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Use of antimicrobial agents in livestock

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Summary

Antimicrobial agents, especially antibacterial agents, are used throughout the world, across a diverse array of extensive and intensive livestock production systems, to protect the health and welfare of livestock and to improve their performance. While some agents that are used in livestock belong to classes that have no counterpart in human medicine, this is not the case for the most widely used agents: the tetracyclines, penicillins, macrolides and sulphonamides. Many bacterial diseases of livestock cause devastating losses of animal life and productivity. As a result, their keepers can lose their livelihoods and see a dramatic reduction in income, so there is often a great sense of urgency to treat affected animals early. However, there are a large number of bacterial pathogens that cause disease and it is frequently difficult to reach a conclusive diagnosis prior to instituting treatment. There are many ways in which existing uses of antimicrobial agents can be improved, amongst the most important are increased utilisation of veterinary professional services, the introduction of enhanced infection control measures, improved point-of-care diagnostic tests, and the application of physiologically based population pharmacokinetic–pharmacodynamic modelling.

Keywords

Antibacterial – Antimicrobial agent – Counterfeit – Critically important antimicrobials – Livestock – Pharmacokinetic–pharmacodynamic – Physiologically based pharmacokinetic – Point-of-care diagnostics – Population pharmacokinetics – Route of administration – Veterinary Services.

Introduction

The term antimicrobial agent has been defined as 'a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kills or inhibits the growth of microorganisms) at concentrations attainable *in vivo*' (292), and includes agents active against bacteria, protozoa, viruses and fungi. The most commonly used category of antimicrobial agent and the one currently of greatest public health interest is the antibacterial class and this overview will focus exclusively on the antibacterial subset of antimicrobial agents and will use the term antimicrobial in this narrower context. Furthermore, this review will focus only on selected terrestrial livestock species, especially cattle, pigs and poultry, which globally provide the top three sources of meat. Information on antimicrobial use in other species (especially buffalo, camels and goats) can sometimes be difficult to find and is often incomplete, although in the case of bees there is an excellent recent review (220).

The use of antimicrobial agents in livestock continues to allow the growth of healthier and more productive animals, with lower incidence of disease, reduced morbidity and mortality, and the production of abundant quantities of nutritious, high-quality and low-cost food for human consumption (192). Sixty years ago the use of antimicrobial agents was reviewed, with findings that would not be unexpected today (232, 233). Penicillin (in the form of procaine and benzathine salts and penethemate) was used to treat various conditions, including bovine mastitis, pneumonia in calves, metritis in cows, and erysipelas in pigs. Streptomycin, especially the less toxic dihydrostreptomycin, was found to be useful for preserving bovine semen and treating bovine mastitis, leptospirosis, pneumonia, intrauterine infections and swine dysentery. Bacitracin was indicated for bovine infectious keratitis, mastitis and topical infections. Chlortetracycline and oxytetracycline were widely and successfully used for bovine pneumonia prophylaxis and treatment of calf and piglet scours, foot rot, metritis and acute mastitis, as well as *Pasteurella multocida*

infections in poultry. At this time erythromycin, the first of the macrolides, was being developed for use in livestock and penicillin, the tetracyclines, and bacitracin had recently been shown to promote the growth of pigs, poultry and calves.

While it is clear that the use of antimicrobial agents has broad and significant benefits, the appropriate use of these agents, including their selection, administration, monitoring and assessment, is a highly skilled discipline that incorporates all of the experience and expertise of veterinarians. Valuable sources of information that veterinarians rely on include textbooks and chapters on infectious diseases of multiple livestock species (47, 86, 97, 213, 244), or specific species such as cattle (7, 10, 48, 283), sheep and goats (3, 175), pigs (33, 80, 177, 298), and poultry (112, 142, 199, 225).

Important subjects that will be addressed in this review include the patterns of antimicrobial use (prophylaxis, metaphylaxis, treatment and nutritional), the extent of use, fundamental elements of appropriate use and refinements to current use (including the role of physiologically based pharmacokinetic–pharmacodynamic modelling and population pharmacokinetics), diagnosis by point-of-care tests (POCTs), quality-assurance programmes, professional intervention by veterinarians and strengthening of measures to ensure the quality of veterinary medicines.

Veterinary and human antimicrobial use

It will quickly become apparent that there are some significant differences between the use of antimicrobial agents in livestock and their use in humans. The most notable differences appear in intensive livestock production systems (that will later be classified as landless livestock production systems) where large populations of livestock are raised at a single site and often in the same airspace. Some important differences between veterinary and human antimicrobial uses are set out in Table I.

Global sales of antimicrobial products for use in livestock

It is helpful to gain an insight into the dimensions of potential antimicrobial use in livestock. While the number of animals treated and the dose regimen implemented provide more information about use (see below), an outline of sales is a useful starting point.

A report by Vetnosis (68) summarises the global animal health anti-infective market in all species. The anti-infective market includes products to treat bacterial and fungal diseases but does not include the medicinal feed additives. Thus, the anti-infective market includes

Table I
Differences between veterinary and human uses of antimicrobial agents

Livestock use	Human use
Populations often treated	Individuals treated
Diagnostic pathway may involve post-mortem	Post-mortem avoided
Cost of treatment very important	Cost less important
Range of bodyweights can be several orders of magnitude across different species	Limited range of weights
Dose rates for oral mass treatment dependent on feed or water intake	Oral dose usually based on age (less frequently on body weight)
Many different monogastric and polygastric species	Only one gastrointestinal type
Withholding period must be observed	No withholding period
Parenteral injections administered to sites that can be trimmed at slaughter	Parenteral injections administered to sites with least pain or reactivity
Long-acting injections preferred	Short-acting injections or oral preparations are normal practice
Prevention of infection most important factor	Treatment of infection usual practice
Diagnosis supported by disease behaviour in population	Diagnosis based on individual features
Majority of animals are young	Full spectrum of ages, neonate to geriatric
Chronic comorbidities rare	Chronic comorbidity common in older individuals
Global antibacterial sales 2009 (all species): US$3.8 billion (Vetnosis 2009 Animal health market)	Global antibacterial sales 2009 : US$42 billion (103)
Top three classes by sales (2009): macrolides (US$0.6 billion), penicillins (US$0.6 billion), tetracyclines (US$0.5 billion)	Top three classes by sales (2009): cephalosporins (US$11.9 billion), broad-spectrum penicillins (US$7.9 billion), fluoroquinolones (US$7.1 billion)

injections, topical preparations, intramammary products and products for oral administration other than by feed (for example, oral liquids, pastes and boluses). For the year ending December 2007, global sales of animal health products totalled US$17.9 billion, with anti-infectives representing 15.5% or US$2.8 billion (and medicinal feed additives, which include the anticoccidial agents as well as antibacterials, representing another 11.7% or approximately US$2.1 billion). In 2007, product sales included macrolides (US$629 million, 22.7%), penicillins (US$550 million, 19.8%), tetracyclines (US$533 million, 19.2%), quinolones (US$531 million, 19.1%) and sulphonamides (US$118 million, 4.3%). Regional sales included West Europe (US$1,110 million, 40.1%), North America (US$725 million, 26.1%), the Far East (US$435 million, 15.7%), Latin America (US$275 million, 9.9%), East Europe (US$150 million, 5.4%) and the Rest of World (US$80 million, 2.9%). Sales by species included cattle (US$1,140 million, 41.1%), pigs (US$670 million, 24.1%), poultry (US$150 million, 5.4%), sheep (US$115 million, 4.1%) and companion animal and other species representing sales of US$700 million (25.2%). Estimated sales of the leading products included oxytetracycline (US$272 million), enrofloxacin (US$259 million), chlortetracycline (US$257 million), ceftiofur (US$200 million), florfenicol (US$114 million) and tulathromycin (US$90 million).

It should be recognised that there is no direct relationship between sales and doses administered. Older products such as the tetracyclines tend to be inexpensive and the cost per dose is likely to be significantly less than the cost of a dose of a more recently marketed quinolone or macrolide.

Global livestock production

The scale of antimicrobial use in livestock is related to the number of animals, the production system, prevailing risk factors for disease and ability to acquire antimicrobial agents.

Animal agriculture is the most widespread use of the world's land surface. In many areas it is the only means of producing food from inedible vegetation. In almost all farming systems it is essential for converting inedible by-products and waste

Table II
Global livestock numbers and the top ten producers for each species

Livestock species	Global animal numbers (millions) 2005	2006	2007	2008	2009	Top 10 producers in 2009 (millions of animals)
Buffalo	176.4	179.5	182.6	185.3	187.9	India (106.6); Pakistan (29.9); China (23.3); Nepal (4.7); Egypt (4.0); the Philippines (3.3); Myanmar (3.0); Vietnam (2.9); Indonesia (1.9); Thailand (1.7)
Camels	23.9	24.5	25.2	25.8	25.9	Somalia (7.0); Sudan (4.5); Ethiopia (2.4); Niger (1.7); Mauritania (1.5); Chad (1.4); Mali (1.2); Pakistan (1.0); Kenya (0.9); India (0.6)
Cattle	1,350.1	1,360.2	1,360.4	1,373.1	1,380.2	Brazil (205.3); India (172.5); USA (94.5); China (84.1); Ethiopia (50.9); Argentina (50.8); Sudan (41.6); Pakistan (33.0); Mexico (32.0); Australia (27.9)
Chickens	16,920.1	17,325.4	17,810.9	18,110.7	18,631.4	China (4,702.7); USA (2,100.0); Indonesia (1,341.8); Brazil (1,234.2); India (613.0); Iran (513.0); Mexico (510.0); Russian Federation (366.3); Pakistan (295.0); Japan (285.3)
Ducks	1,097.7	1,107.7	1,132.7	1,154.1	1,175.6	China (769.4); Vietnam (84.1); Malaysia (48.0); Indonesia (42.4); India (35.0); France (24.3); Bangladesh (24.0); Thailand (16.3); Myanmar (12.5); the Philippines (10.6)
Goats	831.3	832.7	841.4	863.3	879.7	China (152.5); India (126.0); Bangladesh (60.6); Pakistan (58.3); Nigeria (55.1); Sudan (43.3); Iran (25.5); Ethiopia (22.0); Mongolia (20.0); Indonesia (15.8)
Horses	58.7	58.8	59.0	58.9	59.1	USA (9.5); China (6.8); Mexico (6.4); Brazil (5.5); Argentina (3.7); Colombia (2.5); Mongolia (2.2); Ethiopia (2.0); Kazakhstan (1.4); Russian Federation (1.4)
Mules	12.0	11.9	11.7	11.2	11.1	Mexico (3.3); China (3.0); Brazil (1.3); Morocco (0.5); Colombia (0.4); Ethiopia (0.4); Peru (0.3); Argentina (0.2); India (0.2); Iran (0.2)
Pigs	907.8	926.6	919.6	936.4	941.8	China (450.9); USA (67.1); Brazil (38.0); Vietnam (27.6); Germany (26.9); Spain (26.3); Russian Federation (16.2); Mexico (15.2); France (14.8); Poland (14.3)
Sheep	1,094.8	1,099.8	1,100.3	1,089.7	1,077.3	China (128.6); Australia (72.7); India (65.7); Iran (53.8); Sudan (51.6); Nigeria (34.7); New Zealand (32.4); UK (32.0); Pakistan (27.4); Ethiopia (26.0)
Turkeys	446.5	454.4	472.2	483.3	458.0	USA (249.9); Chile (28.5); Italy (24.4); France (23.5); Brazil (23.0); Russian Federation (12.4); Germany (12.0); Poland (8.1); Morocco (7.5); Portugal (6.8)

UK: United Kingdom
USA: United States of America
Source: live animal statistics at: www.faostat.fao.org, updated 17 May 2011

materials into food. For most of the 2.6 billion people depending on smallholder farming systems livestock production is essential for diversifying income sources, maintaining soil fertility and providing draught power and transportation (254). Livestock produce around 30% of the agricultural gross domestic product (AGDP) in the developing world, and about 40% of global GDP.

To provide an overview of the global population of livestock species and annual production of livestock products, Table II summarises animal numbers and the top ten countries for each livestock species while Table III provides information on meat, milk, egg and wool production.

An examination of Table II makes it apparent that for different species of livestock the list of top ten producers varies considerably. Some countries dominate the production of particular livestock species, notably China for duck and pig production, India for buffalo production, the United States (USA) for turkey production, and Brazil and India for cattle production. A number of countries are among the top ten producers of several different species; Ethiopia, for example, has large populations of camels, cattle, goats, horses, mules and sheep. Yet, antimicrobial use may not be related to animal population alone as the production system is possibly of greater importance.

The major food commodities produced by livestock include bovine and buffalo milk, eggs, and pig, chicken and cattle meat.

The world's livestock production systems (LPS) have been shaped by the requirements of linking demand with the availability of feed, water, labour and capital for livestock production. Production systems vary enormously in different regions and are the subject of ongoing and sometimes rapid and dramatic change. A widely used and valuable classification of LPS (239) applies criteria based on degree of integration with crops, land-use, climate zone, intensity of production and source of water to characterise the 11 systems described in Figure 1.

Table IV illustrates the relative global importance in livestock population and production of the four higher-level LPS: landless LPS (LL), grassland-based LPS (LG), mixed rainfed LPS (MR) and mixed irrigated LPS (MI) (Fig. 1).

Table III
Global production of livestock products (million tonnes)*

Livestock product	2005	2006	2007	2008	2009
Milk					
Buffalo milk, whole, fresh	78.8	80.6	83.6	89.4	92.1
Camel milk, whole, fresh	1.6	1.6	1.8	1.8	1.8
Cows' milk, whole, fresh	543.8	559.8	571.2	580.4	583.4
Goats' milk, whole, fresh	14.6	14.7	14.9	15.4	15.5
Sheep milk, whole, fresh	9.0	9.3	9.1	9.1	9.2
Milk, Total	**647.7**	**666.1**	**680.7**	**696.1**	**702.1**
Eggs					
Eggs, primary	61.3	62.5	64.4	67.0	68.0
Meat					
Buffalo meat	3.0	3.1	3.2	3.2	3.3
Camel meat	0.3	0.3	0.3	0.4	0.4
Cattle meat (beef)	59.7	61.7	63.3	61.2	61.7
Chicken meat	70.2	72.3	76.7	80.8	82.5
Duck meat	3.3	3.3	3.5	3.7	3.9
Goat meat	4.7	4.7	4.8	4.9	5.1
Horse meat	0.8	0.8	0.7	0.7	0.7
Pig meat (pork)	99.3	101.1	100.0	103.8	106.4
Sheep meat	7.9	8.1	8.4	8.5	8.5
Turkey meat	5.2	5.2	5.4	5.6	5.3
Meat, Total	**261.1**	**267.7**	**273.9**	**280.1**	**285.3**
Wool					
Wool, greasy	2.3	2.2	2.2	2.1	2.0

Source: www.faostat.fao.org
*Totals are based on original data and presented figures have been rounded, in addition, total meat includes some minor meat sources that are not presented in the table

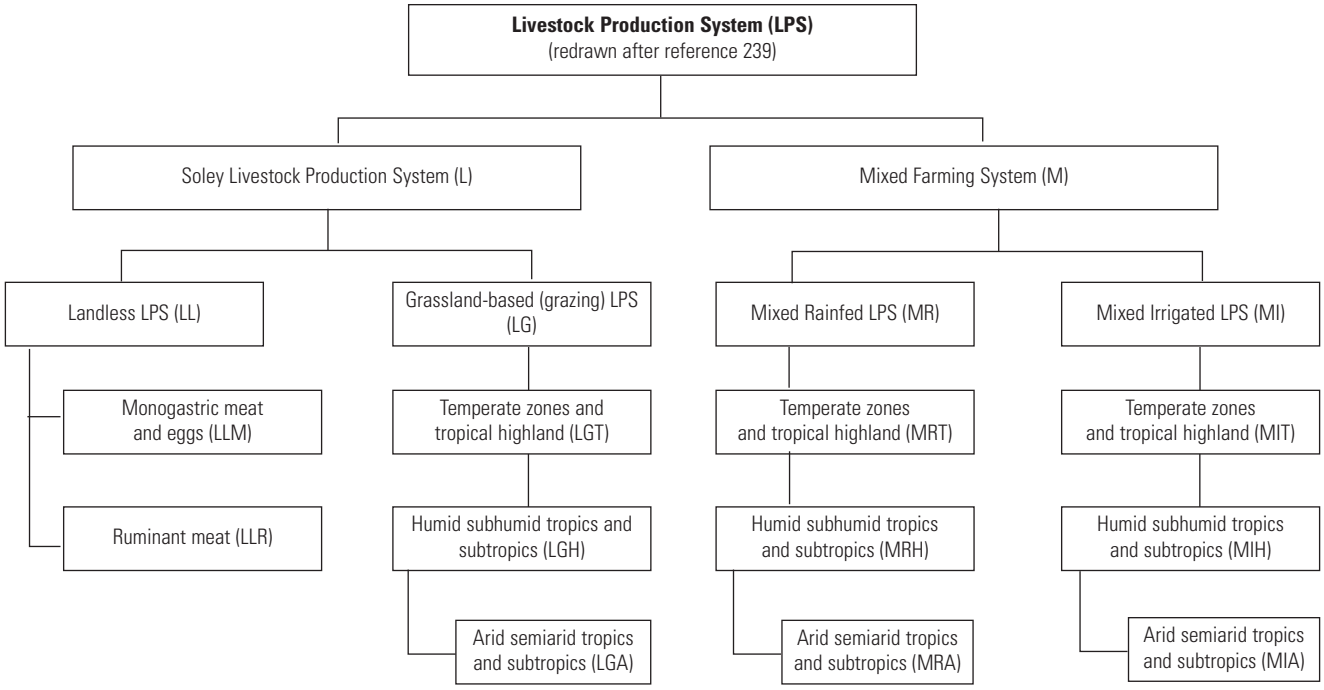


Fig. 1
Livestock production systems

Table IV
Global livestock population and production in different livestock production systems
Figures in bold represent the major livestock production system for each commodity

Parameter	Livestock production system			
	Landless	Grassland	Mixed, rain-fed	Mixed, irrigated
Population (million head)				
Cattle & buffalo	29	406	**641**	450
Sheep & goats	9	590	**632**	546
Production (million tonnes)				
Beef	4	15	**29**	13
Mutton	0.1	**4**	**4**	4
Pork	**53**	1	13	29
Poultry meat	**53**	1	8	12
Milk	–	72	**319**	204
Eggs	**36**	1	6	17

Source: Adapted from Steinfeld *et al.* (249) using global averages for 2001 to 2003

It can be seen that landless systems that produce monogastric animals only (LLM) (otherwise known as intensive production units and often housing tens of thousands of animals in a single environment) are the major source of pig and poultry meat and eggs. Conversely, intensive production systems play only a minor role in global ruminant production (LLR). Most ruminant production takes place in mixed production systems that are rainfed or irrigated (MR or MI), although grazing systems producing ruminants are also important (LG). Similarly, most of the world's milk supply is derived from mixed farming systems.

No systematic studies have been undertaken to explore the relationship between a particular LPS and the use of antimicrobial agents. However, risk factors for the major diseases of livestock are well known (see reference materials on infectious diseases described in the introduction) and the global trend towards intensification has the potential to increase the need for and cost-effectiveness of antimicrobial use, especially in the early stages of intensification when biosecurity, vaccination and other important disease control measures are not as rigorously implemented. As noted recently (201), veterinary medicines are used even in the most remote communities and are often administered by owners with little or no professional input, although the level of use is very low compared with that in intensive LPS.

Due to population growth, increasing urbanisation with increased demand for easily cooked nutritious food, and rising incomes that allow people to express their food preferences, the demand for livestock products, especially the products which smallholders can produce competitively, is the fastest growing market in the agricultural sector (254). By supplying meat, milk, eggs and offal, livestock account for approximately 13% of

worldwide human calorie consumption and 30% of protein consumption, while also contributing to crop production through the provision of transport and manure (249). Livestock production and marketing can help stabilise the food supply, acting as a buffer to economic shocks and natural disasters for individuals and communities. However, the food supply from livestock can be destabilised, particularly by diseases (76), and disease prevention and treatment is an important issue, especially when veterinary infrastructure is unavailable. Much of the future demand for livestock products, particularly from people living in urban areas, will have to be met by intensive medium- and large-scale production units with the potential to increase production per animal, per unit of land and per unit of time. The organisation of farming practice is fluid and dynamic as increasing productivity is sought. For example, in the USA significant increases in farm size between 1987 and 2007 have been associated with increased efficiency, productivity and economics (190). The most notable change was the phenomenal 2,400% increase in the size of farms selling pigs. By 2007, as a result of significant changes in the pig sector, half of all pigs produced in the USA were produced on farms selling 30,000 pigs or more. Livestock production is also shifting geographically, first from rural areas to urban and peri-urban areas, to get closer to consumers, then towards the sources of feedstuffs. There is also a shift in species, with production of monogastric species (pigs and poultry, mostly produced in industrial units – LLM) growing rapidly, while the growth of ruminant production (cattle, sheep and goats, often raised extensively) slows (249). Changes in rapidly growing developing countries are in stark contrast with trends in developed countries, where consumption of livestock products is growing only slowly or stagnating. The shifts in relative importance of the different LPS are likely to be associated with many unpredictable changes in the use of antimicrobial agents and provide an opportunity for strengthened Veterinary Services to deliver advice and guidance on appropriate use.

Infectious diseases of livestock

There are a large number of infectious diseases of livestock caused by a diversity of viral, bacterial, fungal, protozoal and metazoal pathogens. Indeed many diseases are polymicrobial, with several diseases resulting from a complex pathogenesis involving viral and bacterial agents (32, 193). Antiviral and antifungal agents are rarely used in livestock. However, the impact of many important viral diseases is controlled by vaccination. This review is focused on antibacterial agents and Table V presents a summary of the most important bacterial pathogens of cattle, sheep, goats, pigs and poultry. Table V also includes a synopsis of the important protozoal agents (many of which are prevented or treated by agents with a spectrum of activity that includes protozoa as well as bacteria, e.g. the tetracyclines, sulphonamides and fluoroquinolones) and a list of the top five clinical syndromes in each species as reported by Member Countries of the World Organisation for Animal Health (OIE) (274).

There are a multitude of pathogens each involved in one or more disease syndromes. Each pathogen has its own epidemiology, set of risk factors, pathogenic pathway and vulnerable host. Not every pathogen is present in every country or every region of each country. Veterinary clinicians should be familiar not only with the individual diseases of livestock but also with their differential diagnoses and the relative prevalence of each condition likely to be encountered in their area (213). It is only with this knowledge that an initial therapeutic plan can be developed.

In 2000, the International Livestock Research Institute was commissioned to undertake a study to evaluate which diseases of livestock are most important to the poor in three major regions of the world (sub-Saharan Africa, South Asia and South-East Asia). The methodology included a series of consultative workshops with experts working at the front line of veterinary services (drawn from departments of Veterinary Services, non-governmental organisations, research institutions, universities, animal health service development projects and intergovernmental organisations) combined with literature reviews (203). Table VI is based on information contained in this report and identifies the major diseases of livestock in Africa and Asia.

Many of the diseases included in the priority list in Table VI are amenable to prevention by vaccination (see Table VIII), but effective vaccination requires cold chain security to ensure vaccine quality and best practice vaccination, neither of which is readily available in Africa or Asia.

A comparison of Tables VI and VII shows that the priority pig diseases in Africa/Asia are quite different from the bacterial diseases affecting pig production in the USA. It is apparent that bacterial diseases are important in each of the four production categories of pig, but least so in breeding females. Preweaned pigs are affected most by navel and intestinal infections, nursery pigs by *Streptococcal* infection and colibacillosis and the older grower/finisher pigs are affected by respiratory disease and enteric *Lawsonia* infection. As is common with all species (including humans) there is an apparent age predisposition to certain disease syndromes. Interestingly, while neonatal mortality is common to pig production in the USA, Africa and Asia, the survey presented in Table VI did not identify as a priority any of the diseases encountered in pig production in the USA.

Table V
Bacterial and protozoal agents of livestock diseases and major clinical syndromes

Cattle	Sheep and goats	Pigs	Poultry
Bacteria			
– *Actinobacillus lignieresii, seminis* – *Actinomyces bovis* – *Arcanobacterium pyogenes* – *Bacillus anthracis* – *Bacteroides melaninogenicus* – *Borrelia burgdorferi* – *Brucella abortus, canis, melitensis, suis* – *Burkholderia pseudomallei* (Melioidosis) – *Campylobacter coli, fetus* subsp. *venerealis, jejuni* – *Chlamydia* spp. *Clostridium botulinum, chauvoei, haemolyticum, novyi, perfringens, septicum, sordellii, tetani* – *Corynebacterium pseudotuberculosis, renale* – *Cowdria ruminantium* (heartwater) – *Coxiella burnetii* (Q fever) – *Dermatophilus congolensis* – *Escherichia coli* (including Verocytotoxigenic *E. coli*) – *Fusobacterium necrophorum* – *Histophilus somni* – *Leptospira canicola, grippotyphosa, hardjo, icterohaemorrhagiae, pomona* – *Listeria monocytogenes* – *Mannheimia haemolytica, varigena* – *Moraxella bovis* – *Mycobacterium bovis, paratuberculosis* (Johne's disease) – *Mycoplasma bovis, dispar, mycoides* subsp. *mycoides* (contagious bovine pleuropneumonia) – *Pasteurella multocida* – *Prevotella melaninogenica* – *Pseudomonas aeruginosa* – *Salmonella* (many serovars including Dublin, Newport, Typhimurium and others) – *Staphylococcus* spp. (including *aureus* and coagulase negative staphylococci) – *Streptococcus agalactiae, bovis, dysgalactiae, uberis* – *Yersinia enterocolitica, pseudotuberculosis*	– *Actinobacillus licheniformis, lignieresii, pleuropneumoniae, seminis* – *Arcanobacterium pyogenes* – *Bacillus anthracis, cereus, licheniformis* – *Bordetella paratussis* – *Borrelia burgdorferi* – *Brucella ovis, melitensis* – *Burkholderia pseudomallei* (Melioidosis) – *Campylobacter fetus* subp. *fetus, jejuni* – *Chlamydophila abortus, pecorum, psittaci* – *Clostridium botulinum, chauvoei, haemolyticum, novyi, perfringens, septicum, sordellii, tetani* – *Corynebacterium pseudotuberculosis, renale* – *Coxiella burnetii* – *Dermatophilus congolensis* – *Dichelobacter nodosus* – *Ehrlichia ruminantium, ovis* – *Erysipelothrix rhusiopathiae* – *Escherichia coli* – *Fusobacterium necrophorum* – *Histophilus ovis, somni* – *Klebsiella pneumonia* – *Leptospira hardjo, pomona, grippotyphosa, ballum* – *Listeria ivanovii, monocytogenes* – *Mannheimia haemolytica* – *Moraxella* spp. (including *ovis*) – *Mycobacterium avium, bovis, paratuberculosis* (Johne's disease) – *Mycoplasma capricolum* subsp. *capripneumoniae, M. capricolum* subsp. *capricolum, M. mycoides* subsp. *mycoides, M. agalactiae, M. ovipneumoniae, M. conjunctivae, M. arginini, M. bovis, M. putrefaciens* – *Pasteurella multocida, trehalose* – *Pseudomonas aeruginosa, maltophilia, indigofera* – *Salmonella* (many serovars including Typhimurium, Abortusovis, Montevideo, Dublin*)* – *Staphylococcus intermedius, aureus, chromogens* – *Streptococcus* spp. – *Yersinia enterocolitica, pseudotuberculosis*	– *Actinobacillus pleuropneumoniae, suis* – *Actinobaculum suis* – *Arcanobacterium pyogenes* – *Bacillus anthracis* – *Bordetella bronchiseptica* – *Borrelia suilla* – *Brachyspira hyodysenteriae* (swine dysentery), *pilosicoli* – *Brucella suis* – *Burkholderia pseudomallei* (Melioidosis) – *Campylobacter coli, jejuni* – *Chlamydophila psittaci, pecorum, trachomatis* – *Clostridium botulinum, chauvoei, difficile, novyi, perfringens, septicum, tetani* – *Enterococcus faecium* group *(durans, hirae), faecalis* – *Erysipelothrix rhusiopathiae* – *Escherichia coli* (enterotoxigenic *E. coli;* oedema disease *E. coli*; attaching and effacing *E. coli*) – *Fusobacterium necrophorum* – *Haemophilus parasuis* – *Lawsonia intracellularis* (proliferative enteropathy; porcine intestinal adenomatosis, ileitis) – *Leptospira (pomona, tarassovi, bratislava, canicola, icterohaemorrhagiae, grippotyphosa, hardjo, sejroe)* – *Mycobacterium bovis, avium* – *Mycoplasma haemosuis* (formerly *Eperythrozoon suis*), *hyopneumoniae, hyorhinis, hyosynoviae, suis* – *Pasteurella multocida* – *Rhodococcus equi* – *Salmonella* (many serovars, including Choleraesuis) – *Staphylococcus aureus, hyicus* – *Streptococcus dysgalactiae* subsp. *equisimilis, porcinus, suis* – *Yersinia enterocolitica*	– *Avibacterium gallinarum* (formerly *Pasteurella gallinarum), paragallinarum* (formerly *Haemophilus paragallinarum*) (infectious coryza) – *Bordetella avium* (turkey coryza) – *Borrelia anserine* – *Brachyspira* spp. *(intermedia, pilosicoli, alvinipulli, hyodysenteriae*) (avian intestinal spirochetosis) – *Campylobacter coli, jejuni* – *Chlamydophila psittaci* (avian chlamydiosis) – *Clostridium botulinum* (especially type C), *colinum* (ulcerative enteritis), *perfringens* types A and C (necrotic enteritis) – *Enterococcus* spp. *(faecalis, faecium, durans, avium, hirae*) – *Erysipelothrix rhusiopathiae* – *Escherichia coli* (avian pathogenic *E. coli;* colibacillosis) – *Gallibacterium anatis biovar haemolytica* (formerly *Pasteurella haemolytica*) – *Haemophilus paragallinarum* (coryza) – *Listeria monocytogenes* – *Mycobacterium avium* (avian tuberculosis) – *Mycoplasma gallisepticum, iowae meleagridis, synoviae* – *Ornithobacterium rhinotracheale* – *Pasteurella multocida* (fowl cholera) – *Pseudomonas aeruginosa* – *Reimerella anatipestifer* – *Salmonella enterica* subsp. *arizonae* – *Salmonella enterica* subsp. *enterica* serovar Enteritidis (paratyphoid)*;* *Salmonella* Gallinarum-Pullorum (pullorum disease, fowl typhoid); *Salmonella* Typhimurium (paratyphoid) – *Staphylococcus aureus* – *Streptococcus zooepidemicus*

Table V (cont.)
Bacterial and protozoal agents of livestock diseases and major clinical syndromes

Cattle	Sheep and goats	Pigs	Poultry
Protozoa			
– *Anaplasma centrale marginale, phagocytophilum*	– *Anaplasma maestertum, ovis, phagocytophilum*	– *Cryptosporidium* spp.	*Eimeria* spp.
– *Babesia bigemina, bovis, divergens*	– *Cryptosporidium* spp.	– *Eimeria* spp.	
– *Cryptosporidium* spp.	– *Eimeria* spp.	– *Giardia*	
– *Giardia*	– *Neospora caninum*	– *Isospora suis*	
– *Neospora caninum*	– *Sarcocystis*	– *Toxoplasma gondii*	
– *Theileria annulata* (Mediterranean fever), *orientalis (genotypes chitose, ikeda, buffeli and types 4-8), parva* (East Coast fever)	– *Theileria lestoquardi, ovis, separata*		
	– *Toxoplasma gondii*		
– *Tritrichomonas fetus*			
– *Trypanosoma brucei gambiense, T. brucei rhodesiense*			
– *Trypanosoma vivax, congolense, brucei* subsp. *brucei*			
– *Trypanosoma evansi* (Surra)			
Major clinical syndromes in each species*			
– Septicaemia, sepsis, abscess, toxaemia and endotoxaemia	– Digestive diseases	– Digestive diseases	– Digestive diseases
	– Respiratory diseases	– Septicaemia, sepsis, abscess, toxaemia and endotoxaemia	– Respiratory diseases
– Digestive diseases	– Septicaemia, sepsis, abscess, toxaemia and endotoxaemia		– Septicaemia, sepsis, abscess, toxaemia and endotoxaemia
– Mastitis	– Mastitis	– Respiratory diseases	– Skeletal, articular, locomotor, foot
– Respiratory diseases	– Reproductive diseases	– Skeletal, articular, locomotor, foot	– Skin diseases, trauma
– Reproductive diseases		– Reproductive diseases	

** Source*: World Organisation for Animal Health, Biological Standards Commission (274)

Vaccines

A vital component of all disease control plans is consideration of the most effective vaccination programme. Table VIII presents a summary of the bacterial, viral and protozoal pathogens of cattle, sheep, goats, pigs and poultry against which vaccines are available in at least one country.

Vaccine use is an essential part of disease management in intensive animal production and vaccines are also commonly used in extensive livestock production systems and can lead to dramatic improvements in animal health in village livestock (63, 150). From an antimicrobial-use perspective, it should be appreciated that vaccine use can lead to significant reductions in the use of antimicrobial agents. For example, the use of the porcine reproductive and respiratory syndrome virus vaccine has been associated with a significant improvement in the health of pigs and a reduction in the use of antimicrobial agents (15). Increased antimicrobial use is associated with the emergence of the immunosuppressive post-weaning multisystemic wasting syndrome in pigs (121) and vaccination to prevent emergence reduces concurrent bacterial disease and reduces the need to use antimicrobial agents.

Antimicrobial agents

In view of the global importance of bacterial disease in adversely impacting the health and welfare of livestock it is not surprising that there are a large number of antibacterial agents available. Details of antibacterial agents that are approved for use in livestock, together with information on antimicrobial class, site of antibacterial action, importance rating in veterinary and human health and examples of formulations available for cattle, sheep, pigs and broilers are provided in this issue in the paper by Acar, Pastoret, Page and Moulin (2). Box 1 presents information on a selection of government and private veterinary medicine formularies from which the list of antibacterial agents was derived. The information provided in the online formularies includes indications for use, dose regimens and other important product details.

Amongst the antimicrobial agents in use worldwide there are 27 different antibacterial classes used in animals, most of which have human antibacterial counterparts, but there are nine classes exclusively used in animals. Because of concerns about the selection and dissemination of antimicrobial resistance between animals and humans, the concept of 'critically important antimicrobial agents' has been developed.

Table VI
Top-ranked diseases/pathogens, according to their impact on the poor in developing nations (in Africa and Asia) Diseases are listed alphabetically within each group; diseases with a bacterial component are in bold. Adapted from Perry *et al.* (203)

Top 10 diseases in Africa and Asia				
Buffalo	**Cattle**	**Sheep/goats**	**Poultry**	**Pigs**
Anthrax	**Anthrax**	**Anthrax**	Coccidiosis	African swine fever
Brucella abortus	***Brucella abortus***	Ectoparasites	Duck virus enteritis	***Brucella suis***
FMD	**CCPP**	Haemonchosis	Ectoparasites	Cysticercosis
Haemorrhagic septicaemia	FMD	**Heartwater**	**Fowl cholera**	Ectoparasites
Liver fluke (fasciolosis)	**Haemorrhagic septicaemia**	Helminthosis	Fowl pox	FMD
Reproductive disorders	Liver fluke	Liver fluke	Helminthosis	Helminthosis
Respiratory complexes	Nutritional/micronutrient deficiency	**Neonatal mortality**	**Infectious coryza**	Classical swine fever
Rinderpest*	**Reproductive disorders**	Peste des petits ruminants	**Neonatal mortality**	Japanese B encephalitis
Trypanosoma evansi	*Toxocara vitulorum*	**Respiratory complexes**	Newcastle disease	**Neonatal mortality**
Toxocara vitulorum	Trypanosomosis	Sheep and goat pox	Nutritional/micronutrient deficiency	Trypanosomosis
Next ranked diseases in Africa and Asia				
Blackleg	Babesiosis	Bluetongue	Duck virus hepatitis	
Bovine tuberculosis	**Blackleg**	***Brucella melitensis***	Gumboro	
Buffalo pox	**Dermatophilosis**	**CBPP**	**Mycoplasmosis**	
Diarrhoeal diseases	**Diarrhoeal diseases**	**Clostridial diseases**	**Salmonellosis**	
Mastitis	Helminthosis	FMD		
Nutritional/micronutrient deficiency	Infectious bovine rhinotracheitis	**Foot problems**		
	Mastitis	Orf		
	Neonatal mortality	Paratuberculosis		
	Rinderpest*	Rift Valley fever		
	Theileria annulata infection	Trypanosomosis		

* Global freedom from rinderpest was declared by the World Organisation for Animal Health and the Food and Agriculture Organization of the United Nations in June 2011
CCPP: contagious caprine pleuropneumonia
FMD: foot and mouth disease
Available at: www.ilri.org/InfoServ/Webpub/fulldocs/investinginAnimal/Book1/media/index.htm

Critically important antimicrobials

The list of Critically Important Antimicrobials was developed as a reference to help formulate and prioritise risk assessment and risk management strategies for containing antimicrobial resistance due to non-human antimicrobial use (74). A summary of the criteria underpinning the classification of medical (290) and veterinary antimicrobial agents (291) is presented in Table IX.

Antimicrobial use patterns

There are four major use patterns of antimicrobial agents in livestock, as described in Table X and illustrated in Figure 2. It is important to note that these four patterns have been in use for many decades and were thoroughly described in the Swann Report in 1969 (255).

Therapeutic use of antimicrobial agents

Figure 2 shows that prophylaxis, metaphylaxis and treatment are applied at different times during pathogen challenge. In intensive livestock operations (LLM and LLR) the objective is to minimise the occurrence of disease, and significant resources are generally applied to mitigate disease risk factors by ensuring each animal is as robust and resistant to pathogen challenge as possible. Risk mitigation is supported by careful selection of genotype, vaccination, biosecurity, nutrition, environmental controls and sound husbandry. Nevertheless, disease challenge is expected and early intervention is likely to reduce the impact as illustrated in Figure 2.

The value of prophylaxis in reducing pathogen challenge and disease and enhancing animal health and welfare has been demonstrated repeatedly for necrotic enteritis in broilers (31, 132, 286) and bovine respiratory disease (78, 98, 106, 165, 218, 236, 237, 238, 276, 278). In addition, there is abundant evidence that metaphylaxis has significant benefits in reducing the impact of bovine

Table VII
Bacterial diseases of pigs in the United States of America

Bacterial disease	Percentage of sites where each bacterial disease was known or suspected of causing morbidity or mortality* (12 months to May 2006)			
	Breeding females	Preweaned pigs (mean age <19 days)	Nursery pigs (mean age 19–64 days)	Grower/finisher pigs (mean age 65–180 days)
Actinobacillus pleuropneumoniae	4.2		2.9	8.5
Atrophic rhinitis				5.7
Clostridium		16.2		
Colibacillosis (*Escherichia coli*)		47.4	31.8	
Diarrhoea, other			20.7	
Erysipelas	7.1			4.0
Glasser's disease (*Haemophilus parasuis*)	5.0			18.7
Greasy pig disease (*Staphylococcus hyicus*)		27.6	27.5	
Ileitis (*Lawsonia intracellularis*)	16.2			41.7
Mycoplasma pneumonia	17.0		29.4	39.5
Navel infection		43.1		
Oedema disease			9.0	
Salmonella	6.1		8.9	12.0
Streptococcus suis (meningitis, polyserositis, arthritis)		38.5	49.9	
Swine dysentery	1.7		4.8	2.8
Undifferentiated pneumonia		25.0		

* *Source*: United States Department of Agriculture (269, 270)

respiratory disease (4, 180, 258), lameness in ewes (229), and diarrhoea in pre-weaned calves (143). As diagnostic capacity improves, selective metaphylaxis is likely to become more common (88), with reduced use of antimicrobial agents consistent with high animal health. There is growing evidence that another benefit of metaphylactic use of antimicrobial agents may be a reduced propensity to select for resistant bacteria. This is thought to be possible due to the lower bacterial inoculum present in the incipient stages of disease and the lower likelihood of resistant mutants being present in this smaller bacterial population (36, 129). The dose regimen for prophylaxis, metaphylaxis and treatment can be based on knowledge of the expected minimum inhibitory concentration (MIC) of the pathogen expected to be implicated.

Nutritional use of antimicrobial agents

For the nutritional uses of antimicrobial agents (antibiotic growth promotion) it is not possible to select a dose regimen based on the MIC of any particular bacterial species as the specific mode (or modes) of action remains elusive. There are abundant theories to explain the mode of action (for example 59, 82, 123, 206). More recent theories include non-antimicrobial anti-inflammatory effects on the gut (184), modulation of gut immune responses (49) or subtle changes in population composition of the gut microbiome (54, 219).

Examples of use

The most commonly sold antimicrobial classes in the major livestock species in 17 countries are set out in Table XI.

The prominent use of the penicillins, tetracyclines, macrolides and aminoglycosides is notable, especially since each of these classes has been in use for more than 50 years. Although there are no specific findings recently from the USA for antimicrobial use in feedlot cattle, the major diseases that require management include bovine respiratory disease (which attracts the use of macrolides, tetracyclines, florfenicol and cephalosporins by injection) and liver abscess, which is prevented by the use of macrolides in feed (21). In cow-calf herds in Canada, the main antimicrobials reported as used were oral and injectable sulphonamides and injectable tetracyclines, macrolides and penicillins in calves, and injectable tetracyclines and penicillins in cows (89). In terms of used daily doses, a survey of 32 Belgian broiler farms showed that the main antimicrobial agents employed were macrolides, lincosamides, sulphonamide-trimethoprim and penicillins, with necrotic enteritis and the poorly

Table VIII
Infectious agents against which vaccines are available

Cattle	Sheep and goats	Pigs	Poultry
– Aino virus – Akabane virus – *Anaplasma centrale* (also *marginale, phagocytophilum*) – *Arcanobacterium pyogenes* – *Babesia bigemina, bovis, divergens* – *Bacillus anthracis* – Bluetongue virus – Bovine ephemeral fever virus – Bovine herpesvirus type 1 (infectious bovine rhinotracheitis/ infectious pustular vulvovaginitis) – Bovine parainfluenza 3 virus – Bovine respiratory syncytial virus – Bovine viral diarrhoea virus, Type I, Type II – *Brucella (abortus, melitensis, suis)* – *Campylobacter (vibrio) fetus* subsp. *venerealis* biotype 1 – Chuzan virus – *Clostridium botulinum* Types C & D – *Clostridium chauvoei* – *Clostridium haemolyticum* – *Clostridium novyi* Type B – *Clostridium perfringens* Type C & D – *Clostridium septicum* – *Clostridium sordellii* – *Clostridium tetani* (toxoid, antitoxin) – Coronavirus – *Cowdria ruminantium* (heartwater) – *Coxiella burnetii* (Q fever) – *Escherichia coli* – Foot and mouth disease virus – *Fusobacterium necrophorum* – *Histophilus somni (Haemophilus somnus)* – Ibaraki virus – *Leptospira (canicola, grippotyphosa, hardjobovi, icterohaemorrhagiae, pomona)* – Lumpy skin disease virus, Knopvelsiekte, (pox virus) – Malignant catarrhal fever virus (alcelaphine herpesvirus-1) – *Mannheimia haemolytica* – *Moraxella bovis* – *Mycobacterium paratuberculosis* (Johne's disease) – *Mycoplasma bovis* – *Mycoplasma mycoides* subsp. *mycoides* (contagious bovine pleuropneumonia) – *Neospora caninum* – Papillomavirus – *Pasteurella multocida* (including haemorrhagic septicaemia) – Rabies virus – Rift Valley fever virus – Rinderpest virus* – Rotavirus – *Salmonella* serotypes (including Dublin Newport, Typhimurium) – *Serpens* spp. (associated with papillomatous digital dermatitis) – *Staphylococcus aureus* – *Theileria annulata, parva* (East Coast fever) – *Tritrichomonas fetus* – Vesicular stomatitis virus	– *Arcanobacterium pyogenes* – *Bacillus anthracis* – Bluetongue virus – Border disease virus – *Brucella ovis* – *Campylobacter (vibrio) fetus* subsp. *venerealis* biotype 1 – *Chlamydophila abortus* – *Clostridium botulinum* Types C & D – *Clostridium chauvoei* – *Clostridium haemolyticum* – *Clostridium novyi* Type B – *Clostridium perfringens* Types B & D – *Clostridium septicum* – *Clostridium sordellii* – *Clostridium tetani* (toxoid, antitoxin) – *Corynebacterium pseudotuberculosis (ovis)* – *Coxiella burnetii* (Q fever) – *Dichelobacter nodosus* – *Escherichia coli* – Foot and mouth disease virus – *Histophilus somni (Haemophilus somnus)* – *Leptospira (hardjobovi, pomona)* – *Mannheimia haemolytica* – *Mycobacterium paratuberculosis* – *Mycoplasma agalactiae* (contagious agalactia) – *Mycoplasma capricolum* subsp. *capripneumoniae* (contagious caprine pleuropneumonia) – Parapoxvirus (Orf) (contagious pustular dermatitis virus) – *Pasteurella multocida* – Peste des petits ruminants virus – Rabies virus – Sheep and goat pox virus (capripoxvirus) – *Salmonella* serotypes – *Toxoplasma gondii* – Wesselsbron virus	– *Actinobacillus pleuropneumoniae* – Aujeszky's disease virus – *Bacillus anthracis* – *Bordetella bronchiseptica* – *Brucella suis* – Classical swine fever (hog cholera) – *Clostridium perfringens* Type C – *Clostridium tetani* (toxoid, antitoxin) – Enterovirus encephalomyelitis (Teschen/Talfan disease) – *Erysipelothrix rhusiopathiae* – *Escherichia coli* (including O149:K88/O64:K99 / O9:987P) – Foot and mouth disease virus – *Haemophilus parasuis* – Japanese encephalitis virus – *Lawsonia intracellularis* – *Leptospira (bratislava, pomona, tarassovi, icterohaemorrhagiae*) – *Mycoplasma hyopneumoniae* – Parvovirus – *Pasteurella multocida* – Porcine circovirus, Type 2 – Porcine epidemic diarrhoea virus – Porcine reproductive and respiratory syndrome virus – Porcine rubulavirus (La-Piedad-Michoacan paramyxovirus) – Rabies virus – Rotavirus – *Salmonella* serotypes (including Choleraesuis, Typhimurium) – *Streptococcus suis* – Swine influenza (H1N1, H1N2, H3N2) virus – *Taenia solium* (porcine cysticercosis) – Transmissible gastroenteritis (TGE) virus – Vesicular stomatitis virus	– Avian adenovirus – Avian encephalomyelitis virus – Avian haemagglutinating virus – Avian influenza virus – Avian metapneumovirus (avian pneumovirus, avian rhinotracheitis virus virus) – *Bordetella avium* (turkey coryza) – Chicken anaemia virus – *Clostridium perfringens* (necrotic enteritis) – Coccidia (Broilers: *Eimeria acervulina, E. maxima, E. mivati, E. tenella, E. brunetti, E. hagani, E. necatrix, E. praecox*; Turkeys: *E. adenoeides, E. meleagrimitis, E. gallopavonis, E. dispersa*) – Duck virus enteritis (duck plague) – Duck virus hepatitis – Egg drop syndrome virus – *Erysipelothrix rhusiopathiae* (turkeys) – *Escherichia coli* – Fowl pox virus – *Haemophilus paragallinarum* (coryza) – Infectious bronchitis virus – Infectious bursal disease (Gumboro disease) virus – Infectious laryngotracheitis virus – Marek's disease virus – *Mycoplasma gallisepticum* – *Mycoplasma synoviae* – Newcastle disease virus – *Ornithobacterium rhinotracheale* – *Pasteurella multocida* (fowl cholera) – Reovirus (viral arthritis) – *Salmonella* serotypes (including Enteritidis, Gallinarum, Pullorum, Typhimurium)

* Global freedom from rinderpest was declared by the World Organisation for Animal Health and the Food and Agriculture Organization of the United Nations in June 2011

Box 1
Antimicrobial product information sources

Argentina
Vademécum Veterinario
www.caprove.com.ar

Australia
(i) Australian Pesticides and Veterinary Medicines Authority
Public Chemical Registration Information System – PUBCRIS
http://services.apvma.gov.au/PubcrisWebClient/welcome.do
(ii) Index of Veterinary Specialties
MIMS IVS Annual
www.mims.com.au/index.php

Brazil
Sindicato Nacional da Indústria de Produtos para Saúde Animal
Compêndio de Produtos Veterinários
www.sindan.org.br/sd/sindan/index.html
www.cpvs.com.br

Canada
(i) Health Canada
Drug Product Database Online Query
http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
(ii) North American Compendiums
Compendium of Veterinary Products
Over 2,200 pharmaceutical, biological, dietary supplement, feed medication and parasiticide monographs
http://naccvp.com

Europe
European Medicines Authority
European Public Assessment Reports (Veterinary)
www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_epar_search.jsp&mid=WC0b01ac058008d7a8

France
Agence Nationale du Médicament Vétérinaire
Index des médicaments vétérinaires autorisés en France
www.ircp.anmv.anses.fr/

Indonesia
Asosiasi Obat Hewan Indonesia
Indeks Obat Hewan Indonesia
www.asohi.org/

Ireland
Irish Medicines Board
Veterinary Medicines Products List
www.imb.ie/EN/Medicines/VeterinaryMedicines/VeterinaryMedicinesListing.aspx

Kenya
Pharmacy and Poisons Board, Ministry of Health
Registered Drugs
www.pharmacyboardkenya.org/index.php?id=13

New Zealand
(i) New Zealand Food Safety Authority
Agricultural Compounds and Veterinary Medicines Register
https://eatsafe.nzfsa.govt.nz/web/public/acvm-register
(ii) Index of Veterinary Specialties
IVS Annual
www.ivsonline.co.nz

The Philippines
Medicomm Pacific Inc.
Philippine Veterinary Drug Directory
www.ppd.ph/mpinew_pvet.php

South Africa
MIMS
IVS (quarterly index and desk reference)
P.O. Box 182, Pinegowrie 2123, South Africa (011 280 5689)

South America
P.R. Vademecum (Argentina, Brazil, Chile, Columbia, Mexico, Paraguay, Peru, Uruguay, Venezuela)
www.prvademecum.com/pantalla_paises.asp

Switzerland
University of Zurich, Institute of Pharmacology and Toxicology
Tierarzneimittel Kompendium der Schweiz
www-vetpharm.uzh.ch/perldocs/index_t.htm

Uganda
National Drug Authority
List of registered veterinary drugs
www.nda.or.ug/vet_list.php

United Kingdom
(i) National Office of Animal Health
Compendium of Data Sheets for Animal Medicines
www.noahcompendium.co.uk
(ii) Veterinary Medicines Directorate
Product Information Database
www.vmd.defra.gov.uk

United States of America
(i) Food and Drug Administration, Center for Veterinary Medicine
Approved Animal Drugs Green Book
www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/UCM042847
(ii) Drugs.com
Veterinary Product Database
www.drugs.com/vet/
Over 5,000 pharmaceutical, biological, diagnostic, feed medications and parasiticide monographs for products approved in the USA and Canada
(iii) North American Compendiums
Compendium of Veterinary Products
Over 5,000 pharmaceutical, biological, feed medication and parasiticide monographs
http://naccvp.com/

Vietnam
Ministry of Agriculture and Rural Development
List of veterinary drugs permitted for circulation in Vietnam
www.spsvietnam.gov.vn/pages/DongVat-ThuocThuY.aspx

IVS: Index of Veterinary Specialties

Table IX
Criteria underpinning the classification of medical and veterinary antimicrobial agents
An antimicrobial agent can be classified as 'important', 'highly important', or 'critically important', depending on the number of criteria it meets

Criterion	Veterinary critically important antimicrobials [a]	Human critically important antimicrobials [b]
1	Response rate: majority of respondents identified the importance of the antimicrobial class	Antimicrobial agent is used as sole therapy or one of few alternatives to treat serious human disease
2	Treatment of serious animal disease and availability of alternative antimicrobials: agents in class considered essential, few alternatives	Antimicrobial agent is used to treat diseases caused by either: *(i)* organisms that may be transmitted via non-human sources or *(ii)* diseases caused by organisms that may acquire resistance genes from non-human sources
Criteria met	**Classification**	
1 and 2	Veterinary critically important antimicrobials	Critically important antimicrobials
1 or 2	Veterinary highly important antimicrobials	Highly important antimicrobials
Neither 1 or 2	Veterinary important antimicrobials	Important antimicrobials

a) *Source*: World Organisation for Animal Health (291)
b) *Source*: World Health Organization (290)

Table X
Antimicrobial use patterns

Use pattern	Definition	Veterinary examples	Medical example	References
Antimicrobial growth promotion				
– Group administration – In feed – Long duration	'Administration of an antimicrobial, usually as a feed additive, over a period of time to growing animals that results in improved physiological performance (i.e. weight gain, feed conversion)' (43)	Avilamycin, bambermycin, bacitracin, carbadox, chlortetracycline, tylosin and virginiamycin, variously in cattle, pigs and poultry	No medical equivalent	59, 123, 206, 219
Prophylaxis				
– Group administration – In feed, water – Intermediate duration	'Administration of an antimicrobial to exposed healthy animals considered to be at risk, but prior to onset of disease, and for which no etiologic agent has yet been confirmed by culture or other detection method(s)' (43)	Prevention of necrotic enteritis in broilers; intramammary dry cow treatment in dairy cattle; medicated milk replacer in calves to prevent diarrhoea	Pre-operative prophylaxis, mass gatherings; respiratory tract infection in intensive care; post-flood leptospirosis risk	1, 30, 141, 230, 243, 271
Metaphylaxis				
– Group administration – Injection, feed, water – Short duration	'The mass treatment of animal populations currently experiencing any level of disease before the onset of blatant illness' (180)	Control of bovine respiratory disease (BRD) in feedlot cattle	Risk management of those potentially exposed to *Neisseria meningitidis* or *Streptococcus pneumonia* infection	9, 16, 180, 258
Treatment				
– Targeted individual(s) administration – Injection, feed, water – Short duration	'Administration of an antimicrobial to an animal, or group of animals, which exhibits frank clinical disease' (43)	Colibacillosis in calves, pigs or poultry; BRD, swine respiratory disease	Acute bacterial infections of upper or lower respiratory tract, acute urinary tract infection, etc.	9, 97, 298

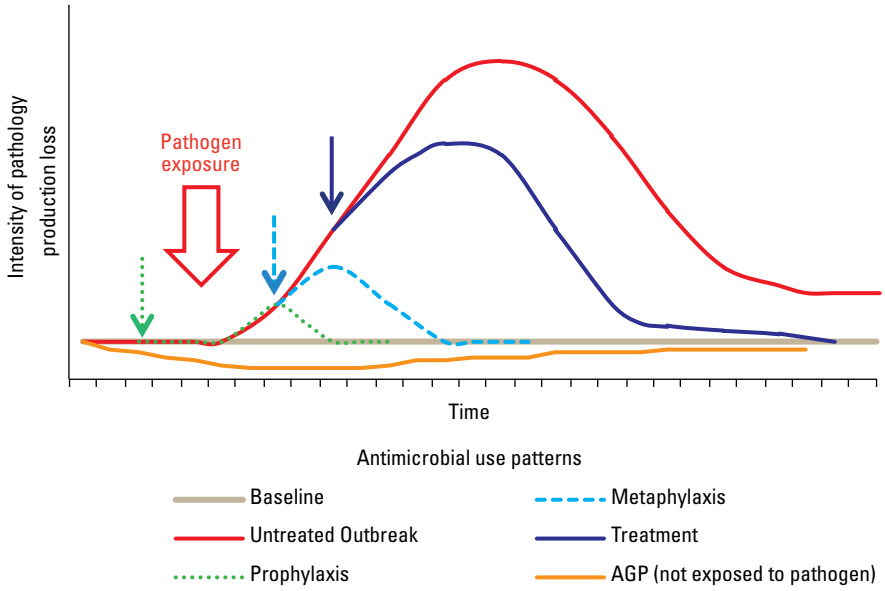


Fig. 2
Antimicrobial use patterns
After exposure to a bacterial pathogen, infecting microorganisms invade target organs and multiply eliciting a complex host response which is usually associated with increasing pathology until (or if) the host immune system is able to gain the upper hand – as illustrated by the red solid line which depicts the time course of pathological response in untreated animals. However, if treatment of a group of animals is initiated prior to exposure (prophylaxis) or soon after exposure (metaphylaxis) the extent of pathology versus time is attenuated, as seen by green dotted and blue dashed lines respectively. Treatment of clinically affected animals (blue solid line) also reduces the extent of the pathology experienced in untreated animals, but to a lesser extent than the reduction associated with earlier intervention. In situations of normal production without acute outbreaks of disease, the use of AGPs can result in an improvement in the health and productivity of livestock, especially during the earlier stages of the life cycle (brown line)

defined 'dysbacteriosis' the major reasons for use (204). Similarly, in the United Kingdom (UK), a survey found that enteric disease, especially necrotic enteritis, and respiratory disease were the major indications for therapeutic use of antimicrobial agents (117) in broilers.

The use of antimicrobial agents in nursery and grower/finisher pigs in the USA is summarised in Table XII.

The primary use of injections was the treatment of respiratory disease in pigs and the primary use of in-feed antimicrobials was the prevention of this disease. The least popular route of administration was by water medication, which was mainly used for respiratory disease treatment. In Danish pig production in 2008 the antimicrobial agents most commonly used to treat enteric disease in nursery or weaner pigs were pleuromutilins, tetracyclines, macrolides and the combination of a sulphonamide and trimethoprim, for respiratory disease the most widely used antimicrobials were pleuromutilins, macrolides and tetracyclines. In finisher pigs, enteric disease was treated with tetracyclines, macrolides and pleuromutilins, while respiratory disease was treated with tetracyclines, pleuromutilins and penicillins (120). In 2008 in Canadian grower-finisher pigs, the use of antimicrobial agents for enteric disease, respiratory disease and disease prevention was very similar to that described in the USA (55).

The use of antimicrobial agents in dairy pre-weaned and weaned heifers and dairy cows is outlined in Table XIII.

While pre-weaned heifers were mainly treated for digestive and respiratory problems, weaned heifers were given in-feed antimicrobial prophylaxis and dairy cows received intramammary antimicrobial agents for mastitis during lactation and at drying off.

Worldwide the treatment of mastitis is one of the most common reasons for administering antimicrobial agents to dairy cattle. Table XIV presents a summary of the antimicrobial agents used in dry cow and lactating cow products in different countries.

There are fewer antimicrobial agents used for dry cow mastitis management, with 19 of the 22 different products containing a beta-lactam and no product containing any active ingredient other than an antimicrobial. There are twice as many lactating cow preparations, with 30 of 44 containing a beta-lactam. In addition to antimicrobial agents a number of other agents are present, including a corticosteroid, a nonsteroidal anti-inflammatory drug or vitamin A.

Table XI
The most commonly sold antimicrobial classes in the major livestock species in 17 countries
Ranked order of each antibacterial class that represents at least 10% of total sales (by mass)

Country	Year of survey	Pigs	Cattle	Cattle (intramammary)	Poultry	Mixed species	Ref.
Australia	2006	Penicillins, tetracyclines, macrolides, sulphonamides	–	–	–	–	124
Belgium	2007/9	–	Veal calves Tetracyclines, penicillins, macrolides, colistin	–	Penicillins, macrolides, TMS	–	197, 204
Canada	2008	Penicillins, tetracyclines, macrolides, lincosamides	–	–	–	–	55
Denmark	2010	Tetracyclines, penicillins, macrolides, pleuromutilins	Penicillins, TMS, tetracyclines	Penicillins, penicillin-aminoglycoside, cephalosporin (G1)	Penicillins, tetracyclines, macrolides, TMS	–	53
Finland	2007	Beta-lactams, TMS, tetracyclines, fluoroquinolones	Beta-lactams, fluoroquinolones	Beta-lactams, aminoglycosides	–	–	259
Finland	2009	–	–	Cloxacillin, penicillin, aminoglycosides	–	All terrestrial species Penicillins, TMS, tetracyclines	72
France	2010	Tetracyclines, polymyxins, macrolides, penicillins	Tetracyclines, macrolides, penicillins	–	Polymyxins, tetracyclines, penicillins	–	79
Germany	2005	–	–	–	–	All species Tetracycline, beta-lactams, sulphonamides	85
Japan	2004	Tetracyclines, sulphonamides, macrolides, aminoglycosides	Macrolides, tetracyclines, cephalosporins	Cephalosporins, aminoglycosides, penicillins	Tetracyclines, aminoglycosides, macrolides	–	119
Kenya (Ekiti State)	2004	–	–	–	–	All farm species Aminoglycoside, penicillin	4
Netherlands	2009	Tetracyclines, TMS, penicillins	Tetracyclines, intestinal antimicrobials (neomycin, colistin), TMS	Penicillins, penicillin-aminoglycoside, cephalosporins (G3)	Penicillins, intestinal antimicrobials (neomycin, colistin), fluoroquinolones, tetracyclines	–	163
New Zealand	2008/9	Macrolides, tetracyclines	Penicillins sulphonamides, aminoglycosides	Penicillins, cephalosporins (G1)	Bacitracin	–	161
Norway	2010	–	–	–	–	All terrestrial species Penicillins, sulphonamides, aminoglycosides	186
South Africa	2002/4	–	–	Penicillins, penicillin-aminoglycoside	–	Food-producing species Macrolides, tetracyclines, sulphonamides, penicillins	66
Sweden	2010	Tetracyclines, macrolides, pleuromutilins, penicillins	Penicillins, TMS	–	Penicillins	–	256
Switzerland	2004/5	Sulphonamides, tetracyclines, polymyxins, penicillins	Sulphonamides, penicillins, tetracyclines, aminoglycosides	–	Sulphonamides, penicillins tetracyclines, aminoglycosides	–	217
USA	2010	–	–	–	–	Food-producing species Tetracyclines, penicillins, macrolides, sulphonamides	38
UK	2010	–	–	–	–	Food-producing species Tetracyclines, penicillins, TMS	281

G1: first-generation cephalosporin
G3: third-generation cephalosporin
TMS: trimethoprim-sulphonamide
UK: United Kingdom
USA: United States of America

Table XII
Antimicrobial use in pigs in the United States of America

Route of administration and primary reason for use	Percentage of sites using the following antimicrobials in the 12 months to May 2006*			
	Nursery pigs		Grower/finisher pigs	
Injection (percentage of sites using)	83.1		75.6	
Disease prevention	Penicillin**	13.4	Penicillin	7.7
	Oxytet.	6.5		
Respiratory disease treatment	Ceftiofur	30.2	Penicillin	47.1
	Penicillin	25.8	Ceftiofur	36.3
	Oxytet.	11.7	Oxytet.	18.8
	Tulathro.	9.0	Tulathro.	10.2
	Tylosin	6.3	Lincomycin	7.0
	Florfenicol	5.9	Florfenicol	5.9
			Tylosin	5.6
Enteric disease treatment	Tylosin	9.2	Tylosin	12.9
	Gentamicin	6.4		
Glasser's disease	Penicillin	22.8	Penicillin	11.1
Feed (percentage of sites using)	82.3		83.6	
Growth promotion	Chlortet.	11.5	Bacitracin	25.7
	Neo. + Oxytet.	5.2	Tylosin	13.3
	Bacitracin	4.8	Chlortet.	12.4
Disease prevention	Chlortet.	29.4	Chlortet.	19.4
	Carbadox	19.3	Tylosin	13.0
	Tiamulin	18.0	Tilmicosin	5.1
	Tylosin	11.6	Tiamulin	4.9
	Lincomycin	5.2		
	Tilmicosin	5.1		
Respiratory disease treatment	Chlortet.	16.3	Chlortet.	25.6
			Tylosin	4.9
Enteric disease treatment	Carbadox	7.1	Tylosin	11.3
	Tiamulin	5.1		
Water (percentage of sites using)	40.3		47.9	
Disease prevention	Amoxicillin	8.1		
Respiratory disease treatment	Amoxicillin	5.8	Chlortet.	17.4
	Chlortet.	5.3	Oxytet.	12.9
			Sulpha.	11.3
			Tetracycline	7.3
Enteric disease treatment			Tylosin	9.1
			Neo.	7.0
			Tiamulin	4.9

*_Source_: United States Department of Agriculture (270)
Chlortet.: chlortetracycline
Neo.: neomycin
Oxytet.: oxytetracycline
**Penicillin: total of ampicillin, amoxicillin, procaine penicillin and benzathine penicillin
Sulpha.: sulphonamide
Tulathro.: tulathromycin

Routes of administration

Antimicrobial agents may be administered directly to the site of infection by topical or intramammary routes or given by mouth (enteral administration) for local action in the gastrointestinal tract or for absorption and systemic action. They may also be administered parenterally, to bypass the gastrointestinal system, e.g. by intravenous, intramuscular (IM) or subcutaneous injection. Examples of the most common routes of administration in pigs and dairy cattle are presented in Tables XII and XIII.

Parenteral injection

Intramuscular

The intramuscular route of injection has traditionally been very popular in ruminants and pigs but can (depending on the irritancy of the active ingredient or its formulation) be associated with tissue damage (160, 187, 189, 294), prolonged and high concentrations of residues (216) and, especially in pigs, broken needles. However, many antimicrobial agents can be formulated to be less tissue reactive and keeping injection volume per site to a maximum of 10 ml has been shown to be less likely to cause reactions (159). It should be noted that the site of

injection can influence the pharmacokinetic response. Differences in plasma drug concentration have been observed when comparing IM injection in the neck with injection in the gluteal muscles (188, 196). To avoid high value muscles and ensure high bioavailability it is usually recommended that IM injections in cattle and pigs be made caudal to the base of the ear.

Subcutaneous

The subcutaneous route in cattle has now become the standard route of injection in many countries. Rapid and widespread adoption of subcutaneous injection followed the recognition that this method of administering antimicrobial agents was associated with pharmacokinetics that were not significantly different from those following intramuscular injection (17) and which resulted in minimal tissue irritation and limited economic losses associated with trimming at slaughter (277). Preferred sites of subcutaneous injection in cattle are high in the neck, at the base of the ear or in the middle third of the posterior aspect of the ear.

Other sites

Less commonly, parenteral injections are given intravenously (usually ear vein or jugular vein) or intraperitoneally.

Enteral

Oral dosing of individual animals

When animal management permits, individual animals can be treated orally with a range of formulations, including tablets, capsules, boli (from simple to intrarumenal controlled release), suspensions, solutions or pastes. Young mammals can have medication added to milk or milk replacer, a common practice in calf-raising units.

Water medication

In the face of an emerging outbreak of disease, particularly in pigs and poultry, antimicrobial agents are frequently added to drinking water. In such situations this form of drug delivery is favoured as the water supply, especially of confined livestock, can be medicated immediately via header tanks or proportioning devices. Furthermore, it is believed that sick animals will continue to drink even though feed intake may be depressed. However, this belief may not be well founded as there is at least one study demonstrating that in pigs challenged with *Actinobacillus pleuropneumoniae* toxins there was a parallel reduction in feed and water intake (207). When water medication is selected it is necessary to know average water consumption in order to determine the inclusion rate of the antimicrobial agent. Factors affecting water consumption of poultry (69, 172), pigs (173) and beef cattle (174) include age and stage of growth, activity level, environmental temperature, humidity, water temperature, water quality (including hardness, mineral content, sulphate content), water palatability, feed composition and, particularly for poultry, lighting programme. In addition there may be variable wastage depending on the type and management of drinkers (140, 263). Failure to ensure these factors are optimised can lead to ineffective drug delivery, as observed in a study of enrofloxacin in chickens (250, 251). Because of the number of factors influencing water intake, it is usually recommended that current water intake is actually measured and used in calculations on

Table XIII
Antimicrobial use in dairy heifers and cows in the United States of America

Target animal	Disease or disorder	Animals treated (%)	Antimicrobials used and percentage of surveyed dairy cattle treated in 2006 for various diseases and disorders*			
Dairy: preweaned heifers	Respiratory	11.4	Florfenicol 25.4	Cephalosporin 24.6	Macrolide 19.8	Tetracycline 13.2
	Diarrhoea or other digestive problem	17.9	Sulphonamide 23.3	Tetracycline 16.5	Aminoglycoside 11.5	Penicillin 11.0
	Navel infection	1.5	Penicillin 69.6	Macrolide 11.6	Tetracycline 6.7	Cephalosporin 5.0
Dairy: weaned heifers	Prophylaxis (in feed)	50.9	Ionophore 84.9	Tetracycline 30.7	Neomycin 9.5	Sulphonamide 5.7
Dairy cow	Mastitis, dry cow	94.1	Penicillin G + DHS 36.9	Cephapirin 31.0	Penicillin G + novobiocin 13.2	Cloxacillin 7.9
	Mastitis, lactating	16.4	Cephalosporin 53.2	Lincosamide 19.4	Penicillin 19.1	Aminocyclitol 2.9
	Reproductive	7.4	Tetracycline 44.4	Cephalosporin 27.9	Penicillin 19.7	
	Lameness	7.1	Tetracycline 42.1	Cephalosporin 27.2	Penicillin 19.5	Sulphonamide 4.2

DHS: dihydrostreptomycin
* *Source*: United States Department of Agriculture (271)

Table XIV
Antimicrobial agents used in dry cow and lactating cow products

Dry cow products (*n*=22)		Lactating cow products (*n*=44)	
Country*	**Active constituents**	**Country**	**Active constituents**
BRL	Bacitracin, neomycin	USA	Amoxicillin trihydrate
IRE	Cefalexin, dihydrostreptomycin	AUS	Amoxicillin trihydrate, clavulanate potassium
SAf	Cefalexin, neomycin	IRE	Amoxicillin trihydrate, clavulanate potassium, prednisolone
BRL	Cefalexin, neomycin, miconazole	IRE	Cefalexin, dihydrostreptomycin
IRE, SAF, AUS	Cefalonium dehydrate	IRE	Cefalexin, kanamycin
USA, SAF, BRL	Cefapirin benzathine	BRL	Cefalexin, neomycin, miconazole, prednisolone
IRE	Cefquinome sulphate	SAf	Cefalexin, neomycin, prednisolone
USA	Ceftiofur hydrochloride	BRL	Cefalonium
IRE, USA, SAF, AUS, BRL	Cloxacillin benzathine	USA, BRL	Cefapirin sodium
BRL	Cloxacillin benzathine, amoxicillin trihydrate	IRE	Cefapirin sodium, prednisolone
IRE, SAF, AUS, BRL	Cloxacillin benzathine, ampicillin trihydrate	IRE, BRL	Cefoperazone
BRL	Gentamicin	BRL	Cefoperazone, dexamethazone
USA	Novobiocin	BRL	Cefoperazone, prednisolone
USA	Penicillin G procaine	IRE, BRL	Cefquinome
USA, SAF	Penicillin G procaine, dihydrostreptomycin	USA, BRL	Ceftiofur hydrochloride
IRE	Penicillin G procaine, dihydrostreptomycin, nafcillin	SAf, AUS	Cefuroxime
IRE	Penicillin G procaine, framycetin, penethamate	IRE, AUS	Cloxacillin benzathine
BRL	Penicillin G procaine, nafcillin	IRE	Cloxacillin benzathine, ampicillin trihydrate
SAf	Penicillin G procaine, neomycin	IRE, USA, BRL	Cloxacillin sodium
IRE	Penicillin G procaine, neomycin, penethamate	BRL	Cloxacillin sodium, amoxicillin trihydrate
BRL	Penicillin G procaine, neomycin, penicillin G potassium	IRE, SAf, AUS, BRL	Cloxacillin sodium, ampicillin sodium
USA, SAF, BRL	Penicillin G procaine, novobiocin	AUS	Dihydrostreptomycin, neomycin, novobiocin
		IRE	Erythromycin
		BRL	Gentamicin
		BRL	Gentamicin, bromhexine
		USA	Hetacillin potassium
		IRE, AUS	Lincomycin hydrochloride, neomycin sulphate
		BRL	Neomycin, nystatin
		AUS	Neomycin, oleandomycin, oxytetracycline
		BRL	Neomycin, oxytetracycline, prednisolone
		BRL	Neomycin, spiramycin, flumethasone
		IRE	Penethamate, dihydrostreptomycin, framycetin, prednisolone
		USA	Penicillin G procaine
		SAf	Penicillin G procaine, dihydrostreptomycin, nafcillin
		IRE	Penicillin G procaine, dihydrostreptomycin, neomycin, novobiocin sodium, prednisolone
		SAf	Penicillin G procaine, dihydrostreptomycin, novobiocin, polymyxin, hydrocortisone
		IRE	Penicillin G procaine, neomycin, oxytetracycline, prednisolone
		IRE	Penicillin G procaine, neomycin, streptomycin, prednisolone
		BRL	Penicillin V potassium, streptomycin, piroxicam
		USA, BRL	Pirlimycin
		BRL	Sulphadiazine, nystatin, prednisolone
		IRE	Sulphadiazine, trimethoprim
		BRL	Sulphanilamide, tetracycline, hydrocortisone, vitamin A
		SAf, BRL	Tetracycline, bacitracin, neomycin, prednisolone

*Examples only
AUS: Australia
BRL: Brazil
IRE: Ireland
SAf: South Africa
USA: United States of America

dilution rates. In addition to an accurate estimate of water intake, it is essential to have a formulation of the antimicrobial agent that allows it to either dissolve or remain evenly suspended in the drinking water while maintaining its chemical stability. Medication may be delivered as a pulse (dose of medication added to water that will be consumed in a short period of time) or continuously throughout the period of treatment. In many cases pulse dosing may be more reliable, though the higher concentration of drug in the water may affect palatability leading to water rejection, as has been reported with florfenicol (100). In some cases, even high administration rates do not overcome inherently low bioavailability. Tetracycline hydrochloride administered to pigs in water at concentrations of up to 500 mg/L led to mean steady-state plasma concentrations of less than 0.8 mg/L – inadequate for treatment of even highly susceptible bacteria (64, 157). In another study, bioavailability of chlortetracycline administered in water was enhanced by the inclusion of citric acid (209). A further important factor influencing the received dose of antimicrobial agent is the variation in the water flow rate in the animal facility. One recent study found that water flow rates varied between farms, between barns within farms and between pens within barns as well as according to type of drinker (64).

Feed medication

Administration of antimicrobial agents in feed is one of the most widely adopted practices worldwide and a practice that should be undertaken in accordance with good animal feeding practices (46). For small groups of animals, feed might be top dressed with the medication, but for larger groups the medication is usually incorporated into the final ration. The medicated feed may be offered as a dry loose mix, a mash, crumbles or pellets. The production of medicated feed must be undertaken by highly skilled workers to ensure the correct inclusion level (8), stability, homogeneity and lack of segregation of the active constituents (235). The carry-over of antimicrobial agents from batch to batch must be avoided to ensure that livestock are not unintentionally medicated, as this can have an impact on safety, residues and resistance selection. To reduce the likelihood of carry-over at the mill, separate delivery systems should be used for higher risk compounds and special consideration paid to feed batch sequencing, flushing and the cleaning of feed processing equipment (107). The physical form of antimicrobial premixes can influence carry-over, as has been demonstrated with sulphamethazine, which has a high propensity for electrostatic attraction when available as a powder but loses this property when granulated (222). Delivery of feed also provides avenues for carry-over. The effective cleanout of feedlot mixer trucks involves sequences of feeds and flushing at various rates (up to 10% of mixer capacity) for various times (2 to 4 minutes) to reduce the likelihood of antimicrobial agent carry-over (279). Once delivered and made available for livestock the constellation of factors that lead to feed intake variability come into operation (144) and consequent pharmacokinetic variability has been described by a feeding-behaviour model (139).

Intramammary infusion

The anatomical construction of the mammary gland or udder of the ruminant (milk-producing cells draining into alveoli which themselves drain into the teat cistern which is connected to the exterior by a teat canal) (96) lends itself to intramammary administration of antimicrobial agents. Bacterial infection of the udder (mastitis) has always been one of the most costly infections of livestock (102, 108) and intramammary treatments were available prior to the modern age of antimicrobial agents, when acridine dyes were widely used (247). It is essential to realise that there are two quite different types of intramammary preparation with distinct formulation characteristics – lactating and dry cow products – that are either quick acting (hours to days) or long acting (weeks to months) respectively.

Other routes of administration

For specific localised infections antimicrobial agents can be administered by intraarticular, intrapleural, intratracheal, ocular, subconjunctival, topical (for example, skin lesions, wounds), interdigital, intravaginal and intrauterine routes, and, in chickens, by the *in ovo* route.

Pharmacology

There are three important enhancements of the pharmacological approach to the veterinary use of antimicrobial agents that for many years have been cultivated and refined by the groups of Professor Jim Riviere at the College of Veterinary Medicine, North Carolina State University, USA; Professor Peter Lees at the Royal Veterinary College, UK; and Professor Pierre-Louis Toutain at the École Nationale Vétérinaire de Toulouse, France. Between them these groups have published more than 200 papers on the pharmacology of antimicrobial agents and put in place a solid foundation for continuing advancements in this critical area of understanding and optimising antimicrobial use. The three areas of pharmacology enhancement include population pharmacokinetics (PPK), physiologically based (mechanism-based) pharmacokinetic (PBPK) modelling, and pharmacokinetic–pharmacodynamic (PKPD) optimisation

of dose regimens. Pharmacokinetics refers to those processes involved in characterising the concentration-time profile of a drug and includes absorption, distribution, metabolism and excretion. Pharmacodynamics refers to those processes that relate drug concentration to biological effect, and for antimicrobial drugs this includes the study of the various biochemical, physiological and microbiological factors that impact the growth, virulence and death of target microorganisms. Before exploring the value that these new approaches can add to optimal use of drugs, it is useful to consider how antimicrobials are used clinically.

Clinical approach to antimicrobial use

As summarised above and presented in greater detail elsewhere (see references), infectious disease of livestock is a complex phenomenon, each episode involving the epidemiological triad: host factors, infectious agents and environmental factors. The most serious disease events combine a large number of host factors for infection, a large number of potential infectious agents, and a diverse array of environmental factors. This makes correct diagnosis of pivotal importance. A flow chart of the clinical approach to antimicrobial use is set out in Figure 3. Continuous review and reassessment of the diagnosis and response to treatment are fundamental features of each episode and each treatment event should be considered a unique experiment requiring professional management.

There is no fixed approach to the management of infectious disease and the use of antimicrobial agents. While it is likely that the majority of cases of infectious disease may have a successful outcome (because of or despite intervention), in other cases the response will not be as anticipated. The checklist set out in Box 2 provides examples of the factors that may help to elucidate why there was apparent treatment failure.

Amongst the causes of treatment failure are those affecting the interface of pharmacology and microbiology, at the site of infection, and include all the inter- and intra-animal sources of variability in pharmacokinetics and pharmacodynamics that lead to less than optimal tissue concentrations of the administered antimicrobial agent. In parallel with the situation with human antimicrobials (70), the dosage regimens on the labels of approved antimicrobial products for animals are usually based on the results of a small number of studies in homogeneous groups of animals. Furthermore, the microbiological characteristics of the pathogens infecting study animals in

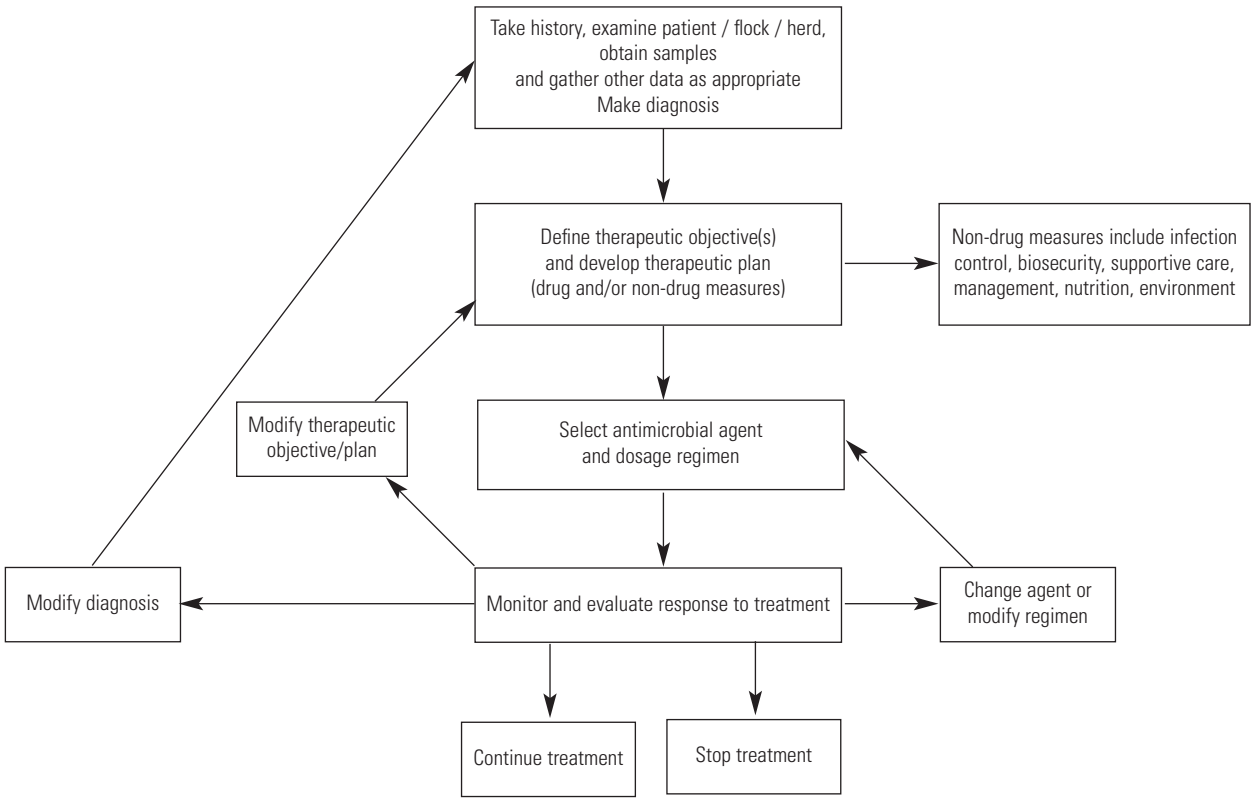


Fig. 3
Steps in the initiation, management and reassessment of antimicrobial therapy

challenge models and field studies that originally supported regulatory approval may not be representative of those encountered in other areas, sometimes many years after the original dose studies were conducted and in another hemisphere. Therefore it may be necessary to review treatment regimens in particular situations and it is guidance on dose individualisation that can be provided by PPK, PKPD and PBPK models.

Box 2
Elements of apparent antibacterial treatment failure

Diagnosis
- Condition not of bacterial origin (non-infectious, other infectious type – viral, protozoal, etc.)

Therapeutic goals
- Unrealistic objective (bacterial eradication versus disease control)

Pathophysiology
- Progression of underlying disease
- Poor management of mixed infection (e.g. mixed aerobic and anaerobic infection)

Host factors
- Predisposing factors uncorrected
- Impaired immune function (e.g. failure of passive transfer of colostral immunoglobulins)
- Nutritional deficits

Pharmaceutical factors
- Substandard product (expired, inappropriate storage, counterfeit)

Treatment
- Compliance (e.g. all intended doses not administered)
- Misadministration (e.g. animal avoided treatment, oral dosage regurgitated, injection misdirected)
- For feed or water medication, sufficient feed or water not consumed, delivered dose inadequate

Pharmacology
- Inappropriate drug selection
- Inappropriate dosage regimen (inadequate dose rate, route, frequency, duration)
- Pharmacokinetic issues (especially changes in absorption, distribution and clearance)
- Impaired perfusion and penetration (blood–brain barrier, abscess, oedema, swollen milk ducts, etc.)
- Interaction with concurrent medication

Supportive therapy
- Omission of concurrent supportive measures (nutrition, hydration, electrolyte balance, nursing, abscess drainage)

Microbial factors
- Toxin elaboration
- Antimicrobial resistance
- Reinfection
- Bacterial dormancy (e.g. non-growth phase)
- Bacterial L-forms
- Phenotypic tolerance (e.g. small-colony variants)
- Dense bacterial loads in infected tissue
- Biofilm formation
- Super-infection (bacteria or fungal)
- Poor correlation of *in vitro* susceptibility and clinical outcome (especially mastitis)

Epidemiology
- External bacterial challenge unabated
- Concurrent immunosuppressive viral infection

Toxicology
- Adverse drug reaction

Failure investigation
- Inappropriate samples collected
- Non-representative animal(s) investigated (e.g. post-mortem of untreated or uninfected animal)

Population pharmacokinetics

Clinical response is affected not only by variability in rate and extent of free drug at the site of action but also variability in pharmacodynamic (PD) activity, which includes the host response to infection and bacterial susceptibility and growth kinetics. Population pharmacokinetics is a discipline designed to address the reality of significant biological and statistical variation in clinical response, as illustrated by the examples below. A PPK evaluation seeks to obtain pharmacokinetic (PK) information from individuals who are representative of the broad and heterogeneous population to which treatment is directed. Population pharmacokinetics recognises that sources of variability (for example, drug absorption, clearance, intersubject, intrasubject, interoccasion) are important and should be quantified and wherever possible investigated and evaluated (67). As the following examples demonstrate, an understanding of PK and PD variability is essential for rational drug therapy (42). Differences in antimicrobial disposition may be related to individual characteristics but also to subpopulation characteristics such as age, breed or physiological or pathological state (156)

Variation

Two recent reviews of the influence of different physiological states on the pharmacokinetics of veterinary medicines included 54 publications that described aspects of the impact of age, infection, inflammation, lactation, pregnancy and hydration on the pharmacokinetic behaviour of antimicrobial agents in camels, cattle, pigs and sheep (153, 162). It was concluded that the astute clinician must be alert to a significant number of variable pharmacokinetic factors that could influence the response to antimicrobial treatment and closely monitor each patient to ensure the desired outcome is attained. While interspecies PK differences are well known (18), a recent example of unpredictable, unexpected and fatal intraspecies variability highlights the importance of monitoring the response to treatment and investigating untoward outcomes. Fatal intoxication of pigs administered valnemulin was experienced in Denmark in 1999 and 2000. Adverse effects were confined to a small number of farms and to pigs from a specific breed, while pigs from other breeds tolerated elevated dose rates. Analysis of liver microsomes from pigs that were intoxicated revealed extremely low expression of those cytochrome P450 isoforms (CYP1A and CYP3A) involved in the metabolism of valnemulin, suggesting that the adverse effects were a result of genetic polymorphism of these CYPs (71).

Inclusion of known important factors contributing to variability into PPK models allows the design of more individualised dose regimens for each subpopulation (42, 156).

There are a slowly evolving number of reports of the application of PPK to inform antimicrobial use in livestock. A PPK approach to evaluation of PK variability of doxycycline in sick pigs group fed with medicated feed (56) found large variation between pigs. The PPK of enrofloxacin and its active metabolite ciprofloxacin has been studied in disease-challenged chickens (99) and ill dairy cows (81). The study in cattle revealed that PK variability was greatly influenced by daily milk production (DMP) and it was suggested that higher doses may be necessary in cows with higher DMP (in which case milk from these cows may not be fit for human consumption). In chickens, PK variability was quantified, and an assessment of the likelihood of achieving the PKPD target (AUC/MIC of 100 for *Escherichia coli*) determined. In this study, variation in MIC of the target pathogen (PD variability) was not assessed but could be readily included in a subsequent analysis.

Physiologically based pharmacokinetic models

Physiologically based pharmacokinetic models are based on compartments that reflect the anatomical and physiological structure of the body (133, 275) and an example of the structure of such a model is set out in Figure 4. The model is constructed as a parallel series of organs interconnected by the arterial and venous arms of the circulatory system. The model can treat each tissue as if it is subdivided into vascular, extracellular and intracellular spaces. The drug permeability of each tissue can be set to reflect known physiological processes (for example, flow-limited or diffusion-limited, as may apply to the brain, the eye and other protected structures). Once the model structure is in place the next step is to apply appropriate species-specific physiological parameters such as organ mass or volume, and blood flow. Of course, the sum of all tissue blood flows must equal cardiac output. Values of these parameters are increasingly accessible in the literature and those for pigs and sheep have been published (272). At this stage the model reflects a physiological species and is ready to interact with a drug delivered by any route. For illustrative purposes only, Figure 4 identifies oral, intramuscular, subcutaneous, intramammary and intravenous routes, however, other routes can be accommodated as required.

The final step in setting up the model is to add drug properties of the agent to be investigated. Important drug information includes physicochemical properties, including lipophilicity, protein binding, membrane

permeability, tissue partitioning and hepatic metabolism, much of which can be derived from *in vitro* or *in silico* sources (176).

The model can be made as complex or as simple as needed to address the questions it is being asked to explore. For example, if there was interest at looking at the PK behaviour of a drug administered directly by intramammary infusion, then the model could be made to focus simply on the mammary gland and possible routes of metabolism in the liver and kidney. Specific features can be added to meet specific situations, for example, complex gastrointestinal dissolution and absorption processes (29), enterohepatic drug circulation (296), protein binding (35) or drug release from a depot injection site (134).

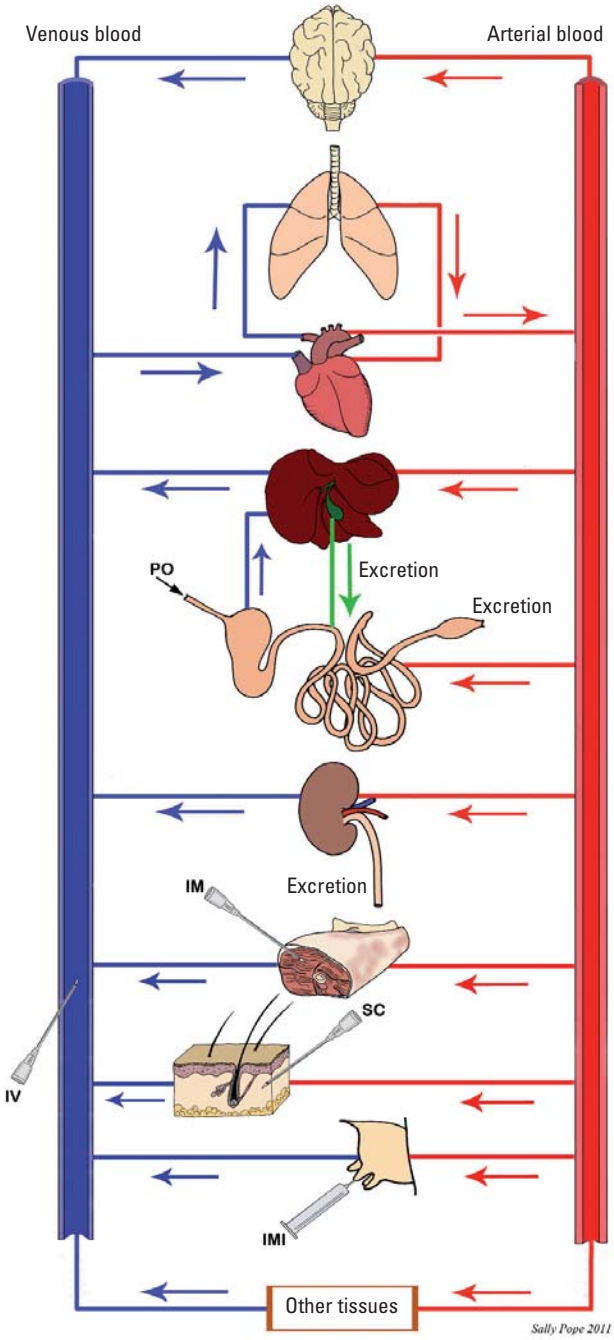
The interconnectedness of every part of the body is made abundantly clear in Figure 4, which becomes an aide-memoire when examining the distribution of antimicrobial agents. For example, in humans it has been found that following oral or parenteral administration of fluoroquinolones (113) and β-lactams (cephalosporins and penicillins) (114) microbiologically active concentrations were present in sweat. It was suggested that this may play an important part in the rapid selection of fluoroquinolone-resistant *Staphylococcus epidermidis* and β-lactam-resistant *S. aureus*. Antimicrobial agents are widely distributed in livestock species as well. Following intramuscular injection of pigs, enrofloxacin (26) and oxytetracyline (25) are present in nasal secretions at concentrations approximately the same as (enroflaxacin) or one third of (oxtetracycline) those in plasma. Fluoroquinolones are substrates for membrane transporters which are responsible for efflux into the gut (5) and into the ruminant mammary gland (210). In either case, gut and mammary gland may be non-target sites and bacteria within each resident microbiome will be exposed to antimicrobial agents. Indeed, a study of enrofloxacin in pigs (288) found that intramuscular administration led to gut concentrations that were similar to those resulting from oral administration, and resistant *Salmonella* and *E. coli* were selected rapidly.

Tissue penetration (168, 170, 185, 234) to the site of action is essential for antimicrobial activity and is best assessed by microdialysis (125, 169), which has significant advantages over other techniques, such as those using whole tissue homogenates or implanted tissue cages. Tissue and protein binding (19) essentially render antimicrobial agents unavailable, as it is the free fraction of the agent that is directly involved in antibacterial activity and it is the free fraction that is best measured by microdialysis.

Physiologically based pharmacokinetic models have been applied in an increasing number of veterinary contexts to establish dose rates and withdrawal periods of antimicrobial agents. For example, PBPK models have been developed to investigate:

– the disposition of chlortetracycline in turkeys (209), valnemulin in pigs (296), and doxycycline in pigs (295)

– the kinetics of residue depletion of sulphamethazine in pigs (34), antimicrobials in eggs (110), and tulathromycin in goats (134).



IMI: intramammary
IM: intramuscular
IV: intravenous
PO: per oral
SC: subcutaneous

Fig. 4
Physiologically-based pharmacokinetic model

It has been suggested that it would be useful to develop a PBPK model for intramammary infusion of antimicrobials (84).

Software available for immediate application to PBPK modelling has been reviewed. It is readily available (29, 91) and can accommodate different routes of administration, complex gastrointestinal tract absorption, customisation of tissue permeability, presence of transporters, hepatic metabolism, *in vitro–in vivo* extrapolation, PD linkages and virtual trials.

Pharmacokinetic–pharmacodynamic models

'The overwhelming obscuring factor in divining the dose–concentration–effect relationship is variability in drug disposition and action' (115), thus a greater understanding of PK and PD and their sources of variability is paramount to improved antimicrobial use. Figure 5 illustrates the pathway that leads from selection of treatment and prescription of dose to effect or outcome. There is first the pharmacokinetic phase, which relates delivered dose to a drug-concentration versus time profile, followed by the pharmacodynamic phase, which describes the biological effects associated with this changing concentration. There are a large number of sources of variability identified, to which other sources could be added.

Many studies have examined the relationship of PK and PD in determining the efficacy of antimicrobial agents (with excellent reviews: 6, 136, 137, 154, 195, 264, 265).

Three PKPD indices have been proposed to allow predictions of antimicrobial efficacy (Fig. 6). The ratio of the maximum unbound (free) concentration and the MIC (fCmax/MIC), the ratio of the free area under the concentration-time curve and the MIC (fAUC/MIC), and the percentage of time that the concentration of free drug is above the MIC (fT>MIC). The daily dose that has been demonstrated by dose-titration studies to provide acceptable antimicrobial activity can be fractionated and delivered as multiple divided doses. By doing this, it is possible, by assessing the response to each dose regimen, to determine whether or not the efficacy of the antimicrobial–bacterial species combination tested depends more on concentration (for example, single large dose leading to fCmax/MIC index of efficacy), or time (for example, frequent divided doses most effective,

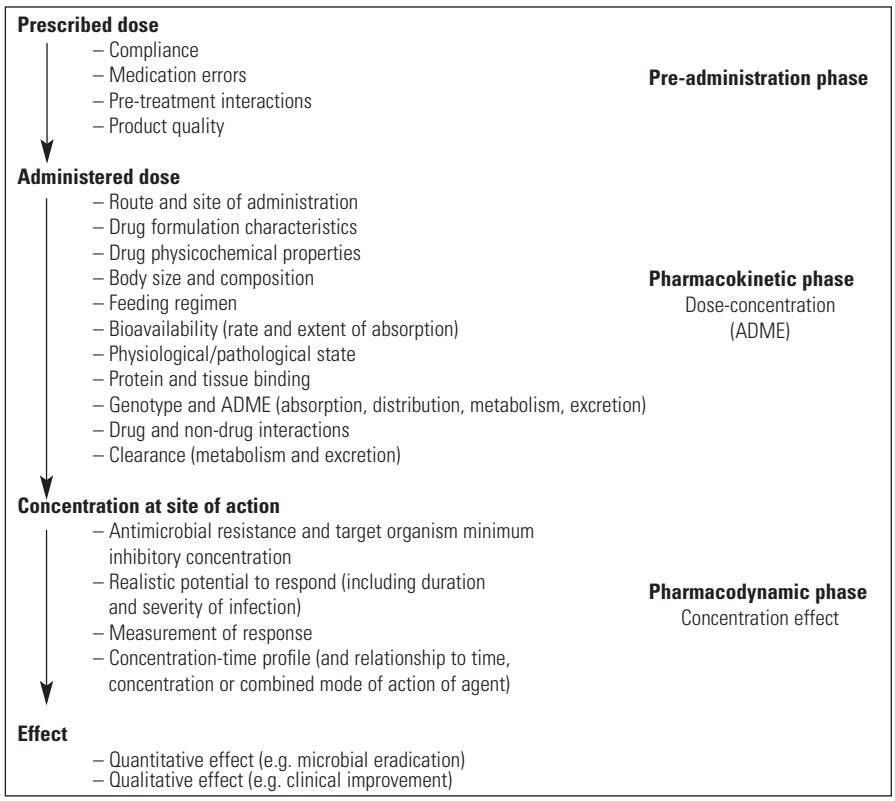
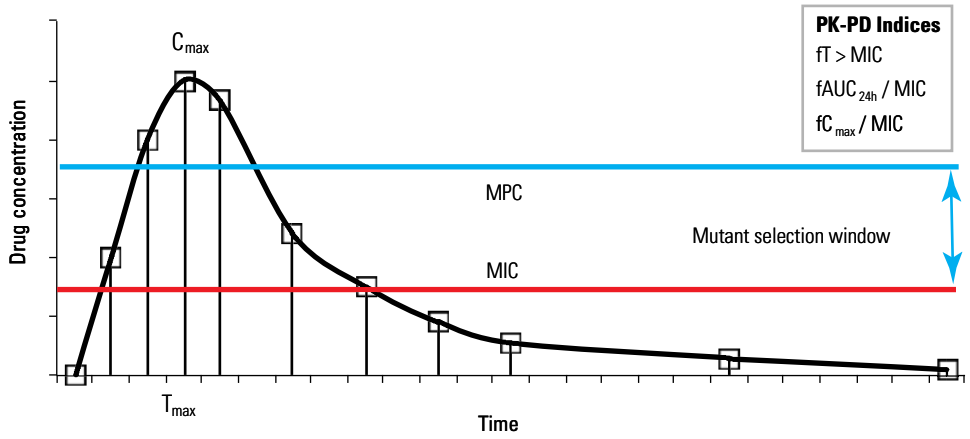


Fig. 5
Factors influencing variability in the relationship between dose and effect



fCmax : maximum unbound (free) concentration
fAUC : free area under the concentration-time curve
fT>MIC : percentage of time that the concentration of free drug is above the MIC

MIC: minimum inhibitory concentration
MPC: mutant prevention concentration
PK–PD : pharmacokinetic–pharmacodynamics

Fig. 6
Pharmacokinetic-pharmacodynamic indices
Note that the pharmacokinetic component of the commonly used pharmacokinetic-pharmacodynamic indices refers only to the unbound or free fraction of the antimicrobial agent of interest (thus use of 'f' to denote free) and that the pharmacodynamic component in each case is the MIC. Further description of the indices is presented in the text

fT > MIC index of efficacy) or is responsive to all regimens (in which case fAUC/MIC may be correlated to efficacy). Such studies have suggested that macrolides, phenicols, tetracyclines, β-lactams, sulphonamides and potentiated sulphonamides are time dependent, and aminoglycosides and fluoroquinolones are concentration dependent (154), but this classification itself is dependent on both the extent and duration of exposure of bacteria to each antimicrobial agent, and fAUC/MIC has been suggested as a universal predictor for all these classes (182).

The PKPD model approach has been applied to a number of dosing regimens in livestock, including the use of danofloxacin in calves (228, 240) and turkeys (104), enrofloxacin in poultry (105, 214, 253), oxytetracycline dose rates in sheep (246), oxytetracycline residues in sheep (51), amoxicillin in sheep (57), and colistin in pigs (101). In several cases the PKPD model was able to demonstrate the benefits of changes in dosing regimens. For example, a study of oxytetracycline use in sheep in South Africa (246) revealed that increases in the MIC of a number of target pathogens meant that the antibacterial spectrum of current dose rates was reduced. In poultry, a modification of the approved dosage regimen of enrofloxacin in water (50 ppm continuously for five days) to a shorter, higher concentration regimen (125 ppm continuously for two days) showed potential for reduced resistance selection while maintaining efficacy (214). Other studies in poultry support the advantages of a short, high-dose strategy with enrofloxacin (105, 253).

One of the most clinically significant variables affecting the success of antimicrobial dose regimens is variability in the susceptibility and MIC of the target pathogens (147). By assessing pathogen susceptibility it has been reported that it is possible to individualise dose regimens in everyday clinical practice (231). However, the success of achieving the appropriate PKPD index by increasing the dose is very dependent on the shape of the dose-target attainment rate curve (154, 155) and it is likely that as MICs rise with resistance selection there will be little improvement in beneficial effect as dose is increased, though adverse effects may become more frequent.

Each of the commonly applied PKPD indices described in Figure 6 relies on the use of the MIC. However, use of the MIC has several disadvantages (182) which include:

– it is measured using serial twofold concentrations, which means the MIC is always less than the reported value

– it is a threshold value, which suggests that there is either activity or there is not, when in reality there can be significant sub- and supra-MIC effects

– it provides a summary measure of a complex set of antibacterial events happening throughout the incubation time

– the MIC is established using a constant concentration of the antimicrobial of interest in contrast to what is encountered *in vivo*

– it is usually based on an inoculum size of 10^{5-6} bacteria, which is considerably less than present in many infections

– as an *in vitro* measure it does not account for the *in vivo* actions of leukocytes and a functioning immune system.

The other important criticism of the conventional PKPD indices is that each of the PK components (T, C_{max} and AUC) are dependent covariates (73) and it has been suggested that it is pointless to search for the best predictive index if all are related.

Consequently, the future of PKPD indices may lie in those indices that can capture the full time-course of *in vitro* (or preferably *in vivo*) bacterial kill kinetics resulting from exposure to the change in concentration with time of the selected antimicrobial agent (52, 167, 171, 182, 257).

In addition to the three conventional PKPD indices illustrated in Figure 6, other indices based on the mutant prevention concentration (MPC) have been proposed in an attempt to preclude selection for resistance (27, 297). The MPC is defined as the antibacterial concentration that inhibits the growth of the least-susceptible, single-step mutant and is essentially the MIC of the least susceptible organism, often determined within an inoculum of 10^{9-10} cfu/ml (36). The concept was developed primarily for the fluoroquinolone class of antimicrobial agent as spontaneous point mutations are the principal resistance mechanism. A new PKPD index, fT>MPC/(time within the mutant-selection window), appeared to be predictive of resistance emergence in one study of marbofloxacin in a *Klebsiella* rat lung infection model (129), however, it is not known if this new index can be generalised to other situations. Caution has been expressed about applying the MPC concept to β-lactams, macrolides or aminoglycosides or even to Gram-negative bacteria, as the primary modes of resistance involve horizontal gene transfer (HGT), inactivating enzymes or target-binding site changes (50, 58) rather than single step mutations.

While the MPC concept has encouraged the use of high-dose regimens to reduce the likelihood of selection of resistant mutants, it appears that this approach may concurrently suppress the transfer of antimicrobial resistance plasmids, at least in *in vitro* studies (145). However, while the MPC concept suggests that there is no selection for mutants at concentrations less than the MIC, this may not be the case, as hypermutation and HGT may be facilitated (36, 50, 149).

The major challenge in developing PKPD indices to prevent resistance is the consequences of exposure of non-target bacteria, particularly the commensal flora, which are inevitably exposed. As indicated above, there is already evidence of resistance selection in *Salmonella* via gut efflux of fluoroquinolones and *Staphylococcus* by β-lactam presence in sweat.

Combined population physiologically based pharmacokinetic–pharmacodynamic models

Physiologically based pharmacokinetic models that incorporate known distributions of physiological and anthropometric properties are already available for use in humans (287) and could readily be adapted for use in veterinary species. PK and PD variability in the animal population of interest can be evaluated by PBPK linked to PD models, the statistical distribution of the PK–PD index that is predictive of clinical efficacy can be established using Monte Carlo simulations and the probability of attaining the desired response (for example, PK–PD breakpoint) in a given proportion of the population can be determined by PPK.

Refinements in antimicrobial use

Measurement of antimicrobial use

A major impediment to any understanding or analysis of global antimicrobial use patterns is the absence of an internationally accepted standard approach to reporting antimicrobial usage (40, 79, 94, 122, 179, 248). The human concept of the defined daily dose or DDD (defined as the assumed average maintenance dose per day for the drug used in its main indication and often expressed as DDDs/1,000 population/day) was first applied to the use of veterinary antimicrobial agents in 1999 (92). This concept in a number of forms (for example, animal defined daily dose, prescribed daily dose and used daily dose) has been the basis of descriptions of the use of antimicrobials in pigs, poultry, and veal calves in Belgium (197, 204, 260), dairy cattle in Switzerland (87), poultry in Norway (93), dairy cattle in Wisconsin (208), cow-calf operations in western Canada (89), pigs in Denmark (120, 282) and turkeys and chickens in France (39, 41). There is still no global consensus on which measure to use, although there is clearly a high level of importance to reach agreement on one or several indices.

Quality assurance programmes

To meet increasing consumer preferences for livestock products that are sourced from enterprises with high

standards of animal health, welfare and food safety the role of quality assurance (QA) programmes has been growing in importance. For example:

– UK: the Responsible Use of Medicines in Agriculture Alliance (www.ruma.org.uk) is well recognised and their programmes for poultry, pigs, cattle and sheep are widely adopted by farmers

– USA: several QA programmes are widely adopted, including the Pork Quality Assurance® Plus Program (www.pork.org/Certification/11/pqaPlus.aspx), the Beef Quality Assurance Program (www.bqa.org) and the National Dairy FARM (Farmers Assuring Responsible Management™) Program (www.nationaldairyfarm.com)

– Canada: the Canadian Quality Assurance Program (www.cqa-aqc.ca) and the Canadian Quality Milk Program (www.dairyfarmers.ca/what-we-do/programs/canadian-quality-milk) are widely adopted by hog producers and dairy farmers, respectively

– Australia: the overwhelming majority of farmers have implemented the measures of either the Livestock Production Assurance Program (www.mla.com.au/Meat-safety-and-traceability/On-farm-assurance/LPA), Australian Pork Industry Quality Program (www.apl.com.au) or PigPass Program (www.pigpass.com.au).

While each QA programme has its own objectives, common elements include (*i*) a philosophy of continuous improvement and (*ii*) ensuring all personnel are appropriately trained and are committed to safe and responsible use of all on-farm chemicals, including veterinary medicines such as antimicrobial agents. Records of medicine use are maintained and are among the documents subject to regular audit within the QA programme. In addition, most QA programmes require that each farm have plans for disease control and biosecurity.

Biosecurity plans

Biosecurity can be defined as 'the implementation of measures that reduce the risk of the introduction and spread of disease agents; it requires the adoption of a set of attitudes and behaviours by people to reduce risk in all activities involving domestic, captive/exotic and wild animals and their products' (77). By providing a strong defence against the introduction of disease, biosecurity plans are associated with a reduction in the need for the use of antimicrobial agents. In addition to discussions of biosecurity in the textbooks recommended in the introduction of this paper, there are excellent descriptions of biosecurity for dairy farmers (241), feedlot enterprises (227), and cow-calf operations (226). Manuals on biosecurity in poultry have been developed by a variety of organisations (12, 13, 44, 45) and the Food and Agriculture Organization of the United Nations has developed a manual on biosecurity in pigs (76). One of the world's major providers of broilers emphasised to its growers that '…prevention is by far the most economical and best method of disease control. Prevention is best achieved by the implementation of an effective biosecurity programme, including appropriate vaccination. Diseases do, however, overcome these precautions and when they do, it is important to obtain professional veterinary advice as quickly as possible' (44).

Regulation

While a survey of OIE Member Countries in 2005 revealed that some countries have no regulations controlling the use of antimicrobial agents in livestock (274) the majority of the respondents noted that their countries do have laws and regulations governing the approval and use of veterinary medicines. However, as emphasised by participants in a World Health Organization (WHO) consultation on antimicrobial use in food animals (289), and more recently by a study in India (224), the implementation and enforcement of regulations is far from universally thorough. Even in developed countries such as the USA it is reported that many antimicrobial agents are readily available to livestock producers without a prescription (95). This should not be surprising in view of the findings of a survey of human antimicrobial use (166). In humans, non-prescription antimicrobial use occurred worldwide and accounted for between 19% and 100% of antimicrobial use outside of northern Europe and North America. It is unlikely that the animal health situation would be any better.

Professional veterinary support

The value of professional animal health intervention provided by veterinarians, paraveterinarians, community animal health workers and other trained health workers has been repeatedly emphasised (22, 75, 83, 152, 200, 242, 267) and most recently the results of a survey of OIE Member Countries reinforced the role of the veterinary sector as 'one of the guarantors of the stability and planned evolution of the world food system' (28). Yet even in developed countries there is no universal use of professional veterinary support. For example, a survey of pig producers in the USA (269) revealed that only 69% had used a veterinarian in the previous year. By contrast a separate survey of cattle feedlots found that veterinarians were used by 97% of operations and their recommendations had a strong or moderate influence on the selection of

antimicrobial agents (268). If such high veterinary input was normal it is likely that there would be significant improvements in disease prevention, diagnosis and antimicrobial use.

Bodyweight estimation and dose delivery

Overestimation and underestimation of bodyweight can lead to inaccurate antimicrobial dose delivery (197). Visual estimation of the bodyweight of sheep by farmers has been found to be potentially inaccurate, with one study finding that only 27% of 273 farmers guessed bodyweights within 20% of the actual value (24). Similarly, a study in Africa found that only 19% of cattle had their bodyweight estimated within 20% by cattle owners, although animal health workers were more accurate and the weight of 77% of cattle was estimated within 20% of the actual value (148). The hipometer is an indirect tool that uses the external width between the greater trochanters of the left and right femurs to estimate the bodyweight of cattle, but in one study of Holstein heifers it was found to be accurate only in heifers between three and fifteen months of age (compared with electronic scales) (62). Measurement of heart-girth (chest circumference) is commonly used to estimate the bodyweight of cattle, but this type of measurement (using weighbands) has been found to be less accurate than electronic scales, with overestimation averaging around 10% in one study (215) and greater errors being present in older rather than younger cattle in another study (194). Both studies observed considerable differences in individual cattle. However, a recent study on weight estimation in Holstein heifers in the USA using a contemporary liveweight prediction equation found that weighbands can be accurate in particular circumstances, especially in Holstein heifers weighing more than 150 kg (109).

Evidence-based clinical decisions

The importance of using antimicrobial agents in a way which evidence suggests is least selective for resistance has been reinforced (158). A recent review (280) reminded us that 'veterinarians involved in food production are required not only to identify what is the best therapeutic option for farm animals but also what is the most cost-effective and economic approach'. Unfortunately there is a dearth of objective systematic reviews of the therapeutic literature. Even for globally important diseases, such as mastitis caused by *S. aureus,* there are few studies guiding veterinarians to the best antimicrobial treatment options (223).

There are two notable and valuable examples of evidence-based decision support systems that rely on databases of relevant pharmacological and microbiological information. The 'Veterinary Antimicrobial Decision Support System' (www.vads.org) (11) regrettably remains a pilot demonstration programme awaiting renewed and ongoing support to keep it up to date and in line with new literature and developments. However, this innovative system clearly shows that it is possible to synthesise a huge dataset from diverse literature sources into a format that can be interrogated and provide information to underpin important clinical decisions. More recently, the 'One health evidence-based prudent use guidelines for antimicrobial treatment of pigs in Denmark' has been described (181), linking pharmacokinetic, pharmacodynamic and microbiological data. Pharmacology reviews and guidelines are currently available to support Danish veterinary decision-making (www.uk.foedevarestyrelsen. dk/forside. htm).

Just as informed veterinarians make better decisions, so too farmers and other end users (202). For example, training farmers in rational drug use has been found to improve the management of infectious disease in cattle in Mali (90).

Product quality

Veterinary medicine production in many countries must comply with demanding codes of good manufacturing practice (GMP). However, there are three main types of poor quality medicines (substandard, degraded and counterfeit) potentially available to end users (178). Substandard products may be the result of poor and unregulated manufacturing practice. Degraded products are derived from those that were originally of high quality but have either exceeded their shelf life or have been stored inappropriately. Counterfeit (or fake) products are defined by WHO as products that are deliberately and fraudulently mislabelled with respect to identity and/or source (128). Counterfeit products include drugs with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging. It has been estimated that up to 10% of the world's pharmaceutical trade, including 25% in developing countries, consists of fakes. It is unlikely that medicines available for animal health use are not as at risk of poor quality as those for human use. There are few cases published in the veterinary literature, although one report observed a preponderance of fake and/or expired drugs in Nigeria (61) and participants in a WHO consultation suggested that expired products were being relabelled and sold (289). In countries where there is no regulatory requirement to demonstrate bioequivalence, some generic versions of pioneer products have been shown to be of variable quality and to have pharmacokinetic profiles unlikely to be associated with effective antimicrobial activity (250, 252).

Improved diagnosis

Observation of livestock and diagnostic description by syndromic classification (for example, 'Dich Ta Heo' – epidemic diarrhoea of pigs [126], 'Libuku' – blackquarter [151], or watery excrements [204]) is the usual first approach to diagnosis of adverse clinical presentations, whether observing pigs in Vietnam (126), sheep in Canada (164), small ruminants in southern Sudan (151) or broilers in Belgium (204). Without further assessment (which often requires the availability of veterinary services) to establish the likelihood of involvement of pathogenic bacteria, such diagnostic categorisation can lead to overtreatment with antimicrobials and in some cases can delay the recognition of serious viral diseases (such as foot and mouth disease or classical swine fever) (126).

The value of enhanced diagnostic capability has been repeatedly emphasised in both medical (60, 221, 266) and veterinary (65, 130, 202) contexts. It is very possible that the greatest improvement in antibacterial use will follow the introduction of POCTs. Targeted treatment guided by the results of such tests has already led to reduced use of antimicrobial agents in medical (198) and veterinary (130, 131) situations. The technology for such tests is improving rapidly (37, 135, 138, 183), driven largely by the need for improvements in medical practice, especially in developing countries, but there should be many applications that can readily be transferred to animal health.

By adding the need to reduce resistance to the WHO criteria for an acceptable POCT, the necessary criteria can be described by the acronym ReASSURED: Resistance-reducing, Affordable, Sensitive (low rate of false negatives), Specific (low rate of false positives), User-friendly (simple to perform in a few steps with minimal training), Robust and Rapid (results available in less than 30 min), Equipment-free, and Deliverable to those who need them (146, 191). It is also vital that POCTs can distinguish colonisation from infection and this can be accomplished by detecting signals from pathogens as well as sensing the response of the host (205).

The importance of accurate and early diagnosis of bovine respiratory disease (BRD) and the value of a chute-side test that improves detection has been emphasised (65). Current methods for identifying cattle with BRD often rely on observation of clinical illness, which has been shown to have low sensitivity (62%) and low specificity (63%) (285). By selecting only those calves with a rectal temperature of ≥39.7°C for targeted metaphylaxis it has been shown that the impact of BRD can be reduced. Moreover, this selective metaphylaxis uses fewer antimicrobial agents than mass medication and involves less handling of calves. (88). Feeding behaviour may be predictive of impending illness (284) and it has been shown that electronic monitoring of the feeding behaviour of newly received feedlot calves permits earlier detection of morbidity than skilled pen-rider observation and earlier implementation of remedial measures, which usually results in a more successful outcome (212). Measurement of the serum concentration of the acute phase inflammatory protein haptoglobin has been demonstrated to be useful in the early detection of metritis (118), but is less predictive of BRD (116) in calves at feedlot arrival. The use of reticulo-rumen temperature boluses to identify visually undetected fever episodes in feedlot cattle (261, 262) is emerging as a possible approach to improving detection of BRD and other diseases associated with pyrexia.

It has been demonstrated that the earlier the detection and treatment of mastitis the higher the likelihood of bacterial elimination (111), leading to the suggestion that an accurate cow-side test (a POCT) would be very valuable, but such tests are still far from ideal (127). It has been reported that up to 40% of cultures from cases of clinical mastitis yield no bacterial growth and so do not require antimicrobial treatment. Use of the Minnesota Easy Culture System, a commercially available on-farm milk culture system for detection of gram-positive and gram-negative bacteria, has been shown to be a useful cow-side test that has the potential to reduce total antibiotic use on dairy farms by 25% (130, 131). Similarly, if farmers can select cows at risk of mastitis and target them for selective dry cow treatment, further reductions in antimicrobial use may be possible (20, 211).

In calf rearing units, diagnostic systems that flag inappetence and other early clinical signs of disease have been proposed as a way to allow targeted treatment of selected calves with diarrhoea (23), avoiding the adverse consequences of antimicrobial-associated diarrhoea when non-discriminatory mass medication is employed.

High herd or flock health and reduced use of antimicrobial agents

Adoption of good farming practices as outlined by OIE (293) should ensure a high degree of health and welfare of livestock and reduce the need to treat clinical disease with antimicrobial agents. A sustained commitment to improved dairy herd health and reduced use of antimicrobials by Danish organic farmers has been described (273). The most significant impediment to success was the presence of mastitis, but determined farmers were able to progressively reduce somatic cell counts in association with improved hygiene, outdoor access, use of nursing cows and drying off infected quarters with chronic mastitis.

A recent survey of antimicrobial use in poultry in Belgium found that 7 of 32 farms examined did not use antimicrobial agents in either of the production cycles monitored (204). In New Zealand it has been reported that while bacitracin is commonly included in the feed for prevention of necrotic enteritis, the poultry meat industry notes that less than three in 100,000 flocks per year are given any class of therapeutic antimicrobial (161). A broiler company in Georgia (USA) commenced drug-free broiler production in 1999 with an objective of raising birds with no use of anticoccidial or antibacterial agents (245). Although production costs are significantly higher than in conventional production systems, increased use of vaccines (especially those against coccidiosis, *E. coli* and necrotic enteritis), probiotics, prebiotics and other agents combined with enhanced biosecurity and careful breed selection has allowed the percentage of flocks requiring interventions with antimicrobial agents to control disease outbreaks to be reduced from 12% per annum to less than 1% in 12 years.

It would appear that under conditions where it is possible to maintain high standards of biosecurity, infection control (including vaccination), animal husbandry, nutrition, and environmental management, antimicrobial use can be more selective and targeted without adversely affecting the welfare or productivity of livestock.

rather than individuals adds another dimension of complexity and source of variation. Furthermore, the existence of target pathogens with a range of susceptibilities to various antimicrobial agents that is in flux and changing with time and place further complicates the current use of such agents. The use of an antimicrobial agent should always be considered a trial. While there is an expected outcome, it is only by monitoring the response to administration that the expected response can be verified or an unexpected outcome can be identified and subjected to investigation. Each stage of the process of use (diagnosis, formulation of a therapeutic plan, selection of the most appropriate antimicrobial agent and administration and monitoring of response) requires the skilful application of detailed knowledge and experience. There are many ways in which existing uses of antimicrobial agents can be improved, amongst the most important are increased utilisation of veterinary professional services, the introduction of enhanced infection control measures, improved point-of-care diagnostic tests and the application of population PBPK-PD modelling. There is a need for a central resource that can provide undergraduate educational materials on antimicrobial use and, for continuing professional development, an ongoing objective assessment of the ever-expanding database that underpins decisions on appropriate antimicrobial use.

Conclusion

There are myriad sources of pharmacokinetic and pharmacodynamic variation in response to the administration of antimicrobial agents by many different routes to a variety of species. The treatment of populations

Utilisation des agents antimicrobiens chez les animaux d'élevage

S.W. Page & P. Gautier

Résumé

Les agents antimicrobiens et notamment antibactériens sont utilisés partout dans le monde dans une grande diversité de systèmes de production animale, aussi bien extensifs qu'intensifs, dans le but de protéger la santé et le bien-être des animaux d'élevage et d'améliorer leurs performances. Si un petit nombre d'antimicrobiens utilisés en production animale appartiennent à des classes sans équivalent en médecine humaine, ce n'est pas le cas de la plupart des agents d'utilisation courante tels que les tétracyclines, les pénicillines, les macrolides et les sulfamides. La plupart des maladies bactériennes du bétail occasionnent des pertes considérables en termes d'effectifs et de productivité des élevages et grèvent dramatiquement les revenus et les moyens de subsistance des éleveurs, de sorte que la nécessité de traiter les animaux

s'accompagne souvent d'une grande sensation d'urgence. Néanmoins, les bactéries pathogènes sont extrêmement nombreuses et il est souvent difficile d'obtenir un diagnostic concluant avant de mettre en place le traitement. Il existe de nombreuses manières d'améliorer les utilisations actuelles des agents antimicrobiens, parmi lesquelles les plus importantes sont un recours plus fréquent aux services professionnels des vétérinaires, l'introduction de mesures renforcées de lutte contre les infections, l'amélioration des épreuves diagnostiques sur les sites d'intervention et l'application de modèles pharmacodynamiques et pharmacocinétiques des populations basés sur la physiologie.

Mots-clés
Agent antibactérien – Agent antimicrobien – Animal d'élevage – Antimicrobiens d'importance cruciale – Contrefaçon – Diagnostic sur le site d'intervention – Pharmacocinétique basée sur la physiologie – Pharmacocinétique des populations – Pharmacocinétique-pharmacodynamique – Services vétérinaires – Voie d'administration.

Uso de agentes antimicrobianos en el ganado

S.W. Page & P. Gautier

Resumen
En todo el mundo y en muy diversos sistemas de producción ganadera, tanto extensiva como intensiva, se utilizan agentes antimicrobianos, en especial antibacterianos, para proteger la salud y el bienestar del ganado y mejorar su rendimiento. Aunque algunos de los fármacos empleados en los animales pertenecen a clases que no tienen equivalente en medicina humana, no es el caso de los más extendidos: tetraciclinas, penicilinas, macrólidos y sulfonamidas. Muchas enfermedades bacterianas del ganado causan devastadoras pérdidas de vidas animales y productividad, además de diezmar dramáticamente los ingresos y medios de vida de los ganaderos. Por ello a menudo cunde la sensación de que urge tratar lo antes posible a los animales afectados. Sin embargo, hay un gran número de patógenos bacterianos que causan enfermedades, y muchas veces es difícil establecer un diagnóstico concluyente antes de poner en marcha el tratamiento. La forma en que actualmente se emplean los antimicrobianos es mejorable en muchos sentidos: entre las posibilidades más importantes están la de recurrir en mayor medida a los servicios de veterinarios profesionales, introducir medidas más eficaces de lucha antiinfecciosa, mejorar las pruebas de diagnóstico efectuadas en el lugar de tratamiento y aplicar modelos de farmacocinética-farmacodinámica de poblaciones basados en datos fisiológicos.

Palabras clave
Agente antimicrobiano – Antibacteriano – Antimicrobianos de importancia crítica – Diagnóstico en el lugar de tratamiento – Falsificación – Farmacocinética basada en datos fisiológicos – Farmacocinética-farmacodinámica – Farmacocinética de poblaciones – Ganado vacuno – Servicios Veterinarios – Vía de administración.

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