HHS Public Access

Author manuscript

Epidemiol Infect. Author manuscript; available in PMC 2015 October 08.

Published in final edited form as:

Epidemiol Infect. 2014 April ; 142(4): 878–881. doi:10.1017/S0950268813001593.

Pre-existing medical conditions associated with *Vibrio vulnificus* septicaemia

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SUMMARY

Vibrio vulnificus (*Vv*) can result in severe disease. Although pre-existing liver disease is a recognized risk factor for serious infection, the relative importance of other comorbidities has not been fully assessed. We analysed reports of *Vv* infections submitted to CDC from January 1988 to September 2006 in order to assess the role of pre-existing conditions contributing to severe outcomes. A total of 1212 patients with *Vv* infection were reported. Only patients with liver disease [adjusted odds ratio (aOR) 5·1)] were more likely to become septic when exposure was due to contaminated food. Patients with liver disease (aOR 4·1), a haematological disease (aOR 3·2), or malignancy (aOR 3·2) were more likely to become septic when infection was acquired via a non-foodborne exposure. As such, patients with these pre-existing medical conditions should be advised of the risk of life-threatening illness after eating undercooked contaminated seafood or exposing broken skin to warm seawater.

Keywords

Pre-existing condition; septicaemia; *Vibrio vulnificus*

Vibrio vulnificus (*Vv*), a Gram-negative rod, was first isolated by the Centers for Disease Control and Prevention (CDC) in 1964 and identified as a human pathogen in 1976 [1]. Blake *et al.* initially described the epidemiology, including mode of transmission, routes of transmission and risk factors of *Vv*, which cause an estimated 200 infections annually in the USA, nearly half of which are foodborne in origin [2, 3]. In the USA, *Vv*, which naturally occur in marine and estuarine environments and are related to a host of environmental parameters including sea surface temperatures, are found in high numbers in the Gulf of Mexico [4, 5]. Massive flooding from the Gulf of Mexico in 2005, consequent to Hurricane Katrina resulted in 14 reported cases of *Vv* wound infection, probably via broken skin contact with seawater, and three *Vv*-attributed deaths [6]. Infection may also result from eating contaminated seafood, typically raw oysters harvested from the Gulf. Although the numbers of annual cases are relatively low, the severity of infection is high, with over 90% of infected patients requiring hospitalization and an estimated case-fatality rate of 34·9% [3].

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DECLARATION OF INTEREST

None.

Severe disease with a fatal outcome is more prevalent in those with pre-disposing medical conditions and *Vv* is a leading cause of seafood-associated fatalities in the USA [7, 8]. Despite continued prevention efforts, data from both active and passive surveillance systems report increasing rates of infection [9].

Although pre-existing liver disease is a recognized risk factor for serious infection, the relative importance of other comorbidities, by route of exposure, has not been fully assessed.

The Cholera and Other Vibrio Illness Surveillance System (COVIS) was initiated by CDC, FDA, and the Gulf Coast states (Alabama, Florida, Louisiana, Mississippi, Texas) in 1988. CDC has maintained a database of *Vibrio* infections from humans in order to obtain data on illnesses associated with *Vibrio* spp. Participating health officials collect clinical data, information about underlying illness, history of seafood consumption, and exposure to seawater during the 7 days before illness. When possible, this information assists in epidemiological investigations to identify the implicated vehicle. Prior to 2007, toxigenic *Vibrio cholerae* O1 and O139, the causative agents of cholera, were the only nationally notifiable species. Despite sporadic reports from other states (non-coastal and Pacific and Atlantic coasts), the expansion of COVIS in 1997 marked the point when nearly all states were voluntarily reporting all *Vibrio* spp. Indeed, by 1997, all but one state had reported *Vibrio* cases to COVIS. Infection with any *Vibrio* spp. (vibriosis) became nationally reportable in 2007.

State and county health departments report infection of all species, along with demographic (e.g. age, sex), clinical (including pre-existing medical conditions), and exposure data (i.e. seafood consumption, travel history, skin exposure to seawater, drippings from raw or live seafood, or contact with marine wildlife) to the CDC via a standardized reporting form. Pre-existing medical conditions, including diabetes, heart disease, haematological disease (e.g. anaemia, thalassaemia), immunodeficiency, malignancy, peptic ulcer disease, gastric surgery, renal disease and liver disease are specified on the reporting form. In this analysis, reported alcoholism was coded as a proxy for liver disease. Data on the source of the specimen and the species isolated are also reported; molecular data are not collected.

We analysed reports of *Vv* infections submitted to COVIS from January 1988 to September 2006. The source of *Vv* exposure was determined by clinical signs and patient's history, and was characterized as either foodborne or non-foodborne. A non-foodborne infection required isolation of *Vv* from a wound or from another source (e.g. external ear, skin) with documented direct contact with saltwater, marine wildlife, raw seafood, or seafood drippings. All other infections were considered foodborne. Septicaemia was defined as isolation of the pathogen from the blood in patients with self-reported fever and hypotension (systolic blood pressure <90 mmHg). We categorized medical conditions as 'present' if the report indicated the patient had the diagnosis. Otherwise, the condition was considered 'not present'. Cases with multiple *Vibrio* spp. were excluded from analysis.

Here we assess pre-existing medical conditions as risk factors for septic *vs.* non-septic *Vv* infection, by route of exposure (foodborne and non-foodborne). We conducted both bivariate analysis [odds ratio (OR), χ^2 test for significance] and logistic regression. The

initial multivariate model included all significant variables from the bivariate analysis. The final model excluded non-significant factors from the initial multivariate model. A population attributable risk percentage was calculated:

$$(\mathrm{OR}-1/\mathrm{OR}) \times \% \text{ of cases with attribute.}$$

A total of 1212 patients with *Vv* infection were reported; 86% were male, 87% were hospitalized, 72% were septic, and 33% died. The median age of patients with an infection was 56 years. Nearly half (48%) were classified as a non-foodborne infection; the remaining cases were classified as foodborne. At least one pre-existing medical condition was reported for 80% of patients; liver disease was most prevalent (40%), followed by heart disease (23%), diabetes (20%), and renal disease (10%). The prevalence of the other pre-existing conditions was each <10%. Patients who acquired infection via contaminated food were significantly more likely to be female (15% *vs*. 11%), younger (55 *vs*. 58 years), non-white (30% *vs*. 15%), have a greater number of pre-existing medical conditions (1·5 *vs*. 1·1) and become septic (87% *vs*. 55%) than those patients who acquired a non-foodborne infection.

Nearly 2/3 (63%) of the septic cases were acquired via contaminated food while the majority (77%) of non-septic cases were non-foodborne infections. Of the patients who were septic, 87% were male. The case-fatality rate of septic cases was 44%; of non-septic cases only 7% died.

Pre-existing medical conditions differed in septic *vs.* non-septic cases and by route of exposure (Table 1). On bivariate analysis of pre-existing medical conditions associated with *Vv* septicaemia from a food-borne exposure, patients with liver disease, haematological disease, diabetes, or peptic ulcer disease were more likely to develop septicaemia. On bivariate analysis of pre-existing medical conditions associated with *Vv* septicaemia from a non-foodborne exposure, patients with liver disease, malignancy, haematological disease, heart disease, or diabetes were more likely to be septic.

Using logistic regression and adjusting for age, sex, and the number of pre-existing conditions, only patients with liver disease (aOR 5·1) were more likely to become septic when exposure was due to contaminated food. Patients with liver disease (aOR 4·1), a haematological disease (aOR 3·2), or malignancy (aOR 3·2) were more likely to become septic when infection was acquired via a non-foodborne exposure (Table 2). Having multiple pre-existing conditions was associated with severe illness. However, in patients with vibriosis who developed septicaemia, only liver disease had an attributable risk percentage >10% (24% of non-foodborne infections; 47% of foodborne infections).

Vv infection results in high morbidity and mortality. Over 70% of infected patients become septic, of which significantly more patients become septic after acquiring infection via a foodborne exposure, and nearly half of septic patients die. Liver disease has already been well characterized as a host risk factor for serious infection, including sepsis and death [4, 5, 8, 10, 11]. In this analysis, we included other potential risk factors and found that only persons with liver disease, were at increased risk of developing septicaemia for both foodborne and non-foodborne exposure. Patients with a haematological disease, or an

underlying malignancy, were at increased risk of developing septicaemia with a non-foodborne infection, but were not at increased risk if the exposure was foodborne. Although the reason for this discrepancy is unknown, both of these conditions may alter the immune system and impair wound healing, and are documented risk factors for other invasive bacterial infections [12].

Given that the results presented here are from a case-series analysis, we cannot determine the individual risk of infection for patients with specific conditions. Due to the relatively low percentage of patients with certain pre-existing conditions [e.g. malignancy (9%) or haematological disease (8%)], this analysis is unable to provide information on the importance of a specific type of condition (e.g. breast cancer). Moreover, this analysis is unable to characterize the severity of conditions (e.g. stage of malignancy, degree of neutropenia) associated with sepsis because such information is not currently collected in this surveillance system. Additionally, as we did not have molecular typing data, we were unable to evaluate the role of risk factors by particular *Vv* strain. This analysis covers data reported to COVIS from 1988 to 2006, which corresponds to the time period from the initiation of this surveillance system until the time that vibriosis became a nationally notifiable disease. While we do not believe the findings presented here will be altered with more recent data, continued analysis of surveillance data is necessary. To provide evidence for more refined recommendations, future iterations of this surveillance system should consider collecting molecular data as well as markers of disease severity.

While the general association between pre-existing medical conditions and *Vv* infection is well known, these results characterize the significance and relative importance of certain pre-existing medical conditions, by route of exposure, associated with *Vv* infection. As such, these results underscore the need for clinicians to advise patients with liver disease, malignancy, or a haematological condition to avoid exposing broken skin to warm seawater. Clinicians should further advise patients, especially patients with liver disease, of the risk of life-threatening illness after eating undercooked contaminated seafood. Clinicians should consider the diagnosis of *Vv* for seriously ill patients presenting with a recent history of raw shellfish consumption or wound exposure to the Gulf of Mexico or other warm marine environments which are likely to harbour *Vv*, culture specimens, and provide prompt treatment, including antibiotics.

Acknowledgments

The authors are grateful to Patricia Griffin (CDC) for her input and support and Anna Newton (CDC) for her technical assistance.

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Table 1

Bivariate analysis of pre-existing medical conditions associated with *Vibrio vulnificus* septicaemia by route of exposure

	Foodborne (*N*=631)			**Non-foodborne (*N*=581)**		
	Septic (*n*=553)	**Non-septic (*n*=78)**		**Septic (*n*=319)**	**Non-septic (*n*=262)**	
	***n* (%)**	***n* (%)**	***P* value**	***n* (%)**	***n* (%)**	***P* value**
Liver disease	328 (59)	19 (24)	<0·01	102 (32)	33 (13)	<0·01
Haematological disease	61 (11)	3 (4)	0·05	25 (8)	6 (2)	<0·01
Diabetes	126 (23)	10 (13)	0·05	71 (22)	40 (15)	0·03
Heart disease	120 (22)	13 (17)	0·31	91 (29)	56 (21)	0·05
Malignancy	57 (10)	5 (6)	0·28	37 (12)	10 (4)	<0·01
Gastric surgery	33 (6)	6 (8)	0·55	11 (3)	4 (2)	0·14
Immunodeficiency	41 (7)	4 (5)	0·46	24 (8)	10 (4)	0·06
Renal disease	56 (10)	6 (8)	0·50	37 (12)	21 (8)	0·15
Peptic ulcer disease	50 (9)	0	<0·01	24 (8)	16 (6)	0·50

Table 2

Pre-existing medical conditions associated with *Vibrio vulnificus* septicaemia

	Foodborne (*N*=631)			Non-foodborne (*N*=581)		
	aOR	**95% CI**	**PAR**	**aOR**	**95% CI**	**PAR**
Liver disease	5·1	2·9–9·0	47	4·1	2·5–6·5	24
Hematological disease				3·2	1·3–8·3	5·4
Malignancy				3·2	1·5–6·7	8·0

aOR, Adjusted odds ratio; CI, confidence interval; PAR, population attributable risk.

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