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A commentary on cholera: The scourge that never dies

Human actions play a large part in creating the conditions that allow cholera outbreaks to occur.

ABSTRACT: The study of cholera is an instructive one that touches on many different fields, including microbiology, epidemiology, marine biology, climatology, waste management, and socioeconomics. We now understand much about *Vibrio cholerae* that was previously perplexing and know more about the organism's ability to survive by colonizing the gastrointestinal tract of copepods. Today cholera outbreaks continue to occur throughout Africa and in other areas affected by war and poverty such as Iraq. Until we combine our understanding of *V. cholerae* with determination to eradicate the disease it causes, many will continue to suffer and die because of this waterborne illness.

In the field of infectious disease, cholera is one of the most instructive diseases to study because it touches on several disciplines, including microbiology, epidemiology, marine biology, climatology, waste management, and socioeconomics. The study of cholera began in earnest more than 100 years ago. In 1854, the city of London was in the grip of a terrible cholera outbreak affecting hundreds and killing dozens. At the same time the scientific world was embroiled in debating the merits of the germ theory (disease is caused by a specific organism) and the miasma theory (disease is caused by poisonous vapors in the air).[1]

Previously, in 1849, Dr John Snow had published an essay about his investigation of an earlier London cholera outbreak that had convinced him water was the carrier and cause of this terrible illness. During the 1854 outbreak he set out to prove his theory. He went from house to house tabulating who was sick, who was healthy, and who had died. He then correlated these data with information about the water supply. During his investigation, Snow received valuable support from a local preacher, Reverend Henry Whitehead, and a local statistician, Dr William Farr.

Snow's investigations eventually implicated a particular pump in Broad Street as an important source of the outbreak. Even though the number of cases was already declining as a result of people leaving the area, Snow managed to reduce the number further by meeting with local officials and having the handle of the pump removed. Investigation eventually identified the index case, an infected child named Frances Lewis, whose mother was throwing her soiled nappies into a cistern that was found to be connected to the pump in Broad Street by chronic rot.

Although Snow's ideas were not immediately accepted, the establishment gradually came to recognize the importance of his findings, and long after his death Snow became known as the father of epidemiology.

Microbiology

In the same year that Dr Snow was carrying out his studies in London, Dr Filippo Pacini, an Italian microscopist, found an organism in stool samples of patients with cholera. While

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studying a cholera epidemic in Florence, he showed clearly that cholera sufferers had numerous such organisms in their stools and healthy people did not. He described a "comma-shaped bacillus" and named it "Vibrio."[2] In a series of publications, he correctly described the basic pathology as involving a massive loss of fluid in the intestinal mucosa. Unfortunately, his published findings were not widely accepted and he did not receive the recognition he deserved. Instead, Dr Robert Koch received credit for the discovery when he confirmed Pacini's findings in 1884. By that time the scientific world was ready to accept microorganisms rather than the so-called miasmata as the cause of the disease. However, Pacini did finally receive posthumous recognition in 1965 when the International Institute of Microbiology renamed the organism in his honor as *Vibrio cholerae pacini 1854*.[3]

Subsequent research has delineated the role of *V. cholerae* in causing disease by describing several pathogenic factors.[4] These include the ability of the organism to survive gastric acidity, to penetrate intestinal mucus, and to withstand gut motility. Other factors identified include the organism's ability to form adhesins and TCP pili (which allow the bacterium to adhere to the intestinal cells) and to form the cholera toxin (which causes massive outpouring of fluid from the mucosa).

While *V. cholerae* has around 200 serotypes, only two are pathogenic—01 and 0139. Serotype 01 is further divided into classical and El Tor strains.[5] The newer serotype 0139 has acquired genetic material from other *Vibrio* species, probably through mechanisms such as transduction, whereby viral DNA is incorporated into the host bacterial genome and confers greater pathologic possibilities, including antibiotic resistance. This factor in particular has made it difficult to produce an effective vaccine against cholera.

Epidemiology

Cholera probably originated in the Bengal area of India and then spread west across Asia in a series of pandemics beginning in 1817.[6] The first six pandemics all began in India, while the seventh pandemic began in 1961 in Indonesia and reached Peru in 1991. This outbreak, caused by the El Tor strain, was especially virulent, and by 1994 over 1 million cases with 9642 deaths were reported from 13 countries in Central and South America. Routes of transmission of *V. cholerae* in this epidemic included "unwashed fruits and vegetables, contaminated food from street vendors, contaminated drinking water and contaminated crabmeat transported in luggage."[7]

Chlolera has continued to be a menace throughout the world. In 2000, 56 countries reported cases, with 87% of these occurring in Africa. Since 2007, cholera has also been reported from several parts of Iraq.

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Marine biology

Dr Rita Colwell first discovered the relationship between the *Vibrio* organisms and a type of zooplankton called copepods, tiny crustacea that feed on phytoplankton.[8] These copepods have an exoskeleton shell composed largely of a polymer called chitin. The *Vibrio* organism possesses an enzyme called chitinase, which allows the bacteria to partially digest the exoskeleton, thus using it as a source of nutrition. In addition the bacteria are able to colonize the gastrointestinal tract of the copepods.

While associated with the copepods, the *Vibrio* organisms can exist in a dormant state, remaining viable but not culturable through ordinary means. These viable non-culturable (VNC) *Vibrio* organisms can thus be protected while moving with the tides and traveling significant distances. The pathogenicity of the copepodassociated bacteria depends upon different environmental factors, such as water temperature, salinity, and acidity. These conditions often exist in estuarine areas where the bacteria can propagate effectively and cause outbreaks. The association of VNC bacteria with copepods explains some previously perplexing observations: the persistence of *Vibrio* organisms despite negative cultures, the frequent recurrence of outbreaks in certain areas, and the simultaneous occurrence of new outbreaks in different locales.[9]

Climatology

Flooding, increased rainfall, and higher aquatic temperatures—all common in a warming world—can lead to increased epidemics of waterborne diseases such as cholera and typhoid. Flooding greatly increases the chance that fresh water will be contaminated with waste products and sewage. It also interferes with the supply of clean water and can cause direct invasion of reservoirs by bacterial overgrowth.

Another weather factor related to disease is El Niño, which is part of a larger phenomenon known as ENSO—El Niño Southern Oscillation. In El Niño years, there is an eastward shift of rainfall and warm water across the equatorial Pacific Ocean toward the west coast of South America along with a decrease in the normal upwelling of ocean nutrients in that area. This warmer water along the Peruvian coast along with increased plankton stimulated by El Niño rains appears to have increased the *V. cholerae* population in the ocean.[10]

The association of warmer water and cholera outbreaks has also been observed in Bangladesh's Bay of Bengal area, where the seasonal pattern of cholera reflects sea surface temperatures and plankton abundance.[11] This relationship appears to have gotten stronger in the last 20 years and primarily involves coastal areas where *V. cholerae* thrives. By comparing the patterns of sea surface temperature and sea surface height with blooms of *Vibrio*-bearing plankton, Colwell and colleagues have been able to predict outbreaks of cholera.

Waste management

Throughout history the story of cholera has been intimately tied to the story of human waste, which has also been closely related to the use of water. In the early 19th century the population of London rose to 2.5 million through rapid urbanization and industrialization. With this population explosion the amount of human waste became overwhelming. Cities contained masses of excrement in cisterns and cesspools, a situation worsened by open sewers harboring germs carrying cholera, typhoid, and other waterborne diseases.

Then in 1831 a cholera epidemic struck the city.[12] The high-density inner-city living combined with inadequate toilet and waste facilities provided a ready means for the *V. cholerae* bacillus to spread through the citizenry, infecting and killing thousands. By 1847 London's sewage problem was even worse with more excrement piling up in cesspits and open sewers.

The first act of the newly formed Metropolitan Commission of Sewers was to close the cesspits, thus directing the sewage into the Thames River, which essentially became a giant sewer. Since the river was also the main source of drinking water, another major cholera epidemic occurred the following year, killing thousands. This epidemic indicated the importance of separating the water intake from the sewage output, a factor still crucial today in preventing cholera outbreaks.

Socioeconomics

The link between socioeconomic conditions and infectious disease is well known, but no disease highlights this connection better than cholera. A clean water source, good personal hygiene, and safe waste disposal are essential to preventing epidemics. But these factors are a gigantic challenge for millions of people living in poverty around the world. Thousands of communities in the nonindustrialized world simply do not have the resources or infrastructure to maintain these necessities of public health. According to Dr Robert Morris,[12] "around the world 1.1 billion people lack access to improved water sources and 2.6 billion lack access to improved sanitation."

Indeed, as the world becomes more heavily populated many related factors are ensuring that diseases such as cholera may never be eradicated because of "urban migration with formation of huge unsanitary slums, increased long distance mobility and trade, changes in personal behaviour and the terrible disruption of wars and conflict."[13] Even as cholera outbreaks continue to occur throughout the world, the last several years have seen a concentration in Africa, especially in Angola, Sudan, Zaire, Democratic Republic of the Congo, Senegal, and Niger.

In September 2007, a cholera outbreak was reported around Kirkuk in northern Iraq. Cholera has since spread to Baghdad and other areas, which is not surprising in a country where war and poverty ensure inadequate access to clean water, disruption of sanitary networks, and the prevalence of raw sewage.[14] Although the general situation in Iraq is improving, continued outbreaks will occur until adequate infrastructure and basic facilities are in place.

Conclusions

A review of the history of *Vibrio cholerae* shows us that cholera is not just a disease but a result of how we interact with the world around us. While the *V. cholerae* organism itself can never be eradicated, the disease it causes can be controlled. Thus, the morbidity and mortality of future outbreaks depends not so much on the organism as on human actions and the environment surrounding the organism. If there is malnutrition there will be cholera; if there is poor sanitation there will be cholera; if there is war there will be cholera.

We have the knowledge and the technology to eradicate this disease, but do we have the will and the determination? If not, then cholera will remain the scourge that never dies.

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Competing interests

None declared.

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