

Antimicrobial Resistance and Responsible Use of Antimicrobials: Information for Veterinary Surgeons

Antimicrobial drugs have played an important role in managing the health of both humans and animals for more than 60 years. In animal health, antimicrobials are used to treat, control or prevent disease caused principally by bacteria.

It is now widely accepted that antimicrobial treatment of animals may contribute to the development of resistant organisms in the treated animals. Similarly, use of antimicrobials in humans may contribute to the development of resistant organisms in humans. It is generally accepted that for the majority of bacteria that cause human infections, the main cause of antimicrobial-resistant infections in people is from the administration of antimicrobial drugs in human medicine. Nevertheless, it is also recognised that the use of antimicrobials in animals is an important factor in the development of resistance in some organisms, particularly those organisms associated with food poisoning in man. The use of antimicrobials in animals can also affect the occurrence of resistance in other bacteria carried by animals. In the same way, the use of antimicrobials in people can result in resistant organisms entering the environment and on occasion being acquired by animals and plants. Government policy continues to promote responsible and appropriate use of antimicrobials in all sectors.

The specific areas of concern are:

- i) Transferable resistance between bacterial species. Resistance genes can transfer between different strains and between different species of bacteria. It is possible for resistance genes of animal origin to transfer to disease-causing bacteria of human origin and *vice versa*.
- ii) The amplification and subsequent dissemination of drug-resistant organisms between animals following antimicrobial therapy. This is particularly relevant to bacteria emanating from animals bred for food.

- iii) Multi-drug resistance. This is regarded as resistance to four or more unrelated antimicrobials. This can result in reduced treatment options, prolonged recovery or in the worst case, treatment failure.
- iv) The increasing occurrence in cases of infection in both humans and animals of bacteria with resistance to critically-important antimicrobials such as fluoroquinolones and third and fourth generation cephalosporins.

What is an antimicrobial or an antibiotic?

Antimicrobials are compounds which exert an action against micro-organisms and exhibit selective toxicity towards them. The term includes any substance of natural, semi-synthetic or synthetic origin, which inhibits the growth of, or kills, micro-organisms (bacteria, fungi, viruses and protozoa).

What is antimicrobial resistance?

Antimicrobial resistance is defined as the ability of a micro-organism to grow or survive in the presence of an antimicrobial at a concentration that is usually sufficient to inhibit or kill micro-organisms of the same species. Micro-organisms may be tolerant, or inherently resistant to particular antimicrobials or they may acquire resistance to an antimicrobial to which they are normally sensitive.

How does antimicrobial resistance occur?

Antimicrobial resistance can arise in one of three ways:

- Micro-organisms can be inherently resistant to an antimicrobial because they do not have the cellular sites required for antimicrobial action, or because they naturally possess special enzymes, which block the action of the antimicrobial. For example, Gram-negative bacteria are resistant to glycopeptides and Gram-positive bacteria are resistant to polymyxins.
- Resistance can arise by spontaneous mutation altering the endogenous genes but not adding new genes. This resistance becomes evident with the extensive use of antimicrobials, as the micro-organisms with the respective mutation for resistance possess a selective advantage. For example, this is the only mechanism of antimicrobial resistance in bacterial genera such as *Mycobacterium*. Chromosomal mutations of this nature are increasingly important in certain salmonella serovars.

- Resistance can be transferable between both related and unrelated bacteria via mobile genetic elements such as plasmids, transposons and integrons. This ability to share genetic information is the major way that multi-drug resistance develops and can do so relatively quickly. For example, plasmid movement into and between strains of *Escherichia coli* and subsequent amplification in the host organism is considered the primary way in which resistance caused by ESBL (extended-spectrum β -lactamase) enzymes is increasing.

What is multi-drug resistance?

There is no single definition of multi-drug resistance. Defra consider multi-drug resistance to be when any bacteria has resistance to four or more unrelated antimicrobials. Multi-drug resistant pathogenic bacteria may compromise treatment choices for both animals and humans, prolong recovery, or lead to treatment failure e.g. meticillin-resistant *Staphylococcus aureus* (MRSA), multiple drug-resistant *Salmonella* Typhimurium definitive phage type (DT) 104.

How does antimicrobial use contribute to the development of antimicrobial resistance?

Both overuse and inappropriate use of antimicrobial drugs contribute to the development of antimicrobial resistance. Treatment may kill all of the susceptible bacteria but any bacteria with a degree of resistance may be able to survive and multiply and are consequently "selected". Under-dosing (including failure to complete a course of antimicrobials) may not kill all the organisms. The development of resistance is also facilitated by overuse or over-reliance on the use of an antimicrobial when there are alternative control measures available; for example, treatment of clinical disease with an antimicrobial rather than vaccination to prevent the disease. Using the wrong type of antibiotic or administration via the wrong route or using a broad spectrum antibiotic where a narrow spectrum one would suffice, will all contribute to the development of resistance. Antimicrobial resistance development is also encouraged by widespread use and possibly unnecessary use of an antimicrobial, for example to treat viral disease, to prevent disease, or to treat in-contact individuals (prophylaxis and metaphylaxis). It is therefore extremely important that the prescribing vet charged with prescribing the correct antimicrobial takes these factors into account when deciding on the appropriate treatment to use.

What can be done in veterinary practice to reduce the emergence of resistance?

- Prevent diseases by implementing good herd or flock health and bio-security practices, good nutrition, hygiene and animal comfort.
- Wherever possible use antimicrobials at an early stage, when clinical signs of disease are first diagnosed and become evident.
- When more than one antimicrobial is indicated for a disease, use the least important for human therapy and least likely to select for resistance first.
- Use a narrow spectrum antimicrobial wherever possible.
- The product's Summary of Product Characteristics (SPC) or product literature instructions must be clearly understood and taken into account, especially when deciding on the dosage and duration of treatment. Do follow the storage advice.
- Emphasise to clients the need to follow the antimicrobial product's labelling instructions.
- Perform sensitivity testing on causal bacteria against antimicrobials of choice whenever possible.
- If the treatment does not appear to work, perform further diagnostic tests and report the treatment failure to the Veterinary Medicines Directorate (VMD) as a Suspected Lack of Efficacy using a yellow form. This is a valuable tool for veterinarians to be part of an alert system to bring an emerging resistance problem to the attention of interested parties.
- Periodically re-evaluate the benefit of any preventative use of antimicrobials. Discontinue use if there is no clear benefit.

What is the VMD doing to combat the emergence of antimicrobial resistance in animal health?

The VMD is responsible for the approval and registration of antimicrobials for use in animal health in the UK. A new drug must satisfy extensive product efficacy, quality (manufacturing) and safety (animal, environment, and human) criteria before being approved. There is a specific requirement for companies to supply, for all new antimicrobial products in all animal species, data to address the area of the development of resistance, before such products are authorised.

The VMD monitors the amounts of antimicrobials used in animals in the UK and, the overall amounts used are decreasing over time. Reports on UK veterinary antimicrobials are available at: www.vmd.gov.uk/Publications/Antibiotic/AntiPubs.htm.

VMD also provides the secretariat to the Defra Antimicrobial Resistance Coordination (DARC) Group, which is a cross-Government Group considering all issues relating to veterinary antimicrobial resistance. Further details about DARC can be found at www.vmd.gov.uk/General/DARC/DARC.htm.

The VMD is currently working with regulators in Europe to develop a coordinated approach to assess and subsequently manage the risks associated with antimicrobial resistance and to reduce the emergence of further resistance as far as possible. The VMD also works with other Government Agencies and expert groups such as the Veterinary Laboratories Agency (VLA), RUMA (Responsible Use of Medicines in Agriculture), Health Protection Agency (HPA), Advisory Committee on Healthcare Associated Infections (ARHAI) and SAGAM (Scientific Advisory Group on Antimicrobials).

Emerging Problems

VMD, via its representation on scientific committees and working groups, is constantly considering emerging problems and horizon scanning the area of antimicrobial resistance in the veterinary sector.

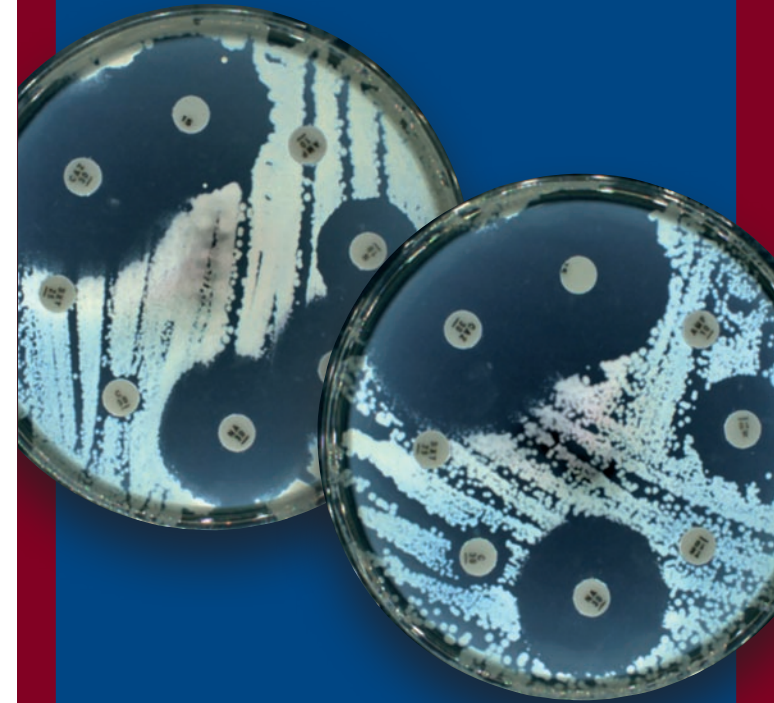
Further Information

www.vmd.gov.uk
www.defra.gov.uk/animalh/diseases/vetsurveillance/antimicrobial-res.htm
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ASSURING THE SAFETY, QUALITY & EFFICACY OF VETERINARY MEDICINES



Antimicrobials



The Veterinary Medicines Directorate is an Executive Agency of the Department for Environment, Food & Rural Affairs