

JUDICIOUS USE OF ANTIMICROBIAL AGENTS

PRINCIPLES OF APPROPRIATE USE

A report commissioned by the

Australian Chicken Meat Federation

Prepared by

STEPHEN PAGE

Updated

September 2011

Advanced Veterinary Therapeutics
PO Box 905 Newtown 2042 NSW AUSTRALIA
swp@advet.com.au

INTRODUCTION

The primary objective of the Australian chicken meat industry is to produce a healthy food. To achieve this objective, chickens need to be healthy and well cared for; in other words, good farming practices are essential. However, even under perfect farming conditions and with preventative treatments such as vaccines in place, chickens may develop diseases. In instances where no vaccine is available or effective against severe bacterial infection, chickens may have to be treated with therapeutic antibiotics. The industry understands that over time, just as in human health, bacteria may develop resistance to antibiotics to which they are exposed. To address this, the industry has taken steps over recent years to minimise the use of therapeutic antibiotics and to seek alternatives. The industry only uses antibiotics that are registered for use in poultry for meat production and consequently, reflecting APVMA's registration policy, does not use antibiotics with significant applications in human health in long-term preventative treatments.

The chicken meat industry is interested not only in the quantity and type of antimicrobial agent that is used but also in the quality of use of antimicrobial agents. Consequently, the chicken meat industry commissioned a review of the principles of judicious use in order that there would be a basis on which to assess the quality of current prescribing practices.

This document presents a summary of the analysis of the principles of judicious use.

TABLE OF CONTENTS

INTRODUCTION.....	2
ABSTRACT:	4
DEFINITIONS OF PRUDENT, APPROPRIATE AND RESPONSIBLE USE	5
PRINCIPLES OF APPROPRIATE USE	7
REVIEW OF PUBLISHED SETS OF JUDICIOUS USE PRINCIPLES	10
APPENDICES: Details of each guideline on appropriate use	13
WHO (2000)	14
WHO (2000). WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food. Report of a WHO Consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties. Geneva, Switzerland. 5-9 June 2000 WHO/CDS/CSR/APH/2000.4.....	14
McDonald's (2003)	15
McDonald's (2003). McDonald's Global Policy on Antibiotic Use in Food Animals.	15
OIE (World Organisation for Animal Health)	16
Anthony F, Acar J, Franklin A, Gupta R, Nicholls T, Tamura Y, Thompson S, Threlfall EJ, Vose D, van Vuuren M, White DG (2001) Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine. Rev Sci Tech 20:829-839..	16
FVE (1999)	20
FVE (Federation of Veterinarians of Europe) (1999). Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine.....	20
RUMA (2005)	23
RUMA (Responsible Use of Medicines in Agriculture Alliance) (2005). Responsible use of antimicrobials in poultry production. Produced by the Poultry Working Group of the RUMA Alliance. May 1999, Revised September 2005.....	23
AVMA (2007).....	25
AVMA (American Veterinary Medical Association) (2007). Judicious use of Antimicrobials.....	25
WVA (2011).....	26
World Veterinary Association (WVA) (2011). Draft Position on Responsible Use of Antimicrobials.....	26
JETACAR (1999).....	29
JETACAR (1999). The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance. Commonwealth of Australia 1999.	29
Antibiotic Expert Group (2006).....	30
Antibiotic Expert Group (2006). Therapeutic guidelines : antibiotic. 13 th edition, Therapeutic Guidelines Limited, North Melbourne, Victoria	30
Guardabassi & Kruse H (2008)	33
Guardabassi L, Kruse H (2008). Principles of Prudent and Rational Antimicrobial Use in Animals. <i>In</i> Guide to Antimicrobial Use in Animals. Edited by Luca Guardabassi, Rachel Williamson and Hilde Kruse, Blackwell Publishing, Oxford, pp 1-12	33
AVA (2005), AVPA (2001)	35
AVA (Australian Veterinary Association) (2005). Guidelines for Prescribing, Authorising and Dispensing Veterinary Medicines.	35
AVPA (2001). AVPA code of practice for the use of antibiotics in the poultry industry. Endorsed by the Australian Chicken Meat Federation and the Australian Egg Industry Association.	35
EPRUMA (2008).....	37
European Platform for the Responsible Use of Medicines in Animals	37

ABSTRACT: JUDICIOUS USE OF ANTIMICROBIAL AGENTS

Prudent use is defined by the World Health Organisation as “usage of antimicrobials which maximizes therapeutic effect and minimizes the development of antimicrobial resistance” (WHO 2000). The Federation of Veterinarians of Europe (FVE 1999) adds that “Prudent use ... 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”. An analysis of 12 of the most highly regarded guidelines to prudent or judicious use resulted in the identification of 22 principles that applied variously to the pre-treatment period, diagnosis, therapeutic objective and plan, drug selection, drug use and post-treatment considerations. The guidelines reviewed included

1. Guardabassi and Kruse (2008). Principles of Prudent and Rational Antimicrobial Use in Animals. In Guide to Antimicrobial Use in Animals.
2. AVMA (American Veterinary Medical Association) (2007). Judicious use of Antimicrobials. & Wages (2008). Antimicrobial therapy. In Diseases of Poultry, 12th edition.
3. FVE (Federation of Veterinarians of Europe) (1999). Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine.
4. World Veterinary Association (WVA) (2011). Draft position paper on responsible use of antimicrobials: The Global Basic Principles.
5. McDonald's (2003). McDonald's Global Policy on Antibiotic Use in Food Animals.
6. OIE: Anthony et al (2001) Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine.
7. RUMA (Responsible Use of Medicines in Agriculture Alliance) (2005). Responsible use of antimicrobials in poultry production.
8. WHO (2000). WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food.
9. AVA (Australian Veterinary Association) (2005). Guidelines for Prescribing, Authorising and Dispensing Veterinary Medicines. & AVPA (2001). AVPA code of practice for the use of antibiotics in the poultry industry. Endorsed by the Australian Chicken Meat Federation and the Australian Egg Industry Association.
10. JETACAR (1999). The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans.
11. Antibiotic Expert Group (2006). Therapeutic guidelines: antibiotic. 13th edition
12. European Platform for the Responsible Use of Medicines in Animals (EPRUMA) (2008)

Interviews with Australian poultry veterinarians indicated that the principles of judicious use were widely recognised and understood and underpinned current prescribing practices. Antimicrobial agents were prescribed sparingly and generally only with confirmed or high index of suspicion (based on flock history, property history and clinical signs) of primary or secondary bacterial infection. Off label use of antimicrobial agents in broiler production was not reported. Responses to treatment were closely monitored. There was a strong emphasis on ensuring high standards of hygiene, biosecurity and infection control to reduce the likelihood of any presence of bacterial disease. In many flocks it was considered usual that no outbreaks of bacterial disease would be encountered during grow outs.

In support of the apparently high standards of judicious use of antimicrobial agents by Australian veterinarians involved in poultry health, a recent survey of retail poultry in three Australian capital cities identified only low levels or no resistance to most antimicrobial agents tested.

DEFINITIONS OF PRUDENT, APPROPRIATE AND RESPONSIBLE USE

WHO (2000)

PRUDENT USE

“Usage of antimicrobials, which maximizes therapeutic effect and minimizes the development of antimicrobial resistance.”

CPSG (Clinical Prescribing Subgroup of the Interdepartmental Steering Group on Antimicrobial Resistance, UK Department of Health) (2001)

APPROPRIATE USE

“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 implies that the choice, route, dose, frequency and duration of administration have been rigorously determined.”

PRUDENT USE

“In line with this definition, the CPSG considered that prudent (or **optimal**) use meant both ‘less’, there still being leeway to reduce unnecessary use, and ‘**appropriate**’ (not only the right antibiotic but also the right dose, administered by the most appropriate route and for the right length of time to effect a clinical cure, while minimising side effects and the development of resistance). Monitoring the *appropriateness* of antimicrobial prescribing presents the greater challenge.”

FVE (Federation of Veterinarians of Europe) (1999)

PRUDENT USE

“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.”

THE RESPONSIBLE USE OF ANTIMICROBIALS IN VETERINARY MEDICINE (Anthony et al 2001)

RESPONSIBLE USE

“The Ad hoc Group described responsible use as follows:

- a) represents the scientific and technically directed use of these compounds that are the responsibility of professionals with the required expertise
- b) 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) aims to reduce the use of antimicrobial agents to their approved and intended uses
- d) 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) should be based on the results of resistance surveillance and monitoring (bacterial cultures and antimicrobial sensitivity testing)
- f) 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.”

ANTIMICROBIAL RESISTANCE AT FARM LEVEL (Acar and Moulin 2006)

PRUDENT USE

“The prudent use of antimicrobial products must be integrated into the whole concept of good management, which includes good husbandry practices, veterinary attention, vaccine programmes, site hygiene, and programmes to control zoonotic pathogen hazards. Safe water, appropriate wildlife control, safe feed, effective effluent management, and stress reduction are key issues. The education of farmers and stockmen is essential to successful on-farm improvement of animal health. Every effort should be made to protect the consumer from resistant as well as susceptible food-borne pathogens.

“The key issues for the prudent use of antibiotics are:

- using them when they can be useful
- knowing when to stop using them (as soon as possible)
- knowing about pK, pD characteristics
- knowing about their residues
- respecting the withdrawal period
- knowing that antibiotics are only part of the treatment of sick animals.”

RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN VETERINARY MEDICINE (OIE Terrestrial Animal Health Code 2011)

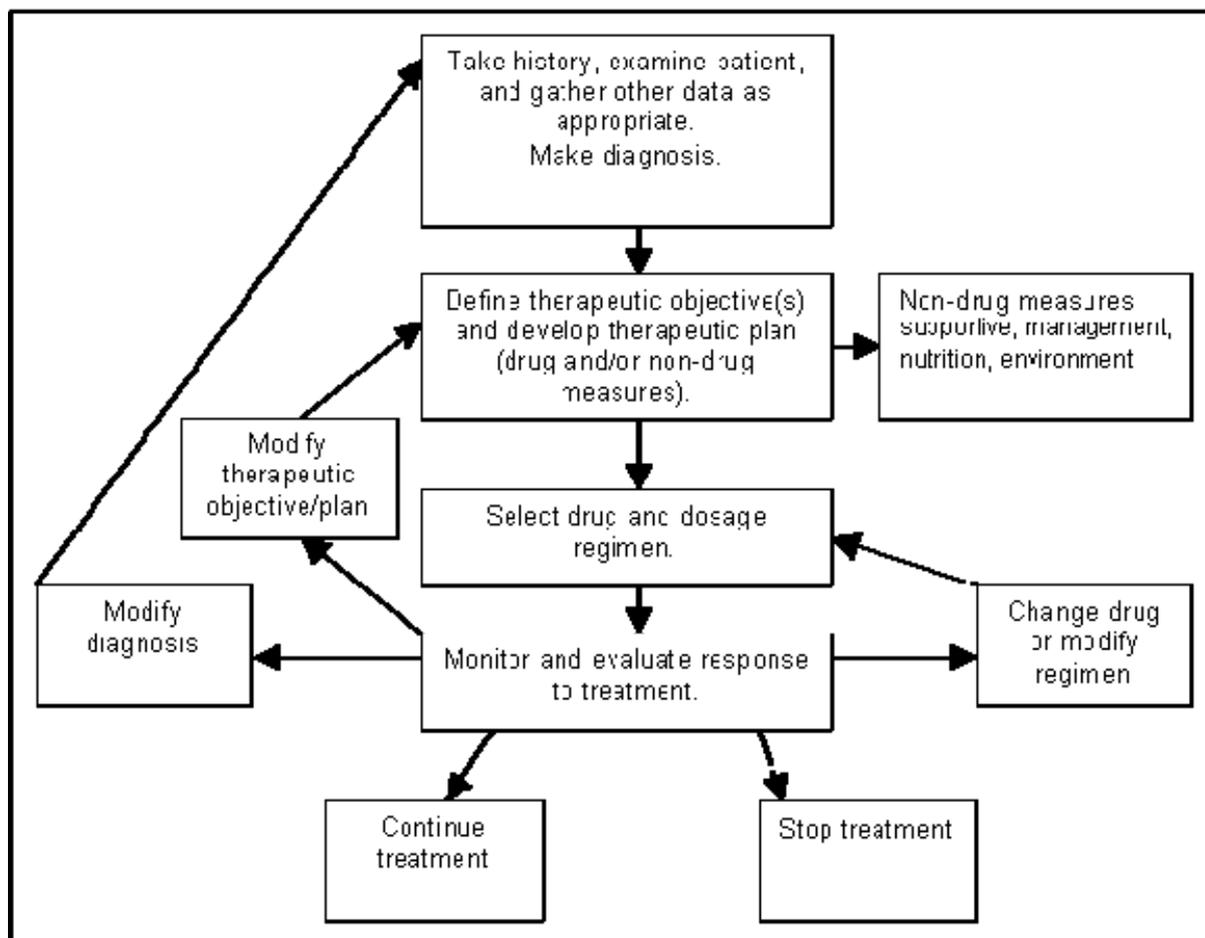
(http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.9.htm)

PRUDENT USE

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

1. 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 in *animals*;
2. comply with the ethical obligation and economic need to keep *animals* in good health;
3. prevent, or reduce, as far as possible, the transfer of micro-organisms (with their resistance determinants) within animal populations;
4. maintain the efficacy of *antimicrobial agents* used in food-producing *animals*;
5. prevent or reduce the transfer of resistant micro-organisms or resistance determinants from *animals* to humans;
6. maintain the efficacy of *antimicrobial agents* used in human medicine and prolong the usefulness of the antimicrobials;
7. prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);
8. 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 micro-organisms to humans.”

PRINCIPLES OF APPROPRIATE USE



#	CATEGORY	PRINCIPLES
1	PRETREATMENT PRINCIPLES	Disease Prevention <ul style="list-style-type: none"> ○ Appropriate (best practice) husbandry and hygiene, routine health monitoring, vaccination, nutrition ○ Codes of Practice, Quality Assurance Programmes, Flock Health Surveillance Programmes (FHSP) and Education Programmes should promote the responsible and prudent use of antimicrobial agents
2		Professional Intervention All uses (labelled and extra-label) of antimicrobials meet all the requirements of a valid veterinarian-client-patient relationship.
3		Distribution of Antimicrobial Agents Veterinarians should work with those responsible for the care of animals to use antimicrobials judiciously regardless of the distribution system through which the antimicrobial was obtained.
4		Alternatives to Antimicrobial Agents Efficacious, scientific evidence-based alternatives to antimicrobial agents can be an important adjunct to good husbandry practices
5	DIAGNOSIS	Accurate diagnosis <ul style="list-style-type: none"> ○ Diagnosis of a bacterial infection (clinical diagnosis complemented with laboratory diagnosis and epidemiological information as appropriate)

#	CATEGORY	PRINCIPLES	
6	THERAPEUTIC OBJECTIVE & PLAN	Therapeutic Objective & Plan Develop outcome objectives (for example clinical or microbiological cure) and implementation plan (including consideration of therapeutic choices, supportive therapy, host and other factors)	
7	DRUG SELECTION	Justification of Antimicrobial Use <ul style="list-style-type: none"> ○ Other therapeutic options should be considered prior to antimicrobial therapy ○ Antimicrobials are a complement to good husbandry practices and should never be used to compensate for or mask poor farm or veterinary practices. ○ Informed professional judgment balancing the risks and benefits for humans and animals 	
8		Guidelines for Antimicrobial Use Disease specific guidelines for antimicrobial selection and use should be consulted.	
9		Critically Important Antimicrobial Agents All antimicrobial agents, including those considered important in treating refractory infections in human or veterinary medicine, should be used in animals only after careful review and reasonable justification.	
10		Culture and Sensitivity Testing Utilize culture and susceptibility when clinically relevant results to aid in the selection of antimicrobials, especially if initial treatment has failed.	
11		Spectrum of Activity Use narrow-spectrum in preference to broad-spectrum antimicrobials whenever appropriate.	
12		Extra-label (off label) Antimicrobial Therapy <ul style="list-style-type: none"> ○ Must be prescribed only in accordance with prevailing laws and regulations. ○ should be confined to situations where medications used according to label instructions have been ineffective and where there is scientific evidence, including residue data, supporting the off-label use pattern 	
13		DRUG USE	Dosage Regimens Regimens for therapeutic antimicrobial use should be optimised using current pharmacological (pharmacokinetic-pharmacodynamic [PK/PD]) information.
14	Duration of Treatment Therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed to meet the therapeutic objective.		
15	Labelling and Instructions Written instructions about the drug use regimen must be given to the end user by the veterinarian with clear details of method of administration, dose rate, frequency and duration of treatment, precautions and withholding period.		
16	Target Animals Limit therapeutic antimicrobial treatment to ill or at risk animals, treating the fewest animals possible.		
17	Record Keeping Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.		
18	Compliance Encourage and ensure that instructions for drug use are implemented appropriately		
19	Monitor Response to Treatment Report to appropriate authorities any reasonable suspicion of an adverse reaction to the medicine in either the treated animals or farm staff having contact with the medicine, including any unexpected failure to respond to the medication.		
20	POSTTREATMENT CONSIDERATIONS		Environmental Contamination Minimize environmental contamination with antimicrobials whenever possible.
21			Surveillance of Antimicrobial Resistance Susceptibility surveillance should be undertaken periodically and the results provided to the prescriber, supervising veterinarians and other relevant parties

#	CATEGORY	PRINCIPLES
22		<p>Continuous Evaluation Veterinarians should continuously evaluate their prescribing practices, based on such information as the main indications and types of antimicrobials used in different animal species and evaluated in relation to available data on antimicrobial resistance and current use guidelines.</p>

REVIEW OF PUBLISHED SETS OF JUDICIOUS USE PRINCIPLES

W	A1	G	R	WH O	Mc D	FVE	OIE	A2	J	TG	EP	#	PRINCIPLES
W03	A1	G1	R	WH O	McD	FVE	OIE	A2,1			EP	1	Disease Prevention <ul style="list-style-type: none"> ○ Appropriate (best practice) husbandry and hygiene, routine health monitoring, vaccination, nutrition ○ Codes of Practice, Quality Assurance Programmes, Flock Health Surveillance Programmes (FHSP) and Education Programmes should promote the responsible and prudent use of antimicrobial agents
W01 W04	A1		R	WH O	McD	FVE	OIE	A2,3 , A2,4	J	TG	EP	2	Professional Intervention All uses (labelled and extra-label) of antimicrobials meet all the requirements of a valid veterinarian-client-patient relationship.
	A1					FVE	OIE	A2,6				3	Distribution of Antimicrobial Agents Veterinarians should work with those responsible for the care of animals to use antimicrobials judiciously regardless of the distribution system through which the antimicrobial was obtained.
W12	A1					FVE					EP	4	Alternatives to Antimicrobial Agents Efficacious, scientific evidence-based alternatives to antimicrobial agents can be an important adjunct to good husbandry practices
W06 W07	A1	G2		WH O		FVE	OIE	A2,1 1	J	TG	EP	5	Accurate diagnosis <ul style="list-style-type: none"> ○ Diagnosis of a bacterial infection (clinical diagnosis complemented with laboratory diagnosis and epidemiological information as appropriate)
											EP	6	Therapeutic Objective & Plan Develop outcome objectives (for example clinical or microbiological cure) and implementation plan (including consideration of therapeutic choices, supportive therapy, host and other factors)
W02 W06	A1	G4	R	WH O	McD	FVE	OIE	A2,2	J	TG	EP	7	Justification of Antimicrobial Use <ul style="list-style-type: none"> ○ Other therapeutic options should be considered prior to antimicrobial therapy ○ Antimicrobials are a complement to good husbandry practices and should never be used to compensate for or mask poor farm or veterinary practices. ○ Informed professional judgment balancing the risks and benefits for humans and animals
		G7		WH O		FVE	OIE			TG		8	Guidelines for Antimicrobial Use Disease specific guidelines for antimicrobial selection and use should be consulted.
					McD	FVE	OIE	A2,8				9	Critically Important Antimicrobial Agents All antimicrobial agents, including those considered important in treating refractory infections in human or veterinary medicine, should be used in animals only after careful review and reasonable justification.
W07	A1	G3				FVE	OIE	A2,1 0	J	TG	EP	10	Culture and Sensitivity Testing Utilize culture and susceptibility when clinically relevant results to aid in the

W	A1	G	R	WH O	Mc D	FVE	OIE	A2	J	TG	EP	#	PRINCIPLES
													selection of antimicrobials, especially if initial treatment has failed.
	A1				McD	FVE	OIE	A2,9	J	TG		11	Spectrum of Activity Use narrow-spectrum in preference to broad-spectrum antimicrobials whenever appropriate.
W08	A1		R		McD	FVE	OIE	A2,5			EP	12	Extra-label (off label) Antimicrobial Therapy <ul style="list-style-type: none"> ○ Must be prescribed only in accordance with prevailing laws and regulations. ○ should be confined to situations where medications used according to label instructions have been ineffective and where there is scientific evidence, including residue data, supporting the off-label use pattern
W09	A1	G5, G7		WH O	McD	FVE	OIE	A2,7	J	TG	EP	13	Dosage Regimens Regimens for therapeutic antimicrobial use should be optimised using current pharmacological (pharmacokinetic-pharmacodynamic [PK/PD]) information.
W09	A1			WH O	McD	FVE	OIE	A2,1 2	J	TG	EP	14	Duration of Treatment Therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed to meet the therapeutic objective.
	A1		R			FVE	OIE				EP	15	Labelling and Instructions Written instructions about the drug use regimen must be given to the end user by the veterinarian with clear details of method of administration, dose rate, frequency and duration of treatment, precautions and withholding period.
					McD		OIE	A2,1 3			EP	16	Target Animals Limit therapeutic antimicrobial treatment to ill or at risk animals, treating the fewest animals possible.
W10	A1		R	WH O	McD	FVE	OIE	A2,1 5			EP	17	Record Keeping Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.
												18	Compliance Encourage and ensure that instructions for drug use are implemented appropriately
	A1		R			FVE	OIE				EP	19	Monitor Response to Treatment Report to appropriate authorities any reasonable suspicion of an adverse reaction to the medicine in either the treated animals or farm staff having contact with the medicine, including any unexpected failure to respond to the medication.
	A1				McD	FVE	OIE	A2,1 4				20	Environmental Contamination Minimize environmental contamination with antimicrobials whenever possible.
W11	A1					FVE	OIE				EP	21	Surveillance of Antimicrobial Resistance Susceptibility surveillance should be undertaken periodically and the results provided to the prescriber, supervising veterinarians and other relevant parties
	A1			WH O		FVE	OIE					22	Continuous Evaluation Veterinarians should continuously evaluate their prescribing practices, based on such information as the main indications and types of antimicrobials used in

W	A1	G	R	WHO	McD	FVE	OIE	A2	J	TG	EP	#	PRINCIPLES
													different animal species and evaluated in relation to available data on antimicrobial resistance and current use guidelines.

ABBREVIATIONS

G	o Guardabassi L, Kruse H (2008). Principles of Prudent and Rational Antimicrobial Use in Animals. <i>In</i> Guide to Antimicrobial Use in Animals. Edited by Luca Guardabassi, Rachel Williamson and Hilde Kruse, Blackwell Publishing, Oxford, pp 1-12
A2	o AVMA (American Veterinary Medical Association) (2007). Judicious use of Antimicrobials. (Approved by the AVMA Executive Board, November 1998; Revised April 2004) http://www.avma.org/products/scientific/jtua.pdf o Wages DP (2008). Antimicrobial therapy. <i>In</i> Diseases of Poultry, 12 th edition, edited by YM Saif, Blackwell Publishing, Ames, Iowa, pp 42-46 o CVM (Center for Veterinary Medicine) (2001). Judicious Use of Antimicrobials for Poultry Veterinarians.
FVE	o FVE (Federation of Veterinarians of Europe) (1999). Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine. http://www.fve.org/news/publications/pdf/antibioen.pdf
W	o World Veterinary Association (WVA) (2011). Draft Position on Responsible Use of Antimicrobials. http://www.worldvet.org/docs/007_draft_WVA_position_on_Antimicrobials_feb2011.pdf
McD	o McDonald's (2003). McDonald's Global Policy on Antibiotic Use in Food Animals. http://www.mcdonalds.com
OIE	o Anthony F, Acar J, Franklin A, Gupta R, Nicholls T, Tamura Y, Thompson S, Threlfall EJ, Vose D, van Vuuren M, White DG (2001) Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine. <i>Rev Sci Tech</i> 20:829-839
R	o RUMA (Responsible Use of Medicines in Agriculture Alliance) (2005). Responsible use of antimicrobials in poultry production. Produced by the Poultry Working Group of the RUMA Alliance. May 1999, Revised September 2005 (www.ruma.org.uk)
WHO	o WHO (2000). WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food. Report of a WHO Consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties. Geneva, Switzerland. 5-9 June 2000 WHO/CDS/CSR/APH/2000.4
A1	o AVA (Australian Veterinary Association) (2005). Guidelines for Prescribing, Authorising and Dispensing Veterinary Medicines. o AVPA (2001). AVPA code of practice for the use of antibiotics in the poultry industry. Endorsed by the Australian Chicken Meat Federation and the Australian Egg Industry Association.
J	o JETACAR (1999). The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). Commonwealth of Australia 1999.
TG	o Antibiotic Expert Group (2006). Therapeutic guidelines : antibiotic. 13 th edition, Therapeutic Guidelines Limited, North Melbourne, Victoria
EP	o European Platform for the Responsible Use of Medicines in Animals (EPRUMA) (2008)
CPSG	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. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4084394

APPENDICES: Details of each guideline on appropriate use

WHO (2000)

WHO (2000). WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food. Report of a WHO Consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties. Geneva, Switzerland. 5-9 June 2000 WHO/CDS/CSR/APH/2000.4

Prudent use of antimicrobials

A. Guidelines on prudent use

24. The strategic aim of policies expressed in guidelines should be to provide advice on optimal therapeutic effect and/or protection of animals at risk and on the control of antimicrobial resistance in animal and zoonotic bacteria.

25. 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.

26. Locally-derived species-specific treatment guidelines should include a list of antimicrobials for 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 and human health concerns. If several antimicrobials can be used, guidelines should make recommendations on different antimicrobials to be used. However, the clinical experience and judgement of the practitioner should determine the final choice.

B. Responsibilities of veterinarians and/or producers

27. For each treated animal or group of animals a health record should be kept to support the choice of empirical therapy. The record should include:

- data on antimicrobial use;
- previous antimicrobial susceptibility test results; and/or
- previous treatment outcomes.

28. Veterinarians should continuously evaluate their prescribing practices. This would be based on information such as the main indications and types of antimicrobials used in different animal species and be evaluated in relation to available data on antimicrobial resistance and current use guidelines.

29. Veterinarians should prescribe antimicrobials only for animals under their direct care. Veterinarians are expected to have examined clinically affected animals, or to be familiar with production practices on the farm and to have developed a written treatment protocol, prior to prescribing medication.

30. Antimicrobials should be prescribed only when indicated, using antibiotics directed against the causative agent/s, given in optimal dosage, dosage intervals and length of treatment to ensure maximum concordance with the treatment regimen.

31. It is the responsibility of the producers to ensure that 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. Such a programme is likely to involve hygiene and disinfection procedures, bio-security measures, management alterations, changes in stocking rate, vaccination and other relevant components.

32. Veterinarians together with producers should be jointly responsible for the health of animals on the farm. Veterinarians and producers should agree on policies and protocols on preventive strategies, health and treatment programmes and veterinary involvement in ongoing animal health management. These policies and protocols should comply with prudent use principles, good farming practice, and quality assurance programmes.

GLOSSARY

Prudent use of antimicrobials

Usage of antimicrobials, which maximizes therapeutic effect and minimizes the development of antimicrobial resistance.

McDonald's (2003)

McDonald's (2003). McDonald's Global Policy on Antibiotic Use in Food Animals.

http://www.aboutmcdonalds.com/etc/medialib/aboutMcDonalds/socialresponsibility.Par.33574.File.dat/antibiotics_policy.pdf

Guiding Principles for Sustainable Use of Antibiotics

Sustainable use of antibiotics is the foundation of McDonald's Antibiotic Policy.

The concept of sustainability is based on conserving natural and social resources in the present and future while creating economic value. The following principles of sustainable use draw from existing frameworks including the World Veterinary Association's *Prudent Use of Antibiotics Global Basic Principles* and the American Veterinary Medical Association's *Judicious Therapeutic Use of Antimicrobials General Principles*.

- 1. Quality and safety:** McDonald's is committed to ensuring wholesome and safe food for our customers. Food safety is McDonald's number one priority and is central to all company operations and supply programs.
- 2. Animal welfare:** Treating animals with care is integral to McDonald's overall quality assurance and animal welfare programs. Disease prevention strategies, such as good husbandry and hygiene, routine health monitoring, and immunization, and other preventative options should be emphasized before the use of antibiotics.
- 3. Antibiotics for animals:** Sustainable use of antibiotics is an integral part of an overall animal care and welfare program. Animals that are ill or at imminent risk of becoming ill must be treated. Sustainable use of antibiotics complements good animal husbandry practices.
- 4. Supervise use:** Antibiotics shall be used in accordance with all applicable regulatory requirements. The use of antibiotics for disease prevention, control or treatment shall occur only under the oversight of a veterinarian who meets all applicable requirements for training and certification. All uses and prescriptions must be based on current pharmacological information and principles. Antibiotics shall be used only in accordance with the product license requirements or as directed by a veterinarian.
- 5. People first:** Antibiotics that are in classes used in human medicine may be used in animals for disease treatment, control or prevention only in accordance with applicable regulatory requirements and after thorough consideration of alternatives, including the use of antibiotics belonging to classes not used in human medicine.
- 6. Limit exposure:** Exposure to antibiotics for disease treatment, control or prevention should be minimized by limiting treatment to ill animals or animals at risk of a specific disease, using the narrowest spectrum antibiotic, treating the fewest animals indicated, and treating only for as long as needed for the desired clinical response. The use of antibiotics for disease control or prevention should be reviewed regularly to determine continued need. Antibiotic use should be confined to appropriate clinical indications. Extra-label therapies should be prescribed only after other treatment options have been exhausted, and should be prescribed in accordance with the most up-to-date laws and regulations that govern drug use and in accordance with McDonald's Antibiotics Use Policy. Dispersal of antibiotics into the environment should be minimized.
- 7. Record keeping:** Suppliers must maintain accurate records of all antibiotic administrations for the purpose of certifying compliance with the policy, including the elimination of growth promotion uses of antibiotics belonging to classes of compounds approved for use in human medicine and compliance with the Guiding Principles for Sustainable Use. Records of extra-label therapies should be delineated.

Definitions

Antibiotic: This policy uses the term 'antibiotic' to refer to both 'Substances of natural origin that are used for treatment of infection or disease that kills or inhibits the growth or multiplication of microorganisms' (*American Veterinary Medical Association Judicious Therapeutic Use of Antimicrobials*, <http://www.avma.org/scienact/jtua/jtua98.asp>), and synthetic agents that have an antibiotic effect (commonly referred to as antimicrobials).

OIE (World Organisation for Animal Health)

Anthony F, Acar J, Franklin A, Gupta R, Nicholls T, Tamura Y, Thompson S, Threlfall EJ, Vose D, van Vuuren M, White DG (2001) Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine. *Rev Sci Tech* 20:829-839

The responsible use of antimicrobials in veterinary medicine

The Ad hoc Group described responsible use as follows:

- a) represents the scientific and technically directed use of these compounds that are the responsibility of professionals with the required expertise
- b) 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) aims to reduce the use of antimicrobial agents to their approved and intended uses
- d) 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) should be based on the results of resistance surveillance and monitoring (bacterial cultures and antimicrobial sensitivity testing)
- f) 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.

RESPONSIBILITIES OF VETERINARIANS

The use of antimicrobials is no substitute for good management practices and the prime concern of the veterinarian is to encourage good farming practice in order to minimise the need for antimicrobial use in livestock. In the frame of good management practice, the veterinarian is responsible for identifying recurrent disease problems and developing alternative strategies to prevent or control disease. These may include changes in husbandry conditions and vaccination programmes where vaccines are available. Veterinarians should only prescribe antimicrobials for animals under their care, which means that:

- the veterinarian must have been assigned responsibility for the health of the animal or the herd/flock by the producer or an agent of the producer
- that responsibility must be real and not merely nominal
- that the animal(s) or herd/flock must have been examined immediately before the prescription and supply or sufficiently recently or frequently for the veterinarian to have personal knowledge of the condition of the animal(s) or current health status of the herd or flock to make a diagnosis and prescribe
- the veterinarian should maintain clinical records of the animal(s)/herd/flock.

It is recommended that veterinary professional organisations develop for their members, species-specific clinical practice guidelines on the responsible use of antimicrobials, with particular reference to the choice of product, disease prevention strategies and treatment protocols. The responsibilities of veterinarians in this area are described below.

USE OF ANTIMICROBIAL AGENTS WHEN NECESSARY

The appropriate use of antimicrobials in practice is a critical decision which, where possible, should be based on the following:

- the experience and local expertise of the prescribing veterinarian
- an accurate diagnosis, based on adequate diagnostic procedures.

On certain occasions, a group of animals which may have been exposed to pathogenic bacteria may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing, to prevent the development of clinical disease and for reasons of animal welfare.

DETERMINATION OF THE CHOICE OF AN ANTIMICROBIAL

The expected efficacy of the treatment

The expected efficacy of the treatment is based on the following:

- the clinical experience of the veterinarian
- the activity towards the pathogenic bacteria involved
- the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogenic bacteria involved. Ideally, the antibiotic profiles should be established before the commencement of treatment. Should a first line antibiotic treatment fail or should the disease recur, the use of a second line antimicrobial agent should be based on the results of the microbiological tests
- the appropriate route of administration
- results of initial treatment
- known pharmacokinetics/tissue distribution to ensure that the selected therapeutic agent is active at the site of infection
- prognosis.

To minimise the likelihood of antimicrobial resistance developing, it is recommended that antimicrobials be targeted to bacteria likely to be the cause of infection.

Absence of selection or limited selection of antimicrobial resistant bacteria

The absence of selection or limited selection of antimicrobial resistant bacteria is influenced by the following:

- the choice of the activity spectrum of the antimicrobial
- the targeting of specific bacteria
- known or predictable susceptibilities using antimicrobial susceptibility testing
- the correct dosing regimens
- the use of combinations of antimicrobial agents
- the importance of the drug to human and/or veterinary medicine. Antimicrobials which are considered important to treat critical diseases in humans and/or animals, should be used only when other therapies are unavailable or inappropriate
- the route of administration.

Combinations of antimicrobials

Combinations of antimicrobials are used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity. Furthermore, the use of combinations of antimicrobials can be protective against the selection of resistance in cases in which bacteria exhibit a high mutation rate against a given antimicrobial. However, a bad choice of a combination of antimicrobials may, in certain cases, lead to an increase of the selection of resistance. If the use of a combination of antimicrobials is justified, the veterinarian should ensure that there is no antagonism between the chosen antimicrobials and should check the ability of these antibiotics to reach the infection site under similar time and concentration conditions, to maintain effective therapeutic concentrations as long as required.

APPROPRIATE USE OF THE ANTIMICROBIAL AGENT CHOSEN

A prescription for antimicrobial agents must precisely indicate the treatment regime, the dose, the dosage intervals, the duration of the treatment, the withdrawal period and the amount of drug to be delivered, depending on the dosage and the number of animals to be treated.

All medicinal products should be prescribed and used according to the conditions of the marketing authorisation, which are reflected in the summary of product characteristics provided by the manufacturer.

If the label conditions allow for some flexibility, the veterinarian should consider a therapeutic regimen that is sufficiently long to allow the effective recovery of the animal, but sufficiently short to limit the selection of resistance in food-borne and/or commensal bacteria.

'Off label use' (extra-label use) of veterinary medicinal products

Although all medicinal products should be prescribed and used in accordance with the specifications of the marketing authorisation, the prescribing veterinarian should have the

discretion to adapt these in exceptional circumstances. The 'off label use' of an antimicrobial agent may be permitted in appropriate circumstances and should be in agreement with the national legislation in force. The veterinarian has the responsibility to define the conditions of responsible use in such a case, including the therapeutic regimen, the route of administration and the duration of the treatment.

Recording

All available information should be consolidated into one form or database, such that this information should:

- allow monitoring of the quantities of medication used
- contain a list of all medicines supplied to each livestock holding
- contain a list of medicine withdrawal periods and a system for allowing information to be updated
- contain a record of antimicrobial susceptibilities
- provide comments concerning the response of animals to medication
- allow the investigation of adverse reactions to antimicrobial treatment, including lack of response due to antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

Labelling

All medicines supplied by a veterinarian should be adequately labelled with the following minimum information:

- the name of the owner/keeper or person who has control of the animal(s)
- the address of the premises where the animal(s) is kept
- the name and address of the prescribing veterinarian
- the date of supply
- the indication 'For animal treatment only'
- the warning 'Keep out of the reach of children'
- the relevant withdrawal period, even if this is nil.

The label should not obscure the expiry date of the preparation or any important information supplied by the manufacturer.

Training

Veterinary professional organisations should participate in the training programmes as defined in the earlier section entitled 'Training of antibiotic users'.

RESPONSIBILITIES OF PRODUCERS

Producers are responsible for preventing outbreaks of disease and implementing health and welfare programmes on their farms. They may, as appropriate, call on the assistance of their veterinarian in undertaking these duties. All those involved with the livestock on the farm have an important role to play in ensuring the responsible use of antimicrobials. Therapeutic antimicrobial products should be regarded as complementing good management, vaccination and farm hygiene. Efforts should be made to ensure that environmental contamination both by antimicrobials and by resistant bacteria is kept to a minimum.

Livestock producers have the following responsibilities:

- a) to draw up a health plan with the veterinarian in charge of the animals that outlines preventative measures (mastitis plan, worming and vaccination programmes, etc.)
- b) to use antimicrobial agents only on veterinary prescription and according to the provisions of the prescription
- c) to use antimicrobial agents in the species, for the uses and at the doses on the approved/registered labels and in accordance with product label instructions or the advice of a veterinarian familiar with the animals and the production site
- d) to isolate sick animals, when appropriate, to avoid the transfer of resistant bacteria
- e) to comply with the storage conditions of antimicrobials in the rearing unit, according to the provisions of the leaflet and package insert
- f) to address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated
- g) to comply with the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer

- h)* to dispose of surplus antimicrobials under safe conditions for the environment. Partially-used medicines should only be used within the expiry date, for the condition for which they were prescribed and, if possible, in consultation with the prescribing veterinarian
- i)* to maintain all the laboratory records of bacteriological and susceptibility tests. These data should be made available to the veterinarian responsible for treating the animals to optimise the use of antimicrobials in that unit
- j)* to keep adequate records of all medicines used, including the following:
- name of the product/active substance and batch number
 - name of supplier
 - date of administration
 - identification of the animal or group of animals to which the antimicrobial agent was administered
 - diagnosis/clinical conditions treated
 - quantity of the antimicrobial agent administered
 - withdrawal periods
 - result of laboratory tests
 - effectiveness of therapy
- k)* to inform the veterinarian responsible for the unit of recurrent disease problems.

See also

Terrestrial Animal Health Code (2011). Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine.

http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.9.htm

FVE (1999)

FVE (Federation of Veterinarians of Europe) (1999). Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine

<http://www.fve.org/news/publications/pdf/antibioen.pdf>

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 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 microorganisms. 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 microorganisms more rapidly than 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.

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 antimicrobial 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.

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 Herd 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.

RUMA (2005)

RUMA (Responsible Use of Medicines in Agriculture Alliance) (2005). Responsible use of antimicrobials in poultry production. Produced by the Poultry Working Group of the RUMA Alliance. May 1999, Revised September 2005

www.ruma.org.uk

21. Responsible use

The use of animal medicines carries with it responsibilities. Under UK legislation most antimicrobial use in poultry is under the direct responsibility of veterinary surgeons. Farmers have, however, a very considerable role to play in ensuring that the directions of the veterinary surgeon are properly carried out, and also in developing and applying disease control measures which minimise the need for antimicrobial medication.

22. Veterinary surgeon responsibilities

Besides meeting regulatory requirements, poultry veterinary surgeons are guided by a specific Code of Practice on Responsible Use issued by the British Veterinary Poultry Association.

Antimicrobials may only be prescribed and used under the direction of a veterinary surgeon when:

- a. the veterinary surgeon has been given responsibility for the health of the animal or flock in question by the owner or the owner's agent; and
- b. the care of the animal or flock by the veterinary surgeon is real and not merely nominal

23. In general, a veterinary surgeon is expected to see the affected animal prior to prescribing medication. However, in poultry medicine, best practice in the control of infectious disease (biosecurity rules) often dictates alternative approaches. There should be formal routes of communication laid down between the veterinary surgeon and the farmer to ensure that reliable and accurate information is provided to enable the veterinary surgeon to make an informed decision regarding treatment of a flock. All such information should be documented, including signed written instructions countersigned by the farmer.

24. The veterinary surgeon involved should perform a health audit (e.g. post-mortem examinations, serology, farm visits and other relevant laboratory investigation) and have a sound knowledge of the production and management systems employed. The veterinary surgeon must visit the farm prior to treatment if he/she does not have this knowledge. In all uses of antimicrobials the best available information should be used to determine treatment, the most prudent regimes and dosages. The aim is to provide optimal efficacy with minimal risk of resistance developing in either the target organisms, potentially zoonotic organisms, or organisms capable of transmitting resistance to pathogens. The veterinary surgeon will be the normal source of such information for the farmer.

25. Farmer responsibilities

It is the responsibility of the farmer to clearly give their veterinary surgeon responsibility for the health of the animals and to co-operate in ensuring that such responsibility is real. Specifically, the farmer should:

- a. Regard therapeutic antimicrobial products as complementing good management, vaccination, and site hygiene.
- b. Initiate medication only with formal veterinary approval, provided either by prescription, a verbal direction or an approved treatment programme or protocol. In the case of in-feed medication, this will be provided by a "Medicated Feedingstuff Prescription" (MFSP or MFS prescription).
- c. Ensure that accurate information is given to the veterinary surgeon in order that the correct dosage can be calculated for the birds concerned, and ensure that clear instructions for dosage and administration are obtained and passed on where necessary to the staff responsible.
- d. Always complete the course of treatment at the correct dosage. Ensure that the dosage is carefully administered in an effective manner.

- e. Accurately record the identity of the flock of birds medicated, the batch number, amount and expiry of the medicine used, the withdrawal period required and the date and time the medication was completed.
- f. For in-feed or in-water medication ensure that the end of medication is accurately determined by cleaning the feed-bin or header tank as appropriate.
- g. For any medicines used, appropriate information should be kept on file – for example, the package inserts, product data sheets, or the safety data sheets as available.
- h. Report to their veterinary surgeon any suspicion of an adverse reaction to the medicine in either the treated animals or farm staff having contact with the medicine. This should include any unusual failure to respond to medication. Such reports may also, if desired, be made directly to the Veterinary Medicines Directorate at Woodham Lane, New Haw, Addlestone, Surrey KT15 3BR. A poultry-specific “green form”, available from the VMD should be used where appropriate. A record of the adverse reaction should also be kept on the farm.
- i. Ensure that the appropriate withdrawal period is complied with prior to the sale or collection of the treated birds or eggs for human consumption. In general the withdrawal time required is specified on the MFSP or prescription, or the label of the medicine. Note that if in the professional judgement of the veterinary surgeon, it is necessary for a product to be prescribed for a species for which it is not authorised or at a dosage higher than the authorised dosage, then an appropriate withdrawal period should be specified to ensure that food produced from the treated animals does not contain residues harmful to consumers. In general this should be not less than the following:
 - Eggs 7 days
 - Meat from poultry 28 days
- j. Co-operate with QA schemes which monitor antimicrobial usage, medication documentation, and withdrawal period compliance. However, such schemes should not constrain the attending veterinary surgeon from preventing suffering in the animals under their care.
- k. Track antimicrobial usage taking account of the potency of various products. The simplest approach is to record the number of kgs. of animal treated/day as a proportion of the total kgs. of animal at risk for each species and class of stock. Any usage where the mg/kg dosage does not match authorised values would need to be highlighted.
- l. Ensure the different medicines are only given at the same time with the specific approval of the veterinary surgeon because adverse interactions sometimes occur.
- m. Maintain a medicine log book on farm together with copies of relevant regulations and Codes of Practice.

AVMA (2007)

AVMA (American Veterinary Medical Association) (2007). Judicious use of Antimicrobials. (Approved by the AVMA Executive Board, November 1998; Revised April 2004)
<http://www.avma.org/products/scientific/jtua.pdf>

- 1 Preventive strategies, such as appropriate husbandry and hygiene, routine health monitoring, and immunizations, should be emphasized.
- 2 Other therapeutic options should be considered prior to antimicrobial therapy.
- 3 Judicious use of antimicrobials, when under the direction of a veterinarian, should meet all the requirements of a valid veterinarian-client-patient relationship.
- 4 Prescription, Veterinary Feed Directive, and extralabel use of antimicrobials must meet all the requirements of a valid veterinarian-client-patient relationship.
- 5 Extralabel antimicrobial therapy must be prescribed only in accordance with the Animal Medicinal Drug Use Clarification Act amendments to the Food, Drug, and Cosmetic Act (AMDUCA) and its regulations.
- 6 Veterinarians should work with those responsible for the care of animals to use antimicrobials judiciously regardless of the distribution system through which the antimicrobial was obtained.
- 7 Regimens for therapeutic antimicrobial use should be optimized using current pharmacological information and principles.
- 8 Antimicrobials considered important in treating refractory infections in human or veterinary medicine should be used in animals only after careful review and reasonable justification. Consider using other antimicrobials for initial therapy.
- 9 Use narrow spectrum antimicrobials whenever appropriate.
- 10 Utilize culture and susceptibility results to aid in the selection of antimicrobials when clinically relevant.
- 11 Therapeutic antimicrobial use should be confined to appropriate clinical indications. Inappropriate uses such as for uncomplicated viral infections should be avoided.
- 12 Therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed for the desired clinical response.
- 13 Limit therapeutic antimicrobial treatment to ill or at risk animals, treating the fewest animals indicated.
- 14 Minimize environmental contamination with antimicrobials whenever possible.
- 15 Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.

WVA (2011)

World Veterinary Association (WVA) (2011). Draft Position on Responsible Use of Antimicrobials. http://www.worldvet.org/docs/007_draft_WVA_position_on_Antimicrobials_feb2011.pdf

THE GLOBAL BASIC PRINCIPLES

- 1. In case of animal disease, the animals should be examined by a veterinarian, who makes a diagnosis, and recommends and plans an effective treatment programme.**

When the decision is reached to use antimicrobials for therapy, veterinarians should strive to optimize therapeutic effectiveness and minimize resistance to antimicrobials in order to protect public and animal health.

- 2. Antimicrobials used for therapy are health management tools that are licensed to be used for the purposes of:**
 - a. disease prevention
 - b. disease control
 - c. disease treatment

Additionally, some countries may license certain antimicrobials to be used in food-producing animals to enhance production through growth promotion and feed efficiency. The antimicrobials may control or prevent disease and thereby enhance production. However like all uses of antimicrobials, these uses should be subjected to risk analysis, including animal and human health benefit assessments, to determine if risk management measures are needed and, if needed, what are appropriate risk management options, for example veterinary oversight.

- 3. Codes of good veterinary practice, quality assurance programmes, herd health control and surveillance programmes, and education programmes should promote the responsible and prudent use of antimicrobials.**

Veterinarians must assume responsibility to stay knowledgeable about the current information on resistance because they are accountable for the safe and effective use of these medicines.

- 4. Antimicrobials should be used only with veterinary involvement.**

Regular, close veterinary involvement is essential for informed advice concerning the effective use of antimicrobials. Regardless of the distribution system available, the use of antimicrobials should be subject to appropriate professional advice, preferably by a veterinarian.

- 5. The availability of effective antimicrobials should be based on risk analysis that considers the OIE list of Antimicrobials of Veterinary Importance.**

The availability of appropriate tools for preventing, controlling and treating disease, which include antimicrobials, are needed for veterinarians to be able to use to relieve animal pain and suffering. The continued availability of all classes of safe, effective antimicrobials for veterinary medicine is a critical component of both a safe food supply and optimal animal health and welfare. The large number of species to be treated and the wide range of diseases encountered requires the wide availability of all classes more so than in human medicine with only one species requiring treatment.

The OIE International Committee unanimously adopted the List of Antimicrobials of Veterinary Importance at its 75th General Session in May 2007. Veterinary antimicrobials are classified according to their importance as critical, highly important or important. Risk analysis should

consider this list as well as the list developed by the World Health Organization that classifies the importance of human antimicrobials.

- 6. Therapeutic antimicrobials may be used when it is known or suspected that an infectious agent is present which will be susceptible to therapy. It is the responsibility of the veterinarian to choose the antimicrobial product, based on his/her informed professional judgment balancing the risks and benefits for humans and animals.**

The veterinarian shall have due regard to the public health risks of using veterinary medicines. Specifically for antimicrobials, the veterinarian shall have due consideration for the potential for decreased antimicrobial susceptibility in zoonotic and potentially zoonotic bacteria and target pathogens in animals, and for the antimicrobial residues of toxicological and microbiological significance. At the same time, benefits such as promoting the health and welfare of animals, assuring safe, wholesome and affordable food from healthy animals, while reducing human exposure to bacteria of animal origin, shall be taken into account.

- 7. When antimicrobials need to be used for therapy, bacteriological diagnosis with antimicrobial sensitivity testing should, whenever possible, be part of the informed professional clinical judgment.**

When treating a disease, the antimicrobial sensitivity of the causal organism should ideally be ascertained before therapy is started. In disease outbreaks involving high case mortality rates or where there are signs of rapid transmission of disease among contact animals, treatment may be started on the basis of clinical diagnosis. Even so, the antimicrobial sensitivity of the suspected causal organism should, where possible, be determined so that if treatment fails the regimen can be changed in the light of the results of sensitivity testing. Antimicrobial sensitivity trends should be monitored over time, and such monitoring used to guide clinical judgment on antimicrobial usage. Further efforts are required to harmonise the methods by which authorities are monitoring the prevalence of resistance. Surveillance systems must be made consistent; otherwise the interpretation of resistance data within regions becomes meaningless.

- 8. Label instructions should be carefully followed and due attention paid to species and disease indications and contra-indications, dosage regimen, withdrawal periods, storage instructions, and expiration dates for products.**

Off label or extra-label use of antimicrobials should be exceptional and as with all use of antimicrobials under the professional responsibility of a veterinarian, with careful justification, written prescription or instructions, and in accord with governmental regulations and guidance (e.g., the European Cascade System; the United States Code of Federal Regulations – 21 CFR 530). When existing, veterinarians have to follow the legal or regulatory systems in their country.

- 9. Antimicrobials used for therapy should be used for as long as needed, over as short a dosage period as possible, and at the appropriate dosage regimen.**

Dosage regimen: It is essential to administer the antimicrobial in accordance with the recommended dosage regimen. This will minimize therapy failures, exploit fully the effective potential of the product, and comply with the applicable withdrawal times. Each class of antimicrobials has its own unique pharmacodynamic properties which are expressed fully when the recommended dosage regimen is applied. Veterinarians and animal owners alike must endeavor to always ensure that the correct dose is given and adhered to for the time of treatment recommended.

As long as necessary: Insufficient duration of administration can lead to recrudescence of the infection. This may lead to increased likelihood of selecting micro-organisms with reduced antimicrobial sensitivity.

As short as possible: Limiting the duration of use to only that required for therapeutic effect will minimize the exposure of the bacterial population to the antimicrobial. The adverse effects on the surviving commensal microflora are minimized and the medical impact of the remaining zoonotic organisms is minimized/reduced. Theoretically, antimicrobial use should be stopped as soon as the animal's own host defense system can control the infection itself.

10. Records should be kept of all antimicrobial administrations

The implementation of record-keeping [ways, means and by whom] should be according to applicable legislation and/or regulations. However, in order to ensure compatibility and usability of recorded data, some harmonization of the principles and of the format is needed.

11. Coordinated susceptibility monitoring and surveillance should be conducted and the results should be provided to the prescriber/supervising veterinarians and other relevant parties.

Monitoring and 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 pre-treatment specimens. Therefore, it is encouraged to also gather data from samples collected at random from farms, slaughterhouses, or food in order to investigate the prevalence and incidence of resistance in veterinary pathogens, zoonotic pathogens, and sentinel organisms. Data should be quickly provided to prescribers/supervising veterinarians and other relevant parties; which will allow the modification of antimicrobial usage to balance the benefits with the risks. Accessibility to the data will vary from programme to programme and should normally be determined beforehand.

12. Efficacious, scientifically proven alternatives to antimicrobials are needed as an important part of good husbandry practices

Among the research needs, it is suggested to look into the development of effective alternatives to the use of antimicrobials and to evaluate the impact that these alternatives [e.g. vaccines, probiotics, competitive exclusion principles and products, nutrition, and new health technologies and strategies, including improved livestock management] might have on selection for resistance while research into new antimicrobial options continue.

WVA wants to maintain the effectiveness of the antimicrobial medicaments for treating sick animals and human beings. The WVA realizes that new types of medicaments should be developed as the effectiveness of the presently known antimicrobials might be limited. The WVA should take part in any position making body in the area.

Notes:

1] The word antimicrobials covers all antimicrobial products administered orally and parenterally to animals, i.e. antibiotics [produced by fermentation of live micro-organisms] but also chemically –synthesized compounds with antibiotic activity such as sulphonamides and quinolones; it does not include disinfectants and sanitizers.

JETACAR (1999)

JETACAR (1999). The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance. Commonwealth of Australia 1999.

Page 164:

Box 12.1 Prudent use principles for antibiotics

General

- Antibiotics should be used only where the benefits are scientifically demonstrable and substantial.
- In general, the spectrum of the antibiotic used should be the narrowest to cover the known or likely pathogen(s).
- Single agents should be used unless it has been proved that combination therapy is required to ensure efficacy or reduce the selection of clinically significant resistance.
- The dosage should be high enough to ensure efficacy and minimise the risk of resistance selection, and low enough to minimise risk of dose-related toxicity.

Therapy

- Choice of therapy should be based on either: (i) culture and susceptibility test results (directed therapy), or (ii) known common pathogens in the condition and their current resistance patterns (empirical therapy).
- Duration should be as short as possible, and should not exceed seven days unless there is proof that this duration is inadequate.

Prophylaxis

- Choice should be based on known or likely target pathogen(s).
- Duration should be as short as possible. Single dose prophylaxis is recommended for surgical prophylaxis. Long-term prophylaxis in human and veterinary medicine should be administered only when it has been demonstrated that the benefits outweigh the risk of resistance selection or propagation.

Antibiotic Expert Group (2006)

Antibiotic Expert Group (2006). Therapeutic guidelines : antibiotic. 13th edition, Therapeutic Guidelines Limited, North Melbourne, Victoria

Therapeutic Guidelines: Antibiotic, version 13, 2006

PRINCIPLES OF ANTIMICROBIAL USE: INTRODUCTION

This chapter outlines acceptable approaches to the use of antimicrobials, both in hospital practice and in the community. General principles are outlined in Box 2.1 and summarised in the antibiotic creed.

In hospitals, drug choice may be influenced by such local factors as trends in susceptibility of current isolates, cost of the drugs, and in some instances traditional preference or familiarity. Each hospital's drug and therapeutics committee should produce its own antimicrobial policies, within the overall framework suggested by these guidelines. Resistance to antimicrobials is common in hospitals and, increasingly, in the community, due to the selective pressure exerted by high drug levels in the biosphere, together with facilitated transfer of organisms between staff and patients. Restraint in prescribing and adherence to the principles discussed in this chapter are equally necessary in both settings.

Principles of use of antibiotics (Box 2.1)

General

Use antibiotics only where the benefits are scientifically demonstrable and substantial.
In general, use the narrowest spectrum antimicrobial to treat the known or likely pathogen(s).
Use single drugs unless it has been proven that combination therapy is required to ensure efficacy or reduce the selection of clinically significant resistance.
Use a dose that is high enough to ensure efficacy and minimise the risk of resistance selection, and low enough to minimise risk of dose-related toxicity.

Therapy

Base choice of therapy on either culture and susceptibility test results (directed therapy), or known common pathogens in the condition and their current resistance patterns (empirical therapy).
Duration should be as short as possible, and should not exceed 7 days unless there is proof that this duration is inadequate.

Prophylaxis

Base choice of antimicrobial on known or likely target pathogen(s).
Duration should be as short as possible. A single dose of antibiotic is recommended for surgical prophylaxis. Administer longer-term prophylaxis only when it has been demonstrated that the benefits outweigh the risk of resistance selection or propagation.

Modified from: The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). Canberra: Commonwealth Department of Health and Aged Care and Commonwealth Department of Agriculture, Fisheries and Forestry; 1999. p.164 <http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubs-jetacar-cnt.htm>

The antibiotic creed (Box 2.2)

- M** microbiology guides therapy wherever possible
- I** indications should be evidence-based
- N** narrowest spectrum required
- D** dosage appropriate to the site and type of infection
- M** minimise duration of therapy
- E** ensure monotherapy in most situations

GENERAL PRINCIPLES OF ANTIMICROBIAL USE

Antimicrobial resistance

Antimicrobial resistance is increasing in many pathogens. Problem organisms include *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA) in both the community and hospitals, vancomycin-resistant enterococci (VRE), strains of *Klebsiella* and *Escherichia coli* with extended-spectrum beta-lactamase resistance, and multiresistant *Acinetobacter* and *Pseudomonas aeruginosa*. Emergence of resistance to reserve antibiotics such as the fluoroquinolones, the carbapenems and vancomycin is also of concern. Antibiotic use is one of the pressures that increases resistance. Appropriate antibiotic use will delay the emergence of resistance and minimise resistance prevalence after it has emerged. The Centers for Disease Control and Prevention website has useful information on how to prevent antimicrobial resistance in health care settings.

Is an antimicrobial needed?

Most viral and minor bacterial diseases are self-limiting and do not benefit from use of antimicrobials.

Unnecessary prescription of antimicrobials exposes patients to adverse drug effects, is costly and helps create conditions favouring the proliferation of resistant organisms in that patient and throughout the community. Before prescribing an antimicrobial, ask yourself, 'Is this really necessary for this patient?'

Antimicrobial choice

When an antimicrobial is indicated, base the choice on factors such as spectrum of activity in relation to the known or suspected causative organism, safety including adverse reactions and drug interactions, previous clinical experience, cost, and the potential for selection of resistant organisms and the associated risk of superinfection, as well as patient factors. The relative importance of each of these factors will be influenced by the severity of the illness and whether the drug is to be used for prophylaxis, empirical therapy or directed therapy.

A history of hypersensitivity or other adverse response to the drug under consideration should be sought and taken into account.

Knowledge of a previous adverse drug reaction may prevent the inadvertent administration of an antimicrobial drug to which the patient is allergic. Failure to take an adequate history can have serious and sometimes fatal consequences.

Take additional care in the elderly, who may have altered pharmacokinetic or toxicodynamic profiles. Renal or hepatic impairment may require adjustment of the dose or dosing interval (see Appendix 2.6). Where therapy is to be self-administered, consider the complexity of the dosage regimen, particularly for those on multiple therapies or with cognitive impairment.

Prophylactic therapy

Restrict prophylactic antimicrobial therapy to situations in which it has been shown to be effective or where the consequences of infection are disastrous (see Cardiac surgery and Orthopaedic surgery). Most surgical prophylaxis should be parenteral and commenced just before the procedure (see Prophylaxis: surgical). A single dose is usually adequate for operations lasting less than 3 hours. The aim is to achieve high plasma and tissue levels at the time that contamination is most likely (ie during the procedure).

Empirical therapy

Base empirical antimicrobial therapy on local epidemiological data, and on potential pathogens and their patterns of antimicrobial susceptibility. Where appropriate, obtain specimens for Gram stain, culture and susceptibility testing before commencing antimicrobial therapy. A Gram stain (eg of sputum) or direct antigen detection methods may allow specific therapy to be commenced even before the pathogen has been cultured. If a noninfective diagnosis is confirmed, early cessation of antimicrobials is warranted. Otherwise, in the absence of a proven causative organism, continue well-chosen empirical antimicrobials for at least 48 hours.

Directed therapy

It is important to review the empirical regimen when culture results have identified the organisms present and their susceptibility to antimicrobial drugs. Remember that organisms found to be present may not necessarily be responsible for the clinical condition. The natural resolution of a bacterial infection may also result from host defences, despite laboratory-reported resistance.

Interpret laboratory data in the context of the overall clinical picture. Antimicrobial therapy directed at specific organisms should include the most effective, least toxic, narrowest spectrum drug available. This practice reduces the problems associated with broad-spectrum therapy (ie selection of and superinfection with resistant microorganisms), and will usually be the most cost-effective.

Oral or parenteral therapy

Compared with oral administration, parenteral use of antimicrobials has several disadvantages including greater risk of serious adverse events (including line-associated sepsis), higher drug product cost, additional cost of equipment, and additional time and expertise needed for administration.

Oral therapy should be used in preference to parenteral therapy unless:

- oral administration is not tolerated or is not possible (eg swallowing difficulties)
- gastrointestinal absorption is an obvious problem (eg vomiting, severe diarrhoea, gastrointestinal pathology), or a potential problem that may accentuate poor bioavailability of an oral antimicrobial
- an oral antimicrobial with a suitable spectrum of activity is unavailable
- high doses are required to achieve effective concentrations at the site of infection (eg for endocarditis, meningitis, osteomyelitis, septic arthritis) and are not readily achievable by oral administration
- urgent treatment is required due to severe and rapidly progressing illness
- the patient is unlikely to adhere to oral treatment.

If parenteral administration is used, reassess the need daily, and convert to oral therapy as soon as possible.

Topical therapy

It is important to restrict topical antimicrobial therapy to a few proven indications (eg eye infections). In general, antimicrobials recommended for topical use should not be from classes used for systemic therapy.

Combination therapy

Avoid antimicrobial combinations, unless indicated to:

- extend the spectrum (eg empirical therapy of suspected mixed infections such as pelvic inflammatory disease, spreading neck infections)
- achieve synergy that is known to improve outcomes (eg enterococcal endocarditis)
- prevent the emergence of resistant microorganisms (eg therapy of tuberculosis).

Duration of therapy

To minimise selection of antibiotic resistance, it is important to limit duration of therapy. In a few infections (eg endocarditis), the minimal effective duration of therapy has been established by clinical trials. In most bacterial infections, the optimal duration of therapy is not well defined and the usual course of 5 days is based on tradition rather than sound evidence.

Guardabassi & Kruse H (2008)

Guardabassi L, Kruse H (2008). Principles of Prudent and Rational Antimicrobial Use in Animals. *In* Guide to Antimicrobial Use in Animals. Edited by Luca Guardabassi, Rachel Williamson and Hilde Kruse, Blackwell Publishing, Oxford, pp 1-12

Disease prevention as a tool for reducing antimicrobial use

- the best way of minimizing the need for, and use of, antimicrobials and thereby aiding the containment of antimicrobial resistance, is by preventing disease.

Accurate diagnosis and antimicrobial susceptibility testing

- empirical use of antimicrobials should be avoided whenever possible and antimicrobials should be preferably prescribed on the basis of laboratory diagnosis and antimicrobial susceptibility testing.
- the use of antimicrobials should always be based upon examination of the clinical case, diagnosis of a bacterial infection and selection of a clinically efficacious antimicrobial agent.
- antimicrobials should only be used when it is known or strongly suspected that the disease is caused by bacteria, since viruses are not susceptible to antibacterial therapy.
- ideally the causal infectious agent should be identified at the species level and its antimicrobial susceptibility be ascertained before initiating antimicrobial therapy. However, in certain situations, such as when the animal is seriously ill or there is an outbreak of with high mortality or rapid spread, therapy may be initiated on the basis of clinical diagnosis (empirical treatment).
- collection of local data on antimicrobial susceptibility is the first step to rational antimicrobial use.
- monitoring reveals the emergence of new antimicrobial resistance trends and is essential in guiding the choice of appropriate drugs for empirical treatment.
- antimicrobial susceptibility testing should be done according to internationally recognised standards.

Justification of antimicrobial use

- before initiating antimicrobial therapy, even in the case of a correct diagnosis, the practitioner should ascertain that such therapy is justified.
- ideally only diseased animals should be treated, and the treatment should be as individual as possible. However, in the case of poultry ... this is not practical and mass treatment is accepted following a relevant diagnosis.
- metaphylaxis, where clinically health animals are treated along with their diseased neighbours, should be avoided.
- prophylaxis should be kept to a minimum.

Choice of an appropriate antimicrobial product and administration route

- from a strictly clinical point of view, four factors have to be considered when selecting an antimicrobial agent:
 1. clinical efficacy
 2. toxicity to the host
 3. risk for development of resistance
 4. adverse effects on commensal flora
- the spectrum of activity of the drug, its importance in human medicine and route of administration are the most important factors in accomplishing prudent and rational antimicrobial use.
- off-label use of antimicrobials should be exceptional and always under the professional responsibility of the veterinarian.

Appropriate dosage regimen

- appropriate dosage regimen (dose level, dose interval and treatment duration) is of fundamental importance to ensure rational antimicrobial use.
- an important aspect of antimicrobial misuse is patients' non-compliance.

Ethical aspects related to prescription and dispensation of antimicrobial drugs

- veterinarians have the ethical obligation to use and prescribe, when indicated, appropriate antimicrobials to cure infections in their patients, thus contributing to the health and well-being of animals.
- ...for the sake of public health, veterinarians also have the responsibility of the adoption of prudent and rational use of antimicrobials
- in addition, they have the important function of informing farmers and animal owners or managers about the potential public health consequences associated with imprudent or irrational use of antimicrobial agents in animals, and instruction them in correct handling and administration of antimicrobial products.
- over-prescription or prescription of unnecessary expensive antimicrobial products is clearly an unethical practice in the veterinary profession

AVA (2005), AVPA (2001)

AVA (Australian Veterinary Association) (2005). Guidelines for Prescribing, Authorising and Dispensing Veterinary Medicines.

AVPA (2001). AVPA code of practice for the use of antibiotics in the poultry industry. Endorsed by the Australian Chicken Meat Federation and the Australian Egg Industry Association.

Professional intervention

- “Professional intervention” can be defined as intervention by a registered veterinarian between the drug wholesaler, premix supplier or feedmill and the end user of the substance, in such a way as to ensure that the drug is necessary, appropriate and will be used (and withheld) correctly.
- Maintenance of records of supply
- Labelling of dispensed products
- Written instructions concerning use

Veterinary care and supervision of recipient stock

- the veterinarian must also demonstrate due care and supervision of the recipient flock

Other areas of responsibility

- the care and welfare of the poultry flock which is the subject of the proposed drug supply

Responsibilities of the veterinarian in the supply of a non-PAR antibiotic

- With the increasing public debate into the use of antibiotics in food-producing animals and the possibility that human health hazards can be created via the occurrence of antibiotic-resistant bacteria or resistance genes that develop in animals, veterinarians should ensure that Prudent Use Guidelines for Antibiotics (whether PAR or non-PAR antibiotics) are understood and should encourage adherence to these guidelines.

Off-label use of antibiotics

- Off-label use of both PAR and non PAR antibiotics by registered veterinarians should be confined to situations where medications used according to label instructions have been ineffective and where there is scientific evidence, including residue data, supporting the off-label use pattern.

WVA ‘Prudent Use of Antibiotics: Global Basic Principles’

1. Antibiotics are health management tools that are licensed to be used to enhance good husbandry practices for the purpose of disease prevention, disease treatment and production enhancement
2. Codes of good practices, Quality assurance programmes, Herd Health Surveillance Programmes (HHSP), and education programmes should promote the responsible and prudent use of antibiotics.
3. Antibiotics shall be used under the supervision of a veterinarian.
4. Therapeutic antibiotics should be used when it is known or suspected that an infectious agent is present which will be susceptible to therapy. It is the responsibility of the veterinarian to choose the antibiotic product, based on his/her informed professional judgement balancing the risks and benefits for humans and animals.
5. When antibiotics need to be used for therapy, bacteriological diagnosis with sensitivity testing should, whenever possible, be part of the informed professional clinical judgement.
6. Label instructions should be carefully followed and due attention paid to species and disease indications and contra-indications, dosage regimen, withdrawal periods, and storage instructions. Off-label use of antibiotics should be exceptional and always be under the professional responsibility of a veterinarian.
7. Antibiotics used for therapy should be used for as long as needed, over as short a dosage period as possible, and at the appropriate dosage regimen.
8. Records should be kept of all antibiotic administrations.
9. Co-ordinated susceptibility surveillance should be conducted and the results be provided to the, prescriber, supervising veterinarians and other relevant parties.

10. Efficacious, scientifically proven alternatives to antibiotics are needed as an important part of good husbandry practices.

EPRUMA (2008)

European Platform for the Responsible Use of Medicines in Animals

1 Introduction

Good health is essential for welfare and for optimal animal performance. Disease control is therefore an essential part of any successful management programme. In turn, safe food is produced by healthy animals. Disease control is part of high quality food production.

2 What is an antimicrobial and how is it made available?

The term 'antimicrobial' is in most cases synonymous with 'antibiotic', and describes a substance that kills or inhibits the growth of bacteria.

3 Ensuring animal health

Animal health starts with good husbandry practices

Farmers should regularly monitor the health and welfare of their animals. Appropriate professional veterinary advice should be sought where necessary on the effective prevention, diagnosis and treatment of disease. These key elements of animal health are in conformity with EISA's IF framework particularly chapter IX.

Management

Animal health is a precondition for animal welfare. A good welfare status will help the animal to maintain its natural resistance against diseases and good health is a precondition for the well being of an animal. Both health and welfare are much influenced by the way animals are kept and must be in compliance with existing EU legislation. Environmental conditions including temperature, humidity, clean air and bedding, amount of light, etc. should be adapted to the animal's needs. Equally important are the availability of clean water, an adequate diet, and enough space to walk and rest. Stress should be avoided as it will have a negative effect on the animal's resistance against infections.

Furthermore, proper monitoring of the animals and keeping records of the observations made is essential for an early diagnosis of conditions affecting the animal's health or welfare. A well-designed animal health plan is a key element for every farm.

Biosecurity

A special point of attention in keeping animals free of infectious diseases is biosecurity. The purpose of biosecurity is to minimise the potential for introducing disease-causing organisms onto the holding by e.g. newly purchased animals, people, vehicles and pets, to mention but a few. Relatively simple measures can be taken without excessive financial investments and these can be very effective and helpful in ensuring the health of animals. Even where a measure doesn't seem to be completely effective, it does not mean that it is worthless. A limited reduction of the risk of introduction of germs is still much better than no reduction at all.

Vaccines

Vaccines are very valuable tools in the prevention and control of many infectious diseases. They are safe and effective in enhancing animals' resistance against infections. However, there are several diseases for which no vaccines are (yet) available. In these cases other means of prevention and control, including the use of veterinary medicines, e.g. antibiotics, may be required. This applies for situations like: E acute infections, which require immediate treatment; E emerging diseases. Acting through the natural immune system, their use should always be considered in the context of a broader strategy. Other measures, such as good hygiene, good animal husbandry and disease monitoring are equally important parts of disease prevention programmes. The optimal strategy depends on the local situation on the farm, and also on factors such as area animal density, presence of pathogens in wildlife, availability of reliable tests, etc. Adequate monitoring of vaccinated animals is an essential part of a vaccination programme.

Veterinarian/farmer interaction

(animal health plan)

An open communication between the farmer and the veterinarian is essential in order to achieve optimal animal health. Preferably, it should take place at regular intervals and not only when a problem occurs. When appropriate, other experts, such as those on housing, feed, nutrition, hygiene, etc., should be consulted. The information obtained from the farmer together with the details obtained by the examination of the animals and local circumstances will allow the veterinarian to propose an optimal solution for a sustainable improvement of the animals' health and welfare. The records also assist the farmer in demonstrating compliance with good farming practice.

4 Diagnosing and treating disease

When a disease occurs, the veterinarian examines the animal(s) and the circumstances in which they are kept.

Disease diagnosis and treatment are closely linked.

When a disease occurs, the veterinarian examines the animal(s) and the circumstances in which they are kept. On the basis of this information s/he will diagnose the disease and decide on an intervention. This could be management advice on the way that the animals are kept (feeding/housing) or the prescription of a suitable (antimicrobial) therapy. If necessary, a sample may be sent to a laboratory for analysis to establish the exact bacterium causing the disease and its sensitivity and so choose the most appropriate treatment. However, if laboratory confirmation is not possible, the choice of antimicrobials is then a matter of experience and of clinical judgement based on the previous bacterial sensitivity on the farm in question. The veterinarian will evaluate the result of his/her treatment of choice and, if necessary, adjust this. Frequently, animals are kept in groups and whilst this is beneficial from practical husbandry and animal welfare aspects, it means that the group may be at risk when a disease strikes. As a result, it is sometimes necessary to treat the group. This would be the case where it is known that an infectious disease is present and where experience shows that the disease will infect most, or even all of the animals in the group once one animal shows symptoms of infection. Such use is sometimes termed 'metaphylaxis'. Bacterial infections in large flocks or herds often appear at identifiable and predictable stages during the life time of the animal, e.g. respiratory problems after regrouping, colibacillosis during the post-weaning period, shipping fever following transport, etc. Treating in situations like this is referred to as prophylactic treatment. The farmer and the veterinarian are familiar with imminent disease hazards on their farms, and early action, carefully and selectively carried out, is a necessary part of disease management. As may be appreciated, preventative action is similar to that practiced in human medicine in cases such as bacterial meningitis outbreaks in schools or colleges where the group of students potentially exposed will be treated in a preventative manner. Having taken a decision to treat with an antimicrobial, the first consideration for a veterinarian is to select the most appropriate one. The next step is to use a specific authorised medicinal product based on the diagnosis made for the disease condition involved and on the expertise of the veterinarian. A range of antimicrobials are available and the veterinarian should use his/her professional knowledge in the context of a specific disease situation to choose the product with the most appropriate spectrum. (A range of products should be used over time to guard against the possible emergence of resistance.) The continuous use of the same product for the same type of indication (e.g. respiratory, intestinal, systemic, etc.) over a long period of time should be viewed with caution, unless preliminary testing in the laboratory has shown satisfactory susceptibility of the bacteria involved. The veterinarian may use a range of products over time to guard against the possible emergence of resistance, sometimes known as a 'rotation programme' in order to safeguard long-term effectiveness and to minimise resistance selection pressure. Several new products have been introduced over the years, and these have strengthened the therapeutic armoury of the veterinarian. Antimicrobials are critical when treating, preventing and controlling animal diseases. In managing animal diseases, veterinarians often focus on controlling the disease on a herd or flock basis. In human medicine, treatment with antimicrobials is almost always directed at the individual. Prophylactic or metaphylactic administration of antimicrobials is a practice that has shown to be beneficial to maintaining herd or flock health, like in mastitis disease management. Availability of a variety of antimicrobials is a critical concern to food-animal veterinarians. It is necessary to have a wide range of safe and effective products from all antimicrobial classes available to the veterinarian in treating animal diseases in order to discourage the potential selection of resistance by the overuse of a restricted number of products. The farmer,

the veterinarian and other experts must work together to ensure that the outcome of treatment is effective. The farmer may be required to administer subsequent treatments. Where this is the case, it is essential that all instructions are followed. The farmer should report any unexpected delay in recovery to the veterinarian. If necessary, an alternative form of treatment may be commenced if the animal is not responding as expected.

Veterinary surgeon to make final choice

Today, a broad range of antimicrobials is available in the market. They vary in many different ways such as route for administration, speed and extent at which they are taken up by the animal, modes of action, speed and extent of penetration into the tissues, etc. At the same time, micro-organisms vary in the way they are affected by the different antimicrobials. For this reason, the selection of an antimicrobial must always be based on several criteria, such as the micro-organism affecting the animal(s), the occurrence of resistance against antimicrobials, the animal species, the way the antimicrobial has to be administered, etc. The selection of the proper treatment must always be made by the veterinarian after examining the animals, the local situation and making a diagnosis.

Cascade

In exceptional cases, where no medicine is authorised, there is a possibility for the veterinarian to use, for example, products that are authorised in other EU countries or for other animal species. This exception exists to avoid unacceptable suffering of animals. In these cases the veterinarian has to follow specific steps, the so-called cascade, and s/he has to make sure that there is no risk for the animal(s) concerned and for consumers of food products of animal origin.

5 Effective administration of a medicine

Successful treatment is determined by proper administration of the antimicrobial coupled with the correct quantity used for the necessary time period.

The dosage recommendation of an antimicrobial medicine has been tested extensively by the company applying for an authorisation. The purpose is to ensure that the dose given is sufficient to ensure that the appropriate quantity of the antimicrobial reaches the site of infection for a sufficient amount of time to ensure that the animal recovers from the disease. Repeated administration may be necessary in order to reach clinical success. In the human medicine context, this is achieved by, for example, taking a tablet three times a day over seven days. For animals, the same principle applies. As with human medicines, the label contains the necessary information for appropriate and safe use and storage.

Maximum residue limit

For food-producing animals, studies are required to see how quickly residues of the medicine are eliminated from the animal. Maximum residue limits (MRLs) are established to set a maximum level of the antimicrobial that may remain in the animal without posing a risk to consumers of produce taken from it. Withdrawal periods (the time between administration of the medicine and slaughter or the taking of food produce, e.g. milk or eggs) are then set to ensure that any remaining residues are below the MRL. Huge safety margins are built into the system to ensure that consumers are protected.

6 Record keeping

In relation to record keeping, in all EU Member States it is mandatory to maintain records for at least five years - irrespective of whether or not the animal is still on the farm - of all medicines used in food-producing animals, including antimicrobial treatments. In addition, it is recommended that the veterinarian, in co-operation with the farmer, keeps track of all the information related to infectious diseases on the farm. Historical information, including laboratory sensitivity data, is very valuable in planning future treatments. For safe transport, storage and disposal of medicines, legislative requirements should be followed in all cases.

Records indicate the ongoing use of antimicrobials on a farm. Trends should be observed and changes in use examined. Overall management conditions should be kept under constant review.

7 Protecting future effectiveness

Pharmacovigilance is the process whereby concerns in relation to safety or effectiveness of medicines are reported to the national authorities. Where a concern arises, the farmer should consult the veterinarian and a report of the incident should be submitted to the authorities if the veterinarian suspects that a safety or efficacy problem has arisen. This system is very beneficial in allowing the ongoing monitoring of products in use under actual field conditions.

Monitoring sensitivity by the animal health industry

Resistance is a phenomenon in which certain bacteria stop responding to treatment by a specific antibiotic. Therefore, it is of great importance to monitor the sensitivity of bacteria to antimicrobials on an ongoing basis. The monitoring of sensitivity is a complex operation which includes collection of representative samples and consistent evaluation of results. The animal health industry is engaged in this type of activity, sometimes concurrently with the regulatory authorities or government agencies. The communication of information on levels of resistance will allow veterinarians to make informed decisions on which antimicrobials they should use for the best chance of success. Moreover, monitoring antimicrobial resistance in animal production is also relevant to public health.

Conclusion

Antimicrobials have a key role to play in protecting animal health and welfare. Protecting animals against disease contributes to the production of high quality food from healthy animals whilst minimising the impact on the environment.

A comprehensive regulatory process applies before these medicines may be placed on the market. Veterinary surgeons have the necessary detailed education to select the most appropriate medicine and to ensure safe use. The farmer has a key role to play in preventing disease and in ensuring that antimicrobials are used correctly. veterinary practice since their introduction more than 60 years ago. Many of these early medicines are still successfully used today although loss of efficacy through resistance development is an ever-present risk.

It is essential that all parties work together to ensure safe use and to minimise the development of resistance. A guiding principle with respect to antimicrobials should be "As little as possible, as much as necessary" since we owe it to both present and future generations to use these agents with care and discrimination. In this way, those to come will benefit, as we have, from these valuable medicines.