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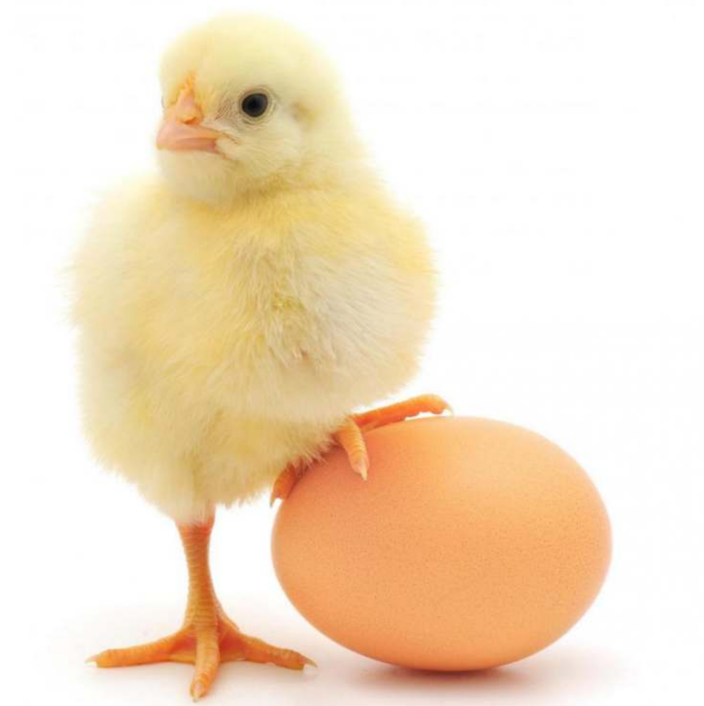

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Antibiotic Resistance in Poultry

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Abstract: The worldwide increase in the use of antibiotics as an integral part of the poultry and livestock production industry to treat and prevent infectious bacterial diseases and as growth promoters at sub-therapeutic levels in feeds has led to the problem of the development of bacterial antibiotic resistance during the past years. Recent scientific evidence has shown that resistance to antibiotics is not only due to the natural ability of a tiny fraction of the bacteria with unusual traits to survive antibiotic's attack, enabling resistant strains to multiply, but also stems from the transmissibility of acquired resistance to their progeny and across to other unrelated bacteria species through extrachromosomal DNA fragment called the plasmid which provide a slew of different resistances. The emergence and spread of resistant bacterial strains like *Campylobacter* sp, *Escherichia coli* and *Enterococcus* sp. from poultry products to consumers put humans at risk to new strains of bacteria that resist antibiotic treatment. Resistant bacteria thwart antibiotics by interfering with their mode of action via a range of effectors' mechanisms, including synthesis of inactivating enzymes, alteration in the configuration of cell wall or ribosome and modification of membrane carrier systems. These mechanisms are specific to the type of resistance developed. Because of the growing global concerns that resistance bacteria can pass from animals to humans, there is an increase in public and governmental interest in phasing out inappropriate antibiotic use in animal husbandry. Improvement in the hygienic practice of handling raw animal products and adequate heat treatment to eliminate the possibility of antibiotic resistant bacteria surviving may play a role in preventing the spread. More attention should be focused on increasing antibiotic surveillance capacity to cope with the spread of emerging resistances and on the alternative approach to sub-therapeutic antibiotics in poultry, especially the use of probiotic micro-organisms that can positively influence poultry health and produce safe edible products.

Key words: Antibiotic, resistance, poultry, probiotic

INTRODUCTION

Poultry is one of the world's fastest growing sources of meat, representing nearly one-fourth of all the meat produced during the year 2000. The modern production unit can produce market ready broiler chickens in less than six weeks. This development arose from genetic selection, improved feeding and health management practices involving usage of antibiotics as therapeutic agents to treat bacterial diseases in intensive farming systems. They may also be used as prophylactic agents in the water of healthy birds and as growth promoters at sub-therapeutic concentrations in feed. Bacitracin, chlortetracycline, tylosin, avoparcin, neomycin, oxytetracycline, virginiamycin and others are used for these purposes. Sub-therapeutic dosing in feed increase the rate of weight gain and improve the efficiency of converting feed to meat. The recommended levels of antibiotics in feed were 5-10g kg^{-1} in the 1950's and have increased by ten to twenty folds since then. In many developing countries, majority of the antibiotics used in poultry is for treatment of infections. Antibiotics are also used to counteract the adverse consequences of stress responses. The economic and health advantages of using antibiotics have revolutionized intensive poultry and livestock production.

In general, when an antibiotic is applied in poultry farming, the drug eliminates the sensitive bacterial strains, leaving behind or selecting those variants with unusual traits that can resist it. These resistant bacteria then multiply, increasing their numbers a million fold a day, becoming the predominant micro-organism in the population. Such bacteria transmit their genetically defined resistance characteristics to subsequent progeny of the strains and to other bacterial species via mutation or plasmid-mediated (Gould, 2008). According to WHO the resistance to antibiotics is an ability of bacterial population to survive the effect of inhibitory concentration of antimicrobial agents (Catry *et al.*, 2003). Potential transfer of resistant bacteria from poultry products to human population may occur through consumption or handling meat contaminated with the pathogens (Van den Bogaard and Stobberingh, 2000). Once acquired, the resistant bacteria can colonize the human intestine and the genes coding resistance to antibiotics can be transferred to other bacteria belonging to the endogenous flora of humans, thereby jeopardizing effective treatment of bacterial infections (De Leener, 2005). For example, the use of flouroquinolone antibiotic in broiler chickens has caused an emergence of resistant *Campylobacter* in poultry which was linked to

10 per cent of human *Campylobacter* diseases found in the area (Randall *et al*., 2003). Administration of avilamycin as a growth promoter resulted in an occurrence of avilamycin-resistant *Enterococcus faecium* in broiler farms (Aarestrup *et al*., 2000). In turkeys fed vancomycin, there was a transfer of vancomycin resistance genes between turkey *Enterococci* strains, from turkey to turkey and from turkey to humans (Stobbering *et al*., 1999).

It is very important to monitor prevalence of resistance to antibiotics not only in human populations but also in animals in order to detect transfer of resistant bacteria or resistant genes from animal origin to humans and vice-versa. While the European Union, USA and Australia have recognized the serious consequences of antibiotic resistance from various areas of animal production for public health, there are large parts of Africa and Asia where we have little idea about antibiotic resistance.

The objective of this review is to provide information on the development of resistance to antibiotics, incidence of antibiotic resistance in poultry, public health implications, strategy for the containment of the evolving bacterial resistances, as well as probiotic application as an alternative approach to sub-therapeutic antibiotic usage in poultry.

Development of bacterial resistance: The development of resistance among bacterial populations exposed to antibiotics is a growing public health issue. For bacteria to develop resistance to antibiotics, they must first receive exposure to them. It is similar in humans and in animals. The source of this in animal husbandry, is their use as feed additives or for care (Fig. 1) which leads to the development of resistant bacteria strains. Broadly speaking there are two groups of resistance to antibiotics. In the first case, resistance is exhibited when some bacteria have the natural ability to resist the effect of a particular antibiotic because of the enzymatic inactivation of the antibiotic. This type of resistance is achieved in the presence of enzymes. An example is found in the penicillinase producing *Staphylococcus* which is able to break down the molecular structure of penicillin and will confer resistance to this antibiotic. In the second case, the resistance depends on the ability of the bacteria to survive in the presence of the antibiotic without direct interaction. This results from gene action in the bacterium and is independent on the destruction of the antibiotic by enzyme action. The two groups create a population of antibiotic resistant bacterial strains. Where bacteria population is exposed to an antibiotic, the sensitive strains will be eliminated, enabling the resistant strains to multiply, thereby increasing the numbers in many folds. Under this selective pressure, antibiotic will acquire resistance and survive antimicrobial treatments and subsequently also act as reservoir for antibiotic resistance genes for other bacteria (Van der Bogaard and Stobberingh, 1999). Resistance determinants could be maintained within the bacterial population even in the absence of the corresponding antibiotics (Khachatourians, 1998).

Bacteria have 2 types of genetic structures, namely chromosomes and plasmids that confer resistance and facilitate the transfer of resistance characteristics within or between different strains and species. Both have DNA sequences that determine antibiotic resistance. Chromosomal resistance to antibiotics depends on a single step or sequential mutations (changes) in the bacterial genes that leads to resistance to a particular antibiotic. It allows resistant mutants to emerge. Plasmid-mediated resistance (R-factor), occurs when the plasmids display their mobility within and between bacteria, thus providing means for the spread of antibiotic resistance. Plasmids may contain from 20-500 genes and carry resistance to a number of bacterial species and various ecosystems (Benzanson *et al*., 2008). Three possible mechanisms by which plasmids may migrate from one bacterium to another are: transformation, transduction and conjugation (Fraser, 1986; Poirel *et al*., 2008). In transformation, naked DNA seems to pass from the donor to the recipient through the growth medium. Transduction takes place where a bacteriophage makes use of its specialized molecular equipment adapted for inserting DNA into recipient bacteria. Thus, the bacteriophage acts as a vector. In conjugation (or conjugative sequence), the DNA passes from the donor cell to the recipient assisted by a bridge formed during direct cell-to-cell contact and then separate after the exchange. Antibiotic resistant generic *Escherichia coli* populating meat from cattle, pigs and poultry are plasmid-mediated (Box *et al*., 2005).

Incidence of antibiotic resistance in poultry: It is now generally known that the widespread use of antibiotics is the main risk factor for an increase in the occurrence of bacterial resistant strains. Bacteria display variable levels of resistance to antibiotics. Resistance of selected *Encherichia coli*, *Staphylococcus sp.* and *Enterococcus sp.* isolates to antibiotics in poultry flocks can be seen in Table 1. In *Escherichia coli*, 97% of strains displayed resistance to tetracycline, 51% to ampicillin and 31% to piperacillin. High frequencies of resistance in 10% of the strains were also found in each of ciprofloxacin and ofloxaxine. In staphylococci, increased numbers of strains resistant to erythromycin (39%), clindamycin (19%), tetracycline (14%) and ofloxacin (13%) were observed. In enterococci, 80%, 59% and 34% of the strains were resistant to tetracycline, erythromycin or nitrofurantoin, respectively. The high incidence of antibiotic resistance among the bacteria populating poultry and rising frequency of the bacterial strains represent a public health hazard.

Table 1: Incidence of Antibiotic Resistance in poultry farm[a]

	Resistance (%)		
Antibiotic	*Escherichia coli*	*Staphylococcus sp.*	*Enterococcus sp.*
Ampicillin	51	-	3
Ampicillin/ sulbactam	0	4	3
Ciprofloxacin	10	-	-
Chloramphenicol	8	3	7
Clindamycin	-	19	-
Erythromycin	-	39	59
Gentamicin	-	-	7
Nitrofurantoin	-	-	34
Ofloxacin	10	13	51
Oxacillin	-	4	-
Piperacillin	31	-	-
Streptomycin	-	-	22
Teicoplanin	-	0	5
Tetracycline	97	14	80
Trimethoprim/ sulfamethoxazole	14	-	-
Vancomycin	-	0	5

[a]After Ref. (Kolar *et al.*, 2002)

Applications of antibiotics in poultry production bring about an increase in resistance to antibiotics not only in pathogenic bacterial strains, but also in commensal bacteria (Lukasova and Sustackova, 2003). In this respect, gastro-intestinal commensal bacteria constitute a reservoir of resistance genes for pathogenic bacteria. Their level of resistance is considered to be a good indicator for selection pressure for antibiotic use and for resistance problem to be expected in pathogens.

Poultry products and meat are common reservoir of emerging antibiotic resistances available to bacteria inhabiting humans. It can be supposed that the transmission of antibiotic-resistant bacteria to people who got in contact with these sources through direct ingestion or handling results in an increase in the human reservoir of these strains which can rapidly spread to the community (Fig. 1). In theory, the birds' waste may serve as a vehicle for expanding the transmission of resistance bacteria to humans. In this direction, the waste ends up in water mainly wells and ponds which represent a significant source of natural water supply for rural population in the developing countries. In addition, there is the possibility that resistance bacteria can get into domestically grown fresh fruits and vegetables to consumers via irrigation with contaminated water (Fig. 1).

Public health implications and strategy for containment: There has been much attention paid to the impact of the introduction of antibiotic resistant bacteria to humans. It can cause significant danger and suffering to individuals, families and the entire community who have common infections that once were easily treatable with antibiotics. The emerging resistant bacterial strains will adversely affect the efficacy of antibiotic chemotherapy for those that acquired the new strains of infectious disease (Anon, 2006; Chastre, 2008). Furthermore, it encourages the need for more expensive and toxic medications. Some resistant infections can cause death. Resistant bacteria thwart antibiotic treatment by interfering with their mode of action via a range of effectors' mechanisms including synthesis of inactivating enzymes, alteration of the specific configuration of target sites and inhibition or changes in membrane transport systems to remove the antibiotic (Cetinkaya *et al.*, 2000).

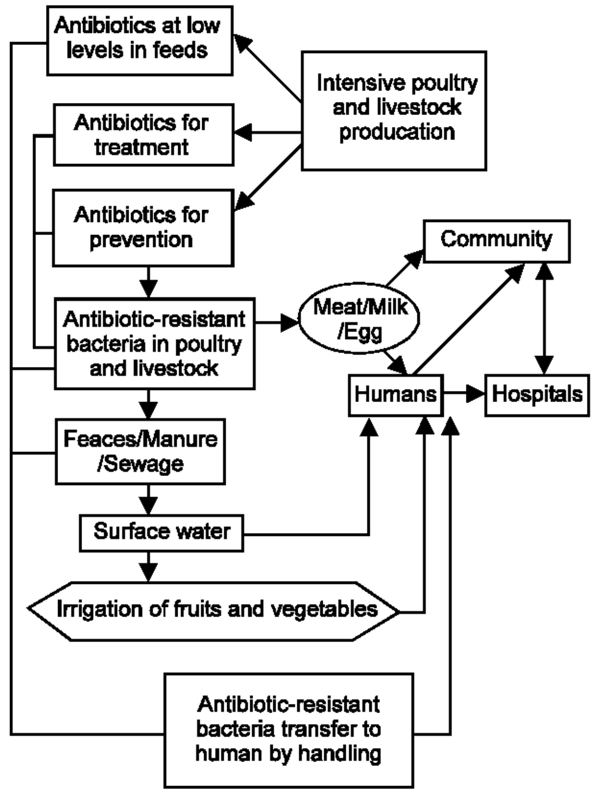

Fig. 1: Sources of Antibiotics and Various Routes for the Transmission of Antibiotic Resistance from poultry and livestock to humans

The strategy to slow down the development of antibiotic-resistant pathogens is to improve resistance surveillance capacity worldwide to cope with rapid spread of emerging resistance mechanisms and clones. Likely measure to prevent spread of antibiotic resistance from poultry to human include improvement in hygienic handling of raw poultry products and adequate cooking, which would sterilize the meat.

Probiotics: Alternatives to antibiotics in poultry: The recognition of the dangers of antibiotic resistance prompted the ban on sub-therapeutic antibiotic usage

Table 2: Beneficial effects of probiotics in poultry[b]

Enhance growth performance	Increase carcass yield and cut-up meat parts
Modify intestinal microbiota	Improve nutrient digestibility
Stimulate immune system	Lower serum cholesterol
Reduce inflammatory reactions	Decrease carcass contamination
Prevent pathogen colonization	Increase feed efficiency

[b]After Ref. Stavric and Kornegay (1995); Jin *et al.* (1998); Zulkifli *et al.* (2000); Simmering and Blaut (2001); Kabir *et al.* (2004); Apata (2008).

in Europe and the potential for a ban in the United States and many developed countries, there is increasing interest in using probiotics that have potential to reduce enteric disease in poultry and subsequent contamination of poultry products (Patterson and Burkholder, 2003). Probiotic, which means "for life" in Greek, has been defined as a live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance. Probiotics can be used in animal feed to enhance production performance and prevent gastro-intestinal infections. A variety of microbial species have been used as probiotics, including species of *Baccilus*, *Bifidobacterium*, *Lactobacillus*, *Lactococcus* and *Saccharomyces* yeast in poultry (Simon *et al*., 2001). The effects of ideal probiotics are shown in Table 2. Proposed mechanisms by which probiotics act include direct bacteria antagonism, competitive exclusion of harmful pathogens, production of toxic compounds that inhibits pathogens and immune stimulation (Jin *et al*., 1997).

Conclusion: Antibiotics have been used widely in poultry industry in order to treat and prevent infectious bacterial diseases. They have also been used at low levels in feed as growth promoters. Such practice has improved poultry performance effectively and economically but an increase in numbers of antibiotic-resistant bacterial strains like *Escherichia coli*, *Staphylococcus sp*. and *Enterococcus sp*. did occur which can be transmitted from poultry to humans through the food chain with serious consequences on public health.

The present situation underlines the increased public and governmental interest in eliminating sub-therapeutic use of antibiotics in poultry and livestock; particularly those that are also used to treat humans. There is need for more rational use of antibiotics in animal production and more prudent use in humans. It is important to take concerted action to improve antibiotic resistance surveillance capacity worldwide with a view to monitoring the emerging resistance genes and their transfer in both animal and human strains. In addition, alternatives to antibiotics should be explored such as the application of probiotics in poultry for production of safe edible products.

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