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Review Article

TRANSFER OF ANTIMICROBIAL RESISTANCE GENE THROUGH LIVESTOCK FOOD PRODUCTS AND ITS IMPACT ON HUMAN HEALTH

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ABSTRACT: Antimicrobial resistance (AMR), is a chief worldwide public health concern with grave health and socio-economic repercussions. Besides improper use of antibiotics, exposure to contaminated water or soil, and close contact with infected individuals; consumption of food products derived from animals carrying antimicrobial-resistant bacteria and genes is a major pathway for transferring AMR to humans. The occurrence of antimicrobial resistance in bacteria can result from both innate and acquired mechanisms, and its spread among bacteria is contributed by the environment, animals, and humans. Analysis of available data shows that non-therapeutic antimicrobial administration to animals increases resistance rates in bacteria in their gut and surroundings. The food supply chain facilitates the transfer of genes associated with AMR and despite considerable efforts to restrict antibiotic overuse, numerous regions of the world are witnessing a surge in clinical antibiotic resistance rates. To address this multifaceted resistance issue effectively, a "One Health" approach is critical, along with concerted efforts across all sectors. Considering the importance and scientific concern of this emerging public health issue, a thorough review of the available literature on the transmission of AMR from animal-derived foods to humans is presented in this paper.

Keywords: Antimicrobial resistance, Livestock products, AMR gene transfer, One health perspective.

INTRODUCTION

The discovery of antibiotics in the 1940s was a transformative event in the history of medicine, and it significantly impacted both human and animal health. Originally designed to treat life-threatening diseases, antibiotics are now widely used to prevent infections in surgical patients, protect cancer patients, stimulate growth, and promote the health of livestock and other food animals. However, the emergence of bacterial populations resistant to multiple antibiotics, including those used as last resort, is an escalating concern, and its impact has progressed from a minor issue to a severe global hazard, regardless of the wealth of a country or the efficacy of its healthcare system. Bacteria can be found in every living organism, as well as in the soil, water, air, and foods, and due to the interconnectedness of ecosystems, there is a continuous transfer of germs. Thus, the antimicrobial resistance (AMR) crisis is no longer limited to the medical sciences, and a multidisciplinary approach involving microbiologists, epidemiologists, evolutionary biologists, engineers, ecologists, sociologists, policymakers, governments, and NGOs is necessary to combat this complex problem [1].

The use of antibiotics in agriculture has been linked to antimicrobial resistance in human infections and even consumption of food is considered a potential means of transmitting antimicrobial-resistant bacteria

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and genes to humans [2]. Antibiotics are administered to animals for various purposes, including the treatment, prevention, and control of diseases, as well as the promotion of growth and improving feed efficiency. Antimicrobial Growth Promoters (AGPs) were first introduced in the mid-20th century when sub-therapeutic doses of antibiotics were found to improve the feed-to-weight gain ratio for poultry, beef cattle, and swine [3]. However, later the administration of antimicrobial growth stimulants has been associated with the presence of antimicrobial-resistant bacteria in farm workers and animals [4], leading to the prohibition of all antimicrobial compounds as AGPs by many countries since the year 2000. A major public health concern in the twenty-first century, according to the World Health Organization, is the rise of bacteria and other viruses that are resistant to antibiotics [5].

An inability to properly treat human illnesses may be a result of the overuse or underdose of antimicrobials used for infection management, prevention, and treatment in animal husbandry and human clinics [1, 5]. One major cause of treatment failure is the eating of potentially resistant bacteria-carrying animal products such as meat, fish, eggs, milk, and dairy products. Indirect routes of transmission for antibiotic-resistant bacteria include contaminated food or drink, human-to-human contact, and the colonized or diseased animals' own fluids, excretions, and secretions. It has been shown that zoonotic transmission occurs because animals raised for human consumption serve as reservoirs of bacteria that contain antimicrobial-resistant genes [6]. This review aims to provide an impartial discussion on the transmission of AMR from animal-derived foods to humans.

THE ANTIMICROBIALS

Substances that can kill or prevent the growth of microorganisms including fungi, parasites, viruses, and bacteria are known as antimicrobials. They play a critical role in treating infectious diseases in humans and animals, and in preventing the spread of harmful pathogens in food production and healthcare settings. Antimicrobials can be classified into various types, including antibiotic, antiviral, antifungal, and anti-parasitic. Among all antimicrobials, the most common ones are those designed to kill or inhibit the growth of germs in animals and people alike [7]. The indiscriminate use of antibiotics in animals is generally associated with the development of AMR bacteria, so our discussion will be mainly focused on these antimicrobials.

ANTIBIOTICS-MODE OF ACTION

Due to differences in structure and affinity for specific target areas within bacterial cells, antibiotics have varying mechanisms of action (Fig. 1).

Inhibitors of cell wall synthesis

The cellular structures of humans and animals lack cell walls, whereas such walls assume a critical role in the survival of bacterial cells. Therefore, one promising approach to treating bacterial infections is the selective targeting of cell walls with antimicrobial medicines. The antibiotic family includes medicines that work in this way, including penicillin, cephalosporin, bacitracin, and vancomycin [8].

Inhibitors of cell membrane function

The cell membrane represents a vital component of the cellular architecture that functions as a selectively permeable barrier, regulating the influx and efflux of various solutes. Cellular viability and survival hinge on the preservation of this membrane, as any harm or disturbance might threaten the delicate cellular environment. While antimicrobials that target the cell membrane have a wide range of effectiveness, their lack of selectivity presents considerable dangers when administered systemically in eukaryotic hosts, such as humans and animals. Thus, topical applications are the favored clinical approach. Polymyxin B and colistin are two examples of drugs that operate using this mechanism [9].

Inhibitors of protein synthesis

Bacterial growth and survival depend on protein synthesis, a basic biological function. In order to inhibit bacterial protein synthesis, several antibiotic classes bind preferentially to the cytoplasmic 30S or 50S ribosomal subunits. Bacterial mortality or reduced proliferation potential may ensue from the subsequent disruption of regular cellular metabolism [10]. Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, and tetracyclines are the antibiotics that function through this mechanism.

Inhibitors of nucleic acid synthesis

Genetic material, including DNA and RNA, is essential for the correct transmission of hereditary information during reproduction in bacteria and other living creatures. Some antibiotics work by attaching selectively to different parts of DNA or RNA production, which disrupts normal cellular processes and eventually kills bacteria [11]. Examples of such antibiotics include quinolones, metronidazole, and rifampicin.

Inhibitors of other metabolic processes

Several antibiotics selectively target critical cellular processes essential for the survival of bacterial pathogens. Both sulphonamides and trimethoprim exert their effects by impeding a metabolic route known as the folic acid pathway. Sulphonamides selectively target dihydropteroate synthase, whereas trimethoprim inhibits dihydrofolate reductase, both of which are enzymes necessary for bacterial vitamin folic acid synthesis [12].

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance denotes the capability of microorganisms to withstand the growth-inhibiting or lethal effects of antibiotics beyond their normal susceptibility. Any agent that can reduce bacterial counts or kill germs is considered an antimicrobial, including chemical biocides used for disinfection in food production environments and antibiotics used for the treatment of bacterial infections in humans and animals. The effectiveness of antibiotics in killing or inhibiting the growth of microbes can be compromised if the microorganisms develop resistance, thereby making them less susceptible to the antibiotic's effects. Antimicrobial resistance in bacteria can arise through both innate and acquired mechanisms.

Innate resistance

Resistance that is inherent to microbes is called innate resistance. To put it simply, antimicrobials cannot overcome intrinsic resistance because it is a natural process that occurs in all members of a certain species. The resistance to antimicrobials is a property that is determined by chromosomes and is closely linked to the overall physiology of the microorganism. In identical environmental conditions and antimicrobial concentrations, innate mechanisms are likely responsible for differences in antimicrobial resistance that occur among various types, genera, species, and strains of microorganisms [13].

Acquired resistance

Acquired resistance can result from either the horizontal transmission of resistance genes or the vertical evolution of structural or regulatory genes [14]. The fast development of antibiotic resistance among several human and veterinary bacterial genera can be attributed to horizontal gene transfer (HGT), the process by which some bacteria acquire resistance through the exchange of mobile genetic components such as transposons, plasmids, and integrons [15]. However, the selection pressure that develops from the long-term abuse of antibiotics is the primary mechanism that causes resistant bacteria to evolve and spread [16]. While antimicrobials are effective against some bacteria, they are often ineffective against resistant strains that have acquired mechanisms to protect themselves from being killed [5].

Mechanism of horizontal gene transfer (HGT)

Conjugation, transformation, and transduction are the three most common possibilities through which bacteria engage in HGT. Certain genetic structures, such as plasmids, integrons, and transposons, greatly aid in the horizontal transmission of genes that confer resistance to antibiotics, their persistence in bacterial populations, and the emergence of resistance to many drugs. Given that they can spread from one location to another, these segments of DNA are called mobile genetic elements (MGEs). The environment, attributes of the recipient and the donor populations, and the MGEs play important roles in determining how often HGT occurs. In nature, there may be additional, less common ways of DNA transfer besides transformation, transduction, and conjugation. Some examples include the movement of genes for virulence and antibiotic resistance through vesicles formed by fusing cells, the transmission of viruses through particle-like structures, and the merging of whole genomes by cellular fusion [17].

Conjugation

An undeviating connection between the recipient and donor cells is necessary for conjugation, the transfer of DNA from one live bacterial cell to another. Plasmids, transposons, and other mobile elements frequently carry antimicrobial resistance genes, while insertion elements, integrons, and genomic islands may also be carriers. It is known that transposons and insertion sequences can move around and inside bacterial cells. Complex assemblies may form from transposable elements and plasmids. A plasmid or transposon can be conjugative or non-conjugative, and either can be transferred through conjugation. Due to the abundance of antimicrobial resistance genes found on mobile elements like plasmids and transposons, conjugation is believed to be the principal mechanism by which bacteria pass these genes to one another [18].

Transduction

The process of transduction is facilitated by bacteriophages. The bacteriophage first binds to the

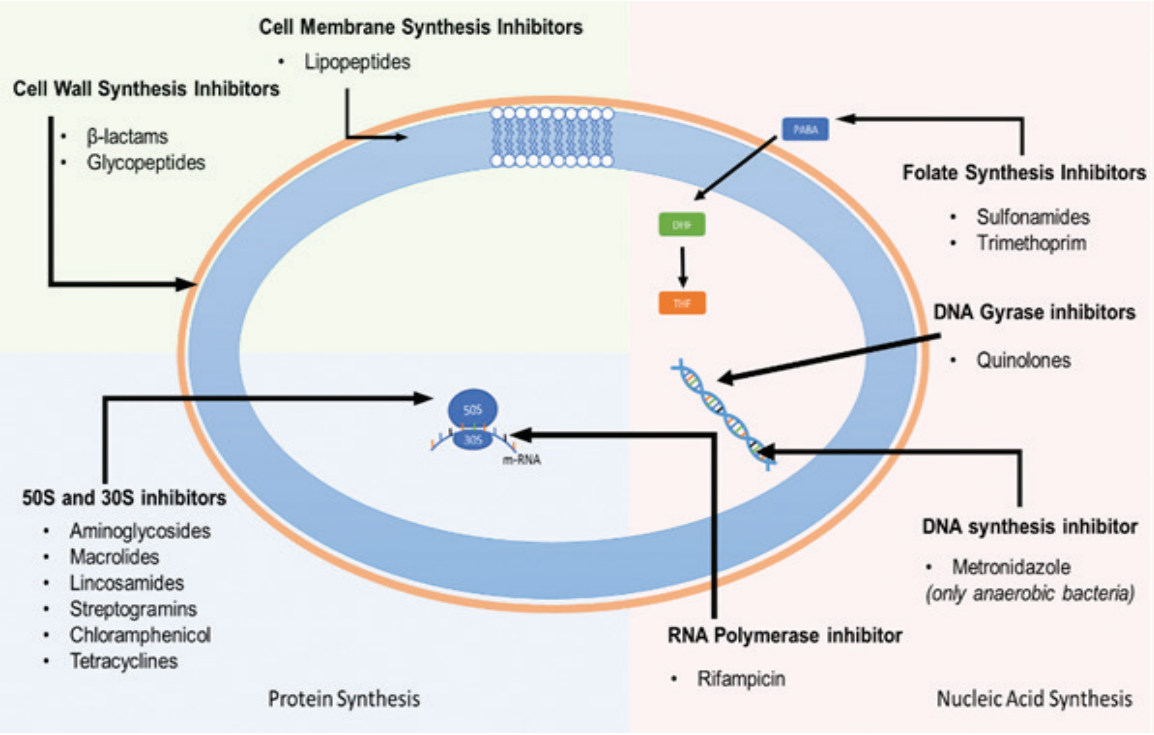

Fig. 1. Mode of action of antibiotics.

bacterium, injecting its genetic material and maybe some of the host bacterium's DNA. DNA needs to be stabilized after entering the bacterial cell, and this can be done by either becoming an independently replicating element or by integrating it into the bacterial genome [19]. The foreign DNA can drive the generation of new phage particles after it has become stable within the bacterial cell. Depending on the kind of phage, this process can be used to transfer genomic DNA of varying lengths from one bacterium to another. A close relationship between bacterial strains is usually necessary for transduction to occur, as bacteriophages are extremely host-specific. The transduction capability of a phage, on the other hand, is not limited to infecting bacteria alone but can reach a far wider variety of organisms [20].

Transformation

The acquisition of bare DNA from the environment by bacteria is known as bacterial transformation. In the stages of transformation, some bacteria at a certain moment in their development cycle, or some bacteria after death and lysis, liberate DNA in the environment. Once that happens, the DNA is successfully absorbed into the recipient bacterial cell present in the nearby environment. The DNA is not degraded by the nucleases of bacteria. Finally, the DNA that has been integrated is expressed [21].

RESISTANCE AGAINST ANTIBIOTICS

There are a number of mechanisms by which bacteria might acquire antibiotic resistance, including the enzymatic destruction of antibiotics, the change of antibiotic targets, alterations to the permeability of bacterial cell walls, and the use of alternate pathways to avoid the activity (Fig. 2).

Enzyme-mediated breakdown or modification

Antibiotic resistance frequently arises through the enzyme-mediated breakdown or modification of antibiotics. Enzymes called β-lactamase can break down the β-lactam ring of β-lactam drugs such as cephalosporins, which can lead to Gram-negative bacteria developing resistance to certain antibiotic classes [22]. The inactivation of aminoglycosides by phosphotransferases, nucleotidyltransferases, and acetyltransferases is another family of antibiotics where enzymatic degradation is a significant route of resistance [23]. There are numerous different forms of each of these enzymes, each with a narrower or broader range against a particular antibiotic.

Target modification

Antibiotic resistance due to target modification occurs when an antibiotic's intended target molecule (often an enzyme) undergoes a change that renders the antibiotic ineffective at binding to its intended target.

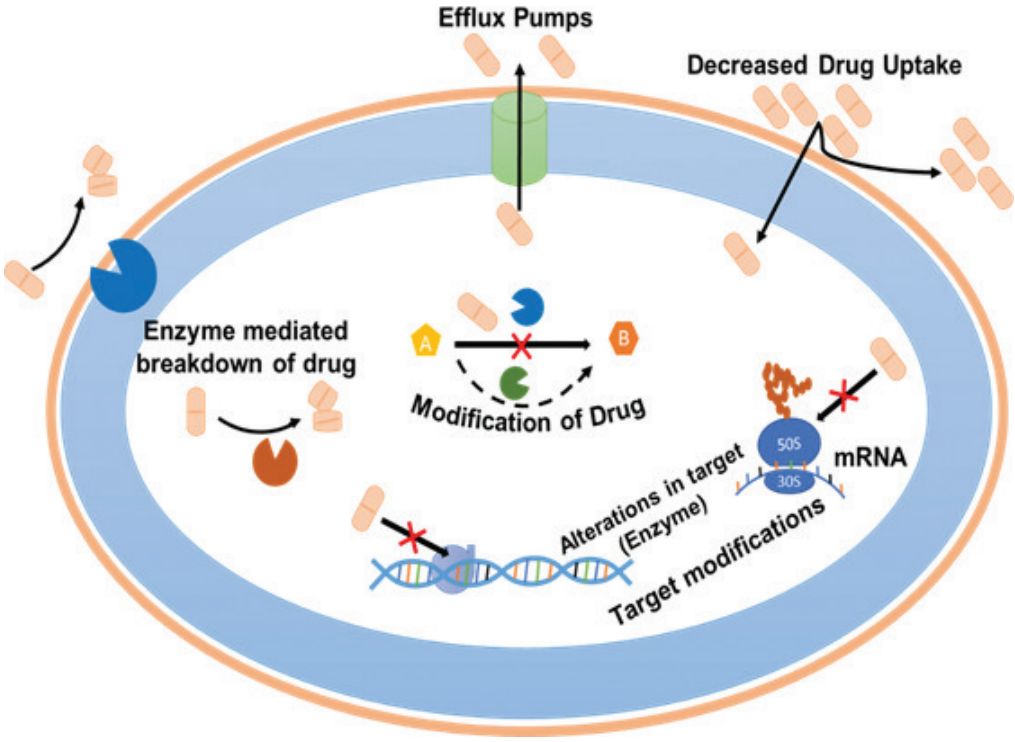

Fig. 2. Mechanism of antibiotics resistance.

Among these mechanisms are mutations affecting the topoisomerase and gyrase genes, which are the targets of antibiotics such as quinolones and fluoroquinolones [24]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an illustration of a horizontally transmissible target alteration. The mecA gene in MRSA encodes for a penicillin-binding protein PBP2A variant with an extremely low affinity for β-lactams. β-lactams inhibit all PBPs except the low-affinity PBP2A [25].

Regulating the internal concentration of antibiotics

To control the amount of antibiotics inside the cell, one must change the permeability of the cell wall or envelope, either by reducing entrance or increasing efflux. Antibiotic penetration into a cell can be influenced or blocked by modifications to cellular pores. Tetracycline resistance is an example of how particular increases in efflux can be achieved through the acquisition of genes [26]. However, an increase in efflux can also occur because of the over-expression of efflux pumps that are normally present in the body, leading to a phenotype that is resistant to many drugs. There is a lack of consensus on the therapeutic significance of the discrete resistance levels created by such efflux pumps.

Adaptive resistance

Adaptive resistance occurs when cells add an extra step to their normal physiological route. In most cases, this is due to a surplus of a certain enzyme. The E. coli and Citrobacter sp. produce an extra dihydrofolate reductase that is resistant to the antibiotic trimethoprim due to the presence of R plasmid. This enzyme binds to many anti-folate compounds differently than the chromosomal enzyme [27]. Quorum sensing was found to exist alongside the mentioned mechanisms. Density sensing, or quorum sensing, is a physiological process of bacteria that regulates a wide range of functions [28]. Quorum sensing (QS) processes are found in both Gram-negative and Gram-positive bacteria, but the signal molecules they utilize to exchange information are distinct. By allowing cells within microbial consortiums to receive signal molecules, quantum sensing (QS) is essential for defining microbial relationships. This triggers a chain reaction that causes genes to be expressed. Because of this, QS can affect food intake and the ensuing metabolism of substances and energy, as well as the architecture of microbial communities by modifying microbial interactions to quickly respond to and adapt to changing circumstances [29]. The QS system controls several aspects of bacterial biology, including

Table 1. Antibiotic resistance genes (ARGs) in fermented foods.

Sample	ARGs	Antibiotic Class	Reference
Dry-cured fermented pork meat product Cheese *L. paracasei* (starter culture) cow , buffalo and ewe's milk	*ermB*, *ermC*, *tetL*, *tetM*, *tetS*, *tetW*	Erythromycin Tetracycline	[82]
Fermented milk *Lactobacillus spp. Streptococcus thermophillus*	*tet*M, *str*A, *str*B, *sul*1	Tetracycline Streptomycin Sulphonamides	[83]
Yogurt , Whey - fermented milk, Dahi, Buttermilk *L. acidophilus, L. brevis, L. elbrueckii* subsp. *Bulgaricus, L. fermentum, L. kefiri, L. plantarum*	*ermB, tetM, tetS* *ant* (*6*), *aph* (*3'*)-*III*	Erythromycin Tetracycline Aminoglycoside	[84, 85]
Cheese *L. casei, L. curvatus, L. fermentum, L. paracasei, L. pentosus, L. plantarum, L. plantarum, L. sakei*	*ermB*, *ermlF, tetM* *aadA*, *aadE*, *aph*(*3'*)-*III*, *vatE-1*	Erythromycin Tetracycline Dalfopristin	[86]
Italian fermented dry pork sausages (*Lactobacillus* spp.)	*tet*(M) ,*erm*(B)	Tetracycline Erythromycin	[87]
Portuguese fermented meat products (*L. sakei*)	*tet*(M)	Tetracycline	[88]

bioluminescence, virulence factors, and tolerance of disinfectants, spore formation, toxin generation, motility, biofilm development, and drug resistance [30]. Bacteria control the behavior of their entire population through the production and secretion of signal molecules, which are also called self-inducing molecules [31]. When the concentration of signal molecules reaches a certain point relative to the density of the bacterial population, genes can be activated to control the adaptability of the bacterial population.

ANTIMICROBIAL RESISTANT BACTERIA AND ITS GENE IN LIVESTOCK FOOD PRODUCTS

The use of antibiotics in cattle production is widespread, serving multiple purposes: illness prevention, control, and growth stimulation. On the other hand, antibiotic resistance can be accelerated in animal husbandry due to the antibiotics' abuse and misuse. Bacteria that are resistant to antibiotics can live in the guts of farm animals and spread to people when they eat food that has been contaminated. This can occur when meat, poultry, eggs, or dairy products from animals carrying resistant bacteria are consumed without proper cooking or heat treatment. It is evident that the use of antimicrobials in animal production and subsequent transmission of resistant microorganisms to humans is heavily reliant on the animal-based food supply chain. Antimicrobial use in animal husbandry has declined during the past decade, yet the problem persists in many farming operations. Furthermore, the animal microbiome has been impacted by the misuse of antimicrobials since the mid-century. Research on the possibility of antibiotic-resistant bacteria or their genes in foods derived from animals is reviewed here.

Beef

Antimicrobials are used in beef cattle production from the beginning of their lives and rising rates of bacterial resistance to antibiotics have been documented in various sectors of the cattle industry and the food supply. Cattle are characterized as "super-shedders" because they shed more *Escherichia coli* O157 than other livestock. Due to the high risk of human infection, especially due to environmental contact, super-shedding has serious ramifications concerning the epidemiology of *E. coli* O157. The Tetracycline resistance protein tet(O) is primarily responsible for promoting tetracycline resistance, which is associated with other resistance mechanisms like ribosome protection and efflux pumps, and is frequently produced through the acquisition of the tet gene [32]. A rise in the prevalence of bacteria harboring tetracycline resistance genes like tet(A), tet(B), and tet(M) has been linked to the extensive use of chlortetracycline [33]. The blaCTX-M gene, which consults resistance to third-generation cephalosporins, was recently found in *E. coli* isolated from bovine fecal samples, confirming the presence of

ESBL-producing *E. coli* in these samples [34]. The Gram-negative bacterial plasmids belonging to the Enterobacteriaceae group create extended-spectrum β-lactamases, which are enzymes that are already resistant to β-lactam antibiotics. *Escherichia coli*, or *E. coli*, is the most well-known ESBL-producing bacteria and is frequently cited as a primary cause of sepsis, pneumonia, and urinary tract infections (UTI). The most prevalent ESBL enzyme in humans is CTX-M β-lactamase, with subtype variations according to region. These nosocomial infections, which produce ESBLs, are becoming more prevalent as infectious agents in the population. In the veterinary industry, ESBL-producing microorganisms are frequently encountered. To determine if these ESBL bacteria are present in both sick and healthy cows, pigs, and poultry farms, research on these bacteria in livestock is crucial [35]. Analysis of plasmids from six isolates revealed that all three AMR genes (blaCTX-M-1, sul2, and tetA) were found clustered together on the same plasmid. Thus, the use of several antibiotics, such as cephalosporin, sulphonamide, and tetracycline, might co-select for the same plasmid [36]. In a similar manner, studies have shown that beef can disseminate blaCTX-M, blaTEM, blaSHV-12, and blaCMY-2 ESBL genes, the latter of which is responsible for plasmid-mediated coding AmpC lactamase resistance (*e.g.*, IncF, IncI1, IncN, and IncHI1) gene transfer [37]. Genes for resistance to vancomycin glycopeptide can be transferred between bacteria, as seen with vanA, which is found mostly in *E. faecium*, and vanB, which is found in both *E. faecium* and *E. faecalis*, and vanC-1, which is responsible for resistance in *E. gallinarum* [38]. These results are very worrisome because vancomycin is often the last line of defense against methicillin-resistant *Staphylococcus aureus* (MRSA) infections in humans. Additionally, MRSA carries resistance to β-lactams via the mecA gene, which encodes a distinct kind of penicillin-binding protein, PBP2a. This protein has a low affinity for certain compounds, giving it the ability to withstand their effects [29]. *S. aureus* bacteria isolated from beef samples exhibit antimicrobial resistance genes, namely gyrA, and gyrB, which provide resistance to fluoroquinolones [39, 40]. Most cases of *Campylobacter* spp. having a cfr gene, that is resistant to a variety of antibiotics - including tetracycline, oxazolidinones, pleuromutilins, lincosamides, and fluoroquinolones - occur in cattle and fowl.

Poultry

Disease control and treatment as well as growth promotion necessitate the use of antimicrobials in the rapidly expanding poultry sector. In recent years, researchers all over the world have focused on how antimicrobials affect the fecal microbiota of birds; as a result, many ARGs are often identified in fecal samples from poultry. It is commonly believed that chicken is a major reservoir for *E. coli* bacteria, and thus, one of the primary matrices responsible for harboring several ARGs. The bla genes blaTEM, blaSHV and blaCTX-M are the most common types in this matrix [41]. The mcr-1 gene, which codes for polymyxin resistance, has been found in *Salmonella* spp. recovered from chickens, while the mecA, blaZe, and tetK genes, which confer resistance to antibiotics in S. aureus, have been found in poultry products [42]. Moreover, *Enterococcus faecalis* with the erm(B), tet(L), and tet(M) resistance genes, as well as optrA, which imparts resistance to lincosamides, one of the final alternative drugs in humans for treating infections, have been isolated from chicken products [43, 44]. Chicken is also a major reservoir of *Klebsiella pneumoniae*, which is a significant human foodborne pathogen. One important characteristic of these bacteria that are resistant to antibiotics is the presence of ARGs that encode ?-lactam resistance, like blaSHV, blaCTX-M-1, and blaCTX-M-10. One possible route of infection in humans with *Yersinia* spp. (having an antibiotics-resistant gene) is through eating chicken [45].

Pork

Pig production makes extensive use of antimicrobials. There is a correlation between the manufacture of these drugs - which are used for both medical purposes and to boost growth - and the emergence and transmission of bacterial strains that are resistant to antibiotics. Additionally, a correlation between resistance genes in pig feces at birth and after slaughter was established, indicating that these ARGs persist in the fecal microbiome and, by extension, in the intestinal microbiome of these animals [46]. The antimicrobials used in swine production have been linked to the presence of *E. coli* ARGs in pig waste, carcasses, and sausages. Most reported are those that confer resistance to beta-lactams (blaTEM, blaCTX-M, blaSHV, and blaOXA), aminoglycosides (ant(3)-I), gentamicin (aac(3)-I), and florfenicol (floR) [47]. The greater prevalence of the mcr-1 gene in pig samples relative to human isolates suggests that mcr-1 genes found in human *E. coli* are acquired from

consuming pork [48]. The presence of *Salmonella* spp. in pork, as reported by Cameron-Veas and coworkers [49], poses public health risks due to the pathogen's resistance to multiple antibiotics, including ampicillin, streptomycin, and sulphonamides, used routinely in humans. Multiple reports have shown that swine bacterial isolates are resistant to many different classes of antibiotics, including aminoglycosides (aphA1, aadA, aadA2, aac(3) IV), sulphonamides (sul1), cephalosporin (blaTEM, blaCTX-M-1 and blaCTX-M-14), trimethoprim (dfrA12) and tetracyclines (tet(A), tet(B)). Additionally, multidrug-resistant strains of *Salmonella typhimurium* have been discovered, highlighting the significance of pork-based foods as human resistance gene carriers [49]. It was discovered in 2013 that the erm(B) gene was positioned on a chromosomal island that confers resistance to numerous antibiotics and it mediates the natural transfer of macrolide resistance between *C. jejuni* and *C. coli* isolated from pigs [50]. Therefore, consuming pork can expose you to harmful levels of resistant bacteria.

Fish

Aquaculture is among the fastest-expanding food production systems globally. Horizontal gene transfer, recombination, and mutation in the human gut microbiota can be facilitated by the widespread use of antibiotics in fish and aquaculture, which in turn leads to bacterial resistance. Utilizing pig and poultry dung as fertilizers during the fish-rearing process is a common practice in integrated fish farming. Numerous resistance genes have been discovered in bacteria that have been isolated from sediments and water used for fish farming. A few examples of these genes are the fox-ampC β-lactamase resistance gene, the sulphonamide resistance genes (sul1 and sul2), the class 1 integron, the tetM ribosome protection gene, and the tetA, tetB, tetC, and tetG efflux pump genes [51]. Multiple types of bacteria, including *E. coli*, and *Vibrio parahaemolyticus* can infect fish, and researchers in Vietnam found that *E. coli* isolated from fish had the ability to produce ESBL and showed decreased susceptibility to tetracycline, trimethoprim/sulfamethoxazole, ampicillin and cefotaxime [52]. They may also harbor beta-lactam resistance genes, notably blaCTX-M group 1 and blaTEM, the latter of which codes for extended-spectrum beta-lactamase. Moreover, since the use of chloramphenicol is now restricted in Vietnam, the detection of chloramphenicol resistance suggests that excessive use in the past had a lasting impact on the bacterial ecosystem [53]. Highly resistant strains of *Enterococcus* spp. harboring the erm(B) gene for erythromycin and the tet(M), tet(L), and tet(S) genes for tetracycline resistance as well as streptomycin resistance gene aadE, were identified from a farm that raises both fish and poultry [54].In salmon farming, sul1 and sul2, strA, and strB, tetA and tetG, blaTEM, dfrA1, dfrA5, and dfrA12 are the most significant AMR genes [55]. Salmon-isolated *E. coli* has also been discovered to carry quinolone resistance genes like those identified in human patient-isolated bacteria. This is concerning since it indicates that horizontal ARG transmission between aquatic microorganisms and human infections is possible and that the resistant bacteria in concern were likely picked up via the ingestion of contaminated fish [56].

Milk and dairy products

As one of the most commonly consumed animal-based foodstuffs, milk significantly impacts the economies of various countries and provides a vital source of income for numerous families. Additionally, this product is used as a raw material in manufacturing several different products. Many different kinds of bacteria can be found in milk and other dairy products. Preventing the spread of infections such as mastitis often involves the use of antimicrobials, but their long-term administration increases the risk that the bacteria being targeted will become resistant, making it more challenging to treat animals infected with these pathogens [57]. High levels of ARGs, including erm(B), blaARL, and tet, which are liable for resistance from antimicrobials generally used in humans, were recognized in isolated *Staphylococci* from milk samples of cows going through antimicrobial treatment [58]. Similarly, isolated *S. aureus* from a tank containing bulk milk has been found to exhibit a functional mecA gene [59]. Dairy products can also serve as a habitat for methicillin-resistant *Staphylococcus aureus* bacteria. *Staphylococcus* spp. strains isolated from milk and dairy products had high levels of the msr resistance genes (msrA and msrB), which activate a drug efflux mechanism and confer resistance to macrolides and streptogamine B [60]. Raw milk and its products, such as cheese, are common sources of E. coli. These are frequently reported to be resistant to streptomycin, tetracycline, and ampicillin. Dairy cows are natural hosts for *Campylobacter* spp., and as a result, milk and dairy food products are often referred to as their "reservoirs." The *Campylobacter* spp. isolates that were collected from milk and products showed high resistance to antibiotics like tetracycline, nalidixic

Table 2. Antibiotic-resistant bacterial food-borne zoonosis.

Sample	Human Patient	Antibiotic Resistance	Related information	Reference
Beef cattle (ground beef) receiving chlortetracycline AGP	Salmonella-infected patients with diarrhoea	Ampicillin, Carbenicillin Tetracycline	Direct genetic tracking of resistance plasmid from hamburger meat to infected patients.	[89]
Swine and chickens	Hospital patients with diarrhoea	Vancomycin	Clonal spread of *E. faecium* and horizontal transmission of the *vanA* gene cluster (Tn1546) found between animals and humans.	[90]
Raw chicken products from processing establishment	Infected people	Multi drug resistance	The 2018 outbreak strain of *Salmonella infantis* has been identified.	[91]
Chicken sandwiches	Bacteremic patients *Salmonella enteritidis*	Nalidixic acid resistance	Outbreak reported in Cauca, Popayan, Colombia.	[92]
Raw meat, animals	*E. coli* - infected indoor patients	Colistin resistance	A retrospective study from 2011 to 2014 showed plasmid-mediated mcr-1 transfer.	[48]
Chickens (slaughtered) Poultry products	Bacteremic hospital patients symptoms of urinary-tract infections (UTIs), bacteremia, and neonatal meningitis	Ciprofloxacin	Multiple molecular and epidemiological typing modalities demonstrated avian source of resistant *E. coli*.	[93]
Pork isolates, the swine herds, slaughterhouse	Bacteremic patients *S. typhimurium* outbreak in Denmark	Nalidixic acid resistance and reduced fluoroquinolone susceptibility	PFGE revealed that a unique resistance pattern.	[94]

acid, and ciprofloxacin [61]. High levels of ampicillin, tetracycline, and amoxicillin resistance have been reported in *Helicobacter pylori* isolates identified from bovine, ovine, and caprine milk [62]. Scientific research has shown that *Listeria monocytogenes* that are isolated from raw milk exhibit a high level of resistance to tetracycline but are sensitive to ampicillin. Because of the widespread use of tetracycline in some countries to prevent infections in the dairy industry, these bacteria have developed resistance to numerous antibiotics [63]. Also, tetracycline and erythromycin resistance genes were shown to be more prevalent in *Enterococcus faecium* which was isolated from mastitic milk samples. The most common erm genes (ermA, ermB, and ermC) and tet genes (tetK, tetL, tetM, tetO, and tetS) were the most frequently discovered [64]. Researchers have shown that *Bacillus cereus* isolated from pasteurized milk had decreased susceptibility against β-lactams like penicillin and ampicillin [65].

Eggs

Bacteria, such as pathogenic *E. coli* can be transmitted from eggs to humans. One study has found that the pathogenic *E. coli* in eggshells had bla genes like blaCTX-M-2, and blaTEM, as well as tet genes like tet(A), tet(B), and tet(C), which characterize resistance to antimicrobials like ampicillin, streptomycin, and tetracycline. Therefore, ARGs can enter the food chain through tainted eggshells [66]. Eggs are a common route for *Salmonella enteritidis*, one of the most common human pathogens. Researchers reported that these bacteria, which were found in chicken eggs and ovaries, harbor β-lactam-resistant (blaCTX-M-1) and fluoroquinolone-resistant (qnrS1)

ARGs [67]. The finding of genetic similarities between methicillin-resistant *Staphylococcus aureus* (MRSA) from human and egg samples provides additional evidence that resistance genes might propagate through the food chain [68]. The β-lactam antimicrobials, such as ampicillin and lincomycin, are ineffective against *Campylobacter* spp., while aminoglycosides, tetracyclines, erythromycin, and fluoroquinolones are ineffective against *Enterococcus* spp. [69, 70].

Fermented animal products

The high concentrations of beneficial bacteria found in fermented foods, including *Lactobacillus* spp., are ingested and find their way to the human digestive system [71]. Research on the isolation and identification of bacterial ARGs in fermented meals made from meat and milk is listed in Table 1.

HUMAN HEALTH IMPLICATIONS OF AMR

One of the most usual ways in which bacteria and their genes for resistance to antibiotics are transferred from animals to humans is via the food chain. The foods that harbor antimicrobial resistance genes, either as whole bacteria or DNA fragments or as bacteriophages, may pose a risk to public health indirectly by expanding the genetic pool of which harmful bacteria might acquire and potentially spread such genes to other pathogenic bacteria. Retail raw foodstuffs like milk, meat, and eggs, as well as processed foods like fermented meat, dairy products, and products containing raw eggs, might have harmful bacteria due to the absence of pasteurization. Some of these bacteria, when used as a starter culture, may create favorable changes in the associated foods, while others may cause spoiling or food-borne illness. Symptoms of bacterial food-borne diseases include diarrhea, abdominal cramping, nausea, vomiting, headaches, and fever. Antibiotics are not usually needed until the infection persists or spreads. Severe infections in the elderly, infants, children, pregnant women, and immune-compromised patients typically necessitate antibiotic therapy [72]. When antibiotics are used in animal feed, farmers and others who deal closely with food-producing animals are at increased risk of contracting antibiotic-resistant flora due to exposure to bacteria found in animal populations [73]. The majority of the population, however, picks up AMR microorganisms from eating contaminated animal products. By 2050, the number of deaths caused by illnesses due to resistance to antibiotics is expected to rise from seven lacs per year to ten million per year, with associated healthcare and reduced productivity expenses exceeding $100 trillion USD [74]. Due to the global nature of this problem, increasing incidences of clinical antibiotic resistance are being detected in nations that have taken strong measures to reduce antibiotic use [75]. According to the World Health Organization, "the highest priority, critically important" antibiotics include those that belong to the macrolide, third - and fourth-generation cephalosporin, glycopeptide, fluoroquinolone, and polymyxin families [76]. Table 2 provides snippets from research that found a link between human food-borne illness and resistant bacteria found in animals and animal products.

A retrospective study of 10 years studied the *Salmonella* strains containing the mcr-1 gene from the investigation of diarrheal outpatients on the consumption of meat products in Shanghai Municipality, China [77]. Orsi and co-workers observed that outbreaks of human listeriosis were possibly caused by lineage II isolates, which were also confirmed in 26% of the illegally imported meat items [78]. According to a study done in the US, tetracycline-resistant clone SA of *C. jejuni* in patients who contracted the infection by drinking raw milk displayed patterns similar to those of raw milk isolates on pulsed-field gel electrophoresis [79]. A case study reported women patients having urinary tract infections due to *E. coli* which is resistant to ampicillin or cephalosporin, through ingestion of retail meat foods mainly chicken and pork products [80]. Similarly, resistance to various antimicrobials was shown in *L. plantarum* and *L. fermentum* strains isolated from yogurt and the human gut [42]. In humans, Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are treated with vancomycin as a last resort [81]. The existence of *Enterobacteriaceae* having carbapenem-resistant has been known for the past two decades, but the spread of carbapenemase-producing *Enterobacteriaceae* (CPE) around the world is a newer problem because carbapenems are the last option drugs capable of curing bacterial infections from the gram-negative organism in humans [5]. Therefore, it is reasonable to conclude that antimicrobial resistance leads to a threat to life expectancies in the event of serious infections since it causes patients to suffer for longer, require hospitalization more often, and possibly die due to treatment failures [76].

FUTURE PROSPECTS

Finding antimicrobial substitutes is crucial for reducing their usage in livestock farming. Public awareness about the risks associated with consuming raw foods wants to be increased. Further research is essential to recognize the mechanisms responsible for the spread of antibiotic resistance genes (ARGs) in farms. Exploring the extent of horizontal transfer (HGT) of ARGs from microorganisms to humans through food is a critical area of investigation. Collaborative and interdisciplinary investigation on ARG pathways of animal-based foods to the human GI tract is urgently needed. Investigation into improved source management, including enhanced ARG removal efficiency during livestock product processing, is also necessary. Additionally, further monitoring initiatives should be implemented in parallel with the current antimicrobial resistance observing system.

CONCLUSION

The prevalence of antimicrobial resistance genes (ARGs) is significantly higher in various livestock reservoirs, highlighting the role of animal-derived food products as a significant basis of ARGs. The extensive use of antimicrobials in the poultry industry has led to the presence of bacteria carrying ARGs in eggs. Similarly, the swine production system, characterized by widespread antimicrobial usage, has contributed to the emergence and dissemination of ARGs. The interconnectedness of fish farming systems with pig and poultry production further exacerbates the issue of ARGs in fish. The ingestion of milk and milk products also leads to a potential avenue for the transmission of ARG-carrying bacteria to consumers. The widespread antimicrobial resistance threatens life in major illnesses, causing patients to suffer longer and sometimes die owing to treatment failures. The judicious and controlled usage of antibiotics in both humans and animals is the need of the hour to mitigate this ever-growing threat of antimicrobial resistance.

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