



# Impact of Antibiotic Use on the Emergence and Characterization of Antimicrobial Resistance: Implications for Public Health

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## ABSTRACT

Antimicrobial resistance (AMR) has become a significant global health issue, making the treatment of infections more complex and leading to higher rates of illness and death. This research explores the various effects of antibiotic usage on the emergence of resistant bacterial strains, particularly examining the gut microbiome's role in this process. The inappropriate use and over prescription of antibiotics in medical settings contribute to the rise of multidrug-resistant organisms, resulting in healthcare-associated infections that pose serious risks to patient safety.

The financial impact of AMR is analyzed, revealing increased healthcare expenses due to extended hospitalizations and the need for more complicated treatment plans. Furthermore, the study identifies risk factors linked to the development of antibiotic-resistant infections in hospitalized patients, highlighting the importance of targeted interventions and effective antibiotic stewardship programs to improve prescribing practices and minimize unnecessary antibiotic use.

Innovative approaches, such as creating new antibiotics and vaccines, are crucial in addressing the growing threat of AMR. This research stresses the urgent requirement for a coordinated global effort to tackle this crisis, involving healthcare professionals, policymakers, and researchers. By raising awareness and implementing effective strategies, it is possible to lessen the effects of antibiotic resistance and protect public health for future generations.

**Keywords:** Antibiotic resistance, gut Microbiome, antibiotic stewardship, microbial diversity

## INTRODUCTION

Antibiotics are crucial for treating infections, with over 250 million outpatient oral antibiotics prescribed annually in the United States alone[1]. The excessive use of antibiotics is one of the main factors contributing to the development of antibiotic resistance[2]. The Centers for Disease Control and Prevention estimates that between 30% and 50% of outpatient antibiotic prescriptions in the United States are unnecessary[1]. Two decades ago, a Dutch study on a neonatology intensive care unit found that amoxicillin drove the overgrowth of  $\beta$ -lactamase producing bacteria, such as *Klebsiella* species, and that third-generation cephalosporins, such as cefotaxime, selected for resistant *Enterobacter* species strains[3]. The human gut microbiome is essential for health, and disturbances early in life are linked to conditions like allergies, obesity, and immune issues. Antibiotic use, especially in neonates, disrupts microbiome diversity, fostering antimicrobial resistance and causing long-lasting ecological effects, particularly when administered during early gut development[4]. A study of more than 200 infants showed that exposure to antibiotics changes the composition and abundance of gut microbiome and antibiotic resistance genes (ARGs). *Bacteroides* species and ARGs, such as CfxA6, were impacted, with attendance at day care also associated with increased *E. coli* and ARGs[5].

A multicenter trial of 266 sepsis patients showed that procalcitonin (PCT)-guided antimicrobial discontinuation reduced infection-related adverse events (7.2% vs. 15.3%) and 28-day mortality (15.2% vs. 28.2%), while shortening antibiotic duration and lowering hospitalization costs[6]. Antimicrobial resistance is a major global health threat, causing at least 25,000 deaths annually in the European Union. To highlight the urgency, the Disease Control and Prevention (CDC) released a report on antibiotic resistance threats in the United States, urging immediate action[7]. Antimicrobial resistance leads to significant morbidity, mortality, longer hospital stays, and higher medical costs due to infections caused by multidrug-resistant organisms (MDROs) and *Clostridioides difficile*[8]. AMR leads to 30,000 deaths annually in Europe and 23,000 in the USA, with the highest spread in low- and middle-income countries, especially Southeast Asia. The rise of multi-drug resistant bacteria is concerning, and without action, AMR could cause 10 million deaths annually by 2050[8]. Prudent antimicrobial use, supported by antibiotic stewardship programs, is crucial to combat antimicrobial resistance. Procalcitonin (PCT) has emerged as a promising host-response marker to guide clinical decisions and help judiciously manage antimicrobial treatment for bacterial infections[9]. Prolonged antibiotic use significantly disrupts gut flora, raising the risk of infections from *C. difficile* and multidrug-resistant organisms (MDROs) in critically ill patients, which can lead to poor clinical outcomes[10]. Even short exposure to extended-spectrum antibiotics

can elevate the risk of MDROs, *Clostridioides difficile* infections, and other antibiotic-related adverse effects, highlighting the urgent need for additional strategies[11]. Enhancing antibiotic use is a critical patient safety and public health priority, recognized by the Centers for Disease Control and Prevention (CDC) as a key strategy to combat antibiotic resistance[12]. Antibiotic stewardship programs (ASPs) improve prescribing practices, optimize infection treatment, and reduce adverse events like *Clostridium difficile* infections. CDC data shows significant variation in antibiotic use across hospitals, indicating opportunities to enhance prescribing in common clinical situations[12].

A cross-sectional audit of Vermont Oxford Network members revealed that no center addressed all seven CDC Core Elements of Hospital ASPs. Of 4127 infants audited, 725 received antibiotics, with a median antibiotic usage rate of 17%, and only 26% had positive cultures[13]. In the US, about half of hospitalized adults receive antibiotics, with pneumonia and UTIs as common indications. Approximately 30% of prescriptions are unnecessary or suboptimal, leading to adverse effects, drug resistance, and increased healthcare costs[14]. Healthcare workers (HCWs) have a key responsibility in managing antimicrobial use, particularly in hospital settings, where their actions are vital in preventing resistance and ensuring the effectiveness of treatments[15]. However, despite increased awareness of the importance of responsible antibiotic use, overprescribing remains a widespread problem[1]. This study aims to investigate the impact of antibiotic resistance on patient outcomes with a focus on multidrug-resistant organisms. It will also assess the burden of antibiotic resistance on healthcare systems globally, particularly in low- and middle-income countries, where environmental factors like wastewater and agricultural runoff contribute to its spread. Lastly, the study will explore innovative strategies to reduce antibiotic resistance and improve clinical outcomes.

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## Global Threat of Multidrug-Resistant Bacteria

Bacteria are often perceived as harmful microorganisms that can damage aging body parts. Antibiotics are used to combat these bacteria, providing an effective solution for various medical problems. These medicines work by either killing or preventing the growth of bacteria and can be administered through different methods[33]. The "ESKAPE" pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Clostridioides difficile*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp./Enterobacteriaceae*—pose significant threats due to their multidrug resistance and associated clinical risks. These organisms are leading causes of healthcare-associated infections in low- and middle-income countries, contributing to rising morbidity and mortality rates. Furthermore, antibiotic-resistant nosocomial infections are increasing fatalities in these regions and spreading to European countries via refugees, presenting a global health threat[34]. The WHO states that watch group antibiotics, which have a relatively high risk of promoting bacterial resistance, should be the focus of stewardship programs and monitoring[35]. Bacteria can develop resistance to antibiotics through new gene mutations or by obtaining genetic information that confers resistance from other bacteria. The extensive use of antibiotics creates a selective environment that allows bacteria with resistance genes to survive and proliferate[36]. The bacteria *Bacillus anthracis*, *Bacillus cereus*, *Bacillus mycoides*, *Bacillus pseudomycoloides*, *Bacillus thuringiensis*, and *Staphylococcus aureus* (strain 29213) are extensively studied in microbiology due to their varied roles in health, agriculture, and ecological systems. These species are renowned for their adaptability, intricate host interactions, and substantial implications in pathogenicity[37].

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## Challenges in Multidrug-Resistant Bacteria and Decolonization Strategies

Infections caused by bacteria that are resistant to multiple antibiotics, including extended-spectrum  $\beta$ -lactamase (ESBL), AmpC  $\beta$ -lactamase (AmpC), and carbapenemase-producing Enterobacteria (CPE), vancomycin-resistant *Enterococcus* (VRE), or naturally resistant non-fermenting bacteria like *Pseudomonas aeruginosa*, are linked to high mortality rates[16][17]. MDR bacterial colonization, linked to prolonged hospital stays and antibiotic use, contributes to the resistome. With slow development of new antibiotics, strategies like probiotics show promise in reducing MDR colonization and preventing the spread of resistant bacteria[18]. In a randomized trial, 80 adult patients colonized with extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae (EPE) received either the probiotic Vivomixx® or placebo. After one year, 12.5% of probiotic patients achieved EPE eradication compared to 5% in the placebo group, though the result was not statistically significant[19]. However, the review examined decolonization approaches for ESBL-E and CPE intestinal carriage, including antibiotics, probiotics, and fecal microbiota transplantation. Although evidence is limited for routine clinical application, some strategies may temporarily reduce colonization, particularly in high-risk individuals[20]. The randomized trial assessed the effectiveness of oral antibiotics followed by fecal microbiota transplantation (FMT) in eliminating ESBL-E/CPE intestinal carriage. Although 41% of the intervention group achieved decolonization compared to 29% in the control group, the difference was not statistically significant. FMT was generally well tolerated[21].

Recent studies on faecal microbiota transplant (FMT) for decolonizing multidrug-resistant organisms suggest that trial design flaws, such as low stool dosage, oxygen exposure during preparation, and insufficient FMT frequency, may have reduced the efficacy in a recent randomized controlled trial[22]. The presence of multidrug-resistant organisms (MDRO) in the intestines of patients with recurrent *Clostridium difficile* infections (CDI), along with FMT's success, has led to exploring FMT's potential to eliminate MDRO in CDI patients. Compared to healthy controls, individuals with CDI carry higher quantities and a broader variety of antibiotic resistance genes (ARG). Sub-studies on ARG in those receiving FMT for recurrent CDI have shown significant reductions in ARG levels post-FMT[23]. The study investigated the impact of antibiotics on the gut colonization of resistant Enterobacteriaceae in UTI patients and their households. Fluoroquinolones increased the prevalence of ciprofloxacin-resistant strains after treatment, while nitrofurans had no effect. Household exposure increased the individual risk of colonization[24]. A study on systemic antibiotics in healthy volunteers revealed long-lasting skin microbiome changes, with doxycycline (100mg) and TMP/SMX causing significant microbial shifts and increased antibiotic-resistant genes,

underscoring risks of antibiotic overuse and resistance development[1]. Antibiotic treatment duration did not affect antibiotic resistance genes or bacterial diversity at day 30. Patients treated for 14 days had reduced faecal phage content compared to other groups[25].

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## The Global Impact of Antimicrobial Resistance: Drivers, Transmission, and Public Health Risks

Addressing antimicrobial resistance requires understanding its mechanisms across health, agriculture, and environment, with integrated strategies targeting resistance drivers, infection control, and comprehensive, multidisciplinary research alongside new drug development[2]. The excessive use of antibiotics in healthcare, agriculture, and veterinary fields substantially contributes to the rise of antimicrobial resistance (AMR), with environmental sources amplifying its spread. Resistant bacteria and their genes enter soil, water, and air through hotspots like hospital wastewater and agricultural runoff. AMR transmission is influenced by infection control standards, sanitation, water access, and global movement[26]. The growing global demand for animal-based protein is driving a projected 67% increase in antimicrobial use in livestock from 2010 to 2030, particularly in middle-income countries adopting intensive farming methods. This surge raises concerns about antimicrobial resistance and its potential impacts on human health[27]. Antimicrobial resistance among the five-species presented demonstrates a major, and increasing, deleterious impact seen in each of the key outcomes measured. These negative changes, at a personal, health system and Societal levels, further emphasise the growing problem of increasing antimicrobial resistance at a global level and the vital need for new antimicrobials[28]. The study examined the diversity of MRSA in pigs and retail foods in China, discovering high levels of multidrug resistance and greater diversity among food-associated isolates. Significantly, community- and hospital-associated MRSA strains were also identified in food samples, suggesting potential transmission risks[29].

The use of antibiotics in food animals, especially those similar to human drugs, promotes antibiotic resistance. Resistant Enterobacteriaceae, including pathogens like *E. coli* and *Klebsiella*, spread through animal waste and food, posing significant public health risks[26]. The study revealed a 33.9% prevalence of *S. aureus* in the Chilean pork supply, with higher rates found in carcasses and farm pigs. Concerning findings included the detection of oxacillin-resistant strains and enterotoxin-producing strains, which pose a potential risk in the food chain[30]. A study of 208 chicken farms in Vietnam found extensive use of antimicrobials, especially for preventive purposes, with significant reliance on tetracyclines, penicillins, and aminoglycosides. Farms focused on meat production and operated by men exhibited higher antimicrobial usage, indicating a need for antimicrobial monitoring to promote responsible use[31]. The study revealed that 84% of antibiotics on Vietnamese chicken farms were used for prevention, 12% for disease management, and 3.8% for both purposes[31]. The consumption of food animals is expected to increase in low- and middle-income countries, leading to a rise in antibiotic use, potentially exceeding current levels in high-income countries. The OECD forecasts that global antimicrobial consumption in food animals will increase from 63,151 tons in 2010 to 105,596 tons by 2030. This increase will be particularly significant in BRICS nations, where antibiotic use may double to meet growing demand[32]. Epidemiologic data show that long antibiotic courses select for collateral resistance in the microbiota, increasing patients' risk of later infections by antibiotic-resistant pathogens[25].

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## Challenges in Antibiotic Resistance and Emerging Treatments

Amoxicillin is a widely used initial treatment for pneumonia in children. Research in low-income nations suggests shorter treatment durations (3-5 days) are effective, but the optimal dosing for higher-income settings remains unclear[38]. The study tested 24 antibiotics against 95 *Bacillus cereus* group bacteria. Most of the bacteria were susceptible to many antibiotics, but resistance to trimethoprim/sulfamethoxazole was widespread. Some were resistant to clindamycin, erythromycin, and quinupristin /dalfopristin. The study highlights the importance of susceptibility testing to guide treatment for *Bacillus cereus* infections[37]. Reduced amoxicillin dosages and shorter 3-day treatment periods for childhood pneumonia were equally effective as standard treatment. However, shorter treatment resulted in slightly longer cough and sleep disturbances. In severe cases, lower doses may be less effective[38]. The typical treatment duration for pediatric pneumonia is 10 days. However, recent studies suggest that shorter durations, like 5 or even 3 days, may be effective for mild cases treated at home. This shorter treatment could be beneficial for patients and reduce the risk of antibiotic resistance[39].

The CAP-IT trial showed that amoxicillin dose and duration did not affect treatment failure for community-acquired pneumonia, questioning current pediatric CAP treatment. Nonetheless, pneumococcal vaccines have shifted CAP epidemiology, and amoxicillin may not effectively treat most cases[40]. The most common causes of pediatric pneumonia are viruses like RSV and influenza. Bacteria like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* are also significant causes. For mild to moderate bacterial pneumonia in healthy, vaccinated children, oral amoxicillin is the first-line treatment[39]. Azithromycin, while effective against bacterial pneumonia, is facing increasing challenges due to growing antibiotic resistance. While generally well-tolerated, some patients experience side effects[41]. The use of macrolide antibiotics has been linked to the development of antibiotic resistance in different microorganisms. Prolonged treatment with macrolides has led to an increase in macrolide-resistant bacteria, which can have significant clinical consequences. Novel non-antibiotic macrolide compounds may provide a potential long-term treatment alternative[42],[43],[41]. The study by Vicki A. Luna et al. found that all tested *Bacillus anthracis* isolates exhibited resistance to trimethoprim/sulfamethoxazole (TMP/SMX) at both 30°C and 35°C, while resistance in other *Bacillus* species was not observed until after 48 hours of incubation at 30°C. The researchers suggested that molecular changes in TMP/SMX enzyme targets at higher temperatures might contribute to these resistance patterns, which could help distinguish *B. anthracis* from closely related species. The study advises against using TMP/SMX for treating infections caused by *Bacillus cereus* or *Bacillus thuringiensis*, particularly in severe cases or suspected *B. anthracis* infections[37].

*H. pylori* infection and reinfection remain prevalent, with increasing antibiotic resistance. Bismuth-containing quadruple therapies and susceptibility-based treatments are effective. Newer regimens, including vonoprazan-based therapies and probiotic combinations, are being explored for improved eradication rates[44]. Genomic analysis of *Streptomyces clavuligerus* strains revealed limited differences in gene presence, with core genes linked to

primary metabolism and variable genes related to secondary metabolism. Industrial strains exhibited smaller chromosomal regions, offering insights for optimizing clavulanic acid production[45]. Antibiotic-resistant Gram-negative bacteria make treating urinary tract infections (UTIs) challenging. Initial options include nitrofurantoin, fosfomycin, or pivmecillinam. Cephalosporins and fluoroquinolones are second-line choices. For resistant strains, carbapenems, piperacillin-tazobactam, and newer agents like ceftiderocol are crucial but should be used cautiously to prevent further resistance[46]. Antibiotic-resistant Gram-negative bacteria, including ESBL, AmpC, and carbapenemase-producing strains, complicate UTI treatment. First-line therapies include nitrofurantoin and fosfomycin. For resistant infections, carbapenems, aminoglycosides, and newer agents like ceftazidime-avibactam and colistin are options. Stewardship is vital to prevent further resistance[47].

The study developed evidence-based guidelines for treating *Corynebacterium striatum* infections, recommending vancomycin as the first-line treatment. Alternatives include linezolid, teicoplanin, or daptomycin for severe cases and amoxicillin-clavulanate for mild infections. Gene sequencing is the gold standard for diagnosis[48]. The study concluded that doxycycline use did not influence the rates of traveler's diarrhoea or ESBL-PE acquisition, but it was associated with higher doxycycline resistance and co-resistance in stool pathogens among users[49]. However, the study found that travel to Asia and diarrhea combined with antimicrobial use were major risk factors for acquiring extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae (ESBL-E) and ciprofloxacin-resistant Enterobacteriaceae (CIPR-E). Of the 445 travelers, 23.4% acquired ESBL-E, mainly *E. coli* with blaCTX-M-15, and 32.5% acquired ciprofloxacin-resistant strains. A single carbapenemase-producing strain was acquired after travel to Egypt. These results emphasize the significant risk posed by travel to high-resistance regions and antimicrobial use[50]. Doxycycline post-exposure prophylaxis (doxy-PEP) effectively reduces *Chlamydia trachomatis* and *Treponema pallidum* infections in men who have sex with men (MSM). Further studies are needed to assess its efficacy for gonorrhoea and in cisgender women, along with potential side effects[51]. Ciprofloxacin, a widely used antibiotic, is facing increasing resistance in pathogens like *Salmonella typhi*, *Staphylococcus aureus*, *E. coli*, and *Pseudomonas aeruginosa*. To address this issue, new strategies, including combinations with other antibiotics, nanoparticles, natural products, bacteriophages, and photodynamic therapy, are being explored to enhance ciprofloxacin's effectiveness against resistant bacteria and biofilms[52]. Ciprofloxacin is a promising antibiotic for *Pseudomonas aeruginosa* lung infections in cystic fibrosis. Inhalation delivery reduces systemic side effects. However, formulation challenges exist due to lung barriers, mucus, and biofilms[53]. This phase 3 trial compared two 4-month rifapentine-based regimens with a standard 6-month regimen for drug-susceptible pulmonary tuberculosis. Rifapentine-moxifloxacin was noninferior to the control, but rifapentine alone showed inferior results[54]. A recent Italian study analyzed 69 anaerobic strains for moxifloxacin susceptibility, finding high resistance rates: 81% for *Bacteroides* spp. and 48% for other anaerobes using EUCAST criteria. CLSI criteria showed lower resistance (35% for all anaerobes, 41% for *Bacteroides*). This highlights a concerning rise in moxifloxacin resistance in Italy[55]. Vancomycin-resistant enterococci (VRE) bloodstream infections pose significant health risks, with high rates of morbidity and mortality. Challenges in managing these infections include dosing complexities, antimicrobial resistance, and limited treatment options[56]. The 2009 vancomycin guidelines target MRSA, emphasizing an AUC/MIC ratio of  $\geq 400$  and trough levels of 15-20 mg/L to combat resistance. Recommendations for MSSA and other bacteria remain cautious due to differing resistance patterns and limited data[57].

Table 1: Overview of Multidrug-Resistant (MDR) Bacteria and Antibiotic Resistance

Bacteria/Pathogen	Antibiotic Resistance Patterns	Associated Risks/Outcomes	Antibiotic/Intervention Strategies
<b>Enterococcus faecium</b>	Vancomycin-resistant (VRE)	Healthcare-associated infections, high mortality rates	Antibiotic stewardship, new antibiotics, probiotics
<b>Staphylococcus aureus</b>	Methicillin-resistant (MRSA)	Common cause of sepsis, pneumonia, skin infections	Methicillin or other beta-lactam resistance management
<b>Klebsiella pneumoniae</b>	Resistant to cephalosporins, carbapenems	Pneumonia, UTIs, bloodstream infections	Carbapenem-sparing agents, colistin, $\beta$ -lactam inhibitors
<b>Acinetobacter baumannii</b>	Carbapenem-resistant (CRAB)	Severe infections in ICU patients	Use of polymyxins, colistin, combination therapies
<b>Pseudomonas aeruginosa</b>	Resistant to multiple antibiotics including beta-lactams, aminoglycosides	Respiratory infections, sepsis, high morbidity	Combination therapy, cephalosporins, aminoglycosides
<b>Enterobacteriaceae (e.g., E. coli)</b>	Extended-Spectrum Beta-Lactamase (ESBL), AmpC $\beta$ -lactamases	UTIs, sepsis, bloodstream infections	$\beta$ -lactam inhibitors, fluoroquinolones, aminoglycosides
<b>Clostridioides difficile</b>	Resistance to some antibiotics (e.g., clindamycin, fluoroquinolones)	Major cause of healthcare-associated GI infections	Discontinuation of unnecessary antibiotics, fecal microbiota transplantation (FMT)
<b>Stenotrophomonas maltophilia</b>	Resistant to multiple classes (including cephalosporins, carbapenems)	Respiratory infections in immunocompromised patients	Trimethoprim-sulfamethoxazole (TMP/SMX), resistant strains

<b>Bacteroides species</b>	Resistance to beta-lactams, metronidazole	Disrupts gut microbiome, linked to infections	Use of metronidazole, alternative agents in resistant cases
<b>Clostridium perfringens</b>	Resistance to beta-lactam antibiotics	Gas gangrene, surgical site infections	Penicillin, clindamycin; adjunctive therapies for resistant strains

**Note:** This table and summary provide a broad overview of the issues surrounding MDR bacteria, the need for appropriate antibiotic stewardship, and the potential strategies to combat these pathogens, focusing on both current therapies and emerging interventions

### The Global Crisis of Antimicrobial Resistance

Infections caused by antibiotic-resistant bacteria, especially those from the "ESKAPE" group (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species), are becoming increasingly prevalent. These pathogens pose a serious threat to public health by causing infections that are difficult to treat with conventional antibiotics[58]. As a result, they contribute to high rates of morbidity, mortality, prolonged hospital stays, and increased healthcare costs. The growing resistance to commonly used antibiotics makes the management of these infections more challenging, leading to the need for novel treatments and better infection control strategies[58]. Antibiotic-resistant infections, including carbapenem-resistant Enterobacteriaceae, lead to significant morbidity and mortality. While new antibiotics are being developed, most are modifications of existing classes, with financial and regulatory challenges hindering progress, complicating long-term resistance management[59]. The Infectious Diseases Society of America (IDSA) highlights concerns over the lack of new antibiotics for drug-resistant infections, particularly gram-negative pathogens, urging urgent action and collaboration to address stagnation in the antibiotic development pipeline[60]. Multidrug-resistant (MDR) Gram-negative bacteria pose a significant global health risk. New antibiotics like cefiderocol, eravacycline, and plazomicin offer hope, but many are modified versions of existing drugs, raising concerns about their long-term effectiveness[61].

The rise of multidrug-resistant Gram-negative bacteria has led to the reconsideration of polymyxins like colistin as a last-resort treatment, but rapid global resistance mechanisms are emerging, complicating their continued effectiveness[62]. Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi, and parasites become resistant to antimicrobial medicines. This makes infections harder to treat, leading to increased illness, disability, and death. AMR is a growing global health crisis, and urgent action is needed to combat it[63]. The economic impact of drug-resistant infections is hard to quantify. These infections require more resources, including healthcare personnel time, longer hospital stays, and costly, less effective medications. However, a standardized method to calculate this burden is lacking[64]. The CDC has been tracking the health burden of drug-resistant infections since 2013. Their latest report in 2019 provides more detailed estimates based on various data sources, including laboratory, population, and electronic health records[64],[65]. Despite significant investments of over US\$ 13.75 billion annually since 2017, experts estimate that an additional US\$ 250-400 million is still needed yearly to sustain antibiotic development[66],[67].

The increasing global problem of antimicrobial resistance has also substantially contributed to the economic burden on healthcare systems worldwide. While quantifying the global cost of antibiotic resistance is challenging, the financial burden associated with AMR is undoubtedly substantial[28]. The study found that Pseudomonas aeruginosa bloodstream infections had significantly higher mortality rates compared to Staphylococcus aureus and other Gram-negative infections, even after accounting for patient, bacterial, and treatment characteristics[16]. ESBL-producing Enterobacteriaceae infections are associated with higher all-cause mortality, attributable mortality, and longer hospital and ICU stays. ESBL infections, especially with E. coli, have a greater clinical impact, particularly in pediatric and cancer patients[17]. Antimicrobial resistance is a worldwide issue, with numerous pathogens becoming resistant to multiple drugs, resulting in higher rates of illness, death, longer hospital stays, and increased treatment expenses[28]. A prospective cohort study in Hanoi, Vietnam, with 296 NICU patients found a 44.3% case fatality rate and 31.8% 30-day mortality. For each additional antibiotic resistance, the odds of death increased by 27%, and length of stay increased by 2.1 days[8].

### The Rising Global Threat of Antimicrobial Resistance

Drug-resistant infections are a rising global health concern. They can spread through travel, contaminated sources, and medical procedures. Resistance genes can be easily shared between germs, making infections more challenging to treat. Some germs may be prevalent in certain regions but less common in others. When people travel internationally, they can acquire infections from other people, animals, contaminated food or water, or through receiving medical care. New forms of resistance can emerge and spread rapidly, particularly resistance shared among germs through mobile genetic elements[68]. Superbugs are infections caused by microorganisms, often bacteria, that are resistant to multiple antibiotics or antifungals. These infections are difficult to treat and pose a significant health threat[69]. Antibiotic resistance is a major global health issue. The 2022 GLASS report shows alarmingly high resistance rates in common bacteria like E. coli and Staphylococcus aureus. This makes treating common infections like urinary tract infections more difficult and less effective[70]. Antimicrobial resistance (AMR) is a growing global health crisis. It occurs when microorganisms like bacteria, viruses, fungi, and parasites become resistant to antimicrobial drugs. This makes infections harder to treat, increasing the risk of severe illness and death[71].

### Tackling Antimicrobial Resistance: Innovation and Action

Antimicrobial resistance causes over a million deaths annually. The WHO's new report highlights the urgent need for innovative strategies to develop new antibiotics and ensure their availability, as the current pipeline is insufficient[66]. The pipeline of new antibiotics is insufficient to combat the

growing threat of drug-resistant infections. Economic challenges and limited private investment hinder antibiotic R&D. Public-private partnerships and innovative funding models are crucial to address this crisis and ensure equitable access to life-saving antibiotics[67]. Inaction against antimicrobial resistance could result in annual economic losses exceeding US\$ 855 billion, but investing in critical interventions could yield returns 7-13 times the initial investment[72]. A new WHO report indicates that vaccines targeting 23 pathogens could potentially decrease global antibiotic consumption by 22%. This would contribute to the fight against antimicrobial resistance. While some of these vaccines are currently available, others still require development and market introduction[73]. A new study estimates that widespread vaccination could prevent millions of deaths and disability-adjusted life-years associated with bacterial antimicrobial resistance, with the highest potential impact in Africa and Southeast Asia, particularly for lower respiratory infections, tuberculosis, and bloodstream infections. The study highlights the crucial role of vaccines in combating AMR and reducing the global health burden[74]. A new WHO report estimates that vaccines against pneumococcus, Hib, typhoid, TB, and *Klebsiella pneumoniae* could prevent up to 649,000 deaths associated with antimicrobial resistance (AMR) annually. While some vaccines are already available, others are still in development[74],[73]. Global leaders have adopted a political declaration at the UNGA High-Level Meeting on AMR, committing to reduce AMR-related deaths by 10% by 2030. The declaration calls for increased funding, including a US\$100 million catalytic fund, to support national action plans on AMR. The goal is to ensure at least 60% of countries have funded national action plans by 2030[75]. Bangladesh faces a significant challenge with antibiotic overuse and misuse due to weak regulatory enforcement, widespread availability, and limited public awareness. The government, with support, is taking steps to strengthen regulations, improve public awareness, and promote rational antibiotic use, including overhauling antibiotic packaging to provide clearer information and discourage inappropriate use[76].

The Global Health Sector Strategies (GHSS) 2022-2030 aims to reduce gonorrhea incidence by 90%. The global action plan on gonococcal AMR outlines strategies for prevention, early diagnosis, and effective management of gonorrhea[77]. The study investigated whether probiotics could prevent gut colonization by multidrug-resistant bacteria during antibiotic treatment. In a randomized trial of 120 elderly patients, a probiotic mixture significantly reduced colonization by *Pseudomonas* and AmpC-producing enterobacteria, with no infections from ESBL bacteria observed up to two years later, suggesting beneficial effects[18]. Multidrug-resistant (MDR) bacteria, such as ESKAPE pathogens and carbapenem-resistant Enterobacteriaceae, represent a significant global health threat, contributing to elevated mortality rates, particularly in low- and middle-income countries. The overuse of antibiotics in healthcare, agriculture, and veterinary practices, combined with environmental contamination, exacerbates the spread of resistance. While decolonization strategies, including probiotics, antibiotics, and fecal microbiota transplantation (FMT), show potential, they lack definitive evidence for routine clinical use. To combat resistance effectively, it is crucial to implement robust antibiotic stewardship, monitoring, and global surveillance, especially to protect vulnerable populations.

Table 2. Summary of Key Findings on Multidrug-Resistant Bacteria and Strategies for Addressing Resistance

Topic	Multidrug-Resistant Bacteria (MDR)	Sources of Resistance	Impact on Health	Decolonization Strategies	Key Pathogens	Global Challenges
<b>Health Threats</b>	MDR bacteria, including ESKAPE pathogens, pose high mortality risk	Antibiotics overuse in healthcare, agriculture, and environment	Increased mortality rates in low- and middle-income countries	Probiotics, FMT, and antibiotics show potential for reducing MDR	ESKAPE pathogens, CPE, VRE, <i>Pseudomonas aeruginosa</i> , Enterobacteriaceae	Rising infections due to resistant bacteria in healthcare settings
<b>Transmission</b>	Resistant bacteria spread in hospitals, agriculture, and environment	Hospital wastewater, agricultural runoff, human movement	Resistance contributes to longer hospital stays and increased infection risks	Studies show limited success in decolonization methods, more research needed	<i>Bacillus</i> spp., <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i>	Antibiotic resistance is a global threat spreading through migration
<b>Antibiotic Use</b>	Inappropriate and overuse of antibiotics fuels MDR bacteria emergence	Antibiotics used for prevention and treatment in animals	Antibiotic resistance increases healthcare costs and reduces treatment effectiveness	FMT and probiotics offer promising alternatives to antibiotics	<i>Enterococcus faecium</i> , <i>Stenotrophomonas maltophilia</i> , <i>Acinetobacter baumannii</i>	Limited new antibiotics, slow development of alternatives
<b>Antibiotic Stewardship</b>	WHO recommends focus on high-risk antibiotics in	Excessive use of broad-spectrum antibiotics	Higher risk of hospital-acquired infections, particularly in	Monitoring and controlled use of antibiotics essential to limit resistance	<i>Clostridioides difficile</i> , <i>Escherichia coli</i> , <i>Klebsiella</i> spp.	Need for global surveillance and coordinated action

	stewardship programs	accelerates resistance	vulnerable patients			
<b>Environmental Spread</b>	Environmental contamination (soil, water, air) amplifies resistance	Antibiotic residues in wastewater and runoff contribute to spread	Antimicrobial resistance spreads globally, posing serious public health risks	Evidence for decolonization strategies is limited but encouraging	Resistant Enterobacteriaceae, MRSA, multidrug-resistant pathogens	Increasing antibiotic use in low- and middle-income countries

**Note:** This table summarizes key findings on multidrug-resistant bacteria and strategies to address resistance, including the impact of specific MDR pathogens, the role of antibiotic misuse, and ongoing research into decolonization methods like probiotics and FMT. It also highlights global trends in antibiotic consumption and the need for strategic monitoring and stewardship to curb resistance.

## Limitations

The current study underscores several limitations that impact its applicability and robustness. Although interventions such as probiotics, antibiotics, and fecal microbiota transplantation (FMT) show potential for decolonizing multidrug-resistant organisms (MDROs), the evidence remains insufficient to support their routine clinical use. Methodological shortcomings, including low stool dosages and inadequate frequency of administration in FMT trials, may have compromised the reliability of recent findings. Furthermore, the study's focus on low- and middle-income countries limits the generalizability of its conclusions to high-income settings with different healthcare infrastructures. While environmental contamination is acknowledged as a factor in antimicrobial resistance, the research does not comprehensively explore this ecological dimension, thereby restricting a broader understanding of resistance transmission. Additionally, the economic implications of antimicrobial resistance are discussed, but a detailed cost analysis of implementing stewardship and decolonization strategies is lacking. The scope of the study is further limited by its narrow examination of specific resistance mechanisms and MDROs, potentially overlooking other critical pathways. Finally, the findings are predominantly based on short-term outcomes, with limited insight into the long-term efficacy and sustainability of these interventions.

To address the limitations identified, future research should focus on several key areas to enhance the understanding and management of antimicrobial resistance (AMR). Longitudinal studies are necessary to evaluate the long-term efficacy and sustainability of decolonization strategies, such as probiotics and fecal microbiota transplantation (FMT), across diverse populations and clinical settings. Comprehensive economic evaluations are also critical to assess the cost-effectiveness of antibiotic stewardship programs and decolonization interventions, considering both direct healthcare expenditures and broader societal impacts. Additionally, further investigation is needed into the role of environmental contamination in the transmission of multidrug-resistant organisms (MDROs), particularly in relation to agricultural practices, wastewater management, and pollution, to identify effective mitigation strategies. Expanding research to include a broader range of populations, especially in high-income countries, will improve the generalizability of findings and inform tailored interventions. Studies should also delve deeper into the mechanisms of resistance across various MDROs to identify novel therapeutic targets. Evaluating the effectiveness of existing antibiotic stewardship programs in diverse healthcare settings will help establish best practices for reducing AMR rates globally. Finally, fostering interdisciplinary research that integrates microbiology, epidemiology, environmental science, and health economics is essential for developing holistic and sustainable strategies to combat AMR.

## Conclusion

The research investigates the substantial influence of antibiotic use on the emergence of antimicrobial resistance (AMR) and its public health implications. It underscores the contributions of over prescription, the variety of resistant strains, and the economic burden linked to AMR. The results highlight the critical need for effective antibiotic stewardship and innovative approaches to address this growing global health challenge.

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