EDITORIAL

Future MICROBIOLOGY

Antimicrobial resistance & 'Man's best friend': what they give to us we might be giving right back

"Antimicrobial resistance follows antimicrobial use…"

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Antimicrobial agents are used to treat infectious diseases in both humans and animals and in many instances the same drug or drug classes are used. Antimicrobial resistance follows antimicrobial use and a central question is do we acquire resistant organisms from animals and/or do animals acquire resistant pathogens from humans? Evidence would seem to suggest it is a two-way street.

The continuing and, in some instances, escalating concerns over antimicrobial resistance is a 'household' reality in all healthcare facilities and in outpatient general practice medicine. Indeed, anywhere patients are examined and antibacterial agents prescribed, antimicrobial resistance is a realistic probability. The aforementioned statements might be assumed to relate to human infectious diseases but in fact, could just as easily relate to veterinary medicine and infectious diseases.

Co-morbidities appear to impact antimicrobial use and therefore antimicrobial resistance. A recent report commenting on antimicrobial use and antimicrobial resistance in various geographical regions in the USA (as determined by the CDC) found the highest usage of antimicrobial agents occurred in geographical regions with the highest incidence of heart disease, diabetes and smoking [1]. Antimicrobial resistance was also highest in this region for *Streptococcus pneumoniae* and macrolides. Both humans and animals may have co-morbidities affecting antimicrobial selection and use. Indeed, Shallcross *et al.* recently reported from humans that any co-morbidity increased the prescribing rate by 44% and prescribing rates to women exceeded those in men by 62% [2].

Animals, like humans, get urinary tract, respiratory tract, skin and skin structure, bone, CNS infections and others including sepsis syndrome [3]. In many instances, similar predisposing or risk factors are common between humans and some animals, however, animals may have some unique risk or predisposing factors for infection. For example, traumatic bites, scratches, ingestion of

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foreign objects, contaminated food and genetic predisposition may occur more regularly in animals than in humans and/or in some breeds more than others [3,4].

Broadly, animals can be classified into food animals, companion animals, exotics and other groupings. The numbers of species is vast and as such, infectious diseases and etiology may relate to habitat, environment, climate and microbial organisms encountered. Geographical variables may also influence human infectious diseases as some pathogens or vector may be geographically restricted or have varying prevalence nationally or regionally.

As in humans, antimicrobials are used to treat bacterial and fungal, parasitic and viral infectious diseases in animals. Human medicine has benefited from countless clinical trials with various antimicrobial agents for a broad range of infectious diseases/pathogens and while similar types of clinical trials have been completed in animals, many aspects of drug use in some clinical conditions in animals are extrapolated from human medicine with limited or no study data. Additionally, human medicine has numerous published therapeutic guidelines that are evidence based with grading of recommendations based on the strength of the evidence [5–7]. Over the past 6 years, therapeutic guidelines for companion animal infectious diseases have been published under the umbrella of the International Society for Companion Animal Infectious Diseases [8] and to date, urinary tract [9], dermatology [10] and respiratory tract [11] documents have been published and currently the urinary tract infection (UTI) guidelines are under revision and update. As with humans, the topic of asymptomatic bacteruria is being addressed.

Many classes of antimicrobial agents routinely used to treat infection are common between human and veterinary medicine: β-lactams (penicillins, ± β-lactamase inhibitors and cephalosporins; 1st, 2nd, 3rd generation), fluoroquinolones, lincosamides, macrolides, tetracycline and trimethoprim plus sulfonamide derivatives. In veterinary medicine, some drugs are not routinely used but may be used as 'rescue' drugs and these include carbapenems, vancomycin, linezolid, tigecycline and others.

'One Health' is a catch all label to consider both human and animal health and within this concept consider antimicrobial use and resistance. First and foremost, the only important implication for antimicrobial resistance is on clinical use and the risks for therapeutic failure, disease escalation and death. Antimicrobial resistance has also captured the attention of regulatory agencies and politicians and is clearly related to the lack of new drug development and the need to preserve/protect our existing agents for clinical utility. For some bug–drug combinations, the preantibiotic era is close, if not already here. The importance of antimicrobial resistance and political interest was recently highlighted by being an agenda item at a United Nations meeting in the USA in September 2016 [12].

So the million dollar question remains, *"Does the use of antimicrobial agents in veterinary medicine give rise to antimicrobial resistant pathogens that subsequently infect humans and for which therapy is compromised due to similar drug classes being used or vice versa?"*

Clearly, some animal pathogens are not pathogens in humans or are rarely recovered from human cases. In other situations, similar pathogens are seen between humans and animals. Many of the food animal bacterial pathogens (or commensals) – for example, *Mannheimia haemolytica* and/or *Pasteurella multocida* causing bovine respiratory disease – are rarely associated with human disease and clearly uncommon in human respiratory tract infections. From swine, *Actinobacillus pleuropneumoniae*, *P. multocida*, *Streptococcus suis* and *Haemophilus parasuis* are infrequently seen causing human disease. One could argue that antimicrobial resistance among the aforementioned organisms would, if present, represent a negligible risk for human infection diseases except in situations where such organisms may share/exchange resistance determinants with human pathogens. For poultry, concerns over fluoroquinolone use and selection of fluoroquinolone-resistant *Campylobacter* species led to a ban on fluoroquinolone use in poultry by the US FDA in 2005 [13].

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The concern related to *Campylobacter* species being commensal organisms of birds and not being eliminated by fluoroquinolones. Exposure of *Campylobacter* species to fluoroquinolones provided selective pressure for resistance selection. As *Campylobacter* species are intestinal pathogens of humans, risks of resistance selection impacting clinical outcomes lead to the ban. Other foodborne bacterial pathogens include *Salmonella* species, *Escherichia coli*

including 0157 strains, enterotoxigenic strains, non-0157 Shiga toxin-producing strains, *Listeria monocytogenes, Vibrio* and *Yersinia* species, *Brucella* species and *Clostridium perfringens* [14].

Swartz suggested that several lines of evidence link antimicrobial-resistant human pathogens to foodborne pathogens of animal origin [14]. These lines of evidence include: direct epidemiologic studies, temporal evidence, additional circumstantial evidence, trends in antimicrobial resistance among *Salmonella* isolates and trends in antimicrobial resistance among other pathogens.

Zoonotic diseases have been known for decades. Zoonosis is described as infectious diseases of animals that can be transmitted to humans. Zoonotic diseases may involve bacteria, viruses, parasites and fungal pathogens. The mechanism of spread of zoonotic diseases include direct contact with blood or body fluids of infected animals or through bites or scratches, indirect contact, which may involve exposure from areas where animals live and roam or by touching objects that have been contaminated with animal sources; vector borne transmission refers to being bitten by an insect or some other vector and foodborne transmission relates from consumption of contaminated food or fluids. While anyone may be infected through a zoonotic process, those that are at higher risk include children under the age of 5 years, pregnant women, adults over the age of 65 years and any immunocompromised patient or patients with weakened immune systems. Measures that have been promoted to reduce the likelihood of zoonotic diseases include handwashing, maintaining the health and safety of pets or other animals where there may be frequent contact, preventing bites from mosquitoes, ticks and fleas, safe handling of food for both human and animal consumption, knowledge of endemic organisms when traveling and where possible avoidance of bites and scratches from animals. Some of the more common zoonotic diseases include Lyme disease, Rocky Mountain spotted fever and West Nile virus infections. Dengue, malaria and chikungunya are common and also geographically restricted and all of the above are usually acquired through either tick or mosquito bites. *Salmonella* and *E. coli* may be acquired through the handling of animals including at petting zoos or other environments where animals may be handled or touched.

Interestingly, Messenger *et al.* commented on 'Reverse Zoonotic Disease Transmission (Zooanthroponosis)' and reviewed human biological threats to animals and found a worldwide disease threat [15]. In their literature review, some 4763 article titles were screened and from these, 56 articles from 56 countries were included in the review. Of interest, articles on reverse zoonosis dated back to 1988 but the number of articles increased from 2008 onward and included fungus, parasites, viruses and bacteria. From their review, the bacterial pathogens and animals infected included: *Mycobacterium tuberculosis* and *Mycobacterium bovis* infecting wildlife, companion animals, livestock; *Streptococcus pneumoniae* and livestock; methicillin-resistant *Staphylococcus aureus* infecting livestock and companion animals; *E. coli* infecting companion animals and livestock; *Helicobacter pylori* and wildlife; *Campylobacter* species, *Salmonella* species, *Shigella* species infecting wildlife.

For viruses, influenza A virus infecting livestock, wildlife and companion animals have been reported as have measles, human metapneumovirus, human adenovirus and rotavirus infecting wildlife, hepatitis E virus infecting wildlife and livestock and human herpes viruses infecting companion animals and wildlife. For parasites, wildlife have been reported to be infected with *Chilomastix mesnili, Endolimax nana, Stronglyoides fuelleborni, Trichuris triciura, Cryptosporidium parvum, Encephalitozoon intestinalis, Giardia duodenalis, Blastocytosis* species, *Ascaris lumbricoides and Isospora* species. Livestock have also been reported to be infection with *C. parvum, Blastocystis* species and *G. duodenalis*. Finally, an assortment of animals has been infected with *Trichophyton* species and *Microsporum* species and specifically wildlife have been infected with *Trichophyton rubrum* and *Microsporum gypseum*. *Candida albicans* have been reported to infect companion animals, wildlife and livestock.

Companion animals (e.g., dogs and cats) suffer from bacterial infections. Of all bacterial infections in dogs and cats, approximately 12% are of the respiratory tract, 23% of eyes and ears, 25% genitourinary, skin and wound are approximately 21% and gastrointestinal infections are approximate 10%. Pathogens common in companion animal infections include *E. coli* and *Staphylococcus pseudintermedius*. *Pseudomonas aeruginosa* is also a bacterial pathogen in dogs

"Pathogens common in companion animal infections include *Escherichia coli* and *Staphylococcus pseudintermedius*."

and cats. Urinary tract infections are more common in dogs than in cats with approximately half of the cases caused by *E. coli* and another 40% caused by *Staphylococcus* species, *Klebsiella pneumoniae* or *Proteus mirabilis*. Also in dogs, *E. coli* may be responsible for up to 40% of lower respiratory tract infections followed by *K. pneumoniae* and other bacterial pathogens as compared with upper respiratory tract infections where *Staphylococcus* species, *Pasteurella multocida* and *E. coli* account for more than 70% of the cases. The primary dermatological pathogen associated with canine skin infections is *S. pseudintermedius*. Secondary bacterial pathogens include *Proteus* and *Pseudomonas* species and *E. coli*.

Rabinowitz *et al.* stated *"Human contact with cats, dogs and other pets results in several million infections each year in the United States ranging from self-limited skin conditions to life-threatening systemic illness."* [16].

"A coordinated approach such as One Health is necessary…"

What antimicrobial resistance threats may be a concern with animals and humans? Drug-resistant pathogens have been documented in animals as they have in humans. For example, Wong *et al.* reported on susceptibility of bacterial pathogens causing urinary tract infections in dogs with data collected between 2010 and 2013 [17]. Multidrug-resistant *E. coli* strains were found more commonly in complicated UTI than in uncomplicated cases. Resistance was more likely for isolates recovered from dogs that had received an antimicrobial agent within the past 30 days prior to specimen collection than from dogs that did not receive drugs. Similar observations with respiratory pathogens in humans have been reported [18].

Extended spectrum β-lactamase (ESBL)-producing Gram-negative bacilli have been reported from companion animals [19,20]. Ljungquist *et al.* reported on the household transfer of ESBL/*ampC*-producing *Enterobacteriaceae* between humans and dogs [21]. The study objective was to determine if colonization of dogs with these multidrug-resistant organisms was more common in household where a known human carrier was present as compared with household without a carrier. Household dogs were more likely to have extended spectrum cephalosporin-resistant *Enterobacteriaceae* if a human carrier was also present in the household and these organisms were not found in dogs in households without human carriers.

Colistin, a polymyxin first introduced in 1959, saw limited use due to renal and neurotoxicity. Renewed interest in this drug related to its activity against multidrug-resistant Gram-negative bacilli and therefore its clinical utility. It has been called a drug of last resort and resistance concerns are escalating. In particular, transferable polymyxin resistance reported from animals, food and humans in China in 2015 solidified the magnitude of these concerns [22]. Indeed, Poirel and Nordmann questioned if the animal world was the culprit and further drew concerns related to *E. coli*, its role in human and animal disease, it being the main reservoir for this resistance (to date) and the fact that it is a gut colonizer and commensal as well as a pathogen [23]. Subsequent reports indicate a broader geographical distribution of colistin-resistance strains, and Richez and Burch suggested that colistin in animals was a high risk for resistance selection in Europe and reviewed that the *mcr-1* gene-encoding colistin resistance has now been found in other genera of *Enterobacteriaceae* and *Campylobacter* species [24].

Schwarz *et al.* in an excellent review indicated that *"…direct contact is likely the quickest and easiest way by which bacteria are transferred in either direction between humans and animals…"* [25]. The data clearly suggest that drug use precedes antimicrobial resistance and such use in humans and animals is expected to give rise to resistant bacteria. Transmission of resistant organism appears to be a bidirectional pathway and we may be sharing with 'man's best friend' what they are sharing with us. A coordinated approach such as One Health is necessary if we are to impact on antimicrobial resistance and preserving clinical utility of existing agents and ensuring longevity of newer compounds and those in clinical development.

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