The Role of Gulf Coast Oysters Harvested in Warmer Months in *Vibrio vulnificus* Infections in the United States, 1988–1996

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***Vibrio vulnificus* infections are highly lethal and associated with consumption of raw shellfish and exposure of wounds to seawater. *V. vulnificus* infections were reported to the Centers for Disease Control and Prevention from 23 states. For primary septicemia infections, oyster trace-backs were performed and water temperature data obtained at harvesting sites. Between 1988 and 1996, 422 infections were reported; 45% were wound infections, 43% primary septicemia, 5% gastroenteritis, and 7% from undetermined exposure. Eighty-six percent of patients were male, and 96% with primary septicemia consumed raw oysters. Sixty-one percent with primary septicemia died; underlying liver disease was associated with fatal outcome. All trace-backs with complete information implicated oysters harvested in the Gulf of Mexico; 89% were harvested in water >22°C, the mean annual temperature at the harvesting sites ($P < .0001$). Control measures should focus on the increased risk from oysters harvested from the Gulf of Mexico during warm months as well as education about host susceptibility factors.**

Vibrio vulnificus is a gram-negative, halophilic bacterium that inhabits marine and estuarine environments and causes three syndromes of clinical illness in humans: gastroenteritis, wound infections, and primary septicemia [1]. Although gastroenteritis is self-limited and rarely reported, wound infections and primary septicemia are highly lethal conditions that occur most often among persons with liver disease or other immunocompromising conditions [2–4]. Primary septicemia with *V. vulnificus* is usually associated with the consumption of raw oysters; it is probably the leading cause of seafood-associated fatalities in the United States.

Since its first recognition as a pathogen in the 1970s [2, 5], much has been learned about the effects of bacterial virulence, host factors, and environmental conditions in the epidemiology of *V. vulnificus* infections. Vibrios proliferate in warm water [6, 7], and infections occur more commonly in warmer months [4, 8]; however, the harvest site temperatures of oysters traced to infections have not previously been studied, and a safe harvesting temperature has not been defined.

Here we summarize data from the Centers for Disease Control and Prevention (CDC) Gulf Coast Surveillance System, which has collected epidemiologic and clinical information about *V. vulnificus* infections in Florida, Alabama, Louisiana, and Texas since 1988. To assess the contribution of environmental factors in the epidemiology of *V. vulnificus* infections, we also studied the association between reported infections and water temperature at oyster harvesting sites. The clinical and environmental information described highlights potential control measures for reducing the number of *V. vulnificus* infections in the United States.

Methods

States participating in the Gulf Coast *Vibrio* Surveillance System were Florida, Alabama, Louisiana, and Texas; other states were also encouraged to report *Vibrio* infections to CDC. Investigators in state and county health departments completed standardized *Vibrio* illness investigation forms on all patients for whom *Vibrio* isolates were reported from physicians, hospitals, and laboratories. Investigators obtained clinical data as well as information about underlying illness and medication use for this cohort of patients. They also obtained epidemiologic data on seafood consumption and exposure to seawater in the week before illness. When a food

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item was implicated in illness, a trace-back investigation was performed by field investigators of the state or US Food and Drug Administration (FDA). FDA trace-back activity often provided CDC with clinical and epidemiologic information about infections in non–Gulf Coast states.

Information on *V. vulnificus* infections was extracted from the *Vibrio* database maintained at CDC. For analysis of data, wound infection was considered to be the source of infection when a patient incurred a wound before or during exposure to seawater or seafood drippings and *V. vulnificus* subsequently grew from a culture of the wound, blood, or a normally sterile site. Primary septicemia was defined as a systemic illness characterized by fever or shock (systolic blood pressure <90 mm Hg) in which *V. vulnificus* was isolated from either the blood or a normally sterile site and no wound infection preceded the illness. Gastroenteritis was defined as an illness with diarrhea, vomiting, or abdominal cramps, no evidence of wound infection, and *V. vulnificus* organisms isolated from stool alone.

Temperature data for the major oyster harvesting sites in each Gulf Coast state were obtained from the Alabama Department of Public Health, Seafood Branch; the Florida Department of Environmental Protection, Division of Marine Fisheries; the Louisiana Department of Wildlife and Fisheries; and the Texas Department of Health, Division of Shellfish Sanitation Control. In Florida and Louisiana, temperatures were recorded as mean monthly surface temperatures gathered from several buoys in each harvesting location associated with *V. vulnificus* infection. In Texas and Alabama, a monthly reading was recorded from a single buoy located in the harvesting regions associated with *V. vulnificus* infections. Oyster production data were obtained from the National Marine Fisheries Service; Eastern oyster *(Crassostrea virginica)* production was recorded in pounds per month for each state.

Statistical analysis of risk factors and temperatures was performed both for the states participating in the Gulf Coast Surveillance System (Alabama, Florida, Louisiana, and Texas) and for all participating states. Univariate and multivariate analyses were done using generalized estimating equations in SAS v. 6.12 [9] to control for clustering within a state. The estimates from the model with all participating states were similar to the estimates from the models that included the cohort from the Gulf Coast Surveillance System states alone. Since these estimates were similar, the results from the models including all states are reported. The association between water temperature and months with reported infections was analyzed using linear regression, with temperature as a continuous variable.

Results

Epidemiologic and Clinical Features

Between 1988 and 1996, 422 total *V. vulnificus* infections were reported to CDC from 22 states and territories (figure 1); 353 (84%) of infections were from states participating in the Gulf Coast *Vibrio* Surveillance System, 68 (16%) were from other states, and 1 isolate was from the territory of Guam. *V. vulnificus* was the leading *Vibrio* species reported in the Gulf Coast region, accounting for 29% of all *Vibrio* isolates reported through the Gulf Coast Surveillance System.

Of the 422 infections reported to CDC, 204 (48%) followed the ingestion of seafood and presented as either primary septicemia or gastroenteritis, and 189 (45%) were wound infections following the exposure of a wound to seafood drippings or seawater. Among ingestion-associated infections, 181 (89%) presented as primary septicemia and 23 (11%) presented as gastroenteritis. An exposure could not be determined for 29 (7%) of the 422 infections, either because insufficient information was available (90%) or because neither an ingestion exposure nor a wound exposure could be ruled out (10%). Of patients whose outcome was reported, 143 (39%) died among all syndromes combined. The proportion of patients who died was similar in all years, ranging from 30% in 1990 to 48% in 1992.

Clinical characteristics among patients with each syndrome are listed in table 1 for patients with interpretable information. Among wound infections, illness was fatal in 32 patients (17%). The median duration of illness was 3 days (range, 1–40) among fatal infections and 11 days (range, 1–90) among nonfatal infections. A wound culture yielded *V. vulnificus* for 122 patients (65%), and the remainder of the wound infection patients had *V. vulnificus* isolated from either blood or a sterile site following the progression of their infection (19% of patients had isolates that grew from both a wound and a sterile site). Coinfection with other *Vibrio* species (*V. parahaemolyticus,* non-O1 *V. cholerae,* and *V. damselae*) was reported for 17 *V. vulnificus* wound infections (9%). Among primary septicemia infections, illness was fatal in 110 patients (61%). The median duration of illness was 3 days (range, 1–89) in fatal infections and 16 days (range, 2–110) in nonfatal infections. In 1 patient, *Vibrio metschnikovii* was also isolated from the blood. Gastroenteritis from *V. vulnificus* was rarely reported, accounting for only 23 (5%) of the infections; 1 patient also had *V. parahaemolyticus* isolated from stool. Two patients with gastroenteritis died; both had underlying medical conditions (alcohol abuse, liver disease) and had eaten raw oysters. It is possible that these patients had primary septicemia that was not documented by blood cultures.

Risk Factors

Shellfish/seawater exposure. Almost all reported primary septicemia and gastroenteritis infections were preceded by eating raw shellfish. Among the 181 patients with primary septicemia, 173 (96%) had ingested raw oysters in the 7 days preceding illness. Of the remaining 8 patients who did not consume oysters, 6 reported eating raw clams, and 2 ate cooked shrimp. Among the 23 patients with gastroenteritis, 19 (83%) reported eating raw oysters in the 7 days preceding illness, 1 ate cooked shrimp, 1 ate fish, and 2 had unspecified seafood exposures. Of primary septicemia patients who ate oysters, 84% ate the oysters at a restaurant or oyster bar. No dose effect was noted as a risk for fatal outcome; among both fatal and nonfatal infections with information available, the median number of oysters consumed was 10 (range, 1–24). All primary

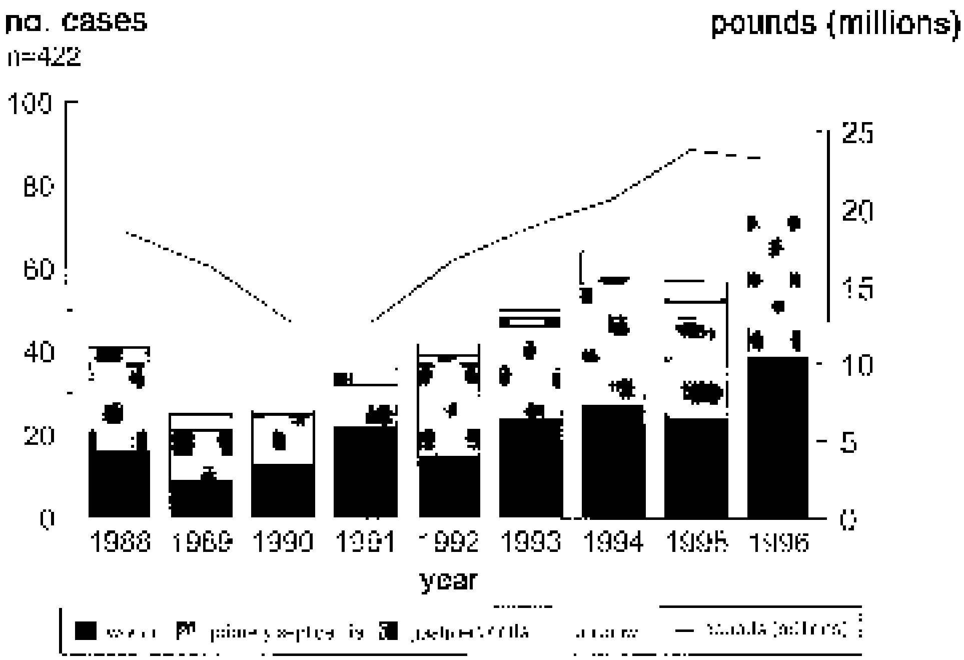

Figure 1. *V. vulnificus* infections reported to Centers for Disease Control and Prevention in United States, by syndrome, and annual oyster meat production in Gulf of Mexico, 1988–1996 (production data courtesy of National Marine Fisheries Service, Fishery Statistics and Economics Division, 1998).

septicemia infections occurred either in states bordering the Gulf of Mexico or states that import oysters from the Gulf. In all instances, when oysters implicated in infections were traced to a single site of origin, including 16 infections (22%) reported from non–Gulf Coast states, the harvesting site was within the Gulf of Mexico.

Among the 189 persons with wound infections, all were exposed to either seawater or raw seafood drippings in the 7 days preceding illness. Ninety patients (50%) sustained a wound at the time of exposure and 39 (21%) reported a preexisting wound; for 53 (29%), the timing of the wound was undetermined. Of the patients with wound infections, 69% reported either fishing or handling raw seafood during the 7 days preceding illness; many of these infections were related to occupational exposures among commercial fishermen and oyster shuckers.

Preexisting conditions. Preexisting medical conditions are reported in table 2 for patients with each syndrome of *V. vulnificus* infection. Preexisting conditions were more common among primary septicemia patients. Liver disease was reported for 122 (80%) of the primary septicemia patients with interpret-

Table 1. Characteristics among patients with *V. vulnificus* infections, by clinical syndrome, 1988–1996.

Characteristic	Wound infections, % (n = 189)	Primary septicemia, % (n = 181)	Gastroenteritis, % (n = 23)
Median age, years (range)	59 (4–91)	54 (24–92)	35 (0–84)
% male	88	89	57
Fever	76	91	59
Diarrhea	—	58	100
Abdominal cramps	—	53	84
Nausea	—	59	71
Vomiting	—	54	68
Shock (systolic blood pressure <90 mm Hg)	30	64	0
Localized cellulitis	91	—	—
Bullous lesions	—	49	0
Hospitalized	89	97	65

NOTE. Values represent % of patients unless otherwise noted. Patients for whom information was not available were excluded from analysis.

Table 2. Preexisting medical conditions among patients with *V. vulnificus* infections, by clinical syndrome, 1988–1996.

Preexisting condition*	Wound infections, % (n = 189)	Primary septicemia, % (n = 181)	Gastroenteritis, % (n = 23)
Liver disease	22	80	14
Alcoholism	32	65	14
Diabetes mellitus	20	35	5
Gastrointestinal surgery	6	7	11
Peptic ulcer disease	10	18	0
Heart disease	34	26	10
Hematologic disorder	8	18[†]	0
Immunodeficiency	9	10	5
Malignancy	10	17	16
Renal disease	7	7[†]	5
Any of above	68	97	35

NOTE. Values represent % of patients. Patients for whom information was not available were excluded from analysis.

* Conditions are not mutually exclusive.

[†] Data were available for <60% of total no. of patients.

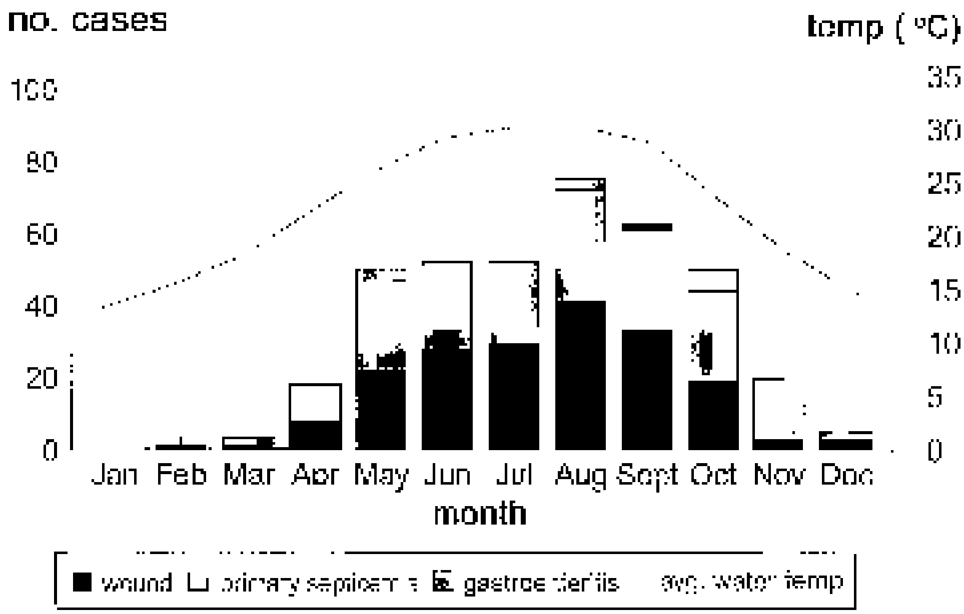

Figure 2. *V. vulnificus* infections in United States reported to Centers for Disease Control and Prevention, by syndrome, and month of symptom onset, 1988–1996. avg = average.

able information and was present in 77 (87%) of the fatal cases compared with 40 (74%) of nonfatal infections (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.6–4.7). Among wound infections with interpretable information, liver disease was reported in 10 (45%) of 22 fatalities compared with 16 (15%) of 104 nonfatal infections (OR, 4.9; 95% CI, 0.95–24.81).

Liver disease was a strong predictor of fatal outcome for all 422 patients combined; among those with interpretable information, 96 (80%) of the persons with fatal infections had liver disease, while only 64 (35%) of those with nonfatal infections had this condition (OR, 7.4; 95% CI, 5.2–10.6). Among 113 patients for whom the type of liver disease was specified, 58% had cirrhosis or alcoholic liver disease, 24% hepatitis or a history of hepatitis, 16% both cirrhosis and hepatitis, 1% metastatic cancer, and 1% liver transplantation. Hematologic conditions included anemia, thrombocytopenia, and leukemia; 1 patient had thalassemia, and 1 patient had hemochromatosis. Immunocompromising conditions included chemotherapy, steroid treatment, and splenectomy. Human immunodeficiency virus (HIV) was noted in 5 patients.

Seasonality/harvest water temperature. All syndromes of *V. vulnificus* infection were more common in warmer months (figure 2). We performed a more detailed analysis of the primary septicemia cases in which complete trace-backs of the oysters implicated in infections were available, and we determined average monthly water temperatures at the harvest sites of these oysters. Because temperature data were only available through 1995 at all sites, we limited our analysis to oysters traced back to their site of origin between 1988 and 1995. Seventy-two infections during this period were caused by oysters that could only have come from a single harvesting site, and that site was determined. These traced cases represented 49% of primary septicemia infections reported during these years. All of these trace-backs implicated oysters harvested in the Gulf of Mexico.

Implicated oysters could be traced to seven major oyster harvesting regions in the Gulf of Mexico: Apalachicola Bay in Florida, Mobile Bay in Alabama, Galveston Bay in Texas, and the bays supplied by four distinct drainage basins in Louisiana (basins 2, 4, 6, and 12). Most (79%) of these infections were traced to oysters harvested in Louisiana and Florida. The average monthly water temperatures did not differ significantly among the seven implicated oyster harvesting sites, and there was no significant difference between the number of oysters harvested during warmer or cooler months for the region as a whole (although variation occurred at individual sites). The 72 traced cases were more likely to occur in months when the water temperature at the time of harvesting was warmer ($P <$ .0001; figure 3). The median water temperature recorded at sites during a month when a case occurred was 27.1°C (range, 13.9–32.0°C), and the median temperature for all months in which no cases occurred was 22.3°C (range, 8.4–32.0°C). Among these 72 traced cases between 1988 and 1995, only 8 *V. vulnificus* infections (11%) occurred in water cooler than the mean annual temperature of 22°C (figure 3), and only 3 infections occurred in persons who consumed oysters harvested in water <20°C.

Because of this seasonal pattern of *V. vulnificus* infections from the Gulf of Mexico, we obtained Gulf Coast oyster production data from the National Marine Fisheries Service to evaluate monthly trends in oyster harvesting. There was little seasonal variation in Gulf Coast oyster production between 1988 and 1996, although total annual production increased by ~30% during these years (National Marine Fisheries Service, Fishery Statistics and Economics Division, 1998, personal

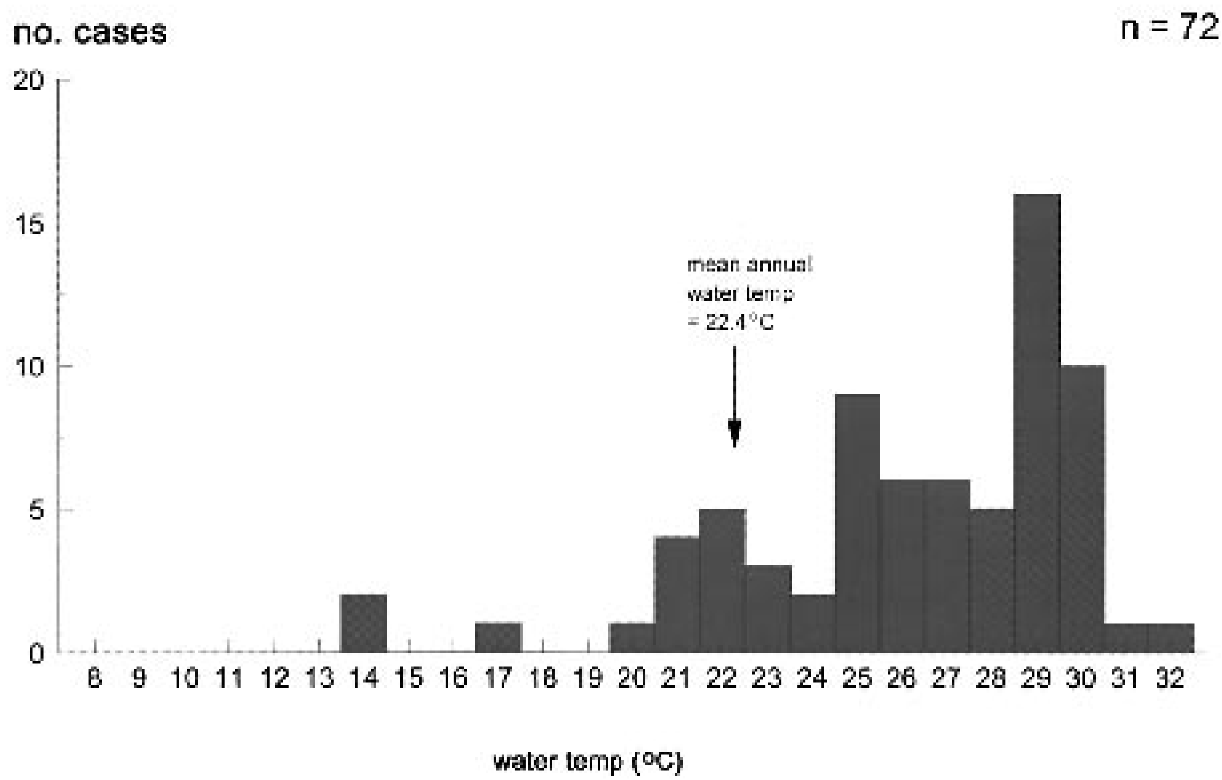

Figure 3. Oyster-associated *V. vulnificus* infections with complete trace-backs, by mean monthly water temperature of harvest site, Gulf of Mexico, 1988–1995.

communication). Production was lowest in August, when an average of 1.05 million pounds (2.31 million kg) was produced in Gulf Coast states, compared with peak production averaging 1.87 million pounds (4.12 million kg) during March (figure 4). Overall, 43% of oyster production in the Gulf of Mexico occurred between May and October during these years, and 57% occurred between November and April (National Marine Fisheries Service, Fishery Statistics and Economics Division, 1998, personal communication).

Discussion

V. vulnificus infections in the United States are rare but highly lethal. This is the largest series reported to date, and the number of reported infections is increasing; of the 418 infections reported since 1988, more than half were reported between 1993 and 1996. Seventy-five cases, 33 of which were fatal, were reported in 1996 alone; this was the largest number of cases and fatalities in any single year since surveillance began in 1988 (figure 1). It is not known whether this represents an increase in the incidence of disease or an increase in reporting. For ingestion-associated infections, an increase in the total annual production of oyster meat between 1988 and 1996 may have been a contributing factor (figure 1). The 61% mortality among patients with primary septicemia and 17% mortality from wound infections is slightly higher than mortality rates reported from Florida between 1981 and 1993 [4]. Liver disease remained a significant risk factor associated with fatal outcome.

Increased saturation of transferrin, either through an excess of iron or a relative decrease in the amount of transferrin, may be associated with the pathogenesis of *V. vulnificus* infection [10, 11]. Among primary septicemia patients, either liver disease or alcoholism was reported in 86% of infections. The underlying iron dysregulation caused by these conditions [12] may have contributed to the high morbidity and mortality in our series, although the effect of iron dysregulation is difficult to separate from other mechanisms of immunocompromise among patients with these conditions.

The report of only 1 patient with hemochromatosis among the 422 infections is low and is in contrast to at least one earlier case series [2]. Because hemochromatosis was not specifically mentioned on the surveillance form, these patients may have been recorded as having either liver disease or diabetes. Since only 3% of patients with primary septicemia reported no preexisting medical condition, it is unlikely that an appreciable percentage of asymptomatic patients with iron overload from hemochromatosis were missed.

Thus, while both in vitro models and experimental murine models have suggested that iron overload is a risk factor for

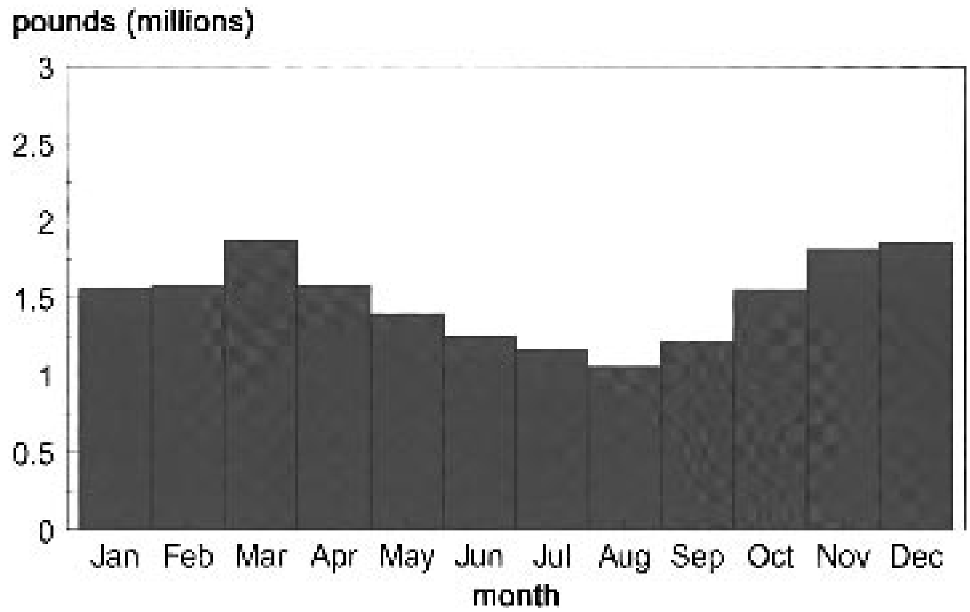

Figure 4. Average pounds of oyster meat produced, by month, Gulf of Mexico, 1988–1996 (courtesy of National Marine Fisheries Service, Fishery Statistics and Economics Division, 1998).

V. vulnificus infection [13–15], it remains unclear what role the iron overloaded state plays in human illness when liver disease is absent; this question deserves further study. Because liver disease and alcoholism were reported frequently, and because liver disease was a strong predictor for mortality in all patients, a poorly functioning liver may pose an additional risk through a mechanism independent of transferrin saturation or iron overload.

Other potential risks for infection may have included the disruption of the gastric acid barrier by peptic ulcer disease (or its treatment) [16] or a weakened immune system caused by malignancy or steroid use [17]. While the presence of HIV has been previously reported in *V. vulnificus* infections [18], the actual risk posed by HIV or AIDS remains unclear. Only 5 (1%) of the 422 patients in our series were reported to have HIV infection. This low number may represent a relatively lower risk than previously suspected; avoidance of raw shellfish among this population; or a failure of reporting, since immunocompromise (rather than HIV) was specified on the surveillance form.

The male-to-female ratio (6:1 for all syndromes combined) is remarkable and may be multifactorial. Surveys throughout the United States have demonstrated that men may be two times more likely to eat raw oysters than women [19, 20]. The difference may also reflect a larger number of men in the population with liver disease, alcoholism, or other risk factors; higher total iron stores in men than in women; or a larger percentage of men with occupational exposures to raw seafood drippings or seawater.

The strong association between illness and the consumption of raw oysters (compared with other seafood) is probably related to the high concentration of *V. vulnificus* within the digestive tracts or tissues of oysters [21] as well as the fact that oysters are commonly eaten raw. Virtually all oysters harvested from the Gulf of Mexico in warmer months of the year harbor *V. vulnificus* [21].

Warmer water temperatures have been shown experimentally to increase the number of endogenous *V. vulnificus* in oysters [7], but the significance of these observations is unknown because the infectious dose for human illness has not been determined. Because only a small fraction of even those in high-risk groups for infection become ill after consuming contaminated raw oysters, the absolute number of organisms present in oysters only partially illuminates our understanding of the risk for infection; specific host factors and *V. vulnificus* strain virulence may also play important roles.

This is the first report of which we are aware of a series of infections traced to individual harvest locations and the mean recorded water temperatures at those sites. The association between oysters harvested in warmer water and infection is strong. We demonstrate that water temperature can serve to predict infections, but we cannot prove a causal relationship through our study, since water temperature may serve as a marker for another environmental factor. Our data strongly support the association between ''summer harvesting'' and illness, but they also demonstrate that ''summer harvesting'' represents at least a 6-month period between May and October when infections commonly occur. Oyster production in the states participating in Gulf Coast surveillance decreases only minimally between May and October. These months represented ~43% of annual production, and since 1972, summer harvesting in the Gulf has increased from 15% to >40% as a percentage of total production (National Marine Fisheries Service, Fishery Statistics and Economics Division, 1998, personal communication).

This 6-month period of risk may help explain the apparent failure of stricter harvesting regulations that went into effect in August 1995. These regulations were intended to decrease the number of ingestion-associated cases by reducing the time allowable between oyster harvesting and refrigeration during the months when water temperatures are >84°F (29°C) to a maximum of 6 h [22]. However, these regulations affected harvesting practices in only the warmest months of the summer. The water temperature data presented here reveal that <40% of the 72 infections traced to a single site between 1988 and 1995 were the result of oysters harvested in waters this warm, and that only 56% of the 1996 infections in the Gulf Coast states actually occurred during months affected by this policy change.

Although the number of infections potentially prevented by these stricter regulations remains unknown, the regulations were modified by the Interstate Shellfish Sanitation Conference (ISSC) in July 1997 to allow up to 10 h before refrigeration during the warmest months (ISSC Executive Director, personal communication). This decision was partly based on the likelihood that *V. vulnificus* burden in an oyster at the time of harvesting plays an important role in infection regardless of postharvest handling and partly on the uncertainty about the ability of postharvesting refrigeration to decrease the number of infections when large numbers of *V. vulnificus* are already present in oysters [7, 23]. Alternative regulatory approaches for harvesting have yet to be identified.

Because Gulf Coast *Vibrio* surveillance is passive and is dependent upon case reporting, which may vary by locality, incidences for *V. vulnificus* infection by site of harvest could not be accurately determined. In addition, differences in oyster marketing and distribution between sites may have created biases in the number of infections traceable to each site, contributing to differences between sites. That only 49% of all infections were traced to an oyster harvesting site was an additional limitation of this study. However, the clinical characteristics among traced cases were similar to those not traced. Because there was no significant difference in the overall mean monthly temperatures recorded between sites, it is unlikely that temperature differences between the harvesting sites influenced the number of cases traced to each site.

Why were all traceable oyster-associated *V. vulnificus* infections between 1988 and 1995 caused by oysters harvested in the Gulf of Mexico? Although clams harvested from the Indian River region of the Atlantic coast of Florida have been implicated in primary septicemia cases (CDC, unpublished data) and wound infections have been reported from exposures in both the Atlantic and Pacific oceans, CDC has not received any accounts of domestic infections that can be clearly traced to the consumption of oysters harvested outside the Gulf of Mexico. One explanation is increased reporting of *Vibrio* infections in the Gulf through the Gulf Coast Surveillance System.

Another explanation may be the high market share of US oyster production from the Gulf states; oysters from the Gulf of Mexico account for ~58% of all oyster production in the United States annually (National Marine Fisheries Service, Fishery Statistics and Economics Division, July 1998, 1993–1996 data, personal communication), and >30% of this production is ''shellstock,'' which is usually consumed raw (the remaining 70% is shucked product, which may be eaten either raw or cooked) (National Marine Fisheries Service, Fishery Statistics and Economics Division, 1997, personal communication).

Water temperature may also be an important factor, since high levels of *V. vulnificus* are supported by Gulf Coast waters throughout most of the year [6] and the Gulf coast is the most important summer harvesting region in the United States. Washington State also has an appreciable summer industry (but colder water temperatures), whereas Atlantic coast states have minimal summer oyster production (National Marine Fisheries Service, Fishery Statistics and Economics Division, 1997, personal communication).

This difference in production between Atlantic and Gulf Coast states during warmer months may be important, since summer water temperatures along the Atlantic coast support ample *V. vulnificus* growth [7], and the numbers of *V. vulnificus* isolated from oysters and seawater in Chesapeake Bay are similar to those for the Gulf of Mexico throughout most of the year [24]. Since the infectious dose of *V. vulnificus* has not been established, the significance of absolute numbers of *V. vulnificus* in oysters from different regions is difficult to determine.

Finally, there may be differences in virulence between the numerous strains of *V. vulnificus,* and variation in these strains may be regional. Studies are underway to evaluate the molecular differences between clinical isolates traced to oysters from the Gulf and environmental isolates, including isolates from oysters, from other bodies of water.

We continue to learn more about the epidemiology and pathogenesis of *V. vulnificus* infections. An important approach for reducing the burden of illness is targeted education and prevention strategies. CDC encourages physicians to educate patients at highest risk to avoid consumption of raw oysters from the Gulf of Mexico, raw seafood drippings, and seawater exposures. It is particularly important that high-risk patients avoid these exposures between May and October. In addition, educational approaches aimed at those who consume raw oysters, as currently required in restaurants in Florida, Louisiana, and California, should be mandated and enforced [25]. Early treatment with antibiotics has been shown to improve survival in septicemic patients [8], so prompt recognition of infection by physicians is critical to reduce mortality from *V. vulnificus* infections. Finally, restricting the use of oysters harvested in warm Gulf waters to cooked or other suitably processed products may significantly reduce morbidity and mortality from *V. vulnificus* infections.

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