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A Comprehensive Review of Antimicrobial Resistance: Historical Perspectives, Current Challenges, and Future Strategies with a Focus on India and Environmental Impacts

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Abstract: Antimicrobial resistance (AMR) is a serious hazard to public health worldwide, with far-reaching effects on healthcare expenditures, patient outcomes, and social welfare. With an emphasis on India and environmental factors, this study gives a general overview of the historical background, present difficulties, and recent developments in the understanding and combating of antibiotic resistance (ABR). It traces the evolution of antibiotic discovery from the "Golden Age of Antibiotics" to the emergence of Multidrug resistance (MDR) bacteria, highlighting key milestones and contributing factors. The review focus on the alarming rise of AMR in India, where overuse, poor regulation, and limited awareness exacerbate the problem. Additionally, it addresses the environmental aspects of antibiotic resistance, highlighting the relationship between environmental, animal, and human health. The study concludes by outlining mitigation methods for AMR, such as global cooperation within the context of One Health framework, surveillance initiatives, and public health programs.

Keywords: Antimicrobial resistance, Multidrug resistance, Antibiotics, Antibiotic resistance

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Introduction

The global increase in infections caused by MDR bacteria is alarming, with a growing number of diseases becoming untreatable (Koulenti *et al.*, 2019). Antibiotic resistance (ABR) is one of the biggest threats to animal and human health, according to the World Economic Forum's Global Risk report (Aslam *et al.*, 2021). Developing novel antibiotics comes with its own set of difficulties. For antibiotics, the link is inquisitive reversed, in contrast to other therapeutic domains where more knowledge facilitates drug discovery (Lewis, 2013; Brown and Wright, 2016). The Waksman platform, which involves looking for growth inhibition zones in soil actinomycetes and ultimately led to the

discovery of streptomycin, marked the beginning of the golden age of antibiotic discovery in the 1940s (Schatz *et al.*, 1944). Large-scale commercial screening programs and the quick identification of important antibiotic classes were sparked by this technique. But this period came to a sudden end in the early 1960s, as knowledge about antibiotic resistance and processes increased (Lewis, 2012).

AMR is one of the top three public health problems of the twenty-first century, according to the World Health Organization (WHO, 2014). Higher death rates and substantial financial costs, estimated at more than $20 billion annually in the United States alone, are linked to MDR organism infections (Diaz Granados *et al.*, 2005; Cosgrove, 2006; Sydnor and Perl, 2011). According to estimates from the Centers for Disease Control and Prevention (CDC), illnesses brought on by microbes resistant to antibiotics claim the lives of at least 23,000 Americans each year (CDC, 2013). Furthermore, according to a recent analysis, ABR may result up to 300 million premature deaths by 2050 and incur up to $100 trillion in economic losses worldwide.

A critical mechanism in the spread of antibiotic resistance is the transfer of resistance genes between bacteria through plasmids, known as horizontal gene transfer (Wang *et al.*, 2024). Plasmids are extrachromosomal DNA molecules that replicate independently and can move between bacteria, carrying genes that provide a selective advantage, such as ABR genes. They are significant vehicles for transferring ABR genes between bacterial species (Partridge *et al.*, 2018; San, 2018). The emergence of AMR in clinical pathogens is often linked to plasmids, presenting a significant challenge to healthcare due to the lack of effective antimicrobials.

To combat the rapid spread of ABR genes and the resurgence of infections, a clearer understanding of ABR is essential. This article examines the origins, spread, and evolution of ABR among bacterial pathogens, providing a comprehensive overview of the historical context, current challenges, and future directions in combating ABR in clinical and environmental settings, with a focus on India. By outlining milestones in antibiotic discovery, resistance mechanisms, and the global health impact of ABR, this article offers valuable insights into the complex nature of the issue. It underscores the urgent need for collaborative efforts across various sectors and disciplines to develop effective strategies for mitigating AMR. By synthesizing recent advances in ABR research and highlighting factors exacerbating AMR in India, the article provides a roadmap for policymakers, healthcare professionals, researchers, and other stakeholders to address this critical public health challenge. Ultimately, the goal is to facilitate informed decision-making, stimulate further research, and catalyze action to preserve the efficacy of antibiotics and safeguard public health.

Antibiotic Discovery

An "antibiotic" is a substance produced by microorganisms that inhibits or kills bacteria, according to Waksman's (1947) definition (Fig. 1). These days, any natural, semisynthetic, or synthetic antimicrobial material can be included under this category (Waksman 1947; Bentley and Bennett, 2003). The "Golden Age of Antibiotics" was defined as the period between the 1930s and 1960s, when the number of newly discovered antibiotics peaked (Aslam *et al.*, 2018). The discovery of penicillin, often attributed to a fortunate mistake, began in 1928 when Alexander Fleming observed that a fungal contaminant, later identified as *Penicillium notatum*, inhibited bacterial growth on a petri dish. Fleming published his findings in 1929, recognizing penicillin's antibacterial properties but failing to purify it (Fleming, 1929; Swann, 1983; Aminov, 2010; Sengupta *et al.*, 2013). In 1939, Howard Florey and Ernst Chain at Oxford, inspired by Fleming's work, developed methods to culture and purify penicillin, with significant contributions from chemist Norman Heatley. By the mid-1940s, they conducted pivotal experiments showing penicillin's efficacy in mice, leading to its

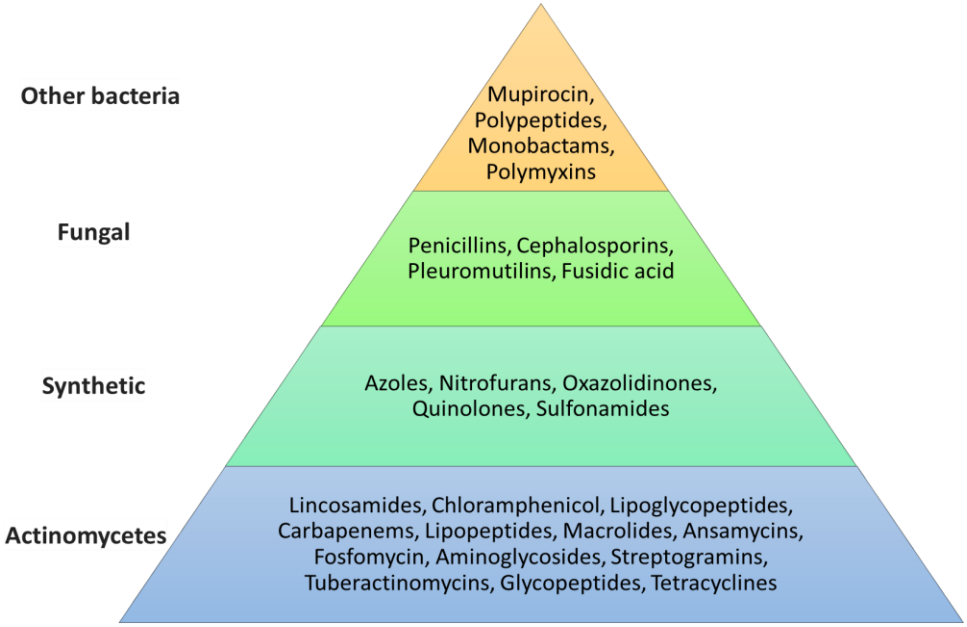

Fig. 1: Natural sources of clinically relevant antibiotics.

recognition as a life-saving drug (Heatley, 2004; Cranston, 2016).

Based on Jean-Paul Vuillemin's (1889) definition of "antibiosis," Rene Dubos discovered Gramicidin in 1939, making it the first antibiotic to be tested in a clinical setting (Schaedler and Dubos, 2006). Tyrothricin, the antibacterial compound found in *Bacillus brevis*, was found to contain tyrocidine and gramicidin by Dubos and Rollin Hotchkiss (Van Epps, 2006). In 1940, Selman Waksman pioneered the systematic screening of soil bacteria like *Streptomyces*, leading to major discoveries including streptomycin in 1944 (Durand *et al.*, 2019). Eli Lilly's program in the 1950s discovered vancomycin from *Streptomyces orientalis*, available to patients by 1958. *Streptomyces* remains a major source of antibiotics (Levine, 2006). Later, the pharmaceutical industry shifted from the Waksman platform to synthesizing new molecules *in vitro*, modifying existing antibiotics (Lewis, 2013).

To sustain the effectiveness of antibiotic treatments, scientists quickly developed new β-lactam antibiotics. However, resistance soon followed, with the first cases of methicillin-resistant *Staphylococcus aureus* (MRSA) reported in the UK in 1962 and in the US in 1968 (Sengupta, 2013; Spellberg and Gilbert, 2014). By 1972, vancomycin was introduced to treat MRSA, and initially, it was believed that resistance to this drug would be unlikely. Nevertheless, the late 1970s and early 1980s saw the emergence of vancomycin-resistant coagulase-negative Staphylococci. Until the early 1980s, new antibiotics continued to be developed, but this pace eventually slowed, and by 2015, approximately 70 years after the first antibiotic treatments, bacterial infections had once again become a significant threat (Aslam *et al.*, 2018). The new antibiotics were primarily modifications or improvements of existing molecules. Figure 2 highlights the continuous fight against ABR by showing the different types of antibiotics and the dates of their clinical availability. As the race to identify new antibiotics rages on to stop the more rapid spread of AMR, this resistance acts like a tornado, destroying the advances made in antibiotic discovery (Iskandar *et al.*, 2022).

Antimicrobial resistance

AMR arises when microorganisms such as bacteria, viruses, fungi, and parasites become resistant to antimicrobial drugs, impacting global

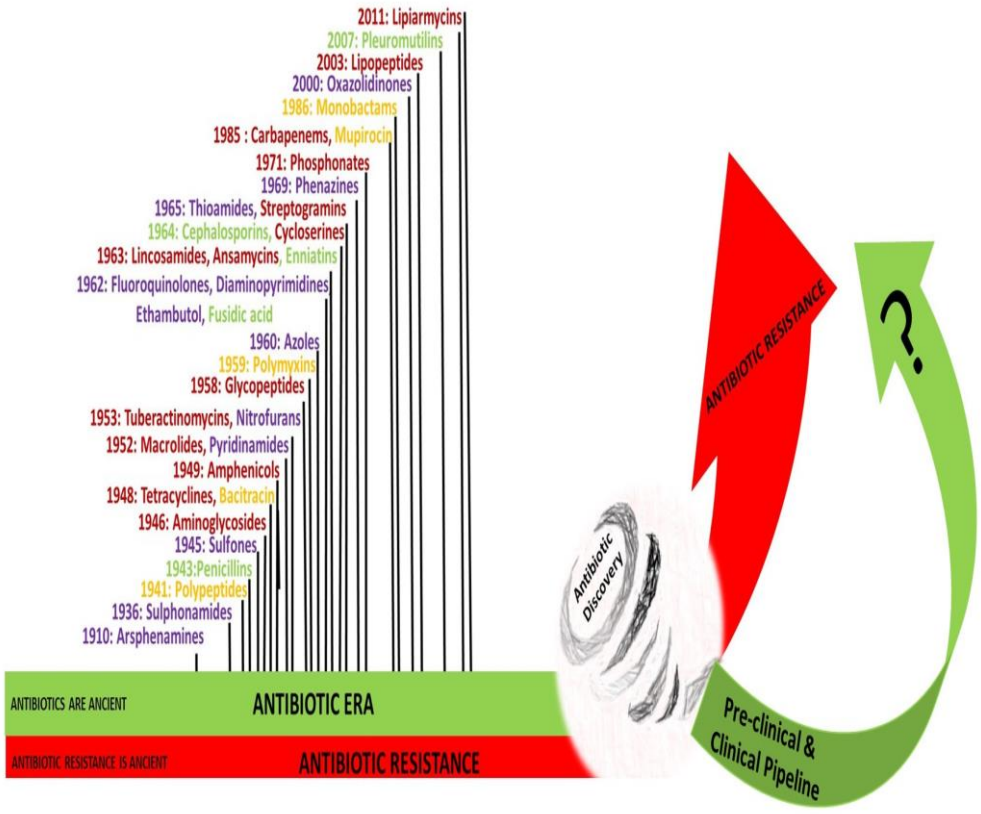

Fig. 2: The pursuit and competition between AMR and antibiotics. The antibiotic classes and the dates of their clinical launch onto the market are displayed. Antibiotics from fungi are green; those from bacteria are gold; those from actinomycetes are red; and synthetic antibiotics are purple (Source: Iskandar *et al.*, 2022).

health regardless of income levels (Founou *et al.*, 2017; CDC, 2019). Key factors include poor access to clean water, sanitation, and hygiene (WASH), insufficient infection control in various settings, limited quality vaccines and medications, and low AMR awareness. Vulnerable and low-resource populations disproportionately suffer from AMR causes and effects (WHO, 2019).

There are two ways that an increase in ABR may affect human health. Firstly, it directly affects the likelihood of treating an infection. Second, it may threaten immunosuppressive treatments (such as transplants) and procedures like catheterization or intubation, sophisticated surgery, or anticancer chemotherapy, which call for the administration of antibiotics to either prevent or treat related infections (WHO, 2014). Indeed, according to the WHO, "commonplace medical procedures once previously taken for granted could be conceivably consigned to medical obscurity" due to the advent and spread of antibiotic-resistant bacteria in hospitals. The consequences are nearly inconceivable (WHO, 2015).

ABR has emerged as a significant global health crisis in the 21st century, with virtually all clinically used antibiotics facing resistance (Bhardwaj *et al.*, 2022). Termed the 'Faceless Pandemic,' it claims around 700,000 lives annually, signaling a shift towards a 'post-antibiotic era' where novel treatments are imperative (Tarin-Pello *et al.*, 2022). While antibiotics have historically revolutionized medicine, their overuse has fueled the rise of MDR bacteria, endangering healthcare efficacy. Despite warnings from pioneers like Sir Alexander Fleming, the scarcity of new antimicrobial drugs exacerbates treatment failures (Aminov, 2010;

Huemer *et al.*, 2020).

Despite the fact that AMR has long existed, it may be simple to think of it as a relatively new problem given the discovery, synthesis, and commercialization of antimicrobials. For example, bacteria that have been isolated from glacial waters and aged over 2000 years exhibit ampicillin resistance, while bacteria that have been isolated from permafrost and aged over 30,000 years exhibit vancomycin resistance (Dancer, 1997; D'Costa *et al.*, 2011). Today's therapeutic settings use a large number of antibiotics that are naturally produced by environmental microbes. For instance, a particular kind of mold produces penicillin as a natural defense against germs (Ligon, 2004). Since penicillin was initially used in medicine, *Staphylococcus aureus* has shown resistance to the antibiotic (Spink, 1947).

Even though ABR is currently posing a threat to the entire world, antibiotics have made significant advances in surgery and medicine. They have extended life expectancy by successfully treating or preventing bacterial infections that occur after chemotherapy and major surgeries such as organ transplants, joint replacements, and cardiac surgery. The average life expectancy in the United States was 56.4 years in the 1920s; it is currently approximately 80 years. Antibiotics have lowered rates of morbidity and mortality from bacterial infections in humans and livestock worldwide, particularly in developing nations with poor public health infrastructure (Piddock, 2012; Wright, 2014).

Overview of ABR Trends/Development of AMR

Bacteria, like all living organisms, have the capacity to adapt and evolve in response to new environments and challenges, including the presence of antibiotics. Shortly after antibiotics were introduced, bacteria began to develop resistance and shared these resistance mechanisms with other bacteria. Table 1 shows timeline highlighting the significant milestones in the development of antimicrobial resistance.

Mechanisms and Dynamics of Antimicrobial Resistance Transmission: From Genetic Transfer to Human-to-Human Spread

A variety of molecular mechanisms of resistance, such as drug target mutations, enzymatic activity that directly inactivates the antibiotic, and the activation of efflux pumps that expel the antibiotic, have been identified through the isolation and genetic characterization of antibiotic-resistant bacterial strains (Gaurav *et al.*, 2023). The term 'resistome' refers to the group of genes implicated in these pathways (Wright, 2010). It was noted in 1944, however, that bacteria were capable of withstanding prolonged antibiotic treatments without developing changes that led to resistance. The words "tolerance" and "persistence" were established to set these survival modes apart from "resistance," although it is still unclear exactly what they mean and how to use them differently. The term "resistance," which is measured by the minimum inhibitory concentration (MIC), describes the innate capacity of microbes to proliferate at high antibiotic doses, irrespective of treatment time (Schultz *et al.*, 2016). On the other hand, "tolerance" refers to the capacity of microorganisms, whether hereditary or not, to withstand brief exposure to high antibiotic concentrations without experiencing a change in minimum inhibitory concentration (MIC), frequently through the inhibition of a crucial bacterial activity (Brauner *et al.*, 2016; Giri *et al.*, 2021). Persistence, as opposed to resistance and tolerance, refers to bacterial cells that lack resistance genes yet are nonetheless resistant to the medication. Because most antimicrobial medicines usually target actively growing and dividing cells, persistence occurs when some cells in a bacterial population adopt a stationary growth phase (dormant) and remain unaffected (Blair *et al.*, 2015; Reygaert, 2018).

ABR is a serious threat to the global public health due to its emergence and spread among bacteria (Davies and Davies, 2010; Ventola, 2015). The transfer of antimicrobial-resistant genes between organisms or within the same organism occurs through several genetic mechanisms. These

Table 1: Timeline of Antibiotic Resistance emergence and spread

S. No.	Year	Resistance	Reference
1.	1928	**Resistance Identified** ✓ Some bacteria became resistant to the antimicrobial Salvarsen	Winslow *et al.* (1920)
2.	1933	**Sulphonamide Resistance** ✓ Certain bacteria developed resistance to sulphonamides	Davies and Davies, (2010)
3.	1944	**Penicillin Resistance** ✓ *Staphylococcus aureus*, a prominent cause of serious infections in humans and animals, was found to have resistance shortly after the introduction of penicillin	Barber and Rozwadowska-Dowzenko (1948)
4.	1961	**Methicillin Resistance** ✓ Methicillin-resistant *Staphylococcus aureus* was described. These bacteria were resistant to all antibiotics in the penicillin class, making infections difficult to treat	Jevons (1961)
5.	1986	**Vancomycin Resistance** ✓ Vancomycin-resistant Enterococcus emerged. These gram-positive bacteria could become resistant to all antibiotics	Leclercq *et al.* (1988); Eubank *et al.* (2022)
6.	1990	**Increasing Resistance** ✓ Resistance to common antimicrobial drugs increased, making previously treatable infections more challenging to manage. ✓ Methicillin-resistant *Staphylococcus aureus*: Emerged as a significant pathogen in hospitals worldwide. ✓ Penicillin-resistant Streptococcus pneumoniae: Increased, especially in the U.S. and Europe	CDC (1997, 1999); Turner *et al.* (2019)
7.	2000	**Spread of Resistance** ✓ Vancomycin-resistant Enterococci (VRE): Became more common in hospitals. ✓ Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae: Spread globally, leading to resistance to many beta-lactam antibiotics. ✓ Carbapenem-resistant Enterobacteriaceae (CRE): Emerged, posing serious treatment challenges.	Ahmed and Baptiste (2018); Akpaka *et al.* (2021); Tompkins and van Duin (2021)
8.	2010	**MDR Resistance** ✓ Both extensively drug-resistant (XDR-TB) and multidrug-resistant (MDR-TB) tuberculosis have become more common, especially in nations with high TB burdens. ✓ Colistin-resistant bacteria: Emerged, often due to the mcr-1 gene, causing concern as colistin is a last-resort antibiotic. ✓ *Neisseria gonorrhoeae*: Resistance to cephalosporins, particularly ceftriaxone, became more common.	Kidd *et al.* (2014); Seung *et al.* (2015) Gao *et al.* (2016)
9.	2020 (upto 2023)	**Continuing Challenges** ✓ Carbapenem-resistant *Acinetobacter baumannii*: Remained a major problem in healthcare settings. ✓ Resistance in *Mycobacterium abscessus*: Increasingly noted in patients with cystic fibrosis and other conditions. ✓ *Clostridioides difficile*: Increased resistance to metronidazole and vancomycin was noted.	Abdelaal *et al.* (2022); Bartal *et al.* (2022)

processes facilitate the rapid spread of resistance, complicating efforts to control AMR.

Transmission of resistance occur between micro-organisms

Apart from gene mutations on a microbe's chromosome leading to AMR, new genetic material can also be transferred across species. Through this exchange, new genetic material encoding antibiotic resistance may be passed on to the host cell and its offspring. This exchange is facilitated by a number of pathways, the most important of which may be plasmid transfer (Wozniak *et al.*, 2010; Walsh *et al.*, 2011; Unemo *et al.*, 2012). Antimicrobials affect this process by causing the transmission of resistance

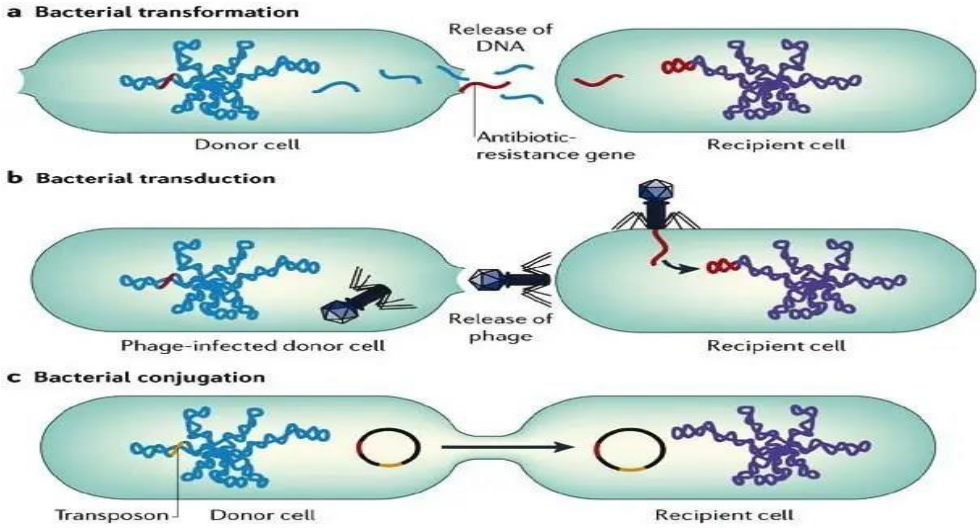

Fig. 3: Gene Transfer Mechanism in Bacteria (Source: Small Things Considered: A Microbial Utopia: Cheese (asmblog.org)); (a) **Transformation:** In this process, bacteria take up free DNA fragments from their environment, which can include resistance genes from lysed (broken down) cells. These fragments can integrate into the recipient's genome; (b) **Transduction:** This mechanism involves bacteriophages (viruses that infect bacteria) transferring resistance genes between bacteria. Phages can accidentally package bacterial DNA, including resistance genes, and transfer them to new bacterial hosts during infection; (c) **Conjugation:** This process involves the transfer of plasmids (circular DNA molecules) between bacteria through direct cell-to-cell contact. Conjugation is a major method for spreading resistance genes across different bacterial species.

determinants between microbes in addition to exerting selective pressure that encourages the establishment of AMR (Beaber *et al.*, 2004).

Bacteria with penicillinase activity were discovered long before antibiotics were commonly employed for medical treatment, indicating their capacity to metabolize penicillin in order to survive in settings that contained the antibiotic (Abraham and Chain, 1940). Early studies on the transfer of genetic information between bacterial cells identified reproductive factors that might treat auxotrophic mutations through R-factors, in addition to spreading AMR (Watanabe *et al.*, 1964). These elements, later named plasmids, were understood to be independent DNA molecules with the ability to move portions of chromosomes through a mechanism known as high-frequency recombination (Hfr) and to self-transmit between cells (Rozwandowicz *et al.*, 2018). Because plasmids can reproduce in a wide variety of hosts and can acquire additional genes through mobile genetic elements like transposons or insertion sequences, they are perfect vectors for the spread of AMR.

Genetic material is transferred between microorganisms through three primary mechanisms: (i) transformation, as seen when *Streptococcus mitis* transfers foreign DNA to *Streptococcus pneumoniae*, leading to penicillin resistance via mosaic gene formation, and when a mosaic penA gene in *Neisseria gonorrhoeae* is linked to ceftriaxone resistance (Unemo *et al.*, 2012); (ii) transduction, where AMR genetic material has been found in phage DNA from wastewater treatment plants, and extended-spectrum β-lactamase (ESβL) genes as well as mecA genes, which confer methicillin resistance in *Staphylococcus aureus*, have been identified in bacteriophages from fecal samples at farms and abattoirs (Colomer-Liuch *et al.*, 2011); and (iii) conjugation, in which plasmids play a crucial role in the global spread of genes encoding carbapenemases, such as New Delhi metallo-β-lactamase, along with ESβLs (Dhanji *et al.*, 2011) (Fig. 3). Additionally, integrative chromosomal

elements can facilitate the transfer of these resistance genes between plasmids and the bacterial chromosome in various Gram-negative species and streptococci (Beaber *et al.*, 2004).

Human-human transmission drive resistance

Modeling the dynamics of transmission has significantly enhanced our understanding of how human-to-human interactions influence the spread of pathogens and AMR. For example, fecal-oral transmission plays a crucial role in disseminating AMR within Enterobacteriaceae, highlighting the importance of sanitation and hygiene in preventing the spread of resistant bacteria in communities (Sharma *et al.*, 2023; Zheng *et al.*, 2023). Similarly, *Neisseria gonorrhoeae*, which causes gonorrhea, is mainly spread through sexual contact. This underscores the necessity of sexual health education, safe sex practices, and regular screenings to manage the spread of antibiotic-resistant gonorrhea (Quillin and Seifert, 2018). Additionally, healthcare-associated infections, such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA), present significant challenges. MRSA often spreads in healthcare environments due to close interactions between patients and healthcare workers, as well as through contaminated surfaces and medical equipment. This situation highlights the need for strict infection control measures, including proper hand hygiene, thorough environmental cleaning, and prudent antibiotic use (CDC, 2024).

Various strategies have been implemented to interrupt human-to-human transmission on a population level. Mass drug administration (MDA) programs, which involve distributing medications to entire populations regardless of individual infection status, have effectively reduced the prevalence of certain infections and the spread of resistance. For instance, MDA has been used to control trachoma and lymphatic filariasis, demonstrating its potential in managing the transmission of other infectious diseases (Gao *et al.*, 2017). Vaccination also plays a vital role in preventing the spread of infectious diseases and AMR. By providing immunity to individuals, vaccines reduce the overall disease burden in the population, thereby limiting opportunities for pathogens to spread and develop resistance. Vaccination programs have successfully controlled diseases such as pneumococcal infections and influenza, reducing the need for antibiotics and the emergence of resistance (Rodrigues and Plotkin, 2020). When implemented effectively, these population-based strategies can significantly reduce pathogen transmission and curb the spread of AMR, thereby protecting public health on a larger scale.

Modeling transmission dynamics, improving hygiene and sanitation, promoting safe sex practices, enforcing strict infection control in healthcare settings, and implementing population-based interventions like mass drug administration and vaccination is essential in combating the spread of AMR. These strategies must be tailored to the specific transmission routes and contexts of different pathogens to be effective.

Factors Contributing to Worsening AMR in India and the Environment

1. *Genetic Insights*: Advances in genomic sequencing technologies have enabled researchers to unravel the genetic basis of ABR in bacteria. This includes the identification of specific genes, mutations, and genetic elements responsible for conferring resistance to various antibiotics (Francine, 2022).

2. *Horizontal Gene Transfer*: Understanding the mechanisms of horizontal gene transfer, such as conjugation, transduction, and transformation, has highlighted how bacteria can acquire resistance genes from other bacterial species, further exacerbating the spread of ABR (Michaelis and Grohmann, 2023).

3. *Emergence of Novel Resistance Mechanisms*: Researchers have identified novel mechanisms of ABR, such as efflux pumps, biofilm formation, and persister cell formation. These mechanisms allow bacteria to evade the effects of antibiotics and survive in the presence of antimicrobial agents

(Reygaert, 2018).

4. *Evolutionary Dynamics*: Studies on the evolutionary dynamics of antibiotic resistance have revealed how bacteria evolve in response to antibiotic exposure, leading to the emergence of MDR strains with enhanced survival and transmission capabilities (Davies and Davies, 2010).

5. *Pharmacokinetic Considerations*: Advances in pharmacokinetic research have highlighted the importance of understanding drug distribution, metabolism, and elimination in the context of antibiotic therapy. This knowledge is crucial for optimizing dosing regimens and combating the development of resistance (Rizk *et al.*,

2017).

6. *Combination Therapies*: Research on combination antibiotic therapies has shown in overcoming resistance mechanisms by targeting multiple pathways simultaneously. Synergistic drug combinations can enhance efficacy and reduce the likelihood of resistance emergence (Morales-Duran, 2024). These recent advances provide valuable insights into the complex mechanisms underlying antibiotic resistance in clinical bacteria and offer opportunities to develop innovative strategies for tackling this growing public health threat.

7. *Overuse and Misuse of Antibiotics*: A significant factor driving AMR in India is the rampant and inappropriate use of antibiotics. Antibiotics are often accessible without a prescription, resulting in widespread and frequently unnecessary consumption (Holloway *et al.*, 2017; Taneja and Sharma, 2019).

8. *Lack of Awareness*: Public awareness of AMR in India is generally low. Many people do not understand the consequences of not completing an antibiotic course or using antibiotics when unnecessary, leading to the development of resistant bacteria (Laxminarayan *et al.*, 2013).

9. *Substandard Infection Control Practices*: Infection control measures in Indian healthcare settings are often insufficient, resulting in high rates of hospital-acquired infections, which are frequently caused by drug-resistant pathogens (WHO, 2019).

10. *Unregulated Antibiotic Use in Animal Husbandry*: The use of antibiotics in animal farming for growth promotion and disease prevention is widespread. This practice can lead to antibiotic residues in meat and other animal products, contributing to antibiotic resistance.

11. *Insufficient Access to Clean Water and Sanitation*: The limited availability of clean water and adequate sanitation facilities increases the incidence of infectious diseases, which in turn raises antibiotic usage and fosters antimicrobial resistance (WHO, 2019).

12. *Weak Surveillance and Regulatory Systems*: India lacks a comprehensive system for monitoring antimicrobial resistance, hindering a full understanding of the problem and the development of effective strategies. Additionally, existing regulations on antibiotic use are poorly enforced (WHO, 2019).

13. *Regulatory Challenges in the Pharmaceutical Sector*: As a major antibiotic producer and consumer, India faces significant issues related to the insufficient regulatory oversight of antibiotic manufacturing and waste management, potentially causing environmental contamination and the spread of antimicrobial resistance (Manyi-Loh *et al.*, 2018).

These factors collectively underscore the complexity of AMR in India and in the world, highlighting the need for comprehensive strategies to address the issue through better regulation, public awareness, and improved healthcare practices.

ABR in the Environment

ABR in the environment is a growing concern globally due to its potential impact on public health. It refers to the ability of bacteria in the environment to withstand the effects of antibiotics, rendering these medications ineffective in treating infections caused by resistant

bacteria. This phenomenon arises from various factors, including the widespread use of antibiotics in human and veterinary medicine, as well as their release into the environment through wastewater, agricultural runoff, and improper disposal of pharmaceuticals. According to Pruden *et al.* (2006), Wellington *et al.* (2013) and Berendonk *et al.* (2015) the key points about ABR in the environment include:

1. *Sources of Antibiotics*: Antibiotics enter the environment through various pathways, including human and animal waste, pharmaceutical manufacturing effluents, and agricultural runoff from the use of antibiotic-containing fertilizers or animal waste.

2. *Selection Pressure*: The presence of antibiotics in the environment creates selective pressure favoring the survival and proliferation of antibiotic-resistant bacteria. These bacteria can transfer their resistance genes to other bacterial species through mechanisms such as horizontal gene transfer.

3. *Environmental Reservoirs*: Antibiotic-resistant bacteria can persist and thrive in various environmental reservoirs, including soil, water bodies, and biofilms on surfaces. These reservoirs serve as potential sources of resistant bacteria that can spread to humans, animals, and other environments.

4. *Human Health Implications*: Antibiotic-resistant bacteria in the environment represent a serious threat to human health by facilitating the spread of resistant infections. People can come into contact with these bacteria through direct interaction with contaminated environments, consumption of tainted food or water, or inhalation of airborne particles.

5. *One Health Approach*: Addressing antimicrobial resistance (ABR) in the environment requires an integrated strategy that recognizes the interconnected nature of human, animal, and environmental health. The One Health framework encourages cooperation among medical professionals, veterinarians, environmental experts, policymakers, and other key stakeholders to effectively control the emergence and transmission of ABR.

6. *Mitigation Strategies*: Efforts to combat ABR in the environment include reducing unnecessary antibiotic use in human and veterinary medicine, improving wastewater treatment processes to remove antibiotics and resistant bacteria, promoting responsible use of antibiotics in agriculture, and implementing surveillance programs to monitor ABR in environmental samples.

In conclusion, combating AMR in India and the environment requires a comprehensive approach that addresses misuse and overuse of antibiotics, enhances public awareness, improves infection control measures, enforces regulations, and fosters international collaboration under the One Health framework.

Approaches to Combat AMR

Antimicrobial resistance (AMR) presents a major challenge to global health, contributing to higher death rates, extended durations of hospitalization, and increased healthcare costs (Prestinaci et al., 2015; Friedman et al., 2016). To address this growing concern, the World Health Assembly (WHA) endorsed the Global Action Plan (GAP) on AMR in 2015 (WHO, 2017). In alignment with this initiative, many nations have formulated their own National Action Plans (NAPs). India's Ministry of Health and Family Welfare launched its NAP to combat AMR in April 2017, which was later showcased during the 70th WHA held in Geneva in May of the same year (NAP-AMR, 2019).

The Food and Agriculture Organization (FAO) emphasized the urgent need to tackle antimicrobial resistance (AMR) in both 2015 and 2019, using World Antimicrobial Awareness Week (WAAW) as a platform to engage and educate various stakeholders. The 2023 WAAW theme, "Preventing AMR Together," highlighted the importance of cross-sector collaboration in combating AMR. India has shown commitment to

Table 2: The National Action Plan outlines five primary goals to combat ABR

GOALS AND OBJECTIVES: Combating Antibiotic-Resistant Bacteria	
Goal 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections	Objectives: Implement public health programs for antibiotic stewardship, eliminate the use of medically-important antibiotics for growth promotion in food animals, and promote veterinary oversight and stewardship in agricultural antibiotic use.
Goal 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance	Objectives: Establish a regional public health laboratory network, enhance national surveillance and reporting infrastructure, build capacity in veterinary and food safety labs, and improve monitoring of ABR patterns and practices in the food production chain.
Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Resistant Bacteria	Objectives: Develop and validate new diagnostics that quickly distinguish between viral and bacterial infections and detect ABR, and expand their availability and use to improve treatment, infection control, and outbreak response.
Goal 4: Accelerate Research to Develop New Antibiotics, Therapeutics, Vaccines, and Diagnostics	Objectives: Enhance understanding of environmental factors and microbial communities related to ABR, intensify research on new therapeutics and vaccines, and develop innovative strategies and non-traditional treatments to address resistant bacterial outbreaks.
Goal 5: Improve International Collaboration and Capacities for Prevention, Surveillance, and Antibiotic Research and Development	Objectives: Strengthen laboratory capabilities to identify key antimicrobial resistant pathogens, collaborate internationally on surveillance, develop communication mechanisms for new resistance trends, and promote the dissemination of information to effectively address ABR.

this cause, notably through the Jaipur Declaration on AMR in 2011, endorsed by health ministers from Southeast Asian countries to strengthen regional efforts. Following the endorsement of the global action plan on AMR by the sixty-eighth World Health Assembly in 2015, India formulated its National Action Plan on AMR (2017-2021) through comprehensive multi-sectoral consultations. This plan aligns with WHO's Global Action Plan and was shared with the global community in April 2017.

According to an IHME report from the University of Washington, AMR is a significant global challenge, causing 4.95 million deaths in 2019 due to drug-resistant infections, with 1.27 million of these directly attributed to AMR. Alarmingly, one in five of these deaths occurred in children under five years old. In India, the AMR burden is particularly severe, with 297,000 deaths attributable to AMR and 1,042,500 deaths associated with AMR in 2019. In 2019, AMR significantly impacted public health in India, with several key pathogens contributing to a high mortality rate. *Escherichia coli* was the leading cause, responsible for 25.9% of AMR-related deaths, translating to 152,700 fatalities. *Klebsiella pneumoniae* followed closely, accounting for 20.9% or 123,200 deaths. *Staphylococcus aureus* was implicated in 18.9% of cases, resulting in 111,400 deaths. *Acinetobacter baumannii* caused 17.6% of the deaths, amounting to 103,500 fatalities, while *Mycobacterium tuberculosis* was responsible for 16.7%, leading to 98,600 deaths. These pathogens are known to cause severe infections such as bloodstream infections, pneumonia, and tuberculosis, which are increasingly difficult to treat due to rising resistance to antibiotics. The growing prevalence of AMR poses a critical threat to public health infrastructure and necessitates urgent measures to combat the spread of resistant strains and develop new treatment strategies. The data

underscores the urgent need for improved antibiotic stewardship, enhanced infection control, and robust public health initiatives to mitigate the impact of AMR in India. The National AMR Action Plan has been approved and implemented in India, with the next steps focusing on financing, monitoring, and utilizing data to ensure effective progression in combating AMR.

The National Action Plan is structured around five key goals to combat antibiotic-resistant bacteria, aiming to enhance healthcare, public health, veterinary medicine, agriculture, food safety, and research and manufacturing sectors (Table 2). These goals focus on slowing the emergence of resistant bacteria by implementing public health programs and stewardship policies, eliminating the use of medically important antibiotics for growth promotion in food-producing animals, and bringing agricultural antibiotic use under veterinary oversight. Additionally, they emphasize enhancing national One-Health surveillance efforts, developing rapid and innovative diagnostic tests, accelerating research for new antibiotics and therapeutics, and improving international collaboration and capacities for prevention, surveillance, and research in antibiotic resistance. These goals emphasize a comprehensive, multi-faceted approach to mitigating ABR, integrating public health initiatives, advanced diagnostics, research, and global collaboration (National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020 – 2025).

Conclusion

The historical journey of antibiotics, from the "Golden Age" of discovery in the 1930s to the 1960s, saw unprecedented advancements with the development of life-saving drugs like penicillin and streptomycin, revolutionizing modern medicine by significantly extending life expectancy and enabling complex medical procedures. However, this era of medical triumph has been overshadowed by the rise of AMR, driven by overuse and misuse of antibiotics, as well as the natural adaptability of bacteria. The emergence of MRSA and vancomycin-resistant bacteria underscores the relentless nature of bacterial evolution, posing a grave threat to global health by undermining the efficacy of existing treatments and endangering essential medical procedures. This "Faceless Pandemic" results in hundreds of thousands of deaths annually and calls for a multifaceted approach to combat AMR. Key strategies include the development of novel antibiotics, improved infection control measures, enhanced global surveillance, and better steward-ship of existing drugs. Raising awareness about AMR and implementing robust public health policies to ensure access to clean WASH, alongside promoting the use of quality vaccines and medications, are equally crucial.

Addressing AMR necessitates coordinated global efforts and comprehensive strategies that encompass global and national action plans, public health initiatives, and stringent infection control measures. The World Health Assembly's Global Action Plan and national strategies like India's National Action Plan emphasize the need for a holistic approach involving healthcare, veterinary medicine, agriculture, and research sectors. Implementing antibiotic stewardship programs, restricting the use of medically important antibiotics in agriculture, enhancing surveillance, and promoting research into new antibiotics and diagnostics are vital steps. Human-to-human transmission dynamics, particularly in healthcare settings, demand improved sanitation, hygiene, and infection control practices. Additionally, population-based interventions such as mass drug administration and vaccination can reduce the prevalence of infections and, consequently, the need for antibiotic use. Addressing environmental AMR through the One Health approach, which recognizes the interconnectedness of human, animal, and environmental health, is essential. This holistic strategy requires collaboration among diverse stakeholders, including healthcare professionals, veterinarians, environmental scientists, and policymakers. By implementing targeted interventions and fostering international

cooperation, it is possible to curb the spread of resistant bacteria and safeguard the efficacy of antibiotics for future generations, ensuring that these vital drugs continue to save lives and support advanced medical treatments.

Ethical Statement

This is a review article hence no Ethical Approval needed.

Author Contributions

Giri Neha: conceived the idea, literature search, manuscript writing and editing; *Tomar Garima*: contributed to literature review, specific section writing, and revisions; *Devi Bindu* and *Singh Karan*: figures/tables, and reviewed the manuscript; *Kotiyal Shalini* and *Negi Priyanka*: manuscript writing and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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