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Essential veterinary education on the development of antimicrobial and antiparasitic resistance: consequences for animal health and food safety and the need for vigilance

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Summary
The role played by the veterinary profession in protecting animal and public health, along with food safety, is unique. Thus, it is important that veterinarians have the necessary knowledge to be pro-active in responding to the emergence of antimicrobial resistance. Many current veterinary educational programmes do not attempt to enhance the understanding of undergraduate students of this complex situation. As a first step, a modern veterinary education programme should provide students with a holistic view of the ecology of resistance and clearly describe how antimicrobial resistance emerges. Understanding the relationships between drug use, natural selection and antimicrobial-resistant organisms, as well as gene mobilisation and recombination, and how these contribute to the emergence of resistant organisms are important facets of a modern veterinary education.

Keywords
Antimicrobial resistance – Antiparasitic resistance – Control – Curriculum – Food safety – Resistance – Vigilance.

Introduction

Antimicrobial resistance is one of the most significant challenges facing modern public health medicine (19). It is an important adverse development with a proven potential for spread in a modern globalised society. Few classes of pharmaceuticals have done as much for health care as antimicrobial compounds; and society has much to lose from the continued erosion of their efficacy. Clearly, one major way in which antimicrobial resistance occurs is through direct human medical use that is not well controlled. The contribution made to the emergence of resistance by antimicrobial consumption outside human medicine remains unclear, but it is generally accepted as a component of the epidemiology that merits specific control (6). The potential of antimicrobial chemotherapy in food animals to increase the occurrence of resistant populations of bacteria, which may subsequently be transferred to humans through the food chain, or other means, has been discussed in many venues (6, 8), and especially recognised by Swann (15).

Chemotherapeutic strategies are based upon their selective toxicity to invading microbes; however, they may also create a selective pressure for the subsequent emergence of resistant populations. Despite its relevance in clinical veterinary medicine and veterinary public health as a food-borne hazard, antimicrobial resistance is not generally the subject of a dedicated course module, nor a specific pro-active risk management course, in the undergraduate curriculum.

This paper explores antimicrobial resistance as a food-borne hazard, the role of veterinary public health in its control and the necessity for veterinary educational programmes based on this model to instruct the undergraduate student.

Antimicrobial drug use and resistance: presenting the challenge to the curriculum developers

Antimicrobial resistance is a global public health issue, arising from human and non-human use of these drugs. Often, the classes of antimicrobial compound(s) used to treat animals are the very same as, or closely related to, those used in human chemotherapy. Developing resistance to these agents is an inevitable consequence of the selective pressure imposed by their use, in both veterinary and human medicine. Over-reliance on and misuse of antimicrobial drugs in both animal production and human medicine have led to an increase in resistant strains being isolated from specimens. The consequences of antimicrobial resistance are severe, leading to an increased risk of therapeutic failure in future cases of infection, where the administration of a drug is indicated. Higher rates of morbidity and mortality associated with antimicrobial resistance are being reported, leading to increased health and economic impacts (10, 18, 20).

Antimicrobial drugs have been used for the control and prevention of infectious disease in food animals, including those in aquaculture, as well as in companion animals and various horticultural situations (18). For food animals, administration of these drugs at sub-therapeutic levels to promote growth is increasingly difficult to justify in the context of a growing antimicrobial resistance problem, and has been banned in many developed societies. Therapeutic administration to food animals with infectious diseases is acceptable practice, as well as being an economic necessity. In the case of large groups of intensively reared food animals, the differences between therapeutic, prophylactic and metaphylactic administration may be more difficult to discern.

Resistance to antiparasitic drugs follows many of the models described for antibacterial drugs. Modern animal husbandry involves overt reliance on antiparasitic drugs to manage helminthoses of grazing herbivores. The intensity of the selection pressure that accrues from 'dose-and-move' approaches to parasite management, mixing pharmacological and management interventions, is immense (4). Resistance to parasitic drugs is a prevalent problem in animal husbandry, with most of these formulations being applied in the absence of any veterinary clinical input. A further example of the reliance on antiparasitic formulations is the way in which feed additives are routinely used in the growing phase of intensive poultry production, in a 'blanket-administration' prophylactic context, to manage protozoal disease. In companion animals and horses, the use of antiparasitic drugs has become a routine part of animal ownership, with regular and frequent dosing regimens receiving at least the tacit endorsement of the veterinary profession, with consequent selection for resistance.

Furthermore, generic antimicrobial drugs used in veterinary practice and agriculture and also used, either in the same type of formulation or its analogue, for human treatments increase the likelihood of human pathogens with animal reservoirs developing resistance/cross-resistance to drugs approved for human use.

Impacts of antimicrobial resistance on animal and public health and food safety: the need for vigilance

In the developed world, the emergence of drug resistance in disease-causing bacteria leads to problems in both animal and human health, through the increased likelihood of treatment failures and subsequent increases in morbidity and mortality. The use and misuse of antimicrobials in agriculture has been cited as one way in which resistance occurs in bacterial populations. This resistance can be subsequently transferred to humans, including, possibly, through foods of animal origin or by direct or indirect contact with animals. In addition, transferable genetic elements, capable of conferring resistance, may move between commensal bacteria and food-borne pathogens of animal origin, either at the pre-harvest phase or in human populations. A picture of the true impact of resistant zoonotic diseases on human health is beginning to emerge. For the period between 1971 and 1983, food animals were linked to 69% of the outbreaks of resistant *Salmonella* in humans investigated by the Centers for Disease Control and Prevention (3, 11), although this development has subsequently been less evident. Human infections with fluoroquinolone-resistant *Campylobacter* have also been associated with chicken and turkey consumption (12). Moreover, it has been suggested that resistance in food-borne pathogens may facilitate infection in people undergoing antimicrobial therapy for unrelated conditions, thus resulting in cases that would otherwise not have occurred (14). Interestingly, people undergoing

antimicrobial therapy may also be more susceptible to certain infections, as commensal bacteria on epithelial surfaces of the gastro-intestinal tract are eliminated, being replaced by pathogenic bacteria. Genes conferring resistance in food-borne pathogens may also be linked to virulence factors. This issue has been reported for infections associated with quinolone-resistant strains of *Campylobacter*, resulting in longer mean durations of illness in patients, compared to those infected with susceptible strains (5). Infection with drug-resistant pathogens can also lead to a delay in treatment with an effective antimicrobial agent, thereby increasing the risk of failure and/or leading to the need to prescribe more toxic or more expensive therapeutic agents.

In recent years, efforts have been made in many countries to minimise selective pressures on bacterial populations in animals and control the spread of resistance. A joint expert group recommended discontinuing the use of antimicrobial growth promoters that belong to antimicrobial classes used in human medicine (18). Denmark and Sweden ceased using antimicrobial growth promoters in livestock in 1999 and 1986, respectively. In 2001, the European Union banned the use of growth promoters in animals which were related to antimicrobial agents used in human medicine. This ban was subsequently extended to all antimicrobial growth promoters in 2006 (9). Ultimately, the ban on antimicrobial agents as growth promoters in these countries led to a reduction in the prevalence of antimicrobial-resistant bacteria in animals, food products and humans, thus justifying the strategy (2, 17).

Strategies to encourage the prudent use of antimicrobial agents in food animal production are being targeted at veterinarians, to further reduce antimicrobial consumption. One such example is a policy introduced in Germany in 2000, that describes the minimum requirements to be followed by veterinarians when administering antimicrobial drugs to animals (16).

Monitoring antimicrobial resistance: learning the lessons

Monitoring antimicrobial drug resistance should promote an increased awareness of antimicrobial resistance in human and animal pathogens and zoonotic and commensal bacteria. This requires a multi-disciplinary approach, in which veterinary professionals play a unique role. Such programmes support measures to control the emergence of resistance to antimicrobial compounds in both animal and human populations. The information provided may:

– assist veterinarians in their choice of appropriate antimicrobial agents for treatment

– aid in monitoring the emergence of resistance to ensure that necessary actions are taken

– aid in afterwards assessing the effectiveness of any intervention measures (reviewed in 13).

Several countries have set up antimicrobial resistance monitoring systems. Two examples are: the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, established in 1995 (1), and, in the United States of America (USA), the National Antimicrobial Resistance Monitoring System, based at the Centers for Disease Control and Prevention, and begun in 1996 as a collaborative effort between several organisations. In the future, the establishment of a co-ordinated global system, based upon sharing data from new and existing national agency databases, would be a welcome development. This would have global impacts on animal and public health, and international trade. Moreover, it would facilitate the understanding of broader environmental and ecological impacts.

Veterinary curriculum: future-proofing the veterinary education programme

A modern veterinary curriculum sits at a crossroads between present and future challenges for the profession. Current veterinary curricula are crowded, and there is often no module specifically dedicated to examining the technical and clinical aspects of antimicrobial use, along with its sociological impacts. In framing the delivery of an education programme on antimicrobial resistance, there is a tendency to concentrate on those elements related to clinical veterinary medicine as the priority. It is reasonable to suggest that improvements could be made at both undergraduate and post-graduate levels. Students could be instructed in appropriate protocols for prescribing antimicrobial drugs, allied with innovative, non-selective mitigation strategies to prevent infection.

An ideally structured programme would contain the necessary elements to enable a veterinary student to clearly understand the decision-making process leading to the use of an antimicrobial compound for treatment, and the subsequent outcome if the process is not followed within safe guidelines. This approach would contribute towards a strategy that could be explained to farmers and other clients, clearly outlining the reasoning behind the need to use a drug or not. It would also have the desired effect of

reducing the selective pressure within the animal and modulate impacts on the broader environment.

A review of current teaching models shows that veterinary education programmes include the basic elements of:
– bacteriology
– parasitology
– molecular biology
– immunology
– pharmacology
– pathology and epidemiology
– animal husbandry and nutrition
– veterinary public health (Fig. 1).

These topics are often presented to students as vertical, 'stand-alone' subjects, without the student having any appreciation of the horizontal connections between them. Moreover, the ways in which these disciplines affect the broader environment are seldom explored. Nonetheless, all these topics are vital building blocks, necessary for a veterinary student to understand the various organisms, and describe genotypic and phenotypic changes in response to selective pressure. Studies in molecular biology should examine resistance mechanisms and the propensity to transfer genetic material. Immunology should empower the veterinarian to aid in enhancing general immunity, as well as to identify specific vaccine-based interventions. Similarly, pharmacology should provide adequate awareness of the modes of action and subsequent spectrums of anti-infective pharmaceuticals, to assist rational selection and effective administration of specific therapeutic substances.

Associated pathology and epidemiology of the identified disease should provide a sound understanding of the disease process and other factors affecting animals. Veterinary involvement in non-chemotherapeutic strategies must be encouraged in the areas of animal husbandry and nutrition, to minimise the emergence of antimicrobial resistance. Such strategies could include, for example, changing the ways in which animals are managed, to limit disease risks through prevention. In attempting to limit the emergence of antimicrobial resistance and reduce transmission, strategies for prudent use of antimicrobial agents should be specifically explored with clinical undergraduates, e.g. the broad principles proposed by the Federation of Veterinarians of Europe (7). Preventive herd-health initiatives should be developed with a clear emphasis on enhanced management, in combination with biosecurity measures, to prevent disease, as opposed to those programmes specifying targets beyond which antimicrobial interventions might be warranted.

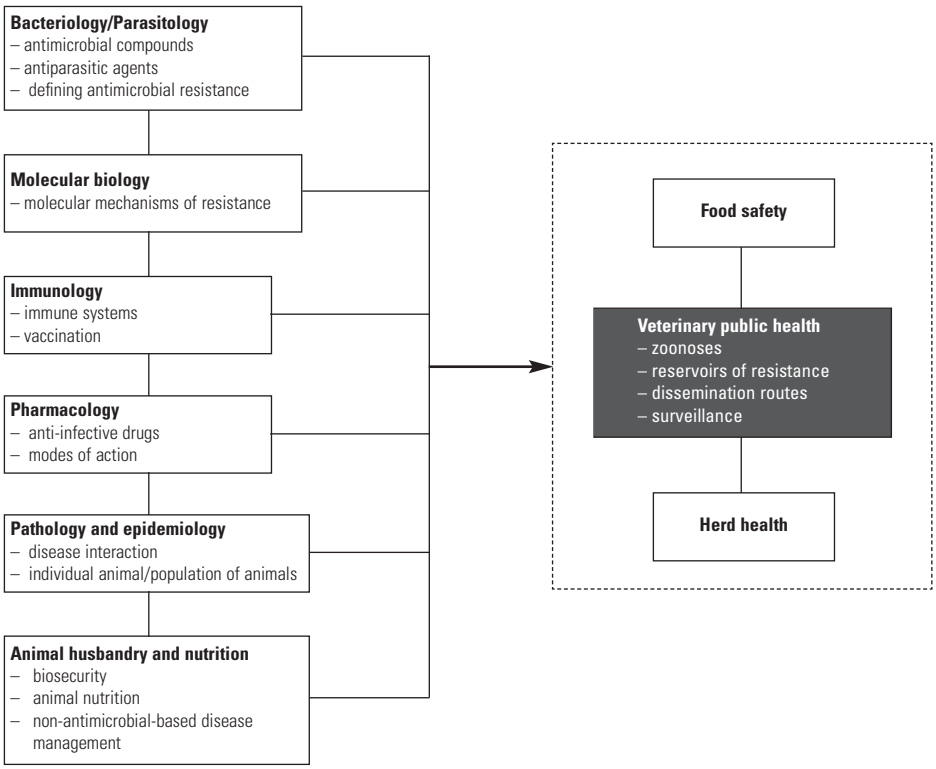

Fig. 1
The essential elements of a modern veterinary education programme containing topics on antimicrobial resistance
The lines represent the vertical and horizontal connections between the individual programme modules

This herd-health approach can be effectively delivered through the development and implementation of hazard analysis and critical control point (HACCP) management programmes at pre-harvest phases of the food chain, where the objectives of disease prevention and management, along with the appropriate use of veterinary medicines, can be incorporated. Whilst empirical clinical diagnosis and treatment may be unavoidable and are perceived as frequently successful, the long-term benefits of informed targeted use of antimicrobial compounds, which accrue from definitive diagnosis and the assessment of pathogens for their susceptibility, should be emphasised. Undergraduate curricula should specifically train undergraduates in the area of veterinary ethics, to underpin these concepts.

Over all, the clinical training of undergraduates should offer an acute awareness of the privilege and responsibility of prescribing these valuable substances into a global ecosystem. In suggesting a suitable approach that could be adopted to teaching antimicrobial resistance, the authors suggest using the model in Figure 1. This learning pathway is designed to build a logical framework to support vertical and horizontal understanding by students of the complex issues associated with antimicrobials, their use and the 'downstream' or consequent challenges that arise. It would draw on many elements that already exist within a modern veterinary education programme, while including novel insights designed to provide a holistic view of the ecology of antimicrobial resistance.

Veterinary public health: a module to broaden student understanding of the control and management of antimicrobial resistance

The teaching of veterinary public health, in particular, should develop the pre-existing understanding of the relevance of antimicrobial resistance at a veterinary clinical level, as outlined previously, and extrapolate this to the ramifications for public health. Concepts such as the spread of resistant zoonotic pathogens and the selection of resistance in human pathogens through residues of animal remedies thus become relatively intuitive extrapolations for veterinary undergraduates. The separate and more intricate concept of reservoirs of resistance determinants in animal commensals being transferred to humans through the food chain, with subsequent incorporation of those determinants into bacterial populations of human relevance, will require specific development in veterinary public health programmes. Rather than focusing on attempts to outline the impact of veterinary and animal use of antimicrobial drug treatments on the burden of public health, the emphasis should be on veterinary clinicians playing their part to minimise the development and spread of resistance. The public health role of the veterinarian in biosecurity, food safety and generic hygiene assurance should be specifically developed as an important component in preventing the transfer of resistance from animals to humans. This would include slaughter hygiene and milk pasteurisation, as well as wider concepts, such as the hygienic management of animal wastes.

The topic of antimicrobial resistance thus represents a unique and important opportunity to develop a role for veterinary public health. This subject uniquely transcends the core of clinical veterinary medicine, with immediate relevance to veterinary public health.

Recommendations

Veterinary undergraduate curricula should harness the unique synergy between clinical medicine and veterinary public health in the field of antimicrobial resistance, to instil deep understanding of this issue in the veterinary undergraduate and hence the veterinary graduate, veterinary clinician and public health veterinarian.

Veterinary curricula should provide an opportunity for students to:

– gain an appreciation of the value and vulnerability of antimicrobial compounds in veterinary and human medicine

– acquire a basic knowledge of the resistance mechanisms involved and understand how resistance to antimicrobial compounds emerges

– appreciate the impact of resistance on zoonotic disease

– understand the relationship between antimicrobial resistance and zoonoses and how resistance is transferred through the food chain

– embrace a culture of considering all other options, minimising over-reliance on antimicrobial drugs through increased awareness of the potential non-drug alternatives to prevent and treat disease at both the individual animal and herd level

– understand the tenets of prudent prescribing in veterinary clinical medicine to minimise the development of resistance

– understand how to balance the clinical priority of rapid effective treatment of diseased animals with the professional ethics of maintaining continuing drug efficacy

– develop skills in the area of herd health and encourage population-based approaches to disease management in food animals

– understand the role of public health veterinarians in managing the risk of food-borne transfer of resistance

– ensure that any programme on antimicrobial and antiparasitic resistance, and their broader impacts on animal health and food safety, is integrated with other core clinical modules.

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Les fondamentaux de l'enseignement vétérinaire dans le domaine de la résistance aux agents antimicrobiens et antiparasitaires : conséquences pour la santé animale et la sécurité sanitaire des aliments et importance de la vigilance

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Résumé

La profession vétérinaire joue un rôle crucial dans la protection de la santé animale, de la santé publique et de la sécurité sanitaire des aliments. C'est pourquoi les vétérinaires doivent avoir les connaissances nécessaires pour intervenir de manière proactive face à l'émergence de la résistance aux antibiotiques. À l'heure actuelle, les programmes d'enseignement initial en médecine vétérinaire ne visent pas particulièrement à approfondir les connaissances des étudiants sur ce phénomène complexe. Les programmes modernes d'enseignement vétérinaire devraient avant tout fournir un aperçu holistique de l'écologie de la résistance et faire le point sur les modalités d'apparition de la résistance aux agents antimicrobiens. Parmi les aspects importants qu'un enseignement moderne doit également aborder figurent les interactions entre l'utilisation des médicaments, la sélection naturelle et les micro-organismes résistants aux antibiotiques, ainsi que la mobilisation et la recombinaison génétiques et leur rôle dans l'émergence de microbes résistants.

Mots-clés

Lutte contre les maladies – Programme d'enseignement vétérinaire – Résistance – Résistance aux agents antiparasitaires – Résistance aux antibiotiques – Sécurité sanitaire des aliments – Surveillance.

Formación veterinaria básica sobre el desarrollo de resistencia a los medicamentos antimicrobianos y antiparasitarios, sus consecuencias en la sanidad animal y la inocuidad de los alimentos, y su necesaria vigilancia

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Resumen

Los veterinarios desempeñan un papel decisivo en materia de protección de la sanidad animal, la salud pública y la inocuidad de los alimentos. Por consiguiente, han de adquirir los conocimientos necesarios para actuar con diligencia y eficacia en caso de aparición de una resistencia a los antimicrobianos. En muchos de los planes de estudios actuales no se contempla la mejora de los conocimientos de los estudiantes universitarios sobre este complejo proceso. Es indispensable que los programas de estudios veterinarios actuales incluyan un panorama global y claro de la ecología de las resistencias y, también, del desarrollo de la resistencia antimicrobiana. Las relaciones existentes entre la administración de medicamentos, la selección natural y los organismos resistentes a los antimicrobianos, por una parte; y entre la movilización y la recombinación de genes, por otra, así como de su contribución a la aparición de organismos resistentes, constituyen otras de las componentes esenciales de toda formación veterinaria moderna.

Palabras clave

Control – Inocuidad de los alimentos – Plan de estudios – Resistencia – Resistencia a los antimicrobianos – Resistencia a los agentes antiparasitarios – Vigilancia.

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