



Eyes on the Prize: Lessons from the Cholera Wars for Modern Scientists, Physicians, and Public Health Officials†

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ASTMH Presidential Address

Eyes on the Prize: Lessons from the Cholera Wars for Modern Scientists, Physicians, and Public Health Officials†

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PROLOGUE

On October 19, 2010, a cholera outbreak was reported in the Artibonite area of Haiti, 10 months after a devastating earthquake had struck the island. Three weeks later on November 6, 2010, then American Society of Tropical Medicine and Hygiene President Edward T. Ryan, MD, gave the following Presidential Address at the American Society of Tropical Medicine and Hygiene Annual Meeting in Atlanta, Georgia.

The American Society of Tropical Medicine and Hygiene traces its origins to 1903, a time when health professions were organizing to address new health threats, including those posed by growing international exchanges and evolving colonialism. One of these threats was cholera, a severe dehydrating illness caused by *Vibrio cholerae*, but we meet here 107 years later with our newspapers filled yet again with news of cholera, this time in Haiti. In October 2010, after a devastating earthquake and displacement of millions of persons in Haiti, a large and spreading outbreak of cholera began that shows no signs of abating. We know a great deal about cholera, but as we gather here tonight, we must acknowledge that we as a species are literally still plagued by it. What lessons can we as scientists, physicians, and health officers garner from the story of cholera's impact on humanity, and perhaps more importantly, humanity's responses to cholera?

I will also preface my Address with the caveat that I am not a historian and that any errors, omissions, or mis-attributions are my fault. They represent my best knowledge after spending the last two decades working on cholera, and I welcome revisions and corrections. As you will see, the story of cholera is both horrifying and rich, with historical details that are extraordinary.

Cholera is caused by a flagellated gram-negative bacterium, *Vibrio cholerae*. Two serogroups of *V. cholerae* (of approximately 200) are associated with epidemic cholera: *V. cholerae* O1 and O139. The pathogen contains two circular chromosomes that have been sequenced, and much is known about its fundamental microbiology. *Vibrio cholerae* exists as a free-living water-based organism, usually in brackish coastal waterways, and often in association with chitin-shelled organisms and zooplankton. With the right temperature and nutrient profile, *V. cholerae* can also exist inland in fresh water, a reality that underpins many of the more recent cholera outbreaks in Africa and now Haiti. Historically, the main eco-

logic niche of *V. cholerae* was probably the top of the Bay of Bengal, where salt and fresh water mix in a large delta system fed by the great eastern rivers of southern Asia.

Although *V. cholerae* may have existed and caused human disease from antiquity, the first relatively well-documented written records that describe what was probably a cholera outbreak date from the 1500s. Gaspar Correia, a Portuguese explorer, described in the *Lendas da India* in 1543 an outbreak among army troops in Calicut and Goa to which 20,000 deaths were ascribed. He noted that the “disease (was characterized) by vomiting with drought of water accompanying it as if the stomach were parched up and cramps that force the sinews of the joints, disease sudden-like which struck with pain in the belly so that a man did not last out 8 hours of time”.

The more modern historical record, however, begins at a time when European colonialism and economic and military exchanges reached sustained engagement in the upper reaches of the Bay of Bengal. Since then, medical historians have declared seven global cholera pandemics. The first pandemic started in 1817 among British troops in what was then Fort William, Calcutta. The disease spread out across India, down through Southeast Asia and across to central Asia, and reached as far as Egypt and the shores of the Caspian Sea before receding. The second pandemic began in 1827, also in the Ganges delta area, and spread across Asia, up through Europe and across Germany to the port city of Hamburg. From there it jumped to England and spread throughout the United Kingdom. It reached France, and was carried by ship to Quebec for its first introduction to the New World, spreading down the Hudson Valley to New York City and then throughout the eastern, southern, and western United States. In 1832, the pandemic entered Australia, and by 1833 had reached Latin America and the Caribbean, probably largely imported from Spain and Portugal to its colonies. This second pandemic receded by 1837 and was the first truly modern global pandemic, affecting all inhabited continents. Despite that, responses to the spread of cholera at this stage were largely local in nature and not particularly effective.

The third pandemic began in 1839 among British troops in Afghanistan and this pandemic spread similarly to the second pandemic, receding only by 1855. However, the third pandemic was associated with a number of major developments. One development concerned the nature of how humans and health professionals perceived the cause of disease and illness. At this point in history, a prevailing concept of disease causation in Western medicine was that of miasma. Miasma (literally from the Greek word for pollution or defilement) initially ascribed disease to unhealthy smells and emanations from decaying matter, but miasmaticism grew to incorporate a wider range of root foulness, including socioeconomic status and moral fiber. A primary tool to fight miasma was hygiene,

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a term that echoes down in the name of our Society. The other model of disease origin at the time, and definitely the minority camp in the 1830s–1850s before the revolutionary work of Pasteur and Koch and the other great founders of microbiology, was the growing field of contagiousness. It was on this background that John Snow first encountered, pondered, and analyzed cholera, and moved the contagiousness concept of disease into its ascendancy.

Although John Snow is best known now for his work on cholera, during his lifetime he was mostly renowned as an anesthesiologist; he was the personal anesthetist to Queen Victoria during delivery of a number of her children. Although these two aspects might seem unrelated, they are actually intimately linked. Within a year of the description of the public successful use of ether at the Massachusetts General Hospital in Boston in October 1846, Snow in England had experimented extensively with ether and published a seminal work *On the Inhalation of Vapour Ether in Surgical Operations*, rapidly becoming a recognized expert in the new field. John Snow's background in gases, ether, chloroform, their gaseous distribution, and their effects on the human body directly informed his view of cholera. He reasoned that gaseous emanations from rotting debris and unclean conditions could not explain the spread of cholera, nor cholera itself, an illness he had personal experience with having served alone as a medical apprentice in a small rural English town during the 1831 outbreak.

By 1849, soon after his work on ether, he published his first work on cholera *On the Mode of Communication of Cholera*, suggesting water as a transmission source of a causative (but unseen) agent. This work was not well received at the time (the devastating and personal reviews in the *Lancet* make for interesting and sobering reading when seen in the context of time). During the third pandemic, Snow continued this cholera work, but focused his response to his critics with data, not conjecture. The core of this response was what he referred to as his Grand Experiment in which he worked with William Farr, the chief biostatistician for London and a pioneer biostatistician, analyzing data from 1848 and 1849 describing cholera-related deaths in London. In this analysis, Snow compared the cholera death burden among London inhabitants who received their water from the Southwark and Vauxhall Water Company, which drew its water downstream of London (after the city's sewage had been added and closer to the Thames River meeting the open sea [i.e., higher salinity]), to the death rate among persons who received their water from the Lambeth Waterworks Company, which drew its water upstream of London. Snow found that the death rate from cholera was 315 deaths/10,000 persons of London for those who received their water from Southwark and Vauxhall, but only 37 deaths/10,000 persons for those who received their water from the Lambeth Company.

Snow was about to publish his analysis when another large cholera outbreak occurred in the Soho area of London on the night of August 31, 1854. This outbreak occurred a few days after a five-month-old baby named Sarah Lewis had died from cholera on Broad Street. On the night of August 31, hundreds of persons became sick in Soho with almost 200 deaths within 24 hours, mostly centering on Broad Street. Snow lived close to Broad Street and personally investigated the distribution of deaths and cases. He recognized that the largest concentration of cases seemed to associate with use

of the water pump at Broad Street, and he petitioned the St. James Parish Council to disconnect the handle on the Broad Street pump. Not really believing Snow, but seeing little downside, the Council agreed. In reality, the outbreak was coming to an end by the time this action was taken, but it should be noted that Sarah Lewis' father became sick with cholera on the day that the pump handle was removed, and the contamination of the water source would have started anew because the draining cesspool from the Broad Street house of the Lewis family had broken down and was in communication underground with the Broad Street pump. John Snow's intervention, therefore, probably prevented a second large outbreak of cholera in Soho.

With his larger Grand Experiment supplemented by the data from the Broad Street outbreak, Snow republished his work in 1855. This time the data were more convincing, were confirmed by subsequent enquiries, and more persons began to recognize the importance of Snow's work. The implications were significant, and facilitated the movement away from considering cholera as being related to inhalation and gases, to being considered the first recognized water-borne illness. Quite simply, miasmaticism had been dealt a deadly blow, and the contagiousness theory of disease took hold. Snow's work is normally considered the birth of evidence and field-based epidemiology, and pointed the way toward practical prevention of disease transmission.

Of note, during this third pandemic in 1854, Filippo Pacini, a clinician and scientist in Florence, Italy, dealing with that city's large outbreak, used microscopy to identify a curved bacillus in the stool of cholera victims, naming the organism *Vibrio cholerae* because it appeared to vibrate under the microscope. Pacini's illustrations leave little doubt that he had visualized the correct organism. However, his work was largely ignored.

The fourth pandemic began in 1863 and in a particularly grim chapter of this pandemic, cholera killed one-third of the 90,000 Mecca pilgrims attending Hajj that year. The infection then spread through Africa, Europe, Latin America, and the United States before receding in 1870. This pandemic marked the ascendancy of the contagiousness theory of disease, and specifically of the water-borne theory relating to cholera. During this pandemic, policy, public health, and engineering interventions were being implemented in countries with the resources to prevent cholera deaths.

The fifth pandemic began in 1881 and is referred to as the Steam and Suez pandemic, spreading from India through Egypt through Africa and Europe, as well as to China and Japan. During this pandemic, Robert Koch did his pioneering work in Egypt and then Calcutta in 1883 and 1884, in which he isolated the cholera organism (which he first called *Kommabazillen* [comma shaped bacillus]). In recognition of Pacini's precedence, the organism was subsequently renamed back to Pacini's *Vibrio cholerae*. Of note, London averted an outbreak during this pandemic largely through the presence of its new sewer system that had been completed in 1875 by Joseph Bazalgette. New York similarly averted an outbreak in 1892 by implementing quarantine in the New York harbor and using the first laboratory-based public health intervention. Specifically, the U.S. National Institutes of Health and Centers for Disease Control and Prevention trace their roots to the predecessor of the U.S. Public Health Service, the Marine Health Service that was formed in 1798 and originally chartered to provide for the medical care of merchant seamen.

By the 1880s, Congress had charged the Marine Health Service with examining passengers arriving with infectious diseases, especially cholera, yellow fever, and tuberculosis. In 1887, Joseph Kinyoun had set up a one-room laboratory in the Marine Hospital on Staten Island, New York. He was trained in microbiology and used a new Zeiss microscope to diagnose cholera cases based on the work of Koch. This development represented the first laboratory confirmation of cases at a public health level, and enabled targeted quarantining of ships and prevention of outbreaks. The fifth pandemic, therefore, showed large advances in microbiology and germ theory with the isolation of the causative agent, as well as development of diagnostic and public health screening protocols. It also represented the first division of the haves and the have nots in the global population. Previous to this time, all persons were equally susceptible to cholera. Now cholera began to be associated with poverty and global social disparity.

The sixth pandemic was prolonged, and stretched from 1899 to 1923, involving Asia, Africa and Europe, but sparing the Western Hemisphere. During the Mecca pilgrimage in 1902, another large outbreak among Hajj pilgrims occurred, and repetitive outbreaks among Mecca pilgrims resulted in the enforcement of strict quarantines. It was at the El Tor Quarantine Camp in the Sinai that El Tor *V. cholerae*, a new biotype, was first identified in 1905.

In 1961, in what is today modern Sulawesi–Indonesia, the seventh pandemic began with El Tor *V. cholerae* re-emerging, and subsequently spanning out in repetitive waves across the globe. By 1970, cholera had extended into Africa and Europe, and by 1991 was introduced into Latin America. It is sobering to note that in the 1970s cholera reappeared in Europe after a hiatus of at least 50 years, causing 30 deaths in Naples, Italy, and more than 2,000 cases in Lisbon, Portugal. Cholera was reintroduced into Africa in 1970, spreading across the continent. It has taken brutal hold in many areas of Africa, becoming endemic in many water systems, and now recurrently plagues that continent. A particularly gruesome outbreak occurred in Goma, Zaire in 1994 in which 50,000 persons died within a 21-day period from a concomitant cholera and shigellosis outbreak.

Cholera has played major roles in many advances of modern science and public health, perhaps noting more firsts than any other pathogen (Table 1). For instance, I have already mentioned that *V. cholerae* was the first causative agent that was identified by microscopy. Cholera also led to the first use of intravenous fluid to treat an ill human. In 1830, Jaehnichen injected six ounces of water intravenously into a cholera patient; the patient improved but then died two hours later. Also in 1830, the German surgeon J. F. Dieffenbach injected whole blood into three cholera patients and once again, although improvement was noted, they died shortly thereafter. During 1831–1832, a prescient W.B. O’Shaughnessy noted that the purpose of treatment should be “to restore specific gravity of blood and replace deficient saline matter” in the blood of cholera patients, prompting Thomas Latta in Scotland to use intravenous fluid replacement therapy with water and salt. Of note, 5 of 15 patients who were in the end stage of disease survived, a report that was sufficient to be published in 1832.

Despite this relative success, intravenous fluid therapy was largely ignored until 1908 and 1909 when Leonard Rogers in Calcutta established sterility and protocol techniques, and showed that sufficient volume replacement with intravenous fluid could reduce mortality rates from 70% to 30%. Intrave-

TABLE 1
Cholera milestones: driven by evidence

First modern global pandemic
Arguably the pathogen that can kill the most number of humans in the shortest period of time
Response to cholera led to major changes in public health and development of governmental and international health boards and agencies
Driver of evidence-based epidemiology
Driver of end of miasmaticism
First described water-borne (non-airborne/contact) illness
First pathogen identified by microscopy (Pacini, Florence, 1854)
First use of laboratory-based public health intervention
Led to discovery of lipopolysaccharide (heat-stable toxin)
Led to the discovery of complement system
First serological basis of diagnosis (vibriocidal and agglutination assays)
Led to development of serotyping of bacteria (agglutination assay)
First enterotoxin identified (cholera toxin) and biochemical mechanism of action determined
First enterotoxin sequenced
First whole-organism analysis of bacterial pathogen gene and protein expression profiling directly in humans
First large field use/trial of laboratory-derived vaccine (Ferran, Spain, 1884; Haffkine, Simpson, India, 1893–1894)
First effective oral vaccine (Sawtschenko and Sabolotny, 1893)
First randomized control group vaccine field trial (Besredka oral bilivaccine vs parenteral, 1920s, India and China)
First use of therapeutic intravenous fluid (Jaehnichen and Hermann, 1830)
Driver of development of oral rehydration solution (ORS)

nous fluid, therefore, became standard treatment at this point. In 1910, Andrew Sellards described acidosis in cholera patients, suggesting that the use of alkali might be of benefit. Once Rogers added alkali to his regimen, mortality rates decreased further from 30% to 20%. During 1958–1964, Phillips, Watten, Carpenter, Gordon, and others measured the exact loss of water and electrolytes in cholera patients, prompting the development of specific intravenous fluid with isotonic saline and alkali. These researchers found that administering this fluid plus oral water could reduce the cholera case-fatality rate to < 1%.

During 1902–1963, physiologists had been examining sodium and glucose transport and their interaction in the intestine, prompting Robert A. Phillips, a U.S. military physician, to question whether the sodium-glucose water-coupled system may be intact during cholera. In 1962, he initiated a trial in the Philippines in which patients received oral solution with glucose that was added for its nutritional value. The addition of glucose led to water absorption and positive fluid and sodium balance, but unfortunately, 5 of 30 patients died, possibly from hypernatremia because the sodium concentration in the solution was high. Because deaths occurred, the protocol was deemed as less efficient than intravenous fluid treatment and was not pursued as practical. Pierce in Calcutta and Hirschhorn in Dhaka continued to use isotonic oral hydration with glucose and sodium in equal concentrations, noting that it decreased the use of intravenous fluid. Nalin, Cash, and others also recognized that oral cholera treatment needed to be tailored to the individual amount of dehydration and ongoing losses, work that was facilitated by the use of a cholera cot (first invented by Watten in Bangkok in 1959) in which fluids passed by an afflicted patient channel down a central hole in a rubber cot into a bucket, facilitating measurement of fluid losses and estimation of required

replacement therapy. These investigator and colleagues in Dhaka noted that using the new protocol of oral fluid replacement decreased intravenous fluid need by 80% in severely dehydrated adult cholera patients, a result that was published in the *Lancet* in 1968.

In 1971 during the Bangladesh War of Independence, there was large displacement of refugees, and cholera broke out in refugee camps and showed a case-fatality rate of 30%. With limited resources and scant access to intravenous fluids and supplies, health providers used oral rehydration solution (ORS), demonstrating a shockingly low mortality rate of 3% under such adverse conditions. This prompted BRAC, a Bangladesh non-government organization, and the Bangladeshi Ministry of Health through its Oral Rehydration Treatment Program, to expand the use of ORS, teaching rural families how to make and use simple home-based ORS. This roll out was facilitated by the work of researchers and clinicians at the International Centre for Diarrhoeal Disease Research in Bangladesh (ICDDR,B), who played critical roles in developing quality control mechanisms for home-based ORS, and conducting clinical trials. It is estimated that ORS has directly saved 40 million lives since its introduction.

Cholera, therefore, has driven many milestones by evidence-based approaches. Cholera was a plague; it was the pandemic that defined much of 19th century life, and it was associated with the global economy and emerging urbanization, presaging influenza and polio. It also played large roles in the field of public health, including being the illness upon which epidemiology was founded, detailed transmission was documented, steps to interrupt transmission were implemented, and cases could be diagnosed. It also played a major role in the development of public health policies and public health organizations, and the development of sanitary procedures and techniques. For instance, in 1851 in Paris, the International Sanitary Conferences began with cholera being the main focus. These meetings eventually led by 1907 to the first international health organization, the Office of International Hygiene, which was also based in Paris and was replaced by the Health Organization of the League of Nations, and eventually by the World Health Organization (WHO). It was also a cholera outbreak in Egypt that prompted the first meeting of the World Health Assembly in 1948.

A number of cholera specific issues remain. It is disconcerting that ORS use is not optimal and decreasing in many locations, pointing out that increased education and communication at the household level are required. It is also disconcerting that cholera cots are not more widely used. The ongoing outbreaks of cholera among the most impoverished persons in the world also highlight some of our failures as a global society. Although the long-term solution to prevent cholera is safe water and improved sanitation, WHO currently estimates that 800 million persons globally lack safe water and 2.6 billion persons lack adequate sanitation. It will therefore be decades, if not longer, before these injustices are rectified, and as such, the use of cholera vaccines in disease control and prevention, especially in the 50 countries in which cholera is endemic, needs to be promoted and evaluated.

So what are the lessons for cholera for us here tonight? First, the cholera wars include fascinating stories of scientific and evidence-based investigation in basic science, physiology,

toxicology, microbiology, environmental sciences, immunology, vaccinology, clinical field trials, epidemiology, health delivery, evaluation, and public health and policy responses. Perhaps the most important lesson in cholera and what I term the eyes on the prize is the development of ORS. Oral rehydration solution is based on science, costs a few pennies, can be made and used by the illiterate, and has saved millions of lives. It requires no special interventions and is as simple as drinking. It is the most practical, cost-effective health intervention driven by basic science yet developed, and it represents the paradigm of the interface of basic science, clinical medicine, and public health.

However, we should take a step back and look at additional lessons from the cholera story. The first lesson is that basic life scientists need to interface with applied science and not operate in a disconnected vacuum, however pure and beautiful that sphere may be. It was applied/translational scientists who took 80 years of wondrous basic science advancements and developed a rational evidence-based intervention that has saved millions of lives. In turn, applied scientists and clinicians need to recognize that they practice in a paradigmatic system and although they can use such systems as constructs to approach patients, they need to enable evidence to dictate their responses. This practice will require fluency with advances in basic science and the ability to question current practice, constantly looking for ways to improve. Public health officials need to reject settling for current policies just because they are good enough. Why are oral cholera vaccines not being more widely used and improved cholera vaccines not being more aggressively pursued? Public health officials will be required to use practical judicious balancing (but accelerated balancing) of what is working versus what would be better.

We as a Society also can garner a number of lessons. Tropical medicine was forged in an earlier wave of globalization, one that grew in part out of imperialism, colonialism, and military intervention. Our diseases always reflect our reality, and cholera is no exception; it was the first global pandemic that was able to capture this new ecologic niche. We are now in a different stage of globalization, one of economic interchange and rapidity of travel on a backdrop of urbanization and mega-cities. Although tropical diseases still affect a large portion of the globe, the traditional tropical diseases now largely affect persons who are being left behind by globalization. We need to continue to serve these persons, but we also need to recognize that they and we are facing new challenges. These challenges include emerging infectious diseases, largely viral and zoonotic in nature, often transmitted by the respiratory route or by vectors. We need to not only address these, but also recognize that severe weather and climate change may change the rules of engagement relating to these emerging infections (and other health issues), and that we need to be flexible and innovative in our responses.

At present, we as a Society are making major contributions in vector biology and arbovirology, but we are not addressing the large global burden of respiratory infections, which currently kill more children than any other category of disease. A second challenge is diseases related to delivery and infrastructure systems. In 2008, the global human population, for the first time in history, largely resided in cities, often in informal settlement areas in resource-limited set-

tings. The lack of adequate infrastructure in many of these settlements means that our current infrastructure systems can actually worsen many health situations and act as efficient vehicles for disease transmission. This finding is especially true for food-borne and water-borne diseases, and we as a Society need to continue to address these important aspects that lead to intestinal infections that are the second leading killer of children globally. The third general area concerns the non-communicable diseases that are increasingly afflicting the human population, including those associated with the use of tobacco and obesity, as well as diabetes, hypertension, and cardiovascular and oncologic conditions. As a Society, we do not do a good job in addressing these new global pandemics. How will we respond to our globalization health threats? Our strength has historically been in generating scientific knowledge on communicable diseases, and this knowledge has been used to support informed and evidence-based decision making for more than a century. A question for us tonight, however, 107 years into the history of our impressive Society, is will we build upon this base. A century from now, will it be said that we as a Society also responded to our global health threats, both ancient and new?

In closing, I would like to say what an honor it has been serving you as President this past year, and God willing, I look forward to working with you going forward.

EPILOGUE

From its onset in 2010 until 2013, the cholera outbreak in Haiti has thus far affected more than 600,000 persons, resulting in more than 8,000 deaths. New cholera cases occur daily. The Haitian outbreak is now the largest in recorded history. Since the outbreak, a more affordable oral killed cholera vaccine has received WHO pre-qualification, and studies are evaluating its use in Haiti and elsewhere, although no large-scale use has yet occurred. The WHO has also formed a cholera vaccine stockpile for possible use in future outbreaks. The quest for the best long-term solutions of safe water and adequate sanitation for the people of Haiti and other resource-limited areas continues, with substantial actions having been taken by national governments, international agencies, and their partners since 2010. Much has been accomplished in the last 36 months; much remains to be done. As we move forward locally and globally, we will all need to keep our eyes on the prize.

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