

# Antibiotic resistance in Australian animals in 2010 - what lies ahead?

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## Introduction

Antibiotic resistance in animal isolates of bacteria is a critical issue. Firstly there is the issue of resistance in animal pathogens and secondly resistance in zoonotic bacteria and transfer of resistance determinants from animal isolates (often commensals) to human pathogens via the food chain or from direct contact. In addition, antibiotic resistance genes are widely distributed in animals, humans and the environment. In recent years there has been much pressure to remove antimicrobial growth promoters from the market and to restrict the range of antibiotics used in animals to those not regarded as important in human medicine.

## What is the background to this issue in Australia?

The Swan Committee (1969) (which recommended separation between antibiotics used in humans from those used in animals) was established in response to the emergence of multi-drug resistant salmonella in humans identical to strains causing problems in calves and the report from Japan (Watanabe, 1963) that resistance genes were carried on plasmids that could transfer from bacteria to bacteria. The UK and Australia and several other countries (but not the USA) responded by removing antibiotics such as penicillin from animal feeds. A few years later the NHMRC established the Working Party on Antibiotics (WPA) to provide advice from a health perspective on registration of antibiotics for use in animals. One of the key decisions of this group was to recommend that fluoroquinolones not be registered for use in food producing animals. The next major development was the report from Denmark on the link between use of avoparcin in animal feeds and the emergence of vancomycin resistance in human isolates of enterococci – VRE. The Europeans quickly responded to this by progressively removing all growth promotant antibiotics from the market. Australia's response to this and the increasing agitation about use of antibiotics in animals was to set up JETACAR which reported in 1999 with 22 recommendations to address the problem of antibiotic resistance in humans and animals. One of the recommendations led to the formation of EAGAR which replaced the WPA. EAGAR worked hard to drive the implementation of the recommendations (although it was not EAGAR's brief to do so) but was discontinued after two NHMRC triennial cycles. Now there is no Australian focus on antibiotic resistance and the issue has dropped off the political agenda.

In considering antibiotic resistance in animals it is important to first consider what are the major antibiotic resistance problems in human medicine in Australia. These would include hospital acquired MRSA, community acquired MRSA, vanB vancomycin resistant enterococci, penicillin-resistant *Streptococcus pneumoniae*, multi-drug resistant Gram-negative bacteria and extended

spectrum beta-lactamase (ESBL) Enterobacteriaceae. So where are the resistant salmonella, E coli and campylobacter that are the basis of the debate about use of antibiotics in animals? Hawkey and Jones (2009) and others before them have described the link between antibiotic use/antibiotic resistance in enteric bacteria in animals and resistance in these organisms in humans. Overall, it is not a major problem compared with some of the other resistant organisms listed above. In the last few years links between humans and animals with regard to MRSA have been reported and ESBLs are an emerging animal issue but vanB VRE (in contrast to vanA VRE) relates to hospital use of vancomycin, S pneumoniae is a human not animal pathogen and multi-drug resistant Gram-negative bacteria appear to be linked to antibiotic use in hospitals.

It is interesting that therapeutic failure in animals is rarely reported and antibiotic resistance data is sparse. In terms of systematic studies, there was an early (1976-1981) Animal Health Committee study (see Barton et al, 2003) and more recently a DAFF pilot surveillance study was carried out in 2004 (DAFF,2007). It is difficult to compare the results of these studies because the methodologies and the populations of animals studied were different. The National Enteric Pathogen Surveillance Scheme (Microbiological Diagnostic Unit, University of Melbourne) and the Salmonella Reference Laboratory (SA Pathology, IMVS, Adelaide) now test salmonella isolates sent to them. In terms of animal pathogens, information is probably readily available in diagnostic laboratory records but is not more widely accessible. However there is anecdotal evidence that E coli and salmonella from calf scours, E coli from neonatal and post-weaning diarrhoea in calves, salmonella from dairy cattle, pigs, chickens and cattle and various isolates from dog ears are often multi-resistant. There are a few Australian publications reporting on resistance patterns but published studies include atypical mycobacteria from cats (Malik et al 2000), cat bite organisms (Love et al 2000), verotoxigenic E coli from various animals (Bettelheim et al 2003), salmonella and E coli from horses (Bucknell et al) and the case studies on multi-drug resistant E coli from Darren Trott's group in Queensland (Sidjabat et al 2006).

As an example of resistance patterns (accepting that it is difficult to compare results between different studies), tetracycline resistance in pig E coli isolates was around 80% in the two surveillance studies but in a South Australian study isolates collected in 1998 showed close to 100% resistance which had declined (on the same piggeries) to just over 80% in 2005 (Peng and Barton, 2005). Interestingly, apramycin resistance declined from over 90% to 0%, and neomycin resistance declined from 80% to just over 10% between 1998 and 2005. The DAFF study found that multiple resistance was absent from cattle isolates, quite common in chicken isolates, and particularly evident in pig isolates. These studies lead to the conclusion that resistance is prevalent in E coli and salmonella, but the pig studies indicate that resistance prevalence changes over time perhaps in response to changing antibiotic use practices.

The DAFF study found that resistance to erythromycin was common in E faecium isolates from pigs and chickens but less common in cattle isolates. Virginiamycin resistance was found in chicken isolates but not cattle or pig isolates. This contrasts with Peng and Barton's study which found over 90% of enterococcal isolates (not speciated) collected in 1998 resistant to virginiamycin although only just over 10% of 2005 isolates were resistant. No high level gentamicin resistance has been reported in animal isolates of enterococci.

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Little or no fluoroquinolone resistance has been found in E coli or salmonella from cattle, pigs and chickens or in campylobacter isolates from chickens and pigs. There may have been illegal use but it is more likely that the resistance detected relates to spontaneous mutation. This has clearly influenced the prevalence of fluoroquinolone resistance in human isolates as this is much lower in Australia compared with overseas countries where fluoroquinolones are used extensively in food producing animals.

It is also clear that there are distinct species differences and possible regional differences as well in resistance patterns and that resistance patterns also change over time.

Multi-drug resistance in salmonella is a potential concern. The problem strains of Salmonella Typhimurium and Salmonella Newport have not been isolated from animals in Australia although as indicated previously multi-drug resistant salmonella are present in food producing animals and horses. Interestingly to date these strains have not shown resistance to ceftiofur (3rd generation cephalosporin) although this is used for a wider range of conditions in cattle than for which it is registered and is used off-label in pigs. Is this because we do not use fluoroquinolones? There has been some discussion about a relationship between the use of fluoroquinolones and 3rd generation cephalosporins in providing selection pressure for emergence of 3rd generation cephalosporin resistance and AmpC  $\beta$ -lactamases and ESBLs. However, it is important to note that AmpC and  $\beta$ -lactamase production in livestock isolates has not been investigated in Australia, although AmpC Enterobacter isolates have been reported from dogs, cats and horses (Gibson et al 2010). ESBLs particularly are a major concern in Australian hospitals although our problem is miniscule in comparison with the prevalence rates reported by SE Asian and other countries in our region (Bell et al 2007). ESBL-producing E coli strains are most common (Denholm et al 2009) in Australian hospitals.

vanB VRE is now endemic in many Australian hospitals. The vanB gene is carried on human anaerobic gut flora and resistance in Australian VRE isolates is probably driven by vancomycin use in hospitals. There is no association with use of avoparcin and no vanB VRE have been isolated from animals. vanA enterococci is rare in humans in Australia, has not been found in pigs or cattle and was last isolated from chickens in isolates collected before avoparcin was withdrawn from the Australian market (Barton and Wilkins, 2001).

Streptogramin resistance is a divisive issue. A streptogramin (quinupristin-dalfopristin [Synercid®]) was re-evaluated to treat multi-resistant Gram-positive infections in humans but virginiamycin had been widely used in animal husbandry for many years. Investigations showed resistance in poultry, pig and cattle isolates in Europe – up to 60% in some European studies. Australian studies have found much less resistance (around 10 to 12% in the latest surveys). A definitive link between handling or consuming poultry treated with virginiamycin and Synercid resistance has been reported (Kieke et al 2006).

Hospital acquired MRSA has been known since the 1960s shortly after methicillin was introduced onto the market and strains have progressively become much more resistant and difficult to treat. In more recent times community acquired MRSA has emerged - not as resistant but more virulent because many isolates carry a virulence factor (Panton Valentine Leukocidin). Animals were not thought to play a role although from time to time MRSA was

isolated from animals – note that antistaphylococcal penicillins such as methicillin, oxacillin, and flucloxacillin are not registered for use in animals. An exception is cloxacillin used to treat mastitis in dairy cattle. However, monitoring in Australia from the 1970s to the 1990s failed to detect any resistance. Now MRSA has been found to be quite widespread in dogs and horses particularly – usually just colonising the animals but occasionally causing infections. Dog isolates have been identified as human hospital acquired strains (Malik et al 2006) and the strain varies depending on which strains are prevalent in the local human population. Dogs appear to be infected by contact with humans carrying or infected with MRSA. However, it is clear that the dogs can infect humans that are in contact with them. The horse strains all appear to be a distinct clone (ST8) which has become horse adapted but which originated from a human hospital acquired strain. Exposure to colonised or infected horses has led to colonising of exposed humans. Thus these strains are a potential occupational threat to veterinarians.

MRSA has also been found in pigs – originating in France in 2005 (Vanderhaeghen et al 2010) it has now spread to many European countries, USA, Canada and Singapore (and probably elsewhere). This ST398 is now a significant coloniser of humans in the Netherlands and has caused human infections in several countries and is now being reported from cattle (mastitis) and infections in chickens. No information is available about the situation in Australia.

So where are we heading? The blame game continues with some in the medical sector attributing human antibiotic resistance problems solely to use of antibiotics in animals whereas some in the animal production/health sectors deny any contribution from animal use and promote unfettered use of antibiotics in animals. Clearly animal use does have an impact on human health – antibiotic resistant enteric zoonotic infections (campylobacter, salmonella, vanA and streptogramin resistant enterococci and possibly extra-intestinal E coli) can be attributed to animal use of antibiotics. ESBL and AmpC  $\beta$ -lactamase producing salmonella and E coli are at least in part associated with animal use of antibiotics overseas and dogs, horses and pigs (at least overseas) can be reservoirs for re-infection of humans with MRSA.

We do need to pay more attention to ESBLs generally and AmpC  $\beta$ -lactamase producing E coli in particular and investigate the role of ceftiofur or other 3rd/4th generation cephalosporins in driving the emergence of such resistance. Resistance in avian pathogenic E coli and extra-intestinal infections in animals, MRSA in pigs, resistance in aquaculture isolates and contamination of water sources and the environment all warrant investigation. Virginiamycin resistance in E faecium should be monitored.

## Conclusion

Australia needs to establish systems for monitoring and surveillance of antibiotic resistance in human and animal isolates. The medical implications of registration and use of animal antimicrobials needs to be taken into account as part of product registration and review. A current issue is registration of 3rd/4th generation cephalosporins – there is no justification for use of such products in livestock, horses or cats and dogs. Nor is there any justification for general off-label use of medical antibiotics such as carbapenems or the newer macrolides in horses or small animals. Antibiotic resistant bacteria and resistance genes are widely distributed

in animals, humans and the environment and although most attention has been on growth promotant antibiotics, any use of antibiotics drives resistance.

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