Therapeutic antibiotics in animal feeds and antibiotic resistance

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Summary
Recent statutory changes involving animal drugs are expected to facilitate the therapeutic use of antibiotics in animal feeds in the United States of America. The use of antibiotics in animal feeds is controversial due to the potential development of resistant bacterial pathogens in food-producing animals which are exposed to the antibiotics and the resultant public health risk. Zoonotic micro-organisms can be transmitted to humans through contact with animal populations, either directly or through the consumption of contaminated food. Recommendations to address the public health concerns include the strengthening of professional education in the areas of infectious diseases and the appropriate selection and use of antimicrobial agents, the development of a comprehensive food safety education programme for food-animal veterinarians and animal producers, and the development of surveillance programmes to monitor antimicrobial resistance among zoonotic pathogens. Early identification of emerging resistance can facilitate a timely and appropriate public health response.

Keywords

Introduction
Recent changes in the Food, Drug and Cosmetic Act concerning the regulation of animal drugs are expected to facilitate therapeutic use of antibiotics in animal feeds in the United States of America (USA). In 1996, the existing law was amended to provide for a new category of drugs approved by the United States Food and Drug Administration (FDA) and intended for use in medicated feed. These drugs can only be used under a Veterinary Feed Directive (VFD) issued by a veterinarian in the course of his or her professional practice.

In addition to inducing a public health hazard, the misuse of antimicrobial agents in feed decreases the value and reliability of the drugs. Bacteria do not exist in discrete populations, but rather flow among humans, animals and the environment and, as a result of this intermixing and flow, the potential exists to transfer resistance factors (6). Resistance factors in human and animal pathogens, particularly those carried on mobile elements, can spread rapidly within human and animal populations and from animals to humans, particularly through contaminated food products. In 1979, the Government of the USA examined the issue of antibiotic resistance and reported several reasons for concern (3), which are as follows:

a) Long-term feeding of antibiotics causes an increase in the proportion of resistant organisms in the intestinal tracts of treated animals.

b) Once in the intestinal tract of an animal, antibiotic-resistant bacteria can thrive, even after the use of the drug is discontinued.
c) The genes which carry resistance, when present on R-plasmids or other mobile factors, can theoretically transfer from non-pathogenic Escherichia coli in animals to human pathogens.

d) The normal course of animal-human contact opens numerous possible routes for the spread of resistance genes, including direct contact, contact with food and contact with faeces or sewage in the environment.

e) The treatment of some human diseases is being compromised by increasing resistance of pathogens to antibiotics.

Preventive action is needed in several areas in order to address these public health concerns adequately. The FDA approval process for drugs used in food-animal production ensures the safety of animal drugs and food additives to the animals and to humans who may consume these animals. Regulatory surveillance by the FDA helps to ensure that antimicrobial agents used in food-producing animals are used safely and appropriately to maintain the continuing effectiveness of these drugs and to minimise the spread of antimicrobial resistance. Consideration should also be given to research on the epidemiology of foodborne pathogens in animals, to more responsible use of antibiotics in food-production medicine, a comprehensive education programme on food safety, and surveillance systems designed to monitor and contain antibiotic resistance.

Animal drug approval process

Premarket approval, post-marketing surveillance and enforcement activities serve as safeguards to maintain safety and efficacy, and also provide controls over the use of new animal drugs. Animal drugs which are not generally recognised as safe and effective may not be legally marketed in the USA unless they are the subject of an approved New Animal Drug Application (NADA). General recognition of safety and effectiveness is determined by scientific experts, qualified by training and experience, and is based on adequate and well-controlled studies in the open scientific literature which demonstrate such safety and efficacy. Review and evaluation of an NADA comprises scrutiny of the following:
- safety and efficacy data
- manufacturing methods and controls
- sources of raw materials
- product labelling, which must contain directions for use and dosages, as well as warnings and precautions including known adverse effects or reactions, and milk withholding and meat pre-slaughter withdrawal times when appropriate.

In addition, FDA approval of animal drugs for use in food-producing animals requires assurance of the safety of edible tissues from these animals. Such approval is conditioned by strict use requirements, which may include withdrawal periods and tolerances.

The FDA is also responsible for determining the marketing status (prescription or over-the-counter) of animal drug products. This decision is based on whether or not it is possible to prepare adequate directions for use under which a lay person can use the drugs safely and effectively. An animal drug which, as a result of toxicity or other potential for harmful effects, method of use or the collateral measures necessary for use, is not safe for use in animals except under the professional supervision of a licensed veterinarian, is a prescription (Rx) drug. These drugs can be dispensed only by – or upon the lawful written order of – a licensed veterinarian. Products for which adequate directions for lay use can be written are labelled for over-the-counter (OTC) use under existing law. If adequate directions cannot be written, the prescription system provides a method of distribution and control which is intended to ensure that the Rx product reaches only the hands of persons trained to use the product. This can include, in addition to the veterinarian, animal owners or managers whom the veterinarian determines are capable of using the product safely under his supervision.

A licensed veterinarian may legally use or dispense a veterinary prescription drug product only within the course of professional practice where a valid veterinarian-client-patient relationship exists. A valid veterinarian-client-patient relationship is defined by the American Veterinary Medical Association as existing when:

'a) the veterinarian has assumed the responsibility for making medical judgements regarding the health of the animal(s) and the need for medical treatment, and the client (owner or caretaker) has agreed to follow the instructions of the veterinarian; and

b) there is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s), and/or makes medically appropriate and timely visits to the premises where the animals are kept; and

c) the practising veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.'

Drugs in animal feeds

(medicated feeds)

Just as each label claim for a new animal drug must be approved, so too must the drug be specifically approved for administration in animal feed. Approvals are issued only for
the uses, claims and drug levels which have been shown to be safe and effective by adequate and well-controlled studies. The feed must be labelled in accordance with the regulations if sold or delivered to a second party.

All commercially available animal drugs intended for use in medicated feed were, until recently, available on an OTC basis. Animal producers were free to purchase, mix and feed these products without the involvement of a veterinarian. In 1985, more than 90% of the animal drugs used in the USA were administered without professional veterinary supervision (5). Certain new therapeutic antimicrobial agents which have been approved for prescription status were unable to be used in animal feeds because of the need for greater control over their use. The VFD process offers an alternative to prescription status, ensuring veterinarian supervision of these types of drugs, while enabling the feed industry to maintain current good manufacturing practices with minimal disruption to feed distribution. The first VFD drug was approved by the FDA in December 1996, and all new antimicrobial agents for therapeutic use in feed will be approved as VFD drugs.

The VFD process is straightforward in practice. A veterinarian, through a professional veterinarian-patient-client relationship, examines and diagnoses animal conditions and determines whether a condition warrants administration of a VFD drug. If so, the veterinarian will issue a signed VFD on a preprinted multi-part form. The veterinarian issues the form to the producer who in turn orders the VFD feed from the feed supplier. A VFD feed may not be distributed to a producer without a signed VFD form. The drug-specific feed directive form is approved by the FDA as part of the NADA approval process.

Licensed feed manufacturers and distributors who ship VFD feed to a downstream distributor or retailer for inventory must receive and retain a copy of a written acknowledgement, stating that the VFD feed will be further distributed only in accordance with FDA requirements. The veterinarian who issues a VFD, the producer and the person or company supplying the VFD feed must retain copies of the signed VFD form for a minimum of two years.

A VFD drug can only be fed to animals in a manner consistent with the FDA conditions of approval. Extra-label use, even if specified by a veterinarian on a feed directive form, is not permitted. The labelling, distribution, holding or use of a VFD drug or feed in a manner inconsistent with FDA approval results in adulterated drug or feed.

Public health concerns

The spectrum of infectious diseases is changing, in part, because of changes in agricultural practices and land use and in food technology. As a consequence of the widespread use and misuse of antimicrobial agents in human and veterinary medicine and in animal production, even drugs used in the treatment of common bacterial infections are becoming increasingly ineffective, which results in prolonged human illness, increased death rates and rising health care costs (7).

Expert scientific groups, such as the Institute of Medicine, the American Society for Microbiology and the World Health Organisation, have identified national and global increases in antimicrobial resistance as a compelling public health problem (1, 8). The development of resistance results from direct use of antimicrobial agents in human beings and acquisition of resistance from animal and environmental bacteria. Antibiotics are used in animals both therapeutically and as growth promoters, and therefore antibiotic-resistant bacteria can emerge in healthy as well as sick animals. The intestinal flora of animals which have been given antimicrobial agents for prevention or therapy is a reservoir of resistance factors (13). Zoonotic micro-organisms are transmitted to humans by contact with animal populations, either directly or through the consumption of contaminated food.

Resistance to antibiotics in humans and animals can result in refractory, untreatable infections, and antibiotic use increases the spread of antibiotic-resistant bacteria by creating selective pressure which favours resistant bacteria (12). The public health impact of resistance on the population includes increased morbidity and mortality from treatment failures and increased health care costs as newer, more expensive antibiotics are needed to treat infections (1).

Selective pressure resulting from widespread antimicrobial use is the underlying force in the development of antibiotic resistance. The association between increased antimicrobial use and resistance has been documented for nosocomial infections (11) as well as for resistant community-acquired infections (2). Due to changes in farm management practices, such as the consolidation of animal production in very large facilities, there is also a concern related to animal health and antibiotic resistance. Factors related to farm management (such as feeding practices, sanitation, space utilisation, housing, environmental controls and drug treatment) influence the pre-harvest food safety environment, including the load of pathogens as well as other contaminants carried by these food-producing animals. In addition to incidents of disease in animals caused by Salmonella, Campylobacter and E. coli, animals are passive carriers of these organisms. On large corporate farms, management techniques are emphasised as a way of minimising and controlling infectious diseases. However, conditions are such that diseases can spread rapidly through a herd or flock.

Antibiotic-resistant pathogens in animals are not only a concern with respect to animal health, but also pose a threat
due to the possibility of transmission to humans as foodborne pathogens. Numerous epidemiological studies have traced *Salmonella* strains to food-animal sources bearing the same plasmid profile as isolates from ill humans who had been in contact with (or had consumed food derived from) the animals (6, 10, 14, 15). In 1976, Lyons et al. (10) observed an outbreak of antimicrobial-resistant salmonellosis in a hospital nursery in which the index infant was born to a woman who had tended calves with diarrhoea ten days before delivery. The mother, as well as another farm worker, infants in the hospital, and the calves were infected by *Salmonella* Heidelberg resistant to three antimicrobial agents. Holmberg et al. (6) investigated an outbreak in which a highly resistant strain of *S. Newport* was epidemiologically related to the consumption of ground beef from cattle which had been fed subtherapeutic levels of tetracycline. From these studies it can be concluded that food animals are a major source of antimicrobial-resistant *Salmonella* infections and that those infections are made more frequent by the use of antimicrobial agents during animal production.

The use of antimicrobial agents in animal production has facilitated confinement housing and allowed higher densities of animals to be maintained. Even if well managed, the increased density of livestock or poultry with similar risk profiles in intensive rearing operations requires an aggressive approach to disease control, which can lead to heavy prophylactic and therapeutic antimicrobial use. If such operations are not well managed, heavy antimicrobial use becomes a management crutch. Poorly managed intensive calf-raising units in the USA in the 1970s demonstrated high rates of salmonellosis and concomitant heavy and indiscriminate use of antimicrobial agents (18). This resulted in an explosion of antimicrobial-resistant *S. Typhimurium* bacteria being isolated from calves.

The United Kingdom (UK) has recently reported a dramatic increase in human cases and epizootic spread of a multiple-drug resistant strain of *S. Typhimurium* definitive phage type (DT) 104 (16, 17, 20). *S. Typhimurium* DT104 was first identified in humans in England and Wales in 1984 (16). This strain has a unique antimicrobial resistance pattern (R-type) with multiple resistance observed for ampicillin (A), chloramphenicol (C), streptomycin (S), sulfonamides (Su), and tetracycline (T) (ACSSuT). In the UK, the number of isolations among humans rose slowly from 1984 to 1990, then more rapidly, so that by 1993, DT104 with R-type ACSSuT accounted for more than 80% of the isolations of this strain (19). In 1995, R-type ACSSuT DT104 accounted for more than 87% of *S. Typhimurium* isolates recovered from humans, with 26.4% and 6.2% of these isolates having additional resistance to trimethoprim and ciprofloxacin, respectively (19, 21).

In the animal population in the UK, DT104 was first recovered in 1989 from cattle. Only one herd was identified. Since that time, isolations have continued to rise and now account for the majority of *S. Typhimurium* isolates. Contact with affected farm animals, particularly cattle, is implicated as a primary factor for transmission to humans (19, 20). A case-control study conducted in the UK demonstrated an association between illness from *S. Typhimurium* DT104 R-type ACSSuT and the consumption of several food items including pork sausages, chicken, and a brand of meat paste, as well as close contact with affected animals (20). Long-term carriage has also been observed in all species, particularly in cats and cattle (4, 9, 20). Illness associated with DT104 from humans and animals has now reached epidemic proportions in the UK.

### Addressing the concerns

There is an urgent need for more prudent use of antibiotics in both human and veterinary medicine, particularly in cases where this use relates to food production. Unless properly managed, food animals being reared in crowded conditions have ample opportunities to transmit infections. The resulting poor performance or disease increases the use of therapeutic, prophylactic and growth-promoting antimicrobial agents. This in turn leads to increased resistance to antimicrobial agents, which then leads to more disease and a greater need for antimicrobial agents. To break this cycle, studies must be performed on the conditions of livestock and poultry production which increase or decrease the presence of foodborne pathogens in live animals, so that measures to prevent the introduction of the pathogens can be implemented.

Current research on treatment with a competitive *Salmonella* exclusion product appears promising. Such treatment advocates that at-risk animal populations receive a mixture of live, non-pathogenic organisms which populate the intestine and compete with *Salmonella* for colonisation of sites where the *Salmonella* invade. Continued research objectives in this area should include studies to increase knowledge of how competitive exclusion increases animal resistance to *Salmonella* invasions, to optimise the choice and ratios of non-pathogenic organisms in competitive exclusion products, and to determine whether there are strains of *Salmonella* which will overcome competitive exclusion efforts.

Professional education, particularly in the medical, nursing, veterinary and dental professions, should be strengthened in the areas of infectious diseases and antibiotics. Greater emphasis should be placed on the appropriate selection and use of antimicrobial agents, the hazards of inappropriate antimicrobial drug use, appropriate diagnosis and treatment of infectious diseases, and antibiotic resistance (1). A comprehensive food safety education programme should be developed for food-animal veterinarians and producers. These educational initiatives should emphasise the appropriate use...
of drugs in food animals to help minimise the occurrence of residues in edible tissues and the presence of resistant pathogens which could be transferred to consumers. The food-animal production community is supported by extensive communication systems which can rapidly provide veterinarians, producers and satellite industry personnel with critical information on animal drug use. Mechanisms which can be used to reach the appropriate audiences include those which follow.

**Producer quality-assurance programmes**

Every major food-animal production industry in the USA is supported by a producer quality-assurance programme. These programmes have been developed by the producers themselves and have high credibility. They provide an excellent mechanism for guiding change.

**Professional organisations**

Veterinarians are supported by professional organisations which provide continuing education on a routine basis. These organisations are often species-oriented and can deliver focused, technical information to guide practitioners in developing appropriate therapies.

**Veterinary colleges and land grant universities**

These institutions are active partners with the food-animal production community. Providing professors with critical information on animal drug therapies can help to ensure up-to-date curricula.

**Federal agencies**

Federal agencies such as the Food and Drug Administration, the Food Safety and Inspection Service, the Animal and Plant Health Inspection Service and the Agricultural Research Service are sources of information on proper animal drug use and animal production practices.

**State agencies**

State departments of agriculture and related agencies can serve as conduits for disseminating critical information. These agencies are linked with Federal agencies and work in concert with them to provide guidance to producers and veterinarians.

Finally, surveillance programmes should be developed or expanded to monitor antimicrobial resistance among animal pathogens which are zoonotic organisms. Information resulting from monitoring programmes and follow-up outbreak investigations can be distributed to veterinarians, physicians and food-animal producer groups in a timely manner. Crisis-driven information campaigns could also be used as needed. Information should be targeted to redirecting drug use so as to diminish the spread and development of resistance over the short term with directives involving long-term use developed in collaboration with the appropriate professional groups.

**Conclusion**

The identification of emerging resistance and the capability to investigate resistance patterns and trends identified through an antimicrobial resistance monitoring system are essential elements to facilitate timely and appropriate public health response. The further development of a multi-agency co-ordinated response would promote punctual communication, informed decision-making and proactivity in assisting practitioners in the appropriate use of antimicrobial agents. The ultimate outcome will be to prolong the efficacy of existing and new antimicrobial agents which are desperately needed to control both human and animal disease and to minimise the spread of resistant zoonotic pathogens to humans through the food supply.

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**L’utilisation thérapeutique d’antibiotiques dans l’alimentation animale et les problèmes liés à l’antibio-résistance**

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**Résumé**

La récente modification de la réglementation des États-Unis d’Amérique sur les médicaments vétérinaires devrait faciliter l’utilisation thérapeutique d’antibiotiques dans l’alimentation animale. L’ajout d’antibiotiques dans les aliments pour animaux est une pratique problématique en raison du risque de développement de bactéries pathogènes antibio-résistantes chez les animaux ainsi traités et du risque qui en découle pour la santé publique lorsque ces
animaux sont destinés à la consommation humaine. En effet, des micro-organismes agents de zoonoses peuvent être transmis à l’homme par contact avec les animaux, soit directement, soit par la voie alimentaire. Les recommandations suivantes devraient contribuer à limiter ces risques pour la santé publique :
- meilleure information des professionnels sur les maladies infectieuses ;
- sélection et utilisation appropriées des agents antimicrobiens ;
- mise en place d’un programme global de formation à l’hygiène alimentaire à l’intention des vétérinaires praticiens ruraux et des éleveurs ;
- élaboration d’un programme de surveillance de l’évolution de la résistance des agents de zoonoses aux antibiotiques.
En effet, l’identification précoce de l’apparition d’une résistance permet de contrecarrer son évolution avant qu’elle ne représente un danger pour la santé publique.

Mots-clés

Antibióticos terapéuticos en piensos animales y resistencia a los antibióticos

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Resumen
Es de esperar que los recientes cambios legislativos concernientes a los medicamentos de uso veterinario faciliten el uso terapéutico de piensos con antibióticos en Estados Unidos de América. El uso de antibióticos en los piensos sigue suscitando controversia, pues la exposición a los antibióticos puede ocasionar el desarrollo de patógenos bacterianos resistentes en animales destinados al consumo humano, con el consiguiente riesgo para la salud pública. Algunos microorganismos zoonóticos pueden transmitirse al ser humano, ya sea por contacto directo con poblaciones animales infectadas, o por la vía alimentaria.
Entre las recomendaciones para evitar posibles problemas de salud pública figuran:
- el refuerzo de la formación profesional en los ámbitos de las enfermedades infectiosas;
- la selección y uso adecuados de agentes antimicrobianos;
- la elaboración de un programa de formación exhaustiva sobre protección alimentaria, destinado a veterinarios especializados en el tratamiento de animales de renta y profesionales de la producción agroalimentaria;
- la creación de programas de vigilancia para controlar la aparición de resistencias a los agentes antimicrobianos entre los patógenos zoonóticos.
La pronta detección de una resistencia incipiente puede facilitar la aplicación de respuestas rápidas y apropiadas en el ámbito de la salud pública.

Palabras clave
References


