

# Anti-infective usage in animals – a risk for human health?

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The use of anti-infectives, (in the following called antibiotics, including chemically synthesised substances) for animals, especially food-producing animals, has been controversial over the last 50 years. The debate has largely been focused on potential consequences for public health. Today, most will agree that resistance to antibiotics of importance for public health has been, and is, generated in animals, but has it spread to people? If so, does it matter? Should something be done about it?

## **Why antibiotics to animals?**

Antibiotics are used for three main purposes in animals; for therapy, for prophylaxis and for performance enhancement (growth promotion). Therapy usually involves an individual animal or a group of diseased animals, while prophylaxis can be anything from routine medication of all animals 'just in case' to targeted interventions to control a diagnosed disease. When groups of animals are medicated, the drug is often administered via feed or water. Routine prophylaxis is particularly common during periods of stress, e.g. around weaning or after transportation and commingling. Generally, the conditions requiring the most extensive use of therapeutic or prophylactic antibiotics are enteric and respiratory diseases in pigs, calves and poultry, and mastitis in dairy cows. Untreated, many of these conditions will lead to a considerable mortality. The antibiotic substances that are used for therapy or prophylaxis are with few exceptions of the same classes that are used in human medicine. However, more recent additions to the therapeutic arsenal such as the most modern cephalosporins, the carbapenems and the oxazolidones, are (still) exclusively used in human medicine.

As for human medicines, regulations and practices vary widely around the globe. In the European Union, all antibiotics for therapeutic or prophylactic use in animals should be 'prescription-only' medicines. As in human medicine, the enforcement of regulations that restrict the use varies between countries.

The growth-promoting effect of antimicrobials for farm animals was discovered in the late 1940s. The practice of feeding subtherapeutic doses of antibiotics was readily adopted and became an integrated part of the systems developed in the animal industry. Apart from increased growth rate and/or increased feed conversion, examples of other observed effects of antimicrobials at low doses are improved egg production in laying hens, increased litter size in sows and increased milk yield of dairy cows. There is a wide range of antibiotic substances, some that are not used in human medicine (e.g. flavophospholipol), and some that are (e.g. tetracyclines, streptogramins).

No prescriptions or other veterinary involvement are required for the use of growth promoters. In the EU, the types of antibiotics and the conditions for use have been restricted gradually over the years. Following the recommendations of the Swann committee (1969), the authorisations of substances active against Gram-negative bacteria (e.g. tetracyclines) were withdrawn. Sweden banned the use of all growth promoting antibiotics in 1986, and Denmark, Norway and Finland abandoned all use in the latter half of the 90s. By 1999, the use of a number of substances active against Gram-positive bacteria (e.g. macrolides, glycopeptides) was discontinued in the EU. From that date, only antibiotics of classes currently not used in human medicine remained authorised. From year 2006, these few remaining substances will also be phased out and no new antibiotics will be authorised for that purpose.

In many countries outside the EU, several other substances such as tetracyclines, macrolides and penicillin are still authorised for growth promotion, and in many countries antibiotics for prophylactic use in feed are also freely available.

## **How much?**

Good quality data on use of antibiotics in animals are still hard to obtain. Estimates are available from some countries, but the source of data and the way of presentation vary. Mostly, data for all animal species are combined. Some countries include pets and horses in the statistics, some present only food-producing animals. There is still no agreed unit of measurement that corrects for potency and population size. Despite the above reservations, data in Table 1 clearly show that the amounts used vary considerably

between countries even when the population size, reflected by the volume of production, is taken into account.

Table 1. Sales of antibiotics as veterinary medicines (i.e. excluding use for growth promotion) animals in some European countries (year in parenthesis)<sup>a</sup>

	Denmark <sup>c</sup> (2004)	Finland (2003)	France (1999)	The Netherlands <sup>c</sup> (2003)	Sweden (2004)	United Kingdom (2002)
<b>Sales in metric tons calculated to active substance</b>						
Tetracyclines	29.5	2.0	661.4	227.0	1.3	217.0
Trimethoprim-Sulphonamides	12.4	2.3	295.3	90.0	2.9	88.0
Beta-lactams & cephalosporins	33.8	7.8	128.3	38.0	9.6	60.0
Aminoglycosides	11.6	0.4	85.7	9.0	0.6	22.0
Macrolides & lincosamides	24.2	0.5	77.2	18.0	1.1	56.0
Fluoroquinolones and quinolones	0.1	0.1	24.5	5.0	0.2	1.4
Other	1.0	0.1	91.5	7.0	0.4	13.0
<i>Total</i>	<i>112.5</i>	<i>13.2</i>	<i>1363.9</i>	<i>394.0</i>	<i>16.1</i>	<i>457.4</i>
<b>Production<sup>b</sup></b>	<b>2,109</b>	<b>211</b>	<b>5,963</b>	<b>2,178</b>	<b>524</b>	<b>2,947</b>

<sup>a</sup> Information compiled from: AFSSA 2003, DANMAP 2004, FINRES–Vet 2002-2003, MARAN 2003, SVARM 2004, VMD 2002; <sup>b</sup> Production of broiler, pork and cattle meat in year 2003 expressed as 1000 metric tons, according to FAOSTAT (<http://faostat.fao.org/faostat/> accessed Sept 1, 2004); <sup>c</sup> Food-producing animals only.

### Resistance - reflecting the use?

In Table 2, figures on resistance to selected antibiotics among *Escherichia coli* from healthy pigs and broilers compiled from resistance monitoring programmes with similar the sampling strategies and methodology for testing. As can be appreciated, the prevalence of resistance varies between the countries and a comparison with data on use given in Table 1 indicates that resistance in commensals is correlated to the overall use in the populations exposed. Similar observations have been made in Denmark, where the prevalence of resistance to certain antibiotics in *Enterococcus faecium* from healthy pigs and broilers dropped notably following the discontinued use of antibiotics for growth promotion (DANMAP 2004).

In the examples above the apparent relation between use and resistance is conspicuous, but it is not always so. The dynamics will vary depending on the specific combination of antibiotic, resistance gene and bacterial host and animal host. All factors affecting spread of infections (e.g. animal density, hygiene and contact rate) will influence, as will co-selection by other, unrelated antibacterial substances.

Table 2. Resistance (%) to selected antibiotics (authorised as veterinary medicines only) in *Escherichia coli* isolated from healthy animals at slaughter.<sup>a</sup>

	Denmark <sup>b</sup> (2004)	Finland (2003)	France (2000)	The Netherlands <sup>b</sup> (2003)	Sweden (2003/2004)
<b>Pigs</b>					
Tetracycline	44	NA <sup>b</sup>	88	70	12
Trimethoprim	21	NA	50	44	4
Nalidixic acid	3	NA	3	0 <sup>c</sup>	1
<b>Broilers</b>					
Tetracycline	11	10	85	60	6
Trimethoprim	5	4	51	46	<1
Nalidixic acid	13	2	28	35 <sup>c</sup>	5

<sup>a</sup> Information compiled from: AFSSA 2003, DANMAP 2004, FINRES–Vet 2002-2003, MARAN 2003, SVARM 2004; <sup>b</sup> NA= not available; <sup>c</sup> Reported as flumequine resistance.

## Zoonotic spread of resistant bacteria

The main source of food-borne bacteria such as *Salmonella* and *Campylobacter* are food-producing animals (Anderson *et al.*, 2003). Contamination of animal products with these zoonotic bacteria may occur whether the bacteria are resistant or not. Many reports provide good circumstantial evidence of spread of resistant salmonellae (e.g. Bezanson *et al.*, 1983; Holmberg *et al.*, 1984; Spika *et al.*, 1987, Mølbak *et al.*, 1999). More difficult is to define where the blame lies – did the resistance emerge as a result of use of antibiotics in animals, or did people who had been treated infect the animals? The pentaresistant clone of *Salmonella* Typhimurium DT104 carries a gene cassette conferring resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines (ACSSuT). The gene conferring resistance to ampicillin (*bla* PSE-1) is similar to a gene conveying carbencillin resistance, but carbencillins are not used in animals. This would incriminate human hospital use. On the other hand, the chloramphenicol resistance gene conveys resistance to florfenicol – an antibiotic that is only used in animals – and there are indications that possibly aquaculture is to blame (Chaslus-Dancla *et al.*, 2000). Whatever the origin, these and other resistant salmonellae are amplified and spread in animal populations which increases the risk of their (re?)transmission to people.

## The pool of resistance genes

Overall, there is strong evidence to support that there is a flow of resistance genes between commensal and pathogenic bacteria, within and between different ecological compartments (Courvalin, 1994). One example of transfer of resistance genes from bacteria colonising animals to human microflora or pathogens is the *aacC4* (apramycin and gentamicin resistance) and *hphB* (hygromycin B resistance). Apramycin and hygromycin B are used exclusively in animals. These genes have been identified in *E. coli* and *Salmonella* Typhimurium from animals, from people as well as from environmental sources in different countries (Chaslus-Dancla *et al.*, 2000).

Another example of putative zoonotic and pandemic spread of resistance genes is that of the *vanA*-gene cluster. In animal production in Europe, a glycopeptide, avoparcin, was used for growth promoting purposes up until 1997. There is a clear association between use of avoparcin and occurrence of vancomycin resistant enterococci (VRE; Bager *et al.*, 1997). VRE harbouring the *vanA* gene cluster have been isolated from humans, both in hospitals and community, but also from pigs, rabbits, dogs, cats, horses, chickens, turkeys, pheasants, ducks, from food of animal origin and from sewage (Bonten *et al.*, 2001). Use of modern molecular techniques indicate that the host bacteria – mostly *E. faecium* – do not frequently spread between different animal species or from these to man. But several studies of the relationships of the gene cluster in bacteria isolated from various animal hosts in different countries have shown that VRE from different animal species and humans in different countries can contain indistinguishable genetic elements coding for resistance (Bonten *et al.*, 2001). Taken together, there is strong evidence for horizontal transfer of this gene cluster.

## The other way around – from people to animals

Bacteria and resistance genes can also spread from people to different animals species. One example is resistance to gentamicin (but not to apramycin, cf. above) conferred by AAC(3)II. The gene encoding this enzyme was demonstrated in *E. coli* from calves in 1986 in a limited area of France but had emerged and become widespread long before that in French hospitals (Chaslus-Dancla *et al.*, 2000).

A more worrying example is that of methicillin resistant *Staphylococcus aureus* (MRSA). Until the mid 90s, no clearly confirmed cases of MRSA in animals had been reported. Since, an increasing number of reports from an increasing number of countries document the emergence of infections with MRSA in dogs and horses. In the vast majority of cases, the animal isolates are indistinguishable from human health-care associated MRSA (Weese *et al.*, 2005; Rich & Roberts, 2005). The emergence is probably linked to the increasing prevalence of humans carrying MRSA in the community, and there is solid evidence for human-to-animal transmission, both from owners and from personnel in animal hospitals (Weese *et al.*, 2005; van Duijkeren *et al.*, 2004). In Canada, a particular clone of MRSA seems to have adapted to horses and spreads in animal hospitals (Weese *et al.*, 2005). This is of concern, as horses travel extensively and the infection may easily spread between animal hospitals, stud farms and racing facilities within and between countries. There are few antibiotics available for treatment of horses, so the burden in terms of mortality may become considerable. And there are no documented strategies for decontamination of healthy carries among animals. But there is also the documented problem of transfer back to people – pets and horses are becoming an additional reservoir for MRSA in the community.

## The impact

The primary consequence of increasing resistance in bacteria of animal origin is the loss of effectiveness of antibiotics for therapy of the animal species concerned. The magnitude of this problem has been poorly documented. Even in Sweden where the situation is still comparatively favourable, there are cases of, e.g. piglet diarrhoea, where none of the antibiotics available for pigs on the Swedish market are likely to be effective (SVARM 2004). Without effective treatment, there will be increased mortality. The emergence of MRSA in pets and horses represents another scenario where alternative treatments are, at best, scarce. And even if treatment is theoretically available, the cost may be prohibitive.

More discussed, and most controversial, is the relative impact of animal use of antibiotics on the overall problem of resistance in relation to public health. The debate is blocked by a number of generalisations. Firstly, animals are bunched together irrespective that broilers are birds and pigs are mammals, and that the husbandry systems and slaughter practices differ, not only by animal species but also between and across countries. Secondly, resistance epidemiology will be more or less bug-drug specific, depending on the mechanism(s) of resistance. Some of the resistant bacteria causing problems in people cannot be linked to animals at all; e.g. multidrug resistant *Mycobacterium tuberculosis*, penicillin resistant *Streptococcus pneumoniae*, and before the mid 90s also MRSA. But other problems can – the food-borne zoonotic agents, VRE and quite a few of the resistance genes conveying resistance to ‘older’ antibiotic classes. Lastly, resistance emerging in one place can influence somewhere else because people travel and food is traded around the globe.

There is no doubt that resistant bacteria and resistance genes can be – and are – transferred between different animal species and man. But how often does this occur, what is the magnitude of the risk? Quantitative risk analysis is hampered by the lack of suitable data, but also by the complexity of the epidemiology.

Even if transfer of resistance genes between different animals and man should be infrequent, it can be very important (Teale, 2002; Turnidge 2004). Even in the best of circumstances, the conditions under which animals are kept allow faecal-oral contact. Genes or organisms introduced to animal populations at low rates can thereby be rapidly amplified, and more so if a selective pressure is applied. Amplifying the resistance reservoir will make (re)transmission via food more likely. The impact of one single transmission can then be amplified in a second step in for example hospitals where the selective pressure is high and where the hygiene is sometimes less than optimal. Recycling and amplification in several steps, both in animals and in people, is often ignored when the risk for public health is discussed. And it complicates the debate – who generates the risk, the farmers who use antibiotics for their animals, or the directors of the hospitals where nosocomial infections are allowed to roam?

## Perspectives

Antimicrobial resistance is problem common to rich and poor, to man and animals. The crisis increases gradually and insidiously rather than in a catastrophic way. In the near future, we cannot expect new antibiotics to be the solution. Because the worst consequences are yet not seen, there is a risk that we do nothing. If we do not, will then future generations of people and animals have access to effective treatments of bacterial infections?

It is time to move on from the debate. Antibiotics should be used only when needed, be it for people or animals. Regarding animals, better management, hygiene and feed can replace the growth-promoting antibiotics. A development towards health-oriented production systems will also remove the perceived need for other routine use. Crucial in the long-term strategy is to minimise the occurrence of diseases, thereby reducing the therapeutic need.

The supranational organisations, the WHO and OIE (World Health Organisation for Animals) have issued recommendations on strategies to contain antibiotic resistance. Now everyone must assume his or her responsibility; we must join forces, move from paper to practice and take action.

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