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ANTI-MICROBIAL RESISTANCE A GLOBAL EMERGING THREAT TO THE PUBLIC HEALTH SYSTEM

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Abstract
This highlights the significance of controlled releasing biodegradable hydrogels as chemotherapeutic drug delivery systems. This study examines the use of hydrogels as drug delivery methods for HCC (Hepatocellular carcinoma), including thermo sensitive, pH-sensitive, photosensitive, dual sensitive, and glutathione responsive hydrogels. Localized chemotherapy, as opposed to systemic chemotherapy, can reduce side effects by delivering a steady supply of chemotherapeutic chemicals directly to the tumor location. Hydrogels have been used for wounds, burns, dressings, contact lenses, tissue engineering applications, and more. Finally, hydrogel can intelligently respond to environmental changes according to internal and external environmental stimuli, allowing for remote control and on-demand release of the anti-cancer active substance. This significantly improves drug targeting, lowering dosages and increasing treatment efficacy.

Keywords: Hydrogels, Controlled release, drug delivery system, Macroscopic design, microgels and nano gels, release mechanism, Drug diffusion coefficient, Applications.

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INTRODUCTION

Alexander Fleming discovered penicillin in 1928, leading to a revolution in antibiotic treatments for bacterial infections. This breakthrough improved the safety of surgeries, childbirth, and cancer therapies [1]. Antiviral drugs have also advanced disease management, notably for COVID-19 and HIV. Antimicrobial drugs are vital for treating infections, but overuse has led to antimicrobial resistance (AMR), increasing healthcare costs. AMR, driven by misuse of antibiotics, is now a major global health threat. The rise of antimicrobial resistance has prompted global discussions, including reports from the WHO and the U.S. Institute of Medicine [2]. The European Union has also hosted scientific sessions and published reviews on the issue. In India, the CDC increased infection surveillance from 5 hospitals in 2016 to 36 by 2021, while NARS-Net expanded antimicrobial monitoring with 35 labs across 26 states. Antimicrobial resistance (AMR) is driven by the overuse and misuse of antibiotics across healthcare, agriculture, and food production [3]. Without action, AMR could become the leading cause of death by 2050, with deaths increasing from 1.2 million to 10 million annually. This study explores AMR's history, mechanisms, impact, future trends, AI applications, and strategies for mitigation. Antimicrobial resistance (AMR) is a growing global threat, leading to millions of deaths and worsening with increased antibiotic use during COVID-19. A drug-resistant *Pseudomonas aeruginosa* outbreak in the U.S., linked to artificial tears, caused severe infections. Rising resistance to carbapenems highlights the urgent need for action. Most studies focus on AMR's burden, risks, and mechanisms [4].

HISTORY

Antimicrobials are substances that eliminate or inhibit the growth of microorganisms, including bacteria, fungi, viruses, and parasites. They encompass antibiotics, antifungals, antivirals, and anti-parasites. The development of

antimicrobials has significantly influenced medical practices and public health

- Early Observations and Discoveries: Ancient civilizations used molds and plant extracts to treat infections over 2,000 years ago. In the 19th century, scientists like Pasteur and Koch discovered that some bacteria inhibit others' growth. This breakthrough led to the development of antimicrobial agents.
- The Golden Age of Antibiotics: The period from the early 1940s to the mid-1960s is often termed the "Golden Age" of antibiotic discovery, during which numerous groundbreaking antimicrobials were introduced:
  - ✓ **Penicillin:** In 1928, Alexander Fleming discovered penicillin, the first widely used antibiotic, which transformed the treatment of bacterial infections. This discovery led to the introduction of antibiotics that greatly reduced the number of deaths from infection.
  - ✓ **Sulfonamides:** Developed in the 1930s, sulfonamides were among the first synthetic antibiotics, paving the way for numerous other antimicrobial agents. In 1935, sulfonamides were developed by Domagk and other researchers.
  - ✓ **Chloramphenicol:** Notably, chloramphenicol became the first naturally occurring antibiotic produced by chemical synthesis, rather than fermentation.

EPIDEMIOLOGY

Antimicrobial resistance (AMR) is a major global health threat, causing 1.27 million deaths in 2019 and contributing to 4.95 million more. It accounted for 9% of infection-related fatalities worldwide [5]. AMR exacerbates poverty in low- and middle-income countries and raises healthcare costs due to prolonged treatments and higher mortality rates. In 2019, six bacterial pathogens caused 73% of AMR-related deaths, with over 330,000 fatalities attributed to them. WHO classified these as high-priority in 2024, overlapping with the ESKAPEE group responsible for hospital infections. Drug-resistant tuberculosis, caused by Mycobacterium tuberculosis, led to 1.3 million deaths in 2022. Addressing AMR requires better data collection, standardized testing, and stronger mitigation strategies [6]. Most AMR infections, including UTIs, STIs, and typhoid fever, are acquired in community settings. Excessive antibiotic use causes 214,000 neonatal deaths annually, mainly in low- and middle-income countries. Poor sanitation, limited healthcare access, and widespread antibiotic misuse worsen AMR, with over 90% of deaths occurring in affected regions [7]. Globalization, travel, and climate change accelerate the spread of antimicrobial resistance (AMR) worldwide [8]. Genomic studies show drug-resistant bacteria like Salmonella Typhi and MRSA spreading through migration and tourism.

Preventing infections requires safe travel, vaccinations, and food safety, as climate change affects disease patterns. In 2017, livestock accounted for 73% of global antibiotic use, with five countries responsible for 58% of consumption [9]. Antibiotic use in food production fosters AMR reservoirs, spreading to humans through zoonotic transmission and gut bacteria. AMR genes in wild animals highlight the need for a One Health approach to assess its impact on ecosystems [10].

FACTORS INFLUENCE OF AMR

Antibiotics are widely used in healthcare and animal farming, with up to 80% given to livestock. This contributes to vancomycin-resistant bacteria in animals, threatening the human food supply. Hospitals can promote the spread of resistant microorganisms, leading to infections. Various additional factors also contribute to this risk.

These can be broadly categorized into four main areas:

- Ecological factors
- Pharmaceutical factors
- Patient-related factors
- Healthcare provider-related factors.

- **Ecological Factors**: Encompass a range of influences, including rapid urbanization and overcrowding, inadequate waste management and sanitation infrastructure, rising incidence of community-acquired resistance, ineffective infection prevention and control measures, increased global mobility and travel, and the extensive use of antimicrobials in agriculture, animal farming, and personal care products.
- **Pharmaceutical-Related Factors**: This exacerbates resistance include the rampant misuse of antibiotics, easy accessibility of antimicrobials without prescription, illogical fixed-dose combinations of antimicrobials, and the proliferation of counterfeit and subpar medications that result in inadequate blood concentrations.
- **Patient-Related Factors**: This contributes significantly to the rise of resistance include non-adherence to prescribed treatment regimens, socioeconomic deprivation, inadequate sanitation, limited education, and self- medication.
- **Healthcare Provider-Related Factors**: such as inappropriate prescribing practices, excessive empiric use of multiple antimicrobials, overreliance on antimicrobials, suboptimal dosing, and inadequate knowledge and training, also perpetuate the growing issue of resistance.

MECHANISM OF AMR

The discovery of penicillin in 1928 led to rapid antibiotic development, but progress declined after the 1980s, increasing reliance on existing drugs. Bacteria have evolved resistance through membrane changes, efflux systems, enzymatic degradation, target modification, and biofilm formation, reducing antibiotic effectiveness. Most resistance develops within six months of exposure, underscoring the urgent AMR challenge [11].

- AMR in the context of next-generation and last-line antibiotics:

Since 2010, 29 antibiotics have been approved, mostly modifications of existing classes, but cross-resistance limits their effectiveness. Last-line treatments like colistimethate and tigecycline are threatened by emerging resistance genes [12]. This highlights the urgent need for new antibiotics targeting novel mechanisms. Teixobactin shows promise as a novel antibiotic but has yet to enter clinical trials. Zoliflodacin and gepotidacin, new topoisomerase II inhibitors, may face fluoroquinolone cross-resistance. Durlobactam, approved with sulbactam for resistant Acinetobacter infections, is ineffective against class B metallo-β-lactamases. Bacterial outer membrane vesicles further spread resistance genes, worsening antibiotic evasion. Despite advances in high-throughput screening and target-based drug discovery, most breakthroughs target Gram-positive bacteria [13]. Gram-negative bacteria remain challenging due to their impermeable outer membrane and efflux pumps. Research on membrane permeability has led to novel compound libraries, including zosurabalpin, an LptB2FGC complex inhibitor identified through extensive screening.

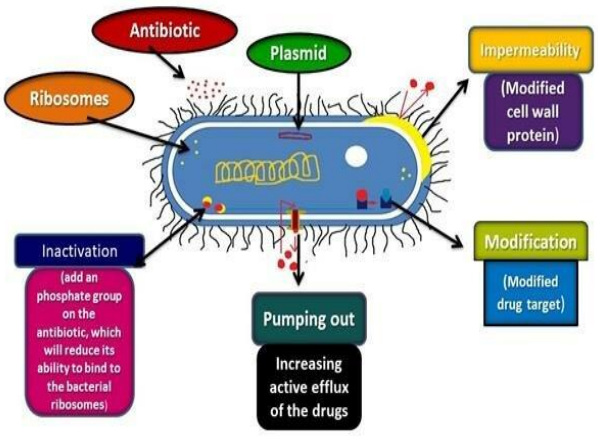

Figure 1: Mechanism of Amr

GLOBAL IMPACT OF AMR

Human Health Impact High Mortality Rates:

- AMR was directly responsible for 1.27 million deaths in 2019, with another 4.95 million deaths associated with drug-resistant infections.
- Increased Healthcare Burden: AMR leads to longer hospital stays, higher medical costs, and more complications in treating infections such as pneumonia, tuberculosis (TB), and urinary tract infections (UTIs).
- Reduced Effectiveness of Medical Treatments: Surgeries, chemotherapy, and organ transplants rely on antibiotics to prevent infections. Without effective antibiotics, these procedures become high-risk or even impossible.

Economic and Social Impact

- High Economic Costs: By 2050, AMR could cost the global economy up to $100 trillion due to lost productivity, increased healthcare costs, and reduced GDP growth.
- Impact on Livelihoods: AMR disproportionately affects low- and middle-income countries (LMICs), where access to healthcare is limited, increasing poverty and inequality.
- Food Security Threats: Antibiotic overuse in livestock and aquaculture promotes the spread of resistant bacteria in food production, affecting global food safety.
- Environmental Contamination: Pharmaceutical waste and agricultural runoff contribute to the spread of resistant bacteria in soil, water, and wildlife.

BASIC OF ANTIBIOTIC RESISTANCE

Antibiotic resistance develops as bacteria evolve to withstand previously effective antibiotics. Through mutations or horizontal gene transfer (HGT), they adapt and become resistant over time [14]. Bacteria develop resistance through target modifications, efflux pumps, or enzymes that degrade antibiotics. They can acquire resistance genes from environmental or commensal bacteria for protection. Resistance can be intrinsic (naturally present) or acquired through mutation or gene transfer [15].

Adaptive resistance is a temporary bacterial response to environmental stress or low antibiotic levels, without permanent genetic changes. It may involve mutation rates, gene amplification, efflux pumps, or biofilm formation and reverts once the stress is removed.

Infection Prevention and Control, Antibiotic Access, and Antimicrobial Stewardship.

Infection prevention programs are crucial in fighting AMR, particularly in LMICs. Improving water, sanitation, hygiene, and vaccine access could prevent 337,000 AMR-related deaths yearly. Vaccines reduce antibiotic use, limit resistance, and curb resistant strain spread [16]. The WHO's 10-20-30 target for 2030 aims to cut AMR deaths by 10%, reduce human antibiotic misuse by 20%, and lower animal misuse by 30%. Its framework categorizes antibiotics into Access, Watch, and Reserve groups. Achieving these goals requires lowering development costs, expanding access to essential drugs, and promoting new antibiotics. Over-the-counter antibiotic use, especially in LMICs, drives AMR, with 63.4% dispensed without prescriptions. Addressing this issue requires education, better healthcare access, and stronger antimicrobial stewardship policies [17]. Strengthening hospital programs is key to combating AMR. This involves improving access to second-line antibiotics, antimicrobial stewardship, and guidelines based on resistance patterns, alongside efforts to reduce unnecessary antibiotic use.

EMERGING NON-ANTIBIOTIC ANTIMICROBIAL THERAPIES

In 2022, WHO reported 80 antimicrobial drugs in development, including 46 antibiotics and 34 non-traditional therapies. With three under regulatory review, 28 antibiotics target priority pathogens, reflecting efforts to combat AMR and improve treatments [19]. Monoclonal antibodies, originally used for cancer and autoimmune diseases, are now promising infection treatments [20]. They enhance immune response, neutralize toxins, and reduce bacterial virulence

while preserving natural microbiota. Approved therapies like Palivizumab and Obiltoxaximab show their potential, with 14 more in development for drug-resistant infections like Staphylococcus aureus and Clostridioides difficile.

Monoclonal antibodies like Tosatoxumab and TRL1068 show promise in treating Staphylococcus aureus infections, enhancing antibiotic effectiveness. Bezlotoxumab reduces recurrent C. difficile infections by 40% and is being explored for other conditions. Antibody-antibiotic conjugates (AACs), inspired by cancer treatments, improve drug delivery and show greater efficacy than vancomycin in preclinical studies, offering a potential breakthrough for resistant infections.

Antimicrobial peptides are being studied for biofilm infections, with iseiganan and omiganan showing potential in reducing microbial load and inflammation. Research is exploring their combination with antibiotics to enhance effectiveness. Bacteriophage therapy, which targets specific bacteria while preserving microbiota, offers a promising AMR treatment but faces challenges like purification, resistance, and personalized treatment needs. Bacteriophage therapy is promising for multidrug-resistant infections like pneumonia and sepsis, with a 58% success rate in one study. Challenges include personalized phage selection, high costs, and resistance, but phage cocktails are being developed to enhance effectiveness [21].

CRISPR-Cas9 gene therapy targets antibiotic-resistant bacteria while preserving beneficial microbiota. Though effective against S. aureus in preclinical studies, challenges include improving delivery, scalability, and broadening its application. CRISPR-based gene therapy offers a targeted alternative to antibiotics by eliminating resistant bacteria and correcting infection-prone genetic defects. Despite challenges in delivery, purity, and scalability, ongoing research supports its potential in AMR treatment [22].

APPLICATIONS OF TECHNOLOGY AGAINST ANTIBIOTIC RESISTANCE

- The evolving antibiotic resistome requires advanced tools like NGS and bioinformatics for better surveillance and analysis. These technologies enhance understanding of AMR and aid in developing effective resistance-combatting strategies [23].
- Metagenomics is a key approach for studying the resistome, identifying resistance genes in diverse environments. Methods like shotgun and functional metagenomics reveal mechanisms such as efflux pumps and beta-lactamases, highlighting gene mobility between bacteria [24].
- Functional metagenomics identifies antibiotic resistance reservoirs by cloning and analyzing DNA fragments. Combining shotgun cloning with advanced sequencing reveals diverse resistance genes, requiring robust databases for accurate AMR tracking.
- The Smart Chip system utilizes qPCR technology for rapid, high-sensitivity detection of antibiotic resistance genes in environmental microbiomes. It enables parallel analysis, making it a powerful tool for AMR research [25].

ACTIVITIES AT GLOBAL AND NATIONAL LEVEL

The global efforts to combat AMR began in the late 1990s and 2000, with the WHO, leading consultative groups and workshops to assess the situation. The result was The Global Strategy 2001 for AMR, which emphasized education for patients, prescribers, and dispensers, Anti-microbial resistance improved implementation of infection control programs, monitoring pharmaceutical company activities, antimicrobial resistance phasing out antimicrobials for growth promotion in animals and plants, and encouraging collaboration between industry, government bodies, and academic institutions for new drug and vaccine development. At the national level, India is a signatory to the "Jaipur Declaration on Anti-microbial Resistance – 2011" for the Southeast Asia Region. While the Government of India formulated the National Policy for Containment of Antimicrobial Resistance in 2011, challenges persist, including inadequate control over the sale of over-the- counter antimicrobials, their inappropriate use, and a lack of coordination in resistance surveillance.

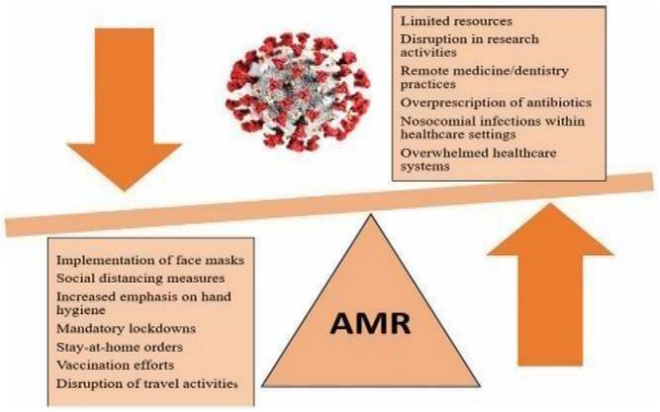

Figure 2: Factors that increase and decrease antimicrobial resistance during COVID-19. AMR

CONCLUSION

The rapid evolution of antimicrobial resistance poses a significant threat to modern medicine, reducing the effectiveness of treatments. Overuse of antibiotics in healthcare and agriculture has accelerated the emergence of resistant strains, making once-powerful drugs ineffective. As multidrug resistance spreads and antibiotic development lags, the risk of untreatable infections increases. Addressing this crisis requires global cooperation, investment in research, and improved infection control measures. Strategies such as antimicrobial stewardship, limiting unnecessary antibiotic use, and promoting vaccination and hygiene can help slow resistance. Advancements in diagnostics and alternative therapies are also crucial. Without immediate action, the growing resistance problem could undermine medical progress and increase global mortality rates.

AUTHOR CONTRIBUTIONS
All authors are contributed equally

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