



The Influencing Factors of Bacterial Resistance Related to Livestock Farm: Sources and Mechanisms

Kaixuan Guo^{1,2†}, Yue Zhao^{1,2†}, Luqing Cui^{1,2}, Zhengzheng Cao^{1,2}, Fan Zhang^{1,2}, Xiangru Wang¹, Jiawei Feng^{1,2} and Menghong Dai^{1,2*}

¹ The Cooperative Innovation Center for Sustainable Pig Production, Huazhong Agricultural University (HZAU), Wuhan, China, ² Ministry of Agriculture Key Laboratory of Food Safety Evaluation, National Reference Laboratory of Veterinary Drug Residue, Huazhong Agricultural University (HZAU), Wuhan, China

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*Correspondence:

Menghong Dai
daimenghong@mail.hzau.edu.cn

[†]These authors have contributed
equally to this work and share first
authorship

Specialty section:

This article was submitted to
Animal Physiology and Management,
a section of the journal
Frontiers in Animal Science

Received: 07 April 2021

Accepted: 23 August 2021

Published: 16 September 2021

Citation:

Guo K, Zhao Y, Cui L, Cao Z, Zhang F,
Wang X, Feng J and Dai M (2021) The
Influencing Factors of Bacterial
Resistance Related to Livestock Farm:
Sources and Mechanisms.
Front. Anim. Sci. 2:650347.
doi: 10.3389/fanim.2021.650347

Bacterial resistance is a complex scientific issue. To manage this issue, we need to deeply understand the influencing factors and mechanisms. Based on the background of livestock husbandry, this paper reviews the factors that affect the acquisition of bacterial resistance. Meanwhile, the resistance mechanism is also discussed. “Survival of the fittest” is the result of genetic plasticity of bacterial pathogens, which brings about specific response, such as producing adaptive mutation, gaining genetic material or changing gene expression. To a large extent, bacterial populations acquire resistance genes directly caused by the selective pressure of antibiotics. However, mobile resistance genes may be co-selected by other existing substances (such as heavy metals and biocides) without direct selection pressure from antibiotics. This is because the same mobile genetic elements as antibiotic resistance genes can be co-located by the resistance determinants of some of these compounds. Furthermore, environmental factors are a source of resistance gene acquisition. Here, we describe some of the key measures that should be taken to mitigate the risk of antibiotic resistance. We call on the relevant governments or organizations around the world to formulate and improve the monitoring policies of antibiotic resistance, strengthen the supervision, strengthen the international cooperation and exchange, and curb the emergence and spread of drug-resistant strains.

Keywords: acquired resistance, antibiotic, heavy metal, biocide, resistance mechanism, mitigation measures

INTRODUCTION

The emergence and spread of bacterial pathogen resistance is a natural response to the selection pressure of antibiotics (Witte et al., 1999). The latest report shows that the total global sales of antimicrobial agents for livestock in 2017 was 93,309 tons, and sales are expected to increase by 11.5% to 1,04,079 tons in 2030 (Tiseo et al., 2020). The application of antibiotics in animals has three main purposes: the treatment of pathogen infection (therapeutic use), the prevention of animal disease outbreak (prevention) and the promotion of growth (Gould, 2016; Roth et al., 2019). Antibiotic resistant bacteria associated with animals are easily transmitted to humans through the food chain, and spread in the environment through animal feces (Van Boeckel et al., 2015; Manyi-Loh et al., 2018). Therefore, when animals are infected by bacterial pathogens, most countries advocate antimicrobial treatment. This treatment can effectively control the spread of disease

and reduce the excretion of pathogens from animals. In addition to treating infections, antibiotics are also used in animals in many developing countries and a few developed countries as a preventive measure to prevent outbreaks of disease, even if the animals are healthy and there are no known infectious diseases in the feeding environment (Prescott, 2017; Collineau et al., 2018). Finally, the use of antibiotics as growth promoters (AGPs) in animal husbandry in developing countries has been controversial. For example, in the review (Sharma et al., 2016), the studies reported the types of antibiotics registered as feed additives for livestock (Hobman and Crossman, 2015) and poultry in the United States, Canada, the European Union and Australia to promote their healthy growth. After antibiotics are fed to farm animals in low or sub-dose concentrations, 75–90% will be lost to the environment in the form of urine and feces (Lekshmi et al., 2017). But the concentration of sub-therapeutic antibiotics in some tissues or organs (such as intestines) will lead to non-specific mutation of bacteria, which may promote the development of bacterial resistance (Cogliani et al., 2011). In addition, the low concentrations of heavy metals in the intestines and feces are often in close contact with bacteria. Usually, some heavy metals are mixed in feed as nutritional additives, because they may be necessary elements to maintain various physiological functions of animal body (Hejna et al., 2018). However, some heavy metals with no established biological functions are considered as pollutants. In recent years, bacteria have developed drug resistance under the influence of heavy metals (especially copper and zinc). Different from the short half-life and biodegradability of antibiotics, heavy metals are not biodegradable in various environments with relatively low concentrations (lower than their minimal inhibitory concentration), and their effects are extensive and lasting (Luo et al., 2014; Waseem et al., 2014; Gumpu et al., 2015; Zhao et al., 2015). All in all, microorganisms can be subjected to long-term selective pressure by metals. Some data show that there is a significant correlation between heavy metal resistance genes and antibiotic and disinfectant resistance genes in food borne *Salmonella* (Yang et al., 2016; Zhang et al., 2016; Deng et al., 2018). In livestock husbandry, biocides are widely used in environmental surface because of their disinfection effect and the treatment of wounds. Biocides used in diverse applications eventually enter the environment. There is no doubt that fungicides exert selective pressure on microorganisms, even at low concentrations (Ons et al., 2020). The mechanisms leading to resistant bacterial populations from antibiotic uses, heavy metals uses, and exposure to biocides have all gained a widespread attention. Furthermore, relevant experiments have proved that bacteria can be induced or selected to produce adaptability when they are exposed to these non-antibiotic antibiotics, thereby reducing sensitivity to one or more antibiotics (Wales and Davies, 2015). For example, after exposure to phenolic fungicides or sub-inhibitory concentrations of triclosan, the frequency of mutations in antibiotic resistance of *Salmonella* increases (Randall et al., 2004). Pathogens will also be transmitted through certain ways, such as, from animals to humans through food chain (Gupta et al., 2020; Lei et al., 2020). Additionally, bacteria can also acquire exogenous resistance genes through other factors in the

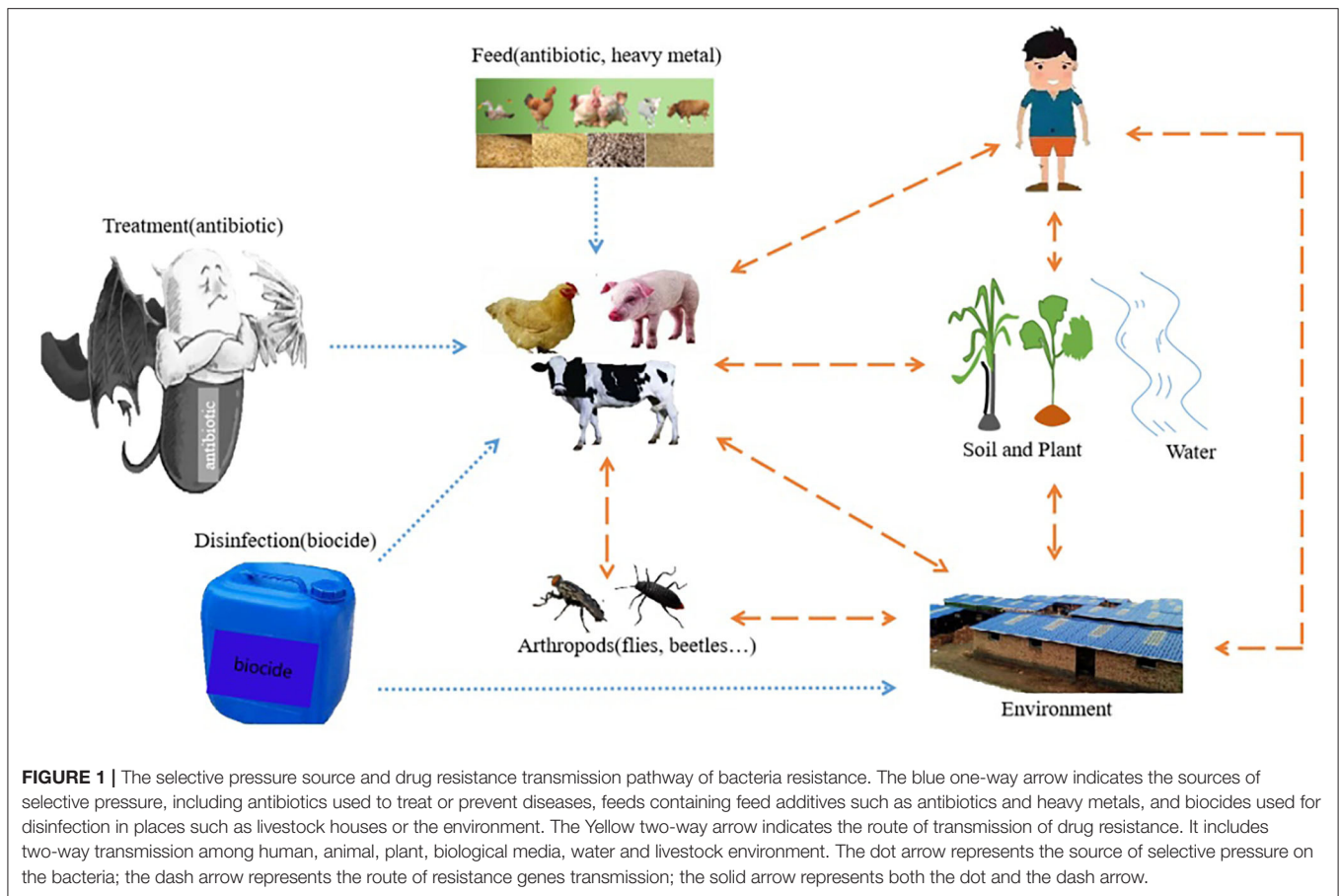
environment, such as flies (Zhao et al., 2019). The sources of selective pressure and the routes of drug resistance transmission are shown in **Figure 1**. Vertical gene transfer (VGT), a process of cell growth (Seoane et al., 2011), and horizontal gene transfer (HGT), the transfer of DNA by mobile plasmids between genera (Li et al., 2019a), coexisted in the natural environments (Qiu et al., 2018). Under the pressure of long-term selection, the inseparable connection among human, animal, environment and food may be an important factor to induce drug resistance and cause vertical or horizontal transmission of drug-resistant factors.

MECHANISM OF BACTERIAL RESISTANCE MEDIATED BY DIFFERENT FACTORS

Antibiotic resistance is a global problem and poses a major threat to human and animal health. Driven by conditions such as selective pressure of antibacterial drugs, spontaneous mutation, recombination and horizontal gene transfer, the unreasonable use of antibiotics has led to the increasing resistance of bacteria to antibiotics. The resistance of bacteria to antibacterial drugs is caused by genetic variation of different mechanisms. The increase in human health risks associated with antimicrobial resistance has prompted us to study the development mechanism of drug resistance, and in-depth exploration of the factors related to the spread of resistance genes in order to take necessary measures to reduce the growing threat. The resistance mechanisms of bacteria to antibiotics, heavy metals and biocides are introduced as follow.

The Resistance Mechanism to Antibiotics

Genetic plasticity is a prominent feature of bacteria, which will enable bacteria to respond to various threats in the environment, including the existence of antibiotic molecules that may endanger their survival. The main bactericidal mechanisms of antibiotics are: hindering the synthesis of cell wall, inhibiting nucleic acid and protein synthesis, affecting bacterial metabolism and the function of cell membrane. From the perspective of evolution, bacteria mainly adapt to the “attack” of antibiotics through two genetic strategies (Munita and Arias, 2016). (i) In general, gene mutation is associated with the mechanism of action of compounds and (ii) horizontal gene transfer (HGT) is used to obtain exogenous DNA encoding the determinants of resistance. Traditionally, bacteria obtain external genetic material through three main methods: transformation, transduction, and combination. Emergence of resistance often involves conjugation. Conjugation is likely to occur in the gastrointestinal tract of animals receiving antibiotic treatment, which involves cell-to-cell contact, and is a relatively effective method of gene transfer. As a common rule, mobile genetic elements (MGEs) are used as carriers to share valuable genetic information. Plasmids and transposons are the most important MGEs, which play an important role in the development and spread of drug resistance in clinical related microorganisms. In addition, integron is one of the most effective mechanisms for accumulating antibiotic resistance genes, and it is also one of the main driving forces of bacterial evolution. It is a site-specific recombination system that can capture mobile gene cassettes carrying resistance genes



and provide an effective mechanism to ensure the expression of new genes. In particular, it is worth noting that carrying plasmids usually results in huge adaptation costs, which means that if the bacteria carrying plasmids want to survive in the population, the cost of plasmids needs to be balanced by the selection pressure brought by antibiotics, for example. In other words, the existence of antibiotics is conducive to the maintenance of plasmid carrying resistance gene. The effects, the use of different types of antibiotics on the generation, spread of bacterial drug resistance and maintenance of drug resistant plasmids will be described in detail in Antibiotics.

The Resistance Mechanism of Copper and Zinc

Metallic oxide played a role in retarding or declining bacterial growth through the generation of active oxygen (Qiu et al., 2018). Copper and zinc compounds are widely used in animal husbandry as feed additives (Yazdankhah et al., 2014). The use of copper compounds causes copper to enter the environment and causes copper pollution in the environment, which leads to the production of copper-resistant genes by many microorganisms (Yazdankhah et al., 2014). The resistance mechanism to copper is basically non-ATP enzyme excretion mode, and its copper resistance system mainly includes *cut* system and *pco* system,

as well as *cusCFBA* efflux system in copper oxidase CueO. Copper-resistant plasmids are often endowed with the gene family *pco* (Tetaz and Luke, 1983; Yang et al., 2020). Some bacteria have strong adaptability to zinc and can automatically change heavy metals from highly toxic state to low toxic state or non-toxic state through biotransformation or physiological metabolic activities. For instance, *E. coli* evolved a genetic system of tolerance to heavy metal zinc, showing resistance to heavy metal zinc (Grass et al., 2002). So far, it has been found that *E. coli* has four systems to keep intracellular Zn^{2+} in balance, namely *znuABC*, *zupT*, *zntA* and CDF system. *ZnuABC* and *zupT* systems are responsible for absorbing Zn^{2+} , while *zntA* and CDF systems are responsible for pumping Zn^{2+} out. Studies have shown that (Rensing et al., 1997) the gene *zntA*, which is usually integrated into the chromosome of bacteria, can encode Zn(II) export protein and is responsible for the specific resistance to Zn(II), Pb(II) and Cd(II) in *E. coli* (Yang et al., 2020). In prokaryotes, the main mechanism of reducing accumulation is the active efflux of cations (Nies, 1992). Up to now, all bacterial cation efflux systems are encoded and induced by plasmids. In gram positive multi metal resistant *Staphylococcus aureus*, membrane bound *cadA* protein (a P-type ATPase) catalyzes the efflux of Cd^{2+} (and possibly Zn^{2+}). The second protein (CADC) is necessary for complete drug resistance, while the third protein (Cadr) is considered to be the decisive factor in

regulating drug resistance. The proteins necessary for CO^{2+} , Zn^{2+} and Cd^{2+} efflux (*czca*, *czcb* and *czcc*) and the determinants of regulatory drug resistance (*czcd*) are all encoded by the determinants of *Czc* from gram negative multi heavy metal resistant bacteria *Alcaligenes eutrophus*. The efflux of chromate catalyzed by the *ChrA* efflux pump leads to chromate resistance (Juhnke et al., 2002). Two determinants of chromate resistance genes were found in this bacterium. That is, the *chr(1)* [genes *chrI*, *chrB(1)*, *chrA(1)*, *chrC*, *chrE*, *chrF(1)*] on the known plasmid pMOL28 and the *chr(2)* on the chromosome [genes *chrB(2)*, *chrA(2)*, *chrF(2)*]. The gene *rcnA* commonly found in *E. coli* is specifically induced by nickel or cobalt and confers resistance to nickel and cobalt based on the efflux system (Rodrigue et al., 2005). Additionally, the research on the effect of heavy metal on bacterial resistance is mainly as a selective pressure to induce antibiotic resistance and promote the spread of resistance genes. The effects of the presence of heavy metal on the generation, spread of bacterial drug resistance will be described in detail in Heavy metals.

The Resistance Mechanism to Biocides

The academic definition of bacterial resistance to biocides are: (i) a bacterial strain that is not killed by a biocide concentration to which the majority of the bacterial species are susceptible and (ii) bacterial cells in a culture that survive biocide exposure that kills the majority of the bacterial population in that culture (Maillard, 2018). Biocides usually put pressure on bacterial cells and cause the bacteria to die (Maillard, 2018). The main bactericidal mechanism is destroying the integrity and permeability of the cell membrane, leading to leakage of intracellular material and DNA degradation (Lin et al., 2019; Yi et al., 2019). It can also affect DNA replication through protein denaturation (Chindera et al., 2016) or inhibit biofilm formation (Wang et al., 2018; Halicki et al., 2020). In response, bacteria express several mechanisms to defend against the adverse effects caused by biocides. These mechanisms include the ability of bacteria to repair damage, which can sufficiently reduce the concentration of biocides so that they no longer cause damage to bacterial cells (Maillard, 2018). Therefore, The resistance mechanisms to biocides include decreasing the concentration of biocides in bacteria (reducing biocide penetration; efflux pumps; enzymatic degradation), changing physiology and metabolism and producing mutations, which has been described in detail in a review (Maillard, 2018). Due to selective pressure of disinfectant, mutations or differential gene expression can significantly contribute to disinfectant resistance (Samantha Mc Carlie, 2020); the mechanism of acquired resistance also includes the effective transfer of mobile genetic elements that can carry single or multiple resistance determinants (Samantha Mc Carlie, 2020). Efflux of biocides is also a major mechanism (Russell, 2001; Mohsen and Brown, 2017). Many biocides can induce adaptive multiple antibiotic resistance phenotypes. This may be due to the increased expression of efflux pump and decreased synthesis of outer membrane porin, or both (Molnar et al., 2015). The effects of the present of biocides on the generation, spread of bacterial resistance will be described in detail in Biocides.

INFLUENCES OF DIFFERENT FACTORS ON BACTERIAL RESISTANCE

Antibiotics

Since the 1940s, antibiotics have been widely used in livestock and poultry production as a kind of medicine with the functions of medical treatment, and have played a huge role in promoting the development of animal husbandry (Kumar et al., 2019). When antibiotics are used to treat the infection of pathogenic bacteria, the premise of bactericidal effect is to reach the effective drug concentration and action time, which is concentration and time-dependent on the action of bacteria. When antibiotics are used for treatment, prevention and feed additive to promote growth, they often expose to the pathogenic bacteria and the common bacteria that are usually in the sub-lethal concentration. Due to the selective pressure of antibiotics, both the pathogenic bacteria and the common bacteria develop resistance. The resistant bacteria and their resistance genes will spread horizontally between animals, environment and humans, thus posing a serious threat to human health. Therefore, relevant national governments or institutions need to improve regulatory measures and strengthen supervision to ensure the healthy, stable and sustainable development of the animal husbandry industry. The main antibiotics commonly used in clinic are β -lactam, tetracycline, aminoglycoside, chloramphenicol, quinolone, sulfonamides and polypeptide. As most countries in the world banned the use of multiple antibiotics as ways to prevent animal diseases or as feed additives, the resistance of bacteria to some antibiotics has declined. For example, the European Commission (EC) issued a decree to ban the use of antibiotics as growth promoters in feed since 2006 (Huyghebaert et al., 2011). Subsequent investigations showed that antibiotic resistance is 6–20% lower in places where the use of antibiotics as growth promoters is prohibited than in places where is no policy (Huyghebaert et al., 2011). In 2015, the 68th World Health Assembly passed the Global Antimicrobial Resistance Action Plan (Laxminarayan et al., 2020). All member states recognized the serious threat that antibiotics pose to human health and advocated specific actions to solve this problem. Since 2015, the implementation of the U.S. Food and Drug Administration (FDA) Veterinary Feed Directive has reduced the sales of antibiotics as growth promoters (Doshi et al., 2020). In the United States, where fluoroquinolone drugs are banned, the drug resistance rate does not exceed 5%, while in Brazil, China, and the European Union, where the drug is registered, the drug resistance rate is not <40 % on average (Roth et al., 2019). In 2016, India decided to ban unreasonable use of drugs and promised to ban colistin as a growth promoter in order to implement better antibacterial management (Laxminarayan et al., 2020). In recent years, the Chinese government has successively published a list of antibiotics banned in agriculture, and has achieved remarkable results in reducing and replacing the use of antibiotics (Xu et al., 2020). Although in the short term, these antibiotic uses appeared to be beneficial, in fact this practice not only caused to bacterial resistance more easily, but may even induce super resistant bacteria (Kumar et al., 2019). There have been many reports on the effect of low level antibiotics on bacterial resistance, as shown in **Table 1**.

TABLE 1 | The impact of low-level antibiotics in some countries or regions on bacterial resistance.

Classification of antibiotics	Antibiotics	Bacteria	Major results	Mechanism	Reference
β-lactam	Ceftiofur	<i>E. coli</i>	Increased prevalence of cefotaxime-resistant strains isolated from the gastrointestinal tract of animals	Propagation of plasmids carrying <i>blaCTX-M</i> and clonal expansion of previously existing resistant strains.	Lin et al., 2017
	Cefotaxime	<i>S. aureus</i>	Resistance to several types of antibiotics and cross-resistance	Free radical production	Bhattacharya et al., 2017
Tetracycline	Tetracycline	<i>E. coli</i>	Two functional mutations in the genome of the recipient strain accompanied plasmid transfer.	Stimulated transfer of the resistance plasmid most	Schuermans et al., 2014
Sulfonamides	Sulfamethoxazole	A complex bacterial community, <i>E. coli</i>	The spread of antibiotic resistance has risen significantly	Promote the horizontal spread of antibiotic resistance among bacteria	Schuermans et al., 2014
Aminoglycoside	Gentamicin	A complex bacterial community and <i>E. coli</i>	The spread of antibiotic resistance has risen significantly	Antibiotic resistance is severe due to increased spread	Jutkina et al., 2018
	Streptomycin	<i>E. coli/S. Typhimurium</i>	Existing resistant mutants are enriched and maintained, and new mutants are reselected	-	Gullberg et al., 2011
	Streptomycin	<i>S. enterica</i>	High levels of resistance evolve under weak selection pressure	(i) Change of ribosomal RNA target (<i>gidB</i> mutation), (ii) reduced uptake of aminoglycosides (<i>cyoB</i> , <i>nuoG</i> and <i>trkH</i> mutations), (iii) aminoglycoside modifying enzyme <i>AadA</i> (<i>znuA</i> mutation) is induced	Wistrand-Yuen et al., 2018
Aminoglycoside	Kanamycin and Streptomycin	<i>E. coli</i>	Facilitates the delivery of the combined plasmids pRK2013, pSU2007 and RP4	Promoted the process of <i>E. coli</i> conjugation	Zhang et al., 2013
	Kanamycin	<i>E. coli</i>	Bacteria with multiple resistance plasmids are selected and enriched	Balance fitness costs	Gullberg et al., 2014
Chloramphenicol	Erythromycin	<i>C. coli/E. faecium</i>	Obtained macrolide-resistant mutants	Mutations in gene	Ge et al., 2017
	Florfenicol	Between <i>S. Typhimurium</i> and <i>E. coli</i>	Significantly increase the average isolation rate of <i>oqxAB</i> positive <i>E. coli</i>	Enhance the <i>oqxAB</i> gene spread	Ge et al., 2017
Quinolone	Enrofloxacin	Between <i>S. Typhimurium</i> and <i>E. coli</i>	Significantly increase the average isolation rate of <i>oqxAB</i> positive <i>E. coli</i>	Enhance the <i>oqxAB</i> gene spread	Chen et al., 2016
	Ciprofloxacin/ Levofloxacin	<i>E. coli</i>	Transfer frequency was significantly increased	The expression of related genes is up-regulated	Chen et al., 2016
Polypeptide	Colistin	<i>K. pneumoniae</i>	The <i>PmrB</i> mutation that mediates colistin resistance is selected	Mutations in gene	Shun-Mei et al., 2018

-presents not mentioned.

Heavy Metals

Heavy metal elements are important components of a series of bioactive substances such as enzymes, hormones and vitamins in human and animal bodies. They participate in the composition of various enzymes and coenzymes, and play an important role in regulating the acid-base balance of body fluids, maintaining the osmotic pressure balance between cells and blood, and promoting the activities of digestive enzymes. It was found that heavy metals such as copper, zinc, chromium, nickel, lead and cadmium were widely used as feed additives in some intensive dairy farming in China (Cannatelli et al., 2014). However, the heavy metal elements may lead to resistance, which is associated with excessive use of Cu and Zn as feed additive. High levels of zinc oxide are also often used as feed additives. This feed contains calcium and iron, which can not only maintain the production of laying hens, but also prevent layers from contracting *Salmonella* (Li et al., 2019b). However, the presence of heavy metals provides a selective pressure on bacteria. Their stability and persistence may encourage bacteria in food and animals to develop resistance to heavy metals when heavy metals reach a critical concentration. For example, zinc rich supplements in pig feed have chosen more zinc tolerant *E. coli* (Noh et al., 2017). It is worth noting that bacteria may develop antibiotic resistance at sublethal concentrations of heavy metals, promote plasmid-mediated horizontal transfer of antibiotic resistance genes, and drive the abundance of ARGs (Sharma et al., 2016). Some metals increase the frequency of bacterial resistance through genetic mutations under long-term exposure to sub-MIC levels (Noh et al., 2017). For example, the MIC of bacteria to ciprofloxacin increased by 24.8, 15.6 and 3.9 times respectively after being induced to be mutated at the sublethal levels of Ag(I), Cu(II) and Zn(II) (Johanns et al., 2019). These resistant mutants also exhibited multi-drug resistance. For example, Zn(II) evolved ciprofloxacin-resistant mutants, and at the same time showed resistance to chloramphenicol and tetracycline (Maillard, 2005). In a pig isolate, it was identified that a plasmid carrying a gene named *tcpB* on a conjugated plasmid made *Enterococcus faecalis* copper resistant (Maillard, 2005). Studies have shown that the use of copper selects new resistance genes. For example, copper-resistant *Salmonella* can be isolated from pig feed supplemented with copper (Aarestrup et al., 2002; Li et al., 2019c). Cu resistance genes *pcoA* was found in multi-resistant *Enterobacteriaceae* with *bla_{NDM-1}* or *bla_{CTX-M-15}* genes, and these genes were mostly located on plasmids (Medardus et al., 2014). The resistance of high-zinc feed may increase due to the correlation between zinc tolerance and antimicrobial resistance. It has recently been found that the copy number of tetracycline and sulfonamide resistance genes is increased in the intestines of weaned piglets fed a high diet of zinc oxide (Poole, 2017). The zinc concentration in liquid pig manure and phenotypic antimicrobial resistance in *E. coli* have been linked in recent publications in Germany (Yang et al., 2018). And the level of pharmacological zinc feeding is related to the increase in the prevalence and persistence of methicillin-resistant *S. aureus* (Vahjen et al., 2015). However, the research found that there was no correlation between phenotypic zinc resistance and multiple antimicrobial resistance in piglet fecal *E. coli* isolates (Hölzel et al., 2012). Observations showed that the MIC of *E. coli* isolated from animals on zinc or

copper did not change when exposed to high concentrations of zinc.

Biocides

Biocides generally refer to all chemicals such as disinfectants and preservatives, fungicides, algacides, rodenticides and insecticides (Hölzel et al., 2012; Slifierz et al., 2015b) and phages and bacteria and other biological agents used to kill pathogenic microorganisms (Slifierz et al., 2015b). In a sense, biocides are a very diverse group of chemicals. Nowadays, chemical biocides are widely used in consumer goods, water, food industry, commodity manufacturing industry, pharmaceutical industry, health care and veterinary departments, as well as oil and gas industry. The universal application reflects the versatility of biocide products in environmental disinfection, product preservation and anti-corrosion (Ghazisaeedi et al., 2020). The biocides used for disinfection and antiseptics mainly include: Alcohols (ethanol, isopropanol); Aldehydes (glutaraldehyde, formaldehyde); Anilides (triclocarban); Biguanides (chlorhexidine, alexidine, polymeric, biguanides); Bisphenols (triclosan, hexachlorophene); Diamideines (propamidine, dibromopropamidine) (Paul et al., 2019). In addition, disinfectants based on quaternary ammonium compounds (QAC) are stable, have low cytotoxicity, and are non-corrosive to farm equipment. Therefore, it has become the most commonly used disinfectant in industry and animal production. The effect of biocides on bacterial resistance is shown in **Table 2**. Although there are many reports that microbial resistance will be affected with the use of fungicides, there are different views in the field of research. The use of disinfectants in the poultry and swine industry and their contribution to the antibiotic and disinfectant susceptibility of *E. coli* strains obtained after cleaning and disinfection were studied. They found that all *E. coli* strains were sensitive to formaldehyde, benzalkonium chloride, acetic acid and hydrogen peroxide at moderate concentrations, indicating that anti disinfectants were not selected in the actual use of disinfectants (Maillard, 2005). Randal and others discussed the adaptability and spread of multi-drug resistant (MAR) *Salmonella* and *Salmonella typhimurium* in the intestines of chickens under the choice of farm disinfectant. Their research shows that the resistant strains screened by farm disinfectants will not be preferentially selected because of the use of disinfectant, and their transmission ability is weak, and will not cause more harm to chickens than other *Salmonella* (McDonnell and Russell, 1999). A large veterinary institution in Australia has detected the pathogenic bacterium *Enterobacter homachi* in the hand washing pool of ICU in a hospital. Despite two subsequent attempts to disinfect it with biocides, the microorganism still survived for several weeks (McDonnell and Russell, 1999). However, the level of disinfectant tolerance can be slightly increased by the disinfectant mutants of *Salmonella typhimurium* (Maertens et al., 2019). In conclusion, improper disinfection program combined with the use of antibiotics may be still at the risk of leading to a higher level of bacterial resistance.

Arthropods

Arthropods, such as flies, beetles, cockroaches and so on, are common in livestock units. The persistent fecal substrate, thermal insulation materials and accumulated dust provide a

TABLE 2 | Effect of biocides on bacterial resistance.

Biocides	Bacteria	Consequence	Mechanism of resistance	References
ABD	<i>S. Typhimurium</i>	Decreased susceptibility to ciprofloxacin	A one- step point mutation in <i>gyrA</i>	Randall et al., 2007a
PFD	<i>S. Typhimurium</i>	Biocide resistance	Obviously promotes the expression of AcrAB-TolC efflux system	Kamatthewatta et al., 2020
QACFG	<i>S. Typhimurium</i>	Reduced susceptibility to several antibiotics	Over-expression of AcrAB efflux pump	Randall et al., 2007b
Triclosan	<i>S. Typhimurium</i>	Reduced susceptibility to several antibiotics	Over-expression of AcrAB efflux pump	Randall et al., 2007b
	Triclosan-tolerant strains of <i>E. coli</i>	Significantly more susceptible to aminoglycoside antibiotics.	The outer membrane is changed, or the plasmid is lost	Karatzas et al., 2007
	<i>K. pneumoniae</i> TRI ^r variants	Causes cross-resistance with antimicrobial agents such as AMP, CIP, CLO, TET and CAZ	Changes in AraC global regulatory agencies (MarA, SoxR and RamA), AcrAB-TolC and/or FabI	Cottell et al., 2009
	<i>E. coli</i>	Antibiotic resistance	The spread of antibiotic resistance is increasing	Curiao et al., 2015
Chlorhexidine	<i>E. coli</i>	Antibiotic resistance	The spread of antibiotic resistance is increasing	Curiao et al., 2015
Benzalkonium chloride	<i>E. coli</i>	Biocide resistance	Mutations in gene	Jutkina et al., 2018
Benzalkonium chloride	MRSA	Antibiotic resistance	Participated in the selection and longevity of MRSA	Sheridan et al., 2012
Five kinds of QACs	<i>E. coli</i>	The transfer of RP4 resistant plasmid in <i>E. coli</i> is facilitated	Bacteria's production of ROS is stimulated, and the permeability of bacterial cell membrane is changed	Slifierz et al., 2015a
Super kill and AQAS	<i>S. Typhimurium</i>	Decreased resistance to multiple antibiotics, but unchanged to fungicides	Over-expressed the AcrEF efflux pump	Han et al., 2019
Five biocides	<i>Campylobacter</i>	Increase the tolerance of itself and other biocides and antibiotics	Active efflux, outer membrane protein profile and cell morphology are changed	Rebekah, 2011
A mix of benzalkonium chloride and glutaraldehyde	<i>E. coli</i> and non-typhoidal <i>Salmonella</i>	Biocide resistance	Glycolytic enzymes and porins are overexpressed or inactivated due to genetic mutations	Mavri et al., 2016
Three kinds of disinfectant	<i>Salmonella</i> enterica Serovar Typhimurium	Biocide resistance	AcrAB-TolC expression increased and outer membrane protein levels decreased	Nhung et al., 2015
Ethanol	<i>B. subtilis</i>	Tn916-like elements and any resistance genes contained in them are induced or transferred	Transfer of mobile genetic elements	Kimon et al., 2008

PFD, a tar oil phenol disinfectant; ABD, aldehyde based disinfectant; QACFG, Quaternary ammonium salt disinfectant containing formaldehyde and glutaraldehyde; Super kill (SK), a mixture of aldehydes and quaternary ammonium compounds; AQAS (AQ), a quaternary ammonium compound. Five kinds of QACs: DTAC, dodecyl trimethyl ammonium chloride; DDDAC, didodecyl dimethyl ammonium chloride; DDBAC, dodecyl dimethyl benzyl ammonium chloride; TDBAC, tetradecyl dimethyl benzyl ammonium chloride; HDBAC, hexadecyl dimethyl benzyl ammonium chloride. Five biocides: triclosan, benzalkonium chloride, cetylpyridinium chloride, chlorhexidine diacetate and trisodium phosphate. Three kinds of disinfectant: An oxidizing compound blend, a quaternary ammonium disinfectant containing formaldehyde, a tar acid-based disinfectant. MRSA, methicillin-resistant *Staphylococcus aureus*; AMP, ampicillin; CIP, ciprofloxacin; CLO, chloramphenicol; TET, tetracycline; CAZ, ceftazidim.

suitable living environment for them. They have a special ability to transfer pathogens and resistance genes from different environmental levels. Flies carrying *Salmonella* with the same serotype and subtype as livestock and poultry can usually be caught around livestock and poultry farms that are positive for *Salmonella* (Hancock et al., 1998; Olsen and Hammack, 2000; Davies and Breslin, 2003; Seier-Petersen et al., 2014). *Clostridium perfringens* can also often be isolated from flies and beetles around infected broiler flocks (Hancock et al., 1998; Olsen and Hammack, 2000; Davies and Breslin, 2003; Kinde et al., 2005; Seier-Petersen et al., 2014). *Salmonella* reported to be isolated from mantis samples from poultry farms in the Middle East (Craven et al., 2001) and in a hatchery and poultry feed mill in the USA (Fathpour et al., 2003). Cockroaches are closely related to people and animals. They have been repeatedly accused of being vectors of food poisoning bacteria (Kopanic et al., 1994). Bacterial pathogens can live on their body surface and digestive tract and spread through direct transfer or during reflux and defecation (Ostrolenk and Welch, 1942). From the above description, we can know flies may be a health indicator of the prevalence of antimicrobial resistance (Schaumburg et al., 2016; Onwugamba et al., 2018). This view was previously confirmed by Zurek and Ghosh (Zurek and Ghosh, 2014). Flies entering the broiler house increase the risk of colonization of multi-drug resistant *E. coli* in broiler chickens (Solà-Ginés et al., 2015; Poudel et al., 2019). However, no similar transfer studies have been found in other arthropods on the farm.

Bacterial resistance is also affected by stress factors. The resistance of diseased livestock and poultry is regulated by nerves, body fluids and endocrine to a certain extent. Under the influence of various stress factors, such as climate upheaval (supercooling or overheating), excessive humidity, strong light, poor ventilation, group transfer, the normal physiological functions of the body will be seriously disordered, and the body's constitution will be reduced, and the resistance will be reduced, and the drug resistance will produce. Studies have shown that some components of the immune system have broad-spectrum antibacterial activity (Andersson et al., 2016). Under long-term action, bacteria can develop resistance to these broad-spectrum antibacterial substances. When the veterinarian uses antibiotics to treat diseased animals, the pathogenic bacteria population will be exposed to sublethal levels of antibiotics. Once some pathogenic bacteria survive, they also may become resistant to antibiotics and spread horizontally or vertically (Andersson et al., 2016). Therefore, to create a good environment for livestock and poultry, reduce the incidence of drug resistance, measures such as reducing stress factors, strengthening feeding management, purifying and disinfecting pens should be taken.

SUGGESTIONS ON REDUCING THE OVERALL LEVEL OF ANTIBIOTIC RESISTANCE IN THE DEVELOPMENT OF ANIMAL HUSBANDRY

The causes of antibiotic resistance are complex. In animal husbandry, bacterial resistance to antibiotics is caused by many factors, such as medication procedure, management system,

breeding environment, selection pressure and so on (Manyi-Loh et al., 2018). Generally, drug resistance is caused by the combination of environmental selection and gene mutation (Manyi-Loh et al., 2018). Long term use of antibiotics in domestic animals may lead to drug resistance in both human and animals. In order to reduce the incidence of bacterial drug resistance, it is necessary to avoid creation of the settings that beneficial for resistance genes persistence in bacterial communities, reduce dispersal routes for resistant bacteria to microbiome, limit the selection pressure for resistant pathogens and strengthen feeding management. Therefore, it is urgent to take appropriate measures to alleviate the generation and spread of drug-resistant strains according to the actual situation.

Ensure that antibiotics are used correctly in humans and animals (van den Bogaard and Stobberingh, 1999). In order to prevent and control the occurrence of epidemic diseases, some farms add antibiotics to feed and drinking water, and frequently use the same kind of antibiotics, so that long-term drug use leads to bacterial resistance to antibiotics. Secondly, not changing the antibiotics in time or increasing the dosage of drugs are also one of the important reasons for the increase of drug-resistant strains. In order to solve this problem, we can consider changing the way of drug use (Friedman et al., 2007). If we use interval or shuttle drug, the frequency of drug resistance will be greatly reduced. Interval medication refers to the use of a drug in the process, not continuous use, can be divided into batches and doses. Shuttle drug use mainly refers to the use of different drugs interspersed, or in different seasons, different years, so as to reduce drug resistance. In addition, the combination of many antibiotics has obvious synergistic effect. For example, the combination of penicillin and aminoglycoside antibiotics, which is the most common in clinic, not only broadens the antibacterial spectrum, but also reduces the drug dosage and plays the role of the best efficacy.

Prevention of bacterial infection and transmission. "There is a correlation between the use of antibiotics in livestock and poultry breeding and the infection of drug-resistant bacteria in humans and livestock," which is still further aggravating (Chen et al., 2018). Improving public and personal health conditions to prevent the generation and spread of pathogens is a crucial measure to solve this problem. The fewer people and livestock are infected, the less antibiotics are needed and the slower resistance develops. Developing countries should focus on improving infrastructure and providing more clean water and sanitation. The focus of other countries should be to reduce the infection of pathogenic bacteria and prevent the emergence of super resistant bacteria.

Develop new antibiotics or find alternative therapies (Cox and Wright, 2013). After the emergence of metallo-lactamase *NDM-1*, the only way to treat it is to use polymyxin as the "last line of defense." Due to its high toxicity, polymyxin has always been a kind of antibiotic that is not easily used by human beings. Therefore, the development of a new generation of antibiotics has become an urgent task in the world. Chemical synthesis and natural product research are two main methods for human beings to discover antibiotics. Compared with chemical synthesis, most of the antibiotics used by human beings are derived from natural products, such as β -lactam antibiotics,

vancomycin and polymyxin, which are the “last line of defense” against bacterial infection (Okano et al., 2017). However, due to the complex structure of natural products and low synthesis efficiency, the production line of new antibiotics is not optimistic, and alternative solutions are needed (Rossiter et al., 2017). One possible alternative is vaccination. In fact, despite the rapid emergence of antibiotic resistance, vaccines can allow infections to be controlled more sustainably (Tagliabue and Rappuoli, 2018).

Participate in international cooperation to reduce the risk of drug resistance transmission. Drug resistance is not a problem that can be solved by a single country, or even by a region. In fact, the world has taken intervention measures from many aspects to deal with the challenges brought by antibiotic resistance (Laxminarayan et al., 2013). For example, the European Medical Agency (EMA) is mainly responsible for the evaluation, monitoring and early warning of EU drugs. There is a special group to carry out specific work, including the Scientific Advisory Group on Antimicrobials (SAGAM), which makes recommendations to the Committee for Medicinal Products for Veterinary Use (CVMP) on the approval and use of veterinary antibiotics, especially the development of guidelines on antimicrobial resistance. The Federation of Veterinarians of Europe (FVE) is a veterinary organization from 35 European countries, including four veterinary groups: industry veterinarians, public health veterinarians, education, research and enterprise veterinarians, and state veterinarians. In 1999, FVE established an *ad hoc* group on antimicrobial resistance and formulated guidelines for the use of antimicrobial agents in animals to reduce the occurrence and spread of drug resistance. However, due to a lack of access to investment, infrastructure and modern equipment some developing countries struggle to adequately implement strategies available to wealthier nations. It can be seen that, to a large extent, there is a lack of coordinated global action, especially at the national and international political levels. At present, countries in the world are more interconnected and interdependent than ever before. Especially in the field of international health care and health, we should advocate the consciousness of “a community of shared future for mankind.”

To improve the monitoring of antibiotics for human and animal use. To this end, the world should first make efforts to monitor and quantify antibiotic resistance in the environment. This requires countries to provide adequate support for the construction of advanced drug resistance monitoring networks and biological risk assessment systems. In 2014, the World Health Organization (WHO) for the first time issued a global antibiotic resistance monitoring report, mainly reports the 7 kinds of common pathogens of antimicrobial resistance of international concern. The World Organization for Animal Health (OIE) launched its first annual data collection on antimicrobial use in animals in 2015, published the first edition of its Annual Report on Antimicrobial Use in Animals in 2016 and the second report in 2017 (Tornimbene et al., 2018). It sorted out the use of veterinary antibiotics in 146 countries and regions from 2013 to 2016. Although these reports may be considered to have limitations on the effectiveness of the impact due to mixed factors such as obsolescence,

national attributes and information bias. These reports still provide valuable reference for the global sharing of information on the development trend of bacterial resistance, and also bring new hope for the global joint response and solution of antibiotic resistance.

Strengthen the propaganda, education and training of antibiotics. Enhance global awareness of antibiotic resistance, disseminate awareness and appropriate information about the risks and consequences of rapidly developing antibiotic resistance. Some countries are looking for alternatives to antibiotics in animal husbandry in order to reduce the use of antibiotics on farms and ensure that the economic benefits of the farm will be further improved under the guidance of the policy (Prescott, 2017; Antão and Wagner-Ahlf, 2018). It is very important to solve this global problem that everyone in the agricultural sector, public sector, health sector, drug administration department and the public at different levels should treat the drug resistance problem of animal origin bacteria as the master. In a word, it is not an overnight thing to solve the problem of antibiotic resistance. The whole world needs an united front to formulate long-term plans and goals, work together in the same boat, and contribute to a better future for the world.

CONCLUSIONS

This paper reviews the influencing factors and mechanisms of bacterial resistance, and puts forward some possible suggestions on how to alleviate the emergence and spread of bacterial resistance. In livestock and its environment, animals are both recipients and providers of selective stress, and ultimately bacteria are survived in a sub-lethal level of antimicrobial environment. Under the selective pressure from low levels of antibiotics, heavy metals and biocides, bacteria produce corresponding resistance. And this pressure can promote the inter-bacterial spread of resistance genes. Most notably, non-antibiotic antibacterial agents can induce or select bacterial adaptation, thereby reducing sensitivity to one or more antibiotics. Apart from antibiotics, heavy metals and biocides, bacterial resistance is also affected by arthropods in the environment. Flies carrying drug-resistant bacteria and resistant genes can transmit them to food animals and bacteria in their environment, and they have the risk of being transmitted to human beings through the food chain, which poses a threat to public health. Furthermore, from the physiological point of view of animals, stress can lead to physiological dysfunction of animals, which indirectly leads to bacterial resistance. Briefly, many factors directly or indirectly cause bacterial resistance. Therefore, countries or alliances around the world should combine the monitoring of animal-derived bacterial resistance and the application of veterinary drug supervision platforms to improve the scientific management of veterinary antimicrobials, effectively promote the reduction of veterinary antimicrobials, and ensure production safety in the global aquaculture industry, Livestock and poultry product quality safety, public health safety and ecological environment safety.

AUTHOR CONTRIBUTIONS

KG, YZ, and MD contributed conception and design of the study. KG, YZ, LC, and MD investigated and surveyed literatures. YZ wrote the first draft of the manuscript. KG wrote the second draft of the manuscript. KG, YZ, LC, ZC, FZ, XW, JF, and MD revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported by the National Key R&D Program of China, grant number 2017YFC1600100, the Fundamental

Research Funds for the Central Universities, grant number 2662017JC034, the Applied Basic Research Programs of Wuhan, grant number 2017020201010228 to MD, and the Earmarked Fund for China Agriculture Research System, grant number CARS-35 to XW.

ACKNOWLEDGMENTS

The authors thank the National Key R&D Program of China, the Fundamental Research Funds for the Central Universities, Applied Basic Research Programs of Wuhan and the Earmarked Fund for China Agriculture Research System for funding this study.

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