Infectious Outbreaks Associated with Bivalve Shellfish Consumption: A Worldwide Perspective

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Outbreaks of shellfish-associated infection have been reported for more than a century. Since the early 1970s, the global consumption of shellfish has increased considerably—and with it, the reports of outbreaks of infection. Most of these reports have originated from the United States, but Europe and, to a lesser extent, Asia and Australia have also been represented. The majority of outbreaks have been linked to oysters, followed by clams and mussels. Hepatitis A virus caused the largest ever shellfish-associated outbreak, but caliciviruses have caused the highest number of outbreaks; Vibrio species lead the list of bacterial pathogens. The prognosis of shellfish-associated infections is generally good, except for outbreaks of Vibrio vulnificus infection, which have a mortality rate of up to 50% in vulnerable people. Conventional and molecular techniques should be applied to better identify the causative agents, thereby enabling more-targeted control measures in growing, harvesting, and shipping bivalves.

"It is unseasonable and unwholesome in all months that have not an “r” in their name to eat an oyster.

—William Butler (1535–1618)

"These may ye eat of all that are in the waters: whatsoever hath fins and scales in the waters, in the seas, and in the rivers, them may ye eat.

—Leviticus 11:9

Shellfish have been known to be an important source of food since the Roman times. For >100 years, ingestion of shellfish has been recognized as a cause of outbreaks of bacterial and viral infections [1]. One of the first recognized outbreaks associated with the consumption of raw oysters was described in 1816 by the French physician J. P. A. Pasquier [2]. He described what appears to have been typhoid fever in a group of people who consumed sewage-contaminated oysters. Since the end of the 19th century, >400 outbreaks and 14,000 cases of infection have been reported in the United States alone [3]. Although data on outbreaks occurring in the United States are continuously displayed at the Web site of the Centers for Disease Control and Prevention (CDC; Atlanta, Georgia), the global picture of outbreaks of shellfish-associated infection is less clear and is not complete.

Classification and nomenclature. The class Bivalvia, sometimes called Pelecypoda, belongs to the phylum Mollusca, one of the most numerous and oldest groups in the animal kingdom. There are ~8500 species
Table 1. Summary of epidemiologic characteristics of 46 outbreaks of infection throughout the world that were associated with ingestion of bivalves, by pathogen, 1969–2000.

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of outbreaks</th>
<th>No. of patients</th>
<th>Country or countries reporting outbreak</th>
<th>Type(s) of bivalve(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calicivirus/Norwalk-like viruses/</td>
<td>18a</td>
<td>5923</td>
<td>USA, UK, Australia, Japan, Spain</td>
<td>Clams, oysters</td>
<td>[6, 7] (and others)</td>
</tr>
<tr>
<td>small round-structured virusb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>8</td>
<td>290,965</td>
<td>USA, Italy, China, Australia</td>
<td>Clams, oysters, mussels</td>
<td>[8–13]</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>5</td>
<td>669</td>
<td>USA, Canada</td>
<td>Oysters, clams</td>
<td>[14]</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>4</td>
<td>120</td>
<td>Malaysia, Italy, USA</td>
<td>“Shellfish,” “bivalves,” oysters</td>
<td>[15, 16]</td>
</tr>
<tr>
<td>Vibrio vulnificus</td>
<td>1</td>
<td>72</td>
<td>USA</td>
<td>Oysters</td>
<td>[17]</td>
</tr>
<tr>
<td>Vibrio mimicus</td>
<td>1</td>
<td>17</td>
<td>USA</td>
<td>Oysters</td>
<td>[18]</td>
</tr>
<tr>
<td>Vibrio hollisae</td>
<td>1</td>
<td>2</td>
<td>USA</td>
<td>Oysters</td>
<td>[19]</td>
</tr>
<tr>
<td>Salmonella species</td>
<td>3</td>
<td>98</td>
<td>Singapore, UK, Japan</td>
<td>Oysters, cockles</td>
<td>[20]</td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td>1</td>
<td>40</td>
<td>France</td>
<td>Shrimps, mussels</td>
<td>—</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>1</td>
<td>24</td>
<td>USA</td>
<td>Oysters</td>
<td>—</td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
<td>2</td>
<td>54</td>
<td>USA, Canada</td>
<td>Roasted oysters</td>
<td>[21]</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>1</td>
<td>4</td>
<td>New Zealand</td>
<td>Smoked mussels</td>
<td>—</td>
</tr>
</tbody>
</table>

a Includes 3 outbreaks of infection in which pathogen identification was inconclusive but the pathogen was presumed to be a virus.
b Small round-structured virus is also designated as “Snow mountain virus.”
c Includes the 290,000 cases from the Shanghai outbreak.

of marine bivalves. Bivalves, commonly called shellfish, include such molluscs as clams (Mercenaria mercenaria), oysters (Crassostrea virginica and Ostrea edulis), mussel (Mytilus edulis and Mytilus galloprovincialis), cockles (Cerastoderma edule). They are all characterized by having a 2-valved shell joined by an elastic ligament. Within the class, the shell forms are used in classification.

Physiology. Understanding the physiology of the bivalves helps clarify why people become infected after eating raw shellfish. The shellfish are common in areas where nutrient levels are high and waters are sheltered. Unfortunately, such conditions prevail in shallow waters, which are frequently contaminated with human sewage. Most of the bivalve species feed on suspended phytoplankton via a pair of specialized gills. Large volumes of water are pumped across the gills by ciliary action. Trapped food particles are transported toward the mouth by specialized cilia. Some bivalves feed on organic material. When pathogenic microorganisms contaminate the harvesting sites, they are filtered by the gills and become highly concentrated in liverlike digestive glands [4, 5].

Distribution. Most bivalves are marine animals and can be found at all depths. They are sometimes cultivated in estuaries, and on rare occasions, they can be found in fresh water. Virtually all bivalves, with few exceptions, are edible. The most important edible oysters are representatives of the genus Crassostrea (notably Crassostrea gigas). Most mussels are cultivated on ropes suspended from floats (notably Mytilus edulis). A wide variety of clams (e.g., Mya arenaria) are cultivated in the North Atlantic and Pacific regions [4]. This review attempts to outline the global dispersion of outbreaks of infection associated with molluscan bivalves.

Data collection. The archives of MEDLINE and EMBASE were extensively searched for articles reporting outbreaks associated with bivalve shellfish. The search covered the period of 1969 through July 2000. Major search terms included such words as “outbreak” combined with “shellfish,” “molluscs,” “bivalves,” “oysters,” “clams,” “mussels,” and “cockles.” Single case reports were not included. Because a previous review on this topic has detailed the American experience [3], and because the present report attempts to give a more balanced worldwide perspective, we refrained from including outbreaks appearing on Internet databases (such as those of the CDC and Morbidity and Mortality Weekly Report in the United States). We did, however, include reports that first appeared in Morbidity and Mortality Weekly Report and then as standard articles elsewhere. Our search identified 46 outbreaks (table 1).

GLOBAL EPIDEMIOLOGY AND TRENDS IN BIVALVE CONSUMPTION

The world fishery production for direct human consumption in 1997 was 93 million tons [22]. From 1988 through 1997, the global fish production grew at an annual rate of 10.3%. The global marine catch of molluscs is twice that of crustaceans, and the great majority are bivalves. In 1997, the global catch of the various bivalves totaled 7.4 million tons, which is 3.6 times the amount caught in 1970.

Most countries have shown a remarkable increase in bivalve...
Outbreaks of bivalve-associated infections have been reported from only 12 countries. Four of these countries are in Europe and 4 are in Asia; 4 reports are from North America and the Australian continent (figure 2). Most reports originate from the United States, but the largest-ever recorded outbreak occurred in Shanghai in 1988. This epidemic involved 290,000 people who contracted hepatitis A after eating clams [23]. In contrast with other bivalve-associated infections, this epidemic is remarkable for the death toll: 47 people died. Large outbreaks of infection involving >800 patients also occurred in Australia in 1979 [6], the United States in 1986 [7], and Japan in 1991 [24].

It is interesting to note that, during the past 3 decades, there has been a constant increase in the number of reports of outbreaks of infection, from merely 3 reports in the 1970s to 22 reports in the 1990s (figure 3). This trend is especially worrisome in light of the constant efforts invested in regulating and inspecting the growth beds of bivalves and their handling, processing, and shipping. It is unclear whether this trend represents a true increase in the number of outbreaks or a heightened vigilance, or whether it parallels the global increase in medical publications. Most reports ($n = 35$) involved oysters, followed by clams, mussels, and other types of shellfish (figure 4).

The commonly cited rule of William Butler, which recommends eating oysters only during autumn and winter, does not seem to reflect custom. Previous reports have found that most shellfish-associated outbreaks of viral infection in the United Kingdom occurred during winter [25], whereas those in the United States peaked in both late spring and late autumn [3]. Experience from Japan in 1987–1992 is similar to that of the United Kingdom: most outbreaks occurred during winter, followed by spring [24]. In contrast, bacterial infec-

Figure 1. Bivalve shellfish consumption in selected countries, 1970 versus 1997. Data are abstracted from the fisheries database of the Food and Agriculture Organization of the United Nations (http://apps.fao.org/fishery/fprod1-e.htm).

Figure 2. Reported infectious outbreaks associated with bivalve shellfish, by region, 1969–2000.
tions caused by *Vibrio* species peaked in the United States during summer months [14, 26]. A similar seasonal distribution was observed in Italy, where 2 outbreaks (one caused by hepatitis A and the other caused by *Vibrio* species) occurred during summer [8, 15].

**REGULATORY AND EDUCATIONAL ASPECTS OF BIVALVE SHELLFISH**

Numerous problems contribute to shellfish-associated infections. These problems regard handling the growth beds and storing, processing, labeling, and shipping the product—as well as lack of education. Both the United States [27] and the European Union [28] have recently established legislative standards to reduce the risk of contaminated shellfish reaching restaurants. The standards are centered on the detection of coliforms and *Escherichia coli*; in the United States, the standards focus on the growing waters of shellfish, and in the European Union, the standards focus on the number of microorganisms per 100 g of shellfish flesh [29, 30]. The fact that outbreaks of infection continue to occur despite apparently adequate control measures highlights the role of viruses, especially Norwalk-like viruses (NLVs). In fact, the published opinion of the scientific committee of the European Union on NLVs has recommended including NLVs in the communicable diseases surveillance network and assuring the implementation of safe food-handling measures [31].

In addition, efforts have been initiated to educate consumers, restaurant proprietors, and physicians about the hazards of eating raw shellfish. An example of the educational efforts to reduce the risk of infection can be found in the 1991 California Code of Regulations, Title 17, Article 10.5: “Eating raw oysters may cause severe illness and even death in persons who have liver disease … cancer, or other chronic illnesses” (p. 13675, 32). Messages such as these should be continuously disseminated to consumers and physicians and posted in restaurants. Physicians who care for patients with chronic liver disease and cancer should be able to provide brochures and other literature detailing the hazards associated with eating raw shellfish.

**CLINICAL ASPECTS OF BIVALVE-ASSOCIATED INFECTION**

The hazards posed by bioaccumulation of harmful microorganisms in shellfish are compounded by the traditional consumption of certain shellfish in raw or only mildly cooked dishes. Human health problems associated with bivalve shellfish are well recognized internationally. Bivalves may transmit various microorganisms, including viruses, bacteria, and parasites, which mostly cause gastroenteritis. Only 2 of the diseases transmitted by shellfish are presently preventable by vaccination: hepatitis A and polio. The majority of reported seafood-associated illnesses have unidentified etiologies and are assumed to be viral.

**Viruses**

Epidemiological evidence gathered in recent years suggests that human enteric viruses are the most common pathogens transmitted by bivalve shellfish [25]. Despite the multiplicity of viruses transmitted feco-orally, only a handful of viruses have been linked to diseases caused by bivalve consumption.
Well-known examples of agents are NLVs and small round-structured viruses (SRSVs), such as astrovirus and coxsackievirus, and hepatitis A virus (HAV), hepatitis E virus (HEV), and poliovirus. These viruses can survive in water for a long time. Furthermore, once these viruses are inside the shellfish, their survival appears to be further prolonged for weeks, and they can withstand depuration.

In most outbreaks of infection, oysters meant for human consumption were harvested from sewage-contaminated water. Satisfactory procedures for eradicating viruses from shellfish are not commonly used. Neither steaming nor freezing has been able to completely eradicate virus particles [33].

The first linkage of viruses with shellfish-associated gastroenteritis was made in the winter of 1976–1977 in the United Kingdom. Small, round, virushlike particles, like those seen in outbreaks of “winter vomiting disease,” were observed in patients’ faces [34]. Since these early reports, >45 publications around the world have documented shellfish-associated outbreaks of gastroenteritis caused by NLVs and SRSVs [25].

NLVs and SRSVs belong to 1 genus of the caliciviruses. This group of small viruses (diameter, 30–35 nm) contains a single-stranded RNA. The caliciviruses include the prototype of Norwalk virus, and other strains, such as the Southampton virus, SRSV, and less well-characterized strains. These viruses appear to have a global distribution. They cannot be grown on culture by means of conventional virological methods, but they can be identified by electron microscopy and by such recent molecular techniques as RT-PCR, which has led to a better understanding of the epidemiological importance of these pathogens.

Caliciviruses emerged as the predominant cause of gastroenteritis associated with shellfish consumption. Gastrointestinal symptoms in such cases are typically described as relatively mild, often including nausea, vomiting, diarrhea, and abdominal cramps after an incubation period of 30–40 h. The symptoms last for 2 days, followed by complete recovery with no complications. The care of a physician is rarely necessary in these cases.

HAV infection is the most serious viral infection linked to shellfish consumption, causing a debilitating disease and, occasionally, death. The first documented outbreak of “infectious hepatitis” occurred in Sweden in 1955, when 629 cases were associated with raw oyster consumption [35]. Subsequently, many HAV-associated outbreaks have been reported worldwide. The most demonstrative one was the outbreak of HAV infection in Shanghai, China, in 1988, in which almost 300,000 cases were linked to the consumption of clams harvested from a sewage-polluted area [23, 36]. In fact, this is the largest virus-associated outbreak of food poisoning ever reported. Smaller outbreaks have been reported from the United States, Italy, and Australia [8, 9–13]. The fairly protracted incubation period (mean duration, 4 weeks) of HAV infection makes it very difficult to determine the association with a particular food vehicle in sporadic cases. Normally, the food will not be available for testing at the time of diagnosis. Thus, it can be safely be assumed that HAV infection associated with shellfish consumption is probably underreported.

Cases of infection due to non-A, non-B hepatitis viruses have also been linked to shellfish consumption [37, 38]. HEV shares morphological and biophysical characteristics with caliciviruses; however, there are significant genomic differences. Recent taxonomic proposals leave HEV without a formally assigned virus group [39]. Like NLVs, characterization of HEV has been achieved largely through molecular methods. The clinical presentation of HEV infection as an acute, self-limiting liver disease shares many features with HAV infection, with some differences—notably the high mortality rate among HEV-infected pregnant women. HEV is endemic in many developing countries, particularly in Asia, where it causes both outbreaks and sporadic cases of infection. In developed countries, cases are usually associated with a history of travel to areas of endemicity. The propensity for waterborne transmission suggests that shellfish could be at risk of contamination with HEV and can act as a vector for transmission of HEV. Although direct evidence is not currently available, the association of shellfish with transmission of HEV is highly suggestive.

A few studies have implicated other viral agents in the pathogenesis of bivalve-related outbreaks of infection. Two epidemiological case-control studies have reported statistically significant or nearly significant relationships between consumption of raw bivalve shellfish and Creutzfeldt-Jakob disease [40, 41]. This is a surprising association, given that a route of transmission is not obvious. However, these studies were fairly small, which makes this association speculative at present.

Human enteroviruses detected in bivalve shellfish include vaccine-strain poliovirus, coxsackievirus, and echovirus. The epidemiological presentations of enterovirus infection do not favor their linkage to a particular food vehicle. Enteroviruses have not generally been associated with shellfish-vectorized (or seafood-vectored) infection. However, this statement should be taken with a grain of salt, given that enteroviruses were found to contaminate shellfish harvested from both polluted and relatively clean sites [38].

A few reports link astrovirus infection to shellfish consumption [42–44]. However, the role of these pathogens seems comparatively minor because of the high levels of adult immunity.

Bacteria
The earliest reports of shellfish-transmitted bacterial diseases were documented in the late 19th and early 20th century. Numerous outbreaks of typhoid fever in Europe, the United States, and elsewhere [45] have been linked to sewage pollution. Other bacterial agents have also been found to cause disease after raw...
shellfish consumption. The most notable examples include Vibrio species, which account for 20% of all outbreaks of disease. Other bacteria are Salmonella species, Shigella species, Plesiomonas shigelloides, and Listeria species.

**Vibrio species.** Vibrio species are halophilic, non–spore-forming bacteria that grow in saline aquatic environments. They produce a wide range of clinical symptoms. Specifically, Vibrio vulnificus infections can result in wound infection and septicemia with a high mortality rate. Other species are associated with gastroenteritis of varying severity, although it is usually much more severe than gastroenteritis associated with other viral pathogens. Among Vibrio species, infection with Vibrio cholerae O1 is the most serious and debilitating.

V. vulnificus has been associated with both ingestion of contaminated seafood, such as raw oysters and clams, or infectious wounds contaminated by seawater [17, 46]. Oyster-associated V. vulnificus sepsis and death were first reported in 1979 [47]. Predisposing factors for severe disease include chronic liver disease, diabetes mellitus, hemochromatosis, and other immunosuppressive disorders. The case-fatality rate among these vulnerable persons is the highest of the shellfish-borne infections and may reach a figure of 50%. In fact, the CDC currently recommends that people with liver disease refrain from eating raw shellfish.

The disease is characterized by a 24-h incubation period, followed by signs of sepsis, including fever, chills, hypotension, nausea, vomiting, and diarrhea. Large hemorrhagic bullae progress to necrotic ulcers. The organism can be readily cultured from blood, stool, or wound samples and is usually susceptible to cefazidime and doxycycline.

**V. cholerae** is a frequent inhabitant of the coastal waters of the Bay of Bengal. Both outbreaks and sporadic cases of infection have been reported in the United States [16]. The US Gulf Coast appears to be the predominant source of infection during summer months, when the waters are warmer [26, 48]. During 1965–1991, 136 cases of infection due to V. cholerae O1 were reported in association with shellfish ingestion [48]. As of this writing, V. cholerae O139 infection has not been associated with shellfish ingestion.

Cholera enterotoxin is the prototype of profuse secretory enteritis. After an incubation period of 6–48 h, profuse watery diarrhea and extensive fluid and electrolyte losses ensue. It is a leading cause of death in several third-world countries. Treatment involves fluid and electrolyte replacement. Oral tetracycline, if administered during the first 48 h of illness, shortens the course of the illness. Since the 1990s, non-O1 serotypes have been reported more frequently. They generally cause a disease that is milder and self-limited.

**Vibrio parahaemolyticus** infection is quite commonly associated with eating undercooked shellfish. It is the leading cause of Vibrio-associated gastroenteritis in the United States. In 1998, a large outbreak of gastroenteritis occurred among 416 people who ate oysters harvested from Galveston Bay, Texas. In Japan and Taiwan, V. parahaemolyticus gastroenteritis infections are frequently reported, but most cases are probably sporadic.

Water temperature has been shown to be closely linked to the growth of V. parahaemolyticus, with infected oysters harvested in water with a temperature >22°C [49]. The organism is readily identified in stool specimens on selective media, such as thiosulfate-citrate-bile salts agar. The median incubation period is 17 h (range, 4–90 h), with a median duration of illness of 6 days. The most common clinical presentation is watery diarrhea. Other symptoms include abdominal cramps, nausea, vomiting, headache, fever, and bloody diarrhea. Sepsis due to V. parahaemolyticus is quite rare and occurs primarily in patients with cirrhosis and neutropenia. The organism is susceptible in vitro to doxycycline, cephalosporins, and imipenem. Antimicrobial treatment has not been shown to shorten the course of uncomplicated gastroenteritis.

**Vibrio mimicus** is a new Vibrio species that was isolated in 1981; it should be considered in the differential diagnosis of acute gastroenteritis in patients who have recently ingested raw oysters [18]. Biochemical and genetics differences defined this pathogen as a new Vibrio species. Vibrio hollisae has been recovered from patients with gastroenteritis who consumed raw seafood before their enteric illness [19]. Rare cases of systemic infections have also been described, particularly in immunocompromised hosts.

**Other bacteria.** Campylobacter, Salmonella, and Shigella species and E. coli, which are commonly implicated in gastroenteritis, are only occasionally traced to seafood [20, 45, 50–52]. One outbreak [21] and several sporadic cases [53, 54] of infection have been reported to be due to Plesiomonas shigelloides. P. shigelloides is interesting in several aspects. First, it is mostly an organism of fresh water and estuaries. Second, the clinical picture of infection may vary from mild diarrhea to bloody diarrhea with fecal leukocytes and, occasionally, extraintestinal manifestations. Third, the laboratory identification from mixed cultures requires selective media.

**Parasites**

Parasites are poorly transmitted via shellfish. Only a few parasites have been isolated from seafood, predominantly fish. These parasites include Giardia duodenalis [55] and Cryptosporidium species [56, 57]. Oocysts of Cryptosporidium species, chiefly Cryptosporidium parvum, are the only ones that have been isolated from oysters to date [58]. C. parvum, a zoonotic waterborne protozoan [59], was found in oysters collected from commercial oyster harvesting sites in Chesapeake Bay [56]. The oocysts were identified by both PCR and immunofluorescent antibody microscopy. Their infectivity at 20°C could be retained for a period of up to 3 months. The best way to eliminate
infectivity was found to be heating to temperatures of \( >72^\circ C \) or freezing to \( -20^\circ C \) for 24 h. Although Cryptosporidium species caused the largest waterborne outbreak of infection in the history of the United States [60], no clinical outbreaks due to Cryptosporidium species have been linked to shellfish. Cryptosporidium infection is probably underdiagnosed, as is the case with other clinical entities.

**CONCLUSION**

Throughout the world, bivalve consumption has increased considerably during the past 3 decades. Along with this trend, infectious outbreaks caused by bivalves have been increasingly reported from almost all continents. The most commonly implicated bivalves are oysters, followed by clams. Most of the infectious syndromes produce self-limiting gastrointestinal symptoms, but a few can be fatal. Mortality was reported in association with HAV and V. vulnificus infections, especially in immunosuppressed patients. People with reduced immunity are at high risk for serious disease—and possibly death—after eating raw or undercooked infected bivalves, and they should be advised to avoid this type of cuisine.

**References**

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