

CASE STUDY: Cholera

BY EDWARD LAWS

Cholera is a classic case study of the interface between the oceans and human health, both in terms of the causes (i.e., a bacterium, copepods, and nutrient pollution of coastal marine waters) and its possible prevention (i.e., the possibility of using *in situ* moorings and satellites to predict its occurrence). Cholera is a serious intestinal disease that has impacted human health for centuries.¹ There are accounts written in Sanskrit of a disease with symptoms resembling cholera on the Indian subcontinent roughly 2,500 years ago (Colwell, 1996). Cholera appears to have been confined to that region of the world until the early 19th century. However, beginning in 1817, a series of seven pandemics evidenced the spread of cholera to regions of Europe, Africa, and the Americas. The first six pandemics all seem to have originated in Bangladesh. Of these, the most noteworthy were probably the second and third, which lasted from 1829 to 1851 and 1852 to 1859, respectively.

JOHN SNOW AND THE CHOLERA OUTBREAK DISCOVERY

During the 19th century, a series of four cholera outbreaks in England left tens of thousands of people dead. Little was done to contain the disease, the prevailing theory being that it was spread by miasma in the atmosphere. Beginning on the night of August 31, 1854 there was a particularly serious outbreak of cholera in the Soho region of London. One month later, 616 people in the area had died of cholera. Dr. John Snow, a physician who was familiar with the Soho district, had recently published a report speculating that cholera was spread by contaminated water. The Soho outbreak provided an opportunity to test that theory.



Figure 1. Drip treatment of cholera victims at a refugee camp in Mozambique. Source: Doctors Without Borders/Médecins Sans Frontières (MSF), New York, NY.

During the month of September, Snow interviewed the families of victims and made a map showing the distribution of cases. He noticed that a pump near the corner of Broad Street and Cambridge Street (a.k.a. the Broad Street pump) was at the epicenter of the outbreak; by interviewing the families of victims, he was able to determine that virtually all the victims had consumed water from the pump (Figure 2). Microscopic examination of a sample of water from the pump revealed particles that Snow concluded were the source of the infection.² He took his findings to the Board of Guardians who, though skeptical of Snow's theory, agreed to have the handle of the pump removed as an experiment. The spread of cholera stopped dramatically.³ Snow's investigation of the 1854 Soho cholera outbreak established him as a pioneer in the fields of public health and epidemiology.

Despite Snow's work and subsequent recognition that cholera was spread by contaminated feces and water, pandemics continued into the first half of the 20th century. The sixth

pandemic, which lasted from 1899 to 1923, was however followed by almost forty years without another outbreak of comparable magnitude. This lull was generally attributed to improvements in the treatment and distribution of public water supplies. However, a seventh cholera pandemic began in 1961 and continues to the present day. This most recent pandemic began in Indonesia and has resulted in hundreds of thousands of cholera cases and tens of thousands of deaths per year (Colwell, 2002). Given modern technology and our understanding that most cholera cases result from the consumption of contaminated water, why has it been so difficult to contain this disease?

THE *VIBRIO* BACTERIUM

Unfortunately, cholera is not a disease that is effectively controlled through the sort of monitoring activities described in Dufour and Wymer (this issue). It therefore provides a provocative case study and contrast. The cause of cholera is the bacterium *Vibrio cholerae*, one of thirty species of *Vibrio* bacteria, twelve

¹Cholera causes severe and profuse diarrhea, vomiting, and rapid severe dehydration and electrolyte imbalance leading to complete collapse (Figure 1). Death may occur within a few hours of onset unless treatment is started in time. The treatment, which includes infusion of water and electrolytes into the veins, produces rapid relief from the symptoms of the disease.

²Subsequent studies indicated that the source of the contamination was a leaking cesspool located only a short distance from the Broad Street well.

³Actually, the outbreak had begun to wane a short time before the pump handle was removed.

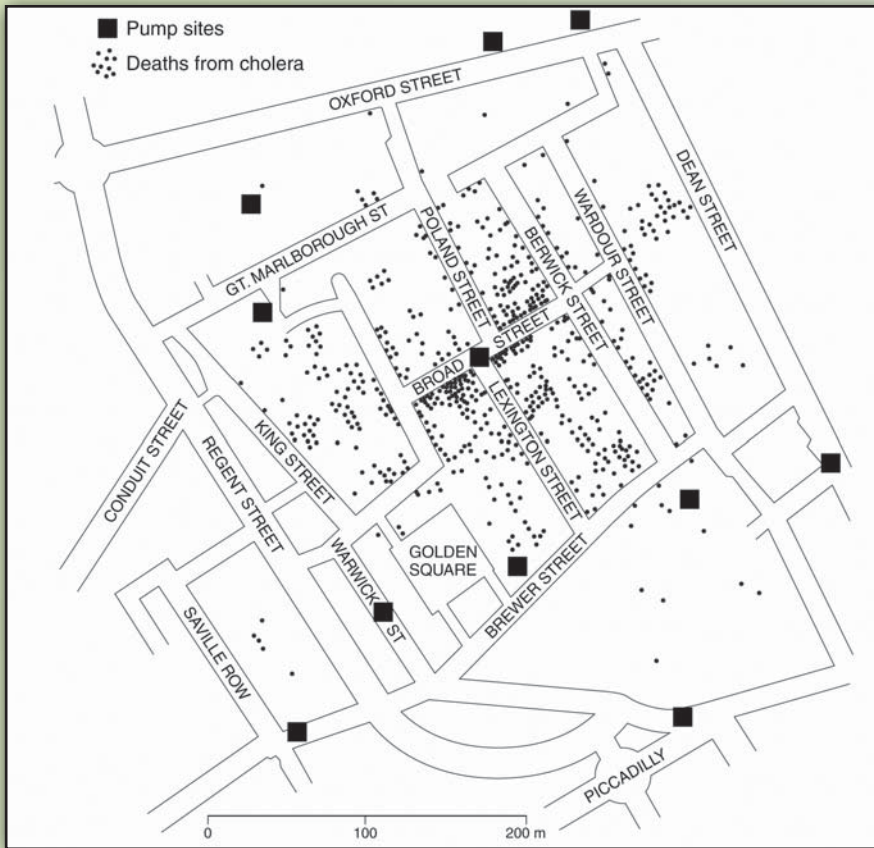


Figure 2. Map of Snow's London. Redrawn from National Geographic, Lesson 9-12 Handout 3, Map of Cholera Deaths and Locations of Water Pumps (Available at <http://www.nationalgeographic.com/education/ideas912/912choleraho3.html>).

transfer; part of the DNA that codes for CT is thought to be the genome of a filamentous phage that lysogenizes *V. cholerae* (Lipp et al., 2002). Lacking at this point is a clear understanding of the environmental conditions associated with the acquisition of virulence genes. Sunlight, pH, and temperature are all known to influence phage infection of *V. cholerae* and the lysogenizing of the host or recipient cell. Although our understanding of the mechanisms is still qualitative, it seems fair to say that, "seasonal environmental factors may affect phage-host dynamics and acquisition of virulence genes to a significant degree" (Lipp et al., 2002).

CHOLERA AND THE OCEANS AND HUMAN HEALTH CONNECTION

Our understanding of the mechanisms responsible for proliferation of *V. cholerae* are more quantitative. There is a commensal relationship between *V. cholerae* and chitinous zooplankton, particularly copepods (Colwell et al., 2003) (Figure 4). All vibrios tested to date, including *V. cholerae*, possess a chitinase that enables them to utilize chitin as a carbon source. *V. cholerae* also possess a chitin-recognition system that undoubtedly accounts for their tendency to colonize the exoskeleton and gut of copepods. A single copepod may contain as many as 10^4 to 10^6 *V. cholerae* (Lipp et al., 2002). Human volunteer studies have shown that the minimum dose required to produce symptoms of cholera is about 10^3 *V. cholerae* (Colwell, 1996). Thus, swallowing a glass of water containing a single copepod colonized by *V. cholerae* could produce clinical symptoms of the disease.

The abundance of *V. cholerae* in tropical and subtropical coastal waters is therefore very much correlated with conditions that cause blooms of chitinous zooplankton. Simple food-chain theory suggests that environmen-

of which are known to cause human disease (Colwell, 2002) (Figure 3). *V. cholerae* is unusual compared to many pathogens of relevance to public health in the sense that it is autochthonous in brackish waters (roughly 1 to 30 practical salinity units [psu]), and *V. cholerae* is virtually always detected in coastal water samples from the tropics and subtropics. With modern technology (monoclonal antibodies, fluorescent dyes, epifluorescent microscopy, and equipment for concentration of samples), it is possible to detect as few as 1–2 cells of *V. cholerae* in a liter of water (Colwell, 1996).

One of the problems with *V. cholerae* is not detection. We know that we can detect it, and we know that it is virtually always present in tropical and subtropical coastal waters. The public health issues with respect to *V. cholerae* are: (1) Is it virulent (i.e., a toxin producer)? (2) Are the concentrations of virulent *V. cholerae* high enough to be of concern? and (3) What do we do to protect people if the

answers to the first two questions are yes?

With respect to the first question, we know that there are roughly 200 serogroups of *V. cholerae*, only two of which (O1 and O139) have been associated with major epidemics. Genes for toxin production (CT) are rarely found in other serogroups (Lipp et al., 2002). There are two biotypes of the O1 serogroup, Classical and El Tor. The first six pandemics are thought to have been caused by the Classical O1 biotype. The seventh pandemic was initially caused by the O1 El Tor biotype; the O139 biotype first appeared in 1992, and appears to be the result of genetic exchange with O1 El Tor (Lipp et al., 2002).

V. cholerae is unusual among bacteria in possessing two chromosomes, both of which are required for metabolism and replication (Colwell, 2002). The genes required to produce CT are located on the larger chromosome. The ability of the O1 and O139 biotypes to produce CT appears to be the result of horizontal gene

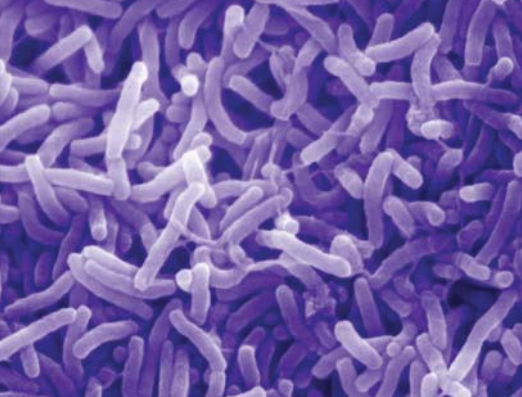


Figure 3. Cholera Bacteria. Source: Dartmouth College, Rippel Electron Microscope Facility, image database (Available at <http://remf.dartmouth.edu/images/Micromondimages/source/32-cholera.html>).



Figure 4. A female copepod whose egg case, on the left, is covered with vibrio bacteria. Source: National Science Foundation multimedia gallery. (Available at http://www.nsf.gov/news/mmg/media/images/094_h.jpg).



Figure 5. A village woman in Matlab, Bangladesh uses layers of sari cloth to filter drinking water. Courtesy of Anwar Huq, University of Maryland.

tal conditions favorable to the rapid growth of phytoplankton will, after a lag in time, be associated with an increase in the zooplankton population. The triggering mechanism for rapid phytoplankton growth is typically an injection of nutrients, either from upwelling or land runoff. In the region surrounding the Bay of Bengal, for example, the peak in cholera cases typically occurs after the summer monsoons, when coastal surface waters are warm and enriched with nutrients derived from river discharge. Because of the close correlation between environmental conditions and the incidence of cholera in such areas, monitoring systems (including *in situ* moorings and satellites) can be used to guide the activities of public health officials, as suggested in Dufour and Wymer (this issue). Colwell (2004), for example, has noted that temperature and salinity conditions alone have been used to predict the presence of *V. cholerae* in the Chesapeake Bay with an accuracy of 76–89 percent.

CHOLERA PREVENTION

Even if we can use environmental monitoring systems to predict the abundance and virulence of *V. cholerae* with great accuracy, how do we protect people who are likely to be drinking water containing even a few copepods colonized with *V. cholerae*? In places such as Bangladesh, much drinking water is obtained from surface sources. These waters are often

contaminated, particularly during the summer monsoons. Boiling water is certainly one way to kill pathogens, but as noted by Colwell et al. (2003), in rural Bangladesh, fuel wood is in short supply and is costly. Furthermore, during periods of severe flooding, building a fire to boil water is not a realistic option. During the 1960s, many wells were drilled to overcome the surface water problem, but the water from as many as half of those wells has been found to contain arsenic at concentrations in excess of 50 ppb. Many people have switched back to surface water to avoid the arsenic problem.

Colwell et al. (2003) have reported at least a partial resolution of this conundrum. In a study involving roughly 133,000 persons in the Matlab region of Bangladesh, they were able to reduce the incidence of cholera by almost a factor of two through encouraging people to filter their drinking water using sari cloth, which is inexpensive and readily available in that part of the world. A filter consisting of eight or more layers of sari cloth was found to have an effective porosity of about 20 microns, sufficient to remove 99 percent of the *V. cholerae* (Figure 5). Colwell et al. (2003) noted that many women who used the sari cloth filtration system noticed a decline in the incidence of diarrhea within their families. This observation on the part of persons participating in the study was expected to be important to the effective implementation of the water filtration

program. As noted by Colwell (2004, p. 289), “Understanding the patterns of infectious disease and developing appropriate treatment that can be readily implemented requires not only knowledge of the biological, physical, and social sciences, but also the ability to integrate this information into an effective response.”

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