Antimicrobial Resistance in Food-Producing Livestock Wastes

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Abstract

Antibiotics used in the treatment of food-producing livestock have been widespread since 1937. That year marked the beginning of antibiotic treatments for pneumonia and mastitis in dairy cattle. By the 1960s, antibiotic growth promoters (AGPs) in feed became common across various livestock industries, particularly poultry, beef cattle, dairy cattle, and pigs. Data indicates in 2013, antibiotic use in the livestock sector reached 131,109 tons, which is 80% higher than that used in humans. The inappropriate and ineffective use of antibiotics has led to increased antibiotic residues and a rise in antibiotic resistance. Resistant bacteria in livestock can contaminate their environment, particularly through improperly disposing of livestock waste (including feces, urine, and livestock disposal). This contamination can extend to the community through waterways (such as rivers and water sources) and soil, facilitated by inefficient irrigation systems, rainwater, and water runoff. These resistant bacteria can transfer their genetic material to other bacteria, contributing to the development of antibiotic resistance within the environmental microbiota. This situation indirectly impacts humans and is a significant risk factor for the rising prevalence of antibiotic resistance worldwide. This chapter aims to determine the status of the situation of antimicrobial resistance in food-producing livestock wastes so that it can be expected to suppress the rising prevalence of antibiotic resistance worldwide.

Keywords: Antimicrobial resistance, Human Health, and Livestock Waste

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Introduction

Antibiotics have been extensively used in food-producing livestock since 1937, primarily for mastitis and pneumonia in dairy cows (Lees et al., 2019). Until 1960, the use of antibiotic growth promoters (AGPs) was widely applied in the livestock industry, especially in poultry, dairy cattle, beef cattle, and pigs (Kirchhelle, 2018). WHO (2012) reported in 2013 that the use of antibiotics in livestock reached 131.109 tons, 80% higher than that used in humans. Improvements in animal health services contribute to the transmission of antibiotic resistance (AMR) because of the use of antibiotics and the interaction between animals and humans (Palma et al., 2020).

Antibiotic growth promoters (AGPs) at subtherapeutic doses in feed and drinking water over a long period without control can increase the risk of residues and antibiotic resistance (Wijayanti et al., 2023). Low or non-lethal concentrations of AGPs found in an animal's gastrointestinal tract can inhibit the growth of susceptible bacterial populations and promote the proliferation of resistant bacteria (Zu et al., 2017). Resistance bacteria and antibiotic residues may be contained in animal products (meat, milk, eggs) and waste from livestock treated with AGPs (FAO, 2018; Loo et al., 2019; Anning et al., 2022). The problem of antibiotic residues has been reported such as chicken meat in the United States and Malaysia, milk and eggs in Bangladesh, and milk in India (Arsène et al., 2022). Several antibiotic residues such as chloramphenicol, erythromycin, and tetracycline were detected in the environment, particularly on animal farms across Southeast Asia, including Bangladesh, India, and Thailand (Lundborg & Tamhankar, 2017).

The environment can be contaminated with surviving bacteria and antibiotics that have passed out of effectiveness from improper disposal of waste (Loo et al., 2019). The research explained that approximately 75-90% of antibiotics used in animals are not metabolized and are excreted in waste (Marshall and Levy, 2011). The pathogenic bacteria and antibiotic residues that contaminate the environment due to poor waste management (feces, urine, and livestock wastewater) is flowing and contaminate the environment through the water system (rivers and irrigation) and the soil (rainwater and runoff) (Dameanti et al., 2023; He et al., 2020; Sore, 2020). An environment contaminated with antibiotic residues creates selective pressure and genetic mutation of bacteria then causes resistance in the environmental microbiome (Ashbolt et al., 2013). Bacterial resistance will transmitted through vertical gene transfer (from one generation to the next) and horizontal gene transfer (between bacteria via plasmids) (Arsène et al., 2022). Dameanti et al. (2023), reported a 14.32% prevalence of multidrug resistant (MDR) *K. pneumoniae* in livestock waste in East Java, Indonesia. Velo et al. (2020), also reported a 58.2% prevalence of MDR bacteria in poultry farm waste in Malaysia. This situation can indirectly affect human health and contribute to the rising prevalence of AMR (Canton et al., 2012).

Antibiotic Resistance in Food-producing Livestock

In animals antibiotics are used mainly for treatment, control, prevention, and as Antibiotic Growth Promoters (AGPs). Livestock farm antibiotics are administered mainly for metaphylaxis (prevention at the herd level), prophylaxis (prevention at the individual level), and AGPs (Economou & Gousia, 2015). Antibiotic Growth Promoters (AGPs), for example, have been demonstrated to reduce the intestines' microbial population, resulting in less competition for nutrition with the intestine's microbial population, decreased pathogenic microbial count, increased immune response, and improved vitamin biosynthesis and metabolism in the hosts (Wijayanti et al., 2023). The use of antibiotics in cattle farming includes penicillin, amoxicillin, erythromycin, gentamicin, tetracycline, quinolones, novobiocin, tylosin, and tilmicosin (Economou & Gousia, 2015). Enrofloxacin, lincomycin, tetracycline, tiamulin, and ceftiofur are common antibiotics used in pig farms. In the poultry industry, common antibiotics include penicillin, aminoglycosides, quinolones, erythromycin, oxytetracycline, doxycycline, tylosin, sulfonamide/trimethoprim combinations, polymyxins (such as colistin), and tiamulin (Marshall & Levy, 2011). In sheep and goat farming, common antibiotics include penicillin G, ampicillin, amoxicillin, amoxicillin/clavulanic acid combinations, ceftiofur, lincomycin, oxytetracycline, enrofloxacin, erythromycin, trimethoprim-sulfonamide, tylosin, sulfonamides, and tilmicosin (Clark, 2013). In sheep and goat farming, common antibiotics include penicillin G, ampicillin, amoxicillin, amoxicillin/clavulanic acid combinations, ceftiofur, lincomycin, oxytetracycline, enrofloxacin, erythromycin, trimethoprim-sulfonamide, tylosin, sulfonamides, and tilmicosin (Clark, 2013).

Antibiotic resistance refers to the inability of antibiotics to inhibit bacterial growth, causing bacteria that were previously sensitive to become resistant to specific antibiotics (Prestinaci et al., 2015). Antibiotic resistance can result from an increase in the use of antibiotic agents in practical industries, especially in livestock. Excessive use of antibiotics, followed by incorrect dosing, extended treatment periods, or incorrect diagnoses, can lead to antibiotic resistance (Astorga et al., 2019; Economou & Gousia, 2015). Antibiotics are generally used in cattle farming for the treatment of pneumonia, diarrhea, fever during delivery, mastitis, and endometritis (Ansharieta et al., 2021; Riyanto et al., 2016). In pig farming, antibiotics are often administered during the early birth period (stress period) and is common to prevent infectious diseases. This stage includes critical procedures like umbilical cord cutting, tail docking, tooth trimming, male castration, and vaccinations, all of which occur in close succession (Economou & Gousia, 2015). In the poultry industry, antibiotics are commonly used therapeutically, administered through drinking water and as growth promoters (AGPs) to enhance chicken performance (Marshall & Levy, 2011).

Antibiotic resistance can occur through natural bacterial processes. Frequent exposure to antibiotics causes the development of microorganisms' survival mechanisms (Munita & Arias, 2016). Antibiotics resistant in bacteria have resistance genes transferred by mobile genetic elements such as plasmids, bacteriophages, integrons, genomic islands, and transposons, or through changes in their own genetic material due to chromatin instability (Muteeb et al., 2023; Partridge et al., 2018). Consequently, these bacteria express resistance genes that can modify antibiotic targets, enable enzymatic degradation, or activate efflux pumps that expel the drugs, all of which depend on the level of gene expression (Bartlett et al., 2013).

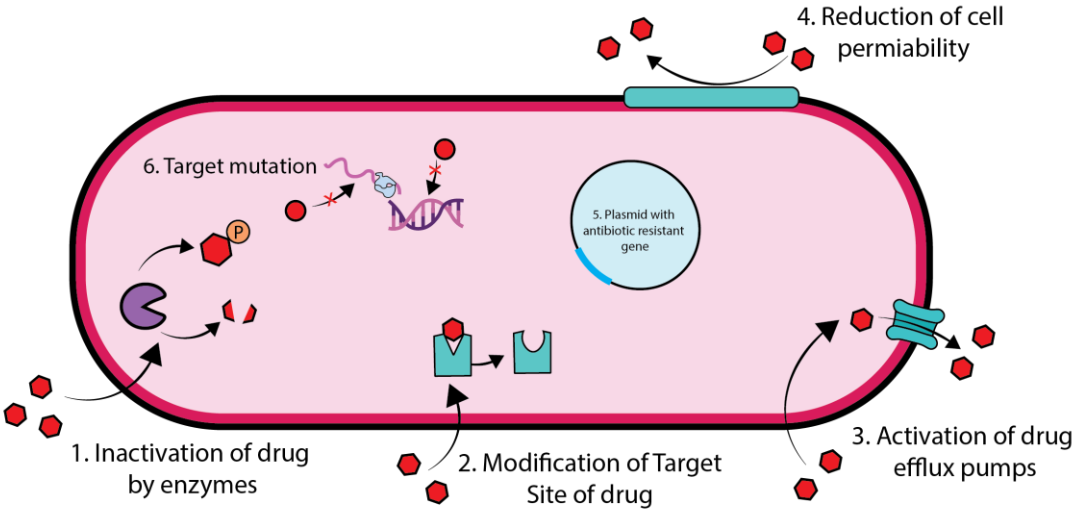

Fig. 1: Antibiotic resistance mechanism

Antibiotic Resistance Mechanisms

Antibiotic resistance in bacteria can arise from two primary mechanisms, the spontaneous mutations in chromosomal genes and the acquisition of resistance genes through horizontal gene transfer from other bacterial species (Cowan & Smith, 2023). Although the likelihood of mutations is quite low. However, given the large population of bacteria in the world and supported by the uncontrolled use of antibiotics, constant mutations can occur. Antibiotic resistance can be attributed to genetic mutations that occur in the bacterial chromosome (Cowan & Smith, 2023). In this scenario, the evolution of resistance happens within a single bacterium before being transferred to another. Bacterial genetic mutations may result from various processes, including duplication, inversion, deletion, addition, and substitution. For instance, resistance to fluoroquinolones is linked to mutations in the DNA gyrase-coding genes gyrB and gyrA (Akiba et al., 2016; Heddle et al., 2002). Similarly, the mutation of the ESBL TEM-1 gene involves the substitution of threonine with methionine at residue 182, a change first identified in *Escherichia coli* isolates in 1965. The ESBL TEM-1 gene continues to evolve, leading to the production of more than 246 derivatives of the TEM beta-lactamase enzyme (Gelalcha & Dego, 2022; Ghafourian et al., 2015; Ghenea et al., 2020; Sideraki et al., 2001).

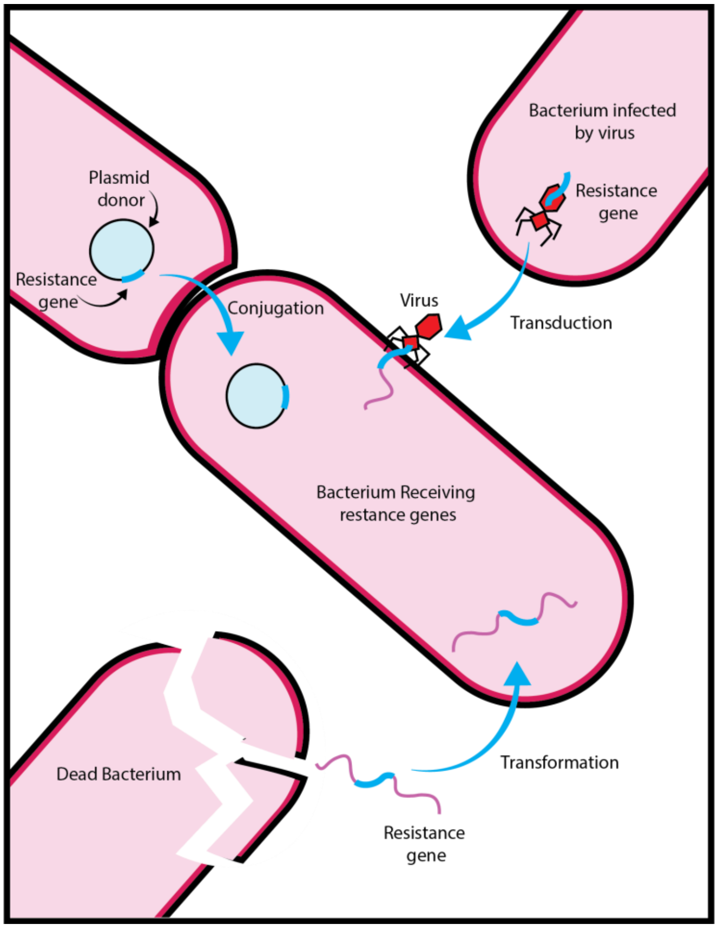

Fig. 2: Horizontal gene transfer mechanism

Bacteria that undergo mutations can transfer their genetic material horizontally through processes, including transformation, transduction, and conjugation, as illustrated in Figure 2 (Amine, 2013). Transformation occurs when bacteria take up DNA from another dead bacteria. Pathogenic bacteria, such as *Streptococcus pneumoniae* have this ability. When they acquire DNA that contains a resistance gene, these bacteria can incorporate it into their own genomes, thereby developing the ability to resist antibiotics. Transduction involves the transfer of DNA with the assistance of bacteriophages, which are viruses that infect bacteria. Typically, bacteriophages can destroy bacterial cells. However, in this process, the bacteriophage facilitates the transfer of resistance genes from one bacterium to another (Davies & Davies, 2010; Guilfoile, 2007).

Conjugation is the bacteria's process of actively taking up DNA fragments known as plasmids, which contain bacterial genes. Genetic material can be transferred from donor bacteria to recipient bacteria during this process. Plasmids may carry antibiotic resistance genes, allowing recipient bacteria to acquire resistance as well. In addition to plasmids, there are other mobile genetic elements, such as integrons and transposons. Transposons move between chromosomes and bacterial strains. Transposition of DNA elements in several species of *Enterococcus* causes resistance to vancomycin (vanR). This type of transposons, known as integrons, can integrate into the genome and new conjugative plasmids, enabling resistance genes to spread widely among different bacterial strains (Babakhani & Oloomi, 2018; Cowan & Smith, 2023; Guilfoile, 2007).

Methicillin-resistant *Staphylococcus aureus* (MRSA) and bacteria that produce Extended Spectrum β-Lactamases (ESBL) are examples of horizontal gene transfer in antibiotic resistance. MRSA first reported in the UK in 1961 and gets resistance through the integration of the mecA gene into the bacterial chromosome (Lakhundi & Zhang, 2018). This gene is located in '*Staphylococcal Cassette Chromosome mec*' (SCCmec), modified and used to produce penicillin-binding protein 2a (PBP2a) then causes a lower affinity for beta-lactam antibiotics compared to PBP in sensitive *S. aureus* strains. Staphylococcus strains with mecA/mecC gene are mostly resistant to beta-lactam antibiotics or semi-synthetic penicillins such as oxacillin, nafcillin, and methicillin (Schnitt & Tenhagen, 2019). Several bacteria produce enzymes that chemically modify or degrade antibiotics. ESBL enzyme can degrade beta-lactam antibiotics such as penicillin and cephalosporins then cause inactivation of the antibiotics before exerting their clinical effects (Muteeb et al., 2023).

Other mechanisms of antibiotic resistance are biofilm formation, efflux pumps, and alternative metabolic pathways (Jamil et al., 2023). Biofilm formation enables bacteria to attach surfaces to inanimate objects or living tissue and protect themselves from antibiotics and the immune system. Biofilm matrix blocks the penetration of antibiotics, making it difficult for these drugs to reach and eliminate the bacteria (Muteeb et al., 2023). Efflux pumps facilitate the expulsion of unwanted foreign substances, including antibiotics, from the cell. Protein pumps are resistance mechanisms commonly associated with tetracycline and are produced when the cell detects tetracycline. The protein pumps bind to tetracycline and remove the antibiotic from the cell, supported by the flow of hydrogen ions back into the cell (Guilfoile, 2007). Some bacteria avoid the effects of antibiotics by using alternative metabolic pathways such as producing different enzymes to make antibiotics ineffective instead of using dihydrofolate to reductase the target enzyme of trimethoprim (Muteeb et al., 2023; Munita & Arias, 2016).

In addition to horizontal transfer, genes encoding antibiotic resistance on chromosomes and plasmids can also be replicated and inherited. This incident is the cause of the rapid proliferation of antibiotic-resistant species. As observed in Figure 3, antibiotics will only kill sensitive bacteria, eventually maintaining pathogenic bacteria in cases of antibiotic resistance. Furthermore, the growth of the resistant bacterial population will inherit the ability to resist antibiotics and repeatedly resistant bacteria then carry out horizontal gene transfer to other bacteria (Cowan & Smith, 2023; Yusuf et al., 2017).

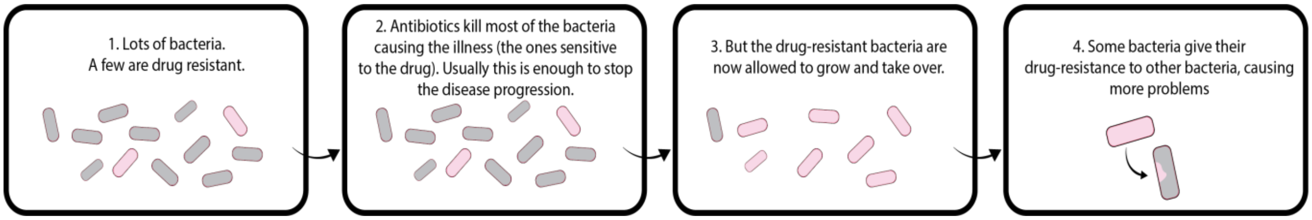

Fig. 3: How antibiotic resistance occurs

The Effect of Livestock Waste on Antibiotic Resistance

The environment has a crucial role in the horizontal gene transfer (HGT) of antibiotic-resistant bacteria. Gene transfer in nature frequently occurs between bacteria, viruses, or other organisms present in the environment (Cowan & Smith, 2023). Livestock waste has become a major reservoir of antibiotics and resistant bacteria in the environment (Maulana et al., 2021). The environment is regarded as the primary transmission pathway for horizontal AMR gene transfer from bacteria to the community (Banu et al., 2021; Normaliska et al., 2019). Environmental factors, livestock waste, and animal feed in dairy cattle are common factors that affect the development and spread of AMR (Collis et al., 2019). Research explains that the AMR issue and environmental pollution are mostly caused by increased food demand coupled with low levels of knowledge in the community (Banu et al., 2021). Awareness about insufficient rational use of antibiotics and improper processing of livestock waste contribute to environmental pollution around livestock locations (Dameanti et al., 2023; Nahar et al., 2023). Bacterial resistance in livestock animals can spread throughout the livestock environment via water sources, irrigation, rivers, rain, and food chain contamination, which in turn affects resistance in environmental microbiota and humans (Soré et al., 2020; He et al., 2020; Ayukekbong et al., 2017). Resistant bacteria can infect humans through environmental exposure, food or water consumption, and contamination at activity sites. The resistant bacteria replicate in the human body (especially in the intestines) and cause either endogenous or exogenous infections, as illustrated in Figure 4 (He et al., 2020).

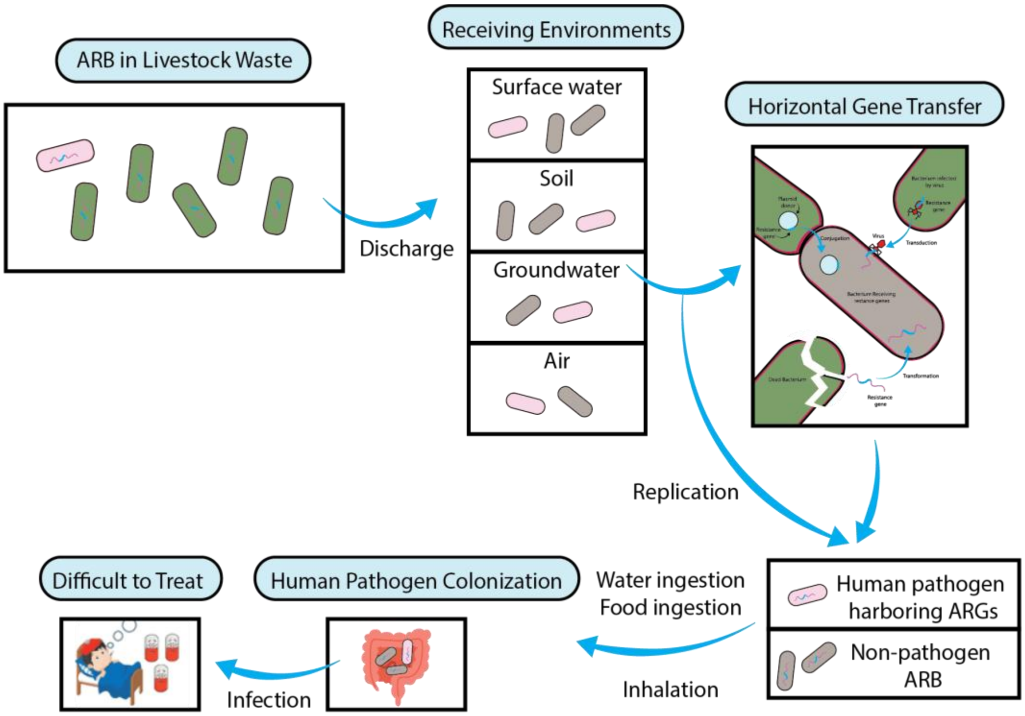

Fig. 4: Potential pathways for transfer of resistant bacteria from livestock waste to human pathogens.

Pathogenesis of antibiotic-resistant bacteria can cause chronic infections. In poultry, this leads to economic and public health problems on a global scale. Commonly, bacterial infections in poultry are associated with salmonellosis, colibacillosis, campylobacteriosis, and other diseases (Wernicki et al., 2017). In livestock, bacterial resistance can cause several diseases, including mastitis, diarrhea, respiratory distress, septicemia, and even death. Bacterial resistance cause urinary tract infections, liver abscesses, and chronic respiratory distress in humans (Aslam et al., 2021; Effendi et al., 2018; Robi et al., 2024; Wareth & Neubauer, 2021). Several effects of antibiotic resistance are heightened risk of complications, more severe diseases, reliance on expensive treatment options, delayed or ineffective treatment, longer hospital stays, admissions to intensive care units, and increased healthcare costs associated with implementing AMR infection control measures (Friedman et al., 2016; Fitranda et al., 2023; Schnitt & Tenhagen, 2020).

Several methods have been explained to reduce the rising incidence of antimicrobial resistance. Higher risk transmission of resistance genes from livestock to humans is important to developing appropriate interventions, strict antibiotic use policies, and infection control, and management on farms (Wee et al., 2020). Surveillance and diagnostics are strategies for early detection and tracking of resistance in microorganisms in livestock waste. Recent research showed that the antibiotic resistance profiles of bacteria from livestock waste correlate with the original isolates (Widodo et al., 2023). Identifying the presence of resistance genes is a confirmed method for a more effective response to the threat of antibiotic resistance (Muteeb et al., 2023). Innovations can used by nanomaterials, antisense RNA, bacteriophages, probiotics, prebiotics, and active ingredient extracts from plants (Cowan & Smith, 2023). He et al. (2020), describe strategies to prevent the increase of antibiotic resistance in livestock:

1. Use alternative material antibiotic such as peptides, prebiotics, and probiotics.
2. Adjusting animal feed diets, decreasing the contact of human-animal, quarantining sick and healthy animals, use existing technologies to improve farm management.
3. Hygiene and sanitation practices of farmers and farms.
4. Use bioreactor technology, anaerobic digestion, and composting to prevent the spread of bacterial resistance in the farm environment.

Conclusion

The problem of antibiotic resistance is on the increase globally and the meat value chain especially the livestock sector has been cited as one of the main contributors to this global problem. The increasing incidence of antibiotic resistance poses a global threat, and the livestock industry plays a significant role in this issue. The study shows that the use of antibiotics in animals for purposes other than for treatment, which includes for promoting growth and preventing diseases account for a large proportion of total consumption. This practice puts pressure on bacteria selection and thus increases the frequency of bacterial resistance to the antibiotics. Animal waste has a role to play in contributing to bio-resistance value in the environment. Bacteria that are resistant to antibiotics can reside in improper disposal areas of livestock wastes, spread around communities and consequently amplify the cases of antibiotic resistance. Several measures including surveillance and diagnostics of antibiotic resistance, use of antibiotic-free treatments, better livestock management, sanitation and hygienic practices for farmers and farms, and appropriate methods of disposal of animal waste will help to fight effects of antibiotic resistance. In addition, it would be possible to experience less transfer of resistant bacteria from the manure of livestock in addition to enhancing the welfare of animals together with sustaining the quantity and quality of people' health.

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