Vibrio Parahaemolyticus: A Review on Distribution, Pathogenesis, Virulence Determinants and Epidemiology

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ABSTRACT

Vibrio parahaemolyticus is a Gram-negative, halophilic bacterium isolated from marine environments globally. After the consumption of contaminated seafood, *V. parahaemolyticus* causes acute gastroenteritis. To initiate infection, a wide range of virulence factors are required. A complex group of genes is known to participate in the pathogenicity of *V. parahaemolyticus*; however, to understand the full mechanism of infection, extensive research is yet required. *V. parahaemolyticus* has become the leading cause of seafood-related gastroenteritis in Japan, the United States and several other parts of the world. In addition, outbreaks caused by the pandemic clone of this organism are escalating and spreading universally. To minimize the risk of *V. parahaemolyticus* infection and warrant the safety of seafood, collaboration between governments and scientists is required. We herein provide an updated review of the pathogenicity determinants and distribution of *V. parahaemolyticus* to deliver a better understanding of the significance of *V. parahaemolyticus* and its host–pathogen interactions.

Key words: Pandemic clone, pathogenesis, *Vibrio parahaemolyticus*, virulence determinants

ملخص البحث:

تؤدي بكتيريا ضمة الدم والتي يمكن عزلها من البيئات البحرية إلى التهاب حاد في الجهاز الهضمي عند تناول أطعمة بحرية ملوثة ولكي تسبب هذه البكتيريا عدوى فأنها تحتاج إلى تواجد عوامل خطورة، والتي لازالت تحتاج إلى مزيد من البحوث. أصبحت هذه البكتيريا المسبب الرئيسي لالتهابات الجهاز الهضمي الناتجة عن تناول الأطعمة البحرية في اليابان، وأمريكا ودول أخرى. يقدم الباحثون تحديثاً عن هذه البكتيريا ومحدداتها المرضية، ولتقليل العدوى بهذه البكتيريا ينصح الباحثون بالتعاون بين العلماء والحكومات على مستوى العالم لمعرفة المزيد عن هذه الجرثومة.

INTRODUCTION

The constant interaction of human populations with their surroundings continues to transform the spectrum of infectious diseases. Therefore, the search of emerging pathogens must not come to a pause. An emerging infectious disease is one for which the rate of incidence has increased within the past two decades or one which threatens to spread rapidly.[1] Examples of these are infections caused by *Vibrio parahaemolyticus*, which is progressing as a significant human pathogen.[2] *V. parahaemolyticus* is a Gram-negative halophilic bacterium that produces a capsule with different somatic (O) and capsular (K) antigens.[3] *V. parahaemolyticus* is isolated from coastal and estuarine environments universally.[4] In addition, it has been recovered from a wide variety

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of marine organisms.[5] The consumption of raw or undercooked seafood contaminated by virulent strains of *V. parahaemolyticus* leads to acute gastroenteritis.[5] The symptoms of the disease include diarrhea, nausea, abdominal pain, vomiting and low-grade fever.[6] In most cases, the disease is self-resolving. However, incidences where *V. parahaemolyticus* caused a more debilitating and dysenteric form of gastroenteritis have been reported.[7] In addition, when open wounds come in contact with contaminated seawater, wound infections occur.[8] Uncommonly, in immunocompromised patients, it may progress into a life-threatening fulminant necrotizing fasciitis characterized by the rapid necrosis of subcutaneous tissue.[9,10] In rare cases, *V. parahaemolyticus* causes septicemia, which is associated with a high mortality rate.[11] It has been mostly reported in individuals who are immunocompromised due to underlying medical conditions such as liver diseases.[12] To initiate infection, a wide range of virulence factors are used by *V. parahaemolyticus* including adhesins, toxins and secretion systems.[11] *V. parahaemolyticus* has become the leading cause of seafood-related gastroenteritis in Japan, the United States and several other parts of the world.[13] Further, outbreaks caused by the pandemic clone of this organism are escalating and spreading universally.[13] To minimize the risk of *V. parahaemolyticus* infection and warrant the safety of seafood, collaboration between governments and scientists is required.[14] Therefore, the objective of this study was to provide an updated review of the pathogenicity determinants and distribution of *V. parahaemolyticus* and use this information to deliver a better understanding of the *V. parahaemolyticus* significance and its host–pathogen interactions.

QUORUM SENSING

Quorum sensing (QS) is a term that defines the cell–cell communication process by which bacteria respond to released signaling molecules (known as autoinducers), on the basis of cell density fluctuations, to regulate gene expression.[11] As the density of QS bacteria increases, the concentration of the autoinducers increases until it reaches a critical threshold, at which point bacteria forms a response.[15] In the process of QS, individual cells' function in unison to coordinately alter their gene expression and control their synchrony-requiring activities such as virulence factor secretion.[16] At high cell densities, *V. parahaemolyticus* bacteria produce their major transcriptional regulator OpaR in response to the QS system.[11] To summarize the role of OpaR in controlling the phenotypic output of *V. parahaemolyticus*, Kernell Burke *et al.*[16] demonstrated 11 transcription

factors under the downstream regulation of OpaR. They fall into the following four broad themes: first, genes related to cell surface and adhesion; second, virulence factors and cell–cell interactions including type III and type VI secretion systems (T3SS and T6SS); third, surface-specific regulon including the lateral flagellar system, chemotaxis and the swarm-specific sRNA and finally, other functions such as competency.[16]

ADHESION TO HOST CELLS

Multivalent adhesion molecules (MAMs) are present in a wide range of Gram-negative pathogens.[17] It enables high-affinity binding to the host cells during preliminary stages of infection, which is essential for delivery of virulence factors.[17] MAM7 is the adhesin expressed constitutionally by *V. parahaemolyticus*. With its aid, *V. parahaemolyticus* is able to attach different types of host cells including macrophages, fibroblasts and epithelial cells.[18] Correct localization and outer membrane anchoring of the protein are achieved by the hydrophobic stretch of 44 amino acids in MAM7 N-terminus.[5] MAM7 has two host surface receptors: host membrane phosphatidic acid lipids (PA), to which MAM7 has a high affinity of binding, and extracellular matrix protein fibronectin, which acts as a co-receptor.[19] MAM7 is constituted of seven mammalian cell entry domains, and each of them is capable of PA binding.[19] The binding of MAM7 to PA in the host membrane causes downstream activation of small GTPase RhoA, which eventually leads to redistribution of epithelial tight junction proteins.[18] The consequences of this pathway are the free migration of bacteria across epithelial layers and the depolarization of the barrier, leaving apical and basolateral surfaces with no particular markers.[18]

IRON ACQUISITION

Iron is essential for the survival of organisms. Therefore, bacteria develop different methods to acquire iron from their hosts.[8] Intracellularly, iron is involved in many processes ranging from signaling to metabolism.[20] Furthermore, many organisms use the intracellular "low-iron conditions" to stimulate the expression of virulence genes.[21] In humans, iron is present as part of multiple molecular complexes such as transferrin and hemoglobin.[8] During infection, *V. parahaemolyticus* utilizes at least two methods of iron acquisition: production of siderophores and use of heme as a direct source of iron.[22] Siderophores are compounds with a low molecular weight and a high iron affinity. They can scavenge extracellular iron, remove transferrin and lactoferrin-bound iron and facilitate its uptake by the

bacteria.[23] *V. parahaemolyticus* produces a siderophore known as vibrioferrin, which is synthesized by proteins from the pvsABCDE operon.[8] An outer membrane receptor, composed of PvuA1 and PvuA2 proteins, recognizes the ferric-charged vibrioferrin.[21] Since this receptor is coupled to the inner membrane ATP-binding cassette, it imports the ferric-charged vibrioferrin to the inner side of the cell.[21] As it acquires the energy required for iron-siderophore transportation across the outer membrane, *V. parahaemolyticus* contains three sets of the TonB energy transduction system.[21] The process of iron uptake should be highly regulated because the concentration of iron inside the cell is critical; too little prevents the completion of certain cellular processes and too much causes the accumulation of free radicals, leading to cell death.[20] In *V. parahaemolyticus*, this vital process is controlled by the ferric uptake regulation protein "Fur."[23] By the downstream regulation of several genes, it represses the iron absorption.[21]

TOXINS

The late 1980s witnessed the study of the first *V. parahaemolyticus* virulence factors: thermostable direct hemolysin (TDH)[24] and the thermostable direct-related hemolysin (TRH).[25] Today, TDH and TRH remain the most distinct virulence factors, as almost all clinically isolated strains of *V. parahaemolyticus* possess hemolytic activity attributed to these two genes.[3] TDH is composed of four soluble monomers, in which a central pore is formed to allow the diffusion of small molecules.[26] In a process termed as Kanagawa phenomenon (KP), tdh + strains of *V. parahaemolyticus* exhibit β-hemolytic activity when plated on special blood media known as Wagatsuma agar.[6] Purified TDH is heat stable after being exposed to 100°C for 10 min.[27] Hemolysis, enterotoxicity, cytotoxicity and cardiotoxicity represent a group of biological activities caused by TDH.[28] TDH is a pore-forming toxin. The fairly large pores it creates on erythrocytes allow both water and ions to flow through membranes.[29] Eventually, this results in colloidal osmotic lysis.[30] The primary targets for TDH activity are the epithelial and intestinal cells. The effect of TDH on these cells is very crucial for biological functions, such as diarrhea, during infection.[27] TDH binds to phospholipid bilayers, in which single channel events occur.[31] The mechanisms of cell binding and calcium ions influx result in the increase of intracellular Ca+ and release of chloride ions in human colonic epithelial cells.[27] When the osmotic pressure of the cell exceeds its limit of self-regulation, pathological changes follow, leading to cell expansion and even death.[32] Homologs of *V. parahaemolyticus* TDH

are expressed in other vibrios causing diarrhea, such as non-O1 *Vibrio cholerae* and *Vibrio mimicus.* They have all been included in the *tdh* family because the coding sequences of these genes share >93% homology.[33] Clinical samples from an outbreak of gastroenteritis in the Republic of Maldives presented KP-negative strains of *V. parahaemolyticus.* However, these strains were found to express a new hemolysin, termed as TRH.[25] TRH is immunologically similar to TDH and their genes share approximately 70% homology.[29] TRH demonstrates hemolytic activity similar to that of TDH on blood cells.[6] Moreover, TRH activates Cl⁻ channels and causes altered ion influx, in a manner analogous to TDH.[29] However, TRH is heat-labile when exposed to 60°C for 10 min.[27] Besides, when compared to TDH, evidence of a lesser role of TRH in the pathogenicity of *V. parahaemolyticus* was proposed.[34] Although the association between the expression of *tdh* and *trh* and the pathogenicity of *V. parahaemolyticus* is well acknowledged, it should be perceived that not all clinical strains possess these genes.[3] Some of the isolated clinical strains do not contain *tdh* and/or *trh* although these main hemolysins are absent, *V. parahaemolyticus* remains pathogenic, indicating the expression of other virulence activities.[29] It should not escape our notice that *V. parahaemolyticus* bacteria express an additional toxin, known as thermolabile hemolysin (TLH).[33] It is encoded by the *tlh* gene, which is targeted during the genetic detection of *V. parahaemolyticus* because it is a species-specific marker.[13] TLH exhibits phospholipase activity and the ability to lyse human erythrocytes.[8] Furthermore, the expression of *tlh* was strongly upregulated under conditions simulating the human–host intestinal environment.[35] Therefore, TLH is assumed to have a role in *V. parahaemolyticus* similar to TDH.[32] However, its direct contribution to the pathogenicity of *V. parahaemolyticus* is yet to be elucidated.[33]

TYPE III SECRETION SYSTEMS

The T3SS bacterial machinery is a needle-like apparatus that injects bacterial proteins (termed effectors) directly into the cytoplasm of eukaryotic cells, without encountering the extracellular environment.[11] Those effectors disrupt the regular cell signaling processes to modify the biological activities of the host cell.[36] The basic structure of the T3SS apparatus is conserved among different species of bacteria. However, their effectors' functions and targets differ.[11] According to the needs of pathogens, the production of effectors may be up- or downregulated.[8] The secretion apparatus of T3SS consists of first, the basal body spanning the

bacterial inner and outer membrane; second, a needle that connects between the bacteria and the host cells and finally, a translocon pore that penetrates the eukaryotic cell membrane.[5] The whole genome sequencing of *V. parahaemolyticus* RIMD 22106633 (O3:K6) revealed the acquisition of two sets of T3SS gene clusters, with one on each of its two circular chromosomes, and thus they were entitled T3SS1 and T3SS2.[37]

Type three III secretion system 1

The T3SS1 gene cluster is encoded in the first pathogenicity island on chromosome 1. Nearly all clinical and environmental strains of *V. parahaemolyticus* encode T3SS1.[32] The sequence homology of T3SS1 gene cluster with *Yersinia* spp. and other vibrios suggests that it was ancestrally acquired and has been evolutionarily conserved.[3] A dual regulatory system consisting of ExsACDE regulatory cascade and heat-stable nucleoid-structuring protein (H-NS) orchestrates the transcription of T3SS1.[38] ExsA, a member of AraC family of transcription regulators, is the master transcriptional regulator of T3SS1 expression.[39] Under noninducing conditions, ExsD (an anti-activator) directly binds to ExcA and renders it inactive. Meanwhile, the anti-anti-activator ExsC binds to ExsE. In inducing conditions, ExsE is secreted to release ExsC. ExsC then sequesters ExsD and liberates ExsA. Free ExsA binds to the promoter genes and activates T3SS1.[39] H-NS is a major component of the bacterial nucleoid.[38] In *V. parahaemolyticus*, H-NS was found to repress the T3SS1-related genes' expression by suppressing *exsA* gene.[38] During *V. parahaemolyticus*

infection, the activation of T3SS1 initiates a reproducible series of events. Their outcome includes the induction of rapid autophagy followed by cell rounding, eventually leading to cell lysis.[11] To date, four T3SS1 effectors have been recognized: Vibrio outer protein (Vop) Q, VopS, VPA0450 and VopR (VP1638) [Table 1].[32] The effector VopQ contributes to T3SS1 cytotoxicity.[40] Through membrane permeations, VopQ manipulates lysosomal homeostasis and autophagic flux, leading to rapid induction of autophagy.[41] The mediated autophagy inhibits recruitment of phagocytosis-related cellular machinery, leading to debilitated phagocytes engulfment of *V. parahaemolyticus* bacteria during infection.[40] Moreover, Vop-Q triggers mitogen-activated protein kinases (MAPKs) pathway that regulates transcription of inflammatory cytokines. Through MAPK, VopQ induces production of interleukin-8, which is known for its leukocyte chemotactic properties and role in inflammatory disease.[42] VopS (VP1686) modifies a conserved threonine residue on Rho, Rac and Cdc42, with adenosine-5′-monophosphate (AMP).[43] The AMPylation of Rho GTPases prevents subsequent interaction with downstream effectors, by which actin assembly is inhibited.[43] The upshots of VopS activities in *V. parahaemolyticus* infection are the interference with the assembly of specks in infected macrophages, the hindrance of inflammasome activation and the assistance in the bacterial evasion from inflammatory responses.[49] VPA0450 is another T3SS1 effector protein contributing to host cell death.[8] In the human host, VPA0450 disrupts the cytoskeletal binding sites on the inner surface of the

Table 1: List of *Vibrio parahaemolyticus* type III secretion systems effectors			
T3SS	**T3SS effectors**	**Activity**	**References**
T3SS1	VopQ	Rapid induction of autophagy leading to debilitated phagocytes engulfment of *V. parahaemolyticus* during infection	[40-42]
	VopS	Actin assembly inhibition	[43]
	VPA0450	Compromises membranes integrity, facilitates cell lysis and participates in cytotoxicity	[8]
	VopR	May play a role in infection by promoting refolding of T3SS effector proteins after their delivery into host cell	[32]
T3SS2	VopA/P (VPA1346)	Suppresses the host innate immune response	[44,45]
	VopL	Actin nucleation, induction of stress fibers and contribute to bacterial uptake into the host cells	[6]
	VopC	Changes in actin cytoskeleton and facilitates bacterial invasion	[46]
	VopT	Cytotoxicity	[47]
	VopV	Enterotoxicity	[36]
	VopZ	Mediates pathological phenotypes during *V. parahaemolyticus* infection	[48]
	VPA1380	Unknown	[32]

T3SS – Type III secretion systems; Vop – Vibrio outer protein; *V. parahaemolyticus* – *Vibrio parahaemolyticus*

membrane. The subsequent plasma membrane blebbing compromises the membrane integrity, facilitates cell lysis and participates in cytotoxicity.[8] Finally, by binding to the phosphoinositide on the host cell, VopR localizes to the cellular membrane. It may also play a role in the infection of *V. parahaemolyticus* by promoting the refolding of T3SS effector proteins after their delivery into host cells.[32]

Type three III secretion system 2

The second cluster of genes encoding T3SS2 is found on the pathogenicity island Vp-PAI (VPaI-7) on chromosome 2. Along with T3SS2 and its known effectors, VPaI-7 typically encodes two *tdh* genes.[37] Accordingly, it is primarily expressed in clinical isolates of *V. parahaemolyticus* and associated with large outbreaks of the disease.[8] The G + C content of VPaI-7 is lower than the genomic average and has a higher number of genes unique to each *Vibri*o spp. These annotations indicate that it was recently acquired by *V. parahaemolyticus* through lateral transfer.[6] The genes of T3SS2 are mainly regulated by two transcriptional regulators, VtrA and VtrB.[38] Gotoh *et al.*[35] demonstrated that *V. parahaemolyticus* recognizes the intestinal environment through detecting bile acids, which induce VtrA-mediated VtrB transcription and subsequent production of T3SS2 effector proteins. Noteworthy, VtrA and VtrB do not only regulate the expression of T3SS2 but also regulate the expression of both *tdh* genes on Vp-PAI. Thus, they play a major role in *V. parahaemolyticus* cytotoxicity.[6] The delivery of effector proteins to host cells requires the presence of a translocon complex. During *V. parahaemolyticus* infection, VopB2, VopD2 and the recently identified VopW are necessary for the T3SS2 effector translocation through permeation of the host cell membrane.[6] While the cytotoxicity of T3SS2 is limited and associated with the function of TDH, T3SS2 appears to be the major contributor to the enterotoxicity occurring in rabbit ileal loop model.[50] In addition, the T3SS2 effectors are capable of adhering to human cells, leading to cytoskeletal disruption and loss of membrane integrity.[51] To date, seven T3SS2 effector proteins have been characterized: first, Vop A/P (VPA1346), which shares around 55% homology with the YopJ-like proteins of *Yersinia* and *Salmonella*.[44] VopA is an acetyltransferase that prevents the activation of MAPK kinases, inhibits MAPK signaling pathway and ultimately suppresses the host's innate immune response.[45] Second, VopL contains three N-terminal Wiskott–Aldrich homology 2 motifs and a unique VopL C-terminal domain. Its main function is actin nucleation and induction of stress fibers.[52] Ham and Orth[6]

suggested that the role of VopL in actin manipulation may contribute to the bacterial uptake into the host cells. Third, VopC, which displays homology to the catalytic domain of cytotoxic necrotizing factor toxins.[46] VopC exhibits transglutaminase activity, by which it modifies Rho family GTPases. Once Rho GTPase is activated, it triggers changes in the actin cytoskeleton of infected cells.[46] In the meantime, the activation of CDC42 facilitates the invasion of *V. parahaemolyticus* into host cells.[46] Fourth, VopT is a cytotoxin and ADP-ribosyltransferase effector that targets Ras GTPase in *V. parahaemolyticus*-infected cells.[47] Fifth, VopV is the homolog of VopM protein that is involved in non-O1/non-O139 *V. cholerae* enterotoxicity. Parallel to VopM, VopP possesses multiple F-actin-binding domains and an enterotoxic activity during infection of *V. parahaemolyticus*.[36] Sixth, VopZ is a multifunctional effector crucial for the pathological phenotypes induced by *V. parahaemolyticus*. Strains lacking *vopZ* genes fail to colonize the intestine and cause diarrhea.[48] VopZ inhibits the activation of transforming growth factor β-activated kinase-1, TAK1, which is essential for MAPK and NF-κB signaling pathway activation. TAK1 has a profound influence on the preservation of intestinal integrity, and its absence leads to different consequences including inflammation, apoptosis and reduced transepithelial resistance.[48] Finally, VPA1380 is the most recently identified T3SS2 effector protein. It is a typical cysteine protease that catalyzes its targeted substrates.[53] VPA1380 possibly contributes to the invasion of the host cell by *V. parahaemolyticus*. However, its direct role in the pathogenicity of *V. parahaemolyticus* has not been fully recognized.[32]

TYPE VI SECRETION SYSTEM

Of Gram-negative bacterial secretion systems, the latest to be described is the T6SS. It is a complex molecular machine that utilizes a bacteriophage-like cell-puncturing device to inject effector proteins into target cells.[54] Homologs of *V. parahaemolyticus* T6SS are found in a range of Gram-negative bacteria. During the infection of those cells, T6SS is predicted to take part in actin cross-linking, intracellular trafficking, secretion and vesicular transport.[55] *V. parahaemolyticus* holds two sets of putative T6SSs, one on each chromosome.[56] VPT6SS1 is mainly associated with clinical isolates, while all strains of *V. parahaemolyticus* encode VPT6SS2. Both systems have different aspects of adherence to Caco-2 and/or Hela cells.[56] Furthermore, there is recent evidence of a significant role of T6SS of *V. parahaemolyticus* in inducing autophagy in macrophages.[57]

Spread of *Vibrio parahaemolyticus* and emergence of pandemic clone

During 1950, Japan witnessed an outbreak of acute gastroenteritis, in which 272 people were infected and 20 died. An investigation of the leading cause, held by Fujino *et al.*, resulted in the first isolation of the Gram-negative rods presently known as *V. parahaemolyticus*.[58] Some of the earliest outbreaks caused by *V. parahaemolyticus* were reported in the United States and Europe [Figure 1].[59,60] The occurrence of *V. parahaemolyticus* cases had a typical sporadic manner, with no clear association between distinct serotypes of *V. parahaemolyticus* and gastroenteritis incidence.[61] This situation remained until 1996, during which a surveillance of *V. parahaemolyticus* gastroenteritis incidence in Kolkata, India, witnessed a sudden surge due to the new unique serotype, O3:K6.[62] Since then, cases of gastroenteritis caused by O3:K6 *V. parahaemolyticus* have been reported worldwide: in Africa,[63] Asia,[64] Europe[65] and the American continent [Figure 1].[66] The rapid spread of O3:K6 marked the first pandemic of *V. parahaemolyticus* and placed this pathogen on the global public health agenda.[3] Matsumoto *et al.*[67] exploited the intraspecies variation of the *toxRS* sequence to develop a group-specific polymerase chain reaction method that permits the confirmation of the clonality of the new O3:K6 strains. During this period, emerging strains that belong to different serovars were found to be almost indistinguishable from the new O3:K6 clone.[67,68] By 2007, 21 different serotypes of *V. parahaemolyticus* appeared to have identical genotypes and molecular profiles to those of O3:K6 and were collectively entitled as "serovariants" of O3:K6 isolates, in which the most common serotypes were O4:K68, O1:K25 and O1:KUT (untypeable).[67,69] The understanding of the genetic diversity of *V. parahaemolyticus* was enhanced by the establishment of a multilocus sequence typing (MLST) scheme.[70] It is the elected method for determining the global epidemiology of bacterial pathogens based on sequence analysis of chosen housekeeping genes.[70] After gathering data from the pubMLST database and different studies, Han *et al.*[71] generated a comprehensive overview of the spread of clinical and environmental pandemic *V. parahaemolyticus* strains [Table 2]. They concluded that 49 serotypes, widely distributed in 22 countries, represent the pandemic isolates. The comparison between the genetic organizations of O3:K6 and other serotypes of *V. parahaemolyticus* disclose the complexity of the pandemic clones.[3] One possible explanation for the widespread of O3:K6 is the acquisition of open reading frame 8 (*orf8*) through phage f237 infection.[110] It was suggested that O3:K6 strains have a higher epidemic potency because the protein product of *orf8* caused them to be more adhesive to host intestine cells.[110] Although *orf8* appears to be a suitable genetic marker for the identification of pandemic clones, its reliability became debatable after findings of O3:K6 strains lacking f237 were reported.[111,112] Soon after that, the gene sequence *VP2905* was proposed as an alternative genetic marker exclusive to the pandemic clones.[113] The gene is located in a 16-kb region inserted in the open reading frame of the histone-like DNA-binding protein HU-α, causing a frameshift in the amino acid sequence. However, its role in the pathogenicity of *V. parahaemolyticus* is yet undecided.[113,114]

CONCLUSIONS AND RECOMMENDATIONS

Studying the virulence determinants used by *V. parahaemolyticus* reveals a complex combination of genes orchestrating the host–pathogen interactions. However, the exact mechanism by which the infection is initiated is yet unknown. Therefore, further research is required to fill gaps in the literature. This is especially emphasized because *V. parahaemolyticus* may act as a reservoir from which genes may be transferred to other bacteria. In addition, the transient nature of the gastroenteritis infection caused by *V. parahaemolyticus* masks the true burden of this pathogen. However, reviewing the emergence of the pandemic clone and its ability to cause large outbreaks highlights the significance of *V. parahaemolyticus* and its impact on the population health as well as calls for the systematic monitoring of its existence and potential pathogenicity in the region.

Figure 1: World map presenting the global dissemination of *V. parahaemolyticus* (illustrative representation of Table 2)

Financial support and sponsorship

Table 2: Overview of the global clinical and environmental distribution of *Vibrio parahaemolyticus*				
Continent	**Country**	**Source(s)**	**Pandemic serotypes**	**Reference(s)**
Asia	Japan	Clinical and environmental	Yes	[72]
	Korea	Clinical and environmental	Yes	[71,73]
	China	Clinical and environmental	Yes	[64]
	Vietnam	Clinical and environmental	Yes	[71,74]
	Laos	Clinical and environmental	Yes	[71,72]
	Indonesia	Clinical and environmental	Yes	[69]
	Malaysia	Clinical and environmental	No	[75]
	Singapore	Clinical and environmental	Yes	[3]
	Thailand	Clinical and environmental	Yes	[76,77]
	India	Clinical and environmental	Yes	[78,79]
	Bangladesh	Clinical and environmental	Yes	[80]
	Jordan	Environmental	No	[81]
Europe	Russia	Clinical and environmental	Yes	[82]
	Sweden	Environmental	No	[83]
	Norway	Environmental	Potentially yes	[84]
	United Kingdom	Clinical and environmental	Yes	[85,86]
	Spain	Clinical and environmental	Yes	[87,88]
	France	Clinical and environmental	Yes	[89,90]
	Italy	Clinical and environmental	Yes	[46,91]
	Switzerland	Environmental	No	[92]
	Germany	Environmental	No	[93]
	Turkey (Black Sea)	Environmental	No	[94]
Africa	Egypt	Environmental	No	[95]
	Tunisia	Environmental	No	[96]
	Nigeria	Environmental	No	[97]
	Kenya	Environmental	No	[98]
	Mozambique	Clinical and environmental	Yes	[63]
	Côte d'Ivoire	Environmental	No	[99]
	Senegal	Environmental	No	[100]
	South Africa	Environmental	No	[101]
	Guinea-Bissau	Environmental	No	[102]
America	Canada	Clinical and environmental	No	[103]
	United States	Clinical and environmental	Yes	[104,105]
	Mexico	Clinical and environmental	Yes	[66]
	Ecuador	Clinical and environmental	Yes	[71,106]
	Brazil	Clinical and environmental	Yes	[107]
	Peru	Clinical and environmental	Yes	[108]
	Chile	Clinical and environmental	Yes	[109]

Conflicts of interest

There are no conflicts of interest.

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