GLOBAL INFECTIOUS DISEASE & PUBLIC HEALTH | NARRATIVE REVIEW

The Silent Pandemic: Antimicrobial Resistance as an Existential Threat to Global Health — Epidemiology, Mechanisms, Clinical Consequences, and a Multisectoral Roadmap for Containment

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ABSTRACT

Background: Antimicrobial resistance (AMR) has emerged as one of the most consequential and complex threats to global public health in the twenty-first century. In 2019, AMR was directly responsible for an estimated 1.27 million deaths globally and contributed to a further 4.95 million deaths — figures that are projected to rise to 10 million annual deaths by 2050 if current trajectories persist unchecked. Unlike conventional pandemics, AMR constitutes a slow-moving but inexorable crisis that erodes the efficacy of the antimicrobial arsenal underpinning modern medicine, threatening not only the treatment of infectious diseases but the viability of surgery, organ transplantation, cancer chemotherapy, and neonatal care. Objective: This narrative review comprehensively synthesizes the current epidemiology of AMR, delineates the principal molecular and ecological mechanisms driving resistance emergence and dissemination, examines the clinical and economic consequences across key pathogen-drug combinations designated as critical priorities by the World Health Organization (WHO), evaluates the current pipeline of novel antimicrobial agents and non-antibiotic therapeutic strategies, and proposes a multisectoral, One Health-aligned roadmap for AMR containment. Methods: A structured literature search was conducted across MEDLINE, EMBASE, and the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) database, encompassing primary research, systematic reviews, meta-analyses, and policy documents published between 2015 and 2025. Priority was given to high-quality epidemiological data from geographically diverse settings and to clinical trial evidence for emerging therapeutic strategies. Key Findings: AMR disproportionately affects low- and middle-income countries (LMICs) due to inadequate infection prevention infrastructure, unregulated antimicrobial access, and constrained diagnostic capacity. The ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.) — alongside Mycobacterium tuberculosis — constitute the most clinically critical resistant organisms globally. The

antimicrobial development pipeline, while marginally improving, remains critically underfunded relative to the scale of need. Phage therapy, microbiome-based strategies, and antivirulence compounds represent promising but pre-commercial adjuncts to conventional antimicrobials. Conclusions: Containing AMR requires a paradigm shift from reactive clinical management to proactive, integrated, cross-sectoral action spanning human health, veterinary medicine, agriculture, and environmental stewardship. Implementation of national AMR action plans with dedicated funding, universal access to diagnostics, stewardship programs scaled to LMIC contexts, and a reformed global antibiotic development incentive structure are non-negotiable prerequisites for reversing current trends.

Keywords: *antimicrobial resistance, AMR, ESKAPE pathogens, antibiotic stewardship, One Health, phage therapy, drug-resistant tuberculosis, beta-lactamase, global health policy, GLASS surveillance*

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1. INTRODUCTION

In 1928, Alexander Fleming's discovery of penicillin inaugurated what many historians of medicine regard as the most transformative revolution in therapeutic history. Within three decades, the introduction of sulfonamides, streptomycin, chloramphenicol, tetracyclines, and cephalosporins had rendered previously fatal bacterial infections reliably curable, dramatically reducing infectious disease mortality across the industrialized world. Fleming himself, in his Nobel Prize acceptance lecture in 1945, sounded what would prove to be a prescient warning: the misuse of penicillin could select for resistant organisms, rendering the antibiotic useless. Eight decades later, that warning has crystallized into a global health emergency of profound dimensions.

Antimicrobial resistance — the capacity of microorganisms to survive and replicate in the presence of antimicrobial agents that would ordinarily inhibit or kill them — is a natural evolutionary phenomenon that has been dramatically accelerated by human activity. The overuse and misuse of antibiotics in human medicine, the massive prophylactic and growth-promotional use of antibiotics in livestock agriculture, the release of antimicrobial compounds into aquatic and terrestrial environments through pharmaceutical manufacturing effluents, and the global mobility of humans, animals, and food products have collectively created conditions for the unprecedented selection, amplification, and international dissemination of resistant organisms and resistance genes.

The scale of the crisis is documented in sobering quantitative terms. The landmark 2022 Global Burden of Antimicrobial Resistance (GRAM) study, published in The Lancet, estimated that in 2019 alone, 1.27 million deaths were directly attributable to bacterial AMR — exceeding the mortality from HIV/AIDS (864,000 deaths) and malaria (643,000 deaths) in the same year. An additional 4.95 million deaths were associated with AMR, meaning that resistant infections contributed to — though were not the sole cause of — these deaths. Sub-Saharan Africa and South Asia bore the greatest burden, with age-standardized mortality rates from AMR several-fold higher than in high-income regions. Projections by the O'Neill Commission, the WHO, and independent modeling groups converge on an estimate of 10 million annual AMR-attributable deaths by 2050 under a business-as-usual scenario, accompanied by cumulative global economic losses of USD 100 trillion.

The consequences of AMR extend beyond mortality statistics. Resistance erodes the antibiotic safety net that enables the entire edifice of modern clinical medicine. Surgical site infections, hospital-acquired pneumonias, bloodstream infections in immunocompromised

patients receiving chemotherapy, and infections in neonatal intensive care units — all of which are managed with the expectation of effective empirical antibiotic therapy — become increasingly difficult or impossible to treat as resistance spreads. The clinical implications are not future projections but present-day realities in many healthcare systems, particularly in LMICs where last-resort antibiotics are often inaccessible and diagnostic capacity for resistance detection is severely limited.

This narrative review was conceived as a comprehensive synthesis of the AMR challenge in its full complexity — spanning the molecular biology of resistance mechanisms, the epidemiology of critical resistant pathogens, the clinical consequences for healthcare systems globally, the state of the antimicrobial therapeutic pipeline, and the policy architecture required to mount an effective coordinated global response. It is intended to serve clinicians, researchers, public health practitioners, and policymakers who require an integrated understanding of AMR as both a biomedical and a governance challenge.

2. EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE

2.1 Global Burden and Geographic Distribution

The GRAM study — based on systematic analysis of 471 million individual records and 7,585 study-years of primary data from 204 countries — remains the most comprehensive quantitative estimate of the global AMR burden. The five leading pathogen-drug combinations responsible for AMR-attributable deaths in 2019 were: (1) fluoroquinolone-resistant Escherichia coli (lower respiratory and bloodstream infections); (2) third-generation cephalosporin-resistant Klebsiella pneumoniae (bloodstream infections and neonatal sepsis); (3) carbapenem-resistant Acinetobacter baumannii (hospital-acquired pneumonia and ventilator-associated infections); (4) methicillin-resistant Staphylococcus aureus (MRSA, skin, soft tissue, and bloodstream infections); and (5) fluoroquinolone-resistant E. coli (urinary tract infections causing secondary sepsis). Collectively, lower respiratory tract infections and bloodstream infections — the two syndromes associated with highest mortality — accounted for 78.8% of all AMR-attributable deaths.

Geographic disparities in AMR burden are stark. Western sub-Saharan Africa had the highest age-standardized AMR-attributable mortality rate globally at 27.3 deaths per 100,000 population, compared with 6.5 per 100,000 in high-income North America and 5.0 per 100,000 in Western Europe. These disparities reflect differences not only in resistance prevalence but in underlying infection rates, healthcare access, infection prevention infrastructure, and availability of effective antibiotics for treatment. Paradoxically, some LMICs face the dual challenge of inadequate access to first-line antibiotics for treatable infections alongside rapidly rising rates of resistance to those same antibiotics — an equity paradox that standard AMR narratives focused on overuse in high-income settings fail to fully capture.

Table 1. WHO Priority Pathogen List — Critical Priority Category (2024 Update)

Pathogen	Key Resistance Pattern	Primary Clinical Syndrome	Attributable Deaths (2019, est.)	Available Last-Resort Agents
Acinetobacter baumannii	Carbapenem-resistant (CRAB)	HAP, VAP, BSI	~105,000	Cefiderocol, sulbactam-durlobactam
Pseudomonas aeruginosa	Carbapenem-resistant (CRPA)	HAP, BSI, UTI	~92,000	Ceftazidime-avibactam, cefiderocol

Pathogen	Key Resistance Pattern	Primary Clinical Syndrome	Attributable Deaths (2019, est.)	Available Last-Resort Agents
Enterobacterales (ESBL/KPC)	3GC/carbapenem-resistant	BSI, UTI, IAI	~240,000	Meropenem-vaborbactam, imipenem-relebactam
Klebsiella pneumoniae (NDM)	Metallo-β-lactamase producing	BSI, neonatal sepsis	~130,000	Ceftazidime-avibactam + aztreonam
M. tuberculosis (XDR-TB)	Rifampicin + fluoroquinolone resistant	Pulmonary, extrapulmonary TB	~190,000	Bedaquiline, pretomanid, linezolid (BPaL)
Staphylococcus aureus (MRSA)	Methicillin-resistant	BSI, SSTI, pneumonia	~150,000	Vancomycin, daptomycin, ceftaroline

HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; BSI = bloodstream infection; UTI = urinary tract infection; IAI = intra-abdominal infection; SSTI = skin and soft tissue infection; 3GC = third-generation cephalosporins; XDR-TB = extensively drug-resistant tuberculosis. Death estimates from GRAM 2022 (Murray et al., Lancet 2022).

2.2 Surveillance Systems and Data Gaps

The WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS), established in 2015, now encompasses 127 participating countries and represents the most ambitious standardized global AMR surveillance initiative to date. GLASS collects data on resistance in priority pathogens causing bloodstream infections, urinary tract infections, gonorrhea, and — more recently — food-borne illness and hospital-acquired infections. Despite this expansion, critical surveillance gaps persist: fewer than 40% of GLASS-enrolled countries meet quality standards for nationally representative data; surveillance capacity in sub-Saharan Africa, Southeast Asia, and the Pacific Islands remains severely limited; and existing systems capture hospital-based clinical isolates while providing minimal data on community-acquired resistance, agricultural reservoirs, and environmental resistance gene pools. The ReAct-commissioned analysis of GLASS 2023 data identified that resistance proportions reported by LMICs were on average 2.3-fold higher than those from high-income countries for equivalent pathogen-drug combinations, underscoring that the global resistance burden is systematically underestimated when surveillance is concentrated in well-resourced settings.

3. MOLECULAR MECHANISMS OF RESISTANCE

3.1 Intrinsic, Acquired, and Adaptive Resistance

Bacterial resistance to antimicrobials is classifiable into three broad categories. Intrinsic resistance denotes inherent structural or physiological characteristics of a bacterial species that render it naturally insensitive to certain antimicrobials — exemplified by the outer membrane impermeability of Gram-negative bacteria to many agents effective against Gram-positives, or the absence of a peptidoglycan cell wall in Mycoplasma spp. rendering them unresponsive to beta-lactams. Acquired resistance arises from genetic changes — mutations in chromosomal genes, or acquisition of exogenous resistance determinants via horizontal gene transfer (HGT) — that confer resistance in organisms previously susceptible. Adaptive resistance represents transient, phenotypic alterations in response to antibiotic exposure (such as biofilm formation or metabolic dormancy) that are not heritably fixed but substantially reduce killing efficacy.

3.2 Horizontal Gene Transfer and Mobile Genetic Elements

Horizontal gene transfer — the movement of genetic material between bacteria outside of reproduction — represents the primary engine of clinically relevant resistance dissemination. The three principal mechanisms are: (1) conjugation, in which plasmids or integrating conjugative elements (ICEs) are transferred through direct cell-to-cell contact via pili or membrane fusion channels; (2) transduction, where bacteriophages inadvertently package and transfer bacterial DNA including resistance genes; and (3) transformation, in which bacteria take up naked DNA from the environment. Of these, conjugation is quantitatively dominant and most clinically important, as plasmids can transfer between phylogenetically distant bacteria — including between Gram-positive and Gram-negative organisms — and a single plasmid may carry multiple resistance genes, co-selecting for multi-drug resistance when any single antibiotic is applied.

Mobile genetic elements — including plasmids, transposons, integrons, and genomic islands — serve as vehicles for resistance gene accumulation and dissemination. Class 1 integrons, which capture and express gene cassettes encoding resistance determinants, have been identified as particularly important in clinical settings and are commonly associated with resistance to aminoglycosides, sulfonamides, and trimethoprim. The mcr gene family, conferring plasmid-mediated colistin resistance, represents one of the most alarming recent examples of HGT-mediated resistance emergence: first identified in China in 2015, mcr-1 had spread to 51 countries within two years of its discovery, demonstrating the extraordinary velocity of global resistance gene dissemination.

3.3 Key Biochemical Resistance Mechanisms

Four principal biochemical strategies underlie clinically important antibiotic resistance. (1) Enzymatic inactivation: beta-lactamases — enzymes that hydrolyze the beta-lactam ring shared by penicillins, cephalosporins, carbapenems, and monobactams — constitute the most clinically significant resistance mechanism. Extended-spectrum beta-lactamases (ESBLs), KPC-type carbapenemases, metallo-beta-lactamases (MBLs, including NDM and VIM), and OXA-type carbapenemases collectively inactivate most clinically used beta-lactam antibiotics, including last-resort carbapenems. Aminoglycoside-modifying enzymes (AMEs) similarly inactivate aminoglycosides through acetylation, adenylylation, or phosphorylation. (2) Target modification: methicillin resistance in S. aureus (MRSA) arises from acquisition of the mecA gene encoding an alternative penicillin-binding protein (PBP2a) with low affinity for beta-lactams, rendering the entire class ineffective. Fluoroquinolone resistance commonly involves mutations in DNA gyrase (gyrA/gyrB) and topoisomerase IV (parC/parE) genes. (3) Efflux pump overexpression: multi-drug efflux pumps such as the MexAB-OprM and MexXY-OprM systems in P. aeruginosa actively expel multiple antibiotic classes from the bacterial cell, reducing intracellular drug concentrations below inhibitory levels. (4) Outer membrane permeability reduction: loss or modification of porins — outer membrane channels through which hydrophilic antibiotics enter Gram-negative bacteria — is a frequent mechanism of carbapenem resistance, often acting synergistically with beta-lactamase production.

Table 2. Key Resistance Mechanisms by Antibiotic Class and Clinical Significance

Antibiotic Class	Primary Mechanism(s) of Resistance	Clinically Critical Examples	Affected Organisms
Beta-lactams (all)	Beta-lactamase hydrolysis; PBP modification; porin loss	ESBL, KPC, NDM, OXA-48; MRSA (mecA)	Enterobacterales, A. baumannii, MRSA
Carbapenems	Carbapenemase production; OprD porin loss; efflux	NDM, KPC, OXA-23, VIM; MexAB-OprM	Klebsiella, Acinetobacter, Pseudomonas

Antibiotic Class	Primary Mechanism(s) of Resistance	Clinically Critical Examples	Affected Organisms
Fluoroquinolones	DNA gyrase/topo IV mutation; efflux pump (QepA); Qnr proteins	QREC (quinolone-resistant E. coli); FQRP	E. coli, Salmonella, P. aeruginosa, M. tb
Aminoglycosides	Aminoglycoside-modifying enzymes; 16S rRNA methylases (rmtB)	AME-producing Enterobacterales; HLGR enterococci	Gram-negatives, Enterococcus, S. aureus
Colistin (polymyxins)	mcr-mediated LPS modification; mgrB mutation	mcr-1 to mcr-9 (plasmid-mediated)	K. pneumoniae, E. coli, A. baumannii
Glycopeptides (vancomycin)	VanA/VanB operons (altered peptidoglycan terminus)	VRE (vancomycin-resistant enterococci); VISA/VRSA	Enterococcus, S. aureus (rare)
Rifampicin	rpoB gene mutation (RNA polymerase alteration)	Rifampicin-resistant M. tuberculosis (RR-TB)	M. tuberculosis, staphylococci

MRSA = methicillin-resistant S. aureus; ESBL = extended-spectrum beta-lactamase; KPC = Klebsiella pneumoniae carbapenemase; NDM = New Delhi metallo-beta-lactamase; VRE = vancomycin-resistant enterococci; VISA = vancomycin-intermediate S. aureus; HLGR = high-level gentamicin resistance; FQRP = fluoroquinolone-resistant Pseudomonas; QREC = quinolone-resistant E. coli.

4. CLINICAL CONSEQUENCES AND ECONOMIC IMPACT

4.1 Impact on Mortality, Morbidity, and Treatment Outcomes

The clinical consequences of AMR extend across virtually every medical specialty and healthcare setting. In critical care, carbapenem-resistant A. baumannii (CRAB) bacteremia carries a 30-day mortality of 50–70% in most published cohort studies, compared with 20–30% for carbapenem-susceptible infections — an excess mortality attributable directly to the absence of effective empirical therapy. MRSA bloodstream infections are associated with significantly greater mortality, longer hospital stays, and higher treatment costs than methicillin-susceptible S. aureus (MSSA) bacteremia, with a meta-analytic excess mortality estimate of 20–30%. In neonatal care — particularly in LMICs — ESBL-producing Klebsiella pneumoniae and E. coli are responsible for an estimated 214,000 neonatal deaths annually, representing one of the most devastating manifestations of AMR in its most vulnerable victims.

Drug-resistant tuberculosis constitutes a distinct and particularly intractable AMR crisis. In 2023, the WHO estimated that 410,000 people globally developed rifampicin-resistant TB (RR-TB), of whom approximately 183,000 had extensively drug-resistant TB (XDR-TB) — defined as resistance to rifampicin, any fluoroquinolone, and at least one of bedaquiline or linezolid. Treatment success rates for XDR-TB historically languished below 40%, though the introduction of the BPaL (bedaquiline, pretomanid, linezolid) regimen in the ZeNix and TB-PRACTECAL trials has improved outcomes substantially, with treatment success rates of 89% demonstrated in the most recent analyses.

4.2 Economic Burden

The economic consequences of AMR are substantial and multi-layered. Direct healthcare costs include longer hospitalizations (AMR infections extend average hospital stays by 3–8 days per episode), higher rates of ICU admission, more expensive second- and third-line antimicrobial agents, increased diagnostics, and greater need for isolation facilities. A 2023 systematic review and meta-analysis of 113 studies quantified the excess direct healthcare cost attributable to AMR

infections at USD 18,400–USD 34,200 per patient in high-income country hospital settings. In the United States alone, the CDC estimates that AMR imposes direct healthcare costs exceeding USD 20 billion annually, with indirect costs — lost productivity, disability, and premature death — adding a further USD 35 billion.

The macroeconomic projections are even more alarming. The O'Neill Commission's 2016 report to the UK government estimated that AMR, if unchecked, could reduce global GDP by 2–3.5% by 2050, with the economic impact disproportionately devastating for low-income countries whose GDP would shrink by up to 5% — an economic shock comparable to the 2008–2009 global financial crisis recurring annually. These projections have been refined and updated by subsequent World Bank modeling that emphasizes the interactive effects of AMR on agricultural productivity, food security, and cross-border trade disruptions.

5. THE ANTIMICROBIAL PIPELINE: STATUS AND INNOVATIONS

5.1 Current Clinical Development Pipeline

The global antibiotic development pipeline has suffered a decades-long drought attributable primarily to market failure: the economics of antibiotic development are fundamentally unattractive to pharmaceutical companies, as antibiotics are used for short treatment courses, are subject to stewardship restrictions limiting use, and generate revenues incompatible with the multi-billion-dollar investment required for drug development. Between 2017 and 2023, 13 new antibiotics were approved by the FDA or EMA; however, most represent modifications of existing chemical scaffolds rather than truly novel mechanisms of action, providing incremental rather than transformative additions to the therapeutic arsenal.

Among the most clinically significant recent approvals are: ceftazidime-avibactam (active against KPC, OXA-48, and AmpC-producing Enterobacterales, but not MBL-producers), ceftolozane-tazobactam (enhanced anti-Pseudomonas activity), meropenem-vaborbactam (KPC-specific activity), imipenem-cilastatin-relebactam, sulbactam-durlobactam (the first specifically approved for CRAB infections), and cefiderocol — a novel siderophore cephalosporin with broad Gram-negative activity including against MBL-producers. The CREDIBLE-CR trial of cefiderocol versus best available therapy for carbapenem-resistant infections, while demonstrating non-inferiority, raised concerns about higher all-cause mortality in the cefiderocol arm for CRAB infections — underscoring the difficulty of clinical trial design in this patient population.

5.2 Novel Therapeutic Strategies

Beyond conventional antibiotics, several alternative therapeutic strategies have advanced to clinical investigation. Bacteriophage therapy — the use of viruses that specifically infect and lyse bacteria — has garnered renewed interest following successful compassionate-use cases, including the landmark treatment of a patient with a disseminated, antibiotic-refractory Mycobacterium abscessus infection using a genetically engineered phage cocktail at Great Ormond Street Hospital in 2019. Phage therapy offers inherent pathogen specificity, self-amplification at infection sites, and the potential for phage engineering to overcome phage resistance. However, regulatory frameworks for phage products remain nascent in most jurisdictions, manufacturing standardization is challenging, and the absence of randomized controlled trial data limits evidence-based adoption.

Antivirulence strategies — targeting bacterial virulence factors rather than viability, thereby avoiding the selective pressure that drives resistance — include anti-toxin antibodies, quorum sensing inhibitors, and biofilm-disrupting agents. The theoretical advantage is that antivirulence agents do not kill bacteria directly, and thus impose less evolutionary pressure for resistance development. Anti-alpha toxin antibodies have demonstrated proof-of-concept in MRSA models, and small-molecule quorum sensing inhibitors targeting LasR and RhlR in P. aeruginosa have

shown activity in murine infection models. Microbiome-modulating strategies — including fecal microbiota transplantation (FMT) for decolonization of carbapenemase-producing organisms from the gastrointestinal tract — have demonstrated promising preliminary efficacy in prospective cohort studies and are being evaluated in randomized trials.

CLINICAL SPOTLIGHT — Sulbactam-Durlobactam for CRAB: A Paradigm of Targeted Development

Carbapenem-resistant Acinetobacter baumannii (CRAB) represents perhaps the most clinically desperate AMR scenario, with infections carrying mortality rates of 40–70% and few therapeutic options beyond polymyxin-based regimens with significant nephrotoxicity and suboptimal efficacy. Sulbactam — a beta-lactamase inhibitor with intrinsic antibacterial activity against Acinetobacter through PBP1 and PBP3 inhibition — has long been recognized as having anti-Acinetobacter activity, but its clinical utility was limited by emerging resistance through PBP modifications and OXA carbapenemases. Durlobactam, a novel diazabicyclooctane beta-lactamase inhibitor, protects sulbactam from inactivation by serine-based OXA carbapenemases while also inhibiting PBP2 — restoring sulbactam's antibacterial efficacy. In the phase III ATTACK trial (2023), sulbactam-durlobactam demonstrated superiority to colistin-based therapy for CRAB infections in a predefined subgroup analysis, with significantly lower 28-day mortality (19% vs. 32%) and substantially lower nephrotoxicity. FDA approval in 2023 marked the first carbapenem-resistant Acinetobacter-specific approval in the modern era.

6. ANTIMICROBIAL STEWARDSHIP: PRINCIPLES AND IMPLEMENTATION

6.1 Core Components of Effective Stewardship Programs

Antimicrobial stewardship programs (ASPs) — systematic, evidence-based interventions designed to optimize antibiotic prescribing to improve patient outcomes, reduce adverse effects, and minimize the selective pressure driving AMR — have become a cornerstone of hospital infection management in high-income countries and are increasingly recognized as essential in LMIC settings. The core components of effective hospital-based ASPs include: prospective audit and feedback (the most evidence-supported intervention, in which a multidisciplinary team reviews antibiotic prescriptions and provides recommendations for de-escalation, dose optimization, or discontinuation); pre-authorization restrictions for high-risk broad-spectrum agents; rapid diagnostic integration (particularly rapid molecular diagnostics and MALDI-TOF mass spectrometry for rapid pathogen identification); pharmacokinetic/pharmacodynamic (PK/PD) optimization of dosing; IV-to-oral switching protocols; and systematic tracking of clinical and resistance outcomes.

A 2022 Cochrane meta-analysis of 221 randomized controlled trials and interrupted time-series studies of ASPs in hospital settings found that ASP interventions significantly reduced broad-spectrum antibiotic use (standardized mean difference −0.48, 95% CI −0.66 to −0.29), reduced inappropriate antibiotic prescribing (relative risk 0.68, 95% CI 0.58–0.80), and were associated with reduced length of hospital stay without adversely affecting clinical cure rates or mortality. Community-level antibiotic stewardship — including point-of-care diagnostic-based prescribing in primary care, public awareness campaigns, and regulatory restrictions on over-the-counter antibiotic sales — is less rigorously evaluated but represents a critical component of comprehensive AMR containment, particularly in LMICs where self-medication and unregulated dispensing are endemic.

6.2 Challenges in Low- and Middle-Income Country Implementation

Implementing ASPs in LMIC healthcare settings presents formidable contextual challenges that render direct transplantation of high-income country models inappropriate. These include: a severe shortage of clinical pharmacists, infectious disease specialists, and microbiologists; absence of functional diagnostic microbiology laboratory infrastructure capable of culture and susceptibility testing; inadequate electronic prescribing systems for data tracking and decision support; competing clinical priorities in overwhelmed health systems; cultural norms around antibiotic prescribing; and patient expectations that may conflict with diagnostic-guided prescribing. Context-adapted stewardship models — such as the WHO Access, Watch, Reserve (AWaRe) classification system, which categorizes antibiotics by access importance and resistance risk and provides a simplified prescribing framework — have shown promising feasibility and impact in LMIC primary care settings in sub-Saharan Africa and Southeast Asia.

7. ONE HEALTH APPROACH AND AGRICULTURAL AMR

The One Health framework — which recognizes the inextricable interconnection between human health, animal health, and ecosystem health — is the conceptually appropriate and operationally necessary lens through which AMR must be understood and addressed. Approximately 73% of global antibiotic consumption occurs in food-producing animals — predominantly cattle, pigs, and poultry — used for growth promotion, disease prevention, and treatment. The use of critically important antibiotics (CIAs) such as fluoroquinolones, third- and fourth-generation cephalosporins, and colistin in veterinary and agricultural contexts has directly contributed to the emergence and dissemination of resistant zoonotic pathogens including fluoroquinolone-resistant Salmonella, ESBL-producing E. coli in poultry, and mcr-mediated colistin-resistant bacteria in livestock.

Molecular epidemiological studies using whole genome sequencing have established direct transmission links between livestock-associated MRSA (LA-MRSA, particularly CC398) and human MRSA infections in communities with intensive livestock farming — most extensively documented in the Netherlands, Denmark, and Germany. Foodborne transmission of resistant organisms — particularly ESBL-producing Enterobacterales via contaminated meat — is increasingly recognized as a significant but underappreciated route of community-level AMR acquisition.

International policy responses to agricultural AMR have been uneven. The EU banned the use of antibiotics for growth promotion in food animals in 2006 and has subsequently mandated significant reductions in antibiotic use in livestock. Several Scandinavian countries have achieved reductions in agricultural antibiotic use of 50–70% over the past decade without adverse effects on animal health or productivity — demonstrating that substantial reductions are achievable. By contrast, major livestock-producing nations including the United States, Brazil, India, and China continue to use antibiotics for growth promotion, though China's 2020 ban on colistin for veterinary growth promotion represented a landmark regulatory achievement. Strengthening Codex Alimentarius standards and incorporating AMR into bilateral and multilateral trade negotiations are essential policy levers for establishing global consistency.

8. POLICY FRAMEWORK AND MULTISECTORAL ROADMAP

8.1 National AMR Action Plans

The 2015 WHO Global Action Plan on Antimicrobial Resistance established a framework of five strategic objectives — improving awareness and understanding, strengthening surveillance, reducing infection incidence, optimizing antimicrobial use, and investing in new medicines and diagnostics — and called on member states to develop National Action Plans (NAPs) aligned with these objectives by 2017. As of 2024, 178 of 194 WHO member states have developed or are

developing NAPs. However, a 2023 WHO/FAO/UNEP tripartite assessment found that fewer than 30% of submitted NAPs were operationally implemented with dedicated funding; the remainder existed primarily as planning documents without budgetary commitments or accountability mechanisms. The gap between policy commitment and implementation — particularly in LMICs constrained by competing public health priorities and limited health system financing — represents the critical bottleneck in global AMR governance.

8.2 Economic Incentive Reform for Antibiotic Development

The market failure in antibiotic development requires structural intervention beyond incremental regulatory streamlining. Two broad categories of economic incentives are under active policy consideration: push incentives, which reduce the cost and risk of development (grants, tax credits, public-private partnerships, streamlined regulatory pathways), and pull incentives, which increase the expected revenue from successful antibiotic development regardless of sales volume. The most promising pull incentive models include subscription-based reimbursement systems (in which payers purchase guaranteed access to a novel antibiotic for a fixed annual fee irrespective of volumes used — analogous to a Netflix subscription) and market entry rewards (large lump-sum payments upon regulatory approval meeting specified criteria). The UK has piloted a subscription payment model for cefiderocol and ceftazidime-avibactam, committing GBP 10 million per antibiotic per year for 10 years. Sweden, Germany, and the United States have implemented or are implementing similar models. International coordination of pull incentive financing — to prevent free-rider dynamics where individual countries defer financing expectations to others — is essential for the system's viability at scale.

Table 3. Multisectoral AMR Containment Roadmap: Priority Actions by Domain

Domain	Priority Actions	Key Actors	Timeline
Human Health	Universal ASPs; rapid diagnostics access in LMICs; infection prevention scale-up	MOH, WHO, hospitals, clinicians	Immediate–5 years
Veterinary & Agriculture	Global ban on growth-promotional antibiotic use; CIA phase-out in food animals	FAO, WOAH, agriculture ministries	2–7 years
Environment	Regulate pharmaceutical effluent discharge; AMR monitoring in waterways	UNEP, EPA agencies, industry	3–10 years
R&D Pipeline	Subscription/market entry reward pull incentives; novel scaffold discovery funding	G7/G20, Wellcome Trust, CARB-X	Immediate–10 years
Surveillance	Expand GLASS to community & agricultural settings; genomic surveillance in LMICs	WHO, Africa CDC, national labs	2–5 years
Global Governance	Binding AMR targets in international treaty; AMR chapter in Pandemic Treaty	UN General Assembly, WHO, WTO	5–10 years

MOH = Ministries of Health; CIA = critically important antimicrobials; CARB-X = Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator; WOAH = World Organisation for Animal Health.

9. DISCUSSION

Antimicrobial resistance represents a uniquely challenging public health emergency in that it lacks the visibility and urgency of acute epidemic threats — its progression is gradual, its causal mechanisms are diffuse across sectors, and its consequences are often attributed to other proximate causes (the patient who dies of 'sepsis' rather than of AMR-complicated sepsis). This invisibility has historically impeded the political prioritization and sustained investment that AMR demands. The COVID-19 pandemic — which paradoxically both increased antibiotic use globally (with reported antibiotic co-prescription rates of 70–80% in hospitalized COVID-19 patients despite bacterial co-infection rates of <10%) and demonstrated the catastrophic consequences of pandemic unpreparedness — has created both challenges and opportunities for the AMR agenda.

The scientific community faces genuine uncertainty about several pivotal questions. The relative contribution of different sectors — human medicine, livestock agriculture, aquaculture, and environmental contamination — to the global AMR burden remains debated, with attribution studies producing highly variable estimates depending on methodological assumptions. The temporal dynamics of resistance emergence — whether contemporary rates of emergence are linear, accelerating, or potentially controllable through stewardship — are incompletely characterized. And the potential of novel therapeutic modalities, from phage therapy to CRISPR-based antimicrobials and bacteriocins, to complement conventional antibiotics in clinical practice remains largely untested in rigorous randomized trials.

What is not uncertain is the trajectory of harm if current trends continue. The GRAM projections, O'Neill Commission estimates, and World Bank modeling all converge on scenarios of cascading human, economic, and social costs from unchecked AMR that should compel urgent action from governments, multilateral institutions, industry, and the clinical community alike. The comparison with climate change — another slow-moving, multi-causal, cross-sectoral global emergency that required decades to achieve meaningful political traction — is instructive both as a cautionary parallel and as evidence that concerted global action on complex systemic challenges is achievable, albeit painfully slowly relative to the pace of the threat.

For clinicians, the implications of AMR are immediately practical: empirical antibiotic selection must increasingly account for local resistance epidemiology; diagnostic stewardship — ensuring cultures are collected before antibiotics and results are acted upon — is as important as therapeutic stewardship; infection prevention (hand hygiene, contact precautions, catheter care bundles) reduces AMR transmission within healthcare settings; and patient communication about antibiotic appropriateness remains a critical but underemphasized competency. For researchers, priority areas include developing rapid point-of-care diagnostics capable of identifying pathogens and resistance patterns within hours rather than days, advancing novel antibiotic and non-antibiotic therapeutic strategies through clinical trials, and generating the economic and epidemiological evidence needed to inform policy decisions.

10. CONCLUSIONS

Antimicrobial resistance is not an inevitable consequence of microbial evolution but an accelerated crisis of human making — and therefore one amenable to human intervention. The evidence reviewed in this narrative synthesis supports a number of firm conclusions. First, the burden of AMR is enormous, immediate, and inequitably distributed, with LMICs — particularly in sub-Saharan Africa and South Asia — bearing disproportionate mortality while possessing the least capacity to respond. Second, the molecular mechanisms of resistance are well characterized, and this mechanistic understanding provides actionable targets for diagnostic innovation, therapeutic development, and stewardship strategies. Third, the antimicrobial therapeutic pipeline is improving but remains inadequate in depth, novelty, and accessibility — requiring structural economic reform of development incentives alongside sustained public investment in basic antimicrobial science.

Fourth, antimicrobial stewardship works: the evidence base for ASPs in hospital settings is robust, and implementation in LMIC-adapted formats should be a global health priority. Fifth, AMR cannot be contained within the human health sector — effective response requires genuine One Health integration encompassing veterinary medicine, agriculture, food systems, and environmental management, coordinated through regulatory and policy frameworks that do not currently exist at the necessary scale. Sixth, global AMR governance requires binding international commitments with accountability mechanisms, dedicated financing, and meaningful engagement of LMICs in decision-making — deficiencies that the ongoing Pandemic Treaty negotiations offer an opportunity to begin redressing.

Fleming's penicillin gave medicine a century of unprecedented therapeutic power. Whether that power persists into the next century will depend not on microbial biology but on the collective will of the global community to mount a response commensurate with the scale of the threat. The scientific evidence reviewed here leaves no ambiguity about what is required. The question is whether the political and economic systems that must translate evidence into action can be mobilized in time.

DECLARATIONS

Conflicts of Interest: All authors declare no conflicts of interest relevant to this manuscript. ANO has received speaking honoraria from Pfizer unrelated to this work. LKB serves on the scientific advisory board of a phage therapy startup; this relationship was disclosed and reviewed by the journal.

Author Contributions: ANO and MAHS conceptualized and designed the review. ANO, FZA, and LKB conducted the literature search and data extraction. ZWC led statistical synthesis of epidemiological data. All authors contributed to writing and revision. ANO acts as guarantor of the review.

Data Availability: All data used in this review are available in published sources cited herein. The GLASS surveillance database is publicly available at https://www.who.int/glass.

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