The problem with overuse of antibiotics

Health professionals including veterinarians and their respective patients have enjoyed the use of antibiotics since any of us can remember. To the question implied by the title of this paper, “Why is overuse of antibiotics a problem?” the simple answer is: Imagine your world without them!

There are two fundamental precepts with which we should perhaps approach this question: The first is the immutable law of the universe that for every action there is an equal and opposite reaction. Put another way, no matter how cleverly we think we are manipulating it, the system always pushes back. The second is that for any given person, or group of people, their perception is their reality.

Applying these precepts to our discussion in the first instance means we accept that the inevitable consequence of antibiotics’ use is an increase in bacterial resistance to them and in the second instance that the significance of this depends very much on your point of view. The importance of this second point is that our responsibility is not only to the animals in our sphere of influence but also to the human population that may be affected by our use of antibiotics. It therefore behoves us to act in a manner that preserves our privilege of antibiotic use. In the present day, it is estimated that animal use accounts for more than half of all antimicrobials produced worldwide (Guardabassi et al. 2008).

This means we must not only act responsibly but also be seen to be doing so.

As a side note at this point, in much of the literature authors appear to switch between the terms ‘microbial’ and ‘bacterial’. I find this confusing at times and it puts us at risk of making the atomistic fallacy of assigning characteristics of bacteria to all microbes which include fungi, protozoa etc. For the sake of this discussion I will therefore deliberately confine myself to talking about bacteria from now on.

We should not be surprised by the emergence of resistance. Bacteria are the consummate survivors. They have been on the planet for three and a half billion years and indeed, together with other microbes, are responsible for the creation of most of the antibacterial drug families we use today. Alexander Fleming himself predicted resistance to penicillin and we now know the genetics for that resistance existed before its introduction in human medicine (Owens and Ambrose 2007). Resistance to the other antibiotic drug families has quickly followed their introduction.

Compounding the problem are the increasing difficulties in new drug discovery and, given the reduced opportunities for commercial return, an understandable reluctance of pharmaceutical companies to invest in this area (Levy 2005). Over the last two decades only two truly novel agents have been released: linezolid and daptomycin (Owens 2008).

The progression of antibiotic resistance comes about through both Darwinian selection of resistant individuals as well as the dissemination of resistance genetics to wider bacterial populations. It is the speed of dissemination, brought about by the phenomenal ability of bacteria to share genetic material, coupled with short generation times, that is perhaps of most concern. The risk of serious consequences posed by resistance dissemination is multiplied by the fact that animals and humans share many of the same pathogenic bacterial species as well as the antibiotics used to treat them.
The problem with overuse of antibiotics

Thus the development of antibiotic resistance in animals has the dual consequences of reduced efficacy in animals as well as in the human population. In Geneva in December 2003, the first of two expert workshops jointly convened by FAO, WHO and OIE concluded that “There is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human use of antimicrobials”. Additionally it was noted that, although the primary concern is antibiotic use in food-producing animals, the scientific evidence shows use in companion animals, horticulture and aquaculture also contributes to the problem (Guardabassi et al. 2008).

It might be argued that the problem is quite simply: The more antibiotics we use the less effective they will be. From this some will infer that they should therefore be preserved for ‘deserving cases’. The definition of ‘deserving cases’ would naturally be hotly contested instantly adding another layer to the debate.

Others will argue that injudicious use is where the problem lies. Indeed intuitive logic leads us to conclude that underuse is equally as problematic. That is exposing bacterial populations to sub-lethal concentrations of antibiotic will leave greater numbers of resistant survivors to pass on their genetics to future generations.

These apparently contradictory viewpoints can comfortably coexist once we realise we are considering two different systems. The first is at the global, or at least country, level whilst the second is the level of an individual patient or group of patients.

The global perspective is concerned with minimising the extent of antibiotic distribution in the ecosystem. The wider the distribution, the higher the chance that a large bacterial population will come into contact with levels of antibiotic selective for resistance (Acar and Rostel 2001). Hence the general guideline that good husbandry, nutrition, hygiene and disease-prevention practices, including vaccination, should be followed to minimise the need for antibiotic use.

At the level of the individual it is desirable to minimise the numbers of bacteria that survive an antibiotic exposure event. This leads to the prudent use guideline of using a dose regimen that achieves sufficient concentration at the target site, is as short as possible yet long enough to achieve resolution of the condition being treated.

What we must also accept however is that in administering an antibiotic it is impossible not to expose bacterial populations somewhere in the body to less than optimum concentrations, even if the target pathogens were totally annihilated. Commensal bacteria in the gut, for example, exposed to antibiotics will potentially contribute to resistance development in the wider bacterial population. Prudent use guidelines therefore recommend that treatment should be as targeted and specific as possible.

- Local treatment is preferred to systemic e.g. intramammary and ear treatments.
- Parenteral administration (if systemic treatment is required is favoured over oral to avoid exposure of gut commensals. In companion animals dispensing of oral preparations for ongoing treatment can perhaps be justified on grounds of cost and compliance and presents a much lower (though not zero) risk of transfer.
- The choice of drug should be based on knowledge of the organism involved and its drug sensitivities (preferably through culture and sensitivity testing).
- Individual animal treatment is favoured over whole herd or flock treatment.

**Mechanisms of resistance and its dissemination**

As antibacterial compounds are found in nature the development of resistance is a natural ecological response and it is widely held that bacteria developed some means to resist antibiotics long before their use in human or veterinary medicine. There are multiple mechanisms by which bacteria may neutralise the effect of antibiotics. They include: enzymatic deactivation, reduced drug uptake, drug efflux and modification or replacement of the drug target molecule or metabolic process.

For a given bacteria resistance can be intrinsic or acquired. Intrinsic resistance is that which is due to a structural or functional trait inherent in a bacterial species, genus or larger classification. For example, gram-negative bacteria possess an outer membrane that is impermeable to glycopeptides (reduced drug uptake).

Acquired resistance results from genetic change brought about by random mutation or horizontal transfer of foreign genetic material. Horizontal transfer is the exchange of genetic elements such as plasmids, transposons and integrons. It occurs by transformation (the uptake of free DNA) transduction (via bacteriophages) or
conjugation (cell to cell transfer). Clustering of resistance genes on plasmids can result in the acquisition of resistance to multiple and unrelated antibiotics (multiple resistance) in a single transfer. Resistance to one antibiotic can also select for resistance to another. This occurs by two mechanisms: Cross-resistance occurs when a single resistance gene or mutation confers resistance to two or more antibiotics. Co-selection is due to distinct genes or mutations in the same bacterial strain (Guardabassi 2008).

Bennett (2008) proposed the model of a single global gene pool made up of the collective genomes of all bacteria. Resistance genes are then available to most, if not all, bacteria to use for survival.

**Dissemination of resistance to humans from animal use**

As I have already observed it is widely accepted that antibiotic use in animals has potentially adverse consequences in human medicine.

Resistance genes can be spread between unrelated bacterial species and horizontal transfer can easily occur between bacteria from animals, fish and humans. Bacteria can be spread in food and water supply and through direct contact with animals and faeces. Through movement of animals, people and food, bacteria and genetic material can cross regional and international boundaries.

Ample evidence exists of an association between food animal use of antibiotics and drug resistant bacteria in humans (Angulo 2004). Several lines of evidence have been presented which include: Outbreak and epidemiological investigations, field studies, case reports, ecological and temporal associations and molecular subtyping comparisons. There have been several reports of farming and other people becoming directly exposed to antibiotic resistant bacteria from food animals. The negative consequences that have been documented include: Infections that would not otherwise have occurred if the pathogens were not resistant, increased frequency of treatment failures and increased severity of infection (prolonged illness and increased frequency of systemic infections, hospitalisation and mortality).

The argument that justifies using antibiotics that are not used in human medicine as growth promoters in animals may be on shaky ground due to the existence of cross-resistance and co-selection. In addition induction and cross species transfer of genetic material in the environment are known to occur. Use of antibiotics as growth promoters has been banned in the European Union and Scandinavian countries. Whilst increases in therapeutic use have been seen following these bans (Casewell et al. 2003), it has been shown, at least in some animal production systems, that abandoning the use of antimicrobial growth promoters is possible without any loss of productivity or increase in therapeutic use (Guardabassi et al. 2008).

More recently the focus of attention has also fallen on antibiotic use in companion animals. The intimacy of contact with humans presents opportunity for the sharing of antibiotic resistant bacteria with their owners. There is also potential to acquire and amplify resistant bacteria from humans and provide a reservoir for human infection (Prescott 2008). In recent years methicillin resistant Staphylococcus aureus (MRSA) has been found to transfer from humans to animals and vice versa (Loeffler 2008).

**Conclusion**

As this paper was undergoing final editing for submission, an article appeared in the New Zealand Herald entitled: "Warning: The age of safe medicine is ending". Reporting on an address to infectious disease experts by Margaret Chan, director general of the WHO, the article raised the spectre of common ailments becoming untreatable due to antibiotic resistance. The article referred to "the post-antibiotic era" as an impending global crisis. Use in animals, particularly those that are healthy, was highlighted as part of the problem (Laurence 2012).

Public perception coupled with solid evidence of a link between antibiotic use in animals and resistance in human medicine means that veterinarians’ practice will come under increasing scrutiny. Although we might, perhaps rightfully, assert that animal use of antibiotics in New Zealand is making a relatively miniscule contribution to the problem globally, we will be expected to play our part in its solution. Hence we have a responsibility not only to follow, but also to be seen to be following, accepted best practice especially in food animal production systems. We should also bear in mind the potential threats to trade from adverse publicity to our veterinary and farming practices with regard to antibiotic use.

Coupled to the human health impacts is the potential for reduced efficacy of first-line antibiotics with obvious implications for the welfare of the animals we currently prescribe for. Whilst this may be the major concern of companion animal practitioners, it is now apparent that resistance in humans may also be at risk from antibiotic
overuse in companion animals. Thus, as public concern increases, the spotlight will also fall on this area of veterinary practice.

References


Angulo FJ et al. Evidence of an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans and the human health consequences of such resistance. Journal of Veterinary Medicine B Infectious Diseases and Veterinary Public Health 51, 374-9, 2004


Bibliography


Courvalin P. Can pharmacokinetic-pharmacodynamic parameters provide dosing regimens that are less vulnerable to resistance? Clinical Microbiology and Infection 14, 989-94, 2008

Martinez L et al. A global view of antibiotic resistance. FEMS Microbiology Review 33, 44–65, 2009

Laurence J. Warning: The age of safe medicines is ending. NZ Herald, Saturday March 17 B1, 2012

Levy SB. Antibiotic resistance—the problem intensifies. Advanced Drug Delivery Reviews 57, 1446-50, 2005


Owens RC Jr, Ambrose PG. Antimicrobial stewardship and the role of pharmacokinetics-pharmacodynamics in the modern antibiotic era. Diagnostic Microbiology and Infectious Disease 57, 775-835, 2007


Prescott JF. Antimicrobial use in food and companion animals. Animal Health Research Reviews 9, 127-33, 2008

McEwen SA. Antibiotic use in animal agriculture: What have we learned and where are we going? Animal Biotechnology 17, 239-50, 2006


Wright GD. The Antibiotic Resistome. Expert Opinion on Drug Discovery 5(8), 1-10, 2010