Overcoming the Bottlenecks: Challenges and Solutions Before the Threshold of The Post-Antibiotic Era

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Abstract
The worldwide threat of antimicrobial resistance (AMR) has given rise to the necessity of new antibiotics. Nevertheless, there are severe economic, scientific and regulatory problems that are encountered in the development of new antibacterial agents. This study focuses on economic barriers to antibiotic development including the excessive cost of development (more than $1 billion) and insufficient returns on investment. The traditional market model that uses high sales volumes cannot be applicable to antibiotics because of low usage and stewardship policies. The paper suggests new economic models, e.g., prepayment and subscription models that would uncouple profits and the sales volume and offer stable revenue sources to the companies without overuse. In addition, the study proposes the implementation of market entry incentives of up to 1 billion dollars to help the companies bear the risk of investing in new antibiotics. The issue of the public-private partnerships and shared investments in helping small firms, which currently dominate most of the antibiotic innovations, is also discussed in the paper. Through the combination of these new economic and policy models, the paper presents a complete solution to jump-start antibiotic R&D, aligning the financial incentives to meet the goals of public health and making the fight against AMR sustainable.

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1. Introduction

The invention of antibacterial substances in the first half of the 20th century revolutionized the field of medicine and radically reduced the number of people dying of infectious diseases [1]. The Salvarsan and Prontosil early chemotherapeutic agents set the precedent that synthetic chemicals could specifically attack the pathogen. The modern antibiotic era came into existence with the serendipitous discovery of penicillin by Alexander Fleming 1928 and the large-scale production of penicillin during World War II [2].

A decline in investment in research, inefficient development of candidate molecules, a poor success rate, and the inappropriate use of antibiotics in the world have been termed a new antibiotic crisis. The ongoing crisis has created a harmful cycle where pathogens develop resistance to new treatments faster than these treatments can be discovered. This threatens public health systems and drives up the costs of hospital stays and therapies [3].

Although it is acknowledged that antibiotic resistance poses the greatest global health threat, the antibiotic research pipeline is at-risk under-funded because of a number of scientific, economic and regulatory factors. The high financial burden of antibiotics development coupled with low profitability has caused the large pharmaceutical companies to lose interest in antibiotics development, leaving the field to academic institutions and small- to medium-sized enterprises that cannot afford the expensive

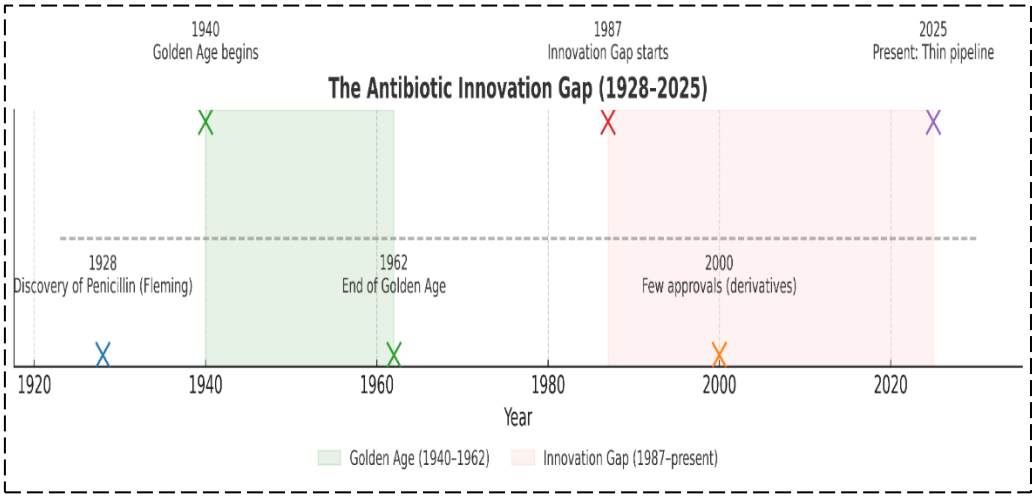

Fig 1: The antibiotic innovation Gaps.

late-stage clinical trials [4]. Awareness of this crisis has recently given rise to a new wave of worldwide policy initiatives and policy support action. Significant efforts have recently been made through the 10- x / 20- Infectious Diseases Society of America project, a plan to produce 10 new antibiotics by 2020 and the WHO Global Action Plan to raise awareness, improve surveillance, and intensify investment in the development of new drugs [5].

To successfully combat this problem, researchers acknowledge that innovative economic models are required that will provide an incentive to develop antibacterial therapies against the infection of inadequate numbers of patients to normally rationalize investment in research by the companies of the traditional private sectors. The reward systems will have to be significant, estimated at a billion dollars in total payout-to be in competition with returns in other therapeutic areas, to maintain investment in antibiotics development [6].

Antimicrobial resistance is now a world health epidemic. In a comprehensive modelling, it was estimated that 4.95million deaths in 2019 were linked to bacterial AMR and 1.27million deaths were directly linked to AMR. More than 1.5 million deaths were recorded because of lower respiratory infections, and six bacterial pathogens such as Escherichia coli, Staphylococcus aureus, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* caused 929 000 deaths linked to AMR [7]. Such statistics are already higher than the HIV/AIDS or malaria mortality worldwide. According to the warning released by the UK Review on Antimicrobial Resistance, by 2050, up to 10 million deaths a year may be the result of AMR unless new medicines and stewardship are introduced, and the cumulative loss of the overall economy globally is forecasted as US$100 trillion [8]. The drop-off in new antibiotic development is coincident with few financial and regulatory incentives. It takes ten to fifteen years and exceeds 1 billion dollars to develop a new antibiotic only to require that new agents be used sparingly to support stewardship, contradicting what justifies the investment [9]. Together with the scientific barriers outlined above, these negative economic incentives can only explain why there has been little in the way of new classes entering clinical trials over the past several decades. Ribeiro da Cunha noted that of the new antibacterial only a single product received approval each year by the U.S. Food and Drug Administration in 20042009 and eight antibiotics or combinations have been filed between 2011 and 2014. The World Health Organization has repeatedly warned that time is running out to prevent the loss of miraculous cures [1].

Despite the fact that there has been exhaustive research on biological issues of antibiotic resistance, there is still a conspicuous gap in the economic and regulatory aspects concerning as to why there is no more development of novel antibiotics. Absence of financial benefits, the difficulties of classic economic approaches, and the lack of support on the part of public-private alliances are the barrier to innovation in this area.

Ultimately, this review paper examines the economic and regulatory challenges affecting the antibiotic research and development pipeline. This study aims to address viable solutions to the issue of developing new antibiotics in the face of incentives (including, but not limited to, proposals of new economic models, like prepayment and subscription systems) and studying policy responses all over the world, which can be used to promote further development of new antibiotics, at the same time being accountable to promote the proper use of the same in combating antimicrobial resistance. Unlike prior reviews that predominantly address antimicrobial resistance from isolated biological, economic, or policy perspectives, this manuscript presents an integrated, stage-linked analysis of the antibiotic research and development (R&D) crisis that connects scientific bottlenecks with economic incentives and regulatory frameworks across the full innovation lifecycle. By systematically aligning emerging discovery technologies, including artificial intelligence–assisted screening, genome mining, and non-traditional antimicrobialswith push and pull economic mechanisms and evolving regulatory strategies, this review offers a unified framework for understanding why antibiotic innovation has stalled and how it may be sustainably revived. In particular, the mapping of policy instruments to discrete R&D stages provides a practical tool for funders, regulators, and policymakers to target interventions where failure risk is greatest. By synthesizing recent scientific advances (2023–2025) with real-world policy pilots such as subscription and delinked reimbursement models, this review moves beyond descriptive accounts to propose a coherent, actionable pathway for restoring antibiotic innovation while preserving stewardship and equitable global access.

2. Historical perspective and the current pipeline

The initial few decades of antibiotic era were characterized by a heroic eruption of chemical ingenuity: a total of twenty-seven chemically distinct classes of antibiotics found their way into markets between 1940 and 1962, yet not even two bona fide novelty classes have emerged since 1962, See figure 2 [10]. A systematic timeline of antibiotic development recognized the golden years of discovery as 1943-1962, when 31 classes were discovered; it was during this period that the antibiotics became amenable to total synthesis, which the timeline states has been in a discovery vacuum since 1987, as those few antibiotics approved since 2000 and which include oxazolidinones, lipopeptides, pleuromutilins, diarylquinolines and lipiarmycins had in fact been discovered decades earlier, in the 197 Since the rebirth of the approvals since 2010, the production was still low: since 2004, the US Food and Drug Administration (FDA) had approved only one new antibacterial each year, and between 2011 and 2014, only eight approvals were achieved [1].

The overview of the modern clinical pipelines demonstrates that the discovery gap exists. In 2021 an analysis of the clinical pipeline projected 76 antibacterial agents in development consisting of 45 conventional small molecule antibiotics and 31 unconventional substances divided between stage I-III and regulatory testing, of which 41 in development were priorities in the WHO priority pathogens, with only nineteen having novel pharmacophores and four having novel mechanisms [11]. In an evaluation of the 2019 pipeline conducted by WHO, it reported that there were only 60 antibacterial products at phase I-III of which only 32 targeted priority pathogens, 12-targeted the Mycobacterium tuberculosis and six the Clostridioides difficile with only 6 agents satisfying any definition of novelty [12]. Values of 1.5-3.5 percent of substances entering the preclinical stage that reach the end of regulation approval and that development line is 10-15 years are provided in the findings of economists [13]. A broader survey of combination agents identified 77 antibiotic or combination therapeutics and 217 antibacterial candidates awaiting testing at the end of 2021 and most (est. 80 %) of those are in classes already represented, further evidence of the derivative nature of the pipeline [14].

Pipelines analyses indicate there are gaps in the targeting of high priority pathogens. Few clinical candidates are highly active against essential Gram-negative pathogens and the percentage, which meets the WHO innovation criteria, is trivial [15]. As of early 2022, there were 47 direct acting antibacterials, five nontraditional small molecule antibacterials, and ten 10 high priority 8 -lactam/1 -lactamase inhibitor combinations in clinical development; however, as demonstrated, the number of truly novel pharmacophores in the later stages is limited [16]. Grand, international schemes like the 10 new antibiotics by 2020 and 5 by 25 programmes have mostly fallen short- both biological challenges and economic disincentives have seen little in the way of new agents beyond a marginal variation of existing classes [17]. Taken together, these data demonstrate that although a minority of the modern antibiotic pipeline shows promise, the pipeline remains narrow, significantly stacked with old designs, and likely to fail to achieve the range of novel agents required absent substantial scientific and economic change.

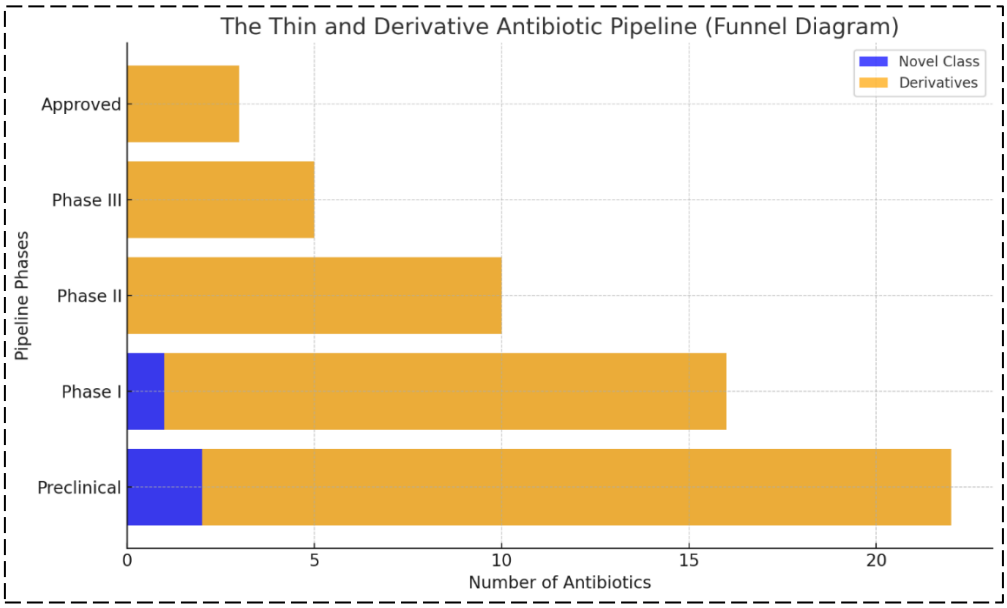

Fig 2: novel and derivate antibiotic pipeline classes.

3. Limitation of the Antibiotics discovery and development

3.1. Scientific and Technical Challenges

Gram-negative pathogens have an impenetrable cell envelope, tentatively providing the initial obstacle to antimicrobial reagents. The two membranes found in the Gram-negative bacteria form an asymmetric outer layer that consists of lipopolysaccharides, phospholipids, lipoproteins and beta barrel porins; the lipopolysaccharide layer is a tightly packed layer that acts as a barrier to the diffusion of hydrophobic drugs [18]. The permeability of this outer membrane is also limited because general porins do not allow molecules greater than ~600 Da to enter the periplasm, and Pseudomonas aeruginosa expresses mainly substrate-specific porins; therefore, many hydrophilic antibiotics cannot permeate the outer membrane [19]. Efflux systems represent a second line of defence: bacteria also use six families of multidrug pumps--ABC, MFS, MATE, SMR, RND and DMT-- and in Gram negative species, RND transporters form tripartite groups that span both membranes to evacuate a wide set of antibiotics [23]. Such pumps work with the outer membrane to maintain the intracellular concentration of

amphiphilic and hydrophobic substances at a concentration below the inhibitory concentration [20].

In addition to physical obstacles, scientific and chemical limitations are preventing the identification of new antibacterial targets. Natural product screens identifying known scaffolds, with a high fraction of hits having cytotoxicity or inadequate ADMET profiles enough times that the number of novel chemotypes remains limited [21]. Irrespective of their success in identifying thousands of initial hits in the process of high throughput pulgionic campaigns, medicinal chemistry hand-offs are inefficient: it has been estimated that only approximately 5 % of hits pass through the hit-to-lead deflagration, and the final success rate of a small-molecule antibiotic discovery project in generating a clinical candidate is in the range of 10 16 [22]. In massive combinatorial libraries and synthetic chemistry and based high-throughput screens, very few antibiotics have, as a result, been identified; success ratios are many orders of magnitudes lower than those of natural products, and tens of thousands of microbial species must, at times, be screened to identify one, new scaffold [24]. These technical limitations are further aggravated by dynamics of resistance: targets of traditional single-target antibiotics generate severe selective pressure and bacteria evolve rapidly by developing point mutations or gaining resistance determinants, whereas multimodal agents, in particular, antimicrobial peptides, are likely to drive more gradually the generation of resistance [25]. Table 1We talked about weaknesses of scientific and technical aspects and how we could resolve them

Table 1: The scientific and technical limitations and potential solutions

Challenge	Description	Examples of Failed Antibiotics	Potential Solutions
Bacterial Membrane Barriers	The complex double membrane of Gram-negative bacteria acts as a barrier, preventing many antibiotics from penetrating. The outer membrane contains lipopolysaccharides, phospholipids, and proteins that reduce permeability.	Penicillin, due to its inability to cross the outer membrane of Gram-negative bacteria [9].	Developing compounds that target membrane proteins to facilitate drug entry or modifying the outer membrane permeability [18].
Efflux Pumps	Bacteria use efflux pumps to expel antibiotics, reducing intracellular drug concentration and preventing antibiotics from reaching effective therapeutic levels.	Fluoroquinolones, such as ciprofloxacin, are ineffective against some resistant Gram-negative strains because of overactive efflux pumps [23].	Inhibiting efflux pumps with adjuvants to increase the effectiveness of antibiotics [26].
Porins and Membrane Channels	Porins are protein channels in the outer membrane of Gram-negative bacteria that permit the passage of small molecules while excluding larger or hydrophobic drugs.	First- and second-generation cephalosporins fail to effectively treat *Pseudomonas aeruginosa* because of restricted porin channels.	Engineering porins to improve penetration of larger drug molecules or developing synthetic analogs that bypass porin-mediated entry [19].
Lipopolysaccharides (LPS)	Lipopolysaccharides in the outer membrane form a rigid barrier that limits the penetration of hydrophobic molecules and many antibiotics.	Penicillin and several cephalosporins show reduced efficacy against certain Gram-negative bacteria because LPS hinder drug penetration [18].	Targeting LPS modification or using adjuvants to enhance antibiotic access across the outer membrane [9].

3.1.1. Trend Solutions to Technical and Scientific Limitations

With recent developments in deep learning, it is possible to train neural networks with high-throughput screening data and use them to predict antibacterial activity and screen virtual libraries of small molecules. A recent review in NPJ Antimicrobials and Resistance explained that AI models have the capacity to screen in large virtual chemical spaces using high-throughput data to predict activity fit and, the more compounds that are screened virtually, the higher that hit rate would be when performing the corresponding experiment in the most predictive compounds. Supervised and unsupervised models are used to predict the connection between chemical structure and biological activity, and they can be used to analyse SMILES encoding and graphs using directed message-passing networks. It resulted in antibiotics found in new classes of molecules including halicin and abaucin [27-29]

In August 2025, a team at MIT reported using generative algorithms (like CReM and F-VAE) to design more than 36 million new compounds, then selected the best based on machine-learning predictions. These algorithms allowed the generation of "virtual" compounds that have never been seen before; the resulting candidates (NG1 and DN1) showed strong activity against resistant bacteria such as *N. gonorrhoeae* and MRSA [30]. The review mentioned above notes the development of models such as MEGAN that help identify molecular substructures responsible for bioactivity, and generative tools like SyntheMol that produce synthesizable molecules with antibiotic activity.

In a review, recent studies indicate that modern science is reappraising nature as a source of antibiotics with a new interest in living organisms in extreme or uneven conditions deserts, hot springs and deep-sea trenches. Such organisms have developed adaptive physiologies and as such have different metabolites providing access to a new range of bioactive compounds. The study observed that genome-mining and next generation sequencing have revealed the genus *Streptomyces* could potentially produce as many as 100 000 distinct antibiotics, with only a tiny fraction having been identified so far [31-32]

In order to solve the problem of culturing of unknown microbes, metagenomics is used to study the DNA of complex environmental samples. Metagenomics is defined as the functional and sequence-based study of collective microbial genomes and to note that untargeted sequencing has millions of fragment units assembled in order to define the microbiome and identify biosynthetic gene clusters [33]. Recent advancements in second- and third-generation platforms offer speed and accuracy in the detection of biosynthetic gene clusters, opening the door to the discovery of new compounds [34-36]

Mining nature The next to be discovered is lariocidin a lasso-shaped peptide, produced by a Paenibacillus bacterium isolated in soil, and grown in culture over a year; this long duration has given an advantage to the slow growing species, Lariocidin is active against a broad spectrum of bacteria by binding an entire site previously not put into practice. Its positivity helps it get into the cells directly through the membrane without having to use the transporters and therefore it allows less chances of the process being resisted. Genomic studies indicate the existence of dozens of comparable biosynthesis systems in many different phyla of bacteria, so a complete family of these peptides remains to be discovered [37].

Finally, in parallel, exploring the natural environment and microbial communities through metagenomics remains a rich source of new natural products, especially when combined with advanced sequencing and AI-driven data analysis.

3.1.2. Emerging Scientific Strategies and Technologies

The decline in antibiotic discovery has been renewing the pool of scientists, who are reinventing screening and dereplication methods. The long-read sequencing-based genome mining platforms with software like antiSMASH and DeepBGC are now routinely used to recover biosynthetic gene cluster (BGC) within microbial genomes, allowing natural product scaffolds to be predicted in silico, with 185 novel compounds being identified between 2018 and 2024 as a result [21]. Most Streptomyces BGCs, though, remain silent in regular conditions, representing no more than 10 % of all detected BGCs even in cases of advanced pipelines; to this end, researchers combine genomics with metabolomics and use high resolution mass spectrometry, NMR and community data resources (such as Global Natural Products Social Networking or GNPS) to annotate cryptic metabolites and apply machine learning models such as SIRIUS and DeepMass to predict their structure [38]. De-replication methods, such as MS/MS based molecular networking, where fragmentation patterns are matched with references in open databases and chemically similar spectra are cross-linked, can enable the researcher to tag a scaffold that has already been reported rapidly, and have the ability to prioritise rare metabolites [39].

Medicinal chemists are also optimizing the physicochemical properties of existing antibiotics to improve penetration through the Gram-negative outer membrane and to defeat efflux. Recognising that efflux pumps have multiple families (ABC, MATE, MFS, SMR, RND and PACE), researchers are designing efflux pump inhibitors such as pyridopyrimidine derivatives and morpholine carboxamide analogues and outer-membrane permeabilisers (e.g., cationic peptides) to be co-administered with antibiotics; however, many candidates exhibit toxicity or lack selectivity [40]. Another strategy uses adjuvant therapy: combining β-lactamase inhibitors, efflux pump inhibitors or membrane permeabilisers with conventional antibiotics can restore activity against multidrug-resistant pathogens and has produced promising results in laboratory and clinical settings. Mechanistic studies show that such potentiators either block the energy supply of efflux pumps or compete with substrates at binding pockets, although the prototypical inhibitor phenylalanine-arginine β-naphthylamide (PAβN) demonstrates dose-limiting toxicity, underlining the need for safer next-generation adjuvants [41].

Lastly, natural product diversity, which was previously not available, is being opened by improving the methods of growing microbes. A multichannel diffusive chamber, the iChip, encapsulates dosing single cells of bacteria into separate growing implements so that bacteria in it grow in their natural soil conditions; in screening extracts of about 10,000 such isolates, its inventors discovered the depsipeptide teixobactin, now known as the dLing, discovery of a new antibiotic that kills Gram positive pathogens resistant to antibiotics with no detectable resistance to it [42]. The ability to access these uncultivable microbes increases the potential biosynthetic potential and demonstrates how access to new technology can reopen the natural products frontier.

3.2. Economic and Financial Challenges

Market commercialization of a new antibacterial would require a lot of time and funds. Analysis of Gram negative antibiotic programme costs in 2025 indicated a total duration of about thirteen years between discovery and launch, a pre-launch expenditure of nearly US$1.2 billion, of which 85 per cent is spent pre-Phase III, but the average antibiotic fifth year sales recorded over the last year is around an US$120 million [43]. Although developers may get to Phase I, the likelihood of a successful outcome is slender: in an economic analysis, it was determined that only 1.5 3.5 % of antibiotic candidates that have proceeded through to preclinical development reach regulatory approval and that it takes 10 15 years on average to translate preclinical research to market [44].

Such negative economics put off investment; one recent Lilliput company review has reported that the cost of developing a new antibiotic is around US$1.4 billion, and that challenges in recovering this have evoked the departure of major pharmaceutical companies from the market [45]. Without blockbuster sales, the broader antibiotic market is compressed by the ease of access to cheap generics, the short durations necessary to conduct curative treatment and antibiotic stewardship policies that conserve the remaining new agents as last-line treatment option-factors that slow sales and cause its conventional sales-based reimbursement system to become impractical [46- 47].

These policy entry barriers have altered the face of antibiotic research and development. Modelling of the WHO preclinical pipeline shows that around 1/3 of developers leave the pipeline annually and the pipeline thus illustrates the vulnerability of early stage programmes and low success of programmers progressing to clinical trials (WHO, 2023) [6]. Small and medium sized companies and academic consortia currently represent the largest source of antibacterial innovation, although lacking in money to develop candidates past the discovery stage. Funding agencies have expressed concern that numerous proposals advanced by such groups are unsuccessful because of insufficient knowledge of toxicology, inadequate data and flawed scientific rationale; a review of ninety one funding application has found widespread scientific and technical deficiencies and stated that project teams did not often possess the needed expertise to maneuver the complicated R&D journey[48] Combined, such financial and operational pressures underpin the necessity of further incentive mechanisms, more accommodating funding regimes and capability building programs to maintain the antibacterial pipeline.

3.2.1. Solutions to Economic challenges

Failure in the market-based incentives has led to the interest in pull mechanisms that give rewards to innovation without providing motivation to overuse in relevance. The UK subscription pilot is an example of how a delinked pull incentive could work: the companies would receive a fixed annual payment based on the benefit of the antibiotic instead of the size of their sales, therefore receive rewards to innovate, and not give any economic incentive to maximize sales [49]. An analysis of broader policy initiatives shows that to jumpstart the late stage antibiotic development pipeline, a combination of pull incentives, covering subscription payments, market entry incentives, transferable exclusivity extensions, and milestone payments, are required; although these pull mechanisms must be accompanied by increased continued push funding (direct grants and nonprofit investment) and aligned internationally to increase access in low- and middle-income countries [13]. In Table 2, we discussed the Policies to Scientific Innovation linkage.

Table 2: Policies linkage to Scientific Innovations to sustain antibiotic development

Development Stage	Scientific Research Needs	Proposed Economic Tools	Suggested Actions
Discovery / Basic Research	AI algorithms, genomics analysis, CRISPR for reviving silent gene clusters	Push grants and community funding (ND4BB, NIAID, CARB-X), open databases	Create unified data platforms and provide educational resources for AI algorithms, support phage engineering and CRISPR projects.
Preclinical Development	Improvement of discovered compounds, toxicity modeling, testing of modified phages	Milestone payments, small project funding, government guarantees	Allocate payments linked to achievement points (e.g., completion of Phase 1), simplify access to funding for small companies.
Clinical Trials / Marketing	Conduct multi-center trials, respond to resistance mutations, human use studies for phage & CRISPR	Subscription models, market entry rewards, value-based health mechanisms	Sign local and international subscription contracts to ensure return for companies and appropriate drug availability, tie rewards to equitable access and sustainability.
Supply Chains & Access	Quality control, development of rapid diagnostic tests, maintaining existing antibiotics	Joint procurements, regulatory waivers, strategic stockpile support	Establish regional alliances for pooling demand, remove registration fees, and develop regional stockpiles for essential antibiotics.

The early pipeline has been extremely important, which has been supported by big push programs. Primary forms of direct funding, like the EU Innovative Medicines Initiative projects ENABLE and TRANSLOCATION and the AMR Accelerator invested over a billion euros to take compounds into the preclinical and phase II stages, evidence of how direct funding can fill in the gap of early development [13]. Several nonprofit consortia--complementary--CARB X, the Global Antibiotic Research and Development Partnership (GARDP) and the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) have rallied hundreds of millions of dollars towards discovery and clinical-development to exemplify how an alliance of investors can derisk antibiotics [49]. Further downstream, there are also programmes (e.g., Novo Nordisk R&D: REPAIR) and funds (e.g. AMR Action Fund) that commit more money--US$165 million and US$1 billion respectively--to see promising candidates through the clinical valley of death and into trials [50]

It would require coordinated prioritization to make sure that it is global investment in R&D that focuses on the pathogens that put excessive burden in the low resource settings. Ethical commentaries on AMR research indicate that priority setting committees tend to be overrepresented by experts in Europe and the Americas; therefore, the research agendas reflect the interests of high income countries, and the needs of low and middle income countries where AMR burden is the greatest are not given a high priority, so to ensure equitable coverage of R&D interests, the representation in funding and priority setting bodies needs to have balanced representation, and it needs to align with the WHO Priority Pathogens List to direct incentives toward pathogens with the highest health impact globally

In the UK, NICE and NHS England have implemented a pilot program that provides companies with a fixed annual fee for antibiotics based on their health value, completely separate from sales volume. This model aims to guarantee a steady income for companies without encouraging overuse of the drugs [51]

The US legislation (PASTEUR Act) aims to establish subscription contracts, which government pays between $750 million and 3 billion dollars initially to access antibiotics within federal programs, over the period of up to 5-10 years. This model provides the decoupling of profits with the sales volume and guarantees that antibiotics are saved and used in cases when it is needed. Whereas, as The World Economic Forum report indicates, Europe is testing a variety of models including subscription fees, entry-reward market, and transferable exclusivity extensions. In the UK, a perma subscription system is all set wherein a predetermined amount per year is charged against antibiotics. [52]. Suggestions to offer a market entry reward (up to 1 billion dollars/new antibiotic) to companies to motivate them to take the risks in developing new drugs have also been offered.

The Swiss Economics Institute suggests payment on the use of antibiotics in less recognizable or literary medication (e.g. agriculture) where funds will go to a worldwide fund that will pay companies to produce alternative antibiotics. The payout payment is a fixed payment and variable payment, which goes up in case of antibiotic targeting resistant bacteria. This self-sustainable mechanism might inspire production of narrow-spectrum antibiotics [53]. The establishment of the AMR Action Fund with approximately $1 billion to assist in the development of antibiotics to clinical stages, and the CARB-X initiative are illustrative of the need to make collective investments and undertake public-private partnerships to give opportunities to small companies. In Figure 3, we link the idea of success in economic policies to the success of antibiotic development.

Figure 3

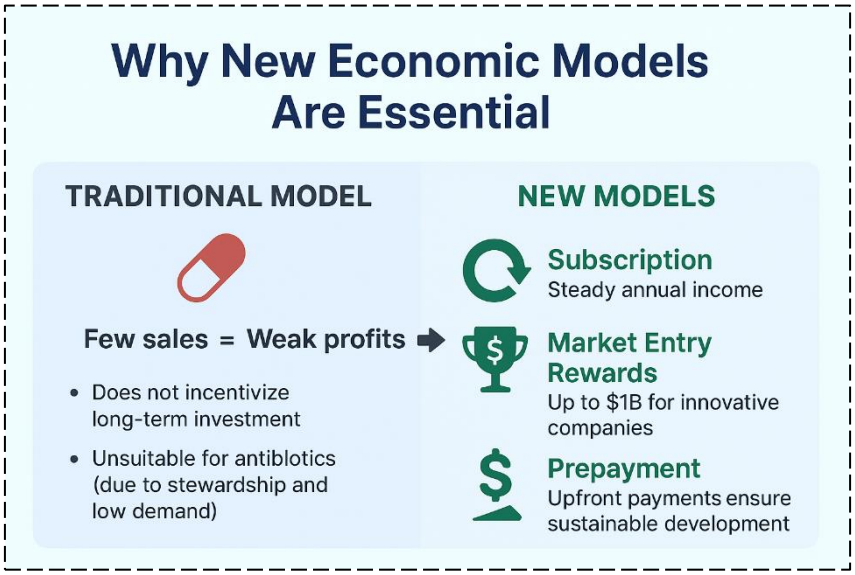

Fig 3: Modern models and their relationship to the sustainability of antibiotic development

3.3. Regulatory and Institutional Challenges

Regulatory oversight for novel antibiotics has become increasingly stringent because previous approvals of drugs such as telithromycin and trovafloxacin were followed by life-threatening hepatotoxicity, prompting agencies to introduce more demanding safety guidelines. New antibiotics must typically be compared with standard therapies through non-inferiority trials that use narrow margins (<10 %), making them difficult to design, requiring larger sample sizes and inflating costs (Shlaes *et al*., 2013, Shaw *et al*., 2007, Sinha & Kesselheim 2016).). Regulators have also shifted from non-inferiority to superiority requirements in some cases; for example, iclaprim and faropenem were rejected despite favourable phase III data when agencies demanded additional toxicity studies and proof of superiority, causing multi-year delays and eventual discontinuation. Recruitment is another obstacle—pathogen-specific trials must enrol patients with resistant infections, yet in a plazomicin trial only 39 of 2,000 screened patients met the inclusion criteria. Adding to the difficulty, regulatory standards differ across regions; inconsistent protocols, divergent endpoints and varying health-technology assessment requirements create uncertainty and prolong the path to approval (Douglas & Laabei, 2023, Huang *et al*., 2018).

Priority setting for antimicrobial-resistance research is also skewed. An analysis of global AMR priority-setting committees found that the European and American regions were over-represented, with limited participation from researchers, clinicians and policymakers in low- and middle-income countries. Such imbalance means research agendas tend to reflect concerns of high-income settings, while infections prevalent in resource-constrained regions receive less attention and funding (Cheah *et al*., 2025, Mendelson *et al*., 2024).

3.4. Regulatory Innovations and Clinical Trial Design

Conventional randomized controlled trials suffer prohibitive costs, the length of time needed to run them has attracted interest in platform, and adaptive trial designs. Platform trials compare multiple interventions by a single infrastructure; they involve shared control groups, shared protocols, and site contracts, thus, being able to decrease costs and populations necessary [54]. The *Staphylococcus aureus* Network Adaptive Platform (SNAP) takes this approach: they build modular domains and leverage routine clinical data to test several interventions against S. aureus infections under the same master protocol and enable addition and drop of intervention arms as evidence is revealed [55]. Pathogen-centered adaptive trials may deliver results more efficiently, with greater potential for actionable findings, and at reduced costs compared to traditional trials. However, they involve more complex governance and present greater statistical challenges in their design [56-57].

Nontraditional therapies have not had their regulatory frameworks fully developed. Bacteriophages are currently classified as biological medicinal products in Europe, although there is no phage-specific pre-approval process, and German clinicians report that phage therapeutic applications are currently limited to single experimental applications with a lack of GMP manufacturing sites and phage clinical trials, outlining the need to provide clear regulations and implement further production capabilities [58]. Antibiotics: Antimicrobial peptides (AMPs) have been put in the spotlight as an antibiotic, although very few have entered the market due to stability and toxicity issues that prevent the early stages of development from reaching the later phases [59]. The alacritous advances in the CRISPR based therapeutics introduce a supplementary wrinkle: genome editing technologies are entering clinical trials, and regulatory bodies, including FDA, EMA and NMPA, will have to design harmonized principles to meet safety and ethical requirements; harmonization of global regulations and involving scientists, ethicists, lawmakers and popular science is crucial towards taking such advances responsibly [60- 62].

Regulators also fragment access to conventional antibiotics. Variation in the process of evaluation implies that antibiotics approved by the U.S. FDA are not yet approved by the European Medicines Agency; regulators responded to the difference by adopting initiatives like the EMAFDA parallel scientific advice programme and tripartite meetings with the Japanese PMDA to standardise systems in their assessment of antibiotics [13]. In addition to such programmes, internationally aligned regulatory channels and dependence systems may help to formalise approvals and enable fair access: adaptive platform trials in themselves are likely to enable international collaborations as they centralise

resources and knowledge internationally [63-64]. Global regulatory convergence will thus needs innovative trial designs as well as coordinated policy innovations to remove unnecessary duplication, expedite approvals, and get novel antimicrobial therapies where they are most needed.

3.5. Production, Stewardship and Access Challenges

The antibiotics manufacturing and supply chain has several structural vulnerabilities. An overview of the report on shortages of essential antimicrobials indicated that fragmented supply chains, insufficient commercial incentives, sole or insufficient active pharmaceutical ingredients, little quality production, and uncomplicated procurement procedures make manufacturers feel unwelcome and lead to frequent shortages [65]. The vulnerability of the supply chains in global APIs implies issues could occur in one plant disrupting supply to the entire world-in one instance, a fire at a plant producing the precursor piperacillin-tazobactam led to an all-over shortage and the unsoundness of forecasting systems compounds supply discontinuity [66]. Forecasting systems are inefficient and pooled procurements are nonexistent in several developing countries with production and supply remaining unstable [67]. Emerging alongside shortages are supply chains fragmented through multiple touchpoints that enable substandard and counterfeit medicines to enter the supply chain, inadequate temperature controls, quality management systems, and regulatory processes permit the presence of counterfeit or out-of-date antimicrobials into the market, destroying treatment and perpetuating resistance [68].

Stewardship is important in that the economic and clinical worth of a new antibiotic depends on restricting it. The potential of antimicrobial resistance implies that new approved drugs must be restricted to multidrug-resistant infection; nevertheless, such a move decreases profitability as the sales volume does not increase [69]. When new agents are dispatched en masse, resistance is likely to crop up soon; cross-resistance can occur with shelved compounds of the same type, as they have common mechanisms of action [70]. Stewardship programmes and rational use policies, therefore, need to be developed in order to allow the new antibiotics to be effective and available to those patients who really need them and not to repeat the patterns of misuse that has been stimulating the development of resistance over time in the past [71].

3.6. Building Capacity, Collaboration and Open Science

Antimicrobial resistance crisis will not be found in the hospitals or research labs; rather it is found at the intersection of human and veterinary medicine, agriculture and the environment. Recent editorial on the AMR emergency has highlighted that the global risks of modern medicine going into collapse demand unified efforts across these sectors, with the authors of that article stating that multi sector collaboration is required at this moment to address AMR [72]. Multi institutional collaborations give a blueprint on the roles that various institutions will play. In one specific example, the D3/CO ADD consortium combined combinatorial synthesis across five university labs with high throughput screening at the Community for Open Antimicrobial Drug Discovery (CO ADD); students created 76 structurally diverse molecules that were screened against pathogenic fungi by CO ADD, eventually identifying two active dipeptides that displayed potency similar to existing lead compounds, and clarifying that parallel research and educational workflows could both discover new compounds and train a new generation of scientists [73]. In addition to academic consortia, nonprofit research organizations funded by the government provide another avenue to capitalize on expertise. A progress report by the Global Antibiotic Research and Development Partnership posits that the nonprofit R&D organizations, with no need to ensure commercial profitability, can easily cooperate with both public and private stakeholders to come up with new antibiotics and get them to the patients that require them as well [74].

Open science initiatives can complement such collaborative initiatives by breaking down the obstacles to data sharing and making learning collaborative. A good example is O AD: the program generates free high throughput screening of compounds donated by academic chemists, gives them back results, and after two years of confidentiality, publishes both positive and negative data in an open database [75]. Not only does this model take advantage of the chemical diversity available in academic collections, it also repays knowledge to that community so that follow on research and patenting can be available to the original contributors. The purpose of other platforms is to aggregate already existing data and not to create new assays.

Sharing a common platform on antibiotic research and knowledge (SPARK) is an open resource in the form of an online database that consolidates data on Gram-negative permeability; it was designed to allow scientists to build on prior research and add their own data and to form new hypotheses [76]. Open science also enables new business models: M4K Pharma has developed an open science drug discovery programmer that is not subject to patents, but regulatory exclusivity; this new model attracts a different portfolio of funders, including government and philanthropic donors and ultimately aims to commercialize therapeutics at lower prices [77].

4. Outlook*:* Is the road dark?

The crisis of antibiotics is composed of several scientific, economic and policy obstacles that strengthen each other. The subsequent demise of the so-called golden age since 1987 is why the majority of drugs passed since are derivations of old classes of compounds that were found several decades earlier[78-79], and there are now few independent scaffolds available to meet the growing resistance. The economic analysis demonstrates that the gestation period of the creation of a novel antibiotic is 10-15 years and that by virtue of stewardship policies, it can be anticipated that the net present value will be between -50 million US$ and +100 million US$, whilst other drug types can be expected to have a present value of hundreds of millions of dollars or more [80-81].

The regulatory and policy framework lacks cohesiveness with global governance sticking in patches with surveillance, enforcement and research funding being divided between states [82]. The problems complement one another these increased costs in R&D puts people off investing in the products, the uncertainty of regulations pegs down the progress of the clinical development, and less international

coordination introduces resistant diseases to travel across the borders. An approach to tackling the crisis by confronting any individual factor will not solve it.

Future research will be central to the provision of this composite solution. The ability of artificial intelligence tools to enhance discovery is already being realized: deep learning models, which have only been trained on tens of thousands of molecules, have the capability of screening millions of structures and identifying candidates that have predicted antibacterial activity, thus circumventing reliance on slow empirical screens [83].

In order to explore the chemical space, scientists are revisiting nature; next generation sequencing and bioinformatics have demonstrated the emergence of identification that of the biosynthetic gene clusters in soil microbes are not expressed in the laboratory, and it is explored that untapped metabolic potential is unlocked by strategies like genome mining, metagenomic analysis and awakening of silent gene clusters [84]. Simultaneously, it is becoming increasingly accepted that classical bactericidal agents alone cannot be used in drug discovery. An overview of the existing pipeline indicates that some alternative therapies (e.g., antibiotic potentiators, bacteriophages, lysins, microbiome modulation, immune modulators and CRISPR based approaches) are reaching the proof-of-concept stage and may need a new regulatory framework [48].

Divergent ecological sources, such as marine environments or animal microbiota in addition to soil, could also be sources of novel scaffolds and could be explored in future, along with how multi omics data and deep learning can prioritize these sources. Lastly, the work of interdisciplinary groups should be aimed at enhancing delivery and stability of nontraditional agents, wherein toxicity suppression and knowledge of resistance mechanisms may be harnessed to keep new therapeutics in use.

To sum up, the future path is not impossible. In recognizing the interdependencies among the science discovery, the economic benefits and policies that govern it, the research community, industry and governments can build a rationalised approach that makes long-term antibiotic development feasible. All of these innovations of AI assisted discovery, exploitation of unexplored ecological diversity, and research into nontraditional therapy and finally integration of these innovations into an ameliorative economic and policy environment will be necessary to prevent a post antibiotic future.

5. Conclusion

This study reveals that not only is the current situation of antibiotic innovation not solely a scientific issue, but it is essentially an economic problem. The conventional sales-oriented model- that has been successful in other therapeutic areas has been thwarted in case of antibiotics because of stewardship, lack of possibility to generate sales and poor profitability. In the absence of new frameworks, the pipeline is set to collapse and the world at risk of antimicrobial resistance.

With a careful dissection on both the bottlenecks and emerging responses, this paper has shown that novel economic frameworks like subscription plans, prepayment plans and even billion-dollar market entry reward plans are not optional, but a necessity to respond to the stated problem. The methods decouple profits and sales volumes, offer long-term incentives, and make incentives consistent with the priorities of public health. The strong aspects of this research are the incorporation of scientific, financial and policy aspects all together. It indicates that only with the help of coordinated global efforts that involve a mixture of both push and pull incentives, public-private partnerships, and access equitability strategies will enable an overhaul of the antibiotic market. Ultimately, this work not only offers a critical diagnosis of a flawed system, but also a guide on the path to sustainable innovation, and thereby protection of the future of modern medicine against the impending post-antibiotic era.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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