Review paper
UDC 636.09:615.33.015.8

REVIEW PAPER ON THE EFFECTS OF ANTIBIOTIC USE IN AGRICULTURAL ANIMALS ON THE HUMAN HEALTH AND FORMATION OF FOOD BORN ANTIBIOTIC RESISTANT MICROORGANISMS

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Abstract

The use of antibiotics in agricultural animals that are bread for human food has allowed for control of disease in livestock, improvement of growth and therefore overall better feed conversion. Although there are many positive sides for the use of antibiotics, in recent years the concern has arisen if excessive use of antimicrobial agents can lead to antibiotic resistant bacteria and how they can impact negatively on the human health and human infections. The purpose of this review is to summarize the published data in food transmitted antibiotic resistant bacteria.

The actual danger may seem small, because in many cases the same antibiotics used in humans are used to treat livestock, but there are papers that state the presence of antibiotic resistant strains of bacteria that derived from animals. Also in this review we look at the potential mechanisms of transferring the antibiotic resistant bacteria from animals to humans. One of the potential ways to transfer these pathogens is from direct infection from the animal. Other papers imply on breaking the species barrier, the antibiotic resistant strain of bacteria if formed in the antibiotic treated animals and then transmitted to humans. Some of the paths of transmission may be the transfer of resistant genes form meat and dairy into human pathogens. Although this potential mechanism is more difficult to study and is least represented in the published data, is most like the most important one to study.

In conclusion the use of antibiotics in agricultural animals and their impact on human health is a vast and under studied matter, that needs to be further analyzed so that the exact mechanisms of transmission are known. But the dangers are present and this matter needs to be dealt with great care and with involvement from all parties, from producer to consumer.

***Key words**: Antibiotics, Animals, Food, Human, Microorganisms, Pathogens.*

1. Introduction

Antibiotics have been used in both human and veterinary medicine for more than 60 years. Almost simultaneously, the use of antimicrobials has been applied in agriculture to prevent, control, and treat infections and to improve growth and feed efficiency [1, 2]. The overuse or misuse of antimicrobials has been blamed for the selection of resistant isolates, giving birth to the term antimicrobial resistance. For antimicrobial resistance the World Health Organization has the following definition: "Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it" [3]. Still, the link between use and overuse of antibiotics and resistance is not easy to follow, as antimicrobial resistance is a very complex phenomenon affecting both human and animal health [4].

Bacteria are quite adaptive organisms that have survived multiple environments during their existence on the planet. Yet, the emergence of antibiotic-resistant bacteria occurred quite shortly after their first use. In 1948, *Staphylococcus aureus* strains isolated from patients in British hospitals were found to be resistant to penicillin [5], and soon after the drug's first use, resistance to streptomycin was observed in *Mycobacterium tuberculosis* isolates [6]. In the 1950s, antimicrobial resistance was confirmed in other pathogenic bacteria, such as: *Escherichia coli*, *Shigella* spp., and *Salmonella enterica*, [7 - 9] whereas in the 1960s, antibiotic-resistant bacteria such as extended spectrum β-lactamases producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant *Acinetobacter baumannii* were encountered [10 - 12]. Concerning outbreaks resulting from resistant bacteria from animals, data are limited, mainly because of the difficulty in discriminating the origin of these bacteria.

2. Reasons for antibiotic administration

Antibiotic administration to animals is often necessary, but the whole heard or flock is treated when illness is recognizes in a small population of the animals. This type of treatments results in a better general welfare of the animals [12]. Mass administration of antibiotics errors on the side of potentially administrating treatment to individuals that are not affected or even ill. Some of the reasons for this are the growth promoting effect of antibiotics. They were first discovered when in an experiment in the 1940s when chickens fed byproducts of tetracycline fermentation were found to grow faster than those that were not fed the byproducts [13]. Since then, many antimicrobials have been found to improve average daily weight gain and feed efficiency in livestock in a variety of applications [14 - 16]. The growth promoting effects are mediated through alterations of the normal intestinal microbiota resulting in more efficient digestion of feed and metabolism of nutrients [17 - 19], others are mediated through pathogen and disease suppression and immune system release [20 - 22].

2.1 Transfer of resistant bacteria from animals to humans by the food chain and other means

It is well known that bacteria from animals may contaminate meat derived from those animals and that such contamination also depends on the human factor of preparing and storing the food. However, most of the studies of the food chain ignore the fact, that there are potential sources of resistant enterococci and *Enterobacteriaceae* other than farm animals given antibiotics. Humans as well as other animals may be a source of resistant bacteria, subsequently isolated from food animals, since pathogens can reach the general environment via sewage [23]. Wild animals, rodents and birds, can acquire these environmental contaminants and pass them on via their excreta in the environment. Vegetables may also be contaminated from sewage. Multiply antibiotic-resistant *E. coli* strains were found to be widespread contaminants of market vegetables in London during the investigation of a community outbreak of *E. coli* infection [24, 25]. Fish farming involves the use of antibiotics (although this is diminishing in Europe), and fish as food may be contaminated with resistant bacteria [26].

Furthermore, antibiotics are widely used to prevent bacterial diseases in plants: tetracyclines and aminoglycosides are used to protect fruit trees from fire blight [27]. Streptogramin-resistant *E. faecium* have been isolated from bean sprouts from sources yet to be identified [28, 29]. Genetic engineering in plants involves the use of a variety of antibiotics including vancomycin [30]. We are aware of no rigorous epidemiological studies of such potential reservoirs, and the assumption that they make negligible contributions to human enteric pathogen resistance is unfounded. Animals that carry, or in certain cases are infected by, resistant organisms are a hazard to those who work with them since the organisms can be transferred by direct contact. This is the probable explanation of the rare but well publicized finding of indistinguishable glycopeptide-resistant enterococci - for example, in the faeces of a Dutch turkey farmer and his flock [31] and of streptogramin-resistant *E. faecium* in the faeces of a Dutch chicken farmer and his chickens [32]. Even in these cases, we cannot exclude the possibility that both animals and humans acquired the strains from a common source, or even that the organisms were transferred from man to his animals. Isolates of enterococci from human and animal faeces that have no evidence of close conventional epidemiological links are often different on molecular testing, depending on the sensitivity of the method used, although in these studies, indistinguishable strains have sometimes been found among human and animal faecal enterococci [33 - 37]. Recent work from Bruinsma *et al*., [38], suggests that whereas human and pig faecal isolates of *E. faecium* have genetic similarities, those from poultry faeces are different. Others have not found such similarities, and clearly more investigations need to be done on this subject. It is generally accepted that adequate cooking destroys bacteria in food. No evidence indicates that antibiotic-resistant strains are more refractory to cooking than are the largely susceptible strains on which the original research was conducted.

We must also assume that as with salmonellae, inadequate cooking fails to decontaminate food. We also know that salmonella cross-contamination between uncooked and cooked food may occur if hygiene measures are inadequate in food outlets, and it may be that such cross-contamination occurs with other bacteria as well, including resistant strains, but again there is no direct information. In the experiment of Sørensen *et al*., [39], ingestion of pig or chicken strains resulted in their excretion for a very limited period of time: in only one experimental subject out of 12 was the same organism detected at 15 days after ingestion but in none thereafter. As already noted, enterococci from chickens do not closely resemble those in human faeces, although those from pigs may have similar molecular characteristics to those from humans, [38] but this does not mean that humans acquire their faecal enterococci from pigs. Zoonoses such as *Salmonella* spp. and *Campylobacter* spp. infection, undoubtedly can reach humans via the food chain, but their immediate source may not be the animal faecal flora. In each case, reports of infection traced from a farm to a human non-epidemic infection are uncommon. Furthermore, a recent study shows that chicken enterococci do indeed belong to a different pool from those of humans and pigs. [38]. Thus, in the absence of adequate conventional and molecular epidemiological studies, we are aware of no evidence of the extent to which resistant enterococci or *E. coli* from food animals are able to colonize the human intestinal tract.

2.2 Gene transfer

The ultimate defense of those who support the farm-to-clinic hypothesis is that provided animal organisms reach the human faeces, they need to survive only for brief periods to pass on their antibiotic resistance genes to resident organisms. There is absolutely no doubt that transfer of resistance genes can occur, and countless *in vitro* experiments have characterized the event in endless variety, including among selected but by no means all strains of enterococci, [40] a phenomenon that may also be demonstrated experimentally in the germ-free animal gut [41]. However, there have been no observations to determine its frequency under natural conditions - or even if it occurs at all in the normal human gut with the 'indicator organisms' from animal sources.

The clearest cases of *in vivo* natural transfer have involved gut pathogens such as salmonella and shigella, *E. coli,* and other *Enterobacteriaceae*. The transfer of vancomycin resistance from vancomycin-resistant enterococci (VRE) to *Staphylococcus aureus* under experimental conditions a decade ago [42] has to date been reported to occur only twice in nature, in the USA, related to intensive vancomycin use in humans - the single case of *S. aureus* with VanA that was presumably acquired from a vancomycin-resistant *E. faecalis* strain from the same patient*,* recently reported, [43] and a second case of a similar nature [44]. However, it is without doubt true that although some genetic elements, such as the transposon Tn*1546*, are heterogeneous both in animal and human faecal enterococci, indistinguishable variants may be found. However animal strains are not the only potential source of resistance, [45] but it cannot be assumed that the genes have passed from these organisms to enterococci rather than vice versa. The truth about gene transfer from animal isolates of indicator organisms to human isolates in the human intestine (or even in other relevant sites) thus remains beyond our grasp and need further investigation and studies. The results of the Danish ingestion experiment in which no human faecal isolates were other than the animal strains swallowed by the experimental subjects, and in which no permanent carriage was demonstrated, suggest that it is not a common event *in vivo* [39].

3. Conclusions

- With this review the possible threats to the human health from consuming food that has been treated with antibiotics and we found no evidence of this except what comes from improperly stored and prepared food, which is a human factor have been summaries. With following simple common sense guidelines this threat can be avoided.

- As for the possibility of forming antibiotic resistant strains of bacteria from animals, the evidence are to say at least, lacking in providing a direct link between animals treated with antibiotics and human infections. This problem with the correct identification of the origin occurs since the same antibiotics are used to treat humans and most probably the antibiotic resistant strains are formed in humans and transmitted to humans. The most precise evidence that can be used to determine the origin of the antibiotic resistant bacteria are molecular identifications of the bacteria, studies which are not conducted enough or thorough enough to give no contradictory evidence. And more molecular studies need to be made and this subject to be further investigated so that all the potential mechanisms of transmission of antibiotic resistant microorganisms can be discovered.

- The biggest threats to humans form animals treated with antibiotics comes from direct contact with them and not form transmission trough food. This subject is popularized a lot by the media in recent years and many fears come from this statements, but with this review we conclude that the use of antibiotics in animals, if done properly and with limited unnecessary administration, has benefits that are unprecedented that outweigh the possible dangers.

4. References

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