Antimicrobial resistance is not a new phenomenon. In nature, microbes are constantly evolving in order to overcome the antimicrobial compounds produced by other microorganisms. Human development of antimicrobial drugs and their widespread clinical use has simply provided another selective pressure that promotes further evolution. Several important factors can accelerate the evolution of **drug resistance**.

Drug Modification or Inactivation

Resistance genes may code for enzymes that chemically modify an antimicrobial, thereby inactivating it, or destroy an antimicrobial through hydrolysis. Resistance to many types of antimicrobials occurs through this mechanism. For example, **aminoglycoside resistance** can occur through enzymatic transfer of chemical groups to the drug molecule, impairing the binding of the drug to its bacterial target. For **β-lactams**, bacterial resistance can involve the enzymatic hydrolysis of the β-lactam bond within the **β-lactam ring** of the drug molecule. Once the β-lactam bond is broken, the drug loses its antibacterial activity. This mechanism of resistance is mediated by **β-lactamases**, which are the most common mechanism of β-lactam resistance. Inactivation of **rifampin** commonly occurs through **glycosylation**, **phosphorylation**, or adenosine diphosphate (ADP) ribosylation, and resistance to **macrolides** and **lincosamides** can also occur due to enzymatic inactivation of the drug or modification.

Prevention of Cellular Uptake or Efflux

Microbes may develop resistance mechanisms that involve inhibiting the accumulation of an antimicrobial drug, which then prevents the drug from reaching its cellular target. This strategy is common among gram-negative pathogens and can involve changes in outer membrane lipid composition, porin channel selectivity, and/or porin channel concentrations. For example, a common mechanism of **carbapenem resistance** among ***Pseudomonas aeruginosa*** is to decrease the amount of its OprD porin, which is the primary portal of entry for carbapenems through the outer membrane of this pathogen. Additionally, many gram-positive and gram-negative pathogenic bacteria produce **efflux pump**s that actively transport an antimicrobial drug out of the cell and prevent the accumulation of drug to a level that would be antibacterial. For example, resistance to β-lactams, **tetracyclines**, and **fluoroquinolones** commonly occurs through active efflux out of the cell, and it is rather common for a single efflux pump to have the ability to translocate multiple types of antimicrobials.

Target Modification

Because antimicrobial drugs have very specific targets, structural changes to those targets can prevent drug binding, rendering the drug ineffective. Through spontaneous mutations in the genes encoding antibacterial drug targets, bacteria have an evolutionary advantage that allows them to develop resistance to drugs. This mechanism of resistance development is quite common. Genetic changes impacting the active site of **penicillin-binding proteins (PBPs)** can inhibit the binding of β-lactam drugs and provide resistance to multiple drugs within this class. This mechanism is very common among strains of ***Streptococcus pneumoniae***, which alter their own PBPs through genetic mechanisms. In contrast, strains of ***Staphylococcus aureus*** develop resistance to **methicillin** (**MRSA**) through the acquisition of a new low-affinity PBP, rather than structurally alter their existing PBPs. Not only does this new low-affinity PBP provide resistance to methicillin but it provides resistance to virtually all β-lactam drugs, with the exception of the newer fifth-generation **cephalosporins** designed specifically to kill MRSA. Other examples of this resistance strategy include alterations in

* ribosome subunits, providing resistance to macrolides, tetracyclines, and aminoglycosides;
* lipopolysaccharide (LPS) structure, providing resistance to **polymyxins**;
* RNA polymerase, providing resistance to **rifampin**;
* DNA gyrase, providing resistance to fluoroquinolones;
* metabolic enzymes, providing resistance to **sulfa drugs**, **sulfones**, and **trimethoprim**; and
* peptidoglycan subunit peptide chains, providing resistance to **glycopeptides**.

Target Overproduction or Enzymatic Bypass

When an antimicrobial drug functions as an antimetabolite, targeting a specific enzyme to inhibit its activity, there are additional ways that microbial resistance may occur. First, the microbe may overproduce the target enzyme such that there is a sufficient amount of antimicrobial-free enzyme to carry out the proper enzymatic reaction. Second, the bacterial cell may develop a bypass that circumvents the need for the functional target enzyme. Both of these strategies have been found as mechanisms of **sulfonamide resistance**. Vancomycin resistance among *S. aureus* has been shown to involve the decreased cross-linkage of peptide chains in the bacterial cell wall, which provides an increase in targets for **vancomycin** to bind to in the outer cell wall. Increased binding of vancomycin in the outer cell wall provides a blockage that prevents free drug molecules from penetrating to where they can block new cell wall synthesis.

Target Mimicry

A recently discovered mechanism of resistance called **target mimicry** involves the production of proteins that bind and sequester drugs, preventing the drugs from binding to their target. For example, ***Mycobacterium tuberculosis*** produces a protein with regular pentapeptide repeats that appears to mimic the structure of DNA. This protein binds **fluoroquinolones**, sequestering them and keeping them from binding to DNA, providing *M. tuberculosis* resistance to fluoroquinolones. Proteins that mimic the A-site of the bacterial ribosome have been found to contribute to **aminoglycoside resistance** as well