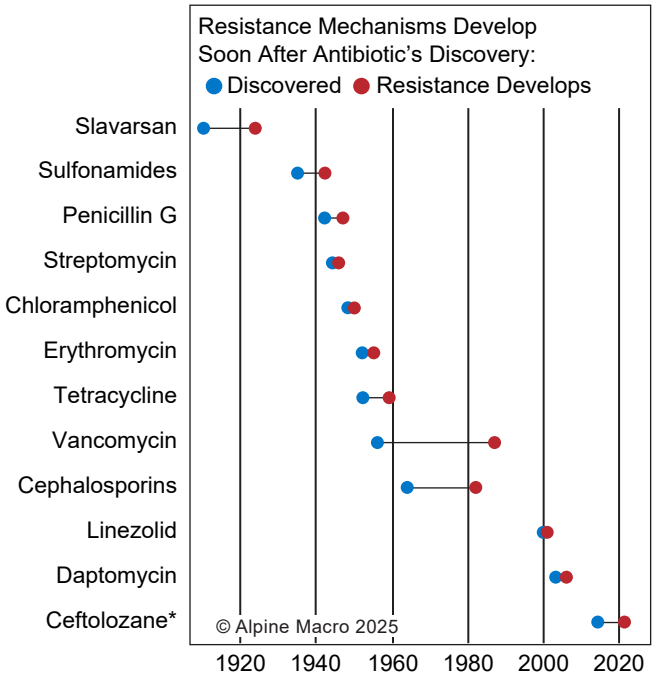
The Silent Pandemic: The Rise Of Antimicrobial Resistance

Essential pillars of modern healthcare, antimicrobial medicines – including antibiotics, antivirals, antifungals, and antiparasitics – are crucial for fighting and preventing infections. However, chronic misuse and overuse of these broad-spectrum medicines in both pharmaceutical and agricultural settings have led to the emergence of antimicrobial-resistant (AMR) "superbugs". These drug-resistant bacteria, viruses, fungi, and parasites pose an existential threat to humanity, arguably making AMR the world's most urgent public health crisis. To date, initiatives to combat AMR from global health bodies lack urgency and an effective coordination road-map to tackle the global challenge.

The most recent figures by WHO indicate that AMR is directly responsible for over 1.2 million deaths annually and is associated with nearly 5 million deaths. The health body consequentially ranked AMR among the top three global public health threats, alongside cancer and cardiovascular diseases. AMR already kills more than HIV, malaria, and tuberculosis combined.

The increasing prevalence of multidrug-resistant organisms (MDROs) represents the most significant health threat. These organisms are categorized into three levels based on their resistance to antimicrobial agents, with each level representing a greater threat. The most severe category, level three, is pan-drug resistant. While pan-drug resistant organisms are considered the most deadly as they show resistance to all available antimicrobial agents, MDROs are on the rise across all three classifications.

Chart 1 AMR Quickly Follows Drug Development



Source: United Nations Environment Programme
*With tazobactum

MDROs pose a dual hazard: they impede doctors' capacity to treat current infections effectively and raise significant safety concerns for common medical procedures. However, the most alarming risk is the increasing possibility of an AMR triggered pandemic. This threat has been exacerbated by several factors, including rapid urbanization, climate change, and the widespread misuse of antibiotics during the COVID-19 pandemic – all of which have contributed to enhancing bacterial resistance to existing medications.

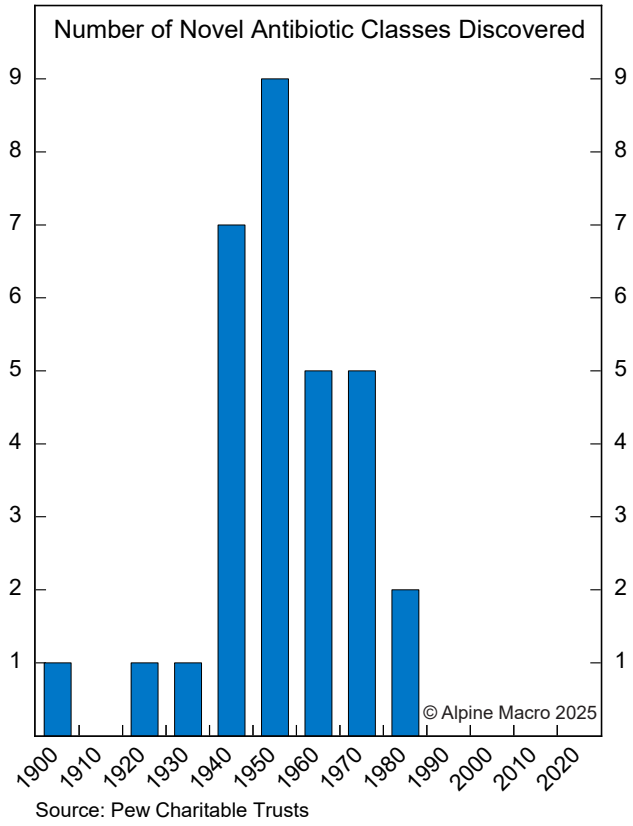
This report will explore the AMR threat and highlight emerging technologies at the forefront of the fight against AMR, including next-generation diagnostics, artificial intelligence, synthetic biology, and phage therapy. Developing innovative tools to combat AMR is not only critical for public health but also essential for ensuring a stable and dependable food supply in the future.

A Rapidly Deteriorating Global Crisis

The impact of AMR is projected to worsen drastically in the coming decades. Bacteria, the primary organisms associated with AMR, can multiply approximately every 20 minutes, leading to exponential growth of resistance. This poses a significant challenge to lengthy drug development timelines, positioning novel therapeutic development always "one step behind" their targets (**Chart 1**). Recent novel analyses of the global impact of AMR highlight the urgency of the situation. Consider the following:

- Since 1990, AMR morbidity rates among the elderly have increased by 80%.[1] Adding fuel to the fire, novel antibiotic development has stagnated with several critical-priority pathogens identified by the WHO not seeing new drugs in over 50 years (**Chart 2**).

Chart 2 Novel Antibiotic Development Has Fallen Off A Cliff

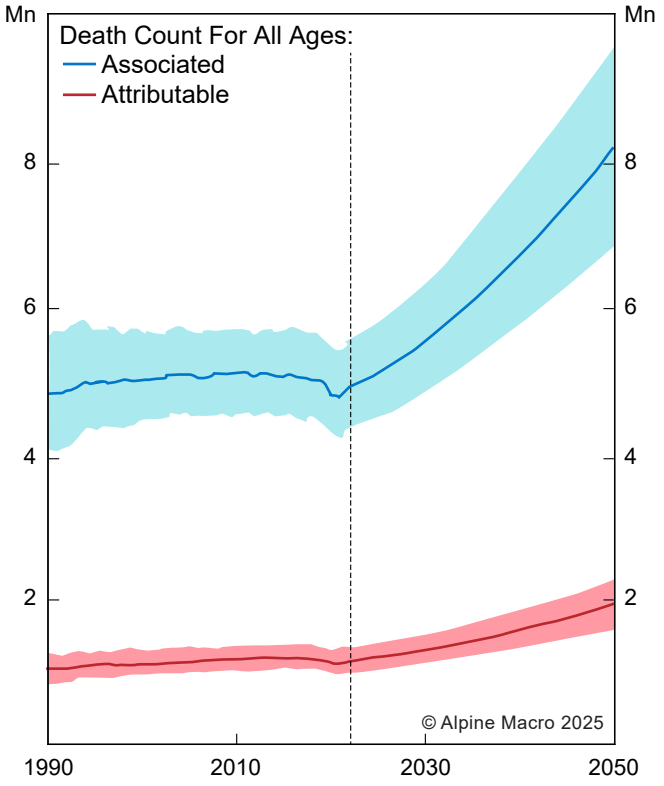


Source: Pew Charitable Trusts

- By 2035, AMR is expected to reduce global life expectancy by an average of 1.8 years, with associated costs of $412 billion annually in healthcare expenses and $443 billion in lost workforce productivity.[2]
- By 2050, AMR-related deaths are anticipated to double (**Chart 3**), claiming nearly 40 million lives over the next 25 years and replacing cancer as the world's most deadly disease[3] (**Chart 4**). This

1 Global Research on Antimicrobial Resistance Project
2 Global Leaders Group on AMR
3 Global Research on Antimicrobial Resistance Project

Chart 3 AMR Becoming Deadlier

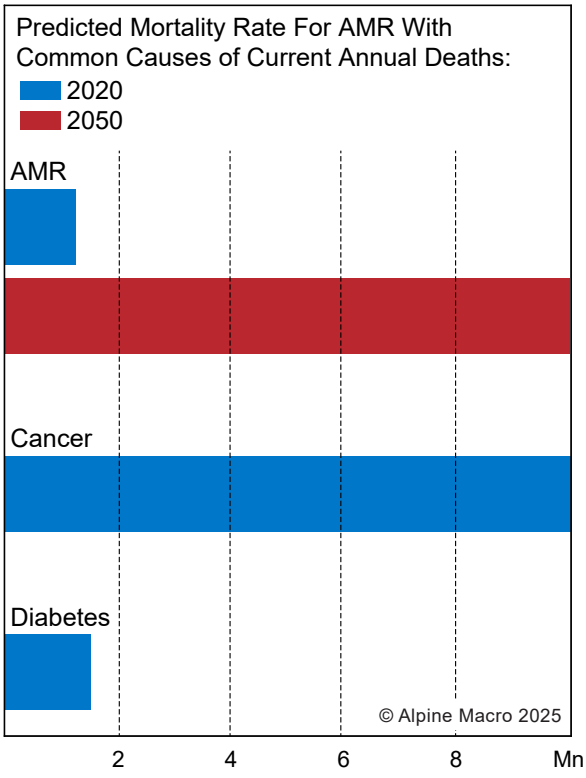


Note: Vertical line denotes start of forecast; source: Naghavi, Mohsen et al, "Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050" (September 2024)

would lead to an estimated $1 trillion in additional annual healthcare costs and $1-3.4 trillion loss to global GDP per year by 2030.[4]

Climate change is a significant driver of AMR. Rising temperatures extend the lifespan and geographic range of bacteria, viruses, fungi, and parasites. In addition, warmer temperatures promote horizontal gene transfer – the exchange of genetic material, including antibiotic resistance genes. Severe rainfall and flooding also exacerbate AMR by contaminating water sources through antibiotic absorption. Wastewater is known as a "reservoir for antibiotic-resistance genes".

Chart 4 AMR Will Eclipse Cancer Deaths By Mid-Century



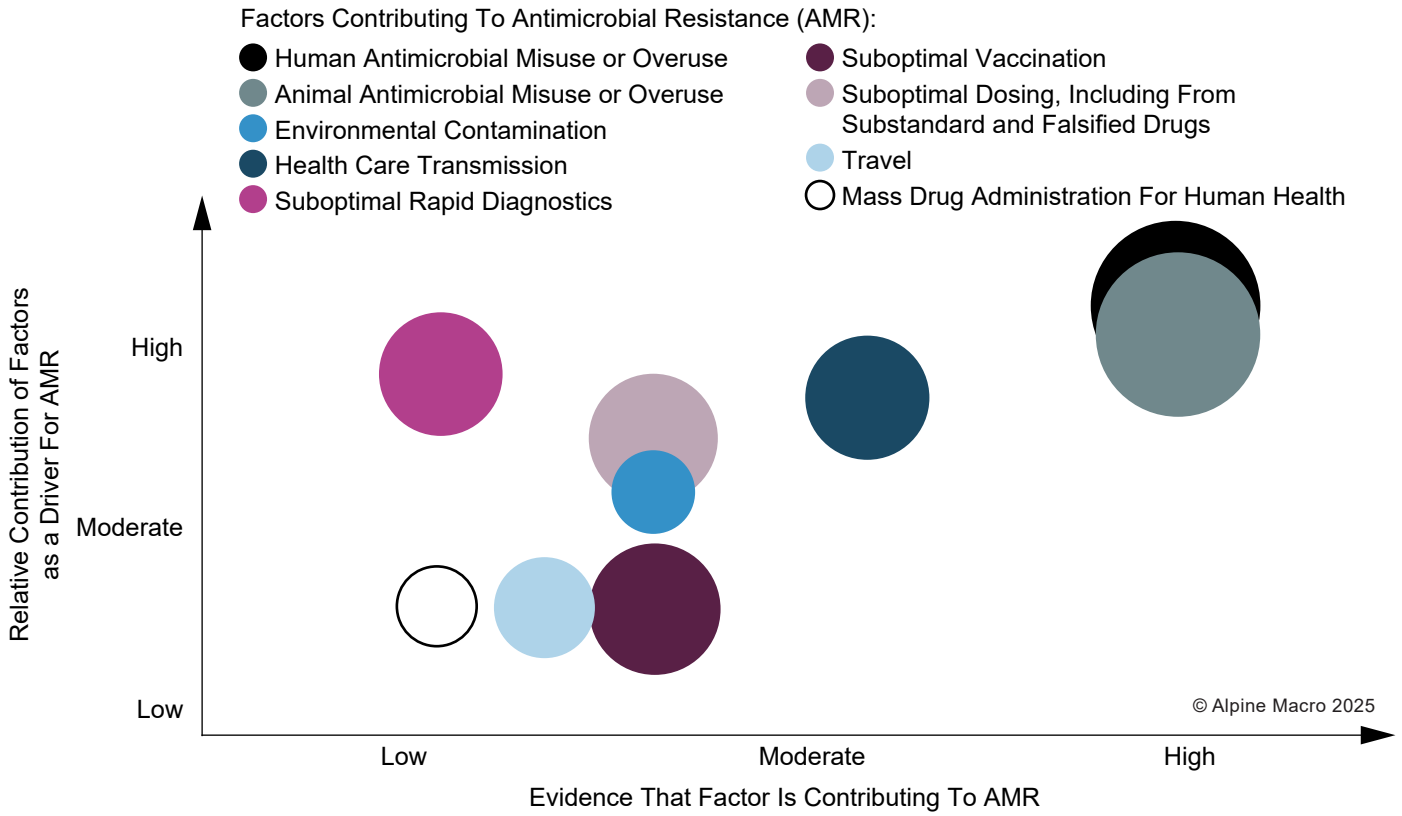
Source: United Nations Environment Programme, adapted from Jim O'Neil's work for Wellcome

Despite these factors, the primary driver of AMR remains the overuse and misuse of antibiotics in healthcare and agriculture (**Chart 5**). In the U.S., 28% of antibiotic prescriptions are unnecessary, while in emerging economies, the number is between 30-50%. Agriculture, where roughly 70% of antibiotics are administered on a yearly basis, is a primary driver for environmental antibiotic contamination due to a lack of agricultural wastewater treatment infrastructure. By mid-century, AMR in livestock could result in production losses equivalent to the annual food consumption requirements of 746 million people.[5]

4 World Bank

5 Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Food-Producing Animals

Chart 5 Anthropogenetic Factors Are Main AMR Drivers



Novel Testing Capabilities Proving Valuable

Rapid diagnostic tests have been a key "missing link" in the AMR fight. Precise and rapid organism identification and antibiotic susceptibility testing are paramount to optimizing patient outcomes. Testing is evolving from the previous "gold standard" of labor-intensive, costly, and slow culture-based techniques to rapid whole genome sequencing (WGS) testing.

Emerging WGS capabilities represent a new weapon in the AMR fight, enabling rapid pathogen identification and antibiotic resistance detection in a single assay without the need for culturing (Table 1). This process requires two key components: an aligner

Table 1 WGS Proving Disruptive

Traditional Screening Vs WGS	
Generalized Approach	**AMR Stewardship**
Empirical diagnosis based on symptoms	Empirical diagnosis based on symptoms
Broad-spectrum antibiotic treatment begins	Culture sample taken for identification (optional AMR screen)
Time with potentially incorrect treatment	Rapid molecular screen (based on empirical narrowing) for ID and AMR
	Begin treatment with targeted therapeutic
Treatment reviewed if patient not responding or from culture information	Improved patient outcomes, Lowered Risk of AMR

Source: "Limitations of current techniques in clinical antimicrobial resistance diagnosis: examples and future prospects" (June 2024)

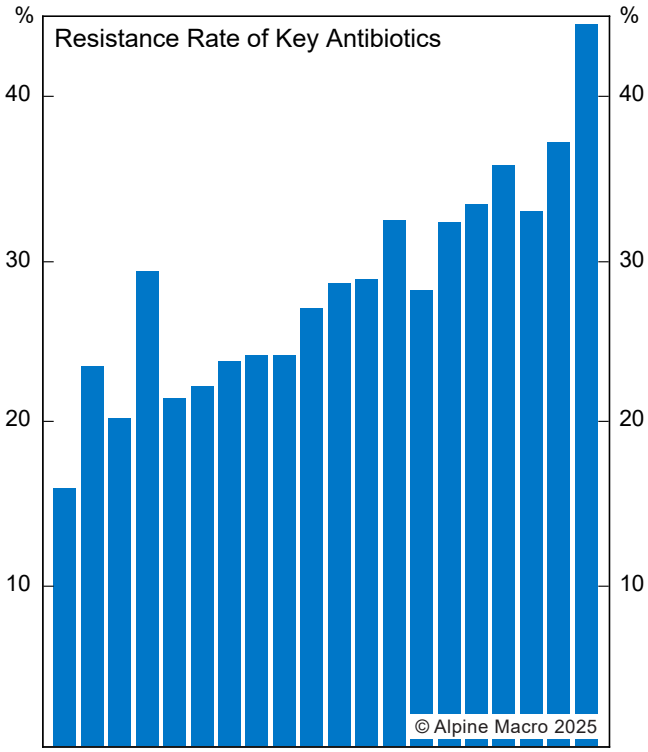
(an algorithmic tool that maps sequencing reads to a reference genome to pinpoint their locations and support genome analysis) and a database of known AMR gene sequences along with their associated resistance phenotypes.

Leveraging WGS is proving to be a highly valuable first line of defense. For example, Oxford Nanopore is using its whole genome sequencing technology to accelerate testing timelines "from days in a Petri dish to hours" using sequencing technology. The platform, the size of a printer, can give its first view on what the pathogen is within half an hour, and a full report in two hours. In another example, Sysmex has developed a smartphone-sized cartridge to detect a bacterial infection in 15 minutes and identify the right antibiotic to treat it in 45 minutes. WGS-based testing is key to mitigating inappropriate antibiotic selection in the treatment process.

AI Driving An AMR Therapeutic Revolution

Novel therapeutic formulation to combat AMR is of critical importance. While the exact resistance rate for pan-drug resistant organisms remains unknown, approximately 44% of antibiotics classified as "essential" are already ineffective depending on the target (**Chart 6**). As a result, AI's most promising application in addressing AMR lies in novel drug development. More specifically, AI's computation capabilities are revolutionizing R&D, shaving timelines from years to weeks or even days. Key AI-driven benefits that accelerate drug discovery include rapid pathogen identification, predictive bioactivity modeling, complex molecular simulations, and the generation of safety profiles for new drug candidates.

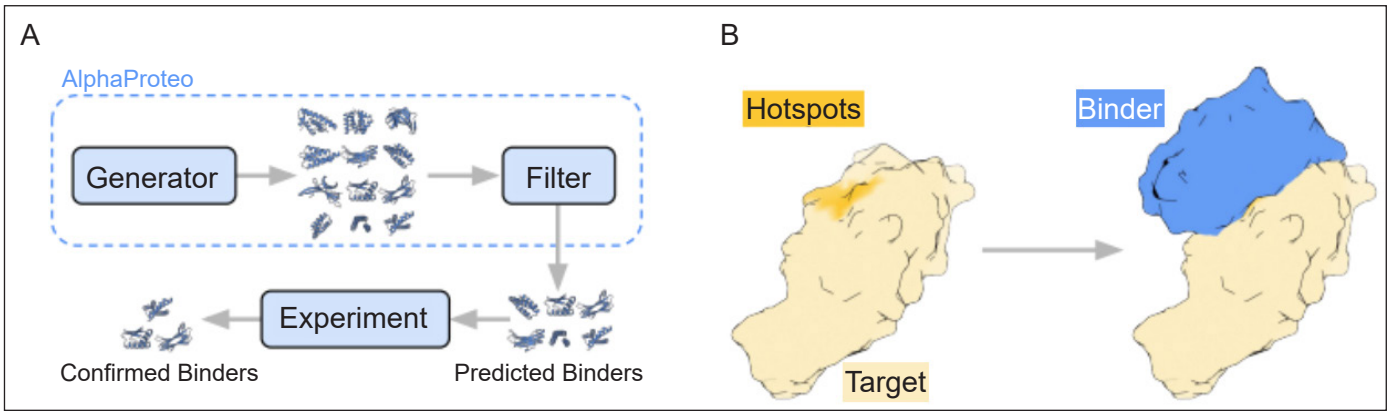
Chart 6 Nearly 50% Of Essential Antibiotics Are Ineffective



Source: McDonnell et al., Center for Global Development, 2023

Scientists estimate that over 10^{60} possible drug-like molecules could be formulated given necessary computing capabilities. Several AI-powered applications are enabling researchers to explore previously inaccessible regions of chemistry. For instance, DeepMind's AlphaProteo model allows researchers to design novel, high-affinity proteins that bind to target molecules with unprecedented precision (**Chart 7**). This model has produced proteins with binding strengths 300 times that of current methods and successfully designed binders across diverse targets, including cancer-related proteins. Similarly, Stanford's SyntheMol AI tool for molecular synthesis has successfully developed novel therapeutic formulations targeting resistant strains of *Acinetobacter baumannii*, a leading AMR-related pathogen. These advanced

Chart 7 AI Tools Unlocking Molecular Level Therapeutic Precision



Source: Unite.AI, "AlphaProteo: Google DeepMind's Breakthrough in Protein Design" (September 2024)

AI tools understand molecular building blocks and validate chemical reaction outcomes with unparalleled accuracy and speed, marking a pivotal shift from trial-and-error approaches to high-confidence biological targeting.

Synthetic Biology, Phage Therapy, And CRISPR Offer Hope

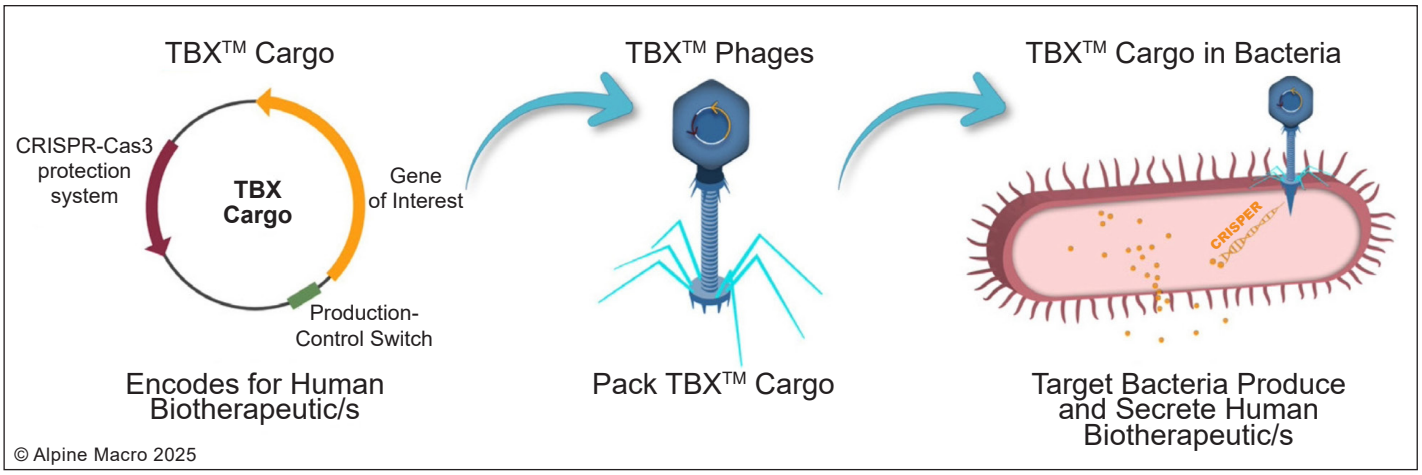
Synthetic biology, a multidisciplinary field focused on engineering new or modified living organisms, is showing efficacy in combating superbugs. As naturally derived antibiotics like penicillin and cephalosporins become increasingly ineffective, synthetic biology is poised to be highly disruptive. Specifically, synthetic biology is critical to the design of engineered molecules that are synthesized with properties/functions to target AMR "weak links".

Bacteriophages (phages), widely used in the 1920s before antibiotics, are regaining interest for their potential efficacy against AMR with support from advanced synthetic biology. Phages are viruses that destroy bacteria. While phages occur naturally, synthetically engineered phages enhance their precision and effectiveness. Unlike broad-spectrum antibiotics, phages specifically target a single bacterial strain or species, reducing collateral damage to the microbiome. They also carry molecular patterns recognized by immune receptors, triggering an immune response.

To date, 5,000 phages have been isolated, with 750 fully sequenced. Of these, 70% infect only 12 bacterial hosts. This diversity is advantageous, if a bacterial strain becomes resistant to one phage, another phage can often be identified to target it. Phages are now being tested against all bacteria on the WHO's critical priority list, including *Salmonella* and *Pseudomonas aeruginosa*.

In 2018, [redacted] established the [redacted] Phage Therapy Center, a world leader in phage therapy research. Albeit data from limited treatment applications, the center reports a 78% success rate in using phages to treat bone infections. In 2019, engineered phages achieved a milestone by successfully treating a cystic fibrosis patient with antibiotic-resistant

Chart 8 **CRISPR Revolutionizing Phage Therapy**



Source: Kathy Liszewski, "Phage Therapy's Neglected Potential Is Finally Being Realized", (September 2024)

Mycobacterium abscessus. Multiple clinical trials are underway exploring phage therapy to combat superbugs.

The advent of CRISPR/Cas9 systems has significantly enhanced phage capabilities, making them more effective at targeting bacteria. CRISPR systems can "guide" phages to target specific virulent genes, enabling the phages to destroy bacteria more efficiently (**Chart 8**). One notable example in clinical development is SNIPR Biome, which has engineered phages with CRISPR-Cas machinery to specifically target *Escherichia coli*.

While both engineered and CRISPR-enhanced phage therapies are still in their early stages, they hold great potential to expand the medical arsenal against AMR. However, challenges remain as no phage therapies in the U.S. are FDA-approved for human use and current phage therapies require extreme customization for each patient, limiting scalability. However, phages' most valuable trait is offering a pathway to less antibiotic use, reducing the self-fueling cycle of AMR and a path forward not totally reliant on antibiotics.

A Novel Age Of Antimicrobial Therapeutics

Currently, pharmaceutical companies are incentivized to maximize antibiotic sale volumes, often contributing to overuse and increased resistance. This is because antibiotic development is plagued by low ROI due to high R&D costs and their "one-and-done" treatment model. Over the past 20 years, all seven publicly traded small antibiotic companies that received FDA approval have either gone bankrupt or been sold in distress.

Advances in AI and automation are helping to create economically viable new classes of therapeutics to combat AMR, but a new pharmaceutical framework is urgently needed. Efforts to reform the business model include initiatives like the U.K.'s subscription-style payment system, which provides pharmaceutical companies with a fixed annual fee for access to new antibiotics, and Sweden's model, which guarantees a minimum annual revenue in exchange for a secure supply.

Table 2 Growing AMR-Focused Therapy Pipeline

Pathogen Category	Phase of Clinical Development				Total
	Phase I	Phase II	Phase III	Preregistration	
Priority Pathogens	22	25	11	4	62
Mycobacterium Tuberculosis	6	12	1		19
Clostridioides difficile	3	8	3		14
H. Pylori	1		1		2
Total	**32**	**45**	**16**	**4**	**97**

Source: WHO

Despite challenges, there is an expanding range of therapeutic development worldwide testing new antibiotics/phages to target critical pathogens (Table 2). This "new wave" of drugs could mark a step-change in solutions against AMR. Notably, novel therapies are proving effective against gram-negative bacteria, which are particularly resistant due to their protective outer membrane. For example, Roche's Zosurabalpin, currently in phase 1 clinical trials, prevents the formation of this membrane and targets carbapenem-resistant *Acinetobacter baumannii* (CRAB), a pathogen with a mortality rate of approximately 60%.

Investment Consideration

AMR is a global crisis that transcends borders, posing severe threats to public health, economic stability, and societal progress. The Investor Action on AMR, a coalition representing over 80 institutions with $13 trillion in assets, has recently called for immediate action from global policymakers. The consortium described AMR as a *"systemic risk akin to climate change... (jeopardizing) global financial markets, economic stability, and long-term value generation."*

Innovation is central to addressing this escalating threat. Government support is emerging as a key accelerator, including initiative like TARGET that aim to transform antibiotic discovery by screening over 107 million molecular candidates with AI and deep learning. Developing new antibiotics and related innovations could boost global GDP by $960 billion by 2050, while delivering significant cost savings to healthcare systems and offering a $28 return on every dollar invested.

Key technologies at the forefront of the fight against AMR present unique long-term public health investment opportunities. AI is positioned as a key enabler across next-generation diagnostics, phage therapy, and CRISPR. Additionally, advanced wastewater treatment technologies are critical for reducing the spread of antibiotic-resistant genes in the environment, acting as a frontline defense against AMR's proliferation and a way to diversify AMR-focused investment.[6]

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6 Alpine Macro *Innovation Themes & Strategy* "Future Water Security Hinges On Innovation" (November 20, 2024).