Antimicrobial resistance in veterinary medicine – issues and controversies from an Australian perspective

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Antimicrobial resistance in veterinary isolates came to renewed prominence in the late 1990s in response to the recognition of an association between the use of avoparcin as a growth promotant in livestock feeds and vanA vancomycin resistance in enterococcal pathogens in humans. Since then there have been many regulatory changes in many countries that have resulted in a reduction in use of antimicrobial growth promoters (AGPs) in livestock feeds. The EU has banned the use of most growth promoters and in Australia post-JETACAR avoparcin (a glycopeptide) has been voluntarily withdrawn from the market by the manufacturer (in 2000), recommendations have been made to restrict the use of virginiamycin (a streptogrammin) to a prescription-only medicine for treatment and prevention of some specific conditions, and a review of macrolide AGPs is in the wings. In addition, many of the industries have voluntarily reduced or ceased their use of some of these products. For example, the pig industry stopped use of avoparcin in 1997 and the use of virginiamycin has been curtailed in the meat chicken industry.

Australia has a very strict national system for registration of all chemicals (including antibiotics) used in animals generally and in food producing animals in particular. As a result of JETACAR almost all antibiotics used in animals – except for some products used in pet fish and aviary birds and the remaining AGPs – are prescription-only medicines. Use of antimicrobials by veterinarians is regulated by state control of use legislation as well as label restraints imposed as part of the registration process. As a result of these processes, unlike the situation in Europe and the USA (and in less-regulated countries in other parts of the world), fluoroquinolones and gentamicin have never been registered for therapeutic use in food producing animals and chloramphenicol was de-registered in 1982, although use of these antibiotics is permitted in cats and dogs. The range of AGP growth promoters is also much more limited than in the USA, for example. Thus it is important not to simply extrapolate reports of AMR in animals from overseas countries to the Australian situation.

Glycopeptide, streptogrammin and high-level gentamicin resistance in enterococci

Many of the AGPs target gram-positive bacteria and as a result of extensive use of these in pigs, chickens and intensively reared cattle, enterococci resistant to glycopeptides and quinupristin-dalfopristin (a streptogrammin) has been reported in foods of animal origin (particularly meats) and in humans consuming such products in Europe in particular. Australian studies of human gut carriage of enterococci have failed to detect vanA VRE. It should be emphasised that only the vanA glycopeptide resistance determinant is associated with avoparcin use, with other determinants such as vanB selected by use of glycopeptides in human medicine. In Australia vanA VRE were found in chickens in a study conducted prior to the withdrawal of avoparcin from the market. However, a pig study carried out in 1998 (twelve months after voluntary withdrawal of avoparcin) found no vanA VRE, although vanC VRE (intrinsically resistant to glycopeptides) were common (R Pratt & M Barton, unpublished). When the same area of pig production was re-sampled in 2003/2004, even vanC VRE had disappeared (H Peng & M Barton, unpublished). The disappearance of vanA VRE from livestock following withdrawal of avoparcin has been well documented in Europe, although the decline has been delayed in some countries due to co-location of vanA with resistance determinants to other antibiotics still used in those countries.
Virginiamycin resistance was found in more than 90% of isolates of *E. faecium* from Australian chicken isolates collected in 2000 and pig isolates from the 1998 survey (R Pratt & M Barton, unpublished); however, in the 2003/2004 survey resistance in pig isolates had fallen to around 10% (H Peng & M Barton, unpublished). It should be noted that *E. faecalis* is intrinsically resistant to streptogramins. Widespread virginiamycin resistance in *E. faecium* isolates from animals exposed to this AGP has been reported overseas (presumably mostly *E. faecalis*). However, ESBLs have been reported in *Enterobacter* spp. isolated from pigs in 2003/2004 (H Peng & M Barton, unpublished). However, ESBLs have been reported in *Enterobacter* spp. isolated from pigs in 2003/2004 (H Peng & M Barton, unpublished). However, ESBLs have not been systematically investigated in Australian livestock although there are increasing numbers of reports from overseas countries. Cefiofur is the only third generation cephalosporin currently registered for use in animals in Australia. It is registered for use in cattle for treatment of respiratory disease but control of use legislation in most states would allow its use in other food producing animals because it is registered for use in one food producing species. Cefiofur resistance has not been detected in salmonella isolates from pigs or chickens or from *E. coli* collected from pigs in 2003/2004 (H Peng & M Barton, unpublished). However, ESBLs have been reported in *Enterobacter* spp. isolated from dogs. AmpC β-lactamases have not been reported from Australian livestock, although ampicillin resistance is reasonably widespread in *E coli* and *Salmonella* in Europe and North America, are not present in Australian livestock. It is interesting to speculate that this may be linked to the absence of fluoroquinolone use in livestock and the so-far somewhat restricted use of third generation cephalosporins such as cefiofur.

Multi-drug resistance in salmonella

Antibiotic resistance is common in Australian animal salmonella isolates. The 2006 IMVS Salmonella Reference Laboratory Annual Report noted that no salmonella isolates (human and animal) were resistant to fluoroquinolones but interestingly nalidixic acid resistance was detected in human (3.4%) and pig (3.6%) isolates and in raw meats other than chicken meat (2.4%). Some cefiofur (third generation cephalosporin) resistance was seen in cattle (0.4%) and human (0.2%) isolates. Overall, pig isolates were more resistant than cattle isolates, followed by meat chicken and raw meats other than chicken isolates; 45-60% of pig isolates were resistant to ampicillin, tetracycline, streptomycin and sulphonamides. Multiple resistance was noted in human isolates, with 8% acquired overseas against 3% acquired in Australia. Resistance to four or more antibiotics was demonstrated in pig (37%), cattle (10%) and meat chicken (3.5%) isolates. However, it is important to note that multiple resistance strains such as *Salmonella* typhimurium DT104 and *Salmonella* newport, which cause significant animal and human infections in Europe and North America, are not present in Australian livestock. It is interesting to speculate that this may be linked to the absence of fluoroquinolone use in livestock and the so-far somewhat restricted use of third generation cephalosporins such as cefiofur.

Fluoroquinolone and macrolide resistance in *Campylobacter jejuni*

*C. jejuni* is not a pathogen in animals but a zoonotic infection transferred via the food chain when foods of animal origin are contaminated during processing. The emergence of fluoroquinolone resistance in human isolates in Europe quickly followed the introduction of fluoroquinolones to treat enteric and respiratory infections in pigs and chickens. Australian studies have found no fluoroquinolone resistance in pigs or chickens. Australian human isolates are largely sensitive to fluoroquinolones and these studies suggested that the more resistant strains were acquired overseas. It is interesting to note that resistance to erythromycin is also relatively uncommon in chicken and human isolates, in contrast to pig isolates (presumably mostly *C. coli*) where resistance to erythromycin and clindamycin is very common. The resistance rates in humans are consistent with those reported overseas.

Extended spectrum β-lactamases (ESBLs) and Amp-C β-lactamases

ESBLs have not been systematically investigated in Australian livestock although there are increasing numbers of reports from overseas countries. Cefiofur is the only third generation cephalosporin currently registered for use in animals in Australia. It is registered for use in cattle for treatment of respiratory disease but control of use legislation in most states would allow its use in other food producing animals because it is registered for use in one food producing species. Cefiofur resistance has not been detected in salmonella isolates from pigs or chickens or from *E. coli* collected from pigs in 2003/2004 (H Peng & M Barton, unpublished). However, ESBLs have been reported in *Enterobacter* spp. isolated from dogs. AmpC β-lactamases have not been reported from Australian livestock, although ampicillin resistance is reasonably widespread in *E coli* and *Salmonella* in *Campylobacter jejuni* and AmpC β-lactamases have been isolated from dogs in a veterinary teaching hospital environment as well as from rectal swabs of staff working in the hospital. Cefiofur is registered for use in dogs and cats and if the use of cefiofur increases, or other third generation cephalosporins are introduced, it is likely that ESBLs and AmpC β-lactamases will become more common in isolates from Australian animals.

Methicillin-resistant *Staphylococcus aureus*

While there have been sporadic reports of methicillin-resistant *Staphylococcus aureus* (MRSA) in animals since 1972, since 1999 there has been a marked increase in the number of papers on this topic. MRSA has been reported in bovine mastitis isolates and various isolates from dogs, cats, horses and, most recently, pigs. With application of molecular tools it has become clear that the isolates from cats and dogs are identical with human hospital acquired strains but that strains from horses often belong to less usual types. MRSA have been found in dogs and cats in Australia and there are anecdotal accounts of infections in foals, but it has not been reported from cattle. Since the end of 2005 it has been clear MRSA has become established in pigs in The Netherlands and France and that pig farmers and their families have been infected with these distinctive pig strains. MRSA has not been reported in Australian pigs. While it is easy to accept that animals could be temporarily colonised with human strains of *S. aureus*, it is difficult to understand the selection pressure that is driving persistent colonisation and allowing these strains to re-infect humans. Antistaphylococcal penicillins such as cloxacillin are often used to treat mastitis in dairy cattle but are not commonly used in other species, at least in Australia.

In conclusion, although AMR is present in Australian bacterial isolates from animals, the livestock industries have responded
to concerns and resistance rates in enteric bacteria from pigs has declined. The removal of avoparcin from the market has reduced the exposure of Australians to the *rara* glycopeptide resistance determinant, the absence of fluoroquinolones and constrained use of ceftiofur from the livestock market has protected Australians from the absence of fluoroquinolones and constrained use of ceftiofur may be contributing to the absence of highly resistant *Salmonella* serovars.

References