholerae*. Control measures implemented included health education for safe household water consumption and early identification and treatment of suspected cholera patients at village level. The cause of the outbreak was suspected to be a combination of contaminated drinking water and person-to-person transmission.

5 Conclusion

The South-East Asia region has always been a hotbed for cholera outbreaks and continues to be so. Importantly, the region has been the source of all the seven pandemics. The ongoing review has been a revelation in the sense that many of the outbreaks have occurred both within as well as outside the purview of the WHO SEARO classification system for the member countries. An important reason could be the following. Those countries that fall within the WHO SEARO classification system could be hesitant in reporting cholera cases. In this regard, it should be noted that Bangladesh reports zero cholera and even in case of India, cholera is grossly under-reported. Various reasons have been cited in this regard, including political connotations, trade embargoes, etc. On the other hand, some countries outside the WHO SEARO system of classification have reported cholera outbreaks, indicating that there is little or no inhibition or hindrance in reporting cholera cases, being outside the purview of the WHO system. Currently, the *modus operandi* for monitoring outbreaks is by carrying out outbreak investigations. In the future, there is a need for good surveillance systems in the region in order to closely monitor the cholera outbreak situation. A robust surveillance system will ensure that outbreaks can be picked up at the very outset and nipped in the bud, so to speak, thereby bringing down both morbidity as well as mortality.

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