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Review

The Impact of Climate Change on Cholera: A Review on the Global Status and Future Challenges

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Abstract: Water ecosystems can be rather sensitive to evolving or sudden changes in weather parameters. These changes can result in alterations in the natural habitat of pathogens, vectors, and human hosts, as well as in the transmission dynamics and geographic distribution of infectious agents. However, the interaction between climate change and infectious disease is rather complicated and not deeply understood. In this narrative review, we discuss climate-driven changes in the epidemiology of *Vibrio* species-associated diseases with an emphasis on cholera. Changes in environmental parameters do shape the epidemiology of *Vibrio cholerae*. Outbreaks of cholera cause significant disease burden, especially in developing countries. Improved sanitation systems, access to clean water, educational strategies, and vaccination campaigns can help control vibriosis. In addition, real-time assessment of climatic parameters with remote-sensing technologies in combination with robust surveillance systems could help detect environmental changes in high-risk areas and result in early public health interventions that can mitigate potential outbreaks.

Keywords: climate change; cholera; vibrio; water-borne disease; water-borne pathogens; infection

1. Introduction

Climate change exposes individuals and organized human societies to risk affecting human health both directly and indirectly. Risks are disproportionately distributed and greater for marginalized and disadvantaged people and communities. The direct impact (for example, heat-related morbidity and mortality or injuries) arises from changing patterns of temperature and rainfall, and changes in the frequency and strength of climatic extremes (heatwaves, hurricanes, and floods) [1,2]. Indirect pathways include effects of climate change on water resources, on food production systems, on population displacement, and on prevalence and incidence of infectious pathogens [3]. Climate change can affect the epidemiological dynamics of multiple infectious agents, including vector-borne, water-borne, and food-borne pathogens. For instance, high temperatures can change the replication, virulence, and survival of microbes; and heavier and frequent precipitation may overwhelm sanitation systems or the viability and geographical distribution of mosquitoes. Even pathogens that pass directly from an infected person to a susceptible one can be influenced by climate change. For instance, human immunodeficiency virus (HIV) and sexually transmitted infections are likely to occur in settings of climate change-related conflicts or in the context of forced population movement, as people will increasingly compete for valuable but scarce natural resources.

Water-borne diseases are those associated with water, i.e., people become infected following contact with water or ingestion of water or consumption of contaminated seafood [4]. Common water-borne transmitted pathogens include *Campylobacter*, *Vibrios*, *Calicivirus*, *Giardia*, and *Cryptosporidium* [5]. Cholera and other diseases caused by *Vibrio* (*V.*) species (*Vibrio parahaemolyticus*, *Vibrio vulnificus*) comprise major water-borne ailments in some areas and a priority health issue given projected further warming and long-lasting impacts on all elements of the climate system, including

oceans and the water cycle [6]. Cholera is a gastrointestinal infectious disease caused by *V. cholerae*, a comma-shaped Gram-negative rod. *V. cholerae* is found in salty and fresh water, commonly in coastal areas or estuaries [6]. Under adverse environmental conditions and organic nutrient depletion, *V. cholerae* can form biofilms and survive in a dormant state [7]. *V. cholerae*, as other pathogenic *Vibrio* species, such as *V. parahaemolyticus*, *V. vulnificus*, and *V. alginolyticus*, have seasonal distribution, with a predominance of infections occurring in the warmer months in temperate zones [6].

This narrative review aimed to summarize the existing evidence and to enhance our understanding of climate-induced changes in the epidemiology of diseases caused by *Vibrio* species and especially from cholera. The review attempts to cover a range of topics including a short introduction to the influence of climate change on oceans, cryosphere, and aquatic systems; basic knowledge about cholera and other *Vibrio* species, their transmission, and previous large-scale epidemics; the association between climatic variability and occurrence of cholera and other diseases from *Vibrio* pathogens; tools and technologies currently available to predict changes in the burden and distribution of cholera and non-cholera vibrio-related disease; and options and potential interventions to manage and mitigate the consequences of vibrio-related diseases due to climate change.

2. Impacts of Climate Change on Aquatic Ecosystems Related to *Vibrio* Infections—An Overview of Evidence

Oceans have certainly become warmer, especially on the surface, with the upper 75 m warmed by 0.11 °C per decade between 1971 and 2010 [8]. Although ocean warming is slower, the pace of climate change and seasonal shift in the ocean is as high as on land [9]. Moreover, around one-third of the emitted anthropogenic CO_2 is stored in the oceans. Oceanic uptake of increased atmospheric CO_2 has resulted in decreased pH of ocean surface water by 0.1, which corresponds to a 26% increase in acidity [8,10]. Ocean acidification poses marine ecosystems, and especially coral reefs and polar ecosystems, significant risk [8]. Moreover, ocean acidification acts in synergy with other global impacts, such as warming and gradually reduced oxygen levels, and with local phenomena, such as pollution and eutrophication, resulting in shifts in species' geographic ranges, seasonal activities, migration patterns, abundances, and interactions with other species [10]. Redistribution or even extinction of marine species and reduced biodiversity can challenge the productivity of fisheries and other services but also propagate growth and transmission of some pathogens, and may result in serious outbreaks (e.g., zoo-plankton blooms and *Vibrio* infections) [2,11–17]. Finally, climate change affects the amount of salt in the oceanic surface. Since the 1950s, seawater of high surface salinity, where evaporation dominates, has become more saline, while areas of low saltiness, where precipitation is frequent, have become fresher [8]. The abundance of some pathogens, like that of cholera, depends on salinity [14–16,18–20].

Table 1 summarizes the environmental risk factors and their effect on *V. cholerae* expansion, spread, or disease potential. Ocean surface temperature, CO_2 and oxygen concentrations, and ocean acidification, pollution, and salinity affect bacterial replication, while ocean level, rainfall, or floods and droughts affect the spread of *V. cholerae*.

Table 1. Risk factors for cholera infection and effect of climate change on these risk factors resulting in altering *Vibrio cholerae* expansion, spread, or disease potential.

Risk Factor	Effect of Climate Change	*Vibrio cholerae* Disease Potential
Ocean surface temperature	Increase	Bacterial replication
CO_2 concentration	Increase	Bacterial replication
Oxygen levels	Decrease	Bacterial replication
Ocean acidification	Increase	Bacterial replication
Ocean pollution	Increase	Bacterial replication

Salinity	Increase or decrease depending on decreasing or increasing precipitation	Bacterial replication
Ocean level	Increase	Flooding events, disruption of water systems/ Increased spread
Rainfall/Flood	Increase	Disruption of water systems/ Increased spread
Drought	Increase	Increased spread

Due to climate change, the amount of sea ice has diminished considerably. Over the period 1992-2011, the Greenland and Antarctic ice sheets have been losing mass, while the yearly averaged Arctic sea-ice extent declined from 1979 to 2012, with a decennial rate between 3.5% to 4.1% [8]. Ice melting and ocean thermal expansion due to warming have largely contributed to sea-level rise [21]. The global averaged sea level rose by 0.19 m between 1901 and 2010, demonstrating a rapid increasing rate since the mid-19th century compared with the mean rate during the previous two millennia [8]. Climate change and especially the upward shift of the sea surface severely affect coastal locations over and above the impact of other important factors, including increased population density, runoff and pollution, and human activities, such as overfishing. According to recent analyses and despite some spatial and seasonal variation, approximately 71% of the coastlines analyzed also showed significant increases in sea surface temperature (SST) [15,22]. Along with oxygen concentration that has decreased in coastal waters [8], warming affects the biodiversity of coastal systems. Moreover, the elevation of sea level is likely to cause an intrusion of seawater into coastlands, coastal rivers, and freshwater, erosion, serious regular flooding events, and even covering of low-lying areas. Under these circumstances, the likelihood of transmission of water-borne (e.g., cholera) and rodent-borne (e.g., leptospirosis) pathogens increases substantially [2,21]. If stagnant water is also trapped following a flooding event, vulnerability to mosquito-borne diseases (e.g., malaria or dengue fever) becomes larger.

In the context of climate change, rainfall patterns are dynamic. Heavier and frequent precipitation in some areas can overwhelm wastewater treatment plants and septic systems, resulting in contamination of surface water and wells. On the other hand, lower rainfall in other regions may cause droughts and water scarcity, leading to increased microbial load in limited water supplies, use of contaminated rainwater, or competition for scarce water [23]. Altered rainfall patterns, higher temperatures, and intense and more frequent weather extremes, often resulting in natural disasters in countries with vulnerable infrastructure, are likely to compromise the supply of clean and safe water, sanitation, and the function of drainage systems with important consequences to the spread of water-borne diseases including cholera [4,11,13,15,24–29,30].

The schematic representation of the major drivers for cholera infection or cholera outbreaks is presented in Figure 1.

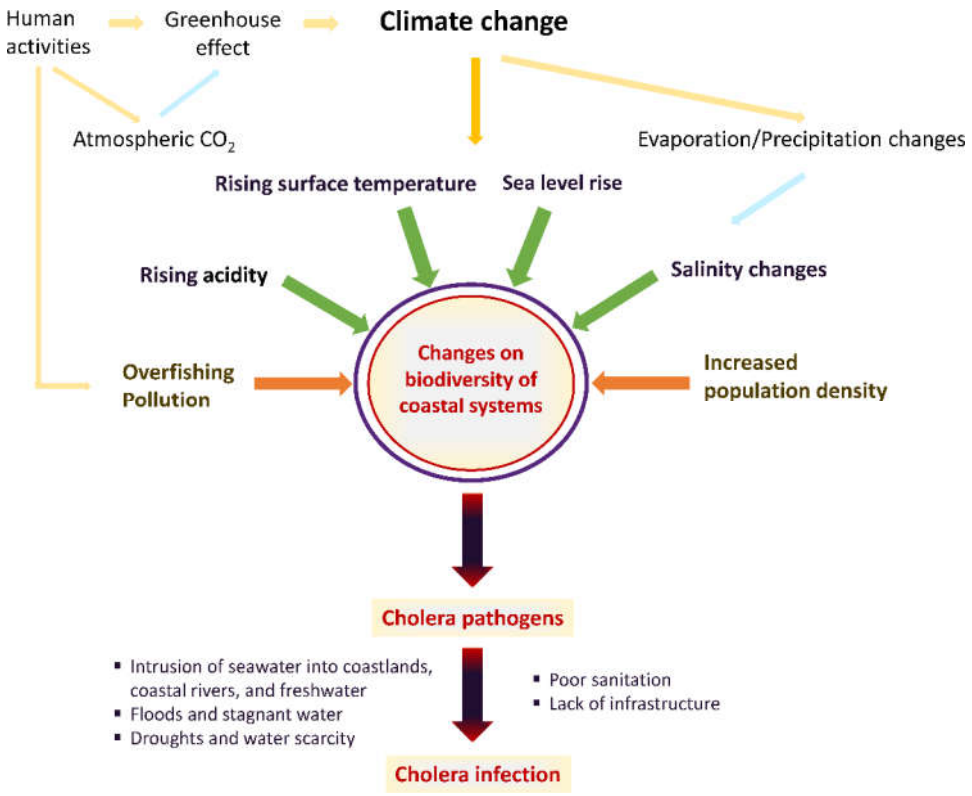

Figure 1. Climate change on oceans and *Vibrio cholerae*: Schematic representation of the major drivers for cholera infection or cholera outbreaks.

3. *Vibrio cholera*—An Overview of Epidemiology, Transmission, and Clinical Disease

It is estimated that about 2.86 million (1.3 m - 4.0 m) cholera cases occur annually in endemic countries with 95,000 (21,000 - 143,000) deaths per year [31]. Cholera is endemic in several developing countries in Asia, Africa, and Latin America. In countries with high population density, limited access to safe drinking water and suboptimal sanitation practices or disruption of public health systems, continue to cause significant morbidity and mortality. On the other hand, in developed countries, there is an increased frequency of *Vibrio* spp. infections, which may be associated with anthropogenic climate change.

Over 200 serotypes of *V. cholerae* have been identified; however, serotypes O1 and O139 are those predominantly causing disease and outbreaks in human populations [31]. Serotype O1 is further characterized based on phenotypic characteristics as classical or El Tor biotype. The El Tor O1 strains have spread around the globe and displaced the classical biotype strains during the last decades [32,33].

V. cholerae spp. are transmitted through the ingestion of contaminated water or food and by the fecal-oral route. The incubation period ranges from 1 to 5 days [34]. Non-cholera *Vibrio* spp., such as *V. parahaemolyticus*, *V. vulnificus*, and *V. alginolyticus*, are transmitted through contaminated seafood and direct exposure to water. They cause a considerable number of infections, especially in the United States (US), where sufficient data are collected due to the strong surveillance system for vibrioses [6]. Most *Vibrios* cause gastrointestinal disease, however, some (i.e., *V. vulnificus*) can cause severe wound infections. Clinically, cholera is characterized by profuse diarrhea resulting in severe dehydration and death without therapeutic intervention. Treatment is supportive, and the most important therapeutic measure is the administration of oral rehydration solution (ORS) or intravenous fluids [12]. Antimicrobials are also effective; however, antimicrobial resistance to sulfamethoxazole–trimethoprim, ciprofloxacin, aminoglycosides, chloramphenicol, and azithromycin has been described [33]. There are four available oral vaccines, two primarily for travelers (Dukoral, Vaxchora)

and two mainly used in mass campaigns for populations at risk (Shanchol, Euvichol) [35]; however global supply is limited. From a public health perspective, prompt detection of an outbreak followed by source identification and control are paramount measures in the management of cholera. Improving sanitation systems, securing access to clean water, and vaccination campaigns have been shown to decrease disease burden associated with cholera.

3.1. Climate-Driven Changes in The Epidemiology of Cholera and Other Vibrio Species

V. cholerae, like other pathogens, requires certain environmental conditions (30 °C temperature, pH 8.5, 15% salinity), to survive and thrive [6]. When encountered with more hostile circumstances, *V. cholerae* persists for long periods in its aquatic niche in a dormant state, or interacts with tiny planktonic crustaceans and animals, such as oysters and copepods [36,37]. Ocean currents can displace plankton together with attached *Vibrios* [38].

During the nineteenth century, six pandemics occurred, first at coastlines, while dispersion was achieved through maritime activity. All pandemics were attributed to contaminated water from rivers or swampy waters. Moreover, they started from Bangladesh and were caused by *V. cholerae* serotype O1 [38,39]. Details about the cholera pandemics are presented in Table 2. During 1926-1960 and in light of improvements in water management, it was assumed that cholera pandemics could be a part of history. However, at the end of the twentieth century, a different spread of a new *V. cholerae* biotype (El Tor) was observed, causing the seventh pandemic. It started in Indonesia in 1961 and spread to Africa and South America over the next decades [38]. Almost all South American countries were involved during the last pandemic, and climate change seems to have played a role. In South America (from January 1991 in Peru until February 1991 in Ecuador), there was an almost simultaneous appearance of outbreaks at a distance of more than 2100 km. The El-Nino event, which causes phytoplacton blooms due to the confluence of rain and nutrients from land into the warm SST, could explain the geographically distant cholera outbreaks since a large "infectious dose" of *V. cholerae* may have originated from river overflow [36]. In detail, the infectious dose of 10^3 *V. cholerae* cells could be provided by one copepod as each one usually carries more than 10^4 *V. cholerae* cells, and during a plankton bloom, several copepods are contained in a glass of untreated water. In 1992 an outbreak of the new *V. cholerae* serogroup 0139 caused a large outbreak in India and Southeast Asia [36,39].

The El Niño/Southern Oscillation (ENSO) periodicity has been connected to many cholera outbreaks and is characterized as a 'powerful natural experiment' [40]. The extreme weather conditions of higher temperature, increased rainfall, and consequent flooding, associated with one of the strongest ENSO events, which occurred in 1997 and lasted until 1998, may explain the global surge of outbreaks observed between 1997 through 1999 [40]. As Mercedes et al. showed in their study [41], the interannual variability of cholera cases correlates with the ENSO time series. In this regard, climate variability seems to affect disease dynamics. During the last two decades of the 20th century, this strong association between ENSO and cholera accounts for more than 70% of the disease variance [42]. Moreover, other events, such as the Northern Hemisphere Temperature and Atlantic Multidecadal Oscillation, are known to correlate positively with *Vibrios* abundance [43].

Climate variations may also affect the genetic diversity of strains between epidemics through environmentally driven changes in the expression of virulence factors [44]. Genetic variability of clinical and environmental strains during and between epidemics occurring in the last 20 years in Bangladesh and neighboring countries, as well as clonal variability of toxigenic *V. cholera*, have been well documented [45–48]. Environmental factors, such as rainfall, seem to influence serotype selection (between O1 and O139 strains), as shown by Goel et al., in two subsequent epidemics in India [49]. Rainfall, as well as increased salinity and water temperature, enhances *V. cholerae* biofilm formation, potentially by affecting the expression of genes responsible for vibrio polysaccharide synthesis (*vps*) [50,51]. Another example is the predominance of the El Tor biotype over the classical one during suboptimal climatic conditions due to its better fitness, owing again to the expression of the *vps* gene [52]. Moreover, transduction, which can give rise to novel toxigenic clones, is enhanced

by certain environmental conditions, including optimal temperature, sunlight, and osmotic conditions [16].

Table 2. Cholera pandemics.

Period	Start from	Spread to	Cholera Strain
1817–1823	India (Bengal)	China, Indonesia, Europe, East Africa	*V. cholerae* serotype O1, classical biotype
1829–1851	India	Russia (Moscow), America (New York, Manhattan, Philadelphia, New Orleans), Hungary, Germany, London, Egypt	*V. cholerae* serotype O1, classical biotype
1852–1859	India	North Africa, South America (Brazil)	*V. cholerae* serotype O1, classical biotype
1863–1879	India (Ganges Delta)	Naples, Spain	*V. cholerae* serotype O1, classical biotype
1881–1896	India	Europe, Asia, South America	*V. cholerae* serotype O1, classical biotype
1899–1923	India	Egypt, Arabian peninsula, Persia	*V. cholerae* serotype O1, classical biotype
1961–ongoing	Indonesia	East Pakistan, the Soviet Union, North Africa	*V. cholerae* serotype O1, El Tor biotype

An increase in SST seems to be a critical factor not only for *Vibrio* persistence but also for the emergence of new *Vibrio* spp. habitats (Table 3). Data from the Baltic Sea during the last decades have confirmed these warming patterns, which correspond closely with the emergence and spread of *Vibrio* infections in the area. Furthermore, many reports of *Vibrio*-associated wound infections were recorded during the warm summers of 1994, 2003, and 2006 when SST exceeded 19 °C for more than three weeks. Baker-Austin et al. [6] showed that climate change has affected aquatic bacterial communities and the emergence of *Vibrio* disease in temperate areas. The authors explain the variability of *Vibrio*-related disease using generalized linear models (GLM) by maximum SST and time, concluding in a very strong association between SST and *Vibrio* cases. Several biological explanations support these results, including increased bacterial replication in high temperatures, temperature mediated pathogenicity of *Vibrio* spp., and increased leisure activities, such as bathing during such circumstances. Vezzulli et al. [53] also proposed a similar relationship between climate change and *Vibrio* disease using generalized additive models. Abundance of *Vibrio* was induced by an increase in SST, up to 1.5 °C during the past 54 years, and this was positively correlated with northern hemisphere temperatures [43,53]. From a different perspective, another study, involving the coastal Bay of Bengal, concluded that the association between SST and cholera could be explained from the presence and dominance of high river discharge [54]. This was proposed after showing that phytoplankton-related chlorophyll and SST were positively correlated during high river discharge and negatively correlated during low river discharge. Based on this finding, the authors suggested that cholera prediction models will benefit from the inclusion of nutrient influx and phytoplankton and zooplankton blooms, in addition to other climatic variables for the early detection of outbreaks. In addition, Lipp et al. [16] highlighted in their review that the likelihood of consuming an infectious dose of *Vibrios* during community use of untreated water is higher during the bloom of copepods. The association of cholera and commensal copepods could also inform models of early outbreak risk recognition based on SST, surface height, and plankton blooms. High salinity and elevated water temperature could influence the expression of regulatory and virulence genes found in *V. cholerae*, such as TfoX and the activity of Chi A2 [55]. Increased water temperature enhances *V. cholerae* growth by decreasing replication time, underlining the importance of environmental conditions and *V. cholerae* transmission dynamics [16]. Finally, another study found that the number of clinical cases in

Bangladesh correlated with an air temperature of more than 28.6 °C and more than 4 hours of sunshine daily [56].

Interestingly, using artificial intelligence applications, it has been shown that cholera cases were associated with periods of low precipitation and higher temperatures. Asadgol and colleagues [57] used artificial neural networks projecting from 2021 to 2050 to study the effect of climate change in cholera disease, using data from 1998 to 2016 of daily cholera infections in Qom city, Iran. A trend towards increasing cholera cases was observed with a significant correlation between low precipitation and cholera infection. Higher temperatures in warmer months could also contribute to this trend [57]. Similar tools, using artificial intelligence methods to model the association between disease cases and environmental conditions, could predict the risk for future outbreaks and thus inform early public health interventions. Other crucial predisposing factors that contribute to the occurrence of cholera outbreaks are rainfall patterns and floodings. After studying an outbreak of cholera in 2015 in South Sudan, investigators analyzed the rainfall patterns using deterministic and stochastic models [58]. They concluded that rainfall patterns are fundamental drivers for a cholera epidemic, and they were able to capture seasonal trends as well as short term seasonal fluctuations. Possible mechanistic ways for this rainfall drive are the increased exposure to contaminated water and contamination with bacteria from open-air defecation sites and overflows. Heavy rainfall and flooding are considered as important as well as common risk factors for cholera outbreaks worldwide during 1995-2005, explaining the global increase in such outbreaks during 1997 and 1999 [38].

Apart from endemic countries, the risk of imported *V. cholerae* is substantial in non-endemic countries with weak healthcare infrastructure and public health systems. The cholera outbreak in Haiti in 2010, following the large earthquake, was believed to have initiated from an imported strain from South Asia via international personnel [59,60]. However, the outbreak may have resulted in propagation due to favorable environmental conditions since the average temperature and rainfall had been above average around that time and before it began [61]. Notably, disruption of the public health system and lack of access to safe water also contributed to its course. Natural disasters and extreme weather events can cause the breakdown of healthcare infrastructure, jeopardize sanitation systems and access to clean water, and, overall, increase vulnerability to cholera epidemics in endemic regions.

Table 3. New or expanding *Vibrio cholerae* habitats driven by climate variability/change.

New or expanding *Vibrio cholerae* habitats	Climate change drivers
North Atlantic and North Sea [6]	Sea surface temperature
Baltic Sea (Northern Europe) [7]	Low salinity and rising water temperatures

4. Prevention of Cholera—Future Directions

The World Health Organization (WHO) has estimated that up to 90% of wastewater is discharged, without treatment, directly into the environment (rivers, lakes, and the ocean), in developing countries [62]. Moreover, approximately 1.8 billion people worldwide drink water from a fecally contaminated source [63]. With overburdened healthcare systems, which lack resources for optimal surveillance, outbreaks of *V. cholerae* can occur. In addition, when there is a breakdown of healthcare infrastructure during catastrophic events or weakened health systems, these outbreaks can cause significant mortality. Water source control, local or centralized sanitation systems, and wastewater management are paramount for the prevention of *V. cholerae* transmission. Improving vaccination effectiveness in developing countries by geographical targeting of routine mass vaccination programs [64] and access to vaccination by increasing global supply will also enhance efforts to reduce the burden of cholera. Overall, strengthening public health infrastructure and laboratory diagnostic capacity in developing countries is of paramount importance in outbreak detection and control of *V. cholerae* transmission.

There is also a need for a robust national, regional, and global surveillance system that would generate epidemiologic data regarding existing and emerging areas of risk for *Vibrio* infections [65,66]. To date, only the US gathers epidemiological data systematically since 1988 through the

Cholera and Other *Vibrio* Information Service (COVIS) CDC program [67]. Assessment of risk should focus on coastal hotspots and regions undergoing rapid warming (i.e., the Pacific northwest, the East China Sea) [22]. Early warning systems that integrate climatic variables, remotely sensed spatial data, and global climate trends could help detect areas with environmental factors conducive to *Vibrio* growth and transmission and thus inform public health measures to mitigate potential cholera outbreaks. However, these systems must be built on previously well-characterized associations between certain environmental phenomena and *V. cholerae*-related disease [68]. Participatory surveillance using cell phone applications for the collection and dissemination of citizen observations may assist in the early detection of unusual cholera activity [69]. High-risk areas with *Vibrio* populations in their coastal estuaries could develop long-term monitoring programs for drinking and recreational water. Intermittent sampling to test for organic nutrient content, salinity, zooplankton concentration, and bacterial abundance is important to maintaining water quality and monitoring for major changes in the microenvironment that could suggest a change in *Vibrio* populations [65]. Furthermore, the development of educational programs about the risks of water-borne diseases and best hygienic practices are of great relevance and importance in view of climate change adaptation [70].

5. Conclusions

Vibrio related diseases cause significant morbidity and mortality worldwide, though some countries, such as Southeast Asia and Africa, are currently more heavily affected. Non-endemic countries are at risk given favorable environmental conditions and disruptions of their public health infrastructure. Global surveillance networks can inform local institutions regarding current cholera or other vibrioses geographic burden. Enforcing local surveillance systems, improving hygiene practices and sanitation systems, combined with educational programs and vaccination campaigns, wherever needed, in vulnerable areas, could reduce the burden of cholera disease in human populations. Moreover, real-time measurement through remote sensing technologies of climate variability, micro-environmental conditions of oceanic regions and coastal areas, as well as the integration of information from population demographics and mobility, could inform predictive models of cholera outbreak risk in endemic and non-endemic areas.

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