Antimicrobial resistance in animal and public health: introduction and classification of antimicrobial agents

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Summary

Bacteria have a remarkable ability to adapt, evolve and survive by developing resistance to therapeutic compounds. This ability is also shared by other pathogenic agents such as viruses, fungi, and parasites. Even when focusing on bacterial resistance only, this phenomenon is quite complex to analyse due to the diversity of animal species, the diversity of rearing environment, the number of antimicrobial classes available and the diversity of pathogenic bacteria involved. This introductory paper includes developments on the place of antiviral compounds in veterinary medicine and a classification of antimicrobials used in food-producing animals.

Keywords

Antimicrobial – Antiviral – Classification – Resistance.

Introduction

For more than 70 years, bacterial infections and, more recently, parasitic, fungal and viral infections have benefited from therapeutic substances of natural, semi-synthetic or synthetic origin. However, all causative microorganisms have revealed a remarkable ability to adapt, to evolve, and to survive by developing resistance to each and every therapeutic compound administered.

At first, resistant strains were considered simply to be a local and undesirable side effect of the treatment, but it is now clear that they reflect a profound change in our environment. These resistant strains have proved to be global, and extremely dangerous. Bacterial resistance to antimicrobials has been most extensively studied in the context of the number of antimicrobials used to satisfy the needs of human and animal health.

Antifungal drug resistance is a clinically important and emerging subject, especially in human medicine, but less so in livestock. Standardised methods for reliable *in vitro* antifungal susceptibility testing are now available from the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. Studies are expanding on azoles and echinocandins, as well as on the epidemiology of fungal infections.

Antiviral compounds, although rarely used in food-producing animals, have had an enormous beneficial impact on human diseases, particularly the human immunodeficiency virus/acquired immune deficiency syndrome complex and influenza. Information about the use of antiviral compounds in veterinary medicine can be found in Box 1.

Parasitic infections in humans and domestic animals, which increasingly involve resistant strains, are a

Box 1
The use of antiviral compounds in veterinary medicine

The world of viruses is vast and highly complex. Although the number of viral species has previously been estimated at around 5,000, this is a gross underestimation.

Two extensively studied species of mammal are humans and cattle; humans are known to host eight different species of herpes virus and cattle five. If we consider that these two species alone host thirteen different identified herpesviruses we get a clearer picture of the extraordinary number of different viruses that must exist in the animal kingdom as a whole. Even if we take into account only vertebrate species (5,416 mammals, 9,723 birds, 9,002 reptiles, 6,570 amphibians and 31,564 fish) it becomes apparent that the total number of viruses among all animal species is huge.

The 1,415 pathogens identified in humans include 217 viruses and prions, 538 bacteria and rickettsiae, 307 fungi, 66 protozoa and 287 helminths. Of these pathogens, 868 (61%) are considered to be zoonotic and 175 to be associated with emerging diseases. Of the 175 agents responsible for emerging infections in humans, 132 (75%) are zoonotic and most have originated in wildlife, emphasising the role of wildlife as a potential source of new emerging diseases, especially viral infections.

The number of viral species identified in humans is also a good indicator of the scale of the virus domain. A key feature of viruses is their extreme variability. In particular, RNA viruses, multi-segmented or not, show great diversity that results from the lack of an error-correction mechanism for use during nucleic acid replication. This variability is underpinned by an exceptionally high mutation rate such that, in a viral RNA genome of around 8,000 nucleotides, all progeny viruses that result from multiplication differ from the parental strain by at least one nucleotide. This exceptional mutation rate leads to the formation of populations of quasi-species.

In the absence of broad-spectrum antivirals, a number of methods have been successful in controlling viral diseases in animals. For production animals they include preventive hygiene measures to avoid possible contamination, disinfection, stamping out (culling) and vaccination.

The most resounding success story in animal health has been the use of routine cattle vaccination to eradicate rinderpest, which is caused by a morbillivirus. In 2011, the World Organisation for Animal Health and the Food and Agriculture Organization of the United Nations declared rinderpest to have been officially eradicated.

A range of measures is also used to tackle other viral infections, the most dreaded of which are legally notifiable transboundary diseases, including foot and mouth disease, classical swine fever, avian influenza (highly pathogenic avian influenza in birds and low-pathogenicity notifiable avian influenza in poultry) and rabies. These measures can even be applied to wildlife, for example, wild carnivores can be vaccinated against rabies or wild boars against classical swine fever.

Experimental therapeutic trials of antiviral drugs have also been conducted, such as a trial of interferon alpha in cattle.

In the absence of effective vaccines (e.g. against African swine fever) and in the presence of newly emerging zoonotic diseases (e.g. Nipah virus infection in pigs), stamping out is often the only choice.

The control of major viral diseases is currently facilitated by the availability of DIVA (differentiating infected from vaccinated animals) vaccines, which allow serological differentiation between animals that have only been vaccinated and those that are infected (whether or not they have been vaccinated).

Although vaccination is the first priority for controlling viral infections in companion animals (except in special situations, such as to control stray dogs, which are potential carriers of rabies), some antiviral drugs are used therapeutically. Only one antiviral compound has been granted a marketing authorisation in Europe: feline omega interferon, which was originally developed for the treatment of canine parvovirus infection. Other drugs approved for humans are also used in veterinary medicine, in accordance with the cascade principle; for example, zidovudine is used to treat feline immunodeficiency virus infection. There are a number of obstacles to the development of antivirals for animals: the high development cost; the often very narrow specificity of the viral target; the diversity of animal species concerned; and the difficulty of developing low-toxicity broad-spectrum molecules. Viruses are obligate cellular parasites and non-selective toxicity is an issue of paramount importance.

In conclusion, antivirals currently play a very limited role in animal health and if their use were to become widespread, resistance would be expected to emerge rapidly because of the exceptionally high mutation rate of viruses, particularly RNA viruses.

significant problem worldwide. A number of types of human parasitosis have been classified as 'neglected diseases', often associated with poor levels of diagnosis, surveillance and management. The incidence of parasitic infection has often been misinterpreted, and in many cases there has been no reliable method to study parasite resistance to therapeutic agents.

Anthelmintic resistance in nematode and trematode parasites of ruminants is an important global issue. Resistance in protozoal infections, including coccidiosis of poultry, is now observed. This subject deserves greater study in humans and other animals, recognising that many antiprotozoal agents have antibacterial activity as well. In specific areas work is already well advanced. For example, the management of resistant malaria is one of the priorities of the World Health Organization.

However, this special issue of the OIE *Scientific and Technical Review*, focuses principally on the topic of

Table I
Antimicrobial classification
In certain countries, some of these antimicrobial agents may be prohibited or have other restrictions on their use.
The inclusion of an antimicrobial in this table does not imply that the OIE or the authors support its use

Antimicrobial class	Antimicrobial sub-classes	Active ingredient*	Species	Main routes of administration				
				Injectable	Oral	Intra-mammary	Intra-uterine	Local
Aminocyclitol		Spectinomycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x			
Aminoglycosides		Streptomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x				
		Dihydrostreptomycin	AVI, BOV, CAP, EQU, LEP, OVI, SUI	x	x	x	x	
	2 Deoxystreptamine	Astromicin (Fortimycin)	SUI		x			
		Framycetin	BOV, CAP, OVI		x			x
		Kanamycin	AVI, BOV, EQU, PIS, SUI			x		
		Neomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, SUI	x	x	x		x
		Paromomycin	CAP, OVI, LEP, BOV, SUI, AVI					
		Apramycin	AVI, BOV, LEP, OVI, SUI		x			
		Gentamicin	AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI	x	x	x		x
		Amikacin	EQU					x
Arsenical		Roxarsone	AVI, SUI		x			
Bicyclomycin		Bicozamycin	AVI, BOV, PIS, SUI		x			
Cephalosporin	Cephalosporin 1st G	Cefacetrile	BOV			x		
		Cefalexin	BOV, CAP, EQU, OVI, SUI	x	x	x		
		Cefalotin	EQU	x				
		Cefapirin	BOV			x	x	
		Cefazolin	BOV, CAP, OVI			x		
		Cefalonium	BOV, CAP, OVI			x		x
	Cephalosporin 2nd G	Cefuroxime	BOV			x		
	Cephalosporin 3rd G	Cefoperazone	BOV, CAP, OVI			x		
		Ceftiofur	AVI, BOV, CAP, EQU, LEP, OVI, SUI	x		x		
		Ceftriaxone	AVI, BOV, OVI, SUI	x				
	Cephalosporin 4th G	Cefquinome	BOV, CAP, EQU, LEP, OVI, SUI	x		x		
Coumarin		Novobiocin	BOV, CAP, OVI, PIS			x		
Fusidane		Fusidic acid	BOV, EQU					x
Glycophospholipid		Bambermycin (Bambermycins [USAN], Flavophospholipol)	AVI, BOV, SUI		x			
Glycopeptide		Avoparcin	AVI, SUI		x			
Ionophores		Lasalocid *(mostly used as anticoccidial agents)*	AVI, BOV, LEP, OVI		x			
		Laidlomycin	BOV		x			
		Maduramicin	AVI		x			
		Monensin	API, AVI, BOV, CAP		x		x	
		Narasin	AVI, BOV		x			
		Salinomycin	AVI, LEP, BOV, SUI		x			
		Semduramicin	AVI		x			
Kirromycin		Efrotomycin	SUI		x			
Lincosamides		Pirlimycin	BOV, SUI, AVI			x		
		Lincomycin	API, AVI, BOV, CAP, OVI, PIS, SUI	x	x	x		
Macrolides	Macrolides C15, C13, triamilide	Tulathromycin	BOV, CAP, LEP, OVI, SUI	x				
	Macrolides C14	Erythromycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x			
	Macrolides C14	Oleandomycin	BOV			x		
	Macrolides C16	Carbomycin	AVI		x			
	Macrolides C16	Josamycin	AVI, PIS, SUI		x			
	Macrolides C16	Kitasamycin	AVI, SUI, PIS		x			
	Macrolides C16	Spiramycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x	x		
	Macrolides C16	Tilmicosin	AVI, BOV, CAP, LEP, OVI, SUI	x	x			
	Macrolides C16	Tylosin	API, AVI, BOV, CAP, LEP, OVI, SUI	x	x			
	Macrolides C16	Tylvalosin (USAN, rINNM)	AVI, SUI		x			
	Macrolides C15, azalide	Gamithromycin	BOV	x				
	Macrolides C16	Mirosamicin	API, AVI, PIS, SUI		x			
	Macrolides C17	Sedecamycin	SUI	x				
	Macrolides C16	Terdecamycin	AVI, SUI		x			
	Macrolides C16	Tildipirosin	BOV	x				
Nitrofuran		Furaltadone	AVI, BOV, SUI		x			x
		Furazolidone	AVI, SUI		x			
Orthosomycins		Avilamycin	AVI, LEP		x			

Table I (cont.)
Antimicrobial classification

Antimicrobial class	Antimicrobial sub-classes	Active ingredient*	Species	Main routes of administration				
				Injectable	Oral	Intra-mammary	Intra-uterine	Local
Penicillins	Natural penicillin (including esters and salts)	Benzylpenicillin	AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI	x	x	x	x	
		Penethamate hydriodide (BAN)	AVI, BOV, SUI, OVI	x		x		
		Benzylpenicillin procaine/ benzathine	BOV, CAM, CAP, EQU, OVI, SUI	x				
	Amidinopenicillin	Mecillinam	BOV		x			
	Aminopenicillin	Amoxicillin	AVI, BOV, CAP, EQU, OVI, PIS, SUI	x	x	x	x	
		Ampicillin	AVI, BOV, CAP, EQU, OVI, PIS, SUI	x	x	x	x	
		Hetacillin	BOV			x		
	Aminopenicillin plus betalactamase inhibitor	Amoxicillin + clavulanic acid	AVI, BOV, CAP, EQU, OVI, SUI	x	x	x		
		Ampicillin + sulbactam	AVI, BOV, SUI	x				
	Carboxypenicillin	Ticarcillin	EQU				x	
		Tobicillin	PIS		x			
	Ureidopenicillin	Aspoxillin	BOV, SUI	x	x			
	Phenoxypenicillin	Phenoxymethylpenicillin (penicillin V USAN)	AVI, SUI		x			
		Pheneticillin	EQU		x			
	Penicillinase-resistant penicillins (i.e. not active against MRSA)	Cloxacillin	BOV, CAP, EQU, OVI, SUI			x		x
		Dicloxacillin	AVI, BOV, CAP, OVI, SUI	x	x			
		Nafcillin	BOV, CAP, OVI			x		
		Oxacillin	AVI, BOV, CAP, EQU, OVI, SUI	x	x			
Phenicols		Chloramphenicol	BOV, EQU, OVI, SUI		x			x
		Florfenicol	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x			
		Thiamphenicol	AVI, BOV, CAP, OVI, PIS, SUI					x
Phosphonic acid		Fosfomycin	AVI, BOV, PIS, SUI		x			
Pleuromutilins		Tiamulin	AVI, CAP, LEP, OVI, SUI	x	x			
		Valnemulin	AVI, SUI		x			
Polypeptides	Active against Gram-positive and anaerobic bacteria	Enramycin	AVI, SUI		x			
		Gramidicin	EQU					x
		Bacitracin	AVI, BOV, LEP, OVI, SUI		x	x		x
	Active against Gram-negative bacteria	Polymyxin B	AVI, BOV, CAP, EQU, LEP, OVI					x
		Colistin (polymyxin E)	AVI, BOV, CAP, EQU, LEP, OVI, SUI	x	x	x	x	
Quinolones	Quinolone 1G	Nalidixic acid	BOV		x			
		Oxolinic acid	AVI, BOV, LEP, OVI, PIS, SUI		x			
		Miloxacin	PIS		x			
		Flumequine	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x			
	Quinolone 2G (Fluoroquinolones)	Ciprofloxacin	AVI, BOV, SUI		x			
		Danofloxacin	AVI, BOV, CAP, LEP, OVI, SUI	x				
		Difloxacin	AVI, BOV, LEP, SUI		x			
		Enrofloxacin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x			
		Marbofloxacin	AVI, BOV, EQU, LEP, SUI	x	x			x
		Norfloxacin	AVI, BOV, CAP, LEP, OVI, SUI	x				
		Ofloxacin	AVI, SUI	x				x
		Orbifloxacin	BOV, SUI		x			
		Ibafloxacin			x			
		Sarafloxacin	PIS		x			
Quinoxalines		Carbadox	SUI		x			
		Olaquindox	SUI		x			
Rifamycins		Rifampicin	EQU		x			
		Rifaximin	BOV, CAP, EQU, LEP, OVI, SUI			x		
Streptogramins		Virginiamycin	AVI, BOV , OVI, SUI		x			

Table I (cont.)
Antimicrobial classification

Antimicrobial class	Antimicrobial sub-classes	Active ingredient*	Species	Main routes of administration				
				Injectable	Oral	Intra-mammary	Intra-uterine	Local
Sulfonamides		Sulfacetamide						x
		Sulfachlorpyridazine	AVI, BOV, SUI	x	x			
		Sulfadiazine	AVI, BOV, CAP, OVI, SUI	x	x		x	
		Sulfadimethoxine	AVI, BOV, CAP, EQUI, LEP, OVI, PIS, SUI	x	x			
		Sulfadimidine (Sulfamethazine, Sulfadimerazine)	AVI, BOV, CAP, EQU, LEP, OVI, SUI	x	x			
		Sulfadoxine	BOV, EQU, OVI, SUI	x				
		Sulfafurazole	BOV, PIS				x	
		Sulfaguanidine Sulfamerazine	AVI, CAP, OVI		x			
		Sulfamethoxazole	AVI, BOV, SUI	x	x			
		Sulfamethoxine (sulfameter, USAN)	AVI, PIS, SUI	x				
		Sulfamonomethoxine	AVI, PIS, SUI		x			
		Sulfanilamide	AVI, BOV, CAP, OVI		x			x
		Sulfapyridine	BOV, SUI		x			
		Phthalylsulfathiazole	SUI		x			
		Sulfamethoxypyridazine	AVI, BOV, EQU, SUI	x	x			
	Sulfonamides + diaminopyrimidines	Sulfonamides + trimethoprim	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	x	x			
	Diaminopyrimidines	Baquiloprim	BOV, SUI	x				
		Ormethoprim	AVI		x			
		Pyrimethamine (*mostly used as antiprotozoal agent*)	AVI, SUI		x			
		Trimethoprim	AVI, BOV, CAP, EQU, LEP, OVI, SUI	x	x			
Tetracyclines		Chlortetracycline	AVI, BOV, CAP, EQU, LEP, OVI, SUI		x		x	x
		Doxycycline	AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI		x			
		Oxytetracycline	API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI	x	x	x	x	x
		Tetracycline	API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI	x	x	x		
Thiostrepton		Nosiheptide	AVI, SUI		x			

* Unless indicated all the names used are INN (International Non-proprietary Name)

Species: API: bee; AVI: avian; BOV: bovine; CAM: camel; CAP: caprine; EQU: equine; LEP: rabbit; OVI: ovine; PIS: fish; SUI: swine

Abbreviations: BAN: British Approved Name; G: generation; MRSA: meticillin-resistant *Staphylococcus aureus*; rINNM: Recommended International Non-proprietary Name Modified; USAN: United States Adopted Name

antimicrobial agents and bacterial infections (mycobacteria have not been included). The severe problems in humans associated with multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis require a specific epidemiological and therapeutic approach. Mycobacterial infections of livestock are rarely treated with antimicrobials; the focus is generally on stamping out or containment.

Even dealing with this limited topic has been a challenge. Antimicrobial resistance is a complex phenomenon, especially in veterinary medicine, because of the number of animal species, the diversity of rearing environments, the differences in the bacteria involved, the range of pathogenicity mechanisms and the complex epidemiology. A number of antimicrobials are available for use in food-producing animals (see Table I) and the mechanisms of resistance are very diverse. The table provides a summary of antimicrobials currently authorised for use in at least one country and is intended to be as comprehensive as possible. The summary is compiled from different sources, including the OIE list of important antimicrobials as well as updated information from a variety of sources such as the pharmaceutical industry. Antimicrobials that are used

only in humans or those used only in non-food-producing animals are not included in this table. In addition, the table does not include agents with antibacterial activity that are intended only for antiparasitic or anticoccidial use. It should also be recognised that a number of antimicrobial classes, for example, the aminoglycosides, polypeptides and streptogramins, are administered by the oral route and show little or no absorption from the intestinal tract.

Given the large number of antimicrobials and the diversity of resistance mechanisms, it has not been possible to cover all aspects and to deal with all issues. It was decided to concentrate greatest attention on the main issues in order to understand the complex phenomenon of antimicrobial resistance in animals, while presenting updated and more precise information on specific aspects.

The reader will find general information on antimicrobial use, antimicrobial resistance and its consequences, and possible actions to contain antimicrobial resistance. More detailed papers provide comprehensive descriptions of antimicrobial resistance mechanisms. This issue of the *Review* also addresses risk analysis and the work of international organisations.

It was not possible to review in detail issues of antimicrobial resistance in particular species or the role of the environment in antimicrobial resistance. However, it is believed that the articles included in this review provide an excellent updated overview of the major issues linked to antimicrobial resistance in animal and public health.

L'antibiorésistance en santé animale et en santé publique : introduction et classification des agents antimicrobiens

J.F. Acar, G. Moulin, S.W. Page & P.-P. Pastoret

Résumé
Les bactéries possèdent une aptitude remarquable à s'adapter, à évoluer et à survivre grâce à la mise en place de mécanismes de résistance aux composés thérapeutiques. Elles partagent cette aptitude avec d'autres agents pathogènes tels que les virus, les champignons et les parasites. Même en se limitant à la seule résistance bactérienne, il s'agit d'un phénomène extrêmement complexe à analyser, en raison de la diversité des espèces animales, de la multiplicité des conditions d'élevage et du nombre de classes d'antimicrobiens disponibles et la diversité des bactéries incriminées. Cet article d'introduction contient également une mise au point sur le rôle des composés antiviraux en médecine vétérinaire et propose une classification des agents antimicrobiens utilisés chez les animaux destinés à l'alimentation humaine.

Mots-clés
Antimicrobiens – Antiviral – Classification – Résistance.

La resistencia a los agentes antimicrobianos en sanidad animal y salud pública: introducción y clasificación de antimicrobianos

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Resumen
Las bacterias tienen una notable capacidad para adaptarse, evolucionar y sobrevivir generando resistencias a los compuestos terapéuticos, capacidad que comparten con otros agentes patógenos como hongos, virus y parásitos. Aun prestando atención únicamente a la resistencia bacteriana, el fenómeno resulta difícil de analizar debido a la diversidad de especies animales, la heterogeneidad de las condiciones de cría, el gran número de clases de antimicrobianos existentes y la diversidad de bacterias patógenas. En este artículo introductorio los autores examinan también el lugar de los compuestos antivíricos en la medicina veterinaria y ofrecen una clasificación de los antimicrobianos utilizados en los animales de consumo humano.

Palabras clave
Antimicrobiano – Antivírico – Clasificación – Resistencia.