Chapter 7
Briefly Summarizing Our Understanding of *Vibrio cholerae* and the Disease Cholera

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Abstract *Vibrio cholerae* is a naturally existing aquatic bacteria that lives in association with the chitinous exoskeletons of crustaceans including copepods. Cholera is an infectious disease of humans which is caused by ingesting those strains of the bacteria *Vibrio cholerae* that carry both of two disease related factors, a toxin gene coded by the bacteriophage CTXΦ which produces the cholera toxin, and the toxin-coregulated pilus which both facilitates attachment of the bacteria to host cells and also serves as the CTXΦ receptor. Cholera is considered a waterborne infection, with the primary route of infection being ingestion of fecally contaminated water and secondary transmission being caused by ingesting fecally contaminated food. Development of mathematical modeling frameworks may help to provide an essential lead time for strengthening intervention efforts to either prevent or ameliorate outbreaks of cholera in regions where the disease is endemic.

7.1 Introduction

The Vibrionaceae are a family of heterotrophic bacteria found in oceanic environments. A few members of the species *Vibrio* have extended their range to occur in brackish and freshwater environments (Takemura et al. 2014). The growth and concentrations of *Vibrio* naturally found in coastal waters increases with warmer water temperatures, often leading to a seasonal distribution of *Vibrio* infections in temperate regions with most of those infections occurring from summer through early autumn (Sinatra and Colby 2018).

Vibrio cholerae naturally exists in association with the chitinous exoskeletons of crustaceans including copepods, and not surprisingly *Vibrio cholerae* produces chitinases (Nalin 1976). Indeed, it is presumed that all *Vibrio* species produce

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chitinases (de Magny et al. 2011) which degrade the crustaceans insoluble exoskeleton chitin polymer into soluble chitin oligosaccharides (Hayes et al. 2017). The chitinases of *Vibrio cholerae* allow that bacterial species to use chitin as a sole carbon and nitrogen source (Mondal et al. 2014) and, correspondingly, *Vibrio cholerae* bacteria that are colonized onto the chitinous surface of copepods are able to utilize the copepods chitin as a sole carbon and nitrogen source (Mondal et al. 2014). One of the two known *Vibrio cholerae* chitinase enzymes, ChiA2, also is secreted by *Vibrio cholerae* within the mammalian intestine and that enzyme hydrolyzes intestinal mucin to release N-Acetylglucosamine. The released sugar then is utilized by *Vibrio cholerae* for growth within the host intestine (Mondal et al. 2014).

Cholera is an infectious disease of humans which is caused by ingesting only those strains of the bacteria *Vibrio cholerae* that carry both of two disease related factors. The pathogenicity factors for *Vibrio cholerae* are the cholera toxin which is encoded by a lysogenic bacteriophage CTXΦ, and a toxin coregulated pilus which is encoded by a pathogenicity island (Faruque and Mekalanos 2012) and also serves as the CTXΦ receptor (Krebs and Taylor 2011).

Cholera primarily is considered to be a waterborne disease with secondary transmission routes that include fecally contaminated food. Vaccination is one of our newest tools in fighting cholera. However, preventing deaths due to cholera will require that we both reduce the risk of exposure to pathogenic strains of the bacteria and that we successfully treat those individuals who contract the illness. Community understanding, along with awareness and intervention, will allow us to resolve this health problem. The goal is that John Snows wish (Snow 1849, 1854) of eliminating the health risk asssociated with cholera finally will be realized.

7.2 Ecology of the Vibrios that Cause Infections in Humans

Understanding a pathogenic microbes ecology is a key factor in comprehending its associated disease.

7.2.1 The Four Horsemen of Vibrio *Disease*

Human health concerns regarding the genus *Vibrio* encompass four environmental species and those are *Vibrio anguillarum*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, and *Vibrio vulnificus*.

Vibrio anguillarum usually is considered to be a pathogen of fish, but it has a wide host range that also naturally encompasses bivalve molluscs plus crustaceans and extends to include larvae of the wax moth *Galleria mellonella* (McMillan et al. 2015). *Vibrio anguillarum* causes economic losses in the fishing and aquaculture industries, and has produced bacteremia in humans as a consequence of people consuming either fish or crustacean seafood which contained the bacteria (Sinatra and Colby 2018).

Both *Vibrio parahaemolyticus* (Letchumanan et al. 2014) and *Vibrio vulnificus* are found in estuaries and coastal waters, where these bacterial species naturally are concentrated into the tissues of filter feeding bivalve molluscs and cause an initially gastrointestinal disease when the contaminated shellfish are consumed either raw or undercooked (Raszl et al. 2016). The resulting human gastrointestinal infections caused by *Vibrio parahaemolyticus* and *Vibrio vulnificus* (Park and Lee 2018) can spread to the bloodstream producing bacteremia. *Vibrio vulnificus* additionally causes disease via wound infections (Raszl et al. 2016).

An examination of archived formalin-preserved plankton samples that included noting the presence of *Vibrio cholerae*, *Vibrio parahaemolyticus*, and *Vibrio vulnificus*, supplemented by using generalized additive models, revealed that long-term increase in *Vibrio* abundance from 1958 to 2011 in the North Atlantic was promoted by increasing sea surface temperatures and positively correlated with the Northern Hemisphere Temperature (NHT) and Atlantic Multidecadal Oscillation (AMO) climatic indices (Vezzulli et al. 2016).

7.2.2 Focusing on the Horseman Named "Pestilence" by Understanding the Ecology of Vibrio cholerae

The natural habitat for *Vibrio cholerae* is the chitinous shells of crustaceans (Grimes 1991) including copepods. Attachment of *Vibrio cholerae* to the surface of live copepods has been suggested as being important for ecological persistence of *Vibrio cholerae* in natural water (Huq et al. 1983) and that attachment beneficially affects multiplication of *Vibrio cholerae* (Huq et al. 1984). The beneficial effect of *Vibrio cholerae*'s association with copepods has been determined to be greatest at an alkaline pH of 8.5 with lesser pH levels of 6.5 and 7.5 also having been examined, at 30 °C with lower water temperatures of 5 through 25 °C having been examined, and with maximum attachment to copepods noted at 15 g/kg salinity as compared against salinities of 5 and 10 g/kg (Huq et al. 1984). It should be remembered that full salinity sea water is considered to be around 35 g/kg. *Vibrio cholerae* is present throughout the year both in the gut and on the surface of its zooplankton copepod hosts and in addition this bacteria has an association with some species of phytoplankton at least in Bangladeshi waters (de Magny et al. 2011). There additionally have been findings of *Vibrio cholerae* associated with *Acanthamoeba castellanii*, and of *Vibrio cholerae* attached to the mucilaginous sheath of the cyanobacteria *Anabaena* (Almagro-Moreno and Taylor 2013). *Vibrio cholerae*, along with copepods which are its presumed primary hosts, has been shown autochthonous to riverine, estuarine, and coastal waters. Copepods have been found as part of the microflora in drinking water distribution systems of even economically well developed countries (van Lieverloo et al. 2012) and this knowledge suggests that microcrustaceans may represent a potentially supportive environment for *Vibrio* contaminants that gain entrance to water distribution systems. Association of *Vibrio* organisms with the chitinous shells of micro crustaceans such as copepods, and macrocrustaceans such as crabs, may facilitate survival of the microbes during passage through the stomach, and that potential increase in gastric survival could be an important factor in waterborne disease if the *Vibrio cholerae* in source waters were attached to microcrustacean copepods when these microcrustaceans inadvertently get ingested along with the water (Nalin 1976; Nalin et al. 1978).

7.3 Characteristics of the Disease Cholera

Cholera is an acute diarrheal disease caused by toxin-producing strains of the bacterial species *Vibrio cholerae* (Lippi and Gotuzzo 2014). More than 200 serotypes of *Vibrio cholerae* have been identified, with several of those serotypes known to be capable of causing mild to serious gastroenteritis including local outbreak situations of diarrheal illnesses with "cholera-like" symptoms. However, it is the toxigenic strains of *Vibrio cholerae* serogroups O1 and O139 that have been identified with cholera epidemics (de Magny et al. 2011).

Cholera disease is noted for its severe watery diarrhea that can lead to dehydration and, if untreated, the disease can result in death. Azman et al. (2013) have provided a good general summary of the incubation period and symptomatology for cholera. It takes between 12 h and 5 days for a person to show symptoms after ingesting either contaminated water or food, and the disease then can kill within hours if left untreated. Susceptibility to infection by *Vibrio cholerae* seems to be determined by a combination of immunologic, nutritional, and genetic characteristics (Harris et al. 2008). Presumably most of those people who are infected with *Vibrio cholerae* will display no symptoms and yet those people still may have the bacteria present in their feces and thus potentially represent a source of infection for other people. Most of the people who do demonstrate symptoms have either mild or moderate illness that can be treated with oral rehydration solution (World Health Organization 2006). A minority of cholera cases will develop acute watery diarrhoea with severe dehydration that can lead to death if left untreated.

Cholera is considered to be a waterborne disease, principally acquired by ingesting fecally contaminated water, with there also being fecally associated secondary transmission (Snow 1849, 1854). It is fortunate that improved personal hygiene standards and improved drinking water quality largely have resulted in the disappearance of cholera from developed countries. Unfortunately, the menace of this disease does continue in many regions of the world due to poor sanitation accompanied by lack of important infrastructure and the complicating factor that flooding results in fecal contamination of water supples (Almagro-Moreno and Taylor 2013). The remaining endemnicity of cholera is in regions of the world where inadequate sanitary practices commonly are associated with consumption of contaminated water and food. It has been estimated that approximately 1.3 billion people are at risk for cholera in endemic countries, with perhaps 2.86 million cholera cases (uncertainty range: 1.3 m–4.0 m) and a possible 95,000 deaths occurring annually (Ali et al. 2015).

7.4 The Association of Cholera Incidence and Climatic Conditions

The incidence rate of cholera disease has been found to correlate both negatively and positively with rainfall patterns. In some studies is has seemed that dry weather periods may result in people using riskier sources of drinking water. Oppositely, surface runoff might overwhelm drinking water treatment systems and flood wells during wet weather seasons. In the study by Camacho et al. (2018) there was a positive correlation between the spring rainy season in Yemen and cholera incidence.

Rainfall, in addition to temperature and salinity, has proven to be an important factor in the ecology of *Vibrio cholerae* (de Magnya et al. 2008). Rainfall and daily hours of sunlight, along with water temperature, water depth, and conductivity, are characteristics that generally affect plankton populations. Phytoplankton blooms naturally are followed by blooms of zooplankton, including copepods, and that has accounted for the observation of an approximate 8 week lag time between the point when a phytoplankton bloom peaks and when cholera cases subsequently appear (Huq et al. 2005).

The results of a study by Fu et al. (2012) have suggested that a predictive model based upon growth curve functions which combined environmental temperature and organic nutrient levels might help to reliably predict *Vibrio cholerae* in the aquatic environment. Ecological analysis research by Jutla et al. (2013) has shown that the use of satellite based radiance observations of the difference between blue (412 nm) and green (555 nm) wavelengths helps to assess the timing and presence of organic matter in coastal waters which in turn can be related to likely incidence of seasonal cholera. Development of such modeling frameworks may help to provide an essential lead time for strengthening intervention efforts to either prevent or ameliorate outbreaks of cholera in regions where the disease is endemic.

7.5 The Role of Crustaceans in Some Other Diseases

Crustaceans are not associated with the transmission of only *Vibrio cholerae*. Several species of crustaceans including freshwater copepods have long been recognized as intermediate hosts of helminths (Leiper 1936). Particularly notable among those is the guinea worm *Dracunculus medinensis* whose larvae develop within a copepod's digestive tract before being transmitted to humans, and that transmission occurs when humans ingest freshwater copepods infested with

Dracunculus medinensis resulting in the disease dracunculiasis also called Guinea worm disease (Centers for Disease Control and Prevention 2012). Marine copepods and other aquatic crustaceans similarly also serve as primary hosts for many helminth species, and the consumption of those infested crustaceans by fish then produces a resultant infestation of the fish (Zander et al. 1994). Fish lice seem paticularly notable as intermediate crustacean hosts for nematodes (Moravec et al. 1999). Additionally, parasitic crustaceans including copepods serve as both hosts as well as vectors for viruses, and those vector relationships may play a role in transmitting the pathogenic agents to other economically valuable crustaceans among which are the penaeid shrimp (Overstreet et al. 2009).

7.6 Additional Transmission Routes for Cholera

In addition to *Vibrio cholerae* causing massive outbreaks of disease associated with the consumption of contaminated water, food also has served as a vehicle for transmission of cholera (Rabbani and Greenough 1999). *Vibrio cholerae* is particularly known to cause illness associated with the consumption of contaminated macrocrustaceans such as crabs (Finelli et al. 1992), and indeed that could be expected as a possible natural contamination of food given that the native habitat of this bacterial organism is the chitinous shells of crustaceans (Grimes 1991). The possibility that association of *Vibrio cholerae* with chitin may provide the bacteria with a natural means of protection from stomach acids (Nalin et al. 1978) indirectly may facilitate the spread of this diease. The natural contamination that occurs with crustaceans is not avoidable but can be ameliorated by adequately cooking food to kill the bacteria before consuming the food.

As with the disease typhoid (Hurst 2018) which is caused by *Salmonella enterica subsp. enterica serovar Typhi*, previously named *Salmonella typhi*, it should be presumed that for cholera ingestion of water contaminated with feces and sewage serves as the primary, or initial, route of transmission (Snow 1849). Careless fecal contamination of food likely is a secondary transmission route (Hurst 2018; Snow 1849). The transmission of cholera by food, aside from the instances of natural contamination as mentioned above for macrocrustaceans such as crab, is an outcome that easily could be avoided by adequate sanitation. Unfortunately, people often just simply do not wash their hands even when adequate means are available for doing that washing. The fact that cholera transmission can be associated with a failure to wash hands and the consequent contamination of food, has been understood at last since the time when it was explained by John Snow nearly two centuries ago (Snow 1849). Social behaviours relating to the sharing of food clearly may increase the risk of gastrointestinal disease transmission. As an example of this, Camacho et al. (2018) found that an increased risk of cholera transmission in Yemen seemingly had been associated with events related to celebration of Ramadan, a month of the Islamic calendar when there are large gatherings for meals in which people share food. That connection of social activity with cholera transmission occured following spring rains which naturally would have increased the chance for *Vibrio cholerae* contamination of water as a primary transmission route and associatively enhanced the risks of food associated cholera as a secondary transmission route.

There also has been a suggestion that synanthropic flies could serve as mechanical transmission vectors for cholera equally as they likey also transmit all other infections that are spread by the fecal-oral route. Vectoring of disease by flies was suspected as contributing to the transmission of the viral disease polio (Cirillo 2016) and has been hypothesized for both bacteria (Graczyk et al. 2001; Junqueira et al. 2017) as well as protozoa (Graczyk et al. 2001).

Once an outbreak of cholera has occurred, *Vibrio cholerae* strains can be traced geographically to understand the development of cholera disease outbreaks (Kiiru et al. 2013). Efforts also have been made by Chao et al. (2014) and Nishiura et al. (2017) to utilize disease transmission models for understanding the dynamics of cholera outbreaks. A basic explanation of compartment modeling and risk estimation for primary waterborne disease transmission accompanied by secondary routes of disease transmission can be found with examples in Hurst (2018).

7.7 Concurrent Infections Can Worsen Gastrointestinal Bacterial Disease

There always is the concern that malnutrition and also concurrent infections caused by other pathogenic organisms, such as those which produce malaria and measles and are known to increase the risk of severe outcome from other gastrointestinal infections, similarly could worsen the severity of cholera. My suggestion of concern relating to malaria is due to the fact that while non-typhoidal *Salmonella* serotypes (NTS) often are associated with gastroenteritis in immunocompetent individuals, individuals with severe pediatric malaria can develop bacteremic infections with NTS during which symptoms of gastroenteritis are commonly absent (Mooney et al. 2014). My concerns about malnutrition and measles were summarized in 2018 (Hurst 2018). The probability of human death from gastrointestinal llness caused by *Cryptosporidium parvum* in the general population is 0.0002 (100 deaths per 403,000 cases of illness) (Hurst 2018). Numbers from a publication by Crawford and Vermund (1988) indicate that the probability of cryptosporidial illness leading to death can be 0.14 (14%, or 1 in 7, or 2/14) if there is underlying malnutrition. The risk of death from *Cryptosporidium* can be 0.20 in the case of underlying measles (20%, or 1 in 5) (Crawford and Vermund 1988) which represents a 2000-fold increase over the rate of death from *Cryptosporidium* infections in the general population. By itself, illness caused by the measles virus *Morbillivirus measles morbillivirus* is almost never fatal but it may be one of the most immunosuppressive viruses that infect humans.

7.8 Prevention of Cholera Including Vaccination and "WASH"

Vaccination and community awareness ultimately will help us to defeat the pestilence known as cholera.

7.8.1 Immunity to Cholera and Vaccination Against the Disease

Vibriocidal antibody is an immunologic marker associated with protection from *Vibrio cholerae*. It has been found that knowledge of the levels of serum IgA to three specific antigens: the B subunit of cholera toxin, lipopolysaccharide, and the major subunit of the toxin-coregulated pilus TcpA that induces mucosal and systemic immunoglobulin A immune responses in patients with cholera caused by *Vibrio cholerae* types O1 and O139, can be used to predict protection in household contacts of patients infected with *Vibrio cholerae* O1 (Harris et al. 2008). Two types of killed-cell vaccines currently are available for helping to prevent cholera (World Health Organization 2017).

7.8.2 International Efforts to Control Cholera

The Global Task Force on Cholera Control (2017) has a goal of reducing cholera deaths by 90% and expresses the hope that as many as 20 of the 47 countries currently affected by cholera could completely eliminate cholera disease transmission by 2030. The task force strategy consists of interventions that include oral cholera vaccines plus a group of water related activities to which they have assigned the acronym "WASH". That acronym is said to represent several points, although the exact number and wording of those points seems to vary.

Firstly, "Basic water supply" is a concept that means having access to safe drinking water, and could be represented by a community supplied potable water distribution network which pipes safe drinking water to each household. Among the alternative possibilities that are considered reasonable for providing an adequate water supply are having access within a 30-minute round-trip to either a public standpipe, borehole, protected dug well, protected spring, or rainwater collection system. If the available water is not potable, meaning safely drinkable, then there should be a provision for either household or community disinfection of the water. That concept of basic water supply helps with preventing both primary transmission and also secondary transmission of waterborne infections. I have addressed elsewhere in this book the subject of providing microbiologically safe drinking water for populations ranging from municipalities to individual households (Chap. 9, "Microbiome of Drinking Water Distribution Systems" pp. 261–311).

Secondly, "Basic sanitation", meaning access to improved sanitation facilities as represented by either having households connected to a public sewer, or a septic system, or a pour-flush latrine, or a pit latrine, will help to prevent secondary transmission.

Thirdly, "Basic hygiene", meaning that every household has access to a hand-washing station with soap and water. Appropriate care when preparing food, including safely either peeling or washing ingredients, cooking things thoroughly, and then protecting the prepared food against inadvertent fecal contamination, will help to avoid secondary transmission. It also is helpful to establish effective community engagement programs to promote safe hygiene.

One of the important aspects of public health programs is to carefully manage the necessary monetary and physical resources that are required for achieving success in disease elimination. There also is a necessity for creating adequate governmental health agencies that will be assigned and comply with the task of monitoring the quality of community water supplies including piped water distribution networks. Disease surveillance and reporting, including the important step of confirming *Vibrio cholerae* infections at the peripheral level for suspected cholera cases, and conducting a monitoring program for identifying outbreaks, represent expensive but helpful efforts that require access to laboratory culture capacity and rapid diagnostic tests. Having an ability to test for antibiotic susceptibility of the causative bacteria during oubreaks, and the ability to geographically track the bacterial strains associated with outbreaks, also are helpful (Camacho et al. 2018; Kiiru et al. 2013) because accurate surveillance data can advance efforts towards achieving the goal of prioritizing preparedness.

The types of advance preparations which can be made for confronting cholera outbreaks include pre-positioning supplies of oral rehydration salt (ORS) solution for performing oral rehydration therapy, which is the administration of fluid by mouth to prevent or correct the dehydration caused by the diarrhoea (World Health Organization 2006), plus having available intravenous fluids for rehydration when instances of diarrhea are so severe that oral rehydration would not be sufficiently effective for saving life. Hypochlorite disinfectant solution should be available for sanitation to prevent iatrogenic infections inadvertently associated with medical examinations during the treatment of cholera patients. The health care system also can be benefited by advance training of health workers to improve patient care and benefited by education about reducing iatrogenic infections. Having dedicated health care facilities which might be either Cholera Treatment Centers or Cholera Treatment Units could further help to reduce the likelihood of nosocomial cholera infections (Global Task Force on Cholera Control 2017).

Compliance with Ethical Standards

Conflict of Interest Christon J. Hurst declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals.

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