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ANTIBIOTIC USE IN BEEF CATTLE

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The major use of antibiotics in beef cattle is associated with feedlot production. This type of intensive animal production with high health surveillance, large numbers of animals in a small area and pressure on stock personnel to minimise losses from disease encourages increased antibiotic usage. I have worked in the beef cattle industry for approximately 30 years and in the feedlot industry for 15 years. During that time I have observed antibiotics used in an indiscriminate fashion 30 years ago, with no regard for a withholding period (WHP), to a much more controlled and responsible usage in recent times. The use of drugs such as long-acting oxytetracycline and Penstrep® have ceased due to problems with WHPs especially in local trade cattle. Antibiotic use now is restricted to drugs with shorter WHPs and single dose treatments if possible

If as veterinarians we are concerned about animal welfare, it is essential that antibiotics for disease treatment and prevention are available.

Use of prophylactic antibiotics at the process stage in feedlots has been widely trialed and has been shown to be effective in decreasing morbidity and mortality, increasing weight gain and improving Feed Conversion Efficiency (FCE) of feeder cattle. In Australia the main products used are Micotil® (tilmicosin Elanco) and Terramycin® (oxytetracycline Pfizer). In trials at large feedlots with which I have been associated it is difficult to justify this practice unless the pull rate (disease morbidity) is over 2.0%. I have reservations about this practice for economic reasons and from a drug resistance point of view.

Antibiotics are used in feedlot cattle for a number of conditions.

PNEUMONIA - this is an important economic disease in feedlot cattle because of treatment cost (ie medicine & labour), morbidity time (weight loss prior to, and regain during, therapy), reduction in performance (irreparable tissue damage decreases efficiency throughout the remainder of the feeding period) and mortality.

The prophylactic use of injectable antibiotics at processing has been widely investigated in the USA and Australia. In the USA several of these products have been shown to be efficacious to improve animal performance through decreasing morbidity and mortality.

A majority of animals evaluated in these trials are young (200 - 250kg), recently weaned and highly stressed. In Australia we observe very few animals of this age or weight classification entering feedlots because it is much less expensive to grow cattle to 300 - 350kg on grass.

In large feedlots with which I have been associated we have evaluated use of several broad-spectrum antibiotics at processing. The results of these trials have failed to show an improvement in animal health or economic gain. Let us remember that we are feeding a slightly more mature and heavier animal than our counterpart in the USA.

When massive respiratory outbreaks do occur and the morbidity rate exceeds 20%, mass injectable antibiotic therapy has been implemented and observed to be efficacious. Again the primary antibiotics used in this scenario are tilmicosin and oxytetracycline.

The practice of feeding prophylactic antibiotics to suppress respiratory disease situations when initiating cattle onto feed is not wide spread in Australia because of lack of animal response. Sick animals rarely have adequate feed intake to obtain therapeutic antibiotic concentrations (minimum inhibitory concentration (MIC)) within the blood stream to suppress respiratory disease. Treatment of these animals is best accomplished with known therapeutic concentrations of an injected antibiotic. Feed antibiotics that may be of use in some situations if animal feed intake is maintained during therapy include oxytetracycline, tylosin and chlortetracycline.

BABESIOSIS - A protozoal disease transmitted by the cattle tick Boophilus microplus. The disease is characterised by fever and intravascular haemolysis creating anaemia, haemoglobinuria and haemoglobinaemia. When feed intake has been maintained an effective feed medication therapy of chlortetracycline can be implemented.

COCCIDIOSIS - Is an elusive parasitic disease because its influence on production is rarely observed as a visible illness (ie bloody diarrhoea with dehydration). Sub clinical losses may be dramatic through depressed feed efficiency, lower Average Daily Gain (ADG) and immune suppression.

Ionophores were developed and used extensively as coccidiostats in poultry production, with later extension into ruminants and progression to intensive ruminant feeding programs. The mode of action is through interrupting coccidia life cycle, requiring continuous feeding for a period of time.

The products with label claims to control coccidiosis in ruminants include: monensin (Rumensin®) and lasalocid (Bovatec®).

RUMINAL ACIDOSIS, BLOAT & LIVER ABCESSES

- Are associated with a disruption of the ruminal fermentation process (ie depressed rumination and/or saliva production = buffering capacity) when feeding high starch (grain) diets. This complex shift of ruminal bacteria species with related metabolites (ie increased D/L lactate & propionic acid production) is caused by inadequate rumen buffering capacity. Disruption of the rumen fermentation process depresses rumen pH, with consequent absorption of hydrogen ions into the blood stream. Lowered blood pH influences the total physiology of the animal. The severity varies with concentration and/or rate of acid production as well as animal ability to respond through saliva production.

Bloat is observed with altered rumen fermentation and suppression of digestive muscle contractions and eructation. A level of bloat is not uncommon when feeding animals high grain diets because of variation among the animal population fed.

Liver abscesses are a consequence of ruminal acidosis. The migration of *F_necrophorum* organisms occurs via rumen wall fissures (ie created through ruminal integument insult) into the blood supply with final deposition in the liver. The true incidence of liver abscesses caused by acidosis is low in Queensland (< 5%), with primary liver condemnation related to fluke migration. The antibiotic commonly used to suppress the severity of liver abscesses is tylosin (Tylan®).

These digestive diseases are not as frequently observed today with improved nutritional management factors such as:
maintaining minimum dietary fibre levels,
improved grain processing (ie large versus fine particle size),
recognised bunk management systems (eg established minimum quantities of feed/energy intake prior to increasing dietary energy level),
Further, ionophores/antibiotics have overcome many historical horror stories once encountered.

RUMEN METABOLIC MODIFIERS - IONPHORES AND NON IONOPHORES

Ionophores (polyether antibiotics) shift ratios or depress various populations of ruminal bacteria species altering metabolites (eg volatile fatty acids) produced and absorbed from the rumen. These compounds are bacteriostatic, not bacteriocidal. They produce the following changes in metabolites:
volatile fatty acids - suppression of acetate, butyrate and increase propionate,
decreased protein degradation and de-ammination of amino acids, improving nitrogen metabolism,
decreased lactic acid production, froth formation and methane production.

This metabolic shift lowers biochemical energy expenditure, increasing efficiency of nutrient metabolism for improved animal performance.

All ionophores are antibiotics, but not all antibiotics are ionophores! Approved rumen metabolic modifiers include:

IONOPHORE	EFFECT ON FEED INTAKE	EFFECT ON BACTERIA
Monensin (Rumensin®)	decrease meal size	G+, broad range
Salinomycin (Posistac®)	none	G+, broad range
Narasin (Naravin®)	none	G+, broad range
Lasalocid (Bovatec®)	none	G+, broad range

The following non-ionophore antibiotics are used to improve feed conversion, or against a specific organism or group of organisms.

NON IONOPHORES	EFFECT ON FEED INTAKE	EFFECT ON BACTERIA
Virginiamycin (Eskalin®)	none	G+, narrow range, *Strep bovis*
Tylosin (Tylan®)	none	G+, narrow range
Flavophospholipol (Flavomycin®)	none	G+, narrow range

The precise mechanism of action of antibiotics in improving growth and enhancing feed conversion is not fully understood. However, it has been long accepted that the primary response is through action on gut microflora. The general modes of action postulated for growth promotion by antibiotics are:

Metabolic effect - the antibiotic directly influences the rate or pattern of the metabolic process;
Nutrient sparing effect - the antibiotic alters bacterial populations resulting in conservation of nutrients;
Control of subclinical disease - the antibiotic suppresses bacteria causing clinical or subclinical infections;
Modification of ruminal fermentation - the antibiotic alters rumen microbial populations to improve fermentation efficiency.

Antibiotics (ionophores and non ionophores) enhance ruminant growth performance through many mechanisms. Ionophores act primarily by modifying ruminal fermentation to increase energetic efficiency

and nutrient flow to lower gut. Whereas the action of non-ionophores is exerted post-ruminally, with the exception of tylosin and virginiamycin.

These pharmaceutical compounds have resulted in decreased animal morbidity and mortality with the advent of intensive animal production.

ANTIMICROBIAL USAGE IN THE DAIRY INDUSTRY

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Current use of antimicrobials in the dairy industry.

Antimicrobials are used in treating the following conditions in dairy cattle:
intramammary infection
uterine infections
sequelae of calving, such as retained foetal membranes.
footrot and lameness
calf diseases such as diarrhoea
control of bloat and acidosis.
injuries

The family of antimicrobials presently in use in the dairy industry include:
beta-lactam drugs - penicillins, cloxacillins
cephalosporins
aminoglycosides
macrolides
tetracyclines
rumen modifiers - monensin, virginiamycin

(Reference: Victorian Dairy Industry Authority, November 1999)

Monitoring for antibiotic residues

At the Dairy Factory
The dairy industry has been proactive in addressing issues of antimicrobial contamination of milk products. Routine testing of all milk tankers upon arrival at the dairy factory has been practiced for many years. The prevalence of antibiotic violations on milk is usually less than 0.1% of all milk pick ups although some states can have much lower prevalences (for example NSW where is the prevalence is less than 0.01%)

Farms with antibiotic violations receive warnings or penalties depending upon the circumstances of the violation. For example the policies of one dairy factory state that if a farmer suspects that antibiotic from a treated cow may have entered the vat and the dairy factory is contacted before milk pick up, the farmer does not receive a financial penalty (normally equivalent to the income from the vat of milk). However, if mistakes continually occur on the same farm, the farmer is penalised despite warning the factory about contamination.

NARM
The National Antibacterial Residue Minimisation Program is a joint program between the cattle industry, State and Commonwealth Governments that focuses on the minimisation of antibacterial residue level in cattle by combining analytical, regulatory and extension processes. In the dairy industry, bobby calves, cull cows and suspect cattle (cattle showing visible signs of illness or recent drug treatment) are targeted by this program as they are considered high risk for violative antibiotic levels.

The following comments relate to the conduct of this program in NSW. During 1999/2000 46 of 78 bobby calves destined for export were found to have levels greater than half MRL (40 greater than MRL). The property of origin of these calves is visited by the Rural Land Protection Board veterinarian to investigate the source of the residue and to give advice on how to further avoid residues and why this practice is important. If there is a repeated incidence of residues above the MRL, a NSW Regulatory Officer investigates with the possibility of prosecution.

Reasons for violative residues included sending calves for slaughter within the withhold period for scour treatment (27 cases), inadequate calf identification, calves suckling antibiotic treated cows within the withhold period (6 cases) or gaining access to recently treated cases (3 cases); calves being fed milk stored in old Scourban containers (6 cases) and a farm management policy of routinely dosing newborn calves with oxytetracycline (7 cases).

(Reference: NSW Meat Chemical Residue Consultative Committee Meeting, May 2000)

TART
The Targeted Antibacterial Residue Testing Program was recently introduced by Australian Quarantine and Inspection Service in all export abattoirs. Kidney samples are collected from cattle suspected to have received antibiotic treatment by the attending AQIS veterinarian. Suspect animals targeted include cows with injection site granuloma, cows with blue dye in the udder, lame cows, fevered or sick animals and animals recovering from recent surgery.

(Reference: Sally Spence, Veterinary Officer, NSW Agriculture, Wollongbar, NSW)

On farm Quality Assurance Programs

In the last five years, the dairy industry has embraced the concept of on farm quality assurance or HACCP schemes (Hazard Analysis Critical Control Points). A national generic program Dairy First was developed with funding provided by major dairy processors in Victoria and the Dairy Research and Development Corporation to address all areas of possible microbial

and chemical contamination of milk and meat. The NSW Dairy Corporation (now a division of Safe Food Production NSW) developed a dairy HACCP program with initial cooperation from the Dairy Farmers Group that is currently being implemented in the majority of NSW dairy farms. All NSW dairy farms will be HACCP certified before July 2000.

The HACCP programs address all activities on a dairy farm where chemical and microbial contamination can occur. The identification of cows treated with antibiotics and the recording of treatment history and withholding period form part of the program.

Count Down Down Under

The responsible use of antibiotics in the treatment of intramammary infections form part of a national mastitis control program, Count Down Down Under. This program has been incorporated into most of the current HACCP programs.

Count Down Down Under program provides a detailed information package for farmers and farm advisers (CDDU Farmer Guidelines and CDDU Technotes). The program also includes a training framework for the training of advisers and farmers in the competencies required to deliver and to implement the program on farm.

The information and training packages cover all aspects of farm management that can influence the prevalence of mastitis on a farm. Improved prevention of mastitis infection by farmers and farm advisers can be achieved by a better understanding of the disease, the causative factors and the impact of different farm management procedures on its prevalence.

(Reference: Pauline Brightling, Project Leader, Count Down Down Under, Dairy Research & Development Corporation)

Lameness

Lameness in dairy cattle has a large economic impact with loss of milk production and cost of treatment. Footrot, white line disease and other foot infections usually have a strong management component that can influence the prevalence of disease. Recent initiatives by DairySA and Gippsdairy (two regional dairy programs) with funding input from Pharmacia -Upjohn have conducted programs examining the cause and control of foot problems in dairy cows.

The construction and management of laneways and how cattle are moved to and from the dairy shed impacts on the prevalence of disease. Management changes could reduce the prevalence of disease and reduce the need for antibiotic treatment.

(Reference: Rod Shaw, Pharmacia-Upjohn)

Nutritional additives

The nutritional requirements of the dairy cow changes throughout lactation as energy demands changes in response to level of milk production and pregnancy. In areas where milk production is required year round, the use of grain and supplements are needed to provide for nutritional shortfalls in pasture and forage. There can be an on-going risk of subclinical acidosis or 'feedlot bloat' which can affect the productivity of the cow and profitability of the enterprise. During drought conditions, where a shortage of forage occurs, the risk of grain poisoning increases.

Monensin and virginiamycin products both have a role in dairy cattle feeding where grain and supplements are given. Monensin has a further role in the prevention of true bloat especially in cattle grazed lucerne or clover pastures. In some dairying areas, monensin is an essential feed additive or bolus treatment because of the high incidence of bloating pastures. Alternative measures for control are either too labour intensive (drenches) or less reliable for ensuring whole herd application (water additives).

Both monensin and virginiamycin act on certain types of rumen bacteria. Milk composition can be marginally changed when these products are used.

To date, the use of these products in dairy cattle feeding has not resulted in detectable antimicrobial activity in the milk (as detected by Delvo SP or by milk functionality).

InCalf

A major National Program has recently been undertaken to identify the current limitation to reproductive performance in Australian Dairy herds. This program is raising the awareness of farmers and advisers to causes of poor reproductive performance in dairy herds. Management issues plays a large part in determining the reproductive health in a herd and the extension of the results from the original study of over 150 dairy herds throughout Australia should identify and improve the current practices in breeding management.

(Reference: John Morton, Project Coordinator - Department of Natural Resources & Environment, Victoria)

Recent research at the University of Sydney by Margaret Curtis (now at Elanco) and Professor Ian Lean have identified nutritional factors which can influence the incidence of post calving metritis in cows. Transitional feeding of the late pregnant cow can lead to lower post calving sequelae such as metabolic disease and calving difficulties These conditions can usually result in

sequelae requiring antimicrobial treatment (mastitis in downer cows and metritis following intrauterine trauma).

Conclusion

The Dairy Industry in Australia has taken a proactive approach towards the reduction of antimicrobial contamination in dairy products. The NSW Dairy Industry, in particular, has almost 100% certification of its herds under a Quality Assurance program specifically aimed at the minimisation of chemical and microbial risks in raw milk.

The national and regional dairy industry are involved in programs specifically aimed at management changes for the improvement of animal health rather than reliance on treatment. The Count Down Down Under program for mastitis control, the Lameness prevention programs in Victoria and South Australia and the recent In Calf program, that assessed the management programs required for improved dairy cattle reproduction, are current initiatives funded by the Australian Dairy Industry and industry sponsors for preventative health programs in dairy cattle.

Antibiotic Usage in the Australian Pig Industry

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The Australian Pig Industry uses a wide range of antibiotics (Table 1) to enhance health and welfare of the Australian Pig Herd.

TABLE 1

PRODUCT	USE	OFF LABEL
Tetracyclines	Feed / Water / Injection	YES
Sulfadimidines (Including potentiated)	Feed / Water / Injection	NO
Amoxycillin	Feed / Water / Injection	YES
Penicillin	Injection	YES (Occasionally)
Lincomycin	Feed / Water / Injection	NO
Tylosin	Feed / Water / Injection	YES
ceftiofur	Feed / Injection	YES
Neomycin	Feed / Water / Injection	NO
Apramycin	Feed / Water	NO
Lincomycin/ Spectinomycin	Feed / Water / Injection	YES
Olaquindox	Feed	YES
Virginiamycin	Feed	NO
Tilmicosin	Feed	YES

Compared to the rest of the world, Australian Pig Producers have limited access to alternate methods of disease control, in particular biologicals. Traditionally the industry has relied heavily on the availability of antibiotics. Key production limiting diseases for which antibiotic control has been of great value are respiratory disease complex, intestinal ileitis and colibacillosis. Growth promotion is a secondary consideration in the selection of antibiotics by Australian Pig Producers and Veterinarians.

Dealing with mixed bacterial infections and / or disease agents which are infective across age groups has resulted in a scatter gun approach to antibiotic use in the Australian Pig Industry. Minimum effective levels of antibiotics required to control clinical disease have traditionally been delivered through feed over extended periods. The inefficiencies of such regimes and potential danger in terms of antibacterial resistance have been recognised by the industry for some time and significant research and extension effort undertaken to facilitate change. The results have been encouraging. The introduction of Mycoplasma hyopneumoniae vaccines has improved herd health and reduced antibiotic use. As the industry restructures to take advantage of emerging export opportunities farrow to finish operations are being replaced with multisite age-segregated rearing facilities which reduce pathogen load and associated antibiotic usage. Advances in diagnostic serology allow major pathogens to be tracked through individual herds and antibiotic control targeted at the most appropriate times. This technology also assists successful implementation of disease eradication programs.

The pig industry, like any other industry or population, will never be antibiotic free nor should they be. Industry self regulation to ensure antibiotics are used in the most appropriate manner is however essential for long term sustainability.

Antibiotic resistance: what is happening now in pigs and poultry?

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Antibiotic resistance remains a key issue for all Australian livestock industries for three main reasons: reduced efficacy of treatment of stock, the risk of transfer of resistant bacteria or resistance genes to people through the food chain, and withdrawal of useful products because of human health concerns. The latter two concerns relate principally to enteric bacteria — E coli, salmonella, campylobacter and enterococci as these organisms (resistant as well as sensitive strains) can pass through the food chain from animals to people.

Antibiotic resistance in enteric isolates from pigs and poultry have been of greatest concern because antibiotic use is more common in these intensive farming systems. Resistance in E coli and salmonella has been recognised since the 1960s as these are pathogens in animals and antibiotic sensitivity tests are part of the routine testing in veterinary diagnostic laboratories. In addition, the potential for transfer of resistance from animal isolates of E coli and salmonella to human strains (as well as direct transfer of resistant strains through the food chain) was also recognised more than 40 years ago. For this reason there are numbers of surveys and case reports in the literature documenting increasing resistance in these organisms. As new antibiotics have been introduced, so resistant populations have emerged.

Enteric campylobacters and enterococci are not pathogens in animals so until resistance problems such as fluoroquinolone resistance in campylobacter and vancomycin/avoparcin resistance in enterococci were recognised, few studies were carried out on animal isolates of these organisms.

The PRDC has funded a project investigating resistance in enteric bacteria isolated from pigs. Resistance to tetracycline, aminoglycosides (streptomycin, apramycin, neomycin) and sulphonamides was widespread. Comparison of these results with an earlier Australian study (Craven, 1982 unpublished) indicates a significant increase in resistance to tetracyclines, streptomycin and also to ampicillin (see Table 1).

Comparison with UK and Danish results indicates that resistance is more common here (Table 1).

In our study no isolates resistant to fluoroquinolones were detected and only a few gentamicin resistant isolates were detected. One surprising finding was that 25% of the isolates were resistant to nitrofurantoin when this antibiotic was withdrawn from use some years ago.

In our study we obtained only 15 salmonella isolates from the 1,000 pigs sampled. Resistance to aminoglycosides, tetracycline and sulphonamides was close to 100%. Again, if these results are compared with an earlier Australian study (Murray et al 1986) and UK and Danish studies (see Table 2 on the next page) resistance is much more widespread in current Australian isolates.

Table 1: Antibiotic resistance in E coli isolated from pigs

Antibiotic	UK Wray et al 1993	Denmark Aarestrup et al 1998	Australia Craven 1982 (unpublished)	Australia — current study (957 isolates)
Tetracycline	58%	28%	72-82%	98%
Ampicillin	25%	10%	7-12%	30%
Streptomycin	47%	56%	49-66%	97%
Sulphonamides	60%	35%		75%

Table 2: Antibiotic resistance in Salmonella spp isolated from pigs

Antibiotic	Denmark – Aarestrup et al 1998	Australia – Murray et al 1986	Australia – current study (15 isolates)
Tetracycline	29%	17%	100%
Ampicillin	3%	9%	7(47)%
Streptomycin	22%	17%	93%
Sulphonamide		37%	93%
Fluoroquinolone		0	0

Multiple resistance (up to 5 classes) was common in both E coli and salmonella isolates in this study.

Resistance to erythromycin, clindamycin, tetracycline and ampicillin was common in campylobacter isolates (116). No resistance to fluoroquinolones was detected.

No vancomycin resistance was detected in 219 isolates of *Enterococcus faecium* from this study. Comparison of results from Denmark and this study confirmed that enterococci are generally resistant to a range of antibiotics (Table 3).

Table 3: Antibiotic resistance of Enterococcus faecium isolates from pigs

Antibiotic	Denmark – Aarestrup et al 1998	Australia – current study
streptomycin	37%	20%
apramycin	89%	100%
spectinomycin	22%	82%
Gentamicin	0	24%
tetracycline	70%	95%

In addition to vancomycin we also tested for resistance to other growth promotant antibiotics and found that resistance to virginiamycin and tylosin were very common but that resistance to bacitracin was very uncommon.

Results from some work we have been doing on chicken carcass rinse isolates are not yet available. DANMAP study results from Denmark have reported less extensive resistance to antibiotics in chicken isolates of E coli, salmonella and campylobacter and similar resistance levels for E faecium – reflecting the intrinsic resistance of this organism.

It is difficult to compare results between studies because different techniques have been used. It is clear that it is exposure to antibiotics that drives resistance so that if different antibiotic regimens are followed in different regions or countries, so different resistance patterns will be seen.

References:

Aarestrup FM, Bager F, Jensen JE, Madsen M, Meyling A & Wegener HC (1998b) Resistance to antimicrobial agents used for animal therapy in pathogenic-, zoonotic- and indicator bacteria isolated from different food animals in Denmark: a baseline study for the Danish Integrated Antimicrobial Resistance Monitoring Programme (DANMAP) APMIS 106, 745-770.

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Issues Concerning Antibiotic Resistance in Cage and Aviary Birds

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Abstract
A connection between antibiotic resistance in pet birds and humans has not yet been established but there are a number of aspects of bird keeping that could theoretically serve to increase antibiotic or bacterial load and prevalence of bacterial resistance. These factors are reviewed in light of the Joint Expert Technical Advisory Committee on Antibiotic Resistance report. Legislation forbidding extra-label usage of antibiotics would have a devastating effect on the ability of veterinarians to treat disease in birds and generic prudent use principles for antibiotics can be applied to avian practice to reduce what is perceived to be a minor risk of resistance spread. Research needs to be conducted to better assess the significance of pet birds in the spread of resistant bacteria before more specific advice regarding appropriate action can be given.

The worldwide use of antibiotics in animals has come under closer scrutiny in recent years because of the increasing ineffectiveness of antibiotics in human medicine due to the rapid emergence of antibiotic resistance. It is generally accepted that overuse or improper use of antibiotics in humans and inadequate infection control procedures are the main reason for this increasing ineffectiveness, but there is evidence that antibiotic use in animals has contributed to the process. The focus of this scrutiny has been on food producing animals and in Australia, in October 1999, the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) produced a comprehensive report: *The use of antibiotics in food producing animals: antibiotic resistant bacteria in animals and humans.*[1]

Antibiotics are used in cage and aviary birds therapeutically and prophylactically but they are not used as growth promotants and these species are not normally consumed by human beings. Consequently the risk of transfer of antibiotic resistance to human pathogens through these species has been perceived to be low. The significance, if any, of birds apart from poultry in the emergence of antibiotic resistance was not mentioned in the JETACAR report, nor did the literature review carried out by JETACAR identify a connection between the keeping of pet birds and the development of antibiotic resistance in human pathogens. However the committee's brief was to focus on food producing animals, not companion animals or wildlife.

While objective evidence of a connection between antibiotic resistance in humans and birdkeeping is lacking, in reviewing the JETACAR report from the perspective of a pet bird practitioner there would seem to be significant theoretical opportunities for antibiotic resistance to be transferred by close contact between humans and their domestic pet birds as well as by international movement of live birds for the pet trade. These comments also apply to other 'minor' species kept as pets, such as small mammals and reptiles, but their specific cases should be considered separately.

Another view on human-animal pathogen transfer
Before speculating on a possible, albeit minor, role of pet birds in the increasing ineffectiveness of antibiotics in human medicine I would like to nest the current debate on human-animal pathogen transfer and emerging antibiotic resistance into a broader historical context. There is strong circumstantial evidence that the major killers of humanity since biblical times - influenza, small pox, tuberculosis, malaria, plague, measles and cholera are all infectious diseases that evolved from close human contact with birds and animals even though human epidemic illnesses are now predominantly confined to people. In order for epidemic illnesses to be sustained, there must be non-resistant populations in which virulent pathogens can spread, so epidemic diseases, for example Measles (related to rinderpest of cattle), would die out in human population numbering fewer than half a million people. It is probably not co-incidence that most shared human-animal pathogens evolved on the huge Eurasian continent where animal domestication first emerged to support dense populations of both animals and people.

When Eurasian-evolved pathogens were spread by European colonisers, they killed vast numbers of indigenous people on islands and other continents. The reverse situation, where local human diseases killed the Europeans occurred but was far less common. The Aborigines had no fatal pathogens to share with the European invaders of Australia two centuries ago and, as was the case in just about every war until World War II, more victims died of war-borne microbes than of battle injuries. Reflecting a common pattern, European victory was due as much to their having the nastiest germs to transmit as it was to the effectiveness of weapons or the military strategy. Globally evolving human-animal pathogen interrelationships have long played a decisive role as shapers of history.[2]

[1] Commonwealth Dept of Aged Care & Dept of Agriculture, Fisheries and Forestry. Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) The use of antibiotics in food producing animals: antibiotic resistant bacteria in animals and humans. Oct 1999

[2] Diamond J (1998) Lethal Gift of Livestock. Chapter in Guns, Germs and Steel. Vintage. pp 195-214

Aspects of birdkeeping that might increase the risk of antibiotic resistance spread.

Birds make popular pets because, appropriately selected, they are beautiful, songful, form close bonds with humans and are generally easy to care for and inexpensive to keep. However, there are potential human health problems that may be associated with keeping birds, including psittacosis, allergic pneumonitis and viral, bacterial and fungal infections. While appreciating that the brief for JETACAR report was to focus on the current day interplay between food producing animals and antibiotic resistance in humans, issues apart from food consumption, for example proximity, relative numbers and susceptibility to infection of humans, birds and animals are all relevant in the evolution of human pathogens, including resistant bacteria. Thinking in this context, there are a number of aspects of birdkeeping that might serve to increase the risk of development or spread of antibiotic resistance factors or indeed other pathogens from birds to people.

Pet birds (budgerigars, pigeons, canaries, aviary birds)

- are often kept as large populations of multi-age flocks where immunosuppression and stress is common. Risk of transfer of resistance factors could be high.
- show clinical signs that are often subtle and non-specific. In such circumstances therapies may not be well targeted and inappropriate antibiotics may be selected.
- are often given drinking water medication. Because of erratic water consumption this mode of delivery may not achieve optimal drug dose rates for all birds.
- are often given antibiotics extra-label, so dosages and treatment times may not be optimal for a particular species. Experimental data is often not available.
- are popular pets for seniors, retirement villages, nursing homes and kindergartens, settings in which they may come into close contact with immunosuppressed people.
- With racing pigeons and at bird dealers stressed birds from many different sources are housed together giving an ideal opportunity to spread pathogens, including antibiotic resistant bacteria or resistance factors.

Birdkeepers

- are often untrained hobbyists and unaware of issues relating to antibiotic resistance. Management may be sub-optimal and open selling or inappropriately obtained antibiotics (eg tetracyclines) are widely and inexpertly used.
- may be elderly and/or immunosuppressed and hence more susceptible to contracting infections.
- may have low disposable incomes or be reluctant to spend money on veterinary care for their birds. Recommendations for specific diagnostics, including antibiotic sensitivity testing, are frequently declined.
- have difficulty in maintaining biosecurity. For example their birds may contact wild birds in outdoor aviaries or sick birds when taken to shows or races.
- frequently have very close contact with their birds as the birds sit on their shoulders, kiss their lips and share their food. Birdkeepers are also brought into close contact with droppings and aerosolled feather dust when cleaning bird enclosures.

Veterinarians

- have generally received limited training in avian medicine so clinical skills and therapies may not be as well targeted as in other species.
- may be perceived by bird owners as self serving rather than acting responsibly if they decline to supply antibiotics except within the requirements of the law and based on prudent use principles for antibiotics. This is particularly so when the value of individual pet birds, and the disposable income of their owners, are both low.

Research

- funds available are far lower for pet birds than for commercial poultry. The need to monitor antibiotic resistance patterns has not been considered a priority.

Resistance patterns in pet bird isolates

In spite of the above concerns, bacterial isolates with multiple resistance patterns are not commonly encountered in companion bird practice in Australia and most pet bird isolates will be sensitive to at least one of the commonly used antibiotics (eg amoxycillin and clavulanic acid, enrofloxacin, lincomycin and spectinomycin). Multi-resistant isolates are commonly reported in literature relating to avian practice overseas, although a connection between resistant bird strains and resistant human strains has not yet been established.

A disconcerting pattern of multi-resistant bacteria was encountered in isolates from budgerigars legally imported through the Spotswood Quarantine Station and seen at Highbury Veterinary Clinic in the mid 1990s. This pattern is perhaps not surprising considering the overseas source of the budgerigars and the procedures to which they were submitted during importation: drinking water treatment with doxycycline, housing in a multi-age/multi-source flock and major stress factors operating during the importation process.

Following their introduction into local aviaries, multiple resistance was not only seen in the imported birds but also in bacterial isolates from birds coming into contact with them. Circumstantially it appeared that mixing birds in the quarantine station may have allowed overseas strains of bacteria to spread resistance factors. There is currently a moratorium on legal importation of

Psittaciformes and this multi-resistant pattern has not been recognised in recent times. Psittacine importation is currently under review.

Relevance of pet birds in emerging antibiotic resistance.
The four key factors that influence the emergence and spread of antibiotic resistance were identified in the JETACAR report as antibiotic load, antibiotic regimen, bacterial load and prevalence of bacterial resistance. Clearly these are all issues with birdkeeping even though pet birds are not consumed as food. The report developed an antibiotic-resistance management program to address these factors contained 22 recommendations grouped into seven categories: Regulatory Controls, Monitoring and Surveillance, Infection Control and Hygiene Measures, Education, Further Research, Communication and Co-ordination of Resistance Management.

Reducing risk of antibiotic resistance is important for the sake of both human and avian patients and many of the initiatives being taken in the food producing industries are recognised as relevant in pet bird practice. However there are significant difficulties in applying these principles in avicultural communities for both social and scientific reasons. With little direct evidence of spread of antibiotic resistance from birds to humans, establishing whether this connection currently exists and continuing to monitor for possible emergence should receive priority. It is readily possible to demonstrate that tetracyclines, which have been widely available over the counter, are far less effective against bacteria encountered in avian practice than S4 antibiotics such as amoxycillin with clavulanic acid, but a human connection is not clear cut. Arguing the case for tighter controls on antibiotics in the avicultural community would be better received if objective evidence of both increased resistance of specifically avian pathogens as well as a bird-human antibiotic resistance connection could be demonstrated.

Benefits of allowing off-label antibiotic use in birds and other 'minor' species
Veterinary practice for avian and exotic pets would be severely compromised if antibiotics were restricted to solely registered uses. Indeed, many of our patients would die or suffer from otherwise treatable diseases if legislation were to forbid off-label use.

It is generally not in the financial interests of drug companies to carry out necessary testing to register their products for minor species because the amount of drug used is often small. Individual species may vary in their response, so testing on a single avian species cannot be confidently extrapolated to all birds, the testing needs to be repeated for each species. While it is not economic for drug companies to conduct trials, an expanding database is accumulating of trials and clinical data conducted by veterinarians working with minor species so that reasonable information on which to base treatment is now available and continues to expand. The overall community benefits of permitting extra-label usage in minor species would seem to far outweigh the potential risk of resistance transfer. However, the situation needs to be carefully monitored and action taken where appropriate to minimise potential risk.

Regulatory Controls
There is scope for tightening regulatory controls on antibiotics used in pet bird medicine. Veterinary Boards currently appear to have difficulty in controlling the activity of several veterinarians who provide dubious diagnosis of avian disease based on faecal samples sent through the mail, then based on this tenuous connection supply antibiotics by post to pigeon fanciers and birdkeepers throughout Australia. Antibiotics are also sold informally thorough bird clubs. The audit trail proposed in Recommendation 3 of the JETACAR report and the proposal to classify all antibiotics as S4 (Recommendation 6) and the harmonising of regulations throughout Australia (Recommendations 7 and 8) could be useful in curtailing these practices.

Monitoring and Surveillance
Monitoring sensitivity patterns of pet bird isolates should be possible by reviewing submissions to commercial veterinary laboratories. Studies could also be done starting from humans infected with multi-resistant bacteria and trying to trace back whether there might be any pet bird connection. Establishing whether this connection currently exists or might be evolving should receive high priority.

Infection Control and Hygiene Measures
Biosecurity, hygiene, vaccination, eradication, husbandry and medication are adjuncts and alternatives to antibiotics that have formed cornerstones of preventative health programs in poultry.[3] The closed aviary concept and biosecurity principles are also taught and advocated by non-poultry avian veterinarians, including geographical isolation, quarantine, control on the movement of people, separation from wild birds and animals, rodent control and secure dead bird disposal. In practice these principles are difficult for many birdkeepers to grasp and implement and they are conscientiously observed by only a minority of aviculturists. There would be scope for wider adaptation if the importance of minimising antibiotic treatment could be clearly demonstrated. Implementation for racing pigeons, dealers and show stock would remain problematic. Hygiene, disinfection and sanitation procedures are generally easier to teach and apply.

[3] Grimes T (2000) Preventative management programs for maintaining health adjuncts to antibiotics. Dander May 2000, pp 8-12

While Australian vaccine manufacturers are willing to develop new vaccines for poultry, the economics are less sustainable for the diversity of species and limited markets that characterise pet bird practice. Eradication is a desirable goal but often elusive. There is scope to adopt husbandry practices that reduce stress and optimise bird immunity. There are medical alternatives to antibiotics including probiotics, prebiotics, organic acids, enzymes, immunomodulators and herbal therapies whose use could perhaps be expanded to enable a reduction in antibiotic use. Given the difficulty in altering current practices, objective data demonstrating the actual occurrence of emerging antibiotic resistance would be important in convincing bird keepers of the need for change and the justification for additional inconvenience and expense involved.

Education

Recommendation 17 of the JETACAR report was that learned professional societies develop continuing education programs on the issue of antibiotic resistance, including a focus on the prudent use principles, antibiotic use guidelines and alternatives to antibiotic usage.

The relevance of the JETACAR report to avian practice is to be discussed in a session planned for the Association of Avian Veterinarians conference later this year . Once there is consensus amongst avian veterinarians regarding recommendations, strategies to educate other veterinarians and birdkeepers about the need to exercise care in the use of antibiotics in birds can be devised. In devising these strategies, it would be useful if comments by avian veterinary practitioners could be backed by authorities that are not perceived to have a conflict of interest in subverting easy access to antibiotics by aviculturists. Involvement in the discussion of a JETACAR representative (or its successor) could be useful in this regard.

Further Research

Highest priority needs to be placed on monitoring avian and human bacterial isolates to determine whether a possible connection between antibiotic resistance in pet birds and in humans exists. This should attract funding ear marked for human health. Other recommendations for research related to antibiotic resistance, eg molecular epidemiology, population dynamics of antibiotic resistance, pharmacoepidemiology, efficacy studies and, particularly, rapid diagnostic tests are relevant to good veterinary medical practice generally and should be supported.

Control of Antimicrobial Resistance in Small Animal Hospitals

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Overview

Investigations into the development of antimicrobial resistance in the veterinary field have been concentrated on production animals due to the widespread use of these drugs in agriculture and the well-recognised transfer of resistant bacteria from animals to humans in food. However, the current trend in companion animal practice towards the management of chronic diseases involving periods of intensive care, often of immuno-compromised individuals, demands a review of antimicrobial practices in small animal hospitals.

What evidence is there for antimicrobial resistance in small animals?

In comparison with the body of literature relating to antimicrobial resistance in human medicine and production animals, there are few comprehensive reports investigating the situation in companion animals. The development of serious antibiotic resistance by *Staphylococcus aureus* in humans has raised concerns that a similar situation might occur in companion animals. In particular, interest has been focussed on veterinary dermatological infections due to their recurrent nature. Repeated exposure to antibiotic courses (reviewed by Schwarz & Noble, 1999) and transmission of resistance between staphylococci has been reported. In contrast with *S. aureus* in humans, cutaneous staphylococcal infections in dogs are usually caused by *S. intermedius*. A high level of resistance by *S. intermedius* to penicillin and oxytetracycline was detected in one study, but despite the widespread usage of first generation cephalosporins, amoxicillin-clavulanate and enrofloxacin to treat this common infection in dogs, the pattern of resistance to these drugs did not change between 1980-1996 (Lloyd, Lamport & Feeney, 1996).

In two recent papers Normand *et al.* (2000a, 2000b) retrospectively examined the trends in antimicrobial resistance of bacterial isolates in a small animal hospital (in Glasgow, UK) and from companion animal practices in the UK. These authors found statistically significant rising trends in the resistance of *E. coli* to amoxycillin, amoxicillin-clavulanate and streptomycin in the hospital population from 1989–1997, and to amoxicillin-clavulanate and streptomycin in the community practice population over the same time. There was a rising trend in the resistance of *Staphylococcus* to erythromycin in the hospital population, but declining trends in this organism's resistance to ampicillin and penicillin in the community practices (Normand *et al*. 2000a, 2000b). Further, in defining multiple drug resistance (MDR) as an organism that was found to be resistant to four or more antimicrobials to which sensitivity may normally be expected (Bulger & Sherris, 1968), these authors also reported a rising trend in MDR of *E. coli*, *Proteus Spp* and *Pseudomonas Spp.* between 1989-1997 (Normand *et al*. 2000b).

The close association between companion animals and humans raises the question of whether pets are a potential source of dissemination of antimicrobial resistance or simply act as a sentinel population. In a survey of the prevalence of transferable drug resistance elements in enteric bacteria isolated from humans and domestic pets in Canberra, Davies & Stewart (1978) demonstrated that the resistance plasmids in the two populations were similar.

The Small Animal Hospital environment

Selection pressures towards antimicrobial resistance in human medicine are greatest in hospitals and the situation might be expected to be similar in veterinary hospitals, especially those that operate intensive care facilities and treat a high number of oncology cases. Pet dogs and cats in these facilities may reasonably be expected to remain hospitalised for longer periods, be naturally immunocompromised, or be immunosuppressed as an integral component of their treatment. In particularly critical patients, bacteria from the alimentary tract or nosocomial organisms may be involved, often with resistance patterns that require more expensive and potentially toxic drugs for effective therapy (Boothe, 1999).

Nevertheless, comparisons with human medicine should be made with care since the shorter natural lifespan of pets, the absence of long-term residential care and the option of euthanasia for cases that would require long term intensive treatment may all reduce selection pressures in veterinary hospitals (Normand *et al*. 2000a).

What precautions should be taken to reduce resistance selection?

Strategies to reduce the intensity of antimicrobial use and selection pressures towards resistance in veterinary hospitals should include the confirmation of the existence of bacterial infection prior to antimicrobial prescription, selection of appropriate antibiotics based on identification of the organism and sensitivity testing, and continual surveillance to detect multiple drug resistance (MDR) and inappropriate antimicrobial practices (Boothe, 1999). The indiscriminate usage of antimicrobials should be avoided, and whenever possible the presence of bacteria confirmed by

cytological evaluation of aspirates and other samples collected from the site of infection. Routine swabbing of endotracheal tubes, indwelling intravenous and urinary catheters on removal has been advocated in veterinary intensive care units, but the results should be interpreted with care, and the difference between colonisation and infection should be considered (Papich, 1999).

Basing drug selection on bacterial culture and sensitivity testing is probably the best method for reducing the risk of resistance developing, but in practice antibiotic therapy is usually started before the results of such testing is known. Empirical antibiotic therapy should anticipate the organism(s) involved, and Gram staining of specimens is often helpful in this regard.

Ensuring that adequate drug concentrations are present at the site of infection is a key component of reducing the development of bacterial resistance, so proper attention should be paid to dose rate, route and frequency of the antibiotic. The necessity of prophylactic antibiotics (perioperatively for example) should be questioned on every occasion and this practice should not be substituted for proper surgical technique. Prophylactic antibiotics, when used, should be administered immediately before the surgical procedure and not any sooner (Papich, 1998). The antimicrobial should target the most likely pathogenic organism and the duration of therapy should be as short as possible. Generally a single dose is given intravenously so that the peak tissue drug concentration coincides with the time of bacterial exposure.

Urinary and gastrointestinal infections are a common sequel of cancer chemotherapy in small animal practice and these immunosuppressed patients require particular attention. In general, prophylactic antibiosis is not routinely employed, white cell counts are carefully monitored and antibiotics prescribed only when severe leucopoenia develops. Only bactericidal drugs should be used in these patients, as their impaired host defences mechanisms would encourage resistance if bacteriostatic drugs were to be prescribed.

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Sweden and the European Union: what is happening in relation to antibiotics in feed?

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The debate concerning antibacterial growth promoters (AGPs) and development of resistance in bacteria is long standing in most countries. In Europe, the recommendations in the report of the Swann committee in the late 60s led to the withdrawal of several substances from the list of authorised AGPs because of a decision to restrict certain antibiotics to therapeutic use (eg penicillin, streptomycin and tetracyclines).
In Sweden, the intensive debate from the 60s never ceased and it was always intertwined with environmental and animal welfare concerns. At the beginning of the 80s, a broad discussion on the use of antibiotics and practices in animal production prompted the Swedish Farmers Union (LRF) to write to the Government and ask for a ban on growth promoting antibiotics. From 1986, antibiotics for animals have been available on prescription only and use is restricted to preventive or therapeutic uses (ie use for growth promotion was no longer authorised).
On a European level, findings of associations between vancomycin resistant enterococci (VRE) in animals and the use of the feed additive avoparcin (1, 2) in the early 90s led to an intensified scientific debate on the possible impacts of antibiotic use in animals on human health. Meanwhile, consumers are getting more and more sensitive to quality aspects of food. As was the case in Sweden, not only safety but also ethical aspects relating to the systems by which food is produced have been highlighted.
In the following, the experiences in Sweden from long-term non-use of antibiotics for growth promotion and some of the recent developments in the European Community are described.

The Swedish experience - what did we learn?
The changes in 1986 had little or no impact on dairy, beef, calves, sheep or layers as these production sectors never or hardly used AGPs. More affected were the chicken and swine industries.

Effects on animal health
Chickens
Before 1986, almost all chicken feed contained both an antibacterial feed additive and a coccidiostat. The chicken producers identified the occurrence of clinical or subclinical necrotic enteritis (caused by *Clostridium perfringens*) as the main problem to tackle subsequent to the ban. It was agreed that a transition period would be necessary. Veterinarians would prescribe virginiamycin as prophylaxis during this period. Field experience and more formal research confirmed that the construction and climate of sheds, hygiene, management and feed composition all contributed to the disease. Further, it was found that coccidiostats of the ionophore type also prevent necrotic enteritis (4).
By 1988 all prophylactic medications had been abandoned. Strong emphasis was placed on improving the animal environment, measures that could be foreseen to prevent other diseases as well. A special bonus was given for good animal management and care, which also led to improvements in the total quality level of production. The most important changes related to feed involved a reduction of protein content, a higher fibre content and supplementation with enzymes. Ionophores are used as coccidiostats for conventionally reared chickens. Goals for the future include replacement of coccidiostats with other preventive strategies such as vaccines.

Pigs
Before 1986, practically all piglets were given AGPs (olaquindox or carbadox), from weaning until delivery to the finishing units at the age of 10-12 weeks. Slaughter pigs were, to a lesser extent, given avoparcin or virginiamycin until slaughter.
The most notable problems arose in weaner pigs. A retrospective study of production averages from 220 piglet-producing herds from the years 1985 and 1986 indicated that post-weaning mortality was about 1.5 percentage units higher the year after the ban and an increased time from birth to 25kg weight(9).
Since the ban of AGPs numerous measures have been, and are continuously, undertaken to optimise rearing and production systems and to employ available techniques (eg sectioning of buildings, age segregation, planned production). The ban also stimulated a development towards new rearing systems. Today, around 40% of piglet production in Sweden uses age-segregated systems. Systems where pigs are reared in the same pen from birth to slaughter have also been introduced. The most prominent changes in feed composition have been a lowering of the protein content, use of water-soluble fibres and supplementing amino acids (6).
In 1992, zinc oxide was approved for incorporation into piglet feed at 2000 ppm of zinc as an aid to prevent weaning diarrhoea. Zinc oxide is presently licensed for sale as a pharmaceutical subject to veterinary prescription. Clearly, the use of zinc oxide is not desirable for environmental reasons. A strategy including education and prescription-only policies for phasing-out the use of zinc has therefore been agreed and successfully implemented. In 1998, the sale of zinc oxide medicated feed had reduced to around 12% of the maximum sales figures in 1995.
Taken together, the changes have greatly improved production results. Still, in 1996 post weaning mortality was slightly higher (0.5 percentage unit) than before the ban (14).
The ban of AGPs did not create obvious clinical problems for growing or finishing pigs. The production

results from this sector are comparable to those from, for example, Danish pig production.

What happened with the consumption of antibacterials?

The use of antibiotics at dosages used for growth promotion also prevents disease. In evaluating the effects of the ban, it is therefore of interest to study the effects on the usage of antibiotics for therapy. The total use of antibacterials for use in animals has been studied in detail (for a review see 10). The statistics are based on sales figures from Apoteket AB (the National Corporation of Swedish Pharmacies) and show the total amount of antibacterials sold by pharmacies or delivered by feed mills during the specified time period. Thus, the figures include antibacterials for all animal species (food animals, fish, pets and horses).

Overall data from 1980-1999

In Table 1, data on sales statistics for antibacterials from 1980-1999 are presented. A marked decrease in total sales can be noted. However, as the substances in question are not equal in their biological activity per weight unit, total figures might be misleading (ie if a substance requiring high dosages for full efficacy is replaced by a more active substance, a false impression of a reduction could be given). Therefore, each substance group should be assessed separately for trends.

Relevant groups of antibiotics

Of special interest in relation to AGPs is the consumption of antibacterials intended for group or flock medication. In Sweden, these are the tetracyclines, macrolides, quinoxalines, streptogramins, pleuromutilins and nitroimidazoles. The penicillins, trimethoprim-sulfonamides, aminoglycosides and fluoroquinolones are mainly or only used for medication of individual animals.

After the ban, a decrease in use of tetracyclines was noted. However, between 1988 and 1993, an increase was again noted. It was found that the increase could almost entirely be explained by the prescriptions of one veterinarian to one herd. The veterinarian was reported and the cause corrected. The total tetracycline consumption is now less than a quarter of that before 1986.

The observed increase over time of macrolides, and that of the pleuromutilins introduced in 1988, is believed to reflect an increase in the incidence of swine dysentery (the major indication for these drugs). Estimates based on these sales figures indicate that today, around 10% of the slaughter pigs are treated for swine dysentery.

Table 1. Total quantity of antibacterial substances (kg active substance) for treatment of animals based on sales statistics from Apoteket AB (National Corporation of Pharmacies) (from 21 and for 1999; Odensvik, in press)

Substance group[1]	**Year**					
	1980	*1984*	*1988*	*1992*	*1996*	*1999*
Tetracyclines	**9819**	**12955**	**4691**	**8023**	**2698**	**2251**
Chloramphenicol	47	49	35			
G-and V penicillins[2]	3222	4786	7143	7446	8818	8692
Aminopenicillins	60	714	655	837	835	809
Other betalactam antibiotics	9	2				245
Aminoglycosides	5274	5608	3194	2139	1164	846
Sulphonamides	6600	4325	3072	2362	2198	2403
Trimethoprim and derivatives	134	186	250	284	339	397
Macrolides and lincosamides	**603**	**887**	**1205**	**1710**	**1649**	**1467**
Fluoroquinolones				147	173	155
Pleuromutilins (eg tiamulin)			**124**	**268**	**1142**	**847**
Other substances[3]	**861**	**1637**	**1567**	**1634**		
Quinoxalines	**6250**	**9900**	**7164**	**4917**	**1098**	
Streptogramins		**8800**	**1088**	**1275**	**525**	**125**
Antibacterial growth promoters	**8380**	**700**				
Total	*41259*	*50549*	*30189*	*31043*	*20639*	*18237*

[1] Substance groups given in bold characters are mainly used for groups or flock medication (ie feed or water)

[2] Calculated to equivalents of benzyl penicillin.

[3] Mainly nitroimidazoles

The major quinoxaline, olaquindox, was exclusively used in pigs. In 1988, the use of olaquindox as a veterinary medicine for prevention of weaning diarrhoea had increased to levels approaching those reported pre-ban. However, as the dosage used was three times higher than before, fewer animals were exposed. After this, use decreased gradually and since July 1997 olaquindox is no longer available in Sweden. As mentioned, zinc oxide has been used as prophylaxis for weaning diarrhoea during the 90s . This practice is now being phased out and the consumption has recently declined to 12% of its maximum amount.

Did the changes affect resistance?

Unfortunately, there are no systematic studies on resistance in bacteria of animal origin from Sweden that are relevant for the AGP discussion from the time before withdrawal of growth promoting antibiotics. Proper monitoring for resistance has only been conducted for salmonellae. The results from that programme show that since 1978, resistance in salmonellae has decreased and today, the situation is very favourable compared to most European countries. However, this can hardly be taken as a direct effect of the ban since few antibiotics active against salmonellae (and thus with potential to select for such resistance) were used as AGPs

For lack of historical data, observations on effects rely on comparisons with other countries. A comparison of the prevalence of resistance in faecal indicator bacteria (*E coli* and enterococci) of pigs in Netherlands and Sweden has been published (13). The data show significantly lower prevalences of resistance to AGPs, but also to therapeutics, in Swedish samples. For VRE, the authors report 39% positive samples from the Netherlands and none from Sweden. The finding of a very low prevalence of VRE in Swedish animals is also supported by other investigations (5, 8). Interestingly, and also in contrast to what is reported from EU countries, Torell and co-workers (12) failed to find carriers of vanA-type VRE in non-hospitalised residents of in Sweden. A plausible explanation for the absence of community carriers in Sweden is that the prevalence of VRE in food is comparatively low due to non-use of avoparcin in local animal production facilities.

Effects on production and economy

Parameters relating to pig production such as farrowing interval, litter size at farrowing and weaning and number of pigs weaned per sow per year, remained largely unaltered by the ban or have gradually improved. The number of pigs weaned per sow averaged 18.7 in 1985 and 20.1 in 1998. The average daily gain in finishers (25-110kg) was 850g per day and feed efficiency 2.85 in 1997. The gross output in percent of the total income was not affected negatively (1984, 7%; 1986, 8% and 1999, 13%) (3).

The combined effect of the removal of growth promoting antibiotics in 1986 and the tough animal welfare laws (eg more space required) from 1988 has been analysed through a comparison with Danish production results. The cost was estimated to be 1.50 Swedish crowns (approx. $A 0.30) per kg pork produced, half of which was due to non-use of antibiotics (11).

The EU perspective - what is going on?

Some background on Community legislation in the area of AGPs (feed additives)

The legislative framework and substances authorised as feed additives may vary substantially between countries. In the EU antibacterial feed additives for performance enhancing purposes (ie AGPs) are regulated separately from veterinary medicines (including medicated feed).

In article 3 of the basic directive regulating the area (Council Directive 70/524/EEC as amended in 96/51/EC) important conditions that must be fulfilled for authorisation are listed. Among other things, the article specifies that i) an authorisation may be given only if the substance does not adversely affect human or animal health or the environment, ii) there should be no serious reasons concerning human or animal health to restrict the use to medical or veterinary purposes and iii) at the level permitted they should not have therapeutic of prophylactic effects. Only substances authorised by the Commission may be used, and authorisations apply in all member states.

If, "*as the result of new information or a reassessment of existing information, a Member State has specific grounds for establishing that the use of one of the authorised additives (or its use in specified conditions) constitutes a danger to animal or human health or the environment, the Member State may temporarily suspend or restrict the application*" (so called "safe-guard clause", Article 11 of Council Directive 70/524/EEC). The Commission examines the grounds, delivers its opinion and takes appropriate measures. The antibacterials that were authorised in EU for use as performance enhances in different animals in 1996 are listed in Table 2.

Table 2. Antibacterials authorised for performance enhancement in 1996 in the European Community (dir 70/524/EEC, Annex I) and their status in May 2000

Class	Substance(s) in 70/524/EEC	Examples of other substances in the class[1]	Date of entry into force of legislative changes
Glycopeptides	Avoparcin	**Vancomycin**	Suspended April 1997
Ionophores	Monensin salinomycin	Other ionophores	
Macrolides	**Tylosin** **spiramycin**	**Erythromycin**	Suspended July 1999
Orthosomycins	Avilamycin	Evernimycin	
Phospho-glycolipids	Flavomycin (syn: bambermycin)		
Polypeptides	**Bacitracin**		Suspended July 1999
Quinoxalines	**Olaquindox** **carbadox**		Suspended September 1999
Streptogramins	**Virginiamycin**	**Quinupristin-dalfopristin**	Suspended July 1999

[1] Substances with therapeutic use in human and/or veterinary medicine are in bold characters.

Some safeguards and applications for amendments relating to antibacterial resistance

Following the accession negotiations with the European Union, Sweden and Finland were granted derogations from community legislation to maintain national legislation in the area until the end of 1998. Finland and Sweden later applied for adaptation of Community legislation and Sweden asked for an EU-wide ban on all use of antibiotics for growth promotion. The claims were that antibiotics should be reserved for use as veterinary and human medicines in order not to compromise further use through increased prevalence of resistance. The applications were accompanied by reports detailing the grounds for this position (7,10). Prior to this, in 1995, Denmark decided to apply the safeguard clause on avoparcin on the ground that VRE, or the *van*A-gene, could transfer to humans or human enterococci.

Parallel activities and reports

During the late 90s, a series of reports and opinions on the medical impact on the use of antimicrobials in food animals have been issued from the EU; the Economic and Social Committee (ECOSOC; 1998), the Copenhagen recommendations (1998) the report of the Scientific Steering Committee (1999). All these pointed in the same direction; the use AGPs that could select for cross-resistance to antibiotics used for therapy should be stopped. Pressure groups such as the Federation of Veterinarians of Europe, Eurocoop and the Consumers Organisation BEUC also voiced concerns and asked for restrictions.

The decisions 1998

The grounds for Danish, Finnish and Swedish applications for adjustments were evaluated by the Commission, by all the member states and, to some extent, by the scientific committee on animal nutrition. By the end of 1998, as a precautionary measure in order to protect human health by preventing an increase of the reservoir of resistance genes through use of substances known to give rise to cross-resistance to drugs used in human medicine, the Commission proposed a suspension of bacitracin, tylosin, spiramycin and virginiamycin. This decision is presently challenged in the European Court of Justice by two of the companies concerned.

What next?

The current debate about the possible impacts of use of antibiotics for growth promotion in agriculture on human health has initiated many research projects within the Union and elsewhere. The need for systems for monitoring of antibacterial resistance and statistics relating to exposure, ie the amounts of antibiotics used and the way they are used, has been highlighted. Presently, these areas are under discussion in several groups in Europe aiming at harmonisation of methodology and at setting minimum standards for all Member States. Discussions on prudent use of antibacterials are being held and recommendations on therapeutic and prophylactic use have been issued by the Federation of Veterinarians of Europe.

The report of the Scientific Steering Committee of the Commission (May 1999) presented numerous recommendations, most with implications for human medicine. The need for a multi-disciplinary approach was emphasised. In relation to AGPs, it was recommended not to use antibiotics that are used for therapy or can give rise to cross-resistance to such

drugs. Further, the importance of implementing disease preventive methods was emphasised. This direction would eventually lead to the phasing-out of *all* routine use of antibacterials.

From the above, it is clear that the debate and the activities in the European Union are not limited to the field of growth promoting antibacterials. All areas of importance are being scrutinised and broad action is being called for. The view that unnecessary use of antibacterials should be removed and the remaining use optimised is becoming predominant among experts and policy makers. According to the Swedish experience, it is possible to reach good results in animal production without AGPs. Today, as well as Sweden, Denmark, Finland, Norway and Switzerland have moved away from such uses. The Netherlands intends to phase out all AGPs within a couple of years. Similar initiatives are also taken on a producer basis. Taken together, the events indicate that the EU is moving towards a system where antibacterials are used only for medical or veterinary purposes and only on prescription and that further strategies for countering antibacterial resistance will be discussed and implemented.

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Medical Uses and Abuses of Antibiotics

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Contributions to Antibiotic Burden
– The Medical Perspective –

- ♥ **Human treatment and prophylaxis**
- × **Veterinary treatment and prophylaxis**
- × **Animal growth promotion**
- × **Agriculture**
- × **Horticulture**
- × **Aquaculture**
- × **Apiculture**
- × **Food production and preservation**

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The medical perspective is such that antibiotics are most important to human medicine and all other uses are subordinate

How much do we use in Australians?

- **Types of data**
  - » Antibiotic import data
  - » Prescription volumes
  - » Defined daily doses
- **Sources of data**
  - » PBS
  - » Pharmacy Guild survey
  - » IMS (commercial)

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Australian import volumes for antibiotics 1992-97
yearly averages

- **Human**
  - » 251,465 kg (36.4%)
- **Stockfeed**
  - » 384,917 kg (55.8%)
- **Veterinary**
  - » 53,750 kg (7.8%)

From JETACAR,

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'Top Ten' Imports 1992-97 yearly average
Human From JETACAR, 1999

Agent	Class	Volume (Tonnes)
Amoxycillin	Penicillins	74.5
Erythromycin	Macrolides	44.3
Penicillin V	Penicillins	14.5
Cephalexin	Cephalosporins	14.4
Flucloxacillin	Penicillins	13.6
K⁺ Clavulanate	ß-lactamase inhibitors	10.4
Sulfamethoxazole	Sulfonamides	8.7
Tetracycline	Tetracyclines	5.7
Metronidazole	Nitroimidazoles	5.6
Doxycycline	Tetracyclines	5.3

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'Top Ten' Imports 1992-97 yearly average
Stockfeed From JETACAR, 1999

Agent	Class	Volume (Tonnes)	X-Resistance to Human agents?
Monensin	Polyethers	77.1	No
Oxytetracycline	Tetracyclines	53.3	Yes
Bacitracin	Polypeptides	45.0	(Yes)
Salinomycin	Polyethers	35.3	No
Lasalocid	Polyethers	27.2	No
Virginiamycin	Streptogramin	23.2	Yes
Chlortetracycline	Tetracyclines	18.7	Yes
Narasin	Polyethers	17.6	No
Tylosin	Macrolides	13.1	Yes
Sulphamethazine	Sulphonamides	12.2	Yes
Avoparcin	Glycopeptides	10.0	Yes

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'Top Ten' Imports 1992-97 yearly average
Veterinary From JETACAR, 1999

Agent	Class	Volume (Tonnes)	X-Resistance to Human agents?
Penicillin G	Penicillins	11.5	Yes
Monensin	Polyethers	8.9	No
Oxytetracycline	Tetracyclines	4.9	Yes
Amoxycillin	Penicillins	4.3	Yes
Dihydrostreptomycin	Aminoglycosides	3.7	Yes
Sulfamethazine	Sulfonamides	3.7	Yes
Sulfadiazine	Sulfonamides	3.1	Yes
Cloxacillin	Penicillins	2.5	Yes
Dimetridazole	Nitroimidazoles	1.9	Yes
Neomycin	Aminoglycosides	1.5	Yes

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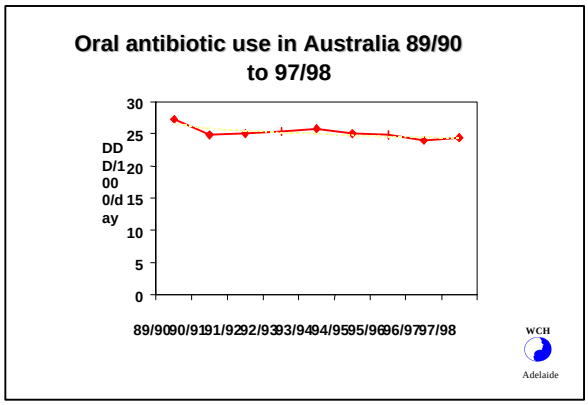
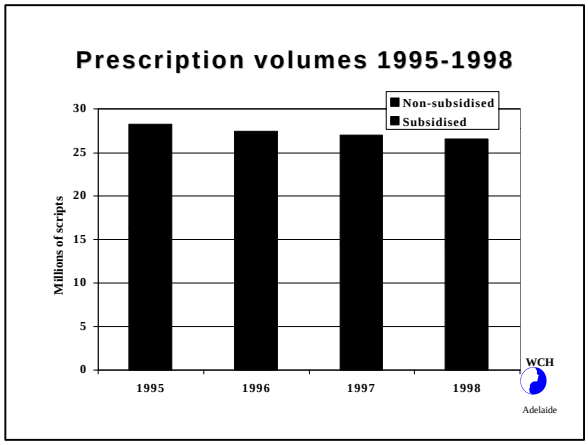
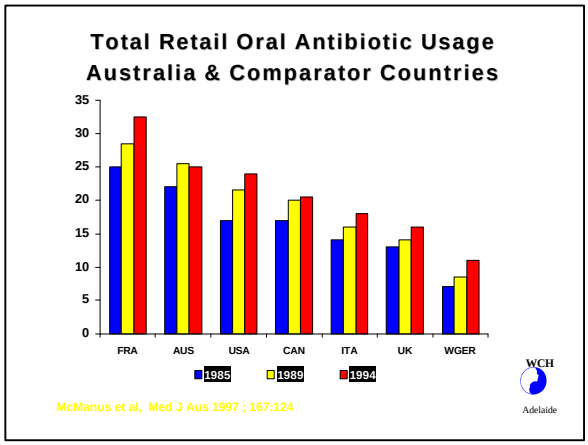


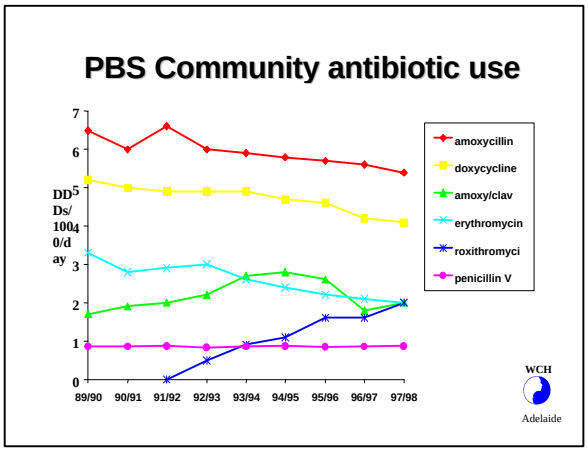
Changes in total oral antibiotic use in humans from financial year 1989-90 to 1997-8 in defined daily doses per 1000 people per year.
Note the slow decline and flattening out in recent years.



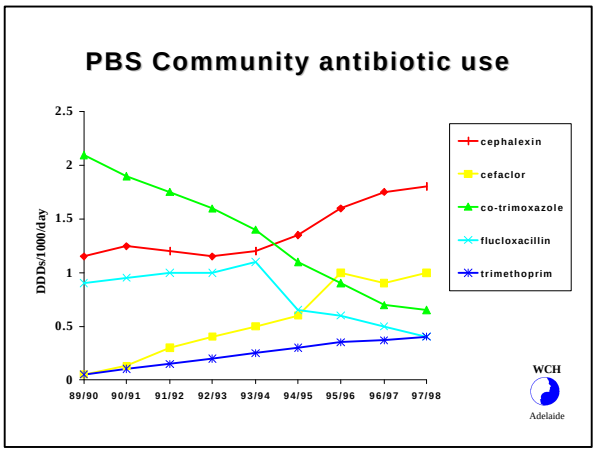
Change in prescription volumes over the last 4 years
Note that there are more prescriptions written per annum than the population of the country.



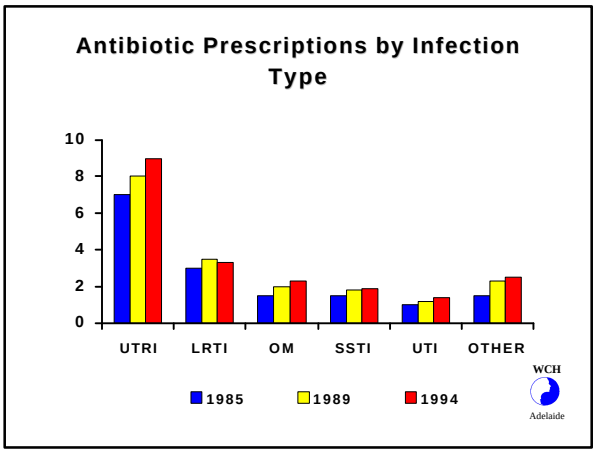
Comparative figures of per capita antibiotic use in Australia and 6 other similar countries. Australia is ahead of the USA but behind that of France. It is the only country that did not increase its per capita use between 1989 and 1994.



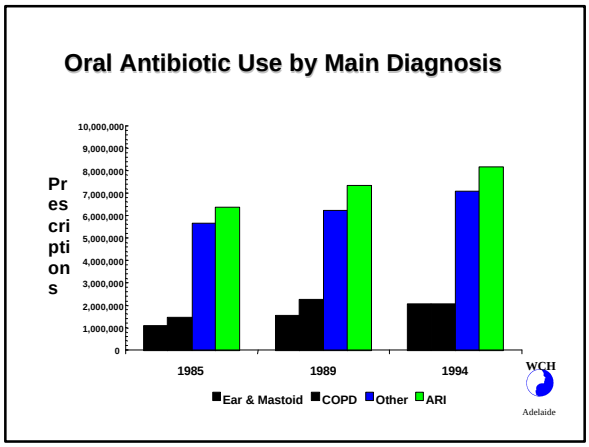
Total per capita use hides a lot of data. These graphs show trends in different antibiotics over a decade. There has been a gradual decline in amoxycillin and doxycycline and a significant rise in the use of the macrolide roxithromycin since it came onto the market in 1992.



This graph shows even more dramatic changes in individual agents over the last decade.



Most antibiotic prescriptions (~75%) are for respiratory tract infection.



Most respiratory tract prescriptions are written for acute undifferentiated respiratory tract infection (almost always viral).

GP prescribing for RTI - before and after intervention

Rogers & Light, 1998

Diagnosis	Frequency	% Antibiotic		
		Before	After	Ideal
Undifferentiated URTI	44.4	14	4	0
Acute bronchitis	16.5	89	64	0
Acute sore throat *	10.8	83	58	10
Acute sinusitis *	8.2	88	71	10
Influenza	6.6	16	0	0
Acute otitis media *	5.1	79	59	50
Chronic bronchitis *	2.1	67	64	50
Pneumonia *	2.1	72	93	90
Otitis media with effusion	1.2	60	21	0
Croup	0.5	20	0	0
Bronchiolitis	0.5	0	0	0
Pertussis *	0.3	100	67	100

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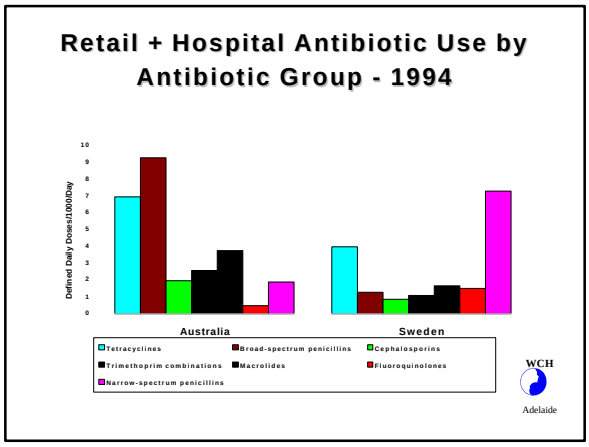
* antibiotics of benefit in some cases

Results of an intervention study involving patient and doctor education simultaneously. It shows the most common presentations with respiratory infections in general practice. A maximum of 30% of patients could be justified on current grounds to be given an antibiotic.



Australia's pattern of antibiotic use is vastly different from that in Sweden, when narrow-spectrum agents are standard.

Main issues in community use

- **High consumer expectation**
  - » poor understanding of difference between bacterial and viral infection – ∴ antibiotics for ALL infections
  - » family pressure
  - » relationship to important events
- **High doctor expectation**
  - » frequent assumption that antibiotics are needed
  - » fear of loss of custom and trust
  - » simplicity of prescribing vs not prescribing

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Main issues in hospital prescribing

- **High outcome expectation**
  - » Broader is 'better'
  - » More is 'better'
  - » Longer is 'better'
- **Strong dependence on antibiotics for both medical and surgical purposes**
  - » therapeutic
  - » prophylactic

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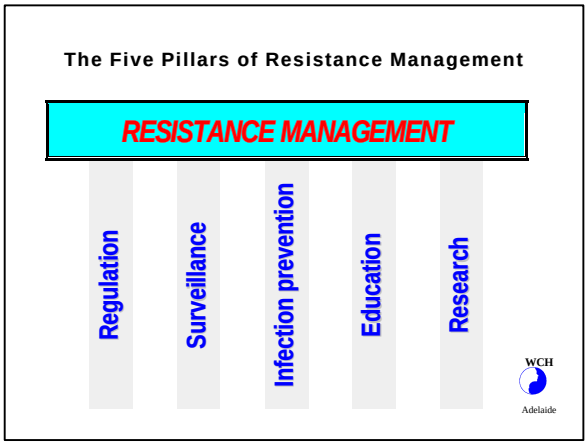

As proposed by the JETACAR report.

Regulation - national

- **Drug evaluation**
  - » microbial resistance safety
  - » resistance data in product information (PI, CPI)
- **Control of access**
  - » e.g. PBS (a two-edged sword)
  - » other restrictions
  - » OTC usage
- **Intervention**
  - » thresholds for action

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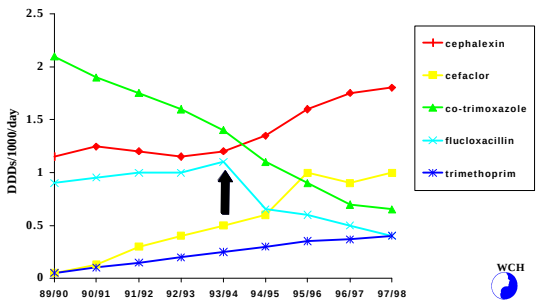
Importance of regulation in controlling antibiotic use in Australia. The Pharmaceutical Benefits Scheme is the most important, but is a two-edged sword as there is great ability to restrict important classes (eg quinolones), but very free access for the common agents.

PBS Community antibiotic use



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Interventions on the PBS can have wanted and unwanted effects: safety warnings about flucloxacillin resulted in a drop in prescribing, but a compensatory rise in the use of cephalexin which is a broader spectrum agent.

Regulation - local

- **Hospital restriction policies**
  - » "It is no longer reasonable the all clinicians should have free access to all antibiotics"
  - » Unrestricted vs Restricted vs Excluded
  - » Problem of "squeezing the balloon"
    - applying inward pressure at one place causes it to bulge outward in a different place
  - » Clinical prescribing standards
    - agreed protocols for each unit, with monitoring or auditing and feedback about deviations from protocol

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Hospitals have a long tradition in Australia of trying to control antibiotic access and use – the value of this has never been formally measured – but experience tells that that uncontrolled access results in the inappropriate use of expensive broad spectrum agents.

Surveillance

- **National monitoring program (passive)**
  - » NARSP (✞)
  - » The Surveillance Network
    - www.thetsn.com
- **Direct programs at problem pathogens (active)**
  - » Australian Group on Antimicrobial Resistance
    - www.ozemail.com.au/~agar/index.html
- **Antibiotic usage surveillance**
  - » Australian Statistics on Medicines
    - www.health.gov.au/haf/docs/asm.htm

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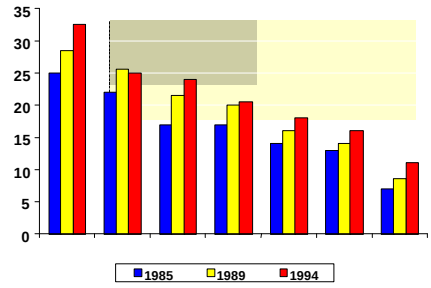
Surveillance in resistance in human medicine in Australia has been established in Australia for many years. A passive computer based system is being installed at the moment. Targeted surveillance is an important adjunct.

Total Retail Oral Antibiotic Usage Australia & Comparator Countries



McManus et al, Med J Aus 1997 ; 167:124

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We need to continue to monitor antibiotic volumes and prescription numbers to show whether our interventions. We believe that a reasonable target is UK or Germany per capita use.

Infection prevention

- **Promotion of current**
  - » Hib
- **Development of better vaccine**
  - » Pneumococcal conjugate
  - » Meningococcal conjugate
- **Infection**
  - » greater efforts in hospitals and community

Preventing infections by vaccines or infection control practices for instance is a vital component of reducing the need for antibiotics in the first place.

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Education

- **Target groups**
  - » Medical profession
  - » Medical students
  - » Allied health professions
  - » Public
  - » High school students
  - » Pharmaceutical industry
- **Risk communication**
  - » Active interchange between stakeholders

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Educations has been a minor component until recently, but is probably the most important tool for the long term. EVERYBODY must be educated.

National efforts so far

- **Quality Use of Medicines program**
  - » www.qum.health.gov.au
- **National Prescribing Service**
  - » www.nps.org.au
- **National Medicines Week 1998**

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Prudent use principles (1)

General

- Antibiotics should only be used where the benefits are scientifically demonstrable and substantial.
- In general, the spectrum of the antibiotic used should be the narrowest to cover the known or likely pathogen.
- Single agents should be used unless it has been proved that combination therapy is required to ensure efficacy or reduce the selection of clinically-significant resistance.
- The dosage should be high enough to ensure efficacy and minimise the risk of resistance selection, and low enough to minimise risk of dose-related toxicity.

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The widespread adoption of prudent use principles is an essential element of education.

Prudent use principles (2)

Therapy

- Choice of therapy should be based on either:
  (i) culture and susceptibility test results (directed therapy),
  or
  (ii) known common pathogens in the condition and their current resistance patterns (empirical therapy).
- Duration should be as short as possible, and should not exceed 7 days unless there is proof that this duration is inadequate.

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Prudent use principles (3)

Prophylactic

- Choice should be based on known or likely target pathogen(s).
- Duration should be as short as possible. Single dose prophylaxis is recommended for surgical prophylaxis. Long-term prophylaxis in human and veterinary medicine should only be administered when it has been demonstrated that the benefits outweigh the risk of resistance selection or propagation.

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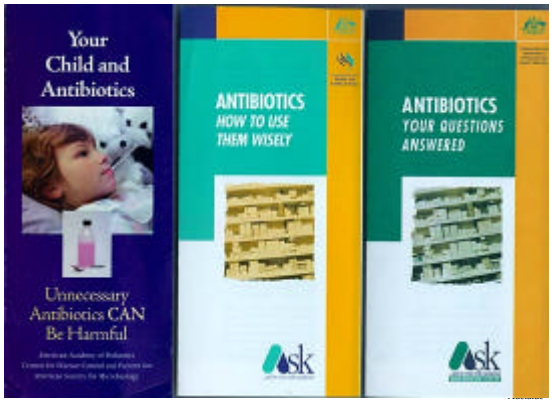

US efforts at controlling the over-prescribing of antibiotics to children by providing information in the doctors' surgeries.

Education

- **Promote ownership of problem by learned and professional societies**
  - » Postgraduate training and directed programs
    - Prudent use principles
    - Antibiotic guidelines
    - Alternatives to antibiotics
- **RACGP, RACP, RCPA, RACS, ASM, University Medical Schools**

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Professional societies must take an active role by impressing on their members their professional responsibilities.

The 'Antibiotic Guidelines' have been a major reference point for prescribing in Australia since the mid-1970s. It is not clear what level of impact they have had, but will continue to act as the 'standard'.

Public education

- **Vital component**
  - » Educate public about inappropriate expectations
  - » Teach basic infection ideas (bacterium versus virus)
  - » Teach high school students about infection
  - » Provide written material at time of consultation
  - » Send out the GREEN message about antibiotics

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We must educate our consumers to expect fewer antibiotics and to be happier to leave the surgery WITHOUT a prescription than with one.

The future standard of care

- **Inappropriate prescription of antibiotics is**
  - » unprofessional
  - » profligate
  - » unsafe
    - puts both the patient & institution in 'danger'

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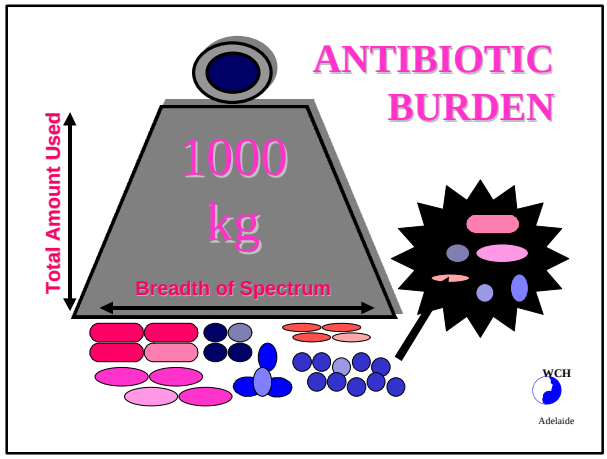
The future professional standard – prescribers must in the end accept that they have a professional responsibility and cannot continue to blame consumer demand.



We all contribute to the antibiotic burden – the amount and breadth of spectrum of antibiotic use that generated the selective and amplification pressure for resistance.

Antimicrobial drug use and resistance in companion animals: what's the problem?

J F Prescott[1], B Hanna[2], R. Reid-Smith[3,4]

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Introduction

The crisis of antimicrobial drug resistance in human medicine has brought every aspect of use of drugs in animals into question. While there is considerable, though often fragmented, data on antimicrobial drug resistance in bacteria of food animal origin[1,2] and increasing, but also fragmented, data on quantities of antimicrobial drug use in food animals, there is little useful data on antimicrobial drug use and resistance in companion animals. Is resistance a problem in companion animals (dogs and cats)?

Intuitively, the problem of antimicrobial resistance in companion animals should be far less severe than in human medicine, because animals are less likely to be exposed to antimicrobial drugs for other than short, sporadic periods, because they are not commonly hospitalized, not kept in old dog's homes, because chronically infected animals are frequently euthanized, because immunocompromised animals are not usually treated with very broad spectrum and potent antimicrobial drugs, and for other reasons.

By contrast to the situation in food animal medicine, the topic of the effect of antimicrobial drug use in companion animals on the acquisition of their resistant bacteria by people, or the acquisition by human pathogens of resistance genes derived from resistant bacteria coming from companion animals, has not been explored in any significant way. Are owners at risk when their companion animals are treated with antimicrobial drugs?

This discussion focuses on antimicrobial drug use and resistance in dogs and cats and addresses the following questions: 1. Is antimicrobial drug resistance in companion animals increasing? Is it a problem? 2. Has there been a change over time in the identity of bacteria isolated from infections in animals, because of antibiotic resistance? 3. What is "prudent use" of antimicrobial drugs in companion animals? Are there any specific guidelines for companion animals other than the generic guidelines promulgated by national veterinary organizations? 4. Are owners at risk when their companion animals are treated with antimicrobial drugs? 5. Who is the enemy? To what extent can resistance problems occurring in bacteria isolated from companion animals be attributed to medical or agricultural use of antimicrobial drugs? 6. Based on these analyses, what recommendations can be made for the future?

Excellent overviews of aspects of this topic are available elsewhere[3,4].

1. Is antimicrobial drug resistance in companion animals increasing? Is it a problem?

It is hard to get a reliable global view of this. Despite a possible wealth of data moldering in filing cabinets in veterinary clinical microbiology laboratories around the world, there has been virtually no systematic investigations of changes in antimicrobial drug resistance in bacteria isolated from companion animals over time using standard methodologies for assessing resistance. There are only a few notable exceptions to this devastating criticism[5-7]. It should also be recognized that reports of resistance coming from diagnostic laboratories may be "worst case" scenarios since they often represent treatment failures rather than treatment successes, which don't reach the laboratory. Antimicrobial drug-treated animals will more likely yield resistant bacteria than untreated animals[8-10]. In addition, variation in resistance patterns between multiple isolates of coagulase-positive staphylococci from the same dog suggests that single swab samples or the usual recommendation to perform susceptibility tests on a limited number of colonies may be of limited value in optimally determining susceptibility patterns[7,11].

There are considerable differences internationally in criteria used for susceptibility testing. In a survey of veterinary clinical microbiology labs around the world done in preparing this paper, these ranged from "all tests are done without standardization on discs and are scored by eye by the same team for 10 years", to the Australian "calibrated dichotomous sensitivity test", to the use of the Veterinary Antimicrobial Susceptibility Test criteria of the United States-based National Committee for Clinical Laboratory Standards, which unfortunately limits itself to US-specific veterinary- or farmer-licenced antimicrobial drugs, mostly for food animals. Apart from differences in susceptibility test methods and interpretive criteria between laboratories, laboratories may change procedures over time, not analyze their data, change computer software which stores data, lose computerized records, so that even the best run clinical microbiology laboratories may have problems with the universality, the reliability and the availability of the data.

The sometimes marked annual variation in reported levels of resistance to antimicrobial drugs is often the result of small sample size from varying populations and may also reflect changing fashions in use of antimicrobial drugs[2-4]. The picture is therefore far more complex than the conclusion based on one study of resistance in canine *Staphylococcus intermedius* that "resistance to commonly used antibiotics appear to have increased dramatically over the last decade"[12]. Because of variation due to small sample size, what is needed is the study of trends over time. For example, in a

retrospective study done in preparation for this Conference, we have noted at Ontario Veterinary College (OVC) a long-term, fifteen year trend for decline in resistance of *S. intermedius* to penicillin G as well as to trimethoprim-sulfonamides, which mirrors a documented declining usage of these drugs at OVC. By contrast, the trend for clindamycin and erythromycin resistance in *S. intermedius* has been to remain stable, which corresponds to maintained usage of clindamycin over time, while enrofloxacin resistance in *S. intermedius* has shown a dramatic increase in resistance, in line with the increasing usage of this drug at OVC in recent years.

Despite the need to be aware of the importance of variation that small sample size or other sampling variables have on apparent prevalence of resistance, some trends are very apparent in the short term. For example, there has been a dramatic increase in resistance of companion animal bacteria to fluoroquinolones[13,14], associated with the rapid introduction of these drugs into companion animal practice. In a recent US study, only 75% of *E. coli* from infections in dogs in 1998 were susceptible to enrofloxacin compared to >95% more than 6 years earlier at the same institution[5,14]. Our own figures for *S. intermedius* resistance have risen from 0% to 12% in eight years.

The congruence of resistance with drug use patterns is an important concept, although the relation is not direct. Resistance is not inevitable. For example, *Streptococcus canis* and *Pasteurella multocida* have remained highly susceptible to antimicrobial drugs over the last 50 years, and we don't know why. Such a debilitating lack of adaptability in these bacteria is not the case for *Escherichia coli* and many other bacteria, whose greater ability to evolve may be reflected not only in the emergence of resistance but perhaps also of virulence. The continued selection pressure of antimicrobial drugs will maintain resistant bacteria in populations. In the absence of such selection pressure, resistance will tend to decline[15]. There is a physiological cost to bacteria to maintain unused resistance genes. For example, Naidoo and Lloyd (1983) showed the rapid rate with which *S. intermedius* lost resistance plasmids in the laboratory[16]. However, the genetic ecology of antimicrobial resistance is highly complex[17]. The physiological cost of possessing resistance genes can be overcome, for example by down-regulating their expression in the absence of antimicrobial drug exposure, by clustering resistance genes on multiple-resistance plasmids, or arranging them as gene cassettes in the order in which they are needed on integrons, which themselves are maintained within plasmids or transposons[18,19].

Although in general it appears that widespread antimicrobial drug use has led to the on-going development and extraordinary refinement of mechanisms for spreading resistance, since bacteria are superb molecular biologists, resistant bacteria isolated from companion animals are conspicuous by their absence as key organisms which have been studied to understand resistance gene organization. In other words, no sufficiently dramatic resistance event has attracted anyone's attention but there are few workers in this field. For example, it seems unlikely that methicillin resistance in *S. aureus* of canine origin (or in *S. intermedius*) is as uncommon as published reports indicate[20,21].

2. Has there been a change over time in the identity of bacteria isolated from infections in animals, because of antibiotic resistance?

If antibiotic resistance is a problem in companion animal practice, then one might expect to observe a change in the identity of bacteria in different infections over time. There are hints that this has happened. For example, a study of the prevalence and susceptibility of obligate anaerobes isolated from a variety of companion animals including dogs and cats associated developing resistance with changes in the prevalence of different anaerobic species over time, although it was acknowledged that changing techniques might have influenced this observation[22]. This trend appears to have continued[23].

There has been a rise in the incidence of enterococci in urinary tract infections (UTIs) in catheterized or hospitalized human patients in recent years, associated with the natural resistance of these bacteria to commonly used antimicrobial drugs. At the OVC, we have only been identifying enterococci generically in the last three or so years; before this they were described as non-hemolytic or as alpha-hemolytic streptococci. Enterococci are naturally resistant to clindamycin (as well as to penicillin G and cephalothin, giving them an antibiotic-resistance fingerprint). We retrospectively examined isolates from canine UTIs at OVC over the last 15 years, classifying all clindamycin-resistant "streptococci" as enterococci. Assuming this is a correct classification, we note a marked increase in the proportion of enterococcal UTIs over the last 15 years (from 6 to 14%). By contrast, *E. coli* and streptococci (including *S. canis*) have remained a stable proportion of UTIs, *Pseudomonas aeruginosa* and *Enterobacter* spp. (both inherently resistant bacterial species) have increased slightly, while *Klebsiella* spp., *Proteus/Morganella* spp. and coagulase-positive *Staphylococcus* spp., have declined as a proportion of the causes of canine UTI. Our tentative conclusion is that we are seeing more enterococcal UTIs in dogs and that this reflects the inherent resistance of this organism to common antibiotics, and so would be expected to emerge among the type of canine patient seen in the OVC Veterinary Teaching Hospital. This is consistent with what has happened in secondary and tertiary care human hospitals[24,25]. More studies of the changing patterns of bacterial infections in companion animals are required, with less assumptions about bacterial identities.

Nosocomial infections with multi-resistant bacteria such as *Acinetobacter baumannii*[26], *Enterobacter* spp[27],

Klebsiella sp[28], and *Salmonella enterica* serovars[29,30], have been recognized in hospitalized dogs, particularly in intensive care units, for many years. Such infections are probably under-recognized and are certainly under-reported. The relatively ready availability of modern, simple, DNA-based fingerprinting systems such as RAPD should make it much easier to more fully document such occurrences in the future.

3. What is "prudent use" of antimicrobial drugs in companion animals? Are there any specific guidelines for companion animals other than the generic guidelines promulgated by national veterinary organizations

All the English-speaking national veterinary associations, including the Australian Veterinary Association, have produced prudent or judicious antimicrobial drug use general guidelines in the last two years.

The essence of prudent use is to ensure that antimicrobial drugs are only used where necessary, for as short a time as possible consistent with clinical efficacy, with optimal dosage and administration, using the narrowest spectrum antimicrobial, guided where possible by laboratory findings, by people who know what they are doing (ie veterinarians), in a manner that does not cause toxicity to the treated animal, and which minimizes the development and spread of resistance and resistant bacteria.

The effort to capture these elements in guidelines has been considerable. In addition to these generic national association guidelines (available on national association web sites), individual species groups have developed or are developing species specific guidelines. For example, the American Animal Hospital Association are developing guidelines under the auspices of the American Veterinary Medical Association Steering Committee on the Judicious Use of Antimicrobials. The British Small Animal Veterinary Association has infection specific guidelines in their Manual on Infectious Diseases (2000), but the British Veterinary Association's companion animal prudent guidelines are very general.

Should some antimicrobial drugs (eg amikacin, imipenem and vancomycin) which are essential in human medicine for the treatment of multi-resistant bacteria or of serious, mixed bacterial infections in tertiary care institutions be unavailable to veterinarians? In a survey of North American Veterinary Teaching Hospitals carried out in preparing for this Conference, only 3 of 21 which replied described having any policy for the "top shelf" drugs, amikacin, imipenem and vancomycin. Several others said they did not use these drugs, or only used them very exceptionally, or had a quality control system based on "rounds" which effectively controlled their use. Others commented that veterinarians didn't like restrictions on their rights to prescribe. The rumours of use of imipenem to treat cat-bite abscesses may be just be hospital rumours, but international agreement about the circumstances under which top-shelf drugs should be used would be helpful. We need to recognize that use of any broad-spectrum antimicrobial drug to treat a bacterial infection affects all the microbes in the body, not just the target organism. More than any other antimicrobial, highly potent and broad-spectrum drugs are like nuclear weapons in their devastating effects on bacteria.

Will prudent use guidelines affect how veterinarians prescribe antimicrobial drugs, which drugs they prescribe, and will their use reduce resistance? How will we know?

Perhaps with the exception of some Scandinavian countries, we won't know. We don't have data on quantities of antimicrobial drug use in companion animal practice and there are no baselines of resistance data against which to judge any effects. We will have to go on faith that highlighted concerns about resistance will make veterinarians think twice before prescribing antimicrobial drugs, will therefore reduce their prescribing of antimicrobial drugs, and that this will reduce resistance.

4. Are owners at risk when companion animals are treated with antimicrobial drugs?

This is an area that has received little if any systematic attention, so the answer must be a mix of "We don't know; possibly; and, of course". Bacteria in animals are often and in some cases markedly adapted to their hosts. There is however evidence, for example, that *S. intermedius* can transfer from dogs to humans[31,32] and somewhat anecdotal evidence that methicillin-resistant *Staphylococcus aureus* (MRSA) has been transferred indirectly from a dog to a patient in an intensive care unit[33]. Clearly, however, this is a two-way street, since MRSA spread from people may have been responsible for an outbreak of MRSA in horses in a veterinary teaching hospital[34] and evidence that cats become colonized by human origin *S. aureus*[35].

The potential for spread of multi-resistant *Salmonella enterica* serovars from companion animals to people as a result of antimicrobial use in infected animals enhancing shedding, though not well documented, must always be recognized[29,36].

5. Who is the enemy? Can resistance problems in companion animals be blamed on medicine or agriculture?

The widespread use of avoparcin as a growth promoter in food animals in Europe resulted in the selection of vancomycin-resistance in their fecal enterococci, which subsequently entered the food chain or in other ways reached people in Europe[1,2]. Dogs and cats in Europe were also infected. Vancomycin-resistant enterococci were isolated from the feces of 48% of 23 dogs and 16% of 24 cats in The Netherlands[37] and from a smaller proportion of dogs and cats in Belgium[38]. This illustrates the apparent spread of resistant bacteria from

food to companion animals. If vancomycin was used in companion animals it could provide the selection pressure for the emergence of vancomycin resistance in other organisms, since the resistance genes are transposable. Recently, in Canada, *Salmonella* reached dogs from infected pig ear "treats", with subsequent infection of dog owners; among the *Salmonella* subsequently isolated from pig ears was a multi-resistant *S.* Typhimurium DT 104[39] .

The resolution to the problems of antimicrobial resistance will not be from finger pointing and blaming others. All who use antimicrobials must accept responsibility for their prudent use, and accept that resistance will always go hand-in-hand with use, even though the story is more complex than this.

6. What recommendations can be made for the future?

Antimicrobial resistant bacteria will always be with us. The resistance crisis in medicine has shown how resistance can emerge in community-acquired infections in a remarkably short time. It is clear that scientific data on the development of drug resistance in companion animal bacteria barely exists, with some few notable exceptions. We have also really no data on the quantities and type of antimicrobial drug use in companion animal practice, and no reliable data on many of the topics raised in this discussion[40].

We need to continue the on-going process of improving and fine-tuning prudent use guidelines in companion animal practice. For example, the Angell Memorial Animal Hospital has three categories of antimicrobial drug use: 1. First choice in the absence or pending culture and susceptibility results (eg amoxicillin with or without clavulanic acid; first generation cephalosporins; trimethoprim-sulphamethazine; tetracyclines); 2. Antimicrobials which can only be used when justified by culture and susceptibility results (eg amikacin, 2nd and 3rd generation cephalosporins, fluoroquinolones, lincosamides, oxacillin); 3. Last resort antimicrobials (vancomycin, imipenem-cilastasin)[41]. It could be extremely helpful to get international agreement among veterinarians on a similar, simple but effective, approach to prudent companion animal drug use.

We need active and effective infection control programs in veterinary hospitals to minimize spread of resistant organisms (or their resistance genes) from patients, especially those treated with broad-spectrum and potent antimicrobials. The science of veterinary hospital infection control is hardly born yet but the increasing numbers of neutropenic or immunosuppressed dogs and cats being treated in veterinary medicine means that we are going to have to embrace this topic not just with enthusiasm but also systematically and with resources.

Veterinary clinical microbiology is also ripe for development as a science rather than an art. As a matter of urgency, veterinary clinical microbiologists around the world should get together to agree on standards for monitoring and reporting resistance in companion animal bacteria, perhaps as part of broader national resistance monitoring of bacteria of food animal origin. This data needs to be coupled with antimicrobial use data. We all need to understand the limitations of the data available and work to improve it.

Companion animal veterinarians need to be prudent, rational, responsible and judicious in their antimicrobial drug use. They also need to recruit owners into partnership in this issue. We need better figures than the recently reported 44% of owners who fully complied with short-term oral antibacterial drug use instructions, perhaps by spending more time over the consultation[42].

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LIFE AFTER JETACAR – REGISTRATION OF VETERINARY ANTIBIOTICS IN AUSTRALIA

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Abstract
The Commonwealth Minister of Health and Aged Care and Commonwealth Federal Minister of Agriculture, Fisheries and Forestry released the JETACAR Report (The use of antibiotics in food-producing animals : antibiotic resistant bacteria in animals and humans) in September 1999. The implementation of 22 recommendations contained in the report are being considered by both government departments as of early June 2000.
The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is the independent statutory authority in Australia responsible for the registration of veterinary chemical products, including all antibiotics, and the control of such products up to the point of retail sale.

The NRA currently seeks advice, on the potential risk of transfer of antibiotic-resistant bacteria, from the Working Party on Antibiotics. A risk assessment approach for new antibiotics and significant extensions to use of registered antibiotics has been introduced.

When the Federal Government determines its implementation strategy with respect to the JETACAR recommendations, the NRA will consider the JETACAR recommendations relating to regulatory controls of veterinary antibiotics (including registration of antibiotics and review of selected antibiotics).

Key issues for the NRA and veterinarians

The Commonwealth Government has yet to issue a Government response to the JETACAR report. The timing and nature of this response cannot be pre-empted in this presentation.

The contributory risk posed by the use of antibiotics in animals to the development of antibiotic resistance in human pathogens needs to be balanced by the risk posed by antibiotic use in humans.

- *New antibiotic product registrations The NRA currently seeks advice from the Working Party on Antibiotics on the potential for antibiotic resistance transfer. The NRA proposes that applicants who seek registration of a new antibiotic (or extensions of use of registered antibiotics) present data as per the revised* Part 10 (Special Data Requirements), *using a risk assessment approach. This risk assessment approach is now in place.*

The important concepts of this risk management approach are :

1. **HAZARD** : antibiotic resistant micro-organisms or their resistance plasmids (that have the potential to transfer to humans) within an animal species, arising from the use of an antibiotic in an animal species
2. **EXPOSURE** : the degree and frequency of exposure of susceptible humans to antibiotic-resistant micro-organisms (or their plasmids) from animal sources
3. **IMPACT** : of infections (caused by antibiotic-resistant pathogens of animal origin) in susceptible humans
4. **RISK** : the probability of infections (caused by antibiotic-resistant pathogens of animal origin) in susceptible humans **AND** the impact of such infections
5. The focus is on commensals and enteric pathogens (and genetic determinants) that may be important to susceptible humans, not on target animal pathogens.
6. The comparative risk of use of antibiotics used in food-producing versus companion animal needs to be considered.
7. Further development of the guideline will occur as a result of a VICH initiative to develop a internationally harmonised guideline for pre-approval studies.

- Drugs and poisons scheduling The JETACAR recommendation that all antibiotics be scheduled as Prescription Animal Remedies, should be considered from a risk point of view. While the concept of re-scheduling all antibiotics to Schedule 4 may be simple, it may not be practical, based on what is considered an ‘antibiotic’ and considering the relative risk of certain products.

- Harmonising State control of use The NRA supports legislation that would harmonise control of use laws between States and Territories. This would allow improved label wording and product use.

- Review of existing antibiotics The JETACAR recommendation that the registration of certain growth promotant antibiotics be reviewed will be considered in the Government response. The NRA conducts special reviews on existing registered chemicals of concern, and is capable of conducting the reviews of virginiamycin and macrolides, as suggested by JETACAR.

- Working Party on Antibiotics The NRA seeks advice on antibiotic resistance from the current WPA and wants to ensure that an external agency is still accessible for this continuing advice. The process for

such advice needs to be open and transparent and subject to timeframes and fee-for-service.

- Alternatives to antibiotics The NRA considers registration of all veterinary chemical products in Australia. The registration of products undergoes scientific assessment with respect to safety to humans, animals and the environment and to efficacy to target animals. Applications for alternatives to antibiotics such as vaccines, herbal products etc. would be considered similarly to other veterinary chemical products, and the NRA would need to be fully satisfied as to such products' efficacy and safety, irrespective of their potential use as antibiotic alternatives.

Veterinary Prescribing – Right or Privilege?

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Definition of veterinary prescribing

This is not a defined term. It is used, particularly by older veterinary surgeons, to describe their ability to write prescriptions for filling by pharmacists, the ability to use, or direct use of, products off-label, the ability to formulate and use their own products and, in some cases, the ability to have products custom manufactured. Much of this concept dates back to the times when veterinary surgeons and pharmacists alike were forced to compound their own products because manufactured products were not available. Few of the remedies made in this way have survived into the twenty first century.

Source of this ability or "right"

Again, there is no specific provision of veterinary prescribing rights in common law or under Australian legislation. Veterinary surgeons have been accorded certain of the above rights in accordance with their professional training in the use and pharmacology of drugs. This has been the basis for incorporation of veterinary rights into Poisons legislation or in veterinary surgeons' registration or controlling legislation.

Poisons legislation usually allows veterinary surgeons to obtain, use and on-supply drugs which are included in certain poisons schedules, ie Schedule 4 (prescription-only products, now known as Prescription Animal Remedies — PAR) and Schedule 8 (drugs of addiction, now known as Controlled Substances). It is not generic, in that it does not apply to all drugs, nor does it control the manufacture and general supply of those drugs.

Legislation can affect these "rights"

Because veterinary surgeons' rights do not somehow exist in common law, they can be overridden by legislation. This is true even in the case of common law situations.

A good example is the control on supply of veterinary drugs which came into effect with the introduction of the Agvet Code of the National Registration Authority for Agricultural and Veterinary Chemicals (NRA).

Prior to the introduction of the Code, veterinary surgeons frequently supplied unregistered products in most states and territories because there was no law prohibiting such action. When the Code was introduced, it allowed veterinary surgeons to continue to supply such products *only where state or territory legislation specifically permitted it*. This meant that in NSW, where veterinary surgeons were only permitted to supply a limited range of unregistered products (human pharmaceuticals and self-compounded medicines), such supply was still permitted.

But in other jurisdictions, such as the Northern Territory, where there was no legislation regulating supply of unregistered products, most such supply immediately became illegal. This would still appear to be the case in a number of jurisdictions, however there appears to be little awareness or enforcement of this restriction.

Controlling veterinary use / prescribing

There are a significant number of reasons for restricting what veterinary surgeons are allowed to do with drugs in this modern world. Just as farmers can no longer use whatever chemicals they like if they expect to market their produce internationally (and even nationally), so veterinary surgeons must ensure that their chemical use is consistent with the needs of contemporary society.

In times past, veterinary surgeons were the repository of most, if not all knowledge relating to the use of veterinary drugs. In the modern world, this expertise has been lost as the demand for relevant knowledge has outstripped the ability of most veterinary surgeons to meet it. Even in such a simple area as providing truly appropriate withholding period advice in relation to an off-label treatment, most veterinary surgeons in general practice have neither the expertise to provide it, nor do they know how to obtain the information (at least if the drug company cannot provide it).

The following areas of concern can be identified.

1 **Residues (Trade)**

The major issue of concern in regard to trade, particularly overseas trade in animal commodities such as meat, is tissue residues.

The Australian beef export industry is worth over $3,500,000,000 annually. Any major residue crisis occurring in relation to that trade could cause many millions of dollars of damage to that trade, with major flow-on effects through the Australian economy.

It is therefore essential that tissue residues do not occur in cattle (or other export-oriented animal industries) as a consequence of the inappropriate use of approved, or the use of unapproved, drugs.

Secondly, the European Union (EU) in particular has already imposed restrictions, and is likely to impose additional restrictions, on the use of certain drugs in countries exporting to the EU. The most obvious are the Hormonal Growth Promotants (HGPs).

Unless Australia can provide evidence that its controls are adequate to deal with these issues, then the only

national option is to ban the drugs entirely, with flow-on losses to animal production and health.

2 **Quality Assurance**

This is closely related to the trade issue, but is more important domestically. The requirements of major food retailers and processors (based on consumer demand) for quality-assured produce mean that they can require that only approved products (registered drugs or chemicals, used as they consider acceptable) will be purchased. Off-label use can be partly compensated for by appropriate withholding periods, but major purchasers still have the ability to dictate what is to be used.

3 **Prohibited chemicals**

Just as the HGPs are prohibited by the EU, other drugs are prohibited for national use (though they may also be prohibited overseas). The most high profile of these are chloramphenicol and diethylstilboestrol (DES).

It is essential that controls exist in each jurisdiction to control the supply and use of these chemicals. This protects both public health and also trade, and provides confidence to consumers both locally and overseas. Current controls over "prescribing" these compounds in some jurisdictions apply only in Poisons legislation. A prohibition on prescribing by veterinary surgeons is not the same as a prohibition on use or supply.

In a jurisdiction without other appropriate controls over veterinary use of drugs, a Health department could consider prohibiting all supply of S4 or S8 products by veterinary surgeons if they believed the matter was not being adequately addressed by the profession. These control restrictions would over-ride the usual NRA supply controls.

4 **Antibiotic resistance**

The recommendations in the report of the Joint Expert Technical Advisory Committee on Antibiotics Resistance (JETACAR) suggest that all users of antibiotics, including veterinary surgeons treating companion animals, will have to reconsider their drug use activities. The report makes 22 recommendations, of which at least eight have immediate implications for veterinary surgeons in regard to use, supply and prescription of antibiotics.

Antibiotic resistance has received extensive coverage by the media, and is a subject close to everyone's heart. The public will only tolerate activities which they consider do not pose a risk to their personal health. Thus veterinary surgeons must take the JETACAR recommendations seriously if they are not to suffer significant loss of their current rights in regard to these products.

The following recommendations impinge on veterinary use of antibiotics.

Recommendation 1

There should be no use of antibiotics in feed unless they are rarely or never used as human or animal medicines and they are unlikely to promote resistant strains of organisms in humans or animals.

Unless control of use legislation exists to restrict this use, veterinary surgeons could continue to use such products contrary to this recommendation. This would stimulate public concern and could lead to the complete loss of the products.

Recommendation 3

There should be an audit trail for use of all (imported) antibiotics.

This is likely to preclude all direct purchase and use or supply of raw antibiotics by veterinary surgeons. It is already illegal under the NRA's Agvet Code for veterinary surgeons to directly import antibiotics.

Recommendation 5

Any identified development of resistance should be dealt with to mitigate its effects.

Again, one way this might be dealt with, in the absence of appropriate control of use legislation, is by the banning of the offending antibiotic from animal use. This could be done by the NRA on a state-by-state basis, so that the product could continue to be available only in those states which could ensure appropriate regulation of its use. Given the difficulty with enforcing this, it is more likely the registration would be stopped.

Recommendation 6

All antibiotics, including those used in feeds, should be prescription only products (Prescription Animal Remedies or PAR).

This has less impact on veterinary surgeons than the other recommendations, but obviously would depend on appropriate poisons legislation being in place. Given that one of the draft recommendations from the National Competition Policy review of Poisons Legislation is for the NRA to take over all poison controls for agricultural and veterinary chemicals, this could in future be dealt with by the NRA.

Recommendation 7

There should be harmonised controls over use in all jurisdictions.

This recommendation was reflected in that of the National Competition Policy review of Agricultural and Veterinary Chemicals. That review acknowledged that a process of national controls had been agreed to by Standing Committee on Agriculture and Resource Management (SCARM — representing all State and

Territory agriculture CEOs), but it re-inforced the need to achieve such controls.
While the Commonwealth cannot directly enforce such controls over states, it has other ways of bringing pressure to bear when it considers that action needs to be taken. Further, any government which was perceived by its population as failing to protect it against misuse of veterinary antibiotics would be at risk.

Without standard use controls in all jurisdictions, the national registration system cannot achieve control objectives which may need to be implemented. Again the likely outcome is that affected products would not be registered.

Recommendation 8
There should be no use contrary to a label restraint statement.

The concerns here, and the likely outcomes, are similar to those for 7 above.

Recommendation 15
Prudent Use Codes of Practice should be promulgated.

Various codes of practice exist in state legislation for issues such as animal welfare and even veterinary practice. If a veterinary surgeon did not comply with a code, which had been adopted by a state veterinary registration board, then they would be liable to disciplinary action by the Board.

Recommendations 16/17
Antibiotic use guidelines and continuing antibiotic use education should be promulgated for all professional training.

Such guidelines are intended to ensure that prudent use of antibiotics is taught and adopted by all training professionals. Failure to do so would again see the Commonwealth seeking to impose appropriate controls by less acceptable means.

Occupational Health and Safety
Because of their privileged access to many drugs and poisons, veterinary surgeons are able to obtain, compound and use many different products.

The process of handling these has implications for veterinary surgeons as employers, under various OH&S Acts, which require them to provide safe workplaces and not jeopardise worker health or safety. One example of such a poison, the preparation of which was "essential" in years gone by due to lack of registered products, was selenium. Certainly in NSW veterinary surgeons would obtain selenium salts and either prepare themselves, or have staff prepare, various mixtures for clients. Selenium is potentially very poisonous to humans, and anyone handling it needs to be appropriately instructed and protected. Now that there are registered selenium concentrates available, all with appropriate first aid and safety directions for users, veterinary surgeons should not need to handle this product any more.

Residues (Health)
This is residues as an immediate health issue, rather than a trade issue as dealt with previously.

Certain chemicals, if present in animal products such as meat or milk, can pose an immediate risk to consumers of those products. Penicillin in meat or milk can adversely affect sensitive individuals. Cases of clenbuterol poisoning (and at least one death) have occurred in the EU following ingestion by consumers of injection site residues (acknowledging that clenbuterol is used much more infrequently in Australia). Chloramphenicol residues pose a risk in relation to even minimal exposure, and this is the main reason it is still banned for use in food animals.

There are undoubtedly a great number of veterinary chemical products for which major risk to consumers would occur if they were used off-label or irresponsibly by veterinary surgeons.

Implications of failing to control veterinary use
The majority of problems arising from inadequate controls over veterinary chemical use (including by veterinary surgeons), have been dealt with in this paper.

There are still some specific issues which should be considered or repeated.

1 **The registration process is undermined**
The whole process of registration of chemicals is based on the expectation that they will generally be used in accordance with their label directions.

Thus residue/trade, environmental and OH&S issues are evaluated by the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) on the assumption that most use, if not all, will be strictly according to label directions. Significant departure from that use exposes users to risks and liabilities they would not otherwise incur.

2 **Trade is threatened**
As discussed earlier, residues resulting from the use of unregistered products, or products off-label, have the ability to jeopardise major (export) trade in animal commodities. Restrictions on certain drugs or uses could also be imposed by Quality Assurance systems.

3 **Human health may be compromised**
This could be an OH&S issue, in regard to the user of a product (eg recommendations to increase the dose rate of organo-phosphate sheep dips) or may impact more indirectly by way of toxic residues affecting consumers of animal products.

4 **There is a risk to animal health**

Many advances in veterinary science have arisen in the past from the endeavours of individual veterinary surgeons in testing novel treatments. But today, animal owners are much more sensitive to issues of negligence, and veterinary surgeons should be much more sensitive to issues of animal welfare associated with off-label treatments.

Even simple changes to label directions, such as increasing or decreasing doses, can affect animals by way of reduced efficacy or increased toxicity. Misuse of antibiotics in individual animals is likely to pose nowhere near the same problems for resistance development as does such misuse in human medicine, but it cannot be discounted. See the presentation by John Prescott in these proceedings.

The other way animal health can be threatened is by way of restrictions imposed on products by either the NRA or Commonwealth Health via the Working Party on Antibiotics. If sufficient concerns were raised about a product, either by way of an NRA review of an existing product, or during the process of registering a new product, registration could possibly be restricted to only those jurisdictions which are able to effectively impose the necessary use controls, or it may be stopped altogether.

This is likely to be an issue with antibiotics in particular, as there is strong pressure from human health professionals to severely restrict animal antibiotic use.

5 **There is a risk to the environment**

While it may seem a minor issue, even the material treated animals excrete has been shown to be a significant problem in regard to environmental concerns.

All new veterinary chemical products are assessed by Environment Australia (EA) for their possible impact on the environment. Such concerns are greater in regard to treatments for intensively housed animals, where large quantities of dung are produced and often spread over soil, or even fed to other animals. When EA approves the use of a new product, its approval is based only on use according to the label directions — environmental impacts are not considered for any other uses.

Concerns about the effects of excreted macrocyclic lactones on dung beetles, and more recently about similar effects in relation to use of synthetic pyrethroids (in pour-on lice treatments), highlight the potential of veterinary treatments to produce environmental consequences. Changes to label uses are more likely to make such problems worse than to improve them.

Conclusions

Contemporary society is increasingly concerned about its exposure to chemicals, its health and the health and welfare of its animals.

Veterinary surgeons, who should be at the forefront in addressing these concerns, must ensure that their practice of veterinary science conforms with social expectations.

Potential impacts on trade, environment and human and animal health all need to be carefully considered whenever veterinary surgeons use any unregistered product, or registered product off-label.

The continuing right to undertake such use depends on veterinary surgeons fulfilling this obligation conscientiously.

Antibiotic resistance - quarantine and trade

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Introduction

The developments in medical concern about antibiotic resistance generated by the use of antibiotics in food-animals have rapidly evolved into a concerted effort, particularly by the EU, to address the issue from a mainly medical perspective. The views and those held by an increasing sector of the general community are that antibiotic growth promotants should be withdrawn from use in food producing animals.

The reality in the EU is that acceptance and implementation of this perspective has become a political imperative. The international trade consequence, based on other EU experience with issues such as hormonal growth promotants and BSE, is that the EU will require third country compliance with their position, no-matter how unscientific and illogical it is, and no-matter what World Trade Organisation (WTO) trade rulings might eventually be.

In the US there is also medical concern on the issue of feeding antibiotic growth promotants to livestock, and this has been most strongly articulated from the Center for Communicable Diseases (CDC). The United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) as well as the Center for Veterinary Medicine (CVM) all have groups looking at this issue. The FDA for example, has commissioned risk assessment model development on the impact of fluoroquinolone resistant Campylobacter on human health.

In 1998 the Departments of Health and Aged Care and Agriculture, Fisheries and Forestry — Australia commissioned an expert group (the Joint Expert Technical Committee on Antibiotic Resistance (JETACAR)) to investigate and make recommendations on the use of antibiotics in food-producing animals in Australia. In October 1999 JETACAR made 22 recommendations covering both the animal and human use of antibiotics. The government has to assess the implications of this report and to decide on full or part adoption of the JETACAR recommendations. Due consideration of costing and international market competition significance is needed. These trade issues are most important because the cost structure and government support for our trade competitors is different. For example the US and EU have embarked on increasingly elaborate and comprehensive government funded programs of antibiotic resistance monitoring and surveillance. The cost of any monitoring and surveillance program on antibiotic resistance that measures ongoing prevalence is likely to be considerable. The issue of who pays for this essential work is a major consideration for government and industry.

Ultimately, however, in the rapidly changing international antibiotic resistance arena, the cost to Australia's export industries of not doing anything to address the issue, for example in monitoring and surveillance, could be exclusion from important markets.

Analysis of the international trade situation and antibiotic resistance

The situation with antibiotic resistance has a number of parallels with chemical residue, animal disease and food contamination issues

Chemical residue issues and trade. The linkage between antibiotic resistance and antibiotic residues is that some people, erroneously, but understandably, assume that antimicrobial residues will have an effect on the generation of antimicrobial resistance in consumers of food, if residues are present. In reality, as discussed in the JETACAR report (Chapter 11, page 141, http://www.health.gov.au/pubs/jetacar.htm) the levels of antimicrobial residues on food are likely to be so low that any effect on the selection of resistant bacteria within the human gut flora is likely to be minimal.

Australia, like other nations, reserves the right to register and use those agricultural and veterinary chemicals that it needs to efficiently conduct its agriculture. The registration process is rigorous and the precautions taken to demonstrate national compliance with the maximum residue levels (MRLs) set for particular chemicals is comprehensive (the National Residue Survey (NRS) monitoring and surveillance programs). The design of these programs incorporates testing requirements from our major trading partners, the EU and the US, who are generally seen as setting international standards in this area under the WTO Sanitary Phytosanitary (SPS) Agreements. Increasingly, however, the EU has been moving from this agreement (based on scientifically defensible requirements) to those determined by the EU political realities and EU community perspectives on issues. This shift in attitude is best demonstrated by the suspension from sale of four antibiotic growth promotants by the EU, and the likely suspension of four others, under the 'precautionary principle'. Scientists and policy experts are increasingly questioning the application of the 'precautionary principle' because it appears to be being used as a veiled form of trade protectionism. This is because of variations in interpretation of the principle are possible. In some

instances absolute proof is needed, in others compliance with international standards is sufficient.

In the international (mainly Codex) arena Australia has promoted the concept of the national right to register the agricultural and veterinary chemicals it needs for internationally competitive agricultural production. For example Australia has internationally peculiar requirements for sheep and cattle anthelmintics. The fact that Australia has particular chemicals legally registered for use, with defined MRLs, should not allow trading partners who have not registered a particular chemical to refuse the importation of Australian beef or sheep meats simply because the importing country has a zero MRL (usually because the chemical is not registered). This, unfortunately, was the cause of the chlorfluazuron crisis in 1994. Australia has been arguing in the international arena that as long as there is a scientifically defensible MRL in Australia, or in Codex, there should be no impediment to exports. If the importing country has concerns these can be dealt with in bilateral consultations where Australia has to demonstrate to the importing country that registration process was scientifically valid and that the particular MRL is not being exceeded in imported product.

In terms of antibiotic residues this is the international trade reality. If another country has legally registered an antibiotic not used in Australia then it would be most unwise and counterproductive for Australia to contemplate any trade restrictions on antibiotic residue grounds.

Animal disease. Australia's privileged quarantine status has long been a source of national pride, and economic advantage, to our food animal industries. However, the practical realities of international trade under the WTO mean that zero-risk quarantine policies are no longer defensible. In fact there has been a series of government papers on the subject of quarantine risk, culminating in the Nairn Report in 1996, that specifically state that the Australian Government does not have a zero-risk quarantine policy. Unfortunately Australia's quarantine position is perceived internationally as a zero-risk position, hence the enthusiasm of a number of international trading nations to challenge Australia's interpretation of its risk analysis approach in the WTO with high profile cases such as the Canadian salmon meat importation challenge (which Australia lost).

What this means in practical terms in the antibiotic resistance situation is that the case for quarantine restriction of animals or food on the grounds of antibiotic resistance needs to be carefully evaluated. In practical terms the existence of a multi-resistant bacteria in a trading partner's animal or human populations could be viewed with concern from the human as well as the animal quarantine perspectives. Antibiotic resistance genes are conceptually no different to virulence genes in bacteria. Scientifically defensible, but not zero-risk, precautions against the importation and establishment of these bacteria in either our human or animal populations could be a reasonable policy.

Enteropathogens in food. Microbiological contamination of food, and in particular meat, with organisms such as *E coli* O157:H7, *Campylobacter* and *Salmonella* species and in more recent times *Enterococci* species is an issue of commercial and international trade concern. This concern dates back to the devastating Salmonella outbreaks in Sweden and the UK in the 1950s and 1960s and the Jack in the Box hamburger and Garabaldi metwurst incidents in the US and Australia, as well as other food safety incidents due to *Escherichia coli* O157: H7 in the UK and Japan in the 1990s.

As a consequence of the earlier Salmonella incidents careful consideration has been given to the registration and use of antibiotics in animals by a number of countries. This is best articulated in the 1969 Swann Report. This is a report produced for the British Government following concerns about the increasing antimicrobial resistance in Salmonella isolated from humans and animals in the 1960s. The tenets of this report are followed today by the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) in the registration of animal antibiotics.

Sweden took its concern with enteropathogens and antibiotic resistance several steps further and has had restricted antibiotic use in animals since 1986, as well as conducting extensive microbiological testing of food, particularly meat, for Salmonella. The net result of the Swedish program is that Sweden has demonstrably lower Salmonella levels in its livestock and on Swedish meat, and cases of human salmonellosis. However Sweden does not have a large beef herd and has to import considerable volumes of EU (and Australian) meat. This requires testing meat imported into Sweden for Salmonella. What is interesting about the Swedish situation is that the majority of Swedish human enteropathogen infections likely to be acquired through the food chain are in people who have recently travelled outside Sweden.

A perspective on antibiotic resistance quarantine and trade

What is a reasonable position for Australia to take on the risk of importing antibiotic resistant bacteria though the movement of people, animals and animal products and food in general?

Clearly, imposing bans on imported food from countries using antibiotics not registered in Australia is not reasonable, politically wise (given Australia's strong international stance on free trade, particularly in primary industry commodities), or defensible in the WTO court in Geneva.

The Swedish situation illustrates that countries can reduce the enteropathogen load on food with a rigorous and comprehensive national approach to the issue. It is interesting to note that concern about the transmission of antibiotic resistant bacteria generated in animals and possibly passed on to humans has been of major concern to Swedish authorities in the 1990s. The EU acceptance of Swedish entry into the EU allowed a derogation on this issue (one of a number of derogations that Sweden was able to get accepted by the EU). That is the public health gains made by Sweden through the limitation of enteropathogen contamination of food were not to be lost. This position has been a strong influence in the momentum of the whole EU debate on antibiotic resistance. A similar situation and concerns exist in Denmark and Finland. Australia may have some similarities with the situation in Sweden.

Australia, as the major beef exporting country in the world, has made significant advances in meat hygiene, and indirectly in the reduction of microbiological contamination of meat through the introduction of ever higher standards of hygiene on slaughter premises, equipment, processing procedures and Hazard Analysis Critical Control Point (HACCP) programs. The potential importance of this progress in limiting antibiotic resistant bacterial contamination of food should not be under-estimated. However, there has been no quantitative or semi-quantitative risk analysis undertaken anywhere in the world to quantify the relative importance of the food chain contribution of antibiotic resistant bacteria to the overall problem of antibiotic resistance in human medicine.

The Swedish experience with Salmonella, and more recently with their removal of antibiotic growth promotants from Swedish animal production systems, raises the issue of considering antibiotic resistant bacteria as a quarantine issue. The resistance genes in bacteria such as the multi-resistant Salmonella Typhimurium DT 104 can be considered in the same way as virulence genes in bacteria such as *Pasteurella*.

If this concept is accepted then a framework to limit the risk of such resistant bacteria gaining entry and becoming established in Australian human or animal populations can be proposed. The same quarantine risk analysis processes that AQIS has already established for the importation of animals and animal products in general can be used.

In summary, the important question to answer is 'Are there international trade implications from either the generation or importation of antibiotic resistant bacteria in Australia?'

Recommendations

- There is a clear need for monitoring and surveillance for antibiotic resistance in a range of bacteria in animals and humans as recommended in the JETACAR Report.
- There is a need to conduct risk analysis to establish relative risks of the various methods of entry (through people, food or animals) of antibiotic resistant bacteria of medical importance into Australia.
- Quarantine risk analysis is then needed and if the risk is judged as significant then appropriate barrier, post barrier and emergency management options devised. Appropriate action could include hospital precautions on isolation of, for example, *Salmonella Typhimurium* DT 104, imported food testing or the requirement for demonstration of specific freedom by exporting countries (this would require concomitant demonstration of freedom in Australia of course).

Conclusions

Antibiotic resistance is an emerging issue of international public health, and hence trade concern. Parallels exist in the food microbiological area for the application of risk analysis methodologies to this issue as a human quarantine and public health problem. This first step should provide justification for action, or no action in the quarantine and emergency management areas of human and animal health.

THE FUTURE OF VETERINARY ANTIBIOTICS

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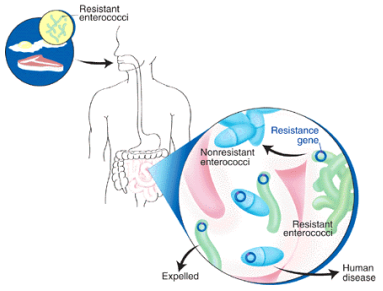
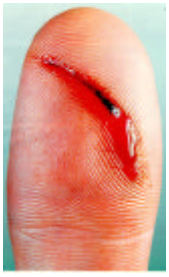
- Current environment for veterinary antibiotics
- A future of improved use
  - reduction
  - replacement
  - refinement
- Quo vadis: concluding remarks



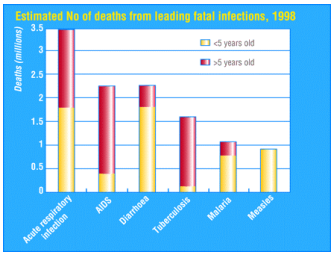
ANTIBIOTIC RESISTANCE:
Superbugs on the Hoof?
Science May 5 2000: 792-794

Disturbing new findings have provided a key link in the chain of evidence connecting antibiotics used on livestock to outbreaks of disease caused by antibiotic-resistant human pathogens



GERM WARFARE

The Australian Magazine June 3 - 4 2000



Superbugs could make existing antibiotics useless by 2010
BMJ 2000;320:1624 (17 June)

MICROBIOPHOBIA

↓

ANTISEPTICOPHILIA

• Triclosan resistant Pseudomonas aeruginosa hyperexpressed a multidrug efflux system resulting in increased resistance levels for several drugs of up to 500 fold (100th ASM, 2000)

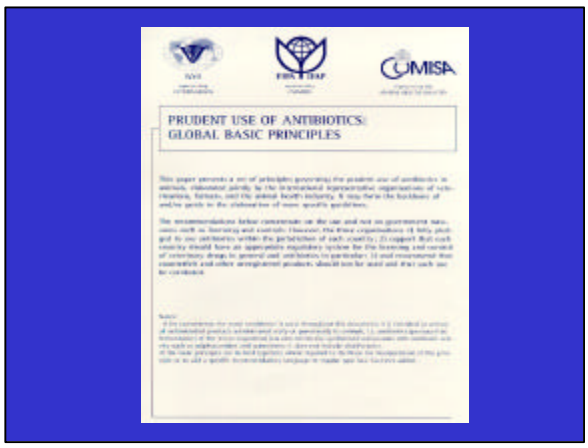
• AMA urges government to increase regulation of household antibacterial products (AMA June 2000)

• In speculating on the role of personal-care products in causing AbR the AMA is diverting attention away from the proven causes of AbR (CTFA June 2000)

• THE DEBATE NEEDS BALANCE

• THEIR NEEDS TO BE A RESTORATION OF CONFIDENCE IN THE DECISION MAKING PROCESS

REDUCTION


PRUDENT USE OF ANTIBIOTICS:
GLOBAL BASIC PRINCIPLES

WHO (12 June 2000)

Global principles for the containment of antimicrobial resistance due to antimicrobial use in animals intended for food

National Consumers League (19 June 2000)

Bacterial Resistance

Beating Bacteria

REPLACEMENT

- Acidulents
- Enzymes
- Probiotics
- In-feed enzymes
- Oligosaccharides
- Conjugated linoleic acid (CLA)

- Competitive exclusion (Nurmi concept)
- Immunostimulants
- Food / carcase irradiation
- Vaccines
- Animal genetics
- Management

REFINEMENT

NEAR PATIENT MICROBIOLOGICAL TESTS

- Increasing use of specific antigen detectors other than antibodies
- Microminiaturisation
- Incorporation into healthcare products such as wound dressings
- Coupling of OTC diagnostic tests and treatments
- Tests can be swallowed or added to any body fluid and results suitable for remote analysis
- Potential disadvantages:

TARGETING

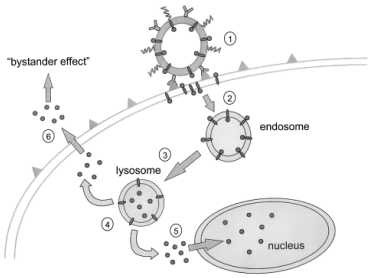
• **Stimulus-responsive controlled drug release systems**

Gentamicin bound to PVA hydrogel via thrombin-sensitive peptide link

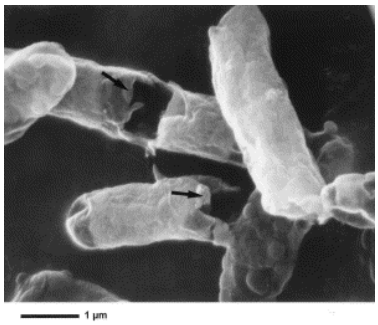
Gentamicin released in presence of Staph aureus infected wound fluid (rich in thrombin-like activity)

• **Other targeting strategies →**

TARGETING: LIPOSOMES



TARGETING: E coli GHOSTS



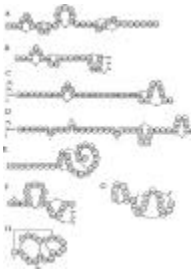
THE SEARCH FOR NEW ANTIBIOTICS

NATURAL APPROACHES TO ANTIBIOSIS

- Berberine (Lancet 354, 1999)
- Bovine aromatherapy (Europe Intelligence Wire 21FEB00)
- Cranberry juice (JAMA 283: 1691, 2000)
- Garlic & VRE (AAC 43: 3045, 1999)
- Tea tree oil (JAC 45: 639, 2000)
- Potato aqueous extract (100th meeting ASM, May 2000)
- Oregano - essential oil fraction IV (ASM, May 2000)
- Ginseng aqueous extract (100th meeting ASM, May 2000)
- Bacteriophages

ENDOGENOUS PEPTIDE ANTIBIOTICS

- Beta-sheet defensins (HNP-1 and HNP-4)
- Alpha-helical peptide LL-37
- Histatins (from human parotid salivary gland)
- Ubiquicidins (murine macrophages)
- Protegrins (porcine leukocytes)
- Magainins / cecropins / mellitins (frogs / insects)
- Temporins (from amphibian Rana temporaria)
- Parasin (from catfish skin)
- Peptide from penaeid (EP 1000153 A2)
- Bacteriocins (eg nisin from Lactobacillus spp)



Selected structures of representative lantibiotics. Nisin (*A*), epidermin (*B*), Pep5 (*C*), and lactocin S (*D*) are typical elongated flexible peptides. Lacticin 481 (*E*) represents a group with a crossbridged C-terminus and an unbridged N-terminal part. The type-B peptides mersacidin (*F*), actagardine (*G*), and cinnamycin (*H*) are conformationally well-defined, globular peptides

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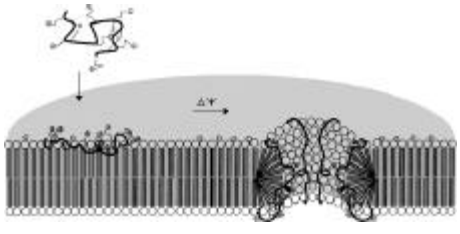
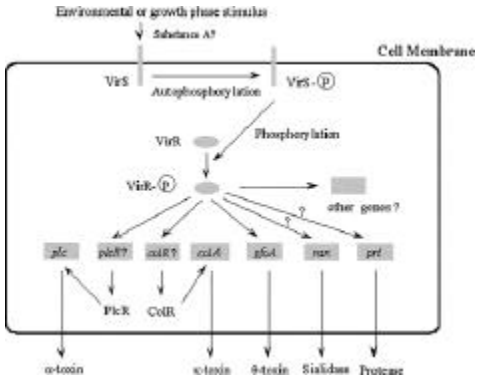


NEW ANTIBIOTIC CLASSES

CLASS	EXAMPLE
Semisynthetic N-alkylated glycopeptide	LY 333328
Ketolides (semisynthetic 14-membered-ring macrolides)	HMR3647
Glycylcyclines	GAR-936 CL 331,002 CL 329,998
Oxazolidinones	Linezolid
Everninomicins (oligosaccharide)	SCH27899
Streptogramin + doxycycline	RP 59500 Doxycycline
Semisynthetic N-alkylated glycopeptide + ampicillin	LY333328 Ampicillin
Lipopeptide	Daptomycin
Trinems	Sanfetrinem
Depsipeptide	Ramoplanin

NEW STRATEGIES

Drugs that might treat infectious diseases without incurring the cost of resistance.



- Agents that inhibit density-dependent expression of virulence factors (Science 280: 438, 1998)
- Production of enterotoxin inhibitors (PNAS 95: 3943, 1998)
- Avirulent E coli expressing shiga-toxin-receptor mimic (Nat Med 6: 265, 2000)

These approaches neutralize or penalize the pathogen rather than killing the microbe

CONCLUSIONS

- DECISION MAKING PROCESS

  Need a thorough, objective, evidence based, transparent, cooperative framework for decision making, permitting sound and defensible decisions with clear identification of benefits and uncertainties

  Decisions should discriminate between scientific and political bases - either may be quite acceptable and reasonable but the foundation of decisions should not be confused

CONCLUSIONS (continued)

- PRECAUTIONARY PRINCIPLE

  Precaution is a reasonable approach, but application of the principle should be based on a sound decision making process

- SCIENTISTS SHOULD NOT DISTORT DEBATE

- POSITIVE OUTCOME OF CURRENT DEBATE

  Renewed interest in alternatives to Abs and increased focus on pathogenesis/MOA ⇒smarter approaches

CONCLUSIONS

- REFINEMENT, REPLACEMENT, REDUCTION

  Essential to optimise use of current tools to reduce the necessity of replacements

- NEW ANTIBIOTIC ENTITIES

  While there is significant activity in the R&D of new antibiotics for human medicine, there cannot be expected to be a lot of developments of antibiotics for animal health

CONCLUSIONS (continued)

- STEWARDSHIP OF RESPONSIBLE USE

  The veterinary profession (ie the AVA) should take the lead to explore how responsible use can be implemented most effectively

- INCREASED INTERACTION OF MEDICAL AND VETERINARY PROFESSIONS
- NEW ANTIBIOTIC ENTITIES

  While there is significant activity in the R&D of new antibiotics for human medicine, there cannot be expected to be a lot of developments of antibiotics for animal health