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Review Article

### Issue of Antibiotics Resistance: From Spot of One Health

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#### ABSTRACT

Antibiotics were considered as an amazing gift to the human and animal healthcare sectors for the treatment of bacterial infections. Antibiotic resistance is the ability of bacteria to resist to the action of an antibiotic. Antimicrobial resistance is a worldwide problem. Antibacterial resistance results in a reduction or elimination of effectiveness of the antimicrobial agent to cure or prevent infection due to this microorganism. Macrolides resisted by gram-negative bacilli particularly members of the family Enterobacteriaceae (intrinsic resistance). Other bacteria like Staphylococci that are normally susceptible to antibiotics (penicillin) become resistant as a result of adaptation through genetic change (acquired resistance). All antibiotic-resistant bacteria survive in the presence of the antibiotic and continue to grow and multiply causing longer illness or even death. Multidrug-resistant microorganism lies in the limited number of remaining options for therapy of patients infected with these microorganisms. The major cause of antimicrobial resistance in microorganisms from humans remains the use of antimicrobials in human medicine, in the community and in hospitals and other healthcare settings. The burden of antimicrobial resistance is mainly due to antimicrobials used in food-producing animals. The current review provides information about antibiotic resistance, its mechanisms responsible for the resistance, role of animal environment and foods of animal origin in spreading the threat and finally suggestions for controlling of antibiotics resistance.

#### INTRODUCTION

Nowadays, antibiotic resistance of various bacteria has emerged as a global threat to the treatment options of bacterial infections (Johansson et al. 2020). Antibiotic resistance of pathogenic bacteria causing bacteremia increases morbidity and mortality therefore is the

challenge around the world (Ježak and Kozajda, 2020). The emergence of AMR is a natural phenomenon in microorganisms, yet it is augmented by the overuse of antimicrobial agents in both humans and animals (WHO, 2018).

Clinical resistance has been observed for all of the more than 100 antimicrobial agents

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available today, It is now apparent that any susceptible bacterial pathogens may develop or acquire resistance. The significance and severity of Healthcare-associated infections are increasing due to the rise in antimicrobial resistance and emergence of multidrug resistance MDR (CDC, 2019). Thus, treatment for patients suffering HAIs resistant to traditional antibiotic therapies is more precarious, costly and, in the worst-case scenario, unsuccessful. The increase in antimicrobial resistance is driven, in part, by the inappropriate use of antibiotics and ineffective disinfectant protocols (CDC, 2020).

The consequence of intensive animal production is a high level of pollution emitted to the environment, the nearest vicinity of farms, but also air, soil, surface water, groundwater, and rainwater. The use of liquid manure as fertilizer poses the risk of polluting the environment with pathogens, antibiotics, metabolites of antibiotics and antibiotic-resistant pathogens (Gordon 2018; Wanot and Domagała 2019).

However, there are limited studies investigating the role of environmental microorganisms, including waterborne pathogens such as *Legionella* spp., *P. aeruginosa* and *Mycobacterium* spp. (Amoureux, 2017). Notably, approximately 80% of chronic and recurrent microorganism infections are caused by biofilms, which are communities of microorganisms, providing protection from adverse environmental conditions and antimicrobial agents (Sharma et al. 2019). The virulence of microbes is key to enabling them to invade a host, surpass its immune system, and cause an infection. The microbial elements accomplishing this invasion are called virulence factors. The function of virulence factors of microbes is not only to instigate the infection but also it aids the bacteria in surviving hostile environments. One of these virulence factors is responsible for biofilm production (Mohamad et al. 2023). Transmission of antibiotic-resistant bacteria (ARB) to humans, immunopathological effects, allergies, mutagenicity, nephropathy, hepatotoxicity, bone marrow toxicity, and even carcinogenicity (e.g., oxytetracycline) are just a few of the side effects of antibiotic resi-

dues (Bacani and Ba,saran 2019).

Awareness of antimicrobial-resistant *Staphylococcus* spp. has become the primary concern in public health because it affects not only animals but also milk products routinely consumed by humans (Kupradit et al., 2020). Antimicrobial resistance (AMR) in the food chain has emerged as a global “One Health” concern (Mdegela et al. 2021). Antimicrobial resistance genes (ARGs) conferring resistance to tetracycline (tet), extended-spectrum  $\beta$ -lactamase (ESBL) genes (*blaCTX-M* and *blaTEM*), carbapenem resistance genes (*blaOXA* and *blaNDM*), and a methicillin resistance gene (*mecA*) are the most commonly detected in ARB present in food and food products and are thought to be widely prevalent in the environment due to the widespread use of the corresponding antibiotics (Ejaz et al. 2021 and 2022). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories as per guidelines. XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories listed and PDR was defined as non-susceptibility to all agents in all antimicrobial categories” according to the European Centre for Disease Control (ECDC) and the CDC (Alkofide et al. 2020). The research community is focusing many efforts on the discovery of new antibiotics, the study of the mechanisms of resistance, epidemiology studies, the development of new tools for a rapid diagnostic of resistant bacteria and the study of the spread of AMR (Soto, 2023).

Bacteria possess unique self-defence mechanisms against their antibiotics. *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. are just a few examples of multiple drug-resistant bacteria. While the Main Difficult-to-Treat Antibiotic-Resistant Pathogens are *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (ESKAPE). (Magiorakos et al. 2012, Peterson and Kaur 2018). Nowadays, there is a rise in the occurrence of these

drug-resistant pathogens due to the availability of a small number of effective antimicrobial agents. It has been estimated that if new novel drugs are not discovered or formulated, there would be no effective antibiotic available to treat these deadly resistant pathogens by 2050 (**Bharadwaj et al. 2022**). However, the widespread availability of antibiotics, accompanied by their over prescription, acts as a double-edged sword, since the overuse and/or misuse of antibiotics leads to a growing number of multidrug-resistant microbes (**Baran et al. 2023**). According to World Health Organization (WHO), AMR is responsible for the deaths of 700,000 people at 2019, while it's estimated that by 2050 the figure will have risen to 20 million (**Watkins and Bonomo 2016**). Excessive utilization of antibiotics in livestock management (poultry, aquatic, etc.), and international travel are a few factors for the outbreak of antibiotic resistance in the human and animal community (**Prestinaci et al. 2015**). All of these factors contribute to the escalation of resistance in the environmental niche, which is also a serious global concern (**Exner et al. 2017**). Furthermore, the "One Health" approach should be adapted to combat antimicrobial residues in animals, food and environment (**Qamar, et al. 2023**).

#### History

Antibiotic defined as is a type of antimicrobial substance active against bacteria. Antimicrobials are medicinal products that kill or stop the growth of living microorganisms (MOs) and include among others ((such as sulfonamides and antiseptics are fully synthetic). Antibiotics revolutionized medicine in the 20th century. Alexander Fleming (1881–1955) discovered modern day penicillin in 1928. Overall, three major elements of AMR development are emergence, transmission, and level of infection. For example, *Neisseria gonorrhoeae* developed resistance to ampicillin, and *Haemophilus* developed resistance to ampicillin, tetracycline and chloramphenicol (Su et al.,2020). Moreover, the first sulphonamide was synthesized at 1935 against Streptococcus infection Similarly, sulfonamide resistance originated in the 1940s (**Uddin et al. 2021**). Antibiotics also developed gradually; methicil-

lin-resistant *S. aureus* (MRSA) strains are among the rapidly propagating bacterial strains (Rossiter, et al.,2017). Once a newly discovered antimicrobial agent is proven to be effective and is approved for therapeutic use or overuse, some bacteria have evolved resistance to them often appears in months to years (**Walsh,2000, Laxminarayan et al. 2013**).

#### Mechanisms of antibiotic resistance in bacteria

Antibiotic resistance evolves when the bacteria can escape the effect of antibiotics by different mechanisms, like neutralizing the antibiotics, pumping them outside of the cell, or modifying their outer structure resulting in inhibition of the drugs' attachment to the bacteria (**Breijyeh, 2020**). Different mode of action of antibiotics and its resistance mechanisms was summarized in Table (1) and Figure (2). The ESKAPE pathogens represent deadly bacteria with rapidly growing multi-drug resistant properties. Although these bacteria are genetically different, the resistance strategies that underlie the emergence and persistence of these pathogens are widely shared among them including decreased drug uptake, drug target alteration, drug inactivation and drug efflux pumps activation (**Mancuso, 2021**). Basically, antibiotic resistance can be related to four causes: (1) natural/intrinsic and (2) acquired resistance. Table (1) summarizes a few mechanisms of resistance to different target drugs having different modes of actions.

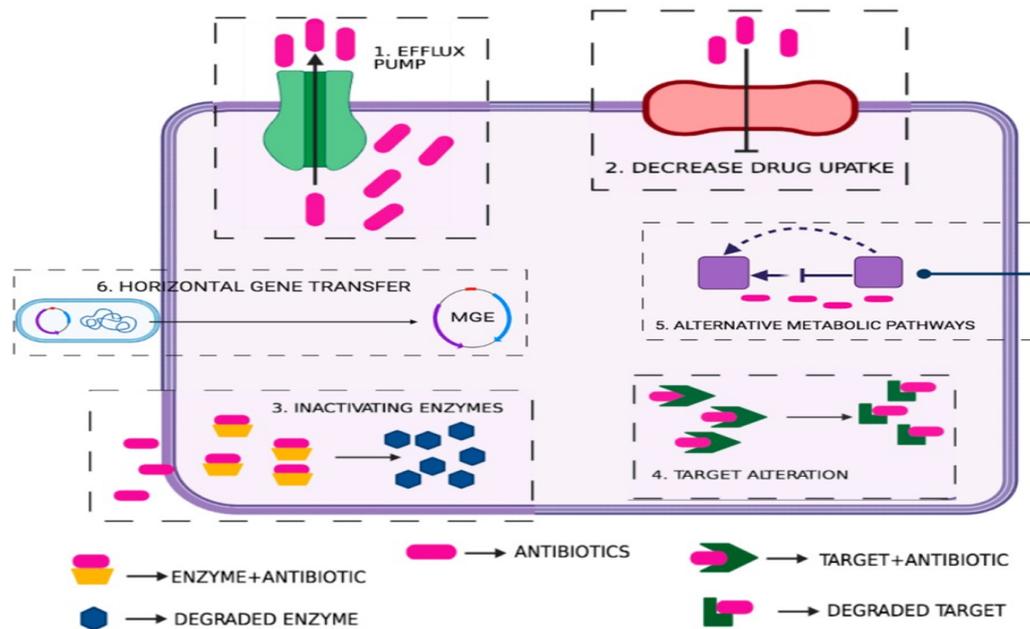


Figure (1): Diagrammatic illustration of possible mechanisms in bacteria contributing towards various antibiotic resistances such as: 1. Active efflux of various antibiotic via pumps; 2. Prevention or decrease drug uptake by the cell; 3. Antibiotic inactivating enzymes; 4. Modification or alteration of targets; 5. Use of alternative or bypass metabolic pathways; 6. Acquired antibiotic resistance mechanism (HGT).

### Intrinsic Resistance

Intrinsic or natural resistance can be defined as the ability of a bacterium to resist the effect of an antibiotic due to its inherent properties. For example, gram-negative bacteria are intrinsically resistant to the activity of the macrolides (Saha and Sarkar 2021). The cytoplasmic membrane of gram-negative bacteria contains the lesser proportion of anionic phospholipids than gram-positive bacteria. Thus, the efficacy of  $\text{Ca}^{2+}$  mediated daptomycin insertion into the cytoplasmic membrane is decreased (Randall et al. 2012). Notably, various genes associated with intrinsic resistance to different classes of antibiotics such as lactams, aminoglycosides, and fluoroquinolones in *P. aeruginosa*, *S. aureus*, and *Escherichia coli* have been identified through high-throughput tools of high-density genome mutant libraries (Lebeaux et al. 2014). Genes responsible for drug-resistant *Salmonella* and *E. coli* include AmpC, bla-TEM-1, bla-CTX-M-15, VIM-1, NDM-1, floR, tetG, and the mcr-1 gene that encodes colistin drug resistance (Darwich et al. 2019) Plasmid coding colistin-resistant (mcr-1

dependent) *E. coli* was first isolated from raw meat, animals, and humans in China (Muktan et al. 2020) Mcr-1 harboring *E. coli* was also reported in migratory birds and human clinical isolates in Pakistan and MDR (ESBLs, quinolones). *E. coli* was reported from poultry farms, wild birds, pigeons, dogs, and humans (Anyanwu et al. 2020). Gram-negative bacteria are intrinsically resistant to many classes of antibiotics, predominantly due to the impermeability of the outer membrane and the presence of efflux pumps (Melander et al. 2023).

**Table 1.** Different mode of action of antibiotics and its resistance mechanisms along-with few bacterial examples.

Antibiotics	Mode of Action	Mechanism of Resistance	Examples
$\beta$ -Lactams (Cephalosporin, Carbapenems, etc.)	Peptidoglycan biosynthesis Cell wall synthesis Inhibition	Hydrolysis, efflux, altered target, reduced permeability, inactivation of antibiotics via $\beta$ -lactamase (extended spectrum $\beta$ -lactamase; carbapenem-hydrolyzing $\beta$ -lactamase)	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , Enteric bacteria, <i>Streptococcus pneumoniae</i> , <i>Vibrio cholerae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i>
Aminoglycosides (Gentamicin, Streptomycin, Spectinomycin, Amikacin, Tobramycin, etc.)	Inhibition of Translation and cell membrane synthesis	Modifying enzyme inactivation by Phosphorylation (phosphorylase), acetylation (acetylase), nucleotidylation, efflux, altered target ribosomal binding site, decrease uptake by reducing permeability, other modifying enzymes includes acetyltransferases, adenyl transferases, phosphotransferases.	Enteric bacteria, Staphylococci, Streptococci, Bacteriodes, <i>Pseudomonas aeruginosa</i> , <i>Vibrio cholerae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i> , etc.
Glycopeptides (Vancomycin, Teicoplanin)	Peptidoglycan biosynthesis	Altered target	Enterococci, Lactobacilli, <i>Staphylococcus haemolyticus</i> , Enterococcus <i>faecium</i> , <i>Enterococcus faecalis</i> , etc.
Tetracyclines (Tigecycline, Minocycline, Doxycycline)	30S ribosomal subunit	Monooxygenation, ABC efflux pump, ribosomal modification, tetracycline inactivating enzyme	Staphylococci, Streptococci, Enterococci, Enterobacteriaceae, Haemophilus, Listeria, <i>Acinetobacter baumannii</i> , etc.
Macrolides (Erythromycin, azithromycin)	Translation	Glycosylation, efflux, methylation of rRNA target	Streptococci, Enterococci, Staphylococci, <i>Acinetobacter baumannii</i> , etc.
Phenicol (Chloramphenicol, Azidamphenicol, Thiamphenicol)	Translation inhibitors	Acetylation by chloramphenicol acetyltransferase, efflux pump, target site alteration	<i>Bacillus subtilis</i> , <i>Streptococcus pneumoniae</i> , Enterobacteriaceae, <i>Haemophilus influenzae</i> , <i>Vibrio cholerae</i> , <i>Escherichia coli</i> etc.
Folate inhibitors (Trimethoprim, Sulfamethoxazole)	Inhibit folate synthesis pathways	Efflux, altered target	Staphylococci, Streptococci, Enterobacteriaceae, Neisseria, <i>Acinetobacter baumannii</i> , etc.
Rifamycins (Rifampin)	Transcription	ADP-ribosylation, efflux, altered DNA-dependent RNA target	Enteric bacteria, Staphylococci, Streptococci, <i>Mycobacterium tuberculosis</i> , <i>Vibrio cholerae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i> , etc.
Quinolone (nalidixic acid, ciprofloxacin, levofloxacin, ofloxacin, norfloxacin)	Inhibitors of DNA synthesis Topoisomerase I and II	Altered DNA gyrase or DNA topoisomerase IV subunit A (parC) efflux or reduced permeability	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus epidermis</i> , <i>Streptococcus pneumoniae</i> , <i>Acinetobacter baumannii</i> etc.
Cationic peptides (Colistin, Polymyxin-B)	Cell membrane Lipopolysaccharide layer of bacteria	Altered target, efflux	<i>Escherichia coli</i> , <i>Salmonella Typhimurium</i> , <i>Acinetobacter baumannii</i> , etc.

## Acquired Resistance

Acquired resistance is the most important trait, and its mechanism can be further subdivided into the following types: (1) decrease uptake of the drug due to reduction in the internal or external membrane permeability or changes in the cytoplasmic membrane composition; (2) enzymatic inactivation or degradation of antibiotics; (3) active efflux pump system; (4) resistance associated with alteration of the target or change in the structure of the target, and; (5) in some cases, the use of alternative metabolic pathways serves as the resistance mechanism (Ndagi et al. 2020). The gene or the genetic elements responsible for acquired resistance may be chromosomal or extra chromosomal. Antibiotic resistance can occur via various mechanisms linked with vir-

ulence factors, outer membrane proteins cell envelope factors specific enzymes, quorum sensing, and biofilm formation and protein secretory systems. Few bacteria harbor various resistance mechanisms (either intrinsic or acquired) that create those strains MDR (Ndagi et al. 2020).

Horizontal gene transfer HGT facilitates the transmission of both resistance and virulence factors between bacterial genera or species. Moreover, features such as mobile genetic elements MGEs and biofilms help bacteria survive and overcome the antibacterial activity of therapeutics. Recombination events or HGT facilitate the transfer of genes from resistant strains to susceptible bacterial cells; genetic elements such as transposons, more precisely

integron, are responsible for antibiotic resistance (Das et al. 2019). As anti-TB drugs were widely used, multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* emerged due to acquired genetic mutations, and this now presents a major problem for effective treatment (Bi et al. 2023).

### 2.1. Antibiotic Efflux

Resistance mechanisms of various pathogens mainly involve permeability barriers for the active efflux of drug molecules. The synergistic action of reduced drug uptake and efflux is involved within the multiplicative action of the outer membrane permeability barrier, and it leads to the acquisition of high-level intrinsic and/or acquired resistance in many clinically important bacteria (Sultan et al. 2018). Ongoing trials targeted toward understanding the physical structures, function, and regulation of efflux systems will facilitate the exploitation of efflux pumps as new drug targets (Alav et al. 2018). The data from numerous studies suggest that heavy metal contamination could affect the dissemination of antibiotic-resistant genes. Environmental pollution caused by anthropogenic activities could lead to mutagenesis based on the synergy between antibiotic efficacy and the acquired resistance mechanism under stressors. Moreover, the acquired resistance includes plasmid-encoded specific efflux pumps. Soil microbiomes have been reported as reservoirs of resistance genes that are available for exchange with pathogenic bacteria (Nguyen et al. 2023). The major obstacle in the antibiotic discovery pipeline is the lack of understanding of how to breach antibiotic permeability barriers of Gram-negative pathogens. These barriers are created by active efflux pumps acting across both the inner and the outer membranes. Overproduction of efflux pumps alone or together with either modification of the outer membrane or antibiotic-inactivating enzymes and target mutations contribute to clinical levels of antibiotics resistance (Manrique et al. 2023).

### 2-2. Use of an Alternative Metabolic Pathway

A similar resistance mechanism was reported in small colony variants (SCVs) of *S.*

*aureus*, the mechanism involved the activation of an alternative transcriptional program, leading to increased ATP production while retaining antibiotic resistance in SCVs. The growth rate of drug-resistant SCVs was also found to be high (Cao, et al. 2017). Similarly, bacteria can acquire the property of utilizing folate present in the environment rather than synthesizing folate (Fernández-Villa et al. 2019).

### 2.3. Reduction of the Inner and Outer Membrane Permeability

Porin mutations in resistant strains result in changes in membrane permeability and decrease drug uptake into the cell (Sultan et al. 2018). For example, in *P. aeruginosa* strains, OprD (specific porin) can cause mutation for carbapenem resistance. Moreover, reduction in permeability of the outer membrane may play an important role in conferring resistance to quinolones and aminoglycosides (Hamed et al. 2018, Pang et al. 2019). Alterations of porins could be achieved by three general processes: (1) a shift in the type of porins expressed, (2) a change in the level of porin expression, and (3) impairment of the porin function. Importantly, changes in permeability through any of those mechanisms frequently end in low-level resistance and are often related to other mechanisms of resistance, such as increased expression of efflux pumps (Fernandez and Hancock 2012). The outer membrane (OM) is a selective permeability barrier that contributes to the intrinsic antibiotic resistance of Gram-negative bacteria. Biophysical characterization of the roles of the component proteins, lipopolysaccharides, and phospholipids is limited by both the essentiality of the OM and its asymmetrical organization (Mikheyeva et al. 2023)

### 2.4. Antibiotic Modification or Degradation

Modification or degradation of antibiotics is one of the most common and important mechanisms of acquired resistance (Ndagi et al. 2020). Bacteria contain genes or gene clusters that encode diverse antibiotic-modifying enzymes. These enzymes are effective against various classes of antibiotics such as aminoglycoside, chloramphenicol, and  $\beta$ -lactam (Sultan et al. 2018). Some of these enzymes

are present in pathogenic strains, whereas other enzymes are present in both pathogenic and non-pathogenic strains. Enzymes can physically modify antibiotics, and they can actively decrease the concentration of drugs in the local environment. Therefore, it is a unique challenge to researchers and clinicians considering new approaches to anti-infective therapy (Baker et al. 2018, Ogawara, 2019). Collective resistance occurs when bacteria work together to decrease the concentration of antibiotics in their environment, for example, by actively breaking down or modifying them. This can help bacteria survive by reducing the effective antibiotic concentration below their threshold for growth. Important aspect of antibiotic degradation is the degree of cooperatively, related to the permeability of the cell wall to antibiotics and enzymes (Geyrhofer et al. 2023).

### Biofilm production

Biofilm is one of the common features of various bacterial strains that aid their survival under stringent conditions. These biofilms restrict the antibiotic from penetrating bacterial cells, and thus protect bacteria from the action of antibiotics, and facilitate the mechanism of resistance (Alav et al. 2018, Verderosa et al. 2019). Sewage and wastewater treatment plants, hospital effluents, aquaculture, agriculture, and slaughterhouse wastes are the hotspots of genetic exchange (Laxminarayan et al. 2013). A study on equine wound reveals that all the wound colonizers could form biofilms. The results demonstrated that the isolates produced biofilms. Gentamicin at the minimum inhibitory concentration (MIC) and  $10\times$  MIC caused biofilm removal between 59.3% and 85.7%, with the highest removal percentage being obtained for the *P. aeruginosa* isolate (at  $10\times$  MIC concentration). It also highlights the possibility of resistance transmission between animals, animals and humans, or animals and the environment (Afonso et al. 2023). The widespread use of metal and metal oxide nanoparticles seems to stimulate the co-selection and co-expression of antibiotic-resistance genes. The selenium nanoparticles (SeNPs) showed an inhibitory effect against all tested planktonic (MIC range: 0.00015 to  $>1.25$  mg/mL) and biofilm-

embedded Carbapenem-Resistant *Acinetobacter baumannii* with a minimum biofilm inhibitory concentration of less than 0.15 mg/mL for 90% of biofilm producers (Smitran et al. 2023). Several studies were established to minimize or eradicate biofilm production pathogens. Rosemary proved to have antibacterial activity against *B. cereus* producing biofilm at a concentration of 1.25% in vitro and in vivo by inoculation in Kariesh cheese (Al.Habaty, SH. and Amin, 2020). Complete inhibition to Streptococcus producing biofilm (SPB) in milking utensils occurred at 10 and 20 minutes when washing by carvacrol nanoemulsions 20% and chitosan nanoparticles 30% (Elsherif, and Elhabtey, 2020).

### Antibiotic resistance transmitted via animal environment

Among the pathogenic zoonotic bacteria on animal farms environment are: *Staphylococcus* spp.; *Salmonella* spp.; *Campylobacter* spp.; *E. coli*; *Listeria* spp.; *Enterococcus* spp. These pathogens are emitted into the air (organic dust) and through surface waters (slurry, faeces of other animals, including poultry) to the environment; where first as viable cell can be a cause of infections in humans and second constitute the source of antibiotic resistance genes (ARG) (Argudín et al. 2017). A number of studies have examined the results of the long-term exposure of environmental bacterial strains to low concentrations of antibiotics. Such exposure appears to have a significant influence on bacterial genomes. This exposure has been found to modulate the transcription levels of bacterial genes which, in turn, increases the frequency of genome mutation and horizontal gene transfer and mobile genetic elements, including those responsible for antimicrobial resistance (Blázquez et al. 2012). The antibiotics used in clinical settings, agriculture and livestock farming, spill over to wildlife, leading to AMR emergence, with potential biological, ecological, and human health effects (Ramos et al. 2022). Moreover, The usage livestock manure from conventional farming as an agricultural lands fertilizer may contribute to spread of antimicrobial resistance (AMR) in the environment (Laconi et al. 2021). Numerous studies, examining the transmission of antimicrobial resistant bacteria

from animal to humans, reported the high prevalence rate of antimicrobial resistant bacteria among individuals that have a direct contact with animals, specifically farm workers and veterinarians (**Jackson, and Villaruel 2012, Nadimpalli, et al. 2018**). Indirect acquisition of antimicrobial resistant bacteria is usually more complex compared to direct acquisition. It is known that a considerable amount of antibiotics used in agriculture, human and animal medicine reaches the environment in their active forms (**Thanner, et al. 2016**). In a study conducted by **Krukowski et al. (2020)** revealed that the first epidemic of Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) in dairy cattle, as well as the first probable case of MRSA transmission between humans and cows in Poland was presented. The authors presented evidence for transmission of MRSA between the cattle and the farm workers and between people in a family environment. The risk of intra and interspecies transmission of LA-MRSA was confirmed.

Dust in livestock premises has high concentration of microorganisms, including those that are antibiotic-resistant. The main factors affecting the environmental conditions inside and outside of animal buildings include concentration and type of animal production, breeding system, organization of the production process, indoor microclimate and the quantity and quality of animal faeces. People working in intensive animal farming are exposed to high concentrations of organic dust and suspended biological agents (**Buczyńska and Szadkowska-Stańczyk 2010**). Qualitative analysis of the dust conducted on 13 poultry farms dust found, i.e., bacteria belonging to the genera *Enterococcus* and *Salmonella*, as well as to the *Escherichia coli* species (**Skóra et al. 2016**). The air in poultry houses at poultry farms is usually heavily contaminated by large quantities of dust particles of biological and non-biological origin. Bio aerosol in poultry houses contains particles released chiefly from settled dust, which originates from feed, manure, litter, feather fragments and animal skin, as well as microorganisms, their bio products and fragments (**Ławniczek-Walczuk et al. 2013**). **Bukowski et al. (2019)** deter-

mined complete plasmid sequences derived from 18 poultry *S. aureus* strains. It has been proven that livestock related *Staphylococcus* are a significant reservoir of factors determining antibiotic resistance, and moreover, that transmission of those genes from animals to humans is possible. Bacteria of the Enterobacteriaceae family are a natural part of the intestinal microflora of humans and animals. They are mostly symptomless or opportunistic species; however, there is also a group of pathogens which are responsible for a significant number of food infections and various gastrointestinal complaints. A characteristic feature of Enterobacteriaceae family Methicillin-resistant *S. aureus* (MRSA) strains are their high capability of acquiring antibiotic-resistance genes, which is passed on to related genera of bacteria (**Krupa et al. 2015, Szewczyk et al. 2019**). **Kucheruk et al. (2018)** studied fallen broilers that had died from a disease. The broilers came from an organic farm. Test samples were taken from heart, liver and stomach muscles of the dead animals. Group D *Salmonella* bacteria were isolated from the pathological material. The results showed that the isolated bacteria were characterized by a significant resistance to a number of traditional antibacterial drugs used in human therapy. Figure (1) show different methods of antibiotic resistance spread among humans, animals and environment.

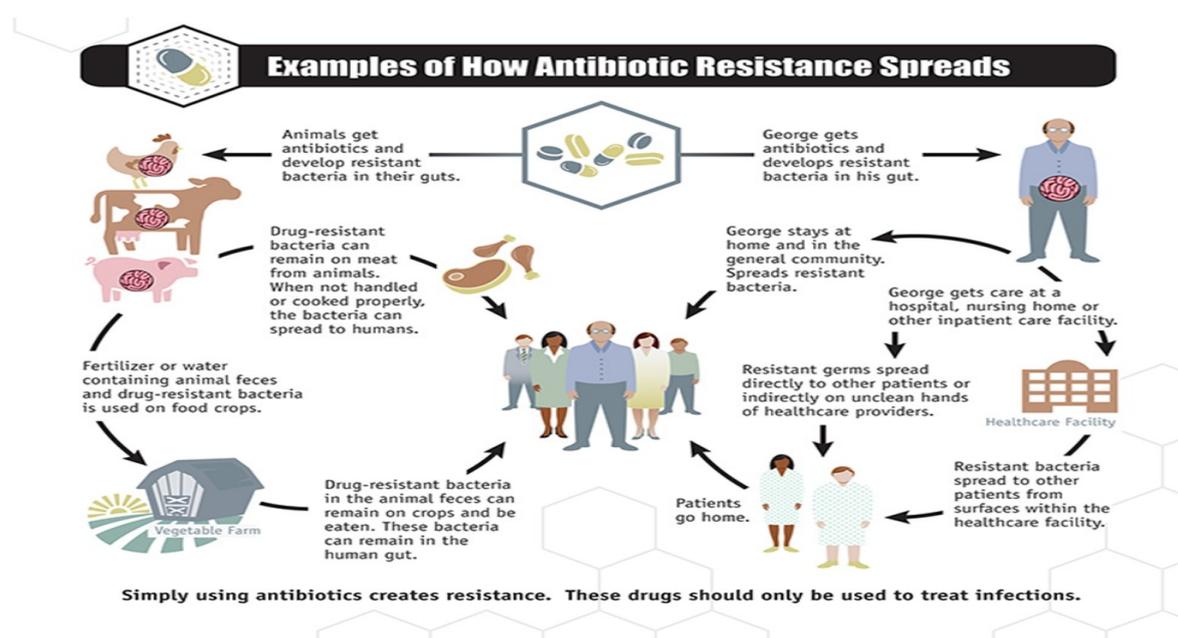


Figure (1): methods of antibiotic resistance spreading among humans, animals and environment

### Emergence of antimicrobial resistance (AMR) in milk and meat

A lack of international harmonization in the investigation of veterinary AMR has led to variations in the methods employed with regard to laboratory methods (culture, and the use of disc diffusion, MIC, Vitek) and the standards followed for interpretation (CLSI, EUCAST, CA-SFM, AHVLA, and so on), making comparisons between countries challenging. Surveillance of AMR in veterinary medicine, therefore, still has some aspects that need to be addressed (Amalia and Rosemarie, 2023). The presence of methicillin- and tetracycline-resistant strains specially *Staphylococcus* spp. in raw milk poses a major risk to public health, as these strains can induce food poisoning outbreaks that spread across populations (Kupradit et al. 2020, Lubna et al. 2023). Most of the isolated *S. aureus* in dairy products are MDR against several antibiotic groups with high MAR index and different prevalence rates like yogurt, cheese and ice cream (Al Habty and Ali, 2023). The *mecA* gene (methicillin), *tetM/tetK* (tetracycline), *blaz* gene (methicillin), and *ermA/ermC* gene (erythromycin), as well as *msrA/msrB*, are common antibiotic resistance genes in the dairy sector that have been reported worldwide

(Wang et al. 2017). Bacterial contamination of dairy products may occur directly from infected animals or through other routes, such as cross-contamination during transport, storage and processing (Moreno-Grúa et al. 2018).

Retail meat products may serve as reservoirs and conduits for antimicrobial resistance, which is frequently, monitored using *Escherichia coli* and other pathogens as indicator bacteria (Lee et al. 2023). *E. coli* which isolated from quail meat and its organs were highly resistant to Amoxicillin, Cephadrine, Neomycin, and Tetracycline by 100 %, 100%, 100% and 83.9 %, respectively (Mohamed and Al-Habaty, 2017). Furthermore, *L. monocytogenes* isolated from ready to eat chicken meals found to be harbor *mefA* gene (macrolides resistance gene) and *Aad6* gene (aminoglycosides resistance gene (El-Hawary et al. 2018). Good observation must focus on the evolution of the antibiotic resistance character in the genus *Salmonella*, *Campylobacters*, *E. coli* and all pathogens transmitted by food producing animals (Motasim et al. 2023).

Also, poultry products contain antimicrobial-resistant strains of *Salmonella*, as well as

genes encoding resistance mechanisms. We need for constant monitoring of not only pathogenic microorganisms but also their sensitivity to antimicrobial agents. The potential threat to human health requires a unified approach to the problem of antibiotic resistance from representatives of both public health and the agro industrial complex (Anara et al. 2023). Mastitis in producing animals can endanger human and animal health by transferring antibiotic resistant bacteria and causing food poisoning (Li et al. 2019). Several bacterial species can cause mastitis, the most common acquired AMR mechanisms employed by both gram-positive (Staphylococcus and Streptococcus genera) and gram-negative (*E.coli*) organisms isolated from bovine milk samples and *Klebsiella* spp. Which act as reservoirs for antimicrobial resistance genes (Amalia and Rosemarie, 2023).

Also in Vietnam a study indicated that the infection of *Klebsiella* spp. associated with bovine mastitis are mostly multidrug-resistant. Results from this study provided information about the distribution and characteristics of pathogenic *Klebsiella* spp. infected bovine mastitis that could support dairy farmers/ owners and veterinarians to improve the usage and management of antimicrobial in mastitis treatment, especially with *Klebsiella* mastitis in large-scale herds (My Trung et al. 2023). An increasing number of scientific studies have referred to the new therapeutic procedures that could serve as alternatives to conventional therapy (Tomani et al. 2023, Zeedan et al. 2023). The introduction of new strategies such as nanotherapy; bacteriophage therapy; animal-, plant-, and bacteria derived antimicrobials; and probiotics, among others, are aiming to replace conventional antibiotic treatment, as well as solving the problem of AMR. The main advantage of the listed non-antibiotic alternatives is the absence of resistance development (Sharun et al. 2021, Prusa, 2020). Potential solutions, which have been promoted through the One Health concept, as well as numerous EU regulations, aim primarily at reducing antibiotic usage by 50% by 2030 and giving preference to alternative approaches before conventional drugs are applied (Weiermayer et al. 2022).

### Control of Antibiotic Resistance

First of all, to overcome the issues of antibiotic resistance, the government must release ample funds as well as set new policies. Personalized medicine and appropriate antibiotic therapy for patients can be novel interventions for antibiotic resistances. At an individual level, we can put some of our effort to combat the expansion of antibiotic resistance by using antibiotics only prescribed by doctors who responsible for appropriate indication, dosage, means, and time of drug intake (Saha and Sarkar, 2021). Moreover, strict implementation of infection control measures, proper hygiene and sanitation standards, and appropriate disposal or discharge of medical wastes must be ensured in hospitals and communities (Huttner et al. 2020). Prescribing antibiotics, their proper use and behavioral change of people to wards health management issues can be a strategy to fight antibiotic resistance, Encouraging hygiene measures but discouraging overuse of disinfectants and antimicrobials must be a scheme to overcome the problem of AMR (Rezasoltani et al. 2020, Rusic et al. 2021). Control of the antibiotics usage in poultry farms should be applied to stop developing a new antimicrobial resistance. In addition to the usage of acidifiers, prebiotics and probiotics instead of antibiotics will decrease the chance of developing a new antimicrobial resistance plus producing poultry without antibiotics residue (Bakheet et al. 2018). Finally, the researchers should be act on application of computational biology in combination with nanotechnology can open new avenues to combat the problem of antibiotic resistance (Sultan et al. 2018).

### CONCLUSION

Good knowledge of the mechanisms of action of antibiotics is crucial for developing innovative strategies, as it enables the prediction of putative bacterial defense mechanisms; therefore, each particular antimicrobial strategy can be made more effective and precise. Overuse and the misuse of antimicrobials contribute the spread of antibiotic resistance globally, therefore, efforts must be done to educate people and implement new policies and control programs on how to use and dispense antibiot-

ics. The research centers and drug companies should be encouraged to produce new and innovative antibiotics. To limit the spread of ESKAPE pathogens and antibiotic resistance more generally, it has become imperative to be more careful in surveillance and implementation of antimicrobial stewardship in both human health and food animals. Application of these programs together with the development of new antibiotics or new approaches (e.g. inhibition of biofilm formation and bacteriophage therapy) are likely the only way to slow the spread of multi-drug resistant strains worldwide.

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