

FROM CURE TO CONCERN: THE BURDEN OF ANTIBIOTIC OVER CONSUMPTION AND MISAPPLICATION

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ABSTRACT

Antibiotics have been one of the greatest discoveries in modern medicine, saving countless lives by effectively treating bacterial infections. However, their over consumption and misapplication have become major global health concerns. This review article provides a comprehensive overview of antibiotics, including their history, classification, and mechanisms of action. It highlights how inappropriate prescribing, self-medication, and use in agriculture have contributed to the rise of antibiotic resistance — a threat that undermines the effectiveness of existing treatments. The paper emphasizes the need for rational antibiotic use, public awareness, and the development of new antimicrobial agents to combat this growing crisis.

KEYWORDS: Antibiotics, Anti-microbial resistance, Penicillin, Over consumption, Misapplication.

1. INTRODUCTION

The term "antibiotics" denotes substances that are produced naturally by various microorganisms, including bacteria and fungi. These substances can inhibit the growth of other microorganisms and destroy their cells.^[1] In contemporary times, with the advent of semi-synthetic derivatives, the terminology has evolved; the term "antimicrobials" now

encompasses natural, semi-synthetic, and synthetic substances that can inhibit the proliferation of microbes, ultimately leading them towards apoptosis.^[2] Prior to the introduction of antibiotics, humans faced significant vulnerability to infections. Diseases such as pneumonia, meningitis, and tuberculosis were challenging to treat or often untreatable. Society lived in constant apprehension of widespread epidemics. Medical fields like surgery, paediatrics, and haematology experienced high mortality rates due to infectious diseases.^[3] Since that time, medical practice has transformed significantly. Freed from the pervasive threat of infection, healthcare professionals were able to expand and innovate their research endeavors. Specialties such as surgery and haematology thrived. Additionally, humanity has enjoyed decades of respite from fears of severe pandemics (e.g., plague, syphilis), with conditions like tuberculosis now being managed effectively. Antibiotics gradually became recognized within the average person's understanding as a life-saving form of treatment.^[4] As time progressed, numerous new antimicrobial agents were discovered, each with distinct mechanisms of action, and it is well-established that the current pharmaceutical inventory offers comprehensive defence against nearly all pathogens.^[5] In modern times, antimicrobials are prevalent not only in clinical settings but also in agriculture, livestock management, and aquaculture, where they serve as growth promoters or protective agents.^[6,7] It is crucial to clarify at this juncture that chemotherapeutic agents that combat bacterial infections and are derived from living organisms are referred to as antibiotics, whereas those synthesized artificially in laboratories are known as antimicrobials.^[8]

2. A BRIEF HISTORY OF ANTIBIOTICS

The application of antibiotic-producing microorganisms to avert disease dates back thousands of years, with historical poultices made from mouldy bread utilized to treat open wounds in regions such as Serbia, China, Greece, and Egypt over 2000 years ago. The Eber's papyrus, dating to 1550 BC, is recognized as the oldest surviving medical document and lists mouldy bread and medicinal soil among its remedies.^[9] Additionally, an Anglo-Saxon recipe from a millennium ago has recently been demonstrated to effectively eliminate MRSA (methicillin-resistant *Staphylococcus aureus*).^[10] Nevertheless, the advancement of anti-infective medications and the foundational idea of chemotherapy is predominantly attributed to Paul Ehrlich, who, around a century ago, developed synthetic arsenic-based pro-drugs salvarsan (salvation arsenic) and neo-salvarsan to combat *Treponema pallidum*, the bacterium responsible for syphilis (Figure 1).^[11] This marked one of the earliest systematic screenings for drug discovery utilizing a library of synthetic compounds, inspired by Ehrlich's research

on dyes that specifically stained bacterial cells. Salvarsan was eventually replaced by the sulphonamide prodrug Prontosil, discovered by Gerhard Domagk^[12], a bacteriologist at Bayer, who employed the drug to prevent his daughter's arm from being amputated. Domagk and his team effectively continued the legacy of Paul Ehrlich, as the sulpha drugs were inspired by dyes used to selectively stain bacterial cells. Sulphonamides were the first truly effective broad-spectrum antimicrobials used in clinical settings and remain in use today; however, they were largely overshadowed by the discovery of penicillin, which was noted on a contaminated Petri dish by Alexander Fleming in 1928.^[13] Penicillin was subsequently purified by Norman Heatley, Howard Florey, Ernst Chain, and their colleagues at Oxford, who played a crucial role in the development of penicillin as a therapeutic agent (Figure 1).^[14] In 1945, Dorothy Hodgkin elucidated the beta-lactam structure of penicillin.^[15] Addressing the well-known discussion involving Robert Robinson, who supported a thiazolidine-oxazolone structure, alongside several prominent chemists such as Chain, Abrahams, and Woodward, who contended that it was a beta-lactam.^[16] This represented a significant advancement as it facilitated the creation of semi-synthetic derivatives to overcome penicillin resistance.

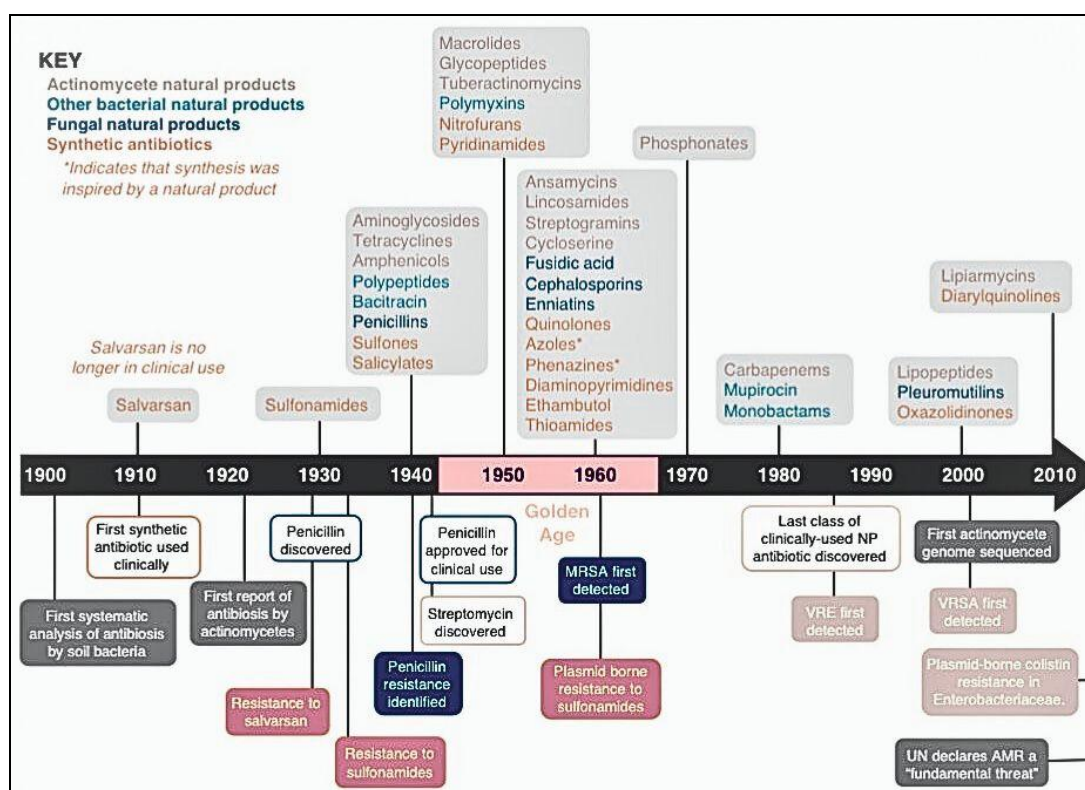


Figure 1: A timeline illustrating the decade in which new classes of antibiotics were introduced to clinical use. Key dates concerning antibiotic discovery and antimicrobial

resistance are displayed at the bottom of the timeline, including the initial reports of drug-resistant strains such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), vancomycin-resistant *S. aureus* (VRSA), and plasmid-mediated colistin resistance in *Enterobacteriaceae*.

Antibiosis among microorganisms was documented well before penicillin was discovered, including by Louis Pasteur, who suggested that microbes had the ability to secrete substances capable of eliminating other bacteria.^[17] By the early 20th century, reports had emerged regarding the generation of diffusible and heat-stable compounds by bacteria.^[18] and investigations into their potential for combating infectious diseases had commenced. It can be argued that the first clinical application of an antibiotic occurred in the 1890s when Emmerich and Low utilized an extract from *Pseudomonas aeruginosa* (then referred to as *Bacillus pycyanus* to treat a substantial number of patients, with this extract, known as pyocyanase, being utilized until the 1910s.^[19] Pyocyanase demonstrated effectiveness against various pathogens and was incorrectly thought to be an enzyme. In reality, the active constituents of pyocyanase were likely comprised of a blend of pyocyanin, a phenazine involved in quorum sensing, and 2-alkyl-4-hydroxy-quinolones.^[20]

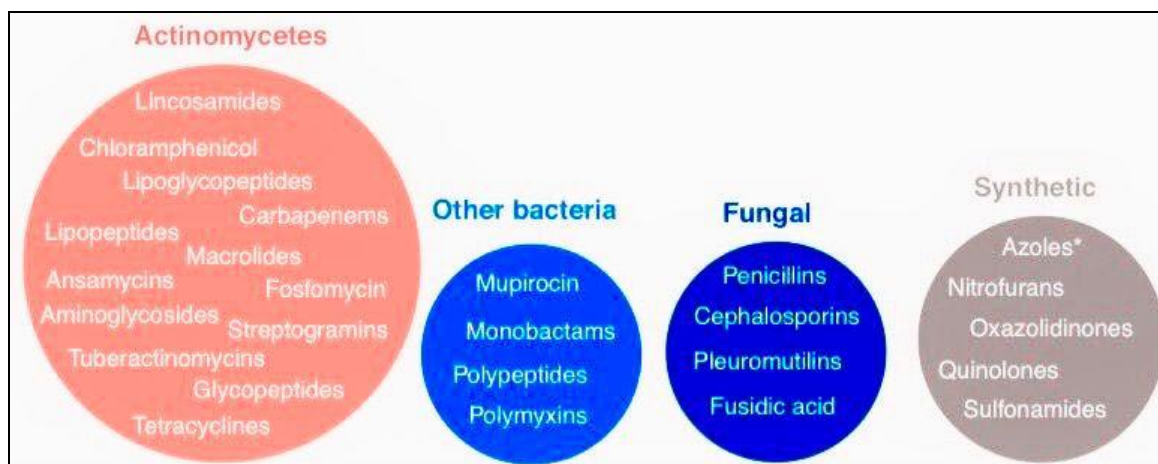


Figure 2: The majority of antibiotic classes that are clinically significant originate from natural products.

The discoveries of penicillin, tyrocidine, and various reports regarding the production of antimicrobial compounds by microorganisms prompted Selman Waksman to initiate a systematic investigation of microbes as sources of antimicrobial compounds in the late 1930s. Waksman characterized an antibiotic as a compound synthesized by a microbe that acts to eliminate other microbes and played a crucial role in recognizing soil-dwelling filamentous

Actinomycetales ('actinomycetes') as abundant sources of antimicrobial substances.^[21] Waksman uncovered numerous antibiotics produced by soil-dwelling actinomycetes, including neomycin and streptomycin, which was the first compound effective against tuberculosis.^[21] Waksman's ground breaking research identified the genus *Streptomyces* as highly productive sources of natural products (NPs), or secondary metabolites, which are compounds not essential for the standard growth, development, or reproduction of an organism in a laboratory setting. Many NPs from streptomycetes exhibit activity against bacteria, fungi, viruses, nematodes, and insects, and they have also been developed for use as anticancer and immunosuppressant medications.^[22]

Waksman's research marked the beginning of the Golden Age of antibiotic discovery, spanning from the 1940s to the 1960s. Many of these antibiotics remain in clinical use today; however, their efficacy has diminished due to the emergence of antimicrobial resistance (AMR) (Figure 1).^[23] The swift and relatively straightforward identification of various classes (and their variations) of natural product (NP) antibiotics within a brief timeframe resulted in their overuse. This situation, combined with a declining antibiotic discovery pipeline since the 1970s, has contributed to the present scenario where there are few new antibiotics undergoing clinical trials.^[23] Consequently, the majority of antibiotics currently in clinical trials are modifications of established classes of NP or synthetic antibiotics, rather than entirely new classes of antibiotics. It is noteworthy that this stagnation in antibiotic discovery coincides with a reduction in the identification of new NP families and the ongoing rediscovery of known compounds during screening campaigns that utilize microbial, predominantly actinomycete, fermentation extracts.^[23] This situation has, in part, fostered the perception that all the 'low-hanging fruit' has been collected, leading many major pharmaceutical and agrochemical companies to close their NP discovery divisions.

The divestment from natural product (NP) research was paired with an investment in various high-throughput screening (HTS) programs aimed at identifying new synthetic antibiotics; however, these efforts have not been fruitful. For instance, GlaxoSmithKline (GSK) conducted 70 HTS campaigns over a span of seven years utilizing a library of around 500,000 compounds, yet this resulted in very few promising leads and no candidates suitable for development.^[24] Likewise, AstraZeneca's 65 HTS campaigns yielded a handful of leads, but none were effective against multi-drug resistant Gram-negative bacteria.^[25] Nevertheless, in recent years, the identification of new antibiotic-producing strains in less-explored

environments, along with advancements in genome mining tools, has revitalized the NP discovery sector, as illustrated by.^[26,27,28]

3. CLASSIFICATION OF ANTIBIOTICS

The wide array of antibiotics has led to multiple suggested classifications, which may be based on chemical structure, mechanism of action, or the type of organism affected. The classification by chemical structure begins with distinguishing between beta-lactam and non-beta-lactam antibiotics. Beta-lactam antibiotics are characterized by a four-membered β -lactam ring, which is essential for their antibacterial efficacy. Numerous classes of antibiotics do not fall under the beta-lactam category,

Classes of antibiotics

Penicillin, Aminoglycoside, 2- and 4-Quinolones, Macrolides, Tetracycline, Carbapenem, Cephalosporin, Sulphonamide, Glycopeptides, Quinupristin and dalfopristin, Rifamycin.

A systematic and practical classification framework that is primarily based on similarities in chemical structure has been proposed, encompassing beta-lactams, aminoglycosides, macrolides, quinolones, fosfomycin, polymyxin, sulphonamides, tetracyclines, and glycopeptides. Another enlightening classification is predicated on the particular mechanism of action, which comprises the following subcategories: inhibitors of cell wall synthesis, inhibitors of protein synthesis, inhibitors of DNA replication, inhibitors of RNA synthesis, inhibitors of folate metabolism, inhibitors of RNA polymerase, inhibitors of mycobacterium tuberculosis, antifungal agents, antimalarial agents, and species-specific inhibitors.^[29,30]

Most classification systems consist of two main categories: the first categorizes according to chemical structure, while the second categorizes based on the mechanism of action. This review will primarily focus on the system based on the mechanism of action, given its detailed nature and functionality. Therefore, the sections on mechanisms and indications can be precisely found under the main category of drug action.^[31, 32]

3.1. Classification Based on Chemical Structure

The primary category consists of β -lactam antibiotics, which can be subdivided into penicillins, cephalosporins, carbapenems, and aztreonam. Penicillins encompass various subclasses, including natural penicillins, penicillinase-resistant variants (such as methicillin and oxacillin, nafcillin), aminopenicillins (like amoxicillin and ampicillin), as well as

antipseudomonal and extended-spectrum penicillins (including piperacillin and ticarcillin). Tazobactam, clavulanic acid, and sulbactam function as β -lactamase inhibitors that, when combined with β -lactam antibiotics, obstruct the bacterial enzyme that targets the drug, thereby enhancing their antibacterial efficacy. Additionally, there are other classes of antibiotics, which include lincosamide, vancomycin, teicoplanin, ansamycin, macrolide, tetracycline, aminoglycoside, fluoroquinolone, and sulphonamide.^[33, 34] Based on their mechanism of action, antibiotics are categorized as either bactericidal or bacteriostatic agents. Bactericidal agents are responsible for killing or destroying bacteria within the infected tissue; examples of such agents include penicillin, cephalosporins, fluoroquinolones, and aminoglycosides. Conversely, bacteriostatic agents inhibit bacterial reproduction, allowing other immune system mechanisms to eliminate the microbes; examples of these include tetracycline, clindamycin, and metronidazole. The antibacterial mechanisms of antibiotics involve disrupting the bacterial cell wall, halting protein synthesis, degrading bacterial nucleic acids (DNA/RNA), inhibiting biochemical metabolism, chelating essential metallic cations for bacterial growth, and damaging bacterial membranes through disintegration. Each antibiotic class is recognized for its ability to eliminate susceptible bacteria through one or more of these mechanisms. Consequently, it is crucial to comprehend each antibiotic classification and its mechanism to ensure appropriate use for specific clinical infections.^[35,36]

3.2. Classification Based on Mechanism of Action^[37-40]

3.2.1. Inhibitors of cell wall synthesis include: a) Beta-lactam antibiotics b) Glycopeptides c) Bacitracin

3.2.2. Agents that inhibit the function of cell membranes

3.2.3. Agents that inhibit protein synthesis: a) Aminoglycosides b) Tetracyclines c) Macrolides d) Chloramphenicol and Thiamphenicol e) Pleuromutilines f) Lincosamides g) Oxazolidinones h) Streptogramins i) Nitroimidazoles

3.2.4. Agents that inhibit nucleic acid synthesis: a) Inhibitors of the DNA gyrase enzyme b) Inhibitors of the DNA-dependent RNA polymerase enzyme c) Inhibitors of the DNA-dependent DNA polymerase enzyme

3.2.5. Antimetabolites: a) Sulphonamides b) Trimethoprim

3.2.6. Inhibitors of RNA synthesis

According to the mechanism of action, antibiotics can be categorized as follows. The primary role of beta-lactam antibiotics and glycopeptides is to obstruct cell wall synthesis. Beta-

lactam antibiotics function by inhibiting the enzymes responsible for constructing the cell wall, which occurs through the suppression of peptidoglycan synthesis during bacterial replication. Glycopeptides, including interprim and vancomycin, inhibit the formation of the peptidoglycan layer in cell walls via a mechanism distinct from that of peptidoglycan precursor formation. A key feature of cell wall synthesis inhibitors is their bactericidal effect. Agents that are concentrated in macrophages and neutrophils demonstrate a concentration-dependent reduction in bacterial numbers in an inoculum, exhibiting a time and concentration-dependent post-antibiotic effect (PAE) in mutants that alter their behaviour. Inhibitors of cell wall synthesis, such as beta-lactam antibiotics and glycopeptides, are influenced during processing, while pre-fasting diminishes the efficacy of aminoglycosides.^[37, 41]

4. OVER CONSUMPTION AND MISAPPLICATION OF ANTIBIOTICS

The over-prescription of antibiotics presents a significant challenge in primary care, where the majority of infections are caused by viruses. Approximately 90% of all antibiotic prescriptions are written by general practitioners, with respiratory tract infections being the primary reason for these prescriptions. Research has shown that multifaceted interventions aimed at reducing antibiotic overuse are more effective than isolated initiatives. Such interventions should include the strict enforcement of policies that prohibit the over-the-counter sale of antibiotics, the implementation of antimicrobial stewardship programs, the active involvement of clinicians in audits, the use of reliable rapid point-of-care tests, the encouragement of delayed antibiotic prescribing strategies, the improvement of communication skills with patients through the provision of informational brochures, and the conduct of more practical studies in primary care that focus on outcomes relevant to clinicians, such as complications and clinical results.^[42]

Antibiotics are often regarded as a "magic bullet," even in instances of viral infections where they will have no impact. Approximately 25 percent of antibiotic prescriptions are not required. Documented cases of antibiotic-resistant superbugs such as pneumonia, tuberculosis, gonorrhoea, and salmonellosis have already been observed. The overuse of antibiotics has become both widespread and pervasive. Such excessive use is a significant contributor to the development of antibiotic resistance. It is the responsibility of physicians to refrain from prescribing antibiotics when not required, for the benefit of both patients and society as a whole.^[42]

Antibiotics are effective solely in treating infections that are caused by bacteria. Utilizing them for viral infections will not improve your condition or expedite your return to work.^[42]

Viruses are responsible for the common cold, influenza, the majority of sore throats, bronchitis, as well as numerous sinus and ear infections. Antibiotics are ineffective against viral infections. Most prevalent respiratory infections do not benefit from antibiotics, as they are caused by a virus. If your healthcare provider concludes that your illness is due to a virus, request advice from them on how to alleviate symptoms and improve your well-being.^[42]

MDR - multi-drug resistance, Side effects associated with antibiotics.

- Antibiotics are linked to a rise in fatal diarrhoea incidents among children.
- Antibiotics have the potential to disrupt delicate gut microbiota.

This disruption may result in additional infections, such as *Clostridium difficile*, as well as other types of antibiotic-associated diarrhoea.

- The use of antibiotics is contributing to a rise in cases of untreatable skin diseases.
- Antimicrobials are contributing to increased Pharmaceutical and Healthcare expenses.
- The use of antibiotics may elevate the likelihood of developing an antibiotic-resistant infection in the future.
- Antimicrobials account for one in five visits to the emergency department due to adverse drug reactions.

To stop the use of antibiotics, Educational Awareness Programs are of very vital. Educational Awareness Programs play a crucial role. Interactive educational interventions prove to be the most effective. These interventions are non-mandatory and are grounded in actual prescriptions from clinical practice. They encompass educational outreach visits, audits, and counselling interviews that provide feedback, along with multifaceted interventions on how to use antibiotics safely.^[42]

- Follow the instructions precisely as prescribed by your provider.
- Please ensure that no doses are missed.
- Do not disclose to others or derive from others.
- Complete the prescribed medication course even if your condition improves.
- Refrain from reserving antibiotics for future use.
- Consume probiotics to assist the body in preserving its beneficial bacteria.

5. CONCLUSION

Antibiotics changed the world, but now our careless use is making them less effective. Over consumption and misapplication have led to dangerous resistant bacteria that no longer respond to treatment. The only way to stop this is through responsible use, good awareness, and strong rules on antibiotic use in both people and animals. Protecting antibiotics today means saving lives tomorrow.

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