

Antibiotic-resistant bacteria in natural water bodies: causes, routes, and remedies

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9.1 Background

Antibiotic resistance (AR) has been a major global health concern, especially with the inception of various ailments that arise through the emergence of different causative organisms that necessitate the use of antibiotics. Antibiotics have been widely used due to their

contribution to the improvement of human and animal health, and their importance to optimum productivity of crops. It has played a remarkable role in the increase of life expectancy recorded in the latter half of the 20th century (Qiao et al., 2017; Kumar et al., 2020). However, a lack of awareness of the various hazards resulting from the use of antibiotics has contributed to the emergence of AR (Komolafe, 2003; Odonkor and Addo, 2011). Indiscriminate use of antibiotics has increased the process of AR, making diseases such as wound infections, tuberculosis, gonorrhea, pneumonia, and related diseases resist treatment using antibiotics drugs. In addition, their imprudent uses have also contributed to the extensive presence of their metabolites, their multiple antibiotic-resistant bacteria (ARBs) and their functional genes in human and animal wastes, in water, in landfills and their leachates, in soil and their sediments, and water-dependent food crops (such as sea-food and produce). The sad story is that this resistance continues for extended periods in many environmental compartments, even after the cessation of antibiotics (Sultan et al., 2020; Akinyemi et al., 2011). The abusive use of many of these antibiotics both in human and animal medicine is well reported.

This chapter, therefore, focuses on the presence of ARBs in water bodies and their impacts on these vital environmental compartments. The long abusive usage history of these antibiotics and other antimicrobial agents have caused the widespread contaminants of their resistance bacteria and genes in water and its related components including wastewater, aquaculture, agriculture water, and infected drinking water. All the roles of these components in the evolution and dissemination of the ARBs were further discussed in this chapter.

9.2 Bacteria

Bacteria are single-cell microscopic organisms that can be found in diverse environments such as soil, animal or man body, plant, water, etc. They are the simplest anatomical, oldest, and most available organisms on earth. They have many important roles in the ecosystem, as they are decomposers that enable the production and distribution of substances that are essential to other organisms. In addition, they are important in the fixation of the nitrogen and carbon cycle. However, some other bacteria are deadly as they cause different types of diseases in humans (Alberts et al., 2002). Bacteria exist in various forms, with slight differences in their characteristics, they are classified primarily based on their metabolic and genetic characteristics. Moreover, their characteristics tend to change as they grow, and this depends on their growth conditions. Infections caused by bacteria can be categorized as aerobic infections or anaerobic infections. Aerobic infections are caused by bacteria that require oxygen for survival and growth. These bacteria can be found in aerated soil which contains organic carbon, as they dominate soil rich in moisture and oxygen content (Singh, 2016). While anaerobic infections are caused by bacteria that do not require oxygen, they live, thrive, and grow in an oxygen-depleted environment. These bacteria exist in deep soil (Singh, 2016). In the human body system, anaerobic bacteria can be found in the mouth, gastrointestinal tract, vagina, and skin. They cause infection when there is damage to body tissue, poor supply of oxygen and leads to infection of wounds, dental diseases, tissues, and internal organs where oxygen is deficient. Infections caused

by anaerobic bacteria are characterized by the foul smell pus, tissue destruction, and abscess formation. Hence, these infections are severe and life-threatening (Brook, 2017).

9.2.1 Essence and effect of bacteria

Bacteria have many positive effects on humans as we cannot survive without them, they live in our digestive tracts to help in the digestion of food, produce vitamins and perform some other vital roles in the human system. On the other hand, bacteria also cause different deadly infections in humans, such as pneumonia, sepsis, wound infections, and sexually transmitted diseases such as gonorrhea. Some infections are spread through water and food media by bacterial pathogens such as *Salmonella*, *Campylobacter*, *E. coli*, etc. Also, infections can be transmitted directly or indirectly from animals to humans, these are referred to as zoonotic infections. Sexual infections are transmitted by bacteria such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

9.2.2 Control of bacteria

Bacteria can be controlled by different means and this includes destroying it at high temperatures, disinfection through chlorination, ozonation, and ultraviolet radiation. In addition, Bacteria infection can also be controlled using antibiotics in the right dose or concentration. The use of antibiotics in a hygienic condition to treat infections has immensely lessened the rate of mortality from bacterial diseases.

9.3 Antibiotics, antibiotic resistance and antibiotic-resistant bacteria

9.3.1 The concept and classification of antibiotics

For over a century, several classes of antibiotics have been manufactured and used all over the world for various purposes, especially after the significant discovery of penicillin by Fleming (1929). Antibiotics, because of their easy access and availability in a wide sense, and in addition to their detrimental effects on human health and the ecosystem have been termed an emerging class of pollutants (Hoa et al., 2011). They have been seen at a great concentration in water bodies, soil components, and biota all over the world (Carvalho and Santos, 2016; Binh et al., 2018; Danner et al., 2019; Felis et al., 2020; Kovalakova et al., 2020; Lyu et al., 2020). Based on their effects or mode of action against bacteria or microorganisms, antibiotics are generally classified as bacteriostatic (which is preventing the development and reproduction of bacteria without killing the cells) and bactericide (which is destroying bacterial cells thus causing heavy damage) (Roose-Amsaleg and Laverman, 2016; Dincer and Yigittekin, 2017). Good examples include tetracyclines, β -lactam antibiotics, and fluoroquinolones (Brandt et al., 2015).

Over time, some definitions have been put forward by different scholars and researchers in explaining the concept of antibiotics. Few of these are presented as follows:

1. Antibiotics are substances produced either entirely or partly by microorganisms and are used “originally” for the treatment and/or prevention of bacterial infections (Bouki et al., 2013; Brandt et al., 2015).
2. Antibiotics are bioactive substances that kill or stunt the growth of the microorganism and have a high effect on synthetic or biological origin (Topal et al., 2015).
3. Antibiotics are a class of secondary metabolites produced by microorganisms that inhibits the growth, survival, and replication of bacteria within or on the body (Serwecinska, 2020; Ben et al., 2019).
4. Antibiotics are drugs, taken orally, intramuscularly, or intravenously, that counter an infection (Drlica and Perlin, 2011).
5. Antibiotics are defined as chemical substances derived from microorganisms, which can inhibit growth, and even destroy other microorganisms in a dilute solution (ICON, 2003).
6. Antibiotics are a diverse group of chemicals that can be grouped by either their chemical structure or mechanism of action (Kummerer, 2009).

Presently, antibiotics are not limited to bacteria only, they can also be referred to as antifungal and antiparasite because of their effectiveness against other forms of microorganisms such as protozoa, viruses, etc. (Kummerer, 2009). Although, some have equated antibiotics to antibacterials alone there exist nowadays many antiviral and antifungal agents that are just as antibiotic as antibacterial penicillin. Every year the production of antibiotics increases, which has been estimated to be about 100,000–200,000 tons (Serwecinska, 2020). Since the discovery of antibiotics many years ago, it has proved to be essential to life in numerous ways, without it many lives could have been lost from an open cut or minor surgeries. Besides antibiotics common use in treating infections, it has been supplemented as additives in livestock feeding (Bouki et al., 2013; Aminov and Mackie, 2007). Some of the antibiotics which can be grouped by their chemical structures or mechanism of action include penicillins (β -lactam antibiotics, such as amoxicillin, cephalosporins), aminoglycosides (such as gentamicin, tobramycin, and amikacin), quinolones (such as ciprofloxacin, levofloxacin, and ofloxacin), macrolide antibiotics (such as erythromycin, clarithromycin, and azithromycin), tetracyclines (such as tetracycline and chlortetracycline), lincosamides (such as clindamycin) and Sulfonamide antibiotics (such as sulfisoxazole and trimethoprim).

From the molecular perspective, antibiotics are designated as small molecules (usually of low molecular mass less than 1500 kDa) which get involved with specific life processes of pathogens, and when these antibiotics enter a pathogen, they attach to a specific component and prevent that component from functioning (Drlica and Perlin, 2011).

9.3.2 Sources and route of antibiotics

The outstanding discovery of antibiotics has been ruined by the flexible behavior and nature of bacteria over the years. Join to that is the abuse consumption of antibiotics without adequate prescription which has wreaked havoc on human health and the environment at large (Berkner et al., 2014). Generally, antibiotic residues and AR microorganisms have the aquatic and soil environment as their main reservoir (Manyi-Loh et al., 2018;

Samie et al., 2012). Concerning surface and groundwater sources, wastewater generated from various industries and sectors such as hospitals, pharmaceuticals, food and dairy, farmlands, and so on is the main source of antibiotic pollution in the environment. Second, to this is the ones consumed by animals and humans which are then egested via feces and urine. As these wastes are being released, they are used as fertilizers (especially animal waste). By this, the antibiotics find their route into agricultural lands contaminating the plants. Fig. 9.1 depicts a typical route of antibiotic residues in the environment and its interaction with the ecosystem in general.

9.3.3 Interrelationship of antibiotics and bacteria

The interrelationship of antibiotics and bacteria explains the theory and mechanism of how antibiotics kill bacteria and how bacteria resist antibiotics. The understanding of how antibiotics induce bacterial cell death has been focused on the important cellular function inhibited by the primary drug-target interaction. Antibiotics are known to either induce cell death using bactericidal drugs or inhibit cell growth via bacteriostatic drugs (Kohanski et al., 2010). Existing antibiotics or antimicrobials have been reported to inhibit DNA synthesis, RNA synthesis, cell wall synthesis, or protein synthesis (Walsh, 2013). More effective antibiotics have been developed via the understanding of drug-target interactions and drug molecule modification.

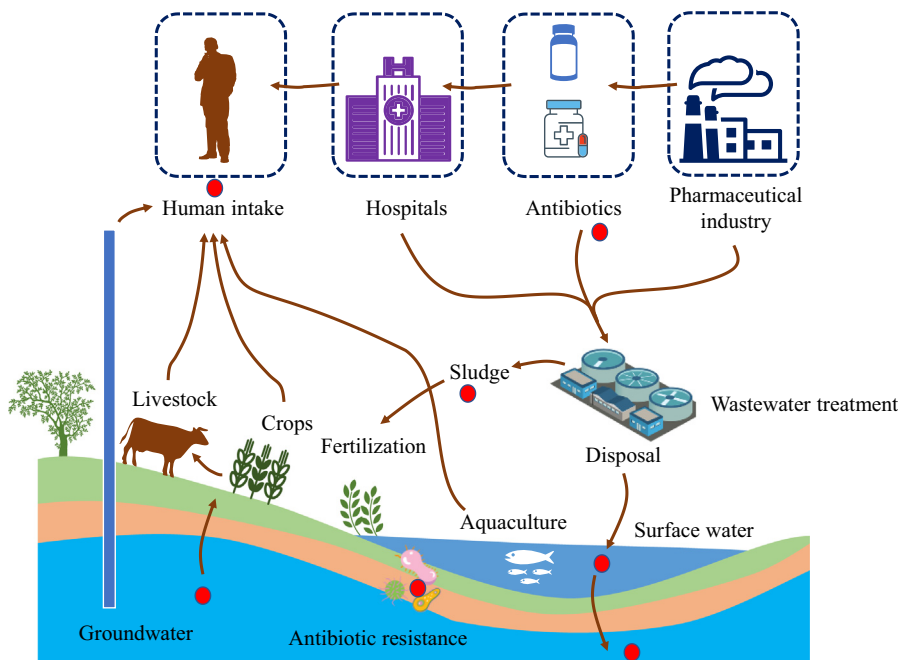


FIGURE 9.1 The sources and routes of antibiotic residue in the environment and their relationship to the ecosystem.

On DNA synthesis, antibiotics that strive to prevent DNA synthesis in a cell will keep a bacterial population from growing and this action may kill affected cells in the long term. Replication of DNA in a cell is a complex process, therefore DNA synthesis machinery includes enzymes known as DNA gyrase and topoisomerase which both assist in the twisting and untwisting of DNA during replication (Drlica et al., 2008). However, some antibiotics such as ciprofloxacin work by aiding topoisomerase to only cut DNA but not attach the ends back together. This then ceases the bacterium to no longer replicate its DNA, thus keeping the bacterial population under control (Guilfoile, 2007). As a matter of importance, this process of DNA damage can activate the death process of the bacterial cell in some bacteria. For RNA synthesis, an enzyme known as polymerase is needed and this enzyme is essential for all types of cells (including bacterial and human cells). Antibiotics such as rifampin can target this enzyme and prevent it from binding to bacterial RNA polymerase to produce RNA. This consequently results in the loss of new protein synthesis and because cell survival is dependent on the continuous supply of these new proteins, these antibiotics will eventually kill the bacteria cell (Campbell et al., 2001; Kohanski et al., 2010).

9.3.4 Common existing antibiotic groups

9.3.4.1 *Beta-lactams antibiotics*

Beta-lactam antibiotics are one of the most common existing antibiotic drugs which have been prescribed to tackle bacterial infectious diseases. They have been largely beneficial in the management and treatment of bacterial infections since their advent in the early 20th century (Pandey and Cascella, 2021). These antibiotics contain a beta-lactam ring found in the nucleus and it causes the antibacterial effect of molecules. They have similar features to other class of drugs which comprises one nitrogen and three carbon rings that are highly reactive (Oncul and Antibiyotikler, 2002). These antibiotics have several clinical indications. They have bactericide effects which include the influencing of cell walls consisting of murine bacteria (Thakuria and Lahon, 2013). Some popular antibiotics in this group include penicillin, cephalosporins, carbapenems, cephalosporins, monobactams, and ampicillin.

9.3.4.2 *Tetracycline antibiotics*

Tetracyclines antibiotics are a group of antibiotics popular for inhibiting bacterial protein synthesis by preventing the association of aminoacyl-t-RNA with the bacterial ribosome (Hlavka et al., 1992; Chopra, 1985). They were discovered in the 1940s and they exhibit activity against a broad range of Gram-positive and Gram-negative bacteria because of their wide-spectrum influence. In addition, they have been extensively used in human and animal infections therapy owing to their excellent property which is the absence of major adverse side effects (Chopra and Roberts, 2001). Other applications include malaria prevention caused by mefloquine-resistant *Plasmodium falciparum* and animal feeds to act as growth promoters, especially in the United States. For tetracyclines to interact with their target, there is a need for traversing one or more membrane systems depending on whether the susceptible organism is Gram-positive

or Gram-negative. This is also due to their inhibiting bacterial protein synthesis by preventing the association of aminoacyl RNA with the bacterial ribosome (Chopra et al., 1992). They affect different types of bacteria and they are highly effective against *Mycoplasma* sp., *Chlamydia* sp., *Rickettsia* sp., *Leptospira* sp., *Spirochaete* sp., and some protozoa (Gurses, 2015).

9.3.4.3 Vancomycin antibiotics

Vancomycin antibiotics are in doubt one of the most used antibiotics in history. It is a glycopeptide antibiotic isolated from a strain of *Streptomyces orientalis* discovered in the mid-1950s in a soil sample (Murray and Nannini, 2010). Its use gained popularity because of the evolution of *Staphylococcus aureus*. Vancomycin exerts its action by binding to a D-alanyl-D-alanine cell wall precursor important for peptidoglycan crosslinking and thus inhibiting bacterial cell wall synthesis. Unlike tetracyclines, Vancomycin has a narrow antibacterial spectrum that is only against most Gram-positive species (with the inclusion of Streptococci and Staphylococci) (Chang et al., 2003; Gurses, 2015). There is adequate knowledge of the changing minimum inhibitory concentrations to select the proper dosage and despite its vast usage over the years, there are still more questions than answers over its optimal use in treatment (Schilling et al., 2011).

9.3.4.4 Aminoglycosides antibiotics

Aminoglycoside antibiotics have a history of use in clinical practice since the 1940s when it was discovered (Ramirez and Tolmasky, 2010). They are broad-spectrum antimicrobials that exhibit activity against both Gram-negative aerobic bacteria and staphylococci (Germovsek et al., 2017). In their early year of discovery, they were surety remedies for tuberculosis and other serious bacterial infections, and they remain relevant today in chemotherapy treatment (Forge and Schacht, 2000; Germovsek et al., 2017). Aminoglycoside antibiotics have a low molecular weight of approximately 300–60 Da and all their types (both natural and semisynthetic) usually possess similar structures having several rings. They contain an aminocyclitol ring on which amino sugars are hinged by glycosidic linkages or bonds. The aminoglycosides include gentamicin, amikacin, tobramycin, neomycin, and streptomycin but their explanation is not covered in this chapter (Becker and Cooper, 2013).

9.3.4.5 Chloramphenicol antibiotics

Chloramphenicol can be described as a synthetically manufactured broad-spectrum antibiotic which in 1948 was initially isolated from the bacteria *S. venezuelae*. This achievement, therefore, put it in the class of the first bulk-produced synthetic antibiotic (Ehrlich et al., 1947; Erel et al., 1999). It belongs to a class of antibiotics that inhibits protein synthesis. Chloramphenicol stops bacterial growth by binding to the bacterial ribosome (blocking peptidyl transferase). Because of its lipid solubility, it can easily diffuse via bacterial cell membrane which then reversibly binds to the L16 protein of the 50S subunit of bacterial ribosomes, where transfer of amino acids to growing peptide chains is prevented. This thus inhibits peptide bond formation and subsequent protein synthesis (Oong and Tadi, 2021). It is very effective in combating various susceptible and serious bacterial infections; however, it is not always used owing to its side effects in long antibiotic courses causing neurotoxicity

and hematologic disorders (Dinos et al., 2016). It is a medication with vast application in the treatment and management of superficial eye infections such as bacterial conjunctivitis, and otitis externa. It is also useful in the treatment of typhoid and cholera and is sensitive to coke, aerobic, anaerobic Gram-positive bacilli, and most of the Gram-negative bacteria (Alcamo, 2001; Oong and Tadi, 2021).

9.3.4.6 *Macrolides antibiotics*

Macrolide antibiotic was first isolated from a *Streptomyces* strain in 1950 and was christened pikromycin due to its bitter taste (Brockmann and Hekel, 1951). It is a class of antibiotics including erythromycin, roxithromycin, azithromycin, and clarithromycin useful in treating respiratory, skin, soft tissue, sexually transmitted, *H. pylori*, and mycobacterial infections (Seiple et al., 2016). Macrolides interfere with bacterial protein synthesis and, depending on concentration and bacterial species, are either bactericidal or bacteriostatic and they have a broad spectrum of activity against many Gram-positive bacteria (Livertox, 2012). They also have immunomodulatory and antiinflammatory effects, which can be beneficial in some situations such as the treatment of cystic fibrosis. Macrolides are effective against Gram-positive (excluding enterococci) and some Gram-negative bacteria (Rossi, 2011). They are classified according to the size of the macrocyclic lactone ring as being either 12-, 14-, 15- or 16-membered ring macrolides with the majority of macrolides containing amino sugar and/or neutral sugar moieties connected to the lactone ring via a glycosylic bond (Dinos, 2017). Just like chloramphenicol antibiotics, macrolides antibiotics inhibit protein synthesis that is dependent on RNA in bacteria by preventing the continuity of the peptide chain and adhesion of t-RNA by binding 70S ribosome to 50S subunit (Allen, 2002).

9.3.4.7 *Quinolones antibiotics*

Quinolones antibiotics are an important family of antibiotics which have gained popularity as therapies in treating both community-acquired and severe hospital-acquired infections since their discovery in the early 1960s (Bisacchi, 2015). The first quinolone antibiotic was reported in 1962 and regarded as nalidixic acid which is part of the 1-alkyl-1,8-naphthyridines series (Leshner et al., 1962). Because of its broad spectrum of activity, high potency, easy bioavailability, convenience of formulations, high serum concentrations, and low side effects, it has been widely used and accepted as a beneficial antibiotic for more than five decades (León-Buitimea et al., 2020). They inhibit the DNA synthesis of bacteria by disrupting the bacterial topoisomerase type II; inhibiting the catalytic activity of DNA gyrase and topoisomerase IV (Anderson and Osherooff, 2001). The activity of the first-generation quinolone was restricted to only Gram-negative organisms, excluding *Pseudomonas* species but this was short-lived after the clinical introduction of nalidixic acid. Rapid resistance was developed in some organisms shortly after its introduction which thus reduces its effectiveness. This is what therefore led to the investigation and discovery of similar antibiotics with improved properties (Gellert et al., 1977; Pham et al., 2019).

9.3.5 The concept of antibiotic resistance and antibiotic-resistant bacteria

Understanding antibiotics is an aspect of achieving one of the important goals of the United Nations on sustainable development goals (SDGs) but it is more pertinent to understand the threat posed by antibiotic-resistant microbes/pathogens to completely achieve a sustainable universal health state. When antibiotics were first discovered in the 20th Century, it was greatly limited but further discovery gave birth to penicillin and streptomycin, bactericidal antibiotics, broad-spectrum bacteriostatic antibiotics, synthetic chemicals, and so on narrowing the broad spectrum of antibiotics to mainly clinical medicine (Baldry, 1976). Notwithstanding, abuse of antibiotics has gradually resulted in the emergence of ABR thus causing global health concerns (Komolafe, 2003). In 2017, the World Health Organization (WHO) published a list of antibiotic-resistant priority pathogens consisting of 12 important bacteria families, considered to pose the greatest threat to human and animal health in the nearest decades (World Health Organization, 2017). The infections of these bacteria are forecast to result in approximately 10 million death all over the world by the year 2050 (O'Neill, 2016). The insusceptibility of target bacterial populations to antibiotics is referred to as AR. Simply put, when bacteria sustain the ability to resist the effect of an antibiotic to which they were previously submitted/sensitive, then the phenomenon is described as AR and these resisting bacteria are referred to as ARB. Another key definition of AR as stated by Drlica and Perlin (2011) is "the capability possessed by a *particular* pathogen population to grow in the presence of a *given* antibiotic when the antibiotic is used according to a *specific* regimen." This definition is more specific and detailed for some reasons: (i) there are varieties of pathogens thus making their susceptibility to antibiotics differ, (ii) that a pathogen is resistant to one antibiotic does not necessarily affect the susceptibility to other antibiotics, and (iii) a specific regime of treatment is vital in properly defining the resistance level of a pathogen. The determination of dose falls between toxicity and effectiveness. Therefore, the dose can be changed to make treatment more or less effective or more or less dangerous (Drlica and Perlin, 2011). Ndagi et al. (2020) reiterated on bacteria or pathogen resistance to antibiotics has been relative in terms of the dose of exposure to an antibiotic. Hawkey (1998) had previously explained this relativity stating that the most resistant bacterium has the greatest possibility of being inhibited or killed by a sufficiently high concentration of antibiotics. However, he strengthened his thought by stating the inability of most patients to tolerate the high concentration required to kill/inhibit the bacteria. ARB infections usually lead to an increase in morbidity rate, mortality rate, and long hospital stay (Cosgrove, 2006). Meanwhile, its control in such states demands that higher doses of antibiotics or a different antibiotic treatment be used or applied.

AR is highly related to evolution which occurs when there is an information change in the DNA molecules and when these changes happen, the phase change(s) is/are called mutation(s) while the organism transformed is called a mutant. This AR mutant is a cell that has acquired a change in its genetic material which has led to the loss of susceptibility to a given antibiotic or class of antibiotics. Generally, AR can be classified into three major types and each category requires a different solution. They are natural or intrinsic resistance, acquired resistance, and transmitted resistance. Natural resistance is possible in bacteria against some antimicrobial agents or groups. This is known as intrinsic resistance.

Their resistance involved bacteria species that are not affected by antibiotics. There is little or no approach that can be taken when it comes to its treatment except to produce vaccines and adopt efficient control infection practices that drives the bacteria/pathogens away from human (Regea, 2018; Drlica and Perlin, 2011). On the contrary, these bacteria can by various mechanisms obtained or build resistance to antibiotics and one of those mechanisms which are very key is mutation. This form of resistance is termed acquired or artificial resistance (Prescott, 2008; Regea, 2018). Mutations are a useful method for bacterial survival in the face of antibiotics; they usually occur when bacteria are exposed to a lower concentration of antibiotics but when there is an emergence of a resistant mutant, the antibiotic eliminates the susceptible population and the resistant bacteria prevail (Ndagi et al., 2020). A mutation conferring resistance to antimicrobials may occur in different parts of the genome, and it may be passed between populations via many mechanisms (Sultan et al., 2018). From a microbial perspective, there are three classifications of antimicrobial resistance determinants based on the source of the mutated gene (Lorian, 2002). They are foreign DNA acquisition, preexisting genetic determinants mutations, and acquired gene mutations. Foreign DNA acquisition in bacteria can occur by transformation, conjugation, and transduction. In brief, transformation focus on the uptake of naked DNA; conjugation refers to plasmid-mediated mating between cells in contact; and transduction involves infection of the bacteria by a nonlethal bacteriophage carrying bacterial genes (Sultan et al., 2018). Meanwhile from a molecular perspective, mutation undermines the interaction between the drug atoms and those of the amino acid from the bacterial enzyme. Therefore, the molecule's drug potency would be compromised and the drug-receptor resident-time would be shortened. In most cases, cell homeostasis is affected by mutational changes leading to resistance (Sultan et al., 2018) and most often with an irreversible reduction in drug fitness (Ndagi et al., 2020). One viable option to slow down the bacteria action is to reduce the consumption of antibiotics or engage the use of a dose that can counteract the growth of the mutant.

9.3.6 Causes of antibiotic resistance and antibiotic-resistant bacteria

AR does not occur naturally without some triggers/causing factors. Some of these factors have been highlighted by Iwu et al. (2020). They include antibiotics overuse, incorrect antibiotic prescriptions, extensive/prolonged antibiotic use in agriculture/veterinary sectors, regulatory barriers, availability of few new antibiotics, and nonexposure to antibiotics. They are briefly explained as follows:

Antibiotic overuse: Antibiotics have been severally used in various applications worldwide. To start with, they have been traditionally utilized for the treatment of bacterial causing diseases in various animals, and plants (including ornamental plants) (Kumar and Pal, 2018). Furthermore, they have been employed extensively in medical, veterinary, and agricultural studies for therapeutic, prophylactic, metaphylactic, and growth-promoting purposes, and the largest consumed antibiotics group by a human is the beta-lactam antibiotics such as penicillins, cephalosporins, and carbapenems (Kumar and Pal, 2018). Antibiotics have also found their usage in animal breeding by increasing the protein content of the meat while decreasing its fat (Gaskins et al., 2002). They are also engaged in

fruit production and beekeeping (Iwu and Okoh, 2019). As a result of its vast usage, a link has therefore been established connecting the evolution of AR to antibiotic use. When there is excessive consumption of antibiotics, drug-sensitive bacteria are eliminated and resistant bacteria are therefore left to proliferate through natural selection (CDC, 2013; Read and Woods, 2014).

Incorrect antibiotic prescriptions: When antibiotics are wrongly prescribed, they could result in AR in bacteria. Luyt et al. (2014) revealed that in about 30%–50% of clinical cases and treatment regimens, the choice of antibiotic and period of antibiotic therapy is not correct. Incorrect antibiotic prescription often results in problematic therapeutic effects that may potentially bring clinical complications to patients (Lushniak, 2014). Meanwhile, sub-therapeutic antibiotics concentration may result in AR thus promoting gene modifications (Viswanathan, 2014).

Extensive/prolonged antibiotic use in agriculture/veterinary sectors: Globally, antibiotics have been used to improve livestock yield via their feeding. This is also proposed to help the health of the animals and improve the quality of their product (Bartlett et al., 2013; CDC, 2013; Michael et al., 2014). Unfortunately, their overuse has affected humans via ingestion of their residues in animal meat and the long run suppresses nonresistant bacteria and permits resistant strains to thrive (Golkar et al., 2014). Moreover, several pieces of information on the evolution and persistence of veterinary antimicrobial agents (VAMAs) residues in animals have been reported globally (Beyene, 2015). In the same vein, antibiotics usage in agriculture has received immense attention too. It has been reported that approximately, 90% of the antibiotics consumed by livestock are egested via feces or urine and dissipated into manure, groundwater, and surface runoff (Bartlett et al., 2013; CDC, 2013). Contamination of four main spheres of the ecosystem which include soil, plant, water, and air by VAMAs have also been lately reported (Sun et al., 2017; Yang et al., 2016; Bartrons and Peñuelas, 2017; Hussain et al., 2016; Chen et al., 2018; Ding et al., 2017; Dong et al., 2016; Zhang et al., 2018; McEachran et al., 2015). ARB selection is enhanced by VAMAs within the environment, subsequently causing serious ecological, plant, and human health problems even at low concentrations (Kuppusamy et al., 2018).

Regulatory barriers: The pursuit of approval for antimicrobials discoveries and development has encountered several bottlenecks. Licensing fluctuation, clinical trial requirements variations, ineffective communication channels, and regulatory rules have all characterized this barrier (Piddock, 2012). Formulating and implementing policies to curb the threat posed by AR have not yielded positive outcomes in several countries and this situation has been influenced by factors such as political will, insufficient funding, poor legal and regulatory framework, and lack of data and technical capacity (IACG, 2018; World Health Organization, 2016).

Availability of few new antibiotics: Investing in the production of a more or new antibiotic is considered an unwise investment by most pharmaceutical companies because the return on production is far less compared to other drugs engaged in treating chronic and terminal diseases such as diabetes, asthma, cancer and psychiatric disorders (Golkar et al., 2014; Wright, 2014). This has therefore resulted in a reduction in the research for new antibiotics. In addition, except in the case where patients are faced with serious illness, most physicians are reluctant in prescribing new antibiotics immediately. They would rather prefer to prescribe existing antibiotics that have shown relative efficacy even though AR can still

occur in the process (Golkar et al., 2014; Gould et al., 2013). To make the matter worst, these physicians are often in fear that prescribing new antibiotics does not totally guarantee the prevention of AR but could also rather promote it (Gould et al., 2013).

Nonexposure to antibiotics: This is the fundamental and the major cause contributing to the accumulation of AR. Studies have shown that there are tendencies for the persistence, accumulation, evolution, and dissemination of AR in the absence of exposure to antibiotics (Andersson & Hughes, 2010; Iwu and Okoh, 2019). Bacteria usually become resistive to antibiotics by altering the target site of the agent mutagenically in a way that they do not influence their target anymore. This phenomenon is often acquired via horizontal gene transfer (HGT).

9.4 Antibiotic-resistant bacteria and natural water bodies

9.4.1 Forms of natural water bodies in the ecosystem

Water constitutes about 71% of the universe and therefore is very important to the sustainability of life and economic development (Annan, 2005; Ugya et al., 2018; Ilori et al., 2019; Akosile et al., 2020; Adewumi et al., 2020; Opafola et al., 2020). It is an important point of focus in the United Nations SDGs which is either a standalone goal or it is interconnected with other goals (Keesstra et al., 2016; Ajibade et al., 2015). A greater proportion of water in the earth's surface exists in water bodies while the remaining fraction exists as a suspension in the air as vapors, which usually come as precipitation (Khatri and Tyagi, 2015). The most common existing natural water bodies include the seas and oceans, lakes, rivers, ponds, gulf, bay, lagoons, and so on. Approximately 96%–97% make up the sea and ocean water bodies while the rest 3%–4% are shared by the groundwater, glaciers, and ice caps both in the Arctic and Antarctic regions.

9.4.2 Antibiotic-resistant bacteria in natural water bodies

One of the major habitats for bacteria on the earth is water. It serves as a major way of easy dissemination medium and also a massive reservoir for AR (Rizzo et al., 2013; Zhang et al., 2009). Several mechanisms have been used to describe this microbial habitat. It may represent the source of resistance genes, act as a bioreactor or make easy the exchange of genes between nonpathogenic and pathogenic bacteria (Baquero et al., 2008; Vaz-Moreira et al., 2014). Several water bodies exist that have been researched for AR and their various effects and impacts as host for ARB on both human health and the environment at large has been largely documented (Bondarczuk et al., 2016; Blaak et al., 2015). Three categories of these water bodies namely freshwater (surface water and groundwater), aquaculture ecosystem, and irrigation water are broadly discussed in the following sections.

9.4.2.1 Freshwater bodies

Freshwater bodies (such as streams, lakes, dams, and rivers) representing a vast aspect of the ecosystems have become a lively domain for resistance evolution and HGT of antibiotic-resistant genes (ARGs) (Nnadozie and Odume, 2019). Most findings on the

evolution and type of AR have largely focused on the clinical settings with limited attention given to the freshwater ecosystem until recently (Chen et al., 2017; Ndlovu et al., 2015; Adelowo et al., 2014). It has been presumed that the antibiotic concentrations in freshwater environments are naturally low, therefore the tendency for resistant bacteria selection occurrence is low. Although, this assumption has been rendered invalid by subsequent studies by showing that, even with a low antibiotic concentration in freshwater environments, the selection of resistant bacteria can occur (Marti et al., 2014; Ndlovu et al., 2015). The occurrence, distribution, and fate of ARBs and ARGs in freshwater environments have mostly been associated with the effluent discharge of wastewater treatment plants (WWTPs) and other factors such as an increase in both industrial and agricultural activities along freshwater bodies' course (Sabri et al., 2018; Chen et al., 2013; Marti et al., 2013; LaPara et al., 2011). Generally, there is usually a high concentration of ARBs and ARGs at the point of effluent discharges from WWTP into streams, but this concentration is gradually reduced downstream of the discharge point (Sabri et al., 2018; Chen et al., 2013). Different factors could be responsible for this reduction in ARGs and ARB's concentration downstream of WWTP effluent discharge points. They include transport, dilution, adsorption, and degradation among which dilution and degradation play a major role in the fate of ARGs in freshwater environments (Collins et al., 2018; Jerde et al., 2016; LaPara et al., 2015; Nelson et al., 2018; Snow et al., 2015; Yoon et al., 2018). Fig. 9.2 depicts the potential spread, transmission, and degradation/dilution of ARBs and ARGs.

Some experimental findings of freshwater bodies harboring ARBs and ARGs are well documented. In South Africa, Odjadjare and Okoh (2010) in their work regarding the prevalence and distribution of *Listeria* pathogens into the final effluents of a rural wastewater treatment facility detected AR *Listeria* spp. harboring the *sulII* (sulfonamide) ARG in

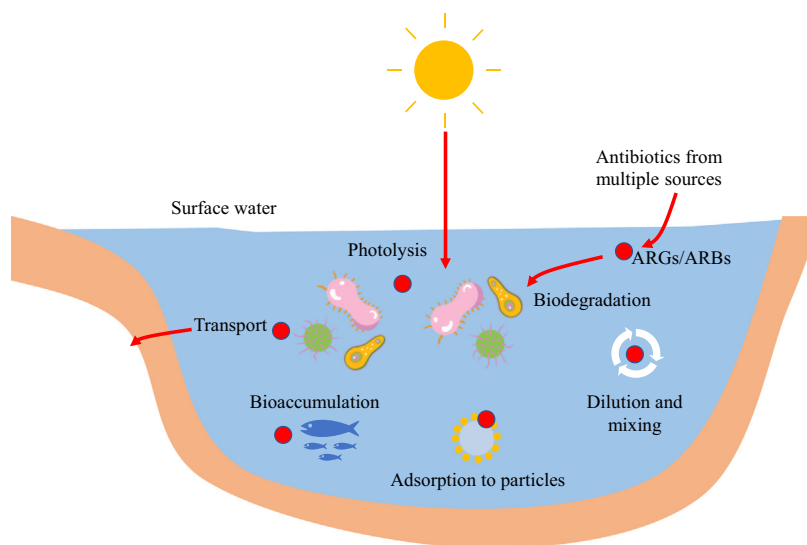


FIGURE 9.2 Antibiotic-resistant bacteria and antibiotic-resistant genes: their spread, transmission, and degradation/dilution.

municipal wastewater effluents which were proposed to be discharged in a freshwater body. Also in South Africa, Adefisoye and Okoh (2016) and Igwaran, et al. (2018) detected AR pathogenic strains of *E. coli* concealing several ARGs belonging to aminoglycosides, phenicols, beta-lactamase, tetracyclines, and macrolide respectively, in final effluents of WWTPs, which was to be discharged into freshwater bodies. In Nigeria, Titilawo et al. (2015) working on the AR determinants of *Escherichia coli* isolates which were recovered from some of the rivers in a state in the South-Western part, detected AR harboring various resistance genes such as the *aacC2*, *aphA1*, *aphA2*, *aadA*, *strA* (aminoglycoside resistance genes), *tetA*, *tetB*, *tetC*, *tetD*, *tetK*, *tetM* (tetracycline resistance genes), *ampC*, *blaTEM*, *blaz*, (beta-lactamases), *catI*, *catII*, *cmIA1* (phenicol resistance genes) and *sulI*, *sulII* (sulfonamide resistance genes) in rivers where anthropogenic activities were carried out frequently. In Spain, Lekunberri et al. (2017) dealing with the bacteriophage and plasmid DNA contribution to the movement of ARGs in Ter River receiving treated wastewater discharges observed that the concentrations of the ARGs including *qnrS* (fluoroquinolone), *ermB* (macrolide), and *tetW* (tetracycline) vary significantly at the upstream and downstream discharge point of WWTP effluent of the River. In China, Chen et al. (2013) in their study on the utilization of appropriate gene indicators to differentiate anthropogenic impacts on ARGs in the Pearl River Estuary (a river known for severe anthropological activities) reported the presence of dominant tetracycline resistance genes including *tetC*, *tetB*, *tetM*, *tetW*, and *tetO*. Also, Ling et al. (2013) working on the occurrence and distribution of ARGs in one of the major rivers in Beijing showed that ARGs such as *tetA*, *tetG*, *tetX*, *tetO*, *tetM*, and *tetC* (tetracycline resistance genes) and *sul1* and *sul2* (sulfonamide resistance genes) were continuously detected in this river. After all, the distribution and occurrence of antibiotics, ARB, and ARGs in freshwater bodies are not limited to the water and sediment alone. They also occur in biofilms and the guts of aquatic animals (Proia et al., 2016; Fu et al., 2017).

9.4.2.2 Aquaculture ecosystem

The aquatic environment is recognized as a reservoir of AR and a channel for possible transmission (Karkman et al., 2018; Suzuki et al., 2017). This situation regarding AR in the aquatic environment is a serious concern especially in developing countries because of ineffective management practices of antibiotic use and antibiotic-related waste (Binh et al., 2018; Kumar et al., 2019). The aquaculture ecosystem has claimed a great stake in the food industry globally. It generates almost half of all seafood which represents about 8% of the total food proteins of animal origin worldwide (Cabello, 2006, Iwu et al., 2020). China tops the list of the producers of aquaculture in the world with about 47.6 million tons produced, followed by India with 5.2 million tons, Indonesia with 4.3 million tons, Vietnam with 3.4 million tons, Bangladesh with 2.1 million tons, Norway with 1.4 million tons and Egypt with 1.2 million tons (FAO, 2017). The dissemination of AR among fish pathogens has economic impacts on the productivity of aquaculture. which also extends to other human pathogens (Cabello, 2006). Similar to the freshwater ecosystem, aquaculture is also regarded as a hotspot for ARBs and ARGs where various genetic activities that often lead to the growth of resistant strains of bacteria occur (Marti et al., 2014; Muziasari et al., 2016). In addition, these resistant bacteria have also found their way into the aquatic environment via aquaculture discharges, treated and untreated sewage, hospital waste, and

agricultural runoff. Therefore, water and sediments which are vital aquatic compartments have played a significant role in driving ARBs' transportation, ecology, and evolution (Taylor et al., 2011). More have been discussed in the previous section on the water with the focus on the evolution, transport, and discharge of ARBs and ARGs in WWTPs. Aquatic sediments are also a sure channel for the occurrence of genetic transfer and recombination. Antibiotics used in these environments are retained and in the long run act as interfaces for a complex and dynamic community of microorganisms, thus facilitating their transfer. Yang et al. (2013) investigated the resistome from marine sediments using high-throughput sequencing and metagenomic analysis. They observed that a lot of contigs shared a high identity with transposons or plasmids from human pathogens. Cummings et al. (2011) in their findings detected five various plasmid-mediated quinolone resistance determinants in the surface sediments obtained from a sewage-impacted coastal wetland along the US–Mexico border while sediments of a close urban wetland not affected by sewage have just three different plasmid-mediated quinolone resistance determinants. Furthermore, Jiang et al. (2012) findings revealed the high levels of ARGs in bacterial strains isolated from fish intestinal samples in a farm fish located in China. Another viable way for the release of antibiotics into water and sediment is via some drugs and metal-containing products used in feeding and treating fishes and also to prevent pollution of the aquaculture. However, in this process, about 70%–80% of these drugs are released into the water which then alters the bacterial or microbial population by choosing the resistant strains of the environmental microbiota (Huerta et al., 2013; BurrIDGE et al., 2010; Seiler and Berendonk, 2012; Ajibade et al., 2021).

9.4.2.3 Irrigation water

Irrigation water is a major source of fresh produce contamination, and it could serve as a potential route of exposure to undesired microorganisms including ARB (Gekenidis et al., 2018). In addition, contaminated fresh produce from the farm can transfer ARB to the consumer, especially when consumed raw (O'Flaherty and Cummins, 2017; EFSA Biohaz Panel, 2013). This incident is common in areas in regions where agriculture is practiced and water is scarce, the water used for irrigation is often reclaimed wastewaters (Christou et al., 2017; Fahrenfeld et al., 2013; Gemmell and Schmidt, 2012). These waters usually become polluted either by direct contact with sewage and manure or by nonpoint pollution sources like agricultural runoffs (Roever, 1999, Gekenidis et al., 2018). Some cases of polluted water sources containing ARBs and ARGs used for irrigation which may be transferred to the food crops or plants are reported (Czekalski et al., 2012; Araújo et al., 2017). Taking for instance the preharvest stage of vegetables cultivated via irrigation water, this phase is usually characterized by dominant contamination of ARBs. In South Africa, Nontongana et al. (2014) in their work detected ARB's strains of *E. coli* in Kat River, South Africa, where the water used for irrigation of the citrus orchard and municipal waterworks is sourced. In Belgium, Holvoet et al. (2013) detected some varying percentages of *E. coli* isolated from rain harvested and borehole water which were used as irrigation water sources for cultivating eight lettuce farms. The *E. coli* were resistant to antibiotics such as tetracycline, ampicillin, streptomycin, sulfonamides, and trimethoprim. There is a high tendency to transfer these strains to the lettuce crops which are consumed without further purification processes. In France, farmland was irrigated for more than

100 years with wastewater and was stopped for about four years. It was then examined for the presence of antibiotics. They discovered that the presence of antibiotics and their concentration on the soil site near the irrigation outlets varies. This outcome suggests that contaminants from irrigation water can be retained in the soil for a long time and can either leach to the groundwater or be absorbed by plants (Tamtam et al., 2011). In China, Chen et al. (2014) examined the occurrence of antibiotics and ARs in soils from wastewater irrigation areas in Beijing and Tianjin. They observed that the soil irrigated with wastewater has more ARBs and ARGs compared to the soil not irrigated at all.

Crucial to all these highlighted research studies is the determination of the number of specific bacteria present in specific irrigation water and a quantitative approach to this has been addressed by Gekenidis et al. (2018). Urgent priority must therefore be given to control the spread of these ARBs via irrigation unto food crops which eventually has potential health risks when consumed. Irrigation water quality monitoring and regulation (with viable and affordable sanitation technologies) thus provide a sustainable way of addressing this concern.

9.4.2.4 Disinfected drinking water

High population densities in urban, semiurban, and even some rural settings have increased the degree of contamination and pollution in water reservoirs. Since a high population also demands a supply of clean and potable water, most of the available water reservoirs such as dams, rivers, lakes, and so on are treated for consumption. However, the total removal of microorganisms from these water or wastewater sources seems impossible because of their high level of contamination in some cases. The provision of safe and clean drinking water thus becomes an essential and basic human right for effective well-being (Vaz-Moreira et al., 2014).

It is believed that disinfected drinking water may contain some bacteria even after disinfection and these bacteria sustain the ability to resist antibiotics. Example of such bacteria are *Sphingobium*, *Sphingomonas*, *Pseudomonas*, and *Acinetobacter* or nonfecal Enterobacteriaceae (Figueira et al., 2012; Narciso-da-Rocha et al., 2013). Tap water, which is one of the trusted sources of drinking water has been reported to display a rich and diversified resistance pattern to some antibiotics such as penicillins, aminoglycosides, and cephalosporins (Vaz-Moreira et al., 2011). ARBs have been studied to be more prevalent in tap than in the water source for some classes of antibiotics (Narciso-da-Rocha et al., 2013; Vaz-Moreira et al., 2012). This has been attributed to the selective effect of the disinfection processes or the preexistence of ARBs downstream of the disinfection point. Although, there is no valid conclusion to support the fact that the water source is the origin of the AR detected in tap water (Narciso-da-Rocha et al., 2013).

9.5 Combating and curbing the impacts of AR and ARBs in natural water bodies: a sustainable approach to water security

Over the decades, the approach to finding effective ways of preventing or curbing the rapid spread of AR and ARBs, especially in water bodies has been challenging (Nnadozie and Odume, 2019). This is because of the easy and quick access water as an environmental

compartment and ecosystem have in harboring and growing microbes of different genes and resistance. As the spread of AR is rapid, even the slightest use of antibiotics will promote the evolution, development, and dissemination of AR. Two well-established methods of adequately curbing the impacts of AR alongside ARBs are limiting antibiotic use and restricting ARB dissemination (Vikesland et al., 2017). As explained in previous sections of this chapter, effluents from WWTPs and hospitals are largely the main contributors of ARBs and ARGs in both freshwater and aquatic ecosystem while irrigation contaminated water and livestock farming serve as pollutant sources of ARBs and ARGs in the agriculture ecosystem. Therefore, focusing on the sources of ARBs in the environment serves as a bail-out system. Some pragmatic approaches which can favor public health by lessening the risk of contamination, that could significantly promote the spread of ARBs are given as follows:

- (i) Provision and implementation of standards and guidelines on the quality of effluent discharge from domestic, hospitals, and industries channels into water bodies.
- (ii) The creation of more effective and efficient methods for treating the wastewater from domestic, hospital, and industries containing ARBs or ARGs before discharging into water bodies is crucial. Existing methods such as ozonation or chlorination used to eliminate pathogens during wastewater treatment are not adequate in eliminating all the genetic materials present in wastewater. The ozonation and chlorination process are liable for AR selection (Li et al., 2016; Chang et al., 2017). Therefore, to prevent the spread of ABRs, their aggressive degradation in wastewater is necessary before discharge into freshwater bodies.
- (iii) Reduction of the use of antibiotics as feed additives in livestock farming with other advantageous substitutes (Tullo et al., 2019) and improving the living condition of the animal will improve their well-being and lessen the dissemination of disease among them.
- (iv) Animal individual distancing activity in conjunction with an appreciable distancing from freshwater bodies will prevent in a great measure the spread of AR. In addition to this, adequate treatment and disposal of their effluent should be ensured.
- (v) Implementation of better waste management strategies backed up by government regulations on the discharge of farm manures should be enforced. Aside from the law implementation of on-farm waste disposal, methods such as anaerobic fermentation and composting can be used to reduce the concentration of antibiotics present in manure.
- (vi) Global and general awareness campaigns and programs (including public media-based awareness programs initiation) that discuss extensively antibiotics, AR, and ARBs and detail their advantages and disadvantages should be staged by global stakeholders in the area of health. A good example of such an agency is the WHO (Tasho and Cho, 2016).

9.6 Conclusion

The existence of ARBs in various environmental compartments and habitats constitutes the natural reservoir of AR and they serve as vehicles between each water body and human microbiota. Imprudent use of antibiotics in all and sundry aspects of the environmental

ecosystem is the principal reason for bacteria gaining resistance, and this has resulted in the emergence of new resistances. This chapter has shed more light on the characteristics nature of AR and ARBs and their impacts on the ecosystems—water bodies being one of the most ideal environmental habitats for AR evolution and dissemination. Bacteria from varying sources such as animals, humans, and other aspects of the environment come together, and their union produces a strong resistance. In addition, residue antibiotics and heavy metals are discharged into water, and this creates an imbalance in ecological activities, resulting in AR. The causes of this AR resistance and their occurrences (including the ARBs or ARGs) in natural water bodies are also explained. This chapter thus serves as an extension and supplementation to research studies on the evolution, dissemination, and grave impacts of AR and ABRs, particularly in natural water bodies.

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