

Ocean Warming and Spread of Pathogenic Vibrios in the Aquatic Environment

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Abstract Vibrios are among the most common bacteria that inhabit surface waters throughout the world and are responsible for a number of severe infections both in humans and animals. Several reports recently showed that human *Vibrio* illnesses are increasing worldwide including fatal acute diarrheal diseases, such as cholera, gastroenteritis, wound infections, and septicemia. Many scientists believe this increase may be associated with global warming and rise in sea surface temperature (SST), although not enough evidence is available to support a causal link between emergence of *Vibrio* infections and climate warming. The effect of increased SST in promoting spread of vibrios in coastal and brackish waters is considered a causal factor explaining this trend. Field and laboratory studies carried out over the past 40 years supported this hypothesis, clearly showing temperature promotes *Vibrio* growth and persistence in the aquatic environment. Most recently, a long-term retrospective microbiological study carried out in the coastal waters of the southern North Sea provided the first experimental evidence for a positive and significant relationship between SST and *Vibrio* occurrence over a multidecadal time scale. As a future challenge, macroecological studies of the effects of ocean warming on *Vibrio* persistence and spread in the aquatic environment over large spatial and temporal scales would conclusively support evidence acquired to date combined with studies of the impact of global warming on epidemiologically relevant variables, such as host susceptibility and exposure.

Assessing a causal link between ongoing climate change and enhanced growth and spread of vibrios and related illness is expected to improve forecast and mitigate future outbreaks associated with these pathogens.

Introduction

Warming of the climate system is unequivocal, with evidence from observations of increases in global average air and ocean temperatures, widespread melting of snow and ice, and rising global average sea level [1]. Global average temperatures have risen by nearly 0.8 °C since the late nineteenth century and approximately 0.2 °C/decade over the past 25 years [1]. It has been estimated that since the 1960s, about 90 % of the excess heat added to the Earth's climate system has been stored in the oceans [2]. In Europe, warming of regional seas has accelerated at an unprecedented rate over the last 25 years, with the Baltic, North, and Black Seas showing greatest increasing temperature [3]. At the global scale, temperature fluctuations in surface waters have been related to large-scale climate patterns such as the North Atlantic Oscillation (NAO) and El-Niño Southern Oscillation (ENSO) [4]. Altered patterns of precipitation and run-off related to global warming are also driving reduction in salinity in estuaries and coastal wetlands [5].

Vibrio spp. are naturally occurring bacteria in riverine, coastal, and estuarine ecosystems around the world and include several human and animal pathogens that can negatively impact human health and ecosystem services (e.g., recreational water use and aquaculture) [6]. Over 80 species have now been described, including at least 12 capable of causing infection in humans (e.g., *Vibrio cholerae*, *Vibrio parahaemolyticus*, and *Vibrio vulnificus*) [7]. *V. cholerae*, the causative agent of cholera, is by far the most important pathogenic species of the genus, accounting for about three million cases of human infections each year, with a case

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fatality rate of about 2.4 % [8]. Overall, *Vibrio* diseases deriving from both water and seafood are increasing worldwide. The number of cholera cases reported to WHO continues to rise, and for 2011 alone, a total of 589,854 cases and 7,816 deaths were reported by 58 countries. Surveillance data from both COVIS and FoodNet indicate the incidence of vibriosis (excluding toxigenic *V. cholerae* O1 and O139) increased in the USA from 1996 to 2010 [9].

Vibrios grow preferentially in warm ($>18^{\circ}\text{C}$), low salinity (<25 ppt NaCl) seawater and brackish waters. Ongoing warming and reduced salinity of coastal regions are expected to support the spread of these bacteria at a global scale, especially in northern latitudes. Increased seawater temperature over the past decade has been linked to outbreaks of *Vibrio*-associated human illness caused by *V. cholerae*, *V. parahaemolyticus*, and *V. vulnificus* including Chile [10], Peru [11], Alaska [12], Israel [13], Spain [14], and Europe [15]. A geographical transition in terms of disease into non-endemic regions has also been observed especially in temperate and cold regions of the world [15] which are the most affected by global warming [16]. Warming patterns have also been correlated with an increase in cholera cases in cholera-endemic countries of sub-Saharan Africa [17] and the Bay of Bengal [18, 19].

In addition to human illnesses, prevalence and severity of a wide range of diseases of marine organisms, e.g., corals, bivalves, and fish, have been linked to elevated sea surface temperature (SST) and *Vibrio* infections. Coral bleaching is the most serious disease affecting coral reefs, and of the eight coral pathogens implicated in the onset of coral diseases worldwide, half belong to the Vibrionaceae family [20, 21]. In the Mediterranean Sea, *Vibrio coralliilyticus* infections were shown to trigger mass mortality events of the purple gorgonian *Paramuricea clavata*, a key structuring species of coralligenous assemblages, related to SST anomalies registered during recent years [22]. Other *Vibrio* species, such as *Vibrio splendidus* and *Vibrio aestuarianus*, are believed to play a role in the abnormal mortality of Pacific oysters (*Crassostrea gigas*), which has increased since 2008 in warmer seasons in some areas of Ireland, France, the Netherlands, and the UK [23, 24].

Notwithstanding the increasing number of reports showing an unequivocal positive correlation between increasing environmental temperature and spread of *Vibrio* diseases, conclusive evidence linking emergence of infections with climate change is lacking. The main concern is that insufficient experimental evidence has been accumulated to date to support a causal link. Contrasting reports such as the recent observation that vibriosis has increased significantly in the USA in the last decade [9, 25] also in areas where long-term coastal temperature trends are weakly cooling or not significant (South Atlantic Bight [$-0.1\pm0.3^{\circ}\text{C}$ (100 years)] and off Florida [$-0.3\pm0.2^{\circ}\text{C}$ (100 years)]) [26] might be also

taken into account suggesting that factors additional than climate are likely to be responsible for driving disease.

More effort should be devoted in the future to study the long-term climate change effects on *Vibrio* pathogen development and survival in the aquatic environment. In addition, for full comprehension of climate change effects on *Vibrio* disease transmission, the influence of a changing climate on exposure patterns (access to drinking and recreational water) and host susceptibility (health status) must be taken into account. Several reports have been published recently that deal with these issues [27, 28]. This review provides succinct update and discussion of the current state of knowledge regarding effects of increasing SST may have on *Vibrio* persistence and spread in the aquatic environment.

Ecology of Vibrios in a Warming Ocean: Knowledge and Gaps

Understanding the ecology of vibrios, namely the role played by environmental factors in survival, growth, and dispersion of these bacteria, is crucial to understand fully their interaction with humans and animals and, consequently, epidemiology of the associated diseases. Vibrios are natural inhabitants of the brackish and marine environment throughout the world and, although our knowledge has increased substantially in recent years [29, 30], we are still far from having a comprehensive view of their global ecology. Most studies have focused on the population ecology of single species (mainly *V. cholerae*) and generally following a reductionist approach, namely lab-scale experiments, and examining the role of a single/few environmental factors affecting *Vibrio* growth and survival [31–33]. Findings from these studies have provided important information about the ecology of vibrios at the molecular, cell, and population levels, namely conditions and resources regulating their metabolism and determining their ecological niche. Conditions include physicochemical parameters, such as temperature, salinity, and pH, whilst environmental resources include carbon and energy needed for metabolism and consumption by microorganisms. Several studies have shown that vibrios are chemoheterotrophic halotolerant microorganisms (optimal NaCl concentration is between 0.2 and 3.0 ‰), with an optimal temperature of growth ranging from 30 to 40 °C and optimal pH of ca. 8.0 [7].

Furthermore, studies conducted both in the laboratory and field showed that, together with environmental conditions and resources, interactions of vibrios with other living organisms and abiotic substrates are the main contributors in shaping the ecological niche of these species [34, 35]. For example, in the aquatic environment, *V. cholerae* has been reported to be associated with a variety of living organisms, including animals with an exoskeleton of chitin, aquatic

plants, protozoa, bivalves, waterbirds, as well as abiotic substrates (e.g., sediments) which represent environmental reservoirs (living or nonliving substrate favoring bacterial persistence and replication in the environment) and/or hosts (living organism that temporarily harbors the bacteria, generally providing nourishment and shelter) [36]. Both the reservoir and host largely influence the ecology of vibrios by favoring their survival and dispersion in the environment and also serving as a vector of their associated disease. Interaction between *Vibrio* and environmental surfaces, namely chitin and the exoskeleton of marine crustaceans, was investigated extensively for *V. cholerae* and exemplifies a successful bacteria–substrate interaction with complex and significant influence on the lifestyle of the bacterium [35]. In fact, the *V. cholerae*–chitin interaction has been shown to positively influence food availability, adaptation to environmental nutrient gradients, tolerance to stress, and protection from predators [35]. Trophic interactions also play a significant role in controlling *Vibrio* proliferation in coastal waters and these include bottom upregulation by the food resource, such as dissolved organic carbon and nutrients [37], as well as top downregulation by protozoan predation [38] and lysis by bacteriophage [39].

In spite of their importance, these studies are limited in not having addressed the influence of environmental variables at the global ecosystem scale. Extreme weather events, human-induced eutrophication, and pollution, as well as large-scale climatic processes (i.e., ENSO and NAO) affect both ecological resources and conditions and the ecological interactions within a biological community. These factors are expected to directly influence multiple levels of organization in an aquatic system, as well as trigger indirect cascading effects, from ecosystem to single cells, all of which are difficult to measure, especially simultaneously. For example, global warming is known to affect the physiology of *Vibrio* cells directly, but also to influence abundance and structure of their main environmental reservoirs [3].

Studies aimed at addressing the challenging field of *Vibrio* global ecology are difficult to design and perform; they are carried out mainly in field investigations of *Vibrio* populations, that is, temporal and spatial occurrence of *Vibrio* populations and their relation to detected ecosystem variables [40–42]. Although very useful, such studies tend to be descriptive and based on correlation and not “cause and effect.” Ecological modeling is a promising method to achieve better understanding of *Vibrio* global ecology, but it is largely constrained by the lack of sufficient experimental observations.

In conclusion, the reductionist approach taken to date, although successful in providing a detailed understanding of *Vibrio* species, underestimates the complexity of the ecosystem, notably that of climate change effects on *Vibrio*

populations (Fig. 1 provides a schematic overview of the direct and indirect influence of ocean warming on vibrios). It should be pointed out that holistic studies are ambitious and difficult to perform in a rigorous scientific way. As a future challenge, macroecological studies investigating statistical patterns of abundance, distribution, and activity of *Vibrio* bacteria over large spatial and temporal scales can help close the gaps providing the basis for dealing with threats that climate linked *Vibrio* proliferation may pose to human health.

Temperature Effects on *Vibrio* Viability, Growth, and Pathogenicity

It has long been established that temperature strongly influences metabolism and growth rates of *Vibrio* species. Early studies of *V. cholerae* showed that by increasing the water temperature up to 30 °C in laboratory microcosms, a pronounced effect on the multiplication of these bacteria is observed [32]. The same phenomenon has been observed for other *Vibrio* species, including those pathogenic for humans, namely *V. parahaemolyticus* [43] and *V. vulnificus* [44].

Most vibrios grow well on culture media when the temperature is above 17 °C. The optimal temperature for growth may vary among different species, but is generally in the range of 30–40 °C [7]. Vibrios are sensitive to cold temperatures below 10 °C when they may enter the viable but nonculturable (VBNC) state. The VBNC state, firstly described for the human pathogen *V. cholerae*, is a dormant condition in which bacteria remain viable, but are not culturable in conventional laboratory media [45]. Temperature upshift was shown to promote regrowth of several VBNC *Vibrio* cells which regain culturability and normal phenotypic traits [46].

Recent studies have shown that temperature has an effect on *Vibrio* pathogenicity. Using proteomic analysis and bioassays, Kimes et al. [47] demonstrated direct temperature regulation of virulence in the coral pathogen *V. coralliilyticus*, including upregulation at 27 °C of several virulence factors involved in motility, host degradation, secretion, and antimicrobial resistance [47]. Increased expression of known and putative virulence-associated traits was also correlated with increased temperature in clinical reference isolates of *V. vulnificus* and *V. parahaemolyticus* [48, 49].

Ultimately, for *V. cholerae*, temperature also appears to play a role in conversion of *V. cholerae* from non-O1 to O1 serogroup [50]. In addition, it regulates transcription of *toxT*, a gene encoding the regulatory protein ToxT which directly activates transcription of virulence factors, including cholera toxin (CT) and the toxin-coregulated pilus (TCP) [51]. The expression of CT and TCP via ToxT is downregulated in *V.*

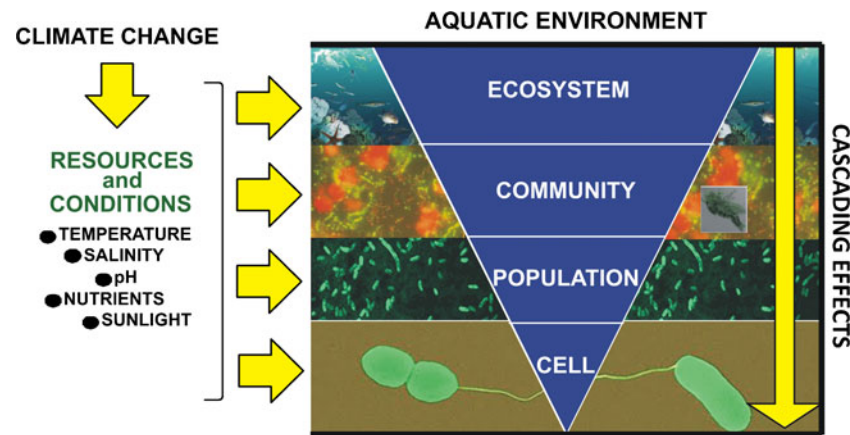


Figure 1 Simplified overview of the impact of climate change on vibrios in the aquatic environment. Climate change is affecting ecological resources and conditions required by biological species. These are directly influencing *Vibrio* cells and populations (e.g., *Vibrio* metabolism and growth) as well as higher levels of organization of the aquatic system (e.g., living communities and the

physicochemical environment). The impact of climate change on the upper levels of ecosystem organization may ultimately trigger indirect cascading effects that could have profound repercussion on the vibrios (e.g., by affecting *Vibrio* environmental reservoirs and trophic interactions)

cholerae at 37 °C and upregulated at 30 °C. It was suggested that negative regulation of ToxT-dependent transcription by temperature and other environmental signals prevents incorrect temporal and spatial expression of virulence factors during the host phase of the *V. cholerae* life cycle [51, 52].

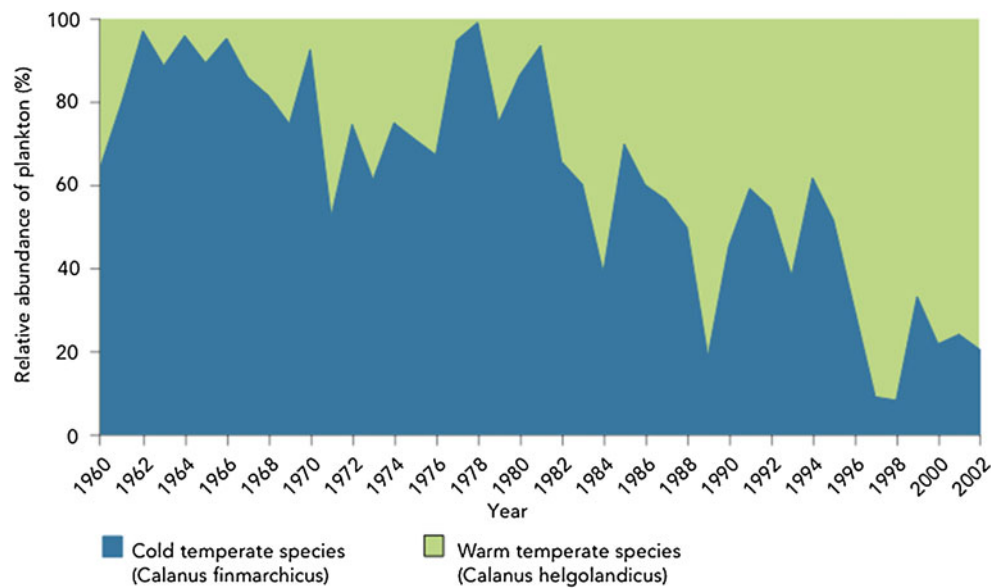
Temperature Effects on *Vibrio* Interaction with Environmental Reservoirs and Hosts

Although much is known about direct effects of temperature on the physiology of *Vibrio* cells, there is very limited information available on the indirect effects that an increase in environmental temperature may have on *Vibrio* populations by altering the abundance and structure of *Vibrio* reservoirs and hosts in the aquatic environment. Vibrios have a high affinity for colonization of chitin surfaces and chitinous organisms, especially zooplankters, which are considered perhaps the main environmental reservoir of these bacteria in the aquatic environment [36]. The copepod exoskeleton has been shown to support large populations of vibrios, including the pathogenic species, *V. cholerae* [53]. Due to its clinical importance, *V. cholerae* has been used as a model to study *Vibrio*–plankton interaction. The exoskeleton surface of a single colonized copepod has been shown to contain up to 10^4 cells of *V. cholerae*, thus providing the required infectious dose for clinical cholera (ranging from 10^4 to 10^{11} depending on the bacterial strain and its host [54]). The importance of copepods in cholera transmission was further demonstrated in a study in which the number of cholera cases in Bangladesh villages was reduced significantly when copepods were removed from drinking water [55].

The role of temperature in *V. cholerae*–plankton interactions was studied by Huq et al. [56] who showed that temperatures ranging from 25 to 30 °C significantly promote attachment of *V. cholerae* to copepods. More recently, Stauder et al. [57] analyzed the molecular basis of the attachment and suggested increased ambient temperature significantly enhanced expression of two colonization factors involved in *V. cholerae* interaction with environmental chitin surfaces, namely *N*-acetylglucosamine-binding protein A (GbpA) and mannose-sensitive hemagglutinin [58, 59]. According to their findings, ocean warming may favor *Vibrio* colonization of plankton, amplifying the role of the plankton reservoir in supporting larger populations of vibrios in the aquatic environment.

Ocean warming affects abundance, diversity, and distribution of plankton communities. In the eastern North Atlantic and on the European shelf, strong biogeographical shifts in copepod assemblages occurred during the last 50 years, with a poleward extension of more than 10° latitude (more than 1,000 km) for warm-water species and a decrease in the number of colder-water species [60] (Fig. 2). This coincided with an observed increase in planktonic biodiversity and parallel reduction in phytoplankton [61] and zooplankton size [3]. Little is known about the effect that ongoing dramatic changes in the plankton community may have on *Vibrio* populations or, as yet unknown environmental reservoirs or hosts of these bacteria [36]. Gaps in our knowledge of *Vibrio* ecology will need to be addressed to answer questions concerning environmental reservoirs of these bacteria including species-specific interaction between vibrios and hosts [62].

Figure 2 Long-term changes in plankton assemblages in the North Atlantic and North Sea spanning four decades. Plankton data recorded by the CPR survey in the North Atlantic and North Sea show the increase in dominance of warm-water copepod species (*Calanus helgolandicus*) (green) and concomitant decrease of cold-water species (*Calanus finmarchicus*) over the period 1960–2002. Copyright© 2010 Sir Alister Hardy Foundation for Ocean Science. All Rights Reserved. SAHFOS



Field Studies of Seasonal Effect of SST on *Vibrio* Abundance and Distribution

Most of the studies cited above employed laboratory model systems to investigate the effect of increased environmental temperatures on *Vibrio* populations. However laboratory experiments are simplified representations of the natural ecosystem and need to be integrated with observational studies in the field.

Field studies conducted worldwide over the last 40 years have clearly showed the number of *Vibrio* in estuarine and coastal waters is strongly associated with seasonal temperature [6]. For example, in temperate regions of the world, the abundance of *V. cholerae* and *V. parahaemolyticus*, both of which occupy similar ecological niches, show a strong seasonal oscillation with higher abundances generally observed during the warmer season of the year, that is when the water temperature typically exceeds 20 °C [63]. Similar temperature-driven dynamics have been observed for *V. vulnificus* [64] and other species of *Vibrio* [22, 65]. Thompson et al. [66] observed that temperature influences the overall structure of *Vibrio* populations in field study conducted in the North Atlantic Ocean by identifying distinct warm-water and year-round populations of vibrios over a 15-month period. Seasonal changes in temperature are known to directly influence both bacteria and their aquatic reservoirs and hosts. In situ data collected in analyses of zooplankton and water samples from coastal waters of the NW Mediterranean Sea over an annual cycle showed that the percentage of plankton-associated *V. cholerae* was positively correlated with SST, increasing dramatically at temperatures above 22 °C [57]. These data are consistent with the laboratory observations showing elevated temperatures promote attachment of *V. cholerae* to copepods [32]. Whether the decline in *Vibrio* abundance during cold seasons of

the year is the result of temperature-mediated cell mortality or induction of the VBNC state or to impact on the bacterial host or vector remains open to debate [67].

Seasonal temperature affects the incidence of *Vibrio*-related diseases and epidemiology [68]. Analysis of cholera outbreaks has shown that temperature and other variables, such as salinity and plankton concentration, influence seasonal transmission of cholera in those regions of the world where the human population relies on untreated water as a source of drinking water [69]. In addition, ENSO events have been found to be related to anomalous patterns in cholera dynamics and other *Vibrio* infections [29, 68]. Using remote sensing, Lobitz et al. [19] were the first to explore the relationship between SST and cholera incidence over a multi-seasonal scale, finding changes in coastal ecosystems to be significantly related to the seasonal pattern of cholera epidemics. Based on those studies, a hierarchical model has been proposed for cholera epidemiology, defining the role of environment, weather, and climate-related variables in cholera outbreaks [29].

Long-term Effects of Increasing SST on *Vibrio* Populations

Long-term effects of ocean warming on abundance and distribution of vibrios in the aquatic environment are difficult to assess because of the lack of historical data. Most recently, an ingenious retrospective study of formalin-fixed plankton samples collected by the Continuous Plankton Recorder (CPR) survey in the North Sea has provided the first evidence for a positive and significant relationship between SST and *Vibrio* abundance over a multidecadal scale (Fig. 3). In the region around the North Sea sampling sites, an unprecedented increase in bathing infections

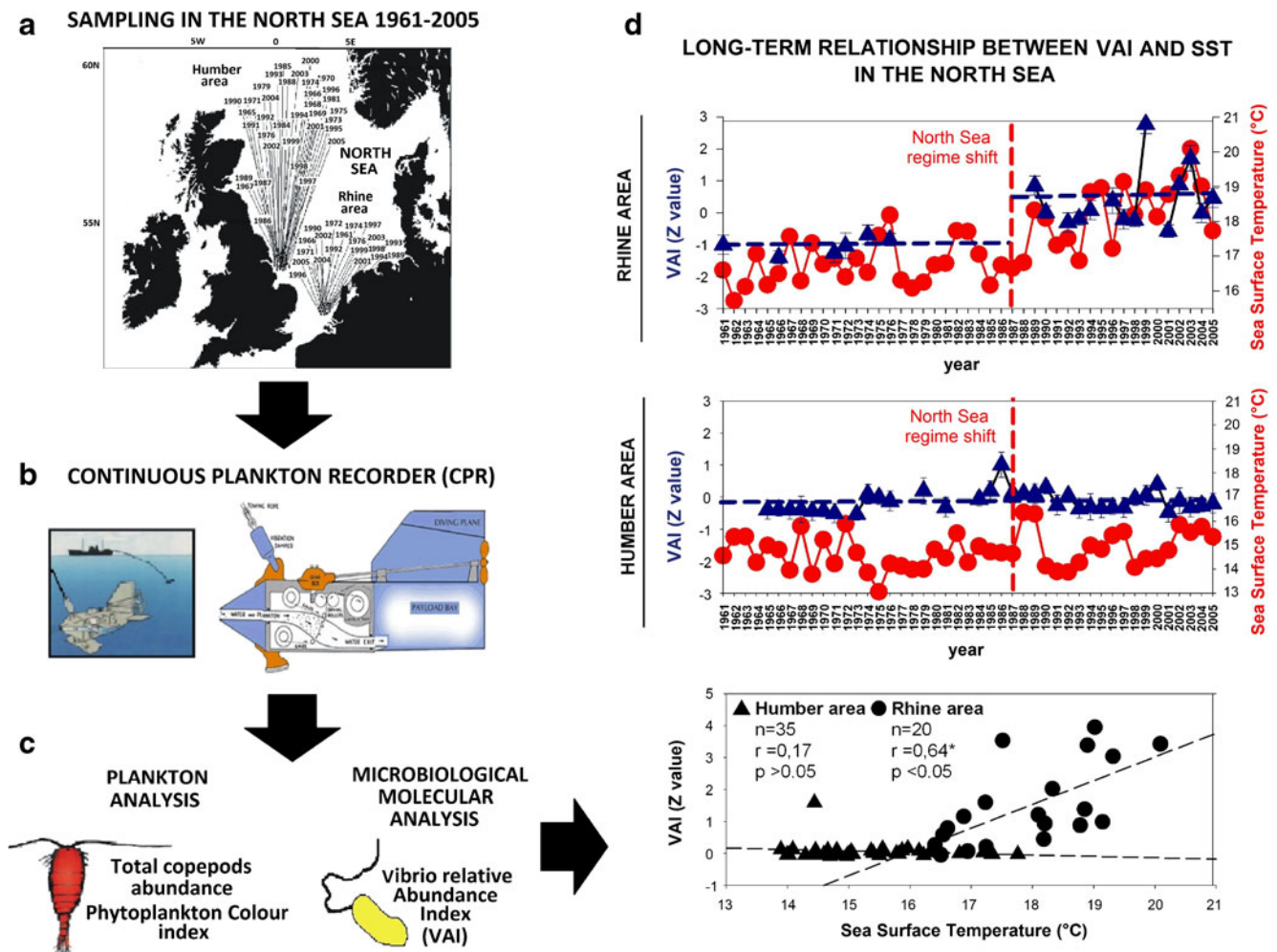


Figure 3 Retrospective assessment of long-term relative abundance of vibrios in the North Sea. Formalin-fixed plankton samples were collected by the CPR survey off the Rhine and Humber estuaries, in August, over the period 1961 to 2005 (a). CPR samples were collected by the continuous plankton recorder (b). Back in the laboratory, the silk containing the formalin-fixed plankton was cut into blocks and microbiological molecular analyses were carried out to assess *Vibrio*-relative abundance (see Vezzulli et al. [70] for details) (c). Phytoplankton and zooplankton analysis was also carried out following standard CPR

methodology [71] (c). Long-term variation in standardized (Z) VAI (triangles; error bars indicate standard deviation, $n=5$) and SST (circles) for 1961–2005 off the Rhine and Humber estuaries in the North Sea (d). Vertical line=regime shift step change in temperature after 1987 [72]. Horizontal lines=average VAI values. The Pearson correlation analysis between VAI and SST in the North Sea (Pearson's correlation on pooled data; $n=55$; $r=0.27^*$; $P<0.05$) (d). Z values are obtained by subtracting the population mean and dividing the difference by the standard deviation. Modified from Vezzulli et al. [70]

associated with *Vibrio* species (*V. cholerae* non O1-O139, *V. vulnificus*, and *Vibrio alginolyticus*) have been reported (Baker-Austin et al. [15] and references therein).

The CPR survey is one of the longest running marine biological monitoring programs in the world and provides a long-term archive of formalin-preserved plankton samples (<http://www.sahfos.ac.uk>). In their work, Vezzulli et al. [70] exploited the well-known association between vibrios and plankton, which is considered to be one of the largest reservoirs of these bacteria in nature, to assess possible linkage between *Vibrio* occurrence in the sea and environmental variables (SST and phytoplankton and zooplankton abundance) over a decadal scale by molecular analysis of the microbial community on these historical CPR samples. To this end, they

recovered environmental DNA from the CPR samples that had been stored for up to ~50 years in formalin-fixed format, which is suitable for molecular analyses of the associated prokaryotic community. An unbiased index of abundance for *Vibrio* quantification in the CPR samples, termed “*Vibrio*-relative abundance index—VAI,” was developed. This index measures the relative proportion of plankton-associated vibrios in comparison to the total number of associated bacterial cells. 16S rDNA pyrosequencing analysis was also carried out to assess the relative contribution of the *Vibrio* genus to the total plankton-associated bacterial community in comparison to other bacterial groups. Using this approach, it was shown that vibrios, including the species *V. cholerae*, have increased in prevalence during the past 50 years in the coastal North Sea

and that this increase is correlated significantly with increasing SST during that time. These findings provide support for the view that global warming is having a strong impact on the composition of marine prokaryotic communities, with potential important implications for human and animal health.

Conclusions

Whether or not ocean warming is significantly promoting growth and distribution of vibrios in the aquatic environment globally is a matter of debate. An increasing number of studies and a significant amount of data support this hypothesis, although there are gaps that preclude conclusive evidence. Implementation of long-term ecological studies that incorporate historical as well as newly produced field data, such as has been gathered for eukaryotic communities (e.g., <http://www.lternet.edu/>; <http://www.sahfos.ac.uk>), is needed. In addition to the biology and ecology of vibrios, epidemiological studies of their associated diseases would be useful, especially those investigating changes in disease transmission patterns (e.g., pathways of exposure and susceptibility of host populations) in a time of climate changes. If a causal link between the spread of *Vibrio* illness and climate change could be proven definitively, it would greatly improve our chance to forecast and mitigate future outbreaks associated with these pathogens.

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