REVIEW

Emergence and spread of antibiotic-resistant foodborne pathogens from farm to table

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Abstract

Antibiotics have been overused and misused for preventive and therapeutic purposes. Specifically, antibiotics are frequently used as growth promoters for improving productivity and performance of food-producing animals such as pigs, cattle, and poultry. The increasing use of antibiotics has been of great concern worldwide due to the emergence of antibiotic resistant bacteria. Food-producing animals are considered reservoirs for antibiotic resistance genes (ARGs) and residual antibiotics that transfer from the farm through the table. The accumulation of residual antibiotics can lead to additional antibiotic resistance in bacteria. Therefore, this review evaluates the risk of carriage and spread of antibiotic resistance through food chain and the potential impact of antibiotic use in food-producing animals on food safety. This review also includes in-depth discussion of promising antibiotic alternatives such as vaccines, immune modulators, phytochemicals, antimicrobial peptides, probiotics, and bacteriophages.

Keywords Antibiotic resistance · Residual antibiotic · Food-producing animal · Farm-to-table · Food safety · Antibiotic alternative

Introduction

Antibiotics, the secondary metabolites produced by microorganisms such as bacteria, fungi, and plants, have been used to kill or inhibit foodborne pathogens. Antibiotics are structurally divided into several classes, including β-lactams, quinolones, fluoroquinolones, macrolides, aminoglycosides, and tetracyclines (Coates et al., 2011). Ever since the discovery of penicillin, the use of antibiotics has been extended from the treatment of infectious diseases caused by pathogens to the growth promoter in animal husbandry, agriculture, fishery, and aquaculture industries (Roca et al., 2015). Over the past few decades, the global meat production has increased with increasing the demand for meat, which can correspond to the increase in antibiotic use. The global antibiotic consumption can be increased up to 110,000 tons by 2030 (Van Boeckel et al., 2015). Antibiotics used in veterinary medicines are about twice as high as those used in humans. In specific, animal husbandry including pigs, cattle, and poultry accounts for the majority of agriculture.

The appropriate use of antibiotics is essential to effectively treat infectious diseases and promote animal growth. However, the residual antibiotics in foods and environments have been increased due to the overuse and misuse of antibiotics, leading to the rapid spread and emergence of antibiotic-resistant bacteria (Ben et al., 2019). A study reported that 700,000 people die from antibiotic-resistant bacterial infections each year, which can be increased to 10 million by 2050 (O'Neill, 2016). The emergence of antibiotic-resistant bacteria, especially multidrug resistance, has become a serious problem in the fields of medical care, animal husbandry, food industry, and public health (Monger et al., 2021). Moreover, the antibiotic prevention and treatment for infectious diseases are limited because the discovery and development of new antibiotics are lagged behind the spread of multidrug resistant bacteria. The new antibiotics require significant investment in research and development. Therefore, understanding the impact of antibiotic use and residues in food animals is essential to prevent misuse and

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overuse of antibiotics. This review discusses the influence of antibiotic resistance and residual antibiotics on food safety from farm to table.

Mechanisms of bacterial resistance to antibiotics

The antibiotic resistance in bacteria occurs through self-protection mechanism which is evolved under natural conditions to acquire resistance against harmful environments. Antibiotics can be commonly classified according to the inhibitory mechanisms, including inhibition of cell wall synthesis, disruption of the cytoplasmic membrane, inhibition of protein synthesis, inhibition of nucleic acid synthesis, and induction of alternative metabolic pathway (Culp et al., 2020; Kapoor et al., 2017) (Fig. 1). Gram-positive bacteria are sensitive to macrolides, cephalosporins, β-lactamase inhibitors, penicillins, and lincosamides, which are mostly bactericidals that inhibit the cell wall synthesis. Gram-negative bacteria are sensitive to aminoglycosides, polymyxins, and quinolones, which are mainly bactericidal through the inhibition of protein synthesis. Bacteria can develop antibiotic resistance mechanisms including antibiotic efflux pump systems, alteration in drug target sites, disruption of membrane permeability, and development of metabolic bypass (Kapoor et al., 2017; Lin et al., 2015).

Alteration of membrane permeability

The limiting uptake of a drug is responsible for bacterial resistance to antibiotics by reducing the envelope permeability, known as intrinsic resistance. Gram-negative bacteria have the outer membrane that acts as a robust barrier against antimicrobial agents. The outer membrane, a unique asymmetric lipid bilayer, consists of phospholipids and polysaccharides (Reygaert, 2018). The hydrophobicity of the outer membrane is attributed to the lipopolysaccharide (LPS) or lipooligosaccharide (LOS), showing strong lateral interactions with divalent cations. The outer membrane can prevent the access antibiotics and bile salts into the cell (Delcour, 2009). Gram-negative bacteria contain β-barrel proteins, called porin channels, in the outer membrane that is permeable to hydrophilic molecules such as ampicillin and amoxicillin (Danelon et al., 2006; Delcour, 2009; Nestorovich et al., 2002). The porin channels are less developed in the outer membrane of antibiotic-resistant bacteria (Delcour, 2009; Khameneh et al., 2016). For example, 44% of β-lactam-resistant *Enterobacter aerogenes* isolated from French hospitals were deficient in the porin channels, and other *Enterobacteriaceae* also showed a low number of porin channels, leading to carbapenem resistance (Charrel et al., 1996; Cornaglia et al., 1996). The porin-deficient *Klebsiella pneumoniae* exhibited the enhanced resistance to β-lactams and fluoroquinolones
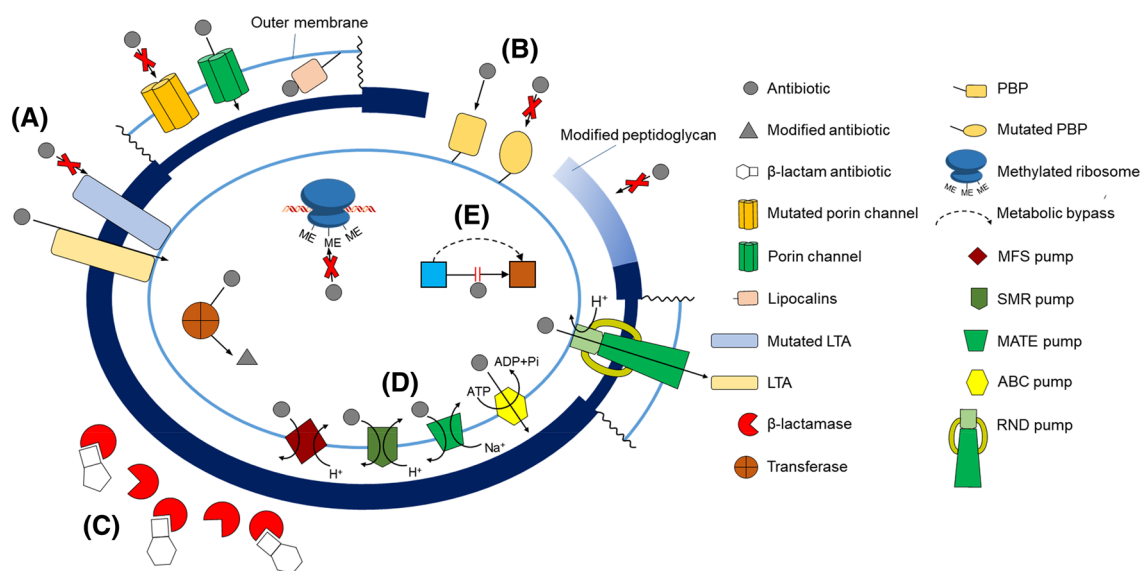

Fig. 1 Schematic illustration of antibiotic resistance mechanisms in bacteria, including **A** alteration of membrane permeability (mutated lipoteichoic acid [LTA], mutated porin channel, and lipocalin), **B** modification of antibiotic target sites (mutated penicillin-binding proteins [PBPs] and modified peptidoglycan), **C** enzymatic degradation of antibiotics (β-lactamases and transferase), **D** activation of bacte-rial efflux pump systems (major facilitator superfamily [MFS], small multidrug resistance [SMR], multidrug and toxic compound extrusion [MATE], ATP binding cassette [ABC], and resistance nodulation division [RND]), and **E** bypass of metabolic pathway inhibited by antibiotics (alternative folic acid synthesis)

(Khalid et al., 2020). The lipocalins, BcnA, in the outer membrane of *Burkholderia cenocepacia* can capture antibiotics, resulting in antibiotic resistance (El-Halfawy et al., 2017). In addition, BcnA induces the resistance of *Pseudomonas aeruginosa* PAO1 to polymyxin B (El-Halfawy et al., 2017). Th hydrophobic block of lipid layer covalently linked to arabinogalactan-peptidoglycan polymer in *Mycobacteria* contributed toward the development of resistance to hydrophilic antibiotics (Nasiri et al., 2017). Unlike Gram-negative bacteria, Gram-positive bacteria lack an outer membrane and have the cell wall consisting of a thick peptidoglycan layer that facilitates the penetration of hydrophobic antimicrobials (Karaman et al., 2020). However, anionic lipoteichoic acid (LTA) embedded in peptidoglycan can restrict the penetration of positively charged antibiotics, leading to antibiotic resistance (Abachin et al., 2002; Malanovic and Lohner, 2016; Peschel et al., 1999).

Modification of antibiotic target sites

The modification of target sites for antibiotics is a self-resistance mechanism under selection pressure of antibiotics (Reygaert, 2018). The β-lactam antibiotics is structurally similar to the penicillin-binding proteins (PBPs) that play an important role in the biosynthesis of peptidoglycan (Sauvage et al., 2008). The structural analogs, penicillin and cephalosporin, irreversibly acylate an active site of PBPs, leading to the inhibition of bacterial growth (Zapun et al., 2008). In this context, *Streptomyces* species and *Streptococcus pneumoniae* are highly resistant to penicillin by overproducing low-affinity PBPs for β-lactams (Beceiro et al., 2013; Blair et al., 2015; Watts et al., 2017). Glycopeptides such as vancomycin and teicoplanin bind to peptidoglycan precursors (D-Ala-D-Ala) and inhibit cell wall transpeptidation and transglycosylation (Kang and Park, 2015). The alteration in peptidoglycan precursor from D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser cause results in a significant decrease in affinity for the glycopeptide (Peterson and Kaur, 2018). The resistance to antibiotics targeting bacterial ribosome can be induced by the methylation of ribosomal subunits, known as erythromycin ribosome methylase (*erm*) (Reygaert, 2018). For example, the resistance to macrolide, lincosamide, and streptogramin B (MLS$_B$) were due to the methylation of ribosomal subunits (Lioy et al., 2014; Reygaert, 2018; Roberts, 2004). The resistance to quinolone and fluoroquinolones targeting DNA gyrase and topoisomerase IV is caused by the structural changes in DNA gyrase and topoisomerase IV, (GryA or ParC), responsible for the reduced binding ability to the DNA gyrase-DNA complex (Hawkey, 2003; Hooper and Jacoby, 2016; Redgrave et al., 2014).

Enzymatic degradation of antibiotics

The hydrolase-type enzymes can cleave substrates such as β-lactams, aminoglycosides, phenicols, and macrolides, leading to antibiotic resistance in bacteria (Blair et al., 2015; Reygaert, 2018). In general, β-lactamases can hydrolyze β-lactam antibiotics such as penicillins, cephalosporins, clavams, carbapenems, and monobactams. Moreover, extended-spectrum β-lactamases (ESBLs) can confer resistance to most β-lactam antibiotics, including oxyimino-cephalosporins (Livermore, 2008). Recently, the emergence and spread of carbapenemase-producing bacteria, including *Klebsiella pneumoniae* and *Enterobacteriaceae*, have been a global health challenge due to high morbidity and mortality (Pitout et al., 2015; Reygaert, 2018). The steric hindrance of the target sites for antibiotics can lead to antibiotic resistance (Blair et al., 2015). The antibiotic-modifying enzymes such as transferases can confer antibiotic resistance by transferring functional groups (acly, phosphate, nucleotidyl and ribitoyl) to aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones (Blair et al., 2015; Ramirez and Tolmasky, 2010; Reygaert, 2018; Robicsek et al., 2006). In addition, the rifamycin phosphotransferases are directly associated with the rifamycin resistance in pathogens (Spanogiannopoulos et al., 2014).

Activation of bacterial efflux pump system

Bacterial efflux transporters are classified into five superfamilies, including ATP-binding cassette (ABC) superfamily, major facilitator superfamily (MFS), drug and metabolite transporter (DMT) superfamily containing small multidrug resistance (SMR) family, multidrug and oligosaccharidyl-lipid/polysaccharide (MOP) exporter superfamily (multidrug and toxic compound extrusion (MATE) family), and resistance-nodulation-cell division (RND) superfamily (Begić and Josić, 2020). These superfamilies are involved in the outer membrane permeability which can render antibiotic ineffective against bacteria. The efflux pump-associated genes are overexpressed in the presence of antibiotics, which confers multidrug resistance (Reygaert, 2018; Van Bambeke et al., 2000).

The ABC transport systems form one of the largest protein families, found in all living organisms (Rees et al., 2009). The ABC transport systems are essential for bacterial survival, involved in the uptake of essential nutrients and the efflux of toxic molecules (Davidson et al., 2008; Szakács et al., 2008). The common ABC transport systems share a conserved core of four domains including two transmembrane domains (TMD) and two nucleotide-binding domains (NBD) (Lewis et al., 2012). The ABC transport systems are able to export antibiotics, for instance, VcaM can transport fluoroquinolones and tetracyclines in *Vibrio cholera* (De,

2021). The ABC transport systems include DrrAB that secretes daunorubicin and doxorubicin in *Streptomyces peucetius* and OleC4-OleC5 oleandomycin transporter in *Streptomyces antibiotics* (Lewis et al., 2012).

The MFS consists of uniporters, symporters, and antiporters, referred to the uniporter-symporter-antiporter (USA) family (Kumar et al., 2013) and are involved in the transport of anions, antibiotics, metabolites, and sugars (Reygaert, 2018). To export specific substrates, the MFS-type efflux pumps generate energy using an ion concentration gradient across the membrane (Kumar et al., 2020). The MFS-type efflux pumps can specifically export erythromycin (SmvA) and chloramphenicol (CraA and CmlA) in *Acinetobacter baumannii* and macrolides (MefB), fluoroquinolones (QepA) and trimethoprim (Fsr) in *Escherichia coli* (Kumar et al., 2020; Reygaert, 2018). The SMR-type efflux pumps are small integral inner membrane proteins that use the proton-motive force (Bay et al., 2008). The hydrophobic property of SMR-type efflux pumps contributes to a narrow range of substrates (Bay et al., 2008; Reygaert, 2018). Few SMR families are involved in antibiotic resistance, including Sau-Smr in *Staphylococcus epidermidis* and Eco-EmrE in *E. coli* (Bay et al., 2008; Nishino and Yamaguchi, 2001). The SMR-type efflux pumps confer the resistance to β-lactam, some aminoglycosides, and glycopeptides (Bay et al., 2008). In addition, the SMR-associated genes are found in chromosomes, plasmids, and transposable elements (Kumar and Schweizer, 2005; Reygaert, 2018).

The MATE-type efflux pumps are classified into three subfamilies, including NorM, DinF, and eukaryotic MATE (eMATE) (Kusakizako et al., 2020; Reygaert, 2018). Bacterial MATE, NorM and DinF, are composed of 12 membrane helices (Kusakizako et al., 2020). The bacterial MATE-type efflux pumps in bacteria have been found in *Vibrio cholerae*, *V. parahaemolyticus*, *Neisseria gonorrhoeae*, and *N. meningitidis* (Kuroda and Tsuchiya, 2009). The substrates of the MATE-type multidrug efflux pumps include fluoroquinolones and aminoglycosides. The RND-type efflux pumps are mostly found extensively in Gram-negative bacteria and have a broad substrate specificity conferring resistance to multiple antibiotics (Khameneh et al., 2016; Kumar et al., 2020; Reygaert, 2018). The major RND-type efflux pumps include proton-driven tripartite systems across the inner membrane, the periplasm, and the outer membrane of Gram-negative bacteria (Li et al., 2015). The AcrAB-TolC system consists of AcrB in the inner membrane, AcrA in the periplasm, and TolC in the outer membrane in *E. coli*, conferring the resistance to penicillin, chloramphenicol, macrolides, fluoroquinolones, and tetracycline (Kourtesi et al., 2013). The MexAB-OprM system confers the resistance of *Pseudomonas aeruginosa* to β-lactam, chloramphenicol, tetracycline, trimethoprim, sulfamethoxazole, and fluoroquinolones (Kumar et al., 2013; Li et al., 2015; Reygaert, 2018).

Change in metabolic pathway

Bacteria can also resist to antibiotics by modifying the metabolic pathway or developing alternate metabolic pathways (Saha and Sarkar, 2021). For example, there are several mechanisms that can produce an additional DNA gyrase subunit for novobiocin resistance, an alternative resistant RNA polymerase for rifamycin resistance, and an alternative fatty acid synthase for platensimycin resistance (Fujimoto-Nakamura et al., 2005; Goldstein, 2014; Peterson et al., 2014). The srrAB is a two-component system that is involved in the overall transcriptional regulation of virulence factors in small colony variants (SCVs) of *Staphylococcus aureus* and survival in anaerobic environments (Cao et al., 2017). The srrAB mutation of SCVs introduces an alternative transcriptional pathway against kanamycin and increasing ATP production in an anaerobic environment, thereby enhancing both resistance to kanamycin and viability (Cao et al., 2017; Saha and Sarkar, 2021). In addition, an antibiotic resistant mechanism can furthers activate metabolic pathways targeted by antibiotics (Munita and Arias, 2016). The trimethoprim-sulfamethoxazole (TMP-SMX) inhibits dihydropteroic acid synthase (DHPS) and dihydrofolate reductase (DHFR) in the folate pathway (Munita and Arias, 2016). The TMP-SMX-resistant bacteria mutate the promoters of the genes encoding DHPS and DHFR to overproduce two enzymes that enhance the antimicrobial activity of TMP-SMX, and also acquires pathways that uses external folates (Eliopoulos and Huovinen, 2001; Flensburg and Skold, 1987).

Acquisition and spreading of antibiotic resistance in food animals

Antibiotics have commonly been used to control the infectious diseases and promote animal growth in husbandry and veterinary care. However, the spread of antibiotic-resistant pathogens has accelerated due to the misidentification of antibiotic-treated animals and misunderstanding of antibiotic use (Oliveira et al., 2020).
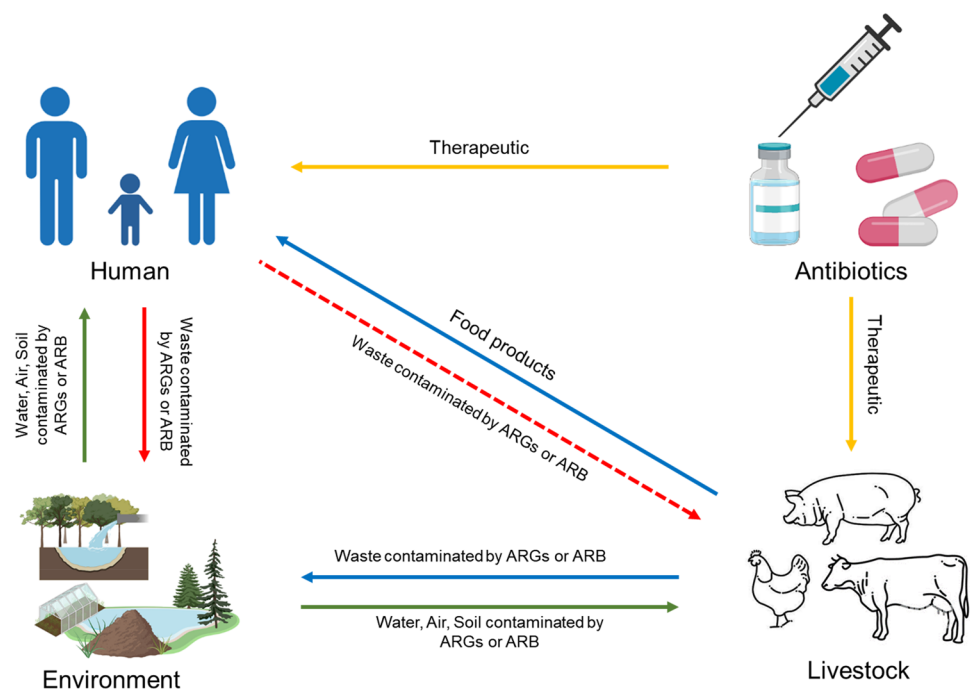
Antibiotic used in pig

Pigs are one of the most important farm animals in terms of both numbers and biomass (Delsart et al., 2020). The largest pork producers include China and the United States, followed by Germany, Spain, and Vietnam (Núñez-Espinoza et al., 2022). These countries represent nearly 65% of global production (Zalewska et al., 2021). Pig husbandry is expected to continue increase up to 8.6% by 2030 and 12.7% by 2050 (Monger et al., 2021). In recent years the use of antibiotics has been restricted worldwide, but antibiotics are commonly used during the suckling period and

post-weaning period (Lekagul et al., 2019). The antibiotics used in pig husbandry include amoxicillin, fluoroquinolones, penicillin, tetracyclines, cephalosporins, lincosamides, tulathromycin, polymyxin (colistin) and macrolid (tylosin) (Coyne et al., 2019; Lekagul et al., 2019). Among these antibiotics, the most commonly used antibiotics are relatively inexpensive and cost-effective antibiotics such as penicillin and the tetracycline (Coyne et al., 2019). The bacterial infections in pig are caused by *Salmonella* spp., *Escherichia coli*, *Actinobacillus pleuropneumoniae*, *Actinobacillus suis*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae*, and *Streptococcus suis*. The increase in sepsis caused by *S. suis* resistant to penicillin, tetracycline, and macrolide significantly affects pig production (Monger et al., 2021). The use of performance-enhancing antibiotics such as chlortetracycline, sulfamethazine, and penicillin can change gut microbiota that include various antibiotic resistance genes (ARGs) (Looft et al., 2012; Zalewska et al., 2021). The most widespread ARGs in the pig husbandry are tetracycline resistance genes, showing 71% of tetracycline resistance in *Enterococcus* spp. (Haack and Andrews, 2000). The tetracycline resistance genes were widespread in pig feces, farm soil, and wastewater (Kang et al., 2018). More than 400 of ARGs were identified in 181 pig herds and 178 poultry farms in European countries and 146 ARGs were identified in 7 Chinese pig farms (Munk et al., 2018; Zhao et al., 2018). In addition, the residual antibiotics can carry over from pig to pork (Monger et al., 2021). The use of antibiotics in animal farms can lead to the deposition of residues in meat that can spread from animals to humans (Chen et al., 2019) (Fig. 2).

Antibiotics used in cattle

The largest beef producers include Brazil, Canada, the USA, Argentina, the EU and Australia. The beef and dairy industries use a variety of antibiotics, including aminoglycosides, β-lactams, chloramphenicol, fluoroquinolones, glycolipid, ionophores, macrolides, quinolones, streptogramins, sulfonamides, and tetracyclines (Zalewska et al., 2021). Chlortetracycline, tylosin, ceftiofur and sulfamethoxazole have commonly been used for cattle in North America (Aust et al., 2008). In Europe, macrolides and lincosamides are commonly used for the treatment of various infectious diseases in cattle. In particular, tetracyclines are widely used to treat respiratory, gastrointestinal, and skin disease in cattle (Zalewska et al., 2021). Major infectious diseases in cattle are caused by *Pasteurella multocida*, *Mannheimia haemolytica*, *Escherichia coli*, *Salmonella* spp., *Staphylococcus aureus*, and *Streptococcus* spp. (Andres-Lasheras et al., 2022; Awosile et al., 2018). With increasing the consumption of beef, the use of antibiotics has been increased in cattle, causing serious antibiotic resistance problem. In addition, cattle manure used as soil fertilizer significantly contributes the dissemination of antibiotic-resistant bacteria and ARGs (Chen et al., 2019; Sachi et al., 2019). The microbial community in the cattle treated with antibiotics contains various transferable genes conferring resistance to MLSB, tetracyclines, and sulfonamides (Alexander et al., 2011; Chen et al., 2008). The excessive use of ceftiofur in cattle plays an important role in the spread of ARGs and multidrug-resistant bacteria (Chambers et al., 2015). The potential transmission

Fig. 2 Diagrammatic representation of the flow of antibiotic residues and the transmission of antibiotic-resistant genes (ARGs) and antibiotic-resistant bacteria (ARBs)

of ARGs from cattle to beef and human can be a serious problem (Zalewska et al., 2021).

Antibiotics used in poultry

The poultry consumption is high in the Asia–Pacific region, and the global poultry market has been increased. The largest poultry producers in 2019 was the USA (19,710,000 tons), followed by Brazil, the EU, and China (Zalewska et al., 2021). Recently, the use of antibiotics in meat and poultry products has been restricted in the USA and EU. However, the use of antibiotics is essential for disease prevention and growth promotion in poultry. The most commonly used antibiotics in poultry are virginiamycin, bacitracin, salinomycin, and tilmicosin (Zalewska et al., 2021). These antibiotics have been used to treat infectious poultry diseases caused by avian pathogenic *E. coli* (APEC), *Salmonella* Pullorum, *S.* Gallinarum, *Pasteurella multocida*, *Avibacterium paragallinarum*, *Gallibacterium anatis*, *Ornitobacterium rhinotracheale*, *Bordetella avium*, *Clostridium perfringens*, *Mycoplasma* spp., *Erysipelothrix rhusiopathiae*, and *Riemerella anatipestifer* (Porter, 1998). The frequent use of antibiotics for disease prevention and growth promotion has inevitably caused the emergence of antibiotic-resistant bacteria (Fletcher, 2015). In particular, APEC has developed resistance to ampicillin, amoxicillin, and tetracycline (Nhung et al., 2017). In addition, *O. rhinotracheale* showed significantly high levels of phenotypic resistance to co-trimoxazole, enrofloxacin, gentamicin, amoxixillin, and ceftiofur (Nhung et al., 2017). The antibiotics used in food animals were tetracyclines in 71% of the United States and 37% of Europe, which remain in meat (Gonzalez Ronquillo and Angeles Hernandez, 2017). The residual antibiotics are contaminated in the laying eggs of poultry, posing a risk to human (Idowu et al., 2010). Furthermore, poultry had the high prevalence of ciprofloxacin-resistant bacteria. Genes resistant to chloramphenicol, quinolones, tetracyclines, and sulfonamides have been detected in poultry (Amador et al., 2019; Zalewska et al., 2021).

Prevalence and transmission of antibiotic resistance from farm to fork

The Center for Disease Control and Prevention (CDC) estimates that 48 million people suffer from foodborne illness each year. Common foodborne pathogens including *Campylobacter* spp., *Bacillus cereus*, pathogenic *Escherichia coli*, *Salmonella* spp., *Staphylococcus* spp., *Enterococcus* spp., and ESBL-producing Gram-negative bacteria can cause diarrhea, fever, vomiting and other symptoms, and even severe cases can be life-threatening or fatal (Economou and Gousia, 2015). Foodborne pathogens that acquire antibiotic resistance through horizontal or vertical gene transfer cause difficult-to-treat infectious diseases (Table 1). Thus, understanding the antibiotic resistance transmission is essential for reducing the occurrence of antibiotic resistance from the animal food sources.

Macro-level determinants of antibiotic resistance transmission

The antibiotic-resistant foodborne pathogens continue to multiply and transfer antibiotic resistance to offspring, and eventually become the main flora (Founou et al., 2016). This phenomenon occurs not only in humans and animals, but also in the natural environment. Food animals, crops, and aquatic products are considered to be a large pool of antibiotic-resistant bacteria because the food production chain is recognized as the major reservoirs of ARGs (Founou et al., 2016). Human-animal-environment is a whole of mutual influence and interaction, and antibiotic resistance can be spread through direct or indirect contact between humans and animals (Fig. 2). For example, methicillin-resistant *Staphylococcus aureus* (MRSA) is quickly disseminated from infected animals to farmers worldwide (Aarestrup, 2015; Lewis et al., 2008; Price et al., 2012). Furthermore, the bovine *S. aureus* CC97 strain was transferred from livestock to humans. The epidemic community-associated MRSA (CA-MRSA) was also spread after host adaptation (Aires-de-Sousa, 2017). Since 1997, the occurrence of vancomycin-resistant *Enterococcus faecium* (VREF) has been decreased because vancomycin analogue (Avoparcin) was banned in Europe (Gouliouris et al., 2018). In case of *Salmonella* strains, fluoroquinolone and cephalosporin resistance cause the biggest global health problem, and these strains pose a major threat to human through feeding animal foods (Aslam et al., 2021; Dutil et al., 2010; Helms et al., 2004). Besides, multidrug-resistant *E. coli*, which can be a source of infection for humans and animals due to contaminated drinking water and food, is a leading cause of public health problems in developing countries (Aslam et al., 2021; Lazarus et al., 2015). Although foodborne pathogens are controlled by physical and chemical interventions, their ARGs are still transferable and infectious (Table 1).

The consumption of food animals that are contaminated with pathogens or ARGs can cause imbalance of the intestinal flora, leading to allergic hypersensitivity, toxic effects, liver toxicity, nephropathy, mutagenesis, carcinogenesis, and antibiotic resistance (Aslam et al., 2021; Malik et al., 2019). Human excrement carrying ARGs may also be passed to animals and environments. The antibiotic resistant bacteria and genes contaminate soil and groundwater or other water resources through feces and water cycle, and then cross-contaminate crops and aquatic products, and eventually reach the table and infect humans (Thanner et al., 2016). However,

Table 1 Antibiotic resistance genes (ARGs) and resistance mechanisms in bacteria

Strain	Food source	Antibiotic resistance	Resistance gene	Resistance mechanism	References
Campylobacter	Poultry products, untreated water	Fluoroquinolone	*gyrA* *cmeR, cmeABC*	Modification of antibiotic target sites Efflux pump activity	Adak et al. (1995), Endtz et al. (1991), Engberg et al. (2001), Iovine (2013),and Tang et al. (2017)
	Raw milk	Macrolide	23S rRNA(*rrn* operon), *erm(B)*, *rplD*, *rplV* *cmeABC*	Modification of antibiotic target sites Efflux pump activity	
		Florfenicol	*cfr* *cmeABC*, *floR*	Modification of antibiotic target sites Efflux pump activity	
		β-lactam	*bla*$_{OXA-61}$ *cmeABC*	Antibiotic inactivation Efflux pump activity	
		Tetracycline	*tet(O)* *cmeABC*	Modification of antibiotic target sites Efflux pump activity	
		Aminoglycoside	*aph(2″)-If, aph(2″)-Ig*	Antibiotic inactivation	
Shiga toxin-producing *Escherichia coli*	Beef, fresh produce,	Macrolide	*mph(A), mph(B), inu(F)* *cmeABC*	Degradation of the antibiotics Efflux pump activity	Ahmed and Shimamoto (2015), Maidhof et al. (2002), Mir and Kudva (2019), and Srinivasan et al. (2007)
	Raw milk,	Phenicol	*catA1, cmlA, floR* *cmeABC, floR*	Modification of antibiotic target sites Efflux pump activity	
	Unpasteurized juice, salami	β-lactam	*bla*$_{OXA-1}$, *bla*$_{TEM}$, *blaAmpC*, *bla*$_{CTX-M}$, *bla*$_{CMY}$, *bla*$_{PSE}$, *bla*$_{SHV}$, *CITM* *cmeABC*	Antibiotic inactivation Efflux pump activity	
		Tetracycline	*tetA, tetB, tetC, tetD, tetE, tetG* *cmeABC*	Modification of antibiotic target sites Efflux pump activity	
		Aminoglycoside	*aac(3)-IV, aac(3)-Id, phA1, strA/B, aadA, aac(6')-Ib*	Antibiotic inactivation	
		Sulphonamide	*sul1, sul2, sat1*	Antibiotic inactivation	
		Trimethoprim	*dfrA1, dfrA7, dfrA12, dfrA17*	Antibiotic inactivation	
		Fosfomycin	*murA*	Modification of antibiotic target sites	
Listeria monocytogenes	Ready-to-eat foods, dairy products,	β-lactam	*anrAB*	Efflux pump activity	Komora et al. (2017) and Olaimat et al. (2018)
	Sea foods, poultry products	Tetracycline	*tetM*	Modification of antibiotic target sites	
		Macrolide	*mdrL*	Efflux pump activity	
		Fluoroquinolone	*lde*	Efflux pump activity	
Salmonella Typhimurium	Poultry products	Aminoglycoside	*aac(3)-Via, aph(3″)-Ib(strA), aph(6)-Id(strB), aadA8, aadA13*	Antibiotic inactivation	Emond-Rheault et al. (2020) and Wang et al. (2019)
	Nuts	β-lactam	*bla*$_{CMY-2}$, *bla*$_{TEM-1}$	Antibiotic inactivation	
		Phenicol	*floR*	Efflux pump activity	

Table 1 (continued)

Strain	Food source	Antibiotic resistance	Resistance gene	Resistance mechanism	References
		Sulfonamide	*sul2*	Modification of antibiotic target sites	
		Tetracycline	*tet(C)*, *tet(D)*	Efflux pump activity	
		Peptide	*mprF(Brucella suis)*	Modification of antibiotic target sites	
		Fluoroquinolone	*qnrB19*	Modification of antibiotic target sites	
Lactobacillus spp.	Fermented foods	Macrolide	*erm*, *ermB*, *ermC*, *ermlF*, *msrC*	Antibiotic inactivation	Abriouel et al. (2015)
	Dairy products	tetracycline	*tetM*, *tetS*, *tetW*, *tetL*, *tetK*, *tetO*	Modification of antibiotic target sites	
	Fermented sausage	β-lactam	*pbp1a*, *pbp2a*, *pbp2x*	Antibiotic inactivation	
	Fermented fish	Aminoglycoside	*ant(6)*, *aph(3')-III*, *aadA*, *aadE*, *aph*, *vatE-1*	Antibiotic inactivation	
Staphylococcus aureus	Dairy products, poultry products	Chloramphenicol	*cat1*	Antibiotic inactivation	da Silva et al. (2020) and Ma et al. (2019)
	Lamb, pork, beef	Sulfonamide	*sul1*	Antibiotic inactivation	
		Aminoglycosides	*Aac(6')/aph(2'')*	Antibiotic inactivation	
		β-lactam	*femA*	Antibiotic inactivation	
		Quinolones	*norA*	Efflux pump activity	
Helicobacter pullorum	Poultry products	Fluoroquinolones, Erythromycin, Tetracycline, Ciprofloxacin, Erythromycin	*gyrA*, *gyrB*, 23S rRNA, 16S rRNA, *cmp*	Modification of antibiotic target sites, Efflux pump activity	Borges et al. (2015)

it is practically difficult to manage the risks of wastewater treatment plants, drinking water, and coastal waters that can be the reservoir of the ARGs (Leonard et al., 2018; Ma et al., 2017). Animal-eating grass containing ARGs or contaminated drinking water can also increase the risk of resistance. In addition, the physical and chemical stresses in food processing, such as acids, oxidants, osmosis, heating, freezing, can also cause resistance to foodborne pathogens (Liao et al., 2020). Therefore, during food processing and transportation, the contamination caused by antibiotic-resistant pathogens needs to be reduced for making sure that safe and reliable foods come to the table. Antibiotics are used for the treatment of infectious diseases and growth promoter for directly humans and animals (Fig. 2). Residual antibiotics are present in water, soil, and animal foods, which can further contaminate various food products. Bacteria exposed to the residual antibiotics can be mutated and directly or indirectly infect humans through ARGs and/or antibiotic-contaminated food products.

Micro-level determinants of antibiotic resistance transmission

ARGs are prevalent in humans, animals, and environments through the farm to the fork at the macro-level and also widespread through genetic elements at the micro-level. There are two main biological pathways, including vertical transmission and horizontal transmission. First, when pathogenic bacteria are mutated under the selective pressure of antibiotics and acquire ARGs that can be passed onto progeny during proliferation, resulting in innate resistance in offspring. The other pathway is to acquire antibiotic resistance through horizontal gene transfer (HGT) so that mobile genetic elements transfer through transformation, transduction, and conjugation within and between bacterial species (Founou et al., 2016). The gene transfer from donor to recipient bacteria through cell-to-cell contact is the main transmission, termed as bacterial conjugation (Leclerc et al., 2019). After contact, the bacterial cells transfer plasmid DNA through a conjugative pilus (Kelly et al., 2009). Bacteria can also actively secrete DNA through membrane vesicles. In natural environment, many bacteria can spontaneously become competent and absorb foreign DNA, which is called transformation. DNAs are prevented from being degraded and integrated into the host genome. This technique has commonly been used in the laboratories for genetic transformation. Mobile genetic elements such as plasmids, integrons, transposons, and phage-mediated gene transfer, are involved in the resistance gene transfer (Hughes and Andersson, 2017).

Plasmids play a pivotal role in the transmission of ARGs from bacteria to bacteria (Vrancianu et al., 2020). Vancomycin-resistant *Enterococcus* (VRE) contains vancomycin resistance genes encoded in mobile genetic elements (Miller et al., 2014; Ray et al., 2003). The broad-host range plasmid, pAMβ1, can transfer from *Lactococcus lactis* donor strains to *Enterococcus spp.* present in the microbiota of human biota-associated (HBA) rats (Tuohy et al., 2002). The transposons can cause the antibiotic resistance transfer from one plasmid to the other, or DNA chromosome to plasmid (Babakhani and Oloomi, 2018). Tetracycline resistance determinants, *tet*(M) and *tet*(L), are located in the genome of *Lactobacillus ingluviei* DSM 15946 [T], and upstream of *tet*(M) are conjugation transfer elements. Integrons are important genetic elements encoding ARGs, acting as a vehicle for disseminating multidrug resistance (Arango-Argoty et al., 2019). The integrons are classified into two major groups; chromosomal integrons (CIs) and mobile integrons (MIs). The MIs are a broad genetic platform that allows bacteria to regulate the expression of antibiotic resistance cassettes by shuffling positions in a common promoter (Souque et al., 2021; Stalder et al., 2012). Class 1 integrons are detected in a significant fraction of isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Souque et al., 2021). The phage-mediated gene transfer, known as transduction, occurs in nature due to abundant bacteriophages that are highly specific for hosts. The genes encoding shiga toxins, *stx1* and *stx2*, are transferable to *E. coli* by bacteriophage-mediated transduction (Wick et al., 2005). *Salmonella* Typhimurium DT104 containing *cam*, *amp*, and *tet* genes conferring chloramphenicol, ampicillin and tetracycline resistance, respectively, was transduced by phage PDT17 and phage ES18 (Colavecchio et al., 2017). ES18 could co-transduce *sul* and *str*, conferring sulfonamide and streptomycin resistance, respectively (Schmieger and Schicklmaier, 1999).

Treatment and preventive strategies to combat antibiotic resistance

Antibiotics have been utilized by treating disease, controlling infection, or promoting productivity and growth of livestock, enhancing feed efficiency. In reality, it is known that 40% of all antibiotics currently produced are used as feed additives. According to estimates, the global average annual consumption of antibiotics per kilogram of food animals is to be 45, 148, and 172 mg/kg for cattle, chicken, and pigs, respectively (Van Boeckel et al., 2015). However, since the wide spreading of antibiotic-resistant bacteria and ARGs caused by the increase in the use of antibiotics in food-producing animals, the discovery and development of antibiotic alternatives are essential to improve food safety. Antibiotic alternatives suggested or used in food animals are bacteriophages, antimicrobial peptides, probiotics, vaccines, immune modulators, and phytochemicals (Table 2).

Vaccines

Vaccines for food-producing animals are currently used to effectively control bacterial infections as antibiotic alternatives. The use of vaccines on pig farms provides cost-effectiveness, antibiotic consumption reduction, and production improvement (Postma et al., 2017; Rojo-Gimeno et al., 2016). For example, vaccination prevented pig from *Laesonia intracellularis* infection causing ileitis and also reduced the consumption of oxytetracyline in the treatment of ileitis (Bak and Rathkjen, 2009). In poultry, vaccination also confers more advantages than other treatments such as antibiotics. As a result, the antibiotic consumption was significantly reduced by the increased use of vaccination against avian colibacillosis (Dalloul and Lillehoj, 2006; Mombarg et al., 2014). In cattle industry, the vaccination is used for the prevention of respiratory infections caused by bacteria and viruses (Richeson et al., 2015, 2019). However, veterinary vaccinations have limitations on efficacy, duration of immunity, and side effect. For instance, vaccine was not effective against *Mycoplasma mycoides* that causes contagious bovine pleuropneumonia with varied duration of protective immunity and serious adverse effects in cattle (Jores et al., 2013). *Salmonella* vaccines are most effective against homologous *Salmonella* but least effective against heterologous serotypes (Barrow, 2007; Hoelzer et al., 2018). Moreover, since vaccine efficacy is associated with active immunity, young animals may not properly respond to vaccines (Hoelzer et al., 2018). In addition, vaccine is not effective against pathogens that can avoid the host are resistant to host immune. Nevertheless, the vaccination is still one promising method to reduce the antibiotic use for food-producing animals.

Immune modulators

Immune modulators such as cytokines, pharmaceuticals, microbial products, nutraceuticals, and traditional medicinal plants play an important role in the prevention of diseases and improvement of production efficiency (Blecha, 2001). These immune modulators are more effective against a wide range of pathogens than vaccines due to the stimulation of animal immune system (Koo et al., 2006). The egg-yolk antibodies (IgY) effectively prevented the diarrhea in food-producing animals and reduced necrotic enteritis in poultry (Diraviyam et al., 2014). Although the IgY in swine gut is not stable and has a narrow host spectrum, the antibodies can be used as alternative over antibiotics because of the potential ability to prevent and treat diarrhea in piglets (Diraviyam

Table 2 Antibiotic alternatives suggested in food-producing animals

Treatment	Mechanism	Characteristic	References
Vaccines	Induction of immune response	*Pros*: Prevention of pathogens, improvement of production, cost-effectiveness, and stimulation of the host immune response *Cons*: Adverse effects, narrow range of inhibitory effect on bacterial growth, host immune response-dependent activity, and difficulty in new vaccine development	Cheng et al. (2014), Hoelzer et al. (2018), Rojo-Gimeno et al. (2016) and Zhang and Sack (2012)
Immune modulators	Stimulation and enhancement of immune system	*Pros*: Broad range of inhibitory effect, less harmful immune response, and enhancement of the host immune system *Cons*: Adverse side effects, host immune response-dependent activity, and few clinical evidences to orally administration	Cheng et al. (2014), Koo et al. (2006), Thacker (2010) and Thanner et al. (2016)
Phytochemicals	Bacterial growth inhibition and animal growth promotion	*Pros*: Animal growth promotion, antioxidative activity, anti-microbial activity, and improvement of gut health *Cons*: Uncertainty of toxicity and interaction with other additives	Cheng et al. (2014), Ghosh et al. (2011), Vakili et al. (2013), Windisch et al. (2008), and Zhang and Sack (2012)
Antimicrobial peptides (AMPs)	Inhibition of bacterial growth	*Pros*: High specificity and stability, good bactericidal effects, and less adverse effect *Cons*: High production cost, narrow range of inhibitory effect, resistance to AMPs, and degradation by protease	Cheng et al. (2014), Cotter et al. (2013), del Castillo et al. (2001), Kramer et al. (2006), Piper et al. (2009), and Zhang and Sack (2012)
Probiotics	Improvement of host health	*Pros*: Inhibition of bacterial growth, animal growth promotion, Production of antimicrobial compounds, and improvement of host gastrointestinal microbial balance *Cons*: Harmful health effect in the immunodeficient host and risk of antibiotic resistance gene transfer	Anee et al. (2021), Cheng et al. (2014), Delia et al. (2012), and Zhang and Sack (2012)
Bacteriophages	Inhibition of bacterial growth	*Pros*: High specificity, low inherent toxicity, degradation of biofilm, and low cost *Cons*: Narrow range of inhibitory effect, removal by host immune system, risk of antibiotic resistance gene transfer, and phage resistance	Cheng et al. (2014), Gambino and Brøndsted (2021), Gigante and Atterbury (2019), Loc-Carrillo and Abedon (2011), Pirnay et al. (2011), and Zhang and Sack (2012)

et al., 2014). In addition, the immunity of swine fed a fodder containing vitamin C and β-glucan was improved and showed effective resistance against bacterial toxins (Eicher et al., 2006). Specific drugs such as avridine, diethyldithiocarbamate, and Isoprinosine have also been used as immune modulators. Interestingly, drugs such as thiabendazole and levamisole are used as immune modulators because they enhance the immune system of food animals with positive side effects (Blecha, 2001). However, immune modulators are highly dependent on the immune system of food animals and are greatly affected by the acquired environment in which food animals are grown (Cheng et al., 2014). For example, immune modulators are ineffective against young animals, whose immune systems are not fully developed, and in animals under extreme environmental stress, and can negatively affect normal immune development (Bricknell and Dalmo, 2005; Cheng et al., 2014). The immune modulators used as adjuvants can effectively reduce the use of antibiotics (Cheng et al., 2014).

Phytochemicals

Phytochemicals such as essential oils and tannins are natural bioactive compounds that are added to animal feed for improving the productivity of food animals (Lillehoj et al., 2018). Recently, phytochemicals have been commonly used as natural growth promoters in the poultry and ruminant industry (Gadde et al., 2017; Lillehoj et al., 2018). In particular, the phytochemicals are used in commercial poultry operations for growth promotion and disease prevention. European Medicines Authority (EMA) and European Food Safety Authority (EFSA) suggested that phytochemicals are effective in promoting growth in chickens. For example, cinnamaldehyde ((2E)-3-phenylprop-2-enal) extracted from cinnamon (*Cinnamomum cassia*) increased the chicken immunity by proliferating chicken spleen lymphocytes (Lee et al., 2011). In addition, *Curcuma longa* (turmeric), *Capsicum annuum* and *C. frutescens* (hot pepper), and *Lentinus edodes* (shiitake mushroom) induced weight gain, reduced fecal oocyst shedding in *E. acervuline*–infected birds, and increased serum antibody titers against profilin (Lee et al., 2009). Capsicum oleoresin, garlic botanical, or turmeric oleoresin fed to *E. coli*-infected pigs improved the intestinal health of the pigs and reduced the adverse effects of *E. coli*. Moreover, phytochemicals relieved the stimulation of immune response and enhanced the physiological defense mechanism in pig (Liu et al., 2014). Capsicum oleoresin in beef cattle feeding improved milk production and immune indicators with increasing neutrophils and decreasing lymphocytes (Oh et al., 2015). However, the use of phytochemicals as alternatives still has a safety concern when used in animal feeding (Lillehoj et al., 2018).

Antimicrobial peptides

Antimicrobial peptides (AMPs) are known as promising antibiotic alternatives because of their strong specificity and high molecular stability. AMPs are mainly classified based on the structural composition and amino acid sequence, including defensins, cathelicidins, hepcidins, histone-derived peptides, and fish specific piscidins (Fasina et al., 2021). Proline-Arginine-39 (PR-39) is a small cationic cathelicidin that has antibacterial activity against *Enterococcus faecalis*, *E. coli*, and *Bacillus subtilis* and relieve intestinal inflammation and diarrhea in pigs (Holani et al., 2016). β-defensin plays an essential role in innate and adaptive immunity of vertebrates and has inhibitory effects against pathogenic bacteria, fungi, mycobacteria, and enveloped viruses (Auvynet and Rosenstein, 2009; Jiao et al., 2017). Pigs fed with fodder supplemented with a specific amino acid and cation mixtures showed the increase in expression of β-defensin genes. These results indicate that AMPs helped improve gut health in pig (Mao et al., 2012). Cecropins are peptides produced in the small intestine of pigs, which show the antimicrobial activity against Gram-negative and Gram-positive bacteria, fungi, and viruses (Song and Lee, 2014). The cecropins also improved the performance of piglets infected with *E. coli* and increased the population of *Lactobacilli* strains that have a beneficial effect on the gut health (Wu et al., 2012). Bovine myeloid antimicrobial peptides (BMAP), bovine cathelicidins, are synthetic host defense peptides, showing antibacterial activity against *S. aureus*, *B. megaterium*, *E. coli*, *P. aeruginosa*, and *S. enterica* serotype Typhimurium (Skerlavaj et al., 1996). Ovodefensins expressed in the oviducts of chickens and ducks show strong antibacterial activity against *E. coli*, avian pathogenic *E. coli*, and *S. aureus* (Whenham et al., 2015). In addition, as avian β-defensins show broad antimicrobial activity against Gram-negative and Gram-positive bacteria and fungi (van Dijk et al., 2008; Whenham et al., 2015). AMPs are one of the most promising antibiotic alternatives applicable to food animals as immune modulators (Pasupuleti et al., 2012).

Bacteriophages

Bacteriophages have been used to treat acute and chronic infections due to their strong host specificity and less adverse effects (Wittebole et al., 2014). Recently, bacteriophages have regained attention as antibiotic alternatives with increasing the emergence of multidrug-resistant bacteria and decreasing the discovery of novel antibiotics (Principi et al., 2019). In particular, bacteriophages can effectively control zoonotic bacterial pathogens such as *Salmonella* spp., *E. coli*, *Campylobacter* spp., and *Listeria* spp., that cause infection of food animals and contamination of food (Gambino and Brondsted, 2021; Gigante and Atterbury,

2019). Broilers infected by *E. coli* were treated with bacteriophages, resulting in the significant reduction in mortality (Huff et al., 2004). The inhibitory effect of bacteriophages was also observed in pigs infected by *Salmonella enterica* in the ileum and cecum (Wall et al., 2010). The US Food and Drug Administration (FDA) and/or the US Department of Agriculture (USDA) has approved the use of bacteriophages to control pathogens in food animals, food crops, and meat (O'Flaherty et al., 2009). For example, FDA has approved the use of 6-cocktails for controlling *Listeria monocytogenes* contamination in ready-to-eat meat (Lang, 2006). Recently, bacteriophage-encoding enzymes such as endolysin, holin, and hydrolases have been used to overcome phage resistance. (Cheng et al., 2014; Loc-Carrillo and Abedon, 2011; Pirnay et al., 2011; Roach and Donovan, 2015). Endolysins are responsible for attacking and disrupting bacterial cell wall peptidoglycan that enables bacteria to withstand turgor and maintains cell shape (Roach and Donovan, 2015; Vollmer et al., 2008). These muralytic enzymes have effective antibacterial activity against MRSA and other Gram-positive bacterial pathogens such as *Staphylococcus*, *Bacillus anthracis*, *L. monocytogenes*, *Clostridium butyricum*, *Enterococcus faecalis*, *C. perfringens*, and Group B *Streptococcus* (Fenton et al., 2010; Low et al., 2005; O'Flaherty et al., 2005).

Probiotics

Probiotics are living bacteria and yeasts that have beneficial effects on humans and animals (Nagpal et al., 2012). Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) defined probiotics as "live microorganisms confer a health effect on the host when consumed in adequate amount". Most probiotics are present in the gastrointestinal (GI) tract of humans and animals, and they beneficially affect host animals by improving the host's intestinal microbial balance or improving the properties of the indigenous microflora (Delia et al., 2012). In addition, probiotics have various beneficial effects on food animals, including the improvement of nutrient absorption ability and milk (or egg) production (Delia et al., 2012; Perdigón et al., 2001). Probiotics effectively prevented diarrhea and reduced mortality in pig infected by *E. coli*. *Bifidobacterium lactis* HN019 also relieved weanling diarrhea of piglets caused by rotavirus and *E. coli* by enhancing the immune system (Shu et al., 2001). Probiotic administration reduced the mortality rate of broilers by 22% and increased the production efficiency (Dersjant-Li et al., 2014). In addition, the broilers treated with probiotics containing *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Pediococcus* strains improved the growth compared to avilamycin-treated broilers (Markowiak and Slizewska, 2018; Mountzouris et al., 2007). In the

cattle, probiotics are widely used for preventing disease and improving productivity (Frola et al., 2012; Nader-Macias et al., 2008). For example, when *Lactobacillus perolens* CRL 1724 was used to treat bovine mastitis in dairy farms instead of antibiotic therapy (Frola et al., 2012). Moreover, probiotic added in the calf diet significantly reduced the incidence of diarrhea and beneficially affected the lactic acid bacteria (Signorini et al., 2012).

Probiotics has been considered as alternatives over antibiotics in food industry, medical field, and agriculture (Reininghaus et al., 2020; Varankovich et al., 2015). However, the use of probiotics is limited due to their potential reservoirs for ARGs. Therefore, probiotics may not be excluded from the transfer of ARGs (Imperial and Ibana, 2016). In general, the antibiotic resistance in bacteria includes inherent and acquired resistance. Antibiotic resistance in bacteria can occur through the mutation of an endogenous gene and the acquisition of exogenous ARGs (Liu et al., 2009). The inhered resistance occurs naturally in all bacterial species, known as nontransferable (Teuber, 1999). The *tet*(W) in *B. animalis* subsp. *lactis* is intrinsic resistance gene that are not transferable (Nøhr-Meldgaard et al., 2021). The acquired resistance confers ARGs through HGT (Lokesh et al., 2019). The mechanisms of acquired resistance in bacteria include membrane permeability modification, efflux pump system, enzymatic degradation, target-site variation, and metabolic rearrangement (Courvalin, 2006; Tóth et al., 2021). The acquired antibiotic resistance in probiotics is involved in the transfer of ARGs in the gastrointestinal tract (GIT) (Selvin et al., 2020). The transferable genes conferring the acquired resistance have been observed in lactobacilli, including *tet*(M) responsible for tetracycline resistance, *erm*(B) for erythromycin resistance, and *cat* for chloramphenicol resistance (Ammor et al., 2007). Therefore, the genetic exchanges and health risk of ARGs need to be assessed based on whether intrinsic or acquired resistance genes (van Reenen and Dicks, 2011).

In conclusion, the risk of antibiotic resistance has been a global problem in food system. Antibiotics are known as effective therapeutic agents for the treatment of bacterial infectious diseases of food-producing animals. However, as the double-edged sword of antibiotics, the possible carry-over of residual antibiotics and the potential reservoir of ARGs through the food chain from farm to table are the high priority health issues. The residual antibiotics in food animals can affect the evolution of antibiotic resistance in foodborne pathogens. Furthermore, the transfer of ARGs can accelerate the emergence and spread of antibiotic-resistant pathogens. The use of antibiotics in farming animals should not be underestimated in terms of food safety and public health. Therefore, other than the regulations that passively restrict the use of antibiotics in farm animals, the discovery and development of effective prevention, control, and

treatment strategies are needed to reduce the risk of residual antibiotics and ARGs.

Declarations

Conflict of interest The authors declare no conflict of interest.

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