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REVIEW ARTICLE

Antibiotic resistance—consequences for animal health, welfare, and food production

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Abstract

Most of the literature on the consequences of emergence and spread of bacteria resistant to antibiotics among animals relate to the potential impact on public health. But antibiotics are used to treat sick animals, and resistance in animal pathogens may lead to therapy failure. This has received little scientific attention, and therefore, in this article, we discuss examples that illustrate the possible impact of resistance on animal health and consequences thereof. For all animals, there may be a negative effect on health and welfare when diseases cannot be treated. Other consequences will vary depending on why and how different animal species are kept. Animals kept as companions or for sports often receive advanced care, and antibiotic resistance can lead to negative social and economic consequences for the owners. Further, spread of hospital-acquired infections can have an economic impact on the affected premises. As to animals kept for food production, antibiotics are not needed to promote growth, but, if infectious diseases cannot be treated when they occur, this can have a negative effect on the productivity and economy of affected businesses. Antibiotic resistance in animal bacteria can also have positive consequences by creating incentives for adoption of alternative regimes for treatment and prevention. It is probable that new antibiotic classes placed on the market in the future will not reach veterinary medicine, which further emphasizes the need to preserve the efficacy of currently available antibiotics through antibiotic stewardship. A cornerstone in this work is prevention, as healthy animals do not need antibiotics.

Key words: *Animal health, antibiotic resistance, consequences*

Introduction

Most of the literature on the consequences of emergence and spread of bacteria resistant to antibiotics among animals relate to risks for transfer to people, and thereby a potential impact on public health. There is ample evidence that resistant *Salmonella*, *Campylobacter*, and methicillin-resistant *Staphylococcus aureus* (MRSA) can spread between animals and people. There is also circumstantial evidence that resistance genes such as the *vanA* gene cluster or genes conveying resistance to higher generations of cephalosporins can spread between bacteria colonizing animals and those colonizing people (1). But the consequences of antibiotic resistance in bacteria of animal origin are not limited to public health. One of the reasons to use antibiotics is treatment of animals suffering from bacterial infections, and antibiotic resistance in animal pathogens can lead to therapy failure with a direct negative effect on animal health and welfare. This aspect has received little or no scientific attention, and the burden of resistance on animal health is unknown. Further, depending on animal species, type of animals, why these animals are kept, and how they are cared for, there may be different social and economic consequences. In the following, potential consequences of antibiotic resistance for animal health, welfare, and production economy will be examined.

Animals kept for social reasons, sports, or breeding

Dogs, cats, and horses are kept for a variety of reasons. In affluent communities, most people keep such

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animals for social reasons and for sports. In the European Union, about 25% of households have a pet (2). Dogs and cats are often considered as family members or companions (3), and there can be strong emotional bonds also to horses. Not surprisingly, people are prepared to spend large sums of money on their companions, and there is a demand for advanced veterinary care. Conditions in dogs for which antibiotics are often used are skin diseases (including wounds) and urinary tract infections, and in horses, diseases of the skin and of the reproductive tract (4).

Regarding veterinary services, dogs and cats are mostly attended at clinics or animal hospitals of varying size. Horses are attended both in ambulatory care and in hospitals. In modern animal hospitals, sophisticated diagnostic equipment is usually available, and there are possibilities both for intensive care and for advanced surgery. In these premises, there can be a high animal density and frequent use of antibiotics—circumstances that cater for nosocomial infections. Indeed, in the last decade there has been an increasing number of reports on community- and hospital-associated infections with MRSA and multi-resistant Gram-negative bacteria with resistance to third-generation cephalosporins or even carbapenems in dogs and horses (5-7), and in dogs also infections with methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) (8). Information on the prevalence of serious infections with such bacteria is scant, and the overall consequences thereof are poorly documented.

The emergence and spread of MRSP may serve as an example to discuss some of the consequences of antibiotic resistance. *Staphylococcus pseudintermedius* is an opportunistic pathogen of dogs and is the main cause of skin, ear, and wound infections (8). Since 2006, MRSP has rapidly emerged worldwide. Studies of isolates from Europe and North America have shown that two major clonal lineages dominate, and both are typically resistant to the major classes of antibiotics used in veterinary medicine (9,10). In a study on outcome of treatment of dogs with pyoderma caused by MRSP or by methicillin-susceptible *Staphylococcus pseudintermedius*, the majority of cases resolved regardless of methicillin susceptibility. However, some cases of MRSP pyoderma took longer to treat, and there were more adverse effects resulting from systemic treatment, in particular for chloramphenicol (11). Topical therapy with antibacterial shampoos or mupirocin alone was used more often in the MRSP group, either initially or after discontinuation of systemic therapy following adverse effects. Treatment with topical antibiotic shampoo is time-consuming but was shown to resolve or markedly improve almost 50% of the cases of pyoderma when used two to three times per week for three weeks (12). It is possible that in the study by Bryan et al. (11) the owner's willingness to comply with this laborious topical treatment was high for the MRSP cases given the lack of options.

While pyoderma in dogs associated with MRSP may still be manageable without systemic antibiotic therapy, deeper infections and some surgical site infections can if untreated be life-threatening or lead to euthanasia for animal welfare reasons. This is also true for infections with MRSA and multi-resistant Gram-negative bacteria in dogs, cats, and horses. Alternative antibiotics such as glycopeptides, oxazolidinones, and carbapenems are now mentioned as options in case reports and clinical reviews (13-15). These drugs are not authorized for use in animals, and knowledge of pharmacokinetics, efficacy, and safety for different animal species and indications is limited. But, more importantly, the veterinarian is faced with an ethical dilemma: should drugs that are critical for treatment of infections with multi-resistant bacteria in humans be used in dogs at all, given the risk of emergence of resistance in pathogenic or commensal bacteria with a potential to spread to humans? Most authors discussing these alternatives emphasize the need to limit their use in animals to situations where no other treatment options are available. In Finland and Sweden, regulators have restricted the possibility of veterinarians to prescribe these drugs. This means that there will be situations when euthanasia is the only alternative. As mentioned above, many owners of dogs and cats view their animal as a member of the family. In a Canadian survey on owner response to companion animal death 30% of the participants experienced severe grief with euthanasia as one of the most prominent risk factors (16). This indicates that among the consequences of infections with multi-resistant bacteria in dogs, but also probably in horses, are negative emotional and social effects on the owners and their families. Even more serious social consequences may affect persons losing service dogs for disabled as the animal may be a prerequisite for coping with daily life activities.

Antibiotic resistance can also have an economic impact for the owner of the animal. If treatment 'at any cost' is chosen, this impact can be considerable. For example, Foster et al. (14) describe treatment of a dog with MRSP bacteraemia and discospondylitis with linezolid. The dog was treated for 23 weeks, and, using the dose used in the case report and prices of Swedish pharmacies, the cost for the antibiotic amounts to 176,000 Swedish crowns (around US$25,600). Clearly, this cost would be prohibitive for most owners. According to information from

Pharmacychecker online,[1] prices in the US are much lower, but the cost for the drug would still amount to US$1,500–4,800. Cost for additional visits, lab work, and other follow-up was presumably also higher than in comparable cases with bacteria that are susceptible to first-choice antibiotics. In surgical site infections in companion animals and horses, there is also a possibility that the original problem does not resolve. If the infection directly leads to the death of the animal, or if euthanasia is chosen, there is a cost for the loss of life of the animal. This aspect is particularly relevant in, for example, service dogs where a lot of money has been invested in training, in valuable breeding animals, and in some of the animals used for sports. In the case of breeding animals, the broader effects of loss of potentially valuable genetic material must also be considered.

Hospitals and clinics affected by outbreaks of multi-resistant bacteria can also be impacted economically in several ways. The costs following one outbreak of MRSA at an equine hospital in Sweden, affecting eight horses, was estimated to 1.2 million Swedish crowns (approximately US$170,000) (17). The financial impact of a more protracted outbreak of a multi-resistant *Salmonella* Newport at a large animal hospital was estimated to US$4.12 million (18). Costs included in the estimate were loss of revenue due to closure, decreased case load, decontamination, reconstruction, and coverage of patient bills. In this outbreak, 61 animals were infected (54 horses), and the case fatality rate was 36%. Thus, there was also a substantial loss for the owners of the animals. Following the outbreak, a modified and strengthened infection control programme was implemented. Costs that were not included in the estimates discussed above and that should apply to all premises are investments in continuously improved infection control and prevention and increased laboratory diagnostics. Finally, the potential loss of client confidence for premises experiencing outbreaks is difficult to quantify but probably important.

For breeding farms and racing stables, costs similar to those of an animal hospital may apply if an infection that is difficult to treat is introduced and spreads. In addition, veterinary costs will probably be higher and there will be a cost for loss of foals or horses not racing as planned, for example. Further, bacteria such as MRSA spread between animals and humans, and people who work with animals are at higher risk of being MRSA-positive than people not working with animals (5). This means that MRSA carriage is an occupational hazard for people working in animal clinics, hospitals, stud farms, or racing stables, and employers are at risk of being sued if personnel have been infected at work.

[1]http://www.pharmacychecker.com/compare-drug-prices-online-pharmacies/linezolid-600+mg/60543/107863/total/

Animals kept for food production

Globally, animals kept for food production are important sources of food, and food production is a significant contributor to world economy. The major commodities produced are meat, milk, and eggs from classical farm animals such as pigs, cattle, buffaloes, sheep, goats, and poultry, and in aquaculture, fish, crustaceans, and molluscs (19). However, also animals such as camels, horses, rabbits, guinea pigs, and bees are regionally kept for production of food.

According to the Food and Agriculture Organization of the United Nations (FAO) (19) 296 million tonnes of meat were produced worldwide in 2010. About 23% of this quantity was beef or buffalo meat, 37% pig meat, 5% goat or sheep meat, and 33% poultry meat. Aquaculture contributed with about 60 million tonnes of fish. Additionally, 69 million tonnes of eggs and over 700 million tonnes of milk were produced. The yearly consumption of meat is about 80 kg/person in high-income countries and about 10 kg/person in low- and middle-income countries (19).

To produce these commodities, the world's stock of animals kept for food production in 2011 totalled about 1.6 billion cattle and buffaloes, 2 billion sheep and goats, 1 billion pigs, and over 20 billion poultry birds according to statistics from FAO.[2] It is conceivable that the settings and conditions under which the animals are kept differ substantially depending on animal species, geographical region, national legislation, and intensity of production. The variation in settings spans from small-scale production, with a few animals kept for household consumption, to large-scale settings where thousands of animals are reared for production of food intended for sale on the national or international market.

A variety of contagious bacterial diseases cause illness and suffering of the animals and thereby bring on economic and welfare losses in food production (20-23). Respiratory and enteric diseases are among the most important in several species, and mastitis is common in animals kept for milk production, mainly cows but also goats, sheep, and buffaloes (21). These diseases are contagious and therefore more problematic when animals are kept in large groups and in close proximity to each other (24). In production forms

[2]www.faostat.org

where animals from different farms are brought together the risk for disease outbreaks is very high, for example in feed-lots where calves are fattened for beef production (23). Bacterial diseases are important also in aquaculture where aquatic animals such as fish and shrimps are raised in large numbers with close contact between individuals (25).

To mitigate the impact of bacterial diseases, antibiotics are used therapeutically to treat sick animals and for prophylaxis when outbreaks of disease in individual animals or groups of animals are anticipated. Poultry, fattening pigs, and fish are mostly treated orally by group medication through feed or water, whereas adult cattle, buffaloes, and breeding pigs usually are treated individually using injectable formulations (21).

Animals kept for food production are examined and treated by ambulatory veterinary services or by their owner or keeper. Globally, access to and the rationales and motives for use of antibiotics in food production vary considerably (26). In some countries there are few restrictions on the access to and use of antibiotics in food animals, but elsewhere this is strictly regulated and antibiotics can only be administered after prescription from a veterinarian (26). To promote responsible use of antibiotics, international and national guidelines have been issued with the dual purpose of ensuring therapeutic efficacy and mitigating resistance (27-29). Compliance to such guidelines varies but is high in some countries (30).

In addition to therapeutic and prophylactic use, antibiotics are utilized to improve growth of food animals by inclusion of low doses in feed. Such use is controversial due to the risk of emergence and selection of antibiotic resistance, of putative concern for animal as well as human health (24,31,32). Use of antibiotics as growth promoters was banned in Sweden already in 1986; later other countries followed suit, and by 2006 growth promoters were phased out in the whole EU (1,33). In December 2013 the US Food and Drug Administration, in its Guidance for Industry #209,[3] recommended that use of antibiotics as growth promoters should be voluntarily phased out. The need and advantages for food production of using antibiotics as growth promoters is questioned, and experiences in some countries show that such use can be replaced by other measures to uphold productivity and animal welfare (26,34-37).

Although antibiotics are not necessary to promote growth, they are needed for effective treatment of sick animals and for prophylaxis for both small- and large-scale food production now and in the future (21,22). Lack of effective treatment for diseases will lead to suffering for the animals and welfare problems, which in turn lead to emotional stress for the keeper of the animals (22). Moreover, there will be financial losses directly through higher mortality and indirectly through decreased feed conversion, reduced production and growth, as well as early culling of breeding animals and dairy cows. Eventually this leads to higher costs of commodities from animal food production for the end consumer.

Thus, access to effective antibiotics is imperative, and emergence and spread of resistance leading to depletion of the available arsenal of antibiotics will therefore have serious consequences. Already some antibiotics are no longer recommended as first-line choices because of widespread resistance. One example is penicillin that has been used to treat mastitis caused by *Staphylococcus aureus* in cattle since the 1950s, but today resistance is regionally so common that penicillin no longer is a relevant empirical first choice for this indication (38). Also emergence of penicillin or tetracycline resistance in *Pasteurella multocida* and *Mannheimia haemolytica* causing pneumonia in calves makes it doubtful to use these antibiotics for first-line treatment in some regions (39,40). Likewise, resistance in *Escherichia coli* causing enteritis in young pigs has regionally ousted trimethoprim-sulphonamide as a relevant first therapeutic choice (41).

To substitute older drugs made obsolete by resistance with newer drugs has consequences that are not immediately evident. One aspect is that newer drugs often are more expensive than older drugs. Of greater importance is that antibiotics recently introduced for use in farm animals mostly have a broader spectrum of activity than older drugs and therefore impose a broader selection pressure for resistance (22). Moreover, to substitute penicillin, tetracycline, and trimethoprim-sulphonamides with fluoroquinolones, third-generation cephalosporins, and newer macrolides can have implications for public health. These antibiotics are critically important in human health care, and reservoirs of resistant bacteria in animals kept for food production is undesired (1,31,41). Despite that, in current literature these antibiotics are often advocated for treatment of respiratory diseases in cattle and pigs (42,43) and mastitis in cattle (44) and are also favoured by practitioners in many countries over older drugs (45).

As the antibiotic arsenal is reduced by resistance, one consequence is that for some diseases there are few alternatives left. One example is swine dysentery, a serious enteric infection of growing pigs caused by the spirochete *Brachyspira hyodysenteriae*. Usually a large proportion of pigs in a herd are affected, and the

[3]http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf

disease often persists, with recurring outbreaks causing suffering for the animals and economic losses due to mortality, reduced feed conversion, and retarded growth. Resistance to drugs previously used to control swine dysentery, such as tylosin and lincomycin, is now widespread, and currently pleuromutilins are recommended (41). However, resistance also to pleuromutilins has been reported, which makes control of swine dysentery difficult and seriously constrains production on farms where resistant *B. hyodysenteriae* occurs (41,46).

Another example is MRSA, which in the last decade has become common among pigs but also among other animals kept for food production (47). Mostly the animals are symptomless carriers of MRSA and clinical disease is rare (47), but there are reports of MRSA in milk from dairy cows and sometimes in association with mastitis (48-52). MRSA isolated from dairy cows has generally been resistant not only to penicillins and cephalosporins but also to tetracyclines and sometimes to other antibiotics as well (48,49). This implies that if MRSA becomes a common cause of mastitis there are few or no antibiotics available for control of the disease (38).

In some regions of the world multi-resistance to anthelminthics is so widespread that parasitic diseases in grazing animals threaten the viability of goat and sheep farms (53). This could be the utmost consequence also of antibiotic resistance if multi-resistance is widespread among bacterial pathogens causing severe endemic diseases in animals kept for food production. The scenario is still in the future and could in single herds probably be managed by depopulation followed by cleaning and subsequent restocking under biosecurity measures. However, widespread multi-resistance in endemic pathogens such as *M. haemolytica* or *B. hyodysenteriae* would have serious consequences for food production in large-scale intensive production systems in affected regions.

Conclusion and perspectives

The consequences of antibiotic resistance in bacteria are basically the same in human and veterinary medicine. Loss of effective antibiotic treatments through resistance will cause suffering for the affected individual, regardless of whether it is a human being or an animal. There will also be economic consequences through increased treatment costs in animal and human health care. These costs are likely to be much higher in human health care because of the more advanced procedures and treatments employed. However, in up-to-date companion animal health care the degree of knowledge and skill is high, and advanced and costly procedures and prolonged treatments are often used. Nevertheless, suffering of the individual animal and the overall costs in companion animal health care can be limited by the possible and relevant alternative to euthanize seriously sick or old animals. In the rearing of animals for food production, it is a normal procedure to put animals down where the cost of treatment goes beyond the benefit in economic terms. Loss of access to effective therapy will also lead to economic losses due to reduced productivity of the animals, and loss of effective therapy in human health care is also associated with losses of productivity and subsequently to societal costs.

Although the consequences of resistance are mostly negative, the insight into the gravity of the problem and the focus from the scientific society and media on these issues have also had positive aspects. The emergence of resistance has been an incentive for development, evaluation, and adaptation of other regimes for treatment or prevention. Examples from companion animal health care are antibacterial shampoos for treatment of pyoderma in dogs, emphasis on debridement instead of antibiotics in wound care, and most importantly infection control in inpatient and outpatient care. Also, in the care of animals kept for food production, the emergence of resistance has brought on insights of the need to reduce morbidity by changes in husbandry and by effective biosecurity routines instead of by use of antimicrobials.

Healthy animals do not need antibiotics. In health care of companion animals and in animals kept for food production alike the main objective of efforts in the future should be to reduce the incidence of infectious diseases and thereby the need for antibiotics. This is even more relevant considering that it is highly unlikely that new antibiotic classes will be available for use in animals. If new antibiotic classes are placed on the market in the future, they will probably be restricted for use in human health care. This further emphasizes the need to mitigate emergence and spread of resistance to the antibiotics currently available in veterinary medicine through antibiotic stewardship, including measures to keep animals healthy without use of antibiotics.

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