ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XV, Issue X, October 2026

Antibiotics from Discovery to Crisis: An Antibiotic History and the Global Emergency of Antimicrobial Resistance

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DOI: https://doi.org/10.51583/IJLTEMAS.2026.151000120

Received: 26 October 2026; Accepted: 31 October 2026; Published: 17 November 2026

ABSTRACT

In the twentieth century, antibiotics revolutionized medicine by making previously lethal infections curable and by enabling organ transplantation, chemotherapy, surgery, and newborn care. Less than a century after penicillin entered clinical use, however, antimicrobial resistance (AMR) has become one of the greatest threats to global health. This review traces the history of antibiotics and examines how the present resistance crisis arose, what it costs, and how it might be addressed. It is a narrative review based on a structured search of PubMed, Scopus, Web of Science, and Google Scholar for literature published up to date, supplemented by reports from the World Health Organization (WHO). It covers the pre-antibiotic period, the "golden age" of discovery (1940s–1960s), the "discovery void" that followed, and the current era of renewed but fragile innovation. The molecular mechanisms of resistance, the human, animal, and environmental drivers of the crisis, the worldwide burden of resistant infections, the economic barriers that have weakened the antibiotic pipeline, and the proposed solutions are summarized in five tables, including a timeline of major milestones, the WHO 2024 bacterial priority pathogens list, and a comparative appraisal of interventions. Bacterial AMR was directly responsible for approximately 1.27 million deaths and was associated with approximately 4.95 million deaths in 2019; the corresponding estimates for 2021 were 1.14 million and 4.71 million, and attributable deaths could reach approximately 1.9 million per year by 2050 if current trends continue. The burden falls disproportionately on older adults and on people in sub-Saharan Africa and South Asia. The crisis reflects a biological inevitability that is amplified by the overuse and misuse of antibiotics, inadequate infection control, and market failure. Our appraisal indicates that no single intervention is sufficient and that major evidence gaps remain, particularly for diagnostics, alternative therapies, and economic incentives in low- and middle-income countries. A coordinated One Health response that combines stewardship, surveillance, new discoveries, alternative therapies, and new economic incentives is necessary to preserve the effectiveness of antibiotics for future generations.

Keywords: antibiotics; antimicrobial resistance; ESKAPE pathogens; antimicrobial stewardship; One Health; WHO priority pathogens; antibiotic discovery

INTRODUCTION

The development of antibiotics is widely regarded as one of the greatest triumphs of modern medicine (Aminov, 2017; Hutchings et al., 2019). Before antibiotics were available, infections such as pneumonia, tuberculosis (TB), sepsis, and wound infections were leading causes of death. Besides curing illness,

ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XV, Issue X, October 2026

antibiotics made complex medical procedures, including cancer treatment and cesarean delivery, possible (Hutchings et al., 2019).

However, AMR is a natural and ancient phenomenon. Over millions of years, antibiotic-producing and resistant bacteria coevolved in the environment, and antibiotic use has created strong selection pressure that favors resistant strains (Aminov, 2017; Larsson & Flach, 2022). Resistance to penicillin was identified within a few years of its introduction, and resistant isolates have emerged after each new class (Gaynes, 2017; Lewis, 2020). Drug-resistant infections now account for more than a million deaths worldwide each year (Antimicrobial Resistance Collaborators, 2022; GBD 2021 Antimicrobial Resistance Collaborators, 2024). Clinicians increasingly speak of a "post-antibiotic era" in which common infections may again become untreatable (Kwon & Powderly, 2021).

Several valuable reviews have addressed either the history of antibiotic discovery or the contemporary burden of AMR. This review brings the two together: it links each phase of the antibiotic story to the resistance that followed, updates the burden estimates using the 2021 Global Burden of Disease analysis and the 2024 WHO Bacterial Priority Pathogens List (World Health Organization [WHO], 2024), and critically compares the main intervention strategies, highlighting where the evidence is weakest.

The objectives of this review are to:

- summarize the history of antibiotic discovery, from the pre-antibiotic era to the present;
- describe the mechanisms and drivers of antibiotic resistance and the global burden it causes; and
- Critically compare the strategies proposed to address the crisis and identify the main evidence gaps.

REVIEW METHODOLOGY

This article is a narrative review. It is based on a structured literature search followed by qualitative, thematic synthesis. It is not a systematic review; no meta-analysis or formal risk-of-bias assessment was undertaken.

Search Strategy

The literature was searched in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Reports and guidance documents were obtained from the website of the World Health Organization. The searches covered publications from January 2000 to November 2026, and older landmark papers were included for the historical sections. The last search was run on 04/11/2026. Search terms were combined with Boolean operators and included "antibiotic history", "history of antibiotic discovery", "antimicrobial resistance", "resistance mechanisms", "global burden", "ESKAPE", "WHO priority pathogens", "antimicrobial stewardship", "One Health", "antibiotic pipeline", "alternative therapies", and "economic incentives"

Eligibility criteria

Sources were included if they were (i) peer-reviewed reviews, original studies, or global burden analyses addressing the history, mechanisms, drivers, burden, economics, or control of bacterial AMR; (ii) reports from international organizations; and (iii) published in English. Conference abstracts, non-peer-reviewed commentary (other than reports from international organizations), and articles dealing only with antifungal, antiviral, or antiparasitic resistance were excluded.

Study selection and synthesis

Titles and abstracts were screened for relevance, and the full texts of potentially relevant articles were read. Records were identified, and [42] sources were included in the final review. Where several sources reported the same finding, primary studies and the most recent authoritative analyses were preferred. Historical dates, epidemiological estimates, and resistance-related claims were cross-checked against the original publications

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or authoritative reports, such as the Global Research on Antimicrobial Resistance (GRAM) publications and WHO documents, wherever possible. Findings were organized thematically (history, mechanisms, drivers, burden, economic impact, and interventions) and synthesized narratively.

Antibiotic History

Early chemotherapy in the pre-antibiotic era

For centuries, wounds and infections were treated empirically with molds, plant extracts, and other natural remedies; the germ theory of disease in the late nineteenth century provided the scientific foundation for antimicrobial therapy (Aminov, 2017). The arsenic compound salvarsan (1910), developed by Paul Ehrlich on the basis of his "magic bullet" concept, was the first systematically designed antimicrobial chemotherapy and was used to treat syphilis. The sulfonamide prontosil, from the laboratory of Gerhard Domagk, was the first widely used antibacterial drug for systemic infection; its activity was discovered in 1932 and reported in 1935 (Aminov, 2017; Hutchings et al., 2019).

Penicillin and the golden age of antibiotics (1928–1960s)

In 1928, Alexander Fleming observed that a *Penicillium* mold had antibacterial activity. It was not until 1940–1941 that Howard Florey, Ernst Chain, and colleagues purified penicillin and demonstrated its therapeutic efficacy, and the Second World War accelerated large-scale manufacture (Gaynes, 2017). Resistance was foreshadowed even before penicillin entered clinical use: a bacterial enzyme able to destroy penicillin, later called penicillinase, was described in 1940 (Abraham & Chain, 1940; Gaynes, 2017).

The following two decades are often called the "golden age of antibiotics." Selman Waksman's systematic screening of soil actinomycetes led to streptomycin (discovered in 1943), the first effective drug against tuberculosis, followed by chloramphenicol, the tetracyclines, the macrolides, the glycopeptides, and several other classes (Aminov, 2017; Hutchings et al., 2019; Lewis, 2020). Most of the antibiotic classes in use today were discovered during this period (Hutchings et al., 2019).

The discovery void (1970s–2000s)

By the 1960s and 1970s, the "Waksman platform" of screening soil microorganisms had begun to yield rediscoveries of known compounds, and synthetic or semisynthetic modifications of existing scaffolds produced only incremental advances (Lewis, 2020). In the 1990s, target-based genomic screening of synthetic libraries largely failed to produce new antibacterials, because compounds that inhibit isolated enzymes often cannot cross the Gram-negative outer membrane or are removed by efflux pumps (Brown & Wright, 2016; Lewis, 2020). Almost no new structural classes entered the clinic between the quinolones of the early 1960s and the introduction of the oxazolidinones and lipopeptides in 2000–2003, and none of the new classes targeted the most dangerous Gram-negative infections (Hutchings et al., 2019; Lewis, 2020). Low financial returns also led major pharmaceutical companies to withdraw from antibacterial research (Årdal et al., 2020).

Renewed innovation (2010s–present)

Development has been modest but real. Recently introduced agents include fidaxomicin (for *Clostridioides difficile* infection), bedaquiline (for multidrug-resistant TB), several β-lactam/β-lactamase-inhibitor combinations (for example, ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam), and the siderophore cephalosporin cefiderocol (Hutchings et al., 2019; Miethke et al., 2021). New discovery approaches include machine learning-guided screening of chemical libraries, which has identified compounds such as halicin and abaucin (Stokes et al., 2020; Liu et al., 2023); genome mining of biosynthetic gene clusters; and cultivation of previously uncultured organisms, which yielded teixobactin (Ling et al., 2015; Lewis, 2020; Miethke et al., 2021). However, few truly novel agents active against critical-priority Gram-negative bacteria are in the preclinical and clinical pipelines (Theuretzbacher et al., 2020).

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Timeline of Key Events

Table 1 summarizes the major milestones in antibiotic discovery and in the emergence of resistance.

Table 1. Timeline of major milestones in antibiotic discovery and resistance emergence

Year	Event	Significance
1910	Salvarsan (Ehrlich) introduced for syphilis	First designed antimicrobial chemotherapy
1928	Fleming observes antibacterial activity of *Penicillium*	Discovery of penicillin
1935	Prontosil / sulfonamides (Domagk); activity found in 1932, reported in 1935	First broadly effective systemic antibacterial
1940	Penicillinase described (Abraham & Chain)	First recognized enzymatic resistance mechanism
1941	Penicillin used clinically (Florey, Chain)	Start of the antibiotic era
1943–44	Streptomycin (Waksman)	First effective anti-tuberculosis drug; soil actinomycete screening
1947–1952	Chloramphenicol, tetracyclines, erythromycin	Broad-spectrum and macrolide classes
1958–1962	Vancomycin; methicillin; quinolones (nalidixic acid)	Glycopeptide, anti-staphylococcal β-lactam, quinolone classes
1961	Methicillin-resistant *Staphylococcus aureus* (MRSA) reported	Resistance to a newly introduced drug within about two years
1950s–1980s	Aminoglycosides (beyond streptomycin), rifamycins, cephalosporins, carbapenems	Expansion of β-lactam and other families
1970s–1990s	Discovery void: no new classes active against Gram-negatives	Pipeline decline; industry exit
1980s	Vancomycin-resistant enterococci (VRE)	Resistance to a last-resort drug
2000–2003	Linezolid (oxazolidinone); daptomycin (lipopeptide)	First new classes in decades (Gram-positive)
2002	Vancomycin-resistant *S. aureus* reported	Further erosion of last-line therapy
2008–2010	NDM-1 carbapenemase described	Rapid global spread of carbapenem resistance
2015–2016	Teixobactin reported; *mcr-1* plasmid-mediated colistin resistance described	New discovery platform; resistance to last-resort polymyxin
2017	WHO priority pathogens list published	Global research priorities defined
2019	Cefiderocol approved	Siderophore cephalosporin for resistant Gram-negatives
2020–2023	Artificial intelligence (AI)-guided discovery of halicin and abaucin	Machine learning enters antibiotic discovery
2022–2024	Global burden analyses (Global Research on Antimicrobial Resistance, GRAM)	Quantification of the AMR crisis
2024	WHO Bacterial Priority Pathogens List updated; UN General Assembly political declaration on AMR	Revised global priorities; global target to reduce AMR deaths by 2030

Note. The data were compiled from Aminov (2017), Gaynes (2017), Hutchings et al. (2019), Lewis (2020), Miethke et al. (2021), Tacconelli et al. (2018), the Antimicrobial Resistance Collaborators (2022), the GBD 2021 Antimicrobial Resistance Collaborators (2024), the WHO (2024), and the United Nations General Assembly (2024), together with the primary reports of Abraham and Chain (1940), Jevons (1961), Leclercq et

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al. (1988), Chang et al. (2003), Yong et al. (2009), Ling et al. (2015), Liu et al. (2016), Stokes et al. (2020), and Liu et al. (2023). The dates are approximate for discoveries and clinical applications.

Antibiotic Resistance Mechanisms

Bacteria can be resistant to antibiotics through intrinsic characteristics, mutation, and horizontal acquisition of resistance genes (Munita & Arias, 2016; Darby et al., 2023). Resistance can spread rapidly across species and ecological niches by horizontal gene transfer through plasmids, transposons, integrons, and bacteriophages (Christaki et al., 2020; Larsson & Flach, 2022). Four main biochemical mechanisms of genetic resistance have been identified (Table 2). In addition, phenotypic tolerance, such as that conferred by persister cells and biofilm formation, allows bacteria to survive treatment and may promote the development of heritable resistance (Darby et al., 2023; Uddin et al., 2021).

Table 2. Principal mechanisms of antibiotic resistance

Mechanism	Description	Examples
Enzymatic inactivation or modification of the drug	Enzymes hydrolyze or chemically modify the antibiotic	β-lactamases (extended-spectrum β-lactamases [ESBLs]; carbapenemases such as KPC, NDM, and OXA-48); aminoglycoside-modifying enzymes
Target alteration or protection	Mutation, modification or protection of the antibiotic's binding site	PBP2a (penicillin-binding protein 2a) in MRSA; *vanA/vanB* altering peptidoglycan precursors; ribosomal methylation (*erm*); *gyrA* mutations
Reduced intracellular accumulation	Decreased permeability or active efflux	Porin loss in Gram-negatives; RND efflux pumps (AcrAB-TolC, MexAB-OprM)
Target bypass / metabolic bypass	Alternative pathways circumvent the inhibited step	Acquired dihydrofolate reductase conferring trimethoprim resistance
Phenotypic tolerance	Non-heritable survival without resistance genes	Biofilms; persister cells

Note. Based on Munita and Arias (2016), Christaki et al. (2020), Uddin et al. (2021), and Darby et al. (2023).

Causes of the Antibiotic Crisis

- **Overuse and misuse in humans:** Global antibiotic use has risen markedly since the early 2000s, especially in low- and middle-income countries (Klein et al., 2018; Browne et al., 2021). Incomplete courses and inappropriate prescribing, such as antibiotics for viral respiratory illnesses, increase selection pressure (Aslam et al., 2018; Salam et al., 2023). Excess use is only part of the problem, however: a lack of access to effective antibiotics also causes substantial mortality (Laxminarayan et al., 2016).

- **Animal agriculture:** Antibiotics are widely used in food animals for growth promotion and disease prevention in some regions, and resistance in animal pathogens and commensal bacteria has increased in low- and middle-income countries (Van Boeckel et al., 2019).

- **Environmental contamination:** Antibiotic residues, resistant bacteria, and resistance genes enter the environment through wastewater, manufacturing effluents, and agricultural runoff. The environment acts as both a reservoir and a mixing vessel for resistance genes (Larsson & Flach, 2022).

- **Infection control, sanitation, and global mobility:** Insufficient infection control in healthcare facilities, poor water and sanitation, and global travel and trade promote the spread of resistant strains (Aslam et al., 2018; Salam et al., 2023).

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- **Economic and regulatory failure:** New antibiotics are used sparingly to preserve their effectiveness, treatment courses are short, and prices are low, so expected returns are small compared with those of drugs for chronic diseases. Several small developers have found newly licensed antibiotics to be a financial burden (Årdal et al., 2020; Dadgostar, 2019).

Antimicrobial Resistance: A Global Crisis

According to the Antimicrobial Resistance Collaborators (2022), in their analysis of data from the Global Research on Antimicrobial Resistance (GRAM) project, bacterial AMR was directly responsible for approximately 1.27 million deaths and was associated with approximately 4.95 million deaths in 2019. An updated analysis estimated 1.14 million attributable deaths and 4.71 million associated deaths in 2021. If current trends continue, attributable deaths could rise to approximately 1.9 million and associated deaths to approximately 8.2 million per year by 2050 (GBD 2021 Antimicrobial Resistance Collaborators, 2024). The same analysis indicates that, between 1990 and 2021, AMR deaths among children under five years fell by more than half, whereas deaths among adults aged 70 years and older rose by more than 80%. People living in sub-Saharan Africa and South Asia bear a disproportionate share of the burden (Antimicrobial Resistance Collaborators, 2022; GBD 2021 Antimicrobial Resistance Collaborators, 2024).

Much of this burden is caused by a small group of bacterial pathogens. The ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) "escape" the effects of many antibiotics and account for a large share of hospital-acquired infections (Rice, 2008; Mulani et al., 2019; Mancuso et al., 2021). To guide research and development (R&D), the WHO published its first priority pathogens list in 2017 (Tacconelli et al., 2018) and an updated Bacterial Priority Pathogens List in 2024 (WHO, 2024) (Table 3). In the 2024 list, the critical group comprises carbapenem-resistant *A. baumannii*, third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales, and rifampicin-resistant *Mycobacterium tuberculosis*. Compared with the 2017 list, carbapenem-resistant *P. aeruginosa* has moved from the critical to the high-priority group, *Helicobacter pylori* and *Campylobacter* are no longer listed, *Salmonella* is divided into *S.* Typhi and non-typhoidal serotypes, and group A and group B streptococci have been added (WHO, 2024).

Table 3. WHO bacterial priority pathogens list (2024) and key resistance phenotypes

Priority	Pathogen	Key resistance
Critical	*Acinetobacter baumannii*	Carbapenem-resistant
Critical	Enterobacterales (e.g., *Klebsiella pneumoniae*, *Escherichia coli*)	Third-generation cephalosporin-resistant
Critical	Enterobacterales (e.g., *Klebsiella pneumoniae*, *Escherichia coli*)	Carbapenem-resistant
Critical	*Mycobacterium tuberculosis*	Rifampicin-resistant
High	*Salmonella* Typhi	Fluoroquinolone-resistant
High	*Shigella* spp.	Fluoroquinolone-resistant
High	*Enterococcus faecium*	Vancomycin-resistant
High	*Pseudomonas aeruginosa*	Carbapenem-resistant
High	Non-typhoidal *Salmonella*	Fluoroquinolone-resistant
High	*Neisseria gonorrhoeae*	Third-generation cephalosporin- and/or fluoroquinolone-resistant
High	*Staphylococcus aureus*	Methicillin-resistant
Medium	Group A streptococci	Macrolide-resistant
Medium	*Streptococcus pneumoniae*	Macrolide-resistant
Medium	*Haemophilus influenzae*	Ampicillin-resistant
Medium	Group B streptococci	Penicillin-resistant

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Note. Adapted from WHO (2024). Carbapenem-resistant *P. aeruginosa* was in the critical group of the 2017 list (Tacconelli et al., 2018).

The Effects on Society and the Economy

Surgery, transplantation, and chemotherapy all depend on effective antibiotic prophylaxis and treatment; AMR prolongs hospital stays, causes treatment failure, increases mortality, and raises healthcare costs (Dadgostar, 2019; Pulingam et al., 2022). The economic burden includes direct healthcare costs and wider productivity losses. A World Bank analysis estimated that AMR could reduce annual global gross domestic product (GDP) by [1.1–3.8%] by 2050 (World Bank, 2017), and other models indicate substantial long-term harm to health systems and economies, especially in low-income regions (Dadgostar, 2019; Pulingam et al., 2022). The COVID-19 pandemic increased antibiotic use in many settings, including among patients with no evidence of bacterial co-infection, and in some regions hospital infections caused by resistant bacteria also increased (Salam et al., 2023).

Strategies to Address the Crisis

The literature converges on a multi-pronged response, which is summarized in Table 4 and compared critically in Section 8.6.

Table 4. Strategies to combat antibiotic resistance

Strategy	Approach	Key challenges	Sources
Stewardship and appropriate use	Prescribing guidelines, delayed prescribing, de-escalation, monitoring of use with the WHO AWaRe classification	Behavioura change; limited capacity in low-resource settings	Aslam et al. (2018); Salam et al. (2023); WHO (2023)
Diagnostic innovation	Rapid and point-of-care tests to distinguish bacterial from viral infection and to detect resistance	Cost, infrastructure, and uptake in low-resource settings	Salam et al. (2023); Laxminarayan et al. (2016)
Infection prevention and sanitation	Hygiene, vaccination, water and sanitation, hospital infection control	Investment and implementation	Laxminarayan et al. (2016); Salam et al. (2023)
Surveillance	National and global monitoring of resistance and consumption	Data gaps in low- and middle-income countries	Antimicrobial Resistance Collaborators (2022); Browne et al. (2021)
New antibiotic discovery	Novel scaffolds, uncultured microbes, genome mining, AI-guided screening	High attrition; Gram-negative penetration	Lewis (2020); Miethke et al. (2021); Brown & Wright (2016)
Alternative therapies	Bacteriophages, antimicrobial peptides, monoclonal antibodies, anti-virulence agents, microbiome-based approaches, resistance breakers	Clinical evidence and regulatory pathways	Mulani et al. (2019); Uddin et al. (2021)
Economic incentives	Push and pull incentives, subscription models, delinked revenue	Political will; international coordination	Årdal et al. (2020); Theuretzbacher et al. (2020)
One Health	Coordinated action across human, animal and environmental sectors	Cross-sector governance	Larsson & Flach (2022); Van Boeckel et al. (2019)

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Stewardship and Prevention

The most pressing issue is reducing the overuse of antibiotics, but this must be balanced against the need to expand access to effective treatment where it is currently lacking (Laxminarayan et al., 2016). The WHO AWaRe classification, which groups antibiotics into Access, Watch, and Reserve categories, provides a framework for monitoring use and guiding prescribing (WHO, 2023). Vaccination, better infection control, and faster diagnosis can reduce both infection rates and antibiotic use (Salam et al., 2023).

Diagnostic Innovation

Rapid and accurate diagnostics support both stewardship and individual patient care by helping clinicians decide whether an antibiotic is needed and which one to use, thereby reducing empirical broad-spectrum prescribing (Salam et al., 2023). Their value is greatest where laboratory capacity is limited, yet these are often the settings in which diagnostics are least available (Laxminarayan et al., 2016). Evidence on how far diagnostic tests change prescribing and patient outcomes in routine practice remains limited, and cost, infrastructure, and clinician uptake are persistent barriers.

Discovery and Development

New targets, such as outer-membrane biogenesis, rational optimization of current scaffolds to avoid resistance, and computational methods that can screen enormous chemical spaces, are promising avenues to pursue (Lewis, 2020; Miethke et al., 2021). Analyses of the pipeline show that a shortage of new ideas, rather than a shortage of candidates, is the bottleneck (Theuretzbacher et al., 2020).

Alternatives and Adjuncts

Current work is exploring phage therapy, antimicrobial peptides, antibodies, and efflux-pump or β-lactamase inhibitors, largely as adjuncts to, rather than replacements for, conventional antibiotics (Mulani et al., 2019; Uddin et al., 2021). Most of these approaches still face limited clinical evidence and unclear regulatory pathways, so their effectiveness at scale remains unproven (Mulani et al., 2019; Uddin et al., 2021).

Governance and Economic Concerns

Because the market alone does not adequately reward antibiotics that are used sparingly, Årdal et al. (2020) proposed combining “push” funding for early research with “pull” incentives, such as subscription-style payments that do not depend on sales volume. Long-term international coordination is widely supported, together with a One Health approach that integrates human medicine, veterinary medicine, and environmental sectors (Larsson & Flach, 2022). The 2015 WHO Global Action Plan on AMR called on countries to develop national action plans (WHO, 2015), and in 2024 the UN General Assembly adopted a political declaration that includes a target to reduce global deaths associated with bacterial AMR by 10% by 2030, against a 2019 baseline of 4.95 million (United Nations General Assembly, 2024).

Three points emerge from this comparison. First, the strategies are complementary rather than competing: stewardship and infection prevention act soonest and cost least but cannot create new drugs, whereas discovery and alternative therapies are slow and uncertain unless economic incentives make their development commercially viable (Årdal et al., 2020). Second, because AMR arises at the interface of human, animal, and environmental sectors, interventions confined to human clinical medicine are unlikely to be sufficient (Larsson & Flach, 2022; Van Boeckel et al., 2019). Third, the evidence base is weakest where the burden is greatest, as surveillance and intervention data from low- and middle-income countries remain scarce (Browne et al., 2021; Antimicrobial Resistance Collaborators, 2022).

EVIDENCE GAPS AND LIMITATIONS

Several evidence gaps emerged from this review. Surveillance data on resistance and antibiotic consumption remain sparse in many low- and middle-income countries (Antimicrobial Resistance Collaborators, 2022;

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Browne et al., 2021), which limits the precision of burden estimates and of forecasts such as the projections to 2050. The long-term effect of stewardship and diagnostics on resistance rates, the clinical efficacy of alternative therapies, and the real-world performance of new economic incentives are all insufficiently studied. It is also unclear how best to deliver integrated One Health interventions across human, animal, and environmental sectors.

Future Perspectives

The next decade is likely to depend on three developments:

- Translation of new discovery technologies, including machine learning and genome mining, into approved drugs with activity against critical Gram-negative pathogens;
- Implementation of sustainable economic models for antibiotics; and
- Strengthened global surveillance and stewardship, especially in low- and middle-income countries where the burden is greatest (Miethke et al., 2021; GBD 2021 Antimicrobial Resistance Collaborators, 2024).

Because resistance is a natural evolutionary response, no single new drug will solve the problem; continued innovation must go hand in hand with the preservation of existing antibiotics (Darby et al., 2023).

CONCLUSION

Antibiotics have a short history but an enormous impact. After a golden age of discovery in the mid-twentieth century and a long discovery void, resistance has become a global health emergency, with millions of deaths associated with resistant infections each year. Because the drivers span human medicine, agriculture, the environment, and economics, effective solutions require coordinated action: prudent use, strong infection prevention, and robust surveillance; investment in innovative discovery and alternative therapies; and new incentives that make antibiotic development sustainable. Our comparative appraisal suggests that no single intervention is sufficient and that closing the evidence gaps identified here, especially in low- and middle-income countries, should be a research priority.

ABBREVIATIONS

AI : artificial intelligence

AMR: antimicrobial resistance

AWaRe :Access, Watch, Reserve

ESBL: extended-spectrum β-lactamase

ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species

GBD:Global Burden of Disease

GDP:gross domestic product

GRAM:Global Research on Antimicrobial Resistance

KPC:*Klebsiella pneumoniae* carbapenemase

MRSA:methicillin-resistant *Staphylococcus aureus*

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NDM: New Delhi metallo-β-lactamase

PBP2a: penicillin-binding protein 2a

R&D:research and development

RND: resistance–nodulation–division

TB: tuberculosis;

UN:United Nations;

VRE:vancomycin-resistant enterococci;

WHO:World Health Organization.

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