Federation of Veterinarians of Europe

Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine

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Abstract

Therapeutic antibiotics are used in the treatment and control of many types of infections in a wide variety of animal species.

This use can lead to the selection of resistant forms of micro-organisms to antibiotics, which is a natural and unavoidable phenomenon. It is an inherent risk associated with the use of antibiotics in any species, including man.

The appearance in human pathogens of multiple resistance to antibiotics has focused attention on both human and veterinary use of these valuable medicines. However, the degree to which usage of antibiotics in veterinary medicine contributes to this problem is yet to be fully understood.

The development of resistance can be minimised provided that a number of measures are observed to prolong the useful life of all antibiotics in both human and veterinary medicine. Antibiotic use should be limited to situations where they are needed and the selection of the right antibiotic should take a number of factors into account.

The purpose of this paper is to increase the awareness of prescribing and supervising veterinary surgeons to the problem of antibiotic resistance and to review the basic principles on the prudent use of antibiotics.

Antibiotic use should not, however, be seen in isolation from the disciplines of animal management, animal welfare, husbandry, hygiene, nutrition, immunology and vaccination. Diseases must be controlled to reduce the need for antibiotic use and they can only be controlled successfully by an holistic approach.

The word antibiotic is used throughout the document; it is intended to cover all antimicrobial agents administered orally, topically or parenterally to animals to produce a curative or protective effect. It includes antibiotics produced by fermentation of live micro-organisms as well as chemically synthesised compounds with antibiotic activity such as sulphonamides, trimethoprim and quinolones. It does not include disinfectants and coccidiostats.

Antibiotic Resistance: Overview

Resistance to antibiotics existed even before antibiotics were used throughout the world. However, this intrinsic form of resistance is not a major source of concern for human and animal health. The vast majority of drug-resistant organisms have instead emerged as a result of genetic changes, acquired through mutation or transfer of genetic material during the life of the micro-organisms, and subsequent selection processes.

Acquired Resistance: mutational vs. transferable resistance

Mutational resistance develops as a result of spontaneous mutation in a locus on the microbial chromosome that controls susceptibility to a given antibiotic. The presence of the drug serves as a selecting mechanism to suppress susceptible micro-organisms and promote the growth of resistant mutants. Spontaneous mutations are transmissible vertically.

Resistance can also develop as a result of transfer of genetic material between bacteria. Plasmids, which are small extra-chromosal DNA molecules, transposons and integrons, which are short DNA sequences, can be transmitted both vertically and horizontally and can code for multi-resistance.

It is estimated that the major part of acquired resistance is plasmid-mediated.

Multiple Resistance

Resistance depends on different mechanisms and more than one mechanism may operate for the same antibiotic.

Micro-organisms resistant to a certain antibiotic may also be resistant to other antibiotics that share a mechanism of action or attachment. Such relationships, known as cross-resistance exist mainly between agents that are closely related chemically (e.g. polymyxin B and colistin, neomycin and kanamycin), but may also exist between unrelated chemicals (e.g. erythromycin-lincomycin).

Micro-organisms may be resistant to several unrelated antibiotics. Use of one such antibiotic will therefore also select for resistance to the other antibiotics.

Epidemiology of Resistance

Resistance patterns

Resistance patterns observed in animals are likely to be affected by antibiotic exposure, but they will also vary according to:

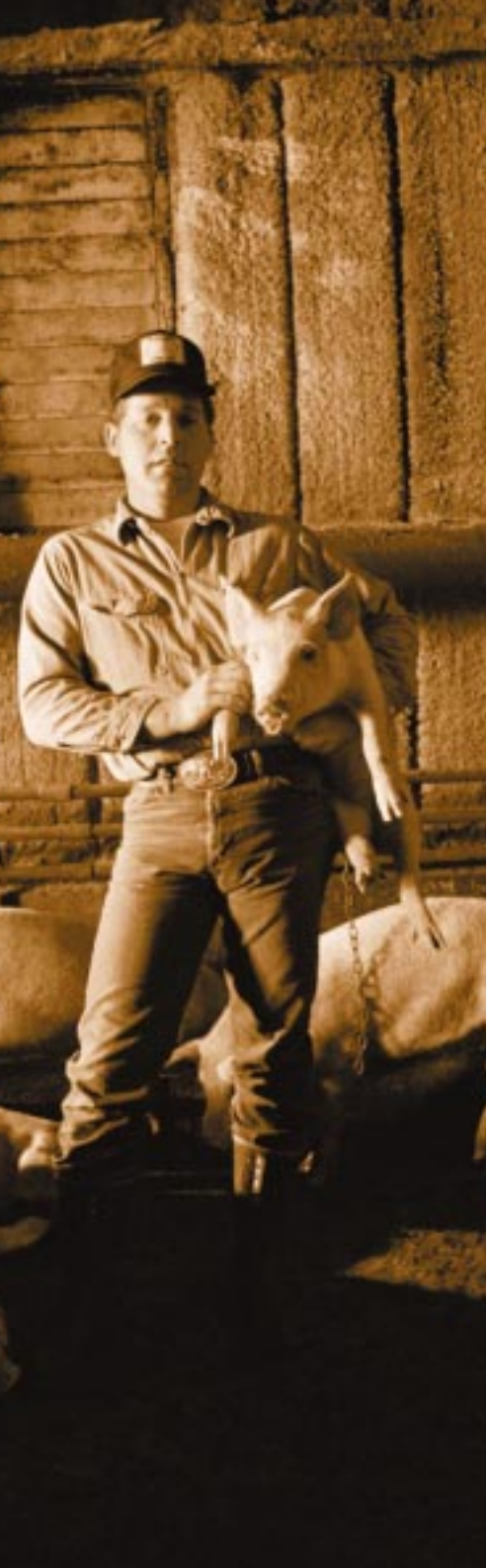
- *the size of the population of micro-organisms;*
- *pre-exposure prevalence of resistance genes;*
- *the fitness of the selected population of micro-organisms in competition with other micro-organisms present in the environment which have not been exposed to antibiotics.*

Resistance transfer

There are multiple sources of resistant micro-organisms, both commensal and pathogenic:

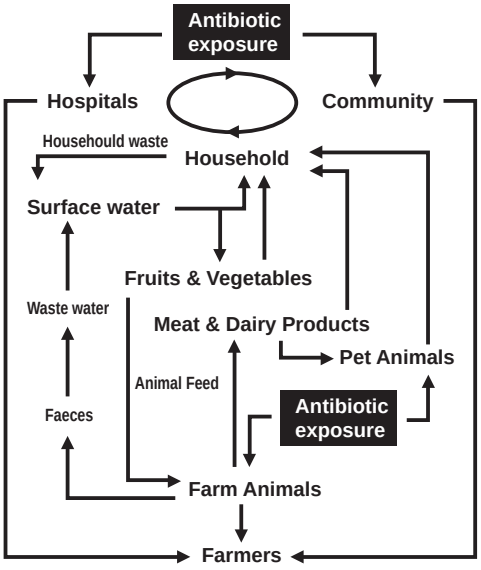
- *Animals and their faeces;*
- *Food of animal origin that may have been contaminated during processing;*
- *Fruits or vegetables that may come from a contaminated environment;*
- *Contaminated water;*
- *Humans.*

Whenever an animal or human host is exposed to antibiotics, there will be some degree of selection for resistant bacterial population. Selection will depend upon the type of antibiotic used, the number of individuals treated, the dosage regimen and the duration of treatment. Therefore, it is vital to limit therapeutic antibiotic use to those situations where they are needed.



The relative contribution of each of these sources as well as the different routes of transfer remain to be fully understood.

However, if the use of antibiotics in human medicine is the main source of resistance in the human population, direct contact with animals and the consumption of contaminated food of animal origin are recognised to be the main routes of transfer of resistance from animals to humans.



In addition, while much attention has focused on transfer of resistant bacteria from food animals to man it must be kept in mind that human and animal populations constitute overlapping reservoirs of antibiotic resistance, as shown in the figure above.

Veterinarians therefore need to educate their clients on the hazards involved. This is true for farmers but also for pet owners, when medicating companion animals known or suspected to be infected with zoonotic organisms, as these animals may share living accommodation with young

children, the elderly, immunocompromised patients or caretakers of food animals.

Finally, given that it will rarely be possible to establish with certainty where the resistance was originally acquired and given the general complexity of the subject, it is important that both medical doctors and veterinarians work together to address the issues.

Prudent use of Antibiotics: Principles

Prudent use of antibiotics is an integral part of good veterinary practices. It is an attitude to maximise therapeutic efficacy and minimise selection of resistant micro-organisms.

Prudent use principles are a guide for optimal use of antibiotics. They should not be interpreted so restrictively as to replace professional judgement of practitioners or to compromise animal health or welfare.

In all cases, animals should receive prompt and effective treatment as deemed necessary by the prescribing or supervising veterinarian.

Choice of the right antibiotic

The choice of the right antibiotic should be based on:

Accurate diagnosis

The use of antibiotics should be based on the clinical evaluation of the animals under the care of the prescribing veterinary surgeon and on the judgement that antibiotic therapy will have a beneficial effect.

When it is not possible to make a direct clinical evaluation, the diagnosis should be based on past experience, on knowledge of the farm epidemiological status and on ongoing sensitivity testing.

Antibiotic therapy should help to contain and limit further extension of the infection, shorten duration of the infection and disease, or reduce risks of systemic complications.

Known products approved for the species and the indication

No medicinal product can be placed on the market unless its quality, safety and efficacy have been demonstrated. Therefore, the first line of choice should be based on the products approved for the species and the indication concerned.

Known efficacy established in well performed field trials

When no suitable product is licensed for a specific condition or species, the choice of an alternative product should be based, whenever possible, on the results of well performed field trials and a proven efficacy for the condition or species concerned. Indiscriminate off-label use should be avoided.

Known or predictable sensitivities of possible micro-organism involved

Antibiotics should only be used when it is known or suspected that an infectious agent, that will be susceptible to the therapy, is present. When treating a disease, the sensitivity of the causal organism should ideally be ascertained before therapy is started. In certain situation such as disease outbreaks involving high mortality or where there are signs of rapid spread of disease among contact animals, treatment may be started on the basis of clinical diagnosis. Even so, the sensitivity of the suspected causal organism, should, where possible, be determined so that if treatment fails, it can be changed in the light of the results of sensitivity testing. Antibiotic sensitivity trends should be monitored over time, and such monitoring used to guide clinical judgement on antibiotic usage.

Susceptibility testing can only give an indication of what the clinical activity of the drug will be. The effect of the drug in vivo depends on its ability to reach the site of infection in a high enough concentration, the nature of the pathological process and the immune response of the host.

Known pharmacokinetics / tissue distribution

The choice of the right antibiotic also need to take into account pharmacokinetics parameters, such as bioavailability, tissue distribution, half-life, tissue kinetics to ensure the selected therapeutic agent reaches the site of infection. Duration of withdrawal periods may be a factor in choosing suitable products.

Considerations must also be given to the available pharmaceutical forms and to the route of administration. Prolonged oral use should be avoided as most of the concerns with regard to resistance is associated with the selection and transfer of resistant bacteria that inhabit the gut.

Susceptibility tests are intended to be a guide for the clinician, not a guarantee that an antibiotic will be effective in therapy.

Known status of immunocompetence

When treating animals with immuno-suppression or life-threatening infections then bactericidal substances should be preferred, as successful use of bacteriostatic antibiotics rely on an active immune system to control the infection.

Appropriate spectrum of activity

The choice of antibiotic should take the susceptibility of the demonstrated or suspected micro-organism into account, while aiming for a minimal effect on other micro-organisms.

The risk for development of resistance in micro-organisms of the individual animal, the population of animals and the risk for transfer to other populations should be considered. Generally, antibiotics with a broad spectrum of activity lead to development of resistance in non-target micro-organisms more rapidly that those with narrow spectrum, because they exert a selection pressure on a greater number of micro-organisms.

Therefore, in order to minimise the likelihood of broad antibiotic resistance developing, where an appropriate narrow spectrum agent is available, it should be selected in preference to a broad spectrum agent.

Consideration should also be given to potential consequences of resistance to the specific substance in question. Selection of antibiotics that are used for animals or man in special, critical, situations where few or no other antibiotics are available, should be carefully justified.

Known antibiotic combinations

The indiscriminate use of antibiotic combinations should be avoided because of the potential for increased toxicity, pharmacological antagonism, and the selection of resistant organisms.

However, the use of multiple antibiotics to provide broader coverage may be justified when failure to initiate effective antibiotic therapy will significantly increase mortality or morbidity or in seriously ill patients when the identity of an infecting organism is not apparent.

Therapy may fail because the causative micro-organisms are or become resistant to the chosen antibiotic. However, there are other causes of failure unrelated to acquisition of resistance. Therapy may also fail because:

- **The animal owner does not comply with the prescription;**
- **The dose prescribed is insufficient or administered for an insufficient duration;**
- **An inappropriate antibiotic is prescribed;**
- **The antibiotic fails to reach the infected site;**
- **Poor host response is encountered due to a systemic disease;**
- **Inactivation of the antibiotic by feed ingredients, mineral salts in water.**

Antibiotic use should not, however, be seen in isolation from the disciplines of animal management, animal welfare, husbandry, hygiene, nutrition, immunology and vaccination. Diseases must be controlled to reduce the need for antibiotic use and they can only be controlled successfully by an holistic approach.

Use of the right antibiotic

Label instructions should be carefully followed and due attention paid to species and disease indications and contra-indications, dosage regimen, withdrawal periods, and storage conditions. Off-label use of antibiotics should be limited to cases where no other suitable product is available and carefully justified, for instance as part of the written prescription.

Dosage regimen

It is essential to administer the selected antibimicrobial agent in accordance with the recommended dosage regimen and recommended route to avoid administration of sub-therapeutic doses, which can lead to a lack of efficacy and, in some cases, may increase the risk of resistance. Correct administration will minimise therapy failures and exploit fully the efficacy potential of the product.

Each antibiotic has its own unique pharmacodynamic properties, which are expressed fully when the recommended dosage regimen is applied.

Duration of treatment

Generally the duration of the treatment should be as indicated on the label. Insufficient duration of administration can lead to recrudescence of the infection. This may also increase the likelihood of selecting organisms with reduced sensitivity.

On the other hand, antibiotic use should be stopped as soon as the animal's own host defence system can control the infection itself. Limiting the duration of use to only that required for therapeutic effect will minimise the exposure of the bacterial population to the antibiotic. Thus, the adverse effects on the surviving micro-organisms are minimised.

Group medication

In some classes of livestock, like fish, pigs or poultry, if a number of animals in a group have overt signs of disease, both sick and healthy animals will usually need to be treated with therapeutic levels of an antibiotic. This is intended to cure the clinically

affected animals, reduce the spread of the disease and prevent clinical signs appearing in the remainder.

Strategic medication

It is recognised that strategic medication may be appropriate in certain precisely defined circumstances. However, this should be part of an integrated disease control programme and the need for such medication should be regularly re-ascertained.

The use of antibiotics in the absence of clinical disease or pathogenic infections should be restricted to situations where past experience indicates that the group of animals may develop the disease if not treated is high. In addition, long-term administration to prevent disease should not be practiced without a clear medical justification.

Each practice should develop a written policy or protocol covering the circumstances in which this is considered appropriate.

Prescribing, delivering and record keeping

All prescribing of antibiotics should be for animals under the care of the prescribing veterinarian.

All therapeutic antibiotics should be supplied by, or with a prescription from a veterinary surgeon. Records of all antibiotics supplied and administered should be kept by the prescriber, the supplier and the end-user.

If part of the treatment regimen is to be undertaken by the animal caretaker, he/she should be given written instructions on dosage, duration of treatment and if appropriate, withdrawal period. The veterinarian should ensure that the animal caretaker has understood fully the instructions. Quantities of antibiotic left with the animal caretaker should correctly reflect the needs, to avoid an oversupply.

Veterinarians should advise the animal caretaker about the disposal of unused antibiotics and containers, in accordance with local requirements.

Errors in antibiotic usage:

- **Incorrect diagnosis**
- **Ineffective levels of the appropriate products are administered**
- **A product that has no established specific effectiveness is prescribed**
- **Treatment of uncomplicated viral infections**
- **Antibiotic therapy is changed too rapidly and incorrectly, assuming therapeutic failure prior to correcting all contributing factors**
- **Non compliance with label or written instructions**

Final Considerations

It is difficult, if not impossible, to have a set of guidelines, which could be applied universally. These general principles therefore only cover the basic principles on the prudent use of antibiotics and have been drawn up in the light of the current state of knowledge. Further work is now required to transform these basic principles into national, local or practice guidelines.

However, when developing such guidelines, species-specific guidelines or formularies, caution should be made not to interpret these principles too restrictively. Prescribing and supervising veterinary surgeons must retain a reasonable freedom of professional judgement.

In addition, it will also be necessary to discuss further a number of items to better understand the problem of antibiotic resistance and of its impact on human and animal health. More data must be generated to fully appreciate the risk associated with the use of antibiotics and to develop appropriate risk management strategies.

Co-ordinated susceptibility surveillance

Good data on antibiotic resistance are lacking. Furthermore, when data are available, they are difficult to compare because of the different methods and different breakpoints used.

Surveillance should target micro-organisms of both veterinary and public health importance. Data from diagnostic laboratories, with collection of samples from pathogenic specimens, have an inherent bias towards a higher percentage of resistant strains than specimens collected prior treatment. Therefore, it is encouraged to also gather data from samples collected at random from farms, slaughterhouses, or food in order to investigate the prevalence of resistance in veterinary pathogens, zoonotic

pathogens and sentinel organisms.

The results of such surveillance schemes should be provided to the prescribing and the supervising veterinary surgeons, which will allow the modification of antibiotic usage whenever necessary.

Monitoring of antibiotic usage

It is also necessary to collect data on consumption of antibiotics to establish:

- *Whether links between antibiotic consumption and resistance trends can be made;*
- *Whether guidelines on the prudent use of antibiotics are correctly implemented and effective.*

The sources and classification of the raw data should be considered and standardised. Technical units of measurement allowing the safe comparisons of incidence of use over time and per animal species need to be developed.

Alternatives to antibiotics and integrated disease control programme

Finally, the importance to develop systematic preventive measures to reduce the need to use antibiotics must be stressed again. Prevention is better than cure.

In food animals, antibiotic use should always be part of, and not a replacement for, integrated disease control programmes, such as Health Heard Surveillance Programmes. These programmes are likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination, etc…

Continued antibiotic use in such control programme should be regularly assessed as to effectiveness and whether their use can be reduced or stopped.

Antibiotics need to be used with care to maintain their efficacy.

Association des Médecins Vétérinaires du Grand-Duché de Luxembourg

British Veterinary Association

Bulgarian Veterinary Association

Bundestierärztekammer

Bundeskammer der Tierärzte Oesterreichs

Chamber of Veterinary Surgeons of the Czech Republic

Chamber of Veterinary Surgeons of the Slovak Republic

Consejo General de Colegios Veterinarios de España

Croatian Veterinary Society

Den Danske Dyrlaegeforening

Den Norske Veterinärförening

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Federazione Nazionale degli Ordini Dei Veterinari Italiani

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Ordem dos Medicos Veterinarios

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Panhellenic Union of State Veterinary Officers

Polish National Veterinary Chamber

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