History of medicine and ethics

The penicillin revolution and the role of the forgotten pioneer Vincenzo Tiberio (1869-1915): discovery, development and legacy

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Keywords

Penicillin • Vincenzo Tiberio • Alexander Fleming • Antibiotics history • Mold-derived antimicrobials • Medical discoveries timeline

Summary

Penicillin's discovery is widely attributed to Alexander Fleming (1881-1955) Professor of Bacteriology at St. Mary's Hospital in London in 1928, who observed the antibacterial effects of Penicillium mold. Fleming found that his "mold juice" was capable of killing a wide range of harmful bacteria, such as streptococcus, meningococcus and the diphtheria bacillus. He then set his assistants, Stuart Craddock and Frederick Ridley, the challenging mission of isolating pure penicillin from the mold juice. It shown to be very unstable, and they were only able to prepare solutions of crude material to work with. Fleming published his findings in the British Journal of Experimental Pathology in June 1929, with only a passing reference to penicillin's potential therapeutic benefits. However, over 30 years earlier, Italian physician Vincenzo Tiberio (1869-1915) had conducted controlled studies on the bactericidal effects of mold extracts, publishing results that went largely unnoticed by the scientific community.This article runs through a work plan timeline and significance of early antimicrobial discoveries, tracing the overlooked work of Tiberio, Fleming's breakthrough, the biochemical properties of penicillin, and the wartime efforts that enabled its mass production. The story of penicillin is not only one of scientific innovation but also of missed recognition, collaboration, and the complex interplay of chance and preparedness.

Introduction

The discovery of antibiotics stands as one of the most transformative and consequential breakthroughs in the entire history of medicine. Before their introduction, bacterial infections – now often considered minor or easily treatable – were among the leading causes of mortality worldwide.

In the pre-antibiotic era, even seemingly trivial injuries such as a scraped knee, a dental abscess, or a mild surgical incision could spiral into life-threatening infections like sepsis. Diseases such as pneumonia, tuberculosis, syphilis, diphtheria, and scarlet fever claimed millions of lives annually.

Before its introduction there was no successful treatment and care also for infections such as gonorrhea or rheumatic fever. Hospitals were full of people with sepsis contracted from a cut, a scratch or abrasion and doctors did not have effective and decisive means or instruments; they could only wait and hope.

The absence of effective antimicrobial treatments meant that physicians were often powerless to intervene once an infection took hold. Clinical management consisted primarily of palliative care, basic antiseptic techniques, patient isolation, and in some cases, the use of toxic compounds that were only marginally effective and frequently harmful.

As a result, mortality rates for bacterial diseases remained unacceptably high, and medical interventions such as surgery, childbirth, or wound care were fraught with lethal risk. The advent of antimicrobial therapies in the 20th century represented a seismic shift. Not only did these drugs revolutionize the treatment of infectious diseases, they also transformed the practice of medicine itself. Suddenly, conditions that had long been untreatable became curable.

Life expectancy rose dramatically in many parts of the world, public health initiatives gained unprecedented efficacy, and medical fields such as surgery, oncology, and intensive care advanced rapidly due to the newfound ability to control postoperative and nosocomial infections. Antibiotics became the cornerstone of modern clinical practice, enabling complex medical interventions that would have been unthinkable just decades earlier. Among the many antibiotics discovered in the 20th century, penicillin occupies a singular place in medical history.

Penicillin, the first widely effective antibiotic, was discovered by Alexander Fleming in 1928 when he observed that a Penicillium mold inhibited bacterial

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growth [1, 2]. His findings, published in 1929, marked a turning point in medicine. However, this standard narrative often neglects earlier contributions, particularly those of Italian physician Vincenzo Tiberio, who reported similar antibacterial effects of mold extracts over thirty years before Fleming [2]. In 1895, Vincenzo Tiberio published a study on the antimicrobial effects of mold [3], inspired by the observation that mold on a family well reduced gastrointestinal infections. He hypothesized that mold released a substance inhibiting bacteria, anticipating later antibiotic concepts [4]. Largely ignored by Italy's scientific community [5], his work was rediscovered in the 20th century by Giuseppe Pezzi and others [6, 7], earning him overdue recognition in the history of penicillin.

Early Observations and Microbial Antagonism

Scientific interest in the antagonistic interactions between microorganisms – a concept now fundamental to microbiology, immunology, and pharmacology – emerged long before the formal discovery of antibiotics. As early as the mid-19th century, scientists began to hypothesize that microorganisms did not merely exist in isolation but could also influence, suppress, or even destroy one another. This idea, which would later be known as microbial antagonism, provided the conceptual groundwork for the development of antibiotic therapies. Early observations of these phenomena were scattered and often anecdotal, but they captured the imagination of a small group of pioneering scientists. Among the most influential figures in shaping this nascent understanding were Louis Pasteur (1822-1895) and Robert Koch (1843-1910), two titans of 19th-century bacteriology whose research fundamentally transformed the medical sciences. Pasteur's work on fermentation and his formulation of the germ theory of disease laid the intellectual foundations for understanding microbes as both causal agents of disease and, potentially, as biological tools that could be harnessed to control other harmful microorganisms [8].

Koch, through his methodical development of postulates and innovations in culturing techniques, established the link between specific pathogens and particular diseases, including tuberculosis and anthrax. Together, these scientists helped shift the perception of microbes from invisible nuisances to biologically active agents with profound implications for health and disease. Building on this evolving framework, Élie Metchnikoff (1845-1916), a Russian zoologist and immunologist working at the Pasteur Institute, introduced key insights into the defensive role of phagocytes in the immune system. He also extended the idea of microbial antagonism by noting how certain beneficial bacteria could suppress pathogenic strains within the gut microbiome. His observations on competitive exclusion anticipated the modern concepts of probiotic therapy and microbial balance, and his work was instrumental in demonstrating that microbial ecosystems could be modulated to promote health rather than simply sterilized to eliminate disease.

Fig. 1. Paul Ehrlich (1854 –1915) - [Public Domain. Wikipedia commons].

A critical leap in this field came with Paul Ehrlich (1854-1915), a German physician, microbiologist, and immunologist, who is often credited as the father of modern chemotherapy (in 1908, he received the Nobel Prize in Physiology or Medicine for his contributions to immunology) (Fig. 1).

Building on the idea that chemical agents could selectively target harmful microorganisms, Ehrlich developed the theory of the "magic bullet"—a compound that could eradicate a pathogen without damaging host tissues. His discovery of *Salvarsan* (arsphenamine) in 1909 as an effective treatment for syphilis marked the first successful application of this principle [9]. Although not an antibiotic in the contemporary sense — it was a synthetic arsenic-based compound — Salvarsan represented the first chemotherapeutic agent specifically designed to combat a microbial disease. Ehrlich's conceptual model not only bridged microbiology and pharmacology but also provided a scientific framework that would later guide the development of penicillin and other antimicrobial drugs. These foundational contributions underscore that the antibiotic revolution did not emerge in a vacuum, nor was it the result of a singular discovery. Rather, it was the culmination of decades of experimental work, theoretical innovation, and interdisciplinary dialogue. The understanding that microorganisms could act as both enemies and allies in human health laid the intellectual and experimental scaffolding for the advent of antibiotics - a leap that would be realized with penicillin in the 20th century, but whose roots lie deep in the scientific soil of the 19th.

Fig. 2. Vincenzo Tiberio (1869-1915) – (Naval medical officer of the Medical Corps of the Italian Navy) London [Public Domain. Wikipedia commons].

Vincenzo Tiberio: a Forgotten Pioneer

In 1895, Vincenzo Tiberio (Fig. 2), a young physician and medical officer in the Italian Navy, published an article titled *Sugli estratti di alcune muffe* ("On the Extracts of Some Molds") in the *Annali di Igiene Sperimentale*, a journal dedicated to experimental hygiene and public health research [3].

His investigation was driven by a keen empirical observation: at his uncle's home in Arzano, near Naples, he noticed a curious pattern. When the walls of the courtyard well—used for household drinking water—were periodically scraped clean of their natural mold layer, outbreaks of gastrointestinal illness, particularly enteritis, would spike among residents. Intrigued by this correlation, Tiberio hypothesized that the mold might play a protective role by inhibiting harmful bacteria in the water supply. To test this theory, he undertook a series of controlled experiments in a laboratory at the University of Naples. Demonstrating methodological rigor unusual for his time, Tiberio isolated several species of mold, including *Mucor mucedo*, *Penicillium glaucum*, and *Aspergillus flavescens*.

He then prepared *aqueous extracts* of these molds and subjected them to a series of *in vitro* assays against pathogenic bacteria, such as *Vibrio cholerae* – the agent responsible for cholera epidemics – and strains of *Staphylococcus*, which were known to cause wound infections and other illnesses.

His results were clear and replicable: the mold extracts exhibited a marked inhibitory effect on bacterial growth, both in culture media and, significantly, in *in-vivo* tests involving animal models [3].

Tiberio concluded that the molds released soluble substances into their environment with potent bacteriostatic and bactericidal properties – a hypothesis that, although he lacked the biochemical tools to isolate or characterize these compounds, foreshadowed the mechanism of action of antibiotics. Importantly, his paper included careful controls, thoughtful discussion of alternative explanations, and proposals for future research.

In many respects, it exemplified the ideals of early scientific microbiology and demonstrated an intuitive grasp of what we now understand as antimicrobial pharmacodynamics. Despite the strength of his data and the novelty of his hypothesis, Tiberio's work went largely unnoticed by the scientific establishment of his day. Several factors contributed to this neglect: his article was published in an Italian-language journal with limited international circulation; his position within the military medical service may have limited his academic visibility; and perhaps most critically, his findings were simply too far ahead of their time.

The dominant scientific paradigms of the late 19th century had not yet fully embraced the concept of inter-microbial chemical warfare or the therapeutic exploitation of microbial products. As a result, Tiberio's research was dismissed as anecdotal or overly speculative by contemporaries who failed to grasp its revolutionary implications. It was not until over half a century later, in the aftermath of World War II, that Tiberio's pioneering work was rediscovered by Giuseppe Pezzi.

In 1946, Pezzi published a commentary highlighting the significance of Tiberio's 1895 study and argued that it represented one of the earliest documented recognitions of mold-derived antibacterial substances [6].

This rediscovery, along with subsequent scholarly efforts to contextualize and re-evaluate Tiberio's research, finally began to secure his place in the history of antibiotic science. Modern historians and microbiologists now recognize Tiberio as a crucial but long-overlooked figure in the pre-history of antibiotics. His observations not only anticipated the discovery of penicillin by several decades but also demonstrated a scientific approach remarkably consistent with the principles of evidence-based medicine.

In retrospect, Tiberio's work stands as a powerful example of how scientific insight can be eclipsed by historical circumstance—and how rediscovering forgotten pioneers can enrich our understanding of medical progress [7].

Alexander Fleming and the Serendipitous Discovery

In 1928, Alexander Fleming, a bacteriologist at St. Mary's Hospital in London (Figs. 3, 4), made what is now regarded as one of the most serendipitous and pivotal discoveries in medical history. Upon returning from a holiday, Fleming noticed that one of his neglected Petri dishes, which had been inoculated with *Staphylococcus aureus*, had become contaminated with a colony of blue-green mold.

What caught his attention, however, was not the contamination itself, but the peculiar halo of inhibition surrounding the mold, in which no bacterial growth could be seen. Intrigued by this phenomenon, Fleming conducted a series of experiments and soon identified the

Fig. 3. Fleming in his laboratory, c. 1943 [Public Domain. Wikipedia commons].

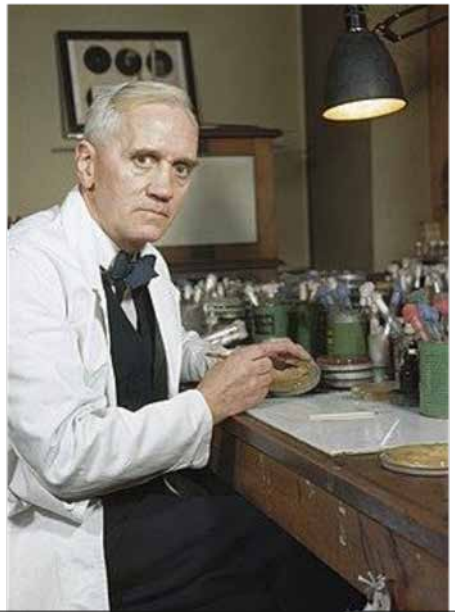
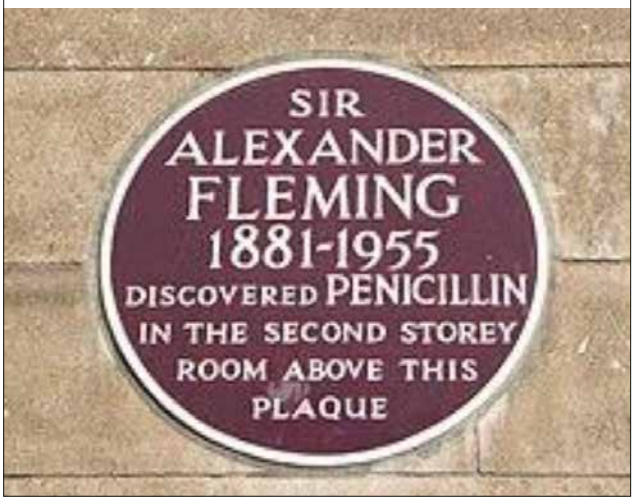


Fig. 4. Commemorative plaque marking Fleming's discovery of penicillin at St Mary's Hospital, London [Public Domain. Wikipedia commons].



mold as belonging to the genus *Penicillium*, specifically *Penicillium notatum* [2]. He deduced that the mold was secreting a substance into its surroundings that killed or inhibited the growth of bacteria. Fleming named this substance "penicillin," after the mold's genus, and published his findings in 1929 in the *British Journal of Experimental Pathology* [2]. His paper documented the antibacterial properties of penicillin against a variety of Gram-positive organisms, including *Staphylococcus* and *Streptococcus*, while leaving mammalian tissues unharmed. This selective toxicity - lethal to bacteria but safe for host cells - was an unprecedented pharmacological feature and would later become the cornerstone of antibiotic therapy. Despite the significance of his discovery, Fleming's ability to develop penicillin as a therapeutic agent was severely limited. The compound was inherently unstable and difficult to isolate in a pure and potent form. Fleming was a skilled microbiologist, but he lacked the chemical expertise and resources necessary to purify penicillin or determine its molecular structure. Moreover, his attempts to attract the interest of pharmaceutical manufacturers and the broader medical community were largely unsuccessful.

For more than a decade, penicillin remained a laboratory curiosity – a promising but impractical substance whose clinical potential was yet to be realized. The breakthrough came in the early 1940s, when a multidisciplinary team of researchers at the University of Oxford took up the challenge.

Led by the Australian pathologist Howard Florey and the German-born biochemist Ernst Boris Chain, and supported by the talented chemist Norman Heatley, the Oxford team set out to purify and stabilize penicillin for clinical use [9]. Building upon Fleming's foundational work, they developed extraction and purification methods that finally allowed penicillin to be produced in biologically active quantities. The team's preclinical studies demonstrated that penicillin was not only highly effective against a wide array of bacterial pathogens but also remarkably well tolerated by host organisms.

In 1941, they conducted the first human trials on patients suffering from life-threatening infections. The results were dramatic: patients who were on the verge of death from septicemia and abscesses began to recover within hours of receiving penicillin. However, early supplies were so limited that the drug had to be recovered from patients' urine and reused.

Recognizing its extraordinary therapeutic potential, Florey and Chain urgently sought means to scale up production. This marked the beginning of a massive international effort to industrialize penicillin manufacturing, especially as World War II created an acute need for effective antimicrobial agents on the battlefield. The Oxford team partnered with scientists and government agencies in the United States, including the USDA and pharmaceutical companies such as Pfizer, to optimize fermentation techniques and boost yields.

These collaborative efforts led to the development of deep-tank fermentation and the eventual mass production of penicillin, which became widely available to Allied troops by 1944 [9].The contributions of Florey, Chain, and their collaborators were so critical to the practical realization of penicillin's promise that they were awarded the Nobel Prize in Physiology or Medicine in 1945, alongside Fleming. While Fleming had discovered penicillin, it was Florey and Chain who transformed it into a usable, life-saving drug - an achievement that would usher in the modern antibiotic era and save countless lives.

Mechanism of Action and Pharmaceutical Development

Penicillin exerts its potent antibacterial effects through

a highly specific mechanism that targets one of the most vital structures in bacterial physiology: the cell wall. The bacterial cell wall is primarily composed of peptidoglycan, a complex polymer consisting of sugar chains cross-linked by short peptides. This mesh-like structure provides mechanical strength and osmotic stability, enabling the bacterium to withstand the high internal pressure generated by its cytoplasm. Without an intact cell wall, most bacteria cannot survive.

The final stages of peptidoglycan synthesis are mediated by a class of enzymes known as transpeptidases, which are part of a broader group collectively referred to as penicillin-binding proteins (PBPs). These enzymes catalyze the formation of peptide cross-links between adjacent strands of peptidoglycan, effectively "sealing" the wall during bacterial growth and division. Penicillin, a β-lactam antibiotic, inhibits this critical enzymatic step by irreversibly binding to the active site of PBPs, thereby halting the cross-linking process and compromising the structural integrity of the cell wall [10].

The molecular secret of penicillin's action lies in its β-lactam ring, a four-membered cyclic amide that mimics the terminal D-Ala-D-Ala dipeptide of the peptidoglycan precursor - a natural substrate for PBPs. This molecular mimicry enables penicillin to "trick" the enzyme into forming a covalent bond with the β-lactam ring, rendering the PBP permanently inactivated. As a result, the bacterium cannot synthesize new peptidoglycan nor repair existing damage, particularly during cell division when the demand for new cell wall material is highest.

The outcome is osmotic lysis, as the weakened cell wall can no longer resist the internal turgor pressure, leading to rupture and cell death. What makes penicillin especially remarkable is its selectivity. The targets of penicillin – PBPs and peptidoglycan – are unique to prokaryotic organisms and entirely absent in eukaryotic cells, including those of humans and animals. This means that penicillin can be used to kill or inhibit bacterial pathogens without harming host tissues, a pharmacological ideal known as selective toxicity [11].

This property set penicillin apart from earlier antimicrobial approaches, such as antiseptics and heavy-metal compounds, which lacked specificity and often caused significant collateral damage to host cells. Furthermore, the discovery of penicillin's mode of action contributed to a broader understanding of bacterial physiology and spurred the development of entire classes of structurally related antibiotics, including cephalosporins, carbapenems, and monobactams – all of which share the β-lactam core and exploit the same biochemical vulnerability. These β-lactam antibiotics differ in spectrum, stability, and resistance profiles, but their common mechanism continues to serve as a foundation for treating a wide array of bacterial infections.

Beyond its immediate clinical utility, penicillin's mechanism also had a profound impact on molecular biology and pharmacology. It provided the first clear example of an antibiotic that interferes with a specific bacterial target through a defined chemical interaction, laying the groundwork for rational drug design. It demonstrated that microbial metabolism could be selectively disrupted without compromising host integrity, thus ushering in a new era of targeted therapeutics and precision pharmacology.

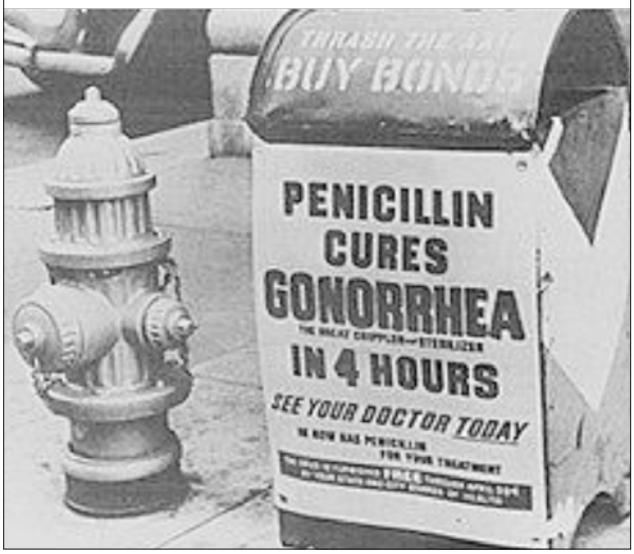
In summary, penicillin's mode of action - centered on the inhibition of transpeptidases and the collapse of peptidoglycan synthesis - is a masterclass in pharmacological precision. Its elegance lies not only in its biochemical efficacy but also in its evolutionary exploitation of a fundamental bacterial vulnerability, all while sparing the host. This combination of potency, specificity, and safety transformed penicillin into the prototypical antibiotic and set the standard by which future antimicrobials would be judged [11].

Industrial Production and Wartime Expansion

World War II served as a crucial accelerant in the transformation of penicillin from a laboratory curiosity into a mass-producible and strategically vital therapeutic agent. In the late 1930s and early 1940s, as global conflict escalated, the demand for effective treatments for battlefield infections became urgent. Wounds sustained in combat were frequently complicated by bacterial contamination, leading to sepsis, gangrene, and high mortality rates. While sulfonamides offered some relief, their efficacy was limited against several key pathogens. The search for a more powerful antimicrobial agent gained urgency and soon centered on the promising but underdeveloped compound known as penicillin. Initial efforts in the United Kingdom were hampered by wartime resource shortages and the bombing of British infrastructure. Despite the Oxford team's success in demonstrating the therapeutic potential of penicillin through animal studies and early human trials, their laboratory-scale production could not meet the pressing medical demands of a world at war. Recognizing the limitations of domestic facilities, Florey and his colleague Norman Heatley made a strategic journey to the United States in 1941 to seek support for large-scale production. Their appeal was received with enthusiasm by American scientific and governmental institutions.

The U.S. Department of Agriculture's Northern Regional Research Laboratory (NRRL) in Peoria, Illinois, was selected as the center of this effort due to its expertise in industrial microbiology and fermentation technologies. There, researchers began optimizing fermentation conditions to increase penicillin yields. A pivotal breakthrough came when they replaced the traditional surface culture method with submerged (deep-tank) fermentation, a more scalable and controllable technique. In this process, mold cultures were grown in large, aerated tanks, dramatically increasing output compared to the shallow tray systems used in earlier trials. One of the most serendipitous contributions to the program came from Mary Hunt, a laboratory technician at NRRL. Tasked with finding more productive strains of *Penicillium*, she brought in a moldy cantaloupe from

Fig. 5. An advertisement advertising penicillin's "miracle cure" [Public Domain. Wikipedia commons].



a Peoria market.

The mold growing on its rind, later identified as Penicillium chrysogenum, was found to be significantly more productive than Fleming's original *P. notatum* isolate. The NRRL team designated this high-yielding strain as NRRL 1951, and it became the genetic foundation for all subsequent industrial penicillin production [9]. To push yields even higher, scientists at NRRL and collaborating pharmaceutical companies employed X-ray and ultraviolet mutagenesis, exposing the fungus to radiation to induce beneficial genetic mutations. This process led to the development of mutant strains capable of producing penicillin at levels more than 1,000 times greater than the original mold. Meanwhile, chemical engineers and microbiologists worked hand-in-hand to optimize every stage of the fermentation process, including aeration, temperature control, nutrient composition, and extraction methods.

The collaboration between academic researchers, government agencies, and private industry – including major pharmaceutical firms such as Pfizer, Squibb, and Merck – was unprecedented in scale and coordination. These companies rapidly adapted their facilities to accommodate the deep-tank fermentation method, effectively creating the first global-scale antibiotic manufacturing infrastructure. By mid-1944, in time for the D-Day invasion of Normandy, penicillin was being produced in quantities sufficient to treat thousands of Allied soldiers. It was distributed to military hospitals across Europe and the Pacific, where it dramatically reduced mortality from wound infections, pneumonia, and venereal diseases such as syphilis and gonorrhea [7] (Fig. 5).

The wartime success of penicillin production not only changed the outcome for countless soldiers but also established a new model for pharmaceutical innovation. It demonstrated the potential of public-private collaboration, government-sponsored research initiatives, and the industrial scalability of biological products. Furthermore, it marked the beginning of what would later be called the antibiotic revolution, laying the groundwork for post-war drug development and the broader transformation of medicine in the second half of the 20th century.

Legacy, Resistance, and Future Challenges

Penicillin's spectacular success in the 1940s did not merely save lives—it also catalyzed a revolution in medicine and public health, ushering in what is now referred to as the "golden age of antibiotics." This period, spanning approximately from the mid-1940s to the early 1970s, witnessed the rapid discovery and commercialization of multiple new classes of antibiotics, each addressing different bacterial targets and broadening the spectrum of treatable diseases. Among the most impactful were streptomycin, the first aminoglycoside antibiotic and the first effective treatment for tuberculosis [11]; tetracycline, which provided broad-spectrum activity against Gram-positive and Gram-negative organisms; and chloramphenicol, a powerful agent effective against life-threatening infections such as typhoid fever and meningitis [12]. Together, these antibiotics transformed clinical practice. Mortality from bacterial diseases plummeted in both developed and developing countries. Conditions that were once fatal or untreatable—such as bacterial endocarditis, septicemia, and osteomyelitis—became manageable. In hospitals, the availability of antibiotics enabled more aggressive surgical interventions, including organ transplants, cancer resections, and joint replacements, by drastically reducing the risk of postoperative infections.

In obstetrics and neonatology, antibiotics helped curb maternal and infant mortality associated with puerperal fever and neonatal sepsis. Public health campaigns and vaccination efforts now had a reliable pharmacological partner, allowing for the integrated control of many communicable diseases. However, the very success of antibiotics sowed the seeds of an emerging crisis. Widespread and often indiscriminate use—in clinical settings, agriculture, animal husbandry, and even household products—created intense selective pressures that favored the survival of resistant bacterial strains. One of the earliest and most formidable forms of resistance was the bacterial production of β-lactamases, enzymes capable of hydrolyzing the β-lactam ring of penicillin and rendering it ineffective [13]. These resistance mechanisms spread rapidly via horizontal gene transfer, turning once-treatable pathogens into stubborn clinical challenges. In response, pharmaceutical scientists developed second- and third-generation β-lactam antibiotics – including cephalosporins, monobactams, and carbapenems – designed to evade enzymatic degradation. Additionally, β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam were formulated to protect primary β-lactam antibiotics from

destruction. These combinations temporarily restored the efficacy of older drugs, but the arms race between pharmaceutical innovation and microbial adaptation was only accelerating. By the late 20th and early 21st centuries, a new and deeply concerning pattern emerged: the rise of multidrug-resistant organisms (MDROs), against which few, if any, antibiotics remained effective. Among the most infamous are methicillin-resistant Staphylococcus aureus (MRSA), which causes severe hospital- and community-acquired infections; vancomycin-resistant enterococci (VRE); and carbapenem-resistant Enterobacteriaceae (CRE), sometimes dubbed "superbugs" due to their extreme resistance and high mortality rates. These pathogens have led to prolonged hospital stays, increased healthcare costs, and a resurgence in mortality from infections previously considered curable. The World Health Organization (WHO), alongside the Centers for Disease Control and Prevention (CDC) and other international agencies, has declared antimicrobial resistance (AMR) one of the top ten global public health threats. According to recent projections, if unchecked, AMR could cause 10 million deaths annually by 2050, eclipsing mortality from cancer and cardiovascular disease [14-16]. Addressing this looming catastrophe requires a comprehensive and coordinated response. At the clinical level, antibiotic stewardship programs are essential to ensure the judicious use of existing antimicrobials, guided by microbiological diagnostics and resistance surveillance. Moreover, several natural antibiotics have been shown to evolve as part of microbial competition in the environment [17].

At the policy level, regulatory frameworks must restrict the non-therapeutic use of antibiotics in agriculture and enforce prescription guidelines in human medicine. Moreover, research incentives and public-private partnerships are urgently needed to reinvigorate antibiotic discovery, particularly since pharmaceutical companies have largely abandoned antibiotic development due to low profitability and high regulatory hurdles. Beyond technical solutions, combating AMR demands global coordination. Resistance knows no borders, and efforts in one country can be undermined by inaction in another. International collaborations such as the Global Antimicrobial Resistance Surveillance System (GLASS), the One Health initiative, and the GARDP (Global Antibiotic Research and Development Partnership) are steps in the right direction, but they require sustained funding, political commitment, and public engagement [18]. In essence, the rise of antibiotic resistance is a stark reminder that scientific breakthroughs, no matter how powerful, are not immune to the consequences of overuse and neglect. The legacy of penicillin is thus twofold: it exemplifies the life-saving potential of biomedical innovation and the ongoing challenge of preserving that legacy in a rapidly evolving microbial world.

Conclusion

While Fleming is rightfully credited, the early work of figures like Tiberio reminds us that the path to discovery is often long, collaborative, and overlooked. Penicillin's story is one of scientific brilliance, global mobilization, and the delicate balance between therapeutic innovation and microbial adaptation. As we navigate the antibiotic resistance crisis, these lessons are more urgent than ever.

Data availability statement

Not applicable.

Informed consent statement

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Conflicts of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

conceived the study: FMG, EV, LI; designed the study: EV, FMG, LI; drafted the manuscript: EV, FMG; performed a search of the literature: MM, LG, LI; critically revised the manuscript: MM; conceptualization and methodology: FMG, EV, MM, LG, LI; investigation and data curation: LG, EV, LI; original draft preparation: EV, FMG; review: MM, EV; editing: MM, FMG, EV, LI All authors have read and approved the latest version of the paper for publication.

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