Reveiw Article

# Antibiotic Resistance: Challenges and Solutions

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## ABSTRACT

Antibiotics have played a pivotal role in modern healthcare. They have been instrumental in treatment and prevention of infections in various clinical settings, but effectiveness of antibiotics is decreasing which is largely because of development of antibiotic resistance. The development of generations of antibiotic-resistant microbes and their widespread distribution in microbes throughout the environment is because of many years of unremitting selection pressure from human and animal applications of antibiotics. This is a manmade situation, and with the help of natural processes, superimposed on nature.[1]

Until recently, the effects of antimicrobial resistance were not felt much as there has been a continuous stream of newer antibiotics. However, over the past 2 decades, there has been dearth of new antibiotics from pharmaceutical companies leading to inability to fight these MDR organisms.[2] This marked increase in antimicrobial resistance among common bacterial pathogens is now threatening this therapeutic accomplishment, jeopardizing the successful outcomes of critically ill patients and is cause of severe infections, complications, longer hospital stays and increased mortality.[3] In fact, the World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century.[4]

## ANTIBIOTIC RESISTANCE

Antibiotic resistance refers to changes in bacteria that reduce or eliminate an antibiotic's ability to destroy it.[5] Drug resistance happens to almost every antimicrobial drug, not just antibiotics, and almost all pathogens and parasites, not just bacteria.[6] Evidence from various published data from around the world indicates an overall decline in antibiotic effectiveness: resistance to all types of antibiotics, including last resort, is rising.[7]

The U.S. Centers for Disease Control and Prevention (CDC) estimates that at least 23,000 deaths and more than 2 million infections are because of antibiotic resistance each year in the United States. Total economic costs are also huge with estimated direct cost of $20 billion and additional productivity losses of $35 billion.[5] Similarly in Europe, an estimated 25,000 deaths are attributable to antibiotic-resistant infections, costing €1.5 billion annually in direct and indirect costs.[8] UK government review recently estimated that deaths from Antimicrobial resistance could rise from approximately 70,000 to around 10 million yearly by the year 2050.[9] Estimates indicate that more than 56,000 neonates die each year from resistance-attributable neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in India alone.[10]

## MECHANISM OF RESISTANCE

Antimicrobial resistance has been there since ages and it is because of the interaction between organisms and their environment. Since most antimicrobial compounds have been developed from natural molecules, the bacteria have evolved mechanisms to overcome their action in order to survive (Figure 1).

Thus, these bacteria are often considered to be "intrinsically" resistant to one or more antimicrobials.[4] However, in clinical settings, we are typically referring to the expression of "acquired resistance" in a bacterial population that was originally susceptible to the antimicrobial compound as the main focus of the problem. But this is a complex problem which will be described in following section.

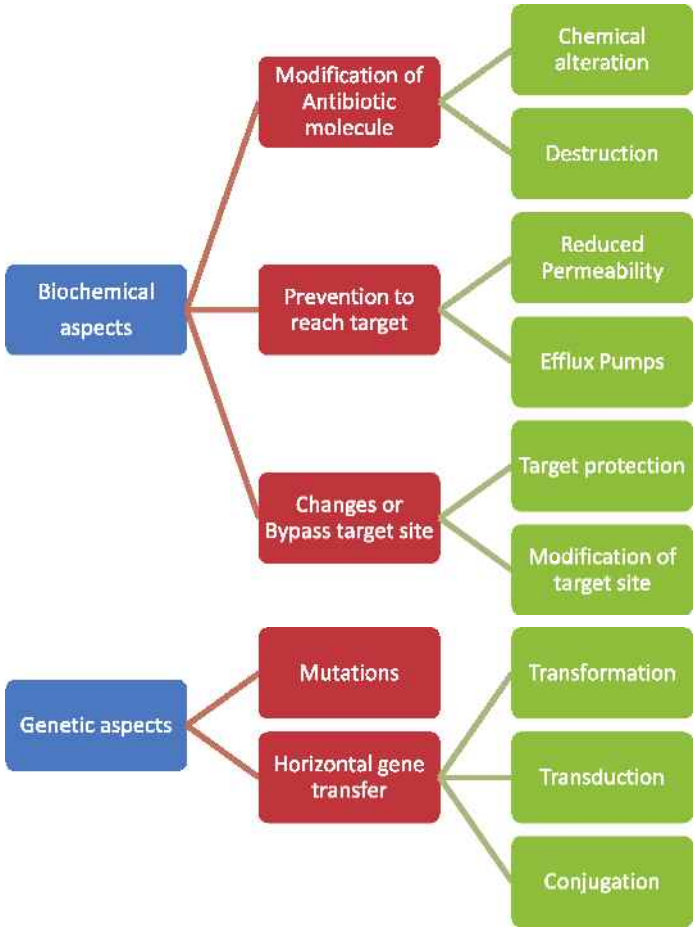


**Figure 1: Mechanism of resistance**

## GENETIC BASIS OF ANTIMICROBIAL RESISTANCE

Bacteria have a remarkable genetic plasticity that allows them to respond to a wide array of environmental threats. Bacteria with genes providing antibiotic resistance are found naturally in microbial populations: they can arise *de novo* because of random mutations in a bacterium or as a method of surviving antibiotics produced by competing bacteria.[11]

From an evolutionary perspective, bacteria use two major genetic strategies for survival against the antibiotics, a) spontaneously during bacterial DNA replication or b) the acquisition of new genes by DNA transfer from other bacteria or uptake of exogenous DNA.[4]

### Mutational resistance

Spontaneous mutation is one of the key mechanism bacteria use to survive stress conditions. In this scenario, in the presence of antibiotic drug, some of the bacterial cells derived from a susceptible population develop mutations in genes that affect the activity of the drug, resulting in preserved cell survival. Once a resistant mutant emerges and the antibiotic drug eliminates the susceptible population and the resistant bacteria predominate.[12]

In general, mutations resulting in antimicrobial resistance alter the antibiotic action via one of the following mechanisms,

a) target modification,
b) decreased uptake of drug,
c) activation of efflux mechanisms, or
d) enzymatic modulations in important metabolic pathways.

Thus, resistance arising due to acquired mutational changes is diverse and varies in complexity.[4]

### Horizontal gene transfer (HGT)

Acquisition of foreign DNA material through HGT is one of the most important drivers of bacterial evolution and it is frequently responsible for the development of

antimicrobial resistance. Furthermore, this genetic exchange has been implicated in the dissemination of resistance to many frequently used antibiotics.[4]

Classically, bacteria acquire external genetic material through three main strategies,

a) Transformation (transfer of free DNA from dead bacteria),
b) Transduction (transfer of DNA by viral delivery) and,
*c*) Conjugation (transfer of plasmid from a resistant bacteria).[13]

Transformation is perhaps the simplest type of HGT. Some bacteria such as *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*, appeared to be capable of uptake, integration, and functional expression of naked fragments of extracellular DNA, but only a handful of them develop clinically relevant resistance.[14] The mobilization or transfer of Antibiotic resistant genes by bacteriophages has been documented for various bacterial species. The transferable DNA sequences range from chromosomal DNA to mobile genetic elements such as plasmids, transposons and genomic islands.[4,14]

Conjugation is a very efficient method of gene transfer that involves cell-to-cell contact. It uses mobile genetic elements (MGEs) as vehicles to share valuable genetic information, although direct transfer from chromosome to chromosome has also been well characterized. The most important MGEs are plasmids and transposons, both of which play a crucial role in the development and dissemination of antimicrobial resistance among clinically relevant organisms. Not uncommonly, many plasmids contain more than one resistance gene. Thus, plasmid acquisition itself can in many cases confer resistance to multiple antibacterial agents.[4]

## BIOCHEMICAL BASIS OF ANTIMICROBIAL RESISTANCE

Antibiotic resistance mechanisms can be categorized according to the biochemical route involved in resistance[4,15]

1) modifications of the antibiotic molecule,
2) prevention to reach the antibiotic target and
3) changes and/or bypass of target sites

### 1. Modifications of the Antibiotic Molecule

Bacteria replace or modify antibiotic molecule by producing enzymes that inactivate the drug by adding specific chemical moieties to the compound or that destroy the molecule itself.

**A. Chemical alterations of the antibiotic**

The production of enzymes that degrade or modifies the antimicrobial molecule is a well-known mechanism of acquired antibiotic resistance in both gram-negative and gram-positive bacteria. The resulting effect is often related to steric hindrance that decreases the avidity of the drug for its target, which, in turn, is reflected in higher bacterial MICs. Many types of modifying enzymes have been described, include acetylation (aminoglycosides, chloramphenicol, streptogramins), adenylation (aminoglycosides, lincosamides), and phosphorylation (aminoglycosides, chloramphenicol).[4]

**B. Destruction of the antibiotic molecule**—One of the earliest and classical recognized mechanism of destruction of antibiotic molecule was by the discovery of β- lactamases. After penicillin became widely available, soon it was realized that, penicillin-resistance is clinically relevant and the mechanism of resistance was found to be a plasmid-encoded penicillinase that was readily transmitted.[1] These enzymes destroy the amide bond of the β-lactam ring, rendering the β-lactam antimicrobial ineffective. In order to overcome this problem, new β-lactam compounds with wider spectrum of activity and less susceptibility to penicillinases (such as ampicillin) were manufactured. However, during the 1960s a new plasmid-encoded β-lactamase capable of hydrolyzing ampicillin was found among gram-negatives (known as TEM-1). From then on, newer generations of β-lactams has been developed, but has systematically been followed by the rapid appearance of enzymes capable of destroying them (e.g. Extended spectrum β-lactamase and Carbapenemase), in a process that is a prime example of antibiotic-driven adaptive bacterial evolution.[4,16]

New Delhi metallo-β-lactamase (NDM-1) is a recently identified broad spectrum carbapenemase with ability to inactivate all β-lactams except aztreonam. However, most of the NDM-1-producers also produce aztreonam hydrolysing-β-lactamases thereby making these pathogens absolutely resistant to all β-lactams.[17] Another worrying concern is the ability of *blaNDM* gene to be readily transmissible among different types of gram-negative organisms, spreading to many countries in a short span of time and becoming one of the most feared resistance determinants in several parts of the world. Particularly in the Indian subcontinent (i.e. India and Pakistan), the *blaNDM* gene is not only extensively

disseminated among nosocomial pathogens, but it is frequently found in community-associated isolates.[4]

**2. Decreased Antibiotic Penetration and Efflux**

**A. Reduced permeability**—Many antibiotics have intracellular bacterial targets or, in case of gram-negative bacteria, targets are located in the cytoplasmic membrane. Therefore, the compound must penetrate the outer and cytoplasmic membrane in order to exert its antimicrobial effect. Bacteria have developed mechanisms to decrease the uptake of the antimicrobial molecule. This mechanism is particularly important in gram-negative bacteria, limiting the influx of substances from the external milieu.

Alterations of porins could be achieved by 3 general processes,

I) a replacement in the type of porins expressed,
ii) alteration in the level of porin expression, and
iii) impairment of the porin function. Importantly, changes in permeability through any of these mechanisms frequently result in low-level resistance and are often associated with other mechanisms of resistance, such as increased expression of efflux pumps.

Example of porin-mediated resistance is the aberrant production of OprD in *Ps. aeruginosa*, which is normally used for the uptake of basic amino acids and antibiotics.[4]

**B. Efflux Pumps**— The efflux pumps are the membrane proteins that export the antibiotics out of the cell and keep its intracellular concentrations at low levels. They not only provide intrinsic resistance to the bacteria but also when overexpressed, efflux pumps can also confer high levels of resistance to previously clinically useful antibiotics. This mechanism of resistance affects a wide range of antimicrobial classes including protein synthesis inhibitors, fluoroquinolones, β-lactams, carbapenems and polymyxins. The genes encoding efflux pumps can be located in MGEs or in the chromosome.[16]

**3. Changes in Target Sites**

Most antibiotics specifically bind to their targets with high affinity, thus preventing the normal activity of the target. So interfering with these target site results in antimicrobial resistance. To achieve this, bacteria have evolved different mechanisms, including protection of the target and modifications of the target site that result in decreased affinity for the antibiotic molecule.

**A. Target protection**—Although some of the genetic determinants coding for proteins that mediate target protection have been found in the bacterial chromosome, most of the clinically relevant genes involved in this mechanism of resistance are carried by MGEs. Examples of drugs affected by this mechanism include tetracycline (Tet[M] and Tet[O]), fluoroquinolones (Qnr) and fusidic acid (FusB and FusC).

**B. Modification of the target site**—Introducing modifications to the target site is a common mechanisms of antibiotic resistance in bacterial pathogens affecting almost all families of antimicrobial compounds. These target changes may consist of:

a) point mutations in the genes encoding the target site,
b) enzymatic alterations of the binding site (e.g. addition of methyl groups), and/or
c) replacement or bypass of the original target.[4]

## TRENDS IN ANTIBIOTIC RESISTANCE

Antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL) producers, and carbapenem-resistant Enterobacteriaceae, are increasing in prevalence worldwide, resulting in infections that are difficult and expensive to treat.

*Escherichia coli*: In five of the six WHO regions, some countries reported *E. coli* resistance of more than 50 percent to fluoroquinolones and third-generation cephalosporins.[18] In India, From 2008 to 2013, *E. coli* resistance to third generation cephalosporins increased from 70% to 83%, and fluoroquinolone resistance increased from 78% to 85%. Resistance to carbapenems in *E. coli* isolates increased from 10% in 2008, to 13% in 2013.[19]

*Klebsiella pneumoniae* resistance rates to third-generation cephalosporins are above 30 percent in most WHO member countries and exceed 60 percent in some regions.[18] In India, amongst *Klebsiella pneumoniae* isolates, third-generation cephalosporin resistance decreased from 90% to 80%, and fluoroquinolone resistance increased from 57% to 73%. Carbapenem resistance among *K. pneumoniae* jumped from just 2% in 2002 to 52% in 2009 in one tertiary-care hospital in New Delhi.[19]

MRSA resistance rates exceed 20 percent in all WHO

regions and are above 80 percent in some regions.[18] In India, a large private laboratory network reported a steep increase in MRSA, from 29 % in 2009 to 47 % in 2014 of *S. aureus* isolates.[7]

High levels of resistance have been reported in *N. gonorrhoeae* isolates (beta-lactamase producers), *Salmonella Typhi* isolates (fluoroquinolones), *Enterococcus faecium* isolates (11% were vancomycin resistant).[19]

*E. coli* and *Klebsiella* spp. carrying NDM-1 now account for the majority of carbapenem resistance in some countries. From their original detection in 2008, NDM-1–carrying Enterobacteriaceae have been identified in more than 70 countries in all regions.[17]

## REASONS FOR INCREASE IN ANTIMICROBIAL RESISTANCE

Following are the reasons for increase in antimicrobial resistance (Figure 2).

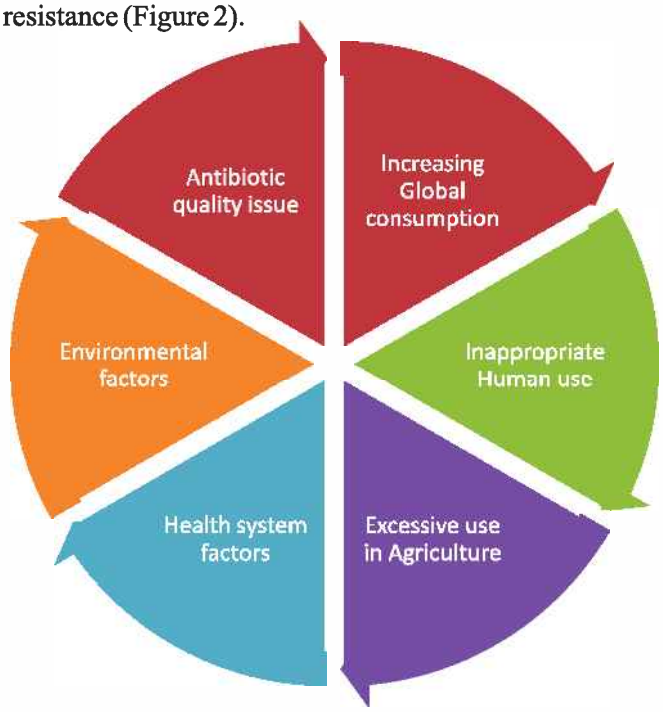


**Figure 2 : Reasons for increase in Antimicrobial resistance**

### 1. GLOBAL CONSUMPTION

Antibiotic use is a major driver of resistance and demand for antibiotics continues to rise and thus the antibiotic resistance.[20] Between 2000 and 2010, total global antibiotic consumption grew by more than 30 percent, from approximately 50 billion to 70 billion standard units, based on data from 71 countries. Although per capita consumption is still generally higher in high-income countries, the greatest increase in antibiotic use between 2000 and 2010 was in Lower to Middle Income countries (LMIC), where use continues to rise. In 2010, India was the world's largest consumer of antibiotics for human health at 12.9 x $10^9$ units (10.7 units per person). The next largest consumers were China at 10.0 x$10^9$ units (7.5 units per person) and the US at 6.8 x$10^9$ units (22.0 units per person). 76 % of the overall increase in global antibiotic consumption between 2000 and 2010 was attributable to BRICS countries.[21] Worldwide, increases were also significant for two "last-resort" antibiotic classes : carbapenems (approximately 40 percent) and polymyxins (13 percent). The growth in retail carbapenem sales was particularly steep in India, Pakistan, and Egypt.[7]

### 2. HUMAN USE OF ANTIBIOTICS

An estimated 80 percent of all antibiotics are used in the community, where prescribing and purchasing of antibiotics without prescription are common, especially in LMICs. In many countries at all economic levels, clinicians have incentives to overuse antibiotics.[7] In hospital settings, the confluence of patients with serious medical conditions, interconnectedness of hospitals through mobile patient populations, and high density of antibiotic use make antibiotic use disproportionately important.

Another issue with antibiotic consumption is inappropriate antibiotic use. It is estimated that from 20 to 50 percent of total antibiotic use is inappropriate.[7] "Inappropriate" can mean use of antibiotics when no health benefit is possible, such as to treat upper respiratory tract infections caused by viruses or malaria or acute diarrhoeas, this may occur because of an absence of clinical training and guidelines on antibiotic treatment available to physicians, or because of a lack of diagnostics and trained personnel to conduct testing and identify the cause and susceptibility of the infection.

It also comprises of suboptimal use of antibiotics for responsive conditions, such as the choice of drugs with an unnecessarily broad spectrum, an incorrect dosage or duration, or poor patient adherence to the prescribed treatment.[7] In addition, more than 50% of patients worldwide fail to take their medications properly. Either overuse or underuse of antibiotics can also result in serious antimicrobial resistance.[22]

## 3. HEALTH SYSTEM FACTORS

Health system factors are also at fault. Infection control in hospitals is poorly monitored and could be improved. Inadequate national commitment to a comprehensive and coordinated response and ill−defined accountability with respect to antimicrobial use and resistance is an issue to be considered. Weak surveillance and regulatory system is also an important determinant of antimicrobial resistance. Samples are generally tested only when patients fail to respond to common treatments.[23] Other structural and behavioral drivers include education, access to insurance, antibiotic costs, and patient demand. Over-the-counter access to antibiotics is a problem, but regulations to restrict access have to be balanced against the need to maintain access for the significant proportion of the population that lacks access to doctors. Indeed, lack of access to effective and affordable antibiotics still kills more children in countries like India than does drug resistance. Use of wide range of fixed-dose combinations in the market, often without scientific or medical merit or evaluation.[19]

## 4. ANTIBIOTICS IN AGRICULTURE

Of all antibiotics sold in the United States, approximately 80% are sold for use in animal agriculture. Global antibiotic consumption in livestock was conservatively estimated at 63,200 tons in 2010, accounting for nearly two-thirds of the estimated 100,000 tons of antibiotics produced annually worldwide. By 2030, consumption is projected to rise by two-thirds, to 105,600 tons.[7]

Antibiotics have three roles in animal production: to treat individual animals with bacterial infections, to prevent infections, and to promote growth. The third role, growth promotion, has no counterpart in human antibiotic use. It accounts for the majority of use in animals and is the focus of most legal and regulatory efforts to reduce antibiotic consumption in livestock and poultry. Growth promotion is accomplished with ultra low doses of antibiotics mixed with feed by the manufacturer or the farmer.[7]

There is growing evidence that antibiotic resistance in humans is promoted by the widespread use of this non-therapeutic antibiotics in animals. Resistant bacteria are transmitted to humans through direct contact with animals, by exposure to animal manure, through consumption of undercooked meat, and through contact with uncooked meat or surfaces meat has touched.[24]

## 5. ENVIRONMENTAL FACTORS

Despite the widespread nature of antimicrobial resistance, limited focus has been placed on the role of environmental factors in propagating resistance. There are only few studies that examine the role of the environment, specifically water, sanitation and hygiene factors that contribute to the development of resistant pathogens. Antibiotics result in contamination of various aspects of the environment and this can result in the introduction of resistance genes and resistant bacteria into the human food chain and clinical environments. These factors are often interlinked with gene transfer going in both directions, perpetuating the cycle of Antimicrobial resistance. There is however scope for both innovative and traditional environmental public health approaches, including the provision and enforcement of adequate standards and guidelines, basic food safety, secondary treatment of water and wastewater/waste products, basic sanitation and hygiene practices, to eliminate or reduce the problem.[25]

## 6. ANTIBIOTIC QUALITY ISSUES

### Substandard manufacturing

Poorly manufactured drugs may enter the market because of insufficient quality control and a lack of necessary microbiological technologies for testing. Even antibiotics that were manufactured to specifications may degrade before they reach consumers because of hot climates, bottlenecks and delays in supply chains, poor storage conditions, and weak distribution systems.[7]

### Counterfeit drugs

Counterfeit medicines may enter the market as a result of crime, corruption, and consumers' reliance on informal drug sellers. It has been estimated that sales of falsified medicines are worth more than $75 billion. The WHO and FDA have estimated that up to 10 percent of drugs worldwide— perhaps even 30 percent in some low- and middle-income countries (LMICs)—may be counterfeit. In Africa and Asia, up to 60 percent of antimicrobials may be falsified, a number that increased 10-fold in the decade from 2002 to 2012.[7]

Experts have recommended stiffer punishments for

counterfeit drug producers and stricter enforcement of current laws. Developing better, simpler, and more accessible testing methods for substandard drugs could bolster both surveillance and control efforts.[7]

## EXTENDING ANTIBIOTIC EFFECTIVENESS

Global Antibiotic Resistance Partnership (GARP) has put emphasis on six strategies will contribute to slowing resistance and maintaining the effectiveness of current drugs[7](Figure 3).

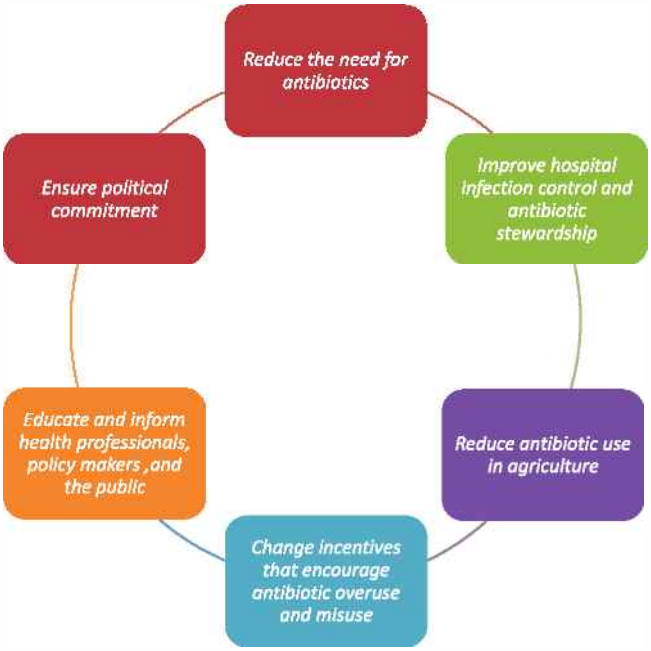


**Figure 3: Strategies to extend antibiotic effectiveness**

**1. Reduce the need for antibiotics.**

The most attractive strategy is to reduce the need for antibiotics by reducing the burden of infectious diseases requiring antibiotics. This can be achieved by improving vaccination coverage, improving access to clean water and sewerage systems, and ensuring a safe and healthful food supply.

**2. Improve hospital infection control and antibiotic stewardship.**

Infections can spread within hospitals. Hand washing with soap or using alcohol disinfectant between patients and good environmental cleaning are necessary but not sufficient to prevent the spread of infections. Other hospital-based interventions to improve antibiotic use include antibiotic stewardship programs and surveillance of resistance and hospital-acquired infections to guide clinical and policy decision making.[7]

**3. Change incentives that encourage antibiotic overuse and misuse**

Economic incentives can encourage the overuse of antibiotics all along the supply chain—in hospitals and communities and in agriculture. Doctors may benefit from prescribing a particular drug or more expensive drugs. Hospitals may also rely on antibiotics to treat infections that could be prevented with improved infection control.[7]

**4. Reduce antibiotic use in agriculture.**

Eliminating antibiotic use for growth promotion and minimizing use for disease prophylaxis need not jeopardize animal or human health. Documenting levels and patterns of antibiotic use in agriculture will provide a sound basis for reviewing and strengthening laws and regulations. Incentivizing the rational use of antibiotics is important in the veterinary field as well.[7]

**5. Educate and inform health professionals, policy makers ,and the public.**

Education and guidelines for healthcare professionals, engagement with policymakers, and national awareness campaigns for the public will begin changing the norms in antibiotic use and promote conservation. The educational component of antibiotic stewardship programs is often conducted at the hospital level, but guidance on antibiotic prescribing, antibiotic stewardship, and infection control can be incorporated into both undergraduate and postgraduate medical programs to instill appropriate prescriber practices early on.[7]

**6. Ensure political commitment.**

Generating local interest and pressure by healthcare professionals and the public and undertaking a thorough situation analysis are necessary to build political commitment and cooperation for combating antibiotic resistance. Thereafter, politicians need to allocate time, money, and resources to designing and implementing strategies to promote the rational use of antibiotics. In addition, government can convene academics and stakeholders from other government sectors to create locally relevant, evidence-based policies. Examples of such political efforts include the Jaipur Declaration on Antimicrobial Resistance, in which WHO Southeast

Asia member states committed to developing multisectoral national alliances to develop national antibiotic policies.[7]

## GLOBAL AND NATIONAL COMMITMENTS

In May 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance, which calls on all countries to adopt national strategies within two years.[26] In the United States, the National Action Plan for combating antibiotic-resistant bacteria stresses the need to slow the spread of antibiotic resistance through stewardship at all levels. The European Union has taken a similar stance. Southeast Asian WHO countries committed to addressing the issue in the Jaipur Declaration.[7]

Government of India released national treatment guidelines for antimicrobial use in infectious diseases in 2016. Recently realizing the need to contain Antimicrobial resistance, Government of India made its National Action Plan on Antimicrobial Resistance which outlines the priorities and interventions planned to be implemented over 2017 – 2021 to tackle the public health challenge of Antimicrobial resistance in India. The National Centre for Disease Control (NCDC) has been appointed as the focal point for implementation and coordination of the Antimicrobial resistance programme. The National action plan has objectives of enhancing awareness, strengthening surveillance, improving rational use of antibiotics, reducing infections, promoting research and to provide leadership on antimicrobial resistance with collaborations.[27]

## SURVEILLANCE SYSTEMS

Many countries have at least partial surveillance systems in place to report and track antibiotic resistance trends. The Indian Council of Medical Research began setting up the Anti-Microbial Resistance Surveillance Network in 2011. Its seven nodes will focus on (i) diarrhea (e.g., *Shigella*, *Vibrio cholerae*), (ii) enteric fever (e.g., *Salmonella* Typhi, *S.* Paratyphi), (iii) sepsis caused by Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella pneumoniae*), (iv) other Gram-negative organisms (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*), (v) Gram-positive bacteria (e.g., MRSA and VRE), (vi) fungal infections (e.g., *Candida* spp.), and (vii) respiratory pathogens (e.g., *Streptococcus pneumoniae*). Each node will focus on certain set of organisms. Medical colleges across the country will act as regional centers.[19]

Antibiotic resistance data in India are also collected as a part of CDDEP's Resistance Map (www.resistancemap.org), which represents invasive isolates from blood and cerebrospinal fluid. Resistance Map tracks the following pathogens: *E. coli*, *K. pneumoniae*, *A. baumannii*, *S. aureus*, *P. aeruginosa*, *Enterobacter* spp., *Salmonella* Typhi, *Salmonella* Paratyphi, and *Enterococcus* spp.[7]

## NEW ANTIBIOTICS AND OTHER INTERVENTIONS

There has been dearth of new antibiotic research and development. Scientific, economic, and regulatory barriers all contribute to the antibiotic market failure. Many scientific solutions have been suggested like finding new screening strategies to identify novel antibiotic scaffolds and to disarm the pathogen without killing it or modulate the host response to the organism without targeting the organism for destruction.[28] As of December 2014, at least 37 new antibiotics, developed by mainly small companies, were in the development pipeline for approval in the United States. Eight of these were in phase 3 trials. In 2015, teixobactin, an antibiotic belonging to a new class, was discovered through the novel growth of uncultured organisms in a laboratory at Northwestern University. Also some older antibiotics that had been largely phased out have been returned to use to treat multi drug resistant infections, colistin being the most prominent one.

Also, for at least some antibiotics, resistance levels decrease with declining use, conserving and even recovering some antibiotic effectiveness. In some high-income countries, where antibiotic stewardship has taken hold and public health is good, antibiotic resistance levels have stabilized or declined. The availability of rapid diagnostics for the healthcare provider would greatly enhance the ability to prescribe more appropriately. A test to distinguish a viral from a bacterial infection, for example, one based on procalcitonin levels, should decrease unnecessary antimicrobial use. More rapid susceptibility tests would aid the initial selection of an antibiotic.[6]

Alternative and complementary approaches to infection control and treatment, such as improved diagnostic tools, new vaccines, and bacteriophages, will also help maintain the effectiveness of current and emerging antibiotics. Global antibiotic stewardship in the broadest sense should make it possible not only to conserve the current

effectiveness of existing antibiotics, but even to reclaim some of effectiveness that has been lost.[7]

## CONCLUSION

The importance and value of antibiotics cannot be overestimated; we are totally dependent on them for the treatment of infectious diseases, but rise in antibiotic resistance in bacteria has lead to therapeutic failure. With the advent of Multi-drug resistant and Pan-drug resistant organisms, antibiotic resistance has become a major public health problem. Factors leading to this problem include increased use and misuse of antibiotics, lack of education and awareness among public and healthcare providers, poor public health infrastructure, widespread antibiotic use in animal farming, and the unregulated sale of cheap antibiotics.

Urgent priorities need to be implemented like improving infection prevention and control practices, optimizing prescribing (through antimicrobial stewardship), improving professional education, training and public engagement, developing new drugs, treatments and diagnostics, better access to and use of surveillance data, better identification and prioritization of research needs and strengthened international collaboration.

A complete understanding of the mechanisms by which bacteria become resistant to antibiotics is of paramount importance to design novel strategies to counter the resistance threat. Otherwise preantibiotic era awaits our future.

## REFERENCES


1. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010 Sep;74(3):417-33. doi: 10.1128/MMBR.00016-10.
2. Infectious Diseases Society of America (IDSA). 2004. Bad Bugs, No Drugs. Alexandria. https://www.fda.gov/ohrms/dockets/dockets/04s0233/04s-0233-c000005-03-IDSA-vol1.pdf
3. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014 Dec;5(6):229-41. doi: 10.1177/2042098614554919.
4. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr 2016 Apr;4(2). doi: 10.1128/microbiolspec.VMBF-0016-2015.
5. Centers for Disease Control and Prevention (CDC). 2013. Antibiotic Resistance Threats in the United States. Atlanta. https://www.cdc.gov/drugresistance/threat report -2013/pdf/ar-threats-2013-508.pdf
6. Levy SB, Marshall B. Antibiotic resistance worldwide: Causes, challenges and responses. Nature Medicine. 2004;10:S122-S129. doi:10.1038/nm1145.
7. Gelband H, Miller-Petrie M, Pant S et al. State of the World's Antibiotics, 2015. Center for Disease Dynamics, Economics & Policy. 2015: Washington, D.C.
8. European Medicines Agency (EMA) and European Centre for Disease Prevention and Control (ECDC). 2009. The Bacterial Challenge: Time to React a Call to Narrow the Gap Between Multidrug-Resistant Bacteria in the EU and Development of New Antibacterial Agents. Stockholm. https://ecdc.europa.eu/sites/portal/files/media/ en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf
9. The PLOS Medicine Editors (2016) Antimicrobial Resistance: Is the World UNprepared? PLoS Med 13(9): e1002130. doi:10.1371/journal.pmed.1002130
10. Laxminarayan R, Bhutta ZA. Antimicrobial resistance-a threat to neonate survival. Lancet Glob Health. 2016 Oct; 4(10):e676-7. doi:10.1016/S2214-109X(16)30221-2.
11. Smith RA, M'ikanatha NM, Read AF. Antibiotic resistance: a primer and call to action. Health Commun. 2015;30(3):309-14. doi: 10.1080/10410236.2014.943634. Epub 2014 Aug 14.
12. Cag Y, Caskurlu H, Fan Y, Cao B, Vahaboglu H. Resistance mechanisms. Ann Transl Med 2016;4(17): 326. doi: 10.21037/atm.2016.09.14
13. Chellat MF, Raguž L, Riedl R. Targeting Antibiotic Resistance. Angew Chem Int Ed Engl. 2016 Jun 1;55 (23):6600-26. doi: 10.1002/anie.201506818. Epub 2016 Mar 22.
14. von Wintersdorff CJ, Penders J, van Niekerk JM, Mills ND, Majumder S, van Alphen LB, Savelkoul PH, Wolffs PF. Dissemination of Antimicrobial Resistance in Microbial Ecosystems through Horizontal Gene Transfer. Front Microbiol. 2016 Feb 19;7:173. doi: 10.3389/fmicb.2016.00173.
15. Džidic S, Šuškovic J, Kos B. Antibiotic resistance mechanisms in bacteria: biochemical and genetic aspects. Food Technol Biotechnol. 2008, 46 (1) : 11-21.
16. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 2015 Jan;13(1):42-51. doi: 10.1038/nrmicro3380. Epub 2014 Dec 1.
17. Shakil S, Azhar EI, Tabrez S, Kamal MA, Jabir NR, Abuzenadah AM, Damanhouri GA, Alam Q. New Delhi metallo-β-lactamase (NDM-1): an update. J Chemother. 2011 Oct;23(5):263-5.
18. Antimicrobial Resistance: Global Report on Surveillance. World Health Organization (WHO).Geneva.2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789

241564748_eng.pdf

19. Laxminarayan R, Chaudhury RR. Antibiotic Resistance in India: Drivers and Opportunities for Action. PLoS Med. 2016 Mar 2;13(3):e1001974. doi: 10.1371/journal.pmed.1001974.
20. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014 Jan 9;14:13. doi: 10.1186/1471-2334-14-13.
21. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014; 14(8):742–50. doi: 10.1016/S1473-3099(14)70780-7.
22. Mao W, Vu H, Xie Z, Chen W, Tang S. Systematic review on irrational use of medicines in China and Vietnam. PLoS One. 2015 Mar 20;10(3):e0117710. doi: 10.1371/journal.pone.0117710.
23. Kumar SG, Adithan C, Harish BN, Sujatha S, Roy G, Malini A. Antimicrobial resistance in India: A review. J Nat Sci Biol Med. 2013 Jul;4(2):286-91. doi: 10.4103/0976-9668.116970.
24. Martin MJ, Thottathil SE, Newman TB. Antibiotics Overuse in Animal Agriculture: A Call to Action for Health Care Providers. Am J Public Health. 2015 Dec;105(12):2409-10. doi: 10.2105/AJPH.2015.302870. Epub 2015 Oct 15.
25. Fletcher S. Understanding the contribution of environmental factors in the spread of antimicrobial resistance. Environ Health Prev Med. 2015 Jul;20(4):243 - 52. doi: 10.1007/s12199-015-0468-0. Epub 2015 Apr 29.
26. Antimicrobial resistance: Draft Global Action Plan on Antimicrobial Resistance. World Health Organization (WHO). Geneva. 2015. http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf
27. National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017 – 2021. April 2017. Government of India.
28. Spellberg B. The future of antibiotics. Crit Care. 2014 Jun 27; 18(3):228. doi: 10.1186/cc13948.

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