Antibiotic resistance in animals

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Abstract

There is currently no systematic surveillance or monitoring of antibiotic resistance in Australian animals. Registration of antibiotics for use in animals is tightly controlled and has been very conservative. Fluoroquinolones have not been registered for use in food producing animals and other products have been removed from the market because of human health concerns. In the late 1970s, the Animal Health Committee coordinated a survey of resistance in *Salmonella* and *Escherichia coli* isolates from cattle, pigs and poultry and in bovine *Staphylococcus aureus*. Some additional information is available from published case reports. In samples collected prior to the withdrawal of avoparcin from the market, no vancomycin resistant *Enterococcus faecium* or *Enterococcus faecalis* were detected in samples collected from pigs, whereas some *vanA* enterococci, including *E. faecium* and *E. faecalis*, were found in chickens. No *vanB* enterococci were detected in either species. Virginiamycin resistance was common in both pig and poultry isolates. Multiple resistance was common in *E. coli* and salmonellae isolates. No fluoroquinolone resistance was found in salmonellae, *E. coli* or *Campylobacter*. ß-lactamase production is common in isolates from bovine mastitis, but no methicillin resistance has been detected. However, methicillin resistance has been reported in canine isolates of *Staphylococcus intermedius* and extended spectrum ß-lactamase producing *E. coli* has been found in dogs. *Commun Dis Intell* 2003;27 Suppl:S121–S126.

Keywords: antibiotic resistance, food-producing animals

Introduction

There is no formal system for monitoring or surveillance of antibiotic resistance in animal bacterial isolates in Australia. Although some investigations were conducted in the late 1970s and into the 1980s, there was little standardisation of sensitivity testing methods so it is difficult to compare this historical data with that which may be produced in the future. The lack of historical data is compounded by the fact that little, if any was published in readily available form and/or was lost with the rationalisation of veterinary laboratories that began in the late 1980s and continues to this day. However, in response to the JETACAR report[1] there is an opportunity to establish *de novo*, a new system of antibiotic resistance surveillance, if agreement can be reached between the relevant government and industry stakeholders on how it should be funded.

Background

Australia has had a conservative approach to registration of antibiotics for use in food-producing animals, particularly since the Swann report[2] recommended that antibiotics important in animal and human health not be used as growth promotants or production enhancers. Initially, the main purpose of controls was to ensure minimal antibiotic (chemical) residues in meat and dairy products, but since the early 1980s the potential for transfer of resistant bacteria and genes from animals to humans has been taken into account. As a result of this approach, neither fluoroquinolones nor gentamicin have been registered for use in food-producing animals and chloramphenicol, furazolidone and carbadox were removed from use in food-producing animals because of human toxicity concerns. Only one third or fourth generation cephalosporin (Ceftiofur) has been registered for use in animals. This product was

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registered specifically for treatment of respiratory infections in cattle, but inconsistencies in state and territory 'control of use' legislation has meant that in some states and territories it has been used in other food-producing animals. Work is underway to have uniform 'control of use' legislation operating in most states and territories by mid-2003.

Antibiotics are used in animals to treat and prevent infections. In food-producing animals, antibiotics have also been used for growth promoting or production enhancing purposes. Antibiotics used in this way are fed to animals at subtherapeutic concentrations for extended periods of time. Invariably, such use is not under the control of a veterinary surgeon—farmers and stock feed manufacturers purchase these products direct from retailers and wholesalers. A restricted range of products is registered for 'growth promotant' use, with the most contentious (from a human health perspective) being avoparcin (a glycopeptide), virginiamycin (a streptogramin) and tylosin (a macrolide). Such antibiotics are used in Australia primarily for the control of chronic enteric infections such as necrotic enteritis in meat chickens and swine dysentery and ileitis in pigs, rather than as 'pure' growth promotants. In addition, ionophores, which are not used in human medicine, are used for control of coccidiosis in chickens and lactic acidosis in cattle and sheep fed high grain rations. Ionophores account for a very large proportion of growth promotant antibiotics used in Australia.

Intensively farmed pigs, poultry, feedlot cattle and sheep account for most antibiotic use in food-producing animals. Therapeutic and prophylactic use (as well as growth promotant use) is often by mass medication through feed or water because of the numbers of animals involved. Antibiotics are rarely used in extensively grazed beef cattle or sheep but individual dairy cows may be treated on occasion and in-feed products can be used to control lactic acidosis. Mass medication (intramammary) can be used at the end of lactation to help control mastitis. Intramammary use during lactation is contra-indicated and is obvious in milk of treated animals through the presence of a blue dye which is a mandatory inclusion in these products.

The extent to which antibiotics are used in aquaculture in Australia is largely unknown. In line with international trends, there is increasing pressure being brought to bear on industry and regulators to use antibiotics to minimise the adverse effects of bacterial and protozoan diseases. Interestingly, Codex Alimentarius, the joint World Health Organization and Food and Agriculture Organization body charged by the World Trade Organization with developing *de facto* international food standards, including maximum residue limits (MRLs), has not yet addressed the issue of MRLs for antibiotics in aquaculture. Nationally, the National Residue Survey (NRS)* has initiated, primarily for market protection purposes, a series of programs to monitor for the presence of antibiotics (and other chemical residues) in a variety of predominantly wild-caught seafood. Reports of these monitoring programs can be found on the NRS website (www.affa.gov.au/nrs).

A wider range of antibiotics is registered for the treatment of disease in cats, dogs and horses with human products frequently used off-label (at least in cats and dogs). Animals are treated individually.

Enteric bacteria

Information on resistance in enteric bacteria isolated from animals is limited. In the late 1970s the then Animal Health Committee (AHC) coordinated a survey of antibiotic resistance in *Escherichia coli* and salmonellae isolates from livestock, and bovine mastitis *Staphylococcus aureus* isolates. The previously unpublished results for *E. coli* from pigs, cattle and miscellaneous sources are shown in Table 1. The results are difficult to interpret and presumably reflect the variation in sources of isolates between years. However, it is clear that in both cattle and pigs resistance to streptomycin and tetracycline was prevalent even 25 years ago. In cattle isolates particularly, there was significant resistance to ampicillin. One thousand two hundred and eighty-seven *Salmonella* isolates from cattle, pigs and poultry were tested between 1975 and 1982.[3] The same antibiotics were used as in the *E. coli* study—resistance to streptomycin and tetracycline was most common. A number of isolates were resistant to more than one antibiotic with the co-resistant combinations of tetracycline and streptomycin (6%) or tetracycline, streptomycin and ampicillin (2%) being the most common.

* The National Residue Survey is part of the Department of Agriculture Fisheries and Forestry—Australia; see: http://www.affa.gov.au/nrs

Table 1. Frequency of antibiotic resistance in Escherichia coli (%)

Species	Antibiotic	Antibiotic concentration*	1976	1977	1978	1979	1980	1981
Pig†			(227)	(196)	(248)	(289)	(270)	(201)
Ampicillin	10 µg/ml	7	12	8	9	6	7	
Chloramphenicol	25 µg/ml	5	3	2	2	3	8	
Furazolidone	25 µg/ml	19	12	18	17	11	12	
Neomycin	4 µg/ml	7	8	7	8	7	13	
Streptomycin	10 µg/ml	50	49	60	56	59	66	
Tetracycline	5 µg/ml	75	82	86	73	72	73	
Bovine†			(91)	(66)	(31)	(89)	(46)	(23)
Ampicillin	10 µg/ml	8	8	23	29	28	9	
Chloramphenicol	25 µg/ml	4	3	24	10	11	4	
Furazolidone	25 µg/ml	19	15	6	4	9	14	
Neomycin	4 µg/ml	4	6	16	24	15	5	
Streptomycin	10 µg/ml	32	45	45	42	39	22	
Tetracycline	5 µg/ml	63	79	71	60	57	39	
Miscellaneous origin†			(17)	(7)	(3)	(1)	(8)	(6)
Ampicillin	10 µg/ml	12	0	0	0	13	0	
Chloramphenicol	25 µg/ml	12	0	0	0	0	0	
Furazolidone	25 µg/ml	24	0	67	0	25	50	
Neomycin	4 µg/ml	12	0	0	0	0	17	
Streptomycin	10 µg/ml	24	29	67	0	25	17	
Tetracycline	5 µg/ml	65	86	100	100	50	50	

* Organisms grew on agar plates containing this concentration of drug.

† Figures in brackets indicate the number of isolates tested.

Source: Animal Health Commission study. J Craven, Director Attwood Veterinary Research Laboratory, Victoria (unpublished results).

Results from the National Enteric Pathogen Surveillance Scheme testing of bovine, chicken and porcine strains of *Salmonella* between 1990 and 1997 are shown in Table 2. The results suggest an increase in prevalence of resistance since the AHC survey in the 1970s (Table 1). There are also differences in the prevalence of resistance in bacteria isolated from different host species, reflecting differences in antibiotic use (e.g., streptomycin was used more commonly in cattle than in pigs and tetracycline is used very commonly in pigs). Fewer isolates from chicken were resistant than isolates from cattle or pigs. Multi-resistant *S.* Typhimurium have been isolated from dairy cattle in Victoria.[4,5] For example, 10 isolates of *S.* Typhimurium PT44 were all resistant to ampicillin, chloramphenicol, kanamycin, neomycin, streptomycin, sulphonamide, tetracycline and trimethoprim but none were resistant to gentamicin or spectinomycin.[5] Interestingly, S. Dublin isolates from the same herds were fully sensitive to the antibiotics tested. It is important to note that the multi-drug resistant serovar *S.* Typhimurium DT104 has not yet been isolated from animals in Australia.

Table 2. Frequency of resistance in *salmonella* 1990 to 1997 (%)a

Chemotherapeutic concentration	Bovine (396)	Chicken (108)	Porcine (51)
Ampicillin 32 µg/ml	31	17	35
Chloramphenicol 10 µg/ml	18	5	10
Streptomycin 25 µg/ml	86	5	10
Tetracycline 20 µg/ml	47	44	92
Sulphathiazole 550 µg/ml	70	19	41
Trimethoprim 50 µg/ml	29	17	35
Kanamycin 10 µg/ml	28	15	31
Nalidixic acid 50 µg/ml	0.5	0	0
Spectinomycin 50 µg/ml	0.6	4	5
Gentamicin 25 µg/ml	0.6	4	5
Ciprofloxacin 0.06 µg/ml	0	5	7

Figures extracted from results provided to the AHC from National Enteric Pathogen Surveillance Scheme by the Microbiological Diagnostic Unit, Department of Microbiology and Immunology, University of Melbourne.

Anecdotal accounts indicate that treatment failure, in part due to antibiotic resistance, is not uncommon in neonatal enteritis in calves and post-weaning diarrhoea in pigs.

The JETACAR report[1] included some results of testing by the Central Veterinary Diagnostic Laboratory of small numbers of *Salmonella* isolates from a range of species with resistance more apparent in cattle and equine isolates than in chicken, cat or dog isolates. Multiple resistance was noted in *Salmonella* isolates from several cattle and one equine isolate. The JETACAR report[1] also included an account of resistance patterns of avian *E. coli* from three chicken meat production companies (T Grimes, personal communication), with widespread resistance to tetracycline and significant resistance to ampicillin and sulphonamides-trimethoprim evident. A study of *E. coli* and *Salmonella* isolates from horses[6] found all 39 isolates resistant to streptomycin and 7 resistant to multiple antibiotics. Resistance to streptomycin was also widespread in *E. coli* isolates and a number of isolates were resistant to at least three antibiotics.

There is very little published Australian information on antimicrobial resistance in *Campylobacter*. A study of 79 chicken isolates[7] found widespread resistance to erythromycin and significant resistance to doxycycline but no resistance to enrofloxacin. Similarly unpublished studies (R Pratt, WS Hart and MD Barton, personal communication) have found significant rates of resistance to erythromycin, tylosin, lincomycin, ampicillin and tetracycline (but no resistance to ciprofloxacin) in pig, pig carcass and pig meat isolates. A study of chickens[8] has reported significant resistance to ampicillin, ceftazidime and tetracycline in *C. jejuni* and *C. coli* isolates. No fluoroquinolone resistance was detected and there was relatively little resistance to erythromycin or tylosin. This study also noted differences in resistance patterns in isolates from different sources, reflecting differences in antibiotics used.

There are no published Australian reports of antibiotic resistance patterns in animal isolates of enterococci. A conference poster[9] reported isolation of one *van*A and one *van*B isolate from animals in the Hunter Valley. Pratt, Hart and Barton (unpublished data) did not detect any *van*A or *van*B *E. faecium* or *E. faecalis* in isolates from pigs, pig carcasses or pig meats. Virginiamycin resistance was found in *E. faecium* isolates, however, no resistance to ampicillin was detected. In the study of chickens mentioned previously[8] about 10 per cent of chicken carcass rinse samples contained *van*A positive enterococci. In keeping with overseas findings that *van*B vancomycin resistance is not associated with avoparcin use in animals, no *van*B resistance was detected in the isolates from chickens. Virginiamycin resistance was detected in *E. faecium* isolates in this study.

Staphylococcus aureus

Frost and Boyle[10] reported the results of testing the 1,657 bovine mastitis *S. aureus* isolates collected in the AHC survey mentioned previously. Sixty-two per cent of the isolates produced penicillinase and around 10 per cent were resistant to streptomycin. Resistance to other antibiotics was negligible and no isolates were resistant to methicillin.

A Tasmanian study of *S. aureus* isolates from bovine milk (Mark Broxton, unpublished results) found 49 per cent of 133 isolates collected in 1992-93 were resistant to penicillin, 11 per cent resistant to streptomycin and none resistant to methicillin. Similarly, Barton (unpublished data) found that of 144 *S. aureus* isolates from South Australian bovine milk samples collected in 1993-94, 54 per cent were resistant to penicillin, 9 per cent were resistant to streptomycin and none were resistant to methicillin.

Bacterial isolates from cats and dogs

Documentation of antimicrobial resistance in isolates from cats and dogs is very limited. A 1995 study[11] of staphylococcal isolates from dogs found that a very high proportion of *S. aureus* and *S. intermedius* isolates were ß-lactamase producers, but all isolates were sensitive cloxacillin/oxacillin. There was considerable resistance to trimethoprim, sulphamixazole and lincomycin. More recently, methicillin resistant *S.* intermedius have been isolated from infections in dogs (J Lucas, personal communication). A Queensland clinic[12] has recently reported isolation of multi-drug resistant *E. coli* with extended spectrum ß-lactamase activity and fluoroquinolone resistance from a nosocomial outbreak of infections in dogs.

Conclusion

Data on antimicrobial resistance in bacterial isolates from Australian animals is sparse but resistance patterns are not dissimilar from those reported from overseas countries and reflect the antibiotics which have been used for treatment. The situation relating to antibiotic resistance in aquaculture needs investigation. It is critical for Australian animal production that there is continued access to antibiotics for treatment and prevention of disease. Use of antibiotics must however, be in accordance with guidelines that minimise the risk of emergence or amplification of resistant bacteria.

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