OPINION
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Antimicrobials and Antibiotic Resistance Genes in Water Bodies: Pollution, Risk, and Control

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The manuscript endeavors to provide a perspective on the role of water bodies in the spread of antimicrobial (antibiotic) resistance (AMR), antimicrobial resistant bacteria (ARB), and antimicrobial resistance genes (ARGs) among pathogens, animals, and humans. We briefly indicate how the AMR problem is globally affecting public health, along with strategies and mechanisms to combat the dissemination of ARB and ARGs. A brief systematic survey of the literature (2015-onwards) for the presence of antimicrobial residues and the occurrence of ARGs and antimicrobial resistant microorganisms in different water bodies/sources indicates the gravity of the situation and suggests their important role in the occurrence and spread of AMR, ARB, and ARGs. The prevalent water treatment methods which tend to reduce ARB and ARGs from water resources are unable to remove them completely, allowing the problem of AMR to continue and spread to organisms of concern. In this opinion article, we attempt to underline the key role of controlling the release/discharge of antimicrobial contaminants in water bodies and their buildup in checking the development and spread of AMR. The reduction in the release of antibiotic residues in the environment, especially water bodies, combined with the development of improved surveillance means and efficacious treatment/removal/decomposition methods could help curb the menace of AMR effectively. We suggest the expansion of the ambit of 'One Health Approach to AMR crises proposed by the World Bank, 2021 to include the 'reduction of antimicrobial contamination of the environment' as the 'seventh domain' of activity to effectively achieve its objective.

Keywords: antibiotic misuse, antimicrobial resistance genes, antimicrobial resistance, pollution, environment, wastewater, water bodies

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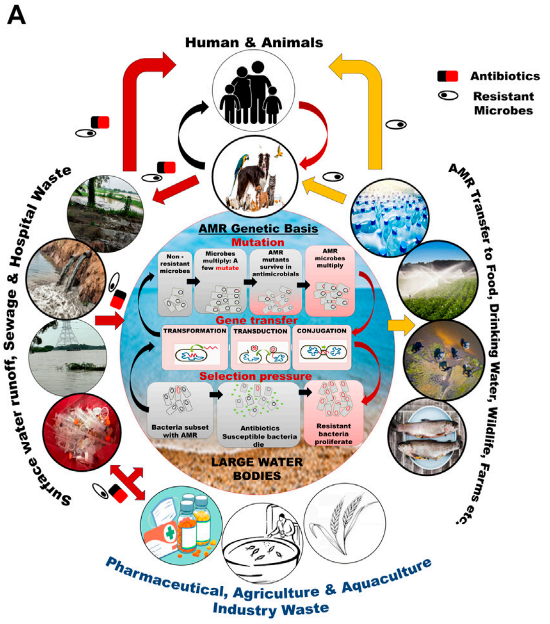
INTRODUCTION

Aquatic ecosystems are very important to maintain the high levels of biodiversity, livelihood, and productivity of the biosphere (Hossain et al., 2018; Vilca and Angeles, 2018; Irfan and Alatawi, 2019; Hassan et al., 2020). The presence of antimicrobials (antibiotics etc.), antimicrobialresistant bacteria (ARB), and antimicrobial resistance genes (ARGs) in the aquatic environment is becoming a cause of great concern as the possibility of development of antibiotic-resistant pathogens, even superbugs, is increasingly posing problems to the environment and human health (Ma et al., 2015; Wang et al., 2020; Zhuang et al., 2021). It is recognized that aquatic environments are one of the key reservoirs and transmission routes for the spread of antimicrobial/antibiotic resistance (AMR/AR) (Amarasiri et al., 2020). Antibiotics reach the environment *via* feces and urine of humans and animals, inappropriate disposal of unused drugs, and direct environmental contamination by waste material from antibiotic



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S. No.	Domains	Activity
1	Awareness Raising	Improve awareness, understanding, and knowledge of AMR through communication, education, and training at local, national, and regional levels.
2	Antimicrobial Stewardship	Promote the optimal use of antimicrobial agents through appropriate prescribing in diverse health care settings, especially in primary care.
3	Reduction of Antimicrobial Contamination of the Environment #	Reduce antimicrobial contamination of environments which is potentially driving AMR selection and spread through identification, monitoring, regulation and implementation of activities and products/innovations that could help minimize antimicrobial residues in the environment (soil, air, water)
4	Surveillance, monitoring, and research for national surveillance systems with a One Health approach	Under a One Health approach, strengthen knowledge and evidence through AMR and associated public health surveillance, monitoring, and research for national systems.
5	Infection prevention and control in human and animal health	Reduce infections (including hospital- and community-acquired infections) in humans and animals.
6	Reduction of the spread of pathogens into the environment	Identify, monitor, and regulate environmentally related activities or products that result in the spread of AMR pathogens
7	Operational Research Agenda	Strengthen and sustain operational research capacity for evidence-based decision-making to improve program performance.

Notes:1. **#Domain "Reduction of Antimicrobial Contamination of the Environment" is suggested by us.**
2. As per World Bank Group (2018), "a One Health approach is: a collaborative approach for strengthening systems to prevent, prepare, detect, respond to, and recover from primarily infectious diseases and related issues such as antimicrobial resistance that threatens human health, animal health, and environmental health collectively, using tools such as surveillance and reporting with an endpoint of improving global health security and achieving gains in development" [WHO, 2018].

FIGURE 1 | (A) Antimicrobial resistance development and transmission of ARGs and ARBs. **(B)** One health approach to AMR crises: Seven domains and activity for guiding the data collection, analyses, and action.

production units (Amaya et al., 2012; World Health Organization, 2017a; United Nations Environment Programme, 2022). Antimicrobials/antibiotics exert selection pressure, accelerating the development of ARB resistant to the used antimicrobial and related compounds (Kolář et al., 2001; Ayukekbong et al., 2017; Serwecinska, 2020). All antibiotics put to use consistently end up in the environment, further accelerating the pace of AMR development (Larsson and Flach, 2021). Globally, AR has been frequently reported from freshwater sources (Kumar et al., 2013; Abdel Rahim et al., 2015; Jabbar Ibrahim and Kareem Hameed, 2015; Guzman-Otazo et al., 2019; Singh et al., 2020; Subbiah et al., 2020), wastewater systems including but not limited to pharmaceutical industries, and wastewater treatment plants (WWTPs) (Ferreira Da Silva et al., 2007; Tesfaye et al., 2019; Adegoke et al., 2020; Obayiuwana and Ibekwe, 2020; Praveenkumarreddy et al., 2020). AMR has emerged as one of the key public health problems of the 21st century that overshadows the efficacy of available effective treatments against a large number of pathogens which are increasingly no longer susceptible to common antimicrobials (Prestinaci et al., 2015). The AMR problem is increasing rapidly and becoming more critical with each passing day. Pathogens causing different common infections have been consistently acquiring and displaying a varying degree of resistance to most of the new antibiotics within <5–10 years of their introduction into the market (**Supplementary Table S1**). AMR is observed in bacteria, fungi, viruses, and parasites as they get adapted to multiply in the presence of antimicrobials (Founou et al., 2017; Dadgostar, 2019). The infection with AMR pathogens is supposed to escalate healthcare costs and treatment failures and cause up to 10 million more deaths annually by 2050 (Dadgostar, 2019; Amarasiri et al., 2020). The World Health Organization (WHO) has declared that due to increasing AR, we are almost out of treatment options (World Health Organization, 2017b; World Health Organization, 2021). Seeing the growing threat of AMR, the WHO has proposed a six-point plan, that is, "One Health Approach" (OHA) (World Bank Group, 2018; Mazimba et al., 2021). The OHA is envisaged as "involvement of human health, animal health, and environmental health and focus on those infectious disease-related issues (including AMR) that undermine overall health and well-being" (World Bank Group, 2018; Mazimba et al., 2021).

Numerous studies across the globe have reported the prevalence of ARB in different water bodies (Kumar et al., 2013; Abdel Rahim et al., 2015; Jabbar Ibrahim and Kareem Hameed, 2015; Guzman-Otazo et al., 2019; Singh et al., 2020; Subbiah et al., 2020) and wastewater systems (Ferreira Da Silva et al., 2007; Tesfaye et al., 2019; Adegoke et al., 2020; Obayiuwana and Ibekwe, 2020; Praveenkumarreddy et al., 2020). The inability of different drinking water treatments and WWTPs to completely remove ARGs and ARBs from water allows for their buildup in large water bodies (Alexander et al., 2020; Amarasiri et al., 2020). Considering the central role of water bodies in the development and spread of AMR (**Figure 1A**), the active monitoring of antimicrobial residues in the environment and control of disposal into the environment are suggested to help reduce the rate of AMR emergence/development (**Figure 1A, B**).

ANTIMICROBIAL RESISTANCE EMERGENCE AND SPREAD

Microbial genome plasticity supported by numerous genetic mechanisms such as conjugation, transformation, and transduction enables them to evolve, adapt, and survive in environments contaminated with antibiotics. The development of AMR in microbes results from selection pressure, mutation, and gene transfer (Serwecinska, 2020; Larsson and Flach, 2021; Michael et al., 2014; Caniça et al., 2019; Van Hoek et al., 2011; Samreen et al., 2021; Kunhikannan et al., 2021; Amábile-Cuevas, 2021; Sriram et al., 2021; von Wintersdorff et al., 2016) (**Supplementary Table S2**), whereas conjugation supposedly remains the most frequently used mode of ARG transmission (**Figure 1A**) (von Wintersdorff et al., 2016).

Selection pressure determines the occurrence, amplification, and dissemination of ARGs in the environment and pathogens. Even low concentrations of antimicrobials/antibiotics can result in the selection of ARGs—making the establishment of a safe concentration of any antimicrobial compound in the environment a challenging task (Wang et al., 2020; Zhuang et al., 2021; Stanton et al., 2020; Yang et al., 2018). Several culture-independent studies on animals, food, humans, and environmental samples had shown the presence of huge reservoirs of ARGs (i.e., resistome) that could be potentially mobilized and transferred to other organisms (Abdel Rahim et al., 2015; Subbiah et al., 2020; Obayiuwana and Ibekwe, 2020; Adzitey, 2020; Forsberg et al., 2012; Hu et al., 2016; Abdel-Rahman et al., 2020; Meng et al., 2020; Morris and Cerceo, 2020; Balakrishna et al., 2017; D'Costa et al., 2011). Aquatic environments are identified as ideal settings for the acquisition and dissemination of AMR/AR. Human exposure to ARB and ARGs from aquatic environments poses an additional health risk (Karkman et al., 2018; Suzuki et al., 2017; Wellington et al., 2013; Leonard et al., 2018; Søraas et al., 2013; Leonard et al., 2015; O'Flaherty et al., 2018). Drinking water and wastewater treatment processes are mostly inadequate to remove ARGs (Li et al., 2015; Rodriguez-Mozaz et al., 2015; McGowan, 2007). The WWTP effluents, agriculture runoffs, *etc.* comprising ARB and ARGs can end up in aquatic environments such as lakes and rivers (**Figure 1A**). Usage of domestic wastewater in agricultural irrigation and recreational activities can introduce new ARB and ARGs to the specific environment (Leonard et al., 2018; Søraas et al., 2013; Leonard et al., 2015; O'Flaherty et al., 2018; Rodriguez-Mozaz et al., 2015; McGowan, 2007; Ben et al., 2017). In addition to drinking water, humans can be exposed to ARB and ARGs *via* different activities such as aquatic sports, bathing, occupational exposure during agricultural irrigation, and consumption of food produce from fields irrigated with reclaimed water (Leonard et al., 2018; Søraas et al., 2013; Leonard et al., 2015; O'Flaherty et al., 2018). However, the extent of human health risk resulting from exposure to ARB and ARGs present in aquatic environments remains poorly understood. It is primarily due to specific information such as the dose–response curves and exposure assessment data related to ARB and ARGs in different water usage scenarios being a prerequisite to conducting a quantitative microbial risk assessment (Ashbolt et al., 2013; Pepper et al., 2018).

ANTIMICROBIAL RESISTANCE IN WATER BODIES: CAUSE AND IMPACT

Antimicrobial Resistance in Aquaculture

The aquaculture field heavily relies on the application of antibiotics either directly in water or mixed with fish food to control infections, causing explosive growth of ARGs in farmed aquatic animals and environments (Heuer et al., 2009; Hinchliffe et al., 2018; Preena et al., 2020). Many antibiotics used in aquaculture are critically important for human treatment, for example, tetracycline, macrolides, and aminoglycosides (World Health Organization, 2021). Several studies indicated the indirect transfer of ARGs from fish origin antibiotic-resistant microbes to human pathogens such as *E. coli, Salmonella spp*., and *Aeromonas* spp through culture-independent studies (West et al., 2008; Heuer et al., 2009; Zou et al., 2012; Amarasiri et al., 2020). The presence of ARGs in *S. enterica* serotype *Typhimurium* DT104 isolates that caused salmonellosis outbreaks in Europe and the United States is also suspected to originate from the aquaculture system (Zou et al., 2012). The incidence of MDR in *Vibrio alginolyticus* and *Vibrio parahaemolyticus* isolates from farmed fishes in Korea further reaffirms the prevalent gene transfer phenomenon (Oh et al., 2011). Metagenomics or culture-independent studies have reported the occurrence of ARGs of different classes in marine sediments, suggesting a vital role for them in lateral gene transfer (Yang et al., 2013; Jiang et al., 2017; Karkman et al., 2018; Lerminiaux and Cameron, 2019; Sun et al., 2019).

Antimicrobial Resistance in Fresh and Wastewater

Freshwater bodies such as rivers, streams, springs, and lakes continuously receive antimicrobials/antibiotics, ARBs, and ARGs through different sources such as effluents from WWTPs, chemical manufacturing plants, animal husbandry, aquaculture, etc. Several studies had reported the presence of different antibiotics and ARGs in surface and groundwater sources (Liang et al., 2013; Shimizu et al., 2013; Ma et al., 2015; Matongo et al., 2015; Deng et al., 2016; Fernando et al., 2016; Madikizela et al., 2017; Danner et al., 2019) (**Supplementary Table S3A**). Even the bacterial communities of *Pseudomonas, Acinetobacter, Bacillus, Arthrobacter, Xanthomonas,* and *Flavobacterium* isolated from Eastern Siberian permafrost sediments had been shown to harbor several ARBs and ARGs by culture-dependent methods (Mindlin et al., 2008). Similarly, ARBs showing resistance to different classes of antibiotics had also been reported from freshwater samples of Antarctica and Siberian lakes (Lobova et al., 2011; Jara et al., 2020).

Wastewater remains a major reservoir of AMR in the environment as it allows ARBs with ARGs to persist and transfer the ARGs in the environment *via* different mechanisms (Rizzo et al., 2013; Fouz et al., 2020) (**Figure 1A**; **Supplementary Table S2**). The prevalent wastewater treatment methods that decrease the ARBs only have a limited impact on ARGs present in the environment (Ben et al., 2017; Hiller et al., 2019a; Singh, 2020). The ARGs present in the environment can get transmitted through horizontal gene transfer (HGT) to different organisms, including the medically important ones (Singh, 2020; Woolhouse et al., 2015). The environment assists the transfer of ARGs from one component to another, *viz.*, animals, soil, water, sediments, and sewage (**Figure 1A**)

(Wellington et al., 2013; Balcazar, 2014; Berglund, 2015; Fouz et al., 2020). ARGs are supposedly ubiquitous. However, their concentration may vary in different environments. The transfer of ARGs is not only limited to closely related species or genera but also occurs among phylogenetically distant species (Jiang et al., 2017). It leads to the ceaseless emergence of new variants of AMR organisms (Bouki et al., 2013; Hocquet et al., 2016; McKinney et al., 2018). The presence of ARGs in the environment represents a more complex and challenging problem concerning containment as they are not degradable and can be easily transmitted (Treangen and Rocha, 2011; Stecher et al., 2012; Beceiro et al., 2013; Hiller et al., 2019b; Ibrahim et al., 2019; Galhano et al., 2021; Koch et al., 2021; Zhuang et al., 2021; Grenni, 2022).

The major source of ARB and ARGs are human and veterinary clinical settings where intestinal bacteria encounter a high concentration of antibiotics, along with the associated WWTPs and land wastes (Karkman et al., 2018; Salyers et al., 2004; Ishikawa et al., 2018; Hendriksen et al., 2019). Bacteria passing *via* the intestinal tract can acquire AR through conjugation and transformation before ending up in human and animal feces (**Figure 1A**) (Salyers et al., 2004; Anderson et al., 2006). The effluent discharges from WWTPs to different environments where the environmental microorganisms can interact with ARB and ARGs may act as primary places of AMR development (Ben et al., 2017; Lee et al., 2017; Fouz et al., 2020; Manoharan et al., 2021).

Antimicrobial Resistance in Marine Environments

The mechanisms responsible for the occurrence of ARBs and ARGs in marine environments can be different from those of fresh water and wastewater. As per a report, marine environments contain about 28% of the ARGs (Hatosy and Martiny, 2015). The major source of increased AMR occurrence in the marine environment is the coastal runoff of the ARBs from the terrestrial environment (Hatosy and Martiny, 2015). In addition, anthropogenic activities are causing direct antibiotic residue outpourings into marine systems, for example, Chilean marine salmonid farms alone had used about 363.4 tons of antibiotics in 2016 that can act as a selection pressure for the development of AR in marine environments (Miranda et al., 2018). Metagenomics studies had reported the same ARGs in the intestines of Baltic Sea farm fishes and farm sediments; the possible reason suggested behind the observation is the usage of antibiotics during the hatching and rearing of juvenile fish or the acquisition of the ARGs by fishes from marine microorganisms in the farms (Rosenfeld and Zobell, 1947; Baam et al., 1966; Miranda et al., 2018; Tortorella et al., 2018). The potential bidirectional transfer of ARGs between these aquatic environments and humans cannot be ruled out.

Studies using both culture-dependent and culture-independent approaches suggest global contamination of the water environments including open oceans and widespread presence of ARBs (Shimizu et al., 2013; Hatosy and Martiny, 2015; Segura et al., 2015; Fekadu et al., 2019). In the natural aquatic environment, bacteria can develop AR due to induced mutagenesis at a low concentration of antibiotics (Kohanski et al., 2010). Although the fraction of resistant mutants is very low, the accelerated selection of ARBs could occur over generations (Gullberg et al., 2011) due to continued antimicrobial presence. Accordingly, attention should be paid to water environments as a key to the origin and spread of ARBs and ARGs.

ANTIMICROBIAL RESISTANCE IN WATER AND PUBLIC HEALTH

It was observed that AMR, including multiresistance and pan-resistance, is rapidly spreading in bacteria, leading to severe infections untreatable with current antimicrobials (World Health Organization, 2014; World Health Organization, 2015; George, 2019). The spread of AMR in the environment had received comparatively less attention as compared to the spread of AMR pathogens in animals and humans (Baekkeskov et al., 2020). There are two types of AMR in bacteria, that is, acquired AMR and intrinsic AMR (World Health Organization, 2015; Baekkeskov et al., 2020) (**Supplementary Table S2**). The release of antimicrobial compounds into the environment allows it to come in direct contact with the naturally occurring microbes and act as a driving force for microbial evolution and the emergence of more resistant strains (European Centre for Disease Prevention and Control, 2019; Graham et al., 2019; Taneja and Sharma, 2019; Singh, 2020).

AMR is beginning to endanger public health worldwide (Prestinaci et al., 2015; Founou et al., 2017; Centers for Disease Control and Prevention, 2019; World Health Organization, 2021; The World Bank, 2021). Infection with AMR pathogens causes serious illnesses requiring longer hospital stays and increased healthcare costs due to the higher cost of second-line drugs and sometimes treatment failure (Llor and Bjerrum, 2014; Prestinaci et al., 2015; Centers for Disease Control and Prevention, 2018; Shrestha et al., 2018; European Centre for Disease Prevention and Control, 2019). AMR in common infections heavily impacts immunocompromised individuals and those undergoing treatments such as chemotherapy, dialysis, joint replacement, surgery, *etc.* (Centers for Disease Control and Prevention, 2018; Centres for Disease Control and Prevention, 2021).

Globally, the frequent incidences of infection with multidrug-resistant Gram-negative bacteria (MDR-GNB) and Gram-Positive bacteria are posing treatment challenges (Llor and Bjerrum, 2014; Bassetti et al., 2019; Ramírez-Castillo et al., 2018; Annavajhala et al., 2019; Centers for Disease Control and Prevention, 2019; World Health Organization, 2017a; Viney et al., 2021). The MDR cases are projected to become a serious issue by 2040 (Friedrich, 2017; Salvatore et al., 2019; Viney et al., 2021). Common pathogens of concern, namely, *Enterococcus faecium, Helicobacter pylori, Neisseria gonorrhoeae, Campylobacter* spp, *etc.* are currently included in the list of priority pathogens by the WHO for the development of new antibiotics due to rapid development of AMR in these pathogens (World Health Organization, 2017b).

The municipal wastewaters contain a high concentration of organic and inorganic matter that supports the growth of AMR microorganisms, further promoting the spread of ARGs and AMR (Da Silva et al., 2006; Baquero et al., 2008; Exner et al., 2017; Karkman et al., 2018). Unrestricted discharge of untreated urban waste had been contributing to an overall rise of ARBs and ARGs in the environment (Da Silva et al., 2006; Moura et al., 2009; Osińska et al., 2016). The WWTPs are the meeting point of most of the ARBs, especially in those processes in which activated sludge or percolator biological filter are used for biological treatment (Baquero et al., 2008; Karkman et al., 2018; Kumar and Pal, 2018). Some studies had shown a higher percentage of MDR bacteria in the effluent than the effluent of treated wastewater (Osińska et al., 2016; Exner et al., 2017). Generally, wastewater treatment regulates the level of bacterial count, but due to differences in treatment plant designs and operations, the fate of ARBs and ARGs may remain unaffected or amplified.

The bacterial communities proliferate in drinking water distribution system pipes even after chlorination (Korzeniewska et al., 2013; Razavi et al., 2017). As the process of chlorination initially lowers the total load of microbes, it may significantly increase the level of ARBs. Expectedly, the effect of chlorination on the secondary effluent of WWTPs had been found to cause reactivation of ARBs (Zhang et al., 2009). The plausible reason for ARB increase could be a decline of antibiotic-susceptible bacteria or the selective rise of the ARB population in wastewater. However, the potential threat to public health from ARBs, whether from reactivation or regrowth, calls for more intensive research on the phenomenon (Blasco et al., 2008; Martinez, 2009; Munir et al., 2011; Huang et al., 2012; Harnisz, 2013; Klanicova et al., 2013). A crucial point of intervention for environmental AMR management could be the removal of ARB and ARG contaminants from wastewater effluents that pose a direct threat to negatively impact other water resources. The enhancement of wastewater treatment technologies and rational use of antibiotics should be promoted to minimize the threat of pathogenic ARB emergence and infection.

The regular uptake of antibiotics through several environmental sources changes the composition of gut microbiota composition and induces the growth of ARB in human and animal gut (Cho and Blaser, 2012; Francino, 2016). This gut microbiota inequity leads to the growth of several AR pathogenic and opportunistic bacteria with the possibility of them evolving into superbugs whose infection could not respond to treatments and lead to untimely death (Cho and Blaser, 2012; Ben et al., 2019). There is a growing need to understand the relationship between antimicrobial/antibiotic exposure and the human microbiome, and its functional aspect related to health (Ben et al., 2019).

The extent of the growing global AMR problem can be gaged by a systematic search of the databases, *viz.,* Web of Science, JSTOR, and PubMed using a combination of pertinent keywords such as antimicrobial, antibiotic resistance gene, water, environmental factors, antibiotics, heavy metals, water bodies, pollutants, etc. for the original research article and review articles. A brief systematic literature search performed for the antibiotic levels, ARBs, and ARGs in fresh and marine water on 17th February 2022 for articles published 2015 onwards (**Supplementary Table S3B, S4**) indicates the widespread presence of the residues of different antimicrobials (amoxicillin, penicillin tetracycline, ofloxacin, ciprofloxacin, *etc.*), a large number of ARGs (tetA, tetB, sulI, qnr, aadA, tetO, ampC, etc), and ARBs of concern (*E. coli, Enterococcus, Salmonella, Shigella, Aeromonas, Vibrio,* etc) in the water bodies (aquaculture, freshwater, wastewater, marine water) as presented in tabular form in **Supplementary Table S3A**, highlighting the severity of the AMR problem in water bodies.

The infections caused by ARBs increase the economic burden in terms of healthcare and associated costs. The infection caused by ARBs drastically inflates the cost of treatment and increases the chances of adverse outcomes, as compared to that caused by antibiotic-susceptible bacteria (World Health Organization, 2014; Centers for Disease Control and Prevention, 2018). The estimated deaths caused by AMR could rise from the current rate of about 0.7 million to 10 million annually by 2050, if comprehensive actions are not taken (World Health Organization, 2019; Samreen et al., 2021). It would further cause a 3–4% reduction in the annual gross domestic product (GDP) globally—translating into an economic cost of 1–6 trillion yearly from 2030–2050 onwards, based upon AMR (low to high) scenarios encountered and depending upon the measures undertaken now (World Bank, 2017).

CONTROL OF ANTIMICROBIAL RESISTANCE EMERGENCE AND DISSEMINATION IN WATER BODIES

Removal of Antimicrobial Resistant Bacteria and Antimicrobial Resistance Genes From Water Supply Systems and Wastewater Treatment Units

The WWTPs were designed for the removal of organic matter, nutrients, and solids, but now they need to be able to remove antimicrobials/antibiotics, ARBs, and ARGs as well. So far, very little is known about the effectiveness of the treatments in the removal of ARB and ARGs. Research is needed to fill a huge knowledge gap in this area to help improve the design of WWTPs and the used methodologies. Water supply systems and WWTPs use a single or a combination of different treatment processes to achieve many log reductions in the number of specific target microbes which show intra- and inter-process variations (Sano et al., 2016; Amarasiri et al., 2017). Specific comprehensive guidelines suggesting minimum reductions for antibiotics, ARB, and ARGs in water/wastewater are desired (Hong et al., 2018).

The membrane bioreactor treatment plants had achieved significantly higher reductions of ARB and ARGs (log reduction range: 2.57–7.06) than conventional treatment methods such as sand filtration, sedimentation, activated sludge, and rotating biological contactor or oxidation ditch (log reduction range: 2.37–4.56; $p < 0.05$) (Munir et al., 2011; O'Flaherty and Cummins, 2017; Su et al., 2018). The retention in the sand filter medium with low nutrient conditions is supposed to cause ARB starvation, leading to plasmid degradation and permanent loss of antibiotic resistance (Griffiths et al., 1990; Tan et al., 2019). Drinking water treatment by conventional methods had achieved variable ARG log reductions (0.03–2.4) that differed with the types of ARGs evaluated (Hu et al., 2019; Zhang et al., 2019). Sulfamethoxazole had killed ARBs immediately, but a delay in ARGs reduction was reported, possibly resulting from a competitive consumption of free radicals by sulfamethoxazole and ARGs (Hu et al., 2019).

Several studies indicate the inability of the water treatment processes to eliminate ARB and ARGs. There had been increased incidences of specific ARGs in the WWTP effluents (Rizzo et al., 2013; Xu et al., 2015; Chu et al., 2018; Karkman et al., 2018). A study revealed no significant differences in the ARGs present in potable source water and treated water, indicating the nonremoval of ARGs during the process (Garner et al., 2018). The activated granular carbon filtration method even enhanced the abundance of ARGs in the filtered water due to the formation of biofilms on the biological activated carbon surfaces where ARB can adhere and grow (Xu et al., 2016; Su et al., 2018; Hu et al., 2019; Tan et al., 2019). The significant correlations ($p < 0.05$) between the effluent ARG concentration (2 μg/l) and residual antibiotic concentration (0.5–0.22 μg/l) suggest a role for selection pressure on ARG enrichment (Mao et al., 2015; Hu et al., 2019).

The search for local solutions to avoid environmental dissemination of these pollutants requires prior information on the specific residues and the AR determinants present in wastewater. There is an urgent need for public health research to increase its pace to keep up with water sustainability technologies and even go beyond. In addition, more research work is essential for the application of effective treatment and disinfection approaches for the complete removal of ARB in WWTPs as the associated immediate environmental and public health risks are high.

Tracking the Sources of Antimicrobial Resistance in Organisms

The modern molecular techniques for the characterization of bacterial organisms can readily increase our ability to track the source of AMR and ARGs. These could provide useful insights, including but not limited to a comprehensive understanding of the population biology of organisms and the genetic diversity of organisms entering water (Olivas and Faulkner, 2008). These techniques could provide fast and accurate AMR source tracking and other genetic mobile platforms involved in AMR dissemination, providing a much more accurate image of the real diversity and complexity of AR in water-borne bacteria, unlike cultivation-dependent approaches (Henriques et al., 2006).

Revision of Domains of "One Health Approach" for Tackling Antimicrobial Resistance

The "One Health Approach" suggested by the WHO that currently focuses on activities to reduce the contamination and usage of antimicrobials and ways to minimize the development and spread of AMR pathogens (World Bank Group, 2018; Mazimba et al., 2021) should consider including active pursuance of the reduction of antimicrobial contamination of the environment as the seventh domain of the OHA for AMR crises to curb the development and spread of AMR (See **Figure 1B**).

DISCUSSION

Antimicrobials/antibiotics are used as both preventive and therapeutic agents in the treatment of animal diseases, human infections, aquaculture, agriculture, and the livestock industry (Baquero et al., 2008; Forsberg et al., 2012; Ben et al., 2019; Dadgostar, 2019; Schar et al., 2020; Schar et al., 2021). Antibiotic residues reach different environments through excretions (stool and urine of animals and human), improper disposal of unused drugs, waste stream from the antibiotic production unit, antibiotics used for plant production, etc. (Baquero et al., 2008; Ishikawa et al., 2018; Karkman et al., 2018; Pepper et al., 2018; Dadgostar, 2019; Larsson and Flach, 2021). Water bodies get contaminated by municipal sewage discharges, animal husbandry, landfill leachates of antibiotic disposal, manufacturing industries, and agricultural runoff (Hernando-Amado et al., 2019; Serwecinska, 2020). The increased frequency of ARGs in various ARBs of different environments is one of the concerning consequences of antimicrobial/antibiotic misuse and subsequent pollution (Kraemer et al., 2019). Studies indicate that aquatic environments act as a key reservoir and means of antibiotic resistance spread (Zhang et al., 2013; Matongo et al., 2015; Binh et al., 2018; Yang et al., 2018; Danner et al., 2019; Kraemer et al., 2019; Amarasiri et al., 2020; Schar et al., 2020; Larsson and Flach, 2021; Liyanage et al., 2021). In an aquatic environment, wastewater and WWTPs are considered one of the key potential hot spots for the spread of AR and transfer of ARGs (Matongo et al., 2015; Amarasiri et al., 2020; Ali et al., 2021; Buriánková et al., 2021; Guo et al., 2021; Markkanen et al., 2021; Obayiuwana et al., 2021; Yoo and Lee, 2021; Zhang et al., 2021). It was estimated that for the production of aquaculture animals, the global consumption of antimicrobials which was 10,259 tons in 2017 is projected to register an increase of 33% to 13,600 tons by 2030 (Schar et al., 2020). Different ARBs and ARGs had been frequently detected in groundwater (Singh et al., 2020; Kunhikannan et al., 2021), surface water (Deng et al., 2016; Binh et al., 2018), wastewater (Karkman et al., 2018; Nguyen et al., 2021), sediments (Liang et al., 2013; Xu et al., 2014; McInnes et al., 2021) and marine water (Buschmann et al., 2012; Shimizu et al., 2013; Vilca and Angeles, 2018). A brief systematic review of the literature aptly highlights the growing menace of ARBs and ARGs in fresh and marine water environments along with the contamination of different antibiotics (**Supplementary Table S3A**).

Both culture-dependent and culture-independent (metagenomics) studies have contributed to our understanding of the AMR problem. The combination of culture-dependent and culture-independent metagenomic techniques is reported to provide better retrieval of ARGs than either method alone (Korzeniewska and Harnisz, 2012; Fenske et al., 2020). Metagenomic studies provide an avenue to study the uncultivable total microorganisms (Forbes et al., 2017). A metagenomics study of municipal wastewater and hospital wastewater revealed the presence of tetracycline, beta-lactam, macrolide–lincosamide–streptogramin resistance gene and multidrug resistance genes ranging from 0.06–0.98 copy/cell, and biocide/metal resistance gene ranging from 0.30–1.99 copies/cell (Zhang et al., 2021). One of the studies reported the presence of different ARGs in the seawater sample at 1.7×10^2 copies/giga base (Zeng et al., 2019). The highest ARG levels of $1.57–700.58 \times 10^2$ copy/ml for penicillin were reported from surface water, whereas $0.37–312.7 \times 10^2$ copy/ml was reported from the groundwater of Sri Lanka. Among the penicillin resistance genes, the highest percentage of bla_{TEM} (700.58×10^2 copy/ml) followed by ampicillin ($0.37–371.7 \times 10^2$ copy/ml) and OPR D (1.57×10^2 copy/ml) resistance genes were reported from aquatic samples, whereas tetM and tetA resistance genes at the levels of $1.35–439.88 \times 10^2$ copy/ml were reported from the surface water samples. Only the tetM resistance gene was reported at 215.99×10^2 copy/ml from the groundwater sample of Sri Lanka (Liyanage et al., 2021). Zhang et al., 2021 reported that the number of ARGs is strongly correlated with the number of biocide/metal resistance genes in the WWTPs with more chemicals (Zhang et al., 2021). The municipal wastewaters had more abundant and diverse ARGs than hospital wastewater. From the urban canals and lakes of Vietnam, different levels of erythromycin, amoxicillin, sulfamethoxazole, ampicillin, clindamycin, tylosin, vancomycin, tetracycline, chloramphenicol, *etc.* were frequently detected (Tran et al., 2019). Metagenomics study of rural and urban water and sediments of Bangladesh reported a significant correlation between ARGs and human origin bacteria ($R^2 = 0.73$; P= < 0.01), suggesting that the release of untreated sewage could act as a driver for the transmission of ARGs in the environment (McInnes et al., 2021). A recent metagenomics study of 79 WWTPs situated in 60 countries reported the differences in diversity and abundance of ARGs among Africa, Asia, North America, South America, Oceania, and Europe (Strange et al., 2021). The Oceanic cluster reported a limited number of ARGs encoding macrolides in high number, whereas Africa, Asia, and South America clusters harbored ARGs representing sulfonamides and chloramphenicol. A study has also reported Vietnam, India, and Brazil to have the most divergent ARG distribution and suggested them as possible hotspots for the emergence of new antibiotic resistance mechanisms (Hendriksen et al., 2019). Several studies reported the prevalence of antibiotics, ARBs, and ARGs in the aquatic environment that was correlated with environmental factors (**Supplementary Table S3A**) (Binh et al., 2018; Tran et al., 2019; Hanna et al., 2020; Anh et al., 2021; Azanu et al., 2021; Duong et al., 2021; Guo et al., 2021; Lai et al., 2021; McInnes et al., 2021; Zhang et al., 2021; Zhuang et al., 2021). A metagenomics study of wastewater in Benin and Burkina showed the prevalence of resistance genes van, blaOXA, blaGES, blaIMP, blaKPC, blaNDM, blaOXA, blaVIM, qnr, and mcr (Markkanen et al., 2021). Recently, a large number of ARGs subtypes, *viz.,* blaNDM-1, blaCTX-M-15, mecA, blaTEM-1, sul1, vanA, blaKPC-2, sul2, blaCTX-M-14, and blaOXA-48 had also been reported in decreasing order from Asia, Europe, Africa, and North and South America (Zhuang et al., 2021).

The major problem to tackle the issue of AMR is existing knowledge gaps comprising incomplete knowledge or information and misperceptions about the use of antibiotics and the relative contribution of the release of ARB or ARGs in the environment from different sources (McCullough et al., 2016; Singh, 2020). Health professionals can play a major role in the prevention and spread of AMR by educating people about the possible risks of inappropriate usage and disposal of antibiotics and contaminated material containing ARBs with ARGs. The effective control of AMR development and spread of ARGs and ARBs can be facilitated by promoting the development of self-contained local wastewater treatment modules, use of antibiotics/antimicrobial degrading contraptions, and implementing strategies to minimize the concentration of antibiotics required for treatment, including the use of nanotechnology (Malakootian et al., 2019; Singh, 2020; Kaur et al., 2021; Singh et al., 2022).

AMR/AR has the potential to threaten human health and inflict huge blows to the economies of both developed and developing countries (Ventola, 2015; World Health Organization, 2021). Estimates for Europe, the United Kingdom, Thailand, and the United States, the project substantial increase in health costs from antibiotic-resistant bacterial infections (Da Silva et al., 2006; World Health Organization, 2015; Osińska et al., 2016; Abdel-Rahman et al., 2020; Obayiuwana and Ibekwe, 2020; Yoo and Lee, 2021). The waterborne AMR is causing an economic impact of $340-$680 billion annually on the health care system (World Economic Forum, 2021). The waterborne AMR is contributing about $1 to $5 billion per year in additional health care expenditure, and it is expected to increase as resistance develops further. The waterborne AMR could be responsible for about 3.5 million additional sicknesses annually at the cost of $300 million (World Economic Forum, 2021). The alarm of AMR crisis raised in recent times by various bodies such as WHO, FAO, CDC, World Bank, etc. (World Health Organization, 2018; Mulani et al., 2019; Centers for Disease Control and Prevention, 2019; Centres for Disease Control and Prevention, 2021) also calls for the strengthening of the synthesis and discovery pipeline of new antibiotics with better activities or activity against various antibiotic-resistant pathogens (**Supplementary Table S5**). Development of new more potent antibiotics with different or multiple modes of action, along with focused steps to curb AMR development and dissemination to pathogens, is required (Mulani et al., 2019; Singh, 2020; Léger et al., 2021). AMR, being a multidimensional problem, requires a proactive holistic, constructive, collaborative, and synergistic strategy and action by different stakeholders to comprehensively implement a One Health Approach to overcome the unfolding AMR crises.

CONCLUSION

The continued antimicrobial overuse, misuse, and uncontrolled contamination of the environment throughout the world are turning the AMR issue into a global health crisis. The tackling of the AMR situation requires implementation of new policies that limit the release of antimicrobial residues into the environment and support appropriate monitoring to minimize their buildups and timely removal. More research efforts are needed toward understanding the extent and mechanistic underpinnings of AMR development and ARG transfer to other pathogenic bacteria to develop better control strategies. The involvement of the public to locally manage and dispose of the antimicrobials and AMB remains a potential area of collaboration and policy development to control the AMR crisis as it could promote both a sense of responsibility and awareness.

AUTHOR CONTRIBUTIONS

SS conceptualized, supervised, prepared, and finalized the manuscript. RK, AKS, and SS prepared the first draft. SV provided critical inputs. RK, AKS, SV, and SS together revised the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fenvs.2022.830861/full#supplementary-material

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