



Review Article

## Antibiotic Resistance: A Review

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### ABSTRACT

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. While a spontaneous or induced genetic mutation in bacteria may confer resistance to antimicrobial drugs, genes that confer resistance can be transferred between bacterial in a horizontal fashion by conjugation, transduction or transformation. Thus, a gene for antibiotic resistance that evolves via natural selection may be shared. Evolutionary stress such as exposure to antibiotics then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacterium carries several resistance genes, it is called multidrug resistant (MDR) or, informally, a superbug or super bacterium. The emerging resistance in today's world has created a major public health dilemma. The major driving force behind the emergence and spread of antibiotic-resistant pathogens is the rapid rise of antibiotic consumption. This trend reflects the growing medicalisation of societies worldwide, with its identification of microbial pathogens as the cause of infectious diseases. Antibiotics promise cure. This together with their ease of use, the usually short treatment requirements, and, for many parts of the world, availability without prescription by a doctor results in a demand that is increasingly met by a growing supply of generic drugs produced in emerging market economies. The same escalation in consumption has occurred in the animal welfare sector, prompting concerns about the transmission of antibiotic resistance through the food chain. An additional set of threats that facilitate the spread of antibiotic-resistant pathogens comes from unpredictable disasters that disrupt human livelihoods and bring about crowding, mass migration, famine and unsafe water supplies. Conflicts within and between states, environmental degradation and climate change can provide scenarios in which infectious diseases thrive and antibiotic resistance may come to the forefront.

**Key words:** *Antibiotic resistance, Multi drug resistance, Antibiotic resistance pathogens*

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### INTRODUCTION

An antibiotic is a kind of antimicrobial substance active against bacteria and is the most significant kind of antibacterial agent for fighting bacterial infections.[1,2] They may moreover kill or inhibit the growth of bacteria.[3] Antibiotics are not effective against viruses such as the common cold or influenza; drugs which slow down viruses are termed antiviral drugs or antivirals rather than antibiotics.[4] Antibiotics

are chemical agents that stop bacterial growth by stopping the bacterial cell from dividing (bacteriostatic) or by killing them (bactericidal).[5] Antibiotics (such as penicillin) are those produced naturally (by one microorganism fighting another), whereas nonantibiotic antibacterials (such as sulfonamides and antiseptics) are fully synthetic. However, each classes have the same goal of killing or

preventing the growth of microorganisms.[4] Antibiotics are used to treat and or stop disease in human and animals. The reductions in death afforded by effective antibiotics for bacterial infections of all types, ranging from easy skin infections to infections of the bloodstream, lung, abdomen, as well as brain, so enormous that the lives of both human and animals are saved due to treatment by using antibiotics.[6]

**MECHANISM OF ACTION OF ANTIBIOTICS**

The next is a list of antimicrobials. The highest division is between antibiotics is bactericidal and bacteriostatic. Bactericidals kill bacteria directly,

whereas bacteriostatics stop them from dividing. However, these classifications are based on laboratory behavior. In practice, both can effectively treat a bacterial infection. In order to appreciate the mechanisms of resistance, it is significant to know how antimicrobial agents act. One of the most general mechanisms of action is targeting the cell wall, which is available in bacteria (prokaryotic cells) but not present in humans (eukaryotic cells). Thus, antimicrobial agents act selectively on vital microbial functions with minimal effects or without affecting host functions. Different classes of antibiotics possess specific modes of action by which they prevent the growth or kill bacteria.[7]

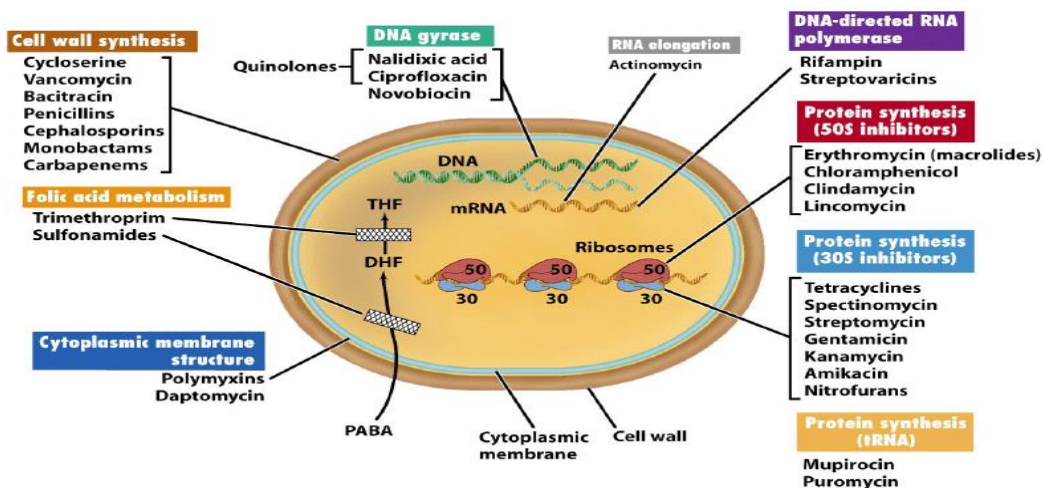
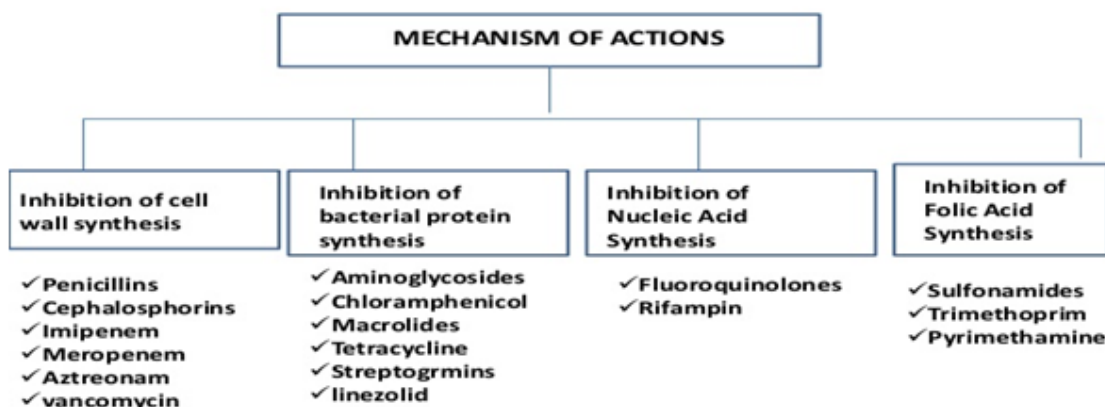


Figure 20-14 Brock Biology of Microorganisms 11/e © 2006 Pearson Prentice Hall, Inc.

Fig. No.1: Mechanism of action of antibiotics (Source taken by Brook biology of microorganism org.com)

Table No. 1: A list of antimicrobial agents and their mechanism of action



## **ANTIBIOTIC RESISTANCE**

The term antibiotic resistance (AR or ABR) is a subset of AMR (antimicrobial resistance), as it applies just to bacteria becoming resistant to antibiotics.[8] Antibiotic resistance is the capability of a microorganism to withstand the effects of an antibiotic. Antibiotic resistance is the capability of a bacterium or other microorganisms to survive and reproduce in the occurrence of antibiotic doses that were previously thought effective against them.[9] Antibiotic resistance was reported to occur when a drug loses its ability to prevent bacterial growth effectively. Bacteria become 'resistant' and keep on to multiply in the presence of therapeutic levels of the antibiotics.[10] Resistant microbes are more hard to treat, requiring alternative medications or higher doses of antimicrobials.[11] Resistance arises through 1 of 3 mechanisms: natural resistance in certain types of bacteria, genetic mutation, or by 1 species acquiring resistance from another.[12]

Usually, a large amount cells in a naive, susceptible bacterial population which can cause an infection are susceptible to particular antibiotic upon exposure. However, there is forever a minute sub-population of resistant bacterial cells that will be able to multiply at higher concentrations in inadequate antibiotic concentration which kill the subpopulation so that micro-organisms survives in the environment.[13] Resistance is often associated with reduced bacterial fitness, and it has been proposed that a reduction in antibiotic utilize will pose selective pressure to acquire resistance would benefit the fitter susceptible bacteria, enabling them to outcompete resistant strains over time.[14]

Antimicrobial resistance is rising globally because of bigger access to antibiotic drugs in developing countries.[15] Estimates are that 700,000 to several million deaths result per year.[16][17] Each year in the United States, at least 2 million people become infected with bacteria which is resistant to antibiotics and at least 23,000 people die as a result.[18] There are public calls for global collective action to address the threat that

include proposals for international treaties on antimicrobial resistance.[19] Worldwide antibiotic resistance is not totally identified, but poorer countries with weaker healthcare systems are more affected.[20]

### **Causes of antibiotic resistance**

Bacteria with resistance to antibiotics predate medical use of antibiotics by humans.[21,22] However, widespread antibiotic use has made more bacteria resistant through the process of evolutionary pressure.[23,24] Reasons for the widespread use of antibiotics in human medicine include:

- increasing worldwide availability over time since the 1950s
- Uncontrolled sale in several low or middle income countries, where they can be obtained over the counter without a prescription, potentially resulting in antibiotics being used when not indicated.[25] This may result in emergence of resistance in any remaining bacteria.

### **Clinical significance**

Increasing bacterial resistance is connected with the volume of antibiotic prescribed, as well as absent doses when taking antibiotics.[26] Inappropriate prescribing of antibiotics has been attributed to a number of causes, such as patients insisting on antibiotics and physicians prescribing them as they do not have time to give details why they are not necessary. Another cause can be physicians not knowing when to prescribe antibiotics or being overly cautious for medical or legal reasons.[27] For example, 70 to 80 percent of diarrhea is caused by viral pathogens, for which antibiotics are not helpful. But nevertheless, approximately 40 percent of these cases are attempted to be treated with antibiotics.[28] In some areas even over 80 percent of such cases are attempted to be treated with antibiotics.[28]

### **Natural occurrence**

Naturally occurring antibiotic resistance is general.[29] Genes for resistance to antibiotics, like

antibiotics themselves, are ancient.[30,31] The genes that confer resistance are identified as the environmental resistome.[32] These genes may be transferred from non-disease-causing bacteria to those that do cause disease, leading to clinically important antibiotic resistance.[32] In 1952 it was exposed that penicillin-resistant bacteria existed before penicillin treatment;[33] and also preexistent bacterial resistance to streptomycin.[34] There is evidence that heavy metals and additional pollutants may choose for antibiotic-resistant bacteria, generating a constant source of them in little numbers.[35]

### **Water pollution**

Antibiotic resistance is a rising problem among humans and wildlife in terrestrial or aquatic environments. In this respect, the extend and contamination of the environment, especially through water pollution "hot spots" such as hospital wastewater and untreated urban wastewater, is a growing and grave public health problem.[36,37] Antibiotics have been polluting the environment since their introduction through human waste (medication, farming), animals, and the pharmaceutical industry.[38] The contribution of the pharmaceutical industry is so important that parallels can be drawn between countries with highest rate of increasing antibiotic resistance and countries with largest footprint of pharmaceutical industry.[39] Along with antibiotic waste, resistant bacteria follow, thus introducing antibiotic-resistant bacteria into the environment. Already in 2011, mapping of sewage and water provide samples in New Delhi showed widespread and uncontrolled infection as indicated by the presence of NDM-1-positive enteric bacteria (New Delhi metallo-beta-lactamase 1).[40] As bacteria replicate rapidly, the resistant bacteria that come in water bodies through wastewater replicate their resistance genes as they carry on to divide. Antibiotic resistance is widespread in marine vertebrates, and they may be significant reservoirs of antibiotic-resistant bacteria in the marine environment.[41]

### **Veterinary medicine**

The World Health Organization (WHO) concluded that inappropriate use of antibiotics in animal husbandry is an underlying supplier to the emergence and spread of antibiotic-resistant germs, and that the use of antibiotics as enlargement promoters in animal feeds should be controlled.[42]

### **Mechanism of antibiotic resistance (ABR)**

The 4 major mechanisms by which bacteria exhibit resistance to antibiotics are:

1. Drug inactivation or modification: for example, enzymatic deactivation of *penicillin G* in some penicillin-resistant bacteria through the production of  $\beta$ -lactamases. Most usually, the protective enzymes produced by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will decrease its capability to attach to the bacterial ribosomes and disrupt protein synthesis.[43]

2. Alteration of target- or binding site: for example, alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria. Another defensive mechanism found among bacterial species is ribosomal protection proteins. These proteins defend the bacterial cell from antibiotics that target the cell's ribosomes to prevent protein synthesis. The mechanism involves the binding of the ribosomal protection proteins to the ribosomes of the bacterial cell, which in turn changes its conformational shape. This allows the ribosomes to keep on synthesizing proteins necessary to the cell while preventing antibiotics from binding to the ribosome to prevent protein synthesis.[44]

3. Alteration of metabolic pathway: for example, some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an significant precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides, instead, like mammalian cells, they turn to using preformed folic acid.[45]

4. Reduced drug accumulation: by decreasing drug permeability or increasing active efflux (pumping out) of the drugs across the cell surface.[46] These pumps within the cellular membrane of certain bacterial species

are used to pump antibiotics out of the cell before they are able to do any harm. They are often activated by a

specific substrate associated with an antibiotic.[47] as in fluoroquinolone resistance.[48]

5.

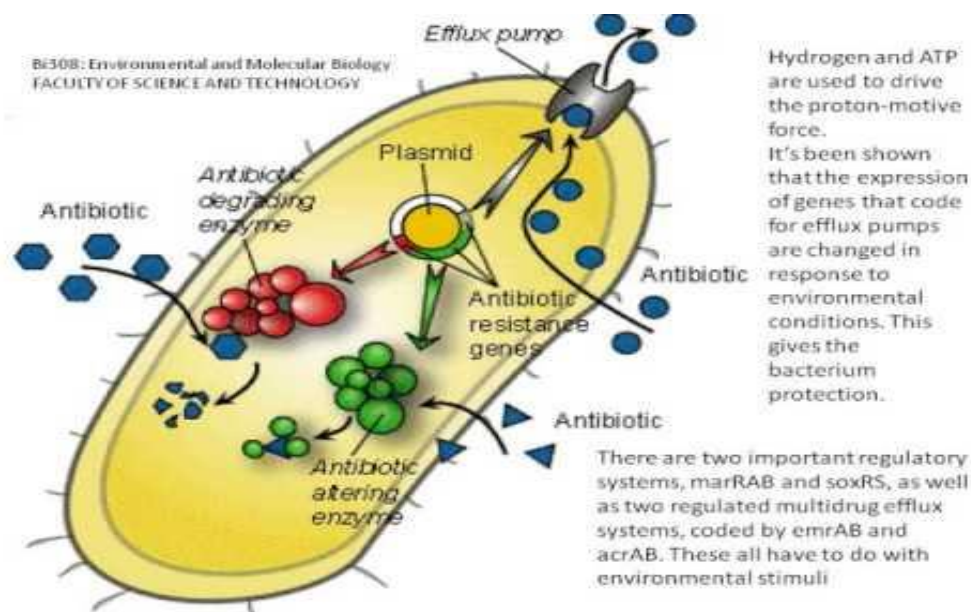


Figure No.2: Resistance mechanism of bacteria (Source taken by : (Adopted from <http://www.chembio.uoguelph.ca>), accessed on April 1, 2017.

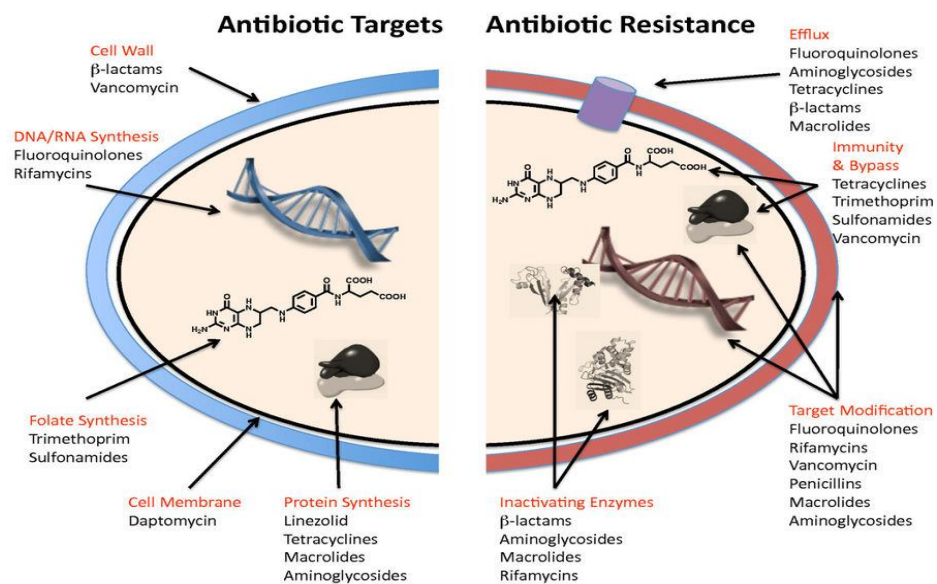


Figure No.3. A number of mechanisms used by common antibiotics to deal with bacteria and ways by which bacteria become resistant to them.

## **PREVENTION OF ANTIBIOTIC RESISTANT**

Defensive measures include only using antibiotics when needed, thereby stopping misuse of antibiotics. Narrow-spectrum antibiotics are preferred over broad-spectrum antibiotics when possible, as effectively and accurately targeting specific organisms is less likely to cause resistance, as well as side effects. There have been increasing public calls for global collective action to address the threat, including a proposal for international treaty on antimicrobial resistance. Further detail and attention is still needed in order to recognize and measure trends in resistance on the international level; the idea of a global tracking system has been suggested but implementation has yet to occur. A system of this nature would supplied insight to areas of high resistance as well as information necessary for evaluation of programs and other changes made to fight or reverse antibiotic resistance. There are a lot of prevention methods of antibiotic resistant and these are following:

### **1. Duration of antibiotics**

Antibiotic treatment duration should be based on the infection and other health problems a person may have. For a lot of infections once a person has improved there is little evidence that stopping treatment causes further resistance. Some therefore feel that stopping early may be reasonable in some cases. Other infections, however, do require long courses regardless of whether a person feels better.[49]

### **2. Monitoring and mapping**

There are multiple national and international monitoring programs for drug-resistant threats, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), extended spectrum beta-lactamase (ESBL), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *A. baumannii* (MRAB).[50]

### **3. Limiting antibiotic use**

Excessive antibiotic use has become 1 of the top contributors to the development of antibiotic resistance. Since the beginning of the antibiotic era, antibiotics have been used to treat a wide range of disease. Overuse of antibiotics has become the main cause of rising levels of antibiotic resistance.[51]

### **4. Industrial waste water treatment**

Manufacturers of antimicrobials need to improve the treatment of their wastewater (by using industrial wastewater treatment processes) to decrease the release of residues into the environment.[52]

### **5. Individuals**

To prevent and manage the spread of antibiotic resistance, individuals can:

- Only use antibiotics when prescribed by a certified health professional.
- Never demand antibiotics if your health worker says you don't need them.
- Always follow your health worker's advice when using antibiotics.
- Never share or use leftover antibiotics.
- Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practising safer sex, and keeping vaccinations up to date.
- Prepare food hygienically, following the WHO 5 Keys to Safer Food (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals.[53]

## **CONCLUSION**

Antimicrobial drug resistance occurs everywhere in the world and is not limited to industrialized nations.

Hospitals and other healthcare settings are battling drug-resistant organisms that spread inside these institutions. Drug-resistant infections also spread in the community at large. Examples include drug-resistant pneumonias, sexually transmitted diseases (STDs), and skin and soft tissue infections. Until the discovery and approval of new compounds, strategies can be employed to slow the development of resistance. For example, we must avoid under-dosing, which is a common yet often unrecognized factor associated with treatment failure and bacterial resistance. Resistance containment depends on very early empirical and aggressive treatment for potentially resistant pathogens, followed by de-escalation and narrowing of the antimicrobial spectrum after identifying the pathogen. Empirical therapy should be discontinued altogether if a diagnosis of infection seems unlikely. Deescalation is a crucial infection-management technique and an effective strategy that balances the need to provide early adequate antibiotic therapy to high-risk patients and the objective of avoiding antibiotic overuse. Current predictions

underestimate the potential role of antibiotic resistance in the emergence and resurgence of infectious diseases in the coming decades. Underestimates are usually due to lack of data, making it difficult to generalize about the impact of antibiotic resistance on treatment outcomes, and on global health and economic burdens. It would thus be justifiable and timely to encourage the implementation of international surveillance systems on antibiotic resistance. This could be achieved by connecting already existing national and international initiatives and by agreements on data collection and exchange. one alternative is to prevent antibiotic resistance by adding cytokines instead of antibiotics to animal feed These proteins are made in the animal body “naturally” after a disease and are not antibiotics, so they do not contribute to the antibiotic resistance problem. One of the major causes of antibiotic resistance is the decrease of effective drug concentrations at their target place, due to the increased action of ABC transporters. Proper planning can help us to overcome the problems associated with drug resistance in bacteria.

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