

Profile of Antibiotic Use in Health Care

Savant Ajit Balasaheb, Mirgane Adesh Ramhari, Wagh Tanay Machindra

-Gaikwad Avinash Santosh, Dr. Kolhe S. A

Aditya Diploma Institute of Pharmacy, Beed

Abstract: *Antibiotics have revolutionized medicine, saving countless lives since their discovery in the early 20th century. However, the origin of antibiotics is now overshadowed by the alarming rise in antibiotic resistance. This global crisis stems from the relentless adaptability of microorganisms, driven by misuse and overuse of antibiotics. This article explores the origin of antibiotics and the subsequent emergence of antibiotic resistance.*

It delves into the mechanisms employed by bacteria to develop resistance, highlighting the dire consequences of drug resistance, including compromised patient care, increased mortality rates, and escalating healthcare costs. The article elucidates the latest strategies against drug-resistant microorganisms, encompassing innovative approaches such as phage therapy, CRISPR-Cas9 technology, and the exploration of natural compounds. Moreover, it examines the profound impact of antibiotic resistance on drug development, rendering the pursuit of new antibiotics economically challenging.

Keywords: Antibiotics

I. INTRODUCTION

Among the greatest discoveries of humankind in the 20th century was the discovery of antibiotics. Antibacterial triumph changed contemporary biomedicine and seeks to define, mold, and grow both its potential and its boundaries. Regrettably, the possibility for resistance to any therapeutic agent to evolve limits its ability to be effective [1,2]. Series of antibiotics must be developed, since resistance compromises efficacy (therapeutic effect). A pathogen's enhanced resistance to the prescribed standard therapy to which it was previously vulnerable is referred to as tolerance to an antibacterial agent (in this case, an antibiotic) [3-5].

The history of using antimicrobial agents to combat infections is rich, dating back to ancient civilizations where various natural extracts were employed for their healing properties. Some of these extracts, originating from plants and molds, exhibited antibacterial properties, even before the term "antibiotics" was coined [6].

The introduction of the term "antibiotics" was the result of pioneering work by American microbiologist Selman Waksman and his team, who successfully isolated chemical substances from microorganisms capable of inhibiting the growth of other microbes [7].

While the concept of using microorganisms to combat infections has ancient roots, it was Alexander Fleming's serendipitous discovery of penicillin in 1928 that marked the inception of modern antibiotic therapy [8].

Fleming's discovery bridged the gap between ancient knowledge, such as

The Egyptians' use of mold bread to treat infection, and the era of antibiotics [8].

The Post-World War II period, often referred to as the "golden era" of antibiotic discovery, witnessed the identification of numerous antibiotic classes that continue to be used today [9].

The advent of penicillin rapidly propagated the belief that infections could be effectively controlled with antibiotics, despite earlier use of sulfonamides as the first antimicrobials, which faced limitations due to emerging resistance mechanisms that persist to this day [10].

Interestingly, the penicillin discovery team identified penicillinase, a bacterium capable of degrading penicillin, even before widespread access to the antibiotic [11,12].



The history of antibiotics :-

Pre-Antibiotic Era

Before antibiotics, bacterial infections were often deadly. Treatments included:

- Herbal remedies
- Bloodletting
- Surgical drainage of abscesses
- Quinine for malaria (not an antibiotic, but an early antimicrobial)

Some ancient cultures, like the Egyptians and Greeks, used molds and plant extracts to treat infections, though they didn't understand the microbial basis of disease.

The Birth of Antibiotics

1928: Discovery of Penicillin

- Alexander Fleming discovered penicillin from the mold *Penicillium notatum*.
- He noticed it killed *Staphylococcus* bacteria in a petri dish.
- At first, the potential wasn't fully realized.

1930s–1940s: Development and Mass Production

- Howard Florey, Ernst Boris Chain, and others turned penicillin into a usable drug.
- By World War II, penicillin was being mass-produced, saving countless lives.
- Marked the start of the antibiotic era.

Golden Age of Antibiotics (1940s–1960s)

This period saw the discovery of many major antibiotics:

Antibiotic	Discovered By	Target Organisms
Streptomycin	Selman (1943) Waksman	TB, gram-negative bacteria
Chloramphenicol	1947	Broad-spectrum
Tetracyclines	1948	Broad-spectrum
Erythromycin	1952	Gram-positive bacteria
Vancomycin	1953	Resistant gram-positive
Rifampin	1957	

Many of these were isolated from soil bacteria, particularly the *Streptomyces* genus.

Rise of Antibiotic Resistance

- 1960s–present: Overuse and misuse led to antibiotic resistance.
- Bacteria like MRSA, VRE, and multidrug-resistant TB emerged.
- Antibiotic development slowed down due to high costs and scientific challenges.

Modern Era and Challenges

- Renewed interest in novel antibiotics, phage therapy, and antimicrobial stewardship.
- New technologies (e.g., genomics, AI) aid drug discovery.
- WHO emphasizes the urgency of combating antibiotic resistance.

Summary

- 1928: Penicillin discovered
- 1940s–60s: Golden Age, many antibiotics developed
- Post-1960s: Resistance emerges, discovery slows



Aim

To analyze and evaluate the patterns, appropriateness, and factors influencing antibiotic use in healthcare settings to promote rational prescribing practices and reduce antimicrobial resistance.

Objectives

1. To assess the types and classes of antibiotics commonly prescribed in healthcare facilities.
2. To evaluate the indications for antibiotic use and their alignment with clinical guidelines.
3. To identify the prevalence of empirical versus culture-guided antibiotic therapy.
4. To determine the level of adherence to antimicrobial stewardship principles among healthcare providers.
5. To investigate the factors influencing antibiotic prescribing behaviors, including physician knowledge, patient expectations, and institutional policies.
6. To examine the rate and patterns of antibiotic resistance associated with common pathogens in the facility.
7. To provide recommendations for optimizing antibiotic use and minimizing the development of antimicrobial resistance.

Methodology

The research is based on a systematic literature review, policy analysis, and, where applicable, hospital audit data and expert interviews. Sources include: Scientific databases (PubMed, Scopus) Guidelines and reports from WHO, CDC, and local health departments Antibiotic stewardship program (ASP) reviews Surveillance data from hospitals and national agencies.

Antibiotic Classes Medication Names

1. Aminoglycosides – Mycin
2. Cephalosporins Cef/Ceph
3. Tetracyclines – Cycline
4. Penicillins – Cillin
5. Sulfonamides Sulfa
6. Fluoroquinolones Floxacin
7. Macrolides Thromycin
8. Carbapenems – Penem
9. Lincosamides – Mycin
10. Glycopeptides – In (Mycin)

1. Based on Mechanism of Action

A. Cell Wall Synthesis Inhibitors Prevent bacteria from forming cell walls.

Examples:

Penicillins (e.g., amoxicillin)
Cephalosporins (e.g., ceftriaxone)
Carbapenems (e.g., imipenem)
Monobactams (e.g., aztreonam)
Glycopeptides (e.g., vancomycin)

B. Protein Synthesis Inhibitors Interfere with bacterial ribosomes.

Examples:

Aminoglycosides (e.g., gentamicin)
Tetracyclines (e.g., doxycycline)
Macrolides (e.g., azithromycin)
Chloramphenicol
Lincosamides (e.g., clindamycin)



C. Nucleic Acid Synthesis Inhibitors Disrupt DNA replication or transcription.

Examples:

Fluoroquinolones (e.g., ciprofloxacin)

Rifamycins (e.g., rifampin)

Metronidazole

D. Antimetabolites Inhibit metabolic pathways (e.g., folic acid synthesis).

Examples:

Sulfonamides (e.g., sulfamethoxazole)

Trimethoprim

E. Cell Membrane Disruptors Compromise bacterial cell membrane integrity.

Examples:

Polymyxins (e.g., polymyxin B, colistin)

Daptomycin

2. Based on Spectrum of Activity

A. Broad-Spectrum Antibiotics Effective against a wide range of gram-positive and gram-negative bacteria.

Examples:

Tetracyclines

Fluoroquinolones

Carbapenems

B. Narrow-Spectrum Antibiotics Target specific types of bacteria (e.g., only gram-positive).

Examples:

Penicillin G (mainly gram-positive)

Vancomycin

3. Based on Origin

A. Natural Antibiotics Produced by microorganisms.

Example:-

Narrow Penicillin (from *Penicillium* fungi)

B. Semi-synthetic Antibiotics Chemically modified natural antibiotics.

Example:

Amoxicillin

C. Synthetic Antibiotics Fully man-made.

Example:

Sulfonamides, fluoroquinolones

Drug Used in Antibiotic in details about the following:

Name:

Amoxicillin

Drug Class:

Beta-lactam antibiotic (Penicillin group)

Mechanism of Action:

Amoxicillin inhibits the synthesis of bacterial cell walls by binding to penicillin-binding proteins (PBPs). This weakens the cell wall and leads to bacterial lysis and death, especially during cell division.

Spectrum of Activity:

Amoxicillin is bactericidal and effective against:

Gram-positive bacteria (e.g., *Streptococcus pneumoniae*, *Enterococcus faecalis*)

Some gram-negative bacteria (e.g., *Escherichia coli*, *Haemophilus influenzae*, *Helicobacter pylori*)



Not effective against:

Beta-lactamase-producing organisms (unless combined with clavulanic acid)

Common Brand Names:

Amoxil

Moxatag

Augmentin (when combined with clavulanic acid)

Indications:

Used to treat a variety of infections including:

Upper respiratory tract infections (e.g., sinusitis, otitis media)

Lower respiratory tract infections (e.g., bronchitis, pneumonia)

Urinary tract infections (UTIs)

Skin and soft tissue infections

Dental abscesses

H. pylori infection (part of combination therapy for peptic ulcer)

Dosage (Adults):

Typical oral dose:

250–500 mg every 8 hours or

500–875 mg every 12 hours, depending on infection severity Note: Dosage may vary for children and based on kidney function.

Side Effects:

Nausea

Diarrhea

Rash

Rare but serious:

Anaphylaxis (in penicillin-allergic patients)

Stevens-Johnson syndrome

Clostridioides difficile-associated diarrhea

Contraindications:

Known allergy to penicillins or cephalosporins (due to possible cross-reactivity) Use with caution in renal impairment.

Drug Interactions:

Oral contraceptives: May reduce efficacy

Allopurinol: Increased risk of rash

Methotrexate: Increased methotrexate toxicity

General Information

Drug Name: Amikacin

Class: Aminoglycoside antibiotic

Route: Usually intravenous (IV) or intramuscular (IM)

Spectrum: Broad-spectrum — effective against aerobic gram-negative bacteria, and some gram-positive bacteria

Mechanism of Action

Amikacin binds to the 30S ribosomal subunit of bacteria, inhibiting protein synthesis. This leads to:

Misreading of mRNA

Defective bacterial proteins

Bactericidal effect (kills bacteria)

Indications (Uses)

Used to treat serious infections, especially when resistance to other antibiotics is a concern:

Copyright to IJAR SCT
www.ijarsct.co.in



DOI: 10.48175/IJAR SCT-27375



Sepsis
Pneumonia (hospital-acquired)
Urinary tract infections (UTIs)
Intra-abdominal infections
Bone and joint infections
Tuberculosis (as a second-line drug)
Multidrug-resistant (MDR) bacterial infections

Dosage and Administration Commonly given IV or IM.
Dosage depends on body weight, kidney function, and severity of infection.
Example: 15 mg/kg/day divided every 8–12 hours.

Therapeutic Drug Monitoring (TDM) is often needed to avoid toxicity.

Side Effects

Amikacin can cause serious toxicities, especially if not carefully monitored:

1. Nephrotoxicity – Kidney damage (reversible if caught early)
2. Ototoxicity – Hearing loss or balance issues (may be irreversible)
3. Neurotoxicity – Rare; includes numbness, muscle twitching, seizure

Contraindications

Known allergy to aminoglycosides
Pregnancy (use only if benefits outweigh risks)
Pre-existing renal impairment (use with caution)

Resistance Concerns

Bacteria may resist amikacin via:
Enzymatic modification (aminoglycoside-modifying enzymes)
Efflux pumps

Reduced permeability of bacterial cell walls

However, amikacin is often used when bacteria are resistant to other aminoglycosides like gentamicin or tobramycin.

Notable Coverage

Effective against:

Pseudomonas aeruginosa
Escherichia coli *Klebsiella* spp.
Enterobacter spp.
Mycobacterium tuberculosis (second-line)

Less effective against anaerobes and some gram-positives unless used in combination therapy

Summary

Feature	Details
Class	Aminoglycoside.
Action	Inhibits 30S ribosome bactericidal.
Used for	Serious gram-negative infections, MDR-TB.
Toxicity	Nephrotoxic, ototoxic monitor levels.
Route	IV or IM.
Monitoring	Renal function, serum drug levels.



Would you like a visual chart or comparison with similar antibiotics like_gentamicin or tobramycin?

Profile of Antibiotic Use in Healthcare

1. Common Uses

Antibiotics are essential in treating bacterial infections such as:

Respiratory infections (e.g., pneumonia)

Urinary tract infections (UTIs)

Skin and soft tissue infections

Surgical site infections (prophylactic use)

Sepsis and bloodstream infections

2. Settings of Use

Hospitals (Inpatient): Used for severe or complicated infections, often via IV.

Primary Care/Outpatient: Prescribed for common infections like sore throats, UTIs.

ICUs: Broad-spectrum antibiotics are commonly used, sometimes empirically.

Long-term care facilities: Used for elderly populations with chronic infections.

3. Routes of Administration

Oral: For mild to moderate infections

Intravenous (IV): For serious infections or when oral administration is not feasible

Topical: Skin infections or eye/ear infections

Antibiotic Stewardship Programs (ASPs)

These are implemented to:

Promote appropriate antibiotic use

Reduce resistance

Improve patient outcome

Decrease healthcare costs

Limitations and Challenges in Antibiotic Use

1. Antibiotic Resistance

Overuse and misuse (e.g., for viral infections) lead to resistant strains.

Emergence of multidrug-resistant organisms (MDROs) like MRSA, VRE, CRE.

Limited treatment options for resistant infections.

2. Diagnostic Uncertainty

Clinicians often prescribe antibiotics empirically before confirmation.

Lack of rapid diagnostic tools contributes to inappropriate use.

3. Patient Expectations and Pressure

Patients often expect antibiotics for viral illnesses (like colds or flu).

This leads to overprescribing in outpatient settings.

4. Lack of New Antibiotics

Pharmaceutical investment in antibiotic development has decreased.

Few new classes of antibiotics have been introduced in recent decades.

5. Inconsistent Stewardship Implementation

Not all healthcare facilities have well-implemented ASPs.

Lack of trained personnel, resources, and data infrastructure.

6. Global Disparities

In some countries, antibiotics are available without prescription.

In others, lack of access leads to untreated infections.

7. Adverse Effects

Side effects include GI disturbances, allergic reactions, and C. difficile infection.

Can lead to longer hospital stays and higher costs.



8. Economic Challenges

High cost of newer antibiotics

Solutions Being Applied

Stronger antibiotic stewardship in hospitals and clinics

Public awareness campaigns about appropriate antibiotic use

Development of rapid diagnostics

Investment in research for new antibiotics

Policies to regulate over-the-counter antibiotic sales (especially in low- and middle-income countries).

9. Modification in Regulatory Process to Facilitate Antibiotic Development

To facilitate antibiotic development and address the challenges posed by antibiotic.

Resistance, several specific changes or improvements in the regulatory process are necessary.

This may include the following:

(i) **Adaptive Pathways and Flexible Trial Designs:** The regulatory process should allow Adaptive trial designs that can be adjusted based on emerging data. This flexibility can Speed up the development process and accommodate the evolving nature of bacterial Resistance.

(ii) **Streamlined Approval Process:** Establishment of a streamlined regulatory pathway Specifically for antibiotics that addresses their unique challenges. This could involve Expedited reviews, accelerated approvals, or priority designations for antibiotics Targeting urgent or unmet medical needs.

(iii) **Tailored Clinical Trial Endpoints:** Development of clinically meaningful endpoints For antibiotic trials that reflect their unique mechanism of action and intended use. These endpoints should consider both short-term efficacy and long-term impact on Antibiotic resistance.

(iv) **Guidance on Combination Therapies:** The regulatory process should provide clear Guidance on developing and testing combination therapies involving antibiotics, Antibodies,probiotics, or other approaches. This guidance should address dosing, Interactions, and potential synergies.

(v) **Biomarker Development:** Investment in research to identify predictive biomarkers That can indicate early in clinical trials whether an antibiotic is effective. Biomarkers Can help streamline development and reduce trial durations.

(vi) **Economic Incentives:** Offering economic incentives such as extended market exclu-Sivity or market entry rewards for antibiotics that target high-priority pathogens or Mechanisms of resistance [205].

(vii) **Adaptive Licensing:** Implementation of adaptive licensing strategies that allow ear-Lier access to antibiotics based on initial safety and efficacy data, with continued Monitoring and data collection post approval.

(viii) **Collaborative Approaches:** Encouragement of collaboration between regulatory agen-Cies, industry, academia, and public health organizations to share data, insights, and Best practices for antibiotic development and regulatory evaluation.

(ix) **Tailored Clinical Trial Endpoints:** Development of clinically meaningful endpoints For antibiotic trials that reflect their unique mechanism of action and intended use.

These endpoints should consider both short-term efficacy and long-term impact on Antibiotic resistance.

Guidance on Combination Therapies: The regulatory process should provide clear Antibodies, probiotics, or other approaches. This guidance should address dosing, Interactions, and potential synergies.

(i) **Biomarker Development:** Investment in research to identify predictive biomarkers That can indicate early in clinical trials whether an antibiotic is effective. Biomarkers Can help streamline development and reduce trial durations.

(ii) **Economic Incentives:** Offering economic incentives such as extended market exclu-Sivity or market entry rewards for antibiotics that target high-priority pathogens or Mechanisms of resistance [205].

(iii) **Adaptive Licensing:** Implementation of adaptive licensing strategies that allow ear-Lier access to antibiotics based on initial safety and efficacy data, with continued Monitoring and data collection post approval.



(iv) Collaborative Approaches: Encouragement of collaboration between regulatory agencies, industry, academia, and public health organizations to share data, insights, and Best practices for antibiotic development and regulatory evaluation.

(v) Real-World Evidence: Incorporation of real-world evidence, such as data from patient Registries and observational studies, to supplement traditional clinical trial data and Support post-approval evaluations.

(vi) Global Harmonization: Working towards global harmonization of regulatory standards for antibiotic development. This can reduce duplication of efforts and create a More efficient pathway for international approvals.

(vii) Antibiotic Stewardship Education: Incorporation of antibiotic stewardship education And responsible-use recommendations into regulatory processes to ensure that new Antibiotics are used appropriately to slow the development of resistance. These changes and improvements aim to strike a balance between fostering innovation, Ensuring patient safety, and addressing the urgent need for effective antibiotics in the face of Growing antibiotic resistance. Collaborative efforts between regulatory agencies, industry Stakeholders, healthcare providers, and researchers will be crucial in implementing these Modifications effectively.

The Intersection of Artificial Intelligence (AI) and Antibiotic Resistance.

AI has the potential to revolutionize how we understand, monitor, and combat antibiotic resistance. AI can play key roles in the following areas:

(a) Predictive Analytics: Predictions that are based on historical and real-time data In order to identify patterns by machine learning techniques make up predictive Analytics. AI algorithms can analyze large datasets, including genetic information From bacteria, patient health records, and environmental factors, to predict which Antibiotics are likely to be effective against specific strains of bacteria. This can aid Clinicians in making more informed decisions about antibiotic treatment. By analyzing Historical patient data, these tools can recommend the most suitable antibiotics, dosage, And duration of treatment. They can forecast patient outcomes, such as the risk of Developing antibiotic resistance, mortality rates, and the length of hospital stays. This Information enables medical professionals to provide more personalized and effective Care. The analysis of extensive datasets on drug interactions, pharmacokinetics, and Microbial genomics, and identifying potential antibiotic candidates and predicting Their effectiveness can assist in development of new antibiotics. Moreover, predictive Analytics is used to investigate the synergistic effects of drug combinations. This Approach can uncover new treatment strategies that enhance the effectiveness of Existing antibiotics and combat resistance [262].

(b) Drug Discovery: The development of antibiotics is a resource-intensive process, often Requiring a long time and significant financial investments. To expedite antibiotic Discovery, there is a growing need for computer-assisted exploration of innovative Drugs with unique action mechanisms. Artificial intelligence (AI) has emerged as A powerful tool for accelerating antibiotic discovery. Large amounts of data can be Analyzed by AI to identify novel potential drug candidates, predict their properties, And optimize their design. In this way, the drug discovery process can be quick and Cheap. Virtual screening for drug discovery is one of the most promising applications Of AI. Virtual screening involves using computers to simulate the interaction between Potential drug candidates and bacterial targets. This can help to identify compounds That are likely to be effective against bacteria, without the need for expensive and Time-consuming laboratory experiments. Another promising application of AI is Drug design. AI algorithms can be used to design new antibiotics that are specifically Targeted to bacterial targets [263,264]. The use of AI in antibiotic discovery is still in its early stages, but it has the capacity to Alter the way we develop new antibiotics. AI has the potential to help us to identify new And effective antibiotics more quickly and efficiently, which could help to save lives in the Fight against antibiotic resistance.

(c) Optimizing Treatment Plans: Artificial intelligence (AI) can optimize antibiotic treatment plans in several ways. For instance, AI can be used to identify the most effective Antibiotic for a particular patient and infection. Medical history, lab results, and Genetic information of the patient can be analyzed by AI, and the antibiotic that is Most likely to be effective against the specific infection can be identified.

AI can be used to determine the optimal dosage and duration of antibiotic treatment For each patient. This can help to ensure that patients receive the right amount of antibiotics For the right amount of time, which can help to prevent antibiotic resistance and improve Patient outcomes. AI can be used to monitor patient data for signs of antibiotic



resistance. This can help To identify patients who are at risk of developing antibiotic-resistant infections, which can Then be treated with appropriate antibiotics [265,266]

(d) Surveillance and Early Detection: AI can analyze large amounts of data from clinical settings, laboratories, and public health records to identify patterns of antibiotic use and resistance. This information can be used to track the spread of resistant bacteria and inform targeted interventions. For example, AI can be used to identify hospitals or regions with high rates of antibiotic-resistant infections and target these areas for additional resources and education. AI can analyze genetic data to identify mutations that confer antibiotic resistance. This information can be used to track the evolution of resistance genes and develop new antibiotics that are less likely to be ineffective. For example, AI can be used to identify new mutations in the genes that code for antibiotic resistance in *Staphylococcus aureus*, a common cause of hospital-acquired infections. AI can develop personalized treatment plans for patients with antibiotic-resistant infections. This can be carried out by analyzing patient data, such as medical history, antibiotic use, and laboratory results. AI can also be used to identify combinations of antibiotics that are more effective against resistant bacteria [267].

II. CONCLUSION

The use of antibiotics in health care plays a critical role in the prevention and treatment of bacterial infections, contributing significantly to improved patient outcomes and reduced mortality rates. However, this benefit is increasingly threatened by the growing problem of antibiotic misuse and overuse, which accelerates the development of antimicrobial resistance (AMR). This review highlights that while antibiotics remain indispensable in modern medicine, their use must be guided by strict stewardship practices, including evidence-based prescribing, patient education, and routine surveillance of resistance patterns.

Efforts to optimize antibiotic use—through hospital antimicrobial stewardship programs, clinician training, and global health policy—are essential to preserving the efficacy of current treatments. A multi-disciplinary approach involving health care providers, policy-makers, and the public is required to address this complex challenge. Moving forward, sustainable antibiotic use in health care must prioritize both individual patient care and broader public health outcomes.

REFERENCES

1. World Health Organization (WHO). Priority Medicines for Europe and the World/Warren Kaplan, Richard Laing 2004. Available.
2. Rehman, M.T.; Faheem, M.; Khan, A.U. An insight into the biophysical characterization of different states of cefotaxime Hydrolyzing β -lactamase 15 (CTXM-15). *J. Biomol. Struct. Dyn.* 2015, 33, 625–638. [CrossRef] [PubMed]
3. Livermore, D.M. Bacterial Resistance: Origins, Epidemiology, and Impact. *Clin. Infect. Dis.* 2003, 36, S11–S23. [CrossRef] [PubMed]
4. Muteeb, G.; Alsultan, A.; Farhan, M.; Aatif, M. Risedronate and Methotrexate Are HighAffinity Inhibitors of New Delhi Metallo- β -Lactamase-1 (NDM-1): A Drug Repurposing Approach. *Molecules* 2022, 27, 1283. [CrossRef]
5. Khan, A.U.; Rehman, M.T. Role of Non-Active-Site Residue Trp-93 in the Function and Stability of New Delhi Metallo- β Lactamase Antimicrob. Agents Chemother. 2016, 60, 356–360. [CrossRef] [PubMed]
6. Gould, K. Antibiotics: From prehistory to the present day. *J. Antimicrob. Chemother.* 2016, 71, 572–575. [CrossRef]
7. Clardy, J.; Fischbach, M.A.; Currie, C.R. The natural history of antibiotics. *Curr. Biol.* 2009, 19, R437–R441. [CrossRef]
8. Fleming, A. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B.Influenzæ. *Br. J. Exp. Pathol.* 1929, 10, 226– 236. [CrossRef]
9. Hodgkin, D.C. The X-ray analysis of the structure of penicillin. *Adv. Sci.* 1949, 6, 85–89.
10. Sheehan, J.C.; Henery-Logan, K.R. The Total Synthesis of Penicillin, V.J. Am. Chem. Soc. 1959, 81, 3089–3094. [CrossRef]
11. Von Döhren, H. Antibiotics: Actions, Origins, Resistance, by C. Walsh. 2003; ASM Press: Washington, DC, USA, 2009; Volume 13,p. 345.
12. Abraham, E.P.; Chain, E. An Enzyme from Bacteria able to Destroy Penicillin. *Nature* 1940, 146, 837. [CrossRef]



13. Aminov, R.I. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. *Front. Microbiol.* 2010, 1, 134. [CrossRef] [PubMed]
14. Durand, G.A.; Raoult, D.; Dubourg, G. Antibiotic discovery: History, methods and perspectives. *Int. J. Antimicrob. Agents* 2019, 53, 371–382. [CrossRef] [PubMed]
15. Iskandar, K.; Murugaiyan, J.; Hammoudi Halat, D.; Hage, S.E.; Chibabhai, V.; Adukkadukkam, S.; Roques, C.; Molinier, L.; Salameh, P.; Van Dongen, M. Antibiotic Discovery and Resistance: The Chase and the Race. *Antibiotics* 2022, 11, 182. [CrossRef] [PubMed]
16. Christensen, S.B. Drugs That Changed Society: History and Current Status of the Early Antibiotics: Salvarsan, Sulfonamides, and B-Lactams. *Molecules* 2021, 26, 6057. [CrossRef]
17. Chait, R.; Vetsigian, K.; Kishony, R. What counters antibiotic resistance in nature? *Nat. Chem. Biol.* 2012, 8, 2–5. [CrossRef]
18. Blair, J.M.A.; Webber, M.A.; Baylay, A.J.; Ogbolu, D.O.; Piddock, L.J.V. Molecular mechanisms of antibiotic resistance. *Nat. Rev. Microbiol.* 2015, 13, 42–51. [CrossRef] [PubMed]
19. Livermore, D.M.; Blaser, M.; Carrs, O.; Cassell, G.; Fishman, N.; Guidos, R.; Levy, S.; Powers, J.; Norrby, R.; Tillotson, G.; et al. Discovery research: The scientific challenge of finding new antibiotics. *J. Antimicrob. Chemother.* 2011, 66, 1941–1944. [CrossRef]
20. Saga, T.; Yamaguchi, K. History of antimicrobial agents and resistant bacteria. *Japan Med. Assoc. J.* 2009, 52, 103–108.
21. Hwang, I.Y.; Tan, M.H.; Koh, E.; Ho, C.L.; Poh, C.L.; Chang, M.W. Reprogramming Microbes to Be Pathogen-Seeking Killers. *ACS Synth. Biol.* 2014, 3, 228–237. [CrossRef]
22. Orfali, R.; Perveen, S.; AlAjmi, M.F.; Ghaffar, S.; Rehman, M.T.; Alanzl, A.R.; Gamea, S.B.; Essa Khwayri, M. Antimicrobial Activity of Dihydroisocoumarin Isolated from Wadi Lajab Sediment-Derived Fungus *Penicillium chrysogenum*: In Vitro and In Silico Study. *Molecules* 2022, 27, 3630. [CrossRef] [PubMed]
23. Davies, J.; Davies, D. Origins and Evolution of Antibiotic Resistance. *Microbiol. Mol. Biol. Rev.* 2010, 74, 417–433. [CrossRef]
24. Bartlett, J.G.; Gilbert, D.N.; Spellberg, B. Seven Ways to Preserve the Miracle of Antibiotics. *Clin. Infect. Dis.* 2013, 56, 1445–1450. [CrossRef] [PubMed]
25. Velez, R.; Sloand, E. Combating antibiotic resistance, mitigating future threats and ongoing initiatives. *J. Clin. Nurs.* 2016, 25, 1886–1889. [CrossRef] [PubMed]
26. Ali, T.; Ahmed, S.; Aslam, M. Artificial Intelligence for Antimicrobial Resistance Prediction: Challenges and Opportunities Towards Practical Implementation. *Antibiotics* 2023, 12, 523. [CrossRef]
27. Melo, M.C.R.; Maasch, J.R.M.A.; de la Fuente-Nunez, C. Accelerating antibiotic discovery through artificial intelligence. *Commun. Biol.* 2021, 4, 1050. [CrossRef]
28. David, L.; Brata, A.M.; Mogosan, C.; Pop, C.; Czako, Z.; Muresan, L.; Ismaiel, A.; Dumitrascu, D.I.; Leucuta, D.C.; Stanculete, M.F.; et al. Artificial Intelligence and Antibiotic Discovery. *Antibiotics* 2021, 10, 1376. [CrossRef]
29. Amin, D.; Garzón-Orjuela, N.; Garcia Pereira, A.; Parveen, S.; Vornhagen, H.; Vellinga, A. Artificial Intelligence to Improve Antibiotic Prescribing: A Systematic Review. *Antibiotics* 2023, 12, 1293. [CrossRef]
30. Lv, J.; Deng, S.; Zhang, L. A review of artificial intelligence applications for antimicrobial resistance. *Biosaf. Health* 2021, 3, 22–31. [CrossRef]

