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# CHALLENGES OF ANTIBIOTIC RESISTANCE AND THE DEVELOPMENT OF NEW ANTIMICROBIAL AGENTS

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**Abstract**

This article provides a comprehensive analysis of the problem of antibiotic resistance, its underlying causes, dynamics of spread, and its impact on the global healthcare system. According to data from the World Health Organization (WHO), antibiotic-resistant bacteria were responsible for 1.27 million deaths worldwide in 2019, a figure projected to reach 10 million per year by 2050. While resistance continues to intensify on one hand, the process of developing new antimicrobial agents is becoming increasingly complex from financial, scientific, and regulatory perspectives on the other. The article discusses the biological mechanisms of resistance, the declining innovative activity of the pharmaceutical industry, and alternative therapeutic approaches including phage therapy, CRISPR-Cas9 technology, and immunomodulatory strategies. In conclusion, the article emphasizes that the problem has assumed a global character that cannot be resolved without systematic international cooperation and a multidisciplinary approach.

**Keywords**

antibiotics, antimicrobial resistance (AMR), superbugs, MDR (multidrug-resistant), XDR (extensively drug-resistant), ESKAPE pathogens, beta-lactamase, phage therapy, CRISPR-Cas9, novel antimicrobial agents.

## Introduction

Since the discovery of antibiotics in 1928, revolutionary changes have taken place in the field of medicine: infections that were once invariably fatal became treatable within a matter of days. In addition to penicillin, discovered by Alexander Fleming, subsequent decades saw the development of powerful agents such as streptomycin, tetracyclines, fluoroquinolones, and carbapenems. However, concurrent with this progress, bacteria began developing resistance to these agents through evolutionary mechanisms. Today, antibiotic resistance has become a complex and multifaceted phenomenon encompassing medicine, veterinary science, agriculture, and environmental ecology. Globally, and particularly in low- and middle-income countries, deaths attributable to antibiotic-resistant infections

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are on the rise. In North America, Europe, and Asian countries, strains of MRSA (methicillin-resistant Staphylococcus aureus), carbapenem-resistant Klebsiella pneumoniae, and pan-resistant Acinetobacter baumannii have become the primary sources of nosocomial infections. At the same time, research and development (R&D) activity in the area of new antibiotic development has declined sharply over the past three decades, as pharmaceutical companies consider short-course antimicrobial drugs to be less economically viable compared to agents used for long-term chronic conditions. This article analyzes the causes, consequences, and potential solutions to this contradictory situation on the basis of the scientific literature.

**Main body**

From a biological standpoint, antibiotic resistance is mediated through several fundamental mechanisms. The first and most widespread mechanism is enzymatic inactivation, whereby bacteria synthesize beta-lactamases, aminoglycoside-modifying enzymes, and other chemically reactive molecules that degrade or modify the antibiotic molecule. Extended-spectrum beta-lactamases (ESBLs) and carbapenemases are the most dangerous representatives of this category; their activity is not limited to resistance against penicillin but extends to neutralizing numerous other beta-lactam antibiotics as well. The second mechanism involves target site modification: penicillin-binding proteins undergo mutation, rendering them unable to bind the antibiotic. The third mechanism is the activation of efflux pump systems, whereby antibiotic molecules that have entered the bacterial cell are expelled by specialized proteins. The fourth mechanism involves a reduction in cell wall or membrane permeability  that is, decreased expression of porins or other channel proteins prevents the antibiotic from entering the cell. All of these mechanisms may coexist simultaneously within the same bacterium, resulting in the formation of an MDR (multidrug-resistant) or XDR (extensively drug-resistant) phenotype.

Horizontal gene transfer plays a particularly important role in the dissemination of resistance. Through plasmids, transposons, and integrons, resistance genes can be rapidly and efficiently transferred from one bacterium to another, and even between bacteria belonging to different species. This is especially hazardous in the hospital environment, where diverse bacteria coexist at high density and antibiotics are in constant use. Six groups designated by the World Health Organization as "ESKAPE pathogens"  Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species  have been officially identified as the most frequently encountered and most resistant causative agents of

nosocomial infections. According to a large-scale epidemiological study published in The Lancet by Murray et al. (2022), 1.27 million deaths directly attributable to antimicrobial resistance were recorded in 2019 a figure exceeding the mortality rates associated with liver disease or malaria.

The global situation regarding the development of new antibiotics is a cause for serious concern. The number of antibiotic candidates currently in preclinical and clinical development stages remains at historically low levels. According to a WHO report (2022), only 45 new antibiotics were in clinical trials, the majority of which were modified variants of already existing drug classes, with very few candidates possessing novel mechanisms of action. The primary reason is economic: developing a new antibiotic requires an investment of between one and two billion US dollars, yet a newly marketed antibiotic is typically held in reserve to prevent the emergence of resistance meaning it is rarely used and consequently generates low revenue. The bankruptcy declarations by major pharmaceutical companies such as Achaogen and Melinta Therapeutics in the antibiotic sector serve as a clear illustration of this reality. Incentive mechanisms such as government subsidies, advance market commitments, and transferable exclusivity vouchers have been proposed, but have yet to be implemented with sufficient effectiveness.

The scientific community is pursuing the discovery of new antibiotics through a combination of natural sources, synthetic chemistry, and in silico approaches (computational modeling). Teixobactin, isolated from soil bacteria in 2015, attracted significant attention as an antibiotic with a novel mechanism of action and demonstrated potent activity against MRSA and Mycobacterium tuberculosis under laboratory conditions. However, teixobactin still requires additional research before it can be considered for clinical use. Furthermore, bacteriocins, antimicrobial peptides, and membrane-disrupting lipopeptides are being investigated as promising research candidates. Modern genomics and bioinformatics have made it possible to identify gene clusters responsible for the biosynthesis of new antibiotics within the genomes of previously unculturable microorganisms, substantially expanding the potential for discovering novel compounds from nature.

Among alternative therapeutic approaches, phage therapy a method of treatment employing viruses that destroy bacteria (bacteriophages) merits particular attention. Phage therapy was practiced in Western Europe and the Soviet Union in the early twentieth century, before falling into decline following the advent of antibiotics. Interest in this approach has been revived in the context of MDR infections. The successful experimental phage therapy case conducted on Thomas Patterson at the UC San Diego Medical Center in 2017 received extensive

coverage in global media. However, the clinical implementation of phage therapy still requires considerable work regarding regulatory frameworks, standardization of phage preparations, and large-scale clinical trials. CRISPR-Cas9 technology is being evaluated in research centers as a means of turning bacteria against themselves that is, by excising resistance genes or targeting virulence genes. This approach may not only eliminate resistance but also treat infection through the selective destruction of the causative bacterium.

Preventing the misuse of antibiotics is a necessary and urgently required measure to slow the spread of resistance. Epidemiological studies have repeatedly documented the widespread sale of antibiotics without prescription in Russia, China, India, and Central Asian countries. This issue is equally relevant for Uzbekistan and neighboring countries: according to data from public health authorities, the population frequently self-prescribes antibiotics without consulting a physician and fails to complete the full course of treatment, thereby contributing to the selection of partially resistant strains. In addition, the use of antibiotics as growth promoters in agriculture particularly in livestock farming contributes significantly to the environmental dissemination of resistance genes. Practice has shown that countries such as Denmark and Sweden, by imposing strict restrictions on antibiotic use in veterinary medicine, have succeeded in significantly reducing resistance rates.

**Conclusion**

Antibiotic resistance is not a narrow problem of medical science, but a global crisis inextricably linked to economics, ecology, politics, and social justice. The mechanisms of resistance are complex and multifaceted, and there is no single "magic bullet" for overcoming them. Systematic efforts are required not only to develop new antibiotics, but also to reduce antibiotic misuse, strengthen surveillance systems, regulate use in veterinary medicine and agriculture, and introduce alternative approaches such as phage therapy and CRISPR into clinical practice. Joint action by international organizations, national governments, academic institutions, and the private sector is the only viable path forward. Failure to do so risks a return, by 2050, to a "pre-antibiotic era" in which even routine surgical procedures carry a risk of death an outcome that would negate all the achievements of modern medicine.

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