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Ancient Roots and Modern Drivers of Antimicrobial Resistance: Resistance is Inevitable, but Crisis is Amplified by Human Activity

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Abstract Antimicrobial resistance (AMR) is both a natural evolutionary phenomenon and a modern public health crisis. Ancient microbial genomes reveal that resistance mechanisms long predate human medicine, underscoring the inevitability of microbial adaptation. However, contemporary human activities, including the widespread use of antibiotics in healthcare, agriculture, and industry, have dramatically accelerated the scale and impact of resistance. This editorial integrates genomic evidence from ancient isolates with current trends to highlight how human behavior amplifies an otherwise natural process into a global threat. By framing AMR as both historically rooted and socially driven, we emphasize the urgent need for coordinated stewardship, innovation in therapeutics, and global policy interventions to mitigate its escalating burden.

Keywords: *Antimicrobial resistance (AMR), Ancient microbial genomes, resistance mechanisms, antibiotics in healthcare, genomic evidence, stewardship, human behavior*

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1. Introduction

Antimicrobial resistance (AMR) is often portrayed as a modern crisis, a consequence of the antibiotic era that began with the discovery of penicillin in 1928. Yet recent findings challenge this narrative. The study of *Psychrobacter* SC65A.3, a strain isolated from the perennial ice block of Scarisoara Ice Cave, Romania, provides critical insights into the genetic reservoir of AMR and virulence determinants preserved in ancient cryoenvironments [1]. Whole-genome sequencing revealed a complex repertoire of resistance genes, underscoring the evolutionary persistence of multidrug resistance (MDR) traits in extreme ecological niches. MDR is the ability of microorganisms (like bacteria) to resist multiple antimicrobial drugs. A total of 107 AMR-associated genes were identified, of which 44 were directly linked to the observed MDR phenotype. Among these, beta (β)-lactam resistance genes (*ampC*, *ftsI*, *ampD*, *ampG*) were prominent, conferring hydrolytic activity against penicillins and cephalosporins. Resistance to fluoroquinolones was mediated by mutations in *gyrA*, *gyrB*, *parC*, and *parE*, which encode deoxyribonucleic acid (DNA) gyrase and topoisomerase subunits. Efflux-mediated resistance was widespread, with genes such as *mexA*, mexB, *oprM*, *emrK*, *mdtA*, *mdtK*, *macB*, *mepA*, *msbA*, *macA*, *bcr*, and *emrE*, enabling broad-spectrum tolerance to aminoglycosides, tetracyclines, macrolides, and other drug classes. Additional resistance determinants included *tetA* and *tetC* (tetracycline efflux), *rpoB* (rifampin resistance), *dfrA* and *folP* (trimethoprim / sulfonamide resistance), and notably *mcr1* (mobilized colistin resistance-1), which confers resistance to colistin, a last-resort antibiotic. Heavy metal resistance genes (*arsA*, *arsB*, *arsC* for arsenic; *merA*, *merP*, *merR* for mercury) further highlighted the strain's adaptive potential in hostile environments.

Beyond resistance, the genome encoded a diverse set of virulence and antimicrobial activity genes, suggesting dual ecological roles as both competitor and survivor. Genes such as *sunS* (sublancin biosynthesis), *pikAII* (pikromycin), *btrK* (butirosin), *rebO* (rebeccamycin), *dpgD* (glycopeptide biosynthesis), *bacC* (bacitracin), *bpoA2* (haloperoxidase), *cetB* (cetoniacytone A), *rdmC* (anthracycline tailoring enzyme), and *sdhE* (succinate dehydrogenase assembly factor) were identified, many of which are associated with the production of bioactive secondary metabolites. These genetic features were corroborated phenotypically: *Psychrobacter* SC65A.3 inhibited the growth of 14 clinically relevant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, *Enterobacter*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. Such activity underscores the strain's potential as a source of novel antimicrobial compounds.

The genome of *Psychrobacter* SC65A.3 from cryoenvironments highlights the dual nature of microbial

survival, encoding both MDR genes such as *mcr1* and biosynthetic pathways for antimicrobial compounds. This demonstrates that AMR is an ancient evolutionary trait shaped by ecological competition, not a modern invention. However, the present global AMR crisis is largely human-driven, with excessive antibiotic use in medicine, agriculture, and industry intensifying selective pressures and escalating a natural process into a public health emergency. Cryoenvironments therefore act as reservoirs of both resistance genes and novel bioactive molecules, offering insights into resistance evolution and opportunities for drug discovery. While resistance is inevitable, its scale and impact are strongly influenced by human behavior [2,3].

Microbial communities have long engaged in chemical competition, producing antimicrobials and evolving mechanisms to withstand them. This ancient "resistome", that refers to the entire collection of AMR genes present in microbial communities, including those expressed, silent, or latent, confirms that resistance is an inherent and enduring feature of microbial life, existing long before clinical antibiotic use [2]. Despite its ancient origins, modern AMR is unprecedented in scale. Widespread and often inappropriate antibiotic use has accelerated the emergence and spread of resistant pathogens, including carbapenem-resistant bacteria that pose serious threats in healthcare settings due to high mortality and limited treatment options [3,4]. Unlike slow natural evolution, modern practices expose microbes to intense and widespread antimicrobial pressure. The contrast between ancient and contemporary AMR underscores that resistance itself is unavoidable, but its amplification is not. In natural ecosystems, resistance was diffuse and ecologically balanced, whereas today it is concentrated, clinically significant, and rapidly disseminated through human activity. Misuse of antimicrobials, agricultural practices, global travel, and weak regulatory oversight have transformed resistance into a global health challenge [3,5]. As shown in Figure 1, the genomic analysis of *Psychrobacter* SC65A.3 reveals a diverse resistome comprising 107 AMR-associated genes. These include efflux pumps and β-lactamases, which are widespread across bacterial taxa, as well as the *mcr1* gene, a determinant of colistin resistance that is of particular clinical concern. The spatial distribution and diversity of these genes emphasize that AMR is not a modern phenomenon but an ancient evolutionary trait. This figure visually reinforces the manuscript's central argument: while resistance is inevitable, its amplification into a global crisis is driven by human activity.

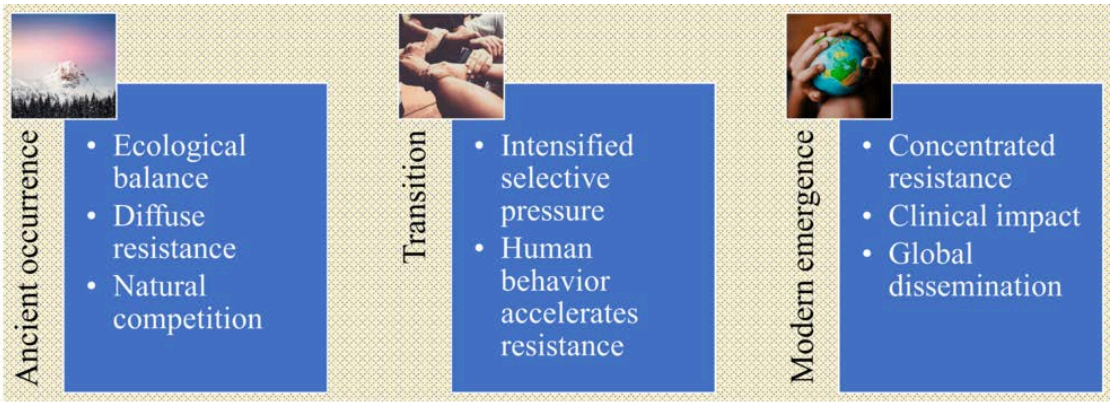

Figure 1. Antimicrobial resistance from ancient ecological occurrence to modern amplification

Table 1. Ancient vs. modern features of antimicrobial resistance and their impact

Feature	Ancient resistome (e.g., Psychrobacter SC65A.3)	Modern crisis drivers	Impact
Origin	Naturally occurring in microbial genomes, predating human antibiotic use	Emerges from widespread clinical and agricultural antibiotic application	Ancient demonstrates inevitability of resistance; modern highlight's human role in accelerating crisis
Balance	Maintained within ecological systems without large-scale disruption	Amplified by human misuse, overprescription, and poor stewardship	Ancient balance preserved; modern imbalance leads to treatment failures
Genetic diversity	Broad spectrum of resistance genes (efflux pumps, β-lactamases, mcr1)	Rapid horizontal gene transfer across pathogens in hospitals and farms	Ancient diversity shows evolutionary adaptation; modern transfer accelerates global spread
Clinical impact	Limited relevance in ancient environments	Direct threat to treatment efficacy in modern healthcare	Ancient resistome poses minimal risk; modern resistome undermines frontline therapies
Transmission	Localized within environmental niches	Globalized through trade, travel, and healthcare networks	Ancient containment; modern dissemination creates worldwide health emergency
Drivers	Evolutionary adaptation to natural microbial competition	Human activity: overuse in medicine, agriculture, and lack of regulation	Ancient drivers inevitable; modern drivers preventable through stewardship
Outcome	Resistance inevitable but contained	Resistance inevitable and amplified into a global health crisis	Ancient resistome informs scientific understanding; modern resistome demands urgent policy action

mcr1: mobilized colistin resistance-1

This image has been created by the authors from references [2,3,4,5].

Table 1. expands the comparative framework by including the impact of ancient versus modern AMR. While ancient resistomes illustrate the inevitability of resistance as an evolutionary trait, modern drivers transform this inevitability into a global health crisis.

This table has been created by the authors from references [1,2,3,4,5].

Beyond clinical misuse, socioeconomic and behavioral

factors play a pivotal role in accelerating AMR. In many community settings, antibiotics are frequently obtained without prescription, leading to inappropriate use for viral infections or incomplete treatment courses. This misuse fosters selective pressure that accelerates resistance development. Pharmaceutical industry practices, including aggressive marketing and insufficient investment in novel antimicrobials, further exacerbate the crisis. Additionally, disparities in healthcare access drive self-medication and reliance on informal drug markets, particularly in low- and middle-income countries (LMICs). Behavioral factors such as patient demand for antibiotics, physician overprescription to satisfy expectations, and lack of public awareness campaigns contribute to widespread misuse. Collectively, these socioeconomic and behavioral drivers transform a natural evolutionary phenomenon into a global public health emergency [6,7,8].

Effective regulatory oversight must be tailored to the realities of diverse healthcare systems and agricultural practices. In high-income countries, robust prescription monitoring, electronic health records, and centralized reporting can enforce stewardship programs. In contrast, LMICs often face challenges such as limited infrastructure, informal drug markets, and uneven access to healthcare. Here, scalable interventions, such as community-based education, stricter controls on over the counter (OTC) antibiotic sales, and partnerships with local health workers, are more feasible. In agriculture, oversight should balance productivity with public health by restricting non-therapeutic antibiotic use, incentivizing alternatives such as vaccines and probiotics, and ensuring compliance through transparent supply-chain audits. These efforts must be supported by robust international collaboration, encompassing surveillance, data sharing, and coordinated action plans that transcend national boundaries. Public awareness campaigns are vital to educate communities about responsible antibiotic use and the risks of misuse, thereby fostering behavioral change at the societal level. Finally, stronger regulatory oversight is required to enforce policies governing antibiotic distribution, sales, and industrial applications, ensuring that human activity does not continue to accelerate an otherwise inevitable biological process [9,10,11].

Looking ahead, the fight against AMR will increasingly rely on forward-thinking strategies that integrate technology, policy, and innovation. Artificial intelligence (AI) offers powerful tools for surveillance, enabling real-time analysis of resistance patterns and predictive modeling to guide interventions before crises emerge. Strengthened global cooperation frameworks are equally vital, ensuring that surveillance data, regulatory standards, and best practices are shared across borders to create a unified response. At the therapeutic level, investment in novel antimicrobials, vaccines, and alternative approaches such as bacteriophage therapy or microbiome modulation will be essential to outpace evolving pathogens. By embracing these future-oriented strategies, the global community can move beyond reactive measures and toward proactive, sustainable management of resistance [12].

In conclusion, AMR is not a modern anomaly but an intrinsic feature of microbial evolution. Genomic evidence from ancient isolates demonstrates that resistance mechanisms have existed for millennia, underscoring the inevitability of microbial adaptation. What transforms this natural process into a global health crisis, however, is the scale and intensity of human activity, particularly the misuse and overuse of antibiotics in medicine, agriculture, and industry. By accelerating the spread and persistence of resistant strains, human behavior has amplified a biological inevitability into a societal emergency. Addressing this challenge requires a dual recognition: resistance cannot be eradicated, but its impact can be mitigated. Coordinated stewardship, investment in novel therapeutics, and global policy frameworks are essential to slow the amplification of resistance and preserve the effectiveness of existing treatments. Ultimately, the crisis of AMR is not solely a scientific problem but a reflection of human choices, and its resolution depends on collective responsibility and sustained action.

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