

Prudent use guidelines: a review of existing veterinary guidelines

C.J. Teale⁽¹⁾ & G. Moulin⁽²⁾

(1) Animal Health and Veterinary Laboratories Agency (Shrewsbury office), Kendal Road, Harlescott, Shrewsbury, SY1 4HD, United Kingdom

(2) French Agency for Veterinary Medicinal Products/French Agency for Food, Environmental and Occupational Health and Safety (Anses), La Haute Marche, B.P. 90203, 35302 Fougères, France

Summary

The World Organisation for Animal Health (OIE) *Terrestrial Animal Health Code* considers the prudent use of antimicrobial agents in veterinary medicine to comprise a series of practical measures and recommendations which confer benefits to animal and public health while preserving and maintaining the therapeutic efficacy of antimicrobials. This paper reviews some of the main veterinary prudent use guidelines which have been published in English and the responsibilities of those involved at all levels in the administration of antimicrobials to animals, including national regulatory authorities. The OIE guidelines are considered comprehensive and cover all of those levels, from regulatory authorities to veterinarians and food producers. Guidelines produced by national authorities, professional veterinary associations or farming associations and which are targeted at particular individuals, for example veterinarians or food animal producers, will, obviously, restrict their coverage to those aspects considered relevant for their target audience.

Keywords

Antimicrobial resistance – Guidelines – Prudent use – Resistance – Responsible use – Veterinary medicine.

Introduction

The World Organisation for Animal Health (OIE) has recognised the need to work on the containment of antimicrobial resistance since 1997, in order to find an appropriate balance between the need to use antimicrobials to promote animal health and welfare and the risk of developing antimicrobial resistance. It is important to work towards the containment of resistance from both the public and animal health perspectives. Regulatory authorities and international organisations that work in this area have important responsibilities, and guidelines for the prudent use of antimicrobials have been introduced and developed by a number of organisations.

In 2003, the OIE published a series of 'International Standards on Antimicrobial Resistance' (24). These standards include a chapter entitled: 'Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine', drawn from the *Terrestrial Animal*

Health Code (Terrestrial Code), as well as a series of chapters on prudent antimicrobial use and containment of resistance. The relevant chapter of the OIE *Terrestrial Code* defines the prudent use of antimicrobial agents in veterinary medicine as comprising a series of practical measures and recommendations which confer benefits to animal and public health whilst preserving and maintaining the therapeutic efficacy of antimicrobials. This chapter (26) lists the responsibilities of those involved at all stages in the use and regulation of use of antimicrobials in animals and recommends that veterinary professional organisations develop species-specific clinical practice guidelines for their members on the responsible use of antimicrobials. A number of codes of practice have been developed by different organisations. Thus, the development of formularies, which has occurred in some countries (for example, the Netherlands), can also be encompassed by the term 'prudent use'. It is not possible within the scope of this document to review all of the guidelines which have been published. Rather, this paper

seeks to review the main guidelines which have been published in English. The terms 'responsible use' and 'prudent use' are considered synonymous in this review.

Definitions and descriptions of prudent use

The OIE *Terrestrial Code*, 2008 (26), considers the prudent use of antimicrobial agents in veterinary medicine to comprise a series of practical measures and recommendations which confer benefits to animal and public health whilst preserving and maintaining the therapeutic efficacy of antimicrobials. The World Health Organization (WHO) defines the prudent use of antimicrobials as usage of antimicrobials which maximises therapeutic effect and minimises the development of antimicrobial resistance (23).

Prudent use, therefore, includes a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals to:

- maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals, with the purpose of optimising both their efficacy and safety
- comply with the ethical obligation and economic need to keep animals in good health
- prevent or reduce, as far as possible, the transfer of microorganisms (with their resistance determinants) within animal populations
- prevent or reduce the transfer of resistant microorganisms or resistance determinants from animals to humans
- maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of these antimicrobials
- prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL)
- protect consumer health by ensuring the safety of food of animal origin with respect to residues of antimicrobial drugs and the ability to transfer antimicrobial-drug-resistant microorganisms to humans.

The OIE *Ad hoc* Group of Experts on Antimicrobial Resistance describes responsible use as follows (5):

a) it represents the scientific and technically directed use of these compounds that are the responsibility of professionals with the required expertise

b) it is part of good veterinary and animal husbandry practice and takes into consideration disease prevention practices, such as the use of vaccination and improvements in husbandry conditions, when disease problems become evident

c) it aims to reduce the use of antimicrobial agents to their approved and intended uses

d) it takes into consideration on-farm sampling and testing of isolates from food-producing animals during their production (where appropriate), and makes adjustments to therapy when problems become evident

e) it should be based on the results of resistance surveillance and monitoring (bacterial cultures and antimicrobial sensitivity testing)

f) it is aimed at all the relevant professionals, including the following:

- administrative and scientific authorities
- the veterinary pharmaceutical industry
- distributors and others handling antimicrobials
- veterinarians, pharmacists and livestock-producers.

The Clinical Prescribing Subgroup (CPSG) of the Interdepartmental Steering Group on Antimicrobial Resistance, part of the United Kingdom (UK) Department of Health (8), considered prudent use to be the use of antimicrobials in the most appropriate way for the treatment or prevention of human infectious diseases, having regard to the diagnosis (or presumed diagnosis), evidence of clinical effectiveness, likely benefits, safety, cost (in comparison with alternative choices), and propensity for the emergence of resistance. The most appropriate way was considered to imply that the choice, route, dose, frequency and duration of administration had been rigorously determined. Prudent use was considered synonymous with optimal use.

Prudent use, by definition, includes the minimisation of misuse and overuse.

The European Platform for the Responsible Use of Medicines in Animals (EPRUMA) aims to promote the responsible use of medicines in animals in the European Union (EU) in order to maintain efficacy and both prevent and minimise adverse reactions. It involves veterinarians, farmers, feed manufacturers, pharmaceutical manufacturers and pharmacists and has developed framework documents available in a number of European languages (12).

Responsibilities in relation to prudent use

The relevant chapter of the *Terrestrial Code* (26) lists the responsibilities of all those involved at all stages in the production, control, distribution and use of veterinary antimicrobials. The national regulatory authority has an important role; however, the guideline is also addressed to the veterinary pharmaceutical industry, wholesale and retail distributors, veterinary practitioners, and food-animal producers. The respective roles and responsibilities of these groups are defined.

Regulatory authorities

National regulatory authorities are responsible for granting marketing authorisations. The terms under which these authorisations are granted are an important tool for promoting subsequent prudent use and for providing appropriate information to the veterinarians administering the antimicrobials. (For countries lacking the resources necessary to develop a national regulatory authority, the *Terrestrial Code* outlines the relevant measures which should be undertaken. It stresses that all countries should take active measures to combat the use of unlicensed and counterfeit antimicrobials.)

The pharmaceutical industry is responsible for submitting the relevant information needed to grant a marketing authorisation to ensure the quality, safety and therapeutic efficacy of the pharmaceutical product. The *Terrestrial Code* (26) states that an assessment should be made of the potential risks and benefits to both animals and humans from using the product in food-producing animals. Differing dosages should be covered and the findings should not be generalised by antimicrobial class.

Quality is considered to include compliance with good manufacturing processes and ensuring that the stability of antimicrobials in the marketed dosage formats is maintained until the stipulated expiry date, under recommended storage conditions.

Assessment of the potential of antimicrobials to select for resistance may be requested by the regulatory authorities and should ideally relate to the target species under the intended conditions of use.

The establishment of an acceptable daily intake or MRL for an antimicrobial should include an evaluation of any potential biological effects on the intestinal flora of humans. In addition, environmental impact should be assessed and efforts made to ensure that any adverse environmental effects of antimicrobial use are restricted to a minimum.

Therapeutic efficacy is determined by measures including pre-clinical trials, which should establish:

- the activity of antimicrobials against pathogens and commensals
- the ability of the antimicrobial to select for resistance both *in vitro* and *in vivo*
- the occurrence of pre-existing resistance.

These measures should also establish an appropriate dosage regime, ensuring therapeutic efficacy but minimising the development of antimicrobial resistance. Clinical trials should be performed to confirm the validity of therapeutic indications and the suitability of the dosage regimes established in the pre-clinical trials.

The OIE chapter (26) stipulates that a summary of product characteristics should be established for each veterinary antimicrobial product, containing the information necessary for its appropriate use. This summary should include the active antimicrobial constituent, antimicrobial class, pharmacological properties, any potential adverse effects, target animal species and type, therapeutic indications, target microorganisms, dosage and route of administration, withdrawal periods, incompatibilities, shelf life, operator safety, precautions and safe disposal. Finally, it should also include information on conditions of use that may be relevant to the potential for selection of resistance.

Post-marketing surveillance for antimicrobial resistance is also mentioned by the OIE. This can fall into three categories:

- pharmaco-vigilance schemes (including monitoring for lack of efficacy)
- general surveillance for antimicrobial resistance, as recommended in the *Terrestrial Code* (25, 27)
- specific surveillance to assess the impact of using a particular antimicrobial.

In terms of the supply and administration of antimicrobials used in veterinary medicine, this chapter stipulates that all antimicrobial agents used in animals should be prescribed by a veterinarian or other authorised person, and supplied only through authorised distribution systems. Administration to animals should similarly be performed by veterinarians, or under their supervision or under the supervision of another authorised person. The relevant authorities should develop procedures for the safe collection and destruction of unused or expired antimicrobials.

Advertising antimicrobials should be controlled in accordance with a code of advertising standards. It should comply with marketing authorisations and be restricted to authorised professionals.

Regulatory authorities also have a role in training. Training should focus on:

- information on disease prevention and management strategies
- the ability of antimicrobials to select for resistance in food-producing animals
- the need to observe recommendations for prudent use.

Finally, regulatory authorities should encourage public and industry-funded research.

The veterinary pharmaceutical industry

The *Terrestrial Code* also describes the responsibilities of the veterinary pharmaceutical industry. These include complying with the requirements of the regulatory authority, supplying any information requested by that authority, ensuring that this information is of good quality and implementing pharmaco-vigilance programmes (and, when requested, specific surveillance for antimicrobial resistance). The *Terrestrial Code* (26) also covers the marketing and export of antimicrobials, the need for authorised distribution, quality certificates and the need to provide the regulatory authority with information on the amounts of antimicrobials marketed. Advertising should be within the terms of the granted authorisation and advertising directly to food-animal producers is discouraged. The veterinary pharmaceutical industry should also participate in training and contribute to research.

Wholesale and retail distributors

The *Terrestrial Code* also considers the responsibilities of wholesale and retail distributors (26). Antimicrobials should only be dispensed on prescription by a veterinarian or suitably trained person, in accordance with national legislation. Appropriate records should be kept and distributors should also be involved in training.

The veterinarian

The *Terrestrial Code* considers that the veterinarian's responsibilities include the prevention, identification and treatment of animal disease, as well as the promotion of both public and animal health and animal welfare (26). It notes that sound animal husbandry methods, hygiene procedures and vaccination strategies can help to minimise the need for antimicrobial treatment. Veterinarians should only prescribe for animals in their care.

Antimicrobial use should be preceded by clinical examination and should be appropriate for the condition

detected. Antimicrobial selection may be based on clinical experience, the expected susceptibility of the target pathogen, the route of administration, expected activity at the site of infection and the epidemiological history of the production unit, especially previous antimicrobial resistance profiles. A recurrence of disease or the failure of first-line treatment should ideally be followed by diagnostic tests to determine second-line treatment. Treatment should be directed at those pathogens likely to be the cause of infection. The *Terrestrial Code* acknowledges that, on occasion, a group of animals which may have been exposed to a pathogen may need to be treated without recourse to an accurate diagnosis or susceptibility testing, to prevent the development of clinical disease and for animal welfare reasons (26). It comments that the use of combinations of antimicrobials should be scientifically supported.

Veterinary prescriptions should include treatment details and the withdrawal period. 'Off-label usage' (i.e. use in non-target animal species or for clinical indications not specified in the authorisation) should be in accordance with national legislation. The *Terrestrial Code* considers the veterinarian to be responsible for defining conditions of prudent use in cases of off-label usage. Appropriate records should be kept of all prescriptions, including the response to treatment. Adverse reactions, including lack of response, should be reported to the regulatory authorities. Farm records should be used to review and evaluate treatment regimes.

Veterinary professional organisations should participate in training programmes and develop guidelines on the responsible use of antimicrobials for their members.

Food-animal producers

Food-animal producers, with the assistance of a veterinarian, are considered by the *Terrestrial Code* to be responsible for implementing health and welfare programmes on their farms to promote animal health and food safety (26).

Food-animal producers should draw up preventive health plans with the attending veterinarian (for example, feedlot health plans, mastitis control plans, vaccination programmes, etc.). They should use antimicrobial agents only on prescription, and according to the provisions of the prescription in the intended species. They should isolate sick animals, when appropriate, to avoid the transfer of pathogens. They should comply with the storage conditions of the antimicrobial specified in the accompanying leaflet and package insert, and with the recommended withdrawal period to ensure that residue levels in animal-derived food do not present a risk for the consumer. The hygiene conditions of the animals

undergoing treatment should be addressed as appropriate, as well as the possibility for transfer of microorganisms during contact between these animals and people. Surplus antimicrobials should be disposed of safely and medicines should only be used before the expiry date, for the condition for which they were prescribed. Appropriate records should be kept of bacteriological and susceptibility tests and of all medicines used. The effectiveness of therapy should be assessed and recurrent problems discussed with the responsible veterinarian.

The World Health Organization (23) considers it the responsibility of food-animal producers to ensure that their production systems promote animal health and welfare. Antimicrobial usage, if necessary, should always be a part of, not a replacement for, an integrated animal health programme and such a programme is likely to involve hygiene and disinfection procedures, biosecurity measures and reviewing management and husbandry, including factors such as changes in stocking rate and vaccination, as well as other relevant components.

In its guidelines, the Responsible Use of Medicines in Agriculture Alliance (RUMA) (18) emphasises biosecurity as a herd-management strategy that is designed to minimise the potential for introducing disease-causing organisms onto farms.

Codex Alimentarius Commission

The Codex Alimentarius Commission (Codex) makes a distinction between responsible use guidelines and national/regional treatment guidelines. Both include non-regulatory controls that apply to the use of antimicrobial agents (10). National/regional guidelines target a specific antimicrobial-resistance, food-safety issue. They are considered to include animal species-specific guidelines, developed to address a specific disease or infection, and can be implemented as a voluntary step before regulatory controls are introduced, such as withdrawing an antimicrobial or restricting its use. Responsible use guidelines are considered to contain broad principles applicable to the administration of antimicrobials. Some of these guidelines may be species-specific. They include the Codex 'Code of Practice to Minimize and Contain Antimicrobial Resistance' (9) and the OIE *Terrestrial Code* (26). These documents contain similar information, reflecting the close collaboration between these international organisations.

The Codex (10) also describes examples of regulatory and non-regulatory risk management options which may be adopted to control foodborne antimicrobial resistance risks. Many of these consist of additional conditions for prudent use and authorisation, as set out in the relevant

chapter of the *Terrestrial Code* (26). An additional area specifically addressed is that of waste management (of human sewage and animal manure). The *Terrestrial Code* also records that developing codes of practice for the use of antimicrobials in animal husbandry is a risk management option (27).

Responsible use in aquaculture

The OIE recently adopted a guideline for responsible and prudent use of antimicrobial agents in aquatic animals. This guideline, based on the equivalent OIE principles for terrestrial animals, recognises the specific needs of aquaculture; in particular, the involvement of an aquatic animal health professional in prescribing or recommending the use of antimicrobials. This approach reflects the reality of aquatic animal production, especially in developing countries (28).

The responsible use of antibiotics in aquaculture has been reviewed by the Food and Agriculture Organization of the United Nations (FAO) (19). There are some prudent use considerations for aquaculture that do not apply in terrestrial farming; for example, large commercial fish ponds may not be drained properly, so high levels of antimicrobials will remain for subsequent batches of new fish. The integrity of the environment is particularly important when fish are raised in open-water systems. The FAO report makes a series of recommendations, including the principle that, in aquaculture, the responsible use of antimicrobials is to reduce their use to therapeutic use alone, and to replace prophylactic use with good husbandry practices, adequate hygiene and vaccination where appropriate. The report notes that producers should promote education and training in proper usage.

The American Veterinary Medical Association (AVMA) has approved a series of guidelines which apply primarily to finfish (4). These include the recommendation not to use antimicrobial drugs prophylactically. The guidelines explain that no antimicrobial drugs are approved for disease prevention in food fish and veterinarians should actively discourage any use of antimicrobials in this way.

Common principles in existing guidelines

In a report called, 'Judicious use of antimicrobial agents' (16), 12 existing prudent use guidelines were reviewed and 22 common principles identified and listed. Only three principles were identified that were not considered to be

covered by the relevant chapter of the OIE *Terrestrial Code* (26); namely:

- using alternatives to antimicrobial agents as an adjunct to good husbandry practices
- selecting a therapeutic objective and plan: the development of outcome objectives and plans for implementation
- compliance: ensuring that instructions for antimicrobial use are implemented appropriately.

The OIE guidelines should therefore be considered relatively comprehensive and as covering all those involved in the administration of antimicrobials to animals, from regulatory authorities to food producers. Guidelines produced by national authorities, professional veterinary associations or farming associations, and which are targeted at particular individuals, for example, veterinarians or food animal producers, obviously restrict their coverage to those aspects considered relevant for their target audience.

The 2000 WHO report (23) additionally comments that guidelines on the prudent use of antimicrobials in animals should be readily accessible, developed with multidisciplinary involvement, subject to peer review, compatible with existing regulations, and should be evaluated and revised at regular intervals.

Guidelines aimed at veterinarians usually develop these ideas further. For example, where the *Terrestrial Code* states that treatment should be directed at pathogens likely to be the cause of infection, the Federation of Veterinarians of Europe (FVE) (13) more explicitly states that, 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. However, the FVE also acknowledges that consideration should be given to the potential consequences of resistance to the specific substance in question. Similarly, the AVMA guidelines (3) prefer the use of narrow-spectrum antimicrobials whenever appropriate and the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (14) similarly states that the spectrum of antibiotic used should be the narrowest to cover the known or likely pathogens.

Most guidelines do not stipulate an average or expected duration of treatment, reflecting the wide diversity of infections that such guidelines must address. However, JETACAR (14) advises that antimicrobial treatment should not exceed seven days, unless there is proof that this duration is inadequate. The FVE (13) considers that prolonged oral use should be avoided, since most of the concerns about resistance are associated with the selection

and transfer of resistant bacteria that inhabit the gut. ‘As little as possible, as much as necessary,’ is stated as the guiding principle of EPRUMA (12) and RUMA (18).

In the United States, the Food and Drug Administration (FDA) Center for Veterinary Medicine recommends two additional principles for the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals (21). The first is that the use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary to ensure animal health. (In light of the risk that antimicrobial resistance poses to public health, the FDA believes that the use of medically important antimicrobial drugs in food-producing animals for production purposes – e.g. to promote growth or improve feed efficiency – represents an injudicious use of these important drugs.) The second is that the use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.

Formularies

Some countries have developed formularies indicating the most appropriate antimicrobials for treating animal diseases, such as the Netherlands and the UK for companion animals (17). The World Health Organization (23) states that locally derived, species-specific treatment guidelines should include a list of antimicrobials or conditions commonly presenting in clinical practice, and offer a rational treatment choice based on:

- scientific data and knowledge
- the disease and resistance situation
- practical experience
- human health concerns.

If several antimicrobials can be used, guidelines should make recommendations on which antimicrobials should be given. However, the clinical experience and judgement of the practitioner should determine the final choice.

The American Association of Avian Pathologists’ ‘Guidelines to judicious use of therapeutic antimicrobials in poultry’ (1) divide antimicrobials into three classes, based on their importance and use in both humans and poultry. Class I antimicrobials are important in human medicine and should be held in reserve for the treatment of poultry while options in the other classes are considered. These guidelines also provide antimicrobial recommendations according to class for various disease conditions that affect poultry.

Farm assurance schemes/ codes of practice

Farm assurance schemes and codes of practice should promote the responsible and prudent use of antimicrobials (18). Some food retailers have incorporated the prudent use guidelines, or aspects of those guidelines, into their company policies. There are a number of examples but, to cite one, McDonald's has a global policy on antibiotic use in food animals (15) which draws on existing frameworks, including the World Veterinary Association (WVA) 'Prudent use of antibiotics: global basic principles' (29) and AVMA's 'Judicious therapeutic use of antimicrobials: general principles' (3). In its guidelines, RUMA states that farm assurance schemes have a very important role to play in promoting the responsible use of antimicrobials on farms (18).

Species-specific guidelines

The FVE has acknowledged the difficulty in developing guidelines which can be applied universally across all species (13). The British Veterinary Association (BVA) (7) has developed recommendations for the use of antimicrobials peri-operatively.

The American Association of Feline Practitioners/American Animal Hospital Association 'Basic guidelines of judicious therapeutic use of antimicrobials' list a number of conditions in domestic cats where bacterial infection is unlikely and thus antimicrobial treatment not usually beneficial (2). For example, they state that most cases of feline lower urinary tract disease do not involve bacterial infection and, in such cases, antimicrobials are not indicated. There are direct parallels here with some medical guidelines; for example, the Standing Medical Advisory Committee report, 'The path of least resistance', which recommends no prescribing of antimicrobials for simple coughs and colds (20).

With regard to the fluoroquinolones and third-/fourth-generation cephalosporins, the BVA guideline states that these should not be administered systemically to groups or flocks of animals, except in very specific situations, and special attention should be given to the risk of antimicrobial resistance as part of the benefit/risk assessment (7).

The British Small Animal Veterinary Association (BSAVA) guideline on companion animals (6) considers there to be a strong argument that 'last resort' antimicrobials, such as imipenem and vancomycin, should not be used for veterinary patients.

Measuring the impact of guidelines

The Codex Alimentarius Commission, in its draft guideline for risk analysis of foodborne antimicrobial resistance (10), stipulates that risk managers should establish a process to monitor and review whether risk management measures have been properly implemented and whether or not the outcome has been successful. Risk management options may, of course, include the adoption of prudent use guidelines. Food safety measurements which could be considered to evaluate the effectiveness of risk management options include not only the prevalence of antimicrobial resistance in animals on the farm and at slaughter, as well as in animal-derived products during manufacture/retail and in humans, but also any adverse effects on public health (e.g. treatment failure, prolonged duration of disease) attributable to foodborne pathogens. Trends in the non-human use of medically important antimicrobials may also be considered. The Codex (10) and *Terrestrial Code* (25) both comment that national surveillance programmes can act as a base-line, against which risk management options can be evaluated.

The CPSG of the UK Interdepartmental Steering Group on Antimicrobial Resistance (8), considered whether the changing pattern of prescribing might affect some outcomes. It stated that the investigation of outcomes – both the gains and the possible losses from using or not using antibiotics, including treatment failures and the incidence of chronic infections or mortality in common conditions – is suitable for special study.

The Food and Drug Administration Center for Veterinary Medicine 'Guidelines on judicious use of antimicrobials for beef cattle veterinarians' (22) uses the bovine respiratory disease complex to show how treatment records may be used to analyse aspects of production, such as whether too many cattle are being treated.

Escher *et al.* (11) described the use of antimicrobials in a veterinary teaching hospital for companion animals in Italy and compared the recorded use with prudent use recommendations. They found that antimicrobials belonging to the last-generation classes were rather frequently used as a first-line therapy and there was a low use of laboratory-testing support.

Off-label usage

The *Terrestrial Code* considers that 'off-label usage' (i.e. usage in non-target animal species or for clinical indications not specified in the authorisation) should be in

accordance with national legislation and that the veterinarian is responsible for defining the conditions of prudent usage in such cases (26). The FVE considers that 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 (13). The Federation also states that indiscriminate off-label use should be avoided (13). Meanwhile, AVMA stipulates in its guidelines (3) that extra-label antimicrobial therapy must be prescribed only in accordance with the relevant legislation.

The WVA, the International Federation of Agricultural Producers (IFAP) and the World Federation of the Animal Health Industry (COMISA) (29) consider that off-label use of antibiotics should be exceptional and always take place under the professional supervision of a veterinarian; that off-label use should be carefully justified; for instance, as part of the written prescription and that, where legal provisions exist, these should serve as a basis for guiding the conditions of off-label use.

The World Health Organization (23) considers that, in exceptional circumstances, where no antimicrobial drug has been authorised for use in a species or for a specific indication, then a product authorised for another indication or another species may be used under direct veterinary supervision. It further comments that the relevant regulatory authorities that oversee the use of antimicrobials in food animals should consider restricting the off-label use of those drugs deemed highly important in human medicine.

The European Platform for the Responsible Use of Medicines in Animals (12) refers to the 'cascade' and states that, in exceptional cases, where no medicine is authorised, the veterinarian may use, for example, products that are authorised in other EU countries or for other animal species. In these cases, the veterinarian must follow specific steps (the so-called 'cascade'), to ensure that there is no risk for the animals concerned or for consumers of food products of animal origin.

The BVA has made some specific recommendations (7); in particular that, wherever possible, fluoroquinolones and third-/fourth-generation cephalosporins should not be used off-label; they should be reserved for clinical conditions that respond poorly to other classes of antimicrobials and when susceptibility testing has been carried out.

Prophylactic or strategic medication

In its guidelines, the FVE states (13) that the use of antibiotics in the absence of clinical disease or pathogenic

infections should be restricted to situations where past experience indicates that there is a high risk of the group of animals developing the disease if they are not treated. In addition, long-term administration to prevent disease should not be practised without clear medical justification, and continued antibiotic use should be regularly assessed for effectiveness and to gauge whether such use can be reduced or stopped. Similarly, WHO (23) considers that routine prophylactic use of antimicrobials should never be a substitute for good animal health management and that prophylactic use of antimicrobials in control programmes should be regularly assessed, both for effectiveness and to see whether such use can be reduced or stopped. Furthermore, efforts to prevent disease should continuously strive to reduce the need for the prophylactic use of antimicrobials.

The BVA describes an eight-point plan for the responsible use of antimicrobials in veterinary practice (7). One of the eight points relates to minimising the prophylactic use of antimicrobials, advising that these should only be used when the animals are at risk and when there is evidence that such use reduces morbidity/mortality. Furthermore, such use should be regularly assessed, written protocols should be developed, when it is considered appropriate, and susceptibility trends should be monitored. The BVA considers that the use of antimicrobials to prevent disease can only be justified where it can be shown that a particular disease is present on the premises and spreading to other animals on the unit, or is likely to do so. The BVA also states that the prophylactic use of antimicrobials is never a substitute for good management.

The BSAVA recommends that prophylactic use of antimicrobials should generally be avoided (6). However, it considers that there are some situations where prophylactic use may be merited, including high-risk, immunosuppressed patients and peri-operatively. The BSAVA comments that it is difficult to define precisely which surgical procedures merit prophylactic antimicrobial use, but also that complex procedures where the consequences of infection would be catastrophic clearly do merit prophylactic antimicrobial use.

Discussion

Prudent use guidelines attempt to strike an appropriate balance between the need to use antimicrobials for the treatment of animal disease and for animal welfare, and the need to minimise the emergence of antimicrobial resistance in target and non-target microorganisms.

A major principle of prudent use guidelines is that antimicrobials should not be used to compensate for poor or deficient husbandry methods. In this regard, WVA, IFAP

and COMISA (29) state that antibiotics are a complement to good husbandry practices and should never be used to make up for or mask bad farm and veterinary practices. This review of some of the existing prudent use guidelines has described some interesting parallels between the guidelines that are evolving to address the responsible administration of antimicrobials to both humans and animals. For example, the American Association of Feline Practitioners/American Animal Hospital Association 'Basic guidelines of judicious therapeutic use of antimicrobials' (2) list a number of conditions in domestic cats where bacterial infection is unlikely and this directly parallels certain medical guidelines, such as the Standing Medical

Advisory Committee's report, 'The path of least resistance', which recommends no prescribing of antimicrobials for simple coughs and colds (20). Prudent use guidelines are an important part of the armoury of risk management options to assist in the control of antimicrobial resistance.

Acknowledgements

The authors are grateful to Dr Stephen Page for sharing his review of prudent use guidelines (16), prior to its publication.



Lignes directrices sur l'utilisation prudente des agents antimicrobiens : tour d'horizon des lignes directrices vétérinaires existantes

C.J. Teale & G. Moulin

Résumé

Le *Code sanitaire pour les animaux terrestres* de l'Organisation mondiale de la santé animale (OIE) préconise une utilisation prudente des agents antimicrobiens en médecine vétérinaire, à travers une série de mesures et de recommandations concrètes destinées à servir les intérêts de la santé publique et de la santé animale tout en préservant et en maintenant l'efficacité thérapeutique des antibiotiques utilisés. Les auteurs examinent les principales lignes directrices vétérinaires qui ont été publiées en anglais sur l'utilisation prudente des antibiotiques, et font le point sur les responsabilités respectives, à différents niveaux, des personnes qui s'occupent de l'administration des antimicrobiens aux animaux, y compris les autorités nationales en charge de la réglementation. Les lignes directrices de l'OIE sont très complètes et abordent tous les niveaux de responsabilité, depuis les autorités en charge de la réglementation jusqu'aux vétérinaires et aux producteurs de denrées alimentaires. Quant aux lignes directrices élaborées par les autorités nationales, par les associations vétérinaires professionnelles ou par les groupements d'éleveurs, elles sont destinées à un groupe particulier de professionnels, par exemple les vétérinaires ou les producteurs d'animaux destinés à la consommation humaine, et de ce fait leur portée se limite aux aspects jugés pertinents pour le public auquel elles s'adressent.

Mots-clés

Antibiorésistance – Lignes directrices – Médecine vétérinaire – Utilisation prudente – Utilisation responsable.



Repaso de las directrices veterinarias existentes en materia de uso prudente de agentes antimicrobianos

C.J. Teale & G. Moulin

Resumen

En su *Código Sanitario para los Animales Terrestres*, la Organización Mundial de Sanidad Animal (OIE) entiende el uso prudente de agentes antimicrobianos en medicina veterinaria como un conjunto de medidas y recomendaciones prácticas que son beneficiosas para la salud pública y la sanidad animal y a la vez preservan y mantienen la eficacia terapéutica de esos agentes. Los autores pasan revista a las principales directrices publicadas en inglés acerca del uso prudente en veterinaria y exponen las responsabilidades de todas las instancias que intervienen a cualquier nivel en la administración de antimicrobianos a los animales, comprendidos los organismos nacionales de reglamentación. Las directrices de la OIE, consideradas exhaustivas, cubren todos los niveles de actuación, desde los citados organismos hasta los productores, pasando por los veterinarios. Obviamente, toda directriz elaborada por autoridades nacionales, colegios veterinarios o asociaciones de productores que vaya dirigida a un colectivo determinado, por ejemplo veterinarios o productores de animales para el consumo humano, se circunscribirá a los aspectos que se consideren pertinentes para esos destinatarios.

Palabras clave

Directrices – Medicina veterinaria – Resistencia a los antimicrobianos – Uso prudente – Uso responsable.



References

1. American Association of Avian Pathologists (2005). – Guidelines to judicious use of therapeutic antimicrobials in poultry. Available at: www.avma.org/issues/policy/jtua_poultry.asp (accessed on 1 September 2011).
2. American Association of Feline Practitioners/American Animal Hospital Association (2009). – Basic guidelines of judicious therapeutic use of antimicrobials. Available at: www.avma.org/issues/policy/jtua_aafp_aaha.asp (accessed on 1 September 2011).
3. American Veterinary Medical Association (2008). – Judicious use of antimicrobials. Available at: www.avma.org/issues/policy/jtua.asp (accessed on 1 September 2011).
4. American Veterinary Medical Association (2008). – Judicious use of antimicrobials for treatment of aquatic animals by veterinarians. Available at: www.avma.org/issues/policy/jtua_fish.asp (accessed on 1 September 2011).
5. Anthony E., Acar J., Franklin A., Gupta R., Nicholls T., Tamura Y., Thompson S., Threlfall E.J., Vose D., van Vuuren M. & White D.G. (2003). – Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine. In OIE International Standards on Antimicrobial Resistance 2003. OIE, Paris, 249–266. Available at: www.oie.int/doc/ged/D9769.pdf (accessed on 1 September 2011).
6. British Small Animal Veterinary Association (2012). – Responsible use of antimicrobial agents. Available at: www.bsava.com/Advice/BSAVAGuidetotheUseofVeterinaryMedicines/Prudentuseofantimicrobialagents/tabid/363/Default.aspx (accessed on 1 September 2011).
7. British Veterinary Association (2009). – Responsible use of antimicrobials in veterinary practice: the 8-point plan. Available at: www.bva.co.uk/public/documents/BVA_Antimicrobials_Poster.PDF (accessed on 19 February 2012).

8. Clinical Prescribing Subgroup of the Interdepartmental Steering Group on Antimicrobial Resistance (2001). – Optimising the clinical use of antimicrobials: report from the Clinical Prescribing Subgroup of the Interdepartmental Steering Group on Antimicrobial Resistance. Available at: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4084394 (accessed on 1 September 2011).
9. Codex Alimentarius Commission (CAC) (2005). – Code of practice to minimize and contain antimicrobial resistance. CAC/RCP 61-2005. CAC, Rome. Available at: www.codexalimentarius.net/download/standards/10213/CXP_061e.pdf (accessed on 14 March 2012).
10. Codex Alimentarius Commission (CAC) (2011). – Draft guidelines for risk analysis of foodborne antimicrobial resistance. In Report of the 4th Session of the Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance, 18–22 October 2010, Muju, Republic of Korea. CAC, Rome. Available at: www.cclac.org/documentos/TFAMR/2010/1%20Alinorm/REP11_AMe.pdf (accessed on 1 September 2011).
11. Escher M., Vanni M., Intorre L., Caprioli A., Tognetti R. & Scavia G. (2011). – Use of antimicrobials in companion animal practice: a retrospective study in a veterinary teaching hospital in Italy. *J. antimicrob. Chemother.*, **66**, 920-927.
12. European Platform for the Responsible Use of Medicines in Animals (EPRUMA) (2008). – Best-practice framework for the use of antimicrobials in food-producing animals in the EU. EPRUMA, Brussels. Available at: www.epruma.eu/publications/all-publications.html?start=10 (accessed on 1 September 2011).
13. Federation of Veterinarians of Europe (1999). – Antibiotic resistance and prudent use of antibiotics in veterinary medicine. Available at: www.fve.org/news/publications/pdf/antibioen.pdf (accessed on 1 September 2011).
14. Joint Expert Advisory Committee on Antibiotic Resistance (1999). – The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth Department of Health and Aged Care and Commonwealth Department of Agriculture, Fisheries and Forestry, Canberra. Available at: [www.health.gov.au/internet/main/publishing.nsf/Content/2A8435C711929352CA256F180057901E/\\$File/jetacar.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/2A8435C711929352CA256F180057901E/$File/jetacar.pdf) (accessed on 1 September 2011).
15. McDonald's (2003). – McDonald's global policy on antibiotic use in food animals. Available at: www.keepantibioticsworking.com/new/Library/UploadedFiles/McDonalds_Policy_About_Antibiotics.pdf (accessed on 14 March 2012).
16. Page S.W. (2011). – Judicious use of antimicrobial agents. Principles of appropriate use. A report commissioned by the Australian Chicken Meat Federation. Available at: www.chicken.org.au/files/_system/Document/ACMF_Review-Judicious_Use_of_Antimicrobial_Agents.pdf (accessed on 2 September 2011).
17. Ramsey I. (2008). – British Small Animal Veterinary Association small animal formulary, 6th Ed. BSAVA Publications, Gloucester, United Kingdom.
18. Responsible Use of Medicines in Agriculture Alliance (2005). – Responsible use of antimicrobials in dairy and beef cattle production. Available at: <http://www.ruma.org.uk/antimicrobials.htm> (accessed on 1 September 2011).
19. Serrano P.H. (2005). – Responsible use of antibiotics in aquaculture. FAO Fisheries Technical Paper 469. Food and Agriculture Organization of the United Nations (FAO), Rome. Available at: <ftp://ftp.fao.org/docrep/fao/009/a0282e/a0282e00.pdf> (accessed on 1 September 2011).
20. Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance (1997). – The path of least resistance: main report. Department of Health, London. Available at: www.advisorybodies.doh.gov.uk/smac1.htm (accessed on 1 September 2011).
21. United States Department of Health and Human Services Food and Drug Administration, Center for Veterinary Medicine (CVM) (2010). – The judicious use of medically important antimicrobial drugs in food-producing animals, draft guidance. CVM, Rockville, Maryland. Available at: www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf (accessed on 1 September 2011).
22. United States Department of Health and Human Services Food and Drug Administration, Center for Veterinary Medicine (CVM) (2012). – Judicious use of antimicrobials for beef cattle veterinarians. CVM, Rockville, Maryland. Available at: www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/default.htm (accessed on 1 September 2011).
23. World Health Organization (WHO) (2000). – WHO global principles for the containment of antimicrobial resistance in animals intended for food. In Report of a WHO consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties, 5–9 June, Geneva, Switzerland. WHO/CDS/CSR/APH/2000.4. Available at: whqlibdoc.who.int/hq/2000/who_cds_csr_aph_2000.4.pdf (accessed on 1 September 2011).
24. World Organisation for Animal Health (OIE) (2003). – OIE International Standards on Antimicrobial Resistance. OIE, Paris. Available at: www.oie.int/doc/ged/D9769.pdf (accessed on 1 September 2011).
25. World Organisation for Animal Health (OIE) (2008). – Terrestrial Animal Health Code, Chapter 6.7. Harmonisation of national antimicrobial resistance surveillance and monitoring programmes. OIE, Paris. Available at: www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.7.htm (accessed on 19 February 2012).

26. World Organisation for Animal Health (OIE) (2008). – Terrestrial Animal Health Code, Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine. OIE, Paris. Available at: www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.9.htm (accessed on 19 February 2012).
 27. World Organisation for Animal Health (OIE) (2008). – Terrestrial Animal Health Code, Chapter 6.10. Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals. OIE, Paris. Available at: www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.10.htm (accessed on 19 February 2012).
 28. World Organisation for Animal Health (OIE) (2011). – Aquatic Animal Health Code, Chapter 6.3. Principles for responsible and prudent use of antimicrobial agents in veterinary medicine. OIE, Paris. Available at: www.oie.int/index.php?id=171&L=0&htmfile=chapitre_1.6.3.htm (accessed on 19 February 2012).
 29. World Veterinary Association, the International Federation of Agricultural Producers and the World Federation of the Animal Health Industry (1999). – Prudent use of antibiotics: global basic principles. Available at: www.worldvet.org/sites/worldvet.org/files/manuals/T-3-2.pdf (accessed on 1 March 2012).
-