Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2025.254

REVIEW ARTICLE

Antimicrobial Resistance Apocalypse and Pan-Drug-Resistant Superbug Challenges: Current Status, Impact and Mitigation Strategies

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ARTICLE HISTORY (25-589)

Received: June 29, 2025
Revised: August 30, 2025
Accepted: September 06, 2025
Published online: September 29, 2025

Key words:
Antimicrobial resistance (AMR)
Low- and middle-income countries
One Health
Public health crisis
Superbugs

ABSTRACT

Antimicrobial resistance (AMR) has emerged as a critical global public health crisis, often described as a silent global crisis threatening human and animal health. While developed nations benefit from advanced healthcare infrastructure, diagnostic capabilities, strong and continuous surveillance systems, low- and lower-middle-income countries (LICs and LMICs) face significant challenges in combating AMR. Limited access to healthcare, high population density, poor sanitation, overuse and misuse of antibiotics, weak regulatory frameworks, and inadequate surveillance accelerate the emergence and spread of AMR in these regions. The unchecked rise of AMR has facilitated the emergence of multidrug-resistant pathogens, or pan-drug-resistant "superbugs," posing severe threats to global health security. However, AMR remains a neglected issue in LICs and LMICs due to economic constraints and weak monitoring systems. This review explores the current status of AMR and superbugs, their impact on human, animal, and environmental health under the One Health framework; primary factors of resistance; and global mitigation strategies, with a particular AMR landscape and identifying appropriate solutions. This review aims to support efforts in reducing antimicrobial consumption and mitigating the growing threat of resistance worldwide.

To Cite This Article: Hossain H, Chowdhury MDSR, Rahman MN, Khan SS, Ahmad T, Akter S, Nitu AS, Brishty KA, Pory FS, K.C. D, Imranuzzaman MD, Abass KS, Rahman MDM and Rahman MDM 2025. Antimicrobial resistance apocalypse and pan-drug-resistant superbug challenges: current status, impact and mitigation strategies. Pak Vet J. http://dx.doi.org/10.29261/pakvetj/2025.254

INTRODUCTION

Antimicrobial resistance (AMR) describes the capacity of microorganisms, such as bacteria, viruses, fungi, and parasites, to resist the effects of antimicrobial medications, making them ineffective in treating infections (Tanni *et al.*, 2025). The global rise of AMR crisis threatens the effectiveness of commonly used antibiotics in treating bacterial infections (Velazquez-Meza *et al.*, 2022). It is a global health concern (Rahman *et al.*, 2024) that incorporates the One Health concept and poses a threat to the therapeutic potency of antibiotics (Velazquez-Meza *et al.*, 2022). The World Health Organization (WHO) has classified multidrug-resistant pathogens, commonly known as superbugs, as a severe global health threat. Reports from the Inter-Agency Coordinating Group (IACG) on AMR predict that AMR could lead to an estimated ten million deaths annually by 2050 (Naghavi *et al.*, 2024). These pathogens bacteria, viruses, fungi, and parasites become resistant to conventional treatments due to factors such as overuse of antimicrobial medications, unhygienic food consumption, poor sanitation, and ineffective infection control (Tanwar *et al.*, 2014). The continuous evolution of resistance mechanisms and the diminishing effectiveness of treatments against recurrent infections result in extended illnesses, higher healthcare costs, more severe disease

progression, and a greater risk of death. Over the last few decades, many infectious agents, including bacteria, viruses, fungi, and parasites, have shown significant resistance and increased morbidity and mortality, earning them the title "superbugs" (Painuli *et al.*, 2023). It is sometimes referred to as the "Silent Pandemic"; however, rather than being viewed as a problem for the future, it requires prompt action and efficient control (Founou *et al.*, 2021).

Since their introduction in the 20th century, antimicrobials have revolutionized medicine by significantly reducing infectious disease mortality and improving public health. Over 15 classes of antimicrobials have been developed, saving millions of lives, with global consumption exceeding 100,000 tons annually (Bacanlı and Başaran, 2019; Chanishvili and Aminov, 2019; Hutchings *et al.*, 2019). However, their widespread use, particularly excessive and inappropriate applications, has contributed to environmental contamination and the rapid emergence of superbugs with multidrug resistance (Danner *et al.*, 2019). More than 150 new antibiotics have been discovered, and their misuse has accelerated resistance, leading to increased treatment failures and rising mortality (Chanishvili and Aminov, 2019). Antimicrobials are also implicated as a primary driver of the emergence and dissemination of antimicrobial-resistant bacteria (ARB) and antimicrobial resistance genes (ARGs) (Shen *et al.*, 2021). Whereas the initial application of antimicrobials gave us a strategic advantage to fight against microbial infections, the increasing threat of AMR now compromises our ability for limiting the spread of infectious diseases (Muteeb *et al.*, 2023).

AMR has rapidly emerged as one of the biggest global challenges of the twenty-first century due to the increasing rate of AMR and the lack of new antimicrobial medications being introduced to combat it (Lobanovska and Pilla, 2017). In 2019, an estimated 1.27 million deaths globally were attributed to AMR infections, either directly or indirectly (Murray *et al.*, 2022). It is a highly documented consequence of antimicrobial usage (AMU), including that even proper and appropriate use results in the development of resistance. However, its excessive and inappropriate use worldwide increase the antimicrobial resistance crisis (Laxminarayan *et al.*, 2013). In developing countries, AMR is fast becoming a threaten use to the widespread misuse of antimicrobials (Byarugaba, 2004). The medications are readily accessible over the counter (OTC), without any prescription, and via unregulated distribution routes (Byarugaba, 2004; Okeke *et al.*, 2005). Suboptimal compliance with prescribed treatments markedly drives AMR emergence, with socioeconomic deprivation serving as a major factor promoting antimicrobial misuse (Okeke *et al.*, 2005). Moreover, the misuse of antimicrobial agents has also led to the development of multidrug resistant (MDR) pathogens and superbugs (Emon *et al.*, 2024). AMR is complicated and results in prolonged hospitalization, high mortality, increased healthcare costs, and a remarkable risk to human health (Salam *et al.*, 2023). The combat against AMR cannot be left only to medical practitioners and researchers. While ongoing education and training are essential to encourage responsible and evidence-based prescribing among doctors, other stakeholders, particularly the general public, also play a vital role in combating antimicrobial resistance (Blakely *et al.*, 2006).

The review explores the current status of AMR, recent resistance mechanisms, and One Health impact and highlights current mitigation strategies to address difficulties in countering AMR in LICs and LMICs. This review covers the etiology and prevalence of pan-drug-resistant (PDR) superbugs in LICs and LMICs, along with the associated threats of antimicrobials and emerging mitigation strategies.

REVIEW METHODOLOGY

This comprehensive review synthesizes current knowledge on antimicrobial resistance, antimicrobial uses (AMU), and antimicrobial consumption (AMC), with a particular focus on LICs and LMICs.

For the "Superbugs: Current Updates in LICs and LMICs" section, a systematic literature search was conducted across several databases, including PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, and ResearchGate, covering the period from January 2014 to October 2024. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords such as "prevalence," "epidemiology," "incidence," "detection," "molecular detection," "pan-drug-resistant bacteria," "PDR bacteria," "superbug," "antibiotic resistance," "drug resistance," "human," "patients," "low-income countries," "lower-middle-income countries," "LMICs," "developing countries," and individual country names classified by the World Bank as LICs and LMICs. Boolean operators "AND" and "OR" were used, along with truncation (e.g., resist, country) to capture variant terms. The literature was reviewed and screened; relevant studies were selected based on inclusion criteria (e.g., human PDR bacterial infections in LICs/LMICs); and data were extracted regarding country, organism, sample size, resistance rate, and confidence intervals, where available. The data were presented descriptively due to heterogeneity in study designs.

For the AMR, AMU, and AMC data reporting component of this review, data were extracted from the Global Antimicrobial Resistance and Use Surveillance System (GLASS) platform operated by the World Health Organization (WHO) (https://www.who.int/initiatives/glass; accessed on 26 February 2025). The primary source was the latest GLASS 2024 report (Global Antimicrobial Resistance and Use Surveillance System (GLASS), which presents global AMR and AMU data updates up to the year 2022. Additionally, we accessed and manually reviewed data from the GLASS online dashboard, focusing on Countries, Territories, and Areas (CTAs) profiles; Global AMU data; and Global AMR data for the period 2016–2022. Data were specifically retrieved for countries categorized as LICs and LMICs according to the World Bank classification. The extracted information included AMU patterns by AWaRe classification (Access, Watch, and Reserve antibiotics); antibiotic consumption levels; and resistance rates among WHO-priority pathogens, including carbapenem-resistant *Acinetobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae*, fluoroquinolone-resistant *Salmonella* spp. and *Neisseria gonorrhoeae*, and methicillin-resistant *Staphylococcus aureus*

(MRSA). Resistance data were stratified by infection sites, particularly bloodstream infections (BSI), urinary tract infections (UTI), and gastrointestinal tract (GIT) infections.

Insights into Recent Mechanisms and Transmission of AMR: Resistance mechanisms of antibiotics/antibacterials can be classified according to type of origin and molecular mechanisms (Fig. 1). The resistance mechanism comprises natural (intrinsic) resistance leading to innate bacterial characteristics, including impermeable outer membranes or efflux systems that can inhibit antibiotic action (Bo *et al.*, 2024). Resistance can be acquired by chromosomal mutations or the acquisition of resistance genes by horizontal gene transfer (HGT), frequently facilitated by plasmids, transposons, or integrons (Fig. 1A). Adaptive resistance is a transient physiological alteration in response to stressors (e.g., antibiotic exposure, biofilm formation) that temporarily enhances survival. It is characterized by the change in bacterial physiology that leads to loss of drug action (Belay *et al.*, 2024).

One of the main AMR factors is decreased permeability, where bacteria change their outer membrane porins (e.g., *OmpF*, *OmpC*, and *OprD*) to reduce drug entry (Belay *et al.*, 2024). In *K. pneumoniae*, mutations in *ompK35*, *ompK36*, *phoQ*, and *mgrB* decrease *β*-lactam and carbapenem penetration (Fig. 1B).

Efflux pumps actively expel antibiotics from bacterial cells, lowering intracellular drug concentrations and contributing to multidrug resistance. Key transporters include *acrB*, *mexB*, *tetA*, and *qacA/B*, which belong to families (Chetri *et al.*, 2019) like resistance-nodulation-division (RND), major facilitator superfamily (MFS), small multidrug resistance (SMR), multidrug and toxic compound extrusion (MATE), and ATP-binding cassette (ABC) (Gao *et al.*, 2022) (Fig. 1C). This gene is commonly plasmid-associated, which increases dissemination. Bacteria can resist antibiotics by altering their target sites through mutations or enzymatic changes that prevent drug binding. Changes in *gyrA*, *parC*, and *rpoB* decrease the binding of quinolone and rifampicin (Brandis *et al.*, 2020). Methylation of *23S rRNA* is the mechanism of erythromycin resistance by *erm* genes. Other vital genes are *mecA* (methicillin), *aac* (aminoglycosides), and *vanA/B* (vancomycin) (Fig. 1D). Bacteria can resist antibiotics by enzymatically inactivating them through degradation or chemical modification. *β*-lactamases (bla_{TEM}, bla_{SHV}, bla_{NDM}, bla_{OXA}) inactivate the *β*-lactams, while aminoglycoside-deactivating enzymes (*aac*, *ant*, *aph*) deactivate the drug (Belay *et al.*, 2024). Mobile genetic elements often associated with these resistance determinants facilitate the dissemination in bacterial populations (Fig. 1E).

tmexCD-toprJ* Gene Cluster: A Novel IncC Plasmid-Borne Resistance Gene for Tigecycline*: Recent developments in research on antimicrobial resistance have revealed new resistances and exposure routes that may seriously threaten the public health. A growing concern is the emergence of tigecycline resistance mediated by the *tmexCD-toprJ* efflux pump system and the *tet(X4)* gene, both of which significantly compromise the effectiveness of tigecycline against multidrug-resistant Gram-negative bacteria (Sun *et al.*, 2022; Hirabayashi *et al.*, 2025). The *tmexCD-toprJ* gene cluster was first identified in *K. pneumoniae* later in *Enterobacter cloacae* (Sun *et al.*, 2022; Wang *et al.*, 2025). The *tmexCD-toprJ* gene cluster encodes an efflux pump belonging to the resistance-nodulation-division (RND) family, which actively expels tigecycline from bacterial cells, thereby lowering intracellular drug concentrations and diminishing therapeutic efficacy (Tong *et al.*, 2021). This efflux system is notably often plasmid-encoded, which allows horizontal gene transfer (HGT) and helps this system spread quickly across numerous Gram-negative populations (Wang *et al.*, 2023). Another study reported the *tmexC3-tmexD5-toprJ2b* cluster in *Oceanimonas* spp., highlighting the spread of these resistance genes in various bacterial species (Wang *et al.*, 2023). The other is the inactivation of tigecycline by the *tet(X4)* gene, which encodes an enzyme that modifies tigecycline with an incorrect chemical group, thus inactivating it (Wang *et al.*, 2025). The gene is commonly located on the mobile genetic elements that can facilitate its dissemination among the bacterial population, including *E. coli* and *K. pneumoniae* (Fan *et al.*, 2024). The finding of these resistance mechanisms in hospital sewage and the environment raises serious concerns and urgency for monitoring and developing new therapeutic options (Li *et al.*, 2023).

Plasmid Replication and Heteroresistance: Bacteria can quickly elevate resistance levels through transient, massive replication of resistance genes on plasmids. This is called heteroresistance, and it permits a small fraction of the bacterial population to survive the presence of the antibiotic even though the majority are still susceptible (Nicoloff *et al.*, 2024). These processes may contribute singly or in combination to the same bacterium.

Porin-Mediated Drug Entry Modulation: A new approach to combat antimicrobial resistance in *K. pneumoniae* is disrupting protein-mediated pathways for drug entry (Belay *et al.*, 2024). Recent findings have also discovered that *CymAKp*, an aminoglycoside uptake facilitating dynamic porin, provides novel strategies for boosting antibiotic efficiency (Gogoi *et al.*, 2023). This builds on earlier findings showing that resistance often arises from the loss or modification of porins like *OmpK35* and *OmpK36*, which reduce *β*-lactam and carbapenem permeability (Elías-López *et al.*, 2024). Therapeutic efficacy against resistant strains can be substantially improved by replenishing or functional substituting porins or combining antibiotic and porin-targeting agents.

Quorum Sensing Disruption: Bacterial communication systems (quorum sensing) regulate behaviors, including biofilm formation and virulence (Preda and Săndulescu, 2019). Breaking this line of communication makes the bacteria less able to defend themselves and also can make antibiotics more effective. RNAIII-inhibiting peptide (RIP) has been shown to interfere with quorum sensing, potentially reducing the need for high-dose antibiotics (Zhou *et al.*, 2020).

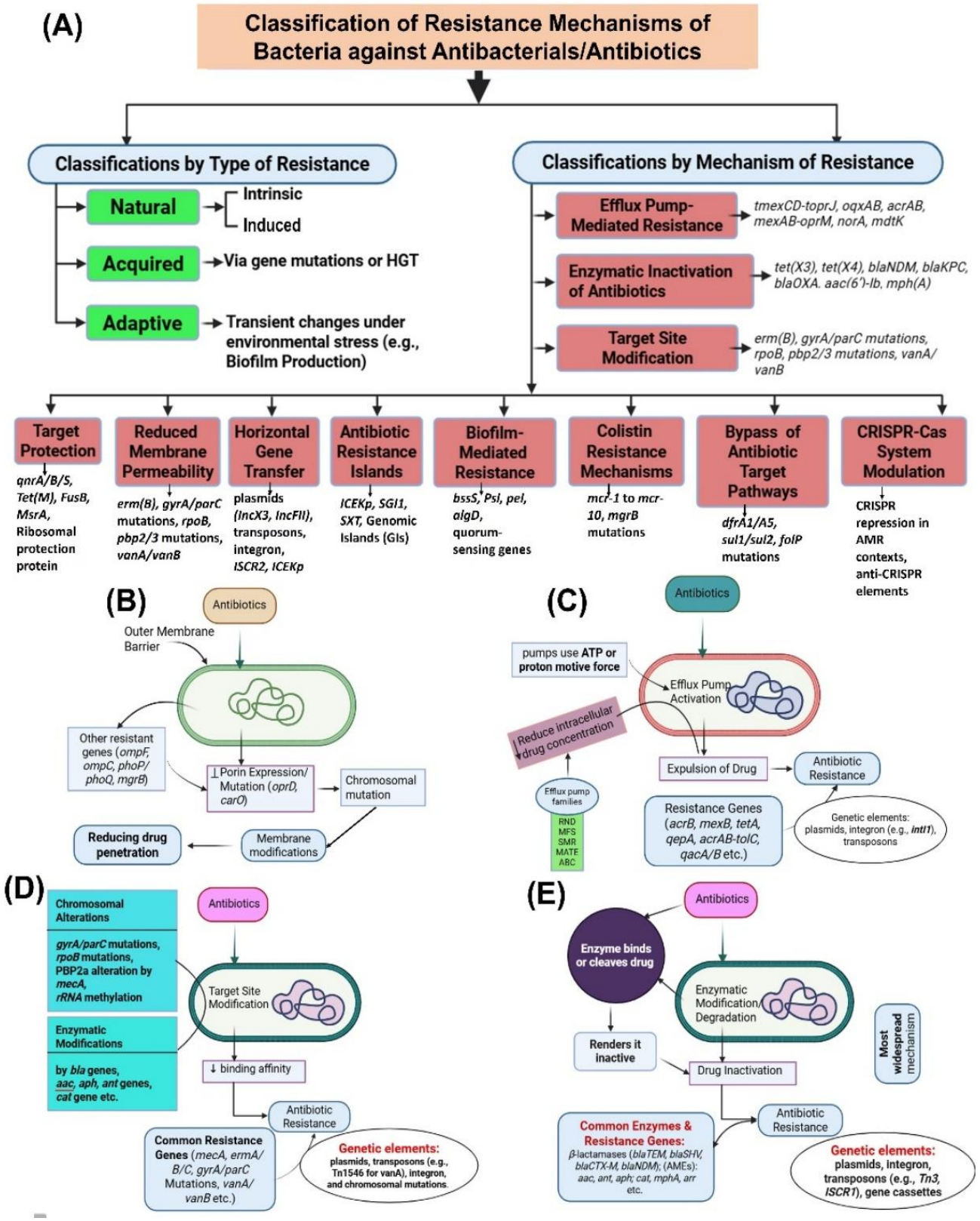

Fig. 1: Schematic representation of the classification and major mechanisms of antimicrobial/antibacterial resistance. (A) Resistance mechanisms are classified by type—natural (intrinsic or induced), acquired (via gene mutation or horizontal gene transfer), and adaptive (temporary changes under stress, e.g., biofilm formation)—and by functional mechanism, including efflux pumps, enzymatic inactivation, and target modification. Additional mechanisms involve reduced permeability, biofilm-mediated resistance, antibiotic resistance islands, CRISPR-Cas modulation, and pathway bypass. (B) Reduced membrane permeability occurs through porin loss or mutation and membrane modifications, limiting drug entry. (C) Efflux pump activation uses ATP or proton motive force to expel antibiotics, reducing intracellular drug concentration. Efflux pump families include RND (resistance–nodulation–cell division), MFS (major facilitator superfamily), SMR (small multidrug resistance), MATE (multidrug and toxic compound extrusion), and ABC (ATP-binding cassette). (D) Target site modification involves chromosomal mutations or enzymatic alterations that lower antibiotic binding affinity. (E) Enzymatic degradation inactivates antibiotics through enzymes like β-lactamases and aminoglycoside-modifying enzymes. Various resistance genes are mobilized by plasmids, transposons, integrons, and gene cassettes. Collectively, these mechanisms contribute to bacterial survival under antibiotic pressure and complicate treatment strategies.

Efflux Pump Overexpression: Efflux pumps are membrane proteins that discharge antibiotics from bacterial cells. Overexpression of these pumps is the major contributory factor for MDR (particularly in Gram-negative bacteria) (Saleh *et al.*, 2024). The resistance–nodulation–cell division (RND) superfamily contributes significantly to this mechanism and pumps such as *AcrAB-TolC* (from *E. coli*), and *MexB* (from *Pseudomonas aeruginosa*) are exemplary (Saleh *et al.*, 2024; Vivekanandan *et al.*, 2025).

Transmission of AMR: AMR spreads through direct human-to-human contact; healthcare settings; and environmental reservoirs such as wastewater, animal feces, and contaminated food and water (Godijk *et al.*, 2022). The overuse of antibiotics in livestock contributes to resistance transmission when humans consume treated animals or come into contact with them (Salam *et al.*, 2023). These pathways facilitate the global dissemination of resistant bacteria, posing a significant public health challenge.

Superbugs: Current Updates in LICs and LMICs: Superbugs, including MDR, XDR, and PDR bacteria and fungi, pose a significant global health threat due to their resistance to nearly all available antimicrobial treatments (Salam *et al.*, 2023). These infections often leave little to no therapeutic options, increasing morbidity, mortality, and treatment costs (Mohsin and Amin, 2023). The ESKAPE pathogens *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. are among the most concerning due to their high resistance potential. Key superbugs such as carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Klebsiella pneumoniae* (CRKP), methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL-producing Enterobacterales, vancomycin resistant *Enterococcus* (VRE), MDR *Pseudomonas aeruginosa*, and *Acinetobacter* continue to emerge worldwide (Salam *et al.*, 2023). In LICs and LMICs, PDR pathogens are frequently reported, particularly within the WHO's critical and high-priority pathogens list (PPL). Due to their presence in human, animal, and environmental niches, these superbugs facilitate the spread of resistance across ecosystems (Reygaert, 2018). Superbugs are the most challenging pathogen due their high potency to make resistance to nearly all classes of antimicrobials. From January 2014 to October 2024, 11 LICs and LMICs have reported PDR-superbug cases (Fig. 2), highlighting an urgent need for enhanced surveillance and antimicrobial stewardship programs.

Several studies have reported the prevalence of superbug bacteria across LICs and LMICs. In Pakistan, Samad *et al.*, (2017) identified *Pseudomonas aeruginosa* in 3/71 (4.2%) isolates. Similarly, Ain *et al.*, (2022) found *Acinetobacter baumannii* in 8/111 (7.2%) isolates. In Ethiopia, Bitew reported *Pseudomonas* and *Acinetobacter* in 14/129 (10.9%) isolates (as PDR) (Bitew, 2019), while Gashaw *et al.*, (2018) found multiple PDR pathogens, including *Staphylococcus aureus, Klebsiella, Escherichia coli*, *Citrobacter*, *Enterobacter*, *Providencia*, *P. aeruginosa*, *A. baumannii*, and *Serratia* in 24/126 (19.0%) isolates. In Europe, CRE prevalence is much lower. In the EU/EEA, average CRE rates are <7%, with northern European countries often reporting <1% cases. In Nigeria, C AGBO *et al.*, (2020) reported *P. aeruginosa* in 38/192 (19.8%) isolates, and Usman *et al.*, (2022) found *Klebsiella pneumoniae* in 3/32 (9.4%) isolates. In Egypt, Tantawy *et al.*, (2020) identified *A. baumannii* in 7/30 (23.3%) isolates, while Al-Baz *et al.*, (2022) found *K. pneumoniae* in 13/142 (9.2%) isolates. In contrast with high income countries, MRSA rates have declined significantly due to strict infection control. In the US, MRSA accounts for nearly 16% of *S. aureus* infections, while in Scandinavian countries it is <5%. These findings highlight the alarming prevalence of PDR bacteria in LICs and LMICs, emphasizing the urgent need for antimicrobial stewardship and surveillance programs.

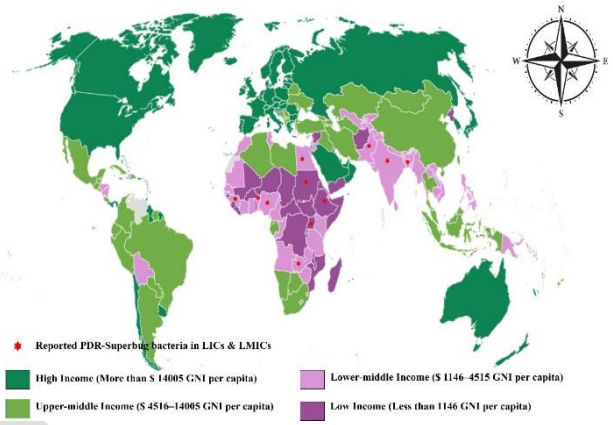

Fig. 2: World Bank country classification by income level (2024–2025) with reported PDR-superbugs in LICs and LMICs (from January 2014 to October 2024). The base map was sourced from the World Bank database, then modified to track reported cases of PDR-superbugs in LICs and LMICs over the specified period.

AMU and AMR Reporting in LICs and LMICs: A Snapshot from the GLASS 2024 Report: According to the Global Antimicrobial Resistance and Use Surveillance System report 2024, global antibiotic consumption surged significantly increased after COVID-19. The top five countries contributing to antimicrobial use (AMU) are Iran (67.68 DDD/1000 inhabitants/day), South Africa (50.93), Bangladesh (48.92), Egypt (46.92), and Jordan (34.27) (Fig. 3a-e), with three of them belonging to LMICs. AMR is a growing issue in LICs and LMICs, whose misuse and inappropriate use of antibiotics ensure the persistence of resistance (Sulis *et al.*, 2022). Time series data from 2016 to 2022 indicate a post-2020 rise in antimicrobial consumption (AMC) across all WHO AWaRe groups, likely driven by COVID-19 (Fig. 3b–d). Among antimicrobial classes, beta-lactams are the most consumed, followed by tetracyclines, macrolides, quinolones, and aminoglycosides (Fig. 3f).

The GLASS Report 2024 also highlights AMU, AMR data, and surveillance gaps in LICs (Table 1). Uganda (21.65) and Burkina Faso (21.04) have the highest antibiotic consumption, possibly due to over-prescription or self-medication (Murungi *et al.*, 2023; Valia *et al.*, 2024). Rwanda (8.66) and Mali (8.42) reported lower usage, which may indicate better stewardship or poor reporting. The WHO AWaRe classification shows Ethiopia

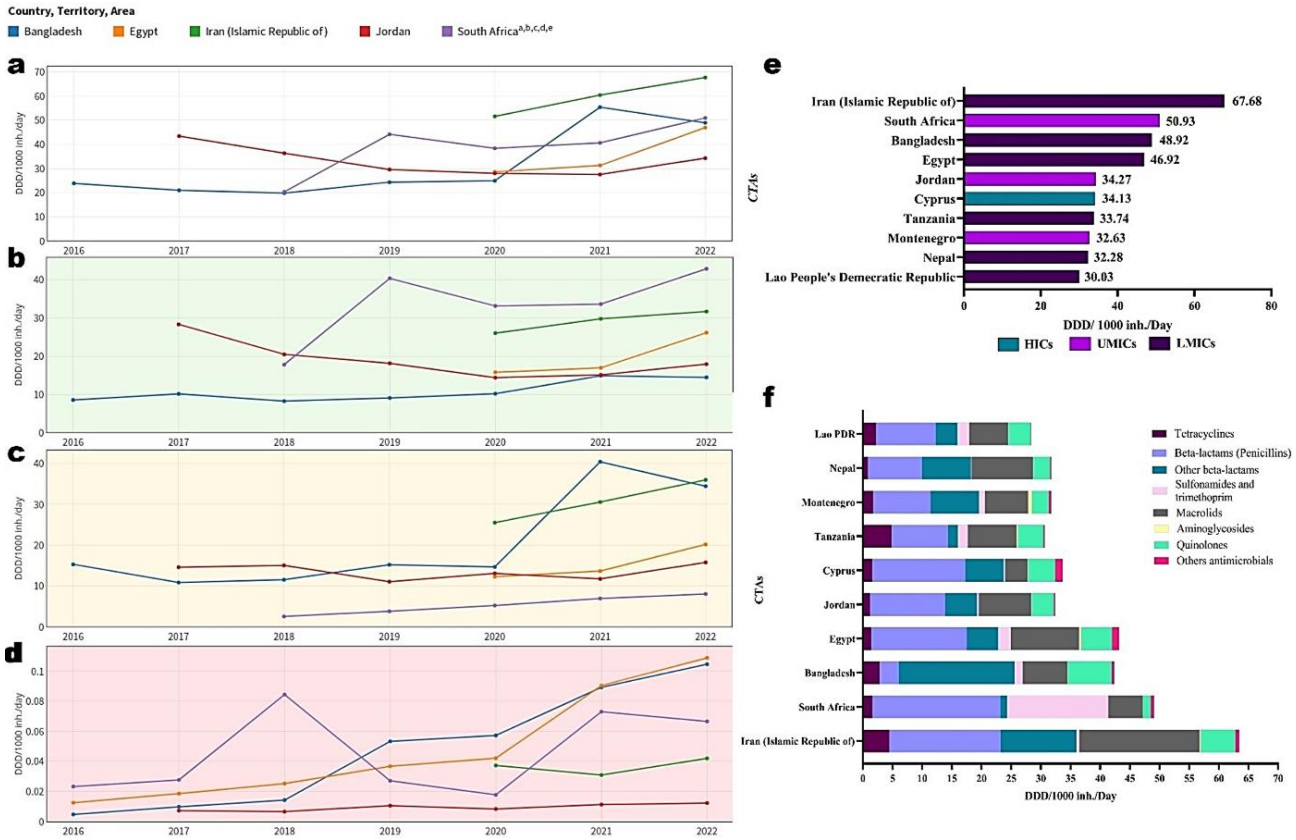

Fig. 3: The time series of the highest (top 5) contributing countries, territories, and areas of antimicrobial uses by AWaRe from 2016 to 2022. (**a**): Total antimicrobial uses in the top five LICs, (**b**): uses of access group of antibiotics, (**c**): watch group, (**d**): reserve group, (**e**): top 10 countries of global AMU, (**f**): AMU with specific classes of antimicrobials.

Table 1: LIC current reporting profile of AMU and AMR data on the GLASS project 2022, WHO.

CTAs	AMU Status	AMR Status	AMU (DDD/1000 inh./Day)	Use of Antibiotics by AWaRe Class (DDD/1000 inh./Day); %	Antibiotic Subgroup (DDD/1000 inh./Day); % (Mostly Used)
Burkina Faso	YY	yy	21.04	A: 17.58 (83.6%) W: 3.34 (15.9%) O: 0.12 (0.6%)	Beta-lactam (penicillins): 8.32 (39.5%); macrolides: 1.93 (9.2%); sulfonamides + trimethoprim: 7.10 (33.7%)
Ethiopia	YY	yy	11.32	A: 8.19 (72.3%) W: 3.13 (27.7%)	Beta-lactam (penicillins): 4.28 (37.8%); quinolone: 2.47 (21.8%); tetracycline: 1.47 (13.0%)
Mali	YY	yy	8.42	A: 3.82 (45.4%) W: 4.39 (52.1%) O: 0.21 (2.5%)	Beta-lactam (penicillins): 2.39 (28.3%); macrolides: 2.06 (28.3%); quinolones: 1.85 (22.0)
Rwanda	YY	yn	8.66	A: 7.34 (84.7%) W: 1.32 (15.3%)	Beta-lactam (penicillins): 4.24 (48.9%); tetracycline: 1.33 (15.4%); quinolones: 0.86 (9.9)
Sudan	YY	yn	15.16	A: 5.4 (35.6%) W: 9.76 (64.4%)	Beta-lactam except penicillins: 9.46 (62.4%); beta-lactam (penicillins): 4.29 (28.3%); tetracycline: 1.09 (7.2)
Uganda	YY	yy	21.65	A: 12.02 (55.5%) W: 7.81 (36.1%) R: 0.01 (0.1%) O: 1.80 (8.3%)	Beta-lactam (penicillins): 8.23 (38.0%); beta-lactam except penicillins 3.48 (16.1%); quinolones: 3.48 (16.0%); macrolides: 1.48 (6.9%)

CTA: countries, territories, areas; DDD: use volume in defined daily dose; inh./Day: inhabitants per day; A: access, W: watch, R: reserve, O: not classified; YY: GLASS AMU enrollment (Yes) and data availability (Yes); yy: GLASS AMR enrollment (Yes) and data availability (Yes); yn: GLASS AMR enrollment (yes) and data availability (no); YN: GLASS AMU enrollment (Yes) and data availability (No); nn: GLASS AMR enrollment (no) and data availability (no); NN: GLASS AMU enrollment (No) and data availability (No); other country status: YN+yn: Afghanistan, Burundi, Central African Republic, Sierra Leone, Somalia; NN+yn: Chad, Congo Dem. Rep., Gambia, Korea Dem. People's Rep., Madagascar, Malawi, Togo; NN+yy: Liberia, Mozambique; NN+nn: Niger, Guinea Bissau, Eritrea; YN+yy: Yemen, Syrian Arab rep.

(72.3%) and Rwanda (84.7%) rely on access antibiotics, aligning with WHO recommendations. However, Sudan (64.4%) and Mali (52.1%) show high watch antibiotic usage, raising AMR concerns (Table 1).

Beta-lactams dominate prescriptions, especially in Rwanda (48.9%) and Burkina Faso (39.5%). Quinolones are commonly used in Ethiopia (21.8%) and Mali (22.0%), while macrolides are widely prescribed in Burkina Faso (9.2%) and Mali (28.3%). Strengthening AMR surveillance, enforcing regulations, and promoting rational antibiotic use is essential to combating AMR in LICs.

AMR trends in LICs and LMICs, emphasizing the growing burden of multidrug-resistant pathogens. Increased participation in AMR surveillance programs is also necessary to effectively assess and mitigate the global AMR threat, given the discrepancy in data availability across nations.

Current AMR Status of WHO Priority Pathogens in LICs and LMICs: Approximately 85% of the global population inhabits in LICs and LMICs, comprising 28 and 54 nations, respectively, out of 218 countries worldwide (Sulis *et al.*, 2022; Ajulo and Awosile, 2024). Many of these countries have high population densities and poor sanitation, contributing to a significant disease spread. The widespread and often unregulated use of antibiotics has aggravated AMR in these regions (Sulis *et al.*, 2022).

Despite the growing threat of AMR, it remains a neglected issue in many LICs and LMICs, leading to an alarming rise in MDR pathogens. To combat AMR, the WHO started the Global Action Plan on AMR in 2015 (Global action plan on antimicrobial resistance). In the same year, on 22 October, the WHO introduced GLASS to monitor AMU and AMR trends globally (Global Antimicrobial Resistance and Use Surveillance System (GLASS). By the end of 2023, 90 countries/territories/areas (CTAs) were recorded in GLASS-AMU, with 63 of them reporting AMU data for 2022 (Global Antimicrobial Resistance and Use Surveillance System (GLASS). However, only a limited number of LICs and LMICs have reported AMU and AMR data to GLASS, highlighting gaps in surveillance. The current AMR status of the WHO's critical and high-priority pathogens in LICs and LMICs has worsened, particularly after the COVID-19 pandemic (Global Antimicrobial Resistance and Use Surveillance System (GLASS). Among bacteriologically confirmed infections (BCIs), urinary tract infections (UTIs) have shown a regular increase, further complicating the AMR problem in these regions (Table 2)

Analysis of Antimicrobial Resistance Trends and Geographic Distribution in LMICs: The AMR patterns in LMICs show a very significant increase in the level of resistance over the years, particularly for multiple key antibiotics (Zhao *et al.*, 2024). Resistance to ampicillin (AMP), cefotaxime (CTX), and ciprofloxacin (CIP) has been on the rise, with a marked increase after 2010. The increasing resistance to cefotaxime is particularly concerning, as it indicates the spread of extended-spectrum beta-lactamase (ESBL) producing bacteria. The increase in ciprofloxacin resistance also threatens the utility of fluoroquinolones for the treatment of infection. While resistance to tetracycline (TET) and trimethoprim-sulfamethoxazole (SXT) remains high, overall trends indicate an alarming rise in AMR against various antibiotics (Fig. 4a). Geographically, AMR is endemic, with some regions in South America, Africa, and Asia reporting over 50% resistance levels. TET and AMP resistance are extremely common, with important area in Southeast Asia, China, and India, where the use of antibiotics in veterinary and human medicine has assisted in spreading resistance. The uneven availability of data shows the need for more surveillance, especially in Africa and South America, where data are scarce (Fig. 4b).

Table 2: Current AMR status of the WHO priority pathogens with BCIs in LICs and LMICs.

Country Income Level	CTAs	BCIs in Bloodstream (pmp)	BCIs in Urinary Tract (pmp)	BCIs in Gastrointestinal Tract (pmp)	Carbapenem-Resistant *Acinetobacter* spp., x/N (%, 95% CI) Source	Carbapenem-Resistant *E. Coli*, X/N (%, 95% CI) Source	Carbapenem-Resistant *Klebsiella pneumoniae*, x/N (%, 95% CI) Source	Fluoroquinolone-Resistant *Salmonella* spp., x/N (%, 95% CI) Source	MRSA, x/N (%, 95% CI) Source	Fluoroquinolone-Resistant *Neisseria gonorrhoeae*, x/N (%, 95% CI) Source
LICs	Burkina Faso	148 (6.6)	2299 (102.1)	94 (4.2)	NA	84/1358 (6.2%; 4.9–7.5), UT	42/336 (12.5%; 9.1–16.5), UT	5/57 (8.8%; 1.4–16.1), GIT	5/7 (71.4%; 29.0–96.3), B	1/18 (5.6%; 5.0–16.1)
	Congo Dem. Republic	581 (5.7)	NA	NA	NA	NA	NA	NA	NA	NA
	Ethiopia	1371 (10.9)	1311 (10.5)	21 (0.2)	77/135 (57.0%; 48.2–65.5), B	20/113 (17.7%; 11.2–26.0), B	67/180 (37.2%; 30.2–44.7), UT	NA	102/165 (61.8%; 54.4–69.2), B	
	Liberia	17 (3.2)	32 (6.0)	3 (0.6)	NA	NA	NA	NA	NA	NA
	Mali	286 (12.4)	487 (21.1)	NA	NA	43/479 (8.9%; 6.6–11.9), UT	13/102 (12.8%; 6.9–20.8), UT	1/66 (1.5%; 1.4–4.5), B	6/44 (13.6%; 3.5–23.8), B	NA
	Mozambique	80 (2.4)	NA	NA	19/40 (47.5%; 31.5–63.9), B	0/14 (0%), B	7/25 (28.0%; 12.1–49.4), B	NA	1/15 (6.7%; 6.0–19.3), B	NA
	Rwanda	101 (7.4)	NA	NA	NA	2/38 (5.3%; 1.8–12.4), B	11/55 (20.0%; 10.4–32.9), B	NA	NA	NA
	Syrian Arab Republic	121 (5.4)	763 (34.0)	1 (0.0)	39/41 (95.1%; 83.5–99.4), B	68/653 (10.4%; 8.2–13.0), UT	39/87 (44.8%; 34.2–55.9), UT	NA	10/34 (29.4%; 14.1–44.7), B	NA
	Yemen	345 (9.0)	59 (1.5)	1980 (51.8)	42/61 (68.9%; 55.7–80.1), B	257/2836 (9.1%; 8.0–10.2), UT	108/366 (29.5%; 24.9–34.5), UT	0/23 (0.0%)	100/107 (93.5%; 88.8–98.1), B	NA
	Uganda	35 (0.7)	124 (2.6)	8 (0.2)	NA	5/187 (2.7%; 0.87–6.13), UT	1/23 (4.4%; 0.1–21.9), UT	NA	NA	42/42 (100%; 100.0–100.0)
LMICs	Bangladesh	129 (0.8)	342 (2.0)	9 (0.1)	NA	22/39 (56.4%; 40.8–72.0), B	6/11 (54.5%; 25.1–84.0), B	1/26 (3.8%; 3.5–11.2), B	NA	NA
	Egypt	383 (3.4)	494 (4.4)	NA	40/50 (80.0%; 66.3–89.9), B	24/61 (39.3%; 27.1–52.7), B	54/78 (69.2%; 57.8–79.2), B	NA	1/1 (100%; 100.0–100.0), B	NA
	United Rep. of Tanzania	2072 (32.0)	2067 (31.9)	NA	80/165 (48.5%; 40.9–56.1), B	56/1264 (4.4%; 3.3–5.6), UT	47/523 (9.0%; 6.5–11.4), UT	0/21 (0.0%), B	439/738 (59.5%; 55.9–63.0), B	NA
	Nepal	2829 (95.2)	12,921 (434.8)	24 (0.8)	274/461 (59.4%; 54.8–63.9), B	657/9226 (7.1%; 6.6–7.7), UT	462/1898 (24.3%; 22.4–26.3), UT	73/125 (58.4%; 49.8–67.0), B	35/42 (83.3%; 72.1–94.6), B	NA
	India	43,929 (30.8)	96,309 (67.6)	26 (0.0)	8632/13,009 (66.4%; 65.5–67.2), B	22,567/131,112 (17.2%; 17.0–17.4), UT	15,043/28,354 (53.05%; 52.5–53.6), UT	1832/3261 (56.1%; 54.4–57.9), B	5071/9245 (54.9%; 53.8–55.9), B	NA

CTA: countries, territories, areas; BCIs: bacteriologically confirmed infections; Pmp: per million population; UT: urinary tract; B: bloodstream; GIT: gastrointestinal tract; x/N: number of resistant isolates/total number of isolates tested; % (95% CI): percentage with 95% confidence interval; N/A: not applicable.

Conversely, Southeast Asia possesses an abundance of data, thereby leading to a lower degree of uncertainty in projections for this region (Fig. 4c). Observed trends highlight the growing AMR crisis in LMICs and underscore the urgent need for global action on surveillance and prevention.

Drivers of the Emergence of AMR and Superbugs: AMR became a global health issue fueled by the interaction of medical, economic, social, and environmental determinants. The dissemination of "superbugs" causes numerous antibiotics ineffective, thereby complicating therapeutic approaches and increasing morbidity and mortality rates on a global scale (Salam *et al.*, 2023). This is driven by a complex array of interlinked factors (Fig. 5) (Endale *et al.*, 2023). One of the primary factors of AMR is the poor access to healthcare and diagnostic services, especially in developing countries (Naser *et al.*, 2024). Most people use empirical treatments because of the expense of medical care and the unavailability of diagnostic facilities, which results in the inappropriate use of antibiotics (Murray *et al.*, 2022). Misdiagnosis and the use of broad-spectrum antibiotics also drive the resistance further (Laxminarayan *et al.*, 2016). An ineffective surveillance and regulation system is one of the key drivers of the emergence of superbugs. Over- the-counter sales of antibiotics without prescriptions are prevalent in most areas, particularly where there is no or

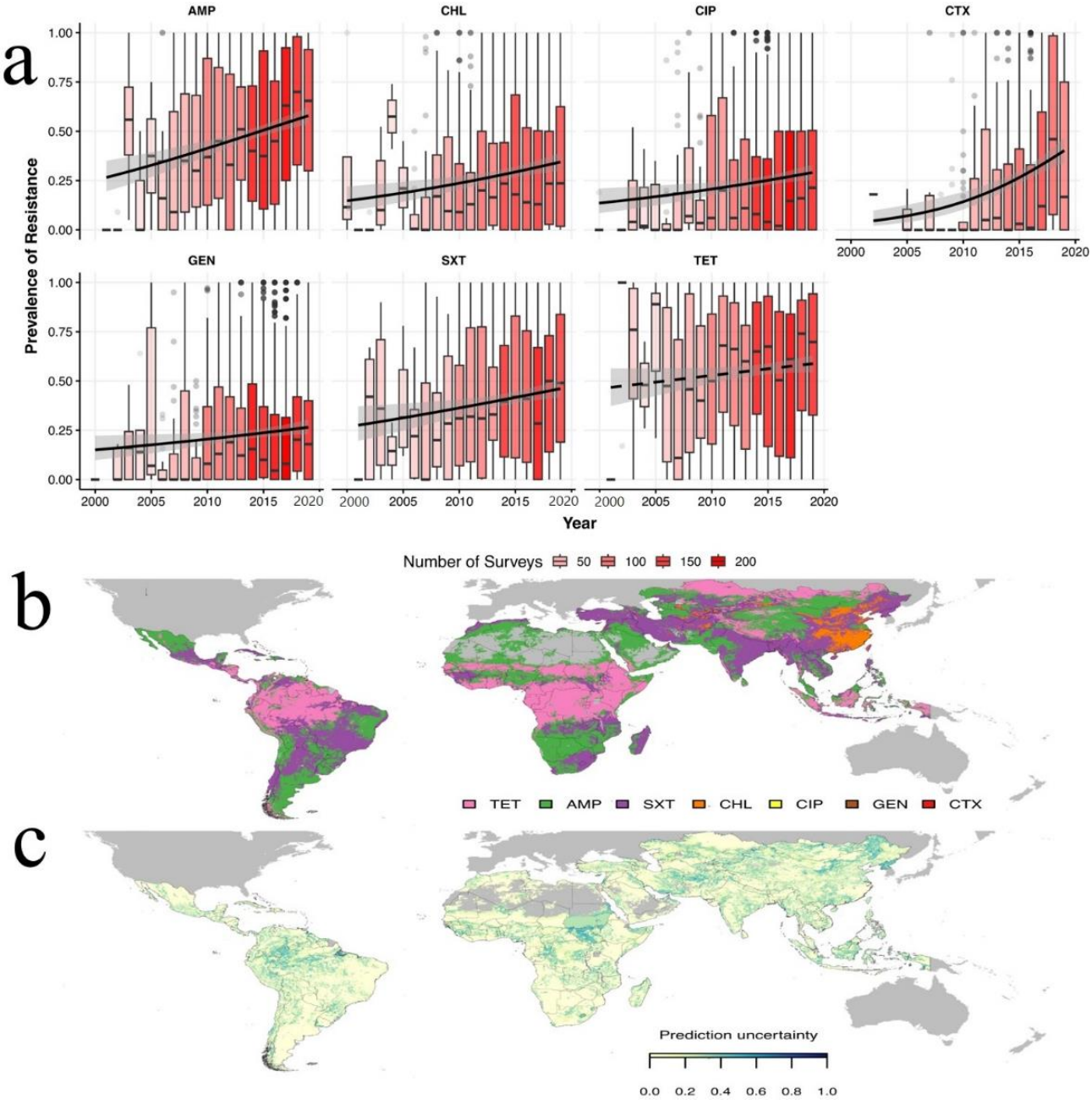

Fig. 4: AMR trends and their distribution in LMICs (a): Twenty-year trends analysis of the prevalence of resistant antimicrobials in LICs and LMICs for ampicillin (AMP), chloramphenicol (CHL), ciprofloxacin (CIP), cefotaxime (CTX), gentamicin (GEN), trimethoprim-sulfamethoxazole (SXT), and tetracycline (TET). (**b**): Geographic distribution of antimicrobials in low- and middle-income countries with a high likelihood of resistance prevalence exceeding 50% in the future (**c**): Estimated uncertainty of the predictions in panel (**b**), arising from the imputation of missing resistance prevalence in the input dataset. Blue shades represent the proportion of Monte Carlo simulations of imputed datasets that produced varying predictions compared to panel (**b**) (Methods). This image is retrieved and modified from Zhao *et al.*, (2024), with appropriate permission.

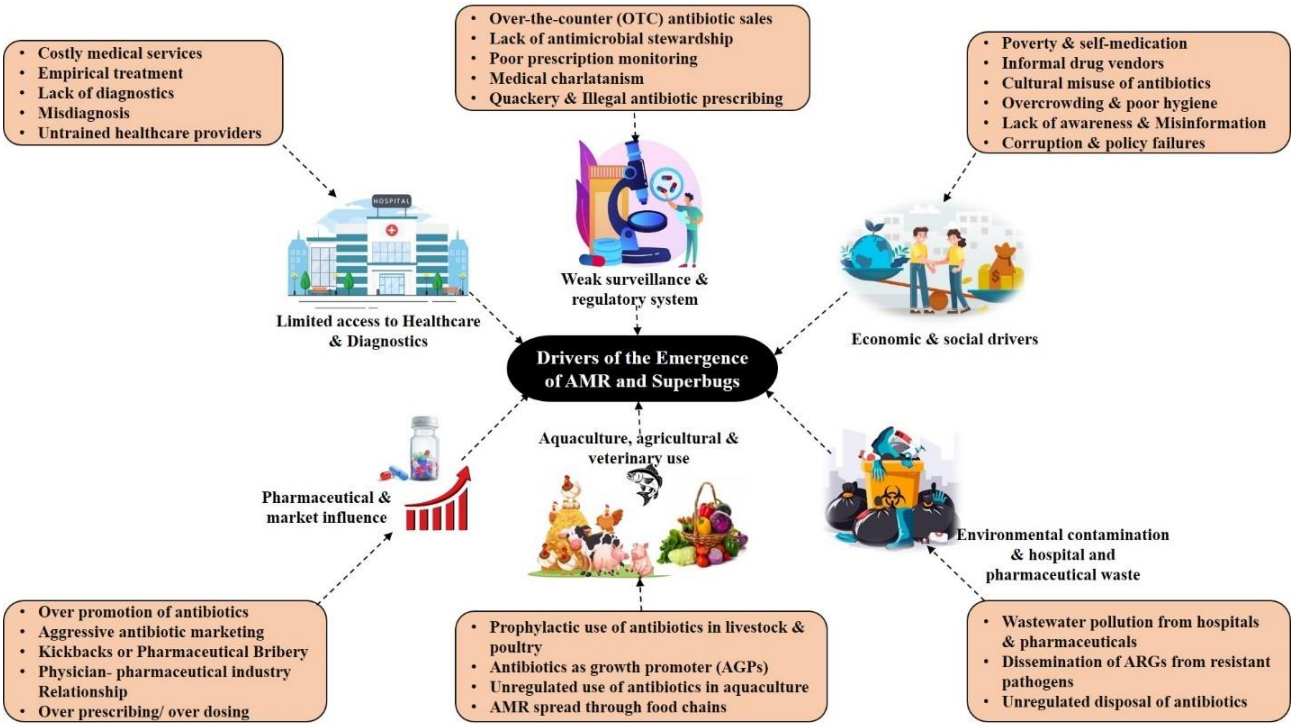

Fig. 5: Probable factors of the emergence of AMR and superbugs in LICs and LMICs.

Table 3: Strengths, weaknesses, opportunities, and threats (SWOT) analysis of AMR alternatives as mitigation strategies.

Strategy	Strength	Weakness	Opportunity	Threat	References
Antibiotic stewardship	Reduces antibiotic misuse, slows resistance development, and improves patient outcomes.	Requires robust infrastructure and significant funding, and faces challenges in both high- and low-resource settings.	Offers potential for nationwide expansion, integration with telemedicine, and incorporation into broader health system strengthening efforts.	Non-compliance among healthcare providers and patients, along with financial incentives driving over-prescription, poses risks.	(Laxminarayan *et al.*, 2013)
Development of new antibiotics	Focuses on high diversity, innovative strategies, and WHO priority pathogens, particularly Gram-negative bacteria.	Faces limited pipeline for novel classes, high scientific barriers, economic disincentives for pharmaceutical companies, and regulatory hurdles.	WHO-led global coordination (e.g., CARB-X, GARDP partnerships) focuses on narrow-spectrum therapies and diagnostics.	Volatility in funding, dependency on public–private partnerships, rapid resistance emergence, regulatory uncertainty, and lack of commercial viability threaten progress.	(Tacconelli *et al.*, 2018; Theuretzbacher *et al.*, 2019)
Immunotherapy	Enhances host immune response, reverses immunosuppression in chronic infections, and combines with antibiotics for synergistic effects.	High cost, complexity, risk of immune-related adverse events, and limited clinical data for bacterial infections are notable weaknesses.	Personalized approaches, such as cytokine modulation and checkpoint inhibitors, show potential for treating antibiotic-resistant infections.	Immune system variability, unintended immune reactions, and bacterial escape mechanisms pose risks.	(Barber *et al.*, 2019; McCulloch, Wells *et al.*, 2022)
Combination therapies	Reduces selection pressure, enhances efficacy through synergistic effects, and delays resistance evolution by requiring multiple mutations.	Risks include drug–drug interactions, increased toxicity, and complexity in dosing and administration.	Integration with One Health approaches and repurposing existing drugs present opportunities.	Pathogens may develop cross-resistance mechanisms, and misuse could still drive resistance.	(Endale *et al.*, 2023)
Phage therapy	Provides natural specificity against bacteria, can be engineered to target resistant strains, and disrupts biofilms.	Narrow host range, complex regulatory requirements, immune response risks, and limited clinical trial data are challenges.	Prophylactic use in agriculture, aquaculture, veterinary medicine, diagnostics, and biocontrol in food safety and environmental decontamination offers opportunities.	Bacterial evolution of phage resistance mechanisms, high costs, logistical challenges, and regulatory hurdles for genetically modified phages threaten adoption.	(Strathdee *et al.*, 2023)
Phage–antibiotic synergy (PAS)	Enhances bacterial eradication through synergistic effects, improves biofilm penetration, reduces antibiotic doses, and	Some antibiotics inhibit phage replication, causing antagonism, and clinical efficacy varies due to host immunity, with long-	Engineered phages targeting resistance genes expand treatments for multidrug-resistant infections.	Emergence of dual resistance, regulatory barriers for phage therapy approval, and toxin release from bacterial lysis pose risks.	(Li *et al.*, 2021)

	delays resistance development.	term safety validation lacking.			
Probiotics and prebiotics	Effective against multidrug-resistant pathogens, enhances immune response, produces antimicrobial substances, and restores gut barrier function.	Variable efficacy depending on strain and host condition, and intrinsic antibiotic resistance in some probiotics raises safety concerns.	Sustainable alternative to antibiotics, reduces antimicrobial resistance, and shows potential in functional foods and combination therapies.	Horizontal gene transfer of antibiotic resistance, insufficient clinical validation, and host-specific dependency are threats.	(Elshaghabee and Rokana, 2022)
Biofilm disruptors	Targets multiple biofilm stages, provides synergistic effects with antibiotics, and includes non-cytotoxic options.	High BIC50 values, limited dispersal activity in preformed biofilms, and potential off-target effects are limitations.	Expanding targets, improved SAR studies, and therapeutic conjugates for targeted delivery offer opportunities.	Biofilm matrix complexity limits penetration, with risks of resistance development, regulatory challenges, and toxicity concerns for some compounds.	(Trebino *et al.*, 2021)
CRISPR-based antimicrobial therapy	Highly specific; uses CRISPR arrays and crRNAs to target and eliminate resistant bacteria via sequence-specific cleavage.	Expensive, requires advanced tools, and needs more in vivo studies to establish therapeutic efficacy.	Potential to revolutionize bacterial treatments by providing genetic memory of infections.	Off-target effects, PAM sequence limitations, and apoptosis induction in some cells are risks.	(Araya *et al.*, 2021; Getahun *et al.*, 2022)
Bacteriocins (antimicrobial peptides from bacteria)	High potency against multidrug-resistant pathogens, non-toxic, biocompatible, selectively targets bacteria, and is amenable to bioengineering for enhanced efficacy.	Low in vivo stability, challenges in large-scale production and purification, and poor oral bioavailability are limitations.	Novel drug delivery systems, combination therapies with antibiotics, and applications in food preservation and safety offer opportunities.	Emergence of bacteriocin-resistant strains, cross-resistance with antibiotics, high production costs, and potential toxicity if used as virulence factors are threats.	(Meade *et al.*, 2020)
Nanotechnology-based antimicrobials	High efficacy against multidrug-resistant pathogens, targeted drug delivery via functionalization, improved drug bioavailability, controlled release, and biocompatibility of lipid-based carriers.	Unclear biocidal mechanisms, potential cytotoxicity, unknown long-term effects, high production costs, scalability challenges, and lack of standardization in studies are limitations.	Combinatorial therapies, multifunctional nanocarriers, and preventive applications (e.g., antiviral coatings, biofilm disruption) offer opportunities.	Environmental risks, regulatory hurdles due to safety uncertainties, and public skepticism about nanotechnology safety are threats.	(Lakshminarayana n *et al.*, 2018)
Vaccine	Vaccines reduce antibiotic use, lowering AMR risk, and reverse vaccinology enables antigen identification without pathogen cultivation.	Long development process, potential for antigenic variation reducing efficacy, and high costs and technical barriers for LMICs are limitations.	Expanding vaccine coverage to priority pathogens, One Health integration, and global distribution partnerships (e.g., COVAX, GAVI) offer opportunities.	Logistical challenges, vaccine hesitancy, and limited protection against evolving bacterial strains are threats.	(Mba *et al.*, 2023)
Monoclonal antibodies	High specificity, low off-target effects, multi-mechanistic action, long half-life, and proven toxin targeting (e.g., bezlotoxumab) are strengths.	Limited FDA approvals, narrow strain/serotype coverage, and limited efficacy against intracellular pathogens/low-abundance antigens are limitations.	Glycosylation to boost stability, mAb-antibiotic combos, and bispecific mAbs for multi-virulence targeting offer opportunities.	Antibiotic resistance complicates targeting, competition from alternatives, and bacterial evolution risks mAb efficacy.	(Vacca *et al.,* 2022)
Antisense oligonucleotides	High specificity for target genes; use of stable analogs; acts as adjuvant enhancing antibiotic efficacy; conjugation with CPPs improves bacterial uptake.	Limited progress in prokaryotes, delivery challenges, and inconsistent activity across bacterial strains/CPPs are limitations.	Targeting diverse resistance mechanisms, novel delivery methods, personalized medicine potential, and combination therapies to extend antibiotic lifespan offer opportunities.	Emergence of bacterial resistance, regulatory/complexity hurdles, high development costs/time, and off-target effects in hosts are threats.	(Jani *et al.*, 2021)
Lysins	High specificity, rapid lysis, low resistance risk, and being effective against multidrug-resistant pathogens are strengths.	Requires permeabilizers for Gram-negative bacteria and has a narrow host range for some variants.	Engineering modular endolysins to broaden spectrum and synergy with antibiotics offer opportunities.	Emergence of rare resistance and immunogenicity concerns in systemic use are threats.	(Rahman *et al.*, 2021)
Fecal microbiota transplant (FMT)	Effective for recurrent Clostridium difficile infection, shows potential for treating various gastrointestinal diseases (e.g., ulcerative colitis, Crohn's disease, IBS), and restores gut microbiota diversity.	Lack of standardized protocols, donor selection criteria, potential risk of pathogen transmission, and variability in patient response are limitations.	Expansion into conditions beyond GI diseases, development of synthetic microbiota-based therapies, and increasing public and scientific interest in microbiome research offer opportunities.	Risk of adverse effects, limited long-term safety data, and resistance to acceptance due to stigma and public perception are threats.	(Tkach *et al.*, 2022)

minimal regulatory oversight. Lack of antimicrobial stewardship programs coupled with insufficient prescription monitoring results in the inappropriate use of antibiotics. Issues of medical fraud, illicit prescribing of antibiotics, and weak enforcement of pharmaceutical regulations further worsen the situation (Salam *et al.*, 2023).

Poverty, self-medication, and lack of information are key economic and social determinants promoting AMR. Due to high costs of healthcare in the majority of developing nations, people practice self-medication. Unauthorized drug sellers would typically provide antibiotics without any guidance, leading to inappropriate dosages and insufficient courses of treatment (Ocan *et al.*, 2015). The cultural misuse of antibiotics as well as the absence of awareness also stimulates resistance. Overcrowding and poor hygiene offer fertile ground for the spread of resistant pathogens. Corruption and policy failure compromise effective AMR containment interventions, particularly in healthcare systems plagued by weak governance (Laxminarayan *et al.*, 2013). The pharmaceutical and market sector also play a major role in the emergence of AMR. Excess prescription of antibiotics is often due to the intensive marketing of antibiotics by pharmaceutical firms, along with financial incentives for healthcare providers (Hoffman *et al.*, 2015). Pharmaceutical corruption and unethical physician–industry relationships also enhance the overuse of antibiotics. Over marketing of antibiotics, particularly in LMICs, has been linked to their high usage in human and veterinary medicine (Sumpradit *et al.*, 2012). The widespread use of antibiotics in agriculture, aquaculture, and veterinary medicine is another key driver of AMR. The prophylactic use of antibiotics as growth promoters in animals and poultry, coupled with the absence of control over antibiotic use in aquaculture, has facilitated the spread of resistance genes along the food chain (Manyi-Loh *et al.*, 2018). The transmission of resistant bacterial strains from animals to humans through food ingestion and environmental exposure has been well documented in the literature (Marshall and Levy, 2011).

Environmental pollution and clinical waste are significant factors in the perpetuation and spread of resistance genes (Naser *et al.*, 2024). Wastewater from healthcare and pharmaceutical facilities frequently has high levels of antibiotics, thereby exerting selective pressure on resistant bacterial populations (Begum *et al.*, 2024). Unregulated release of antibiotics into the environment also increases the development of AMR by facilitating horizontal gene transfer among various bacterial populations (Berendonk *et al.*, 2015).

To combat the AMR problem involves a complex process with multiple components, such as stringent control over antibiotic distribution, better access to health services, increased public awareness, and international cooperation on monitoring and stewardship programs. Antimicrobial stewardship in human and veterinary medicine must be reinforced, and investment in novel therapeutic approaches is required to prevent the risk of AMR and resistant pathogens (O'Neill, 2016).

The COVID-19 Pandemic as a Catalyst for AMR: The COVID-19 pandemic further intensified the global AMR crisis, particularly in low- and middle-income countries, by catalyzing the overuse and misuse of antibiotics (Mahadi, 2021). Despite being a viral disease, a significant proportion of COVID-19 patients especially those hospitalized were empirically treated with broad-spectrum antibiotics such as azithromycin, ceftriaxone, and meropenem to prevent or manage suspected secondary bacterial infections (Langford *et al.*, 2021). However, studies revealed that actual bacterial co-infections were uncommon, and this widespread inappropriate use of antibiotics contributed significantly to the selection pressure on microbial populations (Rawson *et al.*, 2020). The urgency of the pandemic response, lack of proper diagnostic infrastructure, and the fear of missing bacterial co-infections led to prophylactic antibiotic prescribing without confirmation of bacterial involvement.

In LMICs, disrupted healthcare systems, weak antimicrobial stewardship, and panic-driven self-medication during lockdowns made the situation worse. The over-the-counter availability of antibiotics, including those used in COVID-19 management protocols, such as doxycycline and azithromycin, led to irrational use in the community setting (Boccabella *et al.*, 2024). Additionally, misinformation spread via social media and informal health advice promoted unregulated use of antimicrobial agents for COVID-19 prevention and treatment.

Moreover, the pandemic hindered ongoing AMR surveillance, delayed stewardship interventions, and diverted public health resources away from AMR programs. This disruption of regulatory oversight allowed for increased circulation of substandard and counterfeit antimicrobials, further increasing resistance. Waste from overwhelmed healthcare facilities, including antibiotics and disinfectants, also contributed to increased environmental contamination, creating ideal conditions for horizontal gene transfer and evolution of resistant strains (Seneghini *et al.*, 2022).

Post-pandemic data indicate a notable surge in multidrug-resistant organisms (MDROs) such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, especially in intensive care settings where antibiotics were heavily used during COVID-19 waves (Hsu, 2020). The intersection of COVID-19 and AMR highlights the urgent need for integrated pandemic preparedness strategies that emphasize rational antimicrobial use, improved diagnostic capacity, and reinforcement of AMR surveillance systems.

Genetic Drivers of the Emergence of AMR and Superbugs: The genetic drivers contributed to the emergence of AMR and superbugs in addition to the socio-economic, environmental, and healthcare-associated causes in LMICs. The commensals are becoming pathogenic due to the virulent and resistant genes received by horizontal gene transfer (HGT). This transfer may be facilitated by mobile genetic elements (MGEs) such as plasmids, transposons, integrons, and gene cassettes (Waddington *et al.*, 2022). These MGEs (*IncFIB*, *IncFII*, and *IncX3* plasmids) can harbor multiple resistance determinants, enabling the co-selection of multidrug resistance traits when expose to even a single antimicrobial agent. The integrons can disseminate resistance genes like *bla*, *aac*, *sul*, and *tet* to *β*-lactams, aminoglycosides,

sulfonamides, and tetracyclines, respectively (Wang *et al.*, 2024). The high pathogen load is commonly found high in human, animal, and environmental settings in LMICs, and poor antibiotic stewardship favors and occurs in genetic recombination and selection of resistant clones.

Antibiotic use is comparatively found to be higher and irrational in LMICs than in low-income countries, which causes selective pressure on antibiotics. Due to the selective pressure, bacterial mutations occur and enhance bacterial susceptibility to environmental stress (McVicker *et al.*, 2014). Under high bacterial load, the chromosomal integration of resistance genes makes it suitable to adapt them in severe conditions and for them to be hereditary from generation to generation (Liao *et al.*, 2025).

Additionally, clonal expansion of highly resistant lineages such as *Escherichia coli* ST131, *Klebsiella pneumoniae* ST258, and *Staphylococcus aureus* ST239 has been increasingly reported in LMICs, suggesting the genetic adaptation and successful global spread of these superbug lineages (Mathers *et al.*, 2015). Furthermore, sub-inhibitory concentrations of antibiotics in hospital and agricultural waste streams promote mutagenesis and activation of stress response pathways (e.g., SOS response), enhancing genetic plasticity and resistance evolution (Wang *et al.*, 2010). When coupled with environmental and behavioral drivers, these genetic mechanisms accelerate AMR's emergence and persistence in LICs and LMICs.

The One Health Perspective of Global and Regional Impact of AMR: AMR is one of the most pressing threats to global health, food safety, and economic security. AMR is complicated crisis in humans, animals, and the environment with enormous consequences for LMICs whose healthcare infrastructure, regulatory framework, and sanitation infrastructure are not yet strong.

The Human Cost of AMR: A Looming Global Catastrophe: The human cost of AMR is alarming with 39 million predicted deaths between 2025 and 2050, which amounts to 1.91 million deaths annually or one every 20 s due to antimicrobial-resistant infections (Naghavi *et al.*, 2024). In LMICs, as a result of the consequent unavailability of effective interventions, the issue is considered more intensely. BSIs (bloodstream infections) and GIT (gastrointestinal tract)-related BCIs (bacteriologically confirmed infections) caused by drug-resistant organisms have increased sharply, adding a 58% rise in mortality in the affected regions. The financial impact on the healthcare system is similarly alarming. AMR-related bloodstream infections alone cause direct medical expenses of up to USD 12,000 per patient (de Kraker, 2023), a cost that is financially devastating to healthcare facilities in low-resource settings. The total health expenditure due to AMR may cross USD 1 trillion by the year 2050, further widening inequities in access to critical medical care and placing additional stress on already strained health systems. Additionally, 99.65 percent of all deaths from AMR in children under five years occur in LICs and LMICs (Murray *et al.*, 2022).

The Agricultural Crisis: AMR's Devastating Effect on Livestock and Food Security: The animal sector is one of the main reasons in the AMR problem, as an estimated 73% of total antimicrobials sold globally are utilized in food-producing animals (Mulchandani *et al.*, 2023). Excessive and in most instances uncontrolled use of antibiotics, particularly in LMICs where over-the-counter sales still occur, hastens the emergence of resistant bacterial populations (Liza *et al.*, 2024). Its effects reach beyond animal health to rising mortality rates, reduced productivity of livestock, and unjustified culling with a direct impact on farmers' incomes (Salam *et al.*, 2023).

The economic impact to the agricultural sector is substantial. More than half of all antibiotics are consumed worldwide in the food and livestock industries, and by 2030, antibiotics in agriculture are expected to rise by 50% (Rawson *et al.*, 2020). GDP losses annually could be as high as USD 575 billion by 2050 if AMR in food-producing animals is not addressed, and the number of food-insecure individuals would rise to 746 million individuals globally. At worst, the figure would be 2 billion individuals, and the total GDP losses would be USD 953 billion. Animal-to-human transmitted resistant infections would cost the world between an additional USD 1.1 trillion to USD 5.2 trillion in lost GDP by 2050, and tighter controls on the use of antibiotics on farms are necessary (Nelson *et al.*, 2019).

The Environmental impact: A Silent Driver of AMR Propagation: The environmental aspect of AMR is under-investigated but very much a critical driver of resistance spread. Global antibiotic consumption has been steadily increasing, reaching as high as 67.68 defined daily doses (DDD) per 1000 inhabitants per day in Iran. This excessive usage has contributed to widespread environmental contamination including water bodies, soil, and the atmosphere with antimicrobial-resistant microorganisms. LMICs are particularly vulnerable to enhanced risk due to inefficient waste management strategies, weak regulatory frameworks, and high population density. The economic cost of environmental degradation caused by AMR is estimated to be disastrous. By 2030, the annual GDP losses resulting from AMR-induced environmental degradation would range from USD 1 trillion to USD 3.4 trillion, a share that would predominantly fall on LMICs (Murray *et al.*, 2022). The lack of appropriate wastewater treatment facilities, coupled with the uncontrolled disposal of pharmaceutical and agricultural waste, has promoted the pollution of the ecosystems with a fertile breeding ground for the emergence of resistance genes that become readily transmitted within humans, animals, and the environment.

AMR has the potential to destroy global health systems, destabilize food security, and trigger an economic downturn with financial losses reaching into the trillions. A unified One Health approach can make the interconnectedness of human, animal, and environmental health to fight against AMR.

Mitigation Strategies: SWOT Analysis of Antimicrobial Alternatives: AMR in LMICs poses a major challenge due to the inappropriate use of antibiotics, poor healthcare infrastructure, and the limited availability of alternative treatments (Sharma *et al.*, 2022). Resolving this crisis demands creative, low-cost, and scalable solutions that do not rely on conventional antibiotics. Alternative

antimicrobials offer a sustainable solution to combat AMR, though they often come with certain limitations, threats and challenges (Table 3).

AMR is a growing concern. Unlike broad-spectrum antibiotics, phages specifically attack harmful bacteria while preserving beneficial microbiota and can disrupt biofilms, making them useful against resistant infections. However, limited regulatory frameworks, high production costs, and infrastructure challenges hinder widespread adoption in LMICs. Despite these barriers, phage therapy has significant potential in agriculture and veterinary medicine, helping reduce antibiotic overuse in livestock and aquaculture. A key challenge is bacterial resistance to phages, requiring ongoing research and the development of new phage strain.

The success of phage therapy in LMICs depends on cost-effective production, regulatory support, and public awareness, making global collaboration essential for its sustainable implementation.

Probiotics and prebiotics offer an inexpensive and sustainable way to enhance gut microbiota, prevent infections, and reduce dependence on antibiotics (Hossain *et al.*, 2025). In LMICs, incorporating probiotics into food and nutrition programs could significantly improve public health. However, challenges such as variations among probiotic strains and the risk of horizontal gene transfer could contribute to AMR. One of the most notable advantages of probiotics and prebiotics is their affordability, along with their ability to improve gut health and lower AMR (Waddington *et al.*, 2022). However, their effectiveness depends on the specific strain, and there is a risk of transferring resistance genes. Despite these challenges, there is an opportunity to integrate probiotics into local diets and traditional fermented foods, making them more accessible to communities.

The greatest concern lies in the limited clinical research on their long-term effects, as well as the potential risks of overuse, which could lead to unintended health consequences (Ji *et al.*, 2023).

Immunization is a long-term solution to the mitigation of AMR since it decreases the prevalence of infectious diseases, and therefore antibiotics will be needed less. But where there are limited resources, vaccine deployment is challenging, owing to increased initial costs, lower access to healthcare, and challenges in keeping vaccines in a healthy condition of storage. Vaccination is clearly a good thing. It can discourage the abuse of antibiotics, prove cost-effective in the long term, and stave off illness. The vaccine against Human Papillomavirus (HPV) caused a dramatic downturn in cervical cancer and its procedure. Yet, the upfront costs to develop and provide vaccines, especially to developing countries, are the concern (Jit *et al.*, 2021). Additionally, logistic challenges such as maintaining the cold chain for vaccines against diseases like polio, make it more difficult for them to be used more heavily in these parts of the world. There are places where broader access to infectious disease vaccines and better global coordination, including initiatives like the Global Fund's initiative against diseases like malaria and HIV, can occur (Tan *et al.*, 2003). Nonetheless, issues such as refusal of vaccines, as some have observed in terms of people not accepting the vaccine for COVID-19, and evolving germs, which tend to be stronger than vaccines we currently have, are issues that require solution as we try to take advantage of the power of vaccination in combatting AMR (Troiano and Nardi, 2021).

Bacteriocins are antimicrobial peptides from bacteria that are selectively against compete with bacterial strains. Bacteriocins have shown tremendous potential in fighting multidrug-resistant infections and can be genetically modified to make them more stable and potent (Asha *et al.*, 2024). The issues with their production at the industrial level, purification problems, and likelihood of developing resistance also demand ongoing research (Simons *et al.*, 2020). Since these concerns are now being tackled, bacteriocins will become an acceptable alternative to traditional antibiotics. Nanotechnology provides novel antimicrobial technologies, such as nanoparticles with improved antibacterial activity and drug delivery systems designed for maximum bioavailability and specificity. Such technologies have proven to be effective against antibiotic-resistant infections and biofilms but are difficult in terms of production cost, safety, and long-term environmental sustainability (Hetta *et al.*, 2023). Although current limitations on their use widely in LMICs are present, further research on inexpensive and easy-to-use nanotechnology-based antimicrobials can render further applications a possibility in the future. Monoclonal antibodies have emerged as a next-generation therapeutic avenue with extremely high specificity against bacterial pathogens. Their long half-life and neutralization activity of bacterial toxins provide a clear edge over conventional antibiotics. However, issues like limited regulatory approvals, prohibitively high production costs, and reduced activity against intracellular bacteria remain (Singh *et al.*, 2023). Further investment in research in biopharmaceuticals and establishing local production in the LMICs could help make it available to more people.

Bacterial biofilms pose a major challenge to infections treatment since they enhance biofilm antimicrobial resistance. Biofilm disruptors work by preventing the formation of biofilms or breaking down the biofilm matrix to enable drug penetration. These factors are encouraging, although with drawbacks such as inefficacy against mature biofilms and cytotoxicity, prior to their extensive application (Mishra *et al.*, 2023). The combination of existing antimicrobials with biofilm disruptors can make them more effective and thus suitable for use in LMICs where biofilm infections are common.

Phage therapy presents a promising alternative to antibiotics, particularly in veterinary medicine, where antimicrobial resistance is a growing concern. Its application in poultry and livestock has demonstrated efficacy in controlling bacterial infections, reducing antibiotic dependence, and improving animal health (Loponte *et al.*, 2021). However, feasibility in low-resource settings requires cost–benefit analysis, considering infrastructure needs for phage production, storage, and administration. Studies highlight challenges such as regulatory frameworks and scalability (Liang *et al.*, 2023). Addressing these factors can enhance phage therapy's viability as a sustainable solution in veterinary medicine, mitigating AMR while ensuring economic feasibility in LMICs.

Combination of several antimicrobial agents, such as antibiotics, phages, and other bioactive substances, may enhance efficacy and suppress the development of resistance. Synergy between phages and antibiotics (PAS) was observed to enhance bactericidal effects and penetration of biofilms and decrease the use of antibiotic required (Akturk *et al.*, 2023). Certain antibiotics also suppress phage bioactivity, and dual resistance has to be contemplated. Optimization of combination regimens through careful design may help to achieve their maximal advantages in LMICs. Fecal microbiota transplantation (FMT) is a method of transferring normal gut microbiota from healthy donors to diseased patients with conditions such as recurrent *Clostridium difficile* infection (CDI). It has been effective in the reconstitution of gut microbiota diversity and in the reduction of antibiotic usage. However, donor screening issues, the possibility of transmission of pathogens, and variability in patient response are some problems that plague its routine use (Davidovics *et al.*, 2019). Standardization of FMT protocols and the development of synthetic microbiota-based drugs could facilitate its use in LMICs.

Fighting AMR in LMICs requires that the issue is tackled with a multi-faceted approach beyond traditional antibiotics. Other alternatives such as phage therapy, probiotics, antimicrobials based on nanotechnology, vaccines, monoclonal antibodies, and gene-based therapy are exciting avenues towards minimizing antibiotic dependency and resistance. However, each of these necessitates some issues such as high cost, regulatory difficulties, and feasibility barriers. Cooperation among governments, research centers, and global health agencies is extremely crucial in driving these alternatives to manage AMR in an effective manner.

Conclusions: Antimicrobial resistance has become a global crisis, disproportionately affecting LICs and LMICs due to inadequate healthcare infrastructure, poor surveillance, and excessive antimicrobial use. The emergence of MDR and PDR superbugs, including critical WHO-listed pathogens, has escalated morbidity, mortality, and economic burdens. AMR impacts human, animal, and environmental health, disrupting medical advancements and increasing healthcare costs. Post-COVID-19 AMC has surged, intensifying resistance risks. The GLASS 2024 highlights gaps in AMR monitoring, emphasizing the urgent need for antimicrobial stewardship, strengthened regulations, and innovative alternatives. A One Health approach integrating sustainable interventions, surveillance expansion, and global cooperation is essential to mitigate AMR's growing threat. Without immediate action, AMR will continue to compromise global health security, leading to an impending public health catastrophe.

Author Contributions: Conceptualization, HH, MSRC, and MMR (Md Mahfujur Rahman); methodology, HH, MSRC, SSK, MNR, ASN, SA, TA, and KAB, software, HH and MSRC; formal analysis, HH, MSRC, SSK, MNR, ASN, SA, TA, KAB, MI, DKC, FSP, and MMR (Md Mahfujur Rahman); investigation, HH, MSRC, and MMR (Md Mahfujur Rahman); resources, MMR (Md Masudur Rahman) and MMR (Md Mahfujur Rahman); data curation, HH, MSRC, SSK, MNR, ASN, SA, TA, KAB, MI, DKC, FSP, and MMR (Md Mahfujur Rahman); writing—original draft preparation, HH, MSRC, SSK, MNR, ASN, SA, TA, KAB, MI, DKC, FSP, and MMR (Md Mahfujur Rahman), writing—review and editing, HH, MSRC, KSA, MMR (Md Masudur Rahman), and MMR (Md Mahfujur Rahman); validation, KSA, MMR (Md Masudur Rahman), and MMR (Md Mahfujur Rahman); visualization, KSA and MMR (Md Mahfujur Rahman); supervision, MMR (Md Masudur Rahman) and MMR (Md Mahfujur Rahman); project administration, MMR (Md Mahfujur Rahman). All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The original contributions presented in this study are included in the article/ Supplementary Material. Further inquiries can be directed to the corresponding author.

Acknowledgments: During the preparation of this manuscript, the author(s) used Origin 2024b, GraphPad Prism 8.4, BioRender and ArcMap 10.8 for generating the figures. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Competing Interest: The authors declare no conflicts of interest.

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