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Review Article

The Emergence of ARB and ARGs in the Environment

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Abstract

The challenges posed by antibiotic resistant bacteria (ARB) and antibiotic resistant genes (ARGs) in the environment has become issues of concern worldwide. Various research findings revealed that the environment perform a crucial function in the dissemination of ARB and ARGs even though little is known about their emergence. Most studies which have investigated ARB and ARGs in the environment focused mainly on the impact of the anthropogenic activity to the environment. However, the background information regarding these ARB and ARGs that are detected in the environment is yet to be fully researched and thus not clearly understood as of now. This review, therefore, aims to close the gap with uncovering the missing scientific information by discussing factors that are responsible for the emergence and the effects of the existence of ARB and ARGs in the environment. Many findings suggest that the advent of ARB and ARGs is strongly linked with the amplified consumption of antibiotics by human beings as well as animals with the intention of growth enhancement in farm animal stock and domestic fowls also as food preservatives. This study provides a suggestion of strategies and measures that can be followed to mitigate the detection of ARB and ARGs in the environment and further dissemination. All the papers reviewed here were retrieved from databases such as Google Scholar, Science Direct and PubMed.

Keywords: antibiotic resistant bacteria, antibiotic resistant genes, antimicrobial resistance in the environment, dissemination, and emergence of resistance.

1. Background and introduction

The increased utilization of antimicrobials has been prominent globally and the excessive detection of these antimicrobials in the wastewater treatment plants, river and marine environment is an evidence (Klein, 2018), (Rizzo Merlin, 2013), (Boy-Roura, 2018), (Kraemer 2019) [1] [2] [3] [4]. The presence of residues and parent molecules of antimicrobials in the oceanic environment is one factor attributed to the emergence of pathogenic antimicrobial resistance bacteria (ARB) as they tend to thrive and survive in the environment through evolution processes (Anand, 2021).

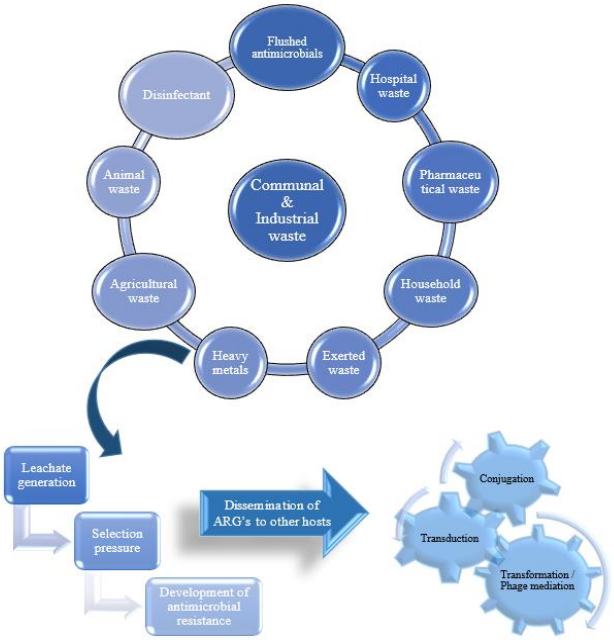

Figure 1: How antimicrobials in the environment result to augmentation of resistant genes in bacteria [5].

Once the pathogens acquire the resistant genes, they turn to be unsusceptible to antimicrobials thus failure to respond to the intended drugs which results into severe illness and deaths of patients. As a result, antimicrobial resistance (AMR) has turned to be one of the pressing public health challenges in the globe which calls for more attention [6]. The antimicrobial agents have lost their efficacy of saving lives due to the emergence of AMR problem [7]. When antibiotic treatment was introduced, it was proclaimed as one of the ways of eliminating infectious diseases as these antibiotics were giving great results in treating bacterial infections, however, antibiotic resistance bacteria (ARB) and antibiotic resistance genes (ARGs) were discovered shortly after an extensive administration of antibiotics [8] [9] [10]. To-date, the evolution and ability of pathogenic microbial organisms to withstand the presence of antibiotics has become amongst the top global leading threats in public health [11] [12]. The decrease in antibiotic development has aggravated the situation resulting into a state declared as "antibiotic crisis" [13] and the foretell call up for a swift reduction of antimicrobial consumption in possible circumstances [14] [15] [16] [10].

2. The emergence of antimicrobial resistance

Antimicrobial resistance refers to a natural phenomenon that occurs when susceptible microorganisms such as bacteria, viruses and fungi are exposed to antibiotic drugs over time and by ways of adapting for survival they mutate or acquire resistant genes from other pathogens enabling them to be unsusceptible to antibiotic drugs [17], as shown in figure 2 below.

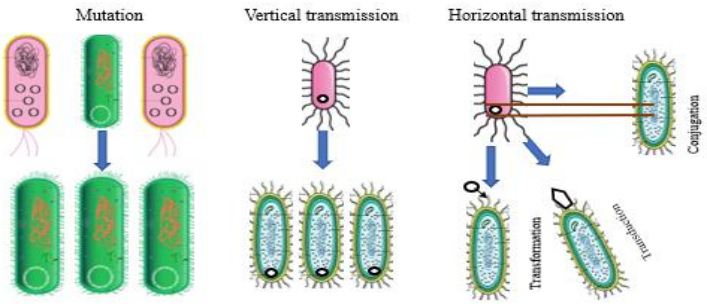

Figure 2: Mutations induced on bacteria due to exposure to antibiotic [18].

Mostly, vulnerable microorganisms are prohibited when exposed to stressors such as antimicrobial, however, pathogenic microorganisms that have acquired antibiotic resistant traits stand better chances to survive and multiply their selection of evolution to become more resistant and enhanced as well as their progeny [19]. Owing to that, antibiotic resistance compels for the introduction of alternative drugs to be employed which may come with toxicity issues in addition to additional costs [20].

3. Factors contributing to the emergence of antimicrobial resistance

The continuous subjection to antimicrobials is now amongst the list of the top consequential factors in the emergence and propagation of ARB [19]. The long exposure is attributed to the inappropriate use or abuse of antimicrobials, scarcity of clean water, poor sanitation, and hygienics for human beings as well as for animals [21]. Antibiotics are extensively used in humans and veterinary medicines with the purpose of managing infections and diseases, growth promotion in livestock and poultry as well as in food preservatives [1,2]. Antibiotics can however be weakly absorbed or incompletely metabolized in human and animal gut and therefore get excreted into the environment as waste [6]. Unused antibiotics are also disposed improperly, and their residues are immensely detected in surface water bodies and thus promote selection of ARB and ARGs [22].

Figure 3: The dissemination of antibiotic resistance bacteria and antibiotic resistance genes from the communal settings to the

environment.

4. Dissemination of antibiotic resistance in the environment

The residues of the un-metabolized antibiotic agents in humans and the disposed unused antibiotics are subsequently found in different natural environmental compartments and surface water bodies such as rivers, lakes, and streams [23] [24], groundwater [25], effluents from hospitals [26] and domestic wastewater [27] [28] and thus promote the selection of ARB and ARGs. The ARB and ARGs have also been found abundantly in river sediments [29] [30] [31], antibiotic-treated manures [32], soil and air as well as in biological systems such as in foods, plants, and animals [31]. There are reports which claim that ARGs originates from microorganisms in the environs and then transmitted to other microorganisms via mobile genetic elements (MGEs) [33]. Consequently, the whole environment including wastewater treatment plants, agricultural operations, and the soil has become one of the recognized reservoirs and a hotspot of ARB and ARGs. Bacteria experience high selective pressure of antibiotics in these hotspots and therefore fight to survive through various mechanisms which brings about the microbial resistance phenomena. Additionally, to the mentioned resistomes, food [34] and drinkable water [35] have been identified as one of the wellspring and hotspots for ARB, ARGs, and antibiotic resistant gene determinants (ARGDs) associated with human infection [36]. The hotspots environments of ARB and ARGs have recently received high scrutiny [37] [38] even though the control of their dissemination has not been established as yet [12].

5. Types of antimicrobial pathogens associated with AMR that are mostly found in the environment

Microbes that are mostly found in the environment includes bacteria, viruses, fungi, and parasites. These pathogens become AMR when they are unresponsive or acquire the ability to survive antimicrobial medicines causing the infections to be harder to treat and leading to severe illness and death. Amongst these pathogens, antibiotic and antifungal resistance are the leading world's public concern [21].

5.1. Bacterial resistant genes

There are commonly known enteric resistant bacteria which are causing antibiotic resistant infections yearly in South Africa (SA). In 2010, the National Institute for Communicable Disease reported a resistant of *Staphylococcus aureus* towards methicillin, *Klebsiella pneumonia* against extended-spectrum β-lactamase (ESBL) in year 2010 to 2012, Enterococci towards vancomycin in 2012, and Entero-bacteriaceae against carbapenemase [36]. The *Klebsiella pneumoniae* which is common to all African regions is one of the popular ARB that belongs to *Salmonella* family and is a common intestinal bacterium. *K. pneumoniae* has a high resistance towards ciprofloxacin rating from 4.1 to 79.4% worldwide and its resistance has led to the use of carbapenem antibiotics which is the last resort at this point and in certain countries half of the patients are resistant to it as well. At most, a lot of hospitalization are due to *K. pneumoniae* infections, and these includes pneumonia, bloodstream infections, as well as infections in newborns and all of these require intensive-care unit patients. *Escherichia coli*, a family of Enterobacteriaceae is a bacterium that is also found in humans' gut and homoiotherms has an antibiotic resistant rate that is ranging from 8.4% to 92.9% against carbapenem. The resistance *E. coli* is also spreading wide. Overall, the last resort for all the sicknesses and diseases related to carbapenem resistant Enterobacteriaceae such as *E. coli* and *Klebsiella* is colistin which is also beginning to have resistance in a couple of countries. In the study that was conducted in 2019, *E. coli* was also proven to be resistant to third generation cephalosporins (3GC) while *Staphylococcus aureus* showed towards methicillin. Several studies that have been conducted on *E. coli* show that these bacteria have a spontaneous mutations occur about 20 times as much on the lagging strand than the leading strand and brings more concerns to public health [40]. The study that was conducted in 2019 also revealed that in 49 countries who provided data on bloodstream infections, about 36% of *E. coli* infections were resistant to third generation cephalosporins and 12.11% of *Staphylococcus aureus* infections were resistant to methicillin. It was also stipulated that about 64% of people who are methicillin resistant are most likely to die compared to people who are not antibiotic resistant [21]. *Pseudodomonas aeruginosa* has also indicated a level of resistance towards aminoglycosides, fluoroquinolones, erythromycin, and ethidium bromide [41] [42] [43] [44] [45] [46] [47].

Table 1: Reported enteric bacteria resistant genes in RSA

Enteric Bacteria spp	Resistant gene sequence	Antimicrobial agent	Reference
Salmonella	*Klebsiella pneumoniae*	Ciprofloxacin	CDC; Fijalkowska 2012 [39, 40]
Enterobacteriaceae	*Escherichia coli*	Third generation cephalosporins	Fijalkowska 2012; Köhler 1996 [40,41]
Enterococcaceae	*Enterococcus faecalis*	Vancomycin-resistant	Van Wyk 1999, Frank 2018 [48, 49]
Enterobacteriaceae	*Shigella*	Ampicillin, chloramphenicol, tetracycline, & cotrimoxazole	Breurec 2018 [50]
Staphylococcaceae	*Staphylococcus aureus*	Methicillin	https://ahpsr.who.int/ [21]
Pseudomonadaceae	*Pseudomonas aeruginosa*	Aminoglycosides, fluoroquinolones, erythromycin, and ethidium bromide	Köhler 1996; Li 1994; Li 1998; [41] [42] [43] [44] [45] [46] [47].

5.2. Virus

Human immunodeficiency virus (HIV) is one of the common viruses that are facing a challenge of drug resistant HIV (HIVDR). Antiretroviral (ARV) drugs are becoming inactive towards HIV due to the emergence of drug-resistant (HIVDR) and this includes newer classes of ARV. This challenge has become a worldwide health concern especially for people that are immunocompromised as viral replication is proceeding and their exposure to drugs is prolonged promoting the selection of resistant strains. This means patients that are under ARV therapy are more prone to acquire HIVDR and the resistance can be further transferred to other people as well because people can be infected with HIV that is drug resistant already [21]. Antiviral resistance has also been observed in Influenza (flue). When flu virus replicates, the genetic makeup also changes resulting to antiviral drugs that are used to inhibit the virus by targeting specific sites being ineffective and result to a resistant virus. As it stands, flu viruses but not many, are resistant to oseltamivir. However, most flu viruses are still susceptible to the antiviral drugs recommended for flu by the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) (zanamivir, peramivir and baloxavir). Nonetherless,influenza B viruses are resistant to adamantane drugs [51].

Table 2: Reported virus resistant genes in Africa regions

Enteric virus spp	Resistant gene sequence	Antimicrobial agent	Reference
Retroviridae	HIV-1	Antiretroviral	Chimukangara 2021 [52]
Orthomyxoviridae	Influenza A (H1N1)	Oseltamivir	Besselaar 2008 [53]
Orthomyxoviridae	Influenza B	Adamantane	Centers for Disease Control and Prevention [51]

5.3. Parasites

There is also an emergence of parasites resistant which threaten the malaria control and raising numbers of morbidity and mortality. In Western Pacific Region and Southeast Region, a partial resistance towards artemisinin and other artemisinin-based combination therapies (ACTs) partnering drugs has been confirmed and this once again a major public health concern. ACT is the first line treatment for uncomplicated *P. falciparum* malaria and highly employed in malaria endemic countries. One of the African countries, Rwanda also confirmed parasite mutations which are associated which are associated with partial artemisinin resistance [21].

Table 3: Reported parasite resistant genes in Africa regions

Enteric Parasite spp	Resistant gene sequence	Antimicrobial agent	Reference
Trichostrongylidae	*Haemonchus*	Anthelmintics	Van Wyk 1999 [48]
Malaria	*Plasmodium falciparum*	Pyrethroid and carbamates	Edwardes 2010 [54]

5.4. Fungi

Certain types of fungi species are naturally resistant to treatment to some type of antifungal drugs. This includes fluconazole which is ineffective in all the infections caused by fungus *Aspergillus* which is a type of mold [55] [56]. So, the ubiquity of fungal drug resistance is infuriating the already existing difficult treatment situation. The most popular invasive fungal infection *Candida auris* has been reported for a widespread resistance towards fluconazole, amphotericin B and voriconazole and now its resistance is emerging towards caspofungin as well [57]. Fungal resistance is causing more difficulties in treating infections because we currently have only three types of antifungal drugs that exist.

The resistance is therefore limiting the treatment options even further because given a situation of *Candida auris*, the infection could be resistant to all three types of drugs [57].

Table 4: Reported fungi resistant genes in SA

Enteric fungi spp	Resistant gene sequence	Antimicrobial agent	Reference
Ascomycetous	*Candida auris*	Fluconazole, amphotericin B & voriconazole and partially in caspofungin	Ostrowsky 2019; Mphanga 2021 [57,58]
Ascomycetous	*Candida albicans*	fluconazole	Owotade 2016 [59]

6. Mechanisms of antimicrobial resistance

Given the prevalent various environment that possess resistance determinant [60], the feasibility is that the antibiotic resistance genes have been transferred from the environment to clinical settings through various mechanisms [61]. The propagation of these ARB pathogens is accomplished through selective mechanisms that the microbial undergo for the acquisition and dissemination of resistance genes. Mostly, new resistance genes are acquired through mobile genetic elements (MGs) such as incorporation of naked DNA, viruses' transposons, integrons and plasmids [62] [63] depending on the type of microorganism. Here we focus on the mechanisms that are employed by bacteria to acquire resistance. Bacterial resistance acquisition is categorized into two major strategies which includes transfer of genetic information between the two individuals: [vertical and horizontal gene transfers (HGT)] [64] and chromosomal mutation [65] [66] [67] [68] [69] [70]. The intrinsic bacterial resistance quandary is not the main problem in the discussion of AMR but the acquired resistance. The acquired resistance occurs by mutation in chromosomal genes or due to the accretion of external genetic determinants of resistance that are probably obtained from intrinsically resistant organisms present in the environment [65]. The HGT mechanism therefore plays a big role in spreading multiple genetic traits especially the ones that are resistant to antibiotics [71], and also ensures a successful adaptation of bacteria to new niches [11]. The masterplan that the bacteria use to acquire external genetic material includes [72] (i) transformation (incorporation of naked DNA) [73] [74], ii) transduction (phage mediated) [75] [76] and, iii) conjugation plasmid (bacterial "sex") [77] [78], then propagate further whether there is presence of antibiotics or not [79].

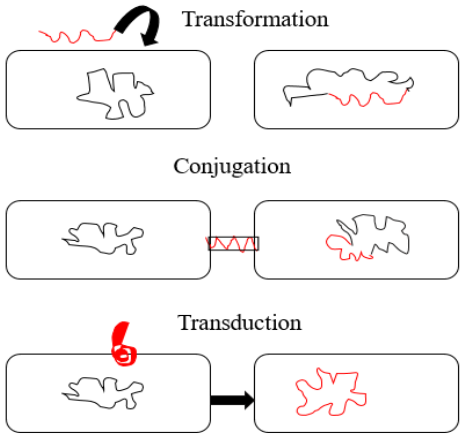

Figure 4: Horizontal mechanism for gene transfer between bacteria *(*adopted from Furuya 2006*)* [79]

6.2. Transformation: Incorporation of naked DNA

Transformation is one of the simplest HGT mechanism but a very difficult clinically relevant bacterial with the ability to "naturally" incorporate naked DNA to establish resistance genes. Some of these bacteria can directly absorb pieces of DNA from its environmental surroundings [65].

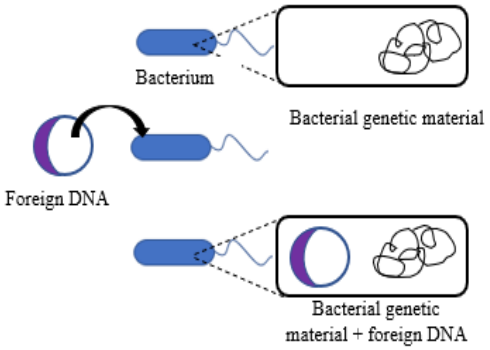

Figure 5: The mechanism for transformation gene transfer (adopted from Ramaswamy) [80].

6.3 Transduction: Phage mediation

Bacteriophages also known as phages are viruses that are capable of infecting bacteria and cause bacterial evolution [81] [82]. The infection process is alleviated by incorporating virulence and ARGs to the DNA of the new bacterial host through transduction [83].

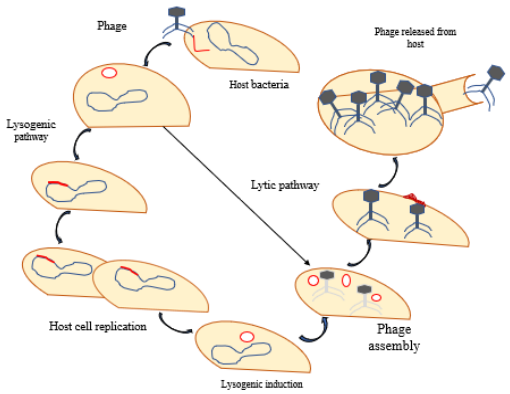

Figure 6: Mechanism for phage mediation gene transfer (adopted from Chiang 2019 [84]).

Temperate and lytic phages are two functional categories of bacteriophage [85]. Temperate infects bacteria and resides in the interior without any disturbance in the bacterial cell in the beginning however, at the end of the multiplication this result to bacterial disruption. On the other hand, in the lysogeny, the bacteriophage uses its host as an assembly factory when viral genome is integrated into the bacterial DNA and recognized as prophage [82] as shown on figure 6 above. The mechanism employed by bacteriophages in gene transfer is still not taken serious as transformation and conjugation [86].

6.4. Bacterial Conjugation

In hospital environments, the emergence of antibiotic resistance most frequently involves conjugation mechanism (Figure 7) which is a very efficient gene transfer method that involves cell-to-cell contact. In this method, two bacteria are able to pair up by their cell membrane and connect through structures [65]. The recruitment of new genes is considered the compensation for the lack of sexual recombination hence the name 'bacterial sex'. The method often occurs at elevated levels in human gastrointestinal tract under antibiotic treatment [87].

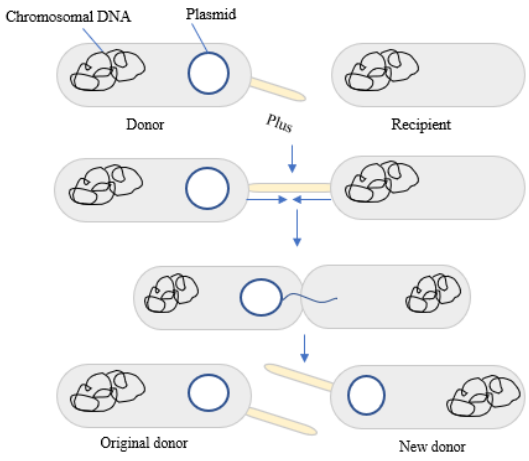

Figure 7: Bacterial conjugation mechanism for the emergence of antibiotic resistance (adopted from Kidwell 2005) [88].

6.5. Mutation

Mutation is one of the bacterial methods that brings about resistance. The phenotypic results of the mutation (the change in the nucleotide) are various depending on the severity as well as the location of the mutation. In the process of mutation, a lot of errors occur during DNA replication or induced by exposure to mutagens (like chemicals and radiation). During the synthesis of a DNA new strand, a nucleotide can be mispaired, added, or omitted [89]. When this occurs, the nucleotide will seem to have substitutes for another leading to one mutated granddaughter DNA strand. Both of the two separate malfunctions should occur in the bacteria's DNA replication machinery for this to happen [90]. These errors may result to a different bacterial structure or colony characteristics or even loos of sensitivity towards antibiotics hence resistance genes.

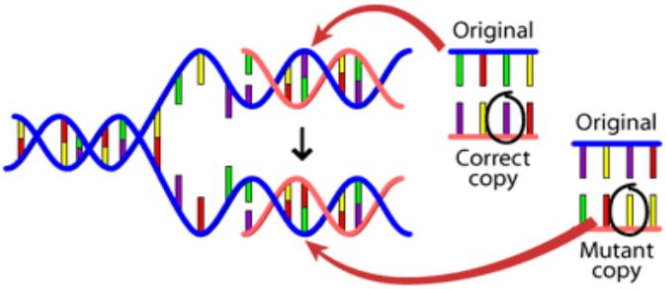

Figure 8: The causes of mutations (adopted from Mutations are the original source of genetic variation) [91].

The consequences of mutation are categorized as follows:

- Auxotrophs: have a mutation that leaves an essential nutrient process dysfunctional.
- Resistant mutants: can withstand the stress of exposure to inhibitory molecules or antibiotics secondary to acquired mutation.
- Regulatory mutants have disruptions on regulatory sequences like promotor regions.
- Constitutive mutants: continuously express genes that usually switch on and off as in operons.

The phenotype variation of these bacteria takes place very quick because of their point of mutation since the majority of their genes are haploid and have a short generation turnover. The rate of spontaneity of mutation takes place at 1 in 10^5 to 10^8 and contribute to random population variation [92]. The spontaneous mutation does not require any induction in order for it to occur hence multiple errors occur during DNA replication [93].

7. Antibiotic resistance

Antibiotics inhibit the microbial infections by disrupting the essential structures or processes in microorganisms and thereby kill the microbes or stops them from multiplying. However, when the antimicrobial pathogens have acquired the resistance genes, they further develop various mechanisms to withstand the effects of an

antibiotic [94] [95]. Currently, each resistance bacterial cell is capable of employing a cadre of mechanisms to give resistance to more than one antibiotic [65]. One of the ways that these resistance bacteria employ to resist several antibiotics is to pump the antibiotic out of the cell and this enables them to identify different antibiotic molecules and thereby pump them out hence called cross-resistance mechanism [96]. The variation of antibiotic resistance mechanisms typically depends on the type of microorganism however the microorganisms use one or more of the mechanisms that are discussed below [97] according to their biochemical route of resistance which includes ***i)*** modifications of the antimicrobial molecule, ***ii***) prevention to reach the antibiotic target (by decreasing penetration or actively extruding the antimicrobial compound), ***iii)*** changes and/or bypass of target sites, and ***iv)*** resistance due to global cell adaptive processes [65].

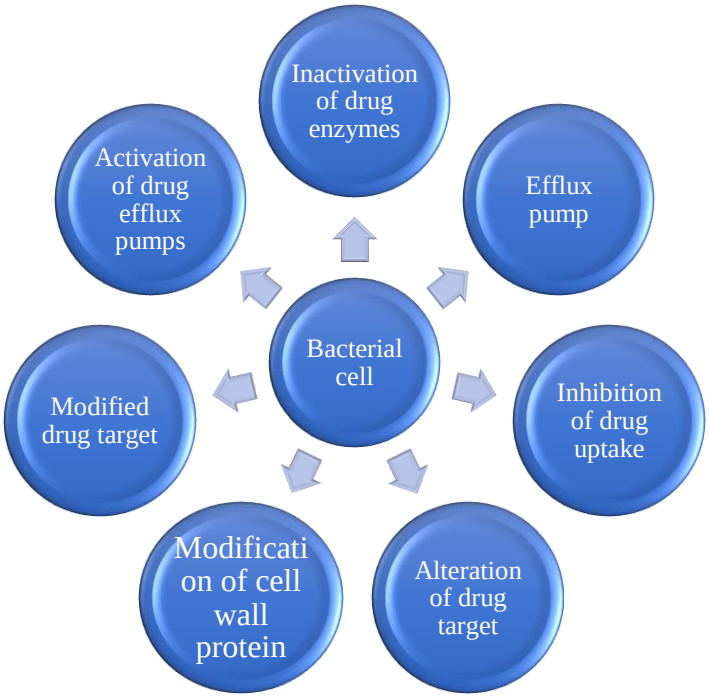

Figure 9: Mechanisms of horizontal gene transfer (HGT) in bacteria and the various antibiotic resistance strategies (adopted form Bbosa 2014) [98].

7.2. Modification of antimicrobial molecule

Microbial pathogens achieve their resistance by modifying the antimicrobial. The drug modification mechanism is done by altering the chemical of the antibiotic or by distracting the antibiotic molecule.

7.2.1.Modification of antimicrobial molecule by chemical alterations of the antibiotic

Bacteria species produces enzymes which are able to introduce different chemical groups to the antibiotics (shielding the antibiotic) which in turn inhibits the antibiotic from reaching and binding to the target site of the bacterial cell [99] [100]**.** This is one of the popular mechanisms and is applied in both gram-negative and gram-positive bacteria [65]. Alternatively, some of the bacteria excrete different proteins from the ones that are inhibited by antibiotics which will be used for their synthesis and become unsusceptible, and the process is called the express of alternative protein. This is observed in *Staphylococcus aureus* bacteria when it has acquired *mecA* resistance gene and produce new penicillin-binding protein which has low affinity towards β-lactam antibiotics and become resistant to the drugs [101]**.**

7.2.2. Modification of antimicrobial molecule by destruction of the antibiotic molecule

The destruction of antibiotic molecule mechanism is often observed in β-lactam resistance whereby the enzymes deactivate or degrades the antibiotic by destroys the amide bond of the β-lactam ring by the process called β- lactamases causing the antimicrobial to be ineffective [65]. Some other time, the bacteria reprogram the target by producing an alternative structure that the antibiotic will not be able to interact with. This is frequently observed when the Vancomycin-resistant bacteria develop a cell wall to inhibit susceptibility [101].

7.3. Activation of efflux and decreasing antibiotic permeability

7.3.1.Decreased antibiotic permeability

Most of the clinical antibiotics inhibit bacterial growth by targeting its intracellular which is found in the cytoplasm membrane in the case of gram-negative bacteria. So, the bacteria use the mechanism to hinder the antibiotics from penetrating the intracellular resulting to a decreased uptake of the antibiotic molecule. This therefore result to less pressure of antibiotic towards bacteria because the outer membrane acts as the first line of defense making it difficult for antibiotic to reach its target hence the resistance [65] [101].

7.3.2. Efflux Pumps

Bacterial also become resistant by pumping out the antibiotics from the bacterial cell. In this mechanism, the bacteria actually produce pumps in their cell walls or cell membranes which will extrude anything that is toxic for the bacteria including antibiotics. These are the same pumps that transport compounds such as signal molecules and nutrients for the bacteria. The pumps are especially good in pumping out tetracycline antibiotics from the cytoplasm of the *E. coli*. In some instances, during bacterial mutation, DNA bacterial can produce plenty of pumps which result to more resistance [65] [101]. Multidrug resistance has been recognized to master the efflux pump mechanism particularly the *P. aeruginosa* [47]. The mechanism has demonstrated even more advanced restrictions on antibiotic substrate spectrums than MexAB-OprM and able to withstand compounds of different structure such as quinolones, chloramphenicol, and trimethoprim [102] [103] [104] [105] [106] [107] [108].

7.4. Changes in Target Sites

Camouflaging the target site of the bacteria or changing its composition is one of the common strategies that are used by the bacteria to accomplish AMR [101].

7.4.1.Target protection

As mentioned above, mutation in the bacterial DNA can result in different structural composition of bacteria and bacteria use this mechanism to change their structure so that they can protect the site that is targeted by antibiotics to reduce the interaction between the bacteria and the antibiotics hence the resistance [101].

7.4.2.Modification of the target site

Modification of target site in bacteria by bacterial DNA mutation can result in decreased affinity of the antibiotic molecule and prevent the interaction of antibiotic with the bacterial target site **[101]**. The modification of targets includes ***i)*** point of mutations in the genes encoding the target site, ***ii)*** enzymatic alterations of the binding site, and/or ***iii)*** complet**e** replacement or bypass of the original target [109]. All these mechanisms they bring about the same final effect which is a decreased affinity of antibiotic to reach the target site of the bacteria [65].

7.5. Resistance Due to Global Cell Adaptations

Bacteria survive in environments that are toxic for them such as human body whereby they are continuously attacked by the immune system and also compete for nutrients. Over decades of evolution, bacterial have acquired some evolution mechanisms to withstand the stressful surroundings that they live on. The mechanism they developed ensures that the pivotal cellular process such as cell wall synthesis and membrane homeostasis is not disturbed [65].

8. Ways to mitigate the spread of antimicrobial resistance

Vaccination is one of the most direct and effective way of preventing the spread of AMR pathogens [110]. More various ways such as immunization, safe food preparation, sanitation, and using antibiotics only when necessary and as directed, can be also employed to minimize drug-resistant infection. Additionally, preventing infections also helps to prevent the spread of bacteria, raising awareness about the bacteria resistance as well as the rational use of antibiotics, taking good measure with regards to antibiotic therapies and revising health and safety policies can also help.

9. Conclusion and recommendations

The emergence of drug resistance has become one of the major public health concerns. The resistance is highly associated with the inappropriate use of antibiotics, poor infection and disease prevention, poor control in health-care facilities and farms, poor access to drugs of high quality, use of just affordable medicines, vaccines, and diagnostics; lack of awareness and knowledge; lack of enforcement of legislation [21] and the presence of antimicrobial residues in the aquatic environment. As thus, ARB and ARGs have been detected immensely in the environment and that has become a threat as they can be transferred either to animals or humans through the food chain. To a certain level, the dissemination of resistance can be minimized by using appropriate antimicrobial regimen. The antimicrobial regimen should aim to minimize the emergence and dissemination of resistance, not only to attain clinical efficacy [111]. Pharmacists, clinicians, and infectious disease specialists should get a better understanding of the mechanisms that are employed by bacteria to attain resistance as this can help to design effective antimicrobial therapies [101]. The limitation for use of antimicrobials in agricultural operations should be drawn as these have been recognized as one of the reservoirs and hotspots of ARB and ARGs.

1. The environment requires more attention to combat the emergence and dissemination of ARB and ARGs.
2. The surveillance and monitoring systems for the wastewater and its sediments should be standardized in order to keep track of the ARB and ARGs that are present in the environment.
3. Strategies to slow down the emergence of microbial resistance and minimizing its propagation should be established. The focus needs to be shifted as the use of standardized regimens in the presence of undiagnosed drug resistance has been determined to be prime driver of drug resistance.

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