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**Derleme**

# Büyüyen Sorun: Antimikrobiyal Direnç

**The Growing Problem: Antimicrobial Resistance**

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## ÖZET

Antimikrobiyaller, daha önce ölümcül ve bulaşıcı olduğu bilinen enfeksiyonların hızlı ve etkili bir şekilde tedavi edilmesini sağlayarak modern tıpta devrim yaratan ilaçlardır. Antimikrobiyaller sayesinde günümüzde insan ömrü 20. yüzyılın başlarına göre yaklaşık 30 yıl daha uzundur. Ancak dünya nüfusundaki artış, en yeni ilaçlara ulaşma isteği, antimikrobiyallerin dikkatsiz ve gereksiz kullanımı sonucunda 1945 yılından beri bilinen antimikrobiyal direnç sorunu 2000'li yılların başından itibaren önemli küresel halk sağlığı sorunlarından biri haline gelmiştir.

Antimikrobiyal direnç, bakterilerin antimikrobiyal ajanların bakterisidal veya bakteriyostatik etkilerine karşı koyabilme yeteneği olarak tanımlanmaktadır. Antimikrobiyal dirençli patojenlerin artan prevalansı, kullanımdaki antimikrobiyallerin etkinliğini kaybetmesine neden olarak enfeksiyon tedavisinin başarısını azaltmaktadır. Antimikrobiyal direnç, hastanede yatış süresini, sağlık hizmetleri için harcanan iş gücünü ve enfeksiyonların mortalite ve morbiditesini artıran küresel bir sağlık sorunudur. Buna ek olarak, birçok ilaç üreticisi 1980'lerde ve sonrasında antimikrobiyal araştırma ve geliştirme çalışmalarını, yatırım getirisinin yetersiz olması nedeniyle tamamen sonlandırmıştır. Bu durum bir yandan dirençli patojenlerin yaygınlığını artırmakta, halen kullanılmakta olan antimikrobiyallerin etkinliğini azaltmakta ve klinik kullanımdan kaldırılmasına neden olmaktadır. Diğer yandan, klinik kullanıma yeni antimikrobiyallerin sunulmamasına neden olmaktadır.

Etkili antimikrobiyal kemoterapi sağlamak ve direnci önlemek amacıyla DSÖ ve EMA, direncin belirlenmesi, izlenmesi ve antimikrobiyal direnç konusunda farkındalığın artırılarak önlem alınmasını içeren eylem planları hazırlamıştır.

**Anahtar Kelimeler:** Antimikrobiyal direnç, Antibiyotik direnci, Antimikrobiyal Direnç Gelişimi.

## ABSTRACT

Antimicrobials are drugs that have revolutionized modern medicine by providing rapid and effective treatment of infections previously known to be lethal and contagious. Thanks to antimicrobials, human lifespan today is about 30 years longer than it was at the beginning of the 20th century. However, as a result of the increase in the world population, the desire to access the latest drugs, the careless and unnecessary use of antimicrobials, the problem of antimicrobial resistance, which has been known since 1945, has become one of the important global public health problems since the early 2000s.

Antimicrobial resistance is defined as the ability of bacteria to resist the bactericidal or bacteriostatic effects of antimicrobial agents. The increasing prevalence of antimicrobial resistant pathogens causes the loss of effectiveness of antimicrobials in use, reducing the success of infection treatment. Antimicrobial resistance is a global health problem that increases the duration of hospitalization, the workforce spent on healthcare, and mortality and morbidity of the infections. Additionally, many pharmaceutical manufacturers completely terminated their antimicrobial research and development efforts in the 1980s and thereafter due to suboptimal return on investment. On the one hand, this situation increases the prevelance of resistant pathogens, decreases the efficacy of antimicrobials currently in use which results in removal from clinical use. On the other hand, it causes lack of new antimicrobials in clinical use.

In order to provide effective antimicrobial chemotherapy and prevent resistance, WHO and EMA have prepared action plans that include identifying and monitoring resistance and taking precautions by increasing awareness on antimicrobial resistance.

**Key Words:** Antimicrobial resistance, Antibiotic resistance, Emergence of resistance.

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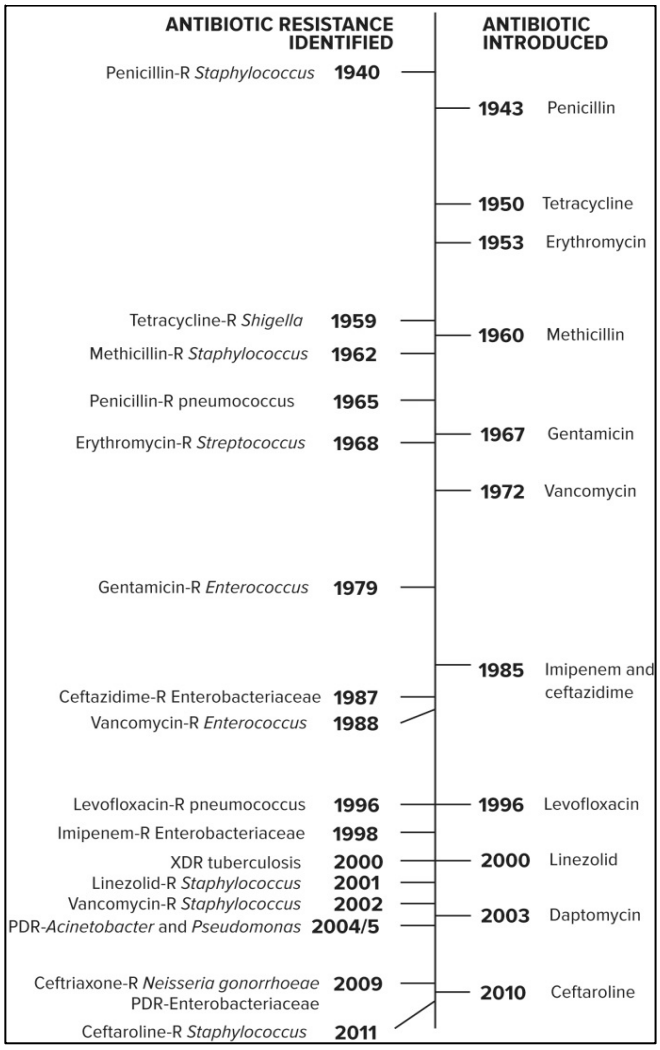
## ABBREVİATİONS

### Origin of Antimicrobial Resistance

Antimicrobials have been used in medicine for therapeutic and research purposes for over 80 years. Also, until 2006, antimicrobials were widely used in agricultural and commercial production areas, and as a result, the intense selective effect on bacterial ecosystems caused changes in the genetic structure of bacteria (1-3). Although a linear relationship between the widespread use of antimicrobials and the development of resistance has not yet been established, it has been shown by some researchers that widespread use may increase the development of resistance (4-7). There are no long periods between introducing an antimicrobial into clinical use and developing resistance to that antimicrobial (Figure 1).

**Figure-1.** Developing Antibiotic Resistance (13)




Although the development of resistance is a predictable process, it cannot be specifically predicted due to its multifactorial and complex structure and the ability of some microorganisms to acquire resistance more easily than others. (5,8).

Although there is no proven data on exactly when antimicrobial resistance occurs or where it originates, the general opinion is that compounds that negatively affect bacterial life in the environment trigger the formation of specific or non-specific antimicrobial resistance (4). Antimicrobial resistance is an adaptation process, and it has been reported that some genes encoding antimicrobial resistance also have metabolic functions (9). For example, the resorption pumps responsible for MDR remove many toxic substances, such as heavy metals, from the cell, in addition to antimicrobials (10,11). It has been reported that bacteria isolated from the intestinal flora of arthropods, which are thought to have never been exposed to antimicrobial agents, create antimicrobial resistance by transferring some genes to E. coli (4,12). More importantly, 11 of the 433 Enterobacterial isolates, known as the Murray collection and isolated before the introduction of antimicrobials, are resistant to many antimicrobials. It was determined that 24% of the bacteria in this collection could transmit plasmids (13).

### Antimicrobial Resistance and the Environment

Antimicrobial resistance is a form of adaptation that has existed for longer than the introduction of antimicrobial compounds and that bacteria have developed to protect themselves from environmental factors. Environmental factors in bacterial ecosystems that risk bacterial life are considered important in forming antimicrobial resistance (4,8).

Antimicrobials are essential for the treatment of bacterial infections in humans and animals. Therefore, the effectiveness of antimicrobials should be preserved (4). The widespread use of antimicrobials, their careless selection, and the selective effect of environmental pollution on bacteria cause changes in the genetic structure of the bacteria, and resistance may develop (2, 3). The problem grows as the resistance transfers to other bacteria. The incidence of infections caused by resistant pathogens increases, causing time, cost, and labor loss. An increase in hospitalization rate and duration, morbidity, and mortality is also observed (Figure 2) (14-16). Antimicrobial resistance is predicted to be the most important cause of death in 2050 (Figure 3) (17).

**Figure-2.** Emergence of Antimicrobial Resistance (13)

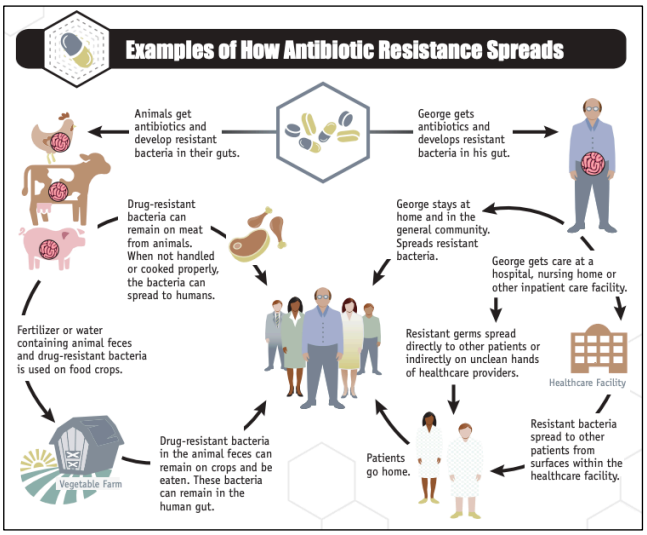
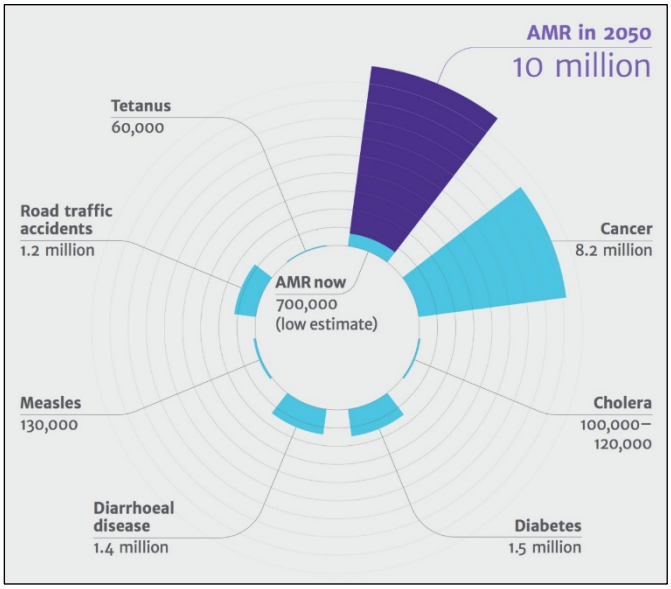


**Figure-3.** Estimated Antimicrobial Resistance Related Deaths in 2050 (17)




The concept of antimicrobial resistance can be classified according to its characteristic features: clinical resistance, microbiological resistance, inherent, acquired, cross, and multidrug resistance (8).

**Clinical Resistance:** Clinical resistance is defined as the failure of a bacterial infection to respond to the applied treatment, and since it is independent of the genetic characteristics of the bacteria, it does not provide detailed information about the character of antimicrobial resistance (8).

**Microbiological Resistance:** Microbiological resistance is determined by whether a bacterium has any resistance genetic factor or mechanism. Microbiological resistance can be measured quantitatively and defined by characteristic features such as sensitive, moderately sensitive, resistant, or methicillin-resistant (8).

**Natural Resistance:** Bacteria may resist some antimicrobials due to their structure. This type of resistance is a fundamental characteristic of the bacteria and is not related to the concentration or application time of the antimicrobial. Natural resistance results from the absence of the target structure of the relevant antimicrobial as a species characteristic of the microorganism or the structural inability of the antimicrobial to reach its target. Since gram-negative bacteria have multilayered peptidoglycan cell walls, they are naturally resistant to vancomycin and methicillin, and enterococci are naturally resistant to cephalosporins. Microorganisms that do not have a cell wall, such as L forms of bacteria and mycoplasmas, are naturally resistant to cell wall synthesis inhibitors such as penicillin. Likewise, metabolically inactive bacterial spores or dormant forms of bacteria naturally resist antimicrobials. Because for many antimicrobials to be effective, the bacteria must be metabolically active (8, 18). Natural resistance is transmitted clonally, and no strain of the naturally resistant strain to an antimicrobial is affected by the applied antibiotic.

**Acquired Resistance:** It is a type of resistance that develops due to changes in the genetic structure of bacteria. Due to genetic changes, a bacterium may not be affected by antimicrobials that are known to be sensitive for a while. Acquired resistance may develop from chromosomal or extrachromosomal sources (8).

**Chromosomal Resistance:** It develops as a result of mutations in the bacterial chromosomal structure and is called de novo resistance. De novo resistance is characterized by the gradual increase of single mutations that initially lead to low-impact resistance, turning into high-impact resistance. De novo resistance develops especially due to mutations in chromosomal regions responsible for synthesizing macromolecules associated with antimicrobial activity, such as proteins or enzymes, and can only be transferred clonally (vertically). Bacterial DNA has a very fragile structure. Environmental factors such as UV rays, oxidation, temperature changes, chemical agents, and antimicrobial compounds can trigger mutations (19, 20).

**Extrachromosomal Resistance (Transferable Resistance):** It occurs when extrachromosomal mobile genetic materials such as plasmids, transposons, integrons, or gene cassettes are transferred between bacteria by methods such as conjugation, transformation, or transposition. Exposure of bacteria to subtherapeutic doses of antimicrobials makes antimicrobial resistance an advantage. For this reason, the presence of antimicrobials in the environment is considered a provoking reason for the transfer of antimicrobial resistance genes (8).

## Extrachromosomal Mobile Genetic Materials

Extrachromosomal genetic materials have evolutionary importance in sustaining genetic diversity, can be transferred between bacteria, and are responsible for developing genetic variation by integrating into fixed structures such as DNA. The most important structures are plasmids, transposons, integrons, and gene cassettes (21).

**Plasmids:** Plasmids are extrachromosomal DNA particles in a circular structure that can replicate independently of the chromosome. In general, plasmids are not necessary structures for bacteria to survive. However, they are important drivers of bacterial evolution as they influence bacterial replication, metabolism, fertility, and, more importantly, resistance to toxins, bacteriophages, and antimicrobials. Many bacterial species are capable of plasmid transfer and expression. This results in the spread of characteristics encoded by plasmids in bacterial ecosystems. Plasmids can be transferred between bacteria belonging to the same or different genera. Plasmids that carry resistance genes against antimicrobial, heavy metal, or chemical agents in their structures are defined as R (resistance)-plasmids. An R-plasmid can carry many resistance factors, so the transfer of R-plasmids between bacteria can cause the development of antimicrobial resistance

more quickly and effectively than chromosomal mutations. Many R-plasmids have been identified to date. R-plasmids obtained from bacterial isolates of human and animal origin show great structural similarities (21,22).

**Transposons:** Transposons are short DNA fragments that can integrate into the structures of chromosomes, plasmids, and bacteriophages and move between these structures. They cannot self-replicate and must be protected within a functional piece of DNA (plasmid or chromosome). Transposons of Gram-negative bacteria are nonconjugative unless integrated into a conjugative plasmid or DNA structure. Bacteroides spp and Gram-positive bacteria may have conjugative characteristics. Transposons carrying resistance genes can easily integrate into the structure of plasmids and subsequently into the structure of bacterial DNA. Many transposons carrying resistance factors can be carried with the same plasmid, so many resistance factors can be transferred between bacteria with a single conjugation. Antimicrobial resistance factors can reach many bacterial populations through the movement of transposons within and between bacteria. However, the most important effect of transposons in the spread of antimicrobial resistance is that they increase the host diversity of antimicrobial resistance genes (8, 23).

**Integrons and Gene Cassettes:** Integrons are defined as mobile gene expression elements. They contain the integrase gene, gene cassettes, and the recombination site for that gene in their structures. The integrase gene is responsible for integrating the gene cassette carried by the integron into other DNA. Integrons are located in the structures of chromosomes, plasmids, or transposons, and many integrons have been reported to carry antimicrobial resistance factors (24, 25).

## Transfer of Mobile Resistance Factors Between Bacteria

Extrachromosomal resistance factors are the most important reason for the spread of antimicrobial resistance. The resistance factor is transferred actively or passively between bacteria from the same and different genera, mainly by conjugation, transformation, or transduction pathways. The NDM1 (New Delhi metallo-β-lactamase 1) gene, identified in 2008 and located on the IncH1 plasmid, shows that resistance to β-lactam antimicrobials is also transferable, and this resistance can spread rapidly. This gene spread to more than 40 countries between 2008 and 2013 (26). Similarly, plasmid-mediated quinolone resistance was first described in 1998 and has now spread globally (27).

**Conjugation:** Conjugation is the most researched mechanism among horizontal gene transfer mechanisms and is defined as the multistage transfer of genetic material due to the contact of two bacterial cells. A cytoplasmic bridge called the sex pilus forms between bacterial cells, and mobile genetic material is transferred from one bacterium to another through this structure. For conjugation to occur, genes encoding conjugative properties or autonomously replicating plasmids must be present in the genetic structure of bacteria (28, 29). Conjugation is considered the most important mechanism responsible for the transfer of antimicrobial resistance genes because it provides more effective gene transfer than transformation and covers a wider variety of bacteria than transduction (30). Transfer of antimicrobial resistance genes via conjugation can occur in many soil- and water-based ecosystems (31). In addition, the fact that plasmids and transposons can be transferred between different taxonomic groups via conjugation shows the importance of this mechanism in the spread of antimicrobial resistance genes (32). Transfer of antimicrobial resistance genes via plasmids is responsible for developing and spreading resistance against β-lactam, quinolone, aminoglycoside, tetracycline, and sulfonamide group antimicrobials (18). More importantly, many antimicrobial resistance genes are located on the same plasmid, which causes multidrug resistance to become widespread. Plasmid transfer is not the only way to transfer resistance genes to new hosts. Transposons and integrons can also be transferred via conjugation. Conjugative transposons, especially found in Gram-positive bacteria, can transfer genes without a plasmid. In recent years, it has been understood that resistance genes are carried, especially by transposons (32).

**Transformation:** Transformation is the incorporation of free DNA into the bacterial cell. The genetic material released by the lysis of a bacterium is recognized by another bacterium through cytoplasmic receptors and taken into the bacterium by the cell membrane. It is thought that changes in penicillin-binding protein (PBP) occur through transformation due to gene transfer between Neisseria species and pathogenic and non-pathogenic streptococcus species. Research has shown that the transformation capacity of bacteria exposed to sub-therapeutic doses of antimicrobials increases. This shows that antimicrobials trigger the transfer of resistance genes (33).

**Transduction:** Transduction is the transfer of resistance genes via bacteriophage. The bacteriophage that infects a bacterial cell is released when the bacterium is lysed and can carry the genetic material of that bacterium to another bacterium. It is often applied for resistance transfer under laboratory conditions. The importance of transduction in terms of clinical resistance developing under in vitro conditions is unknown (1, 2, 34). However, the fact that some bacteriophages have a wide host range of bacteria from different species suggests that transduction has an important potential in spreading antimicrobial resistance genes (36, 37).

**Cross Resistance:** A microorganism species that becomes resistant to an antimicrobial may also develop resistance to other antimicrobials that are similar in structure or mode of action to this antimicrobial agent (Cross Resistance). Although cross-resistance is generally observed between antimicrobials with similar structures, such as erythromycin and other macrolides, cross-resistance can also be observed between

antimicrobials with very different structures, such as erythromycin and lincomycin (1, 2, 34).

**Multidrug Resistance:** The development of resistance of a microorganism against many antimicrobials with different structures and effects is defined as multidrug resistance (MDR). This concept covers many definitions, such as extensively drug-resistant (XDR), Pan drug-resistant (PDR), and multidrug-resistant (MDR). In order to avoid possible confusion, international terminology was created with the joint efforts of the European Center for Disease Control and Prevention (ECDC) and the United States Centers for Disease Control and Prevention (CDC). According to this terminology, disseminated drug resistance is defined as resistance to two or fewer antimicrobial agents belonging to each group from all antimicrobial groups. Fully drug-resistant, resistance to all members within all antimicrobial categories; Multidrug resistance is defined as resistance to three or more antimicrobial agents belonging to different groups (37). MDR, regulated by multiple antibiotic loci (mar), is characterized by a decrease in the intracellular accumulation of the drug due to a structural change in the membrane proteins of bacteria (38). In gram-negative bacteria, MDR develops as a result of the activation of the resorption pump of the resistance nodulation division (RND). The retrograde pump AcrAB-TolC, which is responsible for MDR for Enterobacteriaceae bacteria, ensures the excretion of many compounds, including different groups of antimicrobials (fluoroquinolone, β-lactam, macrolide, tetracycline, and sulfonamide group compounds and trimethoprim), biocides and dyes, out of the cell (16)

### Antimicrobial Resistance Mechanisms

Resistant microorganisms are protected from the inhibitory activity of antimicrobials by preventing the compound from reaching the target site, changing the target structure, protecting the target site, and changing the structure of the compound (35). Preventing antimicrobial agents from reaching their target structures in bacterial cells occurs due to decreasing the permeability of the cell membrane and removing the antimicrobial entering the cell via the efflux pump. The target structure is maintained through mutation and replacement of the molecule with protective structures. Its antimicrobial structure can be changed by enzymatic inactivation or modification (39).

**Preventing Antimicrobials from Reaching Their Target:** Preventing antimicrobials from reaching their targets within the bacterial cell occurs by decreasing the permeability of the cell membrane to the antimicrobial agent and removing the antimicrobial agents from the cell (40).

**Decreased Permeability of the Cell Membrane:** Gram-negative bacteria are less permeable to many antimicrobials than Gram-positive bacteria due to the selective outer layer of their cell membranes. Hydrophilic antimicrobials pass through the cell membrane by binding to porin proteins. The major porin proteins (OmpF and OmpC) found in the Enterobacteriaceae family are nonselective. Bacteria can reduce cell permeability by reducing the number of nonselective porin proteins or replacing them with selective proteins. This is a resistance mechanism that develops against carbapenems and cephalosporins in the Enterobacteriaceae family (35, 40).

**Active Eflux:** Unlike the efflux pump AcrAB-TolC, which is responsible for MDR for Enterobacteriaceae bacteria and is responsible for the extracellular excretion of many antimicrobials, some efflux pumps are more specific. For example, oqxA, oqxB, qepA1, and qepA2 genes enable the removal of hydrophilic fluoroquinolones from the cell (41, 42). Generally, the activities of efflux pumps are regulated through chromosome and plasmid genes. This situation is essential regarding the spread of antimicrobial resistance (35).

**Protection of Target Structure:** Changing the target structure of antimicrobials within the bacterial cell occurs by changing the molecular properties of the target structure as a result of chromosomal mutations and adding protective proteins to the target structure (41)

**Mutation:** Many antimicrobials bind specifically to their target structure in bacteria and prevent the normal activities of these structures. Mutations that cause molecular changes in target structures prevent antimicrobials from binding to these structures (42). Thus, the target structure continues its regular activity. Quinolone resistance-determining region (QRDR) mutations can be shown as an example of this type of resistance. The localization of the mutations are the gyrA and gyrB genes, which encode the DNA gyrase enzyme, and the parC and parE genes, which encode the topoisomerase IV enzyme. As a result of the mutation, the molecular structure of DNA gyrase and topoisomerase enzymes changes, and the bacteria are protected from the inhibition of fluoroquinolones (25, 41-46).

**Reconfiguration of the Target Molecule with Protective Structures:** The target structures of antimicrobials can also be changed by binding protective molecules to these structures. Qnr proteins responsible for transferable fluoroquinolone resistance bind to DNA gyrase and topoisomerase enzymes, causing changes in the molecular structure. As a result of this change, fluoroquinolones are prevented from binding to the DNA gyrase enzyme, and thus, DNA gyrase and topoisomerase IV enzymes are protected from the inhibition of fluoroquinolones (25, 47).

### Altering the Structure of Antimicrobials

The structures of antimicrobials can be changed through enzymes secreted by bacteria. This event occurs by enzymatic inactivation or enzymatic modification (41).

Enzymatic Inactivation: Enzymatic inactivation of antimicrobials occurs due to the decomposition of their

molecular structures through hydrolysis. Today, many enzymes have been identified that inactivate β-lactam, aminoglycoside, phenicol, and macrolide group antimicrobials. There are also isozymes that degrade different antimicrobials belonging to the same group. β-lactamase group enzymes, which decompose the lactam ring in the structures of β-lactam group antimicrobials, can be an example of this situation (35).

**Enzymatic Modification:** Bacteria have many enzymes that prevent antimicrobials from binding to their targets by adding chemical groups such as acetyl, phosphate, and acyl to their molecular structures. The aminoglycoside acetyltransferase enzyme, encoded by the aac(6')-Ib-cr gene, acetylates hydrophilic fluoroquinolones such as ciprofloxacin and norfloxacin, as well as aminoglycosides, and reduces their activities (35, 47-49).

## CONCLUSİON

Antimicrobials are essential for the treatment of bacterial infections in humans and animals. Therefore, the effectiveness of antimicrobials should be preserved (4). The widespread use of antimicrobials, their careless selection, and the selective effect of environmental pollution on bacteria cause changes in the genetic structure of the bacteria, and resistance may develop (2, 3). The problem grows as the resistance transfers to other bacteria. The incidence of infections caused by resistant pathogens increases, causing time, cost, and labor loss. An increase in hospitalization rate and duration, morbidity, and mortality is also observed (14-16). It is predicted that antimicrobial resistance will be the most important cause of death in 2050 (16, 17)

The joint working group of the World Health Organization (WHO), the World Organization for Animal Health (OIE), and the American Food and Agriculture Organization (FAO) aims to prevent the development of resistance in veterinary and human medicine and has prepared a global action plan for this purpose.

**The objectives to be achieved according to this plan are:**

1. To raise awareness at a professional level about antimicrobial resistance through effective communication and training programs,

2. Strengthening and improving scientific evidence on antimicrobial resistance with monitoring programs and scientific research,

3. To reduce the incidence of infection by creating effective sanitation, hygiene, biosecurity, and infection control programs,

4. Optimizing and monitoring the use of antimicrobials in the human and veterinary field,

5. To create sustainable investment resources for developing new antimicrobial agents, antimicrobial resistance detection methods, vaccines, and other measures in all countries.

WHO and EMA recommend identifying and monitoring resistance to prevent effective antimicrobial chemotherapy and resistance (8, 16). In Europe, European Antimicrobial Susceptibility Surveillance in Animals (EASSA) and European Food Safety Authority (EFSA) are programs that aim to monitor resistance in pathogens of animal origin. EFSA focuses on monitoring antimicrobial resistance in nutritional animals and food of animal origin. In addition, many monitoring programs such as GLASS (Global Antimicrobial Resistance Surveillance System) and TATFAR (The Transatlantic Taskforce on Antimicrobial Resistance) are implemented to monitor antimicrobial resistance within the framework of the FDA and WHO (17). Additionally, restricting the use of antimicrobials can reduce the risk of resistance (50).

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