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## Antibiotic residue in animal foods: An alarm

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### Abstract

Human population is growing at a greater pace creating a huge gap between food production and population size. The difference between the two has somehow been managed with the huge utilization of pharmaceuticals be it in agriculture or in farm animals. These antibiotic residues have become a potential hazard for human as well as animal health and a great extent obstacle to export milk, meat and eggs. The consequence of these has shown a negative impact on human health ranging from food allergy to drug resistance. Judicious use of antibiotics and proper maintenance of withdrawal period is the only way to save the mankind from the rapid growing havoc of antibiotic residue in animal foods.

**Keywords:** Pharmaceuticals, residue, milk, meat, egg, food allergy, drug resistance

### Introduction

The rate of food production is far less than the turnover of human population. A report projected by United Nations shows that the current population of India in 2020 is 1,380,004,385, a 0.99% increase from 2019. However, the rate of food production excluding that of animal origin is far beyond the margin. Based on some author to feed today's population with a basic 2900 kcal diet, the average annual rate of cereal production per capita needs to be around 420 kg per year. However, the expected cereal production for 2050 is 360 kg; a 60 kg deficit than what is required <sup>[1]</sup>.

This huge difference between the demand and production has somehow made narrowed with the help of pharmaceuticals be it fertilizers or other common drugs used in animals. In one sense, this lead to indiscriminate use of such drugs in countries where proper enforcement of such laws are lacking. The same is true for food animals as well; animals are prone to various ailments which compel one to use drugs available in market for prevention, control and treatment of such ailments. However, this comes with a cost. The abundant use of antibiotics leads to antibiotic residues in frequently consumed foods. Residual antibiotics in food may have adverse effects on humans by directly causing disease via low-dose exposure and indirect harm via antibiotic resistance and drug allergy.

According to European Union, Residue is "pharmacologically active substances (whether active principles, recipients, or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal products in question has been administered <sup>[2]</sup>." Generally, any xenobiotic once it gets into the body has to undergoes four phases namely Absorption, Distribution, Metabolism and Excretion. Most of the parent product and its metabolites are excreted in urine and feces and to a lesser extent through saliva, sweat, secretions etc. However, after excretion, some portion of the drugs may pass with milk or may persist in eggs, and meat for a certain period of time as residues depending upon the nature of xenobiotics. Antibiotic residue in food animals is taking a greater pace with industrialization particularly in developing countries. The frequent and indiscriminate use of antibiotics in livestock is a crucial factor for the occurrence of antibiotic residues in animal foods such as milk, egg, and meat. Presence of antibiotic residue in animal origin foods can cause problems when the Maximum Residual Limit is crossed.

Maximum Residual limit (MRL) as per FAO is defined as the maximum concentration of a drug or chemical residue (expressed as mg/kg), to be legally permitted in or in food commodities and animal feeds <sup>[3]</sup>. Animal products which contain residues of drug beyond the MRL may causes serious health problems of the consumers ranging from mild allergy to life threatening anaphylaxis. The long term of effect of drug residue in such foods could lead to antibiotic resistance.

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And finally the consequences of such resistance are even more threatening where antibiotics become ineffective for treating mankind. This most of the time happens due to improper maintenance of withdrawal time. Withdrawal time can be broadly described as the time needed after drug administration to a food animal where the products obtained from the animal in which drug has been administered remains below a determined MRL. Different antibiotic may have different withdrawal time depending on their tissue penetration, route of administration and persistence<sup>[4]</sup>. As per survey, the antibiotic contamination of milk was reported to be due to intramammary infusions of antibiotics for treating mastitis and to a lower extent via injections. Likewise for Livestock excluding poultry the contamination of meat was reported to be due to intramuscular injection. In case of eggs, the appearance of drug residues can be mainly attributed to feeding of antibiotics as growth promoter in the feed. The administered antibiotics or their metabolites become deposited in animal tissues and secretions intended to be used for human consumption, where the concentration is beyond the permitted level for a certain period of time. Antibiotic residues in products of animal origin have been one of the major concerns in the recent years. As control policy demands proper detection and quantification approach of Antibiotic residues in milk, a good number of research works, have been published worldwide in this context to meet up the feasibility. Previously, some microbiological tests were used officially though these tests are cheap, rapid, and easy to perform but lack of proper selectivity and accuracy level. Chromatographic techniques, in the other hand, are more precise with higher specificity and accuracy, but requires proper sample preparation, sophisticated instrumentations, well trained personnel<sup>[5]</sup>.

The following factors contribute to antibiotic residue in food animals:

**Antibiotics for treatment:** This is a major cause of presence of Antibiotic residue in animal foods is the indiscriminate usage of antibiotics in therapy of infectious diseases, such as clinical mastitis and other diseases.

**Antibiotics as prevention:** Sometimes, antibiotics are used in therapy of dry cow, management of post-surgical risk and also when used as growth promoter in pigs and poultry which are equally responsible for the residue of parent compound or its metabolites.

**Antibiotics as preservatives:** Antibiotics are authorized for use as preservatives for biological products if used within the limitations. For instance tetracycline are used to prevent the growth of harmful bacteria in poultry, fish, and canned foods. When an antibiotic or combination of antibiotics, the kind and amount of each shall be specified in the outline for such product properly.

If the supplied instructions in the label are not followed accordingly, residues of antibiotics may be found in the final product.

**Extra-label use of antibiotics:** It has been reported in many cases when an antibiotic is approved only for humans become used injudiciously in animals, or usage in different species where it is not approved, or during a condition where it is not approved, or usage beyond the appropriate concentration.

**Lack of maintenance of proper withdrawal time:** Without proper maintenance of withdrawal time of antibiotics in food animal, Antibiotic residue is certain to appear in such foods beyond permissible limits.

**Lacks of rules and detection facilities:** Crisis of skilled manpower or sophisticated instruments or of enforcement system may be one of the crucial factors for the presence of antibiotic residues in animal foods particularly in developing countries.

**Public Awareness:** Lack of awareness of farmers or animal care personnel about withdrawal period of antibiotic and residual effects of antibiotic Residue in long run is also a major contributing factor for developing countries.

**Improper disposal:** After using antibiotic, containers should be kept out of the reach by animal or should be disposed off as per proper guidelines. Presence of empty containers of antibiotics in the farm premises which can contaminate feeds of animals or Animals may come in contact and lick those or even get exposed through contaminated feeds unknowingly<sup>[6]</sup>.

### Major effects of Antibiotic Residue on mankind

Antibiotic resistance: WHO states Antimicrobial resistance is one of the most serious global threat to mankind in the current era, as antimicrobial agents contribute not only to human medicine but also veterinary drug and animal-derived food production. The development of antibiotic residue is so rapid that there are now statements by the WHO and US Centers for Disease Control and Prevention stating a global crisis and an impending disaster involving a return to the pre-antibiotic age<sup>[7]</sup>. Animals raised for food production are known as an important reservoir of antimicrobial-resistant bacteria which can easily pass onto humans. Upon consumption of such foods, these antibiotic resistant bacteria may setup and colonize the human intestinal tract and contribute resistant genes to humans. Microorganism may develop resistance due to following

1. Decreased affinity for the target e.g. pneumococci and staphylococci may develop altered penicillin binding proteins.
2. Development of alternative metabolic pathway e.g. sulfonamide resistant organisms start utilizing preformed folic acid in place of synthesizing it from PABA.
3. Elaboration of the enzymes which inactivate the drug e.g.  $\beta$ -lactamases (penicillins and cephalosporins), chloramphenicol acetyl transferase (chloramphenicol) and aminoglycoside inactivating enzymes (aminoglycosides).
4. Decreased drug permeability due to the loss of specific channels e.g. *aminoglycosides* and *tetracyclines* attain much lower drug concentration in the resistant organisms than in the sensitive organisms.
5. Development of efflux pumps (*tetracyclines*, *erythromycin* and *fluoroquinolones*) results in active extrusion of the drug from the resistant microorganisms<sup>[8]</sup>.

### Allergic reactions

Even though the Residues of antibiotics are little it is often associated with multiple types of allergic reactions, including serum sickness and anaphylaxis, particularly in case of penicillins. Meat and other dietary products from food animals may contain residues of many antibiotics and

antibacterial agents. General surveys have shown a low incidence of detectable residues in most products intended for human consumption. It has been reported that a notable proportion of the general population has true allergic sensitivity to these substances due to prior medical treatment especially in case of penicillin. Although the therapeutic margin of Penicillin is remarkably high, the adverse reactions are attributed to allergy. Allergic reactions to penicillin range from mild skin rashes of little clinical significance to severe anaphylactic shock, which can be life-threatening and even fatal. When penicillin are administered in therapeutic doses, the incidence of severe life-threatening reactions is relatively small (1 in 50000). Conversely, mild skin rashes and eruptions skin papules are common which can be associated as high as 12% of treated patients <sup>[9]</sup>.

### Carcinogenicity

Carcinogenicity has become one of the deadliest and rapidly growing disease of modern society. Environmental factors plays a vital role in the occurrence of cancer and among these food pollution is one. Food pollution is generally defined as the presence in food or associated with food of toxic chemicals (elements or compounds) and/or biological contaminants which are not naturally present in food or are above their natural background levels (for those chemicals which are naturally found in some foods). The antibiotic residue present in animal foods has potential to interact with cellular elements such as DNA by interacting with it causing mutation. Researchers from different Universities have proved the link associated with oral antibiotics and colon cancer. Reports shows that penicillin group of drugs were associated with an increased risk of cancer in the first and middle parts of colon while cancer of the last part of colon was associated with the use of tetracycline <sup>[10]</sup>. The longer the duration of oral antibiotic therapy the worst would be the side effect. This clearly showed that judicious use of antibiotic is of utmost importance to safeguard oneself from such life threatening conditions.

### Teratogenicity

Following Thalidomide disaster in 1960-61, the awareness and monitoring of the drugs associated with teratogenicity has been given greater significance. Long term exposure to Antibiotic Residue during the gestation may end up with numerous congenital anomalies. The main concern for the use of such drug during gestation is their ability to cross the placental barrier and the metabolite which may be of little significance to the mother may pose toxicity to the developing child. Generally speaking, very few antibiotics can be used in pregnancy all along the gestation period while most of the antibiotics are teratogenic in the first trimester which is the period of organogenesis <sup>[11]</sup>. Whatsoever the mother consumes or administered with, it has equal opportunity to invade the fetal circulation depending upon the concentration, lipophilicity, molecular size and plasma protein bindings. Aminoglycosides in adults may cause ototoxicity and nephrotoxicity as adverse effect. Aminoglycosides when administered to a pregnant women may attain as high as 60% of the concentration in the amniotic fluid in comparison to maternal blood <sup>[12]</sup>. This can cause severe intrauterine otological damage and nephrotoxicity of the developing fetus. The chance of causing ototoxicity is higher than nephrotoxicity. On the other hand, tetracycline concentration in umbilical vessels accounts to about 50% of the

concentrations in the maternal blood. These concentration is sufficient to cause intrauterine damage to the feuts depending on the period of gestation. Tetracyclines administered during the period of calcification of the teeth are deposited as a calcium complex in the mineralization zones and cause a yellow discolouration of the teeth as well as hypoplasia and enamel defects. Moreover, tetracyclines has a tendency to deposit on growing long bones and hampers the process of osteogenesis which eventually slows the rate of bond development and mineralization. Other side effect of tetracycline used in pregnancy are fatty liver syndrome in fetus particularly when the fetus is exposed during the last trimester of pregnancy <sup>[13]</sup>.

### Disturbances in the normal intestinal environment

Gut microbes are in equilibrium and coexists with others and colonizes to prevent the pathogenic microbes from producing diseases. Antibiotic residue in animal foods resulting from usage of broad-spectrum antibiotics may kill a wide range of microflora in the intestine including the non-pathogenic organisms, which can make the disease causing microorganisms to expand vigorously and disrupt the normal intestinal environment. This all together can result into another disease. This infection so produced is super-infection. Generally super infection results when a broad spectrum antibiotic is taken to treat an existing bacterial infection. However, in case of drug residue apparently no antibiotic is taken but it is present in small quantity in animal foods. Instead it is the antibiotic residue containing food that makes the second infection possible because it disturbs the normal microbiome in the body. Imbalance in the microbiome, dysbiosis, can last for several months, even up to several years discontinuation of exposure <sup>[14]</sup>.

When the commensal is reduced, the pathogenic microbes get an opportunity to grow and potentially cause a new infection (Superinfection). The chance of getting superinfection is higher when using broad spectrum antibiotics as compared to narrow spectrum antibiotics. Other predisposing factors of superinfection are long duration of antibiotic therapy, lowered immunity and malnutrition. One of the notable example of bacteria causing superinfection is *Clostridioides difficile* <sup>[15]</sup>. It can cause diarrhea which can be severe or even fatal. It has been proved that *C. difficile* infection is mainly associated with broad spectrum antibiotic like fluoroquinolones <sup>[16]</sup>. Apart from bacterial, a common complication following antibiotic treatment is a fungal infection, for example, oral and genital thrush. Many studies have found a direct link between antibiotic use and increased risk of urinary tract infections. For instance, women treated with antibiotics were 4 times more likely to contract a urinary tract infection than untreated women.

### Conclusion

From the above facts, it may be mentioned here that for public health concern, antibiotic residues in food of animal origin produces potential threat in human by causing direct toxicity when consumed in high level and low levels of antibiotic exposure results in alteration of Gastrointestinal microflora, and the possible development of drug allergy and drug resistance, which cause failure of antibiotic therapy in clinical cases. Due to lack of knowledge and effective dairy and poultry principles in developing countries, antibiotics are used indiscriminately and withdrawal periods are not properly maintained. These antibiotic residues have become a potential

hazard for human as well as animal health and a great extent obstacle to export milk, meat and eggs. Judicious use of antibiotics and proper maintenance of withdrawal period is the only way to save the mankind from the rapid growing havoc of antibiotic residue in animal foods.

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