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Review Article

Antibiotic Resistance Genes (ARGs) in the Environment of Saudi Aquaculture as a New Class of Pollutants

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Aquaculture is a productive sector that will be instrumental in addressing the challenges of the forthcoming generation, including the demand for proteins endorsing humans and environmental stewardship. Saudi Arabia (SA) economy heavily depends on aquaculture. However, aquaculture practices, which encompass applying antibiotics for both prophylaxis and treatment, impose a significant impact. Applying antibiotics in aquaculture causes the neighboring microorganisms in the water column, soil particles, and aquaculture-related bacterium species to become resistant to antibiotics. Bacteria can spread antibiotic resistance genes (ARGs) through gene transfer mechanisms, further distributing genetic determinants in aquatic habitats. SA is one of the nations with the highest projected relative growth in aquaculture antibiotic consumption. There have been reports of numerous antibiotic-resistant microorganisms in SA, but the majority of studies focused on isolates from human samples. Several ARGs developing resistance to aminoglycosides, carbapenems, tetracyclines, and beta-lactams were reported in clinical samples in SA; however, limited reviews about aquaculture-related antibiotic resistance genes (AARGs) have been published in SA. In this article, the main drivers of increasing the dissemination of AARGs were poor sanitation systems, human clinical antibiotic resistance (AR), antibiotic misuse, aquatic feed-containing antibiotics, and lack of awareness regarding antibiotics use in both clinical and (AR) aquaculture systems. Saudi national corporations are required to combat AARGs, including reiterating the threat of AR and looking for more cutting-edge knowhows or efficient administration choices to regulate it. It is necessary to educate the general population alongside organizations about AARG dissemination so as to increase understanding and alter the existing circumstances.

1. Introduction

According to the United Nations General Assembly, the antibiotic resistance (AR) problem is equally important to human development as global warming [1]. Some have expected that by 2050, civilization may return to time without antibiotics because of the rising number of bacteria resistant to all popular antibiotics [2]. Antibiotics are applied extensively in both the farming and agriculture sectors, not just for human medical purposes [3, 4]. Such use aims to promote the growth of livestock and crops as well as the prevention or treatment of infectious conditions [5]. Climate change, which has worsened the global food shortage, has exacerbated the problem of AR. According to the predictions, there will be a severe global food insecurity if food production does not increase in the next four decades [6].

Aquaculture is an essential industry for the foreseeable future because it can supply the food needed to feed a population that is expanding quickly. Aquaculture is referred to, as stated by FAO (Food and Agriculture Organization of the United Nations), as "the farming of aquatic organisms, including fish, mollusks, crustaceans, and aquatic plants." 2020 witnessed the production of a record 122.6 Mt of aquaculture-related goods worldwide, valued at an estimated USD 281.5 billion. Aquatic animals accounted for 87.5 Mt, whereas algae made up 35.1 Mt [7]. The global aquaculture industry increased in all regions apart from Africa in 2020, empowered by growth in Norway, China, and Chile, but declined in the two largest African manufacturers, Egypt and Nigeria. Through 2019, the remainder of Africa experienced growth of 14.5%. Asia remains responsible for 91.6% of the aquaculture output worldwide [8]. Considering forecasts for aquaculture in 2030, where fish production is expected to double [9], fish and seafood intake will rise by 27%. These objectives were developed in accordance with the 2030 UN Agenda's Sustainable Development Goals, which encompass the provision of food for all individuals and the preservation of the environment [10]. However, the administration of antibiotics is not entirely prohibited for farmed fish. Contrarily, aquaculture farms frequently use antibiotics to treat a variety of illnesses [11]. Given that this industry uses antibiotics in a vastly unregulated manner, precautions have to be made to protect both human wellness and the ecosystem [12].

Saudi Arabia (SA)'s aquaculture output rose from 6,004 tonnes in 2000 to 75,400 tonnes in 2019. The subregional, regional, and global averages were all surpassing the annual growth rate of 14.25%. Aquaculture now accounts for 52.8% of SA's total fishery production, up from 4.7% in 1990. The extra demand for fish brought on through increasing per capita intake of fish and population expansion would be met by SA's trend of aquaculture growth, but not the additional demand. Between 2019 and 2030, the nation's aquaculture must expand by 14.4% annually to produce enough additional supply to meet the 256,438 tonnes of additional demand brought to by population expansion and increased per capita consumption. According to the latest FAO statistics, "the whiteleg shrimp (*Penaeus vannamei*), with a predicted production of 60,800 mt, is the main farmed species in the country. Leading fish species were the Nile tilapia [*Oreochromis niloticus*] at 8,700 mt, Asian sea bass or barramundi [*Lates calcarifer*; 4,100 mt], and gilt head sea bream [*Sparus aurata*; 1,000 mt]" [13].

The Kingdom's aquaculture yield is anticipated to reach 970,000 tonnes annually by 2029, guided by the constantly rising domestic and global demand. The Ministry of Environment, Water and Agriculture (MEWA) has started a special program with the goal of producing 600,000 tonnes of fisheries products by 2030 in accordance with Vision 2030. The program has allocated Saudi Arabian Riyal 1.3 billion to infrastructure, R&D, and marketing initiatives to stimulate the industry. Additionally, SA became well-known for its high-quality, safe seafood products thanks to its stringent quality and safety assurance programs [14].

It is common knowledge that antibiotic usage in aquaculture increases the prevalence of AR among aquatic microorganisms and, more importantly, transfers AR to human pathogenic agents. As a result, antibiotic residues can spread throughout the marine environment. Many articles regarding AR and antibiotic-resistant microorganisms (ARMs) have been published generally in SA. Eventually, in 198 studies, different ARMs of SA were reported [15]. However, the majority of studies were about isolates from human samples [16–19]. Other animal sample isolates came from camel [20], chicken [21], and minced meat samples [22]. Few studies have studied aquaculture-related antibiotic resistance (AAR) and aquaculture-related antibiotic resistance genes (AARGs).

Additionally, it is understood that the development of AR results from complicated evolutionary and ecological processes. This review reports a description of this important problem, the factors inducing it, and how to confront it in SA.

2. Aquaculture and Antibiotic Use

Since their discovery, antibiotics have been crucial medicines for human wellbeing because they stop pathogen activity or kill bacterial cells [23]. Antibiotics are "any substance with a direct action on bacteria that is used for the treatment or prevention of infections or infectious diseases," according to the European Medicines Agency [24]. According to their modes of action, antibiotics are complex molecules from a chemical perspective that contain a variety of functional groups within their formulae. A few of the numerous ways antibiotics can combat bacteria include inhibitory effects on wall synthesis, cellular membrane modification, suppression of nucleic acid creation, hindering protein manufacturing by antagonistic competition, and antimetabolites action [25].

2.1. Antibiotics as a Double-Edged Weapon. Aquaculture frequently uses antibiotics for the following reasons, especially in nations without alternative preventive measures in place: (i) *prophylactic purposes*: antibiotics are used at subtherapeutic exposure concentrations in bath treatment or combined with feed to stop infections before they happen; (ii) *therapeutic purpose*: administering medicine to sick animals; (iii) *metaphylactic purpose*: applying widespread medicinal products to prevent or lessen an anticipated disease infection; (iv) *growth promoters*: medications like oxytetracycline and florfenicol that are given to animals to increase their rate of growth and food conversion.

However, many countries' aquaculture uses antibiotics improperly or in excess [26]. Furthermore, although it can be challenging to pinpoint the precise levels of contamination, antibiotic quantities in aquaculture can frequently be higher than those used in farming terrestrial animals [27]. Due to a lack of organizational instruction, education, and services for medical diagnosis, the antibiotic usage in aquaculture has been called into question frequently over the past ten years in Asian countries [27–30].

In Asian aquaculture, farmers frequently overuse or misuse antibiotics because of a lack of institutional knowledge. As a result, the EU and the USA have excluded fisheries products from various nations (China, India, Malaysia, Bangladesh, and Vietnam) because they contain prohibited antibiotics like chloramphenicol, nitrofuran, and furazolidone [31].

Additionally, overusing antibiotics in aquaculture may hasten the development of resistance in fish kept in captivity as well as in the environment. Additionally, consuming fish that has received antibiotic treatment may have negative effects on one's health [32].

Through a variety of mechanisms, including feed, which is one of the most significant sources, utilizing antibiotics in aquaculture raises the risk of contaminating both the environment and the organisms being raised [33].

2.2. Potential Antibiotic Sources in Aquaculture. The majority of incompletely metabolized antibiotics from people are delivered to sewage treatment facilities (STFs) through the

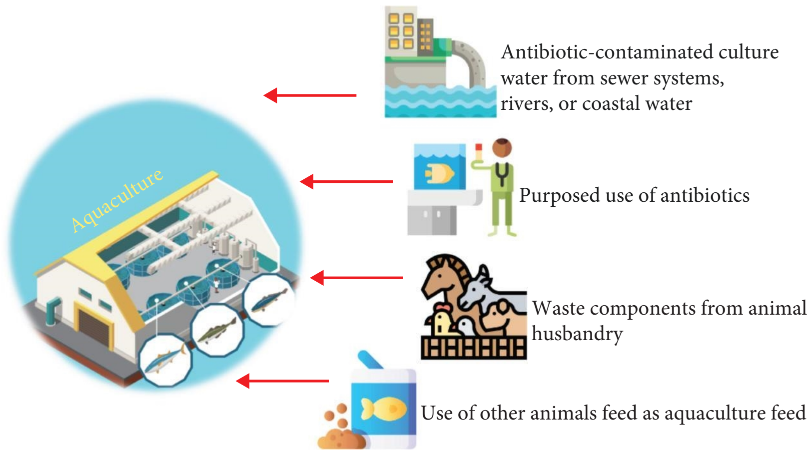

Figure 1: Possible sources of antibiotics in aquaculture.

drainage infrastructure, while the remainder are either discarded into adjacent rivers and streams or dissipate as leakage from locations like landfills [34]. The majority of STFs are not designed to eradicate antibiotics; as a result, antibiotics are emitted by the final treated effluent into the aquatic environment, making the STFs a major source of antibiotic release [35, 36]. Manures produced by farmed animals are often recycled as organic fertilizers to farmland and may partly enter environmental waters through runoff in the practice of animal husbandry. These waste substances possess antibiotics [37] and are significant contributors to the rise in antibiotic concentrations in the water system [38], with accompanying public wellness complications. Figure 1 depicts the potential sources of antibiotics in aquaculture.

Antibiotic concentrations rise after their addition in the water volume, in the deposits underneath boarding facilities, and in the fish itself. A fraction of antibiotic-altered food that the fish do not consume is left behind in the deposits below and close to the aquaculture sites [39]. Approximately 80% of the antibiotics ingested are not absorbed and end up in the environment through fecal matter. Following absorption, antibiotics are then eliminated through the discharges [40]. Such portions of antibiotics build up in the deposits below and near systems for aquaculture and may be carried through flows to far-off sedimentary locations [41].

Oxytetracycline, that is still biologically active, can linger in sediments for quite a long time [42]. Flumequine and oxolinic acid are two antibiotics that can linger near fish farms over several months [43]. Sulfonamide and trimethoprim concentrations are perceptible and functional in debris over several weeks [44]. A few days after being introduced, the antibiotic florfenicol is no longer detectable in the sediments, but the byproduct florfenicol amine can still be found over several months [45]. Tetracyclines continue to be active against bacteria following adhering to deposits and are still aggressive when inhibitory cations such as Mg^{2+} and Ca^{2+} are present [46]. Organic matter can absorb the antibiotics, quinolones, sulfonamides, and tetracyclines, which can then accumulate in the environment and cause serious issues.

2.3. Antibiotic Administration in Aquaculture Varies by Nation. Although antibiotics are frequently used in aquaculture, there is still a dearth of information. The majority of information on antibiotic usage and remainders in fisheries products comes from advanced nations, but the mainstream of fish and shellfish are obtained in developing and/or undeveloped Asian nations, in which there are few or no regulatory strategies or guidelines for aquaculture [26]. About 10,259 tonnes of antibiotics were thought to have been consumed worldwide in aquaculture in 2017. By 2030, the projected global consumption of antibiotics will increase 33% from this baseline, reaching 13,600 tonnes. The vast majority (93.8%) of the world's usage is accounted for by the Asia-Pacific region, and it is expected that this proportion will not change from 2017 to 2030. In 2017, Europe (1.8%) and Africa (2.3%) had the second- and third-highest consumption levels, separately. Africa's portion of global usage is predicted to increase 13% and reach 2.6% by 2030, while Europe's portion is predicted to fall to 1.7%. The largest relative increases in usage between 2017 and 2030 are seen in Latin America and Africa, at 50.9% and 50.6%, respectively. China (57.9%), India (11.3%), Indonesia (8.6%), and Vietnam (5%), which are all in the Asia-Pacific region, accounted for the majority of the world's consumption of antibiotics in 2017. According to projections, these nations will continue to consume the most antibiotics in 2030, with China's share slightly declining to 55.9%, India's share remaining stable, and Indonesia's share rising to 10.1% and 5.2%, respectively [47].

Only five antibiotics from just three classes have received Food and Drug Administration (FDA) approval to be used in fish farming against pathogens [48]. Table 1 lists the FDA-approved antibiotics for aquaculture.

However, a contemporary review article outlined various facets of antibiotic practice in 15 of the world's top fish-producing nations [49]. In these nations, the aquaculture of fish and shrimp still applies certain antibiotics that are no longer authorized and are not FDA-approved. Overall, 55% of them used sulfadimethoxine, erythromycin, amoxicillin, and enrofloxacin in fish farming, while 73% used oxytetracycline, sulfadiazine,

Table 1: List of FDA-permitted antibiotics for aquaculture.

Antibiotic	Commercial name	Class	Application	Species
Oxytetracycline hydrochloride	*OXY Marine*™, *Tetroxy*® *343*, *Pennox 343*®, *Terramycin 343*®, *TETROXY*® *Aquatic*	Tetracyclines	Skeletal marking	Finfish fry and fingerlings
Oxytetracycline dihydrate		Tetracyclines	Control of *Hemophilus piscium*-induced ulcer disease, *Aeromonas salmonicida*-induced furunculosis, *Aeromonas liquefaciens*-induced bacterial hemorrhagic septicemia, and *pseudomonas* disease	Salmonids
			Control of *Aeromonas liquefaciens*—and *pseudomonas*—caused bacterial hemorrhagic septicemia	Catfish
Florfenicol	Aquaflor®	Amphenicols	Manage catfish fatal outcomes brought on by intestinal septicemia attributed to *Edwardsiella ictaluri*	Catfish
			Control of fatal outcomes due to coldwater disease associated with *Flavobacterium psychrophilum*	Freshwater-cultured salmonids
			Control of mortality due to *Aeromonas salmonicida*-induced furunculosis	Freshwater-reared salmonids
			Manage mortality due to *Flavobacterium columnare-induced* columnaris disease	Freshwater-reared finfish
Sulfadimethoxine/ormetoprim	Romet®-30	Sulfonamides	Control of *Aeromonas salmonicida*-induced furunculosis	Salmonids (trout and salmon)
			Control of *Edwardsiella ictalurid*-caused bacterial infections	catfish
Sulfamerazine	Sulfamerazine Fish Grade	Sulfonamides	–	–

or florfenicol. Aquaculture farmers confirmed that while 23% of antibiotics are employed directly to the pond's surface water, 77% of antibiotics are combined with feedstuffs [50]. Table 2 lists the main antibiotics reportedly used in aquaculture.

2.4. Aquaculture-Oriented Antibiotics Used in SA. Available research concerning the actual consumption of antibiotics in aquaculture in SA is limited. However, SA is the second country among the nations with the biggest anticipated rise in consumption of aquaculture antibiotics between 2017 and 2030 (77%), following Brazil (94%).

Fish products, either caught from sea or from aquaculture farms, canned or processed products, eventually reach the consumers through local markets and grocery stores. The maximum residue level (MRL) for some antibiotics in fish has been established via the Saudi Food and Drug Authority (SFDA) at 200 g/kg for oxytetracycline, 200 μg/kg for tetracycline, and 200 μg/kg for chlortetracycline. On the other hand, 0–30 μg/kg/day is the acceptable intake for these three drugs [56]. Sulfamethoxazole and trimethoprim were also found in a treated effluent in SA, with mean concentrations of 145–730 and 41–44 ng/L, respectively [57].

Alanazi et al. [58] carried out a research project in different areas in SA, where various samples of seafood products were gathered and examined for tetracycline antibiotic traces. A total of 249 samples of seafood products were gathered, 71 of which were obtained directly from the sea and were taken in Jeddah, Dammam, and Jazan. The remaining 22 samples came from aquaculture facilities. A total of 106 samples, including 25 cans of tuna and sardines, were bought frozen from neighborhood grocers and supermarkets. The final 24 samples consisted of processed goods. The SFDA has established a clear standard for the maximum allowable level of tetracyclines in seafood products, but this study found that more over half of the observed samples had levels that exceeded the MRL. This suggests that there may have been a lack of adherence to SFDA rules concerning the application of tetracyclines in seafoods.

However, in contrast to the previous study, the SFDA financially supported a study to detect antibiotic residues in fish samples ($n = 20$) collected from local markets [59]. They concluded that the recovered antibiotics (e.g., doxycycline, sulfadimethoxide, and others) were all below the MRLs set by the SFDA.

Table 2: Main antibiotics reported to be used in aquaculture.

Country	Antibiotic classes	References
Bangladesh	Sulfonamides, β-lactams, tetracyclines, macrolides, diaminopyrimidines	[50, 51]
Vietnam	Fluoroquinolones, β-lactams, macrolides, quinolones, diaminopyrimidines, tetracyclines, sulfonamides, aminoglycosides	[52]
Thailand	β-lactams, diaminopyrimidines, sulfonamides, fluoroquinolones, tetracyclines	[52]
China	Macrolides, quinolones, sulfonamides, amphenicols	[49, 53]
United Kingdom	Tetracyclines, quinolones, β-lactams	[54]
Italy	Tetracyclines, β-lactams, sulfonamides, quinolones	[54]
USA	Amphenicols (florfenicol), tetracyclines (oxytetracycline), sulfonamides (sulfa/trimethoprim and sulfadimethoxine/ormetoprim)	[54]
South Korea	β-lactams, fluoroquinolones, tetracyclines, quinolones, sulfonamides, amphenicols, diaminopyrimidines	[55]
Chile	Oxazolidines, aminoglycosides, β-lactams, quinolones, tetracyclines, sulfonamides, macrolides, fluoroquinolones, diaminopyrimidines	[54]

3. Rates of AAR Globally and in SA

Rising AAR rates are anticipated to have an especially negative impact on nations with low and moderate incomes, jeopardizing the advancement made in vulnerable societies' development, escalating income disparities, and causing an increase in absolute poverty by 2030.

A survey has been conducted to determine AAR, specifically in Asia. The survey mapped fresh- and marine-water AAR hotspots. Eastern Turkey, southern India, China's Yangtze River basin, and the Mekong River delta are hotspots for freshwater AAR, whereas the north-eastern and East China Seas, the coastal waters of central Vietnam on the South China Sea, the coastal waters of southern India on the Arabian Sea, the Bay of Bengal across southern India and northern Sri Lanka, and the eastern Mediterranean Sea on coastline of Greece are hotspots for marine water AAR [47].

Most recent Saudi Arabian publications deal with clinical AR in human isolates. However, SA is the nation with the second biggest anticipated relative rise in aquaculture antibiotic consumption between 2017 and 2030. SA is one of the nations with the greatest AA scores for aquaculture. A study used 11,274 distinct isolates of microbes across aquatic organisms and the aquaculture atmosphere to conduct a double meta-analysis and calculate AAR indices for 40 distinct countries. It came to the conclusion that 28 of the 40 studied countries had AAR indices greater than 0.2, a value regarded as a sign of highly hazardous antibiotic pollution [60]. The countries with the highest AAR indices were Zambia, followed by Mexico and Tunisia, while Canada, France, and the USA displayed the lowest. Accordingly, one of the nations with the highest AAR index was SA.

3.1. Stimulation of AAR. As was already stated, AR is currently regarded as one of the most serious risks to the public's well-being [61]. As emerging environmental pollutants, antibiotic resistance genes (ARGs) are now widely acknowledged [62, 63]. ARGs are old and naturally present substances, like most antibiotics. Nevertheless, they are now building up in environments where people have had an impact [64, 65], which may possibly linked to the extensive human-caused use of antibiotics in recent years [66]. It can be difficult to track the spread of resistance determinants in aquatic environments, and there is still a paucity of data on the transfer of AR from aquatic animals to people. Although it may go unnoticed, the aquatic food animal supply chain may be a pathway for the spread of antibiotic-resistant bacteria (ARBs) and ARGs from aquatic organisms and their habitat to humans [67]. Aquaculture and the aquatic environment have been linked to mobile genetic elements (MGEs) carrying ARGs with clinical relevance for humans [68].

Nonetheless, when levels are lower than the minimal inhibitory concentration of the localized bacterial varieties, antibiotic residues can promote the spread of AAR by favoring antibiotic-resistant aquatic bacteria [69]. In an aquatic environment, 90% of the bacteria are resistant to not less than one antibiotic, and 20% are multiantibiotic-resistant bacteria (MARB). When multiple antibiotics are used concurrently in aquaculture, MARB may emerge [70]. Another contaminants and pollutants in the aquatic environment show a key role in promoting AAR. One of the elements of manmade wastes and a naturally occurring component of the earth's crust is "*heavy metals.*" Such deposits have a variety of negative effects, including the poisoning of food, environmental pollution, livestock harm, and irrigation problems. In aquatic species, the buildup of heavy metals alters the immune system and causes oxidative damage [71, 72]. Research suggests that heavy metals affect bacterial AR, leading to ARGs released into the environment and perhaps human hosts [73]. A comparison of the relative significance of antibiotics and heavy metals in the propagation of ARGs is yet missing. Komijani et al. [74] discovered a significant link between waste disposal into waterways and the prevalence of ARGs. The concentration of heavy metals, such as vanadium (V), and the quantity of ARGs correlated more strongly than that of antibiotics. The most often found heavy metals linked to AAR were zinc (Zn) and cadmium (Cd) [75].

Thus, ways of AR transmission among aquatic animals can be stated as follows: (*i*) *selective pressure*: in aquatic environments, antibiotic selective pressure encourages effortless interaction between bacteria and ARGs, further promoting

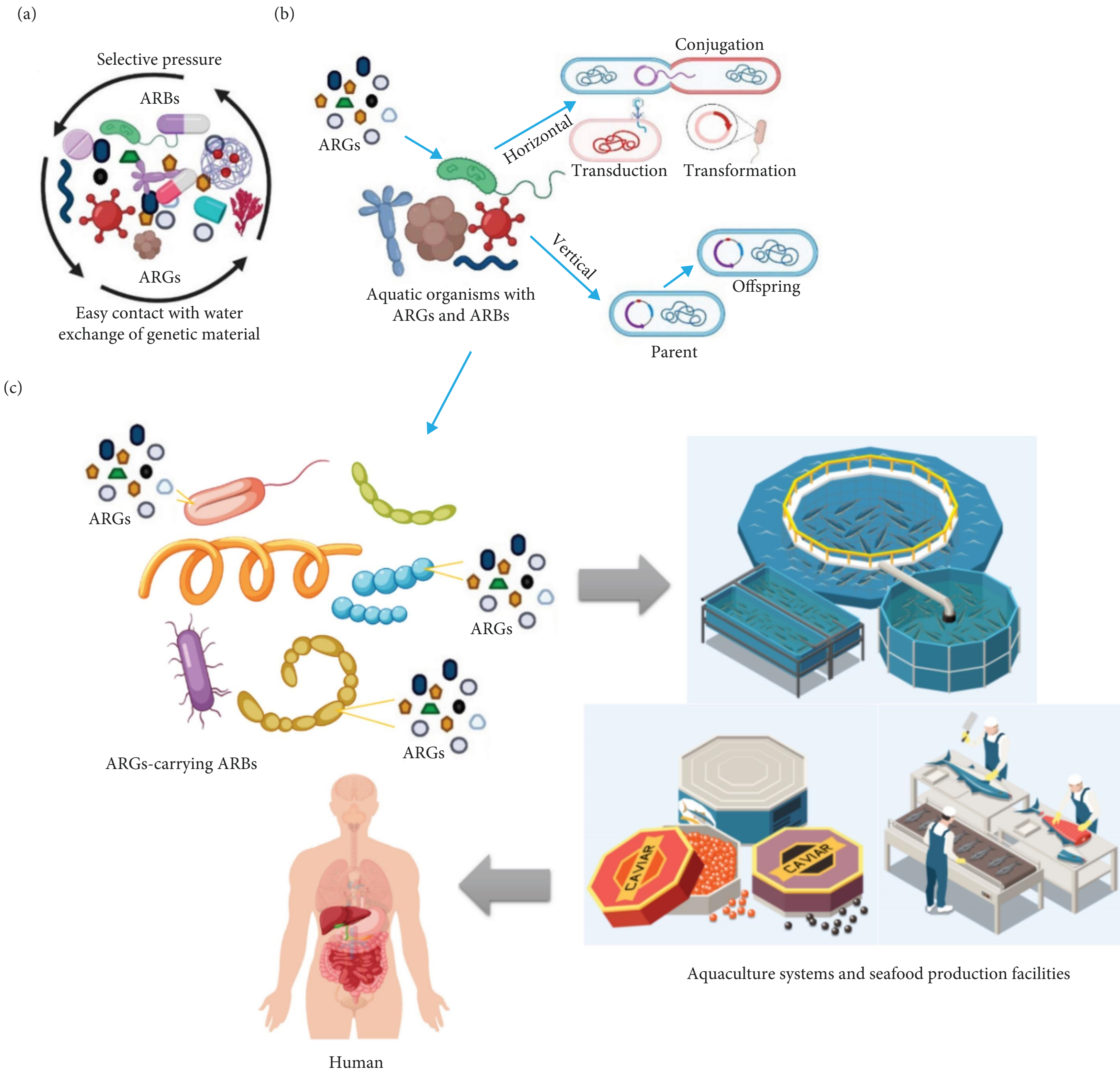

Figure 2: Antimicrobial resistance in aquatic systems: (a) selective pressure may improve the genetic transfer of ARGs; (b) transfer of ARGs in multiple microbial groups leading to ARBs; (c) ARG-carrying ARBs transmission from aquaculture systems and seafood production facilities to human.

simple genome exchange and recombination that leads to the formation of ARBs or ARMs that have the ability to spread infection through other organisms in the water (Figure 2(a)); (*ii*) *biofilms*: aquatic microbes can assemble into intricate microbial communities (biofilms) where genetic information is shared [76, 77]. AR confers a selective advantage to members of resistance-carrying communities by enabling bacteria to survive large concentrations of antibiotics. ARMs or ARBs triumph over the weaker ones. As evidence showing the use of customized antibiotics in fish farming settings has tremendous promise to create selective pressure and raise the occurrence of AR within other ecological microbes; in locations near aquaculture wherever antibiotics have been utilized, increased frequencies of ARB have been documented [78]. Aquaculture bacteria mainly transfer genetic information by two mechanisms (Figure 2(b)): (a) vertical gene transfer from parent to offspring and (b) horizontal gene transfer (HGT) between microbial agents of comparable species or another. The mobilome is made up primarily of various types of MGE that mediate HGT [39]. Bacterial plasmids comprise up to 20% of the shared bacterial genes (plasmidome) that are transferred through HGT processes among the MGEs [79].

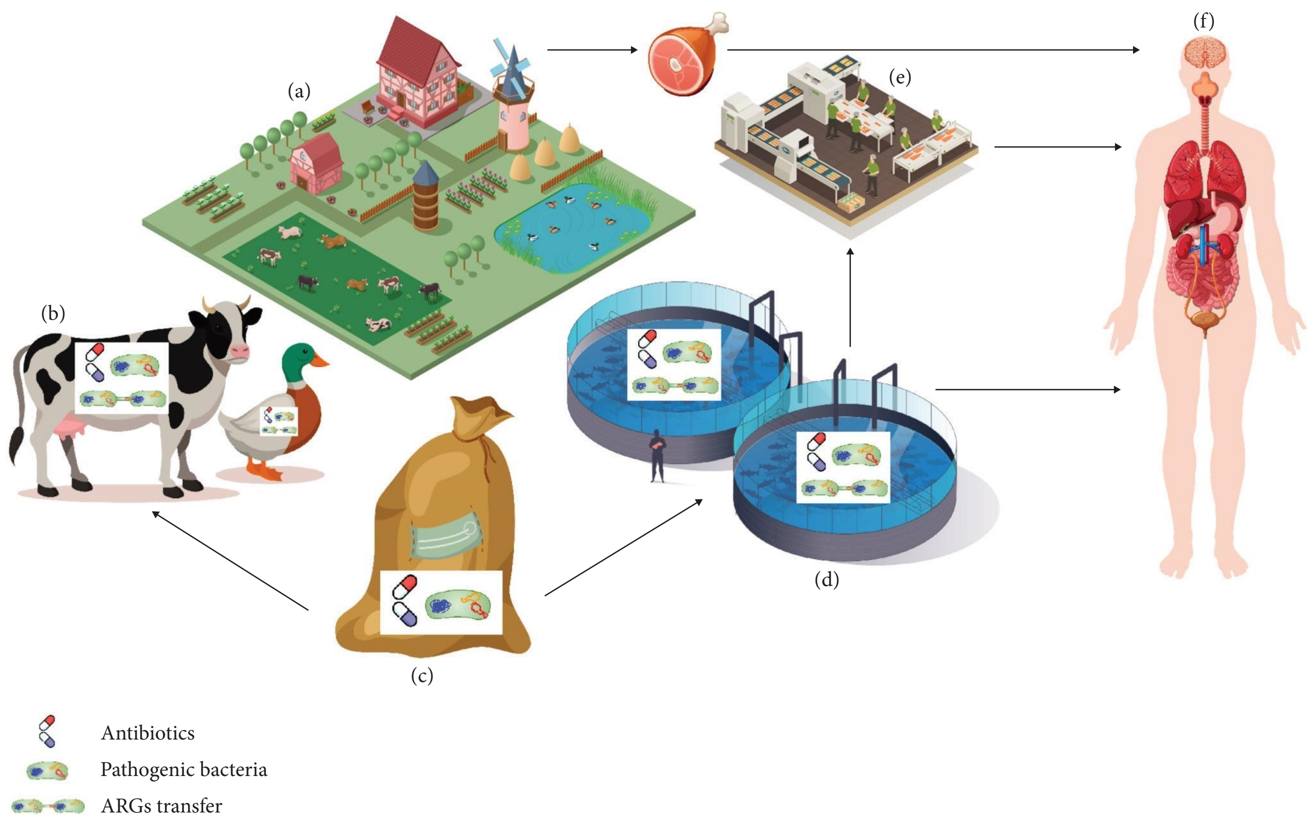

Figure 3: Environmental fate of ARGs/ARBs in the future: (a) animal farm; (b) farm animals receiving antibiotics; (c) antibiotics-containing animal feed; (d) aquaculture system receiving antibiotics; (e) processed fish from aquaculture system; (f) human receiving ARG-contaminated food.

HGT between aquaculture bacteria can occur in three distinct processes: (a) conjugation: transfer intracellular plasmids and transposons containing AARGs through cell-to-cell contact through pili; (b) transduction: transfer intracellular DNA plasmids and intracellular DNA chromosomes containing AARGs via bacteriophages which serve as intermediaries for the transfer of intracellular DNA from a bacterial cell that is infected to a recipient bacterial cell; and (c) transformation: extracellular DNA containing AARGs can enter competent bacteria that are not resistant through the process of natural transformation; (iii) *bioaccumulation*: ARGs continue to bioaccumulate in aquatic settings, which resulting their prevalence at different levels of trophic structure, also in aquatic plants that have the ability to store antibiotics in their roots, where they will be further broken down by other microbes that nourish the roots and allow plants to absorb antibiotics [80]; and (iv) *aquatic food chains*: depending on eating patterns, classification of food chain, and location within the aquatic environment, the amount of antibiotics in aquatic species can change. An investigation of fish collected from wild waters showed that antibiotic concentrations in aquatic species increased gradually from herbivores to omnivores to carnivores, considering carnivorous fish are the primary consumers in the aquatic food web [81].

ARGs can become toxic and endanger the health of people and animals when consumed by fish, plants, and other aquatic species (Figure 2(c)) [82]. Because manure is applied to farmlands and animals are fed with forage that has been harvested from the manure-fertilized fields, production animal husbandry facilities serve as complicated environments in which germs from production animals, as well as farm employees, are constantly combined with farming settings. ARGs from farm animals that have received antibiotics or heavy metals could likewise be transmitted to people indirectly through the animal–environment–human pathways (Figure 3) [82, 83] or directly through contact with farm animals. Several anthropogenic activities, such as manure application and the disposal of farm sewage, are important for the ecological dissemination of ARGs. Because of the aforementioned factors, our livestock systems are not only a rich reservoir of ARGs but also a major global hotspot that poses risks to the environment and population health [84].

3.2. Global Rates of AARGs. All major aquaculture-producing nations on the planet have a high prevalence of ARBs and ARGs detection. *Vibrio* spp., *Aeromonas* spp., *Bacillus* spp., *Pseudomonas* spp., *Enterobacteriaceae*, *Streptococcus* spp., *Exiguobacterium* spp., etc., are among the ARBs that are frequently isolated. Flavobacterium and other bacterial species have also been found in aquaculture environments [85]. Tetracyclines (*tet*A, *tet*B, *tet*K, *tet*M), quinolones (*qnr*A, *qnr*B, *qnr*S), and sulfonamides (*sul*I), among the ARGs that are most frequently found, are those from other antibiotic classes, together with the appropriate antibiotic classes. Some ARBs and ARGs that are harmful to humans and fish/shellfish are frequently found in aquaculture [86]. According to a recent report by Fu et al. [87], ARBs, particularly *Klebsiella pneumoniae*, are present in probiotics used in aquaculture. These bacteria may pose a serious threat to culture organisms besides human health.

Aquaculture ponds in the Southern United States that had received antibiotic treatment were used to isolate Gram-negative bacteria, and compared with bacteria from untreated rivers, these bacteria exhibited higher levels of resistance to ampicillin, chloramphenicol, nitrofurantoin, oxytetracycline, and tetracycline [88]. In total, 292 bacterial strains were isolated from salmon aquaculture in earlier studies, and their susceptibility to quinolones, florfenicol, and oxytetracycline was tested [89, 90]. These studies showed that quinolone, florfenicol, and oxytetracycline resistance were more common in Chilean salmon aquaculture. The doses of florfenicol were nearly two times higher in 2016 than they were in 2013, showing that bacteria in the aquaculture environment were becoming more resistant to this particular antibiotic over time. According to Rozas and Enriquez [91], *Piscirickettsia salmonis* exhibited higher levels of AR than earlier isolates. Globally, AARBs and AARGs are shown in Table 3.

3.3. Rates of AARGs in SA. Previous studies in SA have identified ARGs in soil samples of the southwestern highlands such as bla_{OXA}, *aacC3*, and *aacC4* imparting betalactam and aminoglycoside resistance [108], clinical samples and health care systems such as *OXA-48* and *NDM-1* carbapenem-resistant genes and $bla_{CTX\text{-}M}$, bla_{TEM}, $bla_{CTX\text{-}M\text{-}15}$, $bla_{\text{CTX-MGp1}}$, and $bla_{\text{CTX-MGp26}}$ betalactam-resistant genes [17, 19, 109, 110], and wastewater treatment plant such as tetracycline-resistant genes *tetO*, *tetQ*, *tetW*, *tetH*, *tetZ* [111].

On the flip side, only a few AARG research have been published in SA. According to a survey across Saudi Ministry of Health (MOH) hospitals, the most commonly used antibiotics for human use in SA are beta-lactams, especially 3rd-generation cephalosporin and imidazoles such as sulfamethoxazole [112]. The most prevalent series of antibiotics in Saudi aquaculture farms are tetracyclines, quinolones, betalactams, and sulfonamides because of their affordable price and great effectiveness as a broad spectrum for treating and preventing infectious diseases [113]. Those antibiotic classes were noticed among AARGs studies in the same country in Table 4. Al-Sunaiher et al. [123] identified that multiple *V. vulnificus*, *V. damselae*, *V. fluvialis*, *V. hollisae*, and *V. algi-alginolyticus* species, isolated from Saudi freshwater and marine farms, were highly resistant to various antibiotics, from the ones of highest percentage named amoxycillin, oxytetracycline, ampicillin, penicillin, to the ones of least percentage named chloramphenicol, colistin, tetracycline, lincomycin, trimethoprim, nalidixic acid, nitrofurantoin, and oxolinic acid, respectively. Trimethoprim, tetracycline, sulfamethoxazole, penicillin, oxy-tetracycline, ampicillin, amoxicillin, and lincomycin were absolutely ineffective against the identified *V. vulnificus* species. In a neighborhood seafood marketplace in Shaqra (Riyadh, SA), amoxicillin, bacitracin, chloramphenicol, ciprofloxacin, erythromycin, gentamycin, and tetracycline-resistant strains of Aeromonas, *E. coli*, Enterobacter, Proteus, Enterococcus, and Streptococcus were identified [119]. Nile Tilapia (*O. niloticus*), as the main freshwater fish cultured in SA, were isolated from 2 private aquaculture farms in Al-Qatif (Eastern province, SA). *Aeromonas veronii* isolates from the tilapias proved to be wholly refractory to amoxicillin + Clavulanic acid and ampicillin and showed medium susceptibility to erythromycin and neomycin [120]. This investigation provided that the majority of bacterial isolates from harvested fish and shrimps, which mainly come from aquaculture farms, are Gram-negative AARBs. Wherever chemical substances, particularly antibiotics, are widely used, it is suggested that bacteria with high prevalence could be a possible driver of AARGs dissemination across the cultured fishes and shrimpes. Reported AARB and AARGs in SA are shown in Table 4.

4. AARGs Dissemination from Aquaculture Effluents to Red Sea Coasts

The key pollution origins for the spread of antibiotics and ARGs in estuarine and coastal settings are aquaculture effluents, sewage discharge, WWTPs, and riverine runoff. Due to the favorable aquatic environment and the nutritional preferences of the local population, the aquaculture business has flourished in coastal areas [126]. Antibiotics are frequently included in fish feed as a means of infection prevention or infection therapy [127]. High levels of antibiotic residues are consequently being found more frequently in areas close to aquaculture fields. More precisely, it has been found that areas of coastal aquaculture routinely contain significant quantities of antibiotics [128, 129]. According to Zheng et al. [130], aquaculture effluent was a significant origin of antibiotics and ARGs in 40.00% of the world's estuarine and coastal waters.

Aquaculture operations also contribute significantly to the pollution of ARGs in the coastline and estuarine ecosystems [127–129, 131], where the dominance of ARGs rendered antibiotics worthless and the aquaculture-related species are more vulnerable to disease [132, 133]. Moreover, recent research [134–136] has shown that ARBs and ARGs are quite common in seafood, including marine fish, shrimp, and mussels. For example, 44.4% of *Vibrio parahaemolyticus* isolated strains from maricultural farms in the Bohai and Yellow Seas were resistant to several antibiotics in prawns, crustaceans, sea cucumbers, and half-smooth tongue sole [135]. Although sulfonamides are among the most broadly used antibiotics in aquaculture, a thorough analysis of aquaculture sites throughout the whole Chinese coast indicated that sulfonamide resistance genes, particularly *sul*1 and *sul*2, were the most abundant ARGs in sediments [128].

The Red Sea was created as a result of the African and Arabian plates splitting apart about 24 million years ago [136]. Since then, the Red Sea has been distinguished by unique qualities, including site, a temperature that is often

TABLE 3: Globally reported aquaculture-related antibiotic-resistant bacteria (AARB) and aquaculture-related antibiotic resistance genes (AARGs).

Country	Fish species	Sample	Resistant bacteria	Antibiotics	Resistant genes	Reference
Portugal	Gilthead seabream (*Sparus aurata*)	Intestine fecal samples	Enterococcal isolates (*E. faecium* and *E. faecalis*)	Erythromycin, tetracycline, quinupristin–dalfopristin, ampicillin, gentamicin, streptomycin, kanamycin, ciprofloxacin and chloramphenicol	*erm*(B), *tet*(L) or *tet*(M), *aac*(6′)- *aph* (2′) and *aph*(3′)-IIIa genes	[92]
Portugal	Gilthead seabream (*Sparus aurata*)	Intestine fecal samples	*Escherichia coli*	Beta-lactams, tetracycline, chloramphenicol, streptomycin, gentamicin, trimethoprim/sulfamethoxazole	bla_{TEM-52}, bla_{SHV-12} genes, *cml*A, *tet*A, *aad*A, *sul*1, *sul*2, and *sul*3)	[93]
Italy	Gilthead seabream (*Sparus aurata*)	Skin, gills, muscles, and intestinal content	Vibrio spp.	Ampicillin, amoxicillin, erythromycin, and sulfadiazine	–	[94]
Portugal	Gilthead seabream (*Sparus aurata*)	Intestine fecal samples	*Enterococcus faecalis*, *E. faecium*, and *E. durans*	Vancomycin	vanA	[95]
Italy	Gilthead seabream (*Sparus aurata*)	Skin, gills, muscles, and intestinal content	Aeromonas ssp.	Sulfadiazine, amoxicillin, ampicillin, erythromycin, cephalothin, streptomycin, and trimethoprim	–	[96]
China	–	Wastewater samples	*Aeromonas punctata*		qnrVC	[97]
China	–	Different sample sites in integrated freshwater aquaculture farm	Enterobacteriaceae isolates	Ampicillin, tetracycline, streptomycin, spectinomycin, and trimethoprim	(tet(A), tet(C)), (sul2), aadA22, and *dfr2*	[98]
Chine	Marin fish (Protonibea spp., Epinephelussp spp., Siganus spp., Trachinotus spp., and Nibea spp., etc.)	Tissues (including the liver, spleen, kidney, intestines, and brain)	Vibrio spp.	Vancomycin, amoxicillin, furazolidone, tobramycin, gentamicin, and doxycycline	*aphA*, *vhh*, *hflK*, *chiA*, and *flaC*	[99]
Chile	–	Aquaculture farm water and sediment		Tetracycline, quinolones, and florfenicol	*tetA*, *tetB*, *tetK*, *tetM*, *qnrA*, *qnrB*, *qnrS*, *aac*(6′)*-1b*, and *floR*	[100]
China	–	Water sources, pond water, and sediment in aquaculture farm	–	Tetracycline and sulfonamides.	*Sul1* and *tetC*	[101]
Japan	(15 red seabream Pagrus major, 10 olive flounder Paralichtys olivaceus, 4 Japanese eel *Anguilla japonica*, 1 black seabream *Acanthopagrus schlegelii*)		*Edwardsiella tarda*	β-lactams and aminoglycosides	bla_{CTX-M} *aac*(6′)*-Ib*, *armA and strA-strB*	[102]
Vietnam	(35 red tilapia, 36 striped catfish, 35 wild fish)	Gut contents	Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*	Sulfonamide and colistin	*sul* and *mcr-1*	[103]
Korea	–	Aquaculture fish farm	*Vibrio harveyi*	Tetracycline, beta-lactams, aminoglycosides, and quinolones	*tetB*, *qnrA*, *intI1* (*Class 1 integron integrase*), *aac*(6′)*-Ib*, bla_{SHV}, bla_{CTX-M}, *strA-strB*, *tetA*, *aphAI-IAB*, *qnrC*, *qnrS*, and bla_{TEM}	[104]
Turkey	*C. carpio*, *C. luteus*, *C. umbla*, *C. macrostomum*, *C. gibelio*, *C. trutta*, *C. auratus*, *C. kais*, *L. abu*, *L. regium*, *A. grypus*, *A. marmid*, *A. mossulensis*	Fish muscle samples	*E. coli* O157: H7, *Aeromonas* spp. and *P.shigelloides*	Beta-lactams	(blaCTX-M, blaSHV and blaTEM) and (blaKPC, blaOXA-48, blaVIM, blaIMP)	[105]
India	Freshwater carp (*Labeo rohita*)	Gut	Proteobacteria	Beta-lactams and peptide antibiotics	(*tsnR*), beta-lactams (*CTX-M-1*, *TEM*) and (*mdtA*, *mdtB*, *mdtC*)	[106]
Egypt	*O. niloticus* and *C. gariepinus*	Internal organs	*Pseudomonas aeruginosa*	Beta-lactams and tetracyclines	bla_{TEM}, bla_{CTX-M}, and *tet*A	[107]

Table 4: Aquaculture-related antibiotic-resistant bacteria (AARB) and aquaculture-related antibiotic resistance genes (AARGs) in SA.

Fish species	Province of Saudi Arabia	Fish sample	Aquaculture-related antibiotic-resistant bacteria (AARB) isolates	Antibiotics	Aquaculture-related antibiotic resistance genes (AARGs)	Reference
45 imported mackerel fish samples from supermarkets	Eastern Province	Gills, intestine, and skin	60 isolates of *ESBL*-producing *E. coli*	Beta-lactams	$bla_{CTX\text{-}M}$	[114]
365 Gilthead Sea Bream (*Sparus aurata L.*) samples purchased from wholesale and retail markets	Aljouf	Fish flesh	45 *Aeromonas veronii* Biovar Sobria	Nalidixic acid, carbenicillin, cephalothin, erythromycin, kanamycin, tetracycline, and trimethoprim-sulfamethoxazole	Erolysin (*aero*), elastase (*ahyB*), lipase (*lip*), flagellin (*fla*), enterotoxin (*act*), and DNases (*exu*)	[115]
223 imported frozen freshwater fish purchased from supermarkets and grocery stores	Eastern Province	Gills, intestine, and skin	140 isolates of *Salmonella* spp.	Tetracycline, ampicillin, and amoxicillin-clavulanic acid	–	[116]
405 imported frozen freshwater fish samples from supermarkets	Eastern Province	Gills, intestine, and skin	224 isolates of *ESBL*-producing *E. coli*	Beta-lactams	$bla_{CTX\text{-}M}$	[117]
200 wild fish	Jeddah	Intestine	10 isolates of *Klebsiella pneumoniae* B8 and *Morganella morganii* A4	Beta-lactams	$bla_{CTX\text{-}M}$, bla_{SHV}	[118]
30 fresh fish samples from local market	Shaqa, Riyadh	–	80 isolates of *Aeromonas* spp., *Escherichia coli*, *Enterobacter* spp., *Proteus* spp., *Enterococcus* spp., and *Streptococcus* spp.	Bacitracin, tetracycline	–	[119]
560 Nile Tilapia (*Oreochromis niloticus*) collected from 2 private aquaculture farms	Al-Qatif	Fish organs (liver, kidney, spleen, external lesion if present)	*Aeromonas veronii*	Amoxicillin + Clavulanic acid and ampicillin	–	[120]
35 raw fish samples	Different areas in Riyadh		*Aeromonas* spp.	Ampicillin, carbenicillin, and nalidixic acid	–	[121]
Wastewater from fish market sewage tank	Jazan	–	*S. aureus* and *K. pneumoniae*	β-lactam (methicillin)	Methicillin-resistance gene (mecA)	[122]
370 live fishes with disease signs from 17 freshwater and marine farms	Different provinces	Flesh samples	5 isolates of *Vibrio* spp., including *Vibrio damsela*, *Vibrio fluvialis*, *Vibrio vulnificus*, *Vibrio alginolyticus*, and *Vibrio hollisae*	Sulfonamide, cloistin, tetracycline, lincomycin, trimethoprim, nalidixic acid, nitrofurantoin, amoxycillin, oxytetracycline, ampicillin, penicillin, chloramphenicol, and oxolinic acid	–	[123]
Marketed shrimp (*Penaeus indicus*)	Hail region		Vibrio and Aeromonas genera	Tigecycline, ceftaroline, meropenem, ticarcillin, amikacin, amoxicillin + clavulanic acid, gentamicin, and moxifloxacin	–	[124]
20 samples of marketed shrimps (*Penaeus monodon*)	Al-Ahsa	Muscles	*Aeromonas hydrophila*	Multidrug resistance profiling	Cephalothin, gentamicin, kanamycin, nalidixic acid, neomycin, ampicillin, erythromycin, oxacillin, and oxytetracycline	[125]

high, and a recent geologic history. The Red Sea has a tremendous diversity of life in all areas [137]. Its biosphere is, however, still understudied and little comprehended [138, 139]. The Red Sea serves as a singular source of biological diversity [140–142]. Overall, 80% of the eastern Red Sea coast is covered by western SA. It provides desalinated water to the provinces of Jeddah, Makkah, Yunbu, Al-Lith, and Jazan. The amount of municipal wastewater, aquaculture operations, and recreational activities have all expanded in these cities due to rapid population expansion. A threat to the Red Sea's special status as a global hotspot for marine biodiversity is posed by the discharge of inadequately treated sewage and aquaculture effluents from densely populated cities in several nations [143].

Only a little amount of research has documented the existence of ARGs along SA's Red Sea coast. At several coastal, offshore, and mangrove regions along the Red Sea coast of SA, Ullah et al. [144] conducted research on a variety of ARBs and ARGs. Samples were taken from urban industrial locations, urban beaches, and aquaculture areas. Coastal aquaculture sites showed the highest colony-forming unit (CFU), which was apparently contaminated. In samples from the Red Sea's coast, offshore areas, and mangroves, researchers found about 18 ARGs encoding resistance to tetracyclines, aminoglycosides, quinolones, sulfonamides, and beta-lactam antibiotics. Beta-lactamase and $3'$-aminoglycoside phosphotransferase (APH($3'$)) were also discovered by Elbehery et al. [145] from the Red Sea brine pool (Atlantis II Deep) in the Red Sea's central rift zone, between SA and Sudan.

Moreover, in an offshore site in the Red Sea, several ARGs linked to fluoroquinolones (*par*C, *par*E, *gyrA*, and *gyr*B), tetracycline (*tet*34 and *tet*35), elfamycin (EF-Tu) and β-lactamase (*bla*AmpC and *bla*CARB-4) were found in the genome of virulent strain of *Vibrio alginolyticus* [146]. A sample from the Arabian Sea to identify the most dominant ARGs also included *car*A, *mac*B, *sav*1866, *tlr*C, *srm*B, *tae*A, *tet*A, *oleC*, and *bcr*A, which belonged to the macrolides, glycopeptides, and peptide drug classes. Other Streptogramin-resistant *vga*B, *vgaD*, and *vga*E genes were identified in this sample [147]. Furthermore, ballast and harbor waters in the Gulf of Aden were screened for ARGs to measure the water's quality. The incidence of *sul*1, *dfr*A, and *cfr* genes, which encode for resistance against sulfonamides, trimethoprim, and chloramphenicol-florfenicol antibiotics and have been associated with survival in fish farms and coastal regions sediments, was found to be high [148].

5. Appropriate Strategies to Control and Prevent AAR

Applying antibiotics in aquaculture should be minimized and reduced in order to prevent the spread of ARGs produced from animal use. The spread of ARGs in aquaculture has been shown to be greatly slowed by reducing the use of antibiotics and implementing other remedial measures through (i) *Additives:* probiotics, prebiotics, and synbiotics may become effective substitutes for antibiotics to cut down on the usage of antibiotics and the development of AR in fishes [82]. For example, the synbiotic *Lactobacillus helveticus* and Gum Arabic boosted defense mechanisms and dominated lactic acid bacteria found in the common carp intestinal tract, which might be responsible for the remarkable resistance to *Aeromonas hydrophila* infection. [149]. Another study proved that incorporating 1.5% pot marigold powder into meals has favorable impacts on Rainbow Trout (*Oncorhynchus mykiss*) growth, the activity of digestive enzymes, antioxidant capacity, immunological response, and *Yersinia ruckeri* resistance [150]; (ii) *Immunostimulants*: nutritional factors from bacterial, algal, or animal sources—including hormones and cytokines—can be used to stimulate the immune system. Immunostimulants primarily stimulate the white blood cells, which are crucial to the fish's defense system. If administered prior to situations known to cause stress and impair general performance (such as handling, temperature changes, unfavorable environmental conditions, weaning of larvae to artificial feeds) or prior to anticipated increases in exposure to pathogenic microorganisms and parasites, these substances may also, though not always, keep animals less susceptible to infectious diseases and reduce the risk of disease outbreaks [151]; (iii) *Bacteriophage therapy*: phage therapy has been shown to reduce bacterial populations below critical levels, allowing the host's defenses to control any remaining bacteria. Fish can get bacteriophages via a variety of ways, including injectable, oral, and water bath administration. No phage-neutralizing antibodies were discovered in fish treated with phage, according to several researchers [152]. This demonstrates the ability of some phages to lessen bacterial infections with no adverse effects on fish body. Further research is required to determine whether phages can be used to treat various fish infections in aquaculture instead of antibiotics; (iv) *Vaccination*: the use of antibiotics can be decreased while improving fish health through better aquaculture management, greater farm hygiene, and the use of a prophylactic vaccine to ward off fish infections; (v) *Water system disinfection:* UV application and ozone treatment; and (vi) *Nanotechnology*: applying nanoprobiotics to improve aquaculture's health and immune system, polymeric- and metallic nanoparticles to act as bacteriostatic, bactericidal, antioxidant and immunomodulators, and nanosensors and nanofiltration for fishpond cleaning and stock inspection [153].

6. Discussion

At various trophic levels, aquatic organisms communicate with one another in the aquatic system [154]. Numerous antibiotics are currently entering aquatic environments, and not much is understood about how they interact with aquatic organisms, according to recent studies [155]. ARGs have become more prevalent in aquatic habitats as a result of the continued accumulation of antibiotic treatment [77, 80, 156]. Based on their geographical and temporal distribution, ARGs have been found to differ significantly depending on the region [157]. Figure 3, in this part, depicts one probable method through which ARGs might interact with aquatic species.

It is well known that antibiotics are present in aquatic environments, and over time, aquatic microbes are subjected to these drugs and develop ARGs that they pass on to other organisms [157]. As a result, ARBs or ARMs that can infect other aquatic microbes are created [77]. Such aquatic microbes have the capacity to assemble and form intricate microbial communities (like biofilms), where genetic exchange occurs [158]. These complex microbiomes are more challenging to get rid of because of their sophistication. As shown in Figure 2(b), in such environments, genetic material is transferred from one microbe to another vertically or horizontally. The creation of new ARGs with the ability to induce ARBs and result in widespread bacterial resistance is a risk that may arise during the transfer of genetic material [159]. ARGs become toxic and might be harmful to human health and other animals who consume them as a result of fish, plants, and other aquatic organisms being exposed to them repeatedly (Figure 2(c)). In addition to directly consuming seafood, people run the risk of being exposed to ARGs when they eat meat or animal byproducts that have been subjected to ARGs and ARBs from aquatic habitats.

6.1. Drivers Increasing Dissemination of AARGs. The highest AAR levels were linked to drivers such as (i) poorer sanitation systems, (ii) human clinical AR, (iii) antibiotic misuse, (iv) aquatic feed-containing antibiotics, and (iv) lack of awareness or knowledge regarding antibiotic use in aquaculture systems. These variables provide selective pressure on aquaculture-related microbial populations and favoring AARG growth [160].

In addition, it was found that higher AARBs were correlated with warmer temperatures [47, 60, 161]. Reverter et al. [60] showed that irrespective of the kind of animal cultivated, elevated temperatures nearly invariably result in increased mortality of diseased aquatic organisms. Extreme temperature changes are also known to stress most aquatic organisms and weaken their natural defenses, leaving them more susceptible to disease [162, 163]. It is doubtful that using antibiotics will increase because of increased fatality rates because decisions about antibiotic treatment are typically made at the beginning of a disease outbreak. Even so, the administration of antibiotics is going to rise as a result of the growing problems with fish health (such as higher fatality rates and growing epidemics) [164]. Because AAR is tied to a nation's vulnerability to climate change. These data demonstrate that nations suffering the hardest to find solutions and cope with the changing climate will also be at the greatest risk of AARG dissemination.

Aquaculture excrement is a further reservoir of AARGs disseminated into the environment from aquaculture facilities. A previous investigation found 20 out of 28 AARGs (including genes associated with aminoglycoside resistance *aadA1*, *aadA2*, genes associated with tetracycline resistance *tet*M, and trimethoprim *drfA1*) and a number of transposons (e.g., *tnpA01-tnpA07*) in each of fish intestinal specimens and farming sediment [165]. Additionally, many fish germs that carry AARGs are zoonotic pathogens, which can infect humans as well as animal hosts through direct contact with infected aquaculture facilities and indirect foodborne infections like *Listeria monocytogenes* [166], *Aeromonas* [167], and *Clostridium* spp. [168]. Moreover, some studies suggested that probiotic application represented a driver of AARGs dissemination since probiotic microbes can acquire ARGs from pathogenic microbes and vice versa [169]. The long-run effects of introducing large volumes of probiotics to aquaculture farms, which are still harboring a significant amount of ARGs and antimicrobial agents in situ, must be investigated further.

The abovementioned drivers have been investigated in many regions, such as the Mediterranean Area [161], 40 different countries with low and moderate incomes [60], Asia [47], and Africa [170]. However, such drivers have not been further studied in SA. Here, we investigate these drivers and how they are affecting the dissemination of AARGs in SA. SA represents approximately 80% of the Arabian Peninsula [171] and is primarily made up of desert terrain that suffers extreme temperatures and inadequate rainfall, with the exception of the southwest highlands, which are recognized as having varied flora [172]. Additionally, due to its relatively high moisture content, SA is more susceptible than other nations to climate change and greater temperatures as the average global temperature rises, particularly in the western highlands [173]. Reverter et al. [60] concluded that the average annual temperature positively correlated with the countries AAR index. As previously mentioned, in SA, ARGs were identified in soil samples [108], clinical samples, health care systems [17, 18, 109, 110], and wastewater treatment plants [111].

The Kingdom's health authorities are concerned because SA has been identified as a nation with escalating AR. Antibiotics are easily accessible to the general public, and SA has no restrictions on their availability. The perspective of the health authorities' interventions to stop the unsuitable practice of antibiotics that causes AMR has changed as a result of the common and simple availability of antibiotics [174]. Only a small number of studies on AR in SA have been published so far. The findings of the studies that are currently available, however, indicate that the general public has a very limited understanding of the use of antibiotics and AR [175].

An investigation into patients' understanding of AR in two governmental hospitals in Tabuk City, northwest SA, was conducted using a hospital-based multicenter study. It showed that the study participants had a very high level of ignorance of AR and its contributing components. Therefore, in order to address AR in the Tabuk area, health awareness and education campaigns are strongly advised [176]. Moreover, a self-administered questionnaire was used to investigate public knowledge related to AR among Saudi people in the northern border region of SA. Such a community still has some misconceptions and insufficient knowledge regarding AR [177]. Similar results were reported in the south-western region [174], Jazan, SA [178], university medical Saudi students [179], a tertiary care center, Riyadh, SA [180], Al Wazarat Health Center in Riyadh [181], while Jeddah population have more proper knowledge and awareness

Figure 4: Aquaculture-related antibiotic resistance genes (AARGs) control and management approaches.

about AR [182, 183]. The emergence and spread of AR are causes for great concern because of inadequate awareness of the risks associated with independent medication and antibiotic overuse. Research from the United Kingdom, Sweden, Jordan, and other European nations revealed a higher degree of knowledge concerning the correct application of antibiotics, which contrasts with the results of this research [184–186].

It is crucial to increase public awareness of AR in order to address the pressing problems that it is causing in SA. People can be encouraged to avoid practices and behaviors that spread AR by having a better understanding of how it spreads [187]. Such environment forces aquaculture systems to face the highest risk of AARGs dissemination among aquatic organisms and from organisms to humans.

6.2. Policies and Regulations for AARGs Control: "Prevention Is Better than Cure". These results underline the critical necessity for integrated national and international measures to stop AAR control and AARG dissemination. In an effort to cut down on antibiotic use in aquaculture, a variety of good aquaculture practices have been suggested, from improved disease monitoring and control to enhance animal wellbeing (Figure 4).

AARG management strategies are typically implemented through (i) *biosecurity initiatives*, which primarily stop pathogens from entering farms or hatcheries. Simple biosecurity measures like dehydration of sediments, liming of ponds, elimination of organic waste before restocking by anaerobic digestion and composting, sufficient sanitization of equipment like seine nets, paddle wheels, and vehicles, and processing effluent from the farming industry can greatly diminish the abundance of ARGs/MGEs and effectively control the spread of ARGs/ARBs from animal farming, especially aquaculture [188–190], vaccination and quick screening and testing instruments for pathogens detection (for example, PCR); (ii) *Governmental and nongovernmental organizations* typically offer aquaculture extension services and consultations to farmers in order to help them improve their farming methods [191]. Extension services that enhance information flow can help improve farm management; (iii) *Regulations and interventions* are usually applied to either the immediate antibiotics usage or the antibiotics level in products. Extension agencies can assist and communicate the risks of misapplication and excessive consumption and demonstrate the efficacy of prudent use, ideal usage procedures, innovative possible treatments, and disease avoidance techniques, that all of them can restrict antibiotics use. Regulations for direct use specify when and how to use particular antibiotics; (iv) *Certification* requires farmers to abide by rules limiting and disclosing their use of antibiotics. Similar restrictions apply to current organic certification standards, which all prohibit the use of antibiotics as a preventive measure. Increased public awareness would not only strengthen certification labels but also contribute to a decrease in the overuse of antibiotics by humans.

According to the SA's Vision 2030 plan, MEWA established a code for responsible aquaculture practices to promote the responsible and sustainable development of the Saudi aquaculture industry, with the purpose of assuring the high quality of its products, while respecting environmental and societal considerations and meeting contemporary consumers' food safety requirements. This code focused on stopping disease rather than treating it with chemical substances by (i) not stocking diseased fish, (ii) preventing environmental strain by sustaining high-quality water in culture systems, (iii) not using antibiotics in feeds, pond additives, or any other treatment, (iv) not using antibiotics, antimicrobials, or hormones as growth promoters, and (v) requiring auditors to have access to full records as described during inspections [14].

To combat AAR and AARGs, SA needs to work together nationally, which includes reiterating the threat of AR and looking for more cutting-edge knowhows or efficient administration choices to control AR [192]. It is necessary to educate the general population alongside organizations about AARG dissemination so as to increase understanding and alter the existing circumstances.

7. Conclusion

For both food safety and human wellness, AAR research in Saudi aquaculture enterprises is crucial, and interdisciplinary research is advantageous for reaching numerous financial and ecological advantages. The aim of this research was to examine the status of AARGs pollutants and the main drivers of dissemination in the environment of Saudi aquaculture and to disclose the risks to the aquatic environment and public wellness. The potential sources, ways, and rates for administration of antibiotics, stimulation, and rates of AAR, AARBs, and AARGs in Saudi aquaculture ecosystems were summarized. This AAR research confirmed that SA is one of the nations with the highest AAR index, and such a high index is due to the dissemination of AARBs and AARGs through aquatic animals–environment–human pathways. AARGs spreading with the Saudi aquaculture environment primarily belonged to selective pressure, the ability of AARBs to form persistent biofilms, bioaccumulation, and the nature of the aquatic food chain. Other factors belonged to poor sanitation systems, human clinical AR, antibiotic misuse, aquatic feed-containing antibiotics, and lack of awareness or knowledge regarding antibiotics use in Saudi aquaculture systems. Based on the research, many AARBs and AARGs were discovered in Saudi aquaculture systems, and the majority of AARBs were Gram-negative; such high prevalence could be another possible driver of AARGs spreading. Most detected AARGs in the environment of Saudi aquaculture are conferring resistance to beta-lactams, penicillins, quinolones, and tetracyclines. Methods and strategies to control and prevent AAR were thoroughly explored, though these strategies are not effectively used in practice. Consequently, in subsequent studies, we ought to try to advance Saudi economical and cutting-edge plans to educate and inform stakeholders and the general public about the risk of AARGs/AARBs dissemination with the aim of raising awareness and alleviating the severity of AAR.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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