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A review on the fate, human health and environmental impacts, as well as regulation of antibiotics used in aquaculture

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ABSTRACT

Antibiotics have been a necessary component of animal husbandry and aquaculture since they were first used in clinical settings in the 1940s to meet the rising demand for foods generated from animals. Because of this, large-scale industrial animal production has become a hotspot for the evolution and spread of ARGs (antibiotic resistant genes), potentially posing a threat to public health. The recent advent of quick molecular technologies has substantially increased our understanding of ARGs in cattle systems. From a One Health perspective, detailed analyses of ARGs in the livestock industry and potential mitigation strategies are currently available. In order to clarify the intricacies of ARGs across animals, habitats, and people, this review is focused on human health hazards related to antibiotic usages, ARGs in cattle and aquaculture systems. This review specifically addresses the following topics: (1) antimicrobials used in the animal sector; (2) development of ARGs on animals affected by selected agents; (3) ARG transmission mechanisms (direct/indirect animal-to-human); and (4) mitigating strategies. We emphasize the difficulty of reducing the administering antibiotics to animals for the sake of public and environmental health, as well as the critical necessity to take immediate action to stop the transmission of antibiotic/drug resistance in the livestock and aquaculture sectors.

1. Introduction

The term ‘aquaculture’ (latin word ‘aqua’ meaning water) is generally circumscribed as the commercial rearing of aquatic creatures, primarily fish, mollusks, and crustaceans, in water bodies like seas, lakes, ponds, and rivers (FAO 2016b, c; Shao et al., 2021). It traces its historical origin to nearly 4000 years ago, originating in China and stemming out as a propitious economic zone in recent times (Dias et al., 2012), emphasizing strenuous enquiries on on-field practices of research and innovation. According to FAO, an estimated 45% of fishes were produced worldwide via aquaculture practices, with an annual growth rate of $>$ 8% (FAO 2016b, c). The largest producer of aqua-products was China, accounting for about 15% share of the total aquaculture production followed by Indonesia (8%), Peru (7%), Russian Federation (6%), India (5%), USA (5%), Vietnam (4%), Norway (3%), South Korea (2%), Japan (2%) and Philippines (2%) (FAO 2022) (Fig. 1). Apart from food utilities, the practice of aquaculture has led high economic gains for the traditional fishing activities (FAO 2016a), encouraging the convenient and accessible safe-quality food production for ever-expanding masses, generating jobs and providing a fiscal contribution to overall international economic development. Despite all these pros, a notable ‘call of concern’ need to be addressed pertaining to the matters of environmental impact and risk assessment (Martinez-Porchas and Martinez-Cordova, 2012; Shao et al., 2021). Some of the deleterious effects are listed as: obliteration of natural ecosystems (Rajitha et al., 2007; Martinez-Porchas and Martinez-Cordova, 2012), soil pH changes (Rodrıguez-Valencia et al., 2010), water body pollution (Paez-Osuna 2001; Avnimelech and Kochba 2009), chemical contamination (Justino et al., 2016), biological deterioration brought on by the introduction of non-native species (Molnar et al., 2008), landscape variation

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(Dumbauld and McCoy 2015), and deteriorating fishery management (Granada et al., 2016). Also, the emergence of new illnesses has coincided with a concomitant increase in the usage of antibiotics in aquaculture productivity practices (Lafferty et al., 2015; Zhang et al., 2023).

The aquatic environment is a dynamic medium capable of long-distance pathogen transfer (Murray, 2013; Chen et al., 2020; Bombaywala et al., 2021), owing to substantial organism movement, and thereby crafting a vastly multifarious web of disease spread (Murray, 2013; Bombaywala et al., 2021). In sequence, for orchestrating the stratagem of 'control and combat' of infectious diseases, hefty quantities of veterinary medicinal products (VMPs) (mainly antibiotics) are administered (both controlled and indiscriminate), posing consequential risk to environmental biota and residents of eco-domains (Huang et al., 2015; Lafferty et al., 2015; Xu et al., 2021). Interestingly, many different types of antibiotics have been/are currently being used in aquaculture farms in major producing nations (Fig. 2). Many formulations of antibiotics have been designed and consistently applied as bath treatments or feed augments, devising 'prevent and treat' approaches conferring prophylactic and therapeutic defense lines against bacterial infections (Zhang et al., 2023). In the present review, the effect, regulation and fate of antibiotics in environment and their mitigation strategies were explicitly presented using the newly accessible data. The study also points out critical gaps in our current understanding and future areas in need of investigation in the hopes that this section will inspire readers to get engaged in this hotly debated and rapidly developing field.

2. Methodology: literature search

Screening, identification, and suitability were the three steps in the systematic search approaches used in the present study. The databases of Web of Science, Scopus, and Pubmed/Medline databases, without regard to publication year limits, were used to search for articles specifically about looking into effect of antibiotics in environment. The suitable publications were downloaded in PDF (Portable Document Format) form with conditions of open access or the associated authors were contacted to obtain the full text during the English language literature search. The following were the inclusion requirements: (i) full-text accessibility; (ii) papers that described the methods for preparing, extracting, and analyzing the chosen samples; (iii) papers that described the effects, regulation and entry of antibiotics in environmental domains and that provided information on the mitigation protocols; and (iv) peer-reviewed scientific studies in English language.

3. Entry route into the environment

According to scientific literary estimates, about 75% of feed administered antibiotics enter the environmental domain via (a) metabolic progression of 'secretion and excretion' from cultured species, and

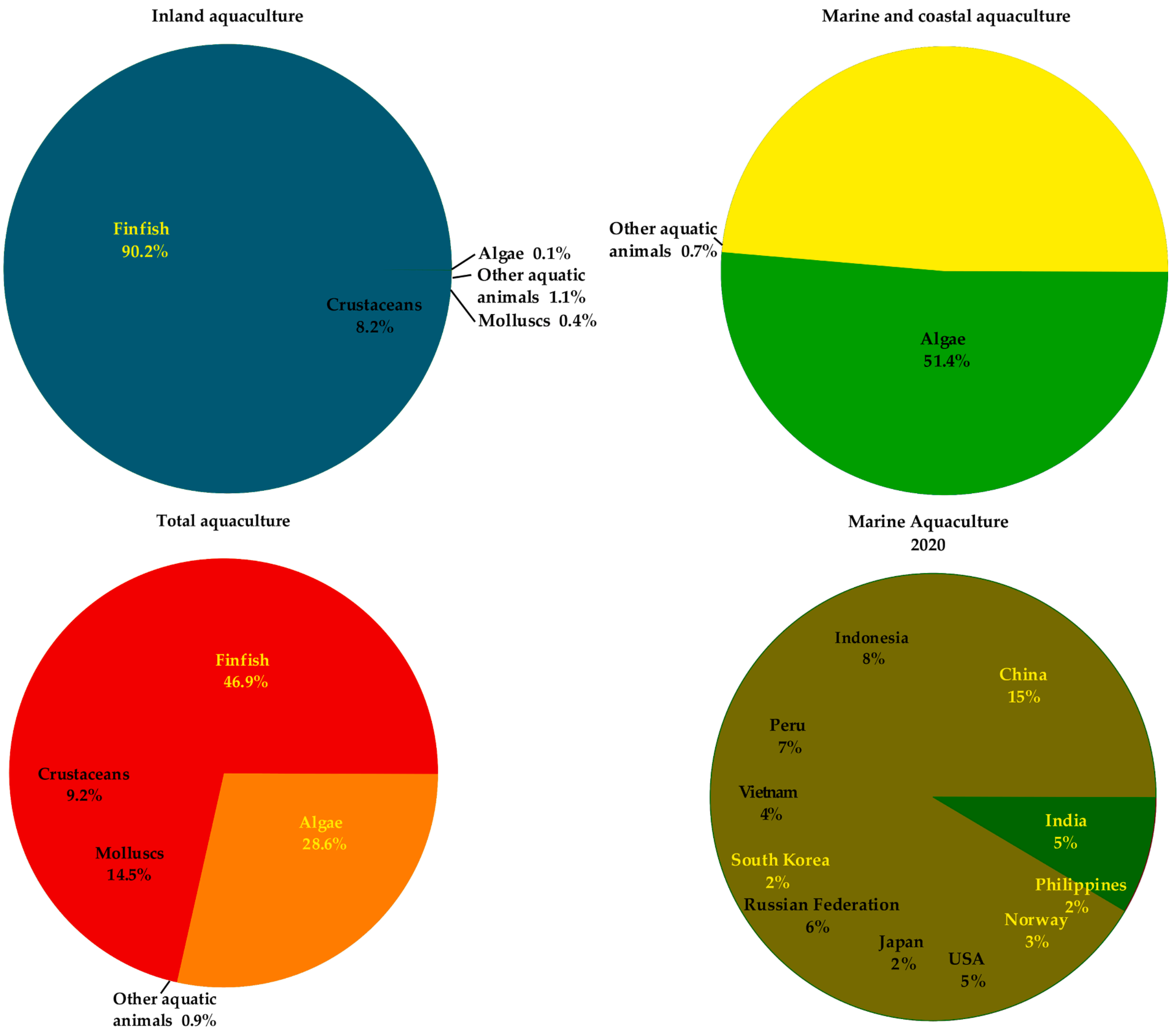

Fig. 1. Aquaculture production data in 2020 (left) and global ten aquaculture-producing countries in 2020 (right) (FAO 2022).

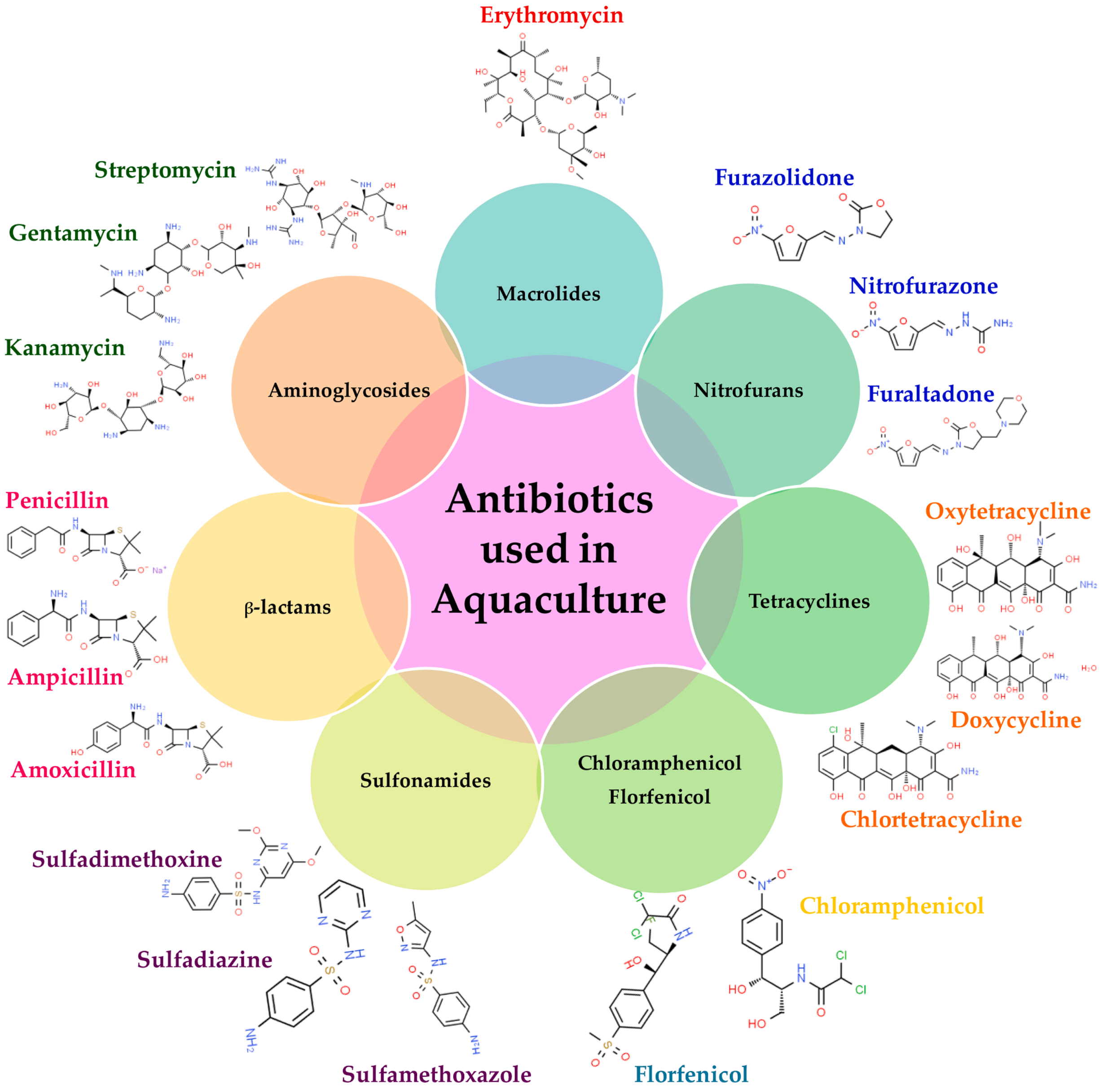

Fig. 2. Antibiotics used in aquaculture.

(b) leaching from unconsumed medicated feed (Lalumera et al., 2004). Antibiotic use and its consequences on aquatic environments have grabbed monumental scientific scrutiny due to their aquaculture-induced pollution and their profound usage in animal husbandry and as human medicine (Santos et al., 2010; Ahmad et al., 2022). The presence of antibiotics has been found to be highly pestilential to microbial entities and primary producers (Zounková et al., 2011). Several toxicological investigations have compiled evidences documenting that aquaculture antibiotics are not hazardous to invertebrates or fish at quantities relevant to the environment (Zounková et al., 2011), although their detrimental effects cannot be eluded on a long-term basis. The study conducted by Wollenberger et al., (2000) discerned for instance lasting effects of oxalinic acid in invertebrates such as disruptive reproduction reported in daphnids at lower concentrations. Fig. 3 depicts entry routes of antibiotics in the environment.

3.1. *Entry and fate of antibiotics in soil systems*

The effectiveness of antibiotics in the environment is influenced by a range of environmental parameters, including soil type, soil chemistry, climate, and physico-chemical characteristics (Shao et al., 2021).The fate and behavior of antibiotics in soil have been identified as one of the newer challenges in environmental chemistry (Table 1). Animals administered antibiotics for veterinary purposes excrete the drugs, which then find their way into the soil when the animals graze or when manure is utilized as fertilizer for farming (Chaturvedi et al., 2021; Ahmad et al., 2022; Zhang et al., 2023). Large quantities of antibiotics per hectare have been evaluated to be lost by manuring. Antibiotics in the dust from exhaust air from stable ventilations may be a major source of other minor agricultural environmental releases. Antibiotics are frequently discharged into the environment with very minor transformations, or even completely unaltered and conjugated to polar compounds (Shao et al., 2021; Chaturvedi et al., 2021). The molecular configuration of pharmaceutical antibiotics affects the chemical and physical behavior in soil. Antibiotics are either ionized, amphoteric or amphiphilic, according to their different structural categories. Several physico-chemical characteristics, such as their molecular arrangement, shape, size, hydrophobicity, and solubility differentially affect the binding, fixation and sorption capacity of antibiotics in soils (Shao et al., 2021). Many antibiotics are polar, only weakly water soluble, and

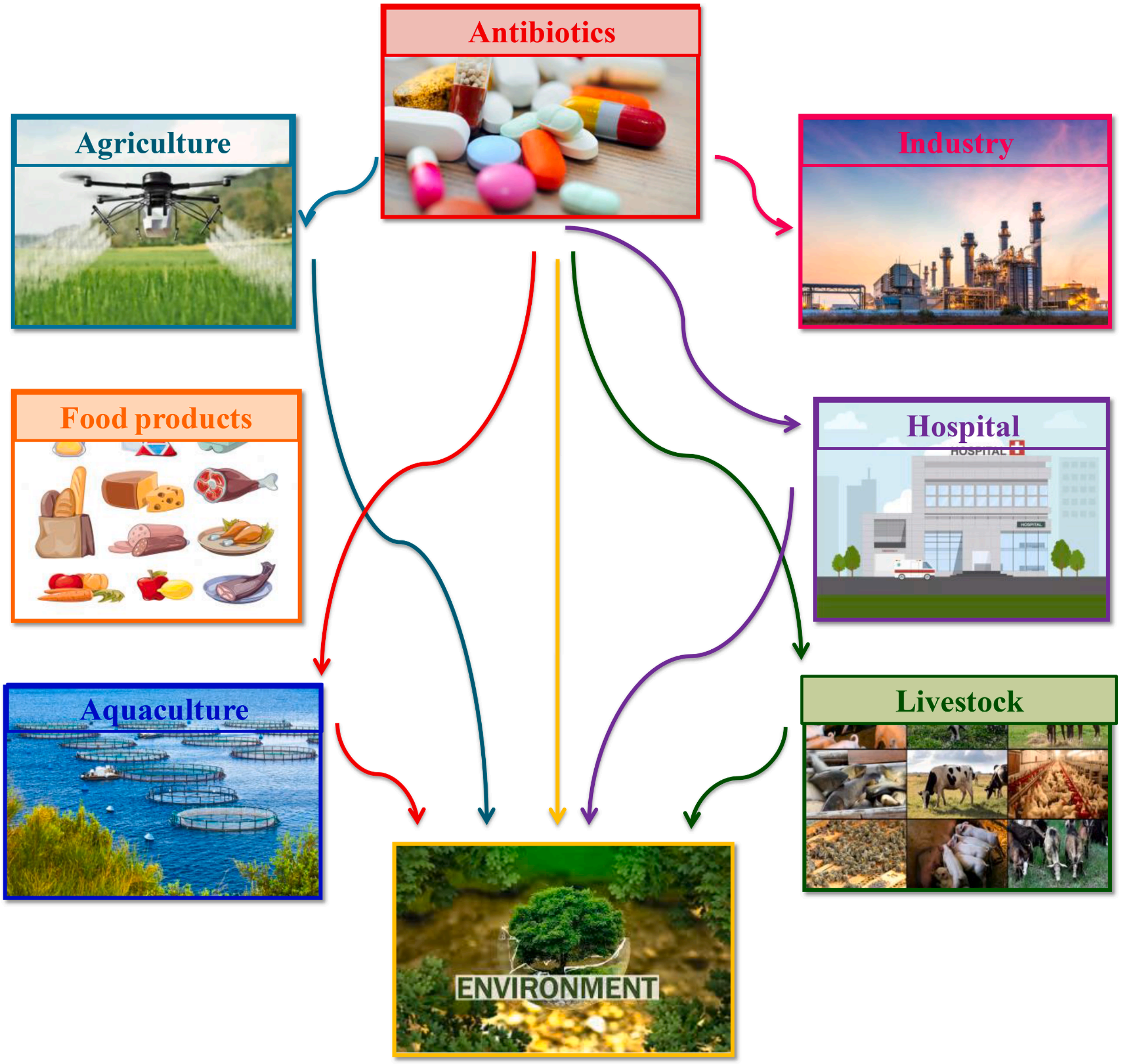

Fig. 3. Entry routes of antibiotics in the environment.

Table 1
Antibiotics in soil systems.

Class	Antibiotics	Refs.
Macrolides	Clarithromycin Lincomycin	Schüller, 1998 Boxall et al., 2004
Sulphonamides	Sulphadiazine Sulphadimidine Sulphametazine	Boxall et al., 2004 Höper et al., 2002 Hamscher et al., 2005
Trimethoprim		Boxall et al., 2004
Fluorochinolones	Ciprofloxacin	Schüller,1998
Tetracyclines	Tetracycline Oxytetracycline Chlortetracycline	Winckler and Grafe, 2000; Hamscher et al., 2002 Boxall et al., 2004 Hamscher et al., 2005

exhibits significant retardation in soils. For instance, the transport of tetracyclines seems to be constrained to quick preferential macropore flow or aided by co-transport by itinerant colloids like dissolved organic materials (Xu et al., 2021). The majority of antibiotics are quickly absorbed and their efficacy is largely diminished by fixation and sorption, although that does not necessarily entail a full eradication of the antibiosis activity (Zhang et al., 2023).Further, research on the antimicrobial activity of tylosin and tetracycline bound to soil has revealed that these antibiotics are still functionally active even when tightly adsorbed to clay particles (Chaturvedi et al., 2021; Xu et al., 2021). This research demonstrated the antimicrobial impacts that lead to the emergence of antibiotic resistant bacteria in the terrestrial environments. In general a chemical compound usually accumulates when its application rate exceeds its removal rate. The amount of antibiotics found in particular soil layers is referred to as 'terracumulation'. These sorbed substances provide a source of contaminants that can be released into soils and affect ground water via leaking or leaching into surface waters (Chen et al., 2020; Bombaywala et al., 2021).

Until now, only a few studies have been reported on the movement and transport of antibiotics in soil. Paez-Osuna (2001) reported the antibiotic contamination of surface waters by diffusion and leakage from agricultural soils. Analysis of ground water and pastoral leachates with manuring and intensive livestock production identified nil to only a few antibiotics in lower concentrations (Bombaywala et al., 2021). In case of tylosin and oxytetracycline, the distributional coefficient was found to be less manure as compared to the soils (Xu et al., 2021). Similar report was also found in sulphachloropyridazine where likewise a lowering effect of manure was ascertained. An increase in the amount of manure in the soil decreases the distribution coefficient, primarily because of the basic nature of manure. Tetracycline was detected for long time periods up to 30 cm soil depth demonstrating its persistence and accumulation in the environmental system (Xu et al., 2021).

Many factors contribute to the degradation of antibiotics. Since the influence of light is diminished when antibiotics are shielded in slurry or sludge, the process of photodegradation does not yield significant effects (Li et al., 2021). Soil based degradation is primarily sponsored by microbe mediated enzymatic reactions, transforming the native compound via the processes of oxidative decarboxylation and hydroxylation. Although these responses are reversible in nature, the antibiotics subsequently degrade in soil and manure (Zhang et al., 2023). The process of biodegradation increases when manure or sludge containing high microbial load is added to the soil. Soil serves as the storehouse of micro-organisms. High bacterial populations are crucial for maintaining the processes of mineral immobilization and breakdown. Antibiotics in soil usually affects in two ways: first, the microbial ecology may be significantly disrupted; second, these environmental bacteria may acquire up and offer gene-coding resistant factors. Certain soil microorganisms have a built-in resistance to antibiotics (Chen et al., 2020; Shao et al., 2021).

3.2. *Entry and fate of antibiotics in water systems*

The need for reliable and secure drinking water is growing due to the demand for the planet Earth's limited freshwater resources, especially in view of the continued exponential development of the human population (Xu et al., 2021). The presence and destiny of antibiotics in the water environments have recently been the focus of numerous studies conducted around the globe (Table 2). In the context of antibiotics used in livestock husbandry, the metabolites or degradation products of antibiotics enter the water cycle through the application of manure or slurry to farming used areas, or directly through the excretion of pasture-raised animals on the land, which is then followed by driftage, surface run-off, or leaching into the deeper earth (Caban and Stepnowski, 2021). The aquatic environment may become contaminated with antibiotics from soils. Since the majority of antibiotics are water-soluble, 90% can be eliminated in urine and 75% through animal faces. Aquaculture is another method by which antimicrobial substances used on animals might be discharged into the environment. Aquaculture residuals and resistant bacteria have been reported in recent years (Okeke et al., 2022). However, the effects of sub-inhibitory amounts against non-marine aquatic bacteria are generally unknown. The influence of several antibiotics continuing to be active against bacteria living in wastewater has been described. The use of sewage sludge as wastewater or manure in irrigation may have directly introduced resistant and multi-resistant bacteria into the food chain. Resistant and multi-resistant bacteria have been detected in wastewater and sewage treatment plants. Most of the investigated antibiotic compounds have been persistent under test settings in aquatic systems, whereas only a small number of antibiotics are partially degraded (Zhang et al., 2023).

Due to the ease of precipitation and accumulation of tetracyclines and hydrolysis of penicillin, they are not present in aquatic environments (Okeke et al., 2022). The β-lactam ring, which is a structural component of β-lactams like cloxacillin, benzylpenicillin, and penicillin, makes them unstable in the environment because β-lactamase, a common enzyme in bacteria, hydrolyzes and breaks open the ring structure (Ahmad et al., 2022). As a result, pristine penicillin molecules are typically absent from the environment. However, antibiotics in agriculture serve as the smallest source of antimicrobials in the marine environment. Only a small number of samples are supposed to have an effect upon animal husbandry on the prevalence of antibiotics in surface waters; the majority of the compounds under investigation came from discharge or sewage into rivers. Human administration of antibiotics via municipal wastewater or hospital effluents accounts for the majority of antibiotic input (Li et al., 2021).

Table 2
Antibiotics in water systems.

Class	Antibiotics	Source	Refs.
Macrolides	Lincomycin	Surface water	Kolpin et al., 2002; Boxall et al., 2004
	Clarithromycin	Surface water	Hirsch et al., 1999
	Erythromycin	Surface water	Hirsch et al., 1999
	Roxithromycin	Surface water	Hirsch et al., 1999
	Tylosin	Surface water	Daughton and Ternes, 1999; Ashton et al., 2004
Sulphonamides	Sulphadiazine	Surface water	Boxall et al., 2004
	Sulphamethazine	Ground water	Hamscher et al., 2005
	Sulphamethoxazole	Ground water	Sacher et al., 2001
		Surface water	Hirsch et al., 1999
		Drinking water	Mückter, 2006
Trimethoprim		Surface water	Boxall et al., 2004
		Surface water	Hirsch et al., 1999
Fluorochinolones	Ciprofloxacin	Effluents	Golet et al., 2001
	Norfloxacin	Effluents	Golet et al., 2001
		Surface water	Kolpin et al., 2002
Tetracyclines	Tetracycline	Ground water	Krapac et al., 2005
	Oxytetracycline	Overland flow water	Kay et al., 2005
	Chlortetracycline	Surface water	Kolpin et al., 2002

4. Antibiotic use in aquaculture: health and environmental safety issues

Although the use of antibiotics benefits enhanced production and the extension of the aquaculture industry, they also cart the vices of harmful effects and risk on human and environmental health (Rico et al., 2013). Scores of scientific literatures have tendered confirmatory accounts on the antibiotic buildup in farmed animal tissues and accumulation in culture and sediments biota, with impending perilous consequences for environmental and human health (Heuer et al., 2009; Shimizu et al., 2013).

4.1. *Effect of antibiotics on the environment*

The rate of metabolic absorption of orally feed administered antibiotics is low to average (Rico et al., 2013; Wang et al., 2015) and nearly 30–90% of the antibiotics gets excreted via the feces or urine (Sarmah et al., 2006). Besides that discarded food seeps into the environment and contains metabolites of antibiotics, fish faeces, and other degradation products. In intensive fish farm practices, over 70% of the antimicrobials amended to feed diffuse into the environment (Thuy and Nguyen 2013; Andrieu et al., 2015; Giang et al., 2015). In the aqueous environment, the antibiotics and their residual products accumulate in sediments, driving significant changes in the native microbial communities and perturbing the existing established natural equilibrium (Samuelsen et al., 2014). Conversely, the continual persistence of multi-drug resistance facades in severe environmental implications to overall microbial profiling and ecological stability (Tamminen et al., 2011).

Once introduced in aquatic ecosystems, the antibiotics entail grave and noxious effects on non-target/indicator species particularly, the diverse populations of microalgae, phytoplanktons and zooplanktons (Yasser and Adli 2015; Song et al., 2016). They disrupt early developmental stages of zooplanktons (Park and Kwak 2018) and chlorophyll production in phytoplanktons (Song et al., 2016), convulsing existing egalitarian complexes of food chains and food webs and deranging every level of ecosystem matrices (Cabello 2004). Also, they have been implicated with growth impairment, immunosuppression and altered gut microbiota in farm cultured species (He et al., 2012a).

Algae are oxygenic autotrophs serving as components that are crucial to aquatic habitats and create organic materials that form the bulk feed for most other life forms like fishes and invertebrates. The structural and functional dynamics of an ecosystem can be adversely affected by any biological or chemical changes to algal cells, leading to oxygen depletion and decreased primary output (Ma et al., 2006). One of the most often used ecotoxicological assays for toxicity evaluation in connection to chemical classification and risk assessment is the algal growth inhibition test (EC, 2003; OECD, 2011). Several studies have typified the concentration ranges which impact microalgal growth to be around one or two orders below those toxic concentration ranges for invertebrates (Lai et al., 2009). Among the diversified complex phyto-planktonic communities, cyanobacteria have been found to be the most susceptible group (Brain et al., 2008), due to their speculative morphological resemblance to the target microorganisms. The drug contamination usually affects all living organisms as algal cells forms the base of the food supply and any deficit in their production will have an immediate impact on the entire aquatic food chain. Further, studies pertaining to antibiotic pollution also pinpoint the negative effects on water-quality parameters and the configuration of innate bacterial communities, severely plaguing the functional processes like nitrification and mineralization of organic matter (Tello et al., 2010). Moreover, the relentless and overuse of antibiotics has forayed in a more gruesome theme of antimicrobial resistance in the strains of bacteria, heftily compromising the efficacy of curative treatments and public health. Tendencia and De la Peña (2001) and Le and Munekage (2004) reported that shrimp farms of Philippines and Vietnam had microorganisms that were resistant to antibiotics. Also, the rampant and pervasive use of bulk quantities of antibiotics have resulted in their high bioaccumulation rate via food chains, which led to derived secondary effects in the succeeding apex orders (Cabello, 2006).

4.2. Effects of antibiotics on human health

An unchecked usage of antibiotics in farmed aquaculture-based food production has shown to be a potential hazard for food safety (Chen et al., 2015, 2018b), reducing the scale of marketability and fiscal gains of aquaculture products (Hassan et al., 2013). Additionally, as wild fish can consume residues of antibiotics, the safety of products from catch fisheries is jeopardized (Chiesa et al., 2018). The uncontrolled use and consumption of antibiotic residue laced aquaculture products accounts for an advanced pattern of antibiotic resistance in clinical pathogens and ADRs (adverse drug reactions) (Liu et al., 2017). Li (2008) documented antigenicity of antibiotics like Penicillin G, tetracycline and sulphonamides rooting severe allergies to consumers; while their bioaccumulation induced organ lesions, resulting in chronic toxicity (Zheng and Su 2010). Also, the transcripts concerning occupational health hazards have long term inhalation or close contact of dust aerosols containing antibiotics by manpower in feed mills and cage farms in aquaculture facilities, causing allergies and toxicity and altering normal dermal flora by ingestion and skin contact (White and McDermott 2009). Furthermore, the findings of Moreau and Neis (2009) and Phu et al., (2016) categorized antimicrobial-occupational hazards as (a) organ-specific and (b) systemic reactions (either singly/ in combinations). Another health hazard referred to as antimicrobial resistance with potential for zoonosis (Martinez 2009), comes typically from long-term high-dose therapy, which causes tissue residue accumulation (Chuah et al., 2016; Monteiro et al., 2016). The infection of *M. albus* by *Aeromonas hydrophila*, followed by red sore disease in *C. carpio* (Saitanu and Wongsawang, 1982), and ulcer disease in walking catfish (*Clarias batrachus*) (Saitanu and Chalarak 1983), were classified as the early imprints of antibiotic resistance by Reungprach and Kesomchandra (1983) from Thailand.

The antimicrobial resistance has been detected in aquaculture across the world in recent research, which is compelling evidence that this danger to human and environmental health is growing.

The culture fish ponds are conceived as the reservoirs of ARGs (antibiotic resistance genes) (Table 3), as the majority of farm used antibiotics (usage either within or outside aquaculture facilities) have been implicated in the development of antimicrobial-resistant microorganisms (Hong et al., 2018; Millanao et al., 2018). In addition, compared to bacteria in areas where there are no aquaculture activity, resident bacteria in commercial aquaculture facilities showed higher ARGs (Gao et al., 2012). The rationale is as follows: Long-term exposure to low doses of antibiotics is necessary for the spread of antibiotic resistance to human biological systems; this is suggestive of the potential for resistance in intestinal resident bacteria and suggests that ARGs may spread horizontally by being conjugated with human pathogenic strains (FAO 2005; Tomova et al., 2015). Moreover, Marshalland Levy (2011) and Rico et al. (2013) exemplified direct transmission of resistant bacterial strains from animals to humans. He et al., (2015) reported the presence of bacteria resistant to antibiotics in aquaculture products in seafood markets of China, hoisting up a major word of consternation in context of health (both of consumers and aquaculture farm workers).

5. The enigmatic problem of multi-antimicrobial resistance (MAMR)

The development of multi-antimicrobial resistant (MAMR; Fig. 4) bacterial strains has severely hampered the existing remedial strategies (Chuah et al., 2016; Pham et al., 2018). The malefic pathogenic strains appropriate resistance to existing schemes of antibiotics, consequential in hysterical breakouts of epidemics and epizootics which are practically terminal and untreatable (Hawkey, 2008). Due to the blanket and wild usage of drug formulations, the MAMR pattern has been confirmed for two *Aeromonas caviae* HG4 isolates (Rahman et al., 2009); members of Bacilli (Fernandez-Alarcon et al., 2010), *V. parahaemolyticus* and

Table 3
Country-specific number of studies on antibiotic resistance among top ten nations.

Nation	No. of studies	%	Refs.
China	74.0	43.5	Liang et al., 2013; Su et al., 2017; Chen et al., 2018a; Hong et al., 2018; Marti et al., 2018
Indonesia	1.0	0.6	Zulkifli et al., 2009
India	20.0	11.8	Elmahdi et al., 2016; Rahiman et al., 2016; Sneha et al., 2016; Stratev and Odeyemi 2016; Mishra et al., 2017
Vietnam	21.0	12.4	Son et al., 2011; Nguyen et al., 2014, 2016; Pham et al., 2018; Thai et al., 2018
Philippines	1.0	0.6	Elmahdi et al., 2016
Bangladesh	2.0	1.2	Rahman et al., 2009; Hossain et al., 2017
South Korea	5.0	2.9	Yi et al., 2014; Germond and Kim 2015; Jang et al., 2018; Kim et al., 2018
Egypt	4.0	2.4	Ishida et al., 2010; Ali et al., 2016; Osman et al., 2016, 2017
Norway	2.0	1.2	Burridge et al., 2010; Midtlyng et al., 2011
Japan	3.0	1.8	Sun et al., 2010; Ahmed et al., 2015; Cao et al., 2016

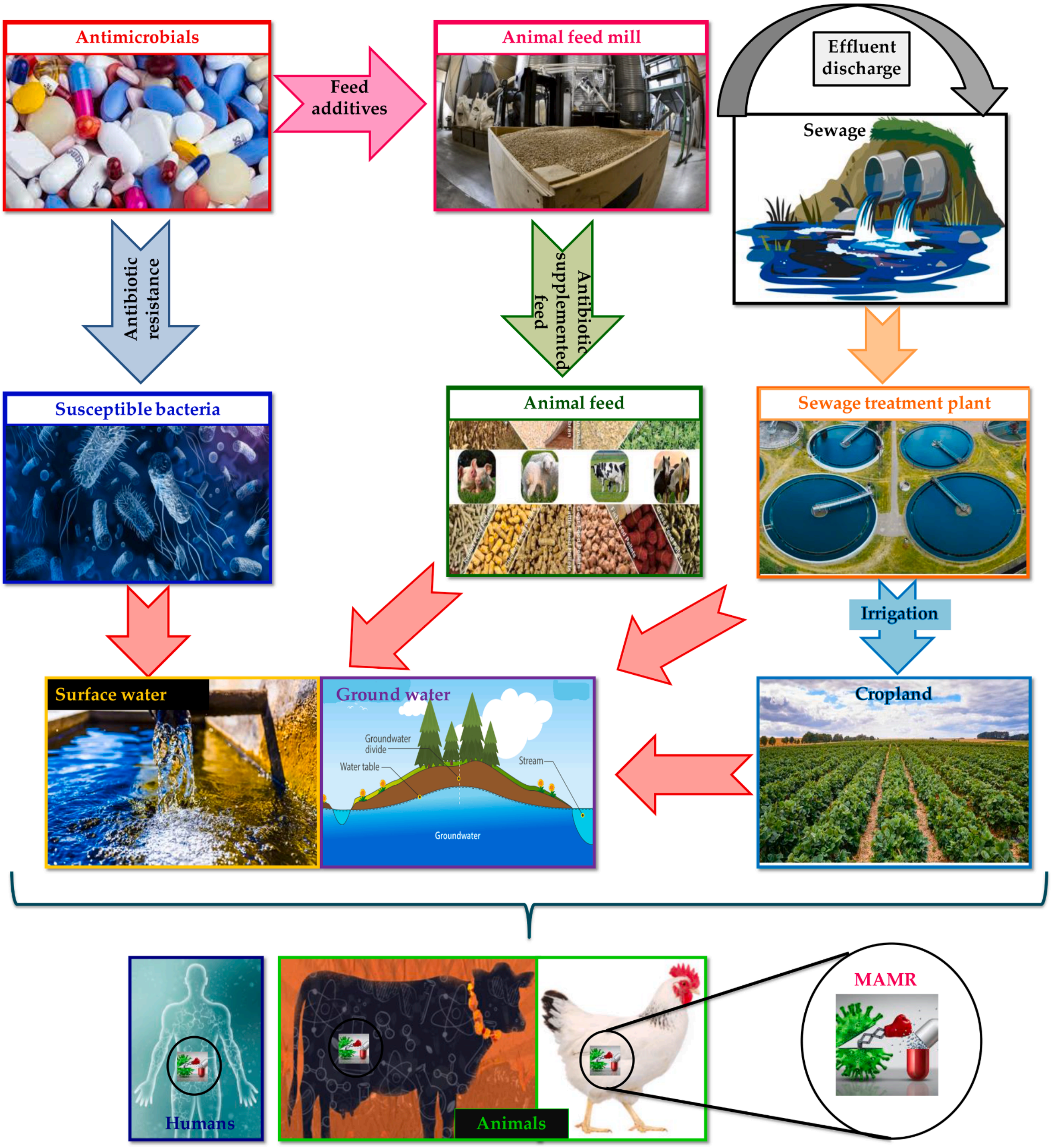

Fig. 4. Environment-to-animal-to-human MAMR transmission pathways in the One Health framework.

V. cholerae (Noorlis et al., 2011); *Vibrio* isolates (Rocha et al., 2016); *V. vulfificus* and *V. parahaemolyticus* (Elmahdi et al., 2016); *Klebsiella pneumoniae* and *A. hydrophila* (Pham et al., 2018). Also, the scenario of MAMR has been reported from coastal sea waters and estuaries for the species of *Vibrio* sp. (*V. parahaemolyticus* and *V. alginolyticus*), *Acinetobacter, Photobacterium* sp., *Aeromonas* and *Klebsiella* (Germond and Kim 2015; de Menezes et al., 2017).

It has been widely noted that plasmid mediation and integron transfer are the two ways by which antibiotic resistance spreads across bacteria (Table 4). The scientific confirmation of integron-mediated MAMR genes has been substantiated in the members of the family of Enterobacteriaceae, *E. coli* (Deng et al., 2014, 2016), *E. coli* isolates from China (Chen et al., 2011), and *Aeromonas* spp. Alternatively, the plasmid-mediated MAMR transfer was verified in the isolates of *Vibrio* (Rocha et al., 2016); *Salmonella* (Budiati et al., 2013) and *V. parahaemolyticus* (Letchumanan et al., 2015a, b). Plasmid mediated single antibiotic resistance was reported in the species of *Pseudomonas, Salmonella* serovars (Budiati et al., 2013), *Edwardsiella ictaluri* (Dung et al., 2008, 2009), *Aeromonas* spp. (Nguyen et al., 2014) and *Flavobacterium psychrophilum* (Henríquez-Nuñez et al., 2012). The presence of antibiotic-resistant *Escherichia coli* (Shah et al., 2014), *Aeromonas, Acinetobacter* (Agersø et al., 2007), *Vibrio* (Reboucas et al., 2011; Tuševljak et al., 2013), isolates of *Streptococcus* and *Enterococcus* (Osman et al., 2017), *Salmonella* and *Edwardsiella* (Tuševljak et al., 2013) have also been reported from aquaculture farmed organisms. Above all, the unbridled prophylactic usage of antibiotics/drug formulations in aquaculture elevates resistance menace due to amplified selective pressure, rendering the progressive ineffectiveness of drugs (Schwarz et al., 2006). Also, due to the inherent and intrinsic unions of aquaculture systems with open water bodies, the antibiotic-resistant

Table 4
Prevalence of multi-antimicrobial resistance (MAMR).

Mode of resistance	MAMR isolates	Refs.
Plasmid mediation	*Aeromonas caviae* HG4	Rahman et al., 2009
Plasmid mediation	Bacilli isolates	Fernandez-Alarcon et al., 2010
Plasmid mediation	*V. parahaemolyticus*	Noorlis et al., 2011
Plasmid mediation	*V. cholerae*	Noorlis et al., 2011
Plasmid mediation	*Vibrio* isolates	Rocha et al., 2016
Plasmid mediation	*V. vulfificus*	Elmahdi et al., 2016
Plasmid mediation	*V. parahaemolyticus*	Elmahdi et al., 2016
Plasmid mediation	*Klebsiella pneumoniae*	Pham et al., 2018
Plasmid mediation	*Aeromonas hydrophila*	Pham et al., 2018
Plasmid mediation	*Vibrio parahaemolyticus*	Germond and Kim 2015
Plasmid mediation	*Vibrio alginolyticus*	Germond and Kim 2015
Plasmid mediation	*Acinetobacter* sp.	Germond and Kim 2015
Plasmid mediation	*Photobacterium* sp.	de Menezes et al., 2017
Plasmid mediation	*Aeromonas* sp.	de Menezes et al., 2017
Plasmid mediation	*Klebsiella* sp.	de Menezes et al., 2017
Integron-mediated MAMR genes	*E. coli*	Deng et al., 2014, 2016
Integron-mediated MAMR genes	*E. coli* isolated from China	Chen et al., 2011
Integron-mediated MAMR genes	*Aeromonas* sp.	Chen et al., 2011
Plasmid-mediated MAMR transfer	isolates of *Vibrio*	Rocha et al., 2016
Plasmid-mediated MAMR transfer	isolates of *Salmonella*	Budiati et al., 2013
Plasmid-mediated MAMR transfer	*Vibrio parahaemolyticus*	Letchumanan et al., 2015a,b
Plasmid mediated single antibiotic resistance	*Pseudomonas*	Budiati et al., 2013
Plasmid mediated single antibiotic resistance	*Salmonella* serovars	Budiati et al., 2013
Plasmid mediated single antibiotic resistance	*Edwardsiella ictaluri*	Dung et al., 2008, 2009
Plasmid mediated single antibiotic resistance	*Aeromonas* sp.	Nguyen et al., 2014
Plasmid mediated single antibiotic resistance	*Flavobacterium psychrophilum*	Henríquez-Nuñez et al., 2012
Plasmid mediation	*Escherichia coli*	Shah et al., 2014
Plasmid mediation	*Aeromonas* sp.	Agersø et al., 2007
Plasmid mediation	*Acinetobacter* sp.	Agersø et al., 2007
Plasmid mediation	*Vibrio* sp.	Reboucas et al., 2011; Tuševljak et al., 2013
Plasmid mediation	isolates of *Streptococcus*	Osman et al., 2017
Plasmid mediation	isolates of *Enterococcus*	Osman et al., 2017
Plasmid mediation	isolates of *Salmonella*	Tuševljak et al., 2013
Plasmid mediation	isolates of *Edwardsiella*	Tuševljak et al., 2013

bacterial strains have been well reported from open water systems (Zhang et al., 2014).

6. Mitigation strategies

6.1. Management of certain agents

The most effective way to stop the spread of MAMRs derived from animal use is to minimize and reduce antibiotic administration in the livestock economy. It has been demonstrated that limiting the use of antibiotics and using other corrective measures can significantly slow the spread of MAMRs in cattle production (Tang et al., 2017).Meanwhile, enhancing animal health through improved livestock management, improved farm hygiene, and the use of a preventative vaccine to fend off animal diseases can aid in reducing the need for antibiotics. In order to decrease the consumption of antibiotics and the emergence of antibiotic resistance in animals, additional additives such as prebiotics, probiotics, and phyto-based products may emerge as reliable alternatives (Yi et al., 2020). Also, due to their potent antibacterial properties and minimal capacity to induce resistance, antimicrobial peptides are suggested as a potent replacement for antibiotics (Li et al., 2018). By taking stock with the cattle waste, it is also possible to lessen the release of MAMRs and antibiotics into the environment. MAMR transmission and proliferation could be less likely in certain environmental niches where antibiotic-driven selection was found to be reduced.

6.2. Management of manure

Fresh manure borne pathogens can be removed through composting, which can also lessen odour emissions and create organic matter for crop productivity. It has been demonstrated that hyperthermophilic composting, which may reach temperatures of up to 90°C during the fermentation phase, removes MAMRs more effectively than traditional composting (Liao et al., 2018). This may be because of the high temperature reached during the hyperthermophilic phase. Composting can effectively remove antibiotics like penicillin, ionophores, macrolides, fluoroquinolones, sulfonamides, and tetracyclines, thereby reducing the potential selection for MAMRs along the pathways (Selvam and Wong 2017). But nevertheless, due to the intricate microbial ecological processes involved in composting, the behavior of MAMRs changes during this process.

To increase the removal effectiveness of MAMRs, additives including coal gasification slags superabsorbent polymers, zeolites, and biochar can be used in composting or soils (Peng et al., 2018). In particular, biochar can immobilize heavy metals, speedup the breakdown of organic waste, and limits nutrient loss and elevates the thermophilic composting temperature (Li Duan et al., 2017). A number of studies have demonstrated that some prominent characteristics of biochar such as porous structure, high surface-to-volume ratio, and microbial affability enable it to restrict the multiplication of MAMR in soils and plants (Zhang et al., 2019). It has been demonstrated that the removal of MAMRs using the regularly utilized livestock waste treatment method of anaerobic digestion is both affordable and effective (Couch et al., 2019). During anaerobic digestion, certain resistance genes, such as *tet* and *erm* genes, have reported reductions in their log copy numbers (Couch et al., 2019). However, a number of variables, including substrate types, operational temperatures, and the microbial hosts of MAMRs, have a significant impact on how effectively anaerobic digestion reduces MAMRs in animal waste. Like composting, additives like wheat straw and biochar can enhance the elimination of MAMR during anaerobic digestion by preventing the re-absorption of metals and antibiotic residues (Yi et al., 2020). Despite the fact that composting and anaerobic digestion are important techniques for effectively disposing of MAMRs, it should be noted that they do not completely eliminate MAMRs. In fact, some MAMRs can still surpass treatment process, even with an increase in the prevalence of resistance. In order to prevent the potential MAMRs surfeit, additional procedures or discharge management may need to be taken into account.

6.3. Treatment of waste water

The abundance of MAMRs can be greatly reduced and their spread from animal husbandry, especially aquaculture, can be effectively controlled by effluent treatments from the pastoral farms. MAMR levels in effluents following wastewater treatment reactors have been found to be decreased in the vast majority of studies. A study by An et al. (2018) reported a reduction in the number of resistance genes and integrons cassettes in the wastewater treatment processes. Although wastewater treatment has been found to be a viable approach for eliminating ARGs, developing nations frequently lack adequate wastewater management or treatment. Therefore, the contaminated effluent may be discarded straight to nearby aquatic bodies (Gros et al., 2019). Moreover, the treatment method can have a significant impact on the elimination of MAMRs. For example, animal effluent from ordinary farms is treated in a bioreactor through an artificial wetland without a full-scale wastewater treatment system. In contrast, ARGs are more effectively eliminated in water treatment plants. The quantity of intake, the kind of biological therapies, and the length of the hydraulic residency are all related to the success of the treatment, influencing the elimination of bacteria and MAMRs (Novo and Manaia, 2010).

6.4. Policies for management and assistance

To manage AMR issues under One Health, regulatory standards for livestock farming and their waste management are crucial. In order to address the worldwide problem of MAMR, it is crucial to involve decision-makers, researchers, farm workers, animal agricultural stockholders, and the community at large in all nations (Góchez et al., 2019; Yi et al., 2020).The discovery of solutions and the provision of a better proposal for concerned authorities on the MAMR danger could be facilitated by standardized procedures and reliable libraries for antibiotics and MAMRs in livestock sectors. Implementing antibiotic limitations may move more quickly if current legislations are improved. This will result in lower financial losses for the livestock sector. Approaches that are both economically viable and environmentally sustainable must be further developed, enhanced, and integrated (Yi et al., 2020). Monitoring and risk evaluations of MAMRs in wastewater and animal waste are required before further applications in order to prevent the spread of MAMRs from animal husbandry to downstream habitats and humans. To combat antibiotic resistance, both regional and global cooperation is required. This includes reiterating the danger that antibiotic resistance poses and searching for new cutting-edge technology or efficient management solutions (Yi et al., 2020). All stakeholders and the general public must be educated and made aware of MAMRs in order to raise awareness and change the current scenario.

Although many decades have passed since the first-time use of antibiotics in feedlots, scientific research on the providence and incidence of antibiotics has only recently emerged from its infancy. Assessments of antibiotic concentrations in the environment and known effects on terrestrial or aquatic microorganisms have not been evaluated, in part due to the lack of appropriate analytical test methods (Yi et al., 2020). The effects of antimicrobial medications in aquatic and terrestrial environments depend not only on the dosage and mode of administration but also on the methods used for animal husbandry, the internal metabolism of the animals, the handling and storage of their manure, and the rates of degradation of the antimicrobials (Gros et al., 2019). Unfortunately, there is a dearth of information regarding the distribution and destiny of antibiotics in the environment, as well as their prevalence.

The propagation of multi-drug resistant bacteria, important for human and veterinary medicine, is one of the greatest issues of prolonged use of antibiotics and their release into the environment (Couch et al., 2019). Pathogenic bacteria may be able to obtain resistance genes from commensal and environmental bacteria. Pathogens, commensal bacteria, and environmental bacteria may develop single, cross, and even multiple resistances as a result of environmental antimicrobials. To find out the role of antimicrobials in the establishment and maintenance of single or multiple populations of antibiotic-resistant bacteria, particularly pathogenic bacteria, further study is still required (An et al., 2018). There is also a lack of reliable information on the relationship between antibiotic residues and the prevalence of resistant bacteria. Even if a general correlation between antibiotic usage and the percentage of resistant strains is anticipated, it is unclear at what threshold concentrations a change towards an increase in resistance bacteria is to be expected. These resistant bacterial strains may spread through direct contact or the food chain, which might lessen the therapeutic effects of using antibiotics to treat both animals and humans (Peng et al., 2018). Emphasis must be placed on multidrug-resistant bacteria's new and existing exposure pathways from animals to humans.

By continuously manuring contaminated faeces from agriculture, it is discovered that resistance is created by repeatedly exposing bacteria to sub-lethal concentrations of antibiotics (Yi et al., 2020). Long-term spreading of liquid manure on fields could lead to major contamination, especially if the environment accumulates specific antibiotics like tetracycline. Despite the fact that certain antibiotics are administered to both humans and animals, human usage is the primary cause of most human resistance problems (Yi et al., 2020). Livestock animal husbandry pollutes the environment with antibiotic residues and resistant microorganisms, yet it appears that people, rather than animals, are the major source of these poisons. Wastewater treatment facilities are the primary source of antibiotic discharge into the environment since the clearance during treatment is inadequate. According to new strategies, sources of faeces pollution of human or animal origin can be identified by analyzing bacteria for signs of resistance to veterinary or human medications (Li et al., 2017).

Although it is clear that dealing with antimicrobial chemicals is necessary for an effective animal production, antibiotics should never be used as the replacement of an appropriate hygiene management system. As the WHO states, "Enhanced monitoring of antibiotic use by data acquisition at various levels is a step towards a science-based, successful intervention." Furthermore, the environmental hazards exerted by antibiotics may have been only now starting to be identified by studies (Liao et al., 2018). Environmentally relevant doses for the vast majority of chemicals are currently found to be substantially lesser than the real concentrations utilized on target species. Due to the difficulties in evaluating controlled comparisons and the variety of natural systems, the advantages of lowering antibiotic resistance are difficult to quantify.

The scientific community is currently debating the best approach to take in order to solve this issue. Experimentation alone cannot determine whether antibiotics have a negative impact on ecosystem health. Laboratory research frequently has limited applicability to the environment due to differences in parameters which includes moisture content, pH, concentration, temperature, and other circumstances such as in experiments on transport, microbial degradability, and the metabolic route of antibiotics (Zhang et al., 2019; Yi et al., 2020). The data collection from pathway mobility and environmental sampling experiments involving significant veterinary pharmaceuticals is one suggested approach to solving this problem; however, the pertinent data have not yet been enough in the analysis of currently used antibiotics (Li et al., 2017). The scientific findings presented in this review illustrate that the occurrence of resistant bacteria and the extent of antibiotic contamination are not constrained by interspecies barriers, geographical differences, or fiscal conditions, even though this deficiency of financial profit worsens the call for extensive actions by the research community. The long-term invisible impacts on numerous species and other interacting effects on living things and the environment as a whole deserve more study, according to scientists. The sensible use of antibiotics as a preventative measure raises questions about the efficacy of both veterinary and human drug therapy (Tables 2–4).

7. Conclusions

The objective of this study was to convey the current level of knowledge about the risks to the environment and public health induced by the excessive use of antibiotics in aquaculture. The unsystematic and random prophylactic uses of antibiotics along with the incidents of MAMRs have put credence on the assessment of health and environmental risks. The major accents spotlighted were: occupational health hazards, food safety issues, altered biodiversity, and antibiotic resistance. Meanwhile, the blanket use of drug formulations/antibiotics remains high in major producer countries. This underscores the call for stern pursuance and enforcement of regulations and policies. Further, meticulous planning, economic investment in research prospects, coordination of policies and regulations, and international collaboration are necessary for attaining sustainable aquaculture production and fine-tuned groundwork in production and marketing. The reduction of antibiotic consumption per unit in the manufacture of environmentally friendly and securely ingestible aquatic food should be the overarching goal. Also, there is an urgent need to survey and ascertain compound specific usage data in aquaculture production.

CRediT authorship contribution statement

Tijo Cherian: Conceptualization, Investigation, Validation, Writing – original draft, Writing – review & editing. **Chinnasamy Ragavendran:** Validation, Writing – review & editing. **Smitha Vijayan:** Writing – review & editing. **Sini Kurien:** Writing – review & editing. **Willie J.G. M. Peijnenburg:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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