

Minireview

In hot water: effects of climate change on *Vibrio*–human interactionsBrett A. Froelich¹ and Dayle A. Daines^{2*}¹Department of Biology, George Mason University, 10900 University Boulevard, Manassas, VA, 20110.²College of Sciences, Office of the Dean, Old Dominion University, Norfolk, VA, 23529.

Summary

Sea level rise and the anthropogenic warming of the world's oceans is not only an environmental tragedy, but these changes also result in a significant threat to public health. Along with coastal flooding and the encroachment of saltwater farther inland comes an increased risk of human interaction with pathogenic *Vibrio* species, such as *Vibrio cholerae*, *V. vulnificus* and *V. parahaemolyticus*. This minireview examines the current literature for updates on the climatic changes and practices that impact the location and duration of the presence of *Vibrio* spp., as well as the infection routes, trends and virulence factors of these highly successful pathogens. Finally, an overview of current treatments and methods for the mitigation of both oral and cutaneous exposures are presented.

Introduction

We are indeed in hot water! The Intergovernmental Panel on Climate Change (IPCC), the United Nations body for assessing the science related to climate change, recently issued a new report focusing on the earth's oceans and cryosphere in which the Panel considered the physical, chemical and biological effects of the well-documented increases in atmospheric and oceanic temperatures (IPCC, 2019). The news is not promising, as the combination of a warming ocean, a concomitant increase in sea levels and increased human activity in coastal waters set the stage for increased *Vibrio*–human interactions. There have been previous reports and reviews of this

subject (Baker-Austin *et al.*, 2016, 2017; Vezzulli *et al.*, 2016; Baker-Austin and Oliver, 2018; Deeb *et al.*, 2018); here we will use those previous studies as seminal points of reference and provide updates from the current literature.

Routes of infection

Although there are over 100 named *Vibrio* species, only a small number have been isolated from humans, including *Vibrio cholerae*, *V. vulnificus*, *V. parahaemolyticus*, *V. alginolyticus*, *V. fluvialis* and *V. anguillarum* (Jacobs Slifka *et al.*, 2017; Sinatra and Colby, 2018; Bonnin-Jusserand *et al.*, 2019; Chowdhury *et al.*, 2019; Miller *et al.*, 2019). A much larger number of *Vibrio* spp. are pathogenic to fish and shellfish, but these will not be considered here. Our focus will be on the three that we consider to be the most significant for their impact on human health: *V. cholerae*, the etiologic agent of human cholera; *V. vulnificus*, responsible for both gastroenteritis as well as for horrifying infections of extremities; and *V. parahaemolyticus*, more recently understood as a significant player by those who study vibrioses (CDC, 2006).

These microorganisms can cause illness via ingestion of untreated water or contaminated fish or shellfish and are routinely isolated from warm coastal waters around the world, including the United States (U.S.). *Vibrio* spp. are susceptible to heat, so most food-related gastroenteritis cases result from eating either raw or undercooked fish or shellfish. Ingestion of *Vibrio* spp. with food protects the organism from the bactericidal effect of stomach acid, so the infectious dose (ID) in contaminated water is considerably higher than when consumed with food: for example, 10^8 – 10^{11} of *V. cholerae* in water is required for an ID in healthy human volunteers, versus 10^4 – 10^8 when ingested with food (Nelson *et al.*, 2009; Almagro-Moreno and Taylor, 2013). Likewise, the use of over-the-counter or prescription proton pump inhibitors designed to decrease stomach acid results in a lower ID due to allowing increased numbers of viable organisms to reach the intestines. Interestingly, *V. cholerae* can only cause

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cholera when carrying the *Vibrio* pathogenicity island (VPI) that includes the toxin co-regulated pilus (TCP) gene cluster, as well as the CTX bacteriophage, which supplies the cholera toxin gene. The cholera exotoxin starts a cascade in intestinal epithelial cells that results in the dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel, causing the massive fluid loss from the intestines that is characteristic of the disease (Kaper *et al.*, 1995). The so-called 'rice water stool' shed by cholera sufferers contains 10^{10} – 10^{12} *V. cholerae* organisms per litre, and patients can lose up to 2 l per day, rapidly causing fatal dehydration unless ameliorated (Nelson *et al.*, 2009). Epidemic cholera is caused by serogroups O1 or O139 if carrying the cholera toxin; however, non-toxigenic non-O1/non-O139 *V. cholerae* are considered opportunistic pathogens and can also cause bloody diarrhoea and gastroenteritis as well as extraintestinal infections (Chowdhury *et al.*, 2016). *V. vulnificus* is ubiquitous in the coastal marine environment and is often associated with fish and shellfish. However, this organism can also be a lethal pathogen when ingested (Jones and Oliver, 2009). In addition, this organism and certain other *Vibrio* spp. can bypass the gastrointestinal route altogether by directly infecting skin cuts or scrapes. Wound infections with *V. vulnificus* can cause a bullous cellulitis resulting in cell death that may require limb amputation and can progress to an overwhelming septic shock that is often fatal due to multiple organ failure (Bhat *et al.*, 2019; Guillod *et al.*, 2019; Leng *et al.*, 2019). The most susceptible populations for fulminant extraintestinal infections from either the oral or cutaneous route are those with a decreased immune response, including patients with thalassemia, diabetes, HIV or liver disease (cirrhosis or hepatitis) as well as those receiving immunosuppressant drugs for other conditions (He *et al.*, 2019). Finally, *V. parahaemolyticus* can cause a seafood-borne rapid-onset gastroenteritis. This illness is usually self-limiting, with severe disease normally observed only in immunocompromised individuals (Yang *et al.*, 2019). It is also associated with outbreaks, evidenced by a recent multistate event in the U.S. linked to eating fresh crab meat imported from Venezuela (CDC, 2018). In addition, similar to *V. vulnificus*, *V. parahaemolyticus* can cause cutaneous infections of open wounds that can be devastating in some patients (Guillod *et al.*, 2019). Overall, those who cultivate, harvest or shuck oysters and other shellfish for a living as well as fish farmers and seafood factory workers have a significantly increased risk of exposure to pathogenic vibrios due to the nature of their work (Penland *et al.*, 2000).

***Vibrio* virulence factors**

Vibrio spp. maintain a number of virulence factors that enhance their ability to cause disease in the host, including siderophores for scavenging iron, haemolysins that

degrade erythrocyte and cellular membranes, capsular polysaccharide that helps the organism resist opsonisation and evade complement fixation, pili and surface proteins to enhance adherence and attachment, and flagella-mediated movement (Jones and Oliver, 2009; Carda-Dieguez *et al.*, 2018; Gao *et al.*, 2018; Guanhua *et al.*, 2018; Duong-Nu *et al.*, 2019; Li *et al.*, 2019; Yamazaki *et al.*, 2019). Indeed, the darting motility of these organisms contributed to their name of *Vibrio*, which comes from the Latin word *vibro*, to vibrate or to set in tremulous motion (Bergey and Holt, 1994). The toxin co-regulated pilus (TCP) of *V. cholerae* facilitates both adherence and biofilm formation in the environment as well as *in vivo* (Yildiz and Visick, 2009). All three species can form biofilms in the environment and within a host during infection, and require flagellar motility to do so (Jung *et al.*, 2019). In addition, some *Vibrio* species maintain type III secretion systems (T3SS) that enable direct translocation of toxic effector proteins from the bacterium into the eukaryotic host cell via a structure that is reminiscent of a hypodermic needle (Zeb *et al.*, 2019). For example, *V. cholerae* translocates a nucleator protein that increases intestinal colonization using a T3SS (Tam *et al.*, 2007) and *V. parahaemolyticus* translocates effectors that regulate the activity of mitogen-activated protein kinase (MAPK) in host cells (Matlawska-Wasowska *et al.*, 2010). All three species also utilize various decarboxylases for acid neutralization to protect the organism from conditions of low pH (Leng *et al.*, 2019). Finally, since *Vibrio* spp. are Gram-negative, each produces lipopolysaccharide (LPS) containing lipid A which can cause polymorphonuclear leukocytes to secrete inflammatory cytokines as well as nitric oxide, inducing vascular permeability, fever and hypotension that can lead to septic shock during infections (Leng *et al.*, 2019).

Environmental factors affecting *Vibrio* concentrations

Numerous studies have sought to correlate environmental conditions with *Vibrio* abundance (Deeb *et al.*, 2018; Coutinho *et al.*, 2019; Green *et al.*, 2019; Liang *et al.*, 2019). *V. cholerae*, *V. vulnificus* and *V. parahaemolyticus* have a temperature optimum of around 37°C, but infections can begin occurring at 15°C for *V. parahaemolyticus* and at 20°C for *V. vulnificus* (Ulitzur, 1974; Kelly, 1982; Kaspar and Tamplin, 1993; Miles *et al.*, 1997; FAO/WHO, 2005; McLaughlin *et al.*, 2005; Sedas, 2007; Martinez-Urtaza *et al.*, 2010). Thus, any increases in environmental temperature, whether short or long-term, have significant effects on the concentrations of these pathogens in the water and in seafoods. Indeed, temperature is the factor most often correlated with *Vibrio* presence, concentration and infection rate (Takemura *et al.*, 2014).

The second most common parameter reported for having the greatest amount of influence is salinity. Together, salinity and temperature are responsible for as much as 50% of the variation in *Vibrio* abundance (Wetz *et al.*, 2008; Nigro *et al.*, 2011; Froelich *et al.*, 2013, 2019). The addition of other factors into descriptive models often only results in smaller improvements (Takemura *et al.*, 2014). The three main pathogens, *V. cholerae*, *V. vulnificus* and *V. parahaemolyticus* all have differing salinity requirements and tolerances, and thus local salinity changes can modify the ratios of these three pathogens. A shift from *V. vulnificus* and *V. parahaemolyticus* to *V. cholerae* was seen when the Bonnet Carre Spillway was opened in the state of Mississippi in the U.S., releasing a flood of freshwater into the estuary (Griffitt and Grimes, 2013). *V. cholerae* can survive in freshwater, whereas the *V. parahaemolyticus* and *V. vulnificus* have strict salinity requirements. Thus *V. cholerae* are often associated with drinking-water-borne infections. *V. parahaemolyticus* appears to be less affected by salinity than *V. vulnificus*, with many studies finding weak or absent correlations. On the other hand, although *V. vulnificus* is often limited by salinity, it has also been shown to be more resistant to higher salinities as the temperature increases (Randa *et al.*, 2004; Froelich *et al.*, 2015).

Because these bacteria have such short generation times (replicating in 20 min or even less), they are able to react quickly to rapid changes in environmental conditions such as flooding, freshening and heatwaves. Thus, there is a potential for *Vibrio* blooms following these changes, which would be a significant health risk to those taking recreation in the area as well as consuming seafood harvested near that location.

Infections increasing with a changing climate

Infections with *Vibrio* spp. have been increasing in the U.S. and around the globe, a trend that has been attributed to the warming of the ocean waters and is predicted to be exacerbated by ongoing climate change (Chowdhury *et al.*, 2017; Logar-Henderson *et al.*, 2019). These infections are seasonal, with the majority of cases occurring traditionally between May and October (CDC, 2017). But the '*Vibrio* season' is expanding as warmer temperatures extend into the Fall months. The ideal *Vibrio* spp. growth conditions are in warm (>15°C) seawater with moderate salinity (<25‰). Biweekly data collected from surface water at a sampling site in the Neuse River Estuary in eastern North Carolina, U.S. (Fig. 1) shows that the concentration of *Vibrio* spp. remains above average beyond the normal *Vibrio* season, increasing the risk of infections that may occur by both aquatic exposure and via consumption of contaminated seafood (Froelich *et al.*, 2015).

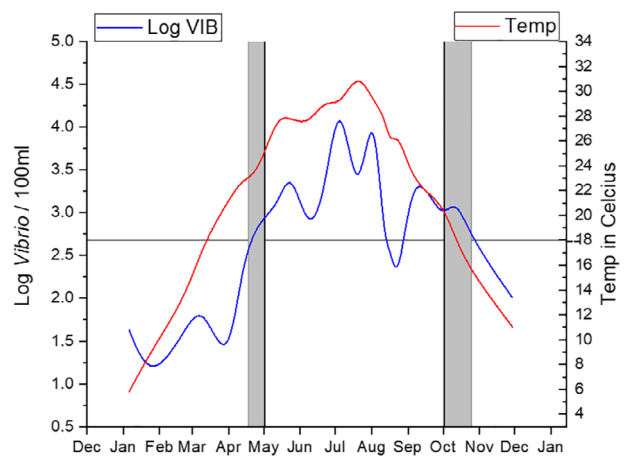


Fig. 1. Log concentration of *Vibrio* (red line, left axis) in the Neuse River Estuary of North Carolina in 2011, compared with water temperature (blue line, right axis). Vertical black lines represent the start and end of '*Vibrio* season', and shaded areas represent the extended period of increased infection risk outside of the traditional period. Horizontal black line is average *Vibrio* concentration.

Additionally, the organism can take advantage of heat waves to appear in higher-latitude areas. For example, in the summer of 2014, there were 89 infections with *Vibrio* spp. in Sweden and Finland, with cases reported within 100 miles of the Arctic Circle (Baker-Austin *et al.*, 2017). This highlights the need for clinicians in northern regions to be aware of possible domestically acquired vibriosis and provides further proof-of-principle that changes in coastal water surface temperature that expands the range of *Vibrio* spp. even temporarily can happen swiftly and have significant public health implications (Chowdhury *et al.*, 2017). Due to their preference for warm, slightly salty water, the brackish water found in estuaries as well as coastal floodwaters provide significant opportunities for *Vibrio* spp. growth. In the U.S., the Gulf coast region states of Texas, Alabama, Florida, Mississippi and Louisiana have had the most reported cases of vibriosis (CDC, 2005). For example, when the floodwaters of Hurricane Rita and Katrina receded in October 2005, the number of pathogenic vibrios (*V. cholerae*, *V. vulnificus* and *V. parahaemolyticus*) in samples taken from both Lake Pontchartrain near-shore sites as well as from canals in New Orleans were highly enriched. Twenty-two cases of *Vibrio*-related illnesses were reported in the 2 weeks following Hurricane Katrina, with five of these resulting in death (Morantz, 2005). As expected for their preferred environmental niche, their numbers decreased in samples with increasing distance from shore (Sinigalliano *et al.*, 2007).

The warming of coastal waters has increased both the temporal range of *Vibrio* spp. as well as heightened the potential for *Vibrio*-human interactions, as when waters

are warmer, people spend more time recreating at the beach. However, when there is increased flooding, non-recreational contact with *Vibrio*-containing waters occurs as well.

The increase in strength and number of named storms, such as hurricanes, nor'easters and tropical storms and cyclones due to elevated climatic energy can also affect *Vibrio* infection risk in a variety of ways. The freshening of coastal systems that result from increased rainfall can extend the boundaries of these pathogens that are normally restricted by fully marine waters (Esteves *et al.*, 2015). Strong winds or storm surge can push the salinity front further upstream than normal, exposing new areas to the non-cholera vibrios, which have a minimal salinity requirement (Fries *et al.*, 2008; Hsieh *et al.*, 2008). Finally, the wind-driven mixing can bring sediments or deeper waters to the surface, potentially exposing those fishing, recreating, or performing rescue operations (Wetz *et al.*, 2008).

The climate crisis is also associated with an impending rise in sea-levels, which will broaden the geographic range of these pathogens. Sea level rise has been called a greater facilitator of a rise in *Vibrio* infection rates than even temperature increases. Predictions of *V. vulnificus* concentrations were modelled by Deeb *et al.* (2018) to the mid-21st century. These investigators reported that in the future, infection risk could be as much as quadruple the current conditions (Deeb *et al.*, 2018).

The El Niño Southern Oscillation was used as a proxy for future climate change, as this climatic event includes changes in sea surface temperature, air temperature, as well as wind and pressure anomalies. An increase in U.S. vibriosis cases is seen with these events and can be expected to double in the year after an El Niño (Logar-Henderson *et al.*, 2019). This indicates that it is not only the high latitude regions of the world that are at risk for increased *Vibrio* concentrations and infections.

Infection trends in the US

The US Centers for Disease Control and Prevention (CDC) administers a system for reporting human infections caused by vibrios, termed the Cholera and Other *Vibrio* Illness Surveillance (COVIS) system. COVIS was initiated in 1988, but *Vibrio* infections only became a nationally reportable disease in 2007. Twenty-one years of reported annual non-cholera infections from 2008 to 2018 are shown in Fig. 2. Infections spike sharply in 2017 and 2018 (Fig. 2), and these increases classify *Vibrio* as an emerging infectious disease pathogen. This is reflected in the data: between 2015 and 2018, the number of *Vibrio* infections diagnosed by culture or culture-independent diagnostic tests increased by 311% in the U.S. (Tack *et al.*, 2019). Though again, these data should

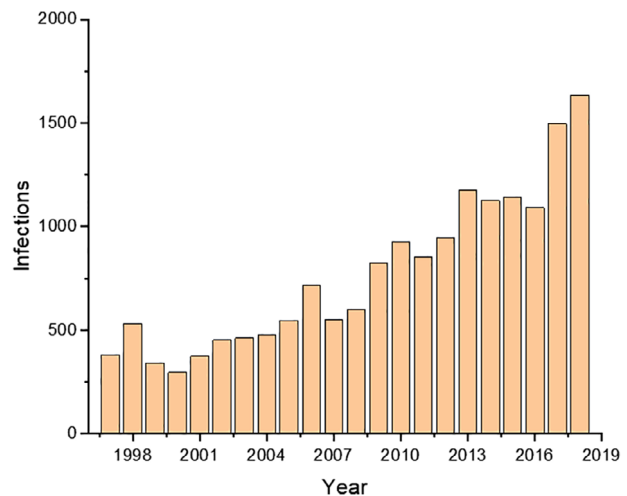


Fig. 2. Annual *Vibrio* (not including toxigenic cholera) infections in the US. Source: Centers for Disease Control (www.data.cdc.gov). [Color figure can be viewed at wileyonlinelibrary.com]

be interpreted with caution as techniques for identifying pathogenic *Vibrio* infections have also improved. Figure 3 shows that the US average annual temperature has been increasing since record-keeping began in 1895, with an average decadal increase of 0.11°F per decade. Furthermore, the 10 years between 2008 and 2018 are well above average (Fig. 3). Figure 3 also shows three extreme temperature spikes occurring between 2000 and 2008, with each being higher than the previous one.

Because only a few of the *Vibrio* infections require medical treatment or hospitalization, many go unreported and the CDC estimates that 80,000 infections occur annually in the United States (Scallan *et al.*, 2011). When the cumulative data is compared for the last 6 years, it is apparent that infections in 2017 were elevated earlier in the year compared with past years, around week 10 (Fig. 4). While in 2018, the increase of infections occurred in the middle of the year, near week 29 and then proceeded to outpace even 2017 numbers. As reported by the Morbidity and Mortality weekly report (CDC, 2019), 2018 exhibited an increase of *Vibrio* incidence by 109% and number of diagnosed infections by 311%, as compared to 2015–2017. It is too early to report if 2019 will be on par with the last 2 years (Fig. 4). These increases have been reported to be primarily driven by increases in *V. parahaemolyticus* infections (Newton *et al.*, 2012). July 2018 was 1.9°F above the 20th-century average, while August was 1.5°F higher than this average. These elevated temperatures likely contributed to the sharp increase in *Vibrio* infections during this period. In 2017, the annual average US temperature was 2.5°F above the 20th-century average and was the third warmest year since record-keeping began. In March 2017, when *Vibrio* cases displayed an earlier than normal

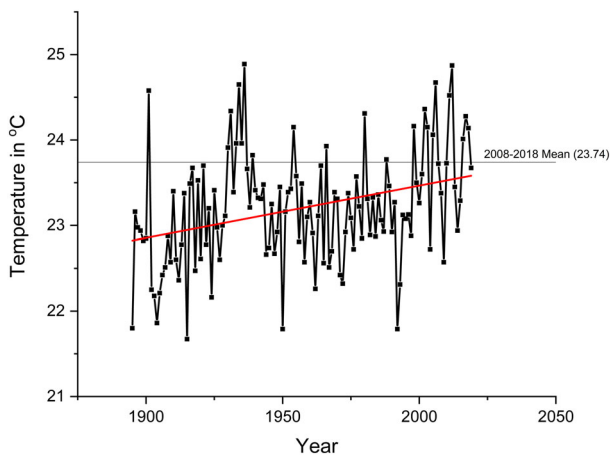


Fig. 3. U.S. average July air temperature (black line with square points) from 1895 to 2019. The decadal mean from 2008–2018 is shown with the black horizontal line, and the overall trend is depicted in red. Data obtained from NOAA National Centers for Environmental Information Climate at a Glance: National Time Series, published December 2019, retrieved on December 28, 2019 from <https://www.ncdc.noaa.gov/cag/>.

increase, the average US temperature was 4.7°F above the 20th-century average. This early warmth likely contributed to the early onset of cases occurring in that year (NOAA, 2017).

Vibrio vulnificus infections are on the rise in the US, with much of this increase being due to wound infections (Newton *et al.*, 2012; Baker-Austin and Oliver, 2018). There was a reported 78% increase of infections between 1996 and 2006, and a 272% increase between 2008 and 2018 (Fig. 2), although the increase from the 1990s to 2006 must be interpreted with caution as *Vibrio* infections were not required to be reported to the CDC

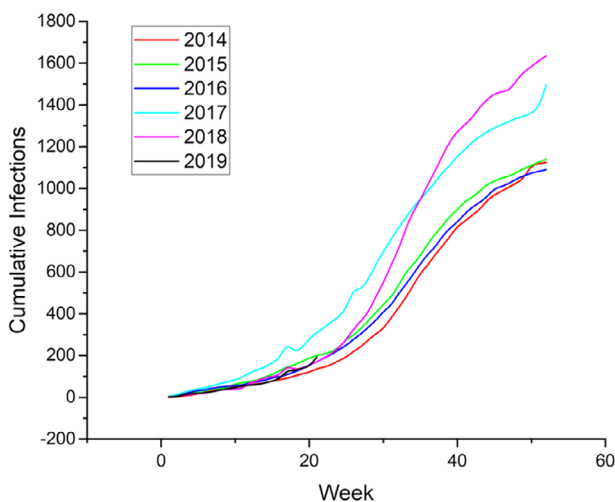


Fig. 4. Cumulative *Vibrio* (excluding toxigenic cholera) infections in the US by week. Year 2019 (black line) is limited by currently available data. Source: Centers for Disease Control (www.data.cdc.gov).

until 2007. *V. vulnificus* infections related to shellfish ingestion are on the rise as well, although this is in part due to increased production and consumption. Controls are being enacted to prevent these. For example, the fishery located in Apalachicola Bay, FL, U.S. had the daily harvest period for un-refrigerated harvest boats reduced by 4 h to address the risk of pathogen replication in contaminated shellfish (Alvarez *et al.*, 2019).

A map of infections by U.S. state in 2013 and 2018 is shown in Fig. 5. From these maps, it is apparent that infections have increased nationally, but the various regions of the U.S. have not been increasing at the same rate. The Atlantic and Gulf Coast regions only had marginal increases, with much of the Atlantic increases occurring in the South Atlantic offset by a reduced number of Northeast infections in 2018 compared to 2013 (Figs 5 and 6). The greatest increases have occurred in the Pacific and, interestingly, in the non-coastal states (Figs 5 and 6). Infections in non-coastal states have more than doubled between these 2 years, and the Pacific region now harbours the greatest number of U.S. infections (Fig. 6). In 2018, the Pacific and Atlantic regions showed far greater than normal average temperatures, while much of the non-coastal states exhibited little or slight deviations from normal. Both the Pacific and South Atlantic regions had annual temperatures that were approaching records (Fig. 7). The high-temperature extremes are likely driving much of the *Vibrio* infection increases seen in coastal states between these periods, while the moderate increases in non-coastal state infections could have been due to either generally warmer temperatures or from the importation and consumption of coastal shellfish.

Vibrio parahaemolyticus has been the causative agent of several U.S. outbreaks recently. The most notable began in 2012, in the U.S. Pacific Northwest (PNW) region. Two serotypes of *V. parahaemolyticus* that had previously caused PNW outbreaks in 1997 and 2004 (McLaughlin *et al.*, 2005; Turner *et al.*, 2013) were subsequently reported on the U.S. Atlantic Coast (Newton *et al.*, 2014; Martinez-Urtaza *et al.*, 2016). *V. parahaemolyticus* with identical genotypes were then eventually isolated on the coast of Spain as well and were responsible for hundreds of illnesses (Martinez-Urtaza *et al.*, 2016).

Current treatments

Treatment for *Vibrio* infections depends upon the pathogen. For toxigenic *V. cholerae*, the standard of care is oral rehydration therapy (ORT), consisting of sodium, chloride, potassium and glucose in water, combined with an appropriate oral antibiotic, such as doxycycline, azithromycin or tetracycline. Antibiotic resistance in *V.*

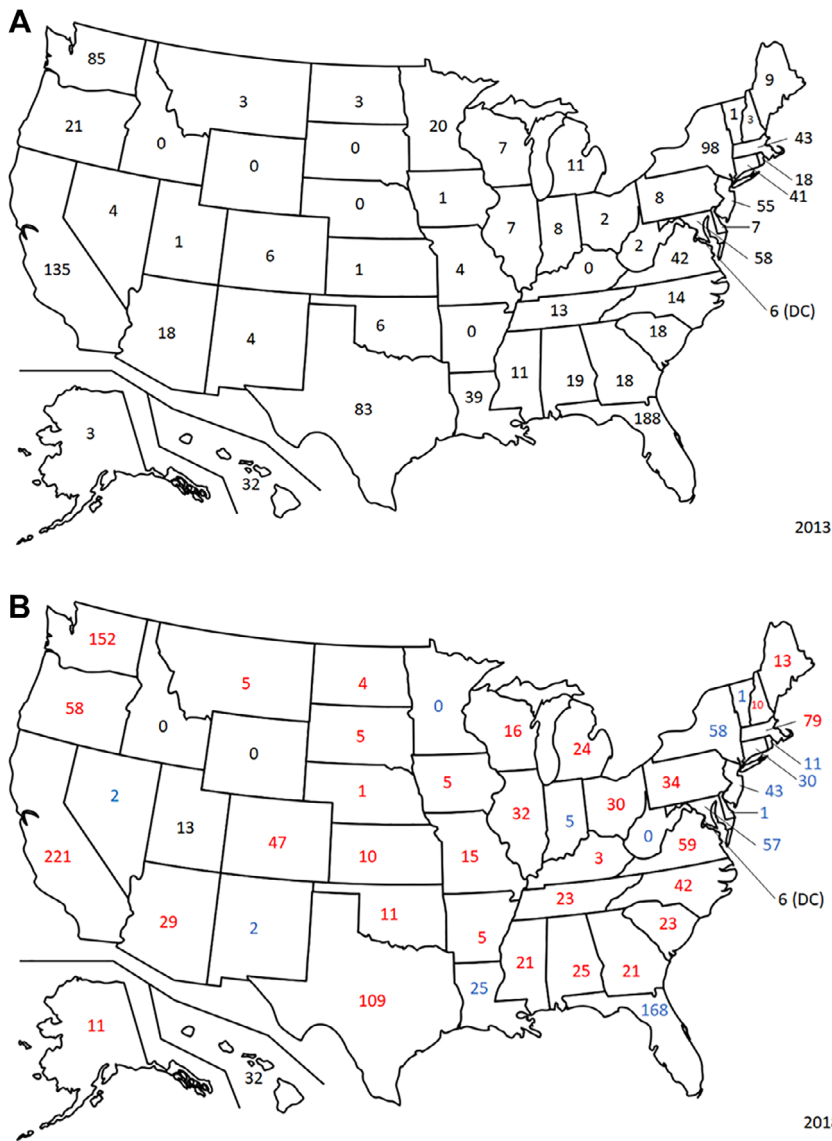


Fig. 5. Number of infections by U.S. state for 2013 (A) and 2018 (B). Red and blue numbers in states on B represent increases or decreases from 2013 respectively. Black numbers indicate no change.

cholerae has been increasing in recent years and is associated with the acquisition of mobile genetic elements, the uptake of which is facilitated by its remarkable competence (Das *et al.*, 2019). If dehydration is severe, intravenous fluids are provided, and if the patient is under the age of five, zinc is also given as an adjunctive therapy (Hsueh and Waters, 2019). ORT is both safe and effective, and its use has decreased the fatality rate of cholera by 97%, but it is not always readily available in some areas (Hsueh and Waters, 2019). Vaccination is recommended for emergency or humanitarian workers in direct contact with cholera patients (Varo *et al.*, 2019). There are currently three oral cholera vaccines that are licensed by the World Health Organization and available for global use: Dukoral, Shanchol and Euvichol (Burnett *et al.*, 2019). All require two doses with a 2-week delay

between doses for full protection for up to 3 years, although a single dose can provide short-term protection (Odeval *et al.*, 2018). As well, while each includes killed whole cells of *V. cholerae*, Shanchol is the first low-cost oral vaccine prequalified by the World Health Organization for international use (Hsiao *et al.*, 2017). However, since all require a cold chain for stockpiling and distribution, their usefulness may be limited in resource-poor countries (Martin *et al.*, 2014).

There is currently no approved vaccine available against *V. vulnificus*. Therefore, approaches for *V. vulnificus* wound infections include antibiotics such as quinolones and tetracyclines as well as early debridement of dead tissues and necessary amputations in cases of necrotizing fasciitis (Leng *et al.*, 2019). These rapidly progressing tissue infections can lead to hypotension, shock and multiple

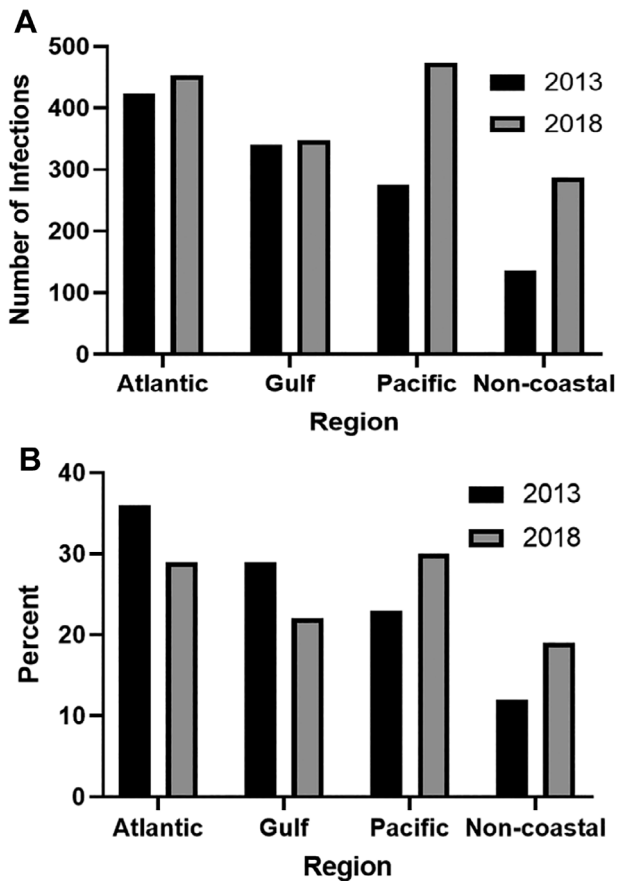


Fig. 6. Number of infections (A) and per cent of total U.S. infections (B) by region in 2013 (black bars) and 2018 (grey bars).

organ failure, resulting in a 50% fatality rate within 48 h (Bhat *et al.*, 2019). In addition, *V. vulnificus* gastroenteritis acquired by eating contaminated raw or undercooked shellfish can allow the pathogen to access the bloodstream, causing septic shock (Jones and Oliver, 2009). A study of the antibiotic resistance profiles of *V. vulnificus* and *V. parahaemolyticus* isolated from oysters revealed higher rates of resistance to single and multiple antibiotics in *V. vulnificus*, with 48% resistant to two or more, although both showed resistance to some antimicrobials used to treat *Vibrio* infections (Elmahdi *et al.*, 2018). One alternative approach that was investigated recently involved treating experimental *V. vulnificus* infections with antimicrobial peptides *in vivo*. At least one of these peptides was shown to provide protection when conjugated to a gold nanoparticle-DNA aptamer and introduced intravenously in mice (Lee *et al.*, 2017). An added benefit of this tactic is that these peptides are unlikely to contribute to increased antimicrobial resistance.

Vibrio parahaemolyticus is the leading bacterial cause of seafood-borne acute gastroenteritis in humans, although this pathogen can also cause cutaneous wound

infections, and the development of sepsis is not rare (Guillod *et al.*, 2019). Since no vaccine has been approved for use, treatment is centred on antimicrobials (Wang *et al.*, 2019). However, many clinical isolates have been found to be resistant to multiple antibiotics, which can further complicate both treatment and convalescence (Li *et al.*, 2019). A recent report of the success of *V. parahaemolyticus*-infected oysters being decontaminated by the application of a specific lytic bacteriophage could potentially provide another avenue for both increased food safety as well as the treatment of diseases caused by this pathogen in the future (Zhang *et al.*, 2018).

Concluding remarks

Global warming leading to a significant rise in planetary ocean temperatures seems unavoidable at this point, and most of the 220 coastal countries and territories of the world have identified a negative cumulative impact of increased anthropogenic stressors on their coastal waters, including fishing, climate change and land-based pressures (Halpern *et al.*, 2019; IPCC, 2019). The overall expansion of *Vibrio*-human interactions, both recreational and non-recreational, will be facilitated by this global change and likely result in an escalation of infections. Likewise, the potential exists that since these infections would increase the contact between pathogenic vibrios and the human microbiome, the movement of mobile genetic elements between microorganisms may be accelerated and could result in enhancing their antimicrobial resistance capability. Besides being more aware of the potential hazards, there are a number of prudent actions that can be taken to decrease the risk of vibriosis. First, limit exposure to possible *Vibrio*-containing waters and ensure that drinking water has been treated and seafood has been properly cooked. This is even more important for the very young, the elderly or those who are immunocompromised by either comorbidities or chemotherapy for other conditions, such as immunosuppressants taken by transplant recipients. For raw seafood products, such as oysters, increased support for research and development of technologies that reduce harmful bacteria without alteration of the product is recommended. In addition, foot protection such as surf shoes should be worn when wading in coastal waters or walking on the beach to avoid cuts or scrapes from rocks and shells that could potentially increase cutaneous exposure to pathogenic vibrios. If contact with coastal floodwaters or brackish water is unavoidable, personal protective equipment such as rubber boots and gloves should be worn, and the handling of raw seafood with cuts or scrapes should be avoided. Utilization of proper hand hygiene after coming into contact with floodwaters or any untreated water (including during a day at the beach) prior to eating is a

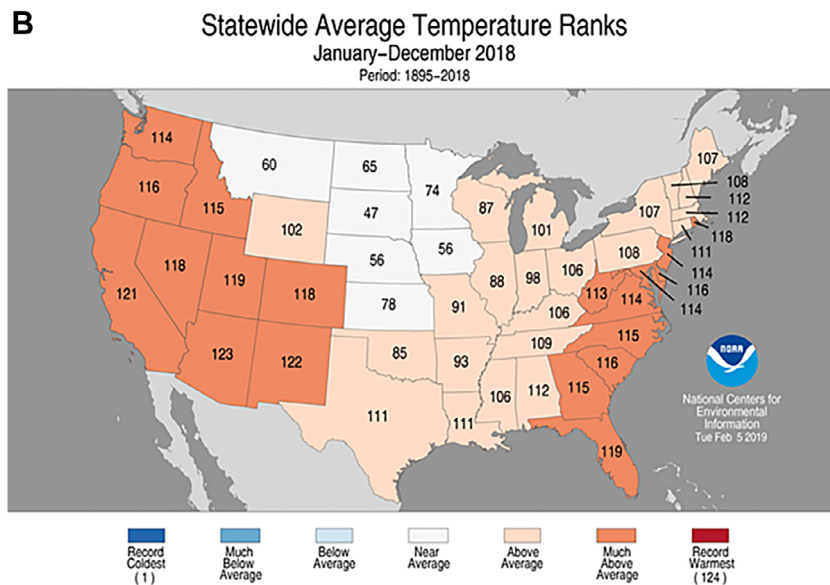
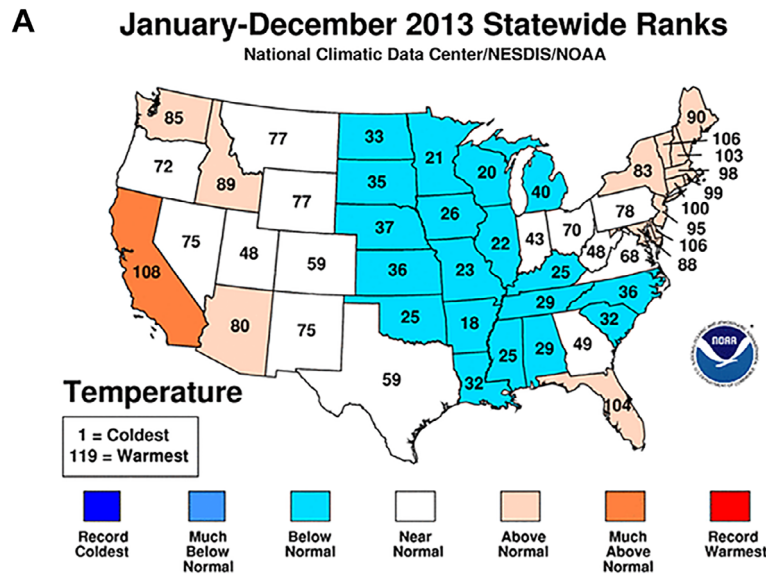


Fig. 7. Ranking, by state, of annual average temperature for 2013 (A) and 2018 (B). A rank of 1 would represent the coldest year on record, and a rank of 119 or 124 would represent the highest temperature on record for 2013 and 2018 respectively. States are colour coded to indicate temperatures above or below normal. Data obtained from NOAA National Centers for Environmental Information, State of the Climate: National Climate Report for Annual 2013 and 2018 from <https://www.nccdc.noaa.gov/sotc/national/201813>.

sensible choice. Finally, education regarding the potential risks, mitigation strategies and the importance of seeking medical attention for any tissue redness and swelling following contact with potential *Vibrio*-containing water is important. These efforts should be aimed at seafood consumers, especially those who are part of the at-risk population, commercial or recreational fishermen, aquaculturists, beach-goers and people who live in coastal areas that are affected by storms or floods. While none of these practices will guarantee protection from possible vibriosis, informed avoidance may be the best approach to maintain health.

Acknowledgements

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References

- Almagro-Moreno, S., and Taylor, R.K. (2013) Cholera: environmental reservoirs and impact on disease transmission. *Microbiol Spectr* **1**: 1–12.
- Alvarez, S., Solis, D., and Hwang, J. (2019) Modeling shellfish harvest policies for food safety: wild oyster harvest restrictions to prevent foodborne *Vibrio vulnificus*. *Food Policy* **83**: 219–230.
- Baker-Austin, C., and Oliver, J.D. (2018) *Vibrio vulnificus*: new insights into a deadly opportunistic pathogen. *Environ Microbiol* **20**: 423–430.
- Baker-Austin, C., Trinanen, J.A., Taylor, N.G.H., Hartnell, R., Siitonen, A., and Martinez-Urtaza, J. (2016) Emerging

- Vibrio* risk at high latitudes in response to ocean warming (vol 3, pg 73, 2013). *Nature Climate Change* **6**: 802.
- Baker-Austin, C., Trinanés, J., Gonzalez-Escalona, N., and Martínez-Urtaza, J. (2017) Non-cholera Vibrios: the microbial barometer of climate change. *Trends Microbiol* **25**: 76–84.
- Bergey, D.H., and Holt, J.G. (1994) *Bergey's manual of determinative bacteriology*. Baltimore: Williams & Wilkins.
- Bhat, P., Bhaskar, M., Sistla, S., and Kadiravan, T. (2019) Fatal case of necrotising fasciitis due to *Vibrio vulnificus* in a patient with alcoholic liver disease and diabetes mellitus. *BMJ Case Rep* **12**: 1–4.
- Bonnin-Jusserand, M., Copin, S., Le Bris, C., Brauge, T., Gay, M., Brisabois, A., et al. (2019) *Vibrio* species involved in seafood-borne outbreaks (*Vibrio cholerae*, *V. parahaemolyticus* and *V. vulnificus*): review of microbiological versus recent molecular detection methods in seafood products. *Crit Rev Food Sci Nutr* **59**: 597–610.
- Burnett, E.M., Francois, J., Sreenivasan, N., Wannemuehler, K., Faye, P.C., Tohme, R.A., et al. (2019) Oral cholera vaccination coverage after the first global stockpile deployment in Haiti, 2014. *Vaccine* **37**: 6348–6355.
- Carda-Dieguez, M., Silva-Hernandez, F.X., Hubbard, T.P., Chao, M.C., Waldor, M.K., and Amaro, C. (2018) Comprehensive identification of *Vibrio vulnificus* genes required for growth in human serum. *Virulence* **9**: 981–993.
- CDC. (2005) *Vibrio* illnesses after hurricane Katrina—multiple states, August–September 2005. *MMWR Morb Mortal Wkly Rep* **54**: 928–931.
- CDC. (2006) *Vibrio parahaemolyticus* infections associated with consumption of raw shellfish—three states, 2006. *MMWR Morb Mortal Wkly Rep* **55**: 854–856.
- CDC. (2017). *Vibrio vulnificus* infections and disasters. Available from <https://www.cdc.gov/disasters/vibriovulnificus.html>.
- CDC. (2018). *Vibrio parahaemolyticus* Infections Linked to Fresh Crab Meat Imported from Venezuela (Final Update). Available from <https://www.cdc.gov/vibrio/investigations/vibriop-07-18/index.html>.
- CDC. (2019). National Notifiable Diseases Surveillance System. Available from <https://www.cdc.gov/nndss/conditions/notifiable/2019/>.
- Chowdhury, G., Joshi, S., Bhattacharya, S., Sekar, U., Birajdar, B., Bhattacharyya, A., et al. (2016) Extraintestinal infections caused by non-toxigenic *Vibrio cholerae* non-O1/non-O139. *Front Microbiol* **7**: 144.
- Chowdhury, F.R., Nur, Z., Hassan, N., von Seidlein, L., and Dunachie, S. (2017) Pandemics, pathogenicity and changing molecular epidemiology of cholera in the era of global warming. *Ann Clin Microbiol Antimicrob* **16**: 10.
- Chowdhury, G., Ramamurthy, T., Ghosh, A., Dutta, S., Takahashi, E., and Mukhopadhyay, A.K. (2019) Emergence of azithromycin resistance mediated by phosphotransferase-encoding mph(a) in Diarrheagenic *Vibrio fluvialis*. *mSphere* **4**: 1–8.
- Coutinho, F.H., Thompson, C.C., Cabral, A.S., Paranhos, R., Dutilh, B.E., and Thompson, F.L. (2019) Modelling the influence of environmental parameters over marine planktonic microbial communities using artificial neural networks. *Sci Total Environ* **677**: 205–214.
- Das, B., Verma, J., Kumar, P., Ghosh, A., and Ramamurthy, T. (2019) Antibiotic resistance in *Vibrio cholerae*: understanding the ecology of resistance genes and mechanisms. *Vaccine* **38**: A83–A92.
- Deeb, R., Tufford, D., Scott, G.I., Moore, J.G., and Dow, K. (2018) Impact of climate change on *Vibrio vulnificus* abundance and exposure risk. *Estuaries Coast* **41**: 2289–2303.
- Duong-Nu, T.M., Jeong, K., Hong, S.H., Puth, S., Kim, S.Y., Tan, W., et al. (2019) A stealth adhesion factor contributes to *Vibrio vulnificus* pathogenicity: Flp pili play roles in host invasion, survival in the blood stream and resistance to complement activation. *PLoS Pathog* **15**: e1007767.
- Elmahdi, S., Parveen, S., Ossai, S., DaSilva, L.V., Jahncke, M., Bowers, J., and Jacobs, J. (2018) *Vibrio parahaemolyticus* and *Vibrio vulnificus* recovered from oysters during an oyster relay study. *Appl Environ Microbiol* **84**: 1–13.
- Esteves, K., Hervio-Heath, D., Mosser, T., Rodier, C., Toumoud, M.G., Jumas-Bilak, E., et al. (2015) Rapid proliferation of *Vibrio parahaemolyticus*, *Vibrio vulnificus*, and *Vibrio cholerae* during freshwater flash floods in French Mediterranean coastal lagoons. *Appl Environ Microbiol* **81**: 7600–7609.
- FAO/WHO. (2005) *Risk Assessment of Vibrio vulnificus in Raw Oysters: Interpretative Summary and Technical Report. Microbiological Risk Assessment Series No. 8*. Rome: FAO/WHO.
- Fries, J.S., Characklis, G.W., and Noble, R.T. (2008) Sediment-water exchange of *Vibrio* sp. and fecal indicator bacteria: implications for persistence and transport in the Neuse River estuary, North Carolina, USA. *Water Res* **42**: 941–950.
- Froelich, B., Bowen, J., Gonzalez, R., Snedeker, A., and Noble, R. (2013) Mechanistic and statistical models of total *Vibrio* abundance in the Neuse River estuary. *Water Res* **47**: 5783–5793.
- Froelich, B.A., Ayrapetyan, M., Fowler, P., Oliver, J.D., and Noble, R.T. (2015) Development of a matrix tool for the prediction of *Vibrio* species in oysters harvested from North Carolina. *Appl Environ Microbiol* **81**: 1111–1119.
- Froelich, B., Gonzalez, R., Blackwood, D., Lauer, K., and Noble, R. (2019) Decadal monitoring reveals an increase in *Vibrio* spp. concentrations in the Neuse River estuary, North Carolina, USA. *PLoS One* **14**: e0215254.
- Gao, X., Pi, D., Chen, N., Li, X., Liu, X., Yang, H., et al. (2018) Survival, virulent characteristics, and transcriptomic analyses of the pathogenic *Vibrio anguillarum* under starvation stress. *Front Cell Infect Microbiol* **8**: 389.
- Green, T.J., Siboni, N., King, W.L., Labbate, M., Seymour, J. R., and Raftos, D. (2019) Simulated marine heat wave alters abundance and structure of *Vibrio* populations associated with the Pacific oyster resulting in a mass mortality event. *Microb Ecol* **77**: 736–747.
- Griffitt, K.J., and Grimes, D.J. (2013) Abundance and distribution of *Vibrio cholerae*, *V. parahaemolyticus*, and *V. vulnificus* following a major freshwater intrusion into the Mississippi sound. *Microb Ecol* **65**: 578–583.
- Guanhua, Y., Wang, C., Wang, X., Ma, R., Zheng, H., Liu, Q., et al. (2018) Complete genome sequence of the marine fish pathogen *Vibrio anguillarum* and genome-wide transposon mutagenesis analysis of genes essential for *in vivo* infection. *Microbiol Res* **216**: 97–107.

- Guilloid, C., Ghitti, F., and Mainetti, C. (2019) *Vibrio parahaemolyticus* induced cellulitis and septic shock after a Sea Beach holiday in a patient with leg ulcers. *Case Rep Dermatol Switzerland* **11**: 94–100.
- Halpern, B.S., Frazier, M., Afflerbach, J., Lowndes, J.S., Micheli, F., O'Hara, C., et al. (2019) Recent pace of change in human impact on the world's ocean. *Sci Rep* **9**: 11609.
- He, R., Zheng, W., Long, J., Huang, Y., Liu, C., Wang, Q., et al. (2019) *Vibrio vulnificus* meningoencephalitis in a patient with thalassemia and a splenectomy. *J Neurovirol* **25**: 127–132.
- Hsiao, A., Desai, S.N., Mogasale, V., Excler, J.L., and Digilio, L. (2017) Lessons learnt from 12 oral cholera vaccine campaigns in resource-poor settings. *Bull World Health Organ* **95**: 303–312.
- Hsieh, J.L., Fries, J.S., and Noble, R.T. (2008) Dynamics and predictive modelling of *Vibrio* spp. in the Neuse River estuary, North Carolina, USA. *Environ Microbiol* **10**: 57–64.
- Hsueh, B.Y., and Waters, C.M. (2019) Combating Cholera. *F1000Res* **8**: 1–8.
- IPCC. (2019) *The Special Report on the Ocean and Cryosphere in a Changing Climate*. Geneva: Intergovernmental Panel on Climate Change (IPCC), pp. 1–44.
- Jacobs Slifka, K.M., Newton, A.E., and Mahon, B.E. (2017) *Vibrio alginolyticus* infections in the USA, 1988–2012. *Epidemiol Infect* **145**: 1491–1499.
- Jones, M.K., and Oliver, J.D. (2009) *Vibrio vulnificus*: disease and pathogenesis. *Infect Immun* **77**: 1723–1733.
- Jung, Y.C., Lee, M.A., and Lee, K.H. (2019) Role of Flagellin-homologous proteins in biofilm formation by pathogenic. *MBio* **10**: e01793-19.
- Kaper, J.B., Morris, J.G., Jr., and Levine, M.M. (1995) Cholera. *Clin Microbiol Rev* **8**: 48–86.
- Kaspar, C.W., and Tamplin, M.L. (1993) Effects of temperature and salinity on the survival of *Vibrio vulnificus* in seawater and shellfish. *Appl Environ Microbiol* **59**: 2425–2429.
- Kelly, M.T. (1982) Effect of temperature and salinity on *Vibrio (Beneckeia) vulnificus* occurrence in a Gulf Coast environment. *Appl Environ Microbiol* **44**: 820–824.
- Lee, B., Park, J., Ryu, M., Kim, S., Joo, M., Yeom, J.H., et al. (2017) Antimicrobial peptide-loaded gold nanoparticle-DNA aptamer conjugates as highly effective antibacterial therapeutics against *Vibrio vulnificus*. *Sci Rep* **7**: 13572.
- Leng, F., Lin, S., Wu, W., Zhang, J., Song, J., and Zhong, M. (2019) Epidemiology, pathogenetic mechanism, clinical characteristics, and treatment of *Vibrio vulnificus* infection: a case report and literature review. *Eur J Clin Microbiol Infect Dis* **38**: 1999–2004.
- Li, L., Meng, H., Gu, D., Li, Y., and Jia, M. (2019) Molecular mechanisms of *Vibrio parahaemolyticus* pathogenesis. *Microbiol Res* **222**: 43–51.
- Liang, J., Liu, J., Wang, X., Lin, H., Liu, J., Zhou, S., et al. (2019) Spatiotemporal dynamics of free-living and particle-associated *Vibrio* communities in the northern Chinese marginal seas. *Appl Environ Microbiol* **85**: e00217-19.
- Logar-Henderson, C., Ling, R., Tuite, A.R., and Fisman, D.N. (2019) Effects of large-scale oceanic phenomena on non-cholera vibriosis incidence in the United States: implications for climate change. *Epidemiol Infect* **147**: e243.
- Martin, S., Lopez, A.L., Bellos, A., Deen, J., Ali, M., Alberti, K., et al. (2014) Post-licensure deployment of oral cholera vaccines: a systematic review. *Bull World Health Organ* **92**: 881–893.
- Martinez-Urtaza, J., Bowers, J.C., Trinanes, J., and DePaola, A. (2010) Climate anomalies and the increasing risk of *Vibrio parahaemolyticus* and *Vibrio vulnificus* illnesses. *Food Res Int* **43**: 1780–1790.
- Martinez-Urtaza, J., Powell, A., Jansa, J., Rey, J.L., Montero, O.P., Campello, M.G., et al. (2016) Epidemiological investigation of a foodborne outbreak in Spain associated with U.S. west coast genotypes of *Vibrio parahaemolyticus*. *Springerplus* **5**: 87.
- Matlawska-Wasowska, K., Finn, R., Mustel, A., O'Byrne, C. P., Baird, A.W., Coffey, E.T., and Boyd, A. (2010) The *Vibrio parahaemolyticus* type III secretion systems manipulate host cell MAPK for critical steps in pathogenesis. *BMC Microbiol* **10**: 329.
- McLaughlin, J.B., DePaola, A., Bopp, C.A., Martinek, K.A., Napoliilli, N.P., Allison, C.G., et al. (2005) Outbreak of *Vibrio parahaemolyticus* gastroenteritis associated with Alaskan oysters. *N Engl J Med* **353**: 1463–1470.
- Miles, D.W., Ross, T., Olley, J., and McMeekin, T.A. (1997) Development and evaluation of a predictive model for the effect of temperature and water activity on the growth rate of *Vibrio parahaemolyticus*. *Int J Food Microbiol* **38**: 133–142.
- Miller, K.A., Tomberlin, K.F., and Dziejman, M. (2019) *Vibrio* variations on a type three theme. *Curr Opin Microbiol* **47**: 66–73.
- Morantz, C.A. (2005) CDC reports on illnesses in hurricane Katrina evacuees and relief workers. *Am Fam Physician* **10**: 2126–2134.
- Nelson, E.J., Harris, J.B., Morris, J.G., Jr., Calderwood, S.B., and Camilli, A. (2009) Cholera transmission: the host, pathogen and bacteriophage dynamic. *Nat Rev Microbiol* **7**: 693–702.
- Newton, A., Kendall, M., Vugia, D.J., Henao, O.L., and Mahon, B.E. (2012) Increasing rates of vibriosis in the United States, 1996–2010: review of surveillance data from 2 systems. *Clin Infect Dis* **54**: S391–S395.
- Newton, A.E., Garrett, N., Stroika, S.G., Halpin, J.L., Tumsek, M., Mody, R.K., and C. Centers for Disease and Prevention. (2014) Increase in *Vibrio parahaemolyticus* infections associated with consumption of Atlantic Coast shellfish—2013. *MMWR Morb Mortal Wkly Rep* **63**: 335–336.
- Nigro, O.D., Hou, A., Vithanage, G., Fujioka, R.S., and Steward, G.F. (2011) Temporal and spatial variability in culturable pathogenic *Vibrio* spp. in Lake Pontchartrain, Louisiana, following hurricanes Katrina and Rita. *Appl Environ Microbiol* **77**: 5384–5393.
- NOAA. (2017). National Climate Report—March 2017. Available from <https://www.ncdc.noaa.gov/sotc/national/201703>. Accessed January 06, 2020.
- Odevall, L., Hong, D., Digilio, L., Sahastrabudde, S., Mogasale, V., Baik, Y., et al. (2018) The Euvichol story—development and licensure of a safe, effective and affordable oral cholera vaccine through global public private partnerships. *Vaccine* **36**: 6606–6614.

- Penland, R.L., Boniuk, M., and Wilhelmus, K.R. (2000) *Vibrio* ocular infections on the U.S. Gulf Coast. *Cornea* **19**: 26–29.
- Randa, M.A., Polz, M.F., and Lim, E. (2004) Effects of temperature and salinity on *Vibrio vulnificus* population dynamics as assessed by quantitative PCR. *Appl Environ Microbiol* **70**: 5469–5476.
- Scallan, E., Hoekstra, R.M., Angulo, F.J., Tauxe, R.V., Widdowson, M.A., Roy, S.L., *et al.* (2011) Foodborne illness acquired in the United States—major pathogens. *Emerg Infect Dis* **17**: 7–15.
- Sedas, V.T. (2007) Influence of environmental factors on the presence of *Vibrio cholerae* in the marine environment: a climate link. *J Infect Dev Ctries* **1**: 224–241.
- Sinatra, J.A., and Colby, K. (2018) Notes from the field: fatal *Vibrio anguillarum* infection in an immunocompromised patient - Maine, 2017. *MMWR Morb Mortal Wkly Rep* **67**: 962–963.
- Sinigalliano, C.D., Gidley, M.L., Shibata, T., Whitman, D., Dixon, T.H., Laws, E., *et al.* (2007) Impacts of hurricanes Katrina and Rita on the microbial landscape of the New Orleans area. *Proc Natl Acad Sci USA* **104**: 9029–9034.
- Tack, D.M., Marder, E.P., Griffin, P.M., Cieslak, P.R., Dunn, J., Hurd, S., *et al.* (2019) Preliminary incidence and trends of infections with pathogens transmitted commonly through food—foodborne diseases active surveillance network, 10 U.S. sites, 2015–2018. *MMWR Morb Mortal Wkly Rep* **68**: 369–373.
- Takemura, A.F., Chien, D.M., and Polz, M.F. (2014) Associations and dynamics of *Vibrionaceae* in the environment, from the genus to the population level. *Front Microbiol* **5**: 38.
- Tam, V.C., Serruto, D., Dziejman, M., Briehner, W., and Mekalanos, J.J. (2007) A type III secretion system in *Vibrio cholerae* translocates a formin/spire hybrid-like Actin nucleator to promote intestinal colonization. *Cell Host Microbe* **1**: 95–107.
- Turner, J.W., Paranjpye, R.N., Landis, E.D., Biryukov, S.V., Gonzalez-Escalona, N., Nilsson, W.B., and Strom, M.S. (2013) Population structure of clinical and environmental *Vibrio parahaemolyticus* from the Pacific northwest coast of the United States. *PLoS One* **8**: e55726.
- Ulitzur, S. (1974) *Vibrio parahaemolyticus* and *Vibrio alginolyticus*: short generation-time marine bacteria. *Microb Ecol* **1**: 127–135.
- Varo, R., Rodo, X., and Bassat, Q. (2019) Climate change, cyclones and cholera - implications for travel medicine and infectious diseases. *Travel Med Infect Dis* **29**: 6–7.
- Vezzulli, L., Grande, C., Reid, P.C., Helaouet, P., Edwards, M., Hofle, M.G., *et al.* (2016) Climate influence on *Vibrio* and associated human diseases during the past half-century in the coastal North Atlantic. *Proc Natl Acad Sci USA* **113**: E5062–E5071.
- Wang, S., Zhang, Z., Malakar, P.K., Pan, Y., and Zhao, Y. (2019) The fate of bacteria in human digestive fluids: a new perspective into the pathogenesis of *Vibrio parahaemolyticus*. *Front Microbiol* **10**: 1614.
- Wetz, J.J., Blackwood, A.D., Fries, J.S., Williams, Z.F., and Noble, R.T. (2008) Trends in total *Vibrio* spp. and *Vibrio vulnificus* concentrations in the eutrophic Neuse River estuary, North Carolina, during storm events. *Aquat Microb Ecol* **53**: 141–149.
- Yamazaki, K., Kashimoto, T., Morita, M., Kado, T., Matsuda, K., Yamasaki, M., and Ueno, S. (2019) Identification of *in vivo* essential genes of *Vibrio vulnificus* for establishment of wound infection by signature-tagged mutagenesis. *Front Microbiol* **10**: 123.
- Yang, C., Zhang, X., Fan, H., Li, Y., Hu, Q., Yang, R., and Cui, Y. (2019) Genetic diversity, virulence factors and farm-to-table spread pattern of *Vibrio parahaemolyticus* food-associated isolates. *Food Microbiol* **84**: 103270.
- Yildiz, F.H., and Visick, K.L. (2009) *Vibrio* biofilms: so much the same yet so different. *Trends Microbiol* **17**: 109–118.
- Zeb, S., Shah, M.A., Yasir, M., Awan, H.M., Prommeenate, P., Klanchui, A., *et al.* (2019) Type III secretion system confers enhanced virulence in clinical non-O1/non-O139 *Vibrio cholerae*. *Microb Pathog* **135**: 103645.
- Zhang, H., Yang, Z., Zhou, Y., Bao, H., Wang, R., Li, T., *et al.* (2018) Application of a phage in decontaminating *Vibrio parahaemolyticus* in oysters. *Int J Food Microbiol* **275**: 24–31.