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Review

Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals

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Abstract

Antimicrobial agents are used in food animals for therapy and prophylaxis of bacterial infections and in feed to promote growth. The use of antimicrobial agents for food animals may cause problems in the therapy of infections by selecting for resistance among bacteria pathogenic for animals or humans. The emergence of resistant bacteria and resistance genes following the use of antimicrobial agents is relatively well documented and it seems evident that all antimicrobial agents will select for resistance. However, current knowledge regarding the occurrence of antimicrobial resistance in food animals, the quantitative impact of the use of different antimicrobial agents on selection for resistance and the most appropriate treatment regimens to limit the development of resistance is incomplete. Surveillance programmes monitoring the occurrence and development of resistance and consumption of antimicrobial agents are urgently needed, as is research into the most appropriate ways to use antimicrobial agents in veterinary medicine to limit the emergence and spread of antimicrobial resistance.

Keywords: Antimicrobial agents; Food animals; Resistance

1. Antibiotic resistance in man

The greatest threat to the use of antimicrobial agents for therapy of bacterial infections is the development of resistance in pathogenic bacteria. Bacteria isolated from patients before antibiotics came into clinical use had virtually no resistance plasmids [1]. Shortly after the introduction of penicillin, the first penicillin-resistant bacteria were observed [2,3]. Since then, the introduction of each new antimicrobial compound has been followed by emergence of antimicrobial resistance [4]. In some cases resistant bacteria emerged shortly after a new agent came into clinical use, whereas in other cases several years or even decades elapsed.

The pharmaceutical industry have tried to limit the consequences of this development of resistance by the search and discovery of new antibiotics but in recent years bacteria resistant to an increasing number of antimicrobial agents have emerged world-wide. It has even been said that we might be approaching the post-antibiotic era.

Numerous studies in human medicine have focused on the increase and decrease of resistance in relation to the increase or decrease in the use of specific antimicrobial compounds and compared the occurrence of antimicrobial resistance in hospitals to the community [5–14]. In general the occurrence of resistance among pathogenic bacteria in different countries follows the consumption of antimicrobial agents relatively closely [15–17]. In human medicine it is generally agreed that the use of antimicrobial agents is the most important factor in the selection of resistance in bacteria and that, in general, a close association exists between the rate of resistance development and the quantities of antimicrobial agents used.

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2. Antibiotic use and resistance in animals

More than half of all antimicrobial use is associated with the production of food animals. World-wide, large quantities of antimicrobials are used for growth promotion and prophylactic purposes and more moderate amounts for therapy. Thus, bacterial species related to food animals are exposed to a substantial and in many cases constant, selective pressure.

Unfortunately, only limited information regarding the consumption of different antimicrobial agents in different countries or for different animal species are available. In most cases studies have to rely on information regarding legislation of different compounds in different countries or for different food animals.

The use of antimicrobial agents for food animals may cause problems in the therapy of infections in animals though the selection for resistance among bacteria pathogenic for animals. In addition, animals frequently harbour bacteria pathogenic for man in their intestinal tract: zoonotic agents (*Salmonella*, *Campylolobacter*, *Yersinia*, *Listeria* and enterohaemorhargic *Escherichia coli*). Development of resistance in these zoonotic bacteria constitute a public health risk, primarily through the increased risk of treatment failures.

Furthermore, use of antimicrobial agents will select for resistance genes in non-pathogenic bacteria, which later may transfer the acquired resistance to different pathogenic bacterial species.

Knowledge regarding associations between use of antimicrobial agents and occurrence of resistance is in many cases based on experience of changes in occurrence of resistance in relation to introduction of new agents. Confirmatory studies giving more detailed information can be performed by comparing the occurrence of antimicrobial resistance among bacteria isolated from different bacterial reservoirs with different use of antimicrobial agents, experimental studies in animals or epidemiological studies under field conditions. In the following paragraphs some of the knowledge available today on these aspects will be discussed.

3. Links between man and animals

3.1. Development of resistance following the introduction of new antimicrobial agents

Bacterial isolates from animals have only rarely been systematically tested for the susceptibility to new antimicrobial agents prior to their introduction. Susceptibility testing of field isolates has normally first been performed after an agent has been used for some time. Nonetheless, some observations on the emergence of new types of resistance after the introduction of new antimicrobial agents into veterinary medicine have been made. Some of these events have had immediate impact for humans, whereas others have been restricted, so far, to pathogens of importance for animals.

3.1.1. Streptothricin

The streptothricin antibiotic nourseothricin was introduced in animal husbandry for growth promotion in the former German Democratic Republic in 1983. No similar compound had been used prior to its introduction and resistance was only observed at a very low frequency. After the introduction *E. coli* with a transferable plasmid mediating resistance appeared [18]. This plasmid-containing strain was found to spread from pigs to pig farmers and their families and was found in *E. coli* from gut flora. The clone also caused urinary tract infections among humans living in the same area, but with no contact with pig farms [19]. Streptothricin resistance has also been found among campylobacter [20] and the spread of resistant *Campylobacter coli* from pig farms to man has been observed [21].

3.1.2. Aminoglycosides

After the introduction of the aminoglycoside antibiotic apramycin for veterinary use at the beginning of the 1980s, resistance to apramycin emerged among *E. coli* isolates found in cattle and pigs in France and the UK [22,23]. Apramycin has never been used for treatment of infections in humans. The gene encoding resistance had not been observed previously, but it also conferred resistance to gentamicin [24]. The same apramycin resistance gene and similar resistance plasmids have since been found in *Salmonella enterica* from animals and in human clinical isolates of *E. coli*, *S. enterica* and *Klebsiella pneumoniae* [25–32]. Direct transfer of resistance plasmids mediating apramycin resistance from *E. coli* in pigs to *E. coli* from a stockman has also been observed [33]. These observations indicate that this resistance gene primarily emerged among food animals because of selection by the use of apramycin in food animals and then was transmitted to humans, and was possibly selected for by the use of gentamicin.

3.1.3. Fluoroquinolones

In The Netherlands water medication with the fluoroquinolone enrofloxacin in poultry production was followed by emergence of fluoroquinolone-resistant *Campylobacter* species among both poultry and humans [34]. Also in the USA and Spain an increase in the occurrence of fluoroquinolone-resistant *Campylobacter* has been observed after the introduction of fluoroquinolones into veterinary medicine [35,36].

In Germany, an increase in the occurrence of fluoroquinolone resistance among *S. typhimurium* DT204c occurred after the introduction of enrofloxacin for veterinary use in 1989 [37]. Most recently, in the UK substantial increases in resistance to fluoroquinolones in *S. hadar* and *S. virchow* and also in multiresistant *S. typhimurium* DT104 have followed the licensing for veterinary use of the enrofloxacin in 1993 and danofloxacin in 1996 [38].

In several countries fluoroquinolones are the drug of choice for treatment of gastroenteritis in man. The emergence of resistance in zoonotic organisms such as *Salmonellae* and *Campylobacter* is, therefore, a matter of increasing concern.

3.1.4. Macrolides

In Denmark an increase in the occurrence of macrolide resistance from before 1980 to the 1990s was observed in two important microorganisms pathogenic for pigs, *Mycoplasma hyosynoviae* and *Streptococcus suis*, [39,40]. Prior to 1982 macrolides had only limited use for food animals in Denmark, but in 1982 the macrolide tylosin was introduced for use as a growth promoter in Denmark. Since then tylosin has gradually become the most widely used growth promoter in pig production in Denmark, constituting more than 60% of all growth promoters used in 1995. The increase in macrolide resistance among *M. hyosynoviae* and *S. suis* is probably linked to this usage.

3.2. Changes in occurrence of resistance following withdrawal of antimicrobial agents

Only limited information about the effects of terminating the usage of an antimicrobial agent on the occurrence of resistance among bacteria from food animals are available. From The Netherlands, van Leeuwen et al. [41–43] reported changes in the occurrence of tetracycline resistance in salmonellae isolated from food animals and man from 1959 to 1983. Between 1959 and 1974 an increase in the occurrence of tetracycline resistance was observed. This was followed by a decrease of tetracycline resistance among *Salmonella* spp. isolated from man and pigs after the 1974 ban on the use of tetracycline for growth promotion in animal feed in 1974.

In Denmark the occurrence of vancomycin-resistant enterococci (VRE) among food animals has been found to be associated with the use of the glycopeptide avoparcin for growth promotion [44]. The use of avoparcin was banned in 1995 and at the same time continuous surveillance for antimicrobial resistance among food animals has been established [45]. Since 1995 the prevalence of VRE isolated from broilers has decreased from 80 to 5%, whereas the prevalence among pigs is at the same level (20%) as in 1995.

4. Differences in quantity of antibiotics and differences in resistances

4.1. Impact of quantities of antimicrobial agents used in different bacterial reservoirs on the occurrence of resistance

More than 30 years ago, Smith [46] noted differences in the occurrence of penicillin resistance among *Staphylococcus aureus* isolated from bovine mastitis in Denmark and the UK. In Denmark the occurrence of penicillin resistance was, at that time, approximately 5%, whereas almost 70% of the isolates in UK were resistant. Smith [46] put this down to the fact that in the UK the farmers were allowed to treat infections in food animals, whereas in Denmark only veterinarians were allowed to use antibiotics. Since that time the occurrence of penicillin resistance among *S. aureus* from bovine mastitis in Denmark has increased to approximately 20% [47]. However, when compared to other countries around the world the highest occurrence of resistance can in general still be observed in countries with a liberal antibiotic policy [47].

In Denmark the use of antimicrobial growth promoters has never been approved in organic farming. Thus, the glycopeptide growth promoter avoparcin has presumably never been used on organic farms, whereas it has been widely used in conventional farming. In 1995 Aarestrup [48] compared the occurrence of VRE isolated from conventional broiler farms and organic farms and found frequent occurrence of resistance in conventional farms and none on organic farms. It was, therefore, concluded that the most likely cause of the occurrence of VRE was the use of avoparcin.

In Denmark the occurrence of resistance to antimicrobial agents used for growth promotion in *E. faecium* isolated from broilers, cattle and pigs was examined in 1996 [45]. Major differences in the occurrence of resistance among *E. faecium* isolated from the different reservoirs to some of the antimicrobial agents were found. Relatively good information regarding the consumption of antimicrobial agents for growth promotion for the different food animals species was available and in general a good relationship between the use of a particular growth promoter for an animal species and the occurrence of resistance was observed. For example, the growth promoter tylosin has been the most commonly used growth promoter for pigs in Denmark and almost 90% of all *E. faecium* were resistant in 1996. In contrast avilamycin has only rarely been used for pigs and the occurrence of resistance was less than 1%. Among broilers avilamycin was the most commonly used growth promoter and the occurrence of resistance amounted to almost 80%.

It can, however, be difficult to base conclusions on data obtained in this way. In many cases only data on susceptibility for a single sample from one reservoir at a single point in time are available. Furthermore, in many cases no data, or, at best very limited data on the consumption of antimicrobial agents in the previous years are available. The occurrence of antimicrobial resistance among bacterial isolates within a given reservoir will not only depend on the consumption of antimicrobial agents in any single year, but may also be influenced by the overall consumption during several previous years. Furthermore, resistance might not emerge and increase immediately after the introduction of antimicrobial agents.

However, comparative studies can give useful indications on the general association between consumption and occurrence of resistance and the value of such data will increase if it is possible to also follow changes over time.

5. Animal experimental and epidemiological findings

Experimental studies can be performed under well controlled conditions and are very useful in giving Confirmatory information on what can happen under normal circumstances. Several experimental studies have been conducted where animal feeds have been supplemented with antimicrobial agents and the occurrence of resistance monitored among bacterial isolates from faeces or the skin. Thus, in feeding experiments it has been shown that the use of enrofloxacin, tetracycline and tylosin in different concentrations will select for resistance among both intestinal and skin bacteria [46,49–54].

Whereas, several dose–response experiments have been performed to establish the most appropriate dose for treatment of bacterial infections, only limited data on the effect of different pharmacodynamic parameters for the selection of resistance are available. Observations in man have indicated that the development of antimicrobial resistance in bacteria is dependent on the bacterial species and antimicrobial agents used as well as dose and time of administration [55,56].

Use of animal models offers the opportunity to study the association between different administration and dosing intervals, as well as different types of antimicrobial agents and the selection for resistance under well controlled conditions. Such studies could give information that would allow us to use antimicrobial agents in a way that would limit the emergence of antimicrobial resistance.

Epidemiological studies are conducted under natural conditions using real life data and are more likely to give precise information regarding associations. Unfortunately, several confounding factors may be present and consequently such studies can be very difficult to perform.

Recently, Dunlop et al. [57] collected data on the use of antibiotics for therapy and on the occurrence of resistance in *E. coli* from 34 pig herds. Most antibiotics were found to select for resistance. However, major differences between the different types of antibiotics in their effect on resistance patterns were found. Furthermore, differences between administration routes were also observed. In general, group treatment was more likely to select for resistance than treatment of individual animals. In Denmark an epidemiological study conducted in 1995 showed a very close association between the use of avoparcin as a growth promoter and the occurrence of resistant enterococci in both broiler flocks and pig herds [44].

So far only a few epidemiological studies have been performed among animals or outside the hospital environment. Correctly performed, epidemiological studies can yield very important information regarding the strength of association between the use of different antimicrobial agents and modes of administration and the selection and spread of antimicrobial resistance. Furthermore, with the increasing information about genes conferring antimicrobial resistance and the availability of DNA technology, it is possible to include characterisation of both bacterial isolates and specific resistance genes in such studies. The scientific knowledge to perform such studies are available today, but it will require the co-operation of scientists with experience in different fields such as microbiology, molecular biology, epidemiology and statistics. Furthermore, to perform valid studies of the global selection and spread of antimicrobial resistance it will be necessary to include information from all relevant bacterial reservoirs (e.g. humans, animals, the environment) from countries around the world.

6. The world-wide problem

The potential risks of selecting resistant bacteria among food producing animals was first discussed in 1955 [58] but no data on selection of resistance were available. After a major epidemic of antibiotic-resistant *S. typhimurium* DT29 in the UK in 1963–65, the Swann Committee recommended that only antibiotics that have little or no application as therapeutic agents in humans and animals and that would not impair the efficacy of a prescribed therapeutic drug through the development of resistance should be used for growth promotion [59] and that therapeutic antibiotics should only be available for use in animals if prescribed by a veterinarian. Unfortunately these guidelines have not been followed and antimicrobial agents have selected for widespread resistance among bacterial isolates causing infection in both animals and humans. It is, however, difficult to quantify the problems caused by antimicrobial-resistant bacteria from food animals and the effects for the human population.

World-wide there are large differences in drug legislation and regulation, policies for drug usage and occurrence of resistance. The occurrence of resistant bacteria is a problem that reaches beyond individual countries or regions. Food animals for breeding and meat products are traded world-wide. Evolving resistant bacterial populations do not respect boundaries between countries.

During the last decade a single clone of multiresistant *S. typhimurium*, phage type DT104 has spread world-wide [60–66]. Within a few years it has emerged as one of the most common causes of human salmonellosis in several countries. Whether the spread of DT104 is to some extent promoted by the use of antimicrobial agents in veterinary medicine or is simply the spread of a successful clone that happens to be multiply resistant is not known. This clone can be expected to have an advantage over other bacterial clones in an environment with intensive use of antimicrobial agents. However, other factors may also influence the emergence of successful bacterial clones and not all these factors have been elucidated. This example clearly shows the ease with which a multiply drug-resistant bacterial clone, given the right conditions, can spread world-wide.

Other cases of similar resistance genes and mobile DNA elements among bacterial isolates of several species distributed around the world have also been observed [67–69]. The origins of these resistance genes are not well known, but such observations strongly indicate that resistance genes can be part of a world-wide pool which can spread easily to and emerge in several countries [70].

7. Conclusions: gaps in our knowledge and future prospects

Numerous studies in man, have shown that the use of antimicrobial agents selects for resistant bacterial strains. In veterinary medicine fewer studies have been published, but the emergence of resistance because of the use of antimicrobial agents are well documented.

Timely actions based on scientific knowledge are needed to limit the emergence and spread of antimicrobial resistance and the consequent problems in relation to treatment of infections in animals and humans. Knowledge of antimicrobial resistance in food animals is incomplete and surveillance programmes aimed at monitoring resistance are strongly desirable. Knowledge regarding the consumption of antimicrobial agents in different food animal species is too limited to quantify the link between consumption and occurrence of resistance. Therefore, programmes to collect data on the consumption of antimicrobial agents are also needed. The establishment of programmes monitoring both the consumption of antimicrobial agents and the occurrence of antimicrobial resistance in both human and animal reservoirs have been strongly encouraged [71,72].

Much knowledge is available regarding the most appropriate treatment regime as in terms of achieving cure of infection. However, virtually no knowledge regarding the most appropriate treatment in relation to limiting the development of resistance is at hand. Research in this area is urgently needed.

In recent years, new mechanisms capable of mediating multiple antimicrobial resistance have been observed [73]. Transposons mediating multiple resistance are being reported with increasing frequency. The emergence of such multiple resistance mechanisms is highly undesirable and it can be speculated that the changing use of different antimicrobial agents might select for multiply resistant bacterial pathogens. Studies into the potential development of such new bacterial defence mechanisms because of the successive use of different antimicrobial agents are strongly encouraged.

The impact of the selection for antimicrobial resistance in the animal reservoir, on human and animal health is not sufficiently well understood. Large scale epidemiological and experimental studies including all relevant information on the use of antimicrobial agents, modes of administration, occurrence of resistance and spread of resistant clones and resistance genes, in all relevant bacterial reservoirs exposed to antimicrobial agents or that might act as reservoirs, are required.

Many factors influencing the selection of resistance have not been elucidated. Consequently programmes aiming at contradicting the development and spread of resistant bacteria or resistance genes may not always be successful.

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