Neglected Tropical Diseases

Alex Loukas *Editor*

Neglected Tropical Diseases - Oceania

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Cholera in Oceania

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Abstract

For approximately 200 years, cholera has been feared globally as a disease that can cause rapid-onset epidemics. The causative organisms, *Vibrio cholerae* O1 and O139 serogroups, are endemic to Southern Asia, but appear to spread globally in waves resulting in seven recognised pandemics to date. The current seventh pandemic has seen the introduction of *V. cholerae* O1 El Tor into the Oceania region. Since 1962 there have been five large outbreaks at a frequency of approximately one per decade. There have also been regular small outbreaks and clusters of disease throughout the region during the seventh pandemic. The most recent outbreak of cholera in the region occurred in Papua New Guinea in 2009–2011, and this was the largest outbreak to occur in the region to date. In Oceania the majority of people live in high-income settings (Australia and New Zealand) so the risk of cholera transmission is low. Despite this, an estimated 6.5 million people living in the region are at risk of cholera. The most important risk factors are inadequate access to safe water and lack of appropriate sanitation and hygiene measures. However, many other factors may contribute to cholera transmission risk, and people living in Pacific Island countries may be at increased risk in the future due to climate change. Strengthening health delivery services in the region will ensure countries are better equipped to handle future cholera outbreaks; and further understanding the epidemiology of cholera and the causative agent in the region could help prevent future transmission.

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Introduction

Cholera is a severe diarrhoeal illness caused by consumption of toxigenic strains of the bacterium *Vibrio cholerae*. More than 200 serogroups of *V. cholerae* have been described, the majority being only mildly pathogenic to humans and causing only sporadic illness. These organisms are well adapted to life in marine and estuarine environments. The serogroups O1 and O139, in addition to being adept at survival in aquatic habitats, are also highly virulent human pathogens. These two serogroups are responsible for epidemics of severe gastrointestinal illness manifesting as acute watery diarrhoea (AWD). The O1 serogroup has a wider geographical distribution and has been associated with illness globally, including the Oceania region. The O139 serogroup is largely restricted to India and Bangladesh. *V. cholerae* O1 causes a higher burden of disease than *V. cholerae* O139, in part due to the wider global distribution.

Cholera is primarily waterborne, and during epidemics the primary mode of infection is ingestion of water contaminated with human waste. Transmission can also occur through consumption of contaminated foods and direct contact of patients, coupled with insufficient hygiene. The infectious dose for *V. cholerae* O1 or O139 is typically around 10^8 cells, although this figure can be much lower in highly susceptible populations (Cash et al. 1974), such as people with gastric hypochlorhydria which can result from *Helicobacter pylori* infection (Clemens et al. 1995; Shahinian et al. 2000). Inside the gastrointestinal tract of the infected person, the organism enters a hyper-infectious stage which is maintained upon excretion (for at least 5 h) to facilitate infection in people who subsequently ingest the organism (Merrell et al. 2002). The most important virulence factor associated with *V. cholerae* is the cholera toxin, responsible for the acute profuse watery diarrhoea observed in severe cases of cholera.

Cholera is readily treatable, and if treatment is received in a timely manner, the mortality rate is typically <1 %. However, without treatment cholera can be rapidly fatal due to the onset of severe dehydration and electrolyte imbalances: a person with cholera can lose up to 20 l of fluid per day. The mortality rate of untreated cholera can be as high as 50 % in vulnerable groups (WHO 2013a).

Definition of Cholera

Early use of the term cholera encompassed diarrhoeal diseases of diverse aetiology, in a time predating the germ theory of disease. The term was first seen in Hippocrates' writings, which predate the *known* occurrence of cholera in Europe by approximately two millennia. Modern use of the term cholera largely coincides with the first pandemic of true cholera which spread to Europe, the Middle East, Asia and Africa in the early 1800s. However, around the time of the first two pandemics, there were reports of 'European cholera', 'mild cholera' and other qualifying terms

which likely describe gastrointestinal illness of an alternative aetiology (Barua 1992; Howard-Jones 1974). Terms such as 'Indian cholera' and 'Asiatic cholera' were sometimes used in the times of the early cholera pandemics to describe true cholera and differentiate from gastrointestinal illness of unknown aetiology. The term cholera gravis has been used to denote cases of AWD resulting in dehydration and severe illness; however, commonly 'cholera' is simply used to describe the illness in contemporary scientific literature.

Although the first two pandemics of cholera predated our understanding of the aetiology of the disease, the term cholera refers to AWD caused by *V. cholerae*. The current WHO case definition for a confirmed case of cholera is when *V. cholerae* O1 or *V. cholerae* O139 is isolated from any patient with diarrhoea (WHO 2004). Cholera cases and outbreaks commonly occur in resource-poor settings, where access to a suitably resourced laboratory is limited; thus, it is important to have a more encompassing case definition of cholera to allow early cases to be identified. In an area where cholera is not known to be present, a patient ≥5 years of age who develops severe dehydration or dies due to acute watery diarrhoea constitutes a suspected case of cholera. In an area where there is a cholera epidemic, a patient who develops acute watery diarrhoea, with or without vomiting, is considered a case of cholera (WHO 2004).

Global Pandemics of Cholera and Associated *V. cholerae* Strains

The natural geographic reservoir of the pathogenic strains of *V. cholerae*, namely, the O1 and O139 serogroups, is the Ganges Delta and Bay of Bengal in Southern Asia. It is difficult to ascertain whether true cholera existed beyond that location in ancient times (Barua 1992). However, with the arrival of Europeans and technologies such as steamships, railroad and canals, new opportunities for dispersal of *V. cholerae* emerged. In 1817, the first cholera pandemic started with the disease spreading along trade routes throughout India, China, Indonesia, Europe and Southern Russia. Throughout the following century, five successive cholera pandemics were recorded, resulting in tens of millions of deaths throughout the world.

The sixth cholera pandemic (and perhaps the preceding pandemics) was caused by a strain of *V. cholerae* O1 known as the 'classical strain'. The seventh and current pandemic is caused by the *V. cholerae* O1 El Tor strain, which is genetically and phenotypically distinct from the classical strain. Following the emergence of the seventh cholera pandemic, the El Tor strain rapidly displaced the classical strain from most regions of the world. Cholera caused by the classical strain re-emerged in Bangladesh in the early 1980s, and the classical and El Tor strains co-circulated until 1993. The final appearance of the classical strain was in Latin American countries from 1991 to 1997 (Alam et al. 2012). Recently, 'hybrid' or 'atypical' strains of cholera have emerged, which have an El Tor genome and a classical cholera toxin (Nair et al. 2006a; Raychoudhuri et al. 2008). The emergence and rapid spread of atypical strains of *V. cholerae* O1 is an important development in global cholera epidemiology. In general, El Tor strains are considered to possess better survival capacity in the environment (Safa et al. 2010), while classical strains possess a more

virulent toxin (Ghosh-Banerjee et al. 2010). The atypical strains produce higher levels of cholera toxin compared to prototype El Tor strains (Ghosh-Banerjee et al. 2010; Son et al. 2011), which may be linked with an increase in disease severity. These strains have recently caused large outbreaks in many regions around the world, including devastating outbreaks in Haiti (CDC 2010) and Zimbabwe (Truscott 2008).

Cholera as a Neglected Tropical Disease

Cholera now has a largely tropical distribution and is considered endemic in 51 countries, mostly in Africa and Asia (Ali et al. 2015). Ali and associates (2015) used spatial modelling techniques to predict cholera endemicity throughout the world and classified eight Oceania countries and Indonesia (encompassing Papua and West Papua provinces) as being 'cholera endemic': Papua New Guinea, Solomon Islands, Vanuatu, Federated States of Micronesia, Kiribati, Marshall Islands, Palau and Narau. Clearly, such an approach is designed to estimate cholera numbers at a macrogeographic, global level and in doing so counteract the problem of underreporting that occurs at the national level. In the case of the 'endemic' countries in Oceania, there is no credible evidence that there is ongoing transmission of cholera; these countries might better be described as 'at-risk' countries where cholera cases can and do occur (Ali et al. 2015).

As with many other 'tropical' diseases, the global epidemiology of cholera for both endemic and at-risk countries is more a reflection of the economic status of countries and their inhabitants than a correlation with climatic conditions. Indeed, the disease once caused widespread, devastating epidemics throughout much of Europe and the Americas, but the 'sanitary revolution' during the nineteenth century resulted in massive declines in the morbidity and mortality associated with cholera and other enteric infections. Unfortunately, the sanitary revolution was not a worldwide occurrence, with much of the world's population continuing to live without adequate sanitation for the entirety of the twentieth century. Currently 2.5 billion people do not have access to improved sanitation, and an estimated 1.8 billion people use a source of drinking water that is faecally contaminated (WHO 2015d). Outbreaks of cholera are invariably linked with inadequate access to sanitation and safe drinking water and more generally poor living conditions.

Neglected tropical diseases (NTDs) are a disparate group of infectious diseases that almost exclusively impact upon people living in poverty. The World Health Organization (WHO) currently lists 17 diseases as NTDs, which include helminthic, protozoan, parasitic, viral and bacterial infectious agents (WHO 2015b). Despite the diversity of infectious agents considered NTDs, there are some commonalities. People living in poverty are most susceptible to NTDs. Moreover, the diseases also impart a considerable burden on the patient and their family, contributing to a vicious circle commonly referred to as the poverty trap. The chronic presentation of many NTDs contributes to this vicious circle of poverty, with patients suffering long-term disabilities such as disfigurement, reduced vision and impeded

cognitive development. These and other impacts of NTDs can often lead to stigma and discrimination, in addition to reduced productivity (thus impacting on earning capacity and quality of life). Another commonality amongst the NTDs is that all of the diseases are largely preventable or treatable with existing interventions; however, the implementation of such interventions has to date proven to be a challenge. In these regards the diseases are neglected, as (a) control is possible but not readily implemented and (b) they impact on poor, often neglected, populations.

Cholera does not feature on the WHO's list of NTDs, despite sharing many of the key traits of the WHO-listed NTDs (WHO 2010c). Cholera is a disease of poverty with considerable disease burden amongst the low-income and politically marginalised people in endemic countries. Despite numerous occasions where cholera has spread to a previously non-endemic country, it presents little threat to inhabitants of high-income communities. The disease is both preventable and treatable; nonetheless, more research is required to improve diagnosis and prevention of the disease. Finally, the burden of cholera is considerable. According to global burden of disease data (Lozano et al. 2012; Murray et al. 2012), cholera causes more deaths than any of the WHO-listed NTDs. Relative to the WHO-listed NTDs, cholera is the second highest contributor to disability-adjusted life years (DALYs), behind only soil-transmitted helminths (listed as intestinal nematode infections by Murray et al. (2012)). Almost 1.5 billion people are at risk of cholera (Ali et al. 2012); thus, it is a risk to more people than are most of the WHO-listed NTDs (Hotez et al. 2007).

The History of Cholera in Oceania

In the early to mid-1800s, during the first and second pandemics, cholera caused considerable morbidity and mortality in many regions of the world. The disease reached Java, Indonesia, in 1820 (Barua 1992); however, there are no credible reports of cholera occurring in the Oceania region during the first pandemic. The earliest reports of cholera in Oceania region are difficult to substantiate. Reports of cholera at the Swan River settlement in Western Australia in the 1830s are based on newspaper records and are not supported by solid evidence (Pollitzer 1954). One local newspaper at the time reported a 'mild form of cholera' that 'bore no resemblance in severity to Indian cholera', suggesting that the gastrointestinal illness was caused by a pathogen other than *V. cholerae*. In New Zealand a death due to 'English cholera' was recorded in 1854 (Gluckman 2000), again, likely a gastrointestinal illness due to a different aetiological agent. There were also reports of cholera in New Zealand during the 1870s, but these reports were met with scepticism at the time (Dow 2012). Similarly, there were reports of a 'cholera-like' illness in the Marshall Islands, Mariana Islands, New Britain (Bismarck Archipelago) and the German colony of New Guinea during the nineteenth and early twentieth centuries, but these outbreaks and their associated aetiological agents are difficult to substantiate (Pollitzer 1954).

The first well-documented outbreak of cholera in the Oceania region occurred in 1885 on board the S.S. Dorunda, a boat travelling from England to Queensland with

367 emigrants and 105 crew. The ship docked in Jakarta overnight to take on supplies. Within 4 days of leaving Jakarta en route to Queensland, a passenger fell ill with what was retrospectively diagnosed as the first case of cholera in this outbreak. The ship docked in or near three ports in northern Queensland before being put into quarantine off the coast of Brisbane. Although no definitive diagnosis was conducted, the epidemiological traits of the outbreak support the notion of this being an outbreak of 'cholera asiatica'. By the end of the outbreak, there were about 75 cases and at least 17 deaths (Cornish 1886). All cases were confined to passengers on the ship; i.e. no reported cases made it to the Australian landmass.

There were scarce reports of cholera in Oceania through the first half of the 1900s, reflecting to some degree global trends during that era, with the disease being largely confined to Asia between 1926 and 1960 (Barua 1992). In 1961, with the onset of the seventh pandemic, cholera returned to the Oceania region. Indeed, this pandemic is generally considered to have commenced in Sulawesi, Indonesia (WHO 2000), thus bordering on the Oceania region. More recent molecular epidemiological data suggests that the origins of the seventh pandemic may have been India (Mutreja et al. 2011), followed by rapid dissemination to Indonesia.

Various sources, most notably the WHO (2000), state that there was a cholera outbreak in Papua New Guinea in 1962, resulting in 1293 cases and 464 deaths. At that time the eastern half of the island of New Guinea was an Australian protectorate, and the western side an overseas territory of the Netherlands. What is now the nation of Papua New Guinea, which gained independence from Australia in 1975, was not the location of this outbreak. Rather, the 1962 outbreak occurred in Dutch New Guinea, which is now the West Papua and Papua provinces of Indonesia. The outbreak in the former Dutch New Guinea resulted in 1400 cases and 500 deaths; most of the cases occurred in 1962, with approximately 100 of the 1400 reported cases occurring in early 1963 (De Moor 1963a, b). This outbreak was linked to consumption of contaminated water (De Moor 1963a).

There were no cases of cholera reported in Oceania between 1964 and 1971. In 1972 a cluster of cases occurred in Australia and New Zealand following an international flight from London to Australia (with some passengers continuing to New Zealand on a subsequent flight). Sutton (1974) documented 47 passengers were found to be excreting *V. cholerae* in their faeces, of which six passengers had continued on to New Zealand. Twenty-five *V. cholerae* O1 El Tor culture-positive passengers had symptoms, while 22 did not develop illness. The WHO (2000) records 40 cases of cholera in Australia in 1972 and 3 cases in New Zealand. On the basis of Sutton's findings, where not all culture-positive passengers developed disease, it seems likely that the number of true cases of cholera in Australia that year was approximately 20, though an additional 20 were culture positive but without symptoms.

Since the 1970s Australia and Guam, and to a lesser extent New Zealand, have reported sporadic cases of cholera. According to WHO reports, between 1970 and 2014, there have been a total of 125 cases reported across 20 separate years in Australia, a total of 33 cases reported across 14 separate years in Guam and a total of 14 cases reported across 8 separate years in New Zealand (WHO 2000; Table 1.1).