Science Journal of Microbiology
ISSN: 2276-626X
www.sjpub.org/sjmb.html

Published By
Science Journal Publication
International Open Access Publisher

Research Article **Volume 2012 (2012), Issue 2**

The Emergence of Antibiotics Resistance and Utilization of Probiotics for Poultry Production

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Accepted December 2011

ABSTRACT

The worldwide increase in the use of antibiotics in farm animals, especially for poultry production to treat and prevent bacterial infections and as growth promoters in feeds has increased microbial resistance to antibiotics. Recent scientific evidences show that resistance to antibiotics is not only due to the ability of bacterial population to survive the effect of inhibitory concentration of antimicrobial agents, but may also arise from several pathways which include the transmissibility of acquired resistance to their progeny and across to other unrelated bacteria species through extra chromosomal DNA fragment called the plasmid which provide a slew of different resistances. The emergence and dissemination of resistant bacterial strains like *Campylobacter* sp, *Escherichia coli* and *Enterococcus* sp. from poultry products to consumer 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, cell wall and ribosomal alteration, and modified 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 combating out imprudent usage of antibiotics in animal husbandry. Improvement in the hygienic practices of handling raw poultry products and adequate heat treatment to eliminate the possibility of antibiotic resistant bacteria surviving which play a role in preventing the spread. More attention should be focused on alternative approach involving the use of probiotic micro-organisms that can similarly enhance poultry productivity and produce safe edible products.

Keywords: Farm Animal Antibiotics; Resistance, Probiotics, Poultry

INTRODUCTION

Poultry represent nearly one-fourth of all the meat produced globally. It is a source of protein that plays an important role in human nutrition. Modern intensive production unit can produce market ready broiler chickens in less than six weeks. This achievement arose from improved productivity via genetic selection, improved feeding and health management practices involving usage of antibiotics as therapeutic agents to treat bacterial diseases and as additives to animal feed. Antibiotics are substances which are metabolically produced by microorganisms and which exhibit either an inhibitory or destructive effect on other microorganisms. In many developing countries, majority of the antibiotics are being used in poultry for treatment of infections by water application for healthy birds In addition, . antibiotics are also used to counteract the adverse consequences of stress responses. Bacitracin, chlortetracyline, tylosin, avoparcin, neomycin, oxytetracycline, virginiamycin, trimethoprim/suiphonamide, lincosamides , cephalosporins etc are the commonly used anbiotics in poultry and some of which are of direct importance in human medicine The economic and health advantages of proper use of many antibiotics and coccidiostats have revolutionized intensive poultry and livestock production. Benefits of poultry antibiotics include production of higher outputs as healthier animals with increased weight put on more weight, and the meat derived from these healthier animals has lower levels of bacteria that can cause food borne illnesses in people. They are used as growth promoters at sub-therapeutic concentrations (50 - 100 $mgkg^{-1}$) in feed and act by suppressing harmful microorganisms. They also improve gut health, which leads to increase in feed conversion efficiency, optimization of genetic potential for growth and reduction of waste product output from intensive poultry production. Antibiotics have made intensive poultry system to become a lucrative form of trade. However, imprudent use of antibiotics in poultry production can lead to increased antibiotic resistant bacteria in poultry products.

In general, when an antibiotic is applied in poultry farming, the drug eliminates the susceptible bacterial strains, particularly at a therapeutic dose, leaving behind or selecting those variants with unusual traits that can resist it. These resistant bacteria then multiply, increasing their numbers a million fold. This shift usually requires several days to occur. The resistant bacteria thus become the predominant micro-organism in the population and they 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). Intensive and extensive antibiotic use can lead to the establishment of a pool of antibiotic resistance genes in the environment. For example, the use of flouroquinolone antibiotics in broiler chickens has caused an emergence of resistant *Campylobacter* in poultry (Randall *et al*., 2003). Administration of avilamycin as a growth promoter resulted in an occurrence of avilamycin-resistant *Enterococcus faecium* in broiler farms (Aarenstrup *et al*., 2000). Potential transfer of resistant bacteria from poultry products to human population may occur through consumption of inadequately cooked meat or handling meat contaminated with the pathogens (Van den Bogaard and Stobberingh, 2000). In turkeys fed vancomycin, there were concerns of glycopeptides resistance among *enterococci* found in turkeys and humans (Stobbering *et al*., 1999). This is an example of cross-resistance. Studies have shown that animal *enterococci* are mostly different from human colonizers, although concerns for transient transfers of resistance remain.(Apata, 2009).

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 antibiotics resistance from various areas of animal production for public health and they have very many surveillance programmes (example European Antimicrobial Resistance Surveillance System,EARSS) already in place and actively tracking resistance levels, there are some countries in Africa and Asia where there are little idea about antibiotics resistance. The aim of this review is to provide information on the development of resistance to antibiotics, resistance mechanisms, on-farm prevalence, potential risks and strategy for the containment of the evolving bacterial resistances. In addition the article also details probiotics application as an alternative approach to sub-therapeutic antibiotics usage in poultry.

Development of bacterial resistance

Bacteria resistance is present when the microorganisms continue to proliferate at a higher rate than the minimal inhibitory concentration (MIC) defined as the lowest concentration of antibiotic required to inhibit 90% of the colonies of a particular organism. The development of resistance among bacterial populations exposed to antibiotics is a pressing issue in animal food production. This trait enables bacteria to survive and continue to grow instead of being inhibited or destroyed by therapeutic doses of the drug. It is also known that resistance is inherent in many populations not routinely exposed to antibiotics. In intensive poultry production, a major source of most resistance is antibiotic usage as feed additive, for treatment, or prevention (Oyeniyi, 1987, Kolar *et al*.,2002, Webster,2009), which leads to the development of resistant bacteria strains. In general, 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 of enzymatic inactivation is found in the penicillinase producing *Staphylococcus* which is able to break down the molecular structure of penicillin by hydrolytic cleavage, and thus 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 most sensitive strains will be eliminated, enabling the resistant strain to multiply, thereby increasing the numbers in many folds. Under this selective pressure, resistant bacteria might be selected which can survive antimicrobial treatments, and subsequently also act as reservoir for antibiotic resistance genes for other bacteria (Van der Bogaard and Stobberingh, 1999).

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. Resistance genes are coded either chromosomally or extra chromosomally by means of plasmids ,transposons and integron. Chromosomal resistance to antibiotics depends on a single step or sequential mutations (changes) in the bacterial genes that lead to resistance to a particular antibiotic. It allows resistant mutant 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 20-500genes and carry resistance to a number of bacterial species and various ecosystems (Benzanson *et al*., 2008).The ease of transfer of genetic materials plays an important role in the spread of bacterial resistance from one bacterial strain to another. Resistant genes therefore have the potential for wide distribution among bacterial Three types of genetic transfer mechanisms have been described namely: transformation, transduction and conjugation (Fraser, 1986; Poirel *et al*., 2008). Transformation involves transfer of naked DNA to recipient bacterium through the growth medium. Transduction takes place where viral DNA is transferred to recipient bacterium. In conjugation (or conjugative sequence), requires contact of donor and recipient cells and in which the genetic material is transferred through a channel between the two mating cells and then separate after the exchange. Transformation and transduction may or may not involve plasmids but always involve DNA (and possibly resistance gene) transfers. Antibiotic resistant generic *Escherichia coli* populating meat from cattle, pigs and poultry are mostly maintained by transformation of plasmids (Box *et al*., 2005).

Apart from transferable resistance, other types of resistance include; natural resistance which is due to a permanent genetically determined insensitivity of a bacterial species towards a certain antibiotic (example all *Pseudomonas aeruginosa* strains are resistant to penicillin G) and primary resistance in which some of the existing strains of a bacterial species are resistant, while others are susceptible (example:30-60% of all *E.coli* strains are resistant to tetracycline).

On-farm prevalence 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 might represent potential sources of resistance.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 gene for pathogenic bacteria. Their level of resistance is considered to

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)

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 of inadequately cooked meat or handling contaminated meat results in an increase in the human reservoir of these strains which can rapidly spread to the community(Apata, 2009). 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 Africa, poultry industry has a sizeable population of village chickens that are practically not exposed to antibiotics . Therefore small scale chicken farming in Africa may be limited in contributing to the selection of resistant bacteria. Other than poultry farms, human sewage treatment plants and runoff discharges can equally contribute to the source of environmental resistance, as well as migrating birds and wild animals.

Potential risks and strategy for containment

The potential risks associated with increased levels of antibiotic resistant bacteria in meat and indeed in food chain have implications for public health. It can result in therapeutic failure in animals and can cause 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 increase the incidence of human infections and affect the efficacy of antibiotic chemotherapy for those that acquired the new strains of infectious diseases (Anon, 2006; Chastre, 2008). Furthermore, it encourages the need for more expensive and toxic medications. Some resistant infections become complicated and are harder to treat. Resistant bacteria thwart antibiotic treatment by interfering with their mode of action via a range of effectors' mechanisms including synthesis of configuration of target sites and inhibition or changes in membrane transport system to remove the antibiotics (Cetinkaya *et al*., 2000).

Various steps for containment include restricting the use of livestock antibiotics to bacterial infections and use only for therapeutic purposes Concerted effort should be made to build surveillance capacity worldwide to obtain reliable data on the development of antibiotic resistant pathogens which will underline the importance of antibiotic policy implementation in animal production and veterinary medicine in many countries .Hygienic handling and adequate cooking of raw poultry are commendable goals that will eliminate both resistant and susceptible food borne pathogens which may reside on raw meats

Probiotics: Alternatives to antibiotics for poultry production

The recognition of the dangers of antibiotic resistance prompted the ban on sub-therapeutic antibiotic usage In European union and the potential for a ban in the United States and many developed countries, there is increasing interest being paid to valuable alternatives for in-feed antibiotics and the adoption of organic farming. Among the modern alternative feed additives being used or investigated include feed acidifiers, which contains blends of organic and inorganic acids that can enhance growth of broiler chickens by reducing the pH value of both the feed and the fore part of the intestinal tract thus controlling harmfull bacterial and improving the digestion of nutrients; prebiotics, which are non-digestible substrates that beneficially affect the host by selectively stimulating growth and/or activity of one or a limited number of bacteria in the colon, and the probiotics, (direct fed microbials) 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 microbial balance.

Probiotics enhance the productivity of animals and their resistance to diseases especially to enteropathic microbes such as *E. coli, Salmonella* .spp ,*Clostridium perfringes* and *Campylobacter* spp . They have potential to reduce enteric disease in poultry and subsequent contamination of poultry products (Patterson and Burkholder, 2003). The aim of probiotic approach is to balance the animal’s intestinal microbial eco-system and restore its resistance to diseases. The most commonly used organisms in probiotic preparations for poultry breeds are the lactic acid bacteria like *Baccilus, Bifidobacterium, Lactobacillus, Streptococcus, Enterococcus and Lactococcus* (Simon *et al.,2001; Kabir, 20091)*,which are found in large numbers in the gut of healthy animals and do not appear to affect them adversely .These species are yet to be fully documented to carry antibiotic resistant markers. Characteristics of ideal probiotics are shown in Table 2 and these should be aimed at when developing new strains for probiotic use. The various stages of such programme are described in Figure 1.The effects of probiotics are shown in Table 3.Apart from bacterial, *Saccharomyces* yeast and *Aspergillus* has been used as probiotics for poultry. Proposed mechanisms by which probiotics act include direct bacteria antagonism, competitive exclusion of harmful pathogens and immune stimulation. Probiotic microorganisms have to be viable to accomplish their putative beneficial effects such as producing antimicrobial factors, inhibiting undesirable organisms and competing for receptor sites on the gut epithelial tissue (Fuller, 1998). The probiotics of choice have to be considered under the environmental conditions of the animal. *Lactobaccillus bulgaricus* addition to broiler chick diet significantly improved growth performance, increased nutrient digestibility and stimulated humoral immune response in the tropics (Apata, 2008).

Conclusion

Antibiotics have been used widely in poultry industry at sub-therapeutic dose for growth promotion, prophylactically for disease prevention, or therapeutically for disease treatment. Such practises are responsible for improved productivity and healthier poultry breeds, but the utility of antibiotics has been questioned given the adverse consequence of an increase in the prevalence of antibiotics-resistant bacterial strains like *Escherichia coli, Staphylococcus* spp. and *Enterococcus* spp. which can be transmitted from poultry to humans through the food chain and other routes ,leading to potential therapeutic failures in both animals and humans. Various steps can be taken to slow down the development of resistance like restricting the use of livestock antibiotics to bacterial infections and use only for therapeutic purposes. National authorities should monitor for inappropriate use of antibiotics in poultry and livestock to ensure prudent use of such substances. Hygienic handling of raw poultry meats and adequate cooking will eliminate both resistant and susceptible food borne pathogens which may reside on raw meats. Because of the increased concerns regarding risk to public health resulting from the use of antibiotic growth promoters,it is essential to have a systematic approach towards replacing such antibiotics with natural alternatives like probiotics. Defining environmental conditions under which they show efficacy and determining mechanisms of action under this condition are important for the effective use of probiotics in poultry for production of safe edible products.

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Table 2. Characteristics of ideal probiotics

- Be of host origin
- Non- pathogenic and non toxic
- Resistance to gastric acid and bile which can be inhibitory in the gut
- Ability to attach to the gut epithelial lining which aids in preventing the organisms being swept out of the gut by peristalsis
- Withstand processing and stable on storage and in the field
- Amenable to cultivation and production on an industrial scale

Table 3: Effects of Probiotics in Poultry[a]

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

[a] After Ref. Stavric and Kornegay (1995); Jin *et al.* (1998); Zulkifii *et al.* (2000); Simmering and Blaut (2001); Kabiru *et al.* (2005); Apata (2008).

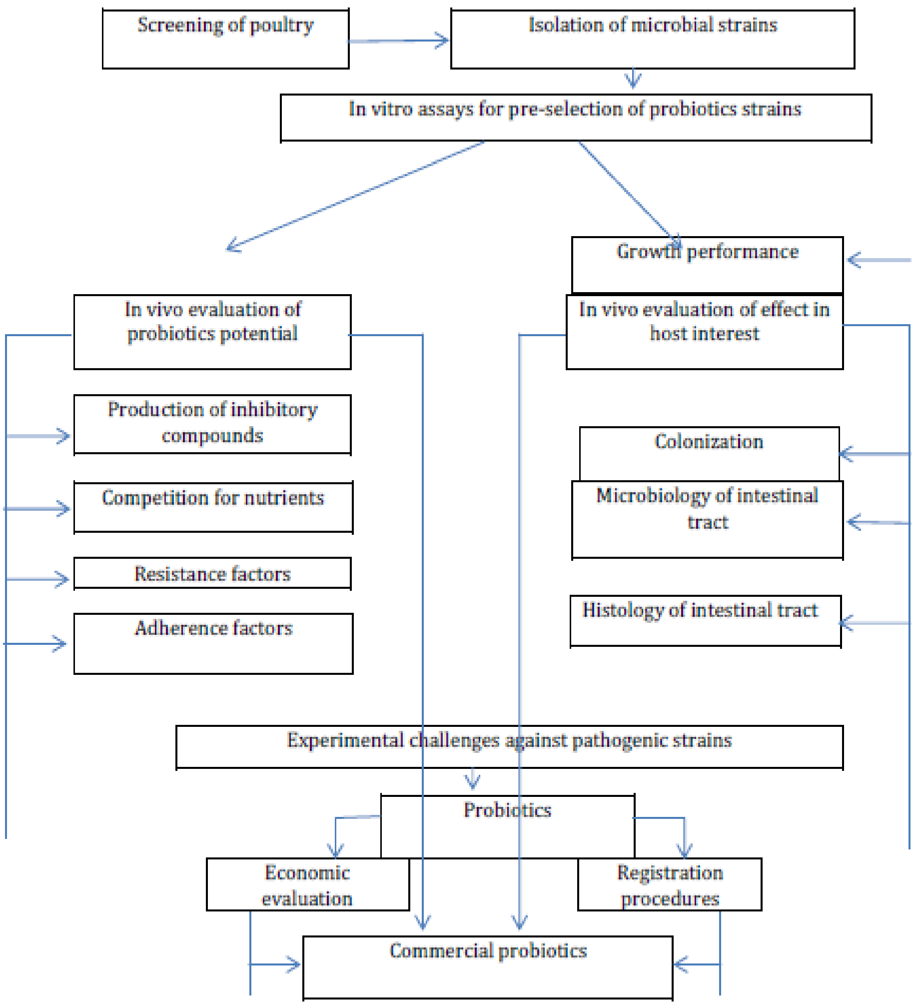

Figure 1 Diagram for selection of probiotics in the poultry industry (modified from Kabir, 2009