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Multidrug-Resistant Bacterial Foodborne Pathogens: Impact on Human Health and Economy

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Abstract

The drug abuse known to occur during growth of animals intended for food production, because of their use as either a prophylactic or therapeutic treatment, promotes the emergence of bacterial drug resistance. It has been reported that at least 25% of the foodborne isolates show drug resistance to one or more classes of antimicrobials (FAO 2018). There are diverse mechanisms that promote drug resistance. It is known that the use of sub-therapeutic doses of antibiotics in animals intended for food production promotes mutations of some chromosomal genes such as *gyrA-parC* and *mphA*, which are responsible for quinolone and azithromycin resistance, respectively. Also, the horizontal transfer of resistance genes as groups (“cassettes”) or plasmids makes the spread of resistance to different bacterial genera possible, among which there could be pathogens. The World Health Organization considers the emergence of multidrug-resistant pathogenic bacteria as a health problem, since the illnesses caused by them complicate the treatment and increase the morbidity and mortality rates. The complication in the illness treatment caused by a multidrug-resistant pathogen causes economic losses to patients for the payment of long stays in hospitals and also causes economic losses to companies due to the absenteeism of their workers.

Keywords: multidrug-resistant bacteria, MDR, foodborne pathogens, antimicrobial resistance, MDR bacteria human health, MDR microorganism economic impact

1. Introduction

Increasing antimicrobial resistance (AMR) is a global public health threat. The excessive use and abuse of drug therapies in humans and in the animals intended for human consumption, and its bad disposition as a waste, have tightened up the problem in recent years [1]. This phenomenon affects any person regardless of sex, age, origin, or social status and threatens the ability to effectively solve the treatments of different diseases and also compromises the food security, economy, and development of the countries [2].

Microorganisms are sensitive to antimicrobials when they do not harbor components involved in degrading them. AMR occurs when bacteria, fungi, viruses, and parasites are exposed for a long time to sub-therapeutic doses of drugs such as antibiotics, antifungals, antivirals, antimalarials, or anthelmintics that modify

the ecology of microorganism. In order to contend with the residues present in their environment, microorganisms may acquire genetic elements that allow them to cope with these compounds and survive. In some cases, the use of poor quality drug, counterfeit products, incorrect product, and modified dosage can accelerate the development of microbial resistance. Another relevant factor for development of AMR is the inadequate disposal of waste generated in the agricultural production and pharmaceutical and wastewater treatment plants as they can be spread through the environment [3]. One of the recently described phenomena observed is the association between the emergence of multiresistant microorganisms (MMR) and the increase in the isolates that show the production of extended-spectrum beta-lactamase enzymes (ESBL). Currently, more than 200 varieties of BLEE enzymes are recognized with different substrates, and the frequency of isolates producing these enzymes varies from country to country (from 20 to 48%) [3].

Although there are many factors that favor the spread of antibiotic resistance, it affects different sectors, such as human health, animal health, agriculture, environment, and commercial trade [4]. It is estimated that 700,000 people die each year from infections caused by microorganisms resistant to antimicrobials and a large number of sick animals that do not respond to treatments [5]. Within the agricultural and food industry, resistant microorganisms represent a risk for production that threatens the global economy. For this reason, it is important to implement supervised agricultural regulations and practices that ensure the responsible use of antimicrobials in the production of animals and crops.

2. Mechanisms and propagation of resistance

In microorganisms, drug resistance arises in order to contend against a harmful stimulus that threatens their survival. In bacteria, the mechanisms that confer the resistance against antibiotics could be classified as intrinsic (mutations originating in the organism itself) or acquired by transfer of genetics elements during the replication of DNA (vertical transfer) or from different species or genera (horizontal transfer) [6] (**Figure 1**).

2.1 Intrinsic mechanisms or natural resistance

The intrinsic mechanisms can be found in the cell in a natural manner. They are conditions that are universally found in bacterial species and that are independent of antibiotic selectivity [7]. Some of the intrinsic mechanisms are described below.

2.1.1 Permeability or impermeability of the outer membrane or cell wall

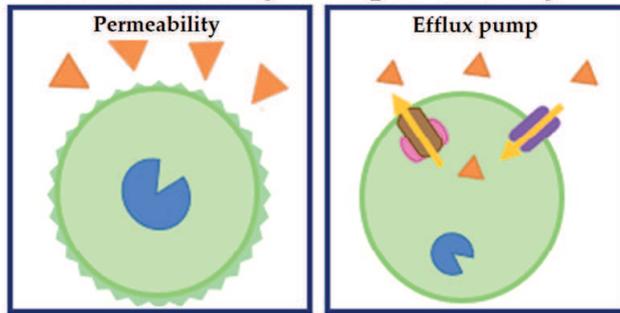
Gram-positive bacteria are more susceptible to various antibiotics since they have a thick outer layer of peptidoglycan with polymers of teichoic acid and covalently bound proteins, which allows the easy penetration of small molecules up to 30–57 kDa [8, 9]. In contrast, Gram-negative bacteria have an outer membrane that surrounds them with a relatively thin peptidoglycan layer. The composition of the outer membrane is based on lipid molecules covalently linked to polysaccharide units [10].

The lipid molecule has a large chain of fatty acids that contribute to reduce the fluidity of the lipopolysaccharide (LPS) membrane [10]. The central region of the LPS plays an important role providing a barrier to hydrophobic antibiotics and other compounds. It has been reported that strains that express full-length LPS have an intrinsic resistance to hydrophobic antibiotic class such as macrolides and aminoglycosides. Another modification observed is the alteration of the anionic nature

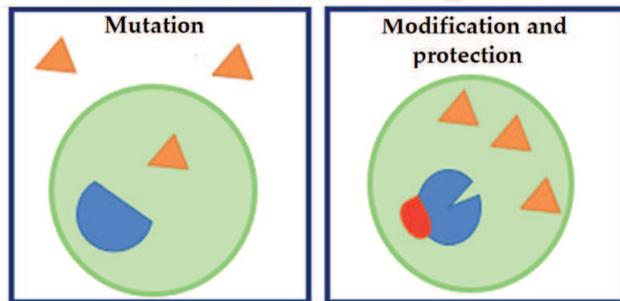
of the LPS; the most common LPS modifications are the cationic substitution of phosphate groups with 4-amino-4-deoxy-L-arabinose (L-Ara4N) or phosphoethanolamine (PEtN), which decreases the net negative load of lipid A from minus 1.5 to minus 1 or from minus 1.5 to 0, respectively [11]. The net positive charge resulting from the LPS modification reduces the binding of some cationic antibiotics such as polymyxins, leading the resistance of the bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella enterica* [12].

Intrinsic resistance mechanisms

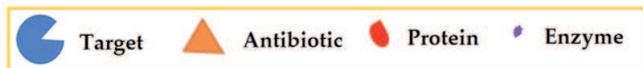
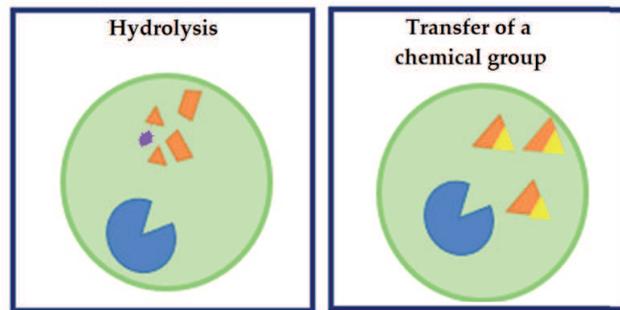
A. Permeability or impermeability



B. Modification of the target site

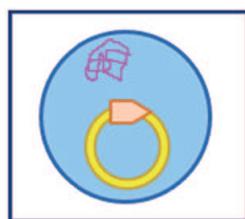


C. Enzymatic inactivation or modification of antibiotics

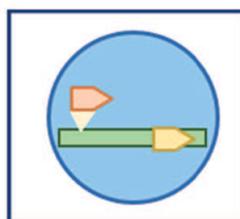


Acquired resistance mechanisms

A. Plasmids



B. Transposons



C. Integrons and cassettes

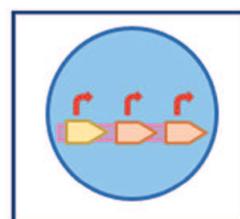


Figure 1.
 Schematic representation of the mechanisms of multidrug-resistance acquisition in bacteria.

On the other hand, embedded in the outer layer membrane of Gram-negative bacteria, there are proteins called porins that function as a channel through which the molecules can diffuse. Porins could restrict the influx of numerous antibiotics and contribute to the resistance against them [13]. The mechanism of resistance promoted by the porins consists in changing the hydrophilic composition of some antibiotics such as beta-lactam, chloramphenicol, fluoroquinolones, and tetracyclines. Likewise, the alteration of the amount or modification of the structure of the porins promotes resistance to antibiotics [11].

2.1.2 Expulsion of the antibiotic by active mechanisms

In general those mechanisms are mediated by bacterial flow pumps that actively transport many toxic molecules out of the cell [14]. The outflow pumps can interact with only one molecule (enzyme substrate specific), or they can have a broader spectrum and export distinct classes of molecules. Antibiotic resistance mediated by active outflow pumps may be incidental, since the pumps exhibit a broad-range substrate [9]. However, efflux pumps associated with antibiotic resistance have been described in Gram-positive and Gram-negative bacterial pathogens. The energy of some flow pumps depends of the antibiotic agents in order to extract it from the periplasm to the outside. The overexpression of one or more of these flow pumps prevents the intracellular accumulation of antibiotics at the thresholds necessary to exert their inhibitory activity [15].

2.1.3 Modification of the target site

Most of the antibiotics bind specifically to their targets with high affinity. Changes in target structure prevent an effective binding to antibiotics but still allow the target to carry out its normal function. The target modification could be originated by a mutation in the gene that encodes for the antibiotic target [14]. An example of this mutation mechanism is the linezolid antibiotic, a member of the oxazolidinone class, which inhibits the initiation of bacterial translation by altering multiple copies of the V domain of the 23S rRNA in Gram-positive bacteria. The mutation in one of these copies of the V domain can confer antibiotic resistance [16].

Another mechanism relies in avoiding or releasing the binding of the antibiotic to their target site [17]. One of the most representative examples of this mechanism and of current importance is that used by quinolones, which exert their function by inhibiting important enzymes of bacterial DNA replication such as gyrase and topoisomerases II and IV. The mechanism of evasion of the antibiotic function is by the expression of repeating pentapeptides (PRP), encoded by *qrn* genes, which bind and promote the release of the quinolone from the target enzymes, allowing the normal activity of the topoisomerases [18].

2.1.4 Enzymatic inactivation or modification of antibiotics

In this case, the mechanism of action could be by enzymatic hydrolysis [19] or modification of chemical groups by transfer or addition of different chemical compounds [14]. The classic example of a hydrolytic enzyme is the beta-lactamase, which hydrolyzes the beta-lactam ring, a common structural element in penicillins, cephalosporins, carbapenems, and monobactams [20]. Four classes of beta-lactamases have been described: the classes A, C, and D have a serine hydrolase activity; in contrast, class B has a metalloenzyme activity [21]. Another example of this type of resistance is provided by the enzymes erythromycin esterases EreA and EreB. These enzymes hydrolyze the macrolactone rings of macrolides such as erythromycin. It should be

noted that EreB enzyme confers resistance to almost all members of the macrolide class, with the exception of telithromycin, a semisynthetic erythromycin derivative, which belongs to a new class of antibiotics called ketolides [22]. In contrast, the EreA enzyme does not hydrolyze azithromycin and also telithromycin [23].

The modification of antibiotics includes the modification of some element of their structure, which is essential in the union with the bacteria target diminishing its affinity. This mechanism involves the addition or transfer of groups such as N-acetyl, phosphoryl, O-nucleoside, O-ribosyl, and O-glycoside. Unlike hydrolysis, this modification does not destroy the essential structures of the antibiotic but obstructs the interaction of the antimicrobial with its target. An example of this mechanism occurs for polycationic antibiotics such as aminoglycosides, which act between the ionic bonds of the amino and hydroxyl groups of the antibiotics and the 16S rRNA region of the A site of the bacterial ribosome, deteriorating the translation mechanism. The enzymes responsible for the modification of the aminoglycosides are the aminoglycoside phosphotransferases (APH) and nucleotidyltransferases (ANT) that modify the hydroxyl groups and the aminoglycoside acetyltransferases (AAC) which modify the amino groups, changing the size, structure, and electronic properties of the antibiotic [24].

2.2 Genetic mobile elements transfer or acquired resistance mechanisms

Once the bacterial cell acquires some degree of antibiotic resistance by an intrinsic mechanism that implies DNA modification, it can transfer the gene or genes encoding for the resistance marker to the offspring (vertical transfer) or to a different specie or genus (horizontal transfer) [25]. The gene resistance can be acquired by genetic mobile elements such as plasmids, transposons, or integrons [19].

The vertical transfer or vertical evolution occurs when a spontaneous mutation in the bacterial chromosome confers resistance to some members of the bacterial population. Once the resistance genes have arisen, they are transferred to the progeny of the bacteria during DNA replication [6]. When the bacterial genes that confer resistance to antibiotics are mobile, because they are contained within plasmids or are flanked by sequences recognized by some DNA transposition enzymes, they can be transferred between bacteria of a different taxonomic and ecological group. Some genetic mobile elements are plasmids, transposons, integrases, and genetic cassettes; in general this mechanism is called horizontal transfer gene [19, 26].

2.2.1 Plasmids

In bacterial cells, there are circular portions of extrachromosomal DNA that improve the survival characteristics of bacteria. This genetic information could be dispensable when it is no longer necessary to contend with the specific stress to which it imparts protection. Plasmids are self-replicating, given that they do so independently of chromosomal DNA replication. When plasmids contain antibiotic resistance genes, they are called plasmids R, and they can be transferred between bacteria of the same or different genera. Plasmids can be transferred to another bacterial cell by mechanisms called transformation or conjugation [19]. Transformation involves the acquisition of free DNA available in the medium. For this process the recipient bacteria must be in a competitive state; and the translocated DNA must be stabilized, either by integration into the host receptor genome or by recircularization (in the case of plasmid DNA) [27]. In contrast, conjugation involves the transfer of DNA through a multistep process that requires cell-to-cell contact, via cell surface pili or adhesins [28]. The conjugative machinery is encoded by genes in plasmids or by integrative conjugative elements in the chromosome [29].

2.2.2 Transposons

These are already known as jumping genes. These are short chains of DNA that jump from chromosome to plasmid or vice versa. DNA transfer can occur between bacterial chromosome, plasmids, and bacteriophages. The most salient feature of transposons is that DNA acquired is easily integrated into the host chromosome or plasmids. Unlike plasmids, jumping genes are not self-replicating, and they must be kept within a self-replicating structure to replicate them [19].

2.2.3 Integrons and cassette system

Both of them provide a simple mechanism for the acquisition of new genes. The DNA acquisition implies a single event of a site-specific recombination that causes the integration or removal of a single gene or a group of antibiotic resistance genes called cassette [30]. The integrons have certain components which allow a site-specific recombination system that recognizes and captures mobile genes. An integron includes a gene that codes for an integrase (IntI) and a site of specific recombination (*attI*) [31]. The sequences of the integrase enzymes allow integron classification in different classes (I–III) [32].

Genetic cassettes are small mobile elements that include a short sequence of 57 to 141 bp that are a specific recombination site. Cassettes can exist as free circular DNA molecules, and frequently they do not contain a promoter [30]. The lack of the promoter and the recombination sites make the recognition of the cassettes by IntI and Int13 and also by integrases encoded in the integrons possible. The integration of the cassettes to the integron structure allows the cassette genes' transcription from the characteristic integron promoter called *Pant* [30].

The dangerous feature of the transfer of antibiotic-resistant genes by transposons, integrons, or cassettes is the possibility that the bacterial receptor could acquire several classes of antibiotic resistance genes in a single event. A summary of the resistance to the different antibiotic classes, obtained by the intrinsic and acquired mechanisms, can be found in **Table 1**.

Antibiotic class/ antibiotics	Mode of action	Mechanism of resistance
Beta-lactam [33] <i>Penicillins</i> [*] Penicillin G and V Cloxacillin Ampicillin Carbenicillin <i>Cephalosporins</i> [*] Cephaloridine Cephalexin Cefuroxime Moxalactam Ceftiofur Cefoperazone Cefepime <i>Inhibitors</i> <i>Beta-lactamase</i> [*] Clavulanate Sulbactam Tazobactam <i>Carbapenems</i> [*] Imipenem/cilastatin Aztreonam	Act as suicide substrates for penicillin-binding proteins (PBP) (transpeptidases) They inhibit cell wall biosynthesis, specifically the peptidoglycan structure	<i>Acquired</i> <ul style="list-style-type: none"> • Plasmids • Transposons • Integrons (<i>bla</i>TEM-1, <i>bla</i>NDM-1, <i>bla</i>KPC, <i>bla</i>SHV, <i>bla</i>CTX-M, <i>AmpC</i>, <i>bla</i>VIM, <i>bla</i>OXA, and <i>bla</i>IMI genes) [34] <hr/> <i>Intrinsic</i> <ul style="list-style-type: none"> • Bacterial flow pumps (RND, ABC, and 233 transporter)

Antibiotic class/ antibiotics	Mode of action	Mechanism of resistance
Monobactams [33, 35] <i>Aminoglycosides*</i> Streptomycin Kanamycin Neomycin Gentamicin Spectinomycin	Inhibits the synthesis of proteins by binding to the ribosomal 30S subunit	<i>Intrinsic</i> <ul style="list-style-type: none"> • Bacterial flow pumps (MexXY and ABC transporter) • Enzymatic modification (<i>bla</i> KPC gene) • Ribosomal point mutation (<i>rrs</i> gene)
Diaminopyrimidines [33] Trimethoprim	They inhibit DNA replication by binding to dihydrofolate reductase, an enzyme involved in the metabolism of folic acid	<i>Acquired</i> <ul style="list-style-type: none"> • Transposon Tn7 (<i>dhfrI</i> gene) [36] <hr/> <i>Intrinsic</i> <ul style="list-style-type: none"> • Competitive inhibition of folic acid synthesis
Phenicols [33] Chloramphenicol Thiamphenicol	They bind to the peptidyl transferase (PTC) center of the 50S ribosomal subunit to inhibit the translation elongation stage	<i>Intrinsic</i> <ul style="list-style-type: none"> • Target modification (<i>cfp</i> gen) • Bacterial flow pumps of amphenicols (Cml transporter)
Fluoroquinolones [37] Enrofloxacin Danofloxacin Marbofloxacin	They inhibit DNA synthesis by topoisomerases II and IV	<i>Intrinsic</i> <ul style="list-style-type: none"> • Target modification (<i>gyrA</i> and <i>parC</i> genes) • Bacterial flow pumps of amphenicols (AcrA transporter)
Glycopeptides [33] Vancomycin Teicoplanin Streptogramins Virginamycin	They inhibit the cell wall biosynthesis in Gram-positive bacteria. They block the binding of the substrate and the transglycosylases	<i>Intrinsic</i> <ul style="list-style-type: none"> • Bacterial flow pumps of amphenicols (AcrF transporter) <hr/> <i>Acquired</i> <ul style="list-style-type: none"> • Transposon Tn1546 (<i>van</i> gene) [38]
Lincosamides [33] Lincomycin Clindamycin Pirlimycin	They prevent protein elongation during translation by causing premature dissociation of the tRNA, inhibiting the 50S ribosomal subunit	<i>Intrinsic</i> <ul style="list-style-type: none"> • Ribosomal modification by methylation or mutation (<i>erm</i> and <i>msr</i> genes) [39] • Bacterial flow pumps (ABC and MFS transporter) • Drug inactivation (<i>Lnu</i> and <i>Mph</i> genes) [39]
Macrolides [33] Erythromycin Oleandomycin Tylosin Spiramycin Tilmicosin		
Nitroimidazoles [40] Metronidazole	They inhibit the synthesis of DNA by oxidation. The nitro group is reduced to toxic radical species	<i>Intrinsic</i> <ul style="list-style-type: none"> • Bacterial flow pumps (RND and BME transporter) • Reductive activation by altering • The metabolism of pyruvate (PFOR) <hr/> <i>Acquired</i> <ul style="list-style-type: none"> • Chromosomal mutations or plasmids acquired (<i>nim</i> gen)

Antibiotic class/ antibiotics	Mode of action	Mechanism of resistance
Peptides [41] Polymyxin B Colistin	They displace the Mg ⁺² and Ca ⁺² ions and interact electrostatically with the lipopolysaccharides (LPS) of the external Gram-negative cell membranes	<i>Intrinsic</i> <ul style="list-style-type: none"> • Reduction of specific proteins of the membrane and LPS • Lipid modifications
Rifamycins [42] Rifampicin	They stop transcription by interacting with the β subunit of RNA polymerase (RNAP)	<i>Intrinsic</i> <ul style="list-style-type: none"> • Point mutations in the rifampicin-binding region of the β subunit of RNAP (<i>rpoB</i> gene) • Bacterial flow pumps (VceB and Acr transporter) [33]
Sulfonamides [36] Sulfanilamide Sulfadiazine Sulfatiazole	They act as competitive inhibitors of DHPS; they block the folate biosynthesis in the bacterial cell	<i>Acquired</i> <ul style="list-style-type: none"> • Integrons (<i>sul1</i> gene) • Plasmids (<i>IncQ</i> class: <i>sul2</i> gene)
Tetracyclines [43] Doxycycline Minocycline Oxytetracycline	They block the access of the tRNA to the ribosome by binding to the 30S ribosomal subunit	<i>Intrinsic</i> <ul style="list-style-type: none"> • Bacterial flow pumps (SMR, RND, or ABC transporter) • Ribosomal modification • Enzyme inhibition (coded by different classes of <i>tet</i>, <i>otr</i>, and <i>tcr</i> genes)

*The subclasses of the class of beta-lactam

Table 1.

Modes of action to different classes of antibiotics and their mechanisms of resistance.

3. Overview of resistant pathogens isolated from food

Fruits, vegetables, and foods from animal origin can be contaminated with antibiotic-resistant bacteria at any time in the food chain FAO [2]. There has been an increase in drug resistance in pathogens isolated from food for human consumption since 2000. *Salmonella enterica* and *Escherichia coli* isolates have been considered among the most important pathogens, because they can make zoonotic transfer of resistant genes [44]. However other pathogens, such as *Vibrio* spp., some species of *Aeromonas*, spores of *Clostridium botulinum* type F, or enteric bacteria such as *Campylobacter*, have been linked to gastrointestinal diseases in humans who have consumed foods of animal and marine origin. It has been reported that multidrug-resistant plasmids are easily transferred to *Aeromonas salmonicida* by *E. coli* [45, 46].

Salmonella is a pathogenic bacterium that cause a gastrointestinal disease called salmonellosis. In Latin America, Asia, and Africa, 200–500 cases of salmonellosis per 100,000 inhabitants per year have been documented, where the 95% of the infections come from the consumption of contaminated foods [47]. Worldwide, it was estimated that the infections caused by *Salmonella enterica* are above 93.8 million cases with 155,000 deaths per year [48].

Salmonella enterica is one of the most frequently isolated foodborne pathogens from different kinds of food. In the United States, between 11 and 20% of strains

isolated from animals destined to human consumption were resistant to more than five different antibiotics [49]. Other studies mention that 82% of the isolates in strains from food are resistant to at least one antibiotic, associated with high resistance levels to tetracycline, streptomycin, sulfamethoxazole, and ampicillin [49]. In Latin American countries, the average of *Salmonella* resistant isolates is dependent on the region and analyzed food. In Brazil in a study conducted in a salami processing line, a 3.7% resistance to 1 antibiotic and 11.1% resistance to 3 or more antibiotics out of a total of 54 isolates have been reported [50]. In contrast, in a study conducted in pork carcasses, 147 out of 155 *Salmonella* strains isolated (94.85%) were resistant to at least one or more antibiotics [51].

Escherichia coli is one of the most widespread microorganisms in nature, and it is a member of the normal intestinal flora of many organisms, including humans. In a study conducted in Havana, Cuba, 74 *E. coli*-resistant strains were isolated from foods involved in foodborne diseases (ETA). Among foods with the highest CFU of *E. coli* serogroups identified, there were soy yogurt (14.3% of isolates), pork steak (11.9%), chicken hash (11.9%), cheese (9.5%), ham (9.5%), and beef hash (7.1%). Resistance to ampicillin was present in 36.4% of the isolates, and some isolates were also resistant to streptomycin, sulfamethoxazole, and tetracycline [52]. In America, Eastern Mediterranean, Africa, Southeast Asia, and the Western Pacific regions, an increased resistance to third-generation cephalosporins and fluoroquinolones into *E. coli* isolates has been reported [53].

On the other hand, studies conducted in dairy products have shown that 73.3% (33/45) of the *E. coli* strains isolated were susceptible to all antibiotics tested and 24.4% (11/45) showed resistance to ampicillin. The phylogenetic analysis of the *E. coli* isolates resulted in grouping into two phylogroups, A and B1, which have a higher frequency of resistance genes than those that were grouped in B2 and D. It is worth to notice that *E. coli* isolates in this study that belonged to phylogroup A and B1 were commensal strains with few or no virulence factors [54]. These results suggest that the food chain is the vehicle for the transfer of resistant genes, and it has been suggested that *E. coli* strains present in food are the original carrier of many mechanisms of antibiotic resistance in the intestinal microbiota of humans.

Studies conducted in different food classes have isolated other bacterial genera different to *Salmonella enterica* and *E. coli*. One of the most studied is *Staphylococcus aureus*, which causes staphylococcal poisoning. Strains of *S. aureus* have been studied in the last decades because they show resistance to methicillin. The analyses done in 282 *S. aureus* strains isolated from food and manipulators showed that 56.1% of the strains were resistant to one or more antimicrobials [55].

Another bacterial genus of health importance is *Mycobacterium bovis*. In the United States, outbreaks by *M. bovis* have been associated with the consumption of contaminated food. In 2007, 203 samples of cheese imported from Mexico were collected at the California customs office. Of the samples collected, 4.9% tested positive for *Mycobacterium* genus, with drug susceptibility test to streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide, showing that they were susceptible to all the antibiotics tested except pyrazinamide [56]. In contrast, in Japan, 58 *M. bovis* strain isolates from dairy cattle reported 7 strains resistant to the fluoroquinolones enrofloxacin, orbifloxacin, and danofloxacin. The fluoroquinolone resistance was associated with the mutation to quinolone resistance-determining regions of *gyrA* and *parC* genes (QRDR). The strains that showed no fluoroquinolone resistance phenotype did not present mutations [57].

Listeria, *Shigella*, and *Campylobacter* are other bacterial genera that have been isolated from foods and have shown antibiotic resistance. *Listeria monocytogenes* strains isolated from cheese have shown resistance to streptomycin, kanamycin, cephalothin, and tetracycline [58]. The analysis of 152 *Shigella* strains isolated

from various foods that caused outbreaks of shigellosis in Brazil showed that several strains were resistant to streptomycin (88.6%), followed by ampicillin (84.6%) and sulfamethoxazole/trimethoprim (80.5%). The resistant strains were grouped into 73 patterns, where pattern A (resistance to ampicillin, sulfamethoxazole/trimethoprim, tetracycline, streptomycin, and chloramphenicol and intermediate resistance to kanamycin) grouped the highest number of isolates ($n = 36$) [59]. In Malaysia, *Campylobacter* spp. was reported with a prevalence of 17.4%, from a total of 340 cattle samples. *Campylobacter* isolates showed resistant to tetracycline (76.9%) and ampicillin (69.2%), while resistance to chloramphenicol was low (7.6%) [60].

Even in farms of goldfish (*Carassius auratus*), 70 strains of bacterial genera such as *Aeromonas hydrophila*, *Vibrio fluvialis*, and *V. furnissii* have been identified, with 45% of the isolates being resistant to 6 of the 14 antibiotics tested; 100% of the strains were resistant to cephalothin, 94% to ampicillin, 89% to chloramphenicol, 88% to tetracycline, 85.3% to nitrofurantoin, 61.3% to carbenicillin, and 65.3% to kanamycin. Twenty three percent of the isolates presented sensitivity to amikacin, trimethoprim, cefotaxime, netilmicin, pefloxacin, and gentamicin. Only one strain, *A. hydrophila*, showed resistance to all antibiotics tested. Twenty strains generated resistance to 7 different antibiotics, and 67 of the 70 strains generated resistance to more than 1 antibiotic [46].

As we can see in this overview, the resistance of the different bacterial genera isolated in a great diversity of foods is alarming, since many of these bacterial genera are the cause of many foodborne diseases. The diseases produced by these resistant pathogenic bacteria are difficult to treat, being able to provoke death in some patients.

4. Economic implications/economic impact of the resistant pathogens in food

As we previously mentioned, the resistance occurs when the antibiotics used for the control of bacterial diseases are no longer optimal for their elimination. The most common routes to get infected with pathogenic bacteria are air, direct contact with sick people, or consumption of contaminated water or food. Pathogenic bacteria can be spread through sick people and contaminated fruits, vegetables, or animals that are intended for consumption. Antimicrobial resistance is a risk factor and complication of the disease, being difficult to treat infections, and it could be eventually lead to death [61]. In 2019, 700,000 deaths worldwide can be attributed to antimicrobial resistance, and the figure would rise to 35 million in 35 years, due to the lack of treatments to cure diseases caused by resistant pathogens; the estimated cost for the treatment of these persons will be 100 billion dollars [62, 63].

Morbidity and mortality increase when the administration of effective treatments to counteract infections caused by resistant pathogens is delayed. The duration of the disease and hospitalization of patients with infections by resistant pathogens have an economic impact, since there are extra procedures for the treatment of the disease, the antibiotics that could be administered usually are more expensive than the ones used as first line, and also there are long hospitalization stays. The economic impact for the patient is due to the loss of productivity for taking care of themselves or a family member [61]. It is highlighted that 63.5% of infections are acquired in hospitals and that the groups with the highest incidence are under 1 year or over 65 years old [62, 63].

In Europe and the United States, more than 50,000 people die every year from infections with drug-resistant pathogens, while in India it is estimated that close to

60,000 newborns die due to resistant infections. There are at least 700,000 deaths every year caused by resistant microorganism that generate diseases such as bacterial infections, malaria, HIV/AIDS, or tuberculosis [64]. The Centers for Disease Control and Prevention estimated that 2 million patients will be treated each year for resistant bacteria, of which 23,000 die [65]. In United States, it was estimated that there are an average of 1400 sick people with infection caused by resistant microorganisms, with a medical cost per patient estimated in \$18,588 to \$29,069 US dollars with a mortality rate of 6.5%. In the European Union, the cost for loss of productivity due to an illness originated by resistant bacteria is estimated in 1.5 billion € per year [66].

It is evident that the problem of bacterial resistance has reached great impact not only in the health of the population but also on its economy. For this reason, it is necessary to undertake actions that help in stopping the acquisition of the genetic elements that promote antibiotic resistance. Without doubt, the implementation of government laws that avoid the excessive use of antibiotics in livestock and fish farming could help to hinder the problem. Also the use of alternative molecules to antibiotics for the prevention of diseases in animals and improvement of the hygiene and vaccination measures in the farming collection and food processes would help to stop the problem of bacterial resistance. It has been proven that countries that have implemented control measures in the use of antibiotics in animals for human consumption and their products reduce up to 39% resistant bacteria. Not less important is the implementation of control measures in hospitals and clinics as well as generation of awareness in the population to avoid the overprescription of antibiotics, elements that all together can make a difference.

Conflict of interest

The authors do not have any conflict of interest.

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