Reviews in Aquaculture

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Antimicrobial Resistance in Malaysian Shrimp Aquaculture and Strategies to Reduce Its Occurrence

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Received: 17 September 2024 | **Revised:** 4 February 2025 | **Accepted:** 21 March 2025

Funding: This work was carried out with financial support from the International Development Research Centre (IDRC), Canada, and the Global AMR Innovation Fund (GAMRIF), part of UK Government's Department of Health and Social Care (DHSC) (Project no: 110342-001 Enhancing Sustainability in Shrimp Aquaculture through Microalgae-Bacteria System with Quorum Sensing Inhibition Properties). T.D. was supported by the Scientific Research Fund of Flanders (FWO; project no: G057725N) and the Special Research Fund of Ghent University.

Keywords: antibiotic alternatives | aquaculture challenges | one health | pathogen control | sustainable practices

ABSTRACT

Shrimp is a commercially important species in several regions and is among the key global aquaculture commodities essential for food production and security. Similar to most shrimp-producing countries, shrimp aquaculture in Malaysia suffers from recurring disease outbreaks that consequently impact the overall economy. The use of antimicrobial agents, particularly antibiotics, in shrimp aquaculture for prophylactic treatment and growth enhancement has increased the spread of antimicrobial-resistant bacteria in the aquatic environment. The development and dissemination of antimicrobial-resistant bacteria and other potential sources of antimicrobial contamination in waterways are facilitated by the continuous application of antibiotics in shrimp farming, municipalities, livestock, hospitals and pharmaceutical sources. This situation contributes to the spread of the antimicrobial resistance (AMR) phenomenon, a One Health issue with detrimental effects on human and animal health as well as the environment. Addressing the risks associated with AMR dissemination remains highly challenging due to the intensification of shrimp farming trends, which heightens disease outbreaks, and the limited availability of alternatives to antibiotics for many farmers seeking to prevent crop failure. In this review, we critically examine the key issues related to AMR in shrimp aquaculture and explore emerging treatment strategies. Our analysis encompasses a comprehensive review of the existing literature on the impact of AMR on shrimp farming in Malaysia, as well as alternative mitigation strategies aimed at fostering more sustainable and resilient aquaculture practices.

1 | Introduction

Shrimp is one of the most heavily traded aquaculture commodities and ranks as the second-largest export group in terms of value [1]. Over the years, shrimp has become the world's most valuable aquaculture organism, with production increasing from approximately 75,000 metric tonnes (mt) in 1980 to over 5.7 million mt in 2020 [2]. In 2022, finfish accounted for 65% of the total value of traded aquatic animal products, followed by crustaceans at 23%, molluscs, and other aquatic invertebrates at 11% [3]. The global shrimp market was valued at USD 56,329 million in 2022 and is projected to grow at a compound annual growth rate (CAGR) of 5.3% from 2023 to 2030, reaching an estimated value of USD 85,995 million in 2030 [4]. According to the Food and Agriculture Organisation (FAO) of the United Nations, aquaculture accounts for 55% of global shrimp production and is the source of approximately half of the seafood consumed worldwide. A significant portion of this production comes from Asian countries including China, India, Thailand, Vietnam, Indonesia and Malaysia.

Global shrimp production is primarily dominated by two penaeid shrimp species, the Pacific white shrimp (*Penaeus vannamei*) and the black tiger shrimp (*Penaeus monodon*) [5]. In 2020, global farmed crustaceans reached approximately 9.4 million mt, with both *P. vannamei* and *P. monodon* contributing around 5.7 million mt [2]. The annual yield of *P. vannamei* alone has reached 4.4 million mt, with the production value of about USD 26.7 billion [6]. This species has gained prominence in the global shrimp market due to its desirable characteristics, including a short culture period and rapid growth [2]. Currently, *Penaeus vannamei* accounts for 83% of all cultured penaeid shrimp, making it the most widely farmed shrimp species [7]. On the other hand, *P. monodon*, once the dominant cultured shrimp species in Asia, now constitutes approximately 15% of total shrimp production, with an annual yield of 0.74 million mt valued at USD 5.59 billion [8]. In 2002, *P. monodon* was largely replaced by *P. vannamei* due to its slower growth rate and higher susceptibility to diseases [9].

Malaysia is recognised as the ninth-largest shrimp producer globally, with its primary export markets being the United States, Japan and China [3]. In Malaysia, shrimp farming was introduced in the 1970s to meet the growing demand for shrimp supply. Today, the sector is a significant contributor to the country's gross domestic product (GDP) [10]. According to the Department of Fisheries Malaysia (DOF), total shrimp production in Malaysia reached 116,722 mt in 2021 but declined to 97,616 mt in 2022 [11]. The local marine shrimp aquaculture market is projected to grow at a compound annual growth rate (CAGR) of 11.9%, increasing from RM1.13 billion in 2020 to RM1.99 billion by 2025 [12]. Approximately 90% of farmed shrimp in Malaysia are *P. vannamei*, which predominantly supplies the domestic market [13]. The species accounts for 89% of total farmed shrimp production, followed by *P. monodon* (at 10%) and other shrimp species [14]. Nevertheless, the industry experienced significant disruption when *P. vannamei* production was severely impacted by Acute Hepatopancreatic Necrosis Disease (AHPND) in 2012, leading to a decline in annual output. In response, 40%–50% of shrimp farmers from the largest shrimp production region began cultivating *P. monodon* intermittently due to its higher export demand and stable farm gate prices ensuring resilience within the sector [15].

Infectious diseases are among the most significant challenges in shrimp aquaculture worldwide [16], with vibrios being the most prevalent bacterial pathogens [17]. To date, 147 *Vibrio* species and 4 subspecies have been identified [18–20]. These Gram-negative marine bacteria regulate their virulence through quorum sensing, a communication mechanism that activates various phenotypes, including pathogenicity, biofilm formation and bioluminescence [21]. *Vibrio* species can infect various aquatic animals and thrive in diverse environments, posing a significant threat to shrimp production and trade, resulting in substantial economic losses to the industry [21–23].

Acute Hepatopancreatic Necrosis Disease (AHPND), also known as Early Mortality Syndrome (EMS), is one of the most devastating shrimp diseases currently affecting the Malaysian shrimp industry, with global economic losses estimated at US$ 11.0 billion between 2009 and 2016 [24]. In Malaysia, AHPND outbreaks were first reported in Perak in late 2010, followed by Penang and Kedah in 2011, Sabah and Sarawak in 2012, Terengganu in 2013 and Johor and Melaka in 2014 [25]. The disease causes high mortalities in shrimp grow-out ponds within 30–35 days of postlarval stocking [26]. Studies on AHPND have originally documented that the *Photorhabdus* insect-associated genes *pirA*^{vp} and *pirB*^{vp}, located on a plasmid (pVA1) and carried by a strain of *Vibrio parahaemolyticus*, encode toxins leading to necrosis and massive sloughing of shrimp hepatopancreatic tubule epithelial cells [27]. Subsequent studies have revealed that these toxin genes were also present in other *Vibrio* species, such as *Vibrio harveyi* [28], *Vibrio owensii* [29], *Vibrio campbellii* [30, 31] and *Vibrio punensis* [32]. The economic impact of AHPND has been substantial across several shrimp-producing nations, with losses reported at USD 11.0 billion in China (2009–2016), USD 2.5 billion in Vietnam (2010–2016), USD 1.2 billion in Malaysia (2010–2016), USD 7.9 billion in Thailand 2012 (2010–2016) and USD 0.7 billion in Mexico (2012–2016) [5].

Antimicrobial resistance (AMR) has reached an alarming level, with its spread across various sectors posing serious threats to human health, animal welfare and environmental safety [33]. This global crisis is projected to escalate further unless decisive actions are taken to regulate antibiotic usage. Notably, no new class of antibiotics has been successfully developed since the golden era of antibiotics discovery between the 1950s and 1970s [34]. By 2050, AMR is projected to cause 10 million deaths annually, surpassing cancer-related fatalities [35]. Recognising the multifaceted nature of this issue, the World Health Organization (WHO) has classified AMR as a One Health priority, acknowledging its interconnected impact on human, animal and environmental health [36].

2 | Good Aquaculture Practices

In Malaysia, Good Aquaculture Practices (GAqP) have been established to assist farmers in mitigating risks associated with disease outbreaks and AMR. The GAqP comprises a set of guidelines, procedures and regulations designed to promote effective and ethical aquaculture practices, safeguard the environment, uphold social responsibility, ensure animal welfare, enhance food safety and enable traceability [37]. Implementing GAqP for food safety minimises production risks for farmers, leading to improved farm performance in the long run. The misuse and overuse of antibiotics remain major contributors to the development of AMR. Therefore, it is crucial to have a strategic and well-regulated approach to antibiotic usage, not only to manage infections effectively but also to preserve the long-term efficacy of antibiotics. Antibiotics should be used judiciously, only when necessary, and under the guidance of a veterinarian. In parallel, exploring alternative treatments and implementing good husbandry practices can further reduce reliance on antimicrobials, while supporting sustainable farming. The efficacy of antibiotics is compromised by their misuse and overuse, especially when coupled with poor farm management, leading to significant risks. These risks include food safety concerns from drug residues and antibiotic-resistant bacteria in aquaculture products, as well as environmental degradation. Such issues ultimately threaten farmers' livelihoods by impacting product quality, eroding consumer trust and impacting revenue.

Good husbandry practices in aquaculture begin from procuring and rearing healthy animals, ensuring their welfare and maintaining proper sanitation and cleanliness throughout the production process. Several countries have successfully reduced antimicrobial use by implementing improved management and husbandry programmes, serving as valuable models for antimicrobial stewardship [38, 39]. Good husbandry practices also play a critical role in biosecurity, which involves measures to minimise the risk of introducing and spreading infectious diseases. Adverse environmental conditions can compromise the animals' immune systems, rendering them more susceptible to diseases. Practices in husbandry to reduce disease susceptibility will lower the need for antimicrobial agent usage, thereby curbing the emergence of antimicrobial-resistant pathogens. Among the key practices highlighted by Yanong [40] are segregating populations to limit the spread of pathogens, such as rearing different life stages in separate systems and adhering to a rigorous schedule of sanitation and disinfection. These measures collectively enhance aquaculture sustainability and health management.

Farmers need to be educated about the potential of pathogen threats, including their modes of entry, survival mechanisms and proliferation within aquaculture facilities. Establishing robust monitoring systems is essential for maintaining optimal water quality and fish health [40]. However, the adoption of these practices remains a challenge, as many farmers often do not fully comply with biosecurity principles. Improving biosecurity and husbandry practices in the aquaculture sector requires investment in education, training and enhanced veterinary services that are accessible and affordable. A survey by Sahidin et al. [41] assessed farmers' knowledge, attitudes and practices concerning *P. vannamei* shrimp disease in Kelantan, Malaysia. The findings revealed that farmers demonstrated strong knowledge and attitudes towards disease management in shrimp pond culture, as evidenced by their positive attitudes toward management and effective aquaculture techniques. This knowledge and proactive approach will later enable farmers to adopt effective cultivation practices, minimising disease incidence and enhancing seed quality.

In response to the growing AMR threat, Malaysia established the National Antimicrobial Resistance Committee (NARC) in 2016 involving both the human and animal health sectors in alignment with the 68th United Nations General Assembly resolution. A Malaysia National Action Plan (NAP) with an aquaculture component related to AMR in Malaysia was also launched in February 2017 with collaborative partnerships particularly between the Ministry of Health and the Ministry of Agriculture and Food Security (MAFS) [42]. The Department of Fisheries (DOF) of Malaysia, under MAFS, oversees the regulation and monitoring of AMR and antimicrobial usage in aquaculture in the country. Among the initiatives are the development and implementation of the National Fish Health Strategy for Malaysia (NFHSM) for 2018–2022 and the Malaysian National Action Plan on AMR (MyAP-AMR) for 2022–2026 [43]. These align with the AMR action plans of WHO, FAO and the World Organization for Animal Health (WOAH) aiming to mitigate the emergence and spread of AMR in Malaysia [44]. The objective of the NFHSM is to minimise the risk of aquaculture diseases threatening the sustainable development of aquaculture while also considering aspects of aquatic biodiversity, food security, food safety and economic sustainability. This includes the establishment of a fish health strategy that supports aquaculture development, protects aquatic biodiversity and meets consumer demands for high-quality products while maximising opportunities for fair profit at all levels of the production chain.

In the MyAP-AMR (2022–2026), the issue of AMR in Malaysian aquaculture is addressed separately from other animal health issues because of the unique dynamics of aquatic ecosystems and aquatic biology [43]. The MyAP-AMR focuses on four key priority areas: (1) increasing public awareness on AMR through education, communication and training, (2) promoting evidence-based research and surveillance, (3) preventing and controlling the spread of AMR and (4) optimising antimicrobial use in human and animal health. Currently, AMR research and awareness programmes are spearheaded by the Department of Veterinary Services (DVS) in Malaysia, which also oversees the registration of vaccines for veterinary use. However, all veterinary drugs must be verified and registered by the National Pharmaceutical Regulatory Agency (NPRA) under the Ministry of Health (MOH). While the DVS actively conducts research on antibiotic residues in aquaculture farms, comprehensive data on antimicrobial usage in aquaculture remain limited. The monitoring programme of AMR is still scarce, and the research conducted by researchers on AMR characterisation and quantification has thus far been inconsistent.

In Malaysia, stringent biosecurity measures are implemented for the import and export of shrimp and shrimp seeds, supported by standard operating procedures (SOPs) as part of monitoring and surveillance protocols to prevent disease outbreaks in shrimp aquaculture. Biosecurity laboratories under the supervision of the DOF of Malaysia play a key role in monitoring and controlling disease outbreaks through routine disease screening analyses. In addition to disease monitoring, the DOF also conducts surveillance for antibiotic residues, heavy metals, pesticide residues, hormones and chemicals in shrimp feed during the import or export processes to uphold high standards of quality and food safety. Shrimp farm operators are required to comply with GAqP, focusing on areas such as reservoir construction, water quality monitoring, chemical usage and waste management. The Environmental Impact Assessment (EIA) works in tandem with the DOF to standardise GAP across the entire aquaculture sector in Malaysia. To further ensure product quality and food safety, certificates are given to shrimp farm operators who meet the prescribed criteria under the Farm Accreditation Scheme. Malaysian farmers are also guided by the Code of Practice (COP), Aquaculture Guidelines and Standard Sanitary Operating Procedure (SSOP), which collectively promote responsible and sustainable aquaculture development.

Chua et al. [44] evaluated NAPs addressing AMR across 10 ASEAN countries with a specific focus on their alignment with the objectives of the Global Action Plan on AMR. The analysis utilised a content-based approach framed within an AMR governance framework emphasising five critical governance areas, including policy design, implementation tools, monitoring and evaluation, sustainability and One Health engagement. The study identified several key factors as essential for translating policies into effective implementation that include accountability, sustained stakeholder engagement, equity, the application of behavioural economics, robust sustainability plans and transparency, international collaborations, as well as the integration of the environmental sector. Notably, in Malaysia, the implementation of the NAP has yielded substantial improvements that led to enhanced biosecurity measures, optimised husbandry practices, strengthened animal health management, improved systems for surveillance and infection prevention and control (IPC), all in accordance with the WOAH standards.

Luthman et al. [45] assessed the regulatory frameworks governing antibiotic use in aquaculture across 17 countries spanning diverse geographic regions covering East Asia, South Asia, Southeast Asia, Europe, America, North America and Oceania (excluding Malaysia). The findings highlighted the positive influence of international commitments to bodies such as FAO/WHO/WOAH on the development of AMR-related policies. The study emphasised the importance of comprehensive national plans that prioritise robust management systems, effective monitoring of antibiotic usage and the integration of best practices for animal health management. It underscored the need for stricter antibiotic use regulations in aquaculture, focusing on limiting prophylactic use, reducing the number of authorised antibiotics and minimising treatments in each production cycle. Thus, understanding regulatory disparities across countries is crucial for identifying gaps in capacity and knowledge to strengthen global efforts in combating AMR.

3 | Antimicrobial Resistance in Shrimp Aquaculture

3.1 | Antimicrobial Resistance (AMR): A Serious Problem

According to the WHO, antimicrobials, which comprise antibiotics, anti-virals, anti-fungals and anti-parasitics, are medications used to prevent and treat infections in humans, animals and plants [46]. For the purpose of this article, we will focus on antibacterial agents, particularly their prolonged and unregulated use in aquaculture, which has been linked to the emergence of bacterial resistance [47]. Prolonged exposure of bacteria to antibiotics can gradually accelerate the evolution of antimicrobial resistance in the bacteria [48]. In aquaculture, antibiotics have been used for over 50 years in three primary ways: (1) therapeutic agents to treat bacterial infections in aquatic organisms, (2) prophylactic use to prevent infection and (3) growth promoters to enhance productivity [49].

The improper use and incorrect dosage of antibiotics in aquaculture have been identified as significant contributors to the development of AMR bacteria [50]. The presence of antibiotics, especially when these substances are not used prudently, imposes strong selective pressure on bacterial populations, allowing only resistant strains to thrive in the presence of these compounds [51]. Moreover, antimicrobial resistance genes are often located on mobile genetic elements that can be transferred horizontally to other bacterial species. Over time, this process facilitates the emergence and proliferation of superbugs or multidrug-resistant bacteria, including human pathogens [52]. Deng et al. [53] investigated five antibiotic resistance genes (ARGs) and one virulence gene in *Vibrio harveyi* 345, demonstrating their role in facilitating horizontal gene transfer (HGT) from other bacterial species, thereby enhancing virulence and antibiotic resistance. Analysis of the complete genome of *V. harveyi* 345 revealed significant genomic exchange, particularly the transfer of virulence genes and drug resistance genes through HGT, which contributed to increased virulence and drug resistance. The risks of AMR dissemination from aquaculture activities are alarming, as water serves as an effective medium for spreading AMR globally. This poses a significant risk to human and animal health. Residual antibiotics in aquatic ecosystems not only stimulate the growth of resistant bacteria but also disrupt the environmental microbiome, leading to broad environmental health implications (Figure 1) [54, 55]. Hence, aquaculture is a recognised source of antimicrobial resistance that can directly impact human pathogens [56].

Water serves as a significant medium for the spread of antimicrobial-resistant bacteria often contaminated by human activities, including from hospital wastewater containing chemicals and pharmaceuticals that could infiltrate aquaculture water sources. Additionally, the excessive use of antibiotics in aquaculture can directly or indirectly impact nearby crops and ecosystems, whereas processed aquaculture products containing antimicrobial-resistant bacteria pose a risk of zoonotic diseases, transferring resistance from animal-associated bacteria to human-associated bacteria.

The indiscriminate use of antimicrobials has driven the rise of antimicrobial-resistant bacteria, thereby complicating the treatment and management of bacterial infections in animals and humans [33]. For example, fluoroquinolones and colistin (polymyxin) are known to be used in aquaculture as growth promoters in some countries, but these antibiotics are also categorised as critically important antibiotics for treating severe multidrug-resistant bacterial infections in humans [57–59]. The use of fluoroquinolones and the recently banned colistin antibiotics as growth promoters in animals resulted in the presence of bacteria that are resistant to these higher classes of antibiotics, thus increasing the risk of therapeutic failure in human infections. This resistance severely limits the availability of robust

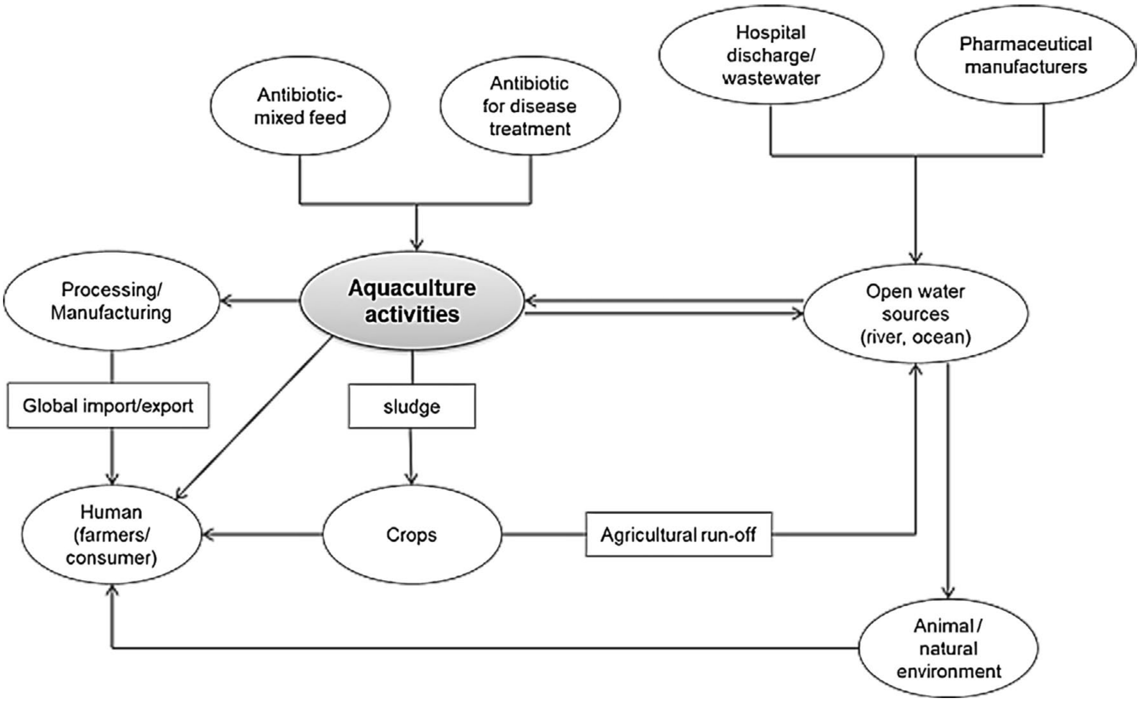

FIGURE 1 | Pathways of antimicrobial resistance dissemination through aquaculture activities within the One Health context, linking animal health, human health and environmental impact.

antibiotics, escalates the severity of infections and eventually results in higher mortality or extended hospital admissions [59, 60]. If left unaddressed, it is projected that the global economic loss caused by AMR would be more than USD 100 trillion between 2014 and 2050, driven by increased treatment costs, higher antibiotics usage, prolonged hospital stays and lost productivity of the patients [61].

3.2 | Antimicrobial Resistance in Global Shrimp Aquaculture

The Asia-Pacific region is among the regions with the highest antimicrobial consumption and is projected to remain the largest consumer until 2030 [54, 62]. Among the commonly used antibiotics are beta-lactams, tetracyclines, sulphonamides, macrolides and fluoroquinolones, which have also been classified by the WHO as important for human medicine [63]. Oxytetracycline, a broad-spectrum antibiotic mainly used for vibriosis, is also reported as a potential antibiotic to treat hepatopancreatic infections in shrimp [64]. In Mexico, florfenicol is used in larval and grow-out facilities to control bacterial diseases [65] and was reported to be effective in treating *V. harveyi* infection in Pacific white shrimp via oral administration of 10 mg kg^{-1} body weight for 10 days.

Quantifying antibiotic use in aquaculture is challenging as each country will have a different antibiotic registration system, and the amounts used in each country can vary significantly. High-income countries tend to implement stricter measures for prudent antibiotic use to control AMR compared to low- and middle-income countries [66]. Shrimp aquaculture activities, however, predominantly occur in low- and middle-income countries, where antibiotic regulation and monitoring are often inadequate [67]. Some countries, for example, the European Union (EU), have prohibited using antibiotics as growth promoters in animal production to curb the emergence of antimicrobial-resistant bacteria [68]. However, in several countries, such as Vietnam, shrimp farmers still continue to rely on antibiotics to enhance shrimp growth and production [69].

Several studies reported on antibiotic residues in shrimps from farms across Southeast Asia and Central America. For example, Swapna and Lakshmanan [70] discovered measurable quantities of chloramphenicol, sulphonamide, tetracycline, erythromycin, streptomycin and β-lactam antibiotics in farmed shrimp in India. In northern Vietnam, three major classes of antibiotics were detected in farmed shrimp: sulphonamides, diaminopyrimidines (trimethoprim) and macrolides [71]. Furthermore, an interview with farmers in Thailand indicated that around 74% of farmers agreed to use antibiotics in pond management. The most commonly used antibiotics were norfloxacin, oxytetracycline, enrofloxacin and different sulphonamides [72]. The improper use of antibiotics in shrimp farming has led to international trade restrictions. Between 2002 and 2019, the United States rejected an average of 341 shrimp-containing imports annually, with antibiotics cited as the main reason [73]. The prophylactic use of antimicrobials in shrimp aquaculture is common and is an authorised practice in veterinary aquaculture [49]. As it is hard to treat infected shrimp individually, the metaphylactic use of antimicrobials, defined as administering antimicrobials to healthy individuals, is still a common practice in shrimp aquaculture [47].

According to Thornber et al. [67], current assessments of AMR severity are not well documented due to the difficulty of obtaining reliable data on antibiotic usage in shrimp-producing countries. Nevertheless, numerous instances of multidrug-resistant bacteria have been recorded in shrimp farm environments and imported shrimp products, suggesting that the improper utilisation of antibiotics within the shrimp industry constitutes a significant threat. Moreover, the traditional shrimp aquaculture practice that is still widely used in Asia often involves the use of antibiotics and has been identified as a potential cause of AMR spread [47]. In this aquaculture practice, the water source for aquaculture activities is usually seawater, and the wastewater that may contain antimicrobials is often released back into the sea, which increases the possibility of AMR dissemination to the natural environment [55, 74].

Antibiotics used in aquaculture often accumulate in the rearing water, plankton and sediments, hence increasing concerns about antibiotic pollution of the environment [49]. Multiple antibiotic-resistant *Klebsiella pneumoniae* and *Aeromonas hydrophila* containing four to seven different antibiotic resistance genes were isolated from water and sediment samples from effluent channels connected to shrimp farms in Long An Province, Vietnam, indicating the dissemination of antimicrobial-resistant bacteria in the natural environment [75]. In South India, sulphonamide-resistant *Salmonella* strains were found in water and sediments from local water sources used by shrimp farms, indicating that AMR contamination can also happen upstream in the water cycle [76].

Other possible ways of AMR spread from shrimp aquaculture include the use of pond sludge containing antimicrobial-resistant bacteria as crop fertilisers, exposure of farmers to water and farm environments that are possibly contaminated with resistant zoonotic agents, and the import and export activities of shrimp that act as transporters for the antimicrobial-resistant bacteria; this can increase the AMR threat on a global scale [67]. In a study of frozen tiger shrimp imported from Thailand to The United States, Shakir et al. [77] found the presence of fluoroquinolone-resistant *Aeromonas* sp. that can threaten humans with an immune deficiency. Different resistant bacteria (including *Aeromonas caviae, Aeromonas hydrophila, Klebsiella pneumoniae* and *Enterobacter aerogenes* resistant to ampicillin, amoxicillin-resistant. *E. aerogenes* and tetracycline-resistant *A. caviae*) were isolated from shrimp samples collected from four fresh markets and Kung Ten salad sold around Bangkok and Nonthaburi, Thailand [78]. In Brazil, 75 out of 100 *Vibrio* sp. strains isolated from Pacific white shrimp were resistant to at least one antibiotic, with resistance observed in species such as *Vibrio parahaemolyticus, Vibrio xuii, Vibrio cholerae, Vibrio alginolyticus, Vibrio diazotrophicus* and *Vibrio vulnificus* [79].

3.3 | Antimicrobial Resistance (AMR) in Retailed and Farmed Shrimps in Malaysia

Pathogenic *Vibrio parahaemolyticus* strains pose a significant threat to shrimp aquaculture, with the emergence of antimicrobial-resistant strains raising serious concerns. In Malaysia, *Vibrio parahaemolyticus* isolates from shrimp demonstrated high resistance rates (63% to 90%) towards ampicillin [80–83]. Resistance to the aminoglycoside class of antibiotics (e.g., amikacin and kanamycin) was also observed in *V. parahaemolyticus* isolated from shrimps. A study by Letchumanan et al. [82] showed that 51% and 28% of the *V. parahaemolyticus* isolated from retail banana prawn (*Penaeus indicus*) and red prawn (*Solenocera subnuda*) were resistant to amikacin and kanamycin, respectively. Additionally, significant resistance to cephalosporin was observed. Up to 56% and 34% of *V. parahaemolyticus* isolated from retail prawns, crabs and clams were resistant to the third-generation cephalosporins cefotaxime and ceftazidime, respectively [81]. A similar observation was reported by Tan et al. [83], where 84% of *V. parahaemolyticus* isolated from retail shrimp (*Penaeus* spp.), blood clam (*Anadara granosa*), surf clam (*Paphia undulata*) and squid (*Loligo* spp.) were resistant to the first-generation cephalosporin cefazolin.

Vibrio parahaemolyticus strains isolated from shrimps in Malaysia have demonstrated a high level of susceptibility to chloramphenicol [82, 83]. However, the Malaysian government has prohibited the use of chloramphenicol in feed and feed additives for treatment and disease prevention due to harmful effects on human health [84]. In contrast, amoxicillin (beta-lactams), oxytetracycline (tetracyclines), florfenicol (amphenicols) and flumequine (quinolones) are among the permitted antibiotics to be used in food-producing aquatic animals for treatment and disease prevention [85]. While their resistance status in shrimp farms remains unclear, previous studies have described high susceptibilities of *Vibrio* isolates from shrimp to amphenicols, tetracyclines and quinolones [81, 86], indicating their potential effectiveness in managing shrimp diseases. Massive AHPND outbreaks may also pose a significant public health risk, as farmers often sell shrimp with a high pathogen load in the market to reduce economic losses [87].

Considering the size and rapid development of shrimp farms in Malaysia, information on the prevalence of MAR bacteria in shrimp farms is still scarce. While studies have described the presence of MAR bacteria in shrimps from wet markets, fewer investigations have focused on the farms themselves. The MAR index is commonly calculated and interpreted using the formula: a/b, where '*a*' represents the number of antibiotics to which an isolate was resistant, and '*b*' represents the total number of antibiotics tested [88]. Meanwhile, $a/(b \times c)$ calculates the MAR index of a sample where '*a*' is the number of resistant cases, '*b*' is the number of antibiotics tested and *c* is the number of isolates [88]. A MAR index above 0.2 indicates a high-risk contamination source where antibiotics are often used [89, 90]. Table 1 summarises the bacterial species, source of isolation, resistance pattern, susceptibility pattern and MAR indices of bacteria isolated from shrimp and other aquatic animals in Malaysia.

3.4 | Sources of Antibiotics in the Malaysian Aquaculture Environment

Over the past decades, various bacteria, including *Vibrio* spp. isolated from water, sediments and various aquatic animals, have shown resistance to multiple antibiotics [93, 96]. The antibiotics enter the aquatic environment from diverse sources, including municipal and hospital sewage, agriculture run-offs, aquaculture farms, and healthcare and pharmaceutical facilities [69]. In Malaysia, antibiotics are commonly prescribed to treat various human infections, with cephalosporins, fluoroquinolones, carbapenems, glycopeptides and penicillin/beta-lactamase inhibitors being the top five antibiotic classes

TABLE 1 | Antibiotic resistance profiles and multiple antibiotic resistance (MAR) index of bacteria isolated from shrimp and aquatic animals in Malaysia.

Bacterial species	Source of isolation	Resistance pattern	Susceptibility pattern	MAR index	Reference
Vibrio parahaemolyticus	Shrimp farm water Sediment Shrimps Effluents	Bacitracin Penicillin G Cephalothin Streptomycin Rifampicin Tetracycline	Spectinomycin Imipenem Amoxycillin/Clavulanic acid Enrofloxacin Meropenem Kanamycin Erythromycin Nalidixic acid	0.14–0.36	[91]
Vibrio species	*Farmed Penaeus monodon* and *Penaeus vannamei*	Ampicillin Vancomycin Penicillin G	NA	0.06–0.75	[92]
Luminescent *Vibrio harveyi*	Farmed *Penaeus vannamei* (Hepatopancreas and haemolymph)	**Tetracycline** Oxytetracycline **Macrolide** Oleandomycin Spiramycin **Quinolone** Nalidixic acid **Aminopenicillin** Amoxicillin Ampicillin **Nitrofuran** Furazolidone **Lincosamide** Lincomycin **Aminoglycoside** Kanamycin **Aminocoumarin** Novobiocin **Colistin/Polymyxin E** Colistin sulphate	**Tetracycline** Tetracycline Doxycycline **Macrolide** Erythromycin **Quinolone** Flumequine Oxolinic acid **Nitrofuran** Nitrofurantoin **Quinolone** Oxolinic acid **Amphenicol** Chloramphenicol Florfenicol **Fosfomycin group** Fosfomycin	0.40	[90]

(Continues)

TABLE 1 | (Continued)

Bacterial species	Source of isolation	Resistance pattern	Susceptibility pattern	MAR index	Reference
Vibrio parahaemolyticus	Retail blood clam (*Anadara granosa*) Shrimp (*Penaeus* spp.) Surf clam (*Paphia undulata*) Squid (*Loligo* spp.)	**Penicillin** Penicillin G (100%) Ampicillin (84.17%) **First-generation cephalosporin** Cefazolin (84.17%)	**Chloramphenicol** Chloramphenicol (100%) **Carbapenem** Imipenem (> 90%) Meropenem (> 90%) **Tetracycline** Tetracycline (> 90%) Doxycycline (> 90%) **Trimethoprim/Sulphonamide** Trimethoprim-sulphamethoxazole (> 90%) **Others** Ampicillin-sulbactam	0.04–0.71	[83]
Vibrio parahaemolyticus	Retail red prawn (*Solenocera subnuda*) Banana prawn (*Penaeus indicus*) Mud crab (*Scylla serrate*) Flower crab (*Portunus pelagicus*) Carpet clam (*Paphia texile*) Hard shell clam (*Meretrix meretrix*) Mud creeper (*Cerithidea obtuse*)	**Penicillin** Ampicillin (85%) **Aminoglycoside** Amikacin (66.8%) Kanamycin (50.1%) **Third-generation cephalosporin** Cefotaxime (55.8%) Ceftazidime (34%)	**Carbapenem** Imipenem (94%) **Tetracycline** Tetracycline (83.1%) **Fluoroquinolone** Levofloxacin (76.1%) **Aminoglycoside** Gentamicin (70.6%) **Trimethoprim/Sulphonamide** Trimethoprim-sulphamethoxazole (75.8%) **Chloramphenicol** Chloramphenicol (92.5%) **First-generation fluoroquinolone** Nalidixic Acid (73.85%) **Others** Ampicillin-Sulbactam (81%)	0.00–0.79	[81]

(Continues)

TABLE 1 | (Continued)

Bacterial species	Source of isolation	Resistance pattern	Susceptibility pattern	MAR index	Reference
Vibrio parahaemolyticus	Retail shrimp	**Penicillin** Ampicillin (90%) **Cephalosporin** Cefotaxime (50%) Cefepime (50%) Ceftazidime (46.7%) **Tetracycline** Tetracycline (36.6%) **Others** Amoxicillin–clavulanic acid (63.3%)	**Carbapenem** Imipenem (100%) Meropenem (93.4%) **Aminoglycoside** Gentamicin (96.7%) Amikacin (73.3%) **Fluoroquinolone** Ciprofloxacin (93.4%) Levofloxacin (93.4%) **Tetracycline** Tetracycline (63.3%) **Third-generation cephalosporin** Ceftazidime (53.3%) **Antipseudomonal Penicillin** Piperacillin (96.7%) **Second generation fluoroquinolone** Ofloxacin (93.4%)	0.07–0.71	[86]
Edwardsiella tarda Enterobacter spp. *Serratia* spp. *Escherichia* spp. *Klebsiella pneumonia. Plesiomonas shigelloides Pseudomonas* spp. *Aeromonas* spp. *Vibrio* spp. *Staphylococcus* spp. *Bacillus* spp. etc	Fish Shrimp Culturing environment	**Penicillin** Ampicillin Penicillin **Macrolide** Erythromycin **Aminoglycoside** Streptomycin **First-generation cephalosporin** Cephalothin	**Aminoglycoside** Gentamicin Tobramycin Amikacin **Fluoroquinolone** Norfloxacin **Chloramphenicol** Chloramphenicol	0–0.63	[93]

(Continues)

TABLE 1 | (Continued)

Bacterial species	Source of isolation	Resistance pattern	Susceptibility pattern	MAR index	Reference
Vibrio parahaemolyticus	Retail banana prawn (*Penaeus indicus*) Red prawn (*Solenocera subnuda*)	**Penicillin** Ampicillin (82%) **Aminoglycoside** Amikacin (51%) Kanamycin (28%) **Third-generation cephalosporin** Cefotaxime (37%) Ceftazidime (15%)	**Carbapenems** Imipenem (98%) **Aminoglycoside** Gentamicin (85%) **Fluoroquinolone** Levofloxacin (83%) **Tetracycline** Tetracycline (82%) **Chloramphenicol** Chloramphenicol (95%) **Trimethoprim/Sulphonamide** Trimethoprim-Sulphamethoxazole (93%) **Others** Ampicillin-Sulbactam (96%)	0.00–0.79	[82]
Vibrio parahaemolyticus	Retail shrimp Cockles	**Penicillin** Ampicillin (63.1%) **First-generation cephalosporin** Cefalexin (35.4%)	**Tetracycline** Tetracycline (97%) **Fluoroquinolone** Ciprofloxacin (49.3%)	NA	[80]
Vibrio species	Farmed *Penaeus vannamei*	Ampicillin Tetracycline Doxycycline	NA	NA	[62]
Vibrio spp.	Farmed *Penaeus vannamei* (PLs and adult-hepatopancreas)	Ampicillin Erythromycin Lincomycin Oleandomycin Amoxicillin Colistin sulphate Sulphamethoxazole Chloramphenicol Flumequine Oxytetracycline Tetracycline Fosfomycin Spiramycin	Oxolinic acid Chloramphenicol Novobiocin Nitrofurantoin Doxycycline Kanamycin Nalidixic acid Florfenicol	0.09–0.30	[94]

(Continues)

used in hospitals [97, 98]. However, unauthorised discharges and inefficient wastewater treatment facilities may lead to antibiotics being discharged into the environment [99]. As described by Low et al. [100], the highest antibiotic occurrence was detected in hospital wastewater effluent, where macrolides (clarithromycin, azithromycin and erythromycin-H_2O), fluoroquinolones (norfloxacin, ofloxacin and ciprofloxacin), sulphonamides (sulphapyridine, sulphadiazine and sulphamethoxazole), tetracycline (tetracycline), chloramphenicol and trimethoprim were detected.

Improper disposal of unused pharmaceutical wastes, including antibiotics, is also a major concern. In Malaysia, surveys showed that most antibiotic users are unaware of proper disposal methods, and unused and expired household pharmaceuticals are commonly discarded in rubbish bins or disposed of through domestic water systems such as toilets or sinks [101, 102]. These wastes could eventually reach the environment through landfill leachates and ultimately contaminate water systems. Importantly, the occurrence of antibiotic residues in drinking water may pose a health hazard to humans. Although previous studies in Malaysia have indicated a low potential human health risk associated with antibiotic exposure through water ingestion, several antibiotics, such as amoxicillin, ciprofloxacin, nitrofurantoin and sulphamethoxazole, were detected in drinking water intended for human consumption.

A wide range of antibiotics is also used in food-producing terrestrial animals such as swine, cattle, goats and poultry for therapeutic purposes and metaphylaxis. Among the permitted antibiotics are aminoglycoside (apramycin, streptomycin, spectinomycin), penicillin (amoxicillin, ampicillin, penicillin G), macrolide (erythromycin, tilmicosin, tylvalosin), sulphonamide (sulphadimethoxine, sulphamethazine/sulphadimidine, sulphadiazine, sulphamonomethoxine, sulphamethoxazole, sulphathiazole), tetracycline (chlortetracycline, doxycycline, oxytetracycline) and quinolone (flumequine) [85]. The waste and effluents from livestock farms can enter aquatic environments and contribute to the increased amounts of antibiotic residues. For instance, wastewater effluent from zoos and slaughterhouses was found to contain fluoroquinolones (norfloxacin, enoxacin, enrofloxacin, ofloxacin and ciprofloxacin), macrolides (azithromycin, erythromycin-H_2O), tetracyclines (oxytetracycline), amphenicol (chloramphenicol), trimethoprim and sulphonamides (sulphapyridine, sulphadiazine, sulphamethoxazole) [100]. Additionally, antibiotics may originate from agricultural activities, where the repeated utilisation of animal manure as fertiliser introduces veterinary antibiotics into the environment. Commonly detected antibiotics in manure-amended agricultural soils include doxycycline, enrofloxacin, flumequine, norfloxacin, trimethoprim and tylosin [103].

4 | Strategies for Reducing Amr in Aquaculture

The production of shrimp is significantly threatened by bacterial diseases, demanding the implementation of effective treatments. This implies that alternative therapeutics will be required to reduce the utilisation of antibiotics. Several strategies have been

TABLE 1 | (Continued)

Bacterial species	Source of isolation	Resistance pattern	Susceptibility pattern	MAR index	Reference
Vibrio harveyi	Farmed *Penaeus monodon* (Haemolymph)	Ampicillin (90%) Sulphamethoxazole (40%)	Kanamycin (0%) Nalidix acid (0%) Tetracycline (3.3%) Furazolidone (3.3%)	NA	[95]

investigated and implemented in Malaysia and globally as alternatives to antibiotics. These strategies are further discussed in the following sections.

4.1 | Probiotics

Probiotics are live microorganisms which, once administered in appropriate amounts, provide a health benefit to the host [104]. Probiotics also play a vital role in improving digestive health, boosting immune responses and enhancing water quality [105, 106]. Various species of *Bacillus* and *Streptomyces* have been used as shrimp probiotics, demonstrating improved growth performance and increased resistance to infectious diseases [107, 108]. For instance, shrimp fed with a commercial probiotic mixture containing *Bacillus subtilis*, *B. natto*, *B. megaterium*, *Lactobacillus acidophilus*, *L. plantarum*, *L. brevis*, *L. casei* and *Saccharomyces cerevisiae* at $2.3\,\mathrm{g\,kg^{-1}}$ feed exhibited higher survival and growth rates compared to untreated shrimp [109]. In addition, this study also found that the synergistic effects of the commercial probiotic mixture and bioflocs helped prevent the development of lesions in shrimp hepatopancreases. Meanwhile, Nguyen et al. [110] reported that *Lactobacillus plantarum* strain T13 effectively protected shrimp from AHPND. Similarly, Chomwong et al. [111] demonstrated that a diet supplemented with *Lactobacillus plantarum* strain SGLAB01 and *Lactococcus lactis* strain SGLAB02 enhanced haemolymph phenoloxidase activity and promoted disease resistance towards AHPND in Pacific white shrimp.

Meanwhile, Chumpol et al. [112] observed that three types of purple non-sulphur bacteria (*Rhodobacter sphaeroides* strains SS15, S3W10 and *Afifella marina* STW181) provided protection to Pacific white shrimp when challenged with AHPND-causing *Vibrio parahaemolyticus*. The tanks inoculated with these bacteria demonstrated an improvement in water quality with reductions in ammonia (NH_4^+), nitrite (NO_2^-) and nitrate (NO_3^-) levels compared to control tanks (without purple non-sulphur bacteria). Wang et al. [113] identified two potential strains (CDM8 and CDA22) isolated from the hindgut of Pacific white shrimp. When the diet was supplemented with these strains, the survival rates increased significantly, with 63.3% for CDM8 and 35% for CDA22, compared to 8.3% survival in the control group fed with commercial feed without supplementation. Moreover, at 9 h post-infection, the group fed with the CDM8-supplemented diet showed a more than 30-fold decrease of pirAvp mRNA gene copy number compared to the unsupplemented group.

Probiotic use in aquaculture has made significant advancements in recent years, with several strategies actively being trialled in the industry. These include probiotic formulations comprising species such as *Bacillus pumilus*, *Micrococcus luteus*, *Pseudomonas fluorescens* and *Pseudomonas putida*, which are marketed as mixtures by Prowins Biotech Private Ltd., India [114]. Kumar Namburu et al. [115] evaluated eight probiotic products (Pro-B Active A, Avant-Bact, Avant-ProW, Black Solve, Bio Cult, Prob Solve, Pond Solve and Micro-PS) widely used by shrimp farmers in India and observed a positive correlation between probiotic use and shrimp growth. Their findings further indicated that probiotics contributed to improved shrimp survival, reduced production costs, decreased disease prevalence and enhanced water quality as well as pond bottom conditions. However, probiotics are not a complete substitute for antibiotics in aquaculture and are better utilised as a complementary approach. For example, while most research on *Bacillus* probiotics emphasises their efficacy as feed additives, their dietary supplementation poses challenges during the early developmental stages of aquatic species due to the underdeveloped digestive systems of larvae and juveniles [116].

4.2 | Quorum Sensing (QS) and Quorum Sensing Interference (QSI)

Vibrio spp. belonging to the Harveyi clade, including *Vibrio harveyi* and closely related species such as *Vibrio campbellii* and *Vibrio parahaemolyticus*, which are among the major bacterial pathogens in shrimp, regulate the expression of their virulence genes through quorum sensing. Quorum sensing is a form of bacterial cell-to-cell communication that mediates various bacterial phenotypes and activities, including the expression of virulence genes, through small signal molecules. The Harveyi clade vibrios contain a three-channel quorum sensing system using three different signal molecules, which are Harveyi autoinducer-1 (HAI-1), autoinducer-2 (AI-2) and *Cholerae* autoinducer-1 (CAI-1) [117]. HAI-1 is a type of acylated homoserine lactone (AHL), specifically identified as the 3-(hydroxybutanoyl)-L-homoserine lactone and is unique to Harveyi clade vibrios [118]. The active molecule structure of AI-2 in *V. harveyi* is identified as a furanosyl borate diester, specifically 3A-methyl-5,6-dihydrofuro(2,3-$_D$)(1,3,2)dioxaborole-2,2,6,6A-tetraol (S-THMF-borate) [119, 120]. This molecule forms through alternative cyclisation, hydration and a subsequent reaction with boric acid [121]. Its presence has been documented in both Gram-negative and Gram-positive bacteria, suggesting a potential role in interspecies communication. Meanwhile, CAI-1 is (Z)-3-aminoundec-2-en-4-one [122] is mostly conserved in *Vibrio* species [123]. The three-channel quorum sensing system has been shown to regulate virulence factor production and is necessary for full virulence in different aquatic organisms [118]. Additionally, another quorum sensing system found in vibrios is indole signalling. This system also controls the virulence of vibrios, as increased indole levels have been shown to decrease the virulence of all vibrios tested thus far [124].

Quorum sensing interference (QSI) is a strategy to disrupt virulence without inhibiting the growth of pathogenic bacteria, allowing the host to activate its defence mechanisms to clear the infection [125]. This approach includes a weaker selective pressure for resistance development than the use of antibiotics [126]. Common modes of QSI are (1) QS signal molecule degradation either through alkaline conditions or enzymatic activity, (2) QS signal molecule receptor blocking (in case of three-channel QS) or activation (in case of indole signalling) and (3) QS signal transduction inhibition [127]. Various aquatic organisms, including bacteria, cyanobacteria, microalgae, macroalgae and others, excrete QSI extracellular substances as part of their survival and defence strategies. For example, QSI enzymes, such as acylase, decarboxylase, deaminase, lactonase and oxidoreductase, are prevalent in various bacterial species [128]. Bacteria with QSI enzymatic activities, such as *Bacillus* spp. including *B. thuringiensis*, *B. cereus*, *B. mycoides*, *B. anthracis*, *B. licheniformis*, *B.*

amyloliquefaciens and *B. megaterium*, can be isolated from healthy aquaculture organisms and have been documented to be able to protect aquatic animals from vibriosis [129].

Algae often coexist with bacteria, forming symbiotic relationships that not only enhance the nutritional value for aquatic animals but also contribute to overall environmental health through their ecosystem services [130]. In fact, the first QSI molecule, the halogenated furanone (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone, was discovered in the red macroalga *Delisea pulchra* [131]. Recent research has shown that an ethanolic extract of the red macroalga *Gracilaria fisheri* interferes with the AI-2 mediated light production in *Vibrio campbellii* [132]. Another red macroalga, *Gracilaria changii*, was found to inhibit the production of purple violacein pigment in *Chromobacterium violaceum* CV026 that is regulated by QS [133]. Meanwhile, culture filtrates of the freshwater microalga *Chlamydomonas reinhardtii* were reported to contain the QS signal-mimic compound lumichrome, a vitamin riboflavin derivative [134]. Other microalgae species such as *Chlamydomonas mutabilis, Chlorella vulgaris* and *Chlorella fusca* also stimulated luminescence responses in *V. campbellii*, although the active compounds remain unknown [134]. Other unknown compounds produced by microalgae include an ethyl acetate extract from the cell-free supernatants of *C. saccharophila*, which inhibited QS-regulated gene expression in all three reporter strains tested [135]. Finally, the auxin plant hormone indole-3-acetic acid, which is also produced by algae, has recently been shown to protect brine shrimp from various pathogenic vibrios, including those AHPND-causing strains [118, 136].

Quorum sensing inhibitors have garnered significant interest for their potential to mitigate bacterial virulence and biofilm formation in various industries, including aquaculture. However, the transition from laboratory research to industrial-scale application remains limited. A comprehensive review by Zhou et al. [137] discusses the regulatory mechanisms and promising applications of QSI agents. The authors highlight the potential of QSI in industrial fields but note that practical applications are still in the developmental stage. Similarly, Elgendy et al. [138] also highlight that industrial-scale applications of QSI are not yet widespread. In the context of aquaculture, while QSIs offer a promising strategy to control bacterial infections without relying on traditional antibiotics, their large-scale implementation faces challenges. These include the need for extensive field trials, regulatory approvals, cost considerations and ensuring environmental safety. Ongoing research and development efforts are crucial to address existing challenges and facilitate the transition from laboratory findings to practical, large-scale applications.

4.3 | Bacteriophages

Bacteriophages are viruses that infect and replicate within bacteria and possess numerous characteristics, including genetic plasticity, self-replication and adaptability to diverse environments and evolutionary changes, making them the most abundant organisms in the biosphere [139]. According to Chen et al. [140], the use of a phage cocktail comprised of five different phages successfully inhibited the growth of pathogenic *Vibrio* species. Besides that, several studies on phage therapy against vibriosis in shrimp also demonstrated promising results [141–143]. For instance, Giant tiger prawns treated with a phage cocktail exhibited survival rates of 83%–93%; significantly higher than the control without phage treatment (32%). Furthermore, the level of pathogenic *V. parahaemolyticus* decreased by up to 4 log units in phage-treated tanks compared to the control tanks [143]. Similarly, Lomelí-Ortega and Martínez-Díaz [142] reported that the survival rate of Pacific white shrimp treated with the phages AS3 and Vpms1 increased to 80% and 77%, respectively, compared to the control group (59%).

Another experiment conducted by Jun et al. [141] revealed that a single dose of the phages Vpms and A3S was sufficient to decrease the mortality rate of shrimp larvae challenged with *V. parahaemolyticus*. Shrimp fed with phage-impregnated feed exhibited a 50% survival when compared to 0% survival in the control group. The untreated larvae challenged with AHPND-causing bacteria demonstrated typical histopathological features of AHPND, including acute sloughing of hepatopancreatic tubular epithelial cells. In contrast, the phage-treated shrimp showed significant recovery from AHPND lesions and a healthy appearance of the hepatopancreas [141]. Phage therapy also reduced shrimp mortality by 4% compared to a control group, delaying mortality by 3 h and shortening the terminal phase [144]. However, single-phage therapy was ineffective in controlling AHPND, suggesting that combined strategies such as phage cocktails and toxin binders should be considered for effective prevention or treatment of AHPND.

Currently, several phage-based products have been developed and implemented in shrimp aquaculture. One such product, V Phages Growout, was tested in four ponds affected with vibriosis on days of culture (DOC) 66 and 69. The application of this phage product resulted in a marked reduction in the prevalence of white gut disease, a consistent increase in feed consumption over the subsequent 14 days until harvest and improved growth performance on DOC 91 and 92. Moreover, it effectively prevented disease outbreaks in adjacent ponds from DOC 73 to 91. In ponds with an AHPND outbreak, the product facilitated recovery and higher shrimp survival rates. However, practical applications of phage therapy are limited by environmental conditions that may inactivate phages or cause off-target adsorption. Encapsulating phages in liposomes has been proposed as a strategy to maintain their stability and concentration, ensuring effective delivery to target bacteria without inactivation [145].

4.4 | Immune Priming

Shrimp do not have a specific adaptive immune system, yet recent research indicates that they can exhibit memory-like properties, known as immune priming or immune training, which refers to the ability of invertebrates to memorise prior encounters with pathogens, thereby enhancing their immune response upon reinfection [146]. A variety of invertebrate species that lack acquired immune systems have now been shown to exhibit immune priming as a form of immune memory. Immune priming has significant implications for effectively preventing infectious diseases in economically valuable shellfish, as it leads to the specific activation of innate immunity upon subsequent infection

[147]. In invertebrates, immune priming is characterised by the induction of defences that follow a biphasic kinetic pattern [147]. This process involves two key phases: (i) a recalled response, where the same immune effectors are activated in response to a secondary challenge, and (ii) an immunisation-induced response, where immune effectors are up-regulated for a sustained period after a primary stimulation. Furthermore, it has recently been demonstrated that the primary and secondary responses, involving distinct immune effector systems, might lead to a transcriptional shift from a cellular to a humoral response.

The concept of immune priming or immune training in shrimp has opened new avenues for enhancing disease resistance despite the absence of a specific adaptive immune system. Immune priming agents such as live, heat-killed pathogens or specific molecules from the original pathogens, such as beta-glucans, lipopolysaccharides and peptidoglycans, are being developed to train shrimp immune systems to respond more robustly to recurring pathogens. However, the success of immune priming can be influenced by temperature, salinity and water quality. Extensive work to understand the mechanism behind the observed protection is ongoing, with no known widely used commercial product used by shrimp farmers thus far [148, 149].

4.5 | Aptamers

Currently, molecular treatments and diagnostics have emerged as dynamic approaches to address the AMR crisis, with the use of aptamers gaining significant interest due to their practicality, flexibility and sensibility. Aptamers are single-stranded oligonucleotides (DNA or RNA) with a length of 50–100 bases that can fold into specific three-dimensional structures, enabling them to selectively bind to target molecules with high specificity and affinity [150]. Aptamer-based antimicrobials offer a potential solution to the increasing gap between drug discovery and the rise of drug resistance. These molecules are able to interfere with critical biochemical processes or bind to extracellular components, thereby acting as therapeutic agents in aquaculture, inhibiting key pathogenic mechanisms such as biofilm formation [151]. Biofilm formation is a multistep process that involves bacterial attachment, maturation and bacterial release, which may lead to virulence and pathogenicity of bacteria. For example, aptamers that bind to the flagella of *Salmonella choleraesuis* restrict its movement by increasing the surface area and preventing mature biofilm formation [152]. This aptamer-mediated binding not only inhibited biofilm development but also rendered bacterial cells more susceptible to antibiotic attack, reducing the required dose of ampicillin and preventing the emergence of AMR strains. Similarly, in *Pseudomonas aeruginosa*, two complex aptamers reduced biofilm formation by over 36% compared to biofilm formation in toxic nanotubes or ciprofloxacin alone. This suggests that the specific identifier aptamer-led complexes target and increase the antimicrobial agent efficiency [153]. These findings indicate that aptamers can disrupt biofilm formation, improve drug efficacy through precise targeting and minimise off-target effects. The application of aptamers for pre-treatment agents could eliminate the need for a high dosage of antibiotics.

In recent years, aptamers have been designed to mediate pathogen recognition by host immune systems, enhance the immune responses and facilitate early detection of infections. Aptamers can be used to inhibit or interfere with superantigen activity and have the potential to be therapeutics for treating various diseases. These functional aptamers are specifically designed to bind to virulence factors such as antigens, toxins, enzymes and pathogenic cells. For instance, Yusof et al. [154] demonstrated the potential of the computationally designed aptamer candidate VPL300 to target the LuxP receptor protein in *Vibrio parahaemolyticus* responsible for AHPND. This aptamer effectively suppressed QS and virulence by inhibiting the expression of polar flagellum genes, which are essential for bacterial motility. To further enhance its bioactivity, modifications to the VPL300 aptamer could improve its binding affinity to the LuxP receptor protein, thereby enhancing its effectiveness as a therapeutic agent for treating *Vibrio* infection in aquaculture.

Aptamers offer distinct advantages over traditional antibodies, including thermal stability, cost-effectiveness, broad applicability and the capacity to detect Gram-negative bacteria and their toxins [155]. Although studies demonstrate the promising potential of aptamers in aquaculture, their application remains in its early stages, with a limited number of aptamers available for targeting specific pathogens in aquaculture settings. The development of a comprehensive series of pathogen-specific aptamers targeting the causative agents of major aquatic diseases is urgently required to establish a foundation for effective therapeutic strategies [156].

4.6 | Phytobiotic

Phytobiotic is known as plant extracts that contain bioactive compounds with anti-inflammatory, antioxidant and anti-cancer properties and are more biodegradable than synthetic molecules, thus being more ecologically friendly and cost-effective [157]. Due to the presence of diverse bioactive molecules with different modes of action, phytobiotics are less likely to induce resistance in pathogens. In shrimp aquaculture, phytobiotics have been extensively tested for their ability to interfere with the bacterial cell wall and viral mRNA synthesis [16]. For example, Zhu et al. [158] demonstrated that dietary hydrolysable tannins significantly increased enzyme activities and oxidative stress in the serum and hepatopancreas of shrimp, impacted the composition of intestinal microbiota and reduced the prevalence of *Vibrio* in the intestines of Pacific white shrimp.

A recent investigation conducted by Shin et al. [157] found that dietary supplementation with piperine, an alkaloid and polyphenol derived from peppers, improved growth performance, feed utilisation, innate immunity, digestibility and disease resistance in Pacific white shrimp, *Penaeus vannamei*. Meanwhile, histopathological analyses revealed that dietary supplementation with methanolic leaf extracts of *Centella asiatica* (Asiatic pennywort) caused fewer alterations in the hepatopancreas at doses ranging from 10 to 30 $mg\,kg^{-1}$ [159]. Specifically, at 30 $mg\,kg^{-1}$, the tissues retained their structural integrity, including the star-shaped tubule lumen and diverse cell types. Another study demonstrated that dietary *Galla chinensis* enhanced total haemocytes, phenoloxidase, phagocytic activity, production of superoxide anion, gene expression, specific growth rate and resistance to *Vibrio parahaemolyticus* in Pacific white shrimp [160].

Commercial phytobiotic products such as Sanacore GM, containing vegetable fatty acids and inactivated *Saccharomyces cerevisiae* and herbal extract, have demonstrated significant improvements in growth performance, feed utilisation and whole-body protein deposition in shrimp *Penaeus vannamei* [161]. Higher dietary inclusion levels of Sanacore GM were associated with a notable enhancement in both cellular and humoral immune responses. Additionally, dietary supplementation of Sanacore GM consistently increased probiotic bacterial counts while reducing the enteric bacterial population in the intestine.

5 | Addressing Amr Through Community Engagement

Community engagement is increasingly recognised as a cornerstone in addressing AMR and in promoting sustainability in shrimp aquaculture. This collaborative approach leverages the collective efforts of societal stakeholders, including non-governmental organisations (NGO), community-based initiatives and small-scale farmers, to mitigate the risks of AMR development and transmission [162]. In Malaysia, the Ministry of Health has taken proactive steps through the organisation of national seminars on antimicrobial stewardship, featuring both local and international experts. A notable milestone was the ASEAN Antimicrobial Stewardship Seminar and Workshop in 2019, hosted as part of the ASEAN Health Cluster 2 Strategic Plan. This event brought together representatives from ASEAN member states across human and animal health sectors to exchange knowledge, best practices and address challenges in implementing antimicrobial stewardship [43]. Similarly, the DOF of Malaysia has contributed significantly to community projects aimed at strengthening capacities, policies and NAPs for the prudent and responsible use of antimicrobials in fisheries and aquaculture [42].

Le et al. [163] identified key risks and preventive measures influencing disease outbreaks in intensive shrimp farming. Their findings highlight the critical role of farmers' adaptive measures such as adjusting feeding schedules, participating in training programmes and utilising extension services in reducing disease prevalence. The study also proposed the development of a comprehensive toolbox by local authorities to integrate various methodologies and predictive models based on data collected from local farmers. This approach could provide more accurate predictions than those generated by farmers alone. Farmers play a pivotal role in managing and mitigating disease risks, making the collection of farm-level data essential. Variables such as feed data, crop duration, adaptive measures and routinely adjusted feed ratios should be regularly recorded and monitored. These measures could support early warning systems and timely interventions, helping farmers minimise the risk of disease outbreaks.

By combining community engagement, data-driven insights and targeted capacity-building initiatives, this approach lays a strong foundation for sustainable shrimp aquaculture while addressing the multifaceted challenges of AMR.

6 | Conclusions

This review highlights the prevalence of AMR and the strategies employed within shrimp aquaculture to counteract it, with a particular focus on Malaysia. A thorough understanding of country-specific disease outbreaks is essential to identifying the underlying drivers of excessive antibiotic usage. Effective management of AMR requires an integrative approach that encompasses human, animal and environmental health within a holistic One Health framework. This approach requires a robust national action plan supported by multi-sectoral collaboration among governments, policymakers, scientists across diverse disciplines and the wider community. Key strategies include strengthening surveillance systems, implementing antimicrobial stewardship programmes and fostering research and development of alternative treatments, in alignment with regulatory guidelines established by the European Union and the United States Food and Drug Administration (FDA). This review also emphasises the need for comprehensive strategies guided by strong and inclusive national action plans to mitigate AMR-associated disease outbreaks in shrimp aquaculture. The extensive use of antibiotics in shrimp farming has significantly contributed to the dissemination of AMR in the natural environment, increasing the risk of transmission to humans, presenting a growing public health concern. Strengthening AMR surveillance and monitoring systems, underpinned by effective national action plans, is therefore essential to mitigate these risks and prevent potential future pandemics.

Author Contributions

Ikhsan Natrah: conceptualization, funding acquisition, writing – review and editing, supervision, writing – original draft, validation, investigation, methodology, project administration, resources. **Sarmila Muthukrishnan:** writing – original draft, writing – review and editing, conceptualization, investigation, validation, visualization, data curation, formal analysis. **Hirzahida Mohd-Padil:** writing – original draft, writing – review and editing, conceptualization, data curation, investigation, validation, formal analysis, visualization. **Nurliyana Mohamad:** writing – original draft, writing – review and editing, conceptualization, data curation, investigation, validation, formal analysis, visualization. **Norfarrah Mohamed Alipiah:** writing – original draft, writing – review and editing, conceptualization, data curation, investigation, validation, formal analysis, visualization. **Mohamed Shariff:** writing – review and editing, conceptualization, data curation, investigation, validation, visualization. **Fatimah Md Yusoff:** writing – review and editing, supervision, conceptualization, data curation, investigation, validation. **Ina Salwany Md Yasin:** writing – review and editing, conceptualization, data curation, investigation, validation, formal analysis. **Sri Devi Devadas:** writing – review and editing, resources, conceptualization, data curation, investigation, validation. **Wan-Haifa Haryani Wan Omar:** writing – original draft, validation. **Wan Nurhafizah Wan Ibrahim:** writing – review and editing, validation, conceptualization, data curation, investigation, visualization, resources, writing – original draft. **Tom Defoirdt:** writing – review and editing, conceptualization, data curation, validation, visualization.

Acknowledgements

This work was carried out with financial support from the International Development Research Centre (IDRC), Canada, and the Global AMR Innovation Fund (GAMRIF), part of UK Government's Department of Health and Social Care (DHSC) (Project no: 110342-001 Enhancing Sustainability in Shrimp Aquaculture through Microalgae-Bacteria System with Quorum Sensing Inhibition Properties). T.D. was supported by the Scientific Research Fund of Flanders (FWO; project no: G057725N) and the Special Research Fund of Ghent University.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The articles supporting this review are accessible, and each article's DOI is included in the references section.

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