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History, Current Situation, and Future Perspectives on Antibiotics and Antibiotic Resistance

AUTHORS DETAIL

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INTRODUCTION

Antibiotics are the most crucial drugs for fighting bacterial infection, widely used to treat and prevent such diseases. Even though these are used against bacterial infections, some antibiotics also possess antiprotozoal activity. The term *antibiotic* means "opposing life," from the Greek roots *anti*, "against," and *bios*, "life," and refers to any compound used against germs (Hutchings et al. 2019).

The records of using antibiotics date back to ancient times. Many civilizations from ancient Egypt, Nubia, China, Serbia, Greece, and Rome topically applied moldy bread to treat infections. John Parkinson (1567–1650) was the first to document infection treatments with molds (Hutchings et al. 2019). Moreover, antibiotics overturned medicine in the 20th century when Alexander Fleming (1881–1955) came upon penicillin in the late 1920s, and the widespread use of which significantly reduced the wartime death rates (Hutchings et al. 2019).

Antibiotic classification can be based upon the mechanism of action as the inhibitors of bacterial cell wall synthesis, protein synthesis, nucleic acid synthesis, folate metabolism, and cell membrane disruptors. Another way to classify antibiotics is according to the spectrum of activity into narrow- and broad-spectrum antibiotics. A narrow-spectrum antibiotic can only kill or inhibit limited bacterial species. On the other hand, a broad-spectrum antibiotic affects two major bacterial groups, Gram+ve and Gram-ve (Joyner et al. 2020).

The continuous use of antibiotics eventually leads to resistance development by infectious bacteria (Christaki et al. 2020). Antibiotic resistance (AR) is the loss of bacterial susceptibility to an antibiotic's bactericidal or bacteriostatic properties (Frieri et al. 2017). AR refers to the increased tolerance to therapeutic regimens to which the pathogen was sensitive before developing resistance. When a resistant strain dominates an infection, it may be untreatable and grievous. Bacterial pathogens have been a significant cause of illness and fatality for a long time. The antibiotic discovery provided a simple and efficient therapy for bacterial infections, and since then, antimicrobials have tremendously impacted human wellness and longevity. However, these are jeopardized by the rise of AR as many infective bacteria have become resistant to the main antimicrobial classes, and multidrug-resistant microbes have caused untreatable diseases (MacLean and San Millan 2019).

AR poses significant health and economic effects, and the yearly cost could rise to 10 million deaths and US$100,000 billion by 2050 (MacLean and San Millan 2019). AR development was reported in the early 1940s following penicillin's initial large-scale uses. Penicillin's massive production was part of World War II's bigger war campaign when the drug was utilized widely by military units and some civilian people (Banks et al. 2019). With penicillin's efficacy in treating wounds, the antibiotic was exalted for reducing sexually transmitted diseases among the troops since it was effective against bacterial pathogens famous for causing syphilis and gonorrhea (Guy 1991).

Penicillin resistance was reported even before the Second World War—firstly, in 1940 by British scientists Chain and Abraham, who reported an enzyme able to destroy the drug. In 1944, several researchers independently described a penicillin-deactivating enzyme released by some microbes (Lima et al. 2020). In the subsequent decades, overexploitation and repeated antibiotic use favored the survival and emergence of many antibiotic-resistant bacteria (Chokshi et al. 2019).

Bacterial cells can acquire AR in two main ways: through mutations in the cell's DNA during replication and resistance acquisition by bacteria through horizontal gene transfer (McInnes et al. 2020). These mechanisms give rise to resistance development since they cause biochemical changes that alter specific bacterial cell properties, rendering the cell susceptible to an antibiotic. These mechanisms include activating efflux pumps that take a drug out of the cell, drug-inactivating enzymes, altering bacterial molecular drug targets, and inhibiting drug uptake (Yelin and Kishony 2018).

Antibiotics are essential for treating medically significant disease cases and are used in animals to treat and prevent infections. Indiscriminative use of antibiotics or incomplete treatment courses causes resistant bacteria to tolerate a sublethal drug dose. This is the leading reason for drug-induced resistance that distributes among humans via food,

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water contaminated by animal waste, and the surroundings where slaughtered animal waste is discarded. The resistance can affect the human population, causing huge socioeconomic costs (Ahmad and Khan 2019).

History of Antibiotic Development

Molecules with antibiotic effects synthesized by various microbes were present long before humanity realized their benefit in treating bacterial diseases. Microbes have been exposed to selection pressures from antimicrobials for a long time, mainly within small areas where antibiotic-producing organisms exist. Mass-production of antibiotics started in the 1940s, mainly semisynthetic products of naturally synthesized molecules and a few completely synthetic antibacterials. Consequently, bacterial populations became exposed to high antibiotic concentrations, leading to speedy resistance among many pathogens today (Chinemerem Nwobodo et al. 2022).

The golden years of antibiotic discovery, development, and production took place from 1940 to the 1960s and continued in the following years but not as speedily as in previous years. The timeline of antibiotic development is depicted in Fig. 1. The most common antibiotics are penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, chloramphenicol, and glycopeptides. Alexander Fleming came upon the first antibiotic, penicillin G, in 1928. Penicillin is a bactericidal drug that acts by adhering the β-lactam ring to DD-transpeptidase. This binding prevents peptidoglycan cross-linking and new cell wall synthesis (Stepek et al. 2019). Cephalosporins are also β-lactam bactericidal antibiotics discovered by the Italian scientist Giuseppe Brotzu in 1945 by isolating a mixture of compounds from *Acremonium*, a mold previously called *Cephalosporium* (Jones 2008).

In 1944, a *Streptomyces qriseus* strain was found to synthesize an aminoglycoside named streptomycin, which prevents protein production by attaching to the bacterial 30S ribosomal subunit. Streptomycin marketing began in 1946 to treat tuberculosis, tuberculous meningitis, and other bacterial infections (Willey et al. 2008).

Chloramphenicol was initially purified from a culture of *Streptomyces venezuelae* in 1947. Chloramphenicol's antimicrobial effect is a reversible binding to the ribosomal 50S subunit, preventing bacterial protein synthesis. Chloramphenicol was the first Food and Drug Administration (FDA)-approved broad-spectrum antibiotic, showing excellent tissue permeability. Nevertheless, various toxicity issues were discovered in the 1960s, and it is presently seldom prescribed (Wiest et al. 2012).

The introduction of tetracyclines started with the discovery of chlortetracycline in 1945. Members of this class exert antibiotic activity by disrupting protein synthesis and acting on the ribosomal 30S subunit. Chlortetracycline, a product of *Streptomyces aureofaciens*, is unstable in strong basic or acidic solutions, leading to its hampered bioavailability (Liu and Myers 2016).

Macrolides are the second most commonly prescribed antibiotics after penicillins. These are naturally synthesized by *Saccharopolyspora erythraea* and were discovered in 1952, starting with erythromycin. Erythromycin is a bacteriostatic antibiotic that binds to a bacterial 50S ribosomal subunit. However, its poor oral bioavailability and instability under acidic conditions hinder its therapeutic use (Cyphert et al. 2017). Virginiamycin, isolated from *Streptomyces virginiae* in 1952, was the first identified streptogramin, a class of antimicrobials formed by a polyunsaturated macrolactone and a cyclic hexadepsipeptide. Either substance binds to the ribosomal 50S subunit, demonstrating a middling activity, but their synergistic effect increases their therapeutic efficacy (Mast and Wohlleben 2014). Fig. 1 indicates the timeline regarding the discovery of various antibiotics.

The first glycopeptide, vancomycin, was discovered in 1956 as a product of *Amycolatopsis orientalis* and is currently a last-line drug. Glycopeptides interrupt cell wall synthesis by interfering with the transpeptidation and transglycosylation steps, inhibiting cross-linking and cell wall maturation (James et al. 2012).

Classification of Antibiotics

The ribosome is one of the best antibiotic targets, and many antimicrobials used presently specifically target the bacterial ribosome. Many antibiotics suppress bacterial growth by inhibiting ribosome functions. For example, macrolides are broad-spectrum bacteriostatic antibiotics inhibiting many Gram+ve bacteria, used for over sixty years. Macrolides hinder bacterial protein synthesis by binding to the ribosomal 50S moiety and targeting the bacterial ribosomal nascent peptide exit tunnel (NPET). The NPET is about 100 A° long and 10–20 A° in diameter and is a hallway that allows synthesized proteins to leave the ribosome (Vázquez-Laslop and Mankin 2018).

Macrolides were thought to inhibit translation merely by obstructing the NPET and inhibiting the movement of newly synthesized polypeptides once they reached a certain length. Structural studies have supported this view by exhibiting that macrolides significantly narrow the NPET (Fig. 2). This concept was confirmed by *in vitro* studies demonstrating that erythromycin causes peptidyl-tRNA accumulation during synthetic mRNAs' translation, suggesting translation disruption in its early stages (Seefeldt et al. 2021). Peptidyl-tRNA accumulation was also detected in macrolide-treated cells (Hasan et al. 2021).

Aminoglycosides are bactericidal antibiotics that bind to the ribosomal 30S subunit. These are thought to adhere to the A-site (aminoacyl) on the 16S rRNA, which is a portion of the 30S ribosomal subunit. This binding causes the genetic code to be misread and disruption of translation, leaving the bacteria incapable of protein synthesis (Block and Blanchard 2021).

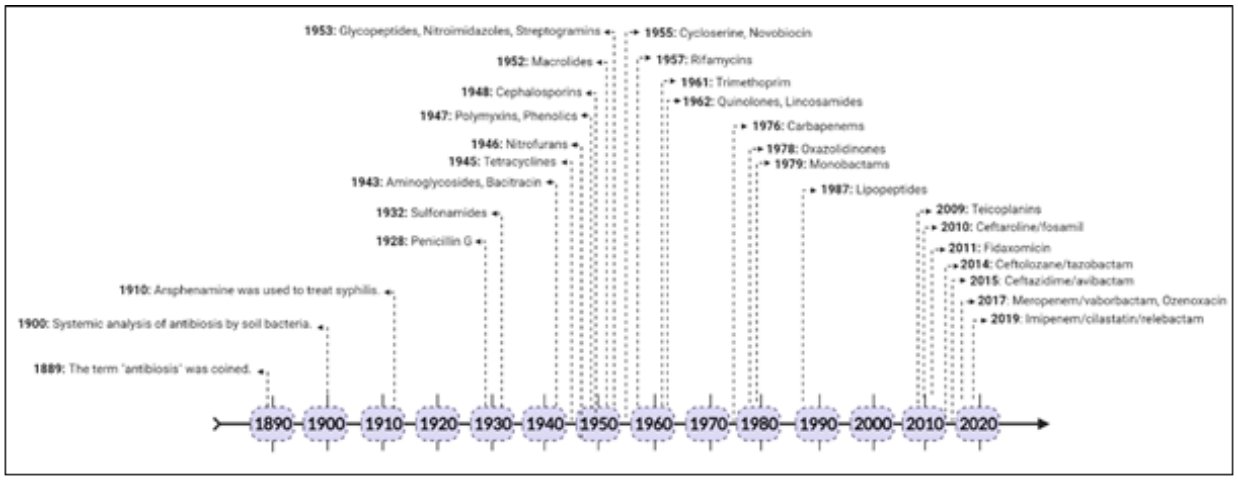

Fig. 1: Timeline of the discovery of antibiotics.

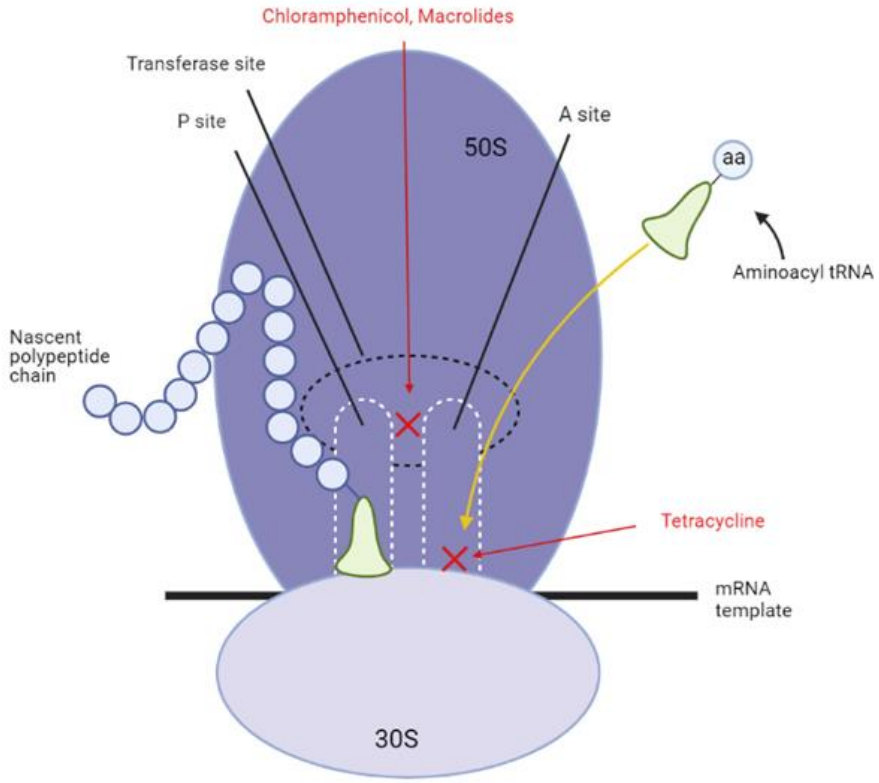

Fig. 2: Inhibition of bacterial protein synthesis by chloramphenicol, macrolides, and tetracyclines. mRNA attaches to the bacterial 30S ribosomal subunit. The nascent polypeptide chain is in the P (peptidyl) site. The aminoacyl tRNA carrying an amino acid (aa) moves into the A (acceptor) site, with base pairing between the mRNA and tRNA. Tetracyclines bind to the 30S subunit and inhibit protein synthesis by blocking tRNA binding to the A site. Chloramphenicol inhibits transpeptidation by binding to the 50S ribosomal subunit at the peptidyltransferase. Macrolides inhibit protein synthesis by binding reversibly to the 50S ribosomal subunits such that the nascent peptide chain temporarily residing at the A site fails to move to the P or donor site.

β-lactam antibiotics comprise penicillins, cephalosporins, carbapenems, and monobactams (Fig. 3). All contain a β-lactam ring and kill susceptible bacteria by suppressing the transpeptidase that triggers the last step in cell wall synthesis (MacDougall 2017). β-lactams inhibit bacterial cell wall, particularly peptidoglycan, synthesis. Peptidoglycans are the bacterial exoskeleton that strengthens the cells' integrity and shape and prevents bursting (Auer and Weibel 2017). These structures cross-link in the last stage of cell wall formation to produce peptidoglycan polymers via membrane -anchored

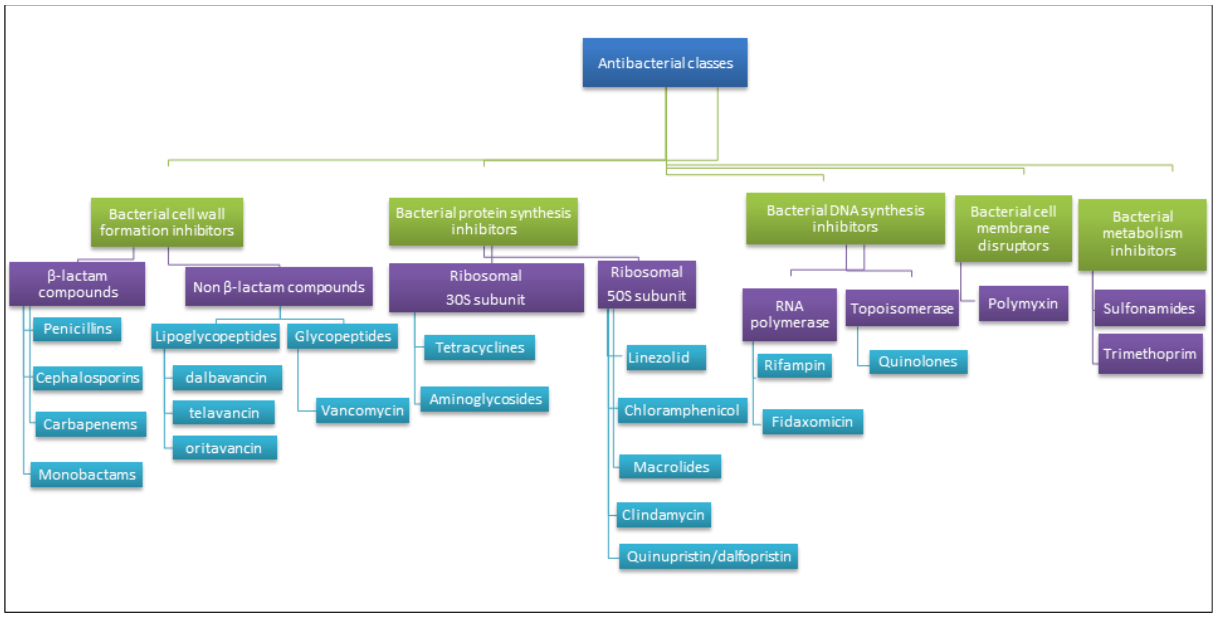

Fig. 3: Major classes of antibacterial compounds.

enzymes such as transpeptidases, carboxypeptidases, and endopeptidases, collectively known as penicillin-binding proteins (PBPs). Penicillin exerts antibacterial activities by inhibiting cell wall formation (Stepek et al. 2019). The drug's binding to the target organism's proteins inhibits PBPs, which are naturally occurring proteins in the cell wall. Once targeted, these proteins are inhibited from completing the peptidoglycan formation, which is essential to bacterial cell wall synthesis. This cell wall synthesis inhibition, combined with the ongoing cell wall degradation via the action of cell wall autolytic enzymes, finally causes bacterial cell lysis and death (Bazakis et al. 2022).

Cephalosporins are a large group of bactericidal β-lactam antibiotics used to treat Gram+ve and Gram-ve bacterial infections that act via β-lactam rings. After the attachment of the β-lactam rings to the PBP, normal activity is inhibited. Consequently, bacteria become incapable of synthesizing a cell wall and die eventually. *Staphylococcus* (*S.*) *aureus,* usually susceptible to cephalosporins, can become resistant by altering the PBPs' structure. Resistant *S. aureus* possesses a gene encoding a modified PBP, inhibiting the cephalosporin's β-lactam rings from deactivating the protein. Resistant bacteria through this mechanism are called methicillin-resistant *S. aureus* (MRSA). Another important resistance mechanism is producing β-lactamase, an enzyme that cleaves the β-lactam ring and inhibits it from attaching to the PBPs, such as peptidoglycan transpeptidase. Inhibitors of β-lactamase can be co-formulated with cephalosporins to improve their activity spectra, such as ceftazidime/avibactam and ceftolozane/tazobactam (Bui and Preuss 2021). Most bacteria have at least one PBP, which is the target for various β-lactam antimicrobials, such as cephalosporins, penicillins, carbapenems, and monobactams (Parsels et al. 2021).

Vancomycin is a non-β-lactam glycopeptide antimicrobial with bactericidal activity by preventing cell wall synthesis and is active against Gram+ve bacteria. It attaches to the D-alanyl-D-alanine (D-Ala-D-Ala), the C-terminal peptide structure of the peptidoglycan precursor in the bacterial cell wall, via hydrogen bonds. When the precursor interacts with vancomycin, transglycosylase cannot handle it, inhibiting cell wall synthesis. Afterward, replicating bacteria die due to a disrupted cell wall, making them susceptible to osmotic pressure (Mühlberg et al. 2020).

Polymyxins are a group of bactericidal drugs that disrupt the bacterial cell membrane. These are basic peptides with a molecular weight of about 1000 Da and act as amphipathic surfactants or cationic detergents. Polymyxins interact powerfully with phospholipids and interrupt cell membranes' integrity via binding to lipopolysaccharides and phospholipids in Gram-ve bacteria cell membranes. The underlying mechanism of action displaces divalent cations from membrane lipids' phosphate groups and destabilizes the cell membrane, causing leakage of the intracellular content and cell death (Ayoub Moubareck 2020).

Quinolones are broad-spectrum antimicrobials active against Gram +ve and Gram -ve bacteria. DNA gyrase is the primary target of quinolones, shown to catalyze the ATP-dependent production of negative supercoiled DNA. Maintaining DNA supercoiling is vital for the proper regulation of various biological processes. The resolution of DNA supercoiling is crucial to maintain DNA replication rates, and topoisomerases manage this resolution. Topoisomerases' activity is necessary and constitutes a prime antibiotic target (Bhagwat et al. 2019). Topoisomerases are necessary for plasmid replication and the regulation of phage recombination (Gutierrez et al. 2017). This discovery offered

new tools to understand the detailed mode of quinolones' bactericidal action.

Fluoroquinolones are an essential broad-spectrum antimicrobial class. Nalidixic acid was the first described quinolone, showing a narrow spectrum of antibacterial activity. Changes in positions 1, 6, 7, and 8 of nalidixic acid's chemical structure have led to newer, more potent quinolones. Quinolones prevent DNA gyrase and topoisomerase IV, which are necessary for bacterial growth (Lapointe et al. 2021).

Chromosomal mutations often cause quinolone resistance by decreasing drug accumulation through reduced drug uptake or increased efflux. Resistance may also occur when quinolone resistance genes are exchanged on plasmids during bacterial conjugation. For example, the *qnr* gene encoding a pentapeptide, which inhibits quinolones' action on the DNA gyrase and topoisomerase IV, can be transported from one bacterium to another through the plasmid. Also, the *aac(6′)-Ib-cr* gene encodes an acetylase that modifies the amino group of fluoroquinolones' piperazine ring and is exchanged via the plasmid (Fàbrega et al. 2009).

Rifampin is a bactericidal antimicrobial that inhibits DNA-dependent RNA polymerase (RNAP). This inhibition occurs via blocking the elongating RNA at the 5′ end or reducing the RNAP affinity for short RNA strands. Rifampin inhibits the microbial RNAP and stops further RNA elongation (Suresh et al. 2021).

Sulfonamides are synthetic bacteriostatic drugs still used today to treat bacterial and other infections (Gulçin and Taslimi 2018). Sulfamethoxazole is a sulfonamide that inhibits folate synthesis inside microorganisms such as bacteria. It is *p*-aminobenzoic acid (PABA) competitor during dihydrofolate synthesis by inhibiting dihydrofolate synthase. Trimethoprim directly inhibits dihydrofolate reductase, inhibiting the synthesis of tetrahydrofolate (the active form of folate). Combining a sulfonamide and trimethoprim creates a synergistic anti-folate effect and inhibits the synthesis of tetrahydrofolate, a compound necessary for producing purines involved in DNA and protein synthesis. These drugs are bacteriostatic when used separately, while the sulfamethoxazole-trimethoprim combination blocks two steps in the bacterial synthesis of essential nucleic acids and proteins and is bactericidal (Kemnic and Coleman 2021).

Antibiotic Resistance (AR)

AR occurs when germs develop mechanisms to defeat the drugs that kill them, which means the bacteria continue to grow. AR is an ancient mechanism since most antibiotics currently used in humans are natural compounds of bacterial or fungal origins. *Streptomyces* are soil bacteria that are the source of most of the currently available antibiotics. Microorganisms have to fight against each other in their natural environment by secreting antimicrobial chemicals and have to become resistant to other antibiotics. Species naturally producing antibiotics are resistant to these substances to avoid self-toxicity (Meade et al. 2020).

Interestingly, multidrug-resistant (MDR) bacterial species and resistance genes to currently available antibiotics have also been purified from environmental and archeological specimens. β-lactamase encoding *blaOXA* genes date back several million years (Bush 2018). D'Costa and coworkers isolated resistance genes to β-lactams, tetracyclines, and glycopeptides from 30,000-year-old permafrost specimens (D'Costa et al. 2011). Kashuba and her colleagues also discovered several resistance genes in a *Staphylococcus* (*S.*) *hominis* genome from permafrost at Mammoth Mountain in Siberia, returning to the Middle Miocene. The recovered *S. hominis* had multiple genes associated with resistance to aminoglycosides, β-lactams, macrolides, lincosamide, and streptogramin B (Kashuba et al. 2017). 177 AR genes in 23 families, representing all resistance mechanisms, i.e., mutation, efflux, and antibiotic deactivation, were discovered in microbes isolated from the Mackay Glacier region (Van Goethem et al. 2018; Durand et al. 2019).

AR has become an issue of increasing concern to the medical community. According to the 2019 AR Threats Report of CDC, more than 2.8 million antimicrobial-resistant infections take place in the U.S. annually, killing more than 35,000 individuals. Annually, >2,000,000 North Americans get AR-associated infections, causing 23,000 deaths. In Europe, about 700,000 antibiotic-resistant cases culminate into over 33,000 deaths yearly (Cassini et al. 2019), costing over €1.5 billion (ECDC 2009). Despite a 36% rise in human use of antibiotics between 2000 and 2010 (Laxminarayan et al. 2016), around 20% of worldwide deaths are due to infectious diseases (Martens and Demain 2017). Unfortunately, nosocomial infections have become a principal cause of morbidity and mortality (Akova 2016), causing lengthier hospital stays and increased healthcare expenditures (McFee 2009). Unfortunately, the outlooks are more pessimistic. For example, a government-accredited study in the United Kingdom forecasts 10,000,000 annual deaths from antimicrobial-resistant infections by 2050 (O'Neill 2018).

Antibiotics are primarily applied in food-producing animals (FPAs) worldwide. These days, the effective production of FPAs is partly due to incorporating growth supplements (Price et al. 2005) and large-scale antibiotic use as growth promoters in livestock farming (Rather et al. 2017). For instance, 60% of the antibiotics sold to the U.S.A. food industry are also used as human therapeutics (Dodds 2017). The average worldwide annual antimicrobial consumption by animals in 2010 was estimated at 45 mg/kg, 48 mg/kg, and 172 mg/kg for cattle, chickens, and swine, respectively. Moreover, using antibiotics in FPAs is projected to increase by 2030 (Price et al. 2005). The widespread antibiotic use in FPAs contributes to selective pressure, favoring AR development and negatively impacting public health.

Antimicrobial-resistant pathogens can be transmitted to humans from the environment or food products and thus become a public health concern (Mohsin et al. 2017).

Pakistan is one of the top 10 animal-producing countries with modern intensive farming practices, and food animals have become crucial for food security. Unfortunately, like in many other countries, animal farming in Pakistan largely depends on consistent antibiotic use as growth promoters and therapies for bacterial diseases (Ur Rahman and Mohsin 2019). The overuse of antibiotics in animal production and the later land applications of manures lead to elevated AR levels in the soil environment. Understanding the fate of antibiotics and how AR genes spread from animal production systems to the soil is essential to minimize AR risks (Chaturvedi et al. 2021).

Veterinary drugs, especially antimicrobials, are one of the most critical issues related to animal feed production. The primary use of antibiotics in animals is to prevent and treat diseases and promote growth (Ahmad and Khan 2019). The application of antibiotics in animals may result in antibiotic residues in foodstuffs such as meat, milk, and egg. These remnants may cause several side effects, such as the spread of antibiotic-resistant bacteria, immunopathological consequences, allergy, mutagenicity, nephropathy (aminoglycosides), hepatotoxicity, reproductive diseases, bone marrow toxicity (chloramphenicol), and carcinogenicity (sulfamethazine, oxytetracycline). Because of these unwanted effects, it is vital to regulate the use of antibiotics. The most crucial adverse effect of antibiotic remnants is transferring antibiotic-resistant bacteria to humans. However, it is crucial not to forget the effect of AR on the animals, as infection by resistant bacteria leads to the loss of animals and flocks due to treatment failure (Bacanlı and Başaran 2019).

Bacteria must not necessarily be resistant to every antibiotic to be life-threatening, and resistance to even one antibiotic can be dangerous. For example, antibiotic-resistant infections necessitating second and third-line therapies can harm patients by causing severe side effects, such as organ failure and prolonged recovery, often lasting months. Many medical procedures depend on handling infections using antibiotics, including orthopedic surgeries, organ transplants, debulking cancer, and treating chronic diseases like asthma, diabetes, and rheumatoid arthritis. These infections usually have no treatment options (Durand et al. 2019).

New Antibiotics in the Last Two Decades

A small number of new antibiotic compounds have been developed since 2000, and none of them is effective against Gram-ve bacteria. These results indicate that new antibiotics targeting the gravest public health threats have not been introduced (World Health Organization 2019). Drugs developed since 2008 fall into four categories: lipoglycopeptides, β-lactam/ β-lactamase inhibitors, quinolones, and protein synthesis inhibitors (Bassetti and Righi 2015). The FDA-approved multi-target antibiotics, their target sites, and their structural classes are listed in Table 1.

Lipoglycopeptide Antibiotics

Modernized lipoglycopeptides are a subclass of glycopeptides distinguished by a lipophilic side chain attached to a glycopeptide moiety. These compounds include teicoplanin and its derivatives dalbavancin, telavancin, and oritavancin (Morphy et al. 2004). The FDA-approved telavancin was used in 2009 to medicate complicated skin and skin structure infections caused by multidrug-resistant *S. aureus* or other Gram+ve pathogens and in 2013 to medicate pneumonia caused by *S. aureus* and *Streptococcus pneumoniae*. The FDA approved the drug in 2014 to treat acute bacterial skin infections caused by pathogenic Gram+ve bacteria. The same year, dalbavancin was licensed for acute bacterial skin infections by antibiotic-resistant pathogenic Gram+ve microbes (Markham 2014). Teicoplanin and its derivatives block the cell wall peptidoglycan layer cross-linking by binding to the lipid II monomer's D-alanyl-D-alanine (D-Ala-D-Ala) terminal (Wetzel et al. 2021).

Oritavancin and telavancin maintain vancomycin's heptapeptide core, consisting of seven amino acids: five aromatics and two aliphatics. On the other hand, dalbavancin contains teicoplanin's cyclic heptapeptide core, consisting of seven aromatic amino acids. D-Ala-D-Ala binding prevents transpeptidase-mediated peptide cross-linking. Telavancin, oritavancin, and dalbavancin also block peptidoglycan construction via impairing transglycosylase-mediated glycan cross-linking. The lipophilic side chains of teicoplanin, oritavancin, and telavancin enhance their dimerization and peptidoglycan binding and may disrupt the bacterial membrane integrity as the third target of these compounds (Wetzel et al. 2021).

The dalbavancin's hydrophobic group enhances dimerization, and bacterial membrane disruption by dalbavancin has not been elucidated (Cheng et al. 2014). The second-generation lipoglycopeptides show better pharmacodynamic and pharmacokinetic characteristics than vancomycin (Das et al. 2017), and these are also less susceptible to resistance development by bacteria. Bacteria can avoid an antibiotic's action on a given target through genetic mutation. Because the second-generation lipoglycopeptides affect more than a single target, random mutations that protect each target are needed and extremely improbable statistically (Zhanel et al. 2010).

Modernized β-lactam Antibiotics

Ceftaroline/Fosamil and Cefiderocol*:* Cefiderocol was approved by the FDA in 2019 for urinary tract infections caused by multidrug-resistant Gram-ve bacteria. FDA also approved ceftaroline fosamil in 2010 to treat community-acquired bacterial pneumonia and acute bacterial skin infections caused by Gram-ve microbes (Moore et al. 2020). These are multi-target antibiotics developed by rational design and belong to the cephalosporin subclass,

Table 1: Structural classes and primary targets of FDA-approved antibiotics since 2008

Cell Wall Synthesis		DNA Replication and Transcription	Protein synthesis inhibitors
Lipoglycopeptides	β-lactam/β-lactamase inhibitors	Quinolones	
dalbavancin	cefiderocol	delafloxacin	eravacycline
oritavancin	ceftaroline fosamil	finafloxacin	plazomicin
telavancin	ceftazidime/avibactam	gatifloxacin	
	ceftolozane/tazobactam	moxifloxacin	
	imipenem/cilastatin/relebactam	ozenoxacin	
	meropenem/vaborbactam	fidaxomicin	

included under the β-lactam antibiotics (Sato and Yamawaki 2019). The cephem moiety of ceftaroline fosamil and cefiderocol is involved in the principal action to inhibit bacterial cell wall formation via irreversible peptidoglycan transpeptidase inhibition (Wetzel et al. 2021).

Ceftolozane/Tazobactam, Ceftazidime/Avibactam, Meropenem/Vaborbactam, and Imipenem/ Cilastatin/Relebactam: Four combinatorial β-lactam/β-lactamase inhibitor combinations were lately approved by the FDA. These combinations are ceftolozane/tazobactam (approved in 2014), ceftazidime/avibactam (approved in 2015), meropenem/vaborbactam (approved in 2017), and imipenem/cilastatin/relebactam (approved in 2019). These combinations are used for urinary tract infections, abdominal infections, and pneumonia (Papp-Wallace et al. 2020).

Modernized Quinolone Antibiotics

Fluoroquinolones: Finafloxacin (approved in 2014) and delafloxacin (approved in 2017) are fourth-generation fluoroquinolone antibiotics. These synthetic compounds have the same bicyclic nitrogen and keto-containing core structures. Quinolones inhibit one or both bacterial DNA gyrase and topoisomerase IV (Yamakawa et al. 2002). DNA gyrase modulates bacterial DNA replication and transcription by regulating the DNA's negative supercoiling, while topoisomerase IV mediates unlinking of post-replication daughter strands (Ashley et al. 2017).

First-generation quinolones (e.g., nalidixic acid) chiefly act on Gram-ve bacteria, while second-generation compounds (e.g., trovafloxacin, ciprofloxacin) exert activity on Gram-ve and some Gram+ve microbes. Third-generation quinolones (e.g., levofloxacin) exert an extended anti-Gram+ve spectrum (Dehbanipour et al. 2019) due to their selective topoisomerase IV inhibition, as opposed to DNA gyrase inhibition by first- and second-generation counterparts. The fourth-generation quinolones (e.g., delafloxacin, gatifloxacin, and moxifloxacin) inhibit DNA gyrase and topoisomerase IV. Hence, these are desirable for treating quinolone-resistant microbial diseases (Pham et al. 2019). Moxifloxacin, gatifloxacin, delafloxacin, and finafloxacin inhibit topoisomerase IV and DNA gyrase at equivalent rates (Saravolatz and Leggett 2003). Trovafloxacin and ciprofloxacin are eight and nineteen times more potent topoisomerase IV inhibitors than DNA gyrase (Wetzel et al. 2021).

The dual-targeting characteristic of fourth-generation quinolones renders them suitable for use against drug-resistant microbes since the simultaneous mutation at two sites of the target proteins is uncommon. Moreover, concurrent inhibition of two enzymes in the same pathway guarantees pathway inhibition (Wagenlehner et al. 2018).

Nonfluorinated Quinolones: Ozenoxacin was the first nonfluorinated quinolone approved in 2017 for topical application to treat impetigo caused by *S. aureus* or *Streptococcus pyogenes* (Wren et al. 2018). Ozenoxacin blocks DNA gyrase and topoisomerase IV, while other quinolones primarily block one enzyme. DNA gyrase and topoisomerase are necessary for bacterial DNA replication and transcription (Vila et al. 2019). Another feature of ozenoxacin is that it cannot be pumped out of the bacterial cell by efflux pumps. These features make the drug a good choice for fluoroquinolone-resistant bacterial infections (López et al. 2013). In addition, since ozenoxacin is not fluorinated, it raises fewer safety issues than fluorinated quinolones (Vila et al. 2019).

Fidaxomicin (lipiarmycin A3, clostomicin B1, tiacumicin B) is a narrow-spectrum antibiotic active against Gram+ve anaerobes, including *Clostridium* (Artsimovitch et al. 2012). It is a natural product isolated from several soil bacteria and contains a glycosylated 18-membered macrolactone ring. Fidaxomicin was marketed in 2011 for intestinal infections due to *C. difficile*. The drug also demonstrates *in vitro* antibacterial activity on resistant *S. aureus* and *Mycobacterium tuberculosis* and exerts antibacterial effects by blocking RNA polymerase (Brauer et al. 2022).

Fidaxomicin and rifampin are bacterial transcription inhibitors. However, the former acts at an earlier step in the transcription initiation pathway (Babakhani et al. 2014), specifically binding to the DNA template-RNA polymerase complex. Fidaxomicin inhibits the initial DNA strand separation that forms the open DNA template-RNA polymerase complex, which precedes messenger RNA synthesis by blocking the σ subunit (Gualtieri et al. 2006). Fidaxomicin has a limited spectrum of antimicrobial activity since it has a unique target site (Tiwari et al. 2010). *C. difficile* isolates resistant to rifampin or other antibiotics (cephalosporins, fluoroquinolones) do not exhibit cross-resistance to fidaxomicin (Zhanel et al. 2015). Fidaxomicin

is the drug of choice for treating colitis caused by *C. difficile*, the third most common nosocomial infection in the United States, causing 29,000 annual deaths (McAlpine 2017).

Protein Synthesis Inhibitors

In the last five years, the U.S. Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved several new antibiotics with prominent anti-Gram-ve bacterial activity, such as plazomicin and eravacycline.

Plazomicin: Plazomicin, approved by the FDA in 2018, is an aminoglycoside that binds to the ribosomal 30S subunit of bacteria, leading to protein synthesis inhibition. Plazomicin displays antibacterial activity against aerobic Gram-ve bacteria, such as β-lactamase-producing and carbapenem-resistant Enterobacteriaceae, and bacteria with aminoglycoside-modifying enzymes (Shaeer et al. 2019). The most common adverse effects of plazomicin are reduced renal activity, diarrhea, hypertension, headache, nausea, and vomiting. Plazomicin may block neuromuscular activity and cause fetal injury in pregnant women and ototoxicity. There is limited efficacy and safety data about plazomicin; hence, the antibiotic is indicated for treating complicated urinary tract infections in adults with few or no treatment choices. If plazomicin is used in patients with severe renal impairment, reducing dosage and drug monitoring are necessary (Clark and Burgess 2020).

Eravacycline: Eravacycline, a fluorocycline that belongs to the tetracyclines, was approved by the FDA in 2018. It is a bacterial protein synthesis inhibitor active against multidrug-resistant organisms, such as *Acinetobacter*, methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, and β-lactamase-producing and carbapenem-resistant Enterobacteriaceae. Eravacycline treats complicated intra-abdominal infections, and the most common adverse effects are infusion site reactions, nausea, vomiting, and diarrhea (Heaney et al. 2019).

Conclusion

Antibiotic resistance is an increasingly common occurrence around the globe, especially in developing countries, and bacteria have developed mechanisms to combat antibacterial product activity. Antibiotic usage must be better regulated locally and globally, including in developed countries. Along with global public awareness, there is a need to stop using over-the-counter antibiotics and educate prescribers to reduce antibiotic resistance.

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