Antimicrobial use in animals and its consequences for human health

Clin Microbiol Infect 1999; 5: 119–124

D. J. Taylor

Department of Veterinary Pathology, University of Glasgow Veterinary School, Bearsden Road, Bearsden, Glasgow, UK

Tel: +44 141 330 5781 Fax: +44 141 330 5602 E-mail: d.taylor@vet.gla.ac.uk

INTRODUCTION

Antimicrobials are used in animals to treat bacterial infections causing identifiable clinical syndromes which cause pain and suffering and which can result in death or chronic disease, and for growth promotion or improvement in productivity. The animal populations in which they are used fall into two groups: the companion animals, which have population structures similar to those of man, with relatively small numbers of young animals, individual housing, a high standard of individual veterinary attention not dependent on economics and the possibility that sick individuals can be nursed; and food animals which are generally young, are kept in large groups and become uneconomic if ill for any length of time. The way in which antimicrobials are used in these two populations differs fundamentally and the risks to human health also differ, although not to such a great extent. It is helpful to understand the ways in which antimicrobials are used in both groups and to examine the risk to human health of each type of practice.

Food animal populations and medication

Food animals include animals such as cattle, sheep, pigs, rabbits, chickens, turkeys, ducks, ostriches, quail, pheasant, trout, salmon and other farmed fish such as sea bass. All of these species exist as adults intended to provide the slaughter generation and required to reproduce for maximum efficiency, and the slaughter generation itself which must grow rapidly to the size appropriate for marketing, usually before sexual maturity and always before physical maturity. These animals are kept in groups (they are all social species) and are often housed for all or part of their rearing process to protect them from climatic extremes. There are two exceptions to this general rule, the dairy cow, which produces milk for sale, and the laying hen. Populations of both these groups are adults in their productive phase, but both must remain at peak productivity to be retained in the herd or flock. The youth of the animals and their housing in groups means that infectious disease can spread rapidly in non-immune animals, as hygiene can be poor and as common airspaces lead to the spread of respiratory disease. Facilities and the capacity for nursing are limited, and individual treatment is often difficult or stressful. Treatment of groups of animals as soon as one member develops disease is essential if infection is to be eliminated from the group, and groups may be treated after infection and before clinical signs develop.

An example of treatment at the onset of disease comes from poultry husbandry where *E. coli* septicaemia may develop in a group of 25000 birds at 10–14 days of age. If untreated, 10% (2500) may die within seven days and another 10% may remain chronically affected and be unsuitable for slaughter at six to seven weeks of age. As the sick birds cannot be identified, treated individually in those numbers or isolated within the same poultry site (the infection spreads by the respiratory route), treatment of the group by medicating food or, particularly, the water is essential. There is no vaccine and prevention by hygiene and management does not always work.

An example of treatment of a group of animals when infection is expected comes from pig husbandry where oedema disease occurs. This disease is caused by verotoxigenic *E. coli* and occurs within seven to ten days of weaning or dietary change in genetically suceptible pigs and cannot be treated once the toxin has been absorbed. Mortality rates reach 30% in successive batches of pigs as they are weaned and outbreaks may continue for months. Antibiotic treatment in food or water from weaning for seven to ten days completely prevents the disease [1]. Vaccine is not yet available, although egg yolk antibody, fimbrial vaccines and recombinant verotoxoids have all been shown to be protective in experiments.

The economics of food animal production are currently poor in Europe, and particularly so in the UK

where some species are currently being produced at a loss. Disease and its associated costs are therefore to be avoided if at all possible but, if disease does occur, the keeper of the animals must safeguard animal welfare or face prosecution under the animal welfare legislation. It is against this background that the use of antimicrobials in food animals should be considered.

Antimicrobials in food animals: regulation and residues

Antimicrobials used in food animals fall into two groups: those used for therapy which can only be supplied and used on veterinary prescription, and those used for growth promotion which are freely available for that purpose from registered suppliers. All have been registered for these uses and are subject to the same general registration process and regulations governing their use throughout Europe. All have been shown to be effective by means of controlled experiments in the target species, to be safe in the target species, and safe handling procedures have been devised to minimize risks to those involved in their supply and administration. Unused antimicrobial must be disposed of as pharmaceutical waste by approved routes. Safety for man has been addressed and the risk of residues in the carcase has been assessed prior to licensing, and a withdrawal period has been specified between the last treatment and slaughter, which must be observed. Monitoring for the effectiveness of this procedure takes place and it is clear that residues of antimicrobial in food of animal origin (meat, milk and eggs) are rare and do not pose a health hazard for man [2].

Benefits to human health from the use of antimicrobials in food animals

One benefit is economic, linked to the price and quality of the food reaching the processor and eventually the public, and the other is reduction in numbers of zoonotic bacteria reaching man in food. The economic argument for the benefits of antimicrobial use in animals to human health is quite clear. Antimicrobial treatment of infectious disease has contributed markedly to the modern developments in animal husbandry which have delivered cheap and available animal protein to Western Europe and other developed parts of the world. They still contribute to traditional systems where animals are not kept in sophisticated buildings, but are less important where investment in housing, health status of stock and good management have occurred. The prompt treatment of disease has led to reductions in mortality, quicker return to health and productivity, and a reduction in valueless chronically-affected survivors of bacterial disease.

A clear example of this comes from milk production, where most mastitis in milking cows is caused by infection with a limited number of organisms: *Staphylococcus aureus, Streptococcus agalactiae, S. dysgalactiae, S. uberis* and *E. coli*. Acute mastitis caused by these organisms can be treated and treatment generally results (with significant nursing support in *E. coli* mastitis) in the rapid reduction in pain and suffering, return of the gland to normal function (both yield and quality of milk return to normal), and a reduction in chronic damage to the affected mammary gland with a cure rate of 81% for a course of treatment [3]. The lifetime yield of milk from the cow is not reduced significantly and more milk is produced per cow than would be the case if the disease were allowed to continue unchecked. In modern mastitis control, treatment is only a part of the whole programme, but it is vital. Similar economic advantages accrue from the prompt treatment of postweaning *E. coli* diarrhoea in pigs. This condition results from the withdrawal of milk protective antibody at weaning and the exposure of the susceptible animal to infection from littermates or imperfectly-cleaned accommodation. Disease occurs within three days of weaning and may kill up to 30% of affected groups, leaving other animals permanently stunted. It is possible to reduce the severity of this condition in a number of ways, but even in the best possible conditions, mortality can still reach 5% if antimicrobial treatment is not given. Prompt and effective treatment with antimicrobial, coupled with nursing (maintenance of temperature, oral rehydration therapy), can reduce mortality to zero and allow growth to continue unchecked, thus reducing losses and allowing more margin over feed and fixed costs [1].

Antimicrobial used for growth promotion provides another example of the economic advantages of the use of antimicrobials. Regardless of the political discussion surrounding the use of antimicrobials as growth promoters, there are some technical facts that are beyond dispute. They are intended for use in clinically-normal animals and have no effect on the major bacterial diseases of livestock (if they had, they would have to be re-registered as therapeutics). They act by killing or disabling bacteria in the gut of animals [4,5], thus reducing the damage caused by the normal flora to the intestinal villi through loss of tissue and inflammation and improving absorption through the now healthy villi. The effects of antimicrobial growth promoters on the gut of young growing animals can be seen clearly by comparing the histological appearance of the intestines of those receiving antimicrobial with those of control clinically-normal animals. The villi of animals receiving antimicrobial growth promoters are longer with more mature epithelial cells and fewer inflammatory cells. The lamina propria of the intestinal mucosa contains fewer plasma cells and lymphocytes, and fewer bacteria

of species such as enterococci and lactobacilli appear to be attached to the epithelium in the small intestine. Antimicrobial growth promoters also prevent bacterial degradation of food before it reaches the host and prevent the destruction of digestive enzymes by bacteria of the normal flora. The growth which results is a consequence of the improvement of gut function and is an indicator of health in normal immature animals. No animal receiving an antimicrobial growth promoter can grow beyond its genetic potential. The use of antimicrobial growth promoters therefore improves the physical welfare of the animals receiving them, as they are better nourished. Improvements of 5–10% in growth rate and feed efficiency are commonplace, resulting in a significant reduction in the cost of rearing food animals. The effects are absent in gnotobiotic animals, and are reduced in the presence of clinical disease or adverse nutritional or environmental conditions.

Benefits from a reduction in zoonotic pathogens are less clear cut, but are most clearly seen in salmonellosis in calves. Calves with salmonellosis pass large volumes of diarrheic feces containing up to 10^9 organisms per gram for several days during the course of the disease. The organisms have the potential to infect other calves, handlers, and cattle and other livestock about to be sent to slaughter. Prompt treatment results in immediate reduction in the diarrhea and in the numbers of salmonellae discharged. Coupled with isolation, disinfection and management, the exposure of man to these organisms by all routes is reduced.

Hazards to man of antimicrobial use in food animals

There are two major areas of risk, one of direct exposure to antimicrobial while administering treatment or incorporating antimicrobial in animal feeds, and the other from antimicrobial resistance in zoonotic pathogens encountered in the workplace, or in food or following the transfer of resistance from normal animal flora in the workplace, or on food to human normal flora or pathogens.

Direct exposure to antimicrobial

Those working with antimicrobial (veterinarians, workers in feed mills, animal handlers) will be exposed to small amounts of the substances in dust or following accidents of administration. It is possible that toxicity may result, but antimicrobials are inherently safe from direct toxicity and would not be licensed if they were toxic. Precautions to avoid contamination are laid down in the data sheets [6] and in safety assessments. Allergy is more difficult to prevent and remains a possibility for those handling animal medicines. In addition the antimicrobial being used may be ingested and may affect the flora of the worker.

Antimicrobial resistance

The second area of risk comes from the effects of the antimicrobial used in the animal on the bacteria present. Regardless of the route of administration or the level of administration, selection pressure is exerted against bacteria in or on some parts of the animal. Most documented resistance occurs in animal pathogens which are of only passing interest to the medical microbiologist as they can only act as donors of resistance for man. The bacteria most likely to cause direct risk to man are the zoonotic pathogens. These include salmonella, campylobacter, verocytotoxic *E. coli*, yersinia, listeria and staphylococci from food and contact, and a range of bacteria such as *Streptococcus suis, Bordetella bronchiseptica, Pasteurella multocida, Leptospira* sp. and *Erysipelothrix rhusiopathiae* acquired by contact. There is clear evidence that salmonellae, campylobacters and yersinias can acquire resistance from antimicrobials used in food animals. In the case of salmonella, this may have resulted from selection during therapy directed against the organism, as salmonellae are capable of producing recognizable syndromes in animals and treatment is directed against them, but in the case of campylobacters, yersinia, *E. coli* O157 and listeria, any resistance results from treatment for other organisms as these organisms rarely cause recognizable clinical syndromes in food animals.

The two types of resistance are best considered in *Salmonella enterica* and *Campylobacter jejuni*. *S. enterica* serotype Typhimurium (*S. typhimurium*) developed multiple resistance in a series of steps in 1964–5 in *S. typhimurium* phage type 29 in the UK [7]. This resistant strain was shown at the time to carry transmissible resistance and caused widespread infection in cattle with some overflow to man to cause both contact and food-borne infection. The concern generated by this development contributed to the Swann Report [8] and to the subsequent Medicines legislation. The organism concerned declined in numbers and disappeared spontaneously at the same time as a cattle dealer ceased trading. Since then, a similar multiply-resistant *S. typhimurium*, phage type 204, has come [9] and gone, and a further resistant *S. typhimurium*, DT104 and related strains, has infected cattle and spread to other species including man where it has caused life-threatening infections [10,11]. The resistance in this case is chromosomal [10], so it is not clear whether this strain will behave in the same way as the earlier strains. *S. typhimurium* DT 104 carries resistance which indubitably arose because of selection during animal treatment, but there is no clear evidence as to when this occurred. The resistance genes may have arisen prior to the development of multi-resistant DT 104, and the organism has certainly spread like an infectious disease along lines of

trade within the UK and into countries such as Denmark with livestock exports. It can be controlled by slaughter and vaccination and does not appear to arise de novo. It therefore illustrates that, although resistance may originally be selected by the animal use of antimicrobials, the organisms themselves can spread in the same way as sensitive organisms and do not necessarily arise as a result of current veterinary therapy although, where multiple resistance is present, selection may occur following the use of any of the antimicrobials concerned. The factors which give rise to a successful clone of this nature and allow it to supplant sensitive strains of *S. typhimurium* and then disappear are not yet known and are the subject of intense study.

The situation with campylobacters is different. In food animals therapy has never been directed against them. The resistance present to macrolides, tetracyclines and to fluoroquinolones has arisen incidentally as a result of exposure to antimicrobial used to treat clinical disease caused by another agent. This exposure may have been as early as the 1960s (macrolide-resistant *Campylobacter coli* were present in pigs in the early 1970s) and have continued until now, or have arisen as recently as this year [12,13]. Fluoroquinolone resistance is a case in point. It was not recorded on any scale in campylobacters until the introduction of this class of antimicrobial for animal therapy. Fluoroquinolones are used to treat *E. coli* septicaemia in young chickens, a life-threatening disease in which mortality rates can reach 10%, recovered birds grow poorly and following which their carcases may be downgraded. It is used in other life-threatening diseases of food animals where its use is justified from a technical and legal point of view. The benefits to the animal may, however, be accompanied by the emergence of fluoroquinolone-resistant campylobacters and other elements of the normal animal flora.

Selection for antimicrobial resistance following veterinary antimicrobial use may occur in yersinias and frequently does so in staphylococci. Most documented antimicrobial resistance occurs in staphylococci in milk where the mandatory pasteurization in Scotland and other EU countries, and the voluntary pasteurization in England and Wales, prevent any threat to human health. Both raw milk and raw milk products such as cheeses can be sources of resistant organisms [14]. *E. coli* O157 isolates in the UK have not been resistant to antimicrobials, but it is clear from other countries that multiple antimicrobial resistance can occur in this organism.

Antimicrobial resistance in the normal human flora as a result of antimicrobial use in animals has been known since the experiments of Williams Smith in the 1950s and 1960s [15,16]. His studies showed that transient colonization of the human gut with resistant *E. coli* from animals could occur, and that that resistance could be transferred to normal human flora in the gut where it remained for a variable length of time unless selection pressure from antimicrobial occurred, when it remained longer [17]. He and other workers demonstrated animal *E. coli* on meat which could act as a source of this resistance for man. In the intervening 30 years, legislation and codes of practice have eliminated the possibility that resistance could arise in *E. coli* and related organisms in animal intestines from the use of antimicrobial growth promoters, but have left the role of therapeutic antimicrobials essentially untouched. Antimicrobials registered for use in the EU as growth promoters were registered because they were not used in animals for therapy in the form used for growth promotion, did not affect antimicrobial resistance in *E. coli* and did not conflict with therapy in man in the form used at the time of registration. The situation has now changed. The identification of antimicrobial-resistant enterococci as threats to human health has altered the focus of attention from the well-established route of transfer of antimicrobial resistance in *E. coli* from animal feces on undercooked meat to consumers and food handlers, to other elements of the animal normal flora, namely the enterococci. It has been known for many years that the use of the antimicrobial growth promoters could select for phenotypic resistance to these antimicrobials and other agents in the same class. Little attention was paid to this phenomenon until it was suggested that vancomycin resistance might be transferred from enterococci to methicillin-resistant *Staphylococcus aureus* (MRSA) and render their control in hospital infections even more difficult. Vancomycin-resistant enterococci were being selected in the normal flora of food animals by the use of avoparcin, a glycopeptide growth promoter used widely in chickens and pigs in Europe for over 25 years. This class of compound is not used in therapy in animals, and the gene concerned had not, in fact, transferred to human staphylococci in the entire period of use.

The intense investigations triggered by the realization that vancomycin resistance was present in animal enterococci confirmed that the species *E. faecium* existed in both man and animals, that the resistance gene of concern, *vanA*, was present in animal *E. faecium*, and that even some flanking sequences could be found in both animal and human *vanA*-resistant enterococci, suggesting that there was contact between the two populations [18,19]. *E. faecium* containing *vanA* was found on chicken meat amongst the normal fecal flora present as contamination. This work led to the suspension of use of avoparcin as a growth promoter in the EU, thus effectively ending the controversy, but

leaving the focus of attention on the role of antimicrobial-resistant enterococci themselves in human disease. They have become prominent as causes of intractable and sometimes fatal infections in immunocompromised patients, and the number of antimicrobials to which they are uniformly sensitive is small. Vancomycin is one such, but vancomycin-resistant enterococci occur in human infections and, as discussed, *may* have originated in animals or received *vanA* resistance from animal enterococci in the past. Regardless of the origin of this resistance, new forms of antimicrobials such as streptogramins and everninomycins not previously used, or not used on a large scale for human medicine, have been developed and are being introduced or evaluated to deal with these enterococci. These two antimicrobials have been used extensively for many years for growth promotion in animals as virginiamycin and avilamycin, respectively. There is no doubt that their use as growth promoters selects for resistance to them-selves in animal enterococci, and that those enterococci are transferred to man with the other elements of the animal fecal flora on meat. The extent to which this results in resistance to either agent in human entero-cocci, and particularly those involved in human infections, is not yet clear. Preliminary data on the susceptibility of enterococci from human infections to streptogramins suggests that few are currently resistant to these agents even after more than 20 years of use of the compound as an animal growth promoter. When this has been clarified, and factors such as the selection pressure exerted by macrolides and lincosamides in therapy in animals have been evaluated, coherent management strategies can be developed to reduce risks to man from these compounds. One such strategy is the recent proposal of the EC to ban the use of tylosin, spiramycin (macrolides), virginiamycin (streptogramin) and zinc bacitracin from 1999 which, if confirmed, will eliminate any risk from these substances used in growth promotion. The influence of growth promoting anti-microbials on the gut flora has been comprehensively reviewed by the Swedish Commission on Antimicrobial Feed Additives [20].

Effects on human health from antimicrobial therapy in companion animals

Antimicrobial growth promoters are not used in companion animals and, with the exception of some horses, these species are not used for human consumption in the EU, so human health cannot be affected by the food route. The carnivorous companion animals receive sterile canned food or high temperature extruded dried foods in most cases and there is little contact with food animal bacterial populations unless owners feed undercooked or raw table scraps. The effects of antimicrobial use are likely to arise directly from therapy given to individuals by the parenteral, oral and topical routes and risks consist of the direct exposure of the owners in a domestic situation to the prescribed antimicrobial they administer to their pets and contact infections with resistant zoonotic bacteria and normal flora from their pets.

A wider range of antimicrobials is regularly used in companion animals than in food animals, and phenotypic resistance to most of those used in companion animal therapy has been identified in veterinary diagnostic laboratories. The onward transmission of this resistance from companion animals to the households in which they are located is poorly documented. Cases of infection of members of a household with salmonella have been associated with infection in cats, dogs and aquarium fish and antimicrobial resistance has been identified in salmonellae transmitted to man. In the case of transmission of *S. typhimurium* DT104 from dogs and cats, the pet has often developed clinical disease before veterinary treatment has begun and treatment has played no part in its selection. The contribution of additional resistance (to fluoroquinolone, for example) following veterinary treatment and the importance of infection of the household during veterinary treatment is not known. Exposure to the feces of infected pets is greatest during clinical disease, as the feces of continent animals is less frequently handled by the household. The situation is different with the infections derived from handling fish and tropical reptiles, especially terrapins. A wide variety of antimicrobials are used to treat and prevent disease in these species in their countries of origin, and antimicrobial resistance can occur in salmonella derived from recently imported animals [21]. Once again, the contribution of any veterinary treatment of the animals in Europe has not been evaluated.

Transmission of campylobacters is also possible. Although resistance to veterinary therapeutics is not uncommonly identified in vitro, resistance to critical antimicrobials such as erythromycin is uncommon and fluoroquinolone resistance rare in campylobacters from UK companion animals at present. The situation with other bacteria is even less clear. Resistance found in canine *Bordetella bronchiseptica* infections to trimethoprim sulphonamide has developed as a consequence of veterinary use of the antimicrobial, but the importance of this has not been assessed formally in infections transmitted onward to man. The same applies to *Pasteurella* sp. from the canine and feline mouth associated with bite wounds in man from those species. Other microbial species where the role of veterinary treatment in the onward transmission of antimicrobial-resistant organisms or resistance to man is not clear include

Staphylococcus intermedius, Pseudomonas aeruginosa, Burkholderia cepacia, Malassezia pachydermatis, and *Microsporum canis.* Enterococci from companion animals are not exposed to vancomycin, streptogramins or everninomycin from veterinary therapy, and veterinary treatment of pets cannot therefore contribute directly to the resistance pool of these antimicrobials in man, but enterococci are exposed to gentamicin during therapy and may contribute resistance to that substance. In spite of the absence of the veterinary use of glycopeptides, vancomycin-resistant enterococci have been identified in dogs and cats [22]. The source of this resistance and its importance is not yet clear.

Conclusions

The use of antimicrobials in animals makes a major contribution to animal welfare and to the economics of farm animal production, with consequent benefits for human health. It has also contributed to the emergence of antimicrobial resistance in bacteria in animals. There are clear examples of the development of resistance in zoonotic pathogens such as *S. typhimurium* following historic animal use of antimicrobials, and there is evidence with regard to fluoroquinolone resistance in campylobacters and salmonellae that this process is continuing. The extent to which this resistance is associated with human health is clear from the statistics related to food-borne infections, where the majority of salmonella infection is associated with sensitive strains, but the extent to which it is related to current veterinary therapy is not clear because of the complicating factor of clonal spread and survival of resistant organisms. The growth-promoting antimicrobials do not affect resistance in salmonellae, but do contribute to resistance in campylobacters and are responsible for resistance to themselves in enterococci. The extent to which this impinges on human health is still not clear, but transfer of organisms and resistance to man will continue as long as animal products remain contaminated with animal flora. The part played by veterinary use of antimicrobials in companion animals in the transmission of antimicrobial-resistant organisms or resistance to man has not been fully explored. The animal use of antimicrobials does not contribute to the major problems of antimicrobial resistance seen in human tuberculosis, pneumococcal infection, typhoid or MRSA. Further study of the transfer of resistance in animal bacteria to man is required in both qualitative and quantitative terms. Policies for the management and reduction of resistance transfer from animals to man are still being formulated.

References

1. Taylor DJ. Pig Diseases, 6th edn. D J Taylor, 31 North Birbiston Rd, Lennoxtown, Glasgow G67 7LZ, ISBN 0-9506932 5-1, 1995, 384 pp.
2. Anon. Medicines Act Veterinary Information Service, Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone Surrey 1998.
3. Kossaibati MA, Hovi M, Esslemont RJ. Incidence of clinical mastitis in dairy herds in England. Veterin Rec 1998; 143: 649–53.
4. Prescott JF, Sivendra R, Barnum DA. The use of bacitracin in the control of experimentally induced necrotic enteritis in chickens. Canad Veterin J 1978; 19: 181–7.
5. Kaukas A, Hinton M, Linton AH. The effect of growth promoting antibiotics on the faecal enterococci of healthy young chickens. J Appl Bacteriol 1988; 64: 57–64.
6. NOAH. Compendium of Data Sheets for Veterinary Products 1998–1999. National Office of Animal Health, 3 Crosfield Chambers, Gladbeck Way, Enfield, Middlesex EN2 7HF. ISBN 0 9526638 4 8.
7. Anderson ES. Drug resistance in *Salmonella typhimurium* and its implications. Br Med J 1968; 3: 333.
8. Anon. Report of the Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine. London: HMSO 1969.
9. Threlfall EJ, Ward LR, Rowe B. Epidemic spread of a chloramphenicol-resistant strain of *Salmonella typhimurium* phage type 204 in bovine animals in Britain. Veterin Rec 1978; 103: 438–40.
10. Threlfall EJ, Frost JA, Ward LR, Rowe B. Epidemic in cattle and humans of multiresistant *Salmonella typhimurium* DT 104 with chromosomally-integrated multiple drug resistance. Veterin Rec 1994; 134: 577.
11. Wray C. Development of antibiotic resistance: a vet's tale. J Med Microbiol 1997; 46: 26–33.
12. Lacey RW. Rarity of tylosin resistance in human pathogenic bacteria. Veterin Rec 1988; 122: 438–9.
13. Moore JE, Madden RH, Kerr JR, Wilson TS, Murphy PG. Erythromycin resistant Campylobacter species isolated from pigs. Veterin Rec 1996; 138: 306–7.
14. Muhammad G, Hoblet KH, Jackwood DJ, Bech-Nielsen S, Smith KL. Interspecific conjugal transfer of antibiotic resistance among staphylococci isolated from the bovine mammary gland. Amer J Veterin Res 1993; 54: 1432–40.
15. Smith HW, Crabb WE. The sensitivity to chemotherapeutic agents of a further series of strains of *Bacterium coli* from cases of white scours: the relationship between sensitivity tests and response to treatment. Veterin Rec 1956; 68: 274–6.
16. Smith HW, Crabb WE. The effect of the continuous administration of diets containing low levels of tetracyclines on the incidence of drug resistant *Bacterium coli* in the faeces of pigs and chickens: The sensibility of the *Bact. coli* to other chemotherapeutic agents. Veterin Rec 1957; 69: 24–30.
17. Smith HW. Transfer of antibiotic resistance from animal and human strains of *Escherichia coli* to resident *E. coli* in the alimentary tract of man. Veterin Rec 1969; 85: 31–3.
18. Bates J, Jordens JZ, Selkon JB. Evidence for an animal origin of vancomycin resistant enterococci. Lancet 1993; 342: 490–1.
19. Jensen LB, Ahrens P, Dons L, Jones RN, Hammerum AM, Aarestrup FM. Molecular analysis of Tn1546 in *Enterococcus faecium* isolated from animals and humans. J Clin Microbiol 1998; 36: 437–42.
20. Report from the Commission on Antimicrobial Feed Additives. Antimicrobial Feed Additives. Swedish Government Official 1. Reports 1997:132. ISBN-38-20707-9 356 pp.
21. D'Aoust JY. Pet turtles: a continuing international threat to public health. Am J Epidemiol 1990; 132: 233–8.
22. Van Belkum A, van den Braak N, Thomassen R, Verbrugh H, Endtz H. Vancomycin-resistant enterococci in cats and dogs. Lancet 1996; 348: 1038–9.