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Review

Antibiotic Resistance: A Global Health Crisis

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Abstract

Antimicrobial Resistance (AMR) has been recognized as a global health crisis. It occurs when the microbial pathogens develop mechanisms by means of which the existing antibiotics become ineffective against them and the management of infections caused by them become difficult. According to the data of World Health Organization (WHO) the most common multidrug resistant (MDR) microbes include *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Clostridium difficile*, *Klebsiella pneumoniae* and many more. Overpopulation, globalization, misuse of antibiotics by humans, injudicious use of antibiotics in livestock, poor hygiene standards in hospitals and lack of development of new antibiotics constitute the major causes for the rise in antimicrobial resistance. Although, the development of new antibiotics is considered as a potential solution to tackle the spread of AMR; newer alternative strategies including vaccines, bacteriophages, monoclonal antibodies, other bioactive molecules like peptides and development of effective diagnostic tools are also being explored by scientists to overcome this issue. This global concern thus requires collaborative efforts from countries across the world. Therefore, different organizations like World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), Infectious Diseases Society of America, World Economic Forum are working tirelessly towards the control of AMR.

Keywords: Antibiotics, anti-microbial resistance, health, global challenge

Introduction

Antibiotics are the chemical substances which kill or stop the growth of microbes including bacteria and fungi. On the basis of their mode of action, antibiotics are divided into two broad categories [1]:

(i) Bacteriostatic: These antibiotics prevent the bacteria from multiplying further mainly by hampering the cell wall synthesis.

(ii) Bactericidal: These antibiotics kill the bacteria by preventing the DNA replication, protein synthesis or by affecting other metabolic pathways (Figure 1).

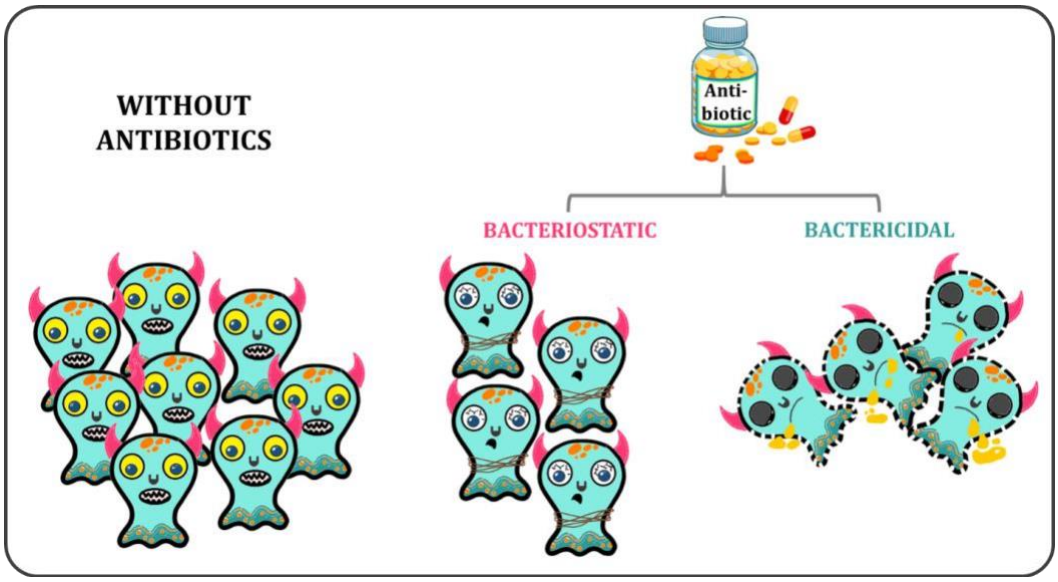

Figure 1: Bacteriostatic and Bactericidal antibiotics

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Multidrug resistant microbes, commonly called "superbugs" is a term used to designate microbes that have developed mechanisms that make them resistant to the effect of these bacteriostatic or bactericidal antibiotics. [Table 1] enlists examples of some microbes which have been reported to have developed resistance against different antibiotics.

Table 1: List of common microbes that exhibit resistance to antibiotics

S. No.	Microorganisms	Resistant to antibiotics	Reference
1.	*Staphylococcus aureus*	Penicillin, Methicillin, Vancomycin, Fluoroquinolones, Tetracycline	[2]
2.	*Mycobacterium tuberculosis*	Amikacin, Ethambutol, Streptomycin, Kanamycin, Quinolones, Rifampicin	[3]
3.	*Neisseria gonorrhoeae*	Aminoglycosides, Cephalosporin, Penicillin, Quinolones	[4]
4.	*Streptococcus pneumoniae*	β-lactam antibiotics, Chloramphenicol, Cephalosporin, Erythromycin, Sulphonamide, Tetracycline, Trimethoprim	[5]
5.	*Pseudomonas aeruginosa*	Aminoglycosides, β-lactams, Polymyxins, Quinolones	[6]
6.	*Clostridium difficile*	Clindamycin, Erythromycin, Moxifloxacin, Rifampicin, Tetracycline	[7]
7.	*Salmonella enterica*	Chloramphenicol, Fluoroquinolone, Tetracycline	[8]
8.	*Klebsiella pneumonia*	Penicillin, Carbapenems, Cephalosporins, Monobactams	[9]

Studies have revealed that the genes that confer resistance in microbes may be present in their own genetic material i.e. chromosomal DNA or may be acquired through horizontal gene transfer which in turn is commonly mediated by conjugation, transformation or mobile genetic elements from other microbes [10]

Mechanism of Antibiotic Resistance

Impermeable barriers which prevent antibiotics to reach their target inside the cell

Many microbes undergo modifications either in their cell wall and cell membrane making them almost impermeable to antibiotics or exhibit alterations in the passage channels located in the outer membrane such as porins which too prevent the entry of antibiotics into the microbial cell. These barriers thus exert a resistive mechanism that barricades the gates for the entry of antibiotics into the cell and reach its destined target. For example, Gram negative bacteria develop resistance against aminoglycosides and β-lactam antibiotics by this mechanism and inhibits the antibiotic from reaching their target of action inside the cell [11]. In some cases, it has been observed that an increase in the thickness of cell walls as in *Staphylococcus aureus* render them resistant to vancomycin. It has also been documented that members of *Enterobacteriaceae* exhibit resistance to carbapenems due to a decrease in the occurrence of porins and also due to a change in the selectivity of porins. A change in porin channels in case of *Neisseria gonorrhoeae* has been related to their resistance to β-lactams and tetracyclines. In some of the microbes, the peripheral formation of biofilm has been shown to inhibit the entry of antibiotics thereby preventing them from reaching their targets in the microbial cell as in *Mycobacterium tuberculosis* [12]. Such instances thus demand a higher concentration of antibiotics to combat the disease causing microbes [10].

Efflux of antibiotics and reduction in their effective concentration inside the cell

Some microbes have membrane transporters which are referred to as the efflux pumps. These pumps expel the antibiotics as soon as they enter into the cell, thereby decreasing their effective concentration required for their action. Depending upon the energy sources, substrates and the number of transmembrane spanning regions, these efflux pumps in bacteria are broadly classified into the following five families [13]:

(i) ABC (ATP Binding Cassette) family

(ii) MATE (Multidrug And Toxic compound Extrusion) family

(iii) MFS (Major Facilitator Superfamily) family

(iv) RND (Resistance-Nodulation-Division) family

(v) SMR (Small Multidrug Resistance) family

Efflux pumps belonging to the RND family are exclusively found in Gram negative bacteria whereas other four families including ABC, MATE, MFS and SMR efflux systems are widely distributed in both Gram negative and positive bacteria. Due to their proficiency in getting away with the

drugs either in the periplasmic space or the cell exterior, these pumps play a significant role in the evolution of multidrug resistance in microbes. While some efflux pumps are selective and specific in expelling a specific class of antibiotics; others either have a broad specificity for several classes of antibiotics or have no effect at all. For instance, AbaF and TetA expel Fosfomycin in *Actinobacter baumanii* [14] and tetracycline in *Escherichia coli* [15] respectively. Unlike these are MexAB-OprM which are responsible for MDR in *Pseudomonas aeruginosa* making them resistant to different classes of antibiotics including fluoroquinolones, tetracyclines, novobiocin, sulfonamides, macrolides, aminoglycosides [16]. There are several other examples that highlight the role of efflux pumps in MDR such as *Escherichia coli* to tetracycline, *Staphylococcus aureus* to fluoroquinolones and tetracycline, and *Salmonella enterica* to Chloramphenicol, Fluoroquinolone, Tetracycline [13, 17-18].

Alteration of target site

In some microbes, resistance is a result of an alteration of the specific antibiotic-target site rendering it unable to bind the target completely or partially. As a consequence, the antibiotic fails to exhibit its desired effect whilst its presence within the cell in an effective concentration [19]. Gram positive bacteria become resistant to the β-lactam antibiotics via alterations in the structure and number of Penicillin-binding proteins (PBPs). For instance, a change in PBPs in *Staphylococcus aureus* makes it resistant to β-lactam antibiotics [20]. Resistance in *Escherichia coli* against quinolones is due to alterations in DNA gyrase and DNA topoisomerase which are caused by chromosomal mutations [21]. Resistance in *Staphylococcus aureus* against vancomycin is because of structural changes in peptidoglycan [22]. Gram positive bacteria exhibit resistance against aminoglycosides and macrolides due to methylation of the ribosomal subunit [23]. Bacteria show resistance against sulphonamides and trimethoprim due to alterations in their target enzyme i.e. dihydropteroate synthase and dihydrofolate reductase, respectively [24].

Alteration and degradation of antibiotics (Enzymatic modification and Enzymatic inactivation)

Microbes develop the resistive mechanisms to either alter or modify the antibiotics in such a manner that they lose the ability to bind to their target site and become ineffective. A well-cited example is the inactivation of β-lactam antibiotics by hydrolytic inactivation of β-lactam rings. This modification prevents the antibiotics from binding to the penicillin-binding proteins (PBPs) which are the target of β-lactam antibiotics and elicit a response by inhibiting the cell wall synthesis. The pathogenic microbes including *Actinobacterbaumannii, Enterococcus, Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae* have developed resistance against β-lactam antibiotics by producing the enzyme β-lactamase. Another example is the modification of aminoglycoside by acetylation or phosphorylation. This type of modification is exhibited by chloramphenicol resistant species of *Enterococci* that undergo acetylation aided by the enzyme chloramphenicol acetyltransferase [25]. Members of Enterobacteriaceae are capable of hydrolysing the macrolactone ring of macrolides such as azithromycin, clarithromycin, and erythromycin A by the production of plasmid-based esterases enzymes EreA and EreB [26]. After the structural changes, the macrolides lose their ability to bind to their target site ribosome. Another example of enzymatic modification is the cleavage of epoxide ring of fosfomycin by the chromosomally-encoded FosX enzyme. There are several other enzymes which modify the Fosfomycin like Fom A and Fom B that are kinases which phosphorylate the oxirane ring of Fosfomycin [27]. Monooxygenanses encoded by microbes break down the tetracyclines and alter the naphthyl group in rifamycin antibiotics thereby preventing them from their action [28].

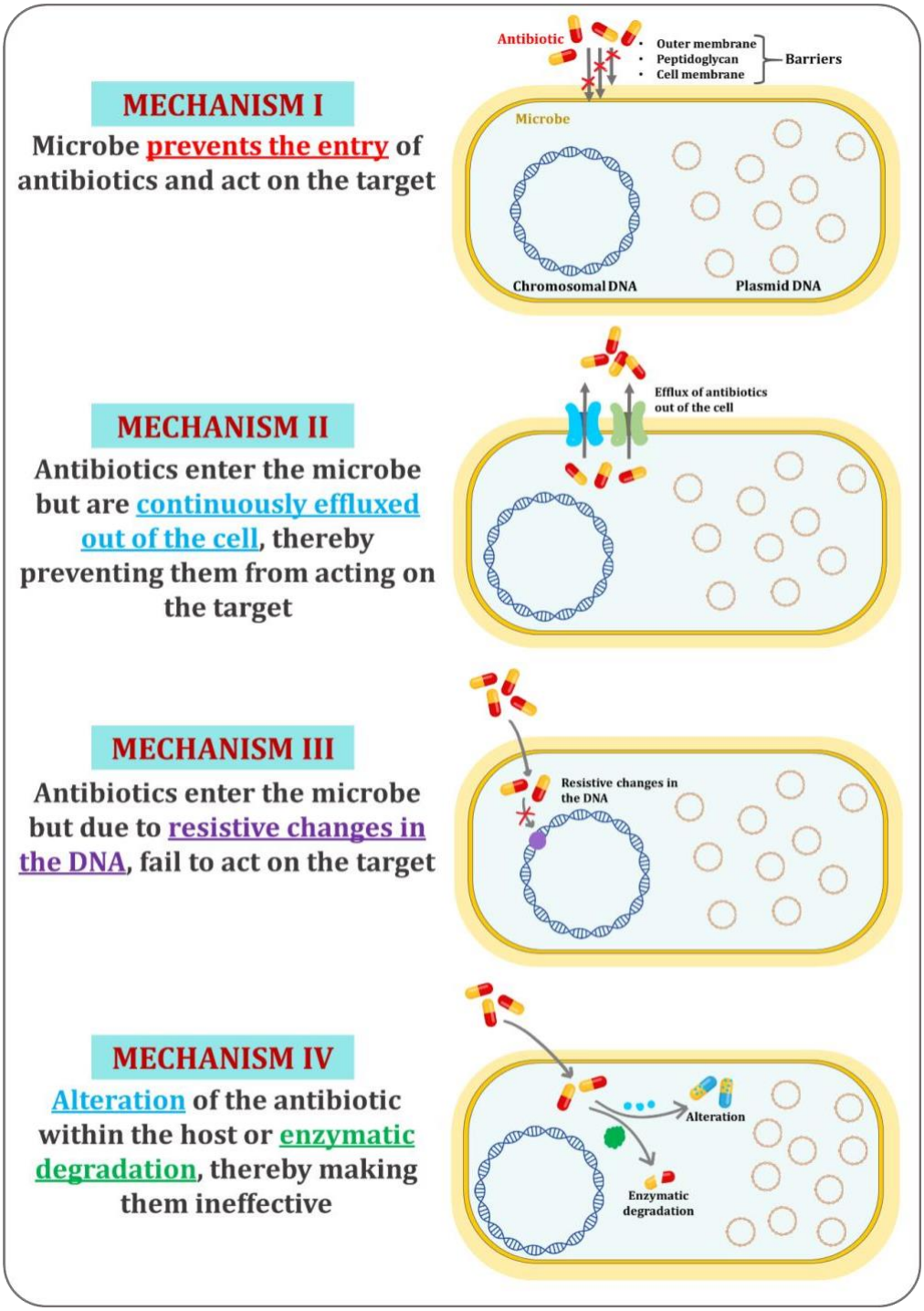

Figure 2: The four primary mechanisms of development of Antibiotic Resistance in microbes

Causes of Antimicrobial resistance

Figure 3: The six main causes resulting in Antibiotic Resistance [29-30]

Overpopulation and globalization

As recorded in June 2021, the population worldwide was reported to be 7.9 billion and is projected to reach 9.7 billion by 2050 [31]. A growing population size also contributes to an escalation in the rate of spread of infections. Globalization has been attributed as another significant factor for a rise and spread of antibiotic resistant microbes. Human migrations and even short distance movements serve as a strong agent for a wide distribution of such resistant microbes throughout the world. Therefore, MDR microbes reported in one country or place may simultaneously be witnessed in other parts of the world [32]. For example, MDR *Neisseria gonorrhoeae* first reported in Southeast Asia during 1960s and 1970s has become a health emergency in United States [33]. Similarly, Methicillin Resistant *Staphylococcus aureus* (MRSA) which has developed resistance to antibiotics such as Penicillin, Methicillin and Vancomycin has become a major health concern in many countries [34].

Misuse of antibiotics

It has been well reported that excessive clinical use of antibiotics, also commonly referred to as the "misuse of antibiotics" is another significant factor responsible for AMR globally. This is because the microbes which experience an increased antibiotic pressure for their survival (which is either due to excessive use of antibiotics or over-the-counter medication) tend to develop ways that cater them with abilities to withstand the pressure. The resulting microbes then tend to become resistant to the administered antibiotics. Another potent contributor to this is the consumption of antibiotics without any doctor's prescription [35-36]. The reason for this over-the-counter medication is largely related to the socio-economic condition of the people too. This problem is more prevalent in developing countries where there is a lack of a strong healthcare sector and universal accessibility of medical facilities is yet to be achieved. The drugs under the "over the counter" category can be purchased without prescription. It has been observed that "over the counter" drugs are generally procured by people for minor symptoms like fever, cold, headache, allergy, constipation, to name a few. Self-medication by consuming "over the counter" drugs save the time and money of the layman. Financially weaker populations prefer to consume medicines on their own rather than approaching the clinicians. Even during this global corona pandemic, prescriptions circulated through social media that probably worked for one individual were presumed to work for all and were used by the majority as self-medication without consulting the doctor. The use of such over the counter drugs need to be regulated which is possible only by framing new policies drugs. There is a growing need for regulatory authorities to streamline and relook the list of essential medicines, drug regulations law and litigations and safety issues of over the counter drugs [37-38].

Excess use of antibiotics in livestock and fish farming

Owing to an increased use of animal products worldwide, antibiotics have been used irrationally in animal farming to meet the demands. These antibiotics are predominantly used to either promote growth, cure the diseases and enhance the milk yield and production of eggs and meat. Antibiotic resistant microbes from such animals when transferred to humans might be pathogenic and their treatment may be an even greater challenge. The most common route of these pathogenic microbes is through the food chain. Additionally, use of animal waste as manure in agricultural fields also results in the release of drug resistant microbes along with their genes into the soil and groundwater which finally might leach out to reach the humans [36, 39-40].

Quality of antibiotics

Quality assurance of antibiotics is a primary requisite before it reaches the general public. But in instances where the antibiotics on the verge of expiry are distributed and even consumed poses a greater threat. Companies for their financial profit change the label of the medicines or sell the expired antibiotics to the people. General public also consumes the expired antibiotics kept at their home in the lack of awareness about the effects of using expired antibiotics [36, 41].

Inadequate hygiene standards and poor infection control in hospitals

Hygiene conditions should be maintained properly in the hospitals otherwise the drug resistant microbes can easily spread from one patient to the other patients. Therefore, healthcare professionals should maintain personal proper hygienic condition as well as the instruments and equipments used in the hospital set up should be sterilized properly before use to avoid the spread of infection [36, 42]. In hospitals mainly in ICUs (intensive care units) large number of patients are on the heavy antibiotic doses which help in the selection of drug resistant microbes and these microbes can infect other patients as well. Consequently, ICUs in hospitals have become the dwelling grounds for antibiotic resistance microbes as the chances of cross contamination are high [36].

Negligence of research and development of new antibiotics

It has been observed that government and private pharmaceutical companies are giving less emphasis on the research to develop new antibiotics which are very promising to combat multidrug resistant microbes. Companies are not interested in developing new antibiotics as it involves less profit with respect to the expenditure. Companies like to invest in the development of medicines which are consumed by a large number of people on a daily basis like the drugs to control blood sugar and blood pressure, painkillers rather than developing antibiotics for drug resistant microbes which are required in treatment of lesser number of diseases [35-36].

Strategies to be used to control multidrug resistance

Development of new antibiotics

As the microbes are developing resistance against the existing antibiotics, it is the need of hour to discover or develop new antibiotics. Governments of every country should introduce policies and schemes to promote and support the research of new antibiotics by companies and researchers collaboratively, for example, In U.S "The Promise for Antibiotics and Therapeutics for Health Act" [43] was introduced in 2015 for encouraging the development of new antibiotics that target "unmet medical needs". Although new antibiotics are the hope to control the infection caused by multidrug resistant microbes, other strategies are being explored and adopted to combat drug resistant microbes.

Vaccines

Vaccination against the multidrug resistance microbes has great potential of reducing the emergence and spread of multidrug resistance. This is evident by the pneumococcal vaccine. Herd immunity which is obtained due to large scale vaccination drive helps breaking the circulation of antimicrobial pneumococcal resistant strains. Vaccination of livestock also help in the decreasing the occurrence of drug resistant microbes. Developing the vaccine against each microbe is not possible because of complexity of pathogens and conducting the efficacy trials. Because of these complications no vaccines are available for *Staphylococcus aureus*, *Clostridium difficile*, *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. Inspite of all these problems development of vaccines against multidrug resistant microbes should be promoted and people should make aware for the vaccination so that large number of people can be vaccinated to achieve the herd immunity. More importantly, vaccination drives effectively reduce the use of antibiotics as the infection rate decreases [44].

Use of Monoclonal antibodies

Use of monoclonal antibodies is being considered as an effective strategy for managing infections of drug resistant microbes and antimicrobial drug resistance. Monoclonal antibodies have the capability to bind various bacterial polysaccharides and proteins. They act through opsonophagocytosis of bacteria, complement-mediated cell lysis and inhibiting the activity of the target. Monoclonal antibodies effective against virulence factor and the exopolysaccharide of *Pseudomonas aeruginosa* and toxins A and B139 of *Clostridium difficile* have been reported. Monoclonal antibodies based approach is more promising in immunocompromised patients as compared to vaccination as their immune system is unable to mount an effective immune response [45].

Use of bacteriophages

Phage therapy seems very promising in dealing with antimicrobial resistance. Mainly the lytic phages are used in these kinds of therapy where the phages cause the lysis of its host bacteria. Phage therapy is highly specific as the phage are bacteria specific against which they are being used and has no adverse effects on the person under treatment and its commensal microbiota [46]. The phage therapy has been effectively used in the successful treatment of 68-year-old diabetic patient with necrotizing pancreatitis complicated by an MDR *Actinobacter baumannii* infection [47]. Similarly, a combination of six phages specific against *Pseudomonas aeruginosa* was used to cure recurrent bladder infection in a 67-year-old woman [48].

Use of antimicrobial peptides

Biomolecules are being explored if they have any activity against the MDR microbes. Antimicrobial peptides have the potential to combat drug resistant microbes, these peptides can be natural, synthetic and semisynthetic [46]. Liu and colleagues reported the applications of cationic peptides against vancomycin resistant *Enterococcus* (VRE). Peptides also increase the efficacy of antibiotics by showing synergistic effects [49].

Effective diagnostic tools

Effective diagnostics tools should be developed to identify a specific microorganism, this will reduce the frequent use of broad-spectrum antibiotics and emergence of multidrug resistant microbes. The tests should be available globally on reasonable prices as it has been reported that invasive non-typhoidal salmonellosis could not be managed effectively in Africa because of non-availability of diagnostic tools [50-51].

Conclusions

Antibiotic resistance is a serious global health problem which has been mainly caused by the mismanagement of antibiotics usage. Microbes which are causative agents of serious infections become resistant to even the most powerful antibiotics available and the situation becomes critical when no antibiotic is available which is effective against them. Consequently, it would be very challenging to manage the public health infectious diseases globally in case of antibiotic failure and development of resistance in almost all clinical isolates. A global and interdisciplinary approach needs to be undertaken against AMR. The measures include increasing the level of awareness among people, developing newer and efficient molecular diagnostic tools to ascertain the actual need of antibiotic therapy and also developing improved strategies. Rules and regulations pertaining to antibiotic usage require a strict implementation as part of the national, regional, and global policies. “Global resistome” can be controlled by the effective tracking, surveillance and the prevention strategies of AMR and MDR pathogens.

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Declaration

Conflict of Interest

The authors declare that they have no conflict of interest.

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