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Review Article

"Antimicrobial resistance in fowl production: cutting-edge status and innovative strategies for bacterial manipulate"

Yamini Bhanot*, Ritik Bhanot, Chitrahans Chowdhary

Department of Microbiology, ICAR-National Research Center on Equines
Department of Pharmaceutical Sciences, Guru Jambeshwar University of Science and Technology

*Corresponding Author
Yamini Bhanot, Department of Microbiology, ICAR-National Research Center on Equines.

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Abstract
The significant increase in the world population has also led to an increase in the Consumption of poultry products, which must meet certain requirements while maintaining Their quality and safety. It is known that in animal production, including poultry, antibiotics (Antibiotics) are used as preventive measures to prevent or treat infectious diseases. Unfortunately, the use and abuse of these compounds has led to the development and Dissemination of antibiotics, which is a major public health problem today. The number of Resistant bacteria is increasing and causing serious harm to humans and animals; Therefore, The aim of this review is to discuss the formation of antibiotics in poultry, focusing on the Current situation in the agricultural sector. New disease control strategies based on research Used in this sector are also described.

Keywords: Antibiotic Alternatives, Antibiotics, Antimicrobial Resistance, Food Safety; Microbiota, Poultry Production.

1. Introduction

The human population is continually increasing, rendering food security a major concern; thus, it is necessary to ensure that food production systems can support this population increase [1]. Animal food products, including meat, play an important role in the human diet. The demand for this foodstuff is on the rise, and meat consumption has increased more than 4-fold in the last 50 years [2].

Nowadays, poultry is one of the most consumed meats worldwide, being the second most produced and consumed meat in the European Union (EU) after pork [3]. In addition, global meat production has increased over the years [2]. From a global perspective, and according to the FAO, in 2020, the production of poultry meat represented almost 40% of global meat production [4]. Consequently, there has been a global shift towards intensive farming systems in which infections, including zoonosis, are transmitted more easily, affecting animal health and productivity [2,5].

Along with the apprehension related to food safety, this increase leads to concerns regarding production sustainability and safety. The production of animal-derived products have inherent impacts to One Health, such as an increase in greenhouse gases, the contamination of drinking water, environmental contamination, the dissemination of antimicrobial drug resistance, and the emergence and re-emergence of zoonotic diseases [6,7]. The production of sufficient amounts of food for the global population is one of the major current challenges [7].

Due to the increasing concentration of animals in intensive farms and the use of conventional antibiotics to safeguard the health of animals and animal products, antimicrobial resistance has developed and spread, which has led to a global public health concern. This review aims to focus on the role of poultry production in the development of AMR and the main bacterial pathogens that affect poultry, and to discuss the potential role of innovative antimicrobial compounds as an alternative or complementary strategy to the use of conventional antibiotics and, consequently, for the reduction and dissemination of AMR between animals, humans and the environment in a One Health Approach.

2. Antimicrobial Drug Resistance

Global Scenario

Antibiotics are natural, semisynthetic or synthetic substances, which interfere with the growth or survival of bacterial microorganisms, and are used to prevent or treat the associated infections [8,9]. Although traditional antimicrobial compounds have been recognized for thousands of years since their discovery by ancient civilizations, it was only in 1928 that the first antibiotic, penicillin, was developed by Alexander Flemming [8].

The advent of antibiotics revolutionized medicine due to their ability to combat bacterial infections, allowing an increase in the average life expectancy of humans and animals, the control of infectious diseases and the reduction in morbidity and mortality, while also contributing to food safety [8,9]. Unfortunately, due to the extensive use of these compounds, multidrug resistant (MDR) microorganisms have emerged and disseminated, which is currently a global concern [10]. If the rate of development of MDR bacteria continues to increase, it is estimated that in 2050 the mortality rate caused by resistant bacterial infections will exceed the mortality rate caused by cancer . In 2000, the World Health Organization (WHO) classified antimicrobial drug resistance (AMR) as a global public health concern. As such, it is urgent to find strategies for the control and mitigation of these strains .In 2015, the World Health Assembly (WHA), which is the decision-making body of the WHO, adopted a global action plan focused on AMR based on five objectives: improve awareness of antimicrobial drug resistance; strengthen knowledge about it through surveillance and research; reduce the incidence of infection by effective sanitation, hygiene and infection prevention measures; optimize the use of antimicrobials in human and veterinary medicine; and increase investment in the development of new medicines, diagnostic tools and vaccines, taking into consideration the necessities of all countries. This action plan highlights the need for an effective One Health approach to tackle this issue and requires coordination among several sectors and groups, including human and veterinary doctors, farmers, economists, environmentalists and informed consumers .

Schematic representation of the coordination between different groups required for a One Health approach.

To help control AMR dissemination, the European Medicine Agency (EMA) developed a categorization of the conventional antibiotics used in veterinary medicine in order to promote their responsible use, focusing on the protection of public and animal health. As such, antibiotics were classified as category A ("Avoid"), which includes antibiotics that are not authorized in veterinary medicine; category B ("Restrict"), which includes critically important compounds for human medicine for which use in animals should be restricted; category C ("Caution"), which includes antibiotics for which alternatives in human medicine generally exist and can be applied in the veterinary settings in the absence of alternatives belonging to category D; and category D ("Prudence), which includes the antibiotics that should be used for first-line treatments in animals [10].

Antibiotics in Poultry Production

Antibiotics have been used in animal production for over fifty years as therapeutic and metaphylactic/prophylactic agents or as growth promoters . The efficacy and cost-effectiveness of the majority of these compounds led to their indiscriminate usage . Consequently, the misuse and overuse of these antimicrobials promoted the establishment of microbial reservoirs carrying AMR determinants in livestock, including poultry. As some of the antimicrobials applied to animals are the same as those administrated to humans, AMR dissemination poses a serious threat to the effective treatment of serious bacterial infections in humans, leading to higher medical costs, prolonged hospital stays and increased mortality .

Antimicrobial growth promoters (AGPs) started being applied in 1951, when the United States (US) Food and Drug Administration (FDA) approved the use of antibiotics as animal additives without prescription, followed by European Union (EU) countries, which approved their own regulations on the use of those substances in animal production . AGPs are antibiotics administrated at subtherapeutic doses, aiming to modify the animal's intestinal microbiota to attain a better performance. AGP dissemination contributes to selecting intestinal bacteria, reducing competition for nutrients and improving animal growth rates. Some authors defend these benefits, arguing that they are important in the early stages of production or that they are useful in the presence of sub-optimal hygiene conditions [2], while others report that they increase productivity, highlighting the importance of good husbandry in animal production .

AGP use has contributed to the evolution and spread of AMR in intestinal microbiota , prompting some countries to ban their application in animal production. Sweden was the first country to prohibit the inclusion of AGPs in animal feed in 1986. In 2006, the EU banned the use of 25 AGPs from animal production. Moreover, EU's decision to ban AGPs has been adopted by several other countries, such as Mexico, New Zealand and South Korea. On the other hand, the USA, Australia, Japan and Canada implemented laws to partially ban or exclude some antibiotic-derived additives . In fact, some important human medicine antimicrobials have been prevented from being used as AGPs in the US since 2016 . Despite these actions, antibiotics are still relevant for the prevention and treatment of bacterial infections, contributing to animal welfare and to the reduction in zoonotic diseases [5,10].

Development of AMR

Antimicrobial drug resistance relates to the capacity of a microorganism to survive the inhibitory or killing activity of an antimicrobial compound [10]. This phenomenon has been reported since the discovery of antibiotics [2]. When an antibiotic is administrated, susceptible bacteria are eliminated, favoring the selection of resistant strains. These strains become the predominant bacterial population, allowing the transmission of genetic resistance determinants to clonal descendants, to other isolates of the same species, or even to members of other bacterial species. This phenomenon occurs either in commensal or pathogenic bacteria from humans, animals and the environment [9].

There are two main pathways associated with the evolution and development of antimicrobial drug resistance. The first is related to resistance mediated by pre-existing phenotypes in natural bacterial populations. During the evolutionary process, bacteria accumulate genetic errors in existing genes (present in the bacterial chromosome or in plasmids) and transfer those genetic determinants responsible for innate/natural or intrinsic resistance to progeny cells via vertical gene transfer (VGT) . The second scenario refers to acquired resistance, which may develop via a direct pathway, which involves gene mutations, or an indirect pathway, by the acquisition of DNA fragments coding for resistance (namely, transposons, integrons, phages, plasmids or insertion sequences) by horizontal gene transfer (HGT) mechanisms that may occur between the same or different bacterial species. HGT takes place via either conjugation, transformation or transduction . VGT and HGT can occur in a variety of settings [19]. As such, farms in which animals and vegetables are produced can act as reservoirs of antibiotic resistant bacteria as the food chain comprises distinct ecological niches, including those in which antibiotics are used and bacteria coexist .

Transmission of AMR.

Drug resistance can disseminate along the food chain through direct or indirect contact between the different actors and settings, both of which are also considered routes of transmission for zoonotic diseases. Direct contact occurs when humans come into contact with resistant bacteria present in animals or in their biological products such as urine, feces, blood, saliva and semen. Occupational workers, such as veterinarians, farmers, abattoir workers and food handlers, and others who have contact with them, have a higher risk of being colonized or infected with resistant strains. At present, it is well established that occupational workers and their families are an entryway for resistant bacteria into the community [9]. Alternatively, indirect contact can also lead to infection, and includes the handling and consumption of contaminated food products, such as meat and eggs, in the case of the poultry industries.

Additionally, a large proportion of antibiotics are not totally degraded, nor are transformed into inactive compounds by animals and humans, and retain their activity after being excreted in urine and feces. The active antibiotic, related metabolites or degradation products, named antibiotic residues, can accumulate in soils, wastewater and manure, causing profound impacts. Hence, the dissemination of antibiotic-resistant bacteria and antibiotic residues via food and animal waste turn the environment into an important reservoir of antimicrobial drug resistance [9]. In fact, it is known that the disposal of manure from animal pens has a significant role in the promotion of HGT of resistance genes among soil bacteria. This way, natural soil can also play a role as a reservoir of resistance determinant. In addition to commensal and environmental bacteria, foodborne pathogens also carry AMR genes.

Strategies to Reduce Antimicrobial Drug Resistance in Poultry Production

Since the consumption of poultry meat is growing, the high density of animals in production flocks increases the risk of the transmission of infectious agents, including AMR bacteria. This prompts the need to find alternatives to replace or complement antibiotic usage in those settings and to evolve to a "post-antibiotic era" .

As previously described, there are several pathogens that are difficult to eliminate from poultry flocks, poultry meat and egg products, requiring improvements in all phases of the poultry production system. In the production phase, the optimization of cleaning procedures, improvement of biosecurity and implementation of adequate hazard analysis and critical control points are fundamental. At the retail level, it is crucial to take action on food handling and worker training, together with consumers' education, to improve food safety awareness. Collectively, these actions offer opportunities to limit foodborne pathogen dissemination and reduce the risk of exposure to susceptible individuals; however, these measures may still be insufficient to protect humans from foodborne pathogens .

Interventions in poultry production can be grouped into two categories: pre-harvest and post-harvest interventions. At pre-harvest, measures to ensure animal health are applied primarily to prevent colonization and broiler infection by foodborne pathogens, via, for example, the administration of compounds in feed or drinking water. At post-harvest, measures applied aim to reduce or eliminate pathogens on carcasses or egg products. These measures focus on direct application on food, food packaging, surfaces and food processing equipment with the goal of minimizing the colonization or multiplication of pathogens and the spoilage of microorganisms during storage or retail .

Despite the availability and research on new substances, investigations usually focus on new methods to be applied at the flock production level, rather than on postharvest operations. This approach can be beneficial for two reasons. First, the ban of AGPs from poultry production led to the emergence of a market opportunity for alternative feed compounds showing health and performance benefits. Second, and from an overall food safety perspective, although reducing foodborne pathogens in processing plants is important, the focus should be on the live bird sector in order to reduce the pathogen loads before they enter the processing plants. However, the administration of alternative antimicrobial compounds to live birds through feed amendments has proven to be more challenging than anticipated . In this sense, this review will focus on the pre-harvest application of nonconventional antimicrobial compounds, approaching, with greater depth, the reduction and eradication of pathogens at the flock level for the improvement of the flock's health.

Conclusions

Infectious diseases are a major cause of illness and death in humans and animals worldwide. Traditionally, antibiotics have been used only to treat infections. However, their widespread use in humans, animals and agriculture has led to increased selection of bacteria in all areas, leading to resistance of the immune system, which in turn forces the immune system to change its behavior. . effectiveness of existing compounds and global health guarantee. It is important that traditional antibiotics play a role in reducing and improving the use of these compounds in all areas of food. Effective control of antibiotic use has proven effective in reducing antibiotic resistance in many European countries. Additionally, the global increase in antibiotic resistance has led to the need to investigate antibiotic use, including in poultry production. These options should be more effective and have new mechanisms of action, including antibiotic peptides, bacteriophages, probiotics, and nanoparticles. Antimicrobial peptides are a broad class of drugs that have many benefits compared to traditional antibiotics due to their unique mechanism of action and immunomodulatory effects. Phages have also demonstrated the ability to control some of the most important diseases affecting poultry and, given their properties, can do this without disrupting the balance of the animal's microbiota.Probiotics are already currently used in production animals because of their immunomodulatory activity and intestinal microbiota-modulation ability, both of which are associated with a reduced propensity to infectious disease development and growth-promoting action. Finally, nanoparticles are used not only due to their antimicrobial potential but also because they enhance the action of conventional antibiotics. Despite all their benefits, each of these innovative approaches also have limitations regarding their antimicrobial potential, resistance development, large-scale production costs and safety.

In conclusion, the application of these non-conventional antimicrobials can contribute to a decrease in antimicrobial use and AMR dissemination, with several of them being already in an advanced phase of research for application in human medicine. However, in vivo investigations regarding the poultry industry are still scarce and should be supported to slow the development of multidrug-resistant bacteria in these settings.

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