

## CHOLERA AND CLIMATE CHANGE: PURSUING PUBLIC HEALTH ADAPTATION STRATEGIES IN THE FACE OF SCIENTIFIC DEBATE

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### ABSTRACT

Climate change will affect the prevalence, distribution, and lethality of many diseases, from mosquito-borne diseases, like malaria and dengue fever, to directly infectious diseases, like influenza, to water-borne diseases, like cholera and cryptosporidia. This Article focuses on one of the current scientific debates surrounding cholera and the implications of that debate for public health-related climate change adaptation strategies.

Since the 1970s, Rita Colwell and her co-researchers have been arguing a *local reservoir* hypothesis for cholera, emphasizing that river, estuarine, and coastal waters often contain more dormant forms of cholera attached to copepods, a form of zooplankton. Under this hypothesis, climatically driven increases in sea surface temperatures, sea surface levels, and phytoplankton production—such as during El Niño years or because of climate change—can then spur cholera outbreaks

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in vulnerable coastal communities. As such, the local reservoir hypothesis has immediate implications for climate change public health adaptation strategies.

In November 2017, however, two teams of scientists published genomic research in *Science* concluding that epidemic and pandemic cholera outbreaks in the Americas and Africa originate from Asia, suggesting that the local reservoir hypothesis needs modification. The two research articles also suggested a very different strategy for dealing with cholera in the Anthropocene—namely, genetic detection and intensely focused control efforts in Asia.

This Article examines in more detail this emerging scientific debate about cholera reservoirs and the ultimate source(s) of cholera outbreaks and epidemics. It then explores the implications of that debate for climate change public health adaptation strategies, suggesting simultaneously that the cholera debate is one concrete example of how identifying the stakes at issue in different climate change adaptation strategies can help communities and nations to choose appropriate adaptation strategies despite scientific uncertainty.

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## INTRODUCTION: CLIMATE CHANGE, DISEASE, AND ADAPTATION

Climate change directly and indirectly changes human health vulnerabilities, including disease vulnerabilities. Indeed, in its 2014 Fifth Assessment, the Intergovernmental Panel on Climate Change (IPCC) devoted an entire chapter of its adaptation report to the human health impacts of climate change.<sup>1</sup> It summarized that:

The health of human populations is sensitive to shifts in weather patterns and other aspects of climate change (*very high confidence*). These effects occur directly, due to changes in temperature and precipitation and occurrence of heat waves, floods, droughts, and fires. Indirectly, health may be damaged by ecological disruptions brought on by climate change (crop failures, shifting patterns of disease vectors), or social responses to climate change (such as displacement of populations following prolonged drought).<sup>2</sup>

As is true for climate change impacts generally, a community's vulnerability to changing disease patterns depends on a complex mix of environmental and social factors.<sup>3</sup> For example, "[t]he background climate-related disease rate of a population is often the best single indicator of vulnerability to climate change—doubling of risk of disease in a low disease population has much less absolute impact than doubling of the disease when the background rate is high."<sup>4</sup> However, the changing climate itself and impacts on environmental attributes also matter:

Climate extremes may promote the transmission of certain infectious diseases, and the vulnerability of populations to these diseases will depend on the baseline levels of pathogens and their vectors. In the USA, as one example, arboviral diseases such as dengue are rarely seen after flooding, compared with the experience in other parts of the Americas. The explanation lies in the scarcity of dengue (and other pathogenic viruses) circulating in the population, before the flooding. On the other hand, the high prevalence of HIV infection in many

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<sup>1</sup> INTERGOVERNMENTAL PANEL ON CLIMATE CHANGE, CLIMATE CHANGE 2014: IMPACTS, ADAPTATION, AND VULNERABILITY 709-54 (2014) [hereinafter 2014 IPCC ADAPTATION REPORT].

<sup>2</sup> *Id.* at 713.

<sup>3</sup> *See id.* at 717.

<sup>4</sup> *Id.*

populations in sub-Saharan Africa will tend to multiply the health risks of climate change, due to the interactions between chronic ill health, poverty, extreme weather events, and undernutrition.<sup>5</sup>

Thus, as other researchers have emphasized, “Because most emerging disease agents are not new but are existing pathogens of animals or humans that have been given opportunities to infect new host populations, environmental and social changes—especially those resulting from human activities which accelerate pathogen traffic—need to be defined.”<sup>6</sup>

The IPCC emphasized that some of the major changes to human health that climate change is bringing involve alterations in food-borne, water-borne, and vector-borne disease patterns.<sup>7</sup> As such, any community’s climate change adaptation strategy should address expected changes in these disease risks, which in turn will often depend on climate change’s particular environmental impacts in and around that community. For example, vector-borne diseases like malaria, dengue fever, and tick-borne encephalitis, which are spread through insect vectors such as mosquitoes and ticks, often have complex relationships to changes in temperature and rainfall.<sup>8</sup> Thus, in malaria-prone regions where climate change is pushing temperatures past mosquitoes’ maximum tolerance, malaria may actually decrease (although heat-related health problems will increase); in contrast, malaria is likely to increase in regions that historically have existed toward the lower end of mosquitoes’ temperature tolerance.<sup>9</sup> Nevertheless, globally, climate

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<sup>5</sup> *Id.*

<sup>6</sup> Rita R. Colwell, *Global Climate and Infectious Disease: The Cholera Paradigm*, 274 *SCI.* 2025, 2025 (1996).

<sup>7</sup> 2014 IPCC ADAPTATION REPORT, *supra* note 1, at 713.

<sup>8</sup> *See id.* at 722-25.

<sup>9</sup> *Id.* at 722. These variable impacts become more pronounced at more extreme increases in global average temperature:

Substantial warming in higher-latitude regions will open up new terrain for some infectious diseases that are limited at present by low temperature boundaries, as already evidenced by the northward extensions in Canada and Scandinavia of tick populations, the vectors for Lyme disease and tick-borne encephalitis. On the other hand, the emergence of new temperature regimes that exceed optimal conditions for vector and host species will reduce the potential for infectious disease transmission and, with high enough temperature rise, may eventually eliminate some infectious diseases that exist at present close to their upper tolerable temperature limits. For example, adults of two malaria-transmitting mosquito species are unable to

change will probably increase significantly the number of people at risk for contracting malaria and increase the number of areas where dengue fever can exist.<sup>10</sup>

Cholera, in turn, is a water-borne disease and “may be transmitted by drinking water or by environmental exposure in seawater and seafood . . . .”<sup>11</sup> The IPCC noted in 2014 that outbreaks of cholera and infections by related *Vibrio* species appear to be linked to temperature and rainfall changes in the relevant environment:

Risk of infection is influenced by temperature, precipitation, and accompanying changes in salinity due to freshwater runoff, addition of organic carbon or other nutrients, or changes in pH. These factors all affect the spatial and temporal range of the organism and also influence exposure routes (e.g., direct contact or via seafood). In countries with endemic cholera, there appears to be a robust relationship between temperature and the disease. In addition, heavy rainfall promotes the transmission of pathogens when there is not secure disposal of fecal waste. An unequivocal positive relationship between *Vibrio* numbers and sea surface temperature in the North Sea has been established by DNA analyses of formalin-fixed samples collected over a 44-year period. Cholera outbreaks have been linked to variations in temperature and rainfall, and other variables including sea and river levels, sea chlorophyll and cyanobacteria contents, and Indian Ocean Dipole (IOD) and El Niño Southern Oscillation (ENSO) event.<sup>12</sup>

While the IPCC offered no specific projections for cholera incidence in the future, its discussion nevertheless suggested that cholera outbreaks may be more likely as temperatures increase and heavy rainfall events become more likely.

At a basic level, what climate change means for future disease risk, including cholera, in a specific community depends on a number of

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survive temperatures much above 40°C in laboratory experiments, although in the external world they may seek out tolerable microclimates. Reproduction of the malaria parasite within the mosquito is impaired at lesser raised temperatures. Larval development of *Aedes albopictus*, an Asian mosquito vector of dengue and chikungunya, also does not occur at or above 40°C.

*Id.* at 736.

<sup>10</sup> *Id.* at 725-26.

<sup>11</sup> *Id.* at 726.

<sup>12</sup> *Id.*

variables, one of the most basic of which is disease etiology—that is, disease causation, especially in terms of where outbreaks actually come from and how they arise. Scientific debates over this etiology, and hence the disease’s relationship to climate change, bring into sharp focus one of the most pervasive impediments to the process of identifying and pursuing public health climate change adaptation strategies: scientific uncertainty regarding what climate change actually means for a given community’s or population’s disease vulnerability. Recent discoveries about cholera’s etiology, at least for some outbreaks, have brought this scientific uncertainty squarely into the realm of identifying cholera climate change adaptation strategies.

This Article examines how nations should be thinking about cholera adaptation in light of a recently sharpened and profound scientific disagreement regarding where cholera epidemics and pandemics come from. Dr. Rita Colwell and her colleagues have been pursuing a local reservoir hypothesis for cholera since the 1970s, based on discoveries that the cholera bacterium, *Vibrio cholera*, exists in local lakes, estuaries, and coastal waters in conjunction with copepods, a common form of zooplankton. Under this hypothesis, changes in climatic conditions can play a direct role in cholera outbreaks, putting cholera prevention squarely within the subject matter of climate change adaptation strategies. Two recent papers in *Science*, in contrast, use genomic analyses to trace all recent cholera epidemics to Asia, suggesting strikingly different strategies for dealing with cholera and a substantially reduced need for public health climate change adaptation strategies.

This Article thus examines cholera as a case study example of the climate change adaptation/scientific uncertainty conundrum. Part I presents a brief history of humanity’s interactions with cholera, especially the seven pandemics that have ravaged the world since the early 19th century. Part II then explains the local reservoir hypothesis of cholera outbreaks, emphasizing how researchers working under this hypothesis have identified environmental changes related to climate variability as both important causes and predictors of cholera outbreaks. Part III, in turn, examines the new “Asia origin” hypothesis and its implications for predicting and managing cholera—including the renewed hope that cholera could be eradicated.

In Part IV, this Article examines the issue of public health climate change adaptation strategies for cholera in light of the ongoing

scientific debate over the disease's etiology, especially debates regarding the importance of climatic variation to cholera outbreaks. After more specifically examining the stakes of the scientific debate over cholera for public health measures and surveying existing strategies for dealing with scientific uncertainty in climate change adaptation planning, it turns to four approaches to on-the-ground cholera prevention and treatment and their places within public health climate change adaptation policies: early warning systems for cholera outbreaks; improved drinking water treatment and sanitation; investment in a cholera vaccine; and efforts to eliminate cholera by eliminating its sources in Asia—a strategy that necessarily assumes that the new science is wholly and exclusively correct. The Article concludes that, in a world of limited resources, multi-benefit adaptation strategies such as investing in improved drinking water and sanitation should probably take first priority in most countries, although it acknowledges that country-specific exigencies and priorities may justify (or allow) investment in disease-specific public health strategies such as the cholera vaccine.

## I. A BRIEF HISTORY OF CHOLERA AS A HUMAN DISEASE

### A. Basic Overview of Cholera

Cholera appears to have a relatively long relationship with humanity. “There are descriptions of a disease resembling cholera in Sushruta Samshita from India, written in Sanskrit -500 to 400 B.C. Historical records tracing back 2000 years, in both Greek and Sanskrit, describe diseases similar to cholera.”<sup>13</sup> The original reservoir of the cholera bacterium, *Vibrio cholera*, was the Ganges River delta in India.<sup>14</sup>

Exposure to the cholera bacterium through contaminated drinking water or shellfish leads to infection of the small intestine and diarrhea.<sup>15</sup> Most infected people display only mild symptoms and readily

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<sup>13</sup> Colwell, *supra* note 6, at 2025.

<sup>14</sup> *Cholera Fact Sheet*, WORLD HEALTH ORG., <http://www.who.int/mediacentre/factsheets/fs107/en/> (last updated Dec. 2017) [hereinafter *Cholera Fact Sheet*].

<sup>15</sup> *See id.*; D. Lippi & E. Gotuzzo, *The greatest steps toward the discovery of Vibrio cholerae*, 20

recover with no or minor treatment, although their feces can still spread the bacterium and disease for one to ten days after infection.<sup>16</sup> However, a minority of infected individuals “develop acute watery diarrhoea with severe dehydration. This can lead to death if left untreated.”<sup>17</sup>

Scientists learned how to control the spread of cholera before they pinned down its actual cause. In 1854, during the third global cholera pandemic (see below),

British physician John Snow succeeded in identifying contaminated water as the transmitter of the disease, a breakthrough in eventually bringing it under control.

Snow carefully mapped the cases of cholera in the Soho area in London and traced the source to a water pump. After convincing officials to remove the pump handle, the number of cholera cases in the area immediately declined.<sup>18</sup>

John Snow’s discovery remains critically important to cholera prevention even today. As the World Health Organization (WHO) emphasizes, “[p]rovision of safe water and sanitation is critical to control the transmission of cholera . . . .”<sup>19</sup>

Connecting cholera to the *Vibrio cholera* bacterium, however, took a little longer. Filippo Pacini actually discovered this bacterium in 1854, the same year as John Snow’s epidemiological discovery.<sup>20</sup> However, the prevailing theory of disease at the time, the miasmal theory of disease, provided no scientific context in which to connect the bacterium to cholera.<sup>21</sup> Later in the 19th century, however, the scientific

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CLINICAL MICROBIOLOGY & INFECTION 191, 191 (2014).

<sup>16</sup> *Cholera Fact Sheet*, *supra* note 14.

<sup>17</sup> *Id.*

<sup>18</sup> *Cholera’s seven pandemics: Disease has killed millions since 19<sup>th</sup> century*, CBC NEWS, (Oct. 22, 2010), <http://www.cbc.ca/news/technology/cholera-s-seven-pandemics-1.758504>. For a longer description of Snow’s investigation and discovery, see Lippi & Gotuzzo, *supra* note 15, at 192.

<sup>19</sup> *See id.*; *see also* Lippi & Gotuzzo, *supra* note 15, at 191 (noting that epidemic cholera “is extremely contagious in communities without adequate sanitation.”).

<sup>20</sup> Lippi & Gotuzzo, *supra* note 15, at 191.

<sup>21</sup> *Id.* at 191-93 (“Although Pacini had discovered the vibriion, his cholera data were ignored by the scientific community and contradicted by influential physicians, who believed in the miasmatic theory, influenced by the localist/contagionist theory of the leading German scientist

transition to the germ theory of disease allowed Robert Koch to connect the bacterium to the disease when he rediscovered *Vibrio cholerae* in 1883.<sup>22</sup> Even then, skepticism over the role of *V. cholerae* in causing cholera persisted until 1959, when Sambhu Nath De discovered the bacterium's toxin and completed the explanation of how it could cause diarrhea.<sup>23</sup>

Cholera disease occurs in three forms: endemic outbreaks, regional epidemics, and global pandemics. As WHO notes, "[c]holera is now endemic in many countries," and "[a] cholera-endemic area is an area where confirmed cholera cases were detected during the last 3 years with evidence of local transmission (meaning the cases are not imported from elsewhere)."<sup>24</sup> Therefore, as Parts II and III will discuss in more detail, local reservoirs of the cholera bacterium probably remain critical sources of endemic cholera outbreaks, which also tend to be far less lethal than the epidemic and pandemic versions. Cholera epidemics, in turn, are a significant increase, often sudden, in cholera cases in a specific area.<sup>25</sup> "[E]pidemic cholera is an acute, painful and often lethal disease" that can lead to death from dehydration in a few hours.<sup>26</sup> Major cholera epidemics continue to occur in South America and Africa.<sup>27</sup> In addition, social unrest and war can foster cholera epidemics,<sup>28</sup> as occurred in Yemen in 2017.<sup>29</sup>

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Max von Pettenkoffer, who considered cholera to be an airborne disease, caused by a combination of three factors: a germ, the local and seasonal conditions, and a constitutional predisposition to infection" (citation omitted).

<sup>22</sup> *Id.* at 191.

<sup>23</sup> *Id.* at 194; see generally S.N. De, *Enterotoxicity of bacteria-free culture filtrate of Vibrio cholerae*, 183 NATURE 1533-34 (1959).

<sup>24</sup> *Cholera Fact Sheet*, *supra* note 14.

<sup>25</sup> See *Epidemic Disease Occurrence*, CENTERS FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section11.html> (last updated May 18, 2012) ("Epidemic refers to an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area.").

<sup>26</sup> Lippi & Gotuzzo, *supra* note 15, at 191.

<sup>27</sup> Colwell, *supra* note 6, at 2026.

<sup>28</sup> *Cholera Fact Sheet*, *supra* note 14.

<sup>29</sup> *Cholera count reaches 500 000 in Yemen*, WORLD HEALTH ORG. (Aug. 14, 2017), <http://www.who.int/mediacentre/news/releases/2017/cholera-yemen-mark/en/> (relaying that cholera outbreaks began in Yemen in April 2017 and, by August 2017, there were over 500,000 suspected cholera cases in that country, including almost 2000 deaths.).

Finally, WHO defines a pandemic to be “the worldwide spread of a new disease.”<sup>30</sup> Seven cholera pandemics have occurred,<sup>31</sup> as the next section explains in more detail.

## B. The Seven Cholera Pandemics

While cholera has been a human disease for over two millennia, cholera pandemics are relatively new and date to 1817.<sup>32</sup> Each cholera pandemic represents the global spread of a new infectious variant of the *V. cholerae* bacterium, and cholera bacteria have a wide range of genetic variations<sup>33</sup>—one reason why genomic studies like those published in 2017 can be revealing. All recent cholera outbreaks have been caused by the toxin-producing *V. cholerae* O1 serogroup.<sup>34</sup> Within this serogroup, cholera exists in two biotypes, classical and El Tor, and both biotypes are further classified into two serotypes, Ogawa and Inaba.<sup>35</sup> Classical strains of *V. cholerae* O1 probably caused the first six cholera pandemics, but El Tor strains are responsible for the seventh.<sup>36</sup> “Compared with the classical strains, El Tor persists for longer in the environment, causes more asymptomatic cases and is shed more extensively in excreta, even in asymptomatic cases.”<sup>37</sup>

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<sup>30</sup> *What is a pandemic?*, WORLD HEALTH ORG. (Feb. 24, 2010), [http://www.who.int/csr/disease/swineflu/frequently\\_asked\\_questions/pandemic/en/](http://www.who.int/csr/disease/swineflu/frequently_asked_questions/pandemic/en/).

<sup>31</sup> *Cholera Fact Sheet*, *supra* note 14.

<sup>32</sup> Colwell, *supra* note 6, at 2026.

<sup>33</sup> WORLD HEALTH ORG., *Cholera vaccines: WHO position paper*, 85:13 WKLY EPIDEMIOLOGICAL RECORD 117, 119 (2010), <http://www.who.int/wer/2010/wer8513.pdf?ua=1> (noting that there are more than 200 serogroups of *Vibrio cholerae*) [hereinafter 2010 WHO Cholera Vaccines Paper].

<sup>34</sup> See *Cholera Fact Sheet*, *supra* note 14 (explaining further that “[t]here are many serogroups of *V. cholerae*, but only two—O1 and O139—cause outbreaks. *V. cholerae* O1 has caused all recent outbreaks. *V. cholerae* O139—first identified in Bangladesh in 1992—caused outbreaks in the past, but recently has only been identified in sporadic cases. It has never been identified outside Asia. There is no difference in the illness caused by the two serogroups.”); see also 2010 WHO Cholera Vaccines Paper, *supra* note 33, at 119 (discussing in more detail the various types of *V. cholera* and their role in human disease.).

<sup>35</sup> 2010 WHO Cholera Vaccines Paper, *supra* note 33, at 119.

<sup>36</sup> *Id.*

<sup>37</sup> *Id.*; see also Colwell, *supra* note 6, at 2026 (“A new biovar or biotype of *Vibrio cholerae* caused the current pandemic—the El Tor biotype of *V. cholerae* O1, which emerged in Celebes, Indonesia, in 1961. The disease caused by this organism is usually not as severe as that of the

The first cholera pandemic was the relatively limited pandemic from 1817 to 1823, which was “related to the two wars – the Oman War and the war between Persia and Turkey.”<sup>38</sup> The pandemic “originated in the Ganges River delta in India,” breaking out near Calcutta and then spreading through the rest of the country.<sup>39</sup> By the early 1820s, “colonization and trade had carried the disease to Southeast Asia, central Asia, the Middle East, eastern Africa, and the Mediterranean coast.”<sup>40</sup> It is difficult to know for certain how many people died in this first pandemic, “but based on the 10,000 recorded deaths among British troops, researchers estimate that hundreds of thousands across India succumbed to the disease. In 1820, 100,000 people died on the Indonesian island of Java alone. By 1823, cholera had disappeared from most of the world, except around the Bay of Bengal.”<sup>41</sup>

The second, more widespread, pandemic of 1829 to 1849<sup>42</sup> or 1851<sup>43</sup> is sometimes said to have begun in Russia<sup>44</sup> but more likely began in India.<sup>45</sup> However, if the latter, it “reached Russia by 1830 before continuing into Finland and Poland. A two-year outbreak began in England in October 1831 and claimed 22,000 lives.”<sup>46</sup> Irish immigrants fleeing the potato famine brought the disease to North America in the summer of 1832, leading to 1,220 deaths in Montreal, Canada, and 1000 more across Quebec.<sup>47</sup> From there, “[t]he disease then entered the U.S. through Detroit and New York, and reached Latin America by 1833. Another outbreak across England and Wales began in 1848, killing 52,000 over two years.”<sup>48</sup>

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classical biotype.”).

<sup>38</sup> Colwell, *supra* note 6, at 2026.

<sup>39</sup> CBC NEWS, *supra* note 18.

<sup>40</sup> *Id.*

<sup>41</sup> *Id.*

<sup>42</sup> *Id.*

<sup>43</sup> Colwell, *supra* note 6, at 2026.

<sup>44</sup> *Id.*

<sup>45</sup> CBC NEWS, *supra* note 18.

<sup>46</sup> *Id.*

<sup>47</sup> *Id.*

<sup>48</sup> *Id.*

The third pandemic, generally considered the most deadly of the seven, occurred from 1852 to 1859.<sup>49</sup> Like all but the last of the cholera pandemics, it began in India, but it then spread to Asia, Europe, North America, and Africa.<sup>50</sup> "In 1854, the worst year, 23,000 died in Britain alone,"<sup>51</sup> even as John Snow was completing his pioneering epidemiological work on cholera.

The fourth cholera pandemic occurred from 1863 to 1879.<sup>52</sup> It "began in the Bengal region [of India] from which Indian Muslim pilgrims visiting Mecca spread the disease to the Middle East."<sup>53</sup> From there it migrated to Europe, Africa and North America. At least 30,000 of the 90,000 Mecca pilgrims fell victim to the disease.<sup>54</sup> Russia was also hard hit: In 1866, cholera killed 90,000 Russians.<sup>55</sup>

The fifth pandemic lasted from 1881 to 1896.<sup>56</sup> It "originated in the Bengal region of India and swept through Asia, Africa, South America and parts of France and Germany."<sup>57</sup> During this pandemic, 90,000 people in Japan died of the disease between 1887 and 1889, while in Russia cholera killed 200,000 people between 1893 and 1894.<sup>58</sup> However, "[q]uarantine measures based on the findings of John Snow kept cholera out of Britain and the United States," and Ukrainian Waldemar Haffkine produced the first cholera vaccine in 1892.<sup>59</sup> The sixth pandemic occurred from 1899 to 1923 (some sources say 1932) and "killed more than 800,000 in India before moving into the Middle East, northern Africa, Russia and parts of Europe."<sup>60</sup>

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<sup>49</sup> *Id.*

<sup>50</sup> *Id.*

<sup>51</sup> *Id.*

<sup>52</sup> *Id.*

<sup>53</sup> *Id.*

<sup>54</sup> *Id.*

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

<sup>57</sup> *Id.*

<sup>58</sup> *Id.*

<sup>59</sup> *Id.*

<sup>60</sup> *Id.*

We are still living with the seventh cholera pandemic, which started in Makassar, Sulawesi, Indonesia, in 1961 and spread to six continents,<sup>61</sup> reaching South Asia in 1963, Africa in 1970, Latin America in 1991, and the Caribbean (Haiti) in 2010.<sup>62</sup> This pandemic most affects Africa, although “little is known about the propagation routes of cholera in this region.”<sup>63</sup> In addition, “in 1991, 100 years after cholera was vanquished from South America, there was an outbreak in Peru that spread across the continent, killing 10,000 people. It was a similar strain to the seventh pandemic that petered out more than a decade earlier.”<sup>64</sup>

### C. The Global Health Burden of Cholera

Researchers currently estimate that, “every year, there are roughly 1.3 to 4.0 million cases, and 21 000 to 143 000 deaths worldwide due to cholera.”<sup>65</sup> According to WHO, “Cholera remains a global threat to public health and an indicator of inequity and lack of social development.”<sup>66</sup>

In 2010, WHO projected that cholera could become even more problematic in the future, based in part on changing climatic conditions but also because of changes in the disease itself:

Concerns about cholera have been heightened by the emergence of new, apparently more virulent, strains of *V. cholerae* O1 that now predominate in parts of Africa and Asia, as well as by the unpredictable emergence and spread of antibiotic-resistant strains. Also, there is a potential for increases in cholera outbreaks resulting from rising sea levels and increases in water temperature, since brackish water and estuaries are natural reservoirs of *V. cholerae*.<sup>67</sup>

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<sup>61</sup> Dalong Hu et al., *Origins of the current seventh cholera pandemic*, 113:48 PNAS E7730, E7730 (2016); Colwell, *supra* note 6, at 2026; *Cholera Fact Sheet*, *supra* note 14.

<sup>62</sup> François-Xavier Weill et al., *Genomic history of the seventh pandemic of cholera in Africa*, 358 SCI. 785, 785 (2017).

<sup>63</sup> *Id.*

<sup>64</sup> CBC NEWS, *supra* note 18.

<sup>65</sup> *Cholera Fact Sheet*, *supra* note 14; Weill et al., *supra* note 62, at 785.

<sup>66</sup> *See generally id.*

<sup>67</sup> 2010 WHO Cholera Vaccines Paper, *supra* note 33, at 119.

Given this latter concern, the connections between a changing climate and its impacts and future cholera outbreaks, epidemics, and pandemics indicate that cholera prevention and control should be a component of many nations' climate change adaptation strategies. However, developing science has recently made the exact nature of those connections between climate and disease, especially for countries not near the Bay of Bengal, more problematic. The next two Parts discuss these contrasting hypotheses regarding cholera etiology.

## **II. THE LOCAL RESERVOIR HYPOTHESIS AND CLIMATE CHANGE: CHOLERA, COPEPODS, AND WARMING WATERS**

The history of cholera pandemics presented in Part I notes that the first six originated in India, while the last originated in Indonesia. India and Indonesia are two of the countries that surround the Bay of Bengal; the others include Bangladesh, Myanmar (Burma), and Malaysia (see Figure 1). Given this history of cholera epidemics, it is perhaps unsurprising that researchers have focused considerable energy on the role of the Bay of Bengal—and changes in coastal environments more generally—in the emergence of cholera outbreaks, epidemics, and pandemics.



**Figure 1: The Bay of Bengal and Surrounding Countries.** This region has been the focus of research regarding the local reservoir hypothesis for cholera; the region has also been the starting point of all seven cholera pandemics.<sup>68</sup>

An environmental theory of cholera outbreaks pre-dated the 20th century. For example, Robert Koch offered such a hypothesis in the late 19th century but could not prove it “because of the ability of *Vibrio cholerae*, the causative agent of cholera, to enter a dormant phase between epidemics.”<sup>69</sup> Beginning in the 1960s, however, Dr. Rita R. Colwell has sought to document the origins of cholera outbreaks and pandemics, focusing on local reservoirs and triggering environmental conditions. In 1996 in *Science*, she reported that cholera bacteria can survive in dormant states in coastal and marine waters. Specifically, “[a]ll *Vibrio* spp. that are

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<sup>68</sup> Map courtesy of QUORA and posted and used in conformity with its re-posting policies. QUORA, <https://www.quora.com/about/tos> and <https://qph.ec.quoracdn.net/main-qimg-e0417b691aed15d5e57a32c2f07d2890-c>.

<sup>69</sup> Rita R. Colwell & A. Huq, *Global microbial ecology: biogeography and diversity of Vibrios as a model*, 85 J. APPLIED MICROBIOLOGY 134S, 134S (1999).

pathogenic are adapted to salinities between 5 per mil and 30 per mil. Salinities favorable for growth of *V. cholerae* are found primarily in inland coastal areas and estuaries, but the bacterium thrives in seawater as well.<sup>70</sup> Cholera bacteria can survive in a dormant and non-infectious state in association with copepods, a form of small marine zooplankton, “but apparently can be resuscitated by heat shock.”<sup>71</sup> In addition:

The association of *V. cholerae* with zooplankton has proven to be a key factor in deciphering the global nature of cholera epidemics. *V. cholerae* preferentially attaches to chitinous plankton, for example, copepods, and can be detected in zooplankton in cholera endemic regions. Ocean currents sweeping along coastal areas thereby translocate plankton and their bacterial passengers.<sup>72</sup>

Thus, according to Colwell, the sea and changes to the sea play an important environmental role in cholera outbreaks and pandemics, although of course “poor sanitation, lack of hygiene, and crowded living conditions” also play important roles in the disease’s spread.<sup>73</sup> Nevertheless, “[t]he history of cholera reveals a remarkably strong association with the sea. The great pandemics followed coastlines of the world oceans.”<sup>74</sup>

Continuing research indicated that the release of dormant cholera bacteria from copepods was linked to algal blooms (on which the copepods feed), changing sea surface temperatures, and changing sea surface heights.<sup>75</sup> All of these tend to occur during El Niño events, and research published in 1999 connected cholera outbreaks in Peru to the 1997-1998 El Niño event.<sup>76</sup> As such, the researchers concluded, advanced computational power in combination with increased interdisciplinary understanding of the role of copepods in cholera

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<sup>70</sup> Colwell, *supra* note 6, at 2027.

<sup>71</sup> *Id.*

<sup>72</sup> *Id.*

<sup>73</sup> *Id.*

<sup>74</sup> *Id.*

<sup>75</sup> Colwell & Huq, *supra* note 69, at 136S.

<sup>76</sup> *Id.*

transmission would allow public health officials to take proactive approaches to controlling cholera outbreaks, not just reactive.<sup>77</sup>

In 2008, Colwell and a large team of researchers published a more comprehensive assessment of the environmental factors associated with cholera epidemics in *Proceedings of the National Academy of Sciences (PNAS)*.<sup>78</sup> As they noted, "Before the late 1970s, transmission of cholera was believed to occur exclusively by person-to-person contact, with epidemics initiated by contaminated water and food."<sup>79</sup> However, "[i]t is now recognized that *V. cholerae* is a component of coastal and estuarine microbial ecosystems, with the copepod species of zooplankton that comprise the aquatic fauna of rivers, bays, estuaries and the open ocean serving as host for the bacterium."<sup>80</sup> Copepods act as a vector for the disease and can each contain up to 100,000 cholera bacteria cells.<sup>81</sup> As a result, ingestion of water containing even a few of these copepods "can initiate the disease," which "was demonstrated in a study showing that the number of cholera cases in Bangladeshi villages was significantly reduced when a simple filtration method that effectively removed the plankton and particulate matter was used to treat drinking water."<sup>82</sup>

Research continued to show that copepod populations in the Bay of Bengal, and consequent cholera epidemics, are causally linked to environmental factors, including changes in sea surface temperatures and sea surface height.<sup>83</sup> Later studies also emphasized the role of precipitation and chlorophyll concentrations in the sea, which is generally a function of algae growth and algal blooms.<sup>84</sup> As a result, the researchers concluded, "the variables related to copepod population dynamics

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<sup>77</sup> *Id.* at 1375.

<sup>78</sup> Guillaume Constantin de Magny et al., *Environmental signatures associated with cholera epidemics*, 105:46 *PNAS* 17676 (2008).

<sup>79</sup> *Id.* at 17676.

<sup>80</sup> *Id.*

<sup>81</sup> *Id.*

<sup>82</sup> *Id.*

<sup>83</sup> *Id.*

<sup>84</sup> *Id.* at 17676-77.

can serve as a proxy for the estimation of *V. cholerae* abundance in the environment.”<sup>85</sup>

Focusing on human cholera incidence in Kolkata, India, and Matlab, Bangladesh, these researchers noted that “[e]nvironmental factors were found to be statistically significant in [both] locations of the Indian continent in directly influencing the dynamics of cholera epidemics.”<sup>86</sup> However, the effect of those environmental factors were “clearly different,” indicating that local variables are still important to cholera transmission.<sup>87</sup> For example, Matlab is farther away from the coast than Kolkata, and human exposure there appeared to be tied to tidal intrusion that carried increased numbers of copepods inland to rivers and streams, where residents were the directly exposed to *V. cholerae* through washing and drinking—as opposed to more direct coastal exposure in Kolkata.<sup>88</sup> Matlab also showed a month’s lag behind Kolkata in cholera incidence after the relevant environmental indicators arose.<sup>89</sup>

Thus, local factors remain important to predictions of cholera incidence—and not just environmental factors. As the researchers noted:

cholera epidemics involve a complex and critical interplay of intrinsic dynamics with extrinsic drivers. For example, cholera is no longer a disease threat for developed countries, including the United States, even though the presence of *V. cholerae* O1 in the waters of the Chesapeake Bay and coastal states of the Gulf of Mexico has long been known.<sup>90</sup>

Nevertheless, the researchers’ main points for public health purposes were that “environmental as well as epidemiological data need to be collected and compiled expediently to provide useful and reliable predictions of the onset, epidemics, and trends of cholera based on environmental variability” and that studies could improve cholera

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<sup>85</sup> *Id.* at 17676, 17678.

<sup>86</sup> *Id.* at 17678.

<sup>87</sup> *Id.*

<sup>88</sup> *Id.* 17678-79.

<sup>89</sup> *Id.* at 17679.

<sup>90</sup> *Id.*

predictive capacities, giving public health researchers increasing and significant lead time to prepare a response and control strategy.<sup>91</sup>

As much of the research above indicates, Bangladesh is a cholera-endemic country.<sup>92</sup> Benjamin A. Cash and his colleagues, expanding upon the local reservoir hypothesis and the postulated importance of climatic changes to cholera outbreaks and epidemics, noted a connection between the autumn incidence of cholera in Bangladesh and El Niño–Southern Oscillation (ENSO) events the previous winter—a potentially important climate connection in terms of predicting cholera outbreaks and epidemics.<sup>93</sup> ENSO affects both sea surface temperatures in the Bay of Bengal and rainfall in Bangladesh, and above-average rainfall in turn “provid[es] a plausible physical link between winter El Niño events and cholera incidence in Bangladesh through increased flooding and breakdowns in sanitation.”<sup>94</sup> The researchers noted that “the El Tor strain of cholera replaced ‘the Classical’ strain in the environment during the mid-1970s” and hence that their research focused purely on the El Tor strain, although they acknowledged that “the two strains may respond differently to environmental drivers.”<sup>95</sup> For the El Tor strain and recent incidences of cholera, they concluded that “that Bangladesh summer precipitation is generally higher following winter El Niño events when the warm [sea surface temperature] anomalies in the central tropical Pacific persist through the summer months,” establishing “a physical basis for the observed correlation between cholera incidence and ENSO.”<sup>96</sup> Their results, moreover, potentially allowed for improved ability to predict cholera risk in Bangladesh, with initial predictions based on sea-surface temperatures and the state of ENSO in the winter and then modified through monitoring of sea surface temperature through the spring and summer.<sup>97</sup>

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<sup>91</sup> *Id.*

<sup>92</sup> Benjamin A. Cash et al., *Disentangling the Impact of ENSO and Indian Ocean Variability on the Regional Climate of Bangladesh: Implications for Cholera Risk*, 23 J. CLIMATE 2817, 2817 (2010).

<sup>93</sup> *Id.* at 2818.

<sup>94</sup> *Id.*

<sup>95</sup> *Id.* at 2822.

<sup>96</sup> *Id.* at 2827.

<sup>97</sup> *Id.* at 2829.

A year later, researchers showed that the Indian Ocean Dipole (IOD) is also relevant to cholera outbreaks in Bangladesh.<sup>98</sup> As these researchers reported, the IOD:

is a climate mode arising from an ocean–atmosphere interaction that causes interannual climate variability in the tropical Indian Ocean. A positive IOD indicates SST [sea surface temperature] anomalies with warmer than usual SSTs over the western basin and cooler than usual SSTs in the eastern basin near Sumatra. A negative IOD occurs when the SST is anomalously warm in the eastern basin and anomalously cold in the western tropical Indian Ocean. Although the extent to which the IOD is independent of ENSO has been debated, there is growing evidence that this air–sea interaction is specific to the Indian Ocean.<sup>99</sup>

The IOD can also affect sea level in the Bay of Bengal and regional climate, including monsoonal rainfall.<sup>100</sup> Specifically, a negative IOD tends to raise sea level in the eastern equatorial region of the Indian Ocean and to increase flooding in Bangladesh.<sup>101</sup>

As is true with other scientists working to elucidate the role of environmental factors in cholera outbreaks, the researchers here hoped to contribute to “the development of accurate early warning systems for cholera epidemics and aid in disease control.”<sup>102</sup> Using a time series analysis, they concluded that a positive IOD was associated with increased hospital visits for cholera 0-3 months later, as opposed to 8-11 months later for ENSO events.<sup>103</sup> They hypothesized that the IOD’s effect on rainfall upstream was partially responsible for increased cholera incidence:

Although the causal pathways are thought to be very complicated, high river levels/flooding are likely to be one of

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<sup>98</sup> Masahiro Hashizume et al., *The Indian Ocean Dipole and Cholera Incidence in Bangladesh: A Time Series Analysis*, 119:2 ENVTL. HEALTH PERSP. 239, 239-44 (Feb. 2011).

<sup>99</sup> *Id.* at 239.

<sup>100</sup> *Id.*

<sup>101</sup> *Id.* at 242.

<sup>102</sup> *Id.* at 240.

<sup>103</sup> *Id.* at 242.

the important causal pathways. Increased river levels and flooding adversely affect water sources and sewerage systems and increase the exposure to water contaminated with *V. cholerae*. The possible link between flooding and cholera may also be associated with the growth and multiplication of *V. cholerae*, because flooding increases the level of insoluble iron, which in turn improves the survival rate of *V. cholerae*. It has also been suggested that flooding washes away the vibriophages that prey on *V. cholerae*, resulting in increased concentration of the bacterium in the water, although a recent simulation study did not support this hypothesis. It is unlikely that these possible pathways explain all cholera cases during the monsoon season, because the incidence of cholera often dips during monsoon flooding. This dip is thought to result from a reduction in salinity levels due to increased river discharge, which reduces the survival of *V. cholerae* and decreases its concentration by monsoon rainfall (dilution effect).<sup>104</sup>

Despite these complexities, however, the researchers concluded that their findings “suggest that Indian Ocean [sea surface temperature] variability should be taken into account when building predictive models for cholera using ocean-climate data,” including the early warning system for cholera that WHO had proposed “based on climatic parameters.”<sup>105</sup>

As the references above to Peruvian cholera outbreaks indicate, the local reservoir (copepod) hypothesis has also been proposed for other locations. In 2009, Colwell and Guillaume Constantin de Magny published a more general proposal that cholera outbreaks are related to climate.<sup>106</sup> Noting that cholera “is reemerging in many parts of the world in epidemic form, especially in tropical areas,” the two researchers emphasized that “*V. cholerae* is naturally present in the

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<sup>104</sup> *Id.* at 243.

<sup>105</sup> *Id.*

<sup>106</sup> Guillaume Constantin de Magny & Rita R. Colwell, *Cholera and Climate: A Demonstrated Relationship*, 120 TRANSACTIONS OF THE AM. CLINICAL & CLIMATOLOGICAL ASS'N 119, 119-28 (2009).

environment," notably in rivers, estuaries, and coastal waters.<sup>107</sup> As a result, they suggested, the same etiology probably applies in all coastal nations where cholera is endemic: "At present, the main geographical regions of cholera endemicity include coastal areas surrounding the Bay of Bengal, Bangladesh, the Indian subcontinent, Africa, and coastal Latin America. In these regions, the same physical or environmental drivers most likely explain the patterns of disease."<sup>108</sup> The theory is relevant even to the United States, where cholera had gradually disappeared in the early 1900s because of improved sanitation and drinking water treatment.<sup>109</sup> The United States is not entirely free of cholera, and "its first reappearance in the twentieth century [was] reported in 1973 in Texas. Since then, sporadic cases are reported each year in the United States, some of which have been confirmed as indigenous in origin."<sup>110</sup> Chesapeake Bay is a proven reservoir of the *V. cholera* bacterium, and de Magny and Colwell developed a model to predict the presence and abundance of cholera bacteria in that bay.<sup>111</sup> While the model itself is not necessary to protect public health in the Chesapeake Bay region, it "illustrate[s] how an interdisciplinary research effort that includes microbiology, ecology and climatology can concretize academic research to a near-operational water-borne pathogen forecasting system."<sup>112</sup>

The linking of cholera outbreaks and epidemics to environmental factors—especially factors such as precipitation, sea surface temperature, and sea surface height—fairly directly renders continued control of cholera a climate change adaptation issue. Indeed, researchers in this field clearly recognize the climate change connection. For example, de Magny and Colwell pointed out in 2009 that:

The relationship between human health and climate is not a new concept, but in the existing context of global change, when most scientists now agree that our climate is

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<sup>107</sup> *Id.* at 119.

<sup>108</sup> *Id.* at 121.

<sup>109</sup> *Id.* at 122-23.

<sup>110</sup> *Id.* at 123.

<sup>111</sup> *Id.* at 123-25.

<sup>112</sup> *Id.* at 125.

changing, there is an increasing need to understand the potential outcome of such changes on human health. This can be achieved by considering how systems interact. With few exceptions, zoonotic and vector-borne diseases are readily understood as having links with the natural environment, and cholera is one of the best examples to illustrate this biocomplexity.<sup>113</sup>

This research also informed the IPCC's conclusions about the links between climate change and human disease. As such, studies of the links between environmental factors and cholera incidence "provide a foundation on which to build a predictive capacity for cholera epidemics, hence, an early warning system for enhancing public health measures, especially for developing countries and areas of the world undergoing social disruption or climate change."<sup>114</sup>

### III. THE ASIAN DISPERSION HYPOTHESIS: IS CLIMATE REALLY RELEVANT?

As noted, although much of the research supporting the local reservoir/copepod hypothesis regarding cholera etiology has occurred around the Bay of Bengal, researchers claim for it a broader application to cholera's origins. However, two genomic studies recently published in *Science* call into question the ubiquity of the local reservoir hypothesis, especially as pertains to cholera outbreaks in Africa and in Latin America.

Focusing on strains of the El Tor variety of the *V. cholera* bacterium, the Africa study<sup>115</sup> identified two El Tor strains "known to have invaded Africa in 1970: one in West Africa (serotype Ogawa) and the other in East Africa (serotype Inaba)."<sup>116</sup> The Ogawa bacteria in Africa were related to three Chinese variations and one Indian variation,

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<sup>113</sup> *Id.* at 122.

<sup>114</sup> de Magny et al., *supra* note 78, at 17679.

<sup>115</sup> Weill et al., *supra* note 62, at 785-89.

<sup>116</sup> *Id.* at 786.

while the Inaba serotype appears to be a mutation of the Ogawa.<sup>117</sup> Overall, the genomic analysis indicated that seventh-pandemic cholera that arrived in Africa in 1970 came from South or East Asia by way of Russia and the Middle East, arriving first in Angola and then spreading to Mozambique and to Portugal and Europe as a result of Portuguese decolonialization wars and the deployment and rotation of Portuguese troops.<sup>118</sup> Moreover, the ten additional cholera introduction events between 1970 and 2008 all appear to have originated in South or East Asia, with seven events involving migration through the Middle East first and three arriving in Africa directly from Asia.<sup>119</sup> From these introductions into West Africa and Eastern/Southern Africa, “[e]pidemic waves then propagated regionally, in some instances spreading to Central Africa, over periods of a few years to 28 years . . . .”<sup>120</sup> The genomic study could also track the cholera bacterium’s acquisition of antibiotic resistance.<sup>121</sup>

Noting that their results are consistent with epidemiological studies of cholera in African countries, the researchers in the Africa study concluded that “the human-related factors play a much more important role in cholera dynamics in Africa than climatic and environmental factors.”<sup>122</sup> Specifically, “[o]ur data do not suggest that aquatic environmental reservoirs are the primary source of epidemic cholera in Africa”; instead, “these results highlight the role that humans play in the long-term spread and maintenance of the pathogen, whether by direct (human-to-human) or indirect (pollution of the environment with feces from cholera patients) transmission.”<sup>123</sup>

The Latin America study focused on the relationship “between local populations and globally circulating pandemic lineages of *V. cholerae*” in the Americas, noting that “pandemic cholera was absent from

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<sup>117</sup> *Id.*

<sup>118</sup> *Id.*

<sup>119</sup> *Id.* at 787.

<sup>120</sup> *Id.*

<sup>121</sup> *Id.* at 787-88.

<sup>122</sup> *Id.* at 788-89.

<sup>123</sup> *Id.* at 789.

Latin America for 100 years."<sup>124</sup> It analyzed 252 cholera isolates from 14 countries spanning 1974 to 2014, about two-thirds of which were seventh-pandemic El Tor varieties of cholera and about one-third of which were other varieties.<sup>125</sup> The strains covered pre-epidemic, epidemic, and interepidemic periods, including the 1991 Peruvian epidemic and 2010 Haitian epidemic.<sup>126</sup> They also included both O1 and non-O1 *V. cholerae*, as well as samples from both clinical and environmental sources.<sup>127</sup>

The genomic analysis "revealed a marked diversity of *V. cholerae* lineages in this region."<sup>128</sup> The cholera samples from the 1991 Peruvian and 2010 Haitian epidemics clustered in the seventh-pandemic El Tor lineages.<sup>129</sup> Nevertheless, 11 cholera lineages were represented in the Latin American isolates, from classical *V. cholerae* found in Mexico in the mid-1990s to *V. cholerae* O1 local lineages to an endemic Latin American lineage.<sup>130</sup> "More than 30 additional isolates sampled across Latin America do not belong to any previously known lineage and comprise at least eight different serotypes . . ."<sup>131</sup>

Thus, a wide range of genetic variations exist in the cholera bacteria found in Latin America. Moreover, "[l]ocal *V. cholerae* O1 lineages in Latin America harbor a wide range of genetic determinants that are associated with pandemic disease,"<sup>132</sup> and the discovery of classical lineages from Mexico dating from 1995 to 1997 demonstrated that this version of the infectious bacterium had not disappeared in the 1980s, as previously believed.<sup>133</sup>

Focusing on the seventh-pandemic El Tor lineage, however, the genomic research showed "that the Latin American cholera epidemics

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<sup>124</sup> Daryl Domman et al., *Integrated view of Vibrio cholerae in the Americas*, 358 *Sci.* 789, 789 (2017).

<sup>125</sup> *Id.*

<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

<sup>128</sup> *Id.*

<sup>129</sup> *Id.*

<sup>130</sup> *Id.*

<sup>131</sup> *Id.*

<sup>132</sup> *Id.*

<sup>133</sup> *Id.* at 790.

were the result of multiple intercontinental introductions . . . .<sup>134</sup> The strains of cholera in Latin America from the first introduction of cholera during the seventh pandemic were most directly related to strains from Western and Central Africa<sup>135</sup>; the strains from the second introduction were related to strains “in South and Southeast Asia, Western Asia (Lebanon) and Eastern Europe (Romania);<sup>136</sup> and the strains from the third introduction were related to the Haitian sublineage.<sup>137</sup>

However, cholera in this part of the world is more complicated than just pandemics, and the researchers outlined “three distinct patterns of diarrheal disease within Latin America.”<sup>138</sup> First, some cholera lineages cause “sporadic cases or limited outbreaks, in which secondary infections are rare or nonexistent.”<sup>139</sup> While these cases *are* cholera, they are far more limited in number than those generated by pandemic strains.<sup>140</sup> “Second, lineages that occupy long-term environmental reservoirs (such as the Gulf Coast lineage) cause illness over longer periods of time and across larger geographic areas”; again, however, they are responsible for far fewer cases of cholera overall.<sup>141</sup> Finally, the “[t]hird pattern, caused by pandemic *V. cholerae*, is visibly distinct. Pandemic lineages are responsible for massive, explosive epidemics that occur over short periods of time,” causing 20,000 cases per week in Peru in 1991 to 250,000 cases over six months in Haiti in 2010.<sup>142</sup>

Importantly, the third pattern cases—the ones that significantly burden the public health system—all arose (directly or indirectly) from strains of cholera bacteria that arrived from Asia.<sup>143</sup> Thus, like the

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<sup>134</sup> *Id.*

<sup>135</sup> *Id.*

<sup>136</sup> *Id.* at 791.

<sup>137</sup> *Id.*

<sup>138</sup> *Id.* at 792-93.

<sup>139</sup> *Id.* at 789-93.

<sup>140</sup> *Id.* at 793.

<sup>141</sup> *Id.*

<sup>142</sup> *Id.*

<sup>143</sup> Kai Kupferschmidt, *Asia is the Cradle of Almost Every Cholera Epidemic, Genome Studies Show*, SCIENCE:NEWS (Nov. 9, 2017), <http://www.sciencemag.org/news/2017/11/asia-cradle-almost-every-cholera-epidemic-genome-studies-show> (“The Americas have seen two major cholera outbreaks in the past half-century: one that began in Peru and raced through almost all of

Africa study, the Latin America study downplayed the importance of local cholera reservoirs to the global cholera disease burden.

#### IV. STRATEGIES FOR CHOLERA PREVENTION IN LIGHT OF SCIENTIFIC UNCERTAINTY AND CLIMATE CHANGE

The debate over the etiology of cholera epidemics and pandemics provides a concrete example of a recurring issue in developing public health climate change adaptation strategies: the problem of scientific uncertainty. This Part looks first at the specific stakes for public health strategies of the cholera etiology debate, then reviews general approaches to climate change adaptation planning in the face of uncertainty. It then uses those approaches to assess four cholera-specific strategies: develop an early warning system; improve drinking water access and treatment and basic sanitation; invest in a cholera vaccine; and seek to control emerging cholera epidemics at their source.

##### A. The Stakes of the Debate: Why Does Cholera's Etiology Matter to a Public Health Climate Change Adaptation Strategy?

Notably, neither of the two 2017 genomic studies of cholera study posits that Asia-derived cholera strains are the *sole* source of cholera infection. The authors of the Africa study specifically noted that their research does not exclude the possibility that other cholera strains cause sporadic disease on that continent.<sup>144</sup> More decisively, the Latin America study explicitly found that there are different types and sources of cholera in Latin America, concluding that “[a]n appreciation of the differences between pandemic and local lineages should inform the design of disease control strategies in Latin America.”<sup>145</sup> Nor does

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Latin America between 1991 and 1993, and another in Haiti that started in 2010 and is ongoing. The analysis confirms previous strong evidence that the Haiti outbreak was inadvertently introduced by United Nations peacekeepers from Nepal, and it shows that the '90s outbreak was also caused by Asian strains, both introduced in 1991. One arrived in Peru by way of Africa, and the other landed in Mexico, having traveled from southern Asia, possibly via Eastern Europe.”).

<sup>144</sup> Weill et al., *supra* note 62, at 785.

<sup>145</sup> Domman et al., *supra* note 124, at 793.

either study refute (and, by affirming a southern Asian origin for many cholera pandemics, might in some ways affirm) the climate-related etiology of cholera epidemics in Bay of Bengal countries like India and Bangladesh.

Nevertheless, as the Latin America study emphasized, epidemic and pandemic strains of cholera impose a much greater global disease burden than the other types. As a result, an Asian origin hypothesis for these forms of cholera outbreaks has direct implications for where public health officials should focus their limited resources. Indeed, the Latin America study researchers discussed the stakes at issue:

[E]xploratory analyses have demonstrated since the 1970s that *V. cholerae* is an integral member of many coastal, estuarine, and brackish water ecosystems, as are other *Vibrio* species, in which it is often associated with copepods and zooplankton. Accordingly, a view of *V. cholerae* epidemiology emerged in the following decades, which posits that locally evolving, but globally distributed, *V. cholerae* populations are responsible for cholera outbreaks, which occur when climatic or environmental stimuli provide favorable bacterial growth conditions in these environs. This perception has had profound effects on all levels of global public health; cholera is now considered to be ineradicable because its etiological agent is ubiquitous in aquatic ecosystems.<sup>146</sup>

The Asian origin hypothesis leads to different cholera public health strategies than the local reservoir hypothesis, particularly in terms of how to assemble early warning systems for developing cholera epidemics and pandemics and of what the eventual global health goal for cholera should be. With respect to early warning systems, such systems based on the local reservoir hypothesis focus on detecting relevant changes in environmental variables, such as sea surface temperature, sea surface height, and chlorophyll or phytoplankton concentrations. In contrast, under the Asian origin hypothesis, early warning systems take the form of genetic detection.<sup>147</sup> As for the ultimate public health goals for cholera, the local reservoir hypothesis means that cholera can never be completely eliminated—only controlled and treated.<sup>148</sup> In contrast, an Asian origin means that cholera—at least in

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<sup>146</sup> *Id.* at 789.

<sup>147</sup> Kupferschmidt, *supra* note 143 (based on an interview with Nicholas Thomson, a researcher at the Wellcome Trust Sanger Institute in Hinxton, U.K.).

<sup>148</sup> Domman et al., *supra* note 124, at 789.

its epidemic and pandemic forms—could be eradicated.<sup>149</sup> Thus, the Asian origin hypothesis could lead the global public health community to invest considerably more into Asia-centric cholera research, perhaps at the expense of learning more about complex cholera etiologies such as exist in Latin America.

## B. General Strategies for Planning Under Uncertainty

So, where should public health officials concerned about cholera and its possible future under climate change invest their time, adaptation efforts, and limited funding? The costs of public health climate change adaptation strategies “may be considerable.”<sup>150</sup> As a result, few individual nations nor the international community at large are likely to be able to afford all-out, multi-stranded disease adaptation efforts. Under these circumstances, the stakes at issue in adaptation choices, as well as potential multiple benefits from certain choices, should become important factors in how the public health sector chooses to adapt to climate change.

At the outset, public health-focused climate change adaptation strategies should reflect well-established public health principles and a proactive approach.<sup>151</sup> One such principle is *prevention*, which can occur at three levels:

Primary prevention aims to prevent the onset of injury or illness; clinical examples include immunization, smoking cessation efforts, and the use of bicycle helmets. Secondary prevention aims to diagnose disease early to control its advance and reduce the resulting health burden; clinical examples include screening for hypertension, hyperlipidemia, and breast cancer. Tertiary prevention occurs once disease is diagnosed; it aims to reduce morbidity, avoid complications, and restore function.<sup>152</sup>

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<sup>149</sup> Kupferschmidt, *supra* note 143.

<sup>150</sup> 2014 IPCC ADAPTATION REPORT, *supra* note 1, at 717.

<sup>151</sup> Howard Frumkin et al., *Climate Change: The Public Health Response*, 98:3 AM. J. PUB. HEALTH 435, 435 (2008).

<sup>152</sup> *Id.*

A second principle, and one directly related to uncertainty, is *preparedness*.<sup>153</sup> New threats such as terrorist attacks and the reemergence of infectious diseases has made the study and anticipation of health impacts a revitalized central tenet of public health practice, and climate change fits easily within this practice.<sup>154</sup> Third, “[*risk management*—systematic ongoing efforts to identify and reduce risks to health—is another relevant framework.”<sup>155</sup> *Co-benefits* offer a fourth “important framework for public health action on climate change. Steps that address climate change frequently yield other health benefits, both direct and indirect.”<sup>156</sup> A fifth consideration is *economics*: “Economic considerations are critical in public health planning. The mandate to maximize health protection at the lowest short-term and long-term cost is highly relevant to climate change.”<sup>157</sup> “Finally, *ethical considerations* guide public health attention to climate change.”<sup>158</sup>

A number of general guidelines and procedures have already been proposed to alleviate the risk planning stagnation in the face of scientific uncertainty, particularly with respect to climate change. For example, scenario planning provides one method of extrapolating a variety of future conditions based on varied assumptions about climatic impacts and social and economic factors.<sup>159</sup> “The central idea of scenario planning is to consider a variety of possible futures that include many of the important uncertainties in the system rather than to focus on the accurate prediction of a single outcome.”<sup>160</sup>

Scenarios may encompass realistic projections of current trends, qualitative predictions, and quantitative models, but much of their value lies in incorporating both qualitative and quantitative understandings of the system and in stimulating people to evaluate and reassess their beliefs about the system. Useful scenarios incorporate imaginative speculation

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<sup>153</sup> *Id.* at 437.

<sup>154</sup> *Id.*

<sup>155</sup> *Id.* (emphasis added).

<sup>156</sup> *Id.*

<sup>157</sup> *Id.*

<sup>158</sup> *Id.*

<sup>159</sup> Garry D. Peterson et al., *Scenario Planning: A Tool for Conservation in an Uncertain World*, 17:2 CONSERVATION BIOLOGY 358, 358-66 (2003).

<sup>160</sup> *Id.* at 359.

and a wide range of possibilities; those based only on what we currently know about the system have limited power because they do not help scenario users plan for the unpredictable.<sup>161</sup>

“Scenario planning aims to enhance our ability to respond quickly and effectively to a wide range of futures, avoiding potential traps and benefiting from potential opportunities.”<sup>162</sup> The scenarios themselves are a form of storytelling about the future: “Scenarios should become brief narratives that link historical and present events with hypothetical future events. Within these storylines the internal assumptions of the scenario and the differences between stories must be clearly visible. To be plausible, each scenario should be clearly anchored in the past, with the future emerging from the past and present in a seamless way.”<sup>163</sup> The goal of scenario planning is to enhance institutional and individual capacity to productively respond to future change:

A successful scenario-planning effort should enhance the ability of people to cope with and take advantage of future change. Decisions can be made, policies changed, and management plans implemented to steer the system toward a more desirable future. New research or monitoring activities may be initiated to increase understanding of key uncertainties, and they may stimulate the formation of new coalitions of stakeholder groups.<sup>164</sup>

A related approach more specific to public health is vulnerability mapping.<sup>165</sup> Vulnerability mapping can reveal potentially increasing vulnerabilities for a number of climate change-related health impacts, including disease.<sup>166</sup> For example, the IPCC has applauded a number of vulnerability mapping efforts in response to climate change:

spatial modeling of geo-referenced climate and environmental information was used to identify characteristics of domestic malaria transmission in 2009–2012 in Greece, to guide malaria control efforts.

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<sup>161</sup> *Id.* at 360 (citation omitted).

<sup>162</sup> *Id.*

<sup>163</sup> *Id.* at 361.

<sup>164</sup> *Id.* at 362.

<sup>165</sup> 2014 IPCC ADAPTATION REPORT, *supra* note 1, at 733 (“Vulnerability mapping is being increasingly used to better understand current and possible future risks related to climate change.”).

<sup>166</sup> *Id.* at 733-34.

Mapping at regional and larger scales may be useful to guide adaptation actions. In Portugal, modeling of Lyme disease indicates that future conditions will be less favorable for disease transmission in the south, but more favorable in the center and northern parts of the country. This information can be used to modify surveillance programs before disease outbreaks occur.<sup>167</sup>

Moreover, as the IPCC noted, vulnerability mapping can inform surveillance and early warning systems, another adaptation strategy that can mitigate uncertainty.<sup>168</sup>

Once future possibilities are understood, a search for “no regrets” measures can become an effective means of starting a climate change adaptation strategy. “No regrets” measures are adaptation strategies that are a good idea under all or at least most future scenarios and generally offer current benefits, as well.<sup>169</sup> “No regrets” strategies are often options that communities or nations should be pursuing anyway but that have been stymied for any of several reasons— “[m]any obstacles explain the current situation, including (i) financial and technology constraints, especially in poor countries; (ii) lack of information and transaction costs at the micro-level; and (iii) institutional and legal constraints.”<sup>170</sup> Climate change adaptation can thus provide the impetus for overcoming these obstacles. For example, as Hurricane Harvey amply demonstrated in late August and early September 2017, toxic sites in the U.S. coastal zone pose both a current health and safety risk and a future vulnerability in light of sea-level rise and the expected increasing numbers of increasingly violent coastal storms.<sup>171</sup> As such, coastal cleanup efforts pursuant to the federal Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund)<sup>172</sup> and parallel state laws qualify as “no regrets” climate change adaptation strategies in the United States.

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<sup>167</sup> *Id.* at 734.

<sup>168</sup> *Id.*

<sup>169</sup> Stéphane Hallegatte, *Strategies to adapt to an uncertain climate change*, 19 GLOBAL ENVTL. CHANGE 240, 244 (2009).

<sup>170</sup> *Id.*

<sup>171</sup> E.g., Michael Biesecker, *EPA orders cleanup at Texas toxic site flooded by Hurricane Harvey*, THE DENVER POST (Oct. 12, 2017), <https://www.denverpost.com/2017/10/12/epa-orders-cleanup-texas-toxic-site-hurricane-harvey/>.

<sup>172</sup> 42 U.S.C. §§ 9601-9628 (2012).

“Second, it is wise to favour strategies that are reversible and flexible over irreversible choices. The aim is to keep as low as possible the cost of being wrong about future climate change.”<sup>173</sup> For example, restrictive land use planning can be a helpful but also changeable legal adaptation strategy, allowing development patterns to reflect evolving understanding of climate change impacts in a community.<sup>174</sup>

“Third, there are ‘safety margin’ strategies that reduce vulnerability at null or low costs.”<sup>175</sup> Such strategies are often most relevant when communities or nations are investing in new infrastructure related to climate change impacts (for example, infrastructure to handle runoff or flooding), when building in additional capacity to handle the worst of expected impacts generally incurs relatively small marginal costs.<sup>176</sup>

Institutional strategies are a fourth form of adaptation strategies.<sup>177</sup> These strategies, often referred to as “soft” and “timing” strategies, are usually flexible and reversible, and they often take the form of ensuring that climate change risk assessment and planning occur more often and at different levels of governance (international, national, local).<sup>178</sup> However, institutional strategies can also be financial, such as through insurance laws or funding schemes to promote certain behaviors or investments.<sup>179</sup>

Finally, adaptation planning in the face of uncertainty requires that planners be cognizant of potential conflicts and synergies among adaptation strategies.<sup>180</sup> “For instance, an increased use of snow-making to compensate for shorter skiing seasons in mountain areas would have negative consequences for water availability and, e.g., agriculture. This example shows that adaptation strategies that look

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<sup>173</sup> Hallegatte, *supra* note 169, at 244.

<sup>174</sup> See *id.* at 243 tbl. 2 (listing this option as a reversible/flexible option for both coastal zones and human settlements).

<sup>175</sup> *Id.* at 244.

<sup>176</sup> *Id.* at 244-45.

<sup>177</sup> *Id.* at 245.

<sup>178</sup> *Id.*

<sup>179</sup> *Id.*

<sup>180</sup> *Id.* at 245-46.

profitable when considering only one sector may be sub-optimal at the macroeconomic scale because of negative externalities.”<sup>181</sup>

### C. The “Preparedness” Option: Early Warning Systems for Cholera Epidemics

From a public health perspective, cholera surveillance and early warning systems clearly serve a public health preparedness function. Most obviously, a few extra months of warning that a cholera epidemic is likely would allow public health officials time to stockpile components for effective treatment—antibiotics, I.V. fluids, disinfectants, and so forth.<sup>182</sup> Moreover, in light of improved vaccines,<sup>183</sup> early warning systems could also allow many cases of cholera to be prevented.

Notably, researchers working under both of the cholera etiology hypotheses are looking to develop an early warning system for cholera. However, the proposed systems are completely different. As several researchers working under the local reservoir hypothesis emphasize, the importance of an environmental theory of cholera etiology is that it allows scientists to develop predictive models, based on indicator environmental conditions, that in turn can provide warnings to public health officials regarding potential cholera outbreaks and epidemics.<sup>184</sup> Climatic events to be monitored for include El Nino events,<sup>185</sup> changes in the IOD,<sup>186</sup> and more general environmental changes and climate change impacts.<sup>187</sup>

In contrast, the early warning system under the Asian origin hypothesis consists of increased genetic testing. Specifically, “When a new cholera case appears, researchers can now sequence the bacterium to determine whether it belongs to the pandemic lineage from Asia.

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<sup>181</sup> *Id.* at 246.

<sup>182</sup> See Donald G. McNeil, Jr., *Turning the Tide Against Cholera*, N.Y. TIMES (Feb. 6., 2017), <https://www.nytimes.com/2017/02/06/health/cholera-vaccine-bangladesh.html> (describing the newer highly effective treatment protocols for cholera).

<sup>183</sup> See discussion *infra* Part IV.E.

<sup>184</sup> Colwell & Huq, *supra* note 69, at 135S.

<sup>185</sup> *Id.* at 137S.

<sup>186</sup> Hashizume et al., *supra* note 98, at 242.

<sup>187</sup> de Magny et al., *supra* note 78, at 17679; de Magny & Colwell, *supra* note 106, at 119.

That could help pinpoint truly dangerous outbreaks that most warrant use of the limited vaccine stocks . . . .”<sup>188</sup>

These two strategies appear to require contradictory investments into both research and public health capacity. What remains to be satisfactorily articulated, however, is whether scientists and public health officials should pursue both approaches—i.e., whether the two types of early warning are in fact complementary and synergistic rather than contradictory, especially with respect to the Bay of Bengal and the countries that surround it. Until that issue can be resolved, it is probably worth pursuing both strategies, particularly in South Asia. Genetic composition is clearly relevant to cholera’s infectious characteristics and lethality; nevertheless, again, nothing in the two new genomic studies directly undermines the importance of the environmental factors to the emergence of cholera epidemics in South Asia—epidemics, if the genomic studies are correct, that can then spread to the rest of the world.

#### **D. The “No Regrets” Option: Improve Drinking Water Access and Treatment and Sanitation**

According to the IPCC’s 2014 report, climate change adaptation strategies for public health impact need to consider a variety of factors:

The degree to which programs and measures will need modification to address additional pressures from climate change will depend on the current burden of ill health; the effectiveness of current interventions; projections of where, when, and how the health burden could change with climate change; the feasibility of implementing additional programs; other stressors that could increase or decrease resilience; and the social, economic, and political context for intervention.<sup>189</sup>

Despite this complexity, however, “[t]he most effective measures to reduce vulnerability in the near term are programs that implement and improve basic public health measures such as *provision of clean water and sanitation*, secure essential health care including vaccination and child health services, increase capacity for disaster preparedness and

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<sup>188</sup> Kupferschmidt, *supra* note 143 (based on an interview with Nicholas Thomson, a researcher at the Wellcome Trust Sanger Institute in Hinxton, U.K.).

<sup>189</sup> 2014 IPCC ADAPTATION REPORT, *supra* note 1, at 733.

response, and alleviate poverty (very high confidence)."<sup>190</sup> Indeed, one of the IPCC's five "take-home messages" about climate change adaptation and public health in 2014 was that:

In the immediate future, accelerating public health and medical interventions to reduce the present burden of disease, particularly diseases in poor countries related to climatic conditions, is the single most important step that can be taken to reduce the health impacts of climate change. Priority interventions include improved management of the environmental determinants of health (*such as provision of water and sanitation*), infectious disease surveillance, and strengthening the resilience of health systems to extreme weather events.<sup>191</sup>

As cholera researchers have observed, "Because infection results from ingesting contaminated water, cholera epidemics typically occur in regions with a limited or damaged infrastructure."<sup>192</sup> Many of the studies discussed above noted that cholera no longer occurs with any frequency in the United States and other developed countries because these countries have safe drinking water and their citizens practice good sanitation and hygiene—*not* because natural reservoirs of the *V. cholerae* bacterium are lacking.<sup>193</sup> As WHO has emphasized repeatedly, improved sanitation and drinking water supplies are and should be the primary goal to address cholera.<sup>194</sup>

Investments in basic sanitation—clean drinking water and human waste facilities—are "no regrets" public health climate change adaptation strategies because such infrastructure provides multiple benefits. The statistics for clean drinking water are somewhat encouraging: "89% of the world population used an improved drinking-water source by end of 2011," meaning a source protected from contamination, especially contamination from feces.<sup>195</sup> Nevertheless, "An

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<sup>190</sup> *Id.* at 714 (emphasis added).

<sup>191</sup> *Id.* at 742 FAQ 11.4 (emphasis added).

<sup>192</sup> Cash et al., *supra* note 92, at 2817.

<sup>193</sup> de Magny et al., *supra* note 78, at 17679.

<sup>194</sup> *Water sanitation hygiene: Cholera prevention and control*, WORLD HEALTH ORG., [http://www.who.int/water\\_sanitation\\_health/emergencies/cholera-prevention/en/](http://www.who.int/water_sanitation_health/emergencies/cholera-prevention/en/) (last visited Feb. 2, 2018).

<sup>195</sup> *Progress on sanitation and drinking-water: Fast facts*, WORLD HEALTH ORG (last updated 2013), [http://www.who.int/water\\_sanitation\\_health/monitoring/coverage/jmp\\_fast\\_facts/en/](http://www.who.int/water_sanitation_health/monitoring/coverage/jmp_fast_facts/en/).

estimated 768 million people did not use an improved source for drinking-water in 2011 and 185 million relied on surface water to meet their daily drinking-water needs."<sup>196</sup> Sanitation statistics are even more troubling. According to WHO, in 2015:

2.3 billion people still do not have basic sanitation facilities such as toilets or latrines.

- Of these, 892 million still defecate in the open, for example in street gutters, behind bushes or into open bodies of water.
- At least 10% of the world's population is thought to consume food irrigated by wastewater.
- Poor sanitation is linked to transmission of diseases such as cholera, diarrhoea, dysentery, hepatitis A, typhoid and polio.
- Inadequate sanitation is estimated to cause 280 000 diarrhoeal deaths annually and is a major factor in several neglected tropical diseases, including intestinal worms, schistosomiasis, and trachoma. Poor sanitation also contributes to malnutrition.<sup>197</sup>

In addition, the number of people lacking basic sanitation is projected to increase throughout the 21st century in concert with generally increasing populations, and various organizations project "that about 1.4 billion people will be without access to basic sanitation in 2050."<sup>198</sup>

A large factor in nations' failure to invest in the "no regrets" options of clean drinking water supply and waste sanitation is cost. In 2008, WHO calculated the cost of achieving the Millennium Development Goal for drinking water and sanitation—i.e., "to 'halve, by 2015, the proportion of people without sustainable access to safe drinking water and basic sanitation'."<sup>199</sup> It estimated the total cost of new services over the implementation period of 2005-2014 to be \$42 billion

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<sup>196</sup> *Id.*

<sup>197</sup> *Fact Sheet: Sanitation*, WORLD HEALTH ORG., (last updated July 2017), <http://www.who.int/mediacentre/factsheets/fs392/en/>.

<sup>198</sup> 2014 IPCC ADAPTATION REPORT, *supra* note 1, at 720.

<sup>199</sup> GUY HUTTON & JAMIE BARTRAM, REGIONAL AND GLOBAL COSTS OF ATTAINING THE WATER SUPPLY AND SANITATION TARGET (2008), [http://www.who.int/water\\_sanitation\\_health/economic/mdg\\_global\\_costing.pdf](http://www.who.int/water_sanitation_health/economic/mdg_global_costing.pdf).

USD for drinking water and \$142 billion USD for sanitation, while the cost of maintaining existing infrastructure would be an additional \$322 billion USD for water supply and \$216 billion USD for sanitation.<sup>200</sup> Combined, the total investment required amounted to about \$72 USD billion per year over the 10-year implementation period,<sup>201</sup> and, even then, not all people would have safe drinking water and good sanitation at the end of it.

Moreover, countries should also be ensuring that any new investment in drinking water and sanitation infrastructure includes a “safety margin” strategy that accounts for potentially worsening climate change impacts on water supplies and contaminating runoff. In places where drinking water supplies are becoming increasingly vulnerable or where extensive retrofitting may be required, however, this “safety margin” strategy could significantly increase the costs of implementing this first, best strategy for preventing water- and hygiene-related disease.

#### **E. The Prevention and Flexibility Option: The Cholera Vaccine**

Improved sanitation, clean drinking water, and internalized hygiene practices are, everyone agrees, the long-term best investment for preventing cholera—and would improve human health more generally in a wide variety of ways. However, as noted, drinking water and sewage treatment infrastructure are expensive, requiring substantial governmental, international organization, or private company investment to build. In addition, such infrastructure investment also often comes off as, well, prosaic. Boring. Far more exciting and newsworthy—and funding-attracting—are new and effective treatments for an individual disease. Thus, for example, in February 2017, *The New York Times* waxed poetic about a new I.V. treatment protocol for cholera “so effective that it saves 99.9 percent of all victims” of the disease and the new “effective cholera vaccine,” enough of which may soon be stock-piled “to begin routine vaccination in countries where the disease has a permanent foothold.”<sup>202</sup> “The world finally has a vaccine that, with

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<sup>200</sup> *Id.*

<sup>201</sup> *Id.* at 16.

<sup>202</sup> McNeil, Jr., *supra* note 182.

routine administration, could end one of history's greatest scourges," it concluded, although acknowledging that, "[w]ith 1.4 billion people at risk, the potential cost of vaccination in cholera-endemic countries is enormous."<sup>203</sup>

WHO has acknowledged the potential role of oral cholera vaccines in cholera prevention.<sup>204</sup> As such, cholera vaccines are among the options available to nations pursuing cholera-specific public health climate change adaptation strategies. What exactly that role should be, however, is an important public health and climate change adaptation planning question, the exact answer to which is likely to vary according to the specific risks faced by and financial circumstances of individual nations and regions.

In 2010, five different cholera vaccines existed: (1) Dukarol, an oral vaccine; (2) Shanchol, an oral vaccine; (3) mORCVAX, an oral vaccine; (4) CVD 103- HgR, an oral, live, attenuated single-dose vaccine that was not being produced at the time; and (5) an injectable vaccine prepared from strains of *V. cholerae* made inactive with phenol.<sup>205</sup> In its 2010 position paper on these vaccines, WHO recommended against use of the injectable vaccine, "mainly because of its limited efficacy and short duration of protection."<sup>206</sup>

With regard to the three oral cholera vaccines that remained in production in 2010, Swedish researchers developed Dukoral and first licensed it in 1991, with over 60 countries eventually approving the vaccine for use.<sup>207</sup> Dukoral is used "primarily as a vaccine for travelers to cholera-endemic areas. However, it has also been used in crisis situations in Indonesia, Sudan and Uganda, and in a demonstration project in an endemic area of Mozambique."<sup>208</sup> The vaccine is relatively safe to take and was "tested in randomized placebo-controlled double-blind precensure efficacy trials in both Bangladesh and Peru"<sup>209</sup> as

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<sup>203</sup> *Id.*

<sup>204</sup> *Cholera vaccines*, WORLD HEALTH ORG., <http://www.who.int/topics/cholera/vaccines/en/> (last visited Jan. 23, 2018).

<sup>205</sup> 2010 WHO Cholera Vaccines Paper, *supra* note 33, at 120.

<sup>206</sup> *Id.* at 121.

<sup>207</sup> *Id.*

<sup>208</sup> *Id.*

<sup>209</sup> *Id.* at 122.

well as in several other studies, including field trials.<sup>210</sup> Moreover, because the vaccine contains a recombinant cholera toxin B subunit, it also protects against ETEC infections.<sup>211</sup>

Shanchol and mORCVAX are so similar that WHO evaluates them together. “Unlike Dukoral, these vaccines do not contain the bacterial toxin B subunit and will therefore not protect against ETEC.”<sup>212</sup> Researchers licensed the original ORCVAX vaccine in Vietnam in 1997, and “[f]rom 1998 to 2009, >20 million doses of this vaccine were administered to children in high-risk areas of Viet Nam, making ORCVAX the first oral cholera vaccine to be used primarily for endemic populations.”<sup>213</sup> ORCVAX was reformulated in 2004 to meet WHO standards, and, “[f]ollowing successful phase II trials in India and Viet Nam, this vaccine was licensed in 2009 as mORCVAX in Viet Nam and as Shanchol in India; mORCVAX is currently intended for domestic use in Viet Nam, whereas Shanchol will be produced for Indian and international markets.”<sup>214</sup>

WHO concluded in 2010 that all three oral vaccines are safe and provide short-term (about two years) protection against cholera in endemic countries.<sup>215</sup> The vaccines can also result in herd immunity if administered extensively in a given population, which provides cholera protection to infants and children too young to receive the vaccine.<sup>216</sup> Finally, while data were limited, cholera vaccine programs appeared to be cost-effective.<sup>217</sup> WHO concluded in 2010 that “[c]holera control should be a priority in areas where the disease is endemic” and

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<sup>210</sup> *Id.* at 121-23.

<sup>211</sup> *Id.* at 123, 125.

<sup>212</sup> *Id.* at 124. ETEC is Enterotoxigenic *E. coli*, “an important cause of bacterial diarrheal illness. Infection with ETEC is the leading cause of travelers’ diarrhea and a major cause of diarrheal disease in lower-income countries, especially among children. ETEC is transmitted by food or water contaminated with animal or human feces.” *Enterotoxigenic E. coli (ETEC)*, CENTERS FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/ecoli/etec.html> (last updated Dec. 1, 2014) (last visited Jan. 23, 2018).

<sup>213</sup> 2010 WHO Cholera Vaccines Paper, *supra* note 33, at 124.

<sup>214</sup> *Id.*

<sup>215</sup> *Id.* at 125.

<sup>216</sup> *Id.* at 125-26.

<sup>217</sup> *Id.* at 126.

that the oral vaccines “should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered in areas at risk for outbreaks.”<sup>218</sup> However, WHO cautioned,

Vaccination should not disrupt the provision of other high-priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented to bring about an immediate response while the longer term interventions of improving water and sanitation, which involve large investments, are put into place.<sup>219</sup>

Moreover, “[i]n cholera-endemic countries, vaccinating the entire population is not warranted. Rather, vaccination should be targeted at high-risk areas and population groups.”<sup>220</sup> Finally, “[p]eriodic mass vaccination campaigns are probably the most practical option for delivering cholera vaccines.”<sup>221</sup>

WHO articulated a different role for cholera vaccines during epidemics. First, “[p]reemptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas.”<sup>222</sup> Second, during large and prolonged epidemics, “reactive vaccination could be considered by local health authorities as an additional control measure . . . .”<sup>223</sup> Both uses, however, required the further development of decisionmaking tools, including risk assessment, and neither use should displace a focus on treating individuals who develop the disease and on improving water and sanitation.<sup>224</sup>

Dukoral (2001) and Shanchol (2011) are WHO prequalified, but mORCVAX is not.<sup>225</sup> The WHO prequalification program seeks to

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<sup>218</sup> *Id.* at 127.

<sup>219</sup> *Id.*

<sup>220</sup> *Id.*

<sup>221</sup> *Id.*

<sup>222</sup> *Id.* at 128.

<sup>223</sup> *Id.*

<sup>224</sup> *Id.*

<sup>225</sup> *Oral Cholera Vaccine (OCV): What You Need to Know*, STOP CHOLERA (Oct. 2017),

ensure that medicines, including vaccines, purchased through or by international procurement agencies—for example, UNICEF or the Global Fund to Fight AIDS—for distribution in resource-limited countries meet acceptable standards of quality, safety, and efficacy.<sup>226</sup> As a result, prequalification status is often critical to a medicine's or vaccine's inclusion in global health programs. However, prequalification is not the only consideration. With respect to cholera vaccines, for example, Dukoral is more expensive and logistically challenging to use than Shanchol<sup>227</sup> because it “ha[s] to be drunk with a large glass of buffer solution to protect it from stomach acid.”<sup>228</sup> Given these impracticalities, Dukoral does not play a prominent role in WHO's recent cholera control programs.<sup>229</sup>

Two more cholera vaccines have been developed since WHO's 2010 report. In late 2015, WHO prequalified Euvichol, an inactivated oral cholera vaccine developed in the Republic of Korea.<sup>230</sup> In 2016, the U.S. Food & Drug Administration (FDA) approved a new version of the CVD 103-HgR attenuated virus oral vaccine known as Vaxchora.<sup>231</sup> Although the FDA granted Vaxchora fast track, priority review, and tropical disease priority review<sup>232</sup> under the Food, Drug, and Cosmetic Act,<sup>233</sup> this new vaccine is intended primarily for U.S. residents

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[https://www.stopcholera.org/sites/cholera/files/oral\\_cholera\\_vaccine\\_what\\_you\\_need\\_to\\_know.pdf](https://www.stopcholera.org/sites/cholera/files/oral_cholera_vaccine_what_you_need_to_know.pdf).

<sup>226</sup> *Prequalification of medicines by WHO*, WORLD HEALTH ORG. (Jan. 2013), <http://www.who.int/mediacentre/factsheets/fs278/en/>.

<sup>227</sup> STOP CHOLERA, *supra* note 225.

<sup>228</sup> McNeil, Jr., *supra* note 182.

<sup>229</sup> “Transporting tanks of buffer was impractical. Making matters worse, it was fizzy, and poor Bangladeshi children who had never tasted soft drinks would spit it out as soon as it tickled their noses.” *Id.* In contrast to Dukarol, the Vietnam vaccine cost only about 25 cents per dose, while the Shanchol vaccine derived from it costs less than US\$2.00 per dose and needs no buffer. *Id.*

<sup>230</sup> *Inactivated oral cholera single-dose vial*, WORLD HEALTH ORG. (Dec. 23, 2015), [http://www.who.int/immunization\\_standards/vaccine\\_quality/pq\\_298\\_euvichol\\_1dose\\_eubiotics/en/](http://www.who.int/immunization_standards/vaccine_quality/pq_298_euvichol_1dose_eubiotics/en/)

<sup>231</sup> *FDA approves vaccine to prevent cholera for travelers*, FDA.GOV, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm506305.htm> (last accessed Jun. 10, 2016).

<sup>232</sup> *Id.*

<sup>233</sup> 21 U.S.C. §§ 301-399f (2012).

traveling to other countries.<sup>234</sup> Vaxchora is not WHO prequalified, and its effectiveness in developing countries has not been established.<sup>235</sup>

In October 2017, WHO supported the launch of the Global Task Force on Cholera Control, a network of United Nations and international agencies, academic institutions, and non-governmental organizations committed to reducing world deaths from cholera by 90 percent by 2030.<sup>236</sup> Oral cholera vaccines are an important component of the Task Force's strategy, particularly in cholera "hot spots," which include many places in Africa.<sup>237</sup> In particular, the Task Force advocates the "[l]arge-scale use of [oral cholera vaccines] to immediately reduce disease burden while longer-term cholera control strategies are put in place."<sup>238</sup>

The Task Force's reliance on cholera vaccines builds from the July 2013 creation of an oral cholera vaccine stockpile and the availability of funding to subsidize the vaccine's cost.<sup>239</sup> Overseen by the International Coordinating Group, the goal of the stockpile was to make many more doses of cholera vaccines available to countries that needed them, particularly during cholera emergencies.<sup>240</sup> The stockpile has dramatically increased use of cholera vaccines (Shanchol and Euvichol), from 1.4 million doses over the 15 years from 1997 to 2012 to 13 million doses administered since 2013, mostly during cholera emergencies.<sup>241</sup> A record 25 million doses of the vaccines are expected to be available in 2018.<sup>242</sup> According to the Task Force, this increased availability of oral cholera vaccines has become "a game-changer in

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<sup>234</sup> FDA.Gov., *supra* note 241.

<sup>235</sup> STOP CHOLERA, *supra* note 225.

<sup>236</sup> See *Partners commit to reduce cholera deaths by 90% by 2030*, WORLD HEALTH ORG. (Oct. 3, 2017), <http://www.who.int/mediacentre/news/releases/2017/partners-reduce-cholera/en/>. See also *OVERVIEW OF ENDING CHOLERA: A GLOBAL ROADMAP TO 2030*, GLOBAL TASK FORCE ON CHOLERA CONTROL, <http://www.who.int/cholera/publications/global-roadmap-summary.pdf?ua=1> [hereinafter 2017 CHOLERA TASK FORCE ROAD MAP]

<sup>237</sup> See generally *id.*

<sup>238</sup> *Id.* at 4.

<sup>239</sup> *Id.* at 10.

<sup>240</sup> *International Coordinating Group (ICG) on vaccine provision for cholera*, WORLD HEALTH ORG., <http://www.who.int/csr/disease/icg/cholera/en/> (last visited Jan. 23, 2018).

<sup>241</sup> 2017 CHOLERA TASK FORCE ROAD MAP, *supra* note 238, at 10.

<sup>242</sup> *Id.*

the fight against cholera. It takes effect immediately and also works to prevent cholera locally for two to three years, effectively bridging emergency response and longer-term cholera control . . . .”<sup>243</sup> Moreover, the vaccine is important not only medically but also psychologically, “help[ing] to dispel the notion that cholera is inevitable, thereby breaking the vicious cycle of inaction and defeatism, motivating national governments and partners, and buying time to implement” longer-term cholera control measures such as water supply and sanitation infrastructure and hygiene practices.<sup>244</sup>

An issue remains, however: Are the cholera vaccines a permanent solution to cholera? In 1997, “Vietnam became the first—and so far only—country to provide cholera vaccine to its citizens routinely, not just in emergencies.”<sup>245</sup> Cholera incidence in Vietnam dropped sharply and disappeared from Hue in 2003.<sup>246</sup>

Nevertheless, almost all players on the international stage emphasize that cholera vaccines, at least in their current form, are an emergency, stop-gap, and/or transitional disease control strategy that targets cholera only—a short-term injection of prevention and flexibility into cholera control intended to be supplanted by the longer-term and more broadly beneficial “no regrets” measures of clean drinking water supplies and effective sanitation. Thus, the International Coordinating Group emphasizes that:

The main objective of the oral cholera vaccine stockpile is to ensure the timely and targeted deployment of vaccine as part of an effective outbreak response. While vaccines provide a short-term effect as an immediate intervention to a potential cholera outbreak, expanding access to improved drinking-water sources and sanitation is a longer term solution for most waterborne diseases, including cholera.<sup>247</sup>

Similarly, WHO maintains that “[i]n the long term, improvements in water supply, sanitation, food safety and community awareness of

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<sup>243</sup> *Id.*

<sup>244</sup> *Id.*

<sup>245</sup> McNeil, *supra* note 182.

<sup>246</sup> *Id.*

<sup>247</sup> 2010 WHO Cholera Vaccines Paper, *supra* note 33.

preventive measures are the best means of preventing cholera and other diarrhoeal diseases."<sup>248</sup>

#### **F. The Ultimate Prevention Strategy: Can We—and Should We—Try to Eliminate Epidemic and Pandemic Cholera at the Source?**

The two 2017 Asian-origin papers in *Science* prompted suggestions that the scientific and public health communities should engage in intensive efforts in South and East Asia to eliminate the epidemic and pandemic forms of cholera at their source. One news story, for instance, emphasized that “the [genomic] research . . . highlights the importance of eliminating natural reservoirs of pandemic *V. cholerae* in Asia . . . . Something in the region allows new strains to evolve and spread across the world, and scientists aren’t sure what it is.”<sup>249</sup>

As with the early warning systems, the proposed strategy of hunting down the source of epidemic and pandemic strains of cholera in Asia, particularly South Asia, underscores the need for scientists and public health researchers to further elucidate the exact relationship between the local reservoir hypothesis and the Asian origin hypothesis in Bay of Bengal countries. Could it be that something in the Bay of Bengal, combined with concentrated populations in India and Bangladesh, is a laboratory for cholera pandemics?

In the meantime, however, many countries need to weigh the costs of a potential cholera eradication program—a disease-specific strategy—against the potentially lost opportunity to invest in climate-resilient drinking water and sanitation infrastructure and the plethora of public health benefits that they bring. If this is the ultimate choice that many poor and developing nations face, then the remaining uncertainties surrounding cholera etiology and the many co-benefits of climate-resilience water and sanitation facilities should weigh strongly in favor of the infrastructure investments.

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<sup>248</sup> *Cholera vaccines*, *supra* note 204.

<sup>249</sup> Kupferschmidt, *supra* note 143.

## CONCLUSION

Climate change is already having, and will continue to have for the foreseeable future, impacts on human health. Given limited resources, both public health norms and strategies for dealing with uncertainty counsel in favor of investment in adaptation strategies that provide broad preparedness and prevention advantages, allow for additional improvements to human quality of life, fulfill human rights such as the right to life and right to water, and help to reduce existing inequalities among populations, including inequalities regarding who bears global health burdens.

For all of these reasons, the scientific debate over cholera epidemic etiology probably should not, at least for the moment, induce the global health community to re-think its basic approach to cholera disease control. Increased investment in climate-resilient drinking water supplies and sanitation facilities remains a “no regrets,” multiple-benefit public health climate change adaptation strategy and should remain a first priority for preventing water-related disease. Where cholera vaccines can bridge a public health transition to such infrastructure or prevent the worst scourges of an epidemic, they become a helpful supplemental strategy for achieving the primary goal.

The dream of eradicating cholera epidemics and pandemics creates a compelling vision of public health heroism, of science triumphing over another of humanity’s microscopic enemies. However, in terms of allocating resources, it should always be remembered that clean drinking water and good sanitation facilities are *also* very effective at preventing cholera infections during epidemics and pandemics—and that, in addition, they can prevent endemic cholera infection, a host of other water-borne diseases, and water-based exposure to toxins, which an Asian eradication strategy would not. At least in this instance, therefore, the prosaic public health adaptation strategy should win.