JOURNAL OF CLINICAL IMMUNOLOGY AND MICROBIOLOGY

E-ISSN: 3068-5168
Journal of Clinical Immunology & Microbiology

ATHENAEUM SCIENTIFIC PUBLISHERS

*Review Article*

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# Pathogenesis of *Vibrio parahaemolyticus* from Clinical and Environmental Perspectives: A Review

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Citation: Dhanush CK, et al. Pathogenesis of *Vibrio Parahaemolyticus* from Clinical and Environmental Perspectives: A Review. J Clin Immunol Microbiol. 2026;7(1):1-10.

https://doi.org/10.46889/JCIM.2026.7101

Received Date: 13-12-2025

Accepted Date: 11-01-2026

Published Date: 17-01-2026



## Abstract

The gram-negative bacteria of the family *Vibrionaceae* are the common inhabitants of the coastal-marine environments, some species of which are important pathogens of both humans and aquatic animals. Of these, *V. parahaemolyticus* is a leading cause of foodborne illness in humans, mainly responsible for gastroenteritis, usually from consumption of raw and undercooked seafood. *V. parahaemolyticus* is associated with a diverse range of marine animals, including fish, clams, oysters, crabs and shrimp. The bacterium is also known to cause wound infections, ear infections and in more severe cases, sepsis in individuals with a compromised immune system. The primary known virulence factor of *V. parahaemolyticus* is a Thermostable Direct Hemolysin (TDH). TDH-Related Hemolysin (TRH), Type 3 Secretion System (T3SS), Type 6 Secretion System (T6SS) and adhesins are also known to play important roles in its survival and pathogenesis. These virulence factors are primarily associated with clinical isolates and, to a lesser extent, with environmental isolates. As an opportunistic pathogen, *Vibrio parahaemolyticus* causes infections of varying intensities in aquatic animals through different virulence factors. This zoonotic pathogen has threatened shrimp farming and associated industries worldwide in recent years, with the emergence of *V. parahaemolyticus* strains harbouring the Acute Hepatopancreatic Necrosis Disease (AHPND) toxin. Compared to clinical isolates, environmental isolates are more genetically diverse and may harbor different, as-yet-unascertained virulence mechanisms that cause acute diarrheal disease. This review aims to provide a comprehensive summary of the pathogenesis and various virulence mechanisms of *V. parahaemolyticus*, as well as current perspectives on managing *V. parahaemolyticus*-related risks by integrating insights from microbiology, epidemiology, public health and aquatic animal health.

**Keywords:** *Vibrio parahaemolyticus*; TDH; TRH; Gastroenteritis; AHPND, Zoonotic Pathogen; Virulence; Pathogenicity Islands

## Introduction

The family *Vibrionaceae* consists of 12 genera, namely *AliiVibrio, Allomonas, Beneckea, Catenococcus, Echinimonas, EnteroVibrio, Grimontia, Listonella, Lucibacterium, Photobacterium, SaliniVibrio* and *Vibrio* and over 142 species [1,2]. *Vibrio* species are gram-negative, non-spore-forming rods that are straight or slightly curved and produce oxidase and catalase [3]. Most *Vibrios* are motile, possessing a single polar flagellum and are widely distributed in coastal and marine environments. Three species of this genus, namely *V. cholerae, V. parahemolyticus* and *V. vulnificus* are well-known human pathogens associated with wild-caught and farmed fish and shellfish [4]. The non-sucrose-fermenting *V. mimicus* is also known to have similar pathogenic characteristics to *V. cholerae* [5]. Members of the genus *Vibrio* are pathogenic to aquatic animals, with the most important species being *V. harveyi, V. parahemolyticus, V. alginolyticus, V. anguillarum, V. splendidus, V. campbellii* and *V. damselae* [6]. *V. harveyi* is responsible for luminous vibriosis, causing mass mortalities in shrimp larval rearing facilities [7]. Other species may cause loose shell disease,

luminous vibriosis, red disease, white gut disease, tail necrosis and the Early Mortality Syndrome (EMS) in aquatic animals. Environmental strains of *Vibrio* are highly diverse; therefore, biochemical identification at the species level requires elaborate tests. Of these, *V. parahaemolyticus* assumes significance as a pathogen of both humans and aquatic invertebrates [8,9]. *V. parahaemolyticus* is primarily known as a human pathogen, responsible for gastrointestinal infections associated with consumption of raw or partially cooked fish and shellfish, particularly the bivalve molluscs such as the oysters [10,11]. However, *V. parahaemolyticus* can cause diverse types of extraintestinal infections in humans, including wound infections and ear infections, as well as sepsis in immunocompromised individuals, which can be life-threatening [12]. *V. parahaemolyticus* is one of the leading causes of foodborne illness, mainly in Japan, Asian countries and the United States [13,14].

In recent years, *V. parahaemolyticus* strains harboring the Acute Hepatopancreatic Necrosis Disease (AHPND) toxin have changed the perspective on bacterial infections in farmed shrimp [15]. The major virulence factor of *V. parahaemolyticus* is a Thermostable Direct Hemolysin (TDH), responsible for β-hemolysis in human erythrocyte cells by membrane pore formation. TDH is present in most clinical isolates (88% to 96%), but only in 1% of natural populations of *V. parahaemolyticus* [16]. TDH is also rarely detected in *V. mimicus* and the non-O1/139 strain of *V. cholerae* [17]. TDH-Related Hemolysin (TRH), which is 69% similar to TDH, is responsible for cytotoxicity by forming channels, causing ion imbalance in cells [18]. Another known species-associated accessory factor is Thermolabile Hemolysin (TLH), which is responsible for phospholipase activity [19]. *V. parahaemolyticus* genome is reported to contain nine genomic islands designated VPaI-1 to VPaI-9 (Fig. 1), with sizes ranging from 10 kb to 81 kb, of which VPaI-7 and VPaI-6 are located on chromosome-2 and others on chromosome-1 (Table 1). T3SS, T6SS and Adhesins are the effectors known to play important roles in survival and pathogenesis [20]. The emergence of environmental pathogenic strains is facilitated by prophages in *V. parahaemolyticus* [21]. The genetic organisation of the *tdh* and *trh* genes, which are present within genomic islands, is flanked by "Direct Repeat Regions" (DRR), involved in genetic exchange. This suggests that the genes were acquired to improve their fitness in specific niches [22,23].

| Pathogenicity Island | Virulence Proteins Encoded | Function/Role | Reference |
|---|---|---|---|
| VPaI-1 | Restriction-modification genes | Genomic defence/fitness | [77] |
| VPaI-2, VPaI-3 | T6SS, Type I pilus, partial T3SS | Virulence and colonization | [76] |
| VPaI-4, VPaI-5, VPaI-6 | Hydrolases, cytotoxin, colicins | Virulence, cytotoxicity, fitness | [76,77] |
| VPaI-7 (Vp-PAI) | TDH, TRH, T3SS2 | Major human pathogenicity factor, enteropathogenicity | [23] |
| VPaI-8 | T6SS, chemotaxis, metabolic and hypothetical proteins | Bacterial competition and environmental fitness | [80] |
| VPaI-9 | T6SS and hypothetical proteins | Aid new modes of virulence, colonization and survival | [80] |

**Table 1:** Summary of different pathogenicity islands reported in *V. parahaemolyticus*.

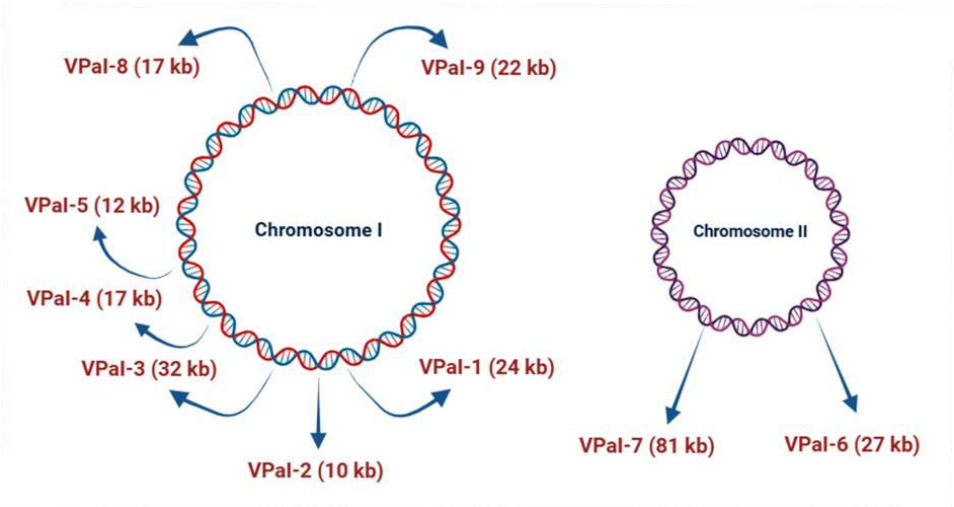

**Figure 1:** Circular representations of *Vibrio parahaemolyticus* Chromosome I and Chromosome II highlighting the genomic positions of pathogenicity islands (VPaI-1 to VPaI-9).

**Occurrence and Epidemiology**

*V. parahaemolyticus* was first discovered in 1950 in Japan from an outbreak of gastroenteritis involving 272 people who consumed small, half-dried sardines [24]. Pathogenic strains were distinguished by Kanagawa-positive phenotype (hemolysis on Wagatsuma agar) by Thermostable Direct Hemolysin (TDH) toxin [25]. An outbreak in the Maldives in 1985, associated with TDH-negative *V. parahaemolyticus* isolates, led to the discovery of TDH-Related Hemolysin (TRH) [26,27]. Since 1996, infections caused by *V. parahaemolyticus* have increased globally, with the emergence of a new strain belonging to the O3:K6 serovar, which has pandemic potential. This pandemic strain was first isolated in Kolkata in 1996 following an increase in diarrheal cases in the region [28]. Subsequently, the strain was reported in Japan among travellers from Southeast Asian countries, followed by Peru in 1998, Mexico and other countries worldwide [29,30]. These isolates were similar across the globe and also, they were different from previous isolates before 1996, hence considered as the pandemic strain with specific nucleotide variation in the *toxR* operon, found only in pandemic strains, based on which a Group-Specific PCR (GS-PCR) was developed to detect this strain rapidly [31].

In the US, first identified as a foodborne pathogen in 1971, *V. parahaemolyticus* has accounted for 34,664 cases of foodborne infections in 2016; in Japan, 837 cases (1993) increased to 12,318 cases (1998), dropped to 14 cases (1999) and 280 cases in 2009 [12,32,33]. In China, 31% of foodborne illnesses in 2000 were attributed to *V. parahaemolyticus*, with the most prevalent serotype being O3:K6 [29]. Even though *V. parahaemolyticus* outbreaks are rare in Europe, the first large outbreak occurred in Spain in 1999, involving 64 illnesses associated with the consumption of raw oysters [34]. A diarrheal outbreak attributed to this pandemic strain of *V. parahaemolyticus* O3:K6 in Kolkata, India, was reported in 2007 [35]. Many cases of acute diarrheal disease caused by *V. parahaemolyticus* have been reported worldwide [14]. *V. parahaemolyticus* isolates from 1951 to 2021 showed a distinct increase in antimicrobial resistance (AMR) and virulence genes in recent decades, based on a study of 1540 genomes collected from the NCBI database, which included 32 different countries or regions worldwide [36]. The increase in antibiotic consumption across the globe in various sectors is one of the important factors contributing to the rise in AMR of *V. parahaemolyticus* [37].

Acute Hepatopancreatic Necrosis Disease (AHPND), also termed Early Mortality Syndrome (EMS), was first reported in China in 2009 and subsequently emerged in Vietnam in 2010, Malaysia in 2011, Thailand in 2012, Mexico in 2013, the Philippines in 2014 and later in Bangladesh, Myanmar and the USA in 2017 [15]. The disease pathology was later attributed to the PirVP toxin, a lethal binary complex of PirA and PirB, encoded on a 69-kb plasmid (pVA1) present in *Vibrio parahaemolyticus* AHPND strains. AHPND can result in very high mortality rates upto 100% within 30 days of stocking and has led to economic losses exceeding one billion USD annually in the Asian shrimp aquaculture industry [38]. AHPND strains generally lack genetic markers associated with human pathogenic strains (TDH and TRH) and strains from Mexico and Thailand lack the 140 Kbp region containing genes coding for the T3SS [39]. These *V. parahaemolyticus* AHPND strains may not be pathogenic to humans and therefore pose no food safety concern. However, multiple virulence factors and combinations must be considered comprehensively in view of diverse infection types caused by *V. parahaemolyticus* strains.

**Human Pathogenesis**

*V. parahaemolyticus* is known to cause various types of illness in humans, mainly gastroenteritis, usually from consumption of raw, undercooked and cross-contaminated seafood. Occasionally, it is responsible for wound infections and ear infections and in more severe cases, sepsis in immune-compromised individuals, which could be life-threatening [12,14]. It is one of the leading causes of foodborne illness, generally associated with seafood consumption [40].

*Toxigenic Strains and Major Virulence Mechanisms*

The most important known virulence factor in toxigenic strains of *V. parahaemolyticus* responsible for human pathogenesis is Thermostable Direct Hemolysin (TDH), which is responsible for β-hemolysis in human erythrocyte cells by forming membrane pores [41]. Additionally, TDH-Related Hemolysin (TRH) is responsible for cytotoxicity by forming channels, leading to an ion imbalance within the cell [42]. The G+C content of the pathogenicity island in the *V. parahaemolyticus* strain carrying the *tdh*/*trh* genes (Vp-PAI, now identified as VPaI-7) was less than the average G+C content of Chromosome II in which it is located. The sequence analysis revealed that Vp-PAI ranged from 1,387,705 to 1,467,746 bp from oriCII (ORFs VPA1310 to VPA1396) and is flanked by 5-bp direct repeats (5'-AACTC-3'), suggesting that this pathogenicity island was inserted into the intergenic region between VPA1309 (ORF coding for hypothetical protein) and VPA1397 (ORF coding for acyl-coenzyme A thioester hydrolase-

related protein). Additionally, the study suggests that the genes encoding the type III secretion system 2 on Vp-PAI are not present in strains lacking TDH/TRH [14,23]. These toxins form tetrameric pore complexes in the host membrane. The pores allow ions to flow freely across the host membrane, leading to haemolysis or cytotoxicity [43]. T3SS1 effectors and T3SS2 effectors are translocated into host cells, causing cytotoxicity in colon epithelial cells or enterotoxicity [32]. The *vopT* (VPA1327), gene coding for one of the T3SS2 effector proteins, plays a role in enterotoxicity [44]. Although the distribution pattern of *vopT* is similar to that of TDH and is reported mainly among clinical isolates, it is observed to be independent of TDH. Hence it has been suggested as an additional virulence marker for more reliable detection of *V. parahaemolyticus* with pathogenic potential to cause human disease [45]. On both chromosomes, *V. parahaemolyticus* possesses two putative type-III and type-VI secretion systems (T3SS and T6SS, respectively). Because they cause both cytotoxicity and enterotoxicity (Fig. 2), T3SS are essential to the infection process [46]. T6SS supports adhesion and virulence linked to interbacterial rivalry in the gut environment [47]. Due to differential expression, the host's interaction with bile salts activates and transcribes other genes, including the type-III secretion system 2 (T3SS2), which is encoded on chromosome 2. On the other hand, T6SS1 is encoded on chromosome 1. Both T3SS2 and T6SS1 are mainly associated with the clinical isolates [46,48].

*Non-Toxigenic Strains and Alternate Virulence Mechanisms*

*V. parahaemolyticus* isolates with no TDH/TRH and T3SS2 present, generally categorised as non-toxigenic, have been reported to cause acute gastroenteritis in humans [49]. Non-toxigenic strains are responsible for a small fraction of gastroenteritis cases reported due to *V. parahaemolyticus* strains, suggesting that they may possess different, yet unknown, pathogenic determinants [49,50]. WGS analysis of clinical non-toxigenic *V. parahaemolyticus* identified the presence of the *mutT* gene, which codes for a nudix hydrolase responsible for the virulence of this isolate. This was further confirmed by experimental infection using *Galleria mellonella* as a model for investigating virulence involving *V. parahaemolyticus mutT* mutant [51]. The virulence of *V. parahaemolyticus* is highly complex in nature and environmental isolates have the potential to be invasive, carrying pathogenic traits common to clinical strains that pose a risk to human health [52,53]. Environmental isolates are more genetically diverse and their role in acute diarrheal disease remains poorly elucidated. More studies on definitive virulence markers are necessary to clearly differentiate between clinical and environmental isolates with pathogenic potential, thereby facilitating the screening and understanding of pathogenomics for this pathogen, which in turn helps mitigate associated risks [54].

Major virulence factors, *tdh* and *trh*, are exclusively associated with clinical isolates, whereas adhesin-encoding genes, *vpadF* and the Mannose-Sensitive Hemagglutinin (MSHA), are mainly found in environmental isolates. The T3SS1 effectors VopQ, VPA0450 and VopS are observed in all isolates, regardless of their origin [55]. In a study, 79 putative virulence-related genes were observed from WGS data, of which *flrBC*, contributing to adhesion and biofilm formation, the *ysc* gene cluster related to the type III secretion system and the *fliCDE* gene cluster coding for virulence via flagellar mobility were identified in *V. parahaemolyticus* isolates from diarrheal patients [56].

The Zonula Occludens Toxin (ZOT), originally described in *V. cholerae*, has been reported in the genomes of highly cytotoxic strains of *V. parahaemolyticus* [57]. The prevalence of the *zot* gene in environmental and clinical *V. parahaemolyticus* isolates possessing different Zot clusters with prophage associations highlights that the co-occurrence of the *zot* gene with classical virulence factors would further augment pathogenicity and survivability [58].

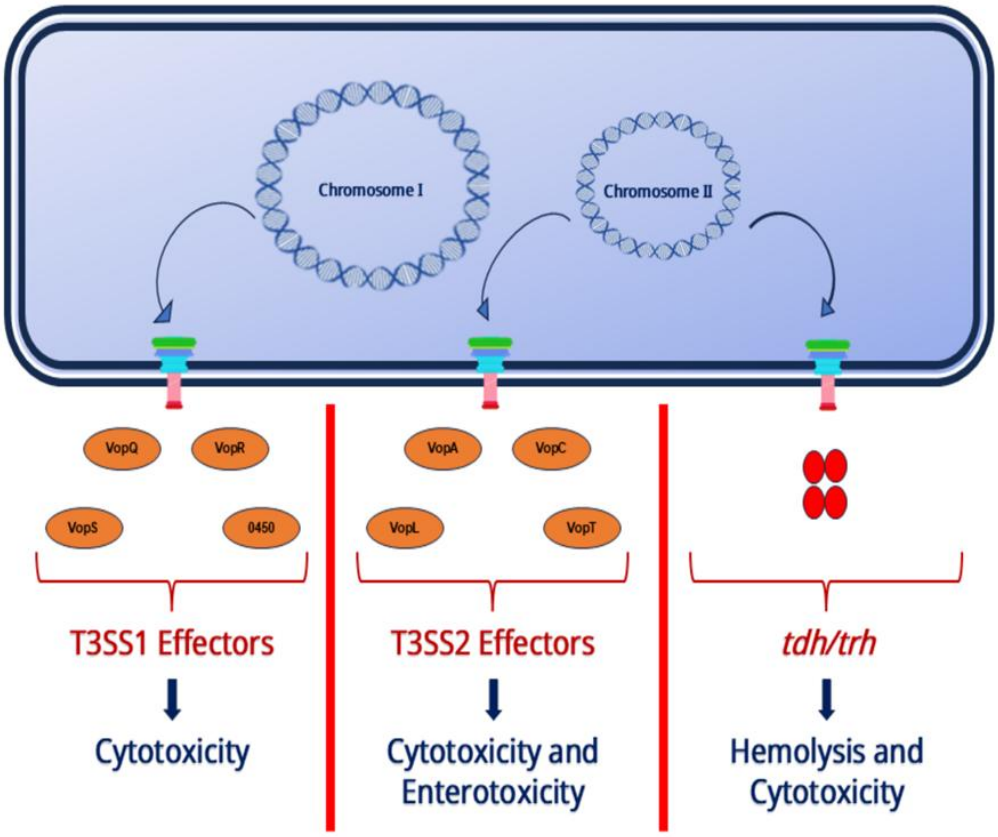


**Figure 2:** Schematic representation of the major human pathogenicity determinants of *Vibrio parahaemolyticus*: T3SS1 (cytotoxicity), T3SS2 (cytotoxicity and enterotoxicity), TDH/TRH (hemolysins and cytotoxicity).

**Pathogenesis in Aquatic Animals**

AHPND, when first reported in 2009, was identified as idiopathic as no distinct causative agent was identified [59]. In 2013, experimental infection and pathological studies ascertained that *V. parahaemolyticus* carrying PirABvp toxin belonging to the *V. harveyi* clade is the causative agent of this disease [60]. PirABvp toxin is secreted into the extracellular environment. Bacteria-free supernatant is sufficient to induce typical AHPND symptoms [60,61]. PirABvp toxin forms a heterodimer and its overall structural topology is very similar to that of *Bacillus thuringiensis* Crystal insecticidal (Cry) toxin, despite a very low sequence identity. Notably, the two toxins share almost identical pore-forming activity [62]. The position of this gene in the genetic organization of pVA1 plasmid harbouring *pirABvp* indicates that this gene can be lost or acquired through mobile genetic elements via transposition or homologous recombination [63]. AHPND pathogenesis studies revealed the effect of the toxin on haemocytes, in addition to the previously described target tissues, hepatopancreas and stomach [38]. The mechanism involves *V. parahaemolyticus* AHPND entering the shrimp and releasing the PirABvp toxin. The binary toxins bind to the LvAPN1 receptor, which is embedded in the cell membrane of shrimp haemocyte [38]. This interaction may induce toxin oligomerization and promote pore formation, thereby facilitating insertion into the membrane. Further haemocyte is lysed and damaged by pore formation and membrane insertion causing mortality [38].

The whole-genome sequence analysis revealed that the non-AHPND strain of *V. parahaemolyticus* harbors different major functional genes associated with multidrug resistance, high pathogenicity and strong adaptability, enabling it to survive various environmental stresses. This non-AHPND strain, which lacked the *pir*, *tdh* and *trh* genes, was responsible for high mortality in shrimp, a finding further confirmed by artificial infection experiments [64]. The Sec-dependent transport system, Twin Arginine Transport (TAT) system, T2SS, T3SS1, T4SS and T6SS were identified in the WGS of this isolate, which are important for toxin delivery, extracellular toxicity and horizontal gene transfers [64]. Disulfide bond proteins (DsbA) have been shown to regulate the expression of virulence factors and attachment in host cells, highlighting their role in animal infections [65]. In recent times,

hypervirulent strains of *V. parahaemolyticus* harbouring *vhvp-1* and *vhvp-2* genes on a large plasmid, known to be responsible for Translucent Post-Larval Disease (TPD) [66]. High mortality occurs within one to two days in young post-larvae with a characteristic translucent appearance, thus emerging as a major concern in shrimp aquaculture with significant economic implications [67].

**Environmental Reservoirs and Ecological Perspectives**

In a comparative genomic study of clinical outbreak isolates and environmental isolates of *V. parahaemolyticus* isolated from 1973 to 2021 in New Zealand, environmental isolates exhibited a significant genetic heterogeneity compared to the clinical isolates with respect to unique nonsynonymous SNPs (nSNPs). A distinct difference was observed not only in clonal relationships and evolutionary profiles, but also in virulence patterns [55]. A study reported that incidence of TDH carrying isolate was detected mostly in fishes (19.3%) and waters (15.6%) compared to the clinical samples (1.04%) and also, the pandemic strains were detected relatively more in water (6%) and fish (5%) samples than in clinical samples (0.7%) [68]. Similar genetic relatedness among isolates from diverse sources suggests possible contamination of food animals and indicates that coastal water bodies may function as reservoirs of pathogenic *V. parahaemolyticus* strains. Whole genome sequence analysis of the six *V. parahaemolyticus* isolated from three edible shellfish species demonstrated significant genome variation mediated by the various mobile genetic elements responsible for horizontal gene transfers [69].

Study on the presence of human pathogenic markers TDH and TRH in *V. parahaemolyticus* isolates from AHPND-associated shrimp and pond water samples have revealed that the TDH and TRH were absent and 10.84% of these isolates were positive for shrimp pathogenic genes *pirA* and *pirB* [70]. Intensive farming environments create reservoirs for pathogenic *Vibrio spp*., with strains isolated from aquatic animals shown to be clonally related to human clinical cases [71]. Aquatic isolates can acquire resistance traits; for instance, a strain from oysters has shown genomic adaptations that enable cadmium tolerance and multidrug resistance, underlining risks to aquaculture and seafood safety [72]. Meta-analyses suggest pathogenic *Vibrios*, including *V. parahaemolyticus*, can spread through birds, further bridging aquatic and terrestrial ecosystems [73]. The gene transfer capacity of *Vibrio* species extends beyond clade classification, demonstrating a new pathogenic capacity in a previously known commensal clade and having significant implications for the spread of emerging diseases. PirVP genes were identified in *Vibrio punensis*, an isolate with the capacity to infect and develop AHPND disease in shrimp, belonging to the Orientalis clade, which was previously identified as the commensal clade [74]. This suggests that environmental surveillance systems with improved point-of-care molecular diagnostic techniques are necessary to discover the risks associated with the emergence of environmental carriers of pathogenic strains (Table 2) [75-85].

| Diagnostic Technique | Principle | Advantages | Reference |
|---|---|---|---|
| PCR (Polymerase Chain Reaction) | Amplification of species/virulence gene targets (e.g., *tlh, TDH, TRH*) | High specificity and sensitivity; widely used | [75,84] |
| LAMP (Loop-Mediated Isothermal Amplification) | Isothermal DNA amplification | Rapid, sensitive; does not require a thermal cycler | [85] |
| ELISA (Enzyme-Linked Immunosorbent Assay) | Antibody-based detection of outer membrane proteins | Specific and reliable; can be coupled with immunomagnetic separation for speed | [82] |
| Fluorescent aptamer-based biosensor | Aptamers bind to target with fluorescence signal | Very sensitive, real-time detection possible | [83] |
| Colorimetric biosensor | Color change response to pathogen detection | Simple, visual detection; can be quantitative | [79] |
| Fluorescence In Situ Hybridization (FISH) | Oligonucleotide probes target rRNA sequences | Detects viable but nonculturable cells; species-specific | [81] |
| Aptamer-based FRET (Fluorescence Resonance Energy Transfer) sensor | Aptamer and quencher system for fluorescence detection | Ultra-sensitive, rapid detection | [78] |

**Table 2:** Major diagnostic techniques developed for the identification of *V. parahaemolyticus*, their principles and advantages.

## Conclusion

As pathogenic strains of *V. parahaemolyticus* are reported in environmental samples, screening for *tdh, trh* and other major virulence genes among the isolates responsible for shrimp disease outbreaks is essential for controlling this zoonotic pathogen. To assess genetic diversity and understand the emergence of genetic traits related to virulence and fitness, there is a paucity of genome information available for the *V. parahaemolyticus* isolates from cases of shrimp *Vibriosis*. *V. parahaemolyticus* is the known causative agent of AHPND syndrome in shrimp, but the plasmid encoding *pirVP* genes responsible for the disease could be transferred among members of the Harveyi clade. Plankton, shellfish and sediments of marine and estuarine ecosystems would play a significant role as environmental drivers of virulence and AMR emergence. Environmental monitoring programs utilizing advanced molecular detection methods can enhance the detection and surveillance of *V. parahaemolyticus* in both clinical and environmental settings. Thus, there is an urgent need for integrated "One Health" approaches employing studies on environmental persistence and AMR with global collaborations in surveillance and outbreak response.

## Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

## Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

## Acknowledgement

The authors are grateful to the Director, ICAR-Central Institute of Fisheries Education, Mumbai for help and support.

## Data Availability Statement

Not applicable.

## Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

## Informed Consent Statement

Informed consent was taken for this study.

## Authors' Contributions

All authors contributed equally to this paper.

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