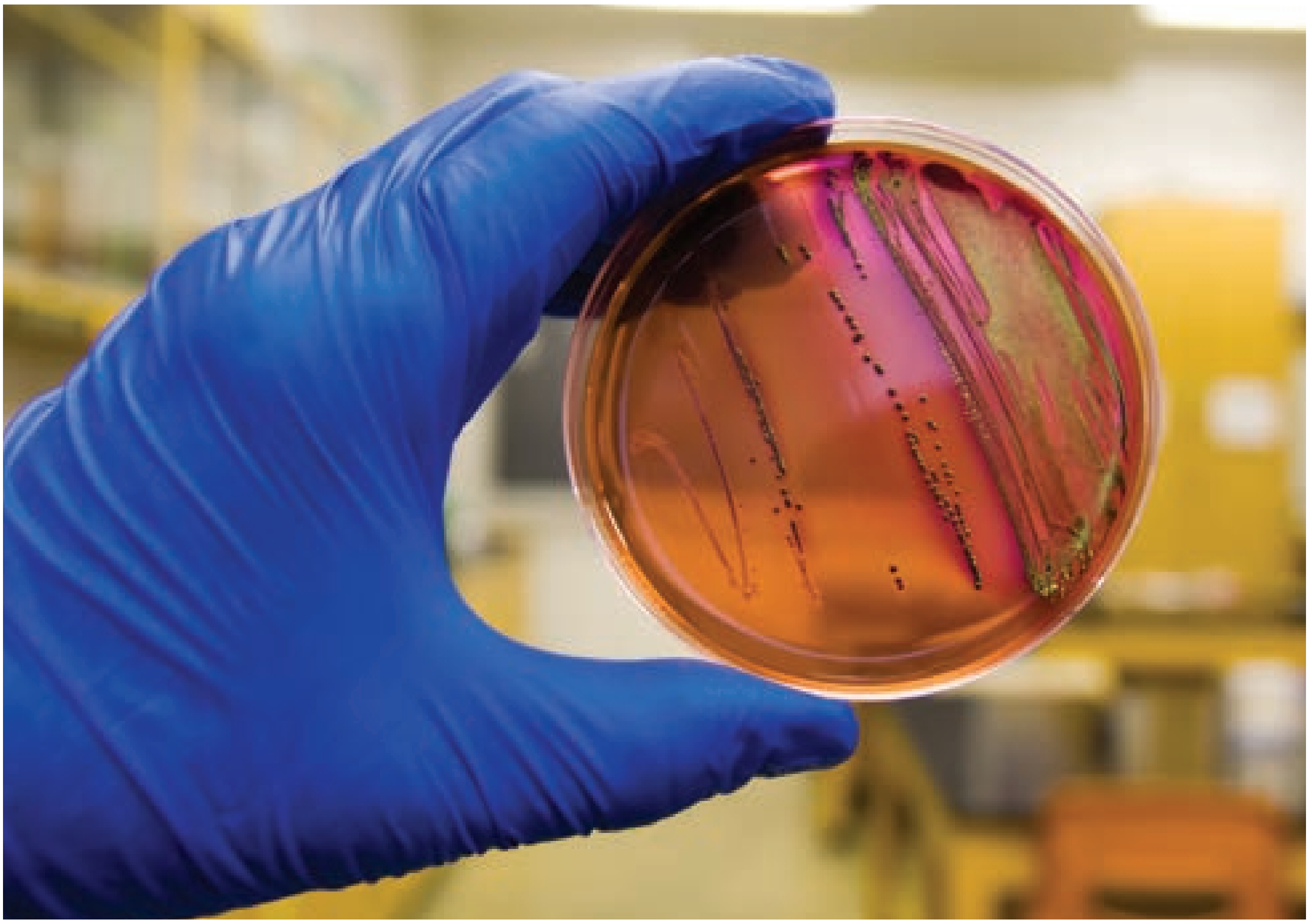
Antimicrobial resistance in Ireland

Multi-drug antimicrobial resistance is a major global issue in medicine. Current thinking is that the main cause of resistance in human medicine is the use of antibiotics in humans. To ensure veterinary medicine does not face the same crisis in the future, responsible practices must be adopted by vets and farmers, writes Charles Chavasse, area veterinary manager, Zoetis



Antimicrobial resistance (AMR) and multi-drug resistant bacteria are causing a therapeutic crisis in human medicine. Over the past 10 years, there has been a dramatic increase in the number of scientific papers written on the subject and much of the evidence is both confusing and contradictory. It is also a subject that is regularly covered in the general press. Unfortunately, many of us have either had a personal experience, or know someone who, due to infection with one of these 'super bugs', has had their time extended in hospital or, worse, never recovered. It is understandably an emotive subject and a growing concern for the general public, politicians, doctors and vets. Fortunately, as yet, with a few exceptions, there is not a therapeutic crisis in veterinary medicine. However, the spotlight is on how and what antibiotics are being used by vets, particularly in agriculture. It is now generally accepted that while the major cause of AMR in human medicine is caused by the use of antibiotics in humans, it is important that the veterinary profession carefully looks after the antibiotics available for use in animals through responsible use programmes. We would do well to learn from the experience and knowledge that has been gained in the medical profession.

AMR is not new. Resistant genes have evolved as part of competition between bacteria over thousands of years, leading to a vast reservoir of resistant genes, including genes coding for resistance to antimicrobials that have never been used.[1,2] What has changed in the past 50 years is that, with an increase in the use of antibiotics, there has been a resultant increased selection pressure. On top of this, there has been a rapid spread of these genes around the world due to widespread international movement of people, animals, food and wildlife.

Bacteria can spread from people to food, from food to people, from people to animals, from animals to the environment, etc. With these transmissions, genes coding for AMR are also moving from one compartment to another. Some of these connections have been extensively studied but others still require further research. It is generally accepted that our understanding is incomplete and that there is a complex web of interconnections between people, animals, food and the environment. See Table 1, adapted from Linton 1977 and Prescott 2000.[3,4] This shows many, but not all, of the potential movements of bacteria and their genes between different 'compartments', ie. humans, their environment, sewage, food animals, manure, slaughter houses, etc. The link between faecal contamination of a carcase in a slaughter house and this eventually entering the food chain is relatively well understood, and throughout history measures have been put in place to reduce this happening. These are constantly being updated, and systems like Hazard Analysis and Critical Control Points (HACCP) have been devised. But these links, and understanding them, have even more importance with the emergence of AMR. An area of particular concern is how both human and animal faeces are treated and where they eventually end up in the environment. If manure which contains bacteria carrying AMR genes is spread on the land, how long do these bacteria survive? Can they enter the food chain? And it is not only animal waste. What happens if a tourist returns from a foreign holiday with a gastro-intestinal infection? There is a possibility that some of the *E. coli* he is passing could be carrying AMR. These should pass into a sewage system. But will this destroy the AMR genes? If there is flooding will all of this be contained within the system, or could it leak out into the waterways? Are cattle drinking from the rivers? Could the AMR genes now enter the farm system? In a few steps, an exotic AMR gene could be transferred from an exotic holiday destination to a farm yard in Ireland.

WHAT IS AMR?

At its simplest, AMR exists when an antibiotic used to treat an infectious condition is no longer effective at that dose. However, it can be difficult to define as there are many variables, including dosage, condition treated, species of patient, etc. Measuring resistance *in vitro* to predict what happens *in vivo* is problematic, and clinical break points have not been well defined for many bacteria in veterinary conditions. It should be remembered that AMR does not cause disease but it does make it more difficult (or even impossible?) to treat some bacterial infections.
There are various mechanisms by which resistance develops. One of the primary concerns are the genes which code for extended spectrum beta-lactamases (ESBLs) in Gram-negative bacteria, particularly *Enterobacteriaceae*. These genes can be located on plasmids as well as on nuclear DNA. The former allow the spread of the coding information both within bacterial species and between different species and genera. As a result, commensal gastrointestinal bacteria may become resistant when a

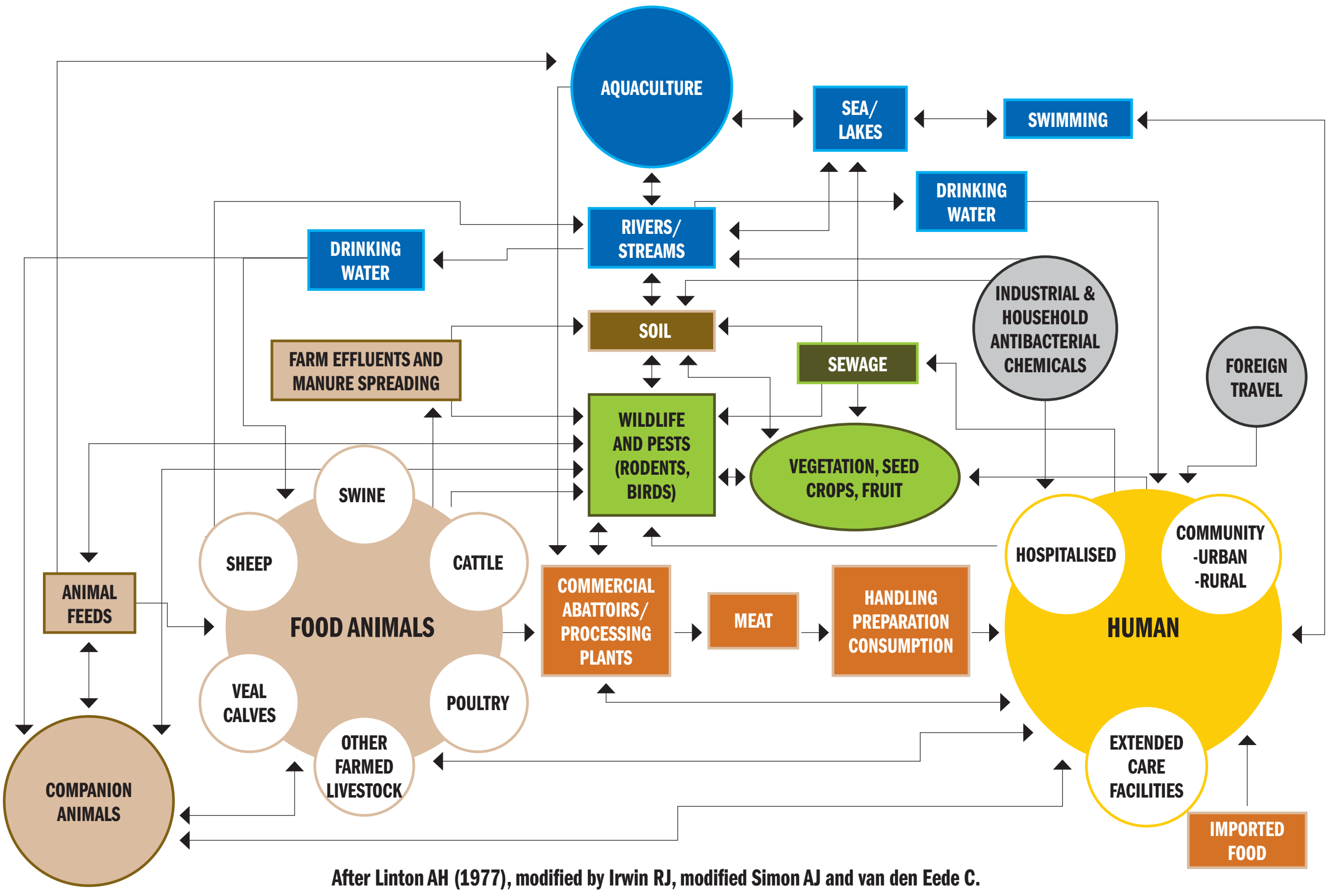


Figure 1: Epidemiology of antimicrobial resistance.

person or animal is being treated for an infection. These ESBL bacteria may be passed into the environment or remain in the gut, but at a later stage come in contact with a pathogenic non-resistant strain of bacteria. The ESBL plasmids may be passed between different species of bacteria while they are multiplying in the same space, resulting in the pathogenic bacteria developing into a resistant strain. This could be of particular relevance on dairy farms where milk containing antibiotic residues is commonly fed to calves. Effectively, the intestinal flora of these calves is subjected to a sub-therapeutic dose of an antibiotic which could select for resistance to that antibiotic.
Among Gram-positive bacteria, the main concern in human medicine is methicillin-resistant *Staphylococcus aureus* (MRSA). The primary epidemiological pattern is by clonal expansion, ie. development of resistance within an individual species of bacteria. MRSA have been further subdivided into hospital-associated (HA-MRSA), community-associated (CA-MRSA) and livestock-associated MRSA (LA-MRSA), but there is overlap between these groups. LA-MRSA has been associated with human disease. The main risk factors for acquiring LA-MRSA appear to be continued close contact with infected animals, particularly pigs.[5]

HAZARD AND RISK

What about the potential impact on human health from ESBL and LA-MRSA bacteria of animal origin? It is relatively straightforward to identify hazards, ie. resistant pathogenic bacteria that may be found in both animals and humans. The risk is generally more difficult to define, ie. what is the probability that AMR genes in the animal reservoirs are a significant contributor to AMR in human pathogens?
It is well recognised that animal origin bacteria can impact directly on human health, as in zoonotic infections. The commensal pool of AMR genes in animal bacteria can also have an impact on human health and this could be on a community level, eg. as foodborne bacteria or as an occupational hazard for people that are in close contact with animals.
If the same strain of ESBL *E. coli* was found in both humans and animals, a hazard would have been identified. However, for this strain to be a risk to human health, the following sequence of events would have to take place:

- The animal-origin *E. coli* containing ESBL genes must contaminate the meat in the slaughterhouse or during processing;
- And must survive storage and transport;
- And must then either be directly ingested or cross contaminate other foodstuffs in the kitchen;
- And must not be killed during cooking;
- And must colonise the human gut;
- And a transfer event of the gene must occur to a potential human pathogen;
- And this pathogen must be one which causes disease in this or other humans;
- And, finally, there must be treatment failure due to AMR.

In vitro AMR genes can readily be transferred between different bacteria but, as shown above, a complex chain of events must occur for this hazard to become a genuine risk. Appropriate controls that are in place in slaughterhouses, processing plants and kitchens greatly reduce the risk to the spread of this hazard. Above all, it should be remembered that AMR does not cause disease in itself; disease is caused by bacteria.

ANTIBIOTIC AVAILABILITY FOR VETERINARY USE

Antimicrobials are a limited resource and there is little evidence of new classes in the pipeline. Additionally, it is likely that EU law would probably restrict any major advances to human use only. It is, therefore, important that veterinarians adopt responsible use practices and use ‘as little as possible, as much as necessary’ to ensure that the antibiotics currently available for veterinary use remain as effective as ever for as long as possible. Restrictions, bans and quotas have all been proposed, but it is important that their primary objective is a meaningful impact on human health and, secondly, a positive impact on animal health. Reducing the use of antibiotics, or certain classes, is not an end in itself and, in fact, could be detrimental; removing a class of antibiotic from veterinary medicine could lead to increased use of another class, and thus lead to increased selection pressure on the remaining antibiotics available for veterinary use.
Proposed changes include the following.

1. Restriction of antibiotic use

- Prohibit the use of certain molecules. This may not have the desired effect since, due to co-selection, other classes may still select for resistance to the molecule that has been withdrawn. There is also evidence that on organic farms with reduced/restricted antibiotic use, ESBLs and MRSA prevalence remains high;[6,7]
- Reduce the use of all antibiotics in veterinary medicine. The use of any antibiotic will select for resistance but at what level should the reduced level be set? And will the reduction have a positive impact on human health? The latter is unlikely if prescribing patterns do not also change in human medicine;
- Identify high-risk practices and do not allow the use of antibiotics to support poor husbandry systems, eg. the feeding of waste milk or medicated milk to dairy calves (this is unnecessary if calves are in a low-risk environment) or unjustified prophylactic use of antibiotics.

Interestingly, in certain environments, reducing antimicrobial use may not lead to improvements in human or animal health. Antibiotic dry cow therapy has been used therapeutically/metaphylactically/prophylactically for over 40 years, but there is no evidence that it is having a significant impact on AMR in mastitis pathogens or on human health.[8]

2. Reduction in the need for antibiotic use

Focus on preventative measures including biosecurity, vaccination and improved environment.
Interventions could have unintended negative consequences:

- Could a ban on an existing antibiotic, or class of antibiotic, create a therapeutic crisis in veterinary that does not exist at present?
- Could animal health suffer? Healthy food comes from healthy animals;
- Could stringent restrictions negatively impact on compliance, eg. under-dosing or incomplete courses of treatment?
- Could stringent restrictions reduce profitability and force farmers out of business? This could lead to increased imports from less regulated markets which possibly could carry higher levels of AMR bacteria.[9]

The main driver behind the AMR debate is to improve human health. This is a long-term goal that will take time. Measuring progress will not be straightforward and, as discussed, simple solutions may not achieve the desired results. However, it is beholden on all prescribers to promote best practice around animal health and, where antibiotics need to be used, to ensure they are used only where needed, by the correct route, for long enough to achieve a result and that withhold periods are observed to prevent residues entering the food chain. Practitioners need to be engaged by farmers to help design systems that will lead to less infected, poor performing animals. But it also needs to be recognised that animals, when sick, deserve to be treated, too. Responsible use of antibiotics can come from some unlikely scenarios; some of the recent, more innovative antibiotic presentations offer advantages over some of the older conventional drugs. For example:

- Long-acting preparations may help to overcome a common problem in both human and veterinary medicine – compliance. It is well recognised that, frequently, antibiotic courses are not completed by both human patients or by farmers administering antibiotics to their animals;
- Nil milk withhold antibiotics. Originally seen as a financial incentive for farmers, but now recognised as less risk of residues entering the food chain but also ensuring that calves are not fed milk containing a subtherapeutic dose of antibiotics that could select for resistance within the commensal gut flora.

It is now possible for a practitioner to call to a farm, make a diagnosis, prescribe and administer a complete course of an antibiotic in one injection, where the farmer doesn't have to withhold the milk. The advantages of this are:

(a) The correct animal is treated for the right condition;
(b) The correct dose is used and the course is completed without relying on the farmer to carry out further injections on what he may now regard as a healthy animal;
(c) Less stress is imposed on 'man and beast' from repeated handling;
(d) Antibiotic residues do not enter the food chain, nor are they fed to healthy calves where they could select for AMR in the commensal gut flora, leading to AMR problems in the future.

CONCLUSION

Multi-drug antimicrobial resistance will continue to be a major global issue in medicine. The current thinking is that the main cause of resistance in human medicine is actually the use of antibiotics in humans. Veterinary medicine, as yet, does not face the same crisis but could in the future if responsible practices are not adopted by vets and farmers. AMR is complex, and simple solutions, like banning or restricting the use of certain drugs, are unlikely to have the desired effect. Vets and farmers should strive to develop systems that result in fewer animals needing treatment but when that need arrives they should be treated promptly using 'as little as possible but as much as necessary'.

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