Research, Society and Development, v. 14, n. 2, e7014248271, 2025
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v14i2.48271

# The importance of rational use of antibiotics in reducing environmental and public health impacts: A critical review

## A importância da utilização racional de antibióticos na redução dos impactos ambientais e na saúde pública: Uma revisão crítica

## La importancia del uso racional de los antibióticos en la reducción del impacto ambiental y en la salud pública: Una revisión crítica

Received: 02/11/2025 | Revised: 02/16/2025 | Accepted: 02/16/2025 | Published: 02/20/2025

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**Abstract**
The consumption of antibiotics in human and animal health has increased significantly over the years, leading to irrational use and the spread of antibiotic resistance in bacteria. This study aims to investigate the impact of antibiotic resistance on the environment and public health through a narrative review of articles and reports published between 2014 and 2024. Searches were conducted using different databases and the search terms were "drug contamination," "water contamination," "medical waste," "drug resistance," "antibiotics," "rational use of medicines," and "environment," and different databases were used. The results show that animal excretions and inappropriate disposal of antibiotics have facilitated the spread of resistance genes through contamination of rivers and water sources, and consumption of contaminated meat and food. This has affected public health through the ineffectiveness of antibiotics and increased mortality from infections with antibiotic-resistant bacteria. Rational use of antibiotics combined with health education is essential to prevent irrational use and inappropriate disposal of antibiotics. These approaches can help reduce the impact on public health and the environment.
**Keywords:** Rational antibiotic use; Resistance of antibiotics; Bacterial resistance genes; Public Health; Environment.

**Resumo**
O consumo de antibióticos na saúde humana e animal aumentou significativamente ao longo dos anos, levando ao uso irracional e à disseminação da resistência a antibióticos em bactérias. Este estudo tem como objetivo investigar o impacto da resistência a antibióticos no meio ambiente e na saúde pública por meio de uma revisão narrativa de artigos e relatórios publicados entre 2014 e 2024. As buscas foram realizadas usando diferentes bancos de dados e os termos de pesquisa foram “contaminação por medicamentos”, “contaminação da água”, “resíduos médicos”, “resistência a medicamentos”, “antibióticos”, “uso racional de medicamentos” e “meio ambiente”, e foram usados diferentes bancos de dados. Os resultados mostram que as excreções animais e o descarte inadequado de antibióticos facilitaram a disseminação de genes de resistência por meio da contaminação de rios e fontes de água e do consumo de carne e alimentos contaminados. Isso afetou a saúde pública por meio da ineficácia dos antibióticos e do aumento da mortalidade por infecções com bactérias resistentes a antibióticos. O uso racional de antibióticos, combinado com a educação em saúde, é essencial para evitar o uso irracional e o descarte inadequado de antibióticos. Essas abordagens podem ajudar a reduzir o impacto sobre a saúde pública e o meio ambiente.
**Palavras-chave:** Uso racional de antibióticos; Resistência de antibióticos; Genes de resistência bacteriana; Saúde Pública; Meio Ambiente.

**Resumen**
El consumo de antibióticos en la salud humana y animal ha aumentado significativamente a lo largo de los años, lo que ha llevado a un uso irracional y a la propagación de la resistencia a los antibióticos en las bacterias. Este estudio pretende investigar el impacto de la resistencia a los antibióticos en el medio ambiente y la salud pública mediante una revisión narrativa de artículos e informes publicados entre 2014 y 2024. Las búsquedas se realizaron utilizando diferentes bases de datos y los términos de búsqueda fueron «contaminación de medicamentos», «contaminación del agua», «desechos médicos», «resistencia a los medicamentos», «antibióticos», «uso racional de medicamentos» y

«medio ambiente», y se utilizaron diferentes bases de datos. Los resultados muestran que las excreciones animales y la eliminación inadecuada de antibióticos han facilitado la propagación de genes de resistencia a través de la contaminación de ríos y fuentes de agua, y el consumo de carne y alimentos contaminados. Esto ha afectado a la salud pública por la ineficacia de los antibióticos y el aumento de la mortalidad por infecciones con bacterias resistentes a los antibióticos. El uso racional de los antibióticos combinado con la educación sanitaria es esencial para prevenir su uso irracional y su eliminación inadecuada. Estos planteamientos pueden ayudar a reducir el impacto sobre la salud pública y el medio ambiente.

**Palabras clave:** Uso racional de antibióticos; Resistencia de los antibióticos; Genes de resistencia bacteriana; Salud Pública; Medio Ambiente.

## 1. Introduction

Antibiotics are important drugs used to treat bacterial infections. Their discovery began in the early 20th century with Alexander Fleming, who discovered that the fungus Penicillium produced penicillin, a substance that inhibits bacterial growth (Fleming, 1929). This was the beginning of the discovery of antibiotics, which led to the golden age of antibiotics from 1940 to 1960, marked by the discovery of several antibiotics such as polymyxin, vancomycin, ampicillin, gentamicin, meropenem and others. In the years that followed, however, the number of innovative antibacterials declined significantly. The World Health Organization (WHO) reported that after the 2000s, new antibiotics were derivatives of existing antibiotics with structural modifications, without new mechanisms of action (World Health Organization, 2022a).

The process of discovering and bringing new medicines to market is extensive and long, requiring clinical trials to prove safety, efficacy and effectiveness (Food and Drugs Administration, 2018). Clinical trials are lengthy, and it can take more than 10 years to get a drug approved if the results are satisfactory, which explains the scarcity of new antibiotics. In addition, large pharmaceutical companies invest in the research and development of antineoplastic drugs and drugs for rare diseases, while few invest in antibiotics due to the high cost, lack of financial return and research challenges (Deloitte, 2023).

The scarcity of new antibiotics and the lack of investment in their development limit the therapeutic options for the treatment of bacterial infections, making the rational use of antibiotics an essential measure. However, the consumption of antibiotics in humans and animals has increased, accompanied by irrational use, such as prescriptions with incorrect doses, self-medication and inappropriate use (Mboya et al., 2018). As a direct result, antimicrobial resistance has increased and is a global threat to human and animal health, increasing hospital stays, health care costs, and reducing the effectiveness of antibiotics due to the development of resistance mechanisms that inhibit their action (Murray et al., 2022).

Antibiotic resistance affects the environment through contamination of soil and water with antibiotic resistance genes (ARG). These genes are excreted in animal manure on farms and then applied as fertilizer in agriculture and through wastewater reuse (Zhu et al., 2021). Improper disposal of antibiotics in waste and wastewater exacerbates environmental contamination by increasing selective pressure on bacteria and accelerating the development of antibiotic resistance (Hanna et al., 2023).

Rational use of antibiotics is a practice necessary to reduce the unnecessary use of antibiotics to prevent antimicrobial resistance and to preserve the efficacy of antibiotics. (Littmann et al., 2018). Together with health education to raise awareness among patients and healthcare professionals about the use and disposal of antibiotics, the impact of antimicrobial resistance on the environment and public health can be reduced.

This study aims to investigate the impact of antibiotic resistance on the environment and public health through a narrative review of articles and reports published between 2014 and 2024.

## 2. Methodology

The search and discussion method are of a qualitative nature (Pereira et al., 2018) and used a critical narrative review (Casarin et al., 2020; Mattos, 2015; Rother, 2007) that included articles and reports that addressed the public health and environmental implications of bacterial resistance to antibiotics and the rational use of antibiotics.

Three databases were used to search for articles using controlled terms from the Medical Subject Headings (MeSH) and keywords related to the topic of interest: PubMed (https://pubmed.ncbi.nlm.nih.gov), Latin American and Caribbean Literature in Health Sciences (LILACS) (https://lilacs.bvsalud.org) and Web of Science (https://clarivate.com/academia-government/scientific-and-academic-research/research-discovery-and-referencing/web-of-science/).

Search terms used were "Drug contamination AND water pollution AND Medical waste AND Drug resistance, microbial AND antibiotics AND Rational Use of Medicines AND environmental". Searches were conducted using the final limit date of December 3rd, 2024. Results were exported to reference management software (Mendeley Reference Manager v.2.92.0).

The following criteria were used to select the manuscripts: published between 2014 and 2024, available in any language. After selection, the titles and abstracts were reviewed, and duplicate articles, those not related to the topic and those of low relevance were excluded. A complete reading of the 24 selected scientific articles was then carried out. Systematic reviews and reports from international organizations were included to complement and contextualize certain topics

## 3. Results and Discussion

### 3.1 Antimicrobial resistance

Antimicrobial resistance (AMR) is defined as the ability of microorganisms to stop responding to antimicrobial drugs (antibiotics, antivirals, antifungals and antiparasitic drugs). Antimicrobial resistance is a natural phenomenon that occurs when microorganisms are exposed to antimicrobial drugs. Under the selective pressure of antibiotics, susceptible bacteria are killed or inhibited, while bacteria that are naturally (or intrinsically) resistant or that have acquired antibiotic-resistant traits have a greater chance to survive and multiply. The overuse of antibiotics and inappropriate use (inappropriate selection, inadequate dosing, poor adherence to treatment guidelines) contributes to the increase of antibiotic resistance (Prestinaci et al., 2015).

Antimicrobial resistance is a natural process that occurred long before antibiotics entered clinical practice (Perry et al., 2016). Phylogenetic analysis shows that the OXA β-lactamase genes have been on plasmids for millions of years. The OXA genes encode a class of β-lactamases, enzymes that break down the β-lactam antibiotics, that confer resistance (Barlow & Hall, 2002). Antimicrobial resistance is considered a natural anthropogenic phenomenon, a mechanism used by microorganisms to gain a competitive advantage that occurs naturally over time through genetic mutation. However, resistance rates and incidence are accelerated by factors such as overuse and misuse of drugs (Sweileh, 2021).

In a process called horizontal gene transfer, pathogens can acquire antibiotic resistance genes (HGT) (McInnes et al., 2020). HGT is the event of a DNA sequence being transferred between species not by inheritance. HGT is the transfer of a DNA sequence between species other than by inheritance. HGT is a critical factor in prokaryotic evolution and is a major source of genomic novelty leading to antibiotic resistance or the emergence of virulent strains (Sevillya et al., 2020).

Conjugation, transduction, and transformation are three mechanisms of horizontal gene transfer. The mechanism of gene transfer is responsible for the most concerning aspects of antimicrobial resistance. Conjugation involves the formation of a sex pilus (small tube) between two bacterial cells through which a plasmid is transferred from one to the other. Transformation involves the uptake of extracellular DNA from lysed bacteria by the recipient bacteria. The DNA is integrated into the genome and promotes new traits in the bacteria. Transduction is the process by which any bacterial gene can be transferred to another bacterium via a bacteriophage. Transduction occurs via a head-first packaging mechanism, followed by infection of the recipient bacterial host and recombination onto the chromosome. The result is the transfer of bacterial genetic information from one strain to another (Holmes et al., 2016).

### 3.1.1 Mechanisms of action of antibiotic drugs

To understand the mechanism of antibiotic resistance, it is important to first understand the mechanism of action of antibiotics on bacteria, which consists of 5 mechanisms of action that will depend on the class and type of antibiotic.

Cell wall inhibitors inhibit the synthesis of peptidoglycan, the major component of the bacterial cell wall, causing damage to the integrity of the wall and leading to cell lysis. Beta-lactam antibiotics are bactericidal agents that disrupt bacterial cell wall formation by covalently binding to essential Penicillin-Binding Proteins (PBPs), enzymes involved in the terminal steps of peptidoglycan cross-linking (Rang et al., 2020).

Protein synthesis inhibitors act by binding to the bacterial 30s ribosome, preventing the tRNA from accessing the acceptor site in the mRNA-ribosome complex and inhibiting the initiation of protein synthesis. Some antibiotics act on the 50s portion of the ribosome, preventing translocation along the mRNA and blocking protein synthesis. They can also inhibit the formation of peptide bonds and make it impossible to elongate protein chains (Goodman & Gilman, 2019).

DNA gyrase and topoisomerase IV are type II topoisomerases found in bacteria that are responsible for maintaining the DNA structure for DNA synthesis. Quinolones are the major class of antibiotics that inhibit nucleic acid synthesis by inhibiting DNA gyrase and topoisomerase IV, which blocks DNA replication and crosslinks DNA strands, preventing cell mitosis (Golan et al., 2021).

Inhibitors of cell membrane function interfere with the structure of the cell membrane, causing leakage of cell contents and disrupting cellular homeostasis, leading to cell death. Antibiotics such as daptomycin bind with calcium ions to form a complex that aggregates within the plasma membrane to form pore-like structures that allow ions to leak out of the cell, causing depolarization of the cell membrane via escape of intracellular cations, ultimately leading to cell death (Goodman & Gilman, 2019).

Antibiotics that inhibit bacterial metabolic pathways interfere with the essential metabolic processes of bacteria. These pathways are critical for bacterial survival, hindering or preventing their growth and multiplication. Sulphonamides are a class of antibiotics that act as competitive inhibitors of dihydropteroate synthetase, the enzyme responsible for the incorporation of p-aminobenzoic acid (PABA) into dihydropteroic acid, the immediate precursor of folic acid, which is essential for DNA and RNA synthesis. Another antibiotic with this mechanism of action is trimethoprim. It acts as a selective inhibitor of the enzyme dihydrofolate reductase, blocking the conversion of dihydrofolate to tetrahydrofolate, the active form of folic acid that is essential for the synthesis of nucleotides required for bacterial DNA replication (Goodman & Gilman, 2019).

### 3.1.2 Mechanism of antibiotic resistance

One study performed a targeted metagenomic analysis of ancient DNA from 30,000-year-old Beringia permafrost sediments and identified a large number of genes encoding resistance to β-lactam antibiotics, tetracyclines and glycopeptides. This shows that resistance is not a recent phenomenon, but a natural phenomenon in which these genes have been used as defenses (Dcosta et al., 2011). Although a natural phenomenon, the indiscriminate and excessive use of antibiotics in human and animal health has greatly accelerated this process. HGT and the selective pressure caused by the survival of more resistant bacteria when exposed to antibiotics are also factors that have contributed to the spread of antibiotic resistance (Larsson & Flach, 2021).

#### 3.1.2.1 Limiting drug uptake

Gram-negative bacteria are intrinsically less permeable to certain antibiotics than Gram-positive bacteria because their outer membrane contains a permeability barrier due to the presence of a lipopolysaccharide (LPS) layer that confers intrinsic resistance (Uddin et al., 2021).

To cross the outer membrane of the gram-negative cell envelope complex, antibiotics permeate through porins, outer membrane proteins that are associated with the modulation of cell permeability, allow the passive transport of hydrophilic compounds such as β-lactam antibiotics and are involved in membrane permeability (Choi & Lee, 2019). Mutations in porins can affect the selectivity of the channel by reducing its size and altering its electrostatic properties, as well as affect porin expression, leading to high levels of resistance (Bartsch et al., 2021).

Biofilm formation is also a mechanism to limit drug absorption. Biofilm is formed by a group of microorganisms surrounded by proteins, polysaccharides, sugars, and other molecules adhering to the surface. This arrangement forms a viscous film, called a viscous polymer matrix, which provides a protective environment by facilitating the survival and proliferation of bacteria and reducing the penetration of antibiotics (Liu et al., 2024). A study evaluated the ability of all the collected isolates to form biofilm in vitro and found that 49.3% were able to do so, with 30.3% of the Escherichia coli isolates, 37.6% of Klebsiella pneumoniae, and 76.5% of Pseudomonas aeruginosa isolates, respectively. The acquisition of specific antimicrobial resistance can compromise or enhance biofilm formation in several species of Gram-negative bacteria (Cepas et al., 2019).

#### 3.1.2.2 Modification of drug targets

Target modification involves protecting the site of action or modifying the structure of the target, thereby reducing the affinity of the antibiotic for it and reducing its effectiveness. Target protection occurs when bacteria express specific proteins that protect the site of action of the antibiotic, preventing the antibiotic from interacting with the site of action and acting as a physical barrier to block the action of the antibiotic (Munita & Arias, 2016).

#### 3.1.2.3 Enzymatic inactivating/ modification

Enzymatic inactivation of antibiotics consists of the bacteria's coding genes expressing enzymes that inactivate the drug by adding a chemical group by catalyzing chemical reactions such as acetylation, phosphorylation, and adenylation. This results in a decreased affinity of the drug for its target. Aminoglycoside modifying enzymes (AMEs) are an example, as they covalently modify the hydroxyl or amino groups of the aminoglycoside molecule (Munita & Arias, 2016).

Enzymes such as β-lactamases are responsible for breaking the amide bond of the β-lactam ring, thereby deactivating the antibacterial properties of antibiotics and conferring resistance to bacteria. Through gene transfer between bacteria, several enzymes have undergone significant mutations and acquired a greater capacity to inactivate antibiotics from different classes, such as extended-spectrum β-lactamases (ESBLs). Carbapenemases are classified into different groups, with notable examples including Klebsiella pneumoniae carbapenemase (KPC), New Delhi metallo-β-lactamase-1 (NDM-1) and OXA-48 (Lawrence et al., 2024).

#### 3.1.2.4 Active drug efflux

Efflux pumps are transmembrane proteins found in the bacterial membrane. Their main function is to actively transport toxic molecules such as metals, detergents, and bile acids from the inside to the outside of the cell. In addition to these molecules, the pumps remove antibiotics from the intracellular to the extracellular environment. This mechanism confers resistance to bacteria, mainly through the overexpression of efflux pumps (Y. Wang et al., 2016).

### 3.2 Impacts of antibiotic resistance

The increase in the consumption of antibiotics by humans and animals is directly related to the crisis of the spread of bacterial resistance. A study evaluating the consumption of antimicrobials in 228 countries reported that in 2017, about 75 percent of antimicrobials sold were used in animal production (Tiseo et al., 2020). And more than 80 percent of the total use of antibiotics in animals was not for therapeutic purposes, but for prophylaxis or as growth promoters (World Animal Protection, 2020).

Human consumption of antibiotics reached 49.3 billion defined daily doses (DDD) in 2023, representing a 20.9 percent increase in total use and a 13.1 percent increase in the rate of consumption compared to 2016. The overuse of antibiotics in human and animal health is an alarming concern, especially in light of studies projecting a 53 percent increase in consumption by 2030 (Klein et al., 2024).

#### 3.2.1 Environmental Dissemination of Antibiotic Resistance

The overuse of antibiotics in animals triggers a chain of dissemination of bacteria and antimicrobial resistance genes because the excreta of cattle and pigs can contain antibiotics, as some of these drugs are not fully metabolized and are excreted in their active form or as active metabolites in feces and urine (Gu et al., 2019).

A team of researchers analyzed and quantified the presence of antibiotics in the feces of poultry and cattle. Twelve antibiotics, including tetracyclines, quinolones, sulfonamides, and macrolides, were the most abundant residues in cattle and poultry manure and were detected in feed, animal waste, and drinking water (Li et al., 2023). The use of fertilizer and wastewater can contaminate soil and water sources near farms, where high levels of antibiotics have already been detected in surface and groundwater (Gu et al., 2019). The excessive use of antibiotics in animals triggers a chain of dissemination of bacteria and antimicrobial resistance genes (ARGs) and selective pressure of resistant strains, especially with the contamination of water resources (Gu et al., 2019).

In addition, the direct application of manure and irrigation with wastewater to the soil resulted in a greater accumulation of tetracyclines, sulphonamides and fluoroquinolones in the soils when compared to fertilization with compost. Growing crops in contaminated soils can lead to the absorption of antibiotics by plants. Studies have identified antibiotic residues accumulated in asparagus (5.83 μg-kg-$^{1}$) and vineyards (3.49 μg-kg-$^{1}$), highlighting the potential for these compounds to be transferred into the food chain (Fang et al., 2023).

Animal meat is also a significant source of ARGs. One analysis evaluated the presence of ARG-containing phages in ground pork, beef, chicken, ham, and mortadella. Bacteriophages can carry ARGs from the host through the process of transduction. The DNA fraction of the phages was analyzed by quantitative polymerase chain reaction (qPCR) to quantify the genes present in these meats. ARGs were detected in most of the samples after propagation of the particles, indicating that at least some of the isolated phage particles were infectious. Eating contaminated meat allows bacteriophages to carry ARGs and transfer these genes to other bacteria, spreading antibiotic resistance through the food chain (Gómez-Gómez et al., 2019).

In addition to animal feces being responsible for the spread of ARGs and antibiotics, one study evaluated the presence of crAssphage, a bacteriophage abundant in the human gut and used as a marker of fecal contamination, in sewage-contaminated environments. In addition, the researchers analyzed public wastewater metagenomes containing exceptionally high levels of antibiotics for ARG detection. A total abundance of ARGs and crAssphage was found in the environment, and the presence of crAssphage was correlated with human fecal contamination and the spread of ARG (Karkman et al., 2019).

### 3.2.2 Incorrect antibiotic disposal and river contamination as a source of resistance spread

Water contamination with antibiotics from animal excretions, sewage, tributaries and effluents from wastewater treatment plants, river water, lake water, drinking water, ground water, sea water, and other water compartments are contaminated with antibiotics on a daily basis due to improper disposal of these drugs by hospitals, the general population, the pharmaceutical industry, and untreated wastewater discharges. Studies show that hospital wastewater has higher levels of antibiotic resistance determinants, approximately 81% higher than community wastewater. Gram-negative patients had higher prevalence of Enterobacteriaceae producing carbapenemase and ESBL pathogens (Hassoun-Kheir et al., 2020). Antibiotics from several classes, such as fluoroquinolones, macrolides, tetracyclines, β-lactams, lincosamides, sulfonamides, amphenicols, glycopeptides, and aminoglycosides, have been reported in wastewater (e.g, from municipal, hospital, and pharmaceutical manufacturing sources), wastewater treatment plant influent and effluent, and aquatic environments in the Eastern Pacific and Southwest Asia regions (Hanna et al., 2023).

Water contamination by antibiotics and other pharmaceuticals is a global problem. One study analyzed the presence of antibiotics and other active pharmaceutical ingredients (APIs) in 258 rivers in 104 countries, including all continents. The contaminants with the highest concentrations were acetaminophen, caffeine, metformin, fexofenadine, sulfamethoxazole (antimicrobial), metronidazole (antimicrobial), and gabapentin. However, 13 antimicrobials were detected and 9 performed safe concentrations. Ciprofloxacin was exceeded at 64 sites and the highest exceedance was in Barisal, Bangladesh, where higher concentrations of metronidazole were observed, exceeding 300 times the safe target. Seven different types of antibiotics were detected in the Danube, Europe's second longest river. These data represent a risk of contamination for aquatic ecology and the spread of antimicrobial resistance (Wilkinson et al., 2022). The presence of antibiotics at these sites exerts a selective pressure on the present bacteria, favoring the survival of resistant bacteria and thus creating environmental reservoirs of antibiotic-resistant bacteria and ARG (Hanna et al., 2023).

The practice of improperly disposing of pharmaceuticals is very common due to a lack of knowledge about the impact they can have and how to dispose of them properly. In one study, participants were asked how they disposed of their medications and 82.1% reported throwing unused medications in the trash. 79.5% reported not knowing how to properly dispose of medications, and 53.1% of participants did not know that improper disposal of medications can affect the environment and public health (Insani et al., 2020).

The presence of antibiotics in water sources exerts selective pressure on bacteria and facilitates the transfer of resistance genes. Studies show that water treatment plants do not have the capacity to effectively remove these genes through filtration and chlorination systems. As a result, research has detected resistance genes even in treated water (Bergeron et al., 2015).

### 3.2.3 Hospitals as a source of resistance dissemination

Hospitals are important sources for the spread of infections and ARGs between immunocompromised patients and healthcare workers. It is estimated that about 7 out of 100 patients acquire an infection in hospitals (World Health Organization, 2022b). Antibiotic-resistant microorganisms, including those with new and emerging resistance, can spread within and between healthcare facilities. These pathogens can cause infections in patients, known as healthcare-associated infections (HAIs) (Center for Disease Control and Prevention, 2019).

The spread of infections can occur in a variety of ways, and hospital surfaces and medical equipment are recurring sources of contamination and the spread of resistant pathogens. Several studies have identified bacteria and ARGs in these environments, particularly the genera Bacillus, Staphylococcus, Pseudomonas and Acinetobacter. In addition, ARGs critical for antibiotic resistance, such as those responsible for resistance to beta-lactams, fosfomycin and cephalosporin, have been found in significant quantities (Hanafiah et al., 2024).

HAI affects millions of patients in hospitals and is common in critical environments such as Intensive Care Units (ICUs) and other critical care areas where antibiotic use is more frequent. Hospital-acquired infections are mostly caused by multi-drug-resistant bacteria, such as Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa (World Health Organization, 2022b).

### 3.2.4 One Health's approach to antibiotic resistance

The data presented make it easier to understand the cycle of dissemination of resistant bacteria and ARGS, in which all environments are susceptible to harboring these pathogens and spreading them to other locations. Promoting a cycle of antimicrobial resistance spread among humans, animals and the environment.

The environmental dimensions of AMR are characterized by cyclical interrelationships, complexities, multiple causalities and dynamics (United Nations Environment Programme, 2022). The United Nations Environment Programme (UNEP) states that a systemic approach is needed, such as 'One Health', which recognizes the interconnection of human, animal and environmental health. It is an integrated and unifying approach that mobilizes various sectors and society to work together to promote well-being and combat threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe food and nutritious food, and combating climate change. It is therefore essential to take into account the environmental dimensions of AMR and understand the importance of a collective effort to combat this global threat (United Nations Environment Programme, 2021).

### 3.2.5 Impacts on public health

Antibiotic resistance is a global public health crisis. Since 2017, the WHO has released the Bacterial Priority Pathogens List (BPPL), a report that identifies bacteria that pose the greatest health risk due to their high levels of antibiotic resistance and the severity of the infections they cause. In the 2024 BPPL, 24 bacteria were identified as priority and grouped, with Gram-negative bacterial pathogens maintaining their critical status, where they have the highest level of resistance (World Health Organization, 2024)

The Centers for Disease Control and Prevention (CDC) released a report identifying the seven main pathogens resistant to antimicrobials in the period 2021-2022 in the United States, of which six showed a 20% increase in infections compared to the pre-pandemic period (Center for Disease Control and Prevention, 2022). Gram-negative bacteria have the highest incidence of resistance levels, and this acceleration in the transmission of AMR was caused by the COVID-19 pandemic (Langford et al., 2023).

Antibiotic resistance rates vary between countries and regions, and a systematic analysis assessed the global burden of AMR by examining pathogen-drug combinations. For example, for methicillin-resistant Staphylococcus aureus, resistance was highest in North African and Middle Eastern countries and lowest in several European countries, demonstrating that a country's economic conditions and level of healthcare influence the burden of AMR (Murray et al., 2022).

Resistance creates a number of problems for healthcare systems as antibiotics that were once effective against common infections become ineffective against the pathogen. This reduces the therapeutic options for treating the infection and requires the use of more potent antibiotics, which may also be ineffective in extreme cases (Founou et al., 2017). The lack of treatment options increases mortality. Studies estimate that in 2021, 4.71 million people will die from antimicrobial resistance and 1.14 million deaths will be attributable to antimicrobial resistance, with an increase in deaths in people aged 70 years and older. With the estimated increase in deaths due to AMR, 46.5 million people could die from AMR between 2022 and 2050 (Naghavi et al., 2024).

In addition to the increase in deaths, antibiotic resistance increases hospital costs, whether in private or public hospitals, by requiring more medical resources due to the use of last-line antibiotics, prolonging patients' hospital stays, increasing the use of medical materials and increasing the rate of complications, which leads to the need for tests, surgeries and health devices (Naylor et al., 2018). The additional costs of increasing patients' length of stay include various support services, such as food and laundry, as well as extra costs to cover additional medical and nursing care. This results in an additional cost of between US$10,000 and US$40,000 to treat a patient infected with a multi-resistant bacterium (Cecchini et al., 2015). The economic cost of treating resistance varies between countries, territories and hospitals, depending on the strain that is widespread there and the clinical condition of the patient, but studies show that the costs range from $21,832 per case to more than $3 trillion in lost GDP (Gross Domestic Product) (Naylor et al., 2018).

### 3.3 Rational use of antibiotics

According to the World Health Organization (2025), the rational use of medicines includes the implementation of a set of practices aimed at ensuring the correct use, in the correct dose, at the appropriate treatment time and for the necessary clinic to maintain their efficacy. The rational use of antibiotics is part of this definition and aims to implement antibiotic control programs to maintain efficacy and minimize the development of resistance rates, which requires the prudent, controlled and appropriate use of antibiotics (Walger, 2016).

The main errors in prescribing antibiotics are incorrect dosage, inappropriate choice of drug, duration of treatment and, in primary care, failure to properly explain the appropriate use of the antibiotic to the patient (Martínez-Domínguez et al., 2022; Sijbom et al., 2023). Programs to promote the rational use of antibiotics help to optimize use and ensure patient safety.

Antimicrobial stewardship is a program of measures to promote the rational use of antimicrobial agents in the hospital environment and, conceptually, to achieve cost savings. The program consists of the review and optimization of antimicrobial prescriptions by pharmacists, who intervene in prescriptions with very long treatment time, inappropriate use for the patient's clinic, reducing excessive doses, changing the route of administration when possible, and removing the antibiotics when the patient's clinic is favorable (Rice, 2018). In addition to promoting rational use, antimicrobial stewardship also provides financial benefits to healthcare organizations. Studies have evaluated the economic impact on hospitals and found an average cost reduction of $448.25 per 100 patient days, or 25% (Huebner et al., 2019).

The AWaRe classification is an initiative developed by the WHO as a tool to also minimize resistance and promote rational use by categorizing antibiotics according to their importance, aiming to limit last-line antibiotics to severe cases. Healthcare professionals use it as a guide to select appropriate antibiotics. The system consists of three categories: Access, which includes low-cost antibiotics used for common infections. Watch, which consists of more limited antibiotics used in more severe cases. Reserve, which includes last-line antibiotics and is used when other therapeutic options fail (World Health Organization, 2023)

However, these measures are restricted to the hospital environment, the use of antibiotics in the community is accompanied by misinformation and unsupervised access. A WHO/Europe survey conducted in 14 member countries of the European Union on the use of antibiotics highlighted that 33% of respondents reported consuming antibiotics without a prescription (Singh-Phulgenda et al., 2023). In addition to taking antibiotics without a doctor's prescription, it is common for people to leave pills left over from treatment at home, which contributes to self-medication and promotes irrational use (X. Wang et al., 2018). The irrational use of antibiotics also includes improper disposal, as a large portion of the population is unaware of how to properly dispose of their medicines and the consequences of throwing them in the trash bin and toilet (Insani et al., 2020).

Several countries have unused medicine take-back programs as a strategy to minimize incorrect disposal and its consequences. These programs, although regulated by legislation, vary between countries in terms of the lack of collection points available and adherence to the program, which is affected by the dissemination of these programs, accessibility to these points and education of the population about the environmental and health impacts. Adherence improved in countries that promoted educational campaigns and had easy access to collection points (L. S. Wang et al., 2024).

In Brazil, the disposal of pharmaceutical waste is regulated by Resolution No. 222/2018 of The Brazilian Health Regulatory Agency (ANVISA) and Decree No. 10.388/2020 from Federal Government, which establishes the guidelines for the management and disposal of medicines, providing for the responsibility of manufacturers and distributors in the implementation of programs for the collection of expired or unused medicines. They must be mainly provided by pharmacies, drugstores and health care facilities (Agência Nacional de Vigilância Sanitária 2018, Brasil, 2020). However, there is no national program to establish guidelines and promote health education campaigns involving different communities.

Pharmacists are health professionals who work in drugstores and pharmacies and are responsible for health education to guide and educate patients and society about the rational use of medicines and health-related issues in Brazil (Conselho Federal de Farmácia, 2013). When dispensing medicines, especially antibiotics, pharmacists can promote the rational use of antibiotics through health education by informing patients where to dispose of medicines left over from treatment, which are in disuse or expired, and informing them of the impacts that can be generated by incorrect disposal. A brochure is attached as a proposal for an educational and informational tool to promote the rational use of antibiotics (See supplementary material).

In this way, the rational use of antibiotics, together with the One Health approach, plays a fundamental role in reducing impacts on human, animal and sustainable health, with practices for the proper prescription of antibiotics and correct disposal contributing directly to the Sustainable Development Goals (SDGs), sustainable goals set by the United Nations General Assembly to be achieved by 2030 (United Nations General Assembly, 2015). Initiatives to minimize the spread of resistance and environmental impacts are aligned with SDG 3 (Good health and well-being), SDG 6 (Clean water and sanitation), SDG 9 (Industry, innovation and infrastructure), SDG 12 (Responsible consumption and production), SDG 14 (Life below water), SDG 15 (Life on land) and SDG 17 (Partnerships towards the goals).

## 4. Conclusion

Promoting the rational use of antibiotics in combination with health education is a legitimate practice to raise public awareness of the impact of antimicrobial resistance and to prevent increased selection of resistant strains and infection with antimicrobial resistance, without intending to prevent the impact of antimicrobial resistance on public health and the environment. However, joint action by different sectors is needed to prevent these effects from increasing, as antimicrobial resistance affects human, animal and environmental health

## Acknowledgments

The authors would like to thank Fundação de Apoio à Pesquisa do Distrito Federal (FAP-DF) for financial support (Grant number 00193-00002067/2023-27)

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