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 *van*A vancomycin resistance in enterococcal pathogens in humans [1]. 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banned the use of most growth promoters and in Australia post-JETACAR avoparcin (a glycopeptide) has been voluntarily withdrawn from the market by the manufacturer (in 2000), recommendations have been made to restrict the use of virginiamycin (a streptogrammin) to a prescription-only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 [2].

Australian studies of human gut carriage of enterococci have failed to detect *van*A VRE [3]. It should be emphasised that only the *van*A glycopeptide resistance determinant is associated with avoparcin use, with other determinants such as *van*B selected by use of glycopeptides in human medicine [4]. In Australia *van*A VRE were found in chickens in a study conducted prior to the withdrawal of avoparcin from the market [5]. However, a pig study carried out in 1998 (twelve months after voluntary withdrawal of avoparcin) found no *van*A VRE, although *van*C 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 *van*C VRE had disappeared (H Peng & M Barton, unpublished). The disappearance of *van*A 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 *van*A with resistance determinants to other antibiotics still used in those countries [1,6,7].

Virginiamycin resistance was found in more than 90% of isolates of *E. faecium* from Australian chicken isolates collected in 2000[5] 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[8]. Widespread virginiamycin resistance in *E. faecium* isolates from animals exposed to this AGP has been reported overseas [9]. No high-level gentamicin resistance was found in isolates in the Australian studies although this has been found overseas [10,11].

Multi-drug resistance in salmonella

Antibiotic resistance is common in Australian animal salmonella isolates. The 2006 IMVS Salmonella Reference Laboratory Annual Report [12] 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 ceftiofur (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 then 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 [13] and *Salmonella newport* [14,15], 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 ceftiofur.

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 [16]. Australian studies have found no fluoroquinolone resistance in pigs or chickens [5,17]. Australian human isolates are largely sensitive to fluoroquinolones [18,19] 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 [5] and human isolates, in contrast to pig isolates [17] (presumably mostly *C. coli)* where resistance to erythromycin and clindamycin is very common. The resistance rates in humans are consistent with those reported overseas [20].

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 [21,22]. Ceftiofur 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. Ceftiofur resistance has not been detected in salmonella isolates from pigs or chickens[12] 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 [23]. AmpC β-lactamases have not been reported from Australian livestock, although ampicillin resistance is reasonably widespread in *E coli* and *Salmonella* [5,12,17], although multi-drug resistant *E. coli* expressing 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 [24]. Ceftiofur is registered for use in dogs and cats and if the use of ceftiofur 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 [25,26]. 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 [27,28] but that strains from horses often belong to less usual types [29]. MRSA have been found in dogs and cats in Australia [28] and there are anecdotal accounts of infections in foals, but it has not been reported from cattle [30]. Since the end of 2005 it has been clear MRSA has become established in pigs in The Netherlands and France [31] and that pig farmers and their families have been infected with these distinctive pig strains [32,33]. 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 *van*A glycopeptide resistance determinant, the absence of fluoroquinolones from the livestock market has protected Australians from fluoroquinolone resistant campylobacter and salmonella, and the absence of fluoroquinolones and constrained use of ceftiofur may be contributing to the absence of highly resistant *Salmonella* serovars.

References

1. Wegener HC. Antibiotics in animal feed and their role in resistance development. *Curr Opin Microbiol* 2003; 6:439-45.
2. Klare I, Konstabel C, Badstüber D *et al*. Occurrence and spread of antibiotic resistances in *Enterococcus faecium*. *Int J Food Microbiol* 2003; 88:269-90.
3 Padiglione AA, Grabsch EA, Olden D *et al*. Faecal colonization with vancomycin-resistant enterococci in Australia. *Emerg Infect Dis* 2000; 6:534-6.
4. Kühn I, Iversen A, Finn M *et al*. Occurrence and relatedness of vancomycin-resistant enterococci in animals, humans and the environment in different European regions. *Appl Environ Microbiol* 2005; 71:5383-90.
5. Barton MD, Wilkins J. Antibiotic resistance in bacteria isolated from poultry. Rural Industries Research and Development Corporation Publication No 1/105 Report of RIRDC Project No USA-9A. 2001.
6. Sørum M, Johnsen PJ, Aasnes B *et al*. Prevalence, persistence and molecular characterization of glycopeptide-resistant enterococci in Norwegian poultry and poultry farmers 3 to 8 years after the ban on avoparcin. *Appl Environ Microbiol* 2006; 72:516-21.
7. Manson JM, Smith JMB, Cook G. Persistence of vancomycin resistant enterococci in New Zealand broilers after discontinuation of avoparcin use. *Appl Environ Microbiol* 2004; 70:5764-8.
8. Duh RW, Singh KV, Malathum K, Murray BF. *In vitro* activity of 19 antimicrobial agents against enterococci from healthy subjects and hospitalized patients and use of an *ace* gene probe from *Enterococcus faecalis* for species identification. *Microb Drug Resist* 2001; 7:39-46.
9. Rshberger E, Oprea ST, Donabedian SM *et al*. Epidemiology of antimicrobial resistance in enterococci of animal origin. *J Antimicrobial Chemother* 2005; 55:127-30.
10. Jackson CR, Fedorka-Cray PJ, Barrett JB *et al*. High-level aminoglycoside resistant enterococci isolated from swine. *Epidemiol Infect* 2005; 133:367-71.
11. Hayes JR, English LL, Carr LE *et al*. Multiple-antibiotic resistance of Enterococcus spp. isolated from commercial poulty production environments. *Appl Environ Microbiol* 2004; 70:6005-11.
12. Australian Salmonella Reference Centre Annual Report. Institute of Medical and Veterinary Science, Frome Road, Adelaide, South Australia, 2006.
13. Humphrey T. *Salmonella Typhimurium* definitive type 104 – a multi-resistant Salmonell. *Int J Food Microbiol* 2001; 67:173-86.
14. Berge ACB, Adaska JM, Sischo WM Use of antibiotic susceptibility patterns and pulsed-field gel electrophoresis to compare historic and contemporary isolates of multi-drug resistant *Salmonella enterica* subsp. *enterica* serovar Newport. *Appl Environ Micobiol* 2004; 70:318-23.
15. Poppe C, Martin L, Muckle A *et al*. Characterisation of antimicrobial resistance of Salmonella Newport isolated from animals, the environment and animal food products in Canada. *Can J Vet Res* 2006; 70:105-14.
16. Allos BM. Campylobacter jejuni infections: update on emerging issues and trends. *Clin Infect Dis* 2001; 32:1201-6.
17. Hart WS, Heuzenroeder MW, Barton MD. Antimicrobial resistance in *Campylobacter* spp., *Escherichia coli* and enterococci associated with pigs. *J Vet Med* B 2004; 51:216-21.
18. Sharma H, Unicomb L, Forbes W *et al*. Antibiotic resistance in *Campylobacter jejuni* isolated from humans in the Hunter Region, New South Wales. *Commun Dis Intell* 2003; 27:S80-S88.
19. Unicomb LE, Ferguson J, Stafford RJ *et al*. Low-level fluoroquinolone resistance among Campylobacter jejuni isolates in Australia. *Clin Infect Dis* 2006; 42:1368-74.
20. Gibreel A, Taylor DE. Macrolide resistance in *Campylobacter jejuni* and *Campylobacter coli*. *J Antimicrobial Chemother* 2006; 58:243-55.
21. Cloeckaert A, Praud K, Doublet B *et al*. Dissemination of an extended-spectrum-β-lactamase blaTEM-52 gene-carrying IncI1 plasmid in various Salmonella enterica serovars isolated from poultry and humans in Belgium and France between 2001 and 2005. *Antimicrobial Agents Chemother* 2007; 51:1872-5.
22. Li X-Z, Mehotra M, Ghimire S *et al*. β-lactam resistance and β-lactamases in bacteria of animal origin. *Vet Microbiol* 2007; 121:197-214.
23. Sidjabat HE, Hanson ND, Smith-Moland E *et al*. Identification of plasmid-mediated extended-spectrum and AmpC beta-lactamases in Enterobacter spp. isolated from dogs. *J Med Microbiol* 2007; 56:426-34.
24. Sidjabat HE, Townsend KM, Lorentzen M *et al*. Emergence and spread of two distinct clonal groups of multi-drug resistant Escherichia coli in a veterinary teaching hospital in Australia. *J Med Microbiol* 2006; 55:1125-34.
25. Leonard FC, Markey BK. Meticillin-resistant *Staphylococcus aureus* in animals: a review. *Vet J* 2007; doi 10.1016/j.tvjl.2006.11.008
26. Malik S, Peng H, Barton MD. Antibiotic resistance in staphylococci associated with cats and dogs. *J Appl Microbiol* 2005; 99:1283-93.
27. Strommenger B, Kehrenberg C, Kettlitz C *et al*. Molecular characterization of methicillin-resistant *Staphylococcus aureus* from pet animals and their relationship to human isolates. *J Antimicrobial Chemother* 2006; 57:461-5.
28. Malik S, Coombs GW, O'Brien F *et al*. Molecular typing of methicillin-resistant staphylococci from cats and dogs. *J Antimicrobial Chemother* 2006; 58:428-31.
29. Moodley A, Stegger M, Bagcigil AF *et al*. Spa typing of methicillin-resistant *Staphylococcus aureus* isolated from domestic animals and veterinary staff in the UK and Ireland. *J Antimicrobial Chemother* 2006; 58:1118-23.
30. Barton MD, Pratt R, Hart WS. Antibiotic resistance in animals. *Commun Dis Intell* 2003; 27:S121-S128.
31. de Neeling AJ, van den Broek MJM, *et al*. High prevalence of methicillin-resistant *Staphylococcus aureus* in pigs. *Vet Microbiol* 2007; 122:366-72.
32. Armand-Lefevre L, Ruimy R, Andremont A. Clonal comparison of *Staphylococcus aureus* isolates from healthy pig farmers, human controls and pigs. *Emerg Infect Dis* 2005; 11:711-4.
33. Huijsdens XW, van Dijke BJ, Spalberg E *et al*. Community-acquired MRSA and pig farming. *Ann Clin Microbiol Antimicrobials* 2006; 5:26 doi:10.1186/1476-0711-5-26.