Pharmaceutical stewardship encompasses three areas: 1) the responsible use of any antimicrobial so as to decrease risk of antimicrobial resistance and to preserve the efficacy of significant antimicrobials for the protection and restoration of animal health; 2) the availability of good quality medicines so veterinarians have access to safe and efficacious medicines in all parts of the world; and 3) the proper disposal of medications no longer being used, whether they are outdated for use, or left over from inadequate compliance with a previous prescription’s directive.

During its 68th General Assembly in May 2015, the World Health Organization (WHO) approved the WHO Global Action Plan on Antimicrobial Resistance, which states that antimicrobial resistance is “happening in all parts of the world for a broad range of microorganisms with an increasing prevalence that threatens human and animal health.” This issue must be addressed so that all healthcare professionals prescribing antimicrobials, and the people who either consume them, or administer them to animals under their care, act responsibly with these medications.

The World Veterinary Association position statement on the use of antimicrobials states that “the WVA:

- supports that each country should have an appropriate regulatory system for the licensing and control of veterinary drugs in general and antimicrobials in particular;
- urges that antimicrobials be used only in compliance with the laws and/or regulations of each country;
- urges that antimicrobials should be used only in accordance with veterinary examination and diagnosis;
- recommends that counterfeit and other unregistered products should not be used and that such use be combated.”

Responsible use of antimicrobials applies to both human and veterinary medical healthcare providers and has two components – 1) appropriate prescriptive direction based on diagnostic assessment, and 2) the proper compliance with those directions by the end user. The use of antimicrobials in human and veterinary medicine has a role in the responsibility for decreasing the development of antimicrobial resistance. The over-prescription of antimicrobials, particularly antibiotics, in the absence of appropriate indications, can be influenced by diagnostic uncertainty, lack of opportunity for patient follow-up, lack of knowledge regarding optimal therapies, and patient/client demand. In some areas of the world, antimicrobial agents are readily available and can be purchased as a commodity without the advice or prescription of a physician, veterinarian, or other trained healthcare provider. Indeed, human behaviour also plays a role in promoting resistance in that we tend to self-medicate or self-diagnose illnesses in ourselves and our animals, and not comply with recommended treatments by forgetting to take (or give) medication, prematurely discontinuing medication as we or the animals begin to feel better, or cannot afford a full course of therapy. Self-medication almost always involves unnecessary, inadequate, and ill-timed dosing.

The use of antimicrobials in animal health has long been a target of much of the blame because of data related to the large volume of antimicrobials sold to the animal sector, yet sales volume data does not equate directly to cause in the case of antimicrobial resistance. The use of antimicrobials in food animal production varies immensely, depending on the level of education of the prescribers and handlers, drug availability, geographic location, degree of revenue generated, regulatory monitoring, and degree of responsible veterinary oversight. In many countries the degree of surveillance is very high, with scrutiny for any sign of medication residues, whether in meat or milk. In some countries there may be very little regulatory reporting or surveillance.

The American-based Food Animal Drug Residue Avoidance and Database (FARAD) is an extensive resource for the safe use of medications in animals with proven withdrawal time periods for many medications for milk and meat. The primary mission of FARAD is to prevent or mitigate illegal or harmful residues of drugs, pesticides, biotoxins and other chemical agents that may contaminate foods of animal origin. Perhaps we need to expand this valuable resource to one of global significance.

In December 2013, the United States Food and Drug Administration (FDA) published a guidance document that called for animal drug manufacturers of approved medically important antimicrobials used in water or feed of food-producing animals to voluntarily stop labelling...
them as animal growth promoters. They also called for a change in the labelling of their products for the remaining uses to require veterinary oversight of these drugs when they are used for therapeutic purposes. All of the affected makers of these drugs committed in writing to participate in the strategy.5

In June 2015, the FDA announced the Veterinary Feed Directive (VFD) final rule6 to restrict antimicrobial use in feeds of food-producing animals. This rule brings in the use of these drugs under veterinary supervision so that they are used only when necessary for assuring animal health. The VFD final rule outlines the process for authorising use of VFD drugs (animal drugs intended for use in or on animal feed that require the supervision of a licensed veterinarian) and provides veterinarians in all states with a framework for authorising the use of medically important antimicrobials in feed when needed for specific animal health purposes. The use of any antimicrobials now needs to be done with a veterinary prescription and oversight under the rules for a veterinary-client-patient relationship. In Europe, many countries have taken measures to stop misuse and overuse of antimicrobials and to reduce the total amounts of antimicrobials used in animals.

At the level of the European Union, comprising 28 member countries, the EU Commission has launched a five-year action plan. This plan contains 12 actions for implementation with EU member countries. It identifies a number of areas where measures are most necessary, such as: preventing microbial infections and their spread, making sure antimicrobials are used appropriately in both humans and animals, improving monitoring and surveillance in human and animal medicine, developing new effective antimicrobials or alternatives for treatment. Proposals for new EU legislation on veterinary medicines and medicated feed are under discussion in the European parliament and Council. Each year in November the European Centre for Disease Prevention and Control (ECDC) organises the European Antibiotic Awareness Day, to raise awareness about the need for the correct use of antibiotics. Total elimination of antimicrobial use in food production animals would be irresponsible, both in terms of humane and appropriate veterinary care for animal health, and as an effective tool in producing a safe and nutritious food supply. Solutions for responsible use vary from one country to another.

The use of antimicrobials in companion animal medicine has remained totally unmonitored, and again depends on many of the same factors – over-prescription of antimicrobials in the absence of appropriate indications and influenced by diagnostic uncertainty, the
pressure to get a quick recovery for pet owner convenience and animal comfort, and the misconception that use of antimicrobials in companion animals may not be as significant to human health as in food animal production. With the increased affection we have for our companion animals, known commonly as the human-animal bond, humans are increasingly co-habituating with their companion animals, sleeping with their pets, and sharing their food with their pets. Children are in close proximity with their pets, including where there may be pet urine and faeces during house-training. These close associations often happen while pets are undergoing treatment with antimicrobials for common respiratory, gastrointestinal, urinary, or skin infections. Yet no data is available on the amount or common uses of antimicrobials in companion animals to determine what role antimicrobials may have in the development of antimicrobial resistance in humans from use in companion animals.

The World Veterinary Association has a good working relationship with the World Medical Association. In fact, in May 2015, the WVA and WMA co-hosted a Global Conference on One Health in Madrid on “Strengthening the Collaboration between Physicians and Veterinarians” as an excellent model of our two professions working together in a “One Health approach” for improved awareness and quality of good public health. Sessions concentrated on a number of One Health issues, but of notable attention were the presentations on antimicrobial resistance and zoonotic disease. The programme and links to presentations can be found at http://www.worldvet.org/uploads/docs/gcoh_-_program_and_presentations.pdf.

Laura Kahn, MD, gave a very interesting evidence-based presentation on the need for genome sequencing of bacteria to better trace the etiologies of resistant bacteria and the development of various antimicrobial resistance schemes (Physicians, Farmers, and the Politics of Antibiotic Resistance: A One Health Analysis). Hospital-associated vancomycin-resistant enterococcus (VRE) appears to be genetically distinct from VRE in livestock and from healthy people in the community. Genetic analysis suggests that the VRE precursor came from an animal, but not the livestock species that everyone assumed. Rather, the VRE precursors (AREF CC17) genetically related to VRE CC17 in hospitals have been isolated in dogs. It is critically important we start to collect data on the amount and use of antimicrobials in all animals, including companion animals, so we can make accurate and informed decisions about the future use and accurate assessment for the relationship, if any, to further development of antimicrobial resistance in human patients. Her presentation made the following conclusions:

- There is no evidence that the EU ban in 2006 decreased VRE in hospitals.
- Antibiotic use varies widely between countries, showing large variations in how medicine is practised.
- Surveillance must include microbial genomes.
- Antibiotic resistance in pets is potentially an important hidden source of resistance in humans.
- Antibiotic resistance surveillance should include pets.

While it has historically been the case to place blame either with physicians or veterinarians for the overuse or misuse of antimicrobials, it seems this is a problem for which both professions are responsible in one way or another. The medical and veterinary professions need to work together, not separately, to discuss future measures for surveillance and protocols to diminish further development of antimicrobial resistance. Those measures should include responsible and accountable use of antimicrobials prescribed in humans and animals, and not only for food production animals, but also for use in companion animal medicine.

A second area of pharmaceutical stewardship involves the availability of good quality drugs. In fact, in some countries the lack of access to good quality drugs magnifies
the problems of non-compliance and self-medication, because significant amounts of available antimicrobials are poorly manufactured, counterfeit, or have exceeded their effective lifetimes. In June 2015, HealthforAnimals (previously the International Federation of Animal Health) hosted the 4th Global Animal Health Conference in Dar es Salaam, Tanzania, funded by the Gates Foundation, with the theme of Regulation Convergence and the goal of assuring that quality medicines can be made available to all countries in Africa. In some countries in the world it is even illegal for veterinarians to be in possession of certain narcotic agents, normally used for pain management or anaesthesia, whereas they are readily available on the street or in the black market. These issues complicate good human and animal healthcare and lead to circumstances that promote further poor practices and likelihood of antimicrobial resistance development.

Innovation for the development of potentially life-saving medicines has become less rewarding and more challenging to recoup a return on a very large investment. Scientific breakthroughs in medicine have saved countless lives, both human and animal, and have improved animal health for the production of a safe and abundant food supply of animal origin for decades. However, occasionally unexpected consequences are observed, sometimes sooner, sometimes years later. Potential complications of a previously acceptable protocol are recognised that require adjustments to be made or even complete termination of a particular drug’s availability or a particular protocol. Obviously the safety of medicines for their intended patients is paramount; however, these developments have led to a decrease of innovation in many areas. Consequently, more clinical trials are required, more regulation is implemented, and governmental trade markets become more difficult to penetrate. We need to encourage innovation in medicine for safer and more efficacious healthcare. We need a viable animal healthcare medicines industry to support veterinarians in keeping animals healthy in the first place, or restore their health, either individually or as a larger population, whether they are food animals, equines, companion animals, aquatic/marine animals, or exotic populations.

The final segment of pharmaceutical stewardship is the responsible disposal of antimicrobials by manufacturers, healthcare professionals, and end users. “Due to very limited options for proper disposal, unused medications become a primary source of abused drugs. These leftover medications also pose serious environmental risks by contaminating waterways and harming aquatic life when flushed or discarded into the trash.” Results of studies demonstrate an increase in resistance among common bacterial pathogens of marine mammals over a time span of six years. We must not only educate providers and consumers on responsible use of antimicrobials, but also on how to decrease leftover product and to educate on proper disposal, including through authorised “take-back programmes”.

In summary, those of us who prescribe antimicrobials, both human medical and veterinary medical professionals, need to do so with appropriate indication and prescription directives based on examination and diagnostic assessment. We need to advocate for continued surveillance and data collection on the use of antimicrobials, and support further research on the development of antimicrobial resistance with genome sequencing. We need to educate and advocate with our human medical association colleagues for the prudent use of these medications in all species to safeguard the efficacy of our current tools against bacterial infections. People who either consume antimicrobials themselves, or administer these medications to animals in their care, need to understand the importance of following the recommended prescription as directed. Finally, we all need to know how to properly dispose of any unused medications in a responsible manner. These measures will help protect the health of both humans and animals from the risk of antimicrobial resistance. The World Veterinary Association will be actively engaged in the advocacy and education process on these issues.

References

2. World Veterinary Association Position on Responsible Use of Antimicrobials (2011).
5. FDA Regulation to Help Ensure Judicious Use of Antibiotics in Food-Producing Animals (2015).

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