e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 13, Issue 5; 2025, 34-39

Antibiotic Resistance: A Persistent Global Health Threat and Pathways to Overcome It

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Received: 16-08-2025 / Revised: 13-09-2025 / Accepted: 29-09-2025
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Conflict of interest: No conflict of interest.

Abstract:

Antibiotic resistance (a major subset of antimicrobial resistance, AMR) has become a leading global health threat: resistance is rising across key bacterial pathogens, undermining treatment of common infections and increasing morbidity, mortality, and healthcare costs. This review summarizes up-to-date epidemiology from global surveillance, describes molecular and phenotypic mechanisms (including biofilms and mobile resistance genes), examines clinical and One-Health drivers (human, animal, environment), evaluates current diagnostics and therapeutic strategies, and outlines public-health, stewardship, and innovation priorities. We highlight surveillance and diagnostic gaps, the dwindling R&D pipeline for new antibiotics, and the urgent need for integrated One-Health actions, equitable access to diagnostics and effective antibiotics, and incentives for antibiotic innovation.

Keywords: antibiotic resistance, antimicrobial resistance, mechanisms, surveillance, stewardship, One-Health, diagnostics etc.

Introduction

Antibiotic resistance occurs when bacteria evolve or acquire the ability to survive exposure to drugs that previously killed them or inhibited their growth. It threatens routine medical care (surgery, chemotherapy, neonatal care), and is driven by antibiotic misuse and insufficient infection prevention across humans, animals, and the environment. Recent global surveillance shows alarming increases in resistance for many common pathogen-drug combinations. Resistance is the ability of a bacteria against the antagonizing effect of an antibacterial agent upon reproduction prevention or bactericidal. The development of resistance to antibiotics in bacteria often develops as a result of unnecessary and inappropriate use of antibiotics. Through the intense use of antibiotics, resistant microorganisms have emerged over the years, and problems were started to be experienced for the treatment of these infections emerged with these resistant microorganisms. Today, on the one hand trying to develop new drugs, on the other hand, there are difficulties in treatment as a result of development of resistance to these drugs rapidly. The development of resistance to antibiotics is a major public health problem in all over the world (1-3).

The main four types of resistance to antibiotics develops; 1. Natural (Intrinsic) resistance 2. Acquired resistance 3. Cross-resistance 4. Multi-drug resistance and pan-resistance

1. Natural (Intrinsic, Structural) resistance: This kind of resistance is caused by the structural characteristics of bacteria and it is not associated with the use of antibiotics It has no hereditary property. It develops as result of the natural resistance, or the microorganisms not including the structure of the target antibiotic, or antibiotics not reaching to its target due to its characteristics. For example, a Gram-negative bacterium vancomycin does not pass in the outer membrane so Gram-negative bacteria is naturally resistant to vancomycin.

Similarly, L-form shape of bacteria which are wall-less forms of the bacteria, and the bacteria such as cell wall-less cell Mycoplasma and Urea plasma are naturally resistant to beta-lactam antibiotics that inhibit the cell wall synthesis (1,4-6).

2. Acquired resistance: As result of the changes in the genetic characteristics of bacteria, an acquired resistance occurs due to its not being affected from the antibiotics it has been responsive before. This kind of resistance occurs due to mainly structures of chromosome or extra chromosomal (plasmid, transposon, etc.).

a. Chromosomal resistance arises from mutations in developing in spontaneous bacterial chromosome (spontaneous). Such mutations may occur according to some physical (ultraviolet, etc.) and chemical factors. This can be a result of structural changes in bacterial cells. The result may be reduced permeability of bacterial drug or changes of the target of the drug may be in the cell. Streptomycin, amino glycosides, erythromycin, lincomycin can develop resistance against these types. Spontaneous chromosomal mutations are 10-7-10-12. Therefore such resistance in the clinic are less and often does not cause a problem (1,4).

b. Extra chromosomal resistance depends extra chromosomal genetic elements that can be transferred in various ways like plasmids, transposons and integro. Plasmids are extra chromosomal DNA fragments that can replicate independently from chromosome. Plasmid genes are usually responsible for the generation of enzymes which inactive antibiotics. Resistance genes and plasmids carrying the genetic material from a bacterium in three ways those are transduction, transformation, conjugation, and transposition mechanism. Transduction by bacteriophage resistance genes, transformation via DNA binding protein called competence factor, conjugation via sex pilus between two live bacteria through transfer of resistance genes. Antibiotic resistance genes on the chromosome or plasmid is interconnected with each other and located near the start of specific units of integration is called integrons. Integrons are in warm regions where recombination (re-edited) is very common (1, 4, and 5).

3. Cross resistance: Some microorganisms which are resistant to a certain drug, that acts with the same or similar mechanism and also resistant to other drugs. This condition is usually observed in antibiotics whose structures are similar: such as resistance between erythromycin, neomycin-kanamycin or resistance between cephalosporins and penicillins. However, sometimes it can also be seen in a completely unrelated drug groups. There is an example of cross-resistance between erythromycin-lincomycin. This may be chromosomal or extra chromosomal origin (4, 5).

4. Multi-drug resistance and pan-resistance: Multidrug-resistant organisms are usually

bacteria that have become resistant to the antibiotics used to treat them. This means that a particular drug is no longer able to kill or control the bacteria. Inappropriate use of antibiotics for therapy resulted in the selection of pathogenic bacteria resistant to multiple drugs. Multidrug resistance in bacteria can be occurred by one of two mechanisms. First, these bacteria may accumulate multiple genes, each coding for resistance to a single drug. This type of resistance occurs typically on resistance (R) plasmids. Second type of resistance, namely multidrug resistance may also occur by the increased expression of genes that code for multidrug efflux pumps, enzymatic inactivation, change in the structure of the target etc. If the bacterial strains resistant to three or more classes of antimicrobials, it is considered as multi-drug resistant. If the strains, resistant to all but one or two antibiotic groups, they are considered as extensively-drug-resistant, if the strains resistant to all available antibiotic, they are classified as pan-drug-resistant. For example, multidrug resistance (MDR) Acinetobacter species (spp.) can be defined as the isolate resistant to at least three classes of antimicrobial agents (namely, all penicillins and cephalosporin's (including inhibitor combinations), fluroquinolones, and amino glycosides).

Extensive drug resistant (XDR) Acinetobacter spp.' shall be the Acinetobacter spp. isolate that is resistant to the three classes of antimicrobials described above (MDR) and shall also be resistant to carbapenems. Pan drug resistant or pan-resistant (PDR) Acinetobacter spp. shall be the XDR Acinetobacter spp. that is resistant to polymyxins (colistin) and tigecycline (6-8).

Global epidemiology and burden

Large surveillance and modeling studies indicate that AMR causes a substantial global burden of disease. Recent WHO GLASS data (2023 surveillance compiled in the 2025 GLASS report) show that roughly **one in six laboratory-confirmed bacterial infections in 2023 were resistant** to commonly used antibiotics — with notable regional variation and rising trends across many bug-drug pairs. The Global Burden analyses and national reports estimate >1 million deaths directly attributable to bacterial AMR annually, with multimillion-death contributions when AMR is a contributing factor; projections without intervention predict much larger future burdens.

Mechanisms of antibiotic resistance

A. The changes that occur in the receptor that connected to the drug and the region of the connection 'Connection of the antibiotics' target areas are different. They can be various enzymes and ribosomes. Resistance associated with alterations in the ribosomal target is the most frequently observed in microcline antibiotics. Mutations in penicillin-binding proteins (beta-lactamase enzymes) and Staphylococcus aureus, Streptococcus pneumoniae, Neustria meningitidis and Enterococcus faecium strains can develop resistance to penicillin. Changes in the structure of the target, beta-laktam, quinolones, glycopeptides, macrolides, and tetracycline and rifampicin resistance are an important mechanism in the development (10-13).

B. Enzymatic inactivation of antibiotics: Most of Gram-positive and Gram-negative bacterias synthesize enzymes that degrade antibiotics. This enzymatic inactivation mechanism is one of the most important mechanisms of resistance. In this group, beta-lactamases, amino glycosides, modifying enzymes (acetylase, fosforiaz adenilaz and enzymes) degrade beta-lactam antibiotics and continually increasing their

number of which inactivates enzymes include chloramphenicol and erythromycin (1, 5, 12).

C. Reduction of the inner and outer membrane permeability: This resistance due to changes in the internal and external membrane permeability, decrease in drug

Resistance mechanisms are diverse and often co-occurring:

- **Enzymatic drug inactivation** — β-lactamases (e.g., extended-spectrum β-lactamases, carbapenemases) hydrolyze antibiotics.
- **Target modification** — methylation (e.g., rRNA methylases), point mutations in target proteins reduce drug binding.
- **Reduced permeability and uptake** — porin loss or modification limits intracellular drug concentration.
- **Efflux pumps** — broad-spectrum transporters expel diverse antibiotics.
- **Biofilm-associated tolerance** — biofilms protect cells via matrix barrier, slow growth, and persister cells and facilitate horizontal gene transfer.
- **Horizontal gene transfer (HGT)** — plasmids, transposons, integrons spread resistance genes across species and ecological niches.

Structural and genomic studies continue to reveal new resistance families and interactions among mechanisms that complicate therapy.

Clinical implications and common resistant pathogens

Critical pathogens include carbapenem-resistant Enterobacterales, multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus (MRSA), and resistant Neustria gonorrhea. Resistance is especially consequential in bloodstream infections, complicated urinary tract infections, pneumonia, and neonatal sepsis — conditions with high case fatality when effective antibiotics are lacking. Regional hotspots (e.g., parts of South-East Asia, Eastern Mediterranean, and some Low- and Middle-Income Countries) report especially high resistance burdens, reflecting gaps in stewardship, diagnostics, and access to appropriate therapeutics.

Drivers of resistance (One-Health perspective)

Key drivers include:

- **Human medicine:** inappropriate prescribing, overuse, and poor adherence.
- **Agriculture and veterinary use:** prophylactic and growth-promotion uses in animals select for resistance that can spill over to humans.
- **Environmental contamination:** discharge of antibiotics and resistant organisms from pharmaceutical manufacturing, hospitals, and farms.
- **Inadequate infection prevention & control (IPC):** poor sanitation, crowded health settings, lack of vaccination and diagnostics.

Integrated One-Health responses that address all sectors are critical to reduce selection pressure and transmission.

Surveillance and diagnostics

Effective containment requires high-quality, timely surveillance and rapid diagnostics:

Surveillance:

GLASS and national systems have expanded reporting, but coverage remains uneven and data gaps persist in many regions. Recent WHO reporting shows improved participation but continuing gaps in the Americas, parts of Africa and the Western Pacific.

Diagnostics: Rapid, point-of-care tests that distinguish bacterial vs viral infections and identify resistance markers would reduce unnecessary antibiotic use; however, uptake is limited by cost, availability, and technical constraints. Investment in affordable, decentralized diagnostics is essential.

Therapeutics and the R&D landscape

Therapeutic strategies include:

Optimize use of existing antibiotics (stewardship; dose optimization; combination therapy when appropriate).

New antibiotics & adjuncts: a small but important pipeline exists (novel β-lactam/β-lactamase inhibitors, siderophore cephalosporin's, etc.), but overall R&D has declined relative to need due to commercial challenges.

Non-traditional approaches: bacterio phages, bacteriocins, monoclonal antibodies, antimicrobial peptides, ant virulence strategies, and therapies targeting biofilms or resistance mechanisms are under study but not yet widely available clinically.
Policy tools (push and pull incentives, market entry rewards, and public–private partnerships) are necessary to revive antibiotic innovation while ensuring equitable access.

Stewardship, infection prevention, and policy responses

Core actions:

Antibiotic stewardship programs (ASPs) in hospitals and community primary care to reduce inappropriate prescribing.

IPC and WASH (water, sanitation and hygiene) in healthcare and community settings to reduce infection incidence.

Regulation of veterinary and agricultural use and promotion of alternatives (vaccination, bio-security).

Global governance: stronger financing of surveillance (GLASS), equitable access to diagnostics and medicines, and international cooperation is essential. Recent WHO recommendations emphasize shifting antibiotic use toward "Access" antibiotics where appropriate and strengthening laboratory capacity.

Knowledge gaps and research priorities

Priority areas:

1. **Affordable rapid diagnostics** for low-resource settings.
2. **Mechanistic research** on persistence, bio-films, and poly microbial interactions.
3. **One-Health transmission pathways** mapping (environmental reservoirs, agriculture-human spillover).
4. **Sustainable incentive models** for antibiotic and diagnostic R&D.
5. **Implementation research** for stewardship and IPC in resource-limited health systems.

Conclusion

Antibiotic resistance is an accelerating global threat that compromises routine healthcare and threatens lives worldwide.

Recent surveillance shows rising resistance across many pathogens and regions; solutions require coordinated One-Health strategies: strengthened surveillance and diagnostics, robust stewardship and IPC, responsible use in agriculture, targeted R&D incentives, and equitable access to effective therapies.

Urgent, sustained global action will determine whether we avert rapidly rising AMR-related disease over the coming decades

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