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Antimicrobial Growth Promoters in Farming Practices Exacerbates Antibiotic Resistance Crisis: A Global Threat

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Abstract: As the world sees increase in the use of antibiotics to reach the market demands, the dependence of man and animals on antimicrobials have tremendously increased leading to an antimicrobial resistance crisis across the globe. Considered as one of the major public health issues and a global threat to man and animals, antimicrobial resistance is widely now talked about as a one health and one world issue.

Use of Antimicrobials has seen its importance in the animal sector not just at therapeutic doses against diseases but also at sub-therapeutic doses as Antimicrobial Growth Promoters (AGPs) for production animals. Resistance of microorganisms to antimicrobials is a major challenge as more and more resistant strains of microbes have evolved. To visualize how the problem of antibiotic resistance might best be addressed, an understanding about what it is and its mechanism is necessary. Solutions can then be drawn and implemented as soon as possible because the time is crucial and the work is vast.

Keywords: antibiotic, antibiotic resistance, global threat, sub-therapeutic dose, antimicrobial growth promoter.

I. INTRODUCTION

With the rapidly increasing population, demands for animal and animal products have risen drastically and this has shown effects on the animal rearing system as more and more emphasis has been recently diverted towards intensive system of farming to meet the huge market demands. This system of rearing faces a lot of incidences of increased disease occurrence as many farms compromise with the basic hygienic conditions of the farm. In scenarios as such that lead to increased levels of stress within the animals in the farm, sub-therapeutic doses of antimicrobials have shown significant decrease in the disease occurrence with even minimum management conditions and thus antimicrobials in animal feeds and drinking water have been invariably used. The major concern of such use of antimicrobials however, has been the development of resistant strains of microorganisms in the long run possessing huge risk of endangering animal and human health. The shrimp and salmon industries have seen significant rise in the use of antimicrobials as growth promoters as an integral part for intensive farming to increase the production. Antimicrobials are administered to animals for reasons that include treatment and control of disease, as growth promoters etc.

Growth promotion use of antimicrobials refers to the use of antimicrobials to increase the rate of weight gain and/or the efficiency of feed utilization in animals by other than purely nutritional means.

The World Health Organization (WHO) identified antibiotic resistance as one of the global threats to public health, while CDC has stated antibiotic resistance as one of the biggest public health challenges of this time.

II. HISTORY

The golden age of antibiotic discovery had begun with Alexander Fleming and his discovery of penicillin in 1928, followed by discovery of newer classes of antibiotics by other pioneers. It was however, not until the 1940s that antibiotics were prescribed to treat illness. This brought about a transformation of modern medicine as was able to save millions of human lives by bringing down the death rate to a remarkable number.

Shortly after the introduction of therapeutic uses of antimicrobials, their effects on the promotion of growth in animals have been discovered. Sub therapeutic or low doses of antimicrobials were then used as growth promoters in production animals and such doses of antimicrobials came to be called as Antimicrobial Growth Promoters (AGP) and were first used in the mid-1950s. Antibiotics like penicillin and tetracycline could increase the feed-to-weight ratio for swine, beef cattle and poultry. However, by the 1950s many microorganisms had already developed resistance against antibiotics like penicillin and tetracycline and thus concerns regarding resistant microorganisms had already been raised. Sir Alexander Fleming in 1945 had warned that "public will demand [the drug and] … then will begin an era … of abuses." Overuse.

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III. EEFECTS OF SUB-THERAPEUTIC USE OF ANTIMICROBIALS

According to a report, NO TIME TO WAIT, published in 2019, drug-resistant diseases cause at least 700,000 deaths globally a year, including 230,000 deaths from multidrug-resistant tuberculosis and this figure could increase to 10 million deaths globally per year by 2050 if no actions are taken. Around 2.4 million people would die in high income countries between 2015 and 2050.

Antimicrobial resistant strains of microorganisms have been selected mainly from use of antimicrobials for therapeutic use in humans but it has also been found that long term use of low doses of antibiotics in animal feed and water also has contributed to development of resistant strains in humans.

IV. ANTIMICROBIALS USED IN ANIMAL FEED

A number of studies show that use of low-dose in-feed antimicrobials (like oxytetracycline, chlortetracycline, sulfamethazine, etc.) as AGP in production animals have led to colonization with drug resistant *E coli.* in chicken and pig. Concerns arise as many drug-resistant organisms have emerged with due course of time and has led to major health issues in animals and man, followed by drug failures.

Long term, low dose use of nontherapeutic antimicrobials possesses the risk of emergence of resistant strains of microbes than therapeutics doses which are generally aimed at shorter durations and at higher doses, controlling the emergence of resistant strains due to relatively short time use and because relatively smaller number of animals are being targeted. The resistant strains that may have even evolved are being diluted by growth of drug susceptible microbes after the therapy has been withdrawn.

V. MECHANISM

Drug resistance is a result of spontaneous mutation within a sequence of genome. The gene for resistance is carried in chromosomal or extra chromosomal elements that are called Resistance (R) plasmids (R factors). R factors may be transferred from one bacterium to other. Resistance to multiple antimicrobials maybe possessed in the same plasmid. Some datas shows that use of antimicrobials have led to an increase in the R^+(resistant plasmid) enteric organisms in the animals. Plasmids confer resistance by encoding for enzymes that cause chemical modification and inactivation of the antimicrobials, by encoding for a substitute enzyme that is insensitive to the antimicrobials or by causing decrease in permeability of the cell to the antimicrobials.

VI. TRANSMISSION OF ANTIBIOTIC RESISTANT BACTERIA THROUGH THE FOOD CHAIN

The food chain is complex and it throws a challenge to determine the direct link between antibiotic use in animals and the emergence of antibiotic resistance in humans. Consumption/handling of meat, shrimp, etc. may lead to transmission of resistant bacteria to humans. Studies have confirmed presence of resistant bacteria in farm premises (in excreta, in air, dust etc.) that use AGPs in the farm animals. These resistant bacteria persisting in the environment act as modes of transmission for other animals and humans. Water environments such as aquaculture, sludge, freshwater, and waste waters may have roles as “mixing pots” leading to transmission of resistant bacteria to other animals and human. The antibiotics used in livestock can also be ingested by humans when they consume animal products.

Antibiotics used in animal as growth promoters leave antibiotic residues in foods like milk meat eggs etc. which may contribute to transfer of antibiotic resistant bacteria to humans through food consumption.

VII. SOLUTION TO THIS PROBLEM

As long as there is a problem, there will also be a solution. The issue of antimicrobial resistance concerned with its use as growth promoters in production animals can be addressed with more careful and newer approaches-

➢ ALTERNATIVES

Promotion of growth of production animals can be achieved with improved use of AGPs or with replacements with other effective alternatives.

• PROBIOTICS

These are live microorganisms that are considered to have positive effects on health when consumed or applied to the body. The use of probiotics awaits a wide field of research as an alternative to AGPs by reducing pathogenicity of opportunistic commensals and by also re-establishing healthy gut commensal micro flora. An ideal probiotic should be resistant to feed processing and to effects of bile salts and digestive enzymes. Probiotics are marketed now by leading feed industries as ‘gut flora stabilizer’. Organisms like *Bacillus subtilis in some species, Bacillus amyloliquefaciens* for poultry and *Enterococcus faecium* for piglets are used as probiotics with positive response as growth promoters by many feed processing companies.

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- **PREBIOTICS**

Prebiotics are non-digestible feed ingredients with selective effects on the intestinal microbiota. These are mainly oligosaccharide compounds. They have similar action as that of probiotics. Prebiotics have beneficial effects on growth or metabolic activity of a limited number of intestinal microbiota species, like *Bifidobacteria* and *Lactobacillus spp*.
An approach of combined use of both probiotics and prebiotics as 'Synbiotics' affecting the host by improving survival and persistence living microbiota in intestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria

- **PHAGE THERAPY**

Bacteriophage are viruses that infect bacteria. They are highly specific to the bacterial species which they kill. A study on phage cocktail SalmoFREE, which is a mixture of 6 *Salmonella* lytic bacteriophages, used as a therapy for Salmonella control in poultry shows evidences that SalmoFREE contributes to the reduction of the presence of Salmonella, when it is used in multiple doses and does not affect the animals and the production parameters, indicating it safety. The effects of phage therapy have caught the attention of many scientists and researchers and studies depict the success status of bacteriophages as therapeutic alternatives of antimicrobials but very less work has been done on its potential use as feed additives and as growth promoters in production animals. A potential application would be the combination of antibiotics with bacteriophages. Such phage-antibiotic combination is reported to have effects superior to the sum of their individual effects. In addition to its superior effects, it also maybe more difficult for microorganisms to develop resistance against both the antibiotic and the bacteriophage than the individual agents. (i.e. the antibiotic or the bacteriophage).

- **NEW ANTIBIOTICS**

Work on new classes of antibiotics that are not affected by known or existing mechanisms of resistance along with chemical modification to form derivatives that are capable of evading resistance mechanisms are necessary and may be one of the solutions to the problem of antimicrobial crisis.

- **ANTIMICROBIAL PEPTIDES**

Antimicrobial peptides (AMPs) are low-mass peptides with antibacterial, antiviral, antifungal, and antiparasitic actions. AMPs are produced by both eukaryotes and prokaryotes. The mechanism of AMPs is based on irreversible damage to the microbial cell membrane, resulting in cell lysis. AMPs produced by bacteria are called bacteriocins. Bacteriocins are characterized by a much greater specificity since their activity is limited to only a few species of bacteria and also have much higher potential.
More compounds are increasingly being explored for their potential roles in growth promotion some include, use of exogenous enzymes that act by the conversion of indigestible compound into readily absorbable Volatile fatty acids (VFAs). The enzyme partially counterbalances the adverse effects of soluble Non-starch polysaccharides (NSPs) on performance. Others include formic acid in protonated form (as 'acidifier') of the intestinal tract in chicken which may reduce diarrhea. A mixture of organic acids and essential oils has been reported to have stimulated body weight gain and decreased *E. coli*. The search for more alternatives has a vast range of scope.
Besides the use of alternatives, management strategies need to be put into account. Maintenance of proper biosecurity measures, hygienic conditions of the farm and the farm animals along with access to clean feed and water to animals and proper sanitation are crucial to fight the problem of antibiotic resistance. Scientific rearing systems are highly essential to reduce the levels of existing stress within the farm animals which would improve the general conditions of the reared animals simultaneously reducing the need for antimicrobial use for growth promotion.
Maintaining a proper vaccination schedule is one of the vital steps in the rearing of animals as vaccinated animals are protected against many diseases which in turn reduce the requirement for antimicrobials in the animals.

- **LIMITATION OF INCORPORATION OF ALTERNATIVES TO AGPs**

Despite the many numbers of studies indicating use of alternatives for growth promotion, there is an unfortunate gap in its introduction to production animals. Some of the limitations include

- Limited funding from public and private sectors for research on antimicrobial alternatives.
- Void in knowledge
- Insufficient interest due to expectations of achieving positive effects.
- Economic conditions of farmers and veterinarians
- Higher production, handling and distribution costs.

❖ Volume of market demand is insufficient as alternatives find their uses only in specific endemic areas (extreme specificity).

Such limitations make it difficult to widen the use of alternatives in animal production. This demands that proper awareness, and marketing needs to come into action.
Professionals like veterinarians have a bigger role to play in guiding and imparting knowledge about the risks related to antimicrobial resistance and the necessity to adopt alternatives to AGPs amongst the farmers and the general public. With the right steps being taken at the right time, a global threat can be mitigated to a great extent.

VIII. CONCLUSION

Antimicrobials are crucial to the survival of man and animals but it's careless and overuse has led to a problem so great in its magnitude, that it has compelled attention for an immediate action. Antimicrobial/antibiotic resistance is not a new concept but one that has been known as early as 1940s. Antimicrobial Growth Promoters have been an integral part of the animal husbandry sector and their incorporation has led to multifold increase in production. This however is a major contributing factor to the entire emergence of the antimicrobial resistance and alternative to AGPs are in high demand. Alternatives like probiotics, prebiotics; phage therapy etc. coupled with proper management practices is now highlighted. These alternatives for AGPs are only of practical significance when they would improve animal performance at levels comparable to that of the AGPs.
However, one should remember that there is no permanent solution to this crisis and it only demands constant modifications over the years. The problem no matter is great but it does have many solutions; the only lacuna is in the fact that more active participation from people belonging to different sectors is the need of the hour.

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