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FROM MIRACLE DRUGS TO GLOBAL RESISTANCE: THE HUMAN COST OF ANTIBIOTIC MISUSE

DAS DROGAS MILAGROSAS À RESISTÊNCIA GLOBAL: O CUSTO HUMANO DO USO INADEQUADO DE ANTIBIÓTICOS

DE LOS MEDICAMENTOS MILAGROSOS A LA RESISTENCIA GLOBAL: EL COSTO HUMANO DEL USO INADECUADO DE ANTIBIÓTICOS

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ABSTRACT

The discovery of antibiotics revolutionized modern medicine and transformed the treatment of infectious diseases, dramatically reducing global mortality and increasing human life expectancy throughout the twentieth century. What was once considered a definitive victory over bacterial infections, however, has progressively evolved into one of the greatest public health threats of the modern era. After nearly eight decades of widespread antibiotic exposure, humanity now faces the accelerating emergence of antimicrobial resistance (AMR), a phenomenon driven largely by inappropriate, excessive, and poorly regulated antimicrobial use across human medicine, veterinary practice, agriculture, and the environment. The current resistance crisis reflects decades of selective pressure imposed on microbial ecosystems. Antibiotics have been excessively prescribed for viral illnesses, used empirically without adequate diagnostic confirmation, consumed through self-medication, and extensively incorporated into livestock production for disease prevention and growth promotion. Simultaneously, inadequate infection control practices, environmental contamination, globalization, and insufficient antimicrobial stewardship have facilitated the rapid dissemination of multidrug-resistant pathogens worldwide. The consequence has been the emergence of highly resistant organisms capable of compromising the effectiveness of even last-line therapies. Beyond its microbiological dimension, AMR threatens the foundation of modern healthcare systems. Procedures that depend on effective antibiotics, including organ transplantation, chemotherapy, intensive care medicine, and major surgery are becoming increasingly vulnerable to therapeutic failure. Resistant infections are associated with prolonged hospitalization, increased mortality, escalating healthcare expenditures, and substantial economic losses that are projected to reach trillions of dollars over the coming decades. Although promising alternatives such as vaccines, bacteriophage therapy, antimicrobial peptides, precision medicine, and artificial intelligence-based drug discovery are under development, none currently possess the capacity to fully replace conventional antibiotics. Until innovative therapeutic strategies become broadly available, preserving the effectiveness of existing antimicrobials through rational prescribing, surveillance, infection

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prevention, and coordinated global stewardship policies remains one of the most urgent priorities in contemporary medicine.

Keywords: Antimicrobial Resistance. Antibiotics. Antimicrobial Stewardship.

RESUMO
A descoberta dos antibióticos revolucionou a medicina moderna e transformou o tratamento das doenças infecciosas, reduzindo drasticamente a mortalidade global e aumentando a expectativa de vida humana ao longo do século XX. O que antes era considerado uma vitória definitiva contra as infecções bacterianas, entretanto, evoluiu progressivamente para uma das maiores ameaças à saúde pública da era moderna. Após quase oito décadas de ampla exposição aos antibióticos, a humanidade enfrenta atualmente a crescente emergência da resistência antimicrobiana (RAM), um fenômeno impulsionado principalmente pelo uso inadequado, excessivo e insuficientemente regulamentado de antimicrobianos na medicina humana, na prática veterinária, na agricultura e no meio ambiente. A atual crise da resistência reflete décadas de pressão seletiva exercida sobre os ecossistemas microbianos. Os antibióticos têm sido excessivamente prescritos para doenças virais, utilizados empiricamente sem confirmação diagnóstica adequada, consumidos por automedicação e amplamente incorporados à produção animal para prevenção de doenças e promoção de crescimento. Simultaneamente, práticas inadequadas de controle de infecção, contaminação ambiental, globalização e insuficiência de programas de stewardship antimicrobiano facilitaram a rápida disseminação mundial de patógenos multirresistentes. Como consequência, surgiram microrganismos altamente resistentes capazes de comprometer a eficácia até mesmo das terapias de última linha. Além de sua dimensão microbiológica, a RAM ameaça os próprios fundamentos dos sistemas modernos de saúde. Procedimentos que dependem de antibióticos eficazes, incluindo transplantes de órgãos, quimioterapia, medicina intensiva e grandes cirurgias, estão se tornando progressivamente mais vulneráveis ao fracasso terapêutico. As infecções resistentes estão associadas a hospitalizações prolongadas, aumento da mortalidade, elevação dos custos em saúde e perdas econômicas substanciais projetadas para alcançar trilhões de dólares nas próximas décadas. Embora alternativas promissoras, como vacinas, terapia com bacteriófagos, peptídeos antimicrobianos, medicina de precisão e descoberta de fármacos baseada em inteligência artificial estejam em desenvolvimento, nenhuma delas possui atualmente capacidade de substituir completamente os antibióticos convencionais. Até que estratégias terapêuticas inovadoras estejam amplamente disponíveis, preservar a eficácia dos antimicrobianos existentes por meio da prescrição racional, vigilância, prevenção de infecções e políticas globais coordenadas de stewardship permanece como uma das prioridades mais urgentes da medicina contemporânea.

Palavras-chave: Resistência Antimicrobiana. Antibióticos. Stewardship Antimicrobiano.

RESUMEN
El descubrimiento de los antibióticos revolucionó la medicina moderna y transformó el tratamiento de las enfermedades infecciosas, reduciendo drásticamente la mortalidad global y aumentando la esperanza de vida humana a lo largo del siglo XX. Lo que alguna vez fue considerado una victoria definitiva contra las infecciones bacterianas, sin embargo, ha evolucionado progresivamente hasta convertirse en una de las mayores amenazas para la salud pública de la era moderna. Después de casi ocho décadas de amplia exposición a los antibióticos, la humanidad enfrenta actualmente la creciente aparición de la resistencia antimicrobiana (RAM), un fenómeno impulsado principalmente por el uso inadecuado, excesivo y escasamente regulado de antimicrobianos en la medicina humana, la práctica veterinaria, la agricultura y el medio ambiente. La actual crisis de resistencia refleja décadas de presión selectiva ejercida sobre los ecosistemas microbianos. Los antibióticos han sido

excesivamente prescritos para enfermedades virales, utilizados empíricamente sin confirmación diagnóstica adecuada, consumidos mediante automedicación e incorporados ampliamente en la producción animal para la prevención de enfermedades y la promoción del crecimiento. Simultáneamente, las prácticas inadecuadas de control de infecciones, la contaminación ambiental, la globalización y la insuficiencia de programas de stewardship antimicrobiano han facilitado la rápida diseminación mundial de patógenos multirresistentes. Como consecuencia, han surgido microorganismos altamente resistentes capaces de comprometer la eficacia incluso de las terapias de última línea. Más allá de su dimensión microbiológica, la RAM amenaza los fundamentos mismos de los sistemas modernos de salud. Los procedimientos que dependen de antibióticos eficaces, incluidos los trasplantes de órganos, la quimioterapia, la medicina intensiva y las cirugías mayores, se están volviendo progresivamente más vulnerables al fracaso terapéutico. Las infecciones resistentes están asociadas con hospitalizaciones prolongadas, aumento de la mortalidad, incremento de los gastos sanitarios y pérdidas económicas sustanciales proyectadas para alcanzar billones de dólares en las próximas décadas. Aunque alternativas prometedoras como las vacunas, la terapia con bacteriófagos, los péptidos antimicrobianos, la medicina de precisión y el descubrimiento de fármacos basado en inteligencia artificial están en desarrollo, ninguna posee actualmente la capacidad de reemplazar completamente a los antibióticos convencionales. Hasta que las estrategias terapéuticas innovadoras estén ampliamente disponibles, preservar la eficacia de los antimicrobianos existentes mediante la prescripción racional, la vigilancia, la prevención de infecciones y las políticas globales coordinadas de stewardship continúa siendo una de las prioridades más urgentes de la medicina contemporánea.

Palabras clave: Resistencia Antimicrobiana. Antibióticos. Stewardship Antimicrobiano.

1 INTRODUCTION

The Promise and Paradox of the Antibiotic Era. The antibiotic era began as one of the most optimistic chapters in the history of medicine because it transformed bacterial infections from frequent causes of death into largely treatable conditions (Lobanovska; Pilla, 2017; Muteeb; Rehman; Shahwan; Aatif, 2023). Before antibiotics became available, pneumonia, septicemia, puerperal infections, meningitis, tuberculosis, and postoperative wound infections were major causes of mortality, and even minor injuries could evolve into fatal conditions (Tang; Millar; Moore, 2023; Vitiello; Sabbatucci; Boccellino; Ponzo *et al.*, 2023).

The discovery of penicillin by Alexander Fleming in 1928 provided the symbolic and practical beginning of modern antibiotic therapy, although large-scale clinical use depended on subsequent purification, testing, and production efforts by the Oxford group during the early 1940s (Lobanovska; Pilla, 2017). The rapid expansion of antibiotic discovery after World War II created what is often described as the golden age of antimicrobial development, during which several major antibiotic classes were introduced into clinical practice (Muteeb; Rehman; Shahwan; Aatif, 2023; Song, 2008). These discoveries changed not only infectious disease treatment but also the safety of modern medical interventions that depend on infection prevention and control, including major surgery, intensive care, organ transplantation, oncology, and neonatal medicine (Tang; Millar; Moore, 2023; Vitiello; Sabbatucci; Boccellino; Ponzo *et al.*, 2023).

The triumph of antibiotics, however, contained a biological paradox because every use of these drugs applies selective pressure that can favor resistant organisms and resistance genes (Colgan; Powers, 2001; McEwen; Collignon, 2018). Fleming himself warned that inappropriate exposure and underdosing could select resistant bacteria, indicating that the danger of resistance was recognized from the earliest years of the antibiotic era (Lobanovska; Pilla, 2017; McEwen; Collignon, 2018). Over the following eight decades, this warning became reality as antimicrobial resistance emerged across hospitals, communities, farms, food chains, water systems, and global ecosystems (McEwen; Collignon, 2018; Tang; Millar; Moore, 2023). The current crisis therefore reflects not only bacterial evolution but also a human-made pattern of excessive prescription, misuse, weak regulation, agricultural dependence, environmental contamination, and insufficient innovation (Palanisamy, 2023; Pulingam; Parumasivam; Gazzali; Sulaiman *et al.*, 2022).

The objective of this editorial is to discuss how inappropriate antibiotic use over the last eight decades has contributed to the emergence of antimicrobial resistance and its consequences for human health. In addition, this study addresses the main factors associated with the resistance crisis, its economic and clinical impacts, and potential

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alternatives to conventional antibiotics (McEwen; Collignon, 2018; Tang; Millar; Moore, 2023).

2 LITERATURE REVIEW

2.1 DISCOVERY OF ANTIBIOTICS AND THE EARLY WARNING SIGNS OF RESISTANCE

The discovery of penicillin was initially based on Fleming's observation that a contaminating Penicillium mold inhibited the growth of nearby staphylococcal. Although Fleming identified the antibacterial potential of penicillin, its transformation into a clinically useful drug required later purification, animal experiments, human trials, and industrial-scale production (Lobanovska; Pilla, 2017).

The first systemic clinical use of penicillin demonstrated that bacterial infections previously considered life-threatening could be reversed with targeted antimicrobial therapy (Muteeb; Rehman; Shahwan; Aatif, 2023). The postwar period brought the discovery and clinical incorporation of multiple antibiotic classes, including aminoglycosides, chloramphenicol, tetracyclines, macrolides, glycopeptides, rifamycins, quinolones, and trimethoprim (Song, 2008).

This rapid expansion created a sense that new antibiotics would continually replace older drugs whenever resistance emerged. That assumption proved unsustainable because the discovery of new classes slowed dramatically after the 1960s and 1970s (Cunha-Ferreira; Vizzotto; Peixoto; Krüger, 2025; Song, 2008).

Resistance to penicillin appeared early, and penicillinase-producing bacteria demonstrated that microorganisms could rapidly neutralize even the most revolutionary antibacterial agents. Resistance later emerged against sulfonamides, penicillins, tetracyclines, fluoroquinolones, cephalosporins, carbapenems, and even last-resort drugs such as colistin (Barbee, 2014; Tang; Millar; Moore, 2023; Wang; Hsieh; Powers; Kao, 2020).

The pattern observed over the antibiotic era shows that each new antimicrobial class can eventually be followed by the emergence of resistance when use is extensive or poorly controlled (Pulingam; Parumasivam; Gazzali; Sulaiman *et al.*, 2022). Thus, the history of antibiotics is not only a history of therapeutic success but also a history of repeated bacterial adaptation to human antimicrobial pressure (Kumar; Sarma; Shubham; Kumawat *et al.*, 2021; McEwen; Collignon, 2018; Pulingam; Parumasivam; Gazzali; Sulaiman *et al.*, 2022).

2.2 THE CURRENT GLOBAL BURDEN OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is now widely described as a silent pandemic because its progression is gradual, global, and often less visible than acute infectious outbreaks (Tang; Millar; Moore, 2023; Vitiello; Sabbatucci; Boccellino; Ponzo *et al.*, 2023). Global estimates indicate that resistant bacterial infections were directly responsible for more than one million deaths in 2019, with several million additional deaths associated with resistant pathogens.

If current trends continue, AMR may cause approximately 10 million deaths annually by 2050, making it one of the leading causes of death worldwide (Tang; Millar; Moore, 2023). The clinical burden of AMR is especially severe for bloodstream infections, ventilator-associated pneumonia, urinary tract infections, surgical site infections, neonatal sepsis, and infections in immunocompromised patients (Watkins, 2022). Healthcare-associated infections caused by multidrug-resistant organisms have increased substantially and are particularly difficult to manage in intensive care units and long-term care facilities(Marino; Maniaci; Lentini; Ronsivalle *et al.*, 2025; Watkins, 2022).

The ESKAPE pathogens are especially relevant because they represent organisms capable of causing severe infections while evading several major antibiotic classes (Wang; Hsieh; Powers; Kao, 2020). These organisms include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species (Boucher; Talbot; Bradley; Edwards *et al.*, 2009). The increasing frequency of MRSA, VRE, ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales, and multidrug-resistant non-fermenting Gram-negative bacteria has narrowed therapeutic options in both hospitals and communities (Baciu; Baciu; Baciu; Gurau, 2024).

The World Health Organization has responded by defining priority pathogen lists to guide research, innovation, surveillance, and drug development for resistant organisms (Abdallah; Alhudhaibi; Dahab; Al Noman *et al.*, 2026; SeyedAlinaghi; Mehraeen; Mirzapour; Yarmohammadi *et al.*, 2025). The 2024 bacterial priority pathogen framework emphasizes critical threats such as carbapenem-resistant *Acinetobacter baumannii*, third-generation cephalosporin-resistant Enterobacterales, carbapenem-resistant Enterobacterales, rifampicin-resistant *Mycobacterium tuberculosis*, and resistant *Neisseria gonorrhoeae* (Supuran, 2024).

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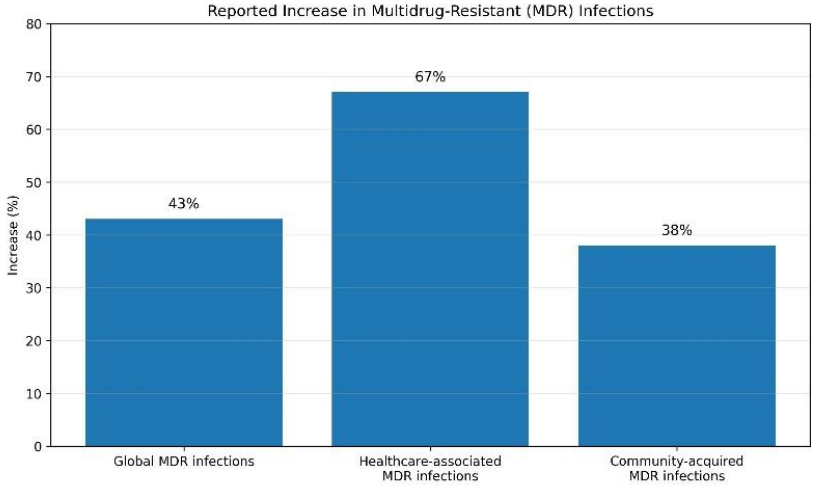
Figure 1

Reported increase in multidrug-resistant (MDR) infections worldwide: global MDR infections, healthcare-associated MDR infections, and community-acquired MDR infections.



Source: Marino et al. (2025), The Global Burden of Multidrug-Resistant Bacteria.

Figure 1 summarizes key indicators of increasing multidrug-resistant infections and visually reinforces that AMR is not restricted to isolated microbiological events but represents a measurable population-level trend (Marino; Maniaci; Lentini; Ronsivalle *et al.*, 2025). The figure shows a 43% reported increase in global multidrug-resistant infections, indicating that resistant organisms have expanded substantially across healthcare systems and communities.

The same figure shows a 67% increase in healthcare-associated multidrug-resistant infections, emphasizing that hospitals remain major amplification environments for resistant pathogens because of antibiotic exposure, invasive devices, severe illness, and patient-to-patient transmission (Marino; Maniaci; Lentini; Ronsivalle *et al.*, 2025; Watkins, 2022).

The 38% increase in community-acquired multidrug-resistant infections shown in Figure 1 demonstrates that resistance has escaped the hospital environment and is increasingly present in general populations. This distinction is essential for the article because it shows that AMR can no longer be understood only as a hospital infection problem but must be interpreted as a societal, ecological, and One Health crisis (McEwen; Collignon, 2018; Tang; Millar; Moore, 2023).

The higher growth of healthcare-associated MDR infections also supports the need for antimicrobial stewardship, infection prevention, hand hygiene, isolation protocols, diagnostic optimization, and surveillance in hospitals (Palanisamy, 2023; Watkins, 2022). The simultaneous rise of community-acquired resistance supports the need for public education, control of over-the-counter antibiotic access, appropriate primary care prescribing, and reduction of unnecessary antimicrobial use in common respiratory infections (Colgan; Powers, 2001).

2.3 WHY WE REACHED THIS SITUATION: EXCESSIVE PRESCRIPTION IN HUMAN MEDICINE

The inappropriate use of antibiotics in human medicine is one of the most important drivers of antimicrobial resistance. A substantial proportion of antibiotic prescriptions are issued for viral infections or self-limited conditions in which the expected benefit is minimal or absent (Colgan; Powers, 2001). Upper respiratory tract infections are a classic example because many are viral, yet antibiotics are frequently prescribed due to diagnostic uncertainty or patient expectations (Watkins, 2022).

When antibiotics are prescribed unnecessarily, they do not benefit the patient but still affect the microbiota and select resistant organisms (Colgan; Powers, 2001). The CDC estimate that approximately 30% of antibiotics in acute care hospitals are unnecessary or suboptimal illustrates the magnitude of inappropriate use even in highly regulated healthcare settings (Watkins, 2022).

The World Health Organization estimates that only about half of antibiotics are used correctly globally further shows that inappropriate use is not a marginal phenomenon but a central structural problem (Palanisamy, 2023).

Diagnostic uncertainty remains a major cause of inappropriate prescribing because clinicians must often decide before culture results or susceptibility tests are available. The fear of missing severe bacterial infection may lead physicians to prescribe broad-spectrum antibiotics empirically, especially in hospitalized or critically ill patients (Chand; Davidson; Megaw; Morgan *et al.*, 2026).

Although empirical therapy may be clinically necessary in severe infection, failure to reassess and de-escalate therapy after diagnostic information becomes available contributes to unnecessary antimicrobial exposure. Antibiotic stewardship programs were developed precisely to address these problems by promoting evidence-based antibiotic selection, dose optimization, treatment duration control, and reassessment after culture results (Noguerol Andrade; Santos; Del Fiol, 2026).

2.4 SELF-MEDICATION, INCOMPLETE COURSES, AND SOCIAL DRIVERS OF MISUSE

Self-medication with antibiotics is another important contributor to AMR, particularly in settings where antibiotics can be obtained without prescription. Patients may use leftover antibiotics, share medications with relatives, stop treatment after symptom improvement, or take antimicrobials for viral infections without clinical evaluation. Incomplete or inappropriate antibiotic exposure can suppress susceptible bacteria while allowing partially resistant organisms to survive and expand (Thaha; K; S, 2026).

Public misunderstanding of antibiotics remains widespread because many individuals still interpret these drugs as general anti-infection or anti-inflammatory agents rather than targeted antibacterial therapies. The social pressure placed on clinicians to prescribe antibiotics also contributes to misuse because patients may expect medication as proof that their illness has been taken seriously In busy clinical environments, prescribing an antibiotic can seem faster than explaining why it is unnecessary, especially when rapid diagnostics are unavailable (Colgan; Powers, 2001; Grada; Chandy; Park; Feldman, 2026).

This behavioral dimension demonstrates that antimicrobial resistance is not only a microbiological issue but also a communication, education, regulation, and health literacy problem. Public campaigns must therefore explain that antibiotics do not treat viral infections, that unnecessary antibiotic use can harm the individual microbiota, and that resistant infections threaten the entire community (Maduko; Kesby; Hale; Olamijuwon, 2026). Health professionals must also be supported with diagnostic tools, prescribing guidelines, audit systems, and institutional policies that make rational prescribing easier than inappropriate prescribing. Without changes in both professional practice and public expectations, the social drivers of antibiotic misuse will continue to amplify biological resistance mechanisms (Bursey; Patey; Etchegary; Aubrey-Bassler *et al.*, 2026).

2.5 AGRICULTURE, LIVESTOCK, GROWTH PROMOTION, AND THE ONE HEALTH DIMENSION

The use of antibiotics in agriculture and livestock production has been one of the most consequential non-human drivers of antimicrobial resistance. Antibiotics have been used in food-producing animals for treatment, prophylaxis, metaphylaxis, and growth promotion (Alabi; Chenia; Lin, 2025). Growth promotion is especially problematic because it often involves prolonged exposure of large animal populations to low antimicrobial concentrations that favor selection of resistant bacteria (Odumosu; Bamidele; Buraimoh; Romiluyi *et al.*, 2026).

Medically important classes such as tetracyclines, macrolides, fluoroquinolones, third-generation cephalosporins, and colistin have been used in animal production systems in different regions. Resistant bacteria selected in animals may reach humans through direct occupational contact, contaminated meat, manure, wastewater, soil, and water systems (Alabi; Chenia; Lin, 2025).

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This transmission pathway illustrates why AMR cannot be solved by hospital policies alone and requires integrated policies across human medicine, veterinary medicine, agriculture, food systems, and environmental management. The One Health approach recognizes that human health, animal health, and environmental health are interdependent and that antibiotic use in one sector can affect resistance patterns in the others (Laxminarayan; Limmathurotsakul; de Abreu; Alimi *et al.*, 2026).

The World Health Organization has recommended reducing routine use of medically important antibiotics in healthy food-producing animals to preserve the effectiveness of drugs essential for human medicine. Alternatives to antibiotic growth promoters, including improved hygiene, vaccination, biosecurity, probiotics, prebiotics, phytobiotics, better nutrition, and husbandry improvements, are central to reducing dependence on antimicrobials in animal production (Bengtsson; Greko, 2014). The statement that healthy animals do not need antibiotics captures the preventive logic of One Health stewardship in veterinary and agricultural settings.

2.6 ENVIRONMENTAL CONTAMINATION AND THE GLOBAL RESISTOME

Environmental contamination is now recognized as a major component of the antimicrobial resistance crisis. Antibiotic residues, resistant bacteria, and resistance genes enter the environment through human sewage, hospital effluents, pharmaceutical manufacturing waste, animal manure, agricultural runoff, and aquaculture systems (Cunha-Ferreira; Vizzotto; Peixoto; Kruger, 2025).

Once present in soil, rivers, wastewater, and sediments, these residues and genes contribute to the environmental resistome and create opportunities for horizontal gene transfer among diverse microbial communities. Environmental antimicrobial concentrations may be below therapeutic levels but still sufficient to select resistant bacteria and maintain resistance genes in microbial populations (Abdallah; Alhudhaibi; Dahab; Al Noman *et al.*, 2026).

Heavy metals, pesticides, microplastics, and other pollutants may also co-select for antimicrobial resistance by favoring bacteria carrying linked resistance determinants. Wastewater treatment systems are therefore important intervention points because they receive resistant organisms from hospitals, communities, farms, and industries (Zhao; Xie; Xie, 2026). The environmental dimension of AMR is especially important in regions with inadequate sanitation, insufficient wastewater treatment, weak pharmaceutical waste regulation, and intensive animal production (Pulingam; Parumasivam; Gazzali; Sulaiman *et al.*, 2022).

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Environmental reservoirs make resistance difficult to reverse because resistant genes can persist and circulate even after clinical prescribing practices improve. This reality reinforces the need for integrated environmental surveillance, regulation of industrial discharge, improved sanitation, and monitoring of antibiotic residues in water and soil. Antimicrobial stewardship must therefore extend beyond hospitals and clinics to include environmental stewardship and ecological control of resistance dissemination (Abdallah; Alhudhaibi; Dahab; Al Noman *et al.*, 2026).

2.7 HOSPITAL AMPLIFICATION, INTENSIVE CARE, AND THE COVID-19 PANDEMIC

Hospitals are major amplification sites for antimicrobial resistance because they concentrate on vulnerable patients, invasive procedures, broad-spectrum antibiotics, and opportunities for pathogen transmission. Intensive care units are especially vulnerable because patients often require mechanical ventilation, central venous catheters, urinary catheters, surgical drains, and prolonged antimicrobial therapy (Marino; Maniaci; Lentini; Ronsivalle *et al.*, 2025; Wang; Hsieh; Powers; Kao, 2020).

These conditions increase the risk of ventilator-associated pneumonia, catheter-associated bloodstream infection, urinary tract infection, surgical site infection, and sepsis caused by resistant organisms. The hospital environment also promotes transmission through contaminated surfaces, healthcare worker hands, inadequate isolation, and patient transfers between units or institutions (Sauerborn; White; Kalteis; Gygax *et al.*, 2026).

The COVID-19 pandemic intensified these risks by increasing hospitalizations, mechanical ventilation, antimicrobial exposure, staffing pressure, and disruption of routine infection control practices. During the early pandemic period, approximately 75% of hospitalized COVID-19 patients received antibiotics despite the viral etiology of SARS-CoV-2 infection. This pattern reflects the difficulty clinicians faced in distinguishing viral pneumonia from bacterial co-infection during a rapidly evolving crisis (Kalasikam; Jimenez-Truque; Kloek; Banerjee, 2025).

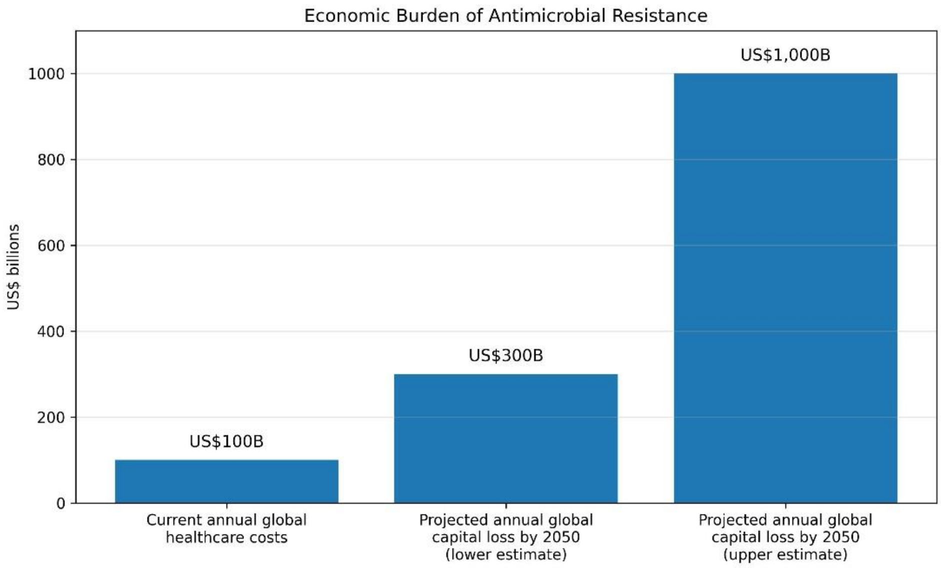
However, widespread empirical antibiotic use during the pandemic likely increased selective pressure and contributed to the spread of resistant hospital-acquired pathogens. The pandemic therefore demonstrated how quickly antimicrobial stewardship can be weakened when healthcare systems are overwhelmed. Future pandemic preparedness must include antibiotic stewardship, rapid diagnostics, infection prevention, and surveillance as essential components rather than secondary activities (Popescu; Petca; Mareș; Petca *et al.*, 2026).

2.8 ECONOMIC IMPACT

The economic burden of antimicrobial resistance is enormous because resistant infections increase direct medical costs, prolong hospitalization, require expensive second-line drugs, and reduce productivity through disability and premature death. Figure 2 illustrates the magnitude of this burden by comparing current annual global healthcare costs with projected future capital losses associated with antimicrobial resistance (Marino; Maniaci; Lentini; Ronsivalle *et al.*, 2025; Pulingam; Parumasivam; Gazzali; Sulaiman *et al.*, 2022). The figure shows current annual global healthcare costs exceeding 100 billion US dollars, emphasizing that AMR already imposes a large economic burden before the most severe future projections occur.

Figure 2

Economic burden of antimicrobial resistance, showing current annual global healthcare costs and projected annual global capital loss estimates by 2050



Sources: Marino et al. (2025) and Pulingam et al. (2022).

The same figure presents projected annual global capital losses by 2050 ranging from approximately 300 billion to 1 trillion US dollars, indicating that AMR may become not only a medical crisis but also a macroeconomic threat. These numbers are important because they show that resistance affects national economies, workforce productivity, social inequality, and development goals, not only hospital budgets. Low- and middle-income countries are expected to suffer disproportionately because they often face higher infectious disease burdens, weaker surveillance, reduced access to newer antibiotics, and greater dependence on labor-based economic productivity (Pulingam; Parumasivam; Gazzali; Sulaiman *et al.*, 2022).

The cost of resistant infection includes additional nursing care, longer hospital stays, diagnostic procedures, isolation measures, last-resort antimicrobial therapy, and intensive care support. Beyond direct healthcare costs, AMR reduces productivity by increasing absenteeism, disability, premature mortality, and long-term health complications. Economic analyses therefore strengthen the public health argument for prevention because reducing inappropriate antibiotic use is far less costly than treating widespread resistant infections (O'Neill; Wei; Machado; Galarraga *et al.*, 2025).

2.9 CONSEQUENCES FOR HUMAN HEALTH AND MODERN MEDICINE

The health consequences of antimicrobial resistance extend far beyond treatment failure in individual infections. Resistant infections are associated with delayed effective therapy, increased mortality, longer illness duration, more complications, and higher risk of disability. Patients with resistant infections often require broader-spectrum or more toxic drugs, including agents that may cause renal, hepatic, hematologic, or neurologic adverse effects. (Hughes; Sathiananthamoorthy; Sergaki, 2026)

Infections caused by carbapenem-resistant Gram-negative bacteria are particularly concerning because treatment options may be limited to last-resort agents such as colistin or tigecycline. Resistance in *Neisseria gonorrhoeae* illustrates how a common community infection can gradually lose susceptibility to successive first-line therapies (Barbee, 2014).

Gonorrhea has developed resistance to sulfonamides, penicillins, tetracyclines, fluoroquinolones, and has shown reduced susceptibility or treatment failures with extended-spectrum cephalosporins. This example supports the broader argument that resistant pathogens can transform previously manageable infections into difficult or potentially untreatable diseases. Modern medicine is structurally dependent on effective antibiotics because procedures such as chemotherapy, transplantation, orthopedic implants, vascular surgery, cesarean delivery, and neonatal intensive care require infection prevention and treatment capacity (Tang; Millar; Moore, 2023).

If antibiotic effectiveness continues to decline, the risk-benefit profile of many advanced medical interventions will worsen. The post-antibiotic era should therefore not be understood as a future without antibiotics but as a future in which antibiotics may no longer reliably protect routine and advanced medical care (Chandra; Mk; Ke; Mukhopadhyay *et al.*, 2021)

2.10 ALTERNATIVES TO ANTIBIOTICS: VACCINES, PHAGES, PEPTIDES, AND NATURAL PRODUCTS

Because resistance is increasing while antibiotic discovery is slow, alternative and complementary strategies are urgently needed. Vaccines are among the most promising long-term strategies because they prevent infections and thereby reduce the need for antibiotic exposure (Gupta; Sharma, 2022). By reducing disease incidence, vaccination also reduces transmission, antibiotic prescribing, and selective pressure on bacterial populations.

Bacteriophage therapy has regained attention because phages can specifically infect and lyse bacterial cells, including multidrug-resistant organisms. A systematic review of phage therapy reported clinical improvement or bacterial load reduction in many treated patients, although evidence remains limited by small studies, case reports, personalization requirements, and regulatory challenges (Aranaga; Pantoja; Martínez; Falco, 2022).

Phage therapy is attractive because it may spare normal microbiota more than broad-spectrum antibiotics, but its specificity also requires careful matching between phage and bacterial strain. Antimicrobial peptides are another promising group because they can disrupt bacterial membranes, interfere with intracellular targets, and modulate immune responses (Rios; Moutinho; Pinto; Del Fiol *et al.*, 2016).

Natural products remain important because many historical antibiotics originated from microbial or natural sources, and plant-derived compounds continue to show activity against priority pathogens. A systematic review of natural products against WHO priority pathogens identified alkaloids, flavonoids, phenols, saponins, tannins, and terpenoids as bioactive classes with antimicrobial potential (SeyedAlinaghi; Mehraeen; Mirzapour; Yarmohammadi *et al.*, 2025). These alternatives are promising, but most still face limitations related to standardization, toxicity, delivery, scalability, clinical trial evidence, regulation, and cost.

2.11 NANOPARTICLES, COMBINATION THERAPIES AND ARTIFICIAL INTELLIGENCE

Nanotechnology has been explored as an unconventional strategy against resistant bacteria because nanoparticles can interact with microbial membranes, enhance drug delivery, and sometimes exert intrinsic antimicrobial effects. Silver nanoparticles have demonstrated activity against Gram-positive and Gram-negative bacteria, including multidrug-resistant strains, and may act through multiple simultaneous mechanisms (Bruna; Maldonado-Bravo; Jara; Caro, 2021).

However, nanoparticle-based strategies require careful evaluation of cytotoxicity, environmental effects, dosing, accumulation, and translational feasibility before broad clinical use. Combination therapy is another important strategy because adjuvants can increase membrane permeability, inhibit efflux pumps, block resistance enzymes, or restore susceptibility to existing antibiotics (Wang; Hsieh; Powers; Kao, 2020). Examples include compounds that permeabilize Gram-negative outer membranes or inhibit efflux systems, thereby allowing older antibiotics to regain activity against resistant organisms (Wang et al., 2020).

Precision medicine may improve antimicrobial stewardship by enabling faster distinction between bacterial and viral infection and by tailoring therapy to the pathogen, resistance profile, host response, and disease severity. Rapid molecular diagnostics and host gene expression assays can reduce unnecessary antibiotic exposure by identifying patients unlikely to have bacterial infection (Watkins, 2022).

Artificial intelligence and machine learning may accelerate antibiotic discovery by predicting antimicrobial activity, identifying resistance genes, mining genomic data, and optimizing molecular design. These technologies can shorten parts of the discovery process, but they do not eliminate the need for pharmacological validation, toxicity testing, clinical trials, manufacturing, and regulatory approval (Wong; de la Fuente-Nunez; Collins, 2023).

Therefore, innovation should be viewed as complementary to stewardship rather than as a justification for continued misuse of existing.

2.12 STEWARDSHIP AND THE NEED TO PRESERVE EXISTING ANTIBIOTICS

Antimicrobial stewardship is the most immediate and practical strategy for preserving antibiotic effectiveness while new alternatives are developed. Stewardship programs seek to ensure that antibiotics are used only when indicated, with the correct agent, dose, route, duration, and reassessment plan. Core stewardship activities include guideline development, prescription auditing, feedback to prescribers, formulary restriction, de-escalation, diagnostic optimization, and surveillance of antibiotic consumption (Palanisamy, 2023).

The AWaRe classification is one tool designed to promote rational use by categorizing antibiotics into Access, Watch, and Reserve groups. The goal of AWaRe-based policy is to increase appropriate use of Access antibiotics while reducing unnecessary use of Watch and Reserve antibiotics. Stewardship must also include infection prevention because every prevented infection is an antibiotic course avoided (Gupta; Sharma, 2022). Hand hygiene, vaccination, sanitation, device management, surgical prophylaxis optimization, environmental cleaning, and isolation measures are therefore part of the resistance prevention strategy.

In animals, stewardship means reducing routine mass medication, eliminating medically important antibiotics for growth promotion, improving husbandry, and preventing disease through vaccination and biosecurity. In the environment, stewardship means reducing antibiotic pollution, improving wastewater treatment, regulating pharmaceutical discharge, and monitoring resistant organisms and resistance genes (Alabi; Chenia; Lin, 2025).

The central ethical principle is that antibiotics are shared societal resources, and each unnecessary use reduces the probability that these drugs will remain effective for future patients.

3 CONCLUSION

The antibiotic era began with extraordinary therapeutic promise and changed the course of human health by reducing mortality from bacterial infections. Over approximately eight decades, however, inappropriate antibiotic use in human medicine, veterinary practice, agriculture, and the environment progressively selected resistant organisms and resistance genes. The data summarized in Figure 1 show that multidrug-resistant infections are increasing globally, with especially strong growth in healthcare-associated infections and important expansion in the community.

The data summarized in Figure 2 show that antimicrobial resistance is also an economic threat, with current and projected costs capable of affecting healthcare sustainability and global productivity. The rise of resistant pathogens, the decline of antibiotic discovery, and the persistence of inappropriate use together create the realistic possibility of a post-antibiotic era in which common infections and routine medical procedures become more dangerous. Promising alternatives such as vaccines, phage therapy, antimicrobial peptides, natural products, nanoparticles, combination therapy, precision diagnostics, and artificial intelligence are important but not yet sufficient to replace conventional antibiotics.

Therefore, the most urgent action is to preserve existing antibiotics through rational prescribing, antimicrobial stewardship, infection prevention, surveillance, public education, environmental control, and One Health policies. The future of infectious disease treatment depends not only on discovering new drugs but also on learning to use current antibiotics with the discipline, restraint, and responsibility that their societal value demands.

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