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A Trend Analysis of *Vibrio vulnificus* Mortality, Using the Cholera and Other *Vibrio* Illness Surveillance System

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2015

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Abstract

A Trend Analysis of *Vibrio vulnificus* Mortality, Using the Cholera and Other *Vibrio* Illness Surveillance System

By Mikala Caton

Background: *Vibrio vulnificus (Vv.)* is an opportunistic gram-negative bacterium commonly found in warm coastal waters. As a rare and severe infection, *Vv.* cases are reported and monitored through the Cholera and other *Vibrio* Illness Surveillance (COVIS) System. While the case fatality ratio was reported to be around 50%, recent COVIS data shows a decrease in the mortality of *Vv.* infections over the past 25 years (from as high as 41% to as low as 18%). Though *Vv.* became nationally notifiable in 2007, it is unlikely this change in surveillance is entirely responsible for the downward trend in mortality. This study aims to determine which factors may be facilitating the downward trend in *Vv.* mortality and develop corresponding models to determine the risk for *Vv.* mortality before and after the implementation of the 2007 policy change.

Methods: *Vv.* cases reported to COVIS between 1988 and 2015 were selected and divided into the pre-policy (1988-2007) and post-policy period (2008-2015). The following variables were analyzed for their association with mortality and potential changes over time: patient characteristics, clinical outcomes, severity, and mode of transmission. Logistic models were created to assess changes in the relationship between each variable and mortality across the pre- and post-policy periods. Predictive margin risk ratios were used to calculate the risk of death per exposure variable over time.

Results: Among all the variables considered, only region and mode of transmission were found to be changing over time. Compared to the Gulf Coast, the Pacific and Atlantic Coasts were increasingly protective against mortality from *Vv.* Compared to non-foodborne infections, cases with foodborne and unknown origins of transmission were at an increased risk for mortality from *Vv.*

Conclusions: The study results demonstrate there is a significant downward trend in *Vv.* mortality partially due to a shift in where cases are reported and how cases are becoming infected. Future interventions surrounding safe-food education are needed across the Gulf Coast and Non-Coastal states to decrease the risk of mortality among raw seafood consumers. Research evaluating the impact of current interventions and environmental factors are needed to understand *Vv.* trends across the regions.

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I. Background and Literature Review

Vibrio vulnificus (Vv.) is an opportunistic gram-negative bacterium commonly found in warm coastal waters (> 22°C) and transmitted through undercooked shellfish consumption or open wounds (1-5). As filter feeders, oysters are the main source of *Vv.* foodborne infections due to high concentrations of the bacteria (2). Because *Vv.* growth is sensitive to both temperature and salinity, oysters harvested from the Gulf Coast during the summer months pose the greatest risk for contamination and potential infection among seafood consumers (2). While most *Vv.* foodborne infections cause gastroenteritis, some *Vv.* infections can be lethal and produce septicemia or necrotizing fasciitis in its hosts (3, 6, 7). Anyone can become infected with *Vv.*, but populations with compromised immune systems, particularly from liver disease, are at the highest risk for severe complications (8).

As a rare and severe infection, *Vv.* cases are reported and monitored through the Cholera and other *Vibrio* Illness Surveillance (COVIS) System. COVIS originated as a collaboration between the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and states within the Gulf Coast region (Texas, Alabama, Florida, Louisiana, and Mississippi) in 1988 (9). Prior to 2007, only *Vibrio cholerea* was nationally notifiable, though many states within and outside the Gulf Coast region routinely reported *Vibrio* cases before 2003 (10).

A study comparing *Vv.* cases reported to COVIS and FoodNet, a network of 10 sites in the United States conducting active surveillance for laboratory-confirmed foodborne infections, found *Vv.* incidence per 100,000 people increased from .03 to .04 in COVIS and from .01 to .05 in FoodNet from 1996 to 2010 (10). Though limited in catchment area, FoodNet provided the most complete picture of *Vibrioses* in the US prior to 2007 by covering 15% of the national population (10). However, COVIS expanded substantially between 1996 and 2010, complementing the lack of coverage in FoodNet. The continued increase in the number of *Vv.* cases reported to COVIS after becoming nationally notifiable in 2007 further validates the incidence trend found in both surveillance systems (10). Though few studies have investigated the cause of the increase in *Vv.*

incidence, the warming of coastal waters, which may increase oyster contamination rates, and increased exposure to seafood and seawater have been suggested explanations (11-14).

In contrast with the overall increase in *Vv.* incidence, current COVIS data shows an overall decrease in the mortality of *Vv.* over the past 25 years (from as high as 41% to as low as 18%) (8, 11, 15, 16). Though *Vv.* became nationally notifiable in 2007, it is unlikely this change in surveillance policy is entirely responsible for these observations (11, 12). A thorough literature review on prior *Vv.* studies and the data available in COVIS suggest transmission mode, clinical outcomes, *Vv.* severity, and patient characteristics to be underlying factors contributing towards the downward trend in *Vv.* mortality.

Literature Review

Transmission Mode and Clinical Outcomes. *Vv.* is transmitted through foodborne and waterborne exposures, causing gastroenteritis, primary septicemia, or wound infections (1-5). Prior studies have shown that cases infected through the consumption of raw seafood are more likely to become septic and twice as likely to die compared to non-foodborne infections (8, 17). While *Vv.* is rare and only 1 out of every 10,000 raw oyster meals results in *Vv.* illness, almost half of all annual *Vv.* cases are related to food consumption.(17-20) However, because the number of reported wound infections increased from 24 cases per year from 1988 through 1999 to 52 cases per year from 2000 through 2010, it is possible there has been a shift from primarily foodborne *Vv.* illnesses to non-foodborne illnesses (16). Route of transmission likely influences the severity of patient symptoms and the trend in mortality.

Changes in *Vv.* infections and illness severity can be further explained through the type of seafood consumed (mollusks, crustaceans, or fish) and how the seafood was prepared (raw or cooked). A study using data from 1973 through 2006 found that 80.5% of *Vv.* cases with foodborne exposures reported eating oysters during the week before illness onset (13). Another study found 96% of the cases with primary septicemia also reported consumption of raw or undercooked oysters

in the last week (3). Changes in the types of seafood consumed and how the seafood was prepared may be related to trends in *Vv.* mortality.

Using current COVIS annual summaries, the overall *Vv.* case fatality rate reported in 2014 was 18% (16). However, the case fatality rate varies when stratified by the three most common *Vv.* related clinical outcomes: septicemia, wound infections, and gastroenteritis. The literature indicates the *Vv.* case fatality rate for primary septicemia to be 50% and 15%-25% for wound infections (3, 21, 22). Because severe symptoms and death are extremely rare among *Vv.* patients with gastroenteritis, there is likely underreporting of these cases and inaccurate estimates of mortality (3, 13). From COVIS data reported from 1988 through 1996, 45% of cases resulted in wound infections, 43% resulted in septicemia, and 5% showed gastroenteritis symptoms (3). A recent study suggests the incidence of septicemia in the US is decreasing, while that of wound infections have increased (12). This shift in case outcomes (septicemia and wound infections) may be influencing the *Vv.* mortality trend found in COVIS (12).

Severity. Length of illness among *Vv.* cases can predict health outcomes and varies across the three major clinical outcomes (12). Though *Vv.* is a fast-acting bacterium with a median incubation period of 16-26 hours, symptoms can be delayed up to 14 days in cases of raw oyster consumption (12). The median duration of illness lasts 3 days for fatal septicemia patients, and 16 days for nonfatal septicemia patients (12). The median duration of illness lasts 3 days for fatal wound infections, and 11 days for nonfatal wound infections (12, 17). Regardless of mode of transmission or clinical outcomes, 70% of all fatal *Vv.* infected patients die within the first 72 hours, often before beginning antibiotic treatment (19). A review of changes in the length of illness may provide insight into the changes in *Vv.* severity.

While *Vv.* can result in mild gastroenteritis, approximately 90% of infected patients require hospitalization for either wound infections or primary septicemia (3, 8, 11 19, 20). Despite underreporting and underdiagnosing, hospitalization often serves as a proxy for *Vv.* severity due to strong associations with *Vv.* mortality (23). The downward trend in *Vv.* mortality may also coincide

with a downward trend in hospitalization, signifying possible shifts in *Vv.* virulence and the severity of infections.

Patient Characteristics. Despite public health warnings about the increased risk of illness after consuming raw or undercooked oysters, eating behaviors remain unchanged (24). Roughly 5.6% of the US population consumes raw shellfish, which is one of the only high risk food categories significantly associated with disease risk (25). Literature from the 1990's suggests food safety practices, risky behaviors, foodborne illness awareness, and pre-existing conditions vary by gender and may contribute to the decrease in *Vv.* mortality (7, 26-28). Previous survey-based behavioral studies found men to be two times more likely to eat raw oysters, and significantly more likely to have liver disease, alcoholism, or high iron states compared to women in the United States (3, 7, 24, 27). In addition, similar studies found that men were more likely to hold high-risk occupations that may expose them to raw seafood drippings or seawater (3, 24). This may help explain why studies found *Vv.* to predominantly occur in men (3, 24). However, studies published as recently as 2014 contradict these findings and suggest patients who acquired infection via contaminated food were significantly more likely to be female, younger, non-white, have a greater number of pre-existing conditions and become septic than those patients who acquired a non-foodborne infection (8, 11, 29). This recent data suggests shifts in *Vv.* patient characteristics that may contribute towards the downward trend of *Vv.* mortality.

While there is conflicting evidence in the literature surrounding a significant difference in the number of *Vv.* infections stratified by sex, research shows sex may play an important role in *Vv.* mortality. Estrogen significantly decreases a woman's risk of lipopolysaccharide-induced septic shock, one of the deadlier complications related to *Vv.* (29, 30). Aligning with the increased female consumption of raw shellfish, it is possible more women are becoming infected with *Vv.* and decreasing the overall case fatality ratio.

Literature surrounding the consumption of raw oysters, the primary vehicle of *Vv.* infection, and *Vv.* mortality also suggests age as an underlying risk factor. The average age of *Vv.* cases is 60

years old, with 95% of cases reported to be over 40 years old (25, 29). Yet, raw oyster consumption is highest among groups between 18 and 29 years of age, indicating a higher risk of *Vv.* infection per exposure among older populations despite variations in at-risk behavior (7, 26, 28). The literature attributes age-based variations in *Vv.* infections to the delayed onset of pre-existing conditions, such as liver disease, and age-based variations in *Vv.* mortality to the decreased risk in developing septicemia (25). Further analysis of age characteristics among *Vv.* infected cases may increase the understanding of the downward trend in mortality, particularly if younger populations are reporting illness.

As an opportunistic infection, *Vv.* predominantly infects people with compromised immune systems or pre-existing conditions (12). The literature suggests 94% of all *Vv.* foodborne infections occur in individuals with at least one chronic condition, and that cases with pre-existing conditions were 80 times more likely to develop severe health outcomes (9, 12). While wound infections are common among previously healthy populations, those with underlying medical conditions, such as: liver disease, hematological disease, malignancy, diabetes, heart disease, gastric surgery, immunodeficiency, renal disease, and peptic ulcers are at an increased risk for developing primary septicemia (2). Compared to other common pre-existing conditions, research using COVIS data from 1988 through 2006 revealed patients with liver disease to be four times more likely to become septic when exposed to *Vv.* through contaminated food (7). Compared to "healthy" patients infected with *Vv.*, patients with liver disease and *Vv.* were 80 times more likely to become septic and 200 times more likely to die from *Vv.* (13). Patients with liver disease are at an increased risk for poor health outcomes due to an overload of iron in their blood, which promotes *Vv.* growth, decreases the effectiveness of the immune system, and increases the probability of developing septicemia (21). Similarly, patients with hematological disease or malignancy are 1.5 times more likely to become septic from non-foodborne *Vv.* exposures compared to other pre-existing conditions as well (7). Analyzing the mortality trend among individuals with these pre-existing conditions may help show if the bacteria's virulence or population at risk has changed.

Though some *Vv.* bacteria have been isolated along the northern Pacific Coast and waters near New England, *Vv.* proliferates along the Gulf Coast due to the warm, brackish estuary and marine environments (3). As a popular area to harvest shellfish and participate in water activities, the Gulf Coast reports the majority of foodborne and non-foodborne *Vv.* cases and initiated the development of COVIS. COVIS collects information on patient demographics, clinical data, epidemiology data, laboratory data, and seafood traceback data. A study analyzing COVIS data from 1988 to 1996 found all oysters consumed by patients with primary septicemia traced back to the Gulf of Mexico (3). The decrease in *Vv.* mortality may be related to a change in where oysters are harvested and consumed.

II. Manuscript

Introduction

Vibrio vulnificus (Vv.) is an opportunistic gram-negative bacterium commonly found in warm coastal waters (> 22°C) and transmitted through undercooked shellfish consumption or open wounds (1-5). As filter feeders, oysters are the main source of *Vv.* foodborne infections due to high concentrations of the bacteria (2). Because *Vv.* growth is sensitive to both temperature and salinity, oysters harvested from the Gulf Coast during the summer months pose the greatest risk for contamination and potential infection among seafood consumers (2). While most *Vv.* foodborne infections cause gastroenteritis, some *Vv.* infections can be lethal and produce septicemia or necrotizing fasciitis in its hosts (3, 6, 7). Anyone can become infected with *Vv.*, but populations with compromised immune systems, particularly from liver disease, are at the highest risk for severe complications (8).

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surveillance systems (10). Though few studies have investigated the cause of the increase in *Vv.* incidence, the warming of coastal waters, which may increase oyster contamination rates, and increased exposure to seafood and seawater have been suggested explanations (11-14).

In contrast with the overall increase in *Vv.* incidence, current COVIS data shows an overall decrease in the mortality of *Vv.* over the past 25 years (from as high as 41% to as low as 18%) (8, 11, 15, 16). Though *Vv.* became nationally notifiable in 2007, it is unlikely this change in surveillance policy is entirely responsible for these observations (11, 12). While researchers attribute 45% of the global increase and spread of *Vibrio* infection rates to rising sea surface temperatures, shifts in transmission mode, clinical outcomes, severity, and patient characteristics likely explain the decrease in mortality (14). Prior studies have shown that cases infected through the consumption of raw seafood are more likely to become septic and twice as likely to die compared to non-foodborne infections (8, 17). However, recent COVIS data show an increase in wound infections from 24 cases per year from 1988 through 1999 to 52 cases per year from 2000 through 2010 (11). It is possible there has been a shift from primarily foodborne *Vv.* illnesses to non-foodborne illnesses, and that route of transmission or even preparation and type of seafood consumed are associated with the downward trend (2, 13, 16). Additional factors, such as sex, age or pre-existing conditions, may also be associated with *Vv.* severity and the resulting clinical outcomes. For example, estrogen significantly decreases a woman's risk of lipopolysaccharide-induced septic shock, one of the deadlier complications related to *Vv.* (29, 30). Coinciding with reported increases in female consumption of raw shellfish, it is possible more women are becoming infected with *Vv.* and decreasing the overall case fatality ratio (8, 11, 29). This study aims to determine which of these factors (patient characteristics, transmission mode, clinical outcomes, or severity) may be facilitating the downward trend in *Vv.* and develop corresponding models to determine the risk for *Vv.* mortality before and after the implementation of the 2007 policy change.

Methods

Data Collection

As a nationally notifiable disease, CDC requests state and local health departments in the US report infections with *Vibrio* species via case report forms within 30 days. Health departments interview cases to collect patient demographics, laboratory data, clinical data, epidemiology data, and seafood traceback data on the case report forms. CDC uses this information to educate seafood consumers, monitor for outbreaks, and assess changes to host, food, and environmental risk factors.

Study Design

Vv. cases reported to COVIS between the years of 1988 and 2015 were selected, providing an initial sample of 2,441 observations. Cases that acquired *Vv.* domestically (no reported international travel history within 7 days of illness onset) were independent (not part of an outbreak), and had data on the outcome (death or survival) were included in further analysis. The inclusion criteria resulted in a remaining sample size of 2,152 *Vv.* cases.

Upon completion of the literature review, four categories of variables were chosen for data analysis: patient characteristics, severity, clinical outcomes, and transmission modes. The following COVIS data elements were selected for data analysis on patient characteristics: sex, age, race, ethnicity, pre-existing conditions, and region reporting each case. Races defined as Hispanic or Latino prior to 1999 were made missing to account for the previous policy that treated race and ethnicity as the same data element. Pre-existing conditions were categorized as none or at least one of the following: alcoholism, diabetes, peptic ulcer, gastric surgery, heart disease, immunodeficiency, liver disease, malignancy, and renal disease. The state reporting each case, usually the case's state of residency, was categorized into the Gulf Coast, Pacific Coast, Atlantic Coast, and Non-Coastal regions. The COVIS data elements selected for data analysis of *Vv.* severity were hospitalization and duration of illness, which was categorized into 0 to 3 days, 4 to 11 days, and greater than 11 days to align with data in the literature (12, 13). The data elements created for clinical outcomes included:

primary sepsis, wound infection (defined as cases providing a positive culture from a wound specimen), and gastroenteritis (defined as cases reporting vomiting or diarrhea). Primary sepsis was defined as septic shock, a data element collected on the COVIS case report form, from cases providing a blood specimen. The COVIS data elements selected for transmission mode analysis were: mode of transmission (defined as foodborne, non-foodborne, and unknown), type of seafood (includes mollusks, crustaceans, and fish), seafood preparation (defined as raw or not raw for mollusks, crustaceans, and fish), and travel (defined as domestic cases that traveled outside their home state in the 7 days before the onset of symptoms). Foodborne transmission included confirmed and probable cases with documented seafood consumption and specimen source. Non-foodborne transmission included confirmed and probable cases with documented water exposure and specimen source. Unknown mode of transmission included cases with missing exposure data and cases with documented seafood consumption, water exposure, and specimen source.

Data Analysis: Descriptive Statistics

Case fatality ratios were calculated for each reporting year, and a chi-square test was used to test for a difference in mortality overall, and during the pre- and post- policy period. To account for potential differences in reporting after *Vv.* became nationally notifiable, all analyses used time or reported year of infection as a dichotomous variable for cases reported between 1988 to 2007 and 2008 to 2015. Cases reported in 2007 were placed in the pre-policy period to account for delays in implementation by states. The proportion of missing surveillance data and case fatality ratios were calculated for each data element, as well as a chi-square test between case outcome and each patient characteristic, severity, clinical outcomes, and transmission mode variable. Descriptive maps displaying the location of *Vv.* cases by the reporting state were also created to visually present the distribution of cases.

Data Analysis: Logistic Regression

Logistic regression models were used to identify which patient characteristics, severity, clinical outcomes, and transmission mode variables were changing over time with mortality. Time or year of reported case served as the predictor variable (before or after 2007) and case outcome (died or not) functioned as the dichotomous outcome variable. Likelihood ratio tests and backwards elimination were used to assess the interaction of time with each patient demographic, severity, clinical outcome, and transmission mode variable. Significant interaction terms were determined when there was evidence that the effect of an exposure of interest changed over time.

Of the regression models found with significant interaction terms, new multivariate logistic models were created to analyze the effect of exposures on mortality. Four sets of models were created to assess the significant variables separately, together, without adjusting for confounders, and while adjusting for confounders. The variables significantly changing over time served as new predictor variables and case outcome (died or not) functioned as the dichotomous outcome variable. Time (pre-policy and post-policy) served as a covariate and interaction term in each model, along with additional potential confounders and interaction terms. Likelihood ratio tests and backwards elimination were used to assess the new interaction terms, and confounding assessments were performed on covariates to obtain the final models. Sex and race were the only eligible variables considered for confounding. Both were associated with mortality among *Vv.* cases in the literature and both were associated with other exposures, such as region, mode of transmission, or the type of seafood prepared and consumed. If the measure of association determined in the reduced model (without the covariate) was more or less than 10% from the measure of association found in the full model (with the covariate), the covariate was kept in the final model to control for confounding. Predicted margin risk ratios were calculated for the measure of association because odds ratios produced from logistic regression models are inflated and do not approximate the risk ratio for non-rare outcomes. The outcome (mortality) in the COVIS dataset was not rare (over 30% died). Variables with more than 10% of the data missing were excluded from the final models as exposures of interest, interaction terms, or covariates (32).

All data were analyzed using SAS version 9.4 (Cary, NC), and the measures of association were calculated using the SAS-callable SUDAAN (Durham, NC) predicted margins risk ratio method. Descriptive maps were made using ArcGIS (Redlands, CA).

Ethics Statement

The Emory University Institutional Review Board determined this study did not require review because COVIS data is publically available and does not meet the definition of research with human subjects.

Results

The distribution of total cases reported per year ranged from 20 to 143 with an average of 77 cases reported per year (standard deviation: 32.6), and the distribution of cases that died per year ranged from 5 to 41 with an average of 26 deaths per year (standard deviation: 8.9 cases). The *Vv.* case fatality ratio steadily decreased from 0.45 in 1988 to 0.18 in 2015 with time as a continuous or categorical variable ($p < .001$; Figure 1). The number of *Vv.* cases reported to COVIS in 1988 was 42, 19 of which died (Figure 2). The number of *Vv.* cases reported to COVIS in 2015 was 143, 27 of which died (Figure 2). A sharp increase in the number of *Vv.* cases reported to COVIS occurred as early as 1998, where the number of *Vv.* cases almost doubled when compared to the number of *Vv.* cases reported in 1988 (Figure 2). Another sharp increase appeared in 2003, where the number of cases almost tripled from those reported in 1988 (Figure 2). Most *Vv.* cases were reported from the Gulf Coast states (Texas, Louisiana, and Florida; Figure 3) across both the pre- and post-policy periods. Non-Coastal states showed an increase in the number of *Vv.* case reported between the pre- and post-policy period (Figure 3).

Among the COVIS cases included in the analysis, the majority were white (84.7%), male (86.0%), over the age of 50 (71.2%), and persons with at least one pre-existing condition (80.4%; Table 1). More than half of the cases reported came from the Gulf Coast (64.7%; Table 1), and only

a small fraction reported out of state traveling the week prior to illness (14.9%; Table 2). Most cases were hospitalized (89.5%) with 24% reporting wound infections and 47% reporting non-foodborne infections (Table 2). The most commonly reported seafood consumed was oysters (93.3%), of which almost all were raw (99.4%; Table 2). All other variables had more than 11% of the data missing (Table 1 and Table 2).

Of the variables with adequate available data, nine were found to be strongly associated with mortality. Among the patient characteristic variables, there was a higher proportion of mortality among women (37.5%, p=.08), patients between the ages of 40-49 (46.7%) and 50-59 (44.8%, p<.001), and patients that identified as black or African American (49.4%), Asian (47.8%), or another race (57.1%) (p< .001; Table 1). There were also higher proportions of mortality among patients reported from the Pacific Coast (46.0%) and the Non-Coastal region (44.0%) (p<.001; Table 1). Patients with at least one pre-existing condition (40.7%; Table 1) and recent hospitalization (35.9%; Table 2) had higher proportions of mortality as well (p<.001; Table 1 and Table 2). Among the clinical outcome variables, the proportion of mortality was higher among patients without a wound infection (40.2%) (p<.001; Table 2). Among the mode of transmission variables, there was a higher proportion of mortality among patients with foodborne (48.4%) or unknown (45.2%) routes of transmission (p<.001), and cases with mollusk consumption (50.5%; p=.003; Table 2).

Of the variables found to be strongly associated with mortality, only the prevalence of cases reported from certain regions and the prevalence of cases reported with certain modes of transmission were changing over the pre-and post-policy period (Table 3). Compared to the Gulf Coast region, there was a strong decrease in the relationship between mortality and the cases reported from the Pacific Coast, the Atlantic Coast, and the Non-Coastal region during the post-policy period (Table 3). Compared to non-foodborne *Vv.* cases, there was an increase in the association between foodborne cases, unknown cases, and mortality during the post-policy period (Table 3).

The unadjusted models for region produced attenuating measures of association without controlling for race (Table 4 and Table 5). After controlling for race, cases reported from the Non-Coastal region were 1.71 (95% CI: 1.31, 2.22) times as likely to die from a *Vv.* infection compared to cases along the Gulf Coast during the pre-policy period (Table 5). However, cases reported from the Pacific Coast (pRR = 0.11 (95% CI: 0.02, 0.80)) and the Atlantic Coast (pRR = 0.65 (95% CI: 0.50, 0.86)) were protective during the post-policy period and less likely to die when compared to the Gulf Coast region (Table 5). The models that assessed region and mode of transmission together produced similar results. The change in *Vv.* risk for region and mode of transmission were not found to be related (p=0.16); the variables were changing independently over the pre-and post-policy period (Table 5).

The unadjusted models for mode of transmission also produced attenuating measures of association without controlling for sex (Table 4 and Table 5). After controlling for sex, the risk of death among foodborne cases remained elevated and relatively constant across the pre- and post-policy period when compared to non-foodborne related cases (Table 5). However, the risk of death among *Vv.* cases with an unknown origin of transmission increased. After controlling for sex, cases with an unknown transmission route were 2.20 (95% CI: 1.79, 2.70) times more likely to die than non-foodborne related cases during the pre-policy period (Table 5). During the post-policy period, cases with an unknown transmission route were 3.42 (95% CI: 2.60, 4.50) times more likely to die than non-foodborne related cases (Table 5).

Discussion

Summary

The main finding from this study is that the surveillance policy change in 2007 is not solely responsible for the increase in the number of *Vv.* cases reported to COVIS and the decrease in the case fatality rate. The relationship between mortality and reporting region, and mortality and mode of transmission changed from 1988 to 2015, contributing to these trends. Cases reported from states in

the Atlantic, Pacific, and Non-Coastal regions are at a decreased risk for mortality during the post-policy period, and cases with foodborne or unknown routes of transmission are at an increased risk for mortality during the post-policy period.

A possible explanation for the decreased risk in mortality in certain regions may be that doctors treating hospitalized or visiting patients in Non-Coastal, Pacific, and Atlantic regions may be getting better at diagnosing, recognizing, and reporting *Vv.* cases. As a rare and fast-acting infection, particularly in Non-Coastal states, it may have been difficult to identify or treat *Vv.* patients in the past. This may be even more important for patients with a recent travel history, which was found to be strongly associated with mortality as well. Improved diagnostics and timely treatment may help explain the decrease in mortality across this time-period. One example is the increasing use of culture-independent diagnostic testing since 2012 (CIDTs), which allows clinics to diagnose patients with the general type of bacteria within hours without growing cultures (33). While CIDTs cannot distinguish between strains or serotypes of bacteria, they may help doctors and clinics treat patients quickly and efficiently (33). It is also likely that only severe cases in the non-Gulf Coast regions were reported during the pre-policy period, thereby creating a biased, elevated risk of death.

While the elevated risk of death for foodborne infections matches the literature, the increased risk of death among the unknown transmission category may be due to misclassification bias (8, 17). Cases are classified with unknown transmission origin if both food consumption and water exposure data are documented or if food consumption and water exposure data are missing. Many COVIS cases have multiple potential routes of exposure, which increases the risk for misclassification if CDC cannot distinguish between foodborne and non-foodborne cases. It is possible that either the exposure information reported to CDC is incomplete or that more severe cases are exposed to *Vv.* through both food and water, rather than one or the other. The continued high risk of death for foodborne infections may also occur if there are increases in raw seafood consumption. However, the latter is less likely, given that the reported consumption of mollusks, crustaceans, and fish was not increasing over time (Table 3) (8, 17).

Connecting to the Literature

The downward trend in *Vv.* mortality found in this study is consistent with recent research and patterns regarding US *Vibrio* cases (11, 14, 15). Given that *Vv.* became nationally notifiable in 2007, it is possible this pattern is driven by an increase in the total number of *Vv.* cases clinically recognized and reported by non-Gulf Coast states and a consistent number of deaths reported over time. However, a significant downward trend in mortality can be seen as early as 2003 in COVIS data with cases voluntarily reported from a variety of Non-Gulf Coast States. In addition, the number of reported annual deaths ranged from 5 to 41 up to 2007 and 21 to 35 annual deaths after 2007 (10). Suggesting, that both the numerator and the denominator of the case fatality ratios are changing.

In response to the severity of many *Vibrio* infections, the National Shellfish Sanitation Program (NSSP) was created by the FDA and the Interstate Shellfish Sanitation Conference to enforce *Vibrio* control plans for all shellfish producing states (35). States must create a risk evaluation plan for the seasonal variations and environmental factors that influence the risk of *Vv.* infections from their harvest areas (34). If there are at least two confirmed *Vv.* cases from the consumption of the state's commercially harvested oysters within the last 10 years, the shellfish producing state must also create specific *Vv.* control plans for additional testing, labeling, and processing to prevent illness (34). While these regulations are implemented nationwide, California took specific actions in 2003 that linked to the downward trend in *Vv.* mortality (10). California enacted policies to restrict oysters harvested along the Gulf of Mexico during the summer and fall months, when the risk for *Vv.* infections are the greatest (4, 10). While this may be reflected in the decrease of reported California cases (Figure 3), these policies likely do not fully explain the national downward trend and regional patterns of mortality (10, 11).

Overall, the characteristics among cases reported to COVIS are consistent with prior literature, which suggests the majority of cases are white males over the age of 40 with a pre-existing condition (3). However, when stratified by the death, the distribution of data for race contradicts the

literature. While most *Vv.* cases are white, this study shows higher case fatality ratios among patients that identified as African American or black (0.49), Asian (0.48), or another race (0.57; Table 1). Little to no literature describes this pattern or these races as high-risk populations for adverse outcomes from *Vv.* infections, yet their case fatality ratios surpass those who identified as white (0.29). Additional research is needed to understand the underlying factors for *Vv.* outcome disparities across race.

Strengths and Limitations

Using the COVIS dataset to analyze the recent downward trend in *Vv.* mortality was a large strength for this study. COVIS provided a large dataset to assess changing trends on a national scale and to account for potential increases in the number of *Vv.* cases reported immediately after becoming nationally notifiable. Despite the surveillance policy change in 2007, the information requested on the COVIS case report form has remained relatively constant and consistently recorded and reported. Calculating the predicted margins risk ratios to properly estimate the measures of association was another strength of the study. This accounted for the non-rare outcome in the dataset and eliminated any inflation that would have occurred if odds ratios were used to estimate risk ratios. This analysis also controlled for confounding variables, such as sex and race, to provide more accurate risk ratios.

There were some limitations to this study. While it was helpful to dichotomize time, collapsing the continuous variable restricted the trend analysis. In addition, analyzing the data with time as continuous variable or with other categories may lead to different results. Underreporting may also affect this study due to the use of surveillance data. It is likely that many less severe *Vv.* infections, particularly those that result in only gastroenteritis, may not see a physician, be reported to a state public health department, or be included in COVIS (20). Therefore, the total number of *Vv.* cases per year is likely larger and the case fatality ratio smaller. In addition to underreporting, important variables such as: ethnicity, duration of illness, primary sepsis, gastroenteritis, crustacean

consumption and preparation, fish consumption and preparation, and travel history had more than 10% of the data missing. Therefore, the study could not make conclusions about their role in the downward trend in mortality or control for them in the logistic regression models (32).

Further Areas of Research

While this study provided an analysis of contributing patient characteristics, severity, clinical outcomes, and mode of transmission variables to explain the possible downward trend in *Vv.* mortality, additional studies on the role of climate change and environmental factors would also be helpful. The warming of coastal waters and environmental factors that contribute to the proliferation of *Vv.* bacterium in oysters may provide insight into the increased incidence rates of *Vv.* reported in the literature and guidance for safer oyster harvesting (11). Identifying and then testing oyster harvest areas with a history of related *Vv.* cases may improve public health interventions and policies to decrease the risk of mortality from *Vibrio*.

In conclusion, the study results demonstrate there is a significant downward trend in *Vv.* mortality partially due to a shift in where cases are reported and the mode of transmission. *Vv.* cases reported from the Pacific and Atlantic Coasts are at a significantly and decreasingly lower risk for death compared to the cases reported from the Gulf Coast over time. *Vv.* cases with a foodborne or unknown transmission route have a significantly and increasingly higher risk for death compared to non-foodborne cases over time. Future public health interventions surrounding safe-food education is needed across the Gulf Coast and Non-Coastal states, particularly for raw seafood consumers. Research evaluating the impact of certain interventions and environmental factors is needed to completely understand *Vv.* trends across the regions.

Tables and Figures

Figure 1. Trend of *Vibrio vulnificus* mortality from 1988 to 2015 using the Cholera and other *Vibrio* Illness Surveillance System (COVIS).

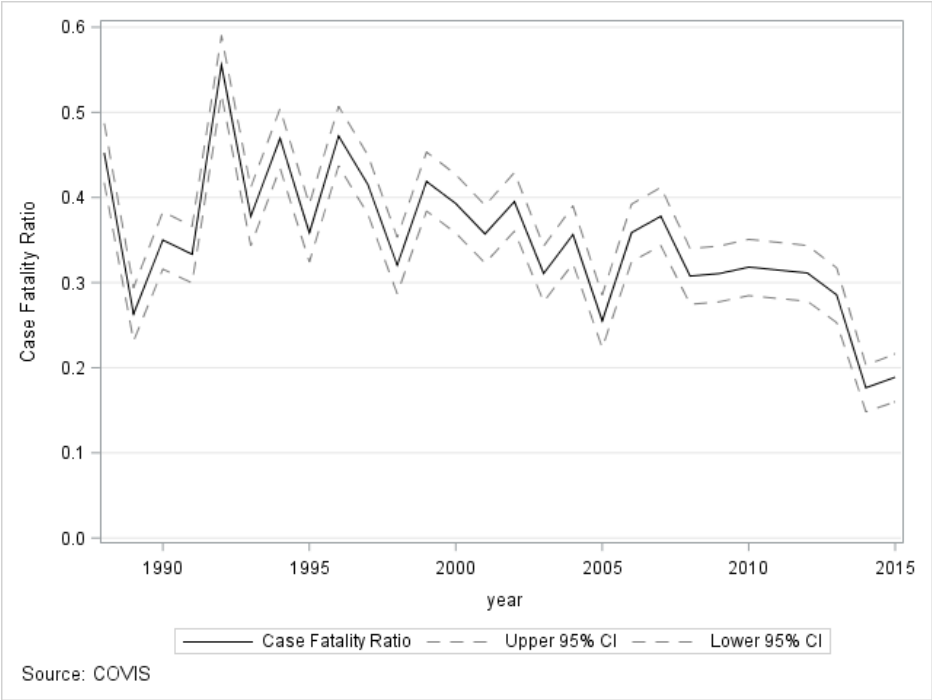

Figure 2. Number of *Vibrio vulnificus* cases from 1988 to 2015 using the Cholera and other *Vibrio* Illness Surveillance System (COVIS)

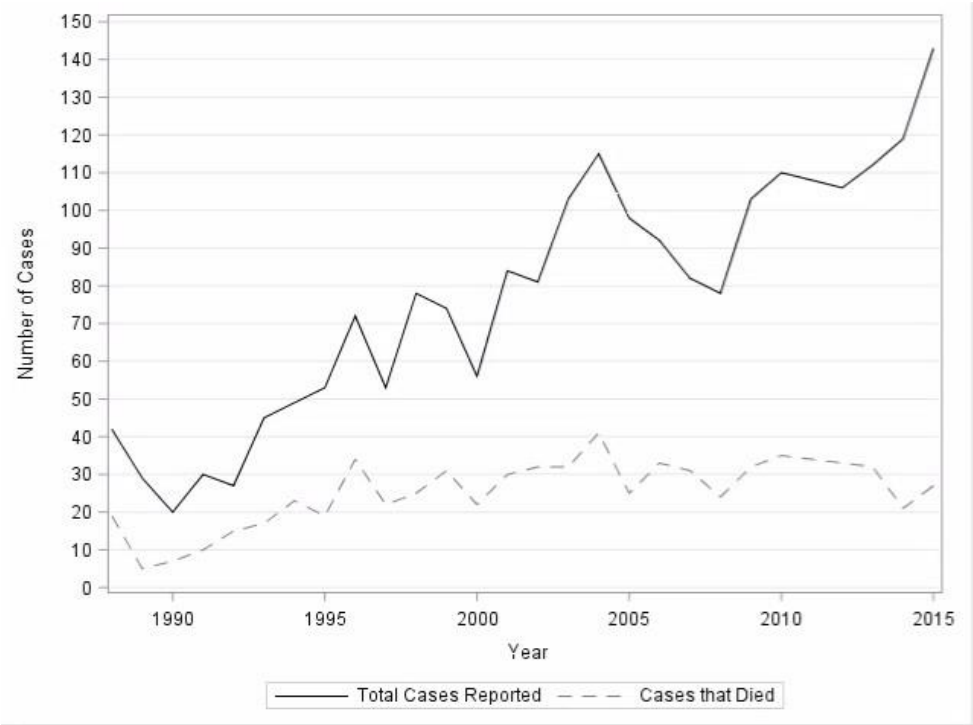

Figure 3. *Vibrio vulnificus* cases reported to the Cholera and Other *Vibrio* Surveillance System (COVIS), by time and state

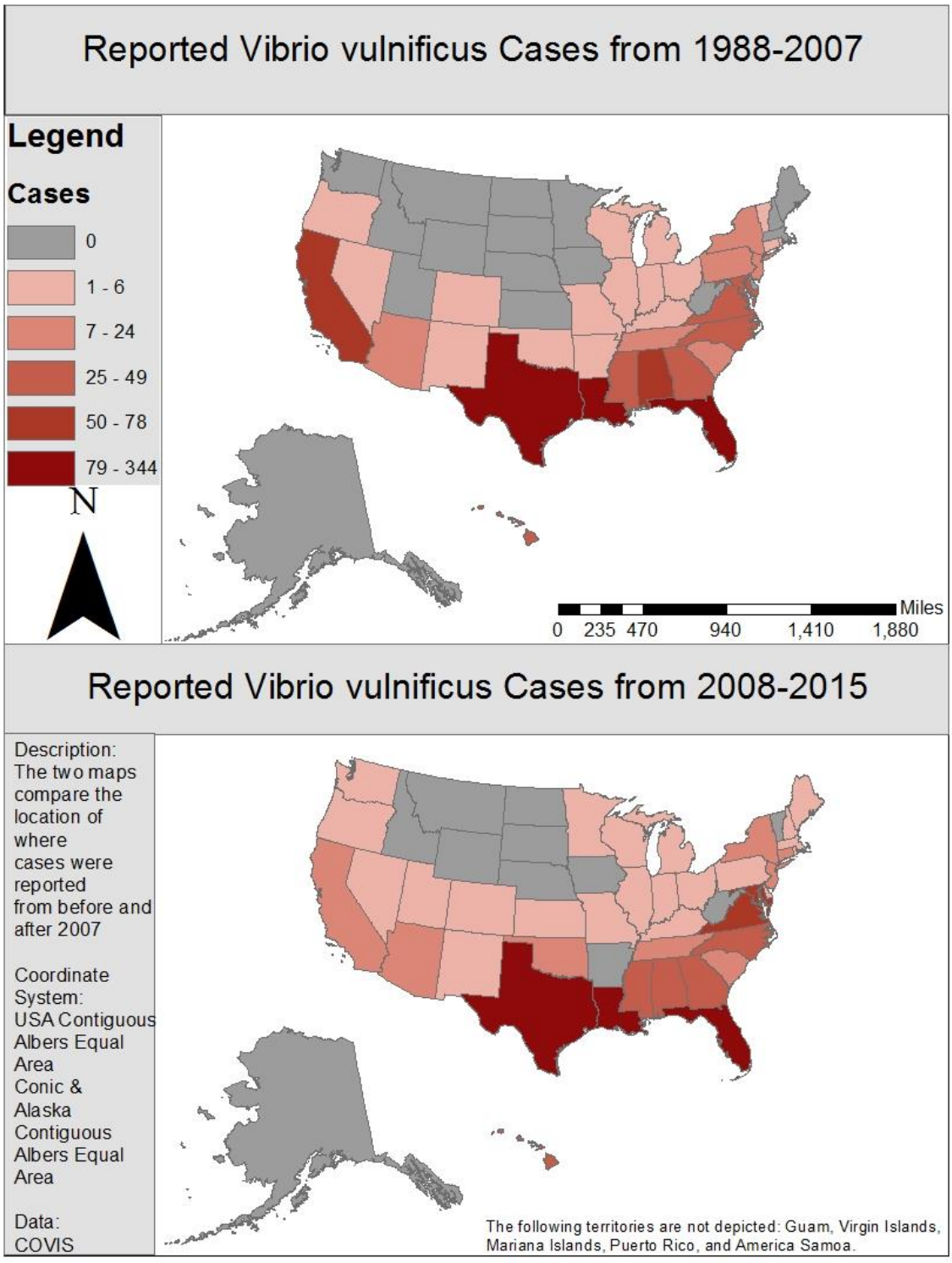

Table 1. *Vibrio vulnificus* patient characteristics and associations with mortality from 1988-2015, using the Cholera and other *Vibrio* Illness Surveillance System (COVIS)

Variables		N	No. (%)	Death n (Row %)	Chi- Square
Patient Characteristics					
Sex		2152	2145 (99.7%)		0.08
	Female		299 (14.0%)	112 (37.5%)	
	Male		1838 (86.0%)	594 (32.3%)	
Age		2152	2122 (98.8%)		<.001
	<5		4 (0.2%)	0 (0%)	
	5-9		14 (0.7%)	0 (0%)	
	10 - 19		44 (2.1%)	2 (4.6%)	
	20 - 29		49 (2.3%)	5 (10.2%)	
	30 - 39		133 (6.3%)	42 (31.6%)	
	40 - 49		366 (17.3%)	171 (46.7%)	
	50 -59		505 (23.8%)	226 (44.8%)	
	60 - 69		444 (20.9%)	122 (27.5%)	
	70 -79		370 (17.4%)	78 (21.1%)	
	79 <		193 (9.1%)	55 (28.5%)	
Race		2152	1918 (89.1%)		<.001
	White		1625 (84.7%)	474 (29.2%)	
	Black or African American		160 (8.3%)	79 (49.4%)	
	Asian		73 (3.8%)	35 (47.0%)	
	American Indian or Alaska Native		4 (0.2%)	1 (25%)	
	Native Hawaiian or Pacific Islander		7 (0.4%)	0 (0%)	
	Other		49 (2.6%)	28 (57.1%)	
Ethnicity[1]		1664	746 (44.8%)		<.001
	Hispanic or Latino		75 (10.1%)	43 (57.3%)	
	Not Hispanic or Latino		671 (90.0%)	187 (27.9%)	
Pre-existing Conditions[2]		2152	1990 (92.5%)		<.001
	At Least One		1600 (80.4%)	651 (40.7%)	
	None		390 (19.6%)	20 (5.1%)	
Region Reported		2152	2152 (100%)		<.001
	Gulf Coast		1393 (64.7%)	453 (32.5%)	
	Pacific		139 (6.5%)	64 (46.0%)	
	Atlantic		479 (22.3%)	132 (27.6%)	
	Non-Coastal		141 (6.6%)	62 (44.0%)	

[1]Ethnicity data was not collected by COVIS until 1999. Calculated for cases reported after 1999.
[2]Includes the following: alcoholism, diabetes, peptic ulcer, gastric surgery, heart disease, immunodeficiency, liver disease, malignancy, and renal disease.

Table 2. *Vibrio vulnificus* severity, clinical outcomes, transmission modes, and associations with mortality from 1988-2015, using the Cholera and other *Vibrio* Illness Surveillance System (COVIS)

Variable	N	No. (%)	Death n (Row %)	Chi-Square
Severity				
Hospitalization	2152	2106 (97.9%)		<.001
Yes		1884 (89.5%)	677 (35.9%)	
No		222 (10.5%)	16 (7.2%)	
Duration of Illness	2152	1179 (54.8%)		<.001
0 to 3 Days		327 (27.7%)	254 (77.7%)	
4 to 11 Days		518 (43.9%)	165 (31.9%)	
>11 Days		334 (28.3%)	72 (21.6%)	
Clinical Outcome				
Primary Sepsis[1]	2152	969 (45.0%)		<.001
Yes		476 (49.1%)	328 (68.9%)	
No		493 (50.9%)	82 (16.6%)	
Wound Infection[2]	2152	2032 (94.4%)		<.001
Yes		488 (24.0%)	50 (10.3%)	
No		1544 (76.0%)	620 (40.2%)	
Gastroenteritis[3]	2152	1710 (79.5%)		<.001
Yes		867 (50.7%)	344 (39.7%)	
No		843 (49.3%)	182 (21.6%)	
Transmission Mode				
Mode of Transmission[4]	2152	2152 (100%)		0.02
Foodborne		612 (28.4%)	296 (48.4%)	
Non-Foodborne		1005 (46.7%)	173 (17.2%)	
Unknown		535 (24.9%)	242 (45.2%)	
Type of Seafood: Mollusks[5,7]	612	581 (94.9%)		0.003
Eaten		542 (93.3%)	274 (50.5%)	
Not Eaten		39 (6.7%)	10 (25.6%)	
Type of Seafood: Crustaceans[6,7]	612	377 (61.6%)		0.41
Eaten		197 (52.3%)	90 (45.7%)	
Not Eaten		180 (47.8%)	75 (41.7%)	
Type of Seafood: Fish[7]	612	336 (54.9%)		0.39
Eaten		107 (31.9%)	49 (45.8%)	
Not Eaten		229 (68.2%)	94 (41.1%)	
Seafood Preparation: Mollusks[5,8]	542	483 (89.1%)		0.55
Raw		480 (99.4%)	244 (50.8%)	
Not Raw		3 (0.62%)	1 (33.3%)	
Seafood Preparation: Crustaceans[6,8]	197	17 (8.6%)		0.48
Raw		13 (76.5%)	4 (30.8%)	
Not Raw		4 (23.5%)	2 (50.0%)	
Seafood Preparation: Fish[8]	107	85 (79.4%)		0.33
Raw		18 (21.2%)	6 (33.3%)	
Not Raw		67 (78.8%)	31 (46.3%)	
Travel History[9]	2152	1888 (87.7%)		0.04
Yes		270 (14.3%)	96 (35.6%)	
No		1540 (81.6)	451 (29.3%)	

[1]Primary sepsis is defined as septic shock from a blood specimen.
[2]Wound infections defined as a wound specimen.
[3]Gastroenteritis defined as cases presenting vomiting or diarrhea.

[4]Includes confirmed and probable cases categorized by CDC's method for classification of transmission routes in the COVIS system
[5]Includes: oysters, clams, and mussels.
[6]Includes: crabs, lobsters, crayfish, and shrimp.
[7]Calculated only for foodborne cases
[8]Calculated only if type of seafood was eaten.
[9]Travel defined as domestic cases that traveled outside home state in the 7 days before the onset of symptoms.

Table 3. Interaction assessment for patient characteristics, severity, clinical outcomes, and transmission mode variables, by time

Variables	β	Standard Error	95% Confidence Interval
Patient Characteristics			
Sex (ref=Female)	0.05	0.27	(-0.48, 0.57)
Age (ref= 20-39)			
≤19	11.94	287.60	(-551.75, 575.64)
20 – 39	0.00	0.00	-
40 - 59	0.16	0.43	(-2.01, 1.23)
60 - 79	0.22	0.43	(-0.68, 0.99)
79 <	-0.14	0.52	(-1.15, 0.88)
Race (ref=White)			
White	0.00	0.00	-
Black or African American	0.68	0.35	(-0.005, 1.37)
Asian	0.53	0.61	(-0.66, 1.71)
Other	-0.68	0.74	(-2.14, 0.78)
Ethnicity (ref= Not Hispanic or Latino)	-12.74	578.20	(-1146.01, 1120.53)
Pre-Existing Conditions (ref=none)	0.22	0.51	(-0.78, 1.22)
Region (ref= Gulf Coast)			
Gulf Coast	0.00	0.00	-
Pacific	-2.53	0.77	(-4.04, -1.02)
Atlantic	-0.64	0.24	(-1.11, -0.17)
Non-Coastal	-0.73	0.37	(-1.45, -0.01)
Severity			
Hospitalization (ref=No)	0.64	0.57	(-0.47, 1.75)
Duration of Illness (ref= 4 to 11 Days)			
0 to 3 Days	-0.48	0.37	(-1.21, 0.26)
4 to 11 Days	0.00	0.00	-
>11 Days	-0.61	0.35	(-1.29, 0.07)
Clinical Outcomes			
Primary Sepsis[2] (ref=No)	-0.11	0.29	(-0.67, 0.46)
Wound Infection (ref=No)	-0.004	0.43	(-0.84, 0.83)
Gastroenteritis (ref=No)	-0.72	0.44	(-1.59, 0.14)
Mode of Transmission			
Mode of Transmission (ref=Non-foodborne)[6]			
Foodborne	0.02	0.25	(-0.46, 0.51)
Non-Foodborne	0.00	0.00	-
Unknown	0.54	0.25	(0.05, 1.02)
Type of Seafood: Mollusks[7,9] (ref=No)	-0.58	0.90	(-2.33, 1.18)
Type of Seafood: Crustaceans[8,9] (ref=No)	0.54	0.44	(-0.33, 1.40)
Type of Seafood: Fish[8] (ref=No)	-0.22	0.50	(-1.20, 0.76)
Seafood Preparation: Mollusks[7,9] (ref=No)	12.78	736.30	(-1455.93, 1430.37)
Seafood Preparation: Crustaceans[8,9] (ref=No)	N/A	N/A	N/A
Seafood Preparation: Fish[9] (ref=No)	0.62	1.17	(-1.67, 2.92)
Travel History[11]	0.50	0.29	(-0.07, 1.07)

Time is categorized into before and after the 2007 surveillance policy change.
[1] Ethnicity data was not collected by COVIS until 1999. Calculated for cases reported after 1999.

[2]Includes the following: alcoholism, diabetes, peptic ulcer, gastric surgery, heart disease, immunodeficiency, liver disease, malignancy, and renal disease.
[3]Primary sepsis is defined as septic shock from a blood specimen.
[4]Wound infections defined as a wound specimen.
[5] Gastroenteritis defined as cases presenting vomiting or diarrhea.
[6]Includes confirmed and probable cases categorized by CDC's method for classification of transmission routes in the COVIS system.
[7]Includes: oysters, clams, and mussels.
[8]Includes: crabs, lobsters, crayfish, and shrimp.
[9]Calculated only for foodborne cases.
[10]Calculated only if type of seafood was eaten.
[11] Travel defined as domestic cases that traveled outside home state in the 7 days before the onset of symptoms.

Table 4. Unadjusted logistic regression models and corresponding predicted margin risk ratios, by time

Exposure	From 1988 to 2007 pRR (95% CI)	From 2008 to 2015 pRR (95% CI)
Considers Region and Mode Separately		
Region Reported[1]		
Gulf Coast	1.0	1.0
Pacific Coast	1.63 (1.34, 1.97)	0.25 (0.07, 0.96)
Atlantic Coast	1.07 (0.88, 1.30)	0.67 (0.51, 0.88)
Non-Coastal	1.64 (1.29, 2.07)	1.11 (0.70, 1.57)
Mode of Transmission[1]		
Foodborne	3.01 (2.25, 4.01)	2.54 (2.10, 3.07)
Non-Foodborne	1.0	1.0
Unknown	3.41 (2.59, 4.49)	2.19 (1.78, 2.9)
Considers Region and Mode of Transmission Together		
Region Reported[2]		
Gulf Coast	1.0	1.0
Pacific Coast	1.38 (1.12, 1.71)	0.29 (0.09, 1.01)
Atlantic Coast	0.97 (0.79, 1.17)	0.73 (0.57, 0.94)
Non-Coastal	1.18 (0.89, 1.57)	0.84 (0.58, 1.22)
Mode of Transmission[2]		
Foodborne	2.41 (1.98, 2.94)	2.98 (2.22, 4.00)
Non-Foodborne	1.0	1.0
Unknown	2.15 (1.75, 2.64)	3.30 (2.50, 4.35)

[1] Considers interaction with time

[2] Considers interaction with time for region and mode of transmission.

Table 5. Adjusted logistic regression models and corresponding predicted margin risk ratios by time

Exposure	From 1988 to 2007 pRR (95% CI)	From 2008 to 2015 pRR (95% CI)
Considers Region and Mode Separately		
Region Reported[1]		
Gulf Coast	1.0	1.0
Pacific Coast	1.27 (0.92, 1.74)	0.11 (0.02, 0.80)
Atlantic Coast	1.05 (0.85, 1.30	0.65 (0.50, 0.86)
Non-Coastal	1.71 (1.31, 2.22)	1.05 (0.73, 1.52)
Mode of Transmission[2]		
Foodborne	2.53 (2.09, 3.07)	2.98 (2.23, 3.98)
Non-Foodborne	1.0	1.0
Unknown	2.20 (1.79, 2.70)	3.42 (2.60, 4.50)
Considers Region and Mode of Transmission Together		
Region Reported[3]		
Gulf Coast	1.0	1.0
Pacific Coast	1.14 (0.82, 1.60)	0.15 (0.02, 0.92)
Atlantic Coast	0.94 (0.76, 1.16)	0.71 (0.55, 0.92)
Non-Coastal	1.22 (0.89, 1.67)	0.81 (0.55, 1.20)
Mode of Transmission[4]		
Foodborne	2.47 (1.99, 3.06)	2.90 (2.12, 3.96)
Non-Foodborne	1.0	1.0
Unknown	2.15 (1.72, 2.68)	3.28 (2.45, 4.39)

[1] Controls for race and considers interaction with time
[2] Controls for sex and consider interaction with time
[3] Controls for sex and race, and mode of transmission; considers interaction with time and interaction of mode of transmission.
[4] Controls for sex and race; considers interaction with time and region with time.

Chapter III. Future Implications for Public Health

This study found that *Vv.* cases infected through foodborne and unknown routes of transmission are at an increased risk for mortality from 1988-2015, which suggests improving oyster harvesting policies, seafood consumer education, and surveillance is needed. Currently, there are three common post-harvesting oyster treatment practices in the seafood industry: individual oyster freezing, mild heat-cool pasteurization, and high hydro-static pressure processing (10). However, these practices alone are ineffective given the overall incidence and risk of death, particularly among oysters harvested along the Gulf Coast (10). These oysters are known to have higher levels of *Vv.* compared to oysters harvested along the Pacific or Atlantic Coasts during the summer months, many of which provide little to no visible warning signs of contamination (10). This influenced California to implement additional annual restrictions on oysters harvested from the Gulf Coast during the summer months (April through May) in 2003, where oysters cannot have more than 3 organisms/gm/oyster meat (10). A recent study found this policy to be effective in reducing both the number of *Vv.* related cases and deaths (10). The median number of California cases dropped from 5.5 to 0, and the median number of deaths in California dropped from 2.5 to 0 after the policy was enacted, suggesting other states may benefit from similar restrictions (10). The results from this study suggest Gulf Coast states, which experienced a significant increase in mortality from *Vv.*, and Non-Coastal states, which experienced an elevated risk, would benefit the most.

The increasing risk of *Vv.* foodborne infections also suggests the need for improved education or warnings to seafood consumers about the potential risks of eating raw oysters. Despite multiple multi-lingual warning labels on consumer products and restaurant menus, the authors found little to no change in the proportion of persons eating raw oysters in California (10). In contrast with the efforts made by the Interstate Shellfish Sanitation Conference (a collaboration between the US Department of Agriculture, the US Environmental Protection Agency, the shellfish industry, and the Gulf Coast states), a 2004 national survey did not find a significant increase in the knowledge among consumers about the potential hazards of consuming raw seafood or the populations at increased

risk for adverse outcomes (10, 35, 36). However, recent decreases in *Vibrio* related illness in Florida suggests educational materials, messages, and presentations for consumers and healthcare providers can be successful and should be studied for future implementation at the national level (35, 36). Increasing the awareness of *Vv.* infections and at-risk populations with certain underlying health conditions will help reduce the overall incidence and case fatality. Additional educational messaging to individuals with occupational and recreational risks for *Vibrio* should also be used (36). Though this study did not find an increased risk for mortality among non-foodborne infections, increased ocean temperatures and increased risk for mortality among cases with unknown origins of infection (classified as both foodborne and water exposures or missing data for foodborne and water exposures) suggest a need for interventions as well (36).

The significant and increased risk for mortality among cases with unknown routes of transmission also suggests the need for improved *Vibrio* surveillance. Additional surveillance metrics measuring the completeness of foodborne and waterborne exposure data reported by states may improve the categorization of cases and monitoring of trends. Information on oyster harvest areas and seafood traceback data for foodborne cases could also be improved and help identify areas associated with *Vv.* outbreaks or patterns of infections. In order to make these improvements, health departments may require additional resources, as the information currently provided is often incomplete.

References

1. Altekruse SF, Bishop RD, Baldy LM, Thompson SG, Wilson SA, Ray BJ, et al. Vibrio gastroenteritis in the US Gulf of Mexico region: the role of raw oysters. Epidemiol Infect. 2000 Jun;124(3):489-95.

2. Daniels NA. Vibrio vulnificus oysters: pearls and perils. Clin Infect Dis. 2011 Mar 15;52(6):788-92.

3. Shapiro RL, Altekruse S, Hutwagner L, Bishop R, Hammond R, Wilson S, et al. The role of Gulf Coast oysters harvested in warmer months in Vibrio vulnificus infections in the United States, 1988-1996. Vibrio Working Group. J Infect Dis. 1998 Sep;178(3):752-9.

4. Dechet AM, Yu PA, Koram N, Painter J. Nonfoodborne Vibrio infections: an important cause of morbidity and mortality in the United States, 1997-2006. Clin Infect Dis. 2008 Apr 01;46(7):970-6.

5. Klontz KC, Lieb S, Schreiber M, Janowski HT, Baldy LM, Gunn RA. Syndromes of Vibrio vulnificus infections. Clinical and epidemiologic features in Florida cases, 1981-1987. Ann Intern Med. 1988 Aug 15;109(4):318-23.

6. Chen SC, Chan KS, Chao WN, Wang PH, Lin DB, Ueng KC, et al. Clinical outcomes and prognostic factors for patients with Vibrio vulnificus infections requiring intensive care: a 10-yr retrospective study. Crit Care Med. 2010 Oct;38(10):1984-90.

7. Klontz KC, B. Timbo, S. Fein, and A. Levy. Prevalence of selected food consumption and preparation behaviors associated with increased risks of food-borne disease. J Food Prot 1995;58:927-30.

8. Menon MP, Yu PA, Iwamoto M, Painter J. Pre-existing medical conditions associated with Vibrio vulnificus septicaemia. Epidemiol Infect. 2014 Apr;142(4):878-81.

9. Centers for Disease C. Cholera and Other Vibrio Illness Surveillance Overview. Atlanta, GA: US Department of Health and Human Services, CDC; 2012.

10. Vugia DJ, Tabnak F, Newton AE, Hernandez M, Griffin PM. Impact of 2003 state regulation on raw oyster-associated Vibrio vulnificus illnesses and deaths, California, USA. Emerg Infect Dis. 2013 Aug;19(8):1276-80.

11. Newton A, Kendall M, Vugia DJ, Henao OL, Mahon BE. Increasing rates of vibriosis in the United States, 1996-2010: review of surveillance data from 2 systems. Clin Infect Dis. 2012 Jun;54 Suppl 5:S391-5.

12. Oliver JD. Vibrio vulnificus: death on the half shell. A personal journey with the pathogen and its ecology. Microb Ecol. 2013 May;65(4):793-9.

13. Iwamoto M, Ayers T, Mahon BE, Swerdlow DL. Epidemiology of seafood-associated infections in the United States. Clin Microbiol Rev. 2010 Apr;23(2):399-411.

14. Vezzulli, L., Brettar, I., Pezzati, E., Reid, P. C., Colwell, R. R., Höfle, M. G., & Pruzzo, C. (2012). Long-term effects of ocean warming on the prokaryotic community: evidence from the vibrios. *The ISME Journal*, *6*(1), 21–30. http://doi.org/10.1038/ismej.2011.89

15. Centers for Disease C. Cholera and other vibrio illness surveillance (COVIS), summary data. Atlanta, GA: CDC; 1999.

16. Centers for Disease C. Cholera and other vibrio illness surveillance (COVIS), summary data. Atlanta, GA: US Department of Health and Human Services; 2014.

17. Horseman MA, Surani S. A comprehensive review of Vibrio vulnificus: an important cause of severe sepsis and skin and soft-tissue infection. Int J Infect Dis. 2011 Mar;15(3):e157-66.

18. Organization WH. Risk assessment of VIbrio vulnificus in raw oysters: an interpretative summary and technical report. Geneva: World Health Organization; 2005.

19. Scallan E, Griffin PM, Angulo FJ, Tauxe RV, Hoekstra RM. Foodborne illness acquired in the United States--unspecified agents. Emerg Infect Dis. 2011 Jan;17(1):16-22.

20. Mead PS SL, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. Emerg Infect Dis. 1999;5:607-25.

21. Strom MS, Paranjpye RN. Epidemiology and pathogenesis of Vibrio vulnificus. Microbes Infect. 2000 Feb;2(2):177-88.

22. Chiang SR, Chuang YC. Vibrio vulnificus infection: clinical manifestations, pathogenesis, and antimicrobial therapy. J Microbiol Immunol Infect. 2003 Jun;36(2):81-8.

23. Chou TN, Lee YT, Lai YY, Chao WN, Yang C, Chen CC, et al. Prognostic factors for primary septicemia and wound infection caused by Vibrio vulnificus. Am J Emerg Med. 2010 May;28(4):424-31.

24. Klontz KC, Desenclos JC, Wolfe LE, Hoecherl SA, Roberts C, Gunn RA. The raw oyster consumer--a risk taker? Use of the Behavioral Risk Factor Surveillance System. Epidemiology. 1991 Nov;2(6):437-40.

25. Nesbitt A, Majowicz S, Finley R, Marshall B, Pollari F, Sargeant J, et al. High-risk food consumption and food safety practices in a Canadian community. J Food Prot. 2009 Dec;72(12):2575-86.

26. Patil SR, Cates S, Morales R. Consumer food safety knowledge, practices, and demographic differences: findings from a meta-analysis. J Food Prot. 2005 Sep;68(9):1884-94.

27. Shiferaw B, Yang S, Cieslak P, Vugia D, Marcus R, Koehler J, et al. Prevalence of high-risk food consumption and food-handling practices among adults: a multistate survey, 1996 to 1997. The Foodnet Working Group. J Food Prot. 2000 Nov;63(11):1538-43.

28. Altekruse SF, Yang S, Timbo BB, Angulo FJ. A multi-state survey of consumer food-handling and food-consumption practices. Am J Prev Med. 1999 Apr;16(3):216-21.

29. Jones MK, Oliver JD. Vibrio vulnificus: disease and pathogenesis. Infect Immun. 2009 May;77(5):1723-33.

30. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. Virulence. 2014 Jan 1;5(1):12-9.

31. Centers for Disease C. Cholera and other vibrio illness surveillance (COVIS), summary data. Atlanta, GA: US Department of Health and Human Services; 2014.

32. Centers for Disease C. *Analyze and Interpret Surveillance Data*. Atlanta, GA: US Department of Health and Human Services; 2013.

33. Aamer Imdad, Fiona Retzer, Linda S Thomas, Marcy McMillian, Katie Garman, Peter F Rebeiro, Stephen A Deppen, John R Dunn, Amy M Woron; Impact of Culture-Independent Diagnostic Testing on Recovery of Enteric Bacterial Infections, *Clinical Infectious Diseases*, , cix1128, https://doi.org/10.1093/cid/cix1128

34. Food and Drug Administration. National Shellfish Sanitation Program: Guide for the Control of Molluscan Shellfish 2015 Revision. Silver Spring, MD: US Department of Health and Human Services; 2015.

35. Vugia DJ, Tabnak F, Newton AE, Hernandez M, Griffin PM. Impact of 2003 State Regulation on Raw Oyster–associated Vibrio vulnificus Illnesses and Deaths, California,USA. Emerg Infect Dis. 2013;19(8):1276-1280. https://dx.doi.org/10.3201/eid1908.121861

36. Weis, K., Hammond, R., Hutchinson, R., & Blackmore, C. (2011). Vibrio illness in Florida, 1998–2007. *Epidemiology and Infection, 139*(4), 591-598. doi:10.1017/S0950268810001354