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Antimicrobial Resistance in Poultry Sector in India

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A B S T R A C T

Misuse and overuse of antimicrobials has led to antimicrobial resistance (AMR) and the outbreak of drug-resistant pathogens, which is acknowledged as the greatest hazard to humankind. The vast majority of antibiotics used are administered to farm animals. This is accelerating the evolution of antibiotic resistant bacteria. Increasing demand for protein supplements and animal protein by today's accelerating fitness industry and by the emerging number of fitness freaks is one of the most contributing factors for developing antimicrobial resistance. This is accelerating the evolution of antibiotic resistant bacteria. According to WHO, the new diseases that have evolved and affected humans in the past 15-20 years are majorly those of animal origin (such as Avian influenza. H5N1) Lack of sanitation, and inadequate prevention and control of infections may promote the spread of microbes resistant to antimicrobial treatment. Therefore, use of antimicrobials should be scrutinized in order to establish an effective set of laws and regulations to safeguard not only the well-being of the population but also for the economic stability of a country.

Introduction

Antimicrobials are substances used to prevent and treat infections in humans, animals, and plants. These can be antibiotic, antifungal, antiviral, or antiparasitic based on the target microbe (i.e., bacteria, viruses, fungi, and parasites) [(1)]. The use of antibiotics in food-producing animals is not just limited to treat infections, antibiotics are administered for metaphylaxis (administration of antibiotics to animals when anticipated to have contacted a diseased animal), prophylaxis (mass administration of antibiotics to animals to prevent disease when risk is established) and as antibiotic growth promoters (AGP's) to boost feed efficiency and increase in weight gain [(2)]. Antimicrobials as growth promoters were first added in chicken and pig feed by Moore and Stokstad in the mid -1950's [(3)].

Poultry is one of the fastest-growing sectors in India owing to an increase in the income of the population and the emergence of vertically integrated poultry producers. India stands fifth and eighteenth in terms of egg and broiler production respectively [(7)]. India accounts for about 3% of the global consumption of antimicrobials in food animals (Florence Mutua, 2020) [(4)]. A surge in antimicrobial resistance due to the unprecedented use of antimicrobials in the poultry industry was reported by the Centre for Science and Environment (CSE).

CSE's Pollution Monitoring Laboratory in a study found that nearly 40% of the samples tested contained antibiotic residues of one or more antibiotics (Centre for Science and Environment, 2014). Antimicrobial resistance (AMR) is a major health problem worldwide [(6)]. AMR occurs when microbes are no longer sensitive to drugs they originally were [(4)]. The first case of antibiotic resistance was reported in 1951 when turkey was fed by streptomycin [(3)]. Misuse of antibiotics leads to the development of antibiotic-resistant bacteria in the animals as well as the farm. Moreover, when the human pathogenic bacteria are exposed to low levels of antibiotic residues over time, they may develop antibiotic resistance (Centre for Science and Environment, 2014).

Poultry is one of the most widely consumed meats and the Indiscriminate use of antibacterials in animal husbandry will hence accelerate the process of AMR [(6)]. The major foodborne bacterial pathogens known to infect raw poultry meat products and their processing environment are *Listeria monocytogenes* and *Salmonella*. The treatment of salmonellosis and listeriosis requires appropriate antimicrobial therapy and since food-borne pathogens have become resistant to regularly used antibiotics, the treatment of patients becomes difficult [(5)].

Antimicrobial Resistance in Poultry in India

With 10.71% of the world's total livestock population, animal husbandry has proven to be of paramount importance for the economy of the country (*Indian Federation of Animal Health Companies*)[(9)]. According to *Indian Journal of Medical Research*, poultry consumption in India is expected to rise by 577% between 2000 and 2030[(11)] and according to a report by McKinsey and company, the per capita chicken consumption is set to grow from 3.2 to 9.1 Kg by 2030 [(12)]. Poultry being a cheaper protein source than others has the potential to increase production manifold leading to the abundant use of antimicrobial agents to enhance productivity [(11)]. Often, subtherapeutic doses are administered as a precautionary measure in case the animals are at risk of developing a certain disease [(10)]. The poultry industry of India produces 1,916×10 tonnes of broiler meat per year with Haryana contributing to the major part in this production (18.4%), West Bengal (17.1%), and Uttar Pradesh (14.1%). ESBL- producing *Enterobacteriaceae* studies, which are among the studies on AMR in poultry, have documented the rate of ESBL producers to vary from 9.4 percent in Odisha to 33.5 percent in Madhya Pradesh to 87 percent in Punjab. Other four studies reported the presence of *Salmonella* species in broilers to vary from 3.3 percent in Uttar Pradesh to 23.7 percent in Bihar in addition to 100 percent isolates being resistant to ciprofloxacin, gentamicin, and tetracycline in Bihar and West Bengal [(11)].

Since poultry production requires less water for maintenance and has proven to be more beneficial in terms of income, farmers in the rural areas around Bangalore are gradually moving to poultry from crop production. Consequently, antibiotic input is also increased for treating various infections and

diseases. An increase in poultry farming at a time of increasing local average temperature (predicted to rise between 1.8°C and 3.3°C in Karnataka by 2030 with respect to the baseline period 1961–90) is likely to result in increased incidences of heat stress-related morbidity[13].

Heat stress is responsible for causing symptoms like diarrhea and reduced appetite that could be mistaken (by less experienced farmers) as infections that need antibiotic treatment [13]. In addition to this, heat stress causes immune-suppressing effects.

According to the observations of Bartlett and Smith, broilers subjected to heat stress had lower levels of total circulating antibodies, and lower IgM and IgG levels, both during primary and secondary humoral responses, leaving broiler chickens more susceptible to bacterial infections hence generating the need for antibiotics [14].

Livestock and poultry are known to harbor various commensal, indicator, and pathogenic bacteria of zoonotic importance. *Escherichia coli* is one of the microorganisms particularly important in the widespread propagation of antimicrobial resistance. Pathogenic strains of *E. coli* may be either diarrheagenic or extraintestinal[15]. Extraintestinal pathogenic *E. coli* (ExPEC) strains may cause urinary tract infection, meningitis, and septicemia in humans [16]. The intestines and environment of healthy chickens can serve as a source for ExPEC strains with zoonotic potential [17]. Researchers have confirmed the role of poultry in fecal excretion of multidrug-resistant, as well as ESBL-positive E. coli strains (S. Bhave *et al.,* 2019) [18].

Salmonella isolates resistant to clindamycin, oxacillin, penicillin, and vancomycin have been detected in poultry and their environment in north India. The samples were found to be sensitive to ampicillin, enrofloxacin, and colistin (Renu Singh *et al.,* 2013) [19]. Multidrug- resistant *Salmonella* isolates were encountered in chicken eggs obtained from poultry farms and various marketing channels in north India (Sangeeta Singh *et al.,* 2010) [20]. Normally birds are raised in open sheds due to which it is difficult to keep disease-carrying rodents and insects away from them. So, farm hygiene and maintenance play an important role in reducing the chances of infections and thus the need for treatment [13].

Optimising the Use of Antimicrobials

Food-borne diseases including both food-borne infections and food-borne intoxications are a major health and financial burden for a country. The Food Safety and Standards Authority of India (FSSAI) in a report estimated that food-borne diseases cost the Indian economy $15 million a year [21]. In a developing country like India, most food-borne diseases go unreported [22]. The emergence of bacteria that are resistant to drugs used in the treatment of food-borne diseases may prove to be fatal for public health and may lead to increased hospitalizations and treatment failures ultimately leading to the death of a vast majority of people [23]. Hence the use of antibiotics needs to be strictly regulated and optimized. Firm laws and regulations for the usage of antimicrobials in the food-processing sector can not only contain antimicrobial resistance but also put the country at an economic advantage, as we have observed in the case of Namibia. Namibia has successfully developed a strong export market for its beef since it introduced a ban for the usage of antimicrobials for growth promotion in animals. Amplified consumer demand for safe and nutritious, antibiotic-free meat proved to be an important factor for putting Namibia at an economic edge [24]. Another option can be to safeguard critically important antibiotics for human use. The World Health Organization

has designated certain antimicrobial classes as "Highest Priority Critically Important Antimicrobials" for human medicine (WHO CIA LIST), these include Quinolones (well known for acting against Quinolone-Resistant Salmonella and E. coli in animals), Third and Higher Generation Cephalosporins (in animals, these act against Cephalosporin-Resistant Salmonella and E. coli, and in man (especially children) are therapeutic for grave Salmonella and E. coli infections), Macrolides and Ketolides (in animals, these act against Macrolide-Resistant Campylobacter spp., especially in poultry where these act against Campylobacter jejuni. Quinolones are not approved for use in the treatment of children who have been seriously infected by Campylobacter. That is where Macrolides turn out to be useful), Glycopeptides (In animals producing food, Glycopeptides help protect against Glycopeptide-Resistant Enterococcus spp. In addition to being a remedy for enterococcal infections) and Polymyxins (In food-producing animals, Polymyxins act against plasmid-mediated polymyxin-resistant *E. coli*. In critically ill patients, these act against grave Enterobacteriaceae and *Pseudomonas aeruginosa* multiresistant infections). (World Health Organization (2019, May). Highest Priority Critically Important Antimicrobials).

Addressing Antimicrobial Resistance

The World Health Organization has been leading multiple initiatives to make the general public aware of the hazards posed by the unprecedented use of antimicrobials including the World Antimicrobial Awareness Week, The Global Antimicrobial Resistance Surveillance System (GLASS), Global Antibiotic Research and Development Partnership (GARDP) and Interagency Coordination Group on Antimicrobial Resistance (IACG)[(1)]. Recognizing the growing concern over antimicrobial resistance in the country, the Government of India came up with various initiatives to contain the problem of antimicrobial resistance one of them being the establishment of the National Task Force on AMR Containment in the year 2010 which further led to the formulation of the National Policy to Contain Antimicrobial Resistance in 2011 following which in November 2014, the WHO Regional Committee Meeting urged the members to accelerate their efforts to contain AMR as outlined in the Jaipur Declaration and the South-East Asia Regional Strategy on Antimicrobial Resistance. The center of attention for the coordination and implementation of the Antimicrobial Resistance Programme is the National Center for Disease Control, New Delhi[(25)]. The National Treatment Guidelines for Antimicrobial Use in Infectious Diseases were published to assist hospitals in developing the local guidelines under which physicians can receive instruction [(25)]. Standardization of antibiotic usage guidelines, restricting the utilization of antibiotic drugs as over-the-counter medications, prohibiting or restricting the use of antibiotics for promotion of growth in livestock, and pharmacovigilance, including prescription audits that include antibiotic use within the hospital and community, were all mandated by the National Health Policy 2017[(25)].

Problems Associated with Unprecedented Use of Antimicrobials

The major problems arising due to unregulated use of antimicrobials are:

Increase in antimicrobial resistance - Misuse and overuse of antimicrobials have resulted in the development of resistant pathogens[(26).] Increase of the length of disease- due to antimicrobial resistance multiple regimes are ineffective in treatment and hence the need for longer hospitalization.

Further, the need for longer hospitalization and the use of intensive care units (ICUs) and isolation beds to prevent the spread of the infection also add to the treatment cost.[26,27,28]

Increase of healthcare costs- AMR has a major impact on healthcare costs. Based on the study conducted by the center for disease control and prevention (CDC) in the United States, AMR can add up to $1,400 to the hospital bill for treating patients with any bacterial infections. According to different studies, it is estimated that AMR cost could range from $300 billion to more than $1 trillion annually by 2050 worldwide. The increased cost can be mainly attributed to the use of expensive treatments and high resource utilization[28].

Rise in mortality rate- By 2050, AMR could be causing 10 million deaths a year[29]. Currently, across the globe, approximately 700,000 people lose their lives because of drug- resistant infections each year[28].

In India, according to a 2019 estimate, about 2 million people may die of antimicrobial resistance by 2050. [30,31]

Increase of more severe diseases- in India the consistently increasing non-communicable disease are also a matter of concern since these diseases are accompanied by a wide variety of infections that are cured by antibiotics in comparison to non-resistant bacteria the resistant forms will double the chances of developing a major disease and triple the chances of death (30,28). Increase the risk of complications- Infections caused by resistant bacteria may be resistant to more than one antibiotic. For instance, previously used antituberculosis agents such as isoniazid and rifampicin are now less efficient.[26,27]

Increase of the risk of adverse effects, some being life-threatening-Antibiotics are responsible for around 20% of all drug-related emergency visits in the United States.

Out of which around 80% are due to allergic reactions and certain other conditions like gastrointestinal, neurologic, and psychiatric disorders. Most of these adverse effects are mild, but some life-threatening adverse effects have been witnessed, such as hepatotoxicity due to amoxicillin and clavulanate[26].

Increase of re-attendance due to infectious diseases.

Increased medicalization

An indicator that monitors the occurrence of bloodstream infections due to two specific drug-resistant pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA); and *E. coli* resistant to third-generation cephalosporins (3GC) was added in the Sustainable Development Goals (SDGs) system for surveillance in the year 2019. The data observed for their median ratewas-[1]

Antiviral drug resistance is most common in immunocompromised patients, where continuing virus replication and long-term drug exposure result in the selection of resistant strains. There are several antivirals to which resistance has grown, including antiretroviral (ARV) medications.[1]

Table.1

Methicillin-resistant *S. aureus*	**11% (IQR 6.4–26.4)**
***E. coli* resistant to third-generation cephalosporins**	**36.0% (IQR 15.2–63.0)**

Many fungal infections cause toxicity, making them difficult to manage, particularly in patients with other infections (e.g. HIV). Candida auris, one of the most prevalent invasive fungal infections, has already established drug resistance to fluconazole, amphotericin B, and voriconazole, along with evolving caspofungin resistance. As a result, fungal infections are becoming harder to cure, medication delays are becoming more likely, hospital stays are becoming longer, and treatment services are becoming much morecostly.(1)

Antimicrobial resistance is a common problem that all the countries of the world are facing right now, be it a developed country or a developing country. The continuous and rapid emergence of antibiotic-resistant pathogens has severely affected the country's medical systems and if stringent policies are not implemented, the pathogens that are resistant to antibiotics, especially multidrug-resistant bacteria, which are also known as 'superbugs' may cause harm to such an extent that the antibiotics will fail to treat the minutest of infections.

Optimizing the use of antimicrobials and stringent implementation of national and international initiatives.

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