



(REVIEW ARTICLE)



## A review on antibiotics in the environment, resistance in microbes, impact on human health and treatment and future strategies for tackling the global problem

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World Journal of Advanced Research and Reviews, 2023, 20(01), 959-971

Publication history: Received on 19 August 2023; revised on 01 October 2023; accepted on 04 October 2023

Article DOI: <https://doi.org/10.30574/wjarr.2023.20.1.2047>

### Abstract

The introduction of antibiotics was a blessing to human civilization as the antibiotics saved several million human and animal lives. Due to overuse and misuse of antibiotics by humans in the healthcare, and agriculture sectors, the residues of the antibiotics were reported in all the segments of the environment (surface water, groundwater, river water, soil, sediments, wastewater effluent, hospital effluent, livestock, fish, fruits, vegetables and milk) from ng to mg/L or kg that results in the rapid increase in the number of antibiotic resistant bacteria. Antibiotic resistance has been listed by the World Health Organization before Covid 19 as one of the top 10 threats to human health globally. Though antibiotic resistance is inevitable it is mainly anthropogenic and is an important factor of increased healthcare costs, longer hospital stay stress on hospital beds and ICU and higher rates of morbidity and mortality. The invention of new antibiotics to cope the resistant bacterial infection is the need of the hour but as bacterial infections is not an ongoing process (have a lower return) unlike chronic diseases hypertension, and diabetes the pharmaceutical companies are not very interested in the inventions. This article discusses the antibiotics in the different compartments of the environment, the antibacterial mechanisms of the antibiotics, causes of development and mechanisms of antibiotic resistance in bacteria and mechanisms/methods to combat antibiotic resistance.

**Keywords:** Antibiotics; Environment; Humans; Antibiotic-resistant bacteria; Preventive mechanisms

### 1 Introduction

Bacteria have long occupied vital roles across diverse ecological niches, shaping Earth's ecosystems and performing essential functions well before humans emerged. This connection has enriched human knowledge and fostered a symbiotic relationship. While most bacterial species are not pathogens, their potential to cause infectious diseases underscores their significance. This delicate interplay highlights the microbial world's balance, with bacteria contributing to ecosystem stability, technological progress, and health challenges. The discovery of antibiotics, starting with Penicillin in 1927, marked a pivotal point in managing bacterial infections. These compounds, from natural and synthetic sources, have been hailed as a "Panacea" against infectious maladies. Antibiotics, with their diverse properties, are crucial for treating bacterial infections, either by eliminating bacteria or hindering their growth. Nevertheless, antibiotics are ineffective against viruses. Initially, antibiotics were substances one microorganism produced to inhibit another, but synthetic versions emerged, like salvarsan [1]. In the medical field, the most influential invention of the 20th century was the invention of antibiotics [2]. In the last decade of the 20th century, antibiotics helped in the development of medical fields like immunosuppressive therapies, and several surgical operations. These antibiotics operate through diverse mechanisms, targeting cell membranes, wall synthesis, metabolic rates, DNA/RNA synthesis, and protein formation [3]. Antibiotics have dual impacts on the environment- immediate effects as bactericidal or bacteriostatic agents, and long-term contributions to antibiotic-resistant bacteria due to factors like concentration and exposure duration. Misuse and overuse across sectors, especially agriculture, disrupt ecosystems (antibiotics residue is present in all the sectors of the environment i.e. surface water, groundwater, wastewater, seawater, sediments, sludge,

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and poultry manure soil) and fosters the spread of antibiotic-resistant genes [4-6]. Resistance extends to aquatic systems, impacting marine life and biodiversity. Livestock farming and soil also suffer from antibiotic-related challenges. Addressing antibiotic resistance requires global initiatives like antibiotic stewardship and environmental measures, particularly in developing nations, to ensure a sustainable future.

The survey of literature indicates that more than half of the antibiotics consumed are used for growth promotion, farm animals, aquaculture and in the agriculture sector [7], 2020 global consumption of antibiotics for food-producing animals was 99502 tonnes and is expected to become 107,472 tons by 2030 [8]. Oxazolidinones and cyclic lipopeptides are the only antibiotics which have been marketed in the last three and half decades [9-10]. If current trends continue, treating infections that are currently easily treatable will likely become impossible and we will enter an era similar to that before antibiotics were discovered. This will lead to not only an inability to prevent and treat bacterial infection but will also increase the risk of severe morbidity and mortality associated with routine medical procedures [11].

One of the major causes of the development of bacterial resistance to antibiotics is the presence of high concentrations in the environment (water, air, soil, sediments) due to anthropogenic activities and an increase in the usage of antibiotics globally (mainly in the developing and low-income countries) [12]. These resistance mechanisms can be associated with mobile genetic elements which can facilitate the dissemination of resistance elements through microbial communities [13]. About 90% of the consumed antibiotics are excreted by humans and animals in the active form via urine and faeces [14] and released into natural environments via sewage sludge, manure, wastewater (soil, waterways) contaminating and harming surrounding environments [15]. Antibiotic-resistant bacteria have been detected in polluted environments, along with measurable antibiotic concentrations that can range from ng/L to µg/L or ng/kg to mg/kg [16].

This study aims to provide data relating to environmental antibiotic resistance and its impact on human health.

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## 2 Antibiotic residues in the environment

Due to economic development, population increase, easy accessibility of antibiotics and to cure ageing persons in low-income and developing countries in the last two decades the consumption of antibiotics has almost doubled. Human and animal gut absorbs only a small fraction of the consumed antibiotic about 80-90% of the active antibiotics are excreted by humans/animals via urine and faeces which enter the environment. Antibiotics enter the environment from the following sources

- Humans,
- Animals,
- Agriculture,
- Aquaculture and
- Pharmaceutical industries.

Wastewater generated from hospitals, medicinal institutions, slaughterhouses, animal houses, dairy farms, drug manufacturing units, pouring of unused/expired medicines in the drain, households and sludge generated from wastewater contains residues of active or metabolites of antibiotics in low to high concentration. These antibiotics are accumulated in agricultural soil fields/crops/plants/vegetables via the use of sludge as soil conditioner and the application of wastewater for irrigation. The leachates from the soil also contaminate groundwater [17-18].

### 2.1 Antibiotic residues in the aquatic environment

Wastewater generated from hospitals, medicinal institutions, slaughterhouses, animal houses, dairy farms, drug manufacturing units, households, pouring of unused/expired medicines in the drain, effluent from leachate is the major source of contamination of groundwater, river water, and surface water by antibiotics. The review of the literature denotes that the residual concentration of antibiotics in river water ranges from ng/L to 2.5 mg/L [17, 19]; in wastewater/ sewage water the concentration of antibiotics ranges from a few ppb to 125 µg/L [20, 21]; in hospital effluent the concentration of antibiotic ranges from few ng/L to more than 100 µg/L [22-24]. The concentrations of antibiotic in surface water ranges from non-detectable to 0.42 mg/L [19, 25]; in the aquaculture effluent, the maximum concentration was of antibiotic ox tetracycline [26]. The data of the literature review also denotes that the antibiotic concentration in surface water near pharmaceutical industries was more than in the blood of patients who are treated with antibiotics.

## 2.2 Antibiotic residues in food (Meat, plant/vegetables)

A survey of the literature denotes that due to anthropogenic activities food (meat, fish, fruits vegetables, and milk) is contaminated with antibiotics. Zhang et al. [27] have reported antibiotics sulfonamides, tetracycline and fluoroquinolones were detected in livestock meat. The maximum concentration was of sulfonamides (424.4 ug/kg), followed by tetracyclines (23.76ug/kg) and fluoroquinolones (5.48 ug/kg). Tetracyclines, ciprofloxacin, streptomycin, macrolides, quinolones, and sulfinalamides were reported in chicken meat, and beef by several researchers [28-31]. Several antibiotics viz. amoxicillin, tetracycline, oxytetracycline, sulfamethoxazole, and erythromycin were reported in the milk samples [32-34]. Several antibiotics were reported in fruits and vegetables [35].

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## 3 The following mechanisms are reported for the anti-bacterial activities of the antibiotics

### 3.1 By inhibiting Cell wall synthesis

Beta-lactam (penicillin, ampicillin, cephalosporins etc) and glycopeptides (vancomycin) antibiotics inhibit the biosynthesis of peptidoglycan (a major component of the bacterial cell wall) resulting inhibition of the cell wall synthesis in bacteria [36, 37]. These antibiotics act on the gram-negative bacteria *E. coli*, *E. faecalis*, *Pseudomonas* and *Staphylococcus aureus*, *Staphylococcus epidermidis* etc. Carbapenems have the broadest activity of all antibiotics.

### 3.2 By inhibiting protein synthesis

Aminoglycosides antibiotics (streptomycin, neomycin, gentamycin) inhibit the protein synthesis in the bacteria (Enterobacteriaceae, *Pseudomonas*, *Rickettsia*, *Mycoplasma spirochetes*) by binding 30s rRNA subunit while antibiotic chloramphenicol inhibits peptide bond formation by binding 50s rRNA subunit of the bacteria viz, *H. influenzae*, *Staph. aureus* etc. [38,39].

### 3.3 By inhibiting nucleic acid synthesis

Some antibiotics show antibacterial activity by inhibiting RNA or DNA synthesis in the bacterial cell.

#### 3.3.1 RNA synthesis inhibitor

Antibiotic rifampin inhibits RNA transcription in *Staphylococcus mycobacterium* by inhibiting bacterial RNA polymerase enzymes [40].

#### 3.3.2 DNA synthesis inhibitor

Quinolones in gram-positive bacteria *Staphylococcus*, and *Pseudomonas* inhibit the DNA synthesis in bacteria by blocking DNA gyrase enzyme and topoisomerase [41].

#### 3.3.3 Metabolic pathways inhibitor

Sulphonamides, pyrimethamine, and trimethoprim inhibit the synthesis of folic acid in the UTI-causing organisms *Proteus enterobacter* [42-44].

#### 3.3.4 Cell membrane function inhibitor

Antibiotics polymyxin destroys the cell membrane in gram-negative bacteria by interacting with the lipopolysaccharide of the bacteria [45, 46].

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## 4 Antibiotic Resistance

Antibiotic resistance stands as one of the most pressing global threats of the 21st century, endangering human health on a scale reminiscent of the pre-penicillin era, where infections could spell death. Sir Alexander Fleming after finding the inappropriate use of penicillin in 1945 during the Nobel Prize acceptance speech warns regarding the resistance of bacteria to penicillin. Antibiotic resistance originating from the use of antibiotics in farm animals was initially observed by Levy et al. in 1976. They discovered that administering tetracycline-laden feed to farm animals led to the emergence of tetracycline-resistant bacteria in their gut within two weeks, subsequently spreading to farm workers within six months. Notably, 80% of farm workers exhibited tetracycline-resistant bacteria in their stool, compared to 7% of neighboring citizens. Pathogens such as *Escherichia coli*, *Klebsiella*, and *Staphylococcus aureus*, known to cause infections in humans, were identified in livestock and retail meat as becoming antibiotic-resistant in the animals' gut or skin [47-50]. These resistant bacteria then transmit resistance genes to other bacteria. Presently, antibiotic resistance leads to

over 1.58 million annual deaths worldwide, with devastating impacts particularly felt among children under five years old and newborns who succumb to blood infections caused by resistant bacteria [51]. Astonishingly, more than 10 million individuals grapple with antibiotic-resistant bacteria annually. Strikingly, the prevalence of resistance varies significantly based on socioeconomic status and population, with low and middle-income countries experiencing 2.67% of total deaths attributed to antibiotic resistance, compared to 1.14% in high-income countries. Forecasts predict that by 2050, unchecked antibiotic resistance could result in over 10 million deaths annually and the global economy will be affected by 100 trillion US dollars [52]. Alarming statistics reveal an annual influx of around 106 million new cases of antibiotic resistance. This phenomenon signifies bacteria's ability to evade drugs designed to eliminate them, rendering traditional treatments ineffective and sometimes futile. As per the literature, the resistance of bacteria to broad-spectrum antibiotics is increasing by 5-10% annually. The report of the Indian Council of Medical Research [53] denotes *E.coli* resistance to antibiotic imipenem increased from 14% in 2016 to 36% in 2021, and the antibiotic susceptibility to bacteria *Klebsiella pneumonia* decreased from 65% in 2015 to 43% in 2021. The ICMR report also stated that 87.5% of the bacteria *Actinobacter baumannii* infected patients showed resistance to broad-spectrum antibiotic carbapenem. As per the WHO report [54], 8.4-92.9% of the bacteria *E.coli* and 4.1% to 79.4 % of bacteria *Klebsiella pneumonia* show resistance to antibiotic ciprofloxacin. Tilahun et al. [55] during their studies found carbapenem (the last discovered antibiotic) resistant Enterobacteriaceae bacteria in several countries. Moreover, critical medical advancements, including surgical procedures, organ transplants, and cancer chemotherapy, depend on effective antibiotics for success. If the species and number of antibiotic-resistant bacteria increase as presently it will become impossible to treat infections we will be in the same era as before antibiotics were discovered and will enhance mortality during routine medical procedures [56]. The economic ramifications are also substantial, impacting not only individuals and societies but entire countries. Treating antibiotic-resistant infections incurs costs of approximately \$700 for a single infection and tens of thousands of dollars for multi-drug-resistant infections. The global GDP could plummet by 3.8% in the next five years if antibiotic resistance remains unchecked. Confronting this issue requires a comprehensive approach involving responsible antibiotic use, robust surveillance, research and development, infection prevention, public education, international collaboration, and regulatory measures. The urgency of the situation underscores the imperative for immediate and concerted action to avert a future where common infections regain their lethal potency. The list of bacteria with high antibiotic resistance is given below:

**Table 1** List of bacteria with high antibiotic resistance

SN	Bacterium	Gram strain	WHO Toxicity	Clinical infection	Problematic resistance
1.	<i>Acinetobacter baumannii</i> (MDR)	Negative	Critical	Pneumonia, UTI, septicaemia	All classes including carbapenem
2.	<i>Escherichia coli</i>	Negative	High	UTI, haemolytic-uremic syndrome, renal failure	B-lactam, fluoroquinolones, quinolones, aminoglycosides, gentamycin
3.	<i>Pseudomonas aeruginosa</i> (MDR)	Negative	Critical	UTI, Cystic fibrosis in lungs, Skin and soft tissue infections	Susceptible only to polymyxins, Carbapenem-resistant
4.	<i>Klebsiella pneumonia</i> (MDR)	Negative	Medium	Pneumonia, surgical wound infections	$\beta$ -lactam, quinolones, aminoglycosides,
5.	<i>Enterobacteriaceae</i> and CRE	Negative	Critical	Blood infections, wound infections, urinary tract infections and pneumonia, low blood pressure	$\beta$ -lactam, quinolones, Carbapenem-resistant
6.	<i>Neisseria gonorrhoeae</i>	Negative	High	Gonorrhoea	B-lactam, quinolones, cephalosporin, fluoroquinolone, tetracycline, macrolides

7.	<i>Helicobacter pylori</i>	Gram negative	High	Peptic ulcer, intestinal problems	clarithromycin-resistant
8.	<i>Campylobacter</i> spp	Gram Negative	High	diarrhoea (frequently bloody), abdominal pain, fever, headache, nausea,	fluoroquinolone-resistant
9.	<i>Salmonellae</i>	Gram Negative	High	Typhoid fever or paratyphoid fever.	fluoroquinolone-resistant
10.	<i>Haemophilus influenza</i> (medium)	Gram Negative	Medium	Bronchitis, Meningitis Cellulitis, Pneumonia, Septic arthritis	ampicillin-resistant
11.	<i>Shigella</i> spp	Gram Negative	Medium	Diarrhea (bloody), Stomach pain or cramps, Fever, Nausea or vomiting	fluoroquinolone-resistant
12.	<i>Staphylococcus aureus</i> and Methicillin-resistant <i>Staphylococcus aureus</i>	Positive	High	Skin and soft tissue infections, nosocomial infections	$\beta$ -lactam, glycopeptides and vancomycin
13.	<i>Streptococcus pneumonia</i> (MDR)	Positive	Medium	Pneumonia, bronchitis, meningitis	$\beta$ -lactam, microlides, quinolones
14.	<i>Clostridium difficile</i>	Positive	Medium	Diarrhoea, colitis	$\beta$ -lactam, quinolones
15.	<i>Enterococci faecalis</i> and VRE	Positive	High	UTI, surgical wound infections, endocarditis	B-lactam, glycopeptides and vancomycin
16.	<i>Mucobacterium tuberculosis</i> (MDR)	Positive	Medium	Tuberculosis	Rifamycin, isoniazid, aminoglycosides, quinolones, pyrazinamide,

## 5 Ways of spreading resistant bacteria to humans:

Antibiotic resistance develops both in the community and the hospitals [57]. Humans and animals excrete approximately 90% of the consumed antibiotics in the active form via urine and faeces which enter the environment via soil, wastewater discharge, and run-off from the agricultural fields. The presence of antibiotics from ng/L to ug/L or ug/kg is reported in surface water, drinking water, soils, sewage water, river water, hospital effluents, and sediments [58, 59].

Several routes facilitate the transmission of antibiotic-resistant bacteria to humans

### 5.1 Direct contact

By touching, coughing and sneezing in the crowd, by exposing bodily fluids and by touching contaminated surfaces, and/or animals. When food that is contaminated with resistant bacteria is prepared or eaten we are exposed to the infection [60].

### 5.2 Indirect

#### 5.2.1 Via food

When bacteria-contaminated food is consumed the resistant bacteria enters the gut of the consumer, the resistant bacteria causes infection later on and spreads to others [61].

### 5.2.2 Via water

Bacterial diseases like typhoid fever and cholera are caused by drinking bacterial-contaminated water. Water sources from drinking wells, river water, and effluents from wastewater plants contain resistant bacteria on drinking such water-resistant bacteria enters the body of the human [62].

### 5.2.3 Via healthcare facilities

Hospitals and other healthcare facilities are the hotspots for resistant bacteria, as high doses of antibiotics are used for the sick people who are in close vicinity; poor hygiene practices by visitors, patients, and healthcare staff; crowded ward; improper cleaning of instruments and other facilities and poor sanitation [63].

### 5.2.4 Via Travel

International travellers are one of the carriers for spreading the resistant bacteria across the world. Several researchers have reported that when travellers visit an area that has a high number of resistant bacteria these travellers carry such bacteria; the risk of carrying the resistant bacteria becomes very high when such persons are hospitalized [64].

### 5.2.5 Via Trade

Resistant bacteria also spread globally via the import and export of fruits, vegetables, meat, seeds, and grains by different countries [65].

## 5.3 Airborne resistant bacteria

Bacteria, viruses and fungi are present in the bioaerosols (the airborne particles of the size 0.001-100 µm). Li et al. [66] reported that the number and other profiles of resistant bacteria in the air of a city are directly correlated with the land use of antibiotics. Pathogens of clinical interest were reported in the airborne culturable bacteria [67-69]. Bacteria *Staphylococci aureus*, *Enterococci fecalis*, *Enterococci faecium*, *Acinetobacter spp.*, *E. coli*, and *P. aeruginosa* were detected in the air samples of the delivery room, intensive care unit, and operation theatre of the hospitals [70,71].

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## 6 Factors affecting the effectiveness of antibiotics

Antibiotic resistance develops both in the community and the hospitals.

Several factors that impact the effectiveness of antibiotics are:

### 6.1 Over-prescription of Antibiotics by Physicians

The unnecessary or improper use of antibiotics by medical professionals contributes significantly to antimicrobial resistance. Prescribing antibiotics for conditions they don't treat effectively, such as viral infections, fuels the development of resistant bacteria. A global survey has denoted that in developing countries 75% of cold patients use antibiotics for it. Studies have shown that the degree of resistance is directly proportional to the frequency of the antibiotic used [50, 57, 72] Due to the overuse of antibiotics during Covid-19, the resistance has been further enhanced.

### 6.2 Overuse/Misuse of Antibiotics in Agriculture and Animal Farming

Antibiotics are often employed in livestock farming to enhance growth and prevent diseases. However, this practice fosters the emergence of antibiotic-resistant bacteria in animals, which can be transmitted to humans through contaminated meat consumption or direct contact. The global consumption of antibiotics which depends on socioeconomic factors, prosperity of the citizenry and cultural differences is expected to be one lakh million tons in this sector by 2030 [73, 74].

### 6.3 Inadequate Hygiene, Infection Control, and Sanitation

Insufficient attention to hygiene and sanitation exacerbates the spread of infections and fuels antibiotic use. Poor infection control measures in healthcare settings facilitate the transmission of drug-resistant pathogens between patients. It is reported that globally more than 2 billion citizens drink feces-contaminated water and cannot access easily basic sanitary facilities. About 670 million people still defecate in the open [75-77].

#### **6.4 Improper Disposal of Healthcare Waste**

Incorrect disposal of waste from healthcare facilities can release antibiotic residues into the environment, amplifying the development of antibiotic-resistant bacteria.

#### **6.5 Global Travel**

As the species of the resistant bacteria differ with climatic, and socioeconomic conditions of the country, when travelling people become infected by consuming contaminated water, food, and contact with animals and/or by receiving medical aids brings these resistant bacteria to their country and pose a threat of spreading antibiotic-resistant bacteria across borders. Infected individuals can carry these bacteria to different regions, accelerating their global dissemination [78].

#### **6.6 Lack of New Antibiotic Discovery**

The discovery of novel antibiotics has slowed considerably due to the complexities and expenses involved in research and development. Since the late 1980s, few new antibiotics have reached the market, leaving gaps in our ability to combat evolving resistance. Since 1987 no antibiotics have been introduced in the market for commercial use and very few are in the advanced development stage for gram-negative bacteria. The discovery is not only expensive but also takes 8-10 years for development.

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### **7 Mechanisms of Antibiotic Resistance in Bacteria:**

Bacteria, a living organism adapt over time to survive, replicate and rapidly spread. So, bacteria adjust to their surroundings to survive and naturally evolve to become resistant to those antibiotics that intend to kill them. Antibiotic resistance in bacteria can arise through various mechanisms, enabling them to evade the effects of antibiotics [9, 46].

These mechanisms can be categorized as follows:

#### **7.1 Intrinsic Resistance**

Some bacteria possess natural mechanisms that render them resistant to certain antibiotics. This resistance often stems from structural characteristics. For instance, bacteria lacking a cell wall are impervious to antibiotics like penicillin, which target cell wall synthesis.

#### **7.2 Acquired Resistance**

When by acquisition of DNA from other resistant bacteria the non-resistant bacteria become resistant is termed as acquired resistance. This transfer of genetic material can confer resistance to specific antibiotics. An illustrative case is the resistance of *Mycobacterium tuberculosis* to rifamycin.

#### **7.3 Genetic Changes**

Bacteria can develop resistance by undergoing genetic alterations that influence the production of enzymes responsible for inactivating antibiotics. Changes in the structure of proteins (by replacing one or more amino acids) or enzymes can also lead to modifications in bacterial components and receptors, making it challenging for antibiotics to identify the bacteria. In addition, bacteria might employ drug efflux pumps to remove antibiotics from their cells. Altered cell wall proteins can prevent antibiotic entry. This mechanism is evident in the resistance of *Escherichia coli* (E. coli) and *Haemophilus influenza* to trimethoprim.

#### **7.4 DNA Transfer**

Bacteria are capable of sharing genetic material with other bacteria, allowing the transfer of resistance-conferring DNA through horizontal gene transfer [73, 79]. This genetic exchange occurs via multiple processes:

#### **7.5 Transformation**

Transformation means incorporation of naked DNA. During transformation intracellular contents with DNA fragments of a dead bacterial cell are taken up by a living bacterium and the DNA of the dead cell is incorporated into the chromosome of a living bacterium which results in the transformation of a susceptible bacterium to become resistant.

## 7.6 Transduction

During transduction process the genetic material transfer through phagocytosis. During transduction bacterium's DNA from one bacterial cell enters another cell via a bacteriophage-carrying genome.

## 7.7 Conjugation

Conjugation means direct contact-based transfer. During conjugation plasmid (Carrying chromosomal DNA) is transferred from one bacterium to another which is in physical contact. Genes present in plasmids encode enzymes that inactivate antibiotics. Plasmid transmission during conjugation is the major mechanism of acquiring bacterial resistance to antibiotics. An example of this is the resistance of *Staphylococcus aureus* to methicillin (MRSA).

These mechanisms collectively highlight the remarkable adaptability of bacteria in developing resistance to antibiotics. Combatting this challenge requires a comprehensive understanding of these mechanisms and the continued development of innovative strategies to counteract antibiotic resistance.

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## 8 Approaches to Combat Antibiotic Resistance

The resistance of bacteria to antibiotics is an ongoing and natural phenomenon, with bacteria constantly attempting to evade the effects of antibiotics. No medication can eliminate bacterial antibiotic resistance due to the vast variability in bacterial properties, making it impossible for a single drug to target all bacterial strains effectively.

### 8.1 Modification of Existing Antibiotics

Scientists have successfully altered antibiotics such as Penicillin and cephalosporin to counter bacterial resistance. However, the potential for modification remains limited.

### 8.2 Development of Novel Antibiotics

Over the past thirty years, the creation of new antibiotics has faced challenges. There have been no introductions of new antibiotics for human use since 1987. Additionally, the slow pace of drug development contrasts with the rapid emergence of resistance.

### 8.3 Global Collaborative Efforts

Similar to the global initiatives for COVID-19 vaccines, a dedicated worldwide endeavour is essential to combat antibiotic resistance. Reports indicate that approval for clinical trials of 43 antibiotics has been pending since December 2020.

### 8.4 Protein Inhibition Strategy

Mavridou et al. [80] have demonstrated a method to counter antibiotic resistance by inhibiting specific proteins in bacteria such as *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, all of which commonly cause human diseases. The inhibition of a protein, DsbA, responsible for antibiotic resistance, was found to be effective. Another study by Furniss et al. [81] suggests that disrupting disulfide bond formation and extracytoplasmic protein folding in bacteria can neutralize antibiotic resistance. Biochemist Wright proposed that bacteria can develop antibiotic resistance by producing proteins that inactivate antibiotics or mutate proteins that bind to antibiotics.

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## 9 Consequences of Antibiotic resistance

Due to antibiotic resistance, the effectiveness of the antibiotics decline so it becomes very challenging to treat the growing number of pneumonia, tuberculosis, gonorrhoea, and salmonellosis infections which leads not only to longer stays at the hospital, higher medical costs but also increased mortality [57,82]. Due to antibiotic resistance about 20% of cancer patients [83] are hospitalized in the intensive care unit to treat pneumonia and sepsis and 8.5% of deaths of cancer patients are due to sepsis [84]. Longer stays in the hospital enhance the chances of illness for more people in the community. To prevent the spread of infection in the community more intensive care units (ICUs) and isolation beds are needed which causes pressure on the healthcare system [85, 86]. Due to more infection, elective surgeries are deferred which not only cost hospital earning but also impacts the health of the patient. As per the Centers for Disease Control and Prevention estimation antibiotic resistance in the USA costs approximately \$55 billion every year (\$20 billion for health care and about \$35 billion for productivity loss) [87] and also estimated that by 2050 the global annual cost of the antibiotic resistance will be from \$300 billion to more than \$1 trillion [88]. The antibiotic-resistant bacteria



also impact organ transplant surgeries as patients are exposed to several infections. Santoro-Lopes and de Gouvea [89] have reported that multi-drug resistant pathogens increase the chances of the failure of liver transplants and may cause death.

World Bank report has stated that due to antibiotic resistance poverty in low-income countries will increase and the gap between developed and developing countries will widen. The World Bank studies have also reported that by 2050 the global GDP due to antibiotic resistance will decrease by 1% and of developing countries by 5-7% [87].

### 9.1 Ways of prevention

- To prevent spread of the antibiotic-resistant bacteria in the community there must be good personal hygiene (the hands must be washed with soap after food handling, going to the toilet etc. and cover our nose and mouth during coughing and sneezing).
- The vaccination must be taken when due.
- Avoid very close contact with sick people, particularly in the hospital.
- Prevent food-borne infections by washing fruits and vegetables, cooking food properly and drinking safe water.
- Understand that antibiotics only work against bacteria. They do not work for colds and cases of flu that are caused by viruses
- Take the antibiotic exactly as prescribed by the Physician and don't take the antibiotic when it is not prescribed by the physician.
- Don't save antibiotics for the next time.
- In the agriculture sector vaccination should be used instead of antibiotics.

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## 10 Conclusion

- Antibiotics due to their resistance to bacteria are considered one of the top 10 toxic pollutants of the 21st century and are present in all the compartments of the environment (groundwater, surface water, river water, hospital effluents, soil, manure, bio solids, milk, vegetables, crops fruits and fish) from ng to mg/L or kg.
- The development of antibiotic resistance and the transfer of antibiotic-resistant genes by bacteria are mainly due to the presence of residual antibiotics in pharmaceutical industries' wastewater, domestic wastewater and hospital effluents.
- The uptake of antibiotics by humans and animals not only causes the development of antibiotic-resistant bacteria but also causes allergies, alteration in intestinal function, optic neuropathy, brain abscess, urticarial, anaphylaxis, bronchospasm, hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness, Stevens-Johnson syndrome; toxic epidermal necrolysis.
- As the bacteria are becoming antibiotic-resistant at a fast pace and new antibiotics are not developed at the same pace there is extreme pressure on the healthcare sector.
- The growing number of antibiotic-resistant bacteria not only led to longer stay at hospital and higher cost of treatment but also widened the gap between developed and developing countries. As per WHO estimation if the number of antibiotic-resistant bacteria and genes increases at the same rate by 2050 the GDP of developing countries will decrease by 5-7%.

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