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Antimicrobial resistance at farm level

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Summary

Bacteria that are resistant to antimicrobials are widespread. This article reviews the distribution of resistant bacteria in farm environments. Humans, animals, and environmental sites are all reservoirs of bacterial communities that contain some bacteria that are susceptible to antimicrobials and others that are resistant.

Farm ecosystems provide an environment in which resistant bacteria and genes can emerge, amplify and spread. Dissemination occurs via the food chain and via several other pathways.

Ecological, epidemiological, molecular and mathematical approaches are being used to study the origin and expansion of the resistance problem and its relationship to antibiotic usage.

The prudent and responsible use of antibiotics is an essential part of an ethical approach to improving animal health and food safety. The responsible use of antibiotics during research is vital, but to fully contribute to the containment of antimicrobial resistance 'prudent use' must also be part of good management practices at all levels of farm life.

Keywords

Antibiotic residue – Antimicrobial resistance – Bacterial clone – Farm – Food safety – Resistance gene.

Introduction

Resistance to an antimicrobial agent was first recognised by scientists soon after penicillin was used for the first time. It became clear that there were two types of bacterial strain: those naturally resistant to penicillin, already known as out of the spectrum of the compound; and those which had acquired an ability to survive and multiply in the presence of the compound. The first type of strain has not been widely studied and deserves epidemiological consideration when exploring the effect of an antibiotic on a microbial community. The second type of strain has been extensively studied because its acquired mechanism of resistance has had major consequences for human health.

The loss of a previously effective antibiotic stimulates research into a means of overcoming the resistance mechanism and developing another therapeutic agent. The story of the discovery of antibiotics, the emergence of resistant bacteria shortly afterwards (usually within two years), and the race to develop new antibacterial agents, is well known and has been reported many times. Antimicrobial resistance is a natural phenomenon which is an inherent risk associated with any use of antimicrobial medication (3).

As a background to this article, it is important to keep the following points in mind:

a) since the late 1980s, the number of new antibiotics coming on to the market has declined. In fact, no new chemical class of antibacterial has been discovered. This situation has prompted a reevaluation of antimicrobial usage and generated multidirectional efforts to optimise the use of antibiotics in hospitals and in the community. In addition, more widespread surveillance of resistant bacteria has opened the door to extensive research into the biochemical mechanisms, molecular identity and genetics of resistance traits (68);

b) since the discovery of plasmids in the early 1960s, bacterial systems that allow the acquisition and transmission of genetic material between members of their community have been explored. Strains of *Salmonella* were among the first species of zoonotic bacteria to be studied (6, 14).

Studies on bacterial resistance have shown that there is a huge diversity of resistance mechanisms, the distribution and interaction of which is complex and mostly unknown. Moreover, resistance mechanisms can change and evolve as quickly as bacterial cells multiply, which sometimes means within very short periods of time (4).

Bacterial clones that are resistant to one or more antibiotics are now everywhere. Containment of bacterial resistance is a key issue in human medicine (nosocomial infections and resistant pathogens acquired in the community). The World Health Organization (WHO) (107) has extensively developed strategies to contain bacterial resistance, e.g.:

– updating knowledge of pathogen resistance

– using appropriate antibiotics in defined circumstances and with a defined treatment duration

– ending the use of antibiotics in cases where bacteria are not likely to be the cause of disease.

It is assumed that reducing the amount of antibiotics used will reduce their selective pressure and will help to control the incidence of resistant strains. Studies are needed to scientifically document this hypothesis.

Antibiotic usage in animals has definitely contributed to the current situation as regards resistant bacteria. Antibacterials contribute to the development of resistance in animal pathogens and commensals, and thus increase the risk that humans will be colonised and/or infected with resistant zoonotic bacteria (1, 37). This important consequence has been reviewed in many previous publications, and will not be detailed in this article (59, 95).

The aim of this paper is to present the actual situation of antimicrobial resistance at farm level and demonstrate how the prudent and responsible use of antibiotics may contribute to its containment and improved food safety, as well as reduce the hazards of the transmission of zoonotic food-borne pathogens that are resistant to antibiotics.

Resistant bacterial clones on the farm

The farm is as a large ecosystem composed of several compartments with different niches. Overlapping between niches and compartments allows microbes to disseminate.

Resistant bacterial strains are found everywhere. A review of the literature reveals that they are reported in all studies exploring animate or inanimate niches. Enterocci, Enterobacteriacae, and non fermentative Gram-negative rods are the most frequently studied species. The prevalence of resistant microorganisms is variable and the species affected depends on the niches explored. Resistant microorganisms have been found in conventional farms and also in organic farms, showing how widespread is the bacterial resistance phenomenon (74, 80, 81, 96, 98).

The principal compartments on the farm are:

– the humans who live and work there

– food animals (cattle, sheep, pigs, poultry), horses, pets, wild animals (rodents, insects, birds)

– the environment, e.g. water, soil, feeds, wastewaters, sewage, manure, lagoons, etc.

Humans on the farm

All human beings, including farm workers and their families, have huge numbers of commensal bacteria on their skin and in their digestive tract.

Only a small number of studies on antimicrobial resistance have been performed in healthy individuals in the community, but they have all shown that humans were colonised with resistant clones of bacteria, even months after having received antibiotics (15, 49, 66).

Studies in adults and children documented that among Gram-positive, Gram-negative and anaerobic bacteria found in intestinal flora a number of strains are resistant to one or more antibiotics; resistance to tetracyclins, β-lactam compounds, sulfonamide and trimethoprim is often found. The extent of the colonisation with resistant strains appears to be related to geographical location and environmental conditions (46).

It is recognised that crowding, poor hygiene, and extensive antibiotic use in the community increase the risk that healthy humans will carry resistant strains. Antibiotic absorption – even in appropriate amounts following a justified treatment – favours the carriage of strains that are resistant to antibiotics.

A large number of studies have been conducted on farms. They were mostly focused on exploring the similarity between resistant strains carried by humans and resistant strains carried by food animals after receiving an antibiotic treatment, e.g. enterococci resistant to glycopeptides (avoparcin, vancomycin) or enteroccoci resistant to virginiamycin (44, 52, 105). The farm workers and farm inhabitants often have strains similar to those isolated in the animals. Comparison with healthy persons living elsewhere or workers less exposed to animals sometimes shows that farm workers carry more resistant bacteria in their faecal flora than the control population. In other studies, such difference is not found. The type of work and the period of exposure may explain the different results (62, 63, 85, 93, 101).

Animals on the farm

Food animals

For four decades food animals have been known to harbour bacteria that are resistant and multiresistant to the antibiotics used in the farm. The resistant strains are found mostly among the commensal flora. Animal pathogens can be also resistant. Antibiotics given orally and for a long period of time have a stronger selective pressure and facilitate the prevalence of resistant strains (26, 42, 48, 53, 70).

The digestive tract of animals is a major bacterial reservoir where resistance genes can be acquired and from where resistant strains can be disseminated (36, 105, 109).

Antimicrobial substances given in low doses for growth promotion were recognised as selectors for resistant strains in the 1960s. The possible consequences for human health were discussed by the Swan committee (1969), which advised that antibiotics used to treat human infections should not be used for growth promotion. More recently, following the Danish experiment (108), the European Community decided to ban the use of antibiotics as growth promoters in Europe.

The food animals on a farm are at present a very large reservoir of resistant bacteria. We will not try to review the large number of publications which have established that all antibiotics used in animals have their corresponding resistant strains. Moreover, as happens in humans, multiple resistant strains are often found since they have a survival advantage in environments where multiple antibiotics are used.

Food animals may be colonised with bacteria present in their feed. *Salmonella* is a dangerous contaminant, often reported in feed, and must be controlled (20, 21, 22, 43, 79).

Other animals

Food animals are not the only reservoir of antibiotic-resistant bacteria: pets, wild rodents, birds, and insects may also harbour resistant bacteria and spread them among all compartments of the farm (18, 33, 103). The ways in which these bacteria spread from animal to animal are very intricate and this complex transmission network has yet to be fully explored.

Environmental sites

Much of the work undertaken on farms contributes to the contamination of the environment with resistant bacteria. The faecal and urine waste of the animals contains both resistant bacteria and antibiotic residues. Sewage, slurries, manure, surface water, sediments, even groundwater may contain, in addition to their specific bacterial flora, resistant bacteria from animals, and some antibiotic residues. This type of environment favours the emergence of resistance, the transfer of genes, and the amplification of resistant strains. New studies are carefully exploring environmental reservoirs and have documented the survival of bacteria in the environment and some of their patterns of antibiotic resistance (11, 12, 13, 41, 45, 84, 88).

Horizontal transfer and the spread of resistant clones

The spread of resistant clones is never monodirectional; it occurs between the different compartments as they overlap. The amplification of resistant bacteria, which facilitates their spread, is generally caused by antibiotics or their residues in the reservoir. When resistant bacteria are pathogens, the amplification occurs in the diseased animals (or humans). Adequate treatment with the appropriate antibiotic and the isolation of the patient are essential for controlling bacterial spread.

The strategy for controlling infections in food animals varies according to the disease and to the species. Bacterial cells, genes, and antibiotic residues interact in various ways. Antibiotics tend to diminish compartmentalisation: i.e. the presence of the same antibiotics in different niches means that resistant bacteria in one compartment can spread and survive in another (64).

It is important to note that clonal transmission and horizontal transfer of genes may occur together in a bacterial population. The relative frequency of each of these mechanisms of spread is unknown. It may depend upon the compartment, the bacteria and the antibiotic being used. However, we do know that horizontal transfer is a slow and complex process that takes place slowly in the environment and in the gut; while clonal transmission can occur very quickly between one host or niche and another.

It has been known for several decades that antimicrobial-resistant bacteria can spread from animals to humans (48). It was shown that small amounts of oxytetracyclin given to animals could select in their intestinal flora *Escherichia coli* resistant to tetracycline. Surprisingly, a few weeks later, resistant *E. coli* were also found in the intestinal flora of people living on the same farm.

A very large number of publications demonstrate that resistant strains in animals can be shared with farm workers and families living on the farm. An early experiment was done with the antibiotic nurseothricin, which is not used in humans; strains resistant to it were recovered in both animals and farm workers (106). More recent studies (principally concerned with enterococci and Enterobacteriaceae [2, 27, 36, 100]) confirm that resistant bacteria can be transmitted from animals to humans.

The transmission from animals to other animals and to humans can happen from direct or indirect contact (7, 93, 97, 103). Resistant bacterial strains originating from a calf were demonstrated to have colonised mice, pigs, chickens, flies, turkeys, and humans (56).

Moreover, airborne transmission has been documented in concentrated swine-feeding operations. The bacterial concentration can be as high as 104 colony-forming units (CFU)/m^3 to 107 CFU/m^3. Enterococci, staphylococci, *Pseudomonas, Listeria, Bacillus, E. coli* were recovered. Resistant enterococci were also recognised as airborne transmissible (16).

The spread of resistant bacteria from humans to animals has not been well documented. A study mentioned by S. Levy, in Ambroseli park in Kenya, showed that baboons that ate human refuse and garbage had a flora with resistant strains similar to those isolated from humans, while baboons from the wild did not (48).

Recently, methicillin-resistant *Staphylococcus aureus* colonising dogs, cats and horses were suspected to have originated from attendant personnel (65, 86). It is likely that the probability of transmission from humans to animals depends upon the geographical location, the level of hygiene, the size of the farm, and the type of integrated farming which takes place.

The magnitude and the dynamic of the spread of resistant strains between the different niches of the farm ecosystems are unknown. Spatial and temporal epidemiology studies might in the future bring new insight into the problem (29, 58).

Farms, like hospitals, are places where a large number of various bacteria coexist and different antibiotics are used. New resistance traits may emerge and horizontal transfer of genes between bacterial cells may result in new resistant microorganisms and new combinations of resistance genes, leading to different patterns of resistance.

In humans and animals the gut is the site for the horizontal transfer of genes. The emergence of clones that have acquired resistance genes in the gut has been documented in several papers (30, 94). A recent study has shown the transfer of plasmid encoding CMY-2 beta-lactamase from *E. coli* to *Salmonella* Newport in turkey intestinal tracts, even without the selective pressure of an antibiotic (73).

Beta-lactamase CMY-2 was discovered in a *Klebsiella* infection affecting a patient in a hospital in Greece in 1990. Four years later CMY-2 was found in a *Salmonella* from Algeria. Since then, CMY-2 has spread and can now be found in a large number of *Salmonella* serotypes. The journey of this beta-lactamase from human *Klebsiella* to *Salmonella* remains a mystery. It is worth noticing that both species are epidemic nosocomial pathogens; in the case of *Salmonella* this is mostly in developing countries (5, 69).

Horizontal transfers have been documented in environmental sites such as wastewater, surface water, sediments and manure. The microbial communities at these sites may contain different amounts of antibiotic residues and genetic material encoding resistance.

There is a lot that is not known about environmental bacteria and which deserves to be investigated, e.g. the role of uncultured bacteria and of *Pseudomonas, Acinetobacter,* anaerobes and enterococci, in the emergence and dissemination of resistance (67, 75).

Recently, two mechanisms of resistance originating in *Shewanella* (class D beta-lactamase and the new plasmid-mediated trait qnR governing quinolone resistance) were reported to have been transmitted horizontally to other bacteria (35, 71, 72).

Bacteria in the genera *Shewanella* and *Xanthomonas* also have chromosomal super-integrons similar to those found in the family Enterobacteriaceae. Are they the origin of such structures (76)?

Exchanges in and out of the farm ecosystem

The farm ecosystem is open: an exchange of bacteria resistant and susceptible to antibiotics occurs at the local level and also at regional, national and international levels as a result of modern systems of farming and export. Resistant strains entering the farm are transported by people, new food animals, birds, rodents, insects, water and feed. Contaminated feed as a vehicle for salmonella is an important problem which needs a surveillance and control strategy (82).

The dissemination of resistant bacteria out of the farm follows multiple pathways, but wastewater, effluent, and manure are important in this regard; in such vehicles, both resistant and susceptible bacteria come into contact with antibiotic residues, and although the amount can be low it is sometimes high enough to maintain the selective pressure. Antibiotics may accumulate in sediments and they take varying amounts of time to degrade.

To antibiotic residues, we must add other pharmaceuticals: disinfectants, heavy metals, coccidiostats and many other compounds that have some antibacterial effect (11, 45).

Animals waste is also an important vehicle of dissemination for resistant bacteria and genes. When used as fertilizer vegetables can be contaminated (40, 87). Contamination of drinking and domestic water has also been documented (8).

If there are any resistant bacteria (pathogenic, commensal or zoonotic) present in food animals at the time of slaughter this can start a chain of contamination which may reach the retail food sector and the consumer (19, 54, 102).

Dissemination from the farm by sewage and neighbouring spread may account for resistant bacteria found in rivers and sediments (9, 17). Human waste may also contribute to that contamination (55, 83).

The big picture of the farm with its different compartments and the constant exchange between a widespread community of bacteria, some of which are resistant and some of which are susceptible to antibiotics, raises a major question about how resistant microorganisms survive.

In sites where some antibiotics are present, the selective pressure maintains the resistant strains and amplifies them. This selective pressure can have a direct effect on strains harbouring the corresponding resistance mechanism. It can also have an indirect effect if cross resistance between bacterial species allows for antibiotics with similar modes of action to select for bacterial species with similar mechanisms of resistance, or if selection by one antibiotic for a sequence in which all traits of resistance are linked together genetically results in co-resistance of a bacterial species to more than one type of antibiotic.

In sites where antibiotics are absent, resistant bacterial strains tend to reach an equilibrium with susceptible strains. Resistant strains may persist at different levels of prevalence; they usually do not disappear completely (78). Several mechanisms have been described which aim to maintain resistant plasmids and to ensure the survival of the resistant strain:

– compensatory mutations, which improve the fitness of the strain, occur in order to adapt to the cost of fitness that occurs in response to the acquisition of resistance (47).

– plasmids themselves may enhance the host fitness (25).

– plasmids may regulate killer genes in the host and maintain themselves by protecting the bacterial cell (31).

Other mechanisms are likely to exist to stabilise resistance genes in the bacterial cell.

It is remarkable to note that resistant traits once acquired are difficult to eliminate (24, 78, 94).

Human and animal bacteria may survive outside of the host for some time in the environment. *Salmonella*, in particular, can survive for long periods in the environment, promoting transmission to a new host. Because *Salmonella* are able to infect a large number of animal species, including flies, there is a complex cycle of host to non-host survival which results in recurring outbreaks that are difficult to manage (104).

The prudent use of antibiotics

We have not detailed the different types of antibiotic use in animals (therapy, metaphylaxis and feed efficiency) as they do not fall within the scope of this paper. However, whatever the reason for using antibiotics, a few important points should be noted:

– selection of resistant strains is more likely to occur when antibiotics are given for a long time. The role of antibiotics used as growth promoters has been established as mentioned earlier. Differences between antibiotics as selectors for resistance should be clarified in the future (39, 43);

– antibiotics facilitate the emergence of resistant strains. High concentrations of antibiotics in contact with the bacterial reservoir (gut, or environment) kill susceptible bacteria and increase the prevalence of pre-existing resistant strains. Subinhibitory concentrations may favour horizontal transfer of genes because at such concentrations, potential receiver strains are not killed. However the effect of various antibiotic concentrations on bacterial cell functions has not been fully explored. The words 'subinhibitory concentrations' are vague because inhibitory concentrations are different for each bacterial species and there is never any definition of what constitutes a subinhibitory concentration;

– no general law or general statement can be applied to the interaction of bacteria and antimicrobials. It depends upon the microbial community, the local and environmental factors, the microbial species and the antibiotic being used;

– a huge number of resistance genes and mechanisms have been recognised to date. Usually resistant strains have multiple mechanisms of resistance for the same antibiotic as well as different mechanisms of resistance for different antibiotics;

– some types of resistance are easy to select among the susceptible bacterial populations: e.g. mutations to quinolones or rifamycin;

– other types of resistance emerge more slowly from a covert evolution of genes whose origin are often unknown: e.g. vancomycin and avoparcin and the VanA gene;

– an advantage for multiple-resistant strains is that they can survive in the presence of various antibiotics; the use of just one antibiotic may maintain the whole set of resistance traits;

– co-selective as well as cross-selective pressure are part of the reason why resistant strains are so difficult to eliminate;

– factors underlying the difficulty in eliminating resistant strains include the dynamics of the ecosystem considered, the fitness and ability to survive of the resistant strains in their community, and the influx of susceptible strains to replace the resistant ones (50).

Future health problems related to infectious diseases depend upon the interplay of the epidemicity, antibiotic resistance, and pathogenicity acquired by bacteria (57).

Antibiotic resistant bacteria are now everywhere in the farm. Antibiotics and their residues contribute to their prevalence. Although the dissemination and transmission pathways of antibiotic resistant bacteria are very complex and not fully understood, the links between the farm on one side and colonised or diseased humans on the other have been documented for *Campylobacter*, *Salmonella*, *E. coli*, enterococci, *Listeria, Yersinia*.

It is important to note that the impact of agricultural antibiotic use on the emergence and dissemination of resistance traits and its contribution to antibiotic resistant pathogens in humans (hospital and community) remains poorly quantified (51, 89, 90, 91).

In human medicine, efforts to decrease the unnecessary use of antibiotics, which includes unnecessary prolonged treatment and use in the treatment of non-bacterial infections, have been going on for 15 years. The prudent use of antibiotics is a large part of the strategy for containment of antimicrobial resistance recommended by the WHO (107). It is legitimate to think that a similar effort among those working in animal medicine may have a positive impact on the problem.

Some experiences are paving the way for a better use of antibiotics in animals. Scandinavian countries, Denmark in particular, have addressed the issue of antibiotics administered as growth promoters and of animals carrying resistant strains. Results of the ban on growth promoters in this country were evaluated and a decline of resistance was observed. Integrated systems which monitor bacteria and the level of antimicrobial use have been established (108).

The treatement of *Campylobacter* infections with fluoroquinolones has been the subject of several studies in the United Kingdom (UK). Many results confirmed that removing bacterial populations from exposure to antimicrobial drugs eliminates the survival advantage of resistant bacteria, thus the carriage of resistant bacteria declines and they are replaced by susceptible strains. It must be mentioned that in most cases, a small number of resistant clones survive the discontinuation of antibiotics. No actions have been proven to completely restore susceptibility (23, 32, 38, 74).

The proper use of antibiotics for treating human diseases in hospitals, in the community, in the farm and in veterinarian hospitals, is likely to help prolong the useful life of antimicrobials. Using antibiotics prudently (appropriately, judiciously) as a strategy to contain antimicrobial resistance is an ethical obligation toward patients (humans or animals).

Treating an infection by eradicating the pathogenic microorganism creates a unique situation where the host, the pathogen, the commensals and the therapeutic agents must be considered. Since the discovery of penicillin we have learnt that antibiotics are a powerful trigger of bacterial evolution. The patient (human or animal) must be effectively treated, taking into account his status, his/its social position (protection of the group) and the ecological aspects of the treatment.

The prudent use of antimicrobial agents in veterinary medicine is a key issue for animal health and one which is inextricably linked to the production of safe food. The principles developed in the last decade to implement the prudent use of antibiotics in veterinary medicine have taken into account the animal species, its bacterial diseases, the most effective approach to delivering the compound, the duration of the treatment, the strategy toward the herd, and the consequences in term of benefits and risks (60). The guidelines developed by the World Organisation for Animal Health (OIE) in agreement with Codex Alimentarius are given in Annex 1 (110). The prudent use of antimicrobial agents in veterinary medicine is just one of the steps that can be taken to control the contamination of food with bacteria of animal origin and the spread of bacterial resistance. Other actions include:

– monitoring zoonotic pathogens and their antibiotic resistance pattern, in animals and in humans (28, 34, 109)

– monitoring animal pathogens and a few indicator bacteria among their commensals to detect new resistance traits (28)

– monitoring antibiotic consumption (61).

The information collected on bacterial surveillance and antibiotic consumption is very important for risk assessment and for interpreting the follow-up studies of management decisions (77, 99).

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

The key issues for the prudent use of antibiotics are:

– using them when they can be useful

– knowing when to stop using them (as soon as possible)

– knowing about pK, pD characteristics

– knowing about their residues

– respecting the withdrawal period

– knowing that antibiotics are only part of the treatment of sick animals.

As a conclusion let us consider the current situation. Resistance now exists everywhere and to all antibiotics used in humans (even to those which were never used in animals), and to all antibiotics used in animals.

There are four large areas where resistant bacteria emerge, amplify, evolve and disseminate:

– wild environment

– farms

– human communities

– hospitals.

Many countries have already established large systems of surveillance (e.g. the United States of America, Canada, Japan, Australia, the UK, Denmark, Sweden, Norway, the European Union) and others are following their example. Integrated and comparative surveillance technologies should be used to analyse national data and provide international comparisons (64).

It is reasonable to expect an improvement in the way in which we handle antimicrobials. The prudent use of them in humans and in animals is an important task and we must develop studies to assess the impact on patients and keep developing research to better understand the interaction between the bacterial world (human, animal, environmental) and antibiotics (92).

It can be expected that the incidence of resistant bacteria will decline, or at least stabilise, in some locations (hospitals, animal husbandry establishments).

Food safety is already improving because of programmes designed to improve the health of food animals, such as those aimed at decreasing the dissemination and the load of *Salmonella* and *Campylobacter* (10).

With our current knowledge it is impossible to quantify the contribution of antibiotics in agriculture to the emergence and incidence of resistant bacteria in human beings. However, we can develop studies to explore the 'portfolio' of antibiotics that are shared between human and animals, and their corresponding resistance mechanisms. It is important to try to establish a science-based rationale to accurately approach the use of old, new and future antibiotics.

Annex 1
The guidelines for antimicrobial use contained in the OIE *Terrestrial Animal Health Code*

Appendix 3.9.3
Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine

Article 3.9.3.1
Purpose

These guidelines provide guidance for the responsible and prudent use of antimicrobial agents in veterinary medicine, with the aim of protecting both animal and human health. The Competent Authorities responsible for the registration and control of all groups involved in the production, distribution and use of veterinary antimicrobials have specific obligations.

Prudent use is principally determined by the outcome of the marketing authorisation procedure and by the implementation of specifications when antimicrobials are administered to animals.

Article 3.9.3.2
Objectives of prudent use

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

a) maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals *b*) comply with the ethical obligation and economic need to keep animals in good health

c) prevent, or reduce, as far as possible, the transfer of micro-organisms (with their resistance determinants) within animal populations

d) maintain the efficacy of antimicrobial agents used in food-producing animals

e) prevent or reduce the transfer of resistant micro-organisms or resistance determinants from animals to humans

f) maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of the antimicrobials

g) prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL)

h) protect consumer health by ensuring the safety of food of animal origin with respect to residues of antimicrobial drugs, and the ability to transfer antimicrobial drug resistant micro-organisms to humans.

Article 3.9.3.3
Responsibilities of the regulatory authorities

Marketing authorisation

The national regulatory authorities are responsible for granting marketing authorisation. This should be done in accordance with the provisions of the *Terrestrial Code*. They have a significant role in specifying the terms of this authorisation and in providing the appropriate information to the veterinarian.

Submission of data for the granting of the marketing authorisation

The pharmaceutical industry has to submit the data requested for the granting of the marketing authorisation. The marketing authorisation is granted only if the criteria of safety, quality and efficacy are met. An assessment of the potential risks and benefits to both animals and humans resulting from the use of antimicrobial agents in food-producing animals should be carried out. The evaluation should focus on each individual antimicrobial product and the findings not be generalised to the class of antimicrobials to which the particular active principle belongs. Guidance on usage should be provided for all dose ranges or different durations of treatment that are proposed.

Market approval

Regulatory authorities should attempt to expedite the market approval process of a new antimicrobial in order to address a specific need for the treatment of disease.

Registration procedures

Countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicinal products (VMPs), and whose supply principally depends on imports from foreign countries, should undertake the following measures:

a) check the efficacy of administrative controls on the import of these VMPs

b) check the validity of the registration procedures of the exporting and manufacturing country as appropriate

c) develop the necessary technical co-operation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

Regulatory authorities of importing countries should request the pharmaceutical industry to provide quality certificates prepared by the Competent Authority of the exporting and manufacturing country as appropriate. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of unlicensed and counterfeit bulk active pharmaceutical ingredients and products.

Quality control of antimicrobial agents

Quality controls should be performed:

a) in compliance with the provisions of good manufacturing practices

b) to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs

c) to ensure that the quality and concentration (stability) of antimicrobial agents in the marketed dosage form(s) are maintained until the expiry date, established under the recommended storage conditions

d) to ensure the stability of antimicrobials when mixed with feed or drinking water

e) to ensure that all antimicrobials are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

Assessment of therapeutic efficacy

Preclinical trials

a) Preclinical trials should:

– establish the range of activity of antimicrobial agents on both pathogens and non-pathogens (commensals)

– assess the ability of the antimicrobial agent to select for resistance *in vitro* and *in vivo*, taking into consideration pre-existing resistant strains

– establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit the selection of antimicrobial resistance. (Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal);

b) the activity of antimicrobial agents towards the targeted micro-organism should be established by pharmacodynamics.

The following criteria should be taken into account:

– spectrum of activity and mode of action

– minimum inhibitory and bactericidal concentrations

– time- or concentration-dependent activity or co-dependency

– activity at the site of infection;

c) the dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:

– bio-availability according to the route of administration

– concentration of the antimicrobial at the site of infection and its distribution in the treated animal

– metabolism that may lead to the inactivation of antimicrobials

– excretion routes

– use of combinations of antimicrobial agents should be scientifically supported.

Clinical trials

Clinical trials should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

a) diversity of the clinical cases encountered when performing multi-centre trials

b) compliance of protocols with good clinical practice, such as Veterinary International Cooperation on Harmonisation guidelines

c) eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses

d) parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

Assessment of the potential of antimicrobials to select for resistance

Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistance. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.
For this the following may be considered:

a) the concentration of active compound in the gut of the animal (where the majority of potential food-borne pathogens reside) at the defined dosage level

b) the route and level of human exposure to food-borne or other resistant organisms

c) the degree of cross-resistance within the class of antimicrobials and between classes of antimicrobials

d) the pre-existing level of resistance in the pathogens of human health concern (baseline determination) in both animals and humans.

Establishment of acceptable daily intake, maximum residue level and withdrawal periods for antimicrobial compounds

a) When setting the acceptable daily intake (ADI) and MRL for an antimicrobial substance, the safety evaluation should also include the potential biological effects on the intestinal flora of humans

b) the establishment of an ADI for each antimicrobial agent, and an MRL for each animal-derived food, should be undertaken

c) for each VMP containing antimicrobial agents, withdrawal periods should be established in order to produce food in compliance with the MRL, taking into account:

– the MRL established for the antimicrobial agent under consideration

– the composition of the product and the pharmaceutical form

– the target animal species

– the dosage regimen and the duration of treatment

– the route of administration

d) the applicant should provide methods for regulatory testing of residues in food.

Protection of the environment

An assessment of the impact of the proposed antimicrobial use on the environment should be conducted. Efforts should be made to ensure that the environmental impact of antimicrobial use is restricted to a minimum.

Establishment of a summary of product characteristics for each veterinary antimicrobial product

The summary of product characteristics contains the information necessary for the appropriate use of veterinary antimicrobial products (VAPs) and constitutes the official reference for their labelling and package insert. This summary should contain the following items:

a) active ingredient and class

b) pharmacological properties

c) any potential adverse effects

d) target animal species and age or production category

e) therapeutic indications

f) target micro-organisms

g) dosage and administration route

h) withdrawal periods

i) incompatibilities

j) shelf-life

k) operator safety

l) particular precautions before use

m) particular precautions for the proper disposal of unused or expired products

n) information on conditions of use relevant to the potential for selection of resistance.

Post-marketing antimicrobial surveillance

The information collected through existing pharmacovigilance programmes, including lack of efficacy, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this, the following should be considered:

General epidemiological surveillance
The surveillance of animal micro-organisms resistant to antimicrobial agents is essential. The relevant authorities should implement a programme according to the *Terrestrial Code*.

Specific surveillance
Specific surveillance to assess the impact of the use of a specific antimicrobial may be implemented after the granting of the marketing authorisation. The surveillance programme should evaluate not only resistance development in target animal pathogens, but also in food-borne pathogens and/or commensals. Such surveillance will also contribute to general epidemiological surveillance of antimicrobial resistance.

Supply and administration of the antimicrobial agents used in veterinary medicine

The relevant authorities should ensure that all the antimicrobial agents used in animals are:

a) prescribed by a veterinarian or other authorised person

b) supplied only through licensed/authorised distribution systems

c) administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons

d) the relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

Control of advertising

All advertising of antimicrobials should be controlled by a code of advertising standards, and the relevant authorities must ensure that the advertising of antimicrobial products:

a) complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics

b) is restricted to authorised professionals, according to national legislation in each country.

Training of antimicrobial users

The training of users of antimicrobials should involve all the relevant organisations, such as regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food-animal owners. This training should focus on:

a) information on disease prevention and management strategies

b) the ability of antimicrobials to select for resistance in food-producing animals

c) the need to observe responsible use recommendations for the use of antimicrobial agents in animal husbandry in agreement with the provisions of the marketing authorisations.

Research

The relevant authorities should encourage public- and industry-funded research.

Article 3.9.3.4
Responsibilities of the veterinary pharmaceutical industry

Marketing authorisation of veterinary antimicrobial products

The veterinary pharmaceutical industry has responsibilities to:

a) supply all the information requested by the national regulatory authorities *b*) guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices

c) implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance.

Marketing and export of veterinary antimicrobial products

For the marketing and export of VAPs:

a) only licensed and officially approved VAPs should be sold and supplied, and then only through licensed/authorised distribution systems

b) the pharmaceutical industry should provide quality certificates prepared by the Competent Authority of the exporting and/or manufacturing countries to the importing country

c) the national regulatory authority should be provided with the information necessary to evaluate the amount of antimicrobial agents marketed.

Advertising

The veterinary pharmaceutical industry should:

a) disseminate information in compliance with the provisions of the granted authorisation

b) ensure that the advertising of antimicrobials directly to the food animal producer is discouraged.

Training

The veterinary pharmaceutical industry should participate in training programmes as defined in point 14 of Article 3.9.3.3.

Research

The veterinary pharmaceutical industry should contribute to research as defined in point 15 of Article 3.9.3.3.

Article 3.9.3.5
Responsibilities of wholesale and retail distributors

Retailers distributing VAPs should only do so on the prescription of a veterinarian or other suitably trained person authorised in accordance with national legislation, and all products should be appropriately labelled.

The guidelines on the responsible use of antimicrobials should be reinforced by retail distributors who should keep detailed records of:

a) date of supply

b) name of prescriber

c) name of user

d) name of product

e) batch number

f) quantity supplied.

Distributors should also be involved in training programmes on the responsible use of antimicrobials, as defined in point 14 of Article 3.9.3.3.

Article 3.9.3.6
Responsibilities of veterinarians

The concern of the veterinarian is to promote public health and animal health and welfare. The veterinarian's responsibilities include preventing, identifying and treating animal diseases. The promotion of sound animal husbandry methods, hygiene procedures and vaccination strategies (good farming practice) can help to minimise the need for antimicrobial use in food-producing animals.

Veterinarians should only prescribe antimicrobials for animals under their care.

Use of antimicrobial agents

The responsibilities of veterinarians are to carry out a proper clinical examination of the animal(s) and then:

a) only prescribe antimicrobials when necessary

b) make an appropriate choice of the antimicrobial based on experience of the efficacy of treatment.

Choosing an antimicrobial agent

a) The expected efficacy of the treatment is based on:

– the clinical experience of the veterinarian

– the activity towards the pathogens involved

– the appropriate route of administration

– known pharmacokinetics/tissue distribution to ensure that the selected therapeutic agent is active at the site of infection

– the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogens involved.

Should a first-line antimicrobial treatment fail or should the disease recur, a second line treatment should ideally be based on the results of diagnostic tests.

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

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

b) Use of combinations of antimicrobials should be scientifically supported. Combinations of antimicrobials may be used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

Appropriate use of the antimicrobial chosen

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

The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used. It is the veterinarian's responsibility to define the conditions of responsible use in such a case, including the therapeutic regimen, the route of administration, and the duration of the treatment.

Recording

Records on veterinary antimicrobial drugs should be kept in conformity with national legislation. Information records should include the following:

a) quantities of medication used

b) a list of all medicines supplied to each food-producing animal holding

c) a list of medicine withdrawal period

d) a record of antimicrobial susceptibilities

e) comments concerning the response of animals to medication

f) the investigation of adverse reactions to antimicrobial treatment, including lack of response due to antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

Veterinarians should also periodically review farm records on the use of VAPs to ensure compliance with their directions and use these records to evaluate the efficacy of treatment regimens.

Labelling

All medicines supplied by a veterinarian should be labelled according to national legislation.

Training

Veterinary professional organisations should participate in the training programmes as defined in point 14 of Article 3.9.3.3. It is recommended that veterinary professional organisations develop for their members species-specific clinical practice guidelines on the responsible use of VAPs.

Article 3.9.3.7
Responsibilities of food-animal producers

Food-animal producers with the assistance of a veterinarian are responsible for implementing health and welfare programmes on their farms (good farming practice) in order to promote animal health and food safety.
Food-animal producers should:

a) draw up a health plan with the attending veterinarian that outlines preventative measures (feedlot health plans, mastitis control plans, endo- and ectoparasite control and vaccination programmes, etc.)

b) use antimicrobial agents only on prescription, and according to the provisions of the prescription

c) use antimicrobial agents in the species, for the uses and at the dosages on the approved/registered labels and in accordance with product label instructions or the advice of a veterinarian familiar with the animals and the production site

d) isolate sick animals, when appropriate, to avoid the transfer of pathogens; dispose of dead or dying animals promptly under conditions approved by the relevant authorities

e) comply with the storage conditions of antimicrobials in the rearing unit, according to the provisions of the leaflet and package insert

f) address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated

g) comply with the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer

h) dispose of surplus antimicrobials under safe conditions for the environment; medicines should only be used within the expiry date, for the condition for which they were prescribed and, if possible, in consultation with the prescribing veterinarian

i) maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the veterinarian responsible for treating the animals

j) keep adequate records of all medicines used, including the following:

– name of the product/active substance and batch number

– name of prescriber and/or the supplier

– date of administration

– identification of the animal or group of animals to which the antimicrobial agent was administered

– clinical conditions treated
– dosage
– withdrawal periods
– result of laboratory tests
– effectiveness of therapy

k) inform the responsible veterinarian of recurrent disease problems.

■

La résistance antimicrobienne au niveau de l'exploitation agricole

J.F. Acar & G. Moulin

Résumé
Les bactéries résistantes aux agents antimicrobiens sont extrêmement répandues. Les auteurs font le point sur la distribution des bactéries résistantes dans les exploitations agricoles. Les populations humaines et animales et les sites dans lesquels ces populations évoluent constituent autant de réservoirs pour les colonies de bactéries susceptibles de devenir résistantes aux antimicrobiens.
L'écosystème des exploitations agricoles offre un cadre dans lequel les bactéries et les gènes résistants ont tout loisir d'émerger, de proliférer et de se propager. La dissémination se produit tout au long de la chaîne alimentaire ou par plusieurs autres voies.
La recherche écologique, épidémiologique, moléculaire et mathématique est mobilisée pour élucider l'origine et le développement du problème de la résistance aux agents antimicrobiens ainsi que ses liens avec l'utilisation d'antibiotiques.
L'utilisation prudente et responsable des antibiotiques est un aspect essentiel de la démarche éthique visant à protéger la santé animale et à assurer la sécurité sanitaire des aliments. Si l'utilisation responsable des antibiotiques est indispensable pour les besoins de la recherche, un réel progrès dans la maîtrise de la résistance aux agents antimicrobiens exige qu'une « utilisation prudente » soit instaurée à tous les niveaux de l'activité des élevages, en tant que partie intégrante des bonnes pratiques de gestion.

Mots-clés
Clone bactérien – Exploitation agricole – Gène de la résistance – Résidu d'antibiotique – Résistance aux agents antimicrobiens – Sécurité sanitaire des aliments.

■

Resistencia a los antimicrobianos en las explotaciones

J.F. Acar & G. Moulin

Resumen
Las bacterias resistentes a los antimicrobianos se han generalizado. En este artículo se examina la distribución de las bacterias resistentes en los seres humanos, los animales y el entorno de las explotaciones, es decir, en los reservorios de las colonias que pueden desarrollar esa resistencia.

Los ecosistemas de las explotaciones constituyen un medio en el que pueden aparecer, desarrollarse y propagarse las bacterias y genes resistentes los cuales, posteriormente, se diseminan por conducto de la cadena alimentaria y otras vías.

Para estudiar el origen y la extensión del fenómeno de la resistencia, así como su relación con la administración de antibióticos, se utilizan métodos ecológicos, epidemiológicos, moleculares y matemáticos.

Para conferir una dimensión ética a los métodos destinados a mejorar la sanidad animal y la seguridad sanitaria de los alimentos deberá incluirse, necesariamente, la administración prudente y responsable de antibióticos. Si bien la "administración responsable" de antibióticos en la investigación es crucial, su "administración prudente" debe formar parte de las buenas prácticas de gestión de las explotaciones para contribuir plenamente a la contención de la resistencia a los antimicrobianos.

Palabras clave

Clon bacteriano – Explotación – Gen de resistencia – Inocuidad de los alimentos – Residuo de antibiótico – Resistencia antimicrobiana.

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