The post-antibiotic era as it relates to veterinary science

Darren Trott
Australian Centre for Antimicrobial Resistance Ecology
School of Animal and Veterinary Sciences
The University of Adelaide, Roseworthy SA 5371

Introduction
Antimicrobial resistance is described as one of the biggest long-term threats to human health, on the same scale as climate change and terrorism. For only the fourth time in its history for a health issue, the United Nations General Assembly met in September 2016 and committed to “a coordinated approach to address the root causes of AMR across multiple sectors, especially human health, animal health and agriculture.” Left unchecked, AMR amongst pathogenic bacteria, protozoa and viruses is predicted to cause 10 million deaths in the year 2050, with a cumulative economic impact exceeding 100 trillion US dollars.

Globally, there is much debate concerning antimicrobial usage in animals, both in livestock produced for food, and pets sharing close contact with humans and its proportional impact on public health. This is largely because the development of AMR is complex, driven by both clonal expansion of multidrug-resistant (MDR) strains and the evolution and horizontal transmission of mobile genetic elements carrying ARGs, including plasmids, transposons, integrons and integrative conjugative elements, under antibiotic selection pressure.

The critically important antimicrobials (CIA) are last line therapies in humans and include third generation cephalosporins (3GCs), fluoroquinolones (FQ), carbapenems and colistin. Internationally, emergence and spread of resistance to CIA has been reported in both food-producing and companion animals. This has resulted in calls for reductions in the veterinary use of antimicrobials especially those also used in humans (i.e. “shared class drugs”) with particular focus on the CIA. Once ARGs encoding resistance to CIA enter livestock systems or companion animals on mobile genetic elements, they can be perpetuated by use of antimicrobials less important to human health but in common use in animals.

MDR AMR in animals-case studies (gram-negative bacteria)
Three recently published papers characterising the genetic basis of resistance to CIA in multidrug-resistant Gram-negative bacteria in Australian animals illustrate this point.

In the first case, a carbapenem-resistant *Salmonella* Typhimurium was isolated from a shelter cat with diarrhoea following treatment of an upper respiratory tract infection with doxycycline. The isolate contained a large multidrug-resistant plasmid encoding resistance to nine antimicrobial agents, including the *bla*IMP-4 carbapenemase gene, but also contained a large array of heavy metal resistance genes, although only phenotypic resistance to arsenic was detected in the laboratory. The plasmid was highly similar to those detected in humans in Asia and in carbapenem-resistant Enterobacteriaceae causing infections in humans in the eastern states.

In the second example, ceftiofur-resistant *Escherichia coli* were detected in commensal *E. coli* isolates at a piggery in Australia with a history of off-label use of ceftiofur in individual piglets with scours. A plasmid containing a *bla*CTX-M-1 gene (encoding resistance to third generation cephalosporins including ceftiofur) and co-resistance to aminoglycosides, sulphonamides and trimethoprim was identified in a large number of different commensal *E. coli* subtypes. The plasmid could still be detected in the faeces
of all age groups of pigs up to four years following removal of ceftiofur from the piggery’s treatment schedule, although prevalence was significantly lower in the latter years. It is important to note that the extended-spectrum beta-lactamase gene identified in the plasmid is not commonly detected in humans and has thus far not been detected in Australian human sepsis isolates during AMR surveillance. Nevertheless, the precautionary principle has driven many pig veterinarians to remove off-label use of ceftiofur from their treatment schedules, particularly for scours.

In the final example, *Salmonella* Typhimurium resistant to third generation cephalosporins were recently detected in sporadic cases of locally acquired salmonellosis in humans in Victoria. Phenotypically resistant isolates of human and animal origin were geographically restricted and were found by whole genome sequencing to all be closely related and to carry *bla*CTX-M-9 in a chromosomal gene cassette. Dairy cattle were the suspected source based on geographical clustering of animal isolates, which were predominantly bovine in origin. It is difficult to hypothesise the reasons for recent emergence of an MDR *Salmonella* serovar in Australian dairy herds, but increased off-label use of ceftiofur for the treatment of foot diseases because of the nil withholding period is one possible precipitating factor. There is no evidence that the use of ceftiofur for its labelled indication in beef feedlots in Australia is causing any resistance issues- in studies by the author (unpublished data) or Barlow et al. MDR AMR in animals-case study (gram-positive bacteria)

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) has recently emerged in Australian companion animal practice. Characterisation of the isolates causing infection in Australian dogs has revealed some interesting findings. Sequence types (ST) 71 (the most common in Europe) and ST45 have been detected in Australia, but we also have our own home grown new STs in ST496 and ST497, which predominate in our largest cities. MRSP should be regarded as our “golden staph”, with every effort made to prevent transmission between dogs within veterinary hospitals, given their resistance to multiple classes of antimicrobial agent including CIAs. One particular case study provides a cautionary tale- a MRSP stifle joint infection in a Great Dane with pyoderma following a cruciate repair (submitted for publication). The dog eventually had to be treated with linezolid, an important human antimicrobial agent at exorbitant cost, but fortunately with a good outcome.

The future

Australia has been largely shielded from the antimicrobial resistance in animals debate, as much of its livestock production is extensive and it has adopted a conservative position regarding registration of antimicrobials. Australia is the only country never to have permitted use of FQs in livestock produced for food, while 3GCs are not used in poultry and colistin has not been used in animals for more than 25 years. The level of AMR in animals in Australia is likely to be low by international standards, giving our primary producers significant local and international trade advantages, however this needs to be documented by evidence. Co-ordinated surveillance programmes for monitoring AMRIA to confirm this advantage have only just commenced.

Australia’s livestock and veterinary industries, particularly those involved with intensive farming of animals, will require innovation to rapidly adapt to the changing international climate in the post-antibiotic era, according to the following caveats:

- Any new classes of antimicrobial will be for human use only, the animal health industry will need to preserve the lifespan of “shared class” drugs and explore new or repurpose existing “animal only” drug classes.
• There will be an increasingly profitable market for animal products produced with demonstrably minimal antimicrobial interventions and industries will be increasingly reliant on good management, improved diagnosis of infectious disease and a range of novel non-antimicrobial control measures to treat and prevent infections.

• Confirming freedom from ARGs that have the most impact to public health (i.e. those imparting resistance to last line or CIA), both in animal products and the animal production environment, will become part of future livestock quality assurance programmes.

• New vaccine development, with some notable exceptions, is unlikely to provide protection from the full spectrum of microbial infections in animals (e.g. bovine mastitis).

• Off-label use of CIAs (e.g. use of cefiofur) in food-producing animals will come under increased scrutiny with the first detection of resistance in Australia.

• Off-label use of CIAs (e.g. use of linezolid) in companion animals as last resort options requires clear governance, a reporting system and a hierarchy of permission, as occurs in human medicine.

References


Acknowledgments
The author wishes to acknowledge the financial support of Zoetis, without which much of the research undertaken on AMR in Australian animals would not have been possible.