

**A REVIEW OF THE IMPACT OF THE USE OF
ANTIMICROBIALS IN ANIMALS AND PLANTS ON THE
DEVELOPMENT OF ANTIMICROBIAL RESISTANCE IN
HUMAN BACTERIAL PATHOGENS**

Report of the Expert Panel on Antibiotic Resistance

July 2005

ISBN 0-478-079-6-0

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Executive Summary

This report was prepared by an Expert Panel appointed by the Antibiotic Resistance Steering Group in 2004. The Panel's purpose is to:

- review and update the report of the 1999 Expert Panel (*Antibiotic Resistance and In-feed Use of Antibiotics in New Zealand*);
- extend the review of the public health impacts of antimicrobial use to include all formulations of antimicrobials used in animals and plants by all routes of administration;
- review the compliance of the New Zealand systems for regulation of the use of antimicrobials in animals and plants with guidelines that have been or are being promulgated by the World Health Organization (WHO), the Office International des Epizooties (World Animal Health Organization, OIE) and the Joint FAO/WHO Food Standards Programme (Codex Alimentarius); and
- suggest how advice might be given to the Agricultural Compounds and Veterinary Medicines (ACVM) Group of the New Zealand Food Safety Authority (NZFSA) and Medsafe in the future.

The focus of this report is the New Zealand situation and perspective, and the extensive international literature on antimicrobial resistance has not been reviewed in detail except as is relevant to New Zealand and the recommendations in this report.

Antimicrobial Resistance in New Zealand

The development of resistance in bacteria is a natural response to exposure to antimicrobials, and the prevalence of resistance is directly related to the degree of exposure. A summary of resistance mechanisms is provided in Chapters 3 and 6.

The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA), bacteria possessing extended spectrum β lactamases (ESBLs) and resistant *S. pneumoniae* in human isolates, is increasing but rates remain low by comparison with Australian, European and American data. Vancomycin-resistant enterococci (VRE) in human isolates remain relatively rare. Levels of resistance in *Salmonella* and *Campylobacter* isolates of human and non-human origin are also low. The Expert Panel considers the preservation of this relatively favourable status to be a priority.

Information on antimicrobial resistance in animal and plant bacteria indicates that where antimicrobial use is high, such as in mastitis control/treatment and in-feed use of antimicrobials, antimicrobial resistance has developed. However, the data are fragmentary and do not allow conclusions on the transfer of resistance to human pathogens or any specific relationship with resistance among human pathogens in New Zealand to be drawn. Nonetheless, the Panel has concluded that the potential for transfer continues to exist and this justifies the continuation of a prudent approach to the use of antimicrobials.

The need for more structured examination of resistance in animal bacteria is highlighted by observations such as the identification of *S. aureus* strains isolated from bovine udders resistant to oxacillin and penicillin, vancomycin-resistant *Enterococcus* spp. isolated from chickens fed avoparcin and bacitracin-resistant *Enterococcus faecalis* isolated from chickens.

Reducing antibiotic resistance in bacterial pathogens requires:

- using antibiotics in humans or animals only when they are proven to be of benefit;
- complying with infection control principles in both animal husbandry and human health care settings;
- using control mechanisms that do not use antibiotics wherever possible, e.g. vaccination and infection control systems (this applies to both human and animal health); and
- controlling the pathways by which resistant bacteria or their resistance determinants can be transmitted to other bacteria. Food safety programmes, such as those administered by NZFSA, are an integral component of the management of the transfer of resistance determinants through food.

The Use of Antimicrobials in Animals and Plants

The raw data on sales of antimicrobials for animal use are not helpful in getting an understanding of how and why they are used. This understanding is critical for undertaking risk assessments and, in particular, for estimating the public health costs versus the animal health and welfare benefits of their use, and understanding the consequences of withdrawing antimicrobials from use in animals.

The total sales of antimicrobials (excluding the ionophores) have increased by 60% from 1999 to 2003 with the largest increases in the penicillins (60%) and bacitracin (150%). In the other groups, sales appear to be relatively static. In the same period, the numbers of dairy cows, pigs and poultry have increased substantially. The increase in the use of the penicillins appears to be attributable mainly to intramammary use whereas bacitracin is used almost exclusively in poultry production.

Intramammary antimicrobial products account for about 90% of the total amount of antimicrobials used in cattle. The very strong financial incentive to achieve low somatic cell counts in raw milk is a significant driver of this use. There is an equally strong disincentive to supply raw milk that contains antimicrobial residues. There are no particular short-term incentives to avoid the development of antimicrobial resistance through this use.

The anecdotal evidence available to the Expert Panel indicates a high degree of awareness of the consequences of using antimicrobials among veterinarians and industry organisations, particularly in the intensive industries. The Panel has been told of the efforts being made to ensure that the use of antimicrobials is not a panacea for poor husbandry practices. The Panel was given examples of husbandry programmes designed to achieve high health status and the performance benefits of doing so.

The horticultural (mainly pip and summer fruit sectors) industries that use streptomycin appear to do so responsibly. The amount used is reducing as the industries adopt management strategies to limit its use. Sales of streptomycin in 2003 were less than half that sold in 1999. Notwithstanding the apparently reduced threat of bacterial diseases to these industries, there is no satisfactory alternative to streptomycin in those situations where outbreaks of bacterial disease occur.

Because of the timing of applications, the fruit produced from treated trees or plants presents a low risk to humans of the transfer of streptomycin residues, resistant pathogens or

resistance determinants. Streptomycin applications in orchards may contribute selection pressure for resistance to plant-associated and soil organisms but the significance of this is unknown. It is not considered to be a significant pathway for human exposure.

The Expert Panel endorses ERMA New Zealand's policy on the release of genetically modified organisms that include antibiotic resistance marker genes (see Chapter 4).

Regulation and Management of the Use of Antimicrobials

The Panel concluded that the regulatory system as represented by:

- the Agricultural Compounds and Veterinary Medicines (ACVM) Act;
 - the administrative procedures operated by the ACVM Group, including collaboration with Medsafe and ERMA New Zealand; and
 - the New Zealand Veterinary Code of Professional Conduct meets the recommendations of the international guidelines in most respects but noted the following:
1. The ACVM Act does not currently provide for conditions of registration to be applied to antimicrobial veterinary medicines in furtherance of public health objectives. A Bill to amend the Act is being drafted to provide the statutory basis for what is currently done administratively.
 2. The surveillance and monitoring systems do not meet the recommended standards because no surveillance or monitoring of antimicrobial resistance in animal bacteria is undertaken.
 3. The regulation of antimicrobials does not comply with the draft OIE Guidelines for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine, which recommend that “all the antimicrobial agents used in animals are prescribed by a veterinarian or other authorised person” (Article 3.9.3.3 Paragraph 12). However, the Expert Panel does not consider that antimicrobials that are of no concern to human antimicrobial resistance (e.g. ionophores, carbadox) should be subject to veterinary prescription.
 4. Statistical data on antimicrobial sales have been collected since 2000 but the methodology of collection and analysis has been evolving. Comparisons between years are problematic. It is noted that the supply of sales statistics became compulsory from 2003 and a method of presentation has been determined. Sales data do not provide an adequate picture of the use of these medicines and are of little value on their own.
 5. While risk analysis methodology has been applied on a case-by-case basis, there has not been an adequate examination of the pathways by which human exposure to resistant animal bacteria or resistance determinants could occur. The Expert Panel considers that, if these assessments were done and adopted by the Ministry of Health (MoH) and the ACVM Group, decisions relating to the registration of antimicrobial products would be facilitated.
 6. Unlike their medical counterparts, veterinarians have few resources to turn to in obtaining guidance on the prudent use of antimicrobials. There is an unfulfilled need for development and documentation of ‘best practice’ that offers advice on the choice of treatments that are designed to achieve the intended clinical result while preserving the efficacy of veterinary antimicrobial products in the long term and reducing the risk of resistance transfer. The Panel has been informed of how this is done in the medical sphere and has formed the view that more could be done to assist veterinarians in matters of prudent use. Such an approach could preserve

veterinarians' right to access the spectrum of available antimicrobials and may be as effective in achieving some of the objectives of management of antimicrobial resistance as regulation of use. This approach would require a collaborative effort involving the expertise that resides within the New Zealand Food Safety Authority (NZFSA), the New Zealand Veterinary Association (NZVA) and its membership, the pharmaceutical industry and elsewhere. The Panel notes that NZVA has an established 'best practice' vehicle.

A proposed classification of the antimicrobials used in New Zealand based on the classification developed by the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) is presented in Table 5.2. This is intended to assist in risk assessment on individual actives.

Recommendations for the Regulation of the Use of Specific Antimicrobials in Animals

Recommendations relating to the use of aminoglycosides, bacitracin, the cephalosporins, the fluoroquinolones, macrolides, anti-mycobacterial antimicrobials and the streptogramins are discussed in Chapter 6.

Informing Regulation Policy

Current policy settings are based on a qualitative assessment of the risks and, while they are consistent with international guidelines on prudent use, they represent a precautionary approach. This is appropriate in the present state of knowledge, but the application of a precautionary approach assumes that risk assessments will be carried out as scientific data come to hand. The international guidelines propose that such assessments be done.

Obtaining data on the existence and prevalence of antimicrobial resistance in animal bacteria is necessary to being able to make an informed assessment of the risks of exposure of humans to zoonotic bacteria or the transfer of resistance determinants to human pathogens. This will assist in determining whether current policy settings are appropriate.

The application of risk analysis to the issue of antimicrobial resistance is in its infancy and will require more research before it can be used with confidence as a tool to inform policy decisions.

There is a widespread scientific debate on the importance of antimicrobial use in food animals as a contributor to the evolution of antimicrobial resistance in human pathogens. While there is good international evidence for exposure of humans to resistant zoonotic pathogens, such as *Salmonella* and *Campylobacter*, that have acquired their resistance through the use of antimicrobials in animals, the evidence for transfer of resistance determinants from animal commensals to human pathogens does not allow any conclusions to be drawn. Considering the possible pathways by which humans and their pathogens might be exposed (see Figure 7.1), it is clear that, in New Zealand at least, the food pathway is not the only one that should be considered. However, the lack of data allows no more than speculation.

A Surveillance Programme

A pragmatic surveillance programme employing existing microbiological sampling systems is proposed, and considerable detail has been provided to show how it can work. It is seen as an appropriate first step in acquiring better information about antimicrobial resistance in the so-called indicator organisms *Salmonella*, enterococci and *E. coli* associated with meat. It is hoped that *Campylobacter* can be added in the future.

The proposed surveillance programme is intended to have objectives similar to those of the UK programme, which are to:

- provide information on the prevalence, patterns and trends of antimicrobial resistant micro-organisms in animals and their environment and their spread;
- produce this information so that it can be related to patterns detected in similar micro-organisms in foodstuffs and humans;
- investigate any relationship that might exist between the prevalence of resistance to antimicrobials in animals, the pattern of use and the amounts of antimicrobials sold for use in animals;
- investigate any relationship that might exist between the prevalence of resistance to antimicrobials in animals and husbandry methods, non-antimicrobial constituents of animal feed, vaccination or hygiene procedures;
- use the data generated to guide and encourage the responsible, prudent and judicious use of antimicrobials by the veterinary profession and producers and thus prolong the efficacy of these valuable drugs;
- address the issue of cross-correlation with parallel human antimicrobial resistance surveillance schemes; and
- use the data generated to identify areas for further research and investigation.

New Zealand's agricultural practices are sufficiently different from those of other countries that assumptions based on overseas data and experience may be irrelevant and are potentially misleading. Equally important is the evidence of changing practices that are likely to alter the rates of exposure of animal and plant bacteria to antimicrobials.

The Panel considers that the management of the programme must involve careful analysis of the value of the data produced so that timely changes are made. Evaluation must take account of whether improved risk assessments can be made and that, in turn, policy settings can be re-examined.

The Future Role of an Advisory Group

The role of a future advisory group is to give advice to the ACVM Group and Medsafe on all aspects of antimicrobial resistance including related public health consequences where any application for registration of a veterinary antimicrobial medicine involves a new active, a new use, a changed risk profile or some other novel feature.

The advisory group could offer advice or peer review on the results of surveillance and monitoring programmes, including recommendations on changes to surveillance and monitoring programmes to reflect changes in information needs.

The advisory group would be expected to maintain oversight on international issues and trends, and advise on research, education and any other technical matters pertinent to the regulation of antimicrobial use.

The Expert Panel suggests a regular review of the registration of antimicrobial products and their conditions of use on a schedule to be determined by the ACVM Group and Medsafe. Those antimicrobials of high concern to public health should be reviewed every five years.

SUMMARY OF RECOMMENDATIONS

Use of Antimicrobials

1. The development of animal disease management and good husbandry practices that minimise the routine prophylactic use of antimicrobials should be actively promoted by NZFSA, NZVA, animal industry organisations and the pharmaceutical industry.
2. The use of streptomycin in the pipfruit and summerfruit industries should continue to be permitted under present controls.
3. The use of streptomycin for the treatment of tomato seedlings should be phased out.
4. The horticultural industries should be encouraged to continue to seek alternative strategies to control bacterial diseases so that the use of streptomycin can be phased out in the future.
5. Ongoing monitoring of resistance in the plant pathogens that are targets for streptomycin treatment should be undertaken.

Regulation and Management of the Use of Antimicrobials

6. The ACVM Act amendment to give statutory authority for applying conditions of registration to antimicrobial veterinary medicines in furtherance of public health objectives should be passed as soon as possible.
7. The ACVM Group should continue its present policy of classification of antimicrobial veterinary medicines for the purpose of registration (Stratification of Class I Prescription Animal Remedies, 2001), notwithstanding the potential non-compliance of the policy with the OIE Guideline (as presently drafted).
8. A programme of surveillance and monitoring of antimicrobial resistance of animal bacteria as described in Chapter 7 should be implemented as soon as practical.
9. The annual summary of statistics on sales of antimicrobial veterinary medicines should be accompanied by an analysis that shows how the medicines are used. Information on use should be obtained from industry sources and veterinarians who service the various industries. Consideration should be given to commissioning selected veterinarians to undertake periodic sentinel quantitative surveys of use within species/industries.
10. The ACVM Group and MoH should commission the development and documentation of generic risk analyses of pathways by which humans are exposed to resistant zoonotic bacteria, and human pathogens may acquire resistance determinants of animal origin as a basis for future decisions on the registration and classification of antimicrobial veterinary medicines.
11. The development and documentation of 'best practice' guidelines for veterinarians in the prudent use of antimicrobials drawing on the expertise within NZFSA, NZVA and its membership, the pharmaceutical industry and elsewhere should be given high priority.
12. The proposed classification of antimicrobials used in New Zealand set out in Table 5.2 should be adopted as a resource.

Recommendations on Specific Antimicrobials

Aminoglycosides

13. Evidence of synergistic effect and enhanced efficacy of mixtures of β lactam and aminoglycoside should be required at the time of their next registration.
14. Oral aminoglycosides, alone or in combinations, should not be used to treat non-specific enteric infections in groups of food-producing animals. If used to treat gut infections, their selection should be confirmed by bacteriology and susceptibility tests.

Bacitracin

15. Bacitracin resistance should be monitored as part of the surveillance system to investigate any correlation of bacitracin and vancomycin resistance trends. If no correlation is seen, this surveillance could safely be stopped.

Cephalosporins

16. Third and fourth generation cephalosporins should be registered for use in animals with a condition that they are for use only in life-threatening conditions in individual animals where culture and susceptibility testing (done prospectively or retrospectively) provides evidence of their unique clinical value.
17. Registration of current third and fourth generation cephalosporins for intramammary use and any new applications for registration should be reconsidered.
18. Conditions of the use of first and second generation cephalosporins in dry cow therapy should be that the criteria of Appendix 2 of the *New Zealand Veterinary Code of Professional Conduct* be applied and that they are the treatment of choice based on herd culture and susceptibility tests.

Fluoroquinolones

19. The first two conditions applied to marbofloxacin boluses should be applied to all use of fluoroquinolones in food animals.
20. The first condition should be applied to all fluoroquinolone use in non-food animals, and any registered indication for use that does not meet this criterion should be reconsidered.

Macrolides

21. The use of macrolides and similar drugs in cattle should be discouraged.
22. Macrolide resistance should be included in the surveillance system screens.

Anti-mycobacterial drugs

23. None of these drugs should be registered for use in animals without a condition that they are for use only in life-threatening conditions where a culture and susceptibility has shown that no other drug is likely to work or where there are sound clinical grounds to believe they are the drug of choice.

Streptogramins

24. Streptogramin resistance should be monitored as part of the surveillance system.

Informing Regulatory Policy

25. The present policy settings are prudent and conservative. No further general restriction on the use of antimicrobials in animals seems justified. Some specific adjustments are proposed in Chapter 6.
26. Risk assessment protocols acceptable to both the ACVM Group and Medsafe should be developed hand in hand with the surveillance and monitoring programme proposed above. These protocols must reflect New Zealand practices because they differ from practices in other countries.

A Surveillance Programme

27. A surveillance programme, as outlined in Chapter 7, utilising existing/proposed microbiological sampling in the food animal industries and existing laboratory resources should be established forthwith.
28. The programme should be managed by an oversight committee made up of persons with the requisite expertise, nominated by the funding parties.
29. The pilot studies described in Chapter 7 should be initiated to run in parallel with the surveillance programme.

Future Technical Advice

30. The ACVM Group and Medsafe should appoint a standing advisory group comprising expertise in medical microbiology, epidemiology, veterinary pharmacology, animal nutrition and veterinary practice to advise them on any matters related to the use of antimicrobials in animals and plants that influence the evolution of antimicrobial resistance and on the design and interpretation of the surveillance programme.

CHAPTER 1: INTRODUCTION

In 1999 the Antibiotic Resistance Steering Group convened by the Ministry of Agriculture and Forestry (MAF) commissioned an Expert Panel to undertake a review of the impact of feeding antibiotics to animals on the evolution of antibiotic resistance among human bacterial pathogens. The Expert Panel's report, *Antibiotic Resistance and the In-feed Use of Antibiotics in New Zealand*, reviewed the world's literature on the subject through May 1999, drew attention to the emerging international concern about the increasing prevalence of resistant bacteria that threatened to outstrip the availability of effective antimicrobial drugs and made 29 recommendations.

Prior to the commissioning of the 1999 report, assessment of antimicrobial resistance potential was not a part of the registration process for veterinary antimicrobial medicines although the availability of the majority of antimicrobials was controlled through veterinary prescription. In 2000 MAF's Agricultural Compounds and Veterinary Medicines (ACVM) Group undertook a complete review of the antimicrobial resistance potential of all currently registered antimicrobial active ingredients (see definition in Chapter 2), using a standardised qualitative risk assessment framework.

The actives were classified as high, medium, low or of no concern in respect to their public health significance. Management of identified risks is achieved via a system of stratified control (see Chapter 5) through veterinary prescription that ranges from 'no prescription required' for those veterinary medicines that are of no public health concern to a ban on their use in veterinary medicines (there are none in this category at present).

This re-classification of actives included acceptance of all the product specific recommendations of the 1999 report. 'Growth promotion' is no longer a permitted claim except for those actives that have been classified as having no public health concern, and registered products containing these actives may be sold 'over the counter' without veterinary prescription.

An important issue for regulators is to strike an appropriate balance between ensuring the prudent use of antimicrobials in animals and plants to minimise any potential transfer of resistance to human pathogens and ensuring animal health and welfare are not compromised through the unavailability of effective antimicrobials for the treatment of disease and the control of infections (Casewell *et al*, 2003). An emerging concern is the potential increase in microbiological load in animal products to which humans are exposed as the result of less effective infection control through the reduced use of effective antimicrobials (Cox, 2005; Cox and Popken, 2003).

The Antibiotic Resistance Steering Group reconvened the Expert Panel in 2004 to review and update the 1999 report. The Expert Panel's terms of reference have been extended to include all formulations of antimicrobial drugs used in animals and plants by all routes of administration and to take account of the guidelines that have been or are being promulgated by the international standard setting organisations: the World Health Organization (WHO), the Office International des Epizooties (World Animal Health Organization, OIE) and the Joint FAO/WHO Food Standards Programme (Codex Alimentarius). These guidelines, which are a response to the international concern mentioned above, are designed to assist countries

to promulgate policies and regulations to manage the use of antimicrobials and to contain the development of resistant micro-organisms and transferable resistance determinants.

The use of antimicrobials in animals, especially their use at low concentrations to promote growth and improve food conversion efficiency, has been singled out as a possible avenue for transferring resistant bacteria and resistance determinants to human pathogens. The international interest in the subject has spawned a burgeoning scientific and non-scientific literature and an increasingly politicised international debate over the significance of this pathway. The members of the Expert Panel have used the international literature to inform their conclusions in this report but the focus of this report is the New Zealand situation and perspective. We have not attempted to provide a review of antimicrobial resistance literature except as is relevant to New Zealand.

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CHAPTER 2: APPROACH TO THE REVIEW AND METHODOLOGY

Terms of Reference

The Expert Panel was asked to:

1. prepare a technical report on the impact of antibiotic (antimicrobial) use in animals and horticulture on the development of antibiotic resistance in human pathogens;
2. develop a framework for the ongoing provision of technical advice to the ACVM Group and Medsafe for the approval of antibiotic products under the ACVM Act; and
3. make recommendations on the priorities for action in the area of antibiotic resistance over the next two - five years.

In addition, the Expert Panel was asked to address a number of matters identified in a technical brief prepared by the ACVM Group and Medsafe. These matters included:

- the use of aminoglycosides, in particular streptomycin, dihydrostreptomycin and spectinomycin, in animals and plants in view of their importance in human medicine;
- the risks to human medicine of the use of the macrolides and lincosamides in animals, including the relative risks of using actives within the group in conferring resistance to other actives;
- risk management of the use of cephalosporins;
- the use of antimicrobials in dry cow therapy.

The full text of the technical brief is in Appendix 2.

Scope

The Panel elected to limit its consideration of the topic to the hazard of the use of antimicrobials in animals and plants to the emergence of resistance in human pathogens. The importance of extending the effective life of antimicrobials in veterinary medicine and horticulture is acknowledged but not specifically considered.

Focus

The focus of this report is on matters that are relevant in the New Zealand context. Reviews of the literature and the experience of other countries have been used to inform the Panel's thinking but no comprehensive review of these sources is provided.

Definitions

For the purposes of this report, definitions from the Agricultural Compounds and Veterinary Medicines Act 1997 and from Codex Alimentarius have been used.

Agricultural compound (ACVM Act)

...any substance, mixture of substances, or biological compound used or intended for use in the direct management of plants and animals or to be applied to the land, place or water on or in which the plants and animals are managed for the purposes of –

- a. managing or eradicating pests, including vertebrate pests; or

- b. maintaining, promoting or regulating plant or animal productivity and performance or reproduction; or
 - c. fulfilling special nutritional requirements; or
 - d. the manipulation, capture or immobilization of animals; or
 - e. diagnosing the condition of animals; or
 - f. preventing or treating conditions of animals; or
 - g. enhancing the effectiveness of an agricultural compound used for the treatment of plants and animals; or
 - h. marking animals; -
- and includes any veterinary medicine, any substance, mixture of substances or biological compound used for post-harvest pest control or disinfection of raw primary produce and any substance, mixture of substances or biological compound declared to be an agricultural compound for the purposes of this Act by Order in Council made under section 2.

Growth promotion (Codex Alimentarius)

Use of antimicrobial substances to increase the weight gain and/or the efficiency of feed utilisation in animals by other than purely nutritional means. The term does not apply to the use of antimicrobials for the specific purpose of treating, controlling or preventing infectious diseases even when an incidental growth response may be obtained.

Prophylactic use (Codex Alimentarius)

Use of antimicrobial(s) in healthy animals considered to be at risk of infection or prior to the onset of clinical disease. This treatment includes:

- control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals;
- prevention of an infectious disease that has not yet been clinically diagnosed.

Therapeutic use (Codex Alimentarius)

Use of antimicrobial(s) for the specific purpose of treating an animal(s) with a clinically diagnosed infectious disease or illness.

Veterinary antimicrobial drug (abbreviated to antimicrobial) (Codex Alimentarius)

Naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of organisms). Where anti-coccidial products have antibacterial activity, they should be considered as veterinary antimicrobial drugs, except where this is precluded by national legislation.

Veterinary medicine (ACVM Act)

Any substance, mixture of substances or biological compound used or intended for use in the direct management of an animal. The term ‘animal remedy’ does not appear in the Act but is used in the term ‘prescription animal remedy’.

CHAPTER 3: ANTIMICROBIAL RESISTANCE

Mechanisms of Antimicrobial Resistance and the Transfer of Resistance Determinants between Bacteria

Antimicrobial resistance is a measure of the ability of bacteria to survive a defined concentration of an antimicrobial (Acar and Röstel, 2003). It can be defined in clinical terms (survival of therapeutic doses of an antimicrobial), pharmacodynamic terms (survival of antimicrobial concentrations found in physiological compartments), microbiological and genetic terms (mechanisms that induce the requirement for higher than normal minimum inhibitory concentrations) or epidemiological terms (resistant subpopulations within a population). Resistance may be an intrinsic characteristic presumed to have evolved through exposure of the bacteria (e.g. many enterobacteriaceae) to natural antimicrobial substances or be acquired through exposure to antimicrobial drugs.

Acquired antimicrobial resistance appears to develop over time in bacterial populations in relation to the quantity of antimicrobial used (Goossens *et al*, 2005). Although variation exists in the rate of resistance development for a particular bacterium-antimicrobial combination, this general ‘rule’ seems to apply. Factors that may hasten the development of resistance include:

- inappropriate or unnecessary use of antibiotics;
- the use of broad-spectrum antimicrobials;
- long durations of treatment; and
- low concentrations of antimicrobial.

Resistance mechanisms include efflux pumps, altered cell wall antimicrobial receptors or targets, resistance to penetration of the antimicrobial, metabolic pathways that by-pass the toxic effects of the antimicrobial and detoxification of the antimicrobial (Acar and Röstel, 2003). The by-pass and detoxification mechanisms are often associated with high levels of resistance. Details of the mechanisms that alter the efficacy of specific antimicrobials are given in Chapter 6.

Resistance determining genes may arise through:

- chromosomal mutation with spread of the resistant clone favoured through continuing exposure to the antimicrobial (so called vertical transmission);
- horizontal transfer of plasmids, transposons or even naked DNA containing resistance genes;
- conjugation; or
- transduction by a bacteriophage.

Large plasmids or transposons may carry an array of resistance genes leading to transfer of resistance to more than one antimicrobial (Summers, 2002). This is of particular significance in the evolution of resistance because the induction of resistance through the use of one antimicrobial may lead to bacteria that are resistant to a group of related antimicrobials (cross-resistance) or to resistance to antimicrobials in other groups (co-resistance). Although mutations and horizontal transfer events are likely to be random, the presence of an antimicrobial in the environment of a bacterial population is likely to influence the ecology of

that population by eliminating or reducing the numbers of susceptible bacteria and favouring the multiplication of resistant organisms.

Reduction in the frequency of resistant bacteria in populations following withdrawal of antimicrobial use has been observed, for example avoparcin resistance in *Enterococcus faecium* (Bager, Emborg and Heuer, 2002), but persistence of many resistance genes in bacterial populations is not dependent on continued exposure to antimicrobials (Summers, 2002). The use of antimicrobials in humans and animals has created an expanded pool of transferable resistance genes that may be recruited and exchanged by both pathogens and commensals (O'Brien, 2002).

While it is generally acknowledged that resistance to antimicrobials among human pathogens is due mainly to the use and misuse of antimicrobials in the human population (Harbarth and Samore, 2005), transfer of resistance determinants from animal and environmental bacteria has been identified as significant in the evolution of antimicrobial resistance in human pathogens and, in particular, the use of antimicrobials in food animals has been singled out as an important pathway. The pathways by which transfer might occur and the evidence that transfer does occur are discussed in more detail in Chapter 7. The animal bacteria that are most frequently incriminated are the zoonotic *Salmonella* serotypes and *Campylobacter* spp. The animal commensals *Enterococcus* spp. and *Escherichia coli*, because they are found in the food chain, are known to develop resistance, and the gastrointestinal tract is considered to be prime site for bacterial populations to mix and for transfer to occur.

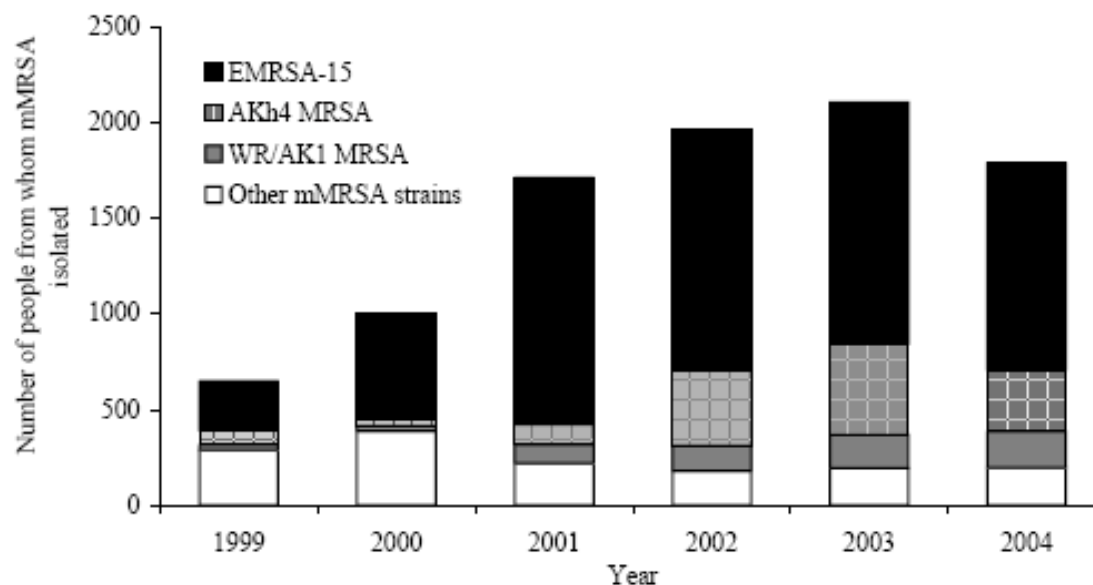
The Status of Antimicrobial Resistance in the New Zealand Human Population

Human health has benefited enormously in the last 60 years from the use of antimicrobials because it has been possible to treat the majority of bacterial infections with antibiotics. The public health importance of infection and antibiotic resistance is recognised as a priority by the Ministry of Health in New Zealand (Ministry of Health, 2001).

Antibiotic resistance rates show great regional variation, which can be related to some extent to variations in the amount of antibiotic prescribed to humans (Goossens *et al*, 2005). This report does not review the international literature on antimicrobial resistance to any great extent. However, there are numerous reports describing much higher rates of antimicrobial resistance in human bacterial isolates overseas than in New Zealand (see Bell and Turnidge, 2003; Biedenbach *et al* 2004, Stelling *et al* 2005). The incidence of antibiotic-resistant organisms has increased, including methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae, and penicillin resistant *Streptococcus pneumoniae* (ESR, 2004).

- In spite of wide regional differences, multiresistant MRSA comprises less than 10% of all *S. aureus* isolates in New Zealand hospitals, which is much lower than most Australian, European and American hospitals. Current rates are illustrated in Figure 3.1.

Figure 3.1: MRSA resistance rates in New Zealand hospitals and the community



Source: www.esr.cri.nz

- ESBL organisms have been increasing in New Zealand over the last five years from <20 a year to 305 isolates in 2003 (Table 3.1) and 282 in 2004. This increase is due partly to better detection but there has also been local spread within some health care facilities. Again the problem is small compared to other countries, but there is no room for complacency.

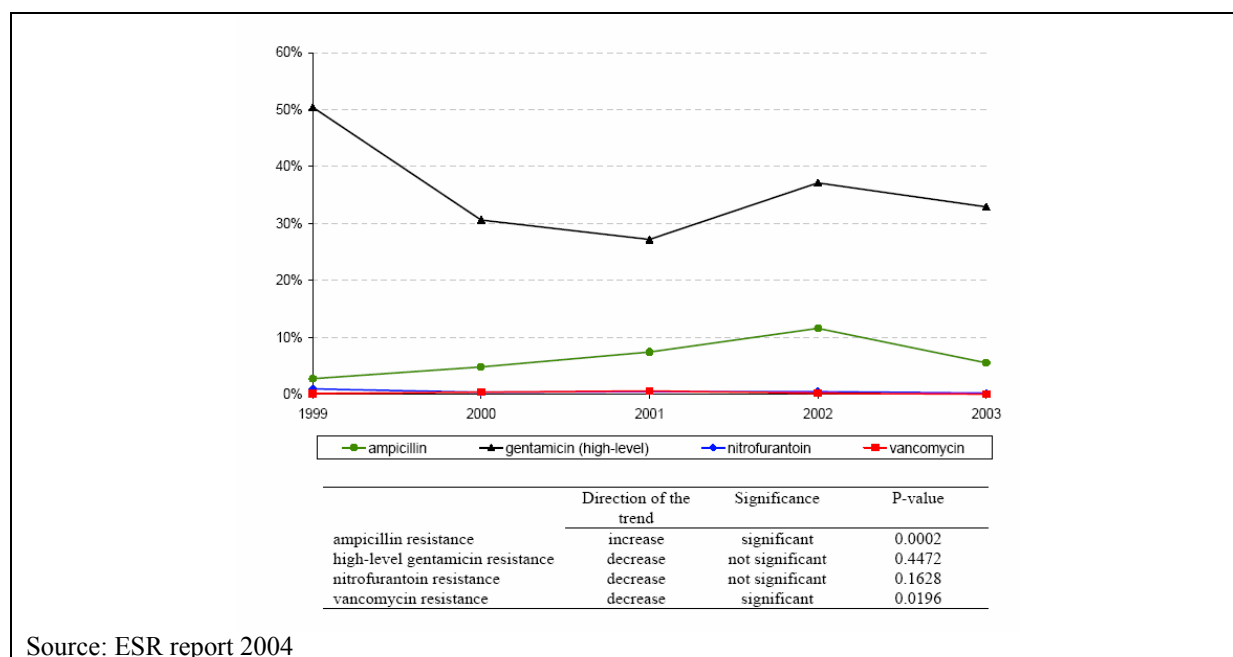
Table 3.1: Antimicrobial resistance in *Escherichia coli*: comparison of hospital and community rates

	Percent resistance (1999 rate - 2003 rate)	
	Hospital	Community
ampicillin	55.0 – 52.4	54.3 – 51.7
co-amoxiclav	19.3 – 13.9	6.1 – 6.8
cephalothin	20.4 – 16.4	-
cefuroxime	0.9 – 1.7	-
cefotaxime	0.1 – 0.9	-
fluoroquinolone	1.2 – 3.1	1.2 – 4.9
gentamicin	1.5 – 2.7	-
nitrofurantoin	1.2 – 1.0	1.5 – 2.8
trimethoprim	24.9 – 24.9	24.1 – 22.9

Source: www.esr.cri.nz

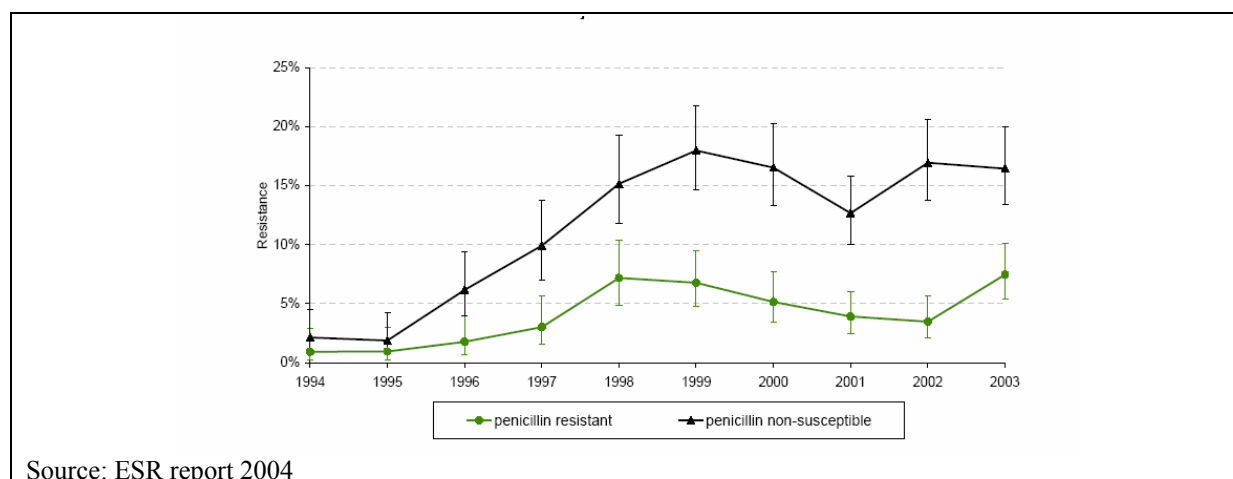
- Vancomycin-resistant enterococci (VRE) remain rare in New Zealand with fewer than 20 clinical isolates since 1996 (ESR, 2004; Heffernan and Blackmore, 2004) (Figure 3.2). In 2004, two *E. faecium vanA* and one *E. faecalis vanA* were seen at ESR. All three were infections acquired overseas. Many of the larger hospitals conduct surveillance for VRE and other multiresistant organisms, but <0.5% of hospitalised patients were colonised with VRE in one study by Briggs *et al* (2002). Like ESBL-containing Gram negative organisms, some strains of VRE have greater capacity for causing outbreaks that have caused disruption to hospital services overseas (CDC, 1995, 2005).

Figure 3.2: Antimicrobial resistance rates in *Enterococcus* spp. hospital isolates 1999-2003



- The rates of *S. pneumoniae* with reduced susceptibility/resistance have increased dramatically, from <3% to 28% over the past ten years (ESR, 2004) (Figure 3.3). The increase has been due largely to the circulation of particular serotypes that possess greater penicillin and cephalosporin resistance (Bean and Klena, 2005).

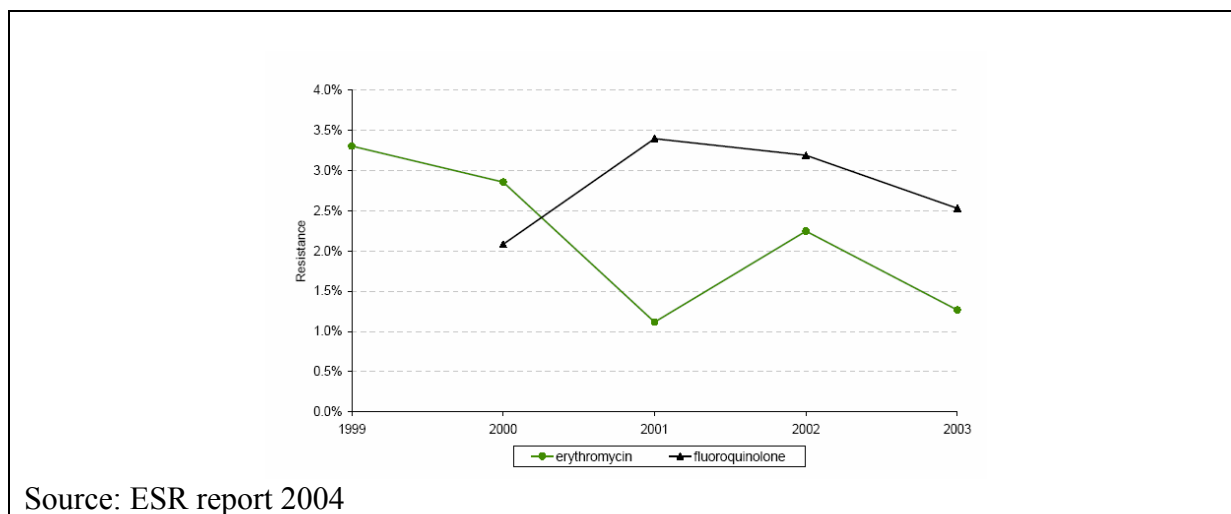
Figure 3.3: Antimicrobial resistance in *Streptococcus pneumoniae*: change over the decade 1994 to 2003



- There has been a slow but definite increase in fluoroquinolone resistance in *E. coli* and other enterobacteriaceae. The explanation for this increase has not been specifically studied.

Of food-borne pathogens, New Zealand has a high rate of *Campylobacter* and *Salmonella*-related diarrhoea (Lake *et al*, 2003). While these infections in humans only occasionally require antimicrobials for treatment, resistance to macrolides and quinolones remains low compared to other countries (Dowling *et al*, 1998) (Figure 3.4).

Figure 3.4: Changes in the resistance of *Campylobacter* spp. to erythromycin and fluoroquinolone



Antimicrobial Resistance in Animal Bacteria

While antimicrobial resistance in animal bacteria in New Zealand is well recognised, no systematic monitoring of the occurrence of antimicrobial resistance has been undertaken. Reports of resistance relate mainly to two forms of use of antimicrobials:

1. the use of antimicrobials to treat mastitis in dairy cows; and
2. in-feed use of antimicrobials in poultry.

Streptococcus* spp. and *Staphylococcus

Following the introduction of penicillin for the treatment and control of streptococcal mastitis caused by *Streptococcus agalactiae*, penicillin-resistant staphylococci emerged as the most significant cause of mastitis (Elliott, 1971; Buddle and Cooper, 1980). Streptomycin/penicillin combinations, new generation penicillins and cephalosporins have become the treatments of choice.

Carman and Gardner (1997) have described the trend in bacterial isolates from the bovine udder from 1976 to 1995 based on 36,000 milk samples examined in the Ruakura Animal Health laboratory. Their study confirmed the progressive replacement *S. agalactiae* by *S. aureus* as the principal pathogen and as the control of cow-to-cow transmission of *Staphylococcus* infections was achieved, infections by the environmental opportunists *Streptococcus uberis* and *S. dysgalactiae* have become more prevalent. Other environmental organisms are occasionally implicated in mastitis.

Approximately 25,000 disc susceptibility tests were performed on the most prevalent pathogens. No evidence of resistance to cephalothin and nafcillin was found. All *Staphylococcus* species were sensitive to cloxacillin and tetracycline. The numbers of *Staphylococcus* isolates resistant to lincomycin rose from 0% to 6% over the period. Up to 5.5% of *S. uberis* exhibited resistance to tetracycline and lincomycin but no trends were apparent.

Situmbeko (2004) examined minimum inhibitory concentrations of a range of antimicrobials on 115 *S. aureus* isolates from milk from mastitis-affected cows. The selected antimicrobials were ampicillin, cefuroxime, cephalexin, cephalothin, dihydrostreptomycin, erythromycin, neomycin, novobiocin, oxacillin, penicillin and tetracycline. In comparison with other New Zealand and Denmark studies in 1998, the minimal inhibitory concentration values that inhibited 90% of isolates tested were slightly higher for ampicillin and penicillin, slightly lower for novobiocin and the same for cephalothin, erythromycin and oxacillin.

Gibson (2005) reported the occurrence of penicillin resistance in *S. aureus* isolates from 23.6% of farms sampled and isolates from 6.2% of these farms had combined oxacillin/penicillin resistance.

Enterococcus spp.

Vancomycin-resistant *Enterococcus faecalis*, *E. faecium* and *E. durans* have been isolated from chickens administered avoparcin and the bacteria were shown to carry the *vanA* gene. The VRE clone of *E. faecalis* has persisted after the cessation of avoparcin treatment (Manson, Smith and Cook, 2004). Approximately 65% of isolates carried the *ermB* gene conferring resistance to macrolides but no resistance to gentamicin or ampicillin was found.

Manson, Keis *et al* (2004) demonstrated that acquired bacitracin resistance in poultry *Enterococcus faecalis* isolates is mediated by a plasmid-located ABC transporter and a novel regulatory protein, and that the plasmid transferred at high frequency to another strain of *E. faecalis*. A survey of 382 poultry enterococci showed 98% to have minimum inhibitory concentrations of bacitracin to be $\geq 256 \mu\text{g/ml}$.

Other records

It can be inferred from the results of testing human and non-human isolates of non-typhoidal salmonellae and *Campylobacter* tested by ESR that antimicrobial use does not appear to have had a significant impact on the prevalence of antimicrobial resistance in these species. Harrow *et al* (2004) examined 251 isolates of *Campylobacter jejuni* and *C. coli* from South Canterbury and found most were susceptible to the clinically significant antimicrobials. However, five isolates from pig offals were resistant to erythromycin.

Over the period 1999 to 2002, ESR examined antimicrobial susceptibilities of isolates from veterinary laboratories but the programme was discontinued after 2002 because it was felt that the isolates obtained were not representative of the food animal population. Most isolates were from cattle, dogs and cats and small numbers of isolates from a wide range of other species. *Escherichia coli* and *S. aureus* were the two species tested. The conclusions were that the pattern of resistant *E. coli* was similar to, but generally lower than, human isolates (although fluoroquinolone and tetracycline rates were similar) and that there was no clear trend over the four years. In contrast, *S. aureus* exhibited more variability with resistance to clindamycin, co-trimoxazole, fluoroquinolones, gentamicin and tetracyclines being more common among animal isolates than human, and a trend of increasing resistance among isolates from dogs and cats. Isolates from cattle exhibited much lower levels of resistance.

Antimicrobial Resistance in Plant Bacteria

The only antibiotic registered for control of bacterial diseases in New Zealand is streptomycin. It is used for control of fire blight on pipfruit and different diseases on stone fruits. It is also used to a lesser extent for control of diseases on tomato seedlings.

Resistance to streptomycin in *Erwinia amylovora*, the fire blight pathogen, was first reported in 1991 (Thomson *et al*, 1993). Streptomycin resistant strains of *E. amylovora* were limited to the Hawke's Bay region. Subsequent surveys showed that only a relatively low percentage of strains were resistant to this antibiotic. No survey has been carried out for several years.

Following the discovery of resistance in *E. amylovora*, other plant-associated bacteria (plant pathogens such as *Pseudomonas syringae* and epiphytes such as *Pseudomonas fluorescens* and *Pantoea agglomerans*) from Hawke's Bay were found to carry genes that conferred streptomycin resistance. These genes were carried by transposons or plasmids (Vanneste and Voyle, 2001).

Recently, streptomycin resistance was also found in plant pathogens from stone fruit orchards from Hawke's Bay and Central Otago (Vanneste *et al*, 2005). In at least a few cases from Hawke's Bay, a link between streptomycin resistance and copper resistance has been established (Vanneste and Voyle, 2003).

Conclusions

The incidence of MRSA, ESBLs, VRE and resistant *S. pneumoniae* in human isolates is increasing but rates remain low by comparison with Australian, European and American data. Levels of resistance in *Salmonella* and *Campylobacter* isolates of human and non-human origin are also low. The Expert Panel considers the preservation of this relatively favourable status to be a priority.

Information on antimicrobial resistance in animal and plant bacteria indicates that where antimicrobial use is high, such as in mastitis control/treatment and in-feed use of antimicrobials, antimicrobial resistance has developed. However, the data are fragmentary and do not allow conclusions on the transfer of resistance to human pathogens or any specific relationship with resistance among human pathogens in New Zealand to be drawn.

Nonetheless, the Panel has concluded that the potential for transfer continues to exist and this justifies the continuation of a prudent approach to the use of antimicrobials. The need for more structured examination of resistance in animal bacteria is highlighted by observations such as the identification of *S. aureus* strains isolated from bovine udders resistant to oxacillin and penicillin, vancomycin-resistant *Enterococcus* spp. isolated from chickens fed avoparcin and bacitracin-resistant *Enterococcus faecalis* isolated from chickens. A proposal for a structured surveillance and monitoring programme is discussed in Chapter 7.

Reducing antibiotic resistance in bacterial pathogens requires:

- using antibiotics in humans or animals only when they are proven to be of benefit;
- complying with infection control principles in both animal husbandry and human health care settings;

- using control mechanisms that do not use antibiotics wherever possible, e.g. vaccination and infection control systems (this applies to both human and animal health); and
- controlling the pathways by which resistant bacteria or their resistance determinants can be transmitted to other bacteria. Food safety programmes, such as those administered by NZFSA, are an integral component of the management of the transfer of resistance determinants through food.

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CHAPTER 4: THE USE OF ANTIMICROBIALS IN ANIMALS AND PLANTS IN NEW ZEALAND

The Use of Antimicrobials in Animals

Data on the sales of antimicrobials have been collected since 1999 but the method of collection and analysis has been evolving so that comparison of data between years is problematic. Supply of sales data to the ACVM Group was voluntary up to 2003. There are also problems in equating sales data to the actual use of the products because of factors such as registration for use in multiple species and off-label use. The recently developed practice by the ACVM Group of obtaining informed comment on the use of antimicrobial products from industry sources and veterinarians has helped clarify some of the ambiguities apparent in the raw data.

Sales data for the years 1999 to 2003 are shown in Table 4.1.

Table 4.1: Sales of antimicrobial actives for animal use

	1999	2000	2001	2002	2003
	kg active compound				
Macrolides/lincosamides	6082	6601	5293	6279	5011
Penicillins	8476	10423	13747	11065	13709
Cephalosporins	763	839	879	1176	1076
Tetracyclines	2311	3167	2840	1509	3458
Sulphonamides/trimethoprim	2066	5571	5930	2998	4429
Aminoglycosides	2207	2122	1692	2325	2132
Glycopeptides (avoparcin)	1060				
Virginiamycin	891		15		29
Fluoroquinolones	18			23	28
Clavulanic acid				73	141
Nitro-imidazoles				60	105
Nitrofurans				168	111
Bacitracins	10905			26579	27263
Orthosomycins				453	
Others	549	15461	25013	63	65
TOTAL	35328	44184	55409	51629	57557
Ionophores	18032	36215	50169	53107	

Source: ACVM Group, NZFSA

In 1999 sales of antimicrobials for use in animals, excluding the ionophores, were 47% of total sales in New Zealand (Expert Panel, 1999). Data for total sales or sales for human use are not available for subsequent years.

Because of changes made to the way that data have been derived and analysed, comparison of quantities used within species by year or by purpose is unreliable. The following commentaries are based on indicative trends suggested by the data. Table 4.2 shows a ranking of the specific antimicrobials used by class of antimicrobial with what are considered to be the principal uses. The ionophores are not discussed because they are considered to have no public health significance.

Table 4.2: Ranking of antimicrobials used in animals by the amount used for what is considered to be the principal uses. The % total column is the proportion of the specific antimicrobials sold as a percentage of the total amount of that class of antimicrobials sold based on 2003 sales figures

Rank of to quantity used	Antimicrobial class	Antimicrobial	Species	Principal routes of administration	% of total for class
High	Macrolides/ lincosamides	tylosin	pigs	feed, water,	94
	Penicillins	cloxacillin	poultry	intramammary	18
		procaine penicillin G	cattle	parenteral	63
Medium	Penicillins		all	intramammary (with streptomycin)	
				feed	
				feed,	
	Bacitracin	zinc bacitracin	pigs,poultry		100
	Macrolides/ lincosamides	tilmicosin	pigs		4
	Penicillins	amoxycillin	companion	oral	5
		ampicillin			5
		penethamate			5
		benzathine penicillin G			4
	Cephalosporins	cephalexin	companion	oral	40
			cattle	intramammary	
	Tetracyclines	cephalonium	cattle	intramammary	41
		oxytetracycline	principally cattle, pigs and poultry	feed, water, parenteral	99
			mainly cattle and pigs	oral	26
	Sulphonamides/ trimethoprim	sulphadiazine	mainly cattle	oral	15
		sulphaguanidine	mainly cattle	oral	15
		sulphamethazine	cattle, pigs, poultry	oral, feed	40
		trimethoprim	all	Mainly oral	9
	Aminoglycosides	streptomycin,	all mammals	oral	82
		dihydrostreptomycin		parenteral (50%) intramammary (27%)	

The production data presented in this chapter were obtained from MAF (2004) and industry sources.

Pastoral sector

Pastoral farming of dairy and beef cattle, sheep, deer, goats and other grazing species relies on the animals harvesting forage; the animals are at pasture for 12 months of the year and only dairy animals are husbanded on a daily basis. Mass antimicrobial medication of animals through feed or water is generally not a practical option. The majority of antimicrobials used are applied therapeutically, prophylactically or metaphylactically. The most important examples of mass medication are:

- intramammary administration of therapeutic doses of antimicrobials to control or prevent mastitis during the non-lactational period to prevent the onset of clinical mastitis or subclinical mastitis with elevated somatic cell counts in milk in the subsequent lactation (dry cow therapy);
- oral medication of adult dairy cows with ionophores to prevent bloat – daily administration over a period of several weeks; and
- oral or parenteral treatment or metaphylaxis of enteric infections in hand-reared calves – oral medication may be in feed.

In the pastoral system, dairy cow numbers have increased by 33% since 1990 and productivity per cow by 25%. Beef cattle numbers fluctuate around a mean number depending on markets, especially the USA, while productivity has increased by 10%. A significant number of dairy animals are represented in the beef kill either as culled dairy cows or hand-reared dairy calves that are sold to beef farmers after weaning. Sheep numbers fell from about 70 million to 39 million over the period 1990 to 2004 and have now stabilised. However, productivity has increased substantially to a point where more sheep meat was produced in 2000 than was produced in 1990.

Intramammary preparations containing penicillin, cloxacillin, the cephalosporins cephalexin and cephalonium, and streptomycin and dihydrostreptomycin (usually in combination with penicillin) make up more than 90% of all antimicrobials used in cattle in 2003 and will have been used almost exclusively in dairy cattle.

The total amount of antimicrobials used in cattle has increased by about 30% since 2000. It appears that most of this increase can be explained by the increase in the numbers of dairy cows, but the high penalty costs of high somatic cell counts in milk has stimulated the use of dry cow therapy.

One practice that is of concern is the diversion of milk from antimicrobial-treated cows to hand-reared calves, creating at least a theoretical opportunity for the development of resistance in gut organisms by exposure to low doses of antimicrobials.

Tetracyclines, sulphonamides and streptomycin are all used for the prophylaxis and treatment of enteric infections in hand-reared calves but the amounts used are comparatively small.

It is considered that antimicrobial use in other pastoral species is largely therapeutic and limited in quantity.

Pigs

Consumer demand for lean white meat continues to fuel growth in poultry and pork production. Pork production increased 10% between 2003 and 2004, 5% from increased numbers and 5% from increased pig weights.

In recent years the number of herds in the commercial pork industry has reduced to around 200 but the size of herds has increased. This has been accompanied by a shift towards high health status herds free of most of the major diseases. Vaccination against endemic diseases is widely practised and this has reduced the use of antimicrobial treatment for conditions such as pneumonia. A high proportion of locally produced pork is derived from these commercial herds.

There are substantial numbers of people who 'keep a few pigs' primarily for their own use, but small numbers may enter commercial marketing channels.

A high proportion (about 33%) of the pig meat products consumed in New Zealand is imported. Most, but not all, of these products are cooked before release to the retail market. This is a factor to be accounted for in the design of surveillance programmes.

The method of analysis of the 2003 sales figures does not allow precise estimates of antimicrobial use in pigs, but the annual report on the regulatory control of antimicrobials (ACVM Group, 2004) includes a description of pig management and the use of veterinary medicines. From the point of view of antimicrobial use in the intensively managed commercial piggeries, the key points are:

1. Routine in-feed medication to control endemic diseases has largely been replaced by infection control and eradication programmes, vaccination strategies and hygiene management, which contribute to reduced use of antimicrobials.
2. Some infection control and eradication programmes involve prolonged periods of treatment with antimicrobials e.g. in-feed tiamulin to eradicate swine dysentery, tiamulin, tilmicosin and lincomycin to eradicate mycoplasmosis.
3. When antimicrobials are used, there is a greater use of single or episodic pulsed therapeutic doses of antimicrobials rather than continuous medication. Control of proliferative ileitis is achieved through periodic pulsed treatments with tylosin or lincomycin at therapeutic doses.

The commercial industry is mainly serviced by a small number of specialist veterinarians who have a high degree of awareness of antimicrobial resistance and of the risks to the image of the industry and its products of perceptions of high antimicrobial use.

Poultry

There are approximately three million birds kept for egg production and 87.5 million broilers are produced per year in New Zealand. Poultry meat production has increased from approximately 60,000 tonnes in 1990 to 160,000 tonnes in 2004. Production increased 8% between 2003 and 2004 mainly through growth in numbers, but there has been an increase in bird weights of 2% per year over the past decade.

Data on antimicrobial use in the poultry industry can be reliably obtained because of the high degree of vertical integration of the industry.

The New Zealand poultry industry enjoys a high health status and its freedom from most of the major virus diseases of poultry means that routine treatments on farms target a relatively narrow range of infections. In particular, freedom from infectious bursal disease means that infections consequent to compromised immune status are a significantly smaller problem than in many other countries.

The annual report on the regulatory control of antimicrobials (ACVM Group, 2004) includes a description of current management practices in the broiler, egg layer and turkey segments of the industry. In respect of antimicrobial use, the key points are:

1. The short growing period for broilers (28 to 52 days) limits the opportunity to use antimicrobials and the choice of those that can be used. This is less of a constraint in egg layers and turkeys.
2. Zinc bacitracin (95% of the time) and avilamycin (5% of the time) are fed to broilers throughout the growing period.
3. Therapeutic feed medication with apromycin or amoxicillin has limited use. Other products registered for this purpose are not used by the major companies.
4. Sixteen per cent of laying birds receive continuous tylosin medicated feed to control mycoplasmosis. A smaller number receive pulsed treatment with therapeutic doses of tylosin.

5. Barn-raised and free-range layers (10% of the total number of layers) receive zinc bacitracin and may be treated with amoxicillin to control fowl cholera.

Companion animals

Approximately 2% of all prescription antimicrobials were used in companion animals in 2003 but the range of products available for use is wider than for the food animal species. Some off-label use of human antimicrobial medications is known to occur but the amounts used are not known. Sales figures for 2003 indicate use of the following antimicrobials: clindamycin hydrochloride, amoxicillin, clavulanic acid, cephalexin, doxycycline, sulphamethoxazole, sulphathiazole, trimethoprim, framycetin, gentamicin, spiramycin and enrofloxacin.

The potential significance of antimicrobial resistance in companion animals as a pathway for transfer of resistance is discussed in Chapter 7.

Antimicrobial Use in Horticulture

Antimicrobial use in horticulture is currently limited to the use of streptomycin for the treatment of fire blight in apples and pears, and bacterial diseases of stonefruit and tomato seedlings. Alternatives to the use of this antibiotic are limited. The most frequently used alternatives are the copper-based compounds, which can lead to resistance problems and toxicity.

There is good evidence of success of streptomycin for control of fireblight in pipfruit but the evidence of efficacy when used to control bacterial blast and bacterial spot on stonefruit and bacterial diseases on tomato seedlings is less convincing.

The Expert Panel sought the views of Pipfruit New Zealand, Summerfruit New Zealand and Vegfed on the consequences of discontinuing or phasing out the use of streptomycin or the introduction of tighter controls over its use. Each industry indicated that improvements in management practices had significantly reduced the amount of streptomycin used but they would be very reluctant to see it withdrawn from use when there are no current satisfactory alternatives.

Streptomycin is of greatest importance to the pipfruit industry for the control of fireblight. Applications are subject to GROWSAFETM controls. The frequency of application to summerfruit species has been significantly reduced over the past five years from an average 0.75 to 0.175 applications per year. Vegfed advises streptomycin use on tomato seedlings is minimal if used at all. It may be used by small-scale growers who raise their own seedlings.

The belief that the amount of streptomycin used currently is significantly reduced is borne out by current sales figures. In the 2003/04 season, 495 kgs of streptomycin active ingredient were sold as compared to the 1,200 kgs reported in the 1999 Expert Panel's report. It is likely that actual usage was less than the amount sold because some would be held in retail outlets.

The following analysis provides a basis for assessing the risk of this use to human exposure to resistant bacteria or resistance determinants.

Hazards

- Development of resistance to streptomycin in plant pathogens
- Development of resistance to streptomycin in other plant-associated bacteria
- Transfer of resistance determinants to plant-associated bacteria.

Exposure

Fruit trees are treated at the flowering stage up to shuck fall or as nursery stock, and tomato plants are treated at the seedling stage. Risk of direct exposure to streptomycin from consumption of fruits from treated plants is probably very close to nil. However, reports of the antibiotic entering the food chain through honey have been published overseas. (Reybroeck, 2003). Large numbers of non-target organisms are exposed to the antibiotic.

Impact

Streptomycin is used infrequently because of the nature of plant bacterial diseases. Its future use might be impacted by our competitors and customers producing and demanding food that has not been treated with antibiotics. Few alternatives are available.

Benefits

The principal beneficiary is the pipfruit industry where streptomycin can reduce the impact of serious outbreaks of fireblight. However, the benefit of using streptomycin has not always been clearly established, especially in areas where resistance is common and persistent.

Potential for Antimicrobial Use in Other Industries

Antibiotics for control of bee diseases

There is no use of antimicrobials for the control of bee pathogens known to the Expert Panel. Fumagillin, used in the past for control of nosema, has not been registered under the Hazardous Substances and New Organisms (HSNO) Act 1996 and is not on the market in New Zealand. Two pathogens present in New Zealand are treated with antibiotics overseas:

1. nosema, caused by the protozoan *Nosema apis*, is treated with the sulphonamide fumagillin;
2. American foulbrood (AFB), caused by *Paenibacillus larvae* subsp. *larvae*, is treated with oxytetracycline. Recently, strains of *P. larvae* subsp. *larvae* resistant to oxytetracycline have been isolated in the USA (Miyagi *et al*, 2000) and in Argentina (Alippi, 2000).

European foulbrood (EFB), caused by *Melissococcus plutonius*, is not present in New Zealand. However, if it were detected in this country, the bee industry would most probably ask to be permitted to administer oxytetracycline as a treatment. The use of oxytetracycline for control of EFB overseas has not led to strains of the EFB pathogen, *M. plutonius*, resistant to tetracycline (Hornitzky and Smith, 1999; Waite *et al*, 2003).

The use of tetracycline would also affect *P. larvae* subsp. *larvae*, the causal agent of AFB, rendering the early diagnosis of this disease more difficult. So far New Zealand has been very successful at keeping AFB under control without the use of antibiotic (Goodwin, 2005). This strategy relies mostly on the ability to detect the early signs of the disease (Goodwin and Van Eaton, 1999). Therefore, the use of oxytetracycline for control of EFB might lead to the

current strategy for control of AFB becoming unreliable. It would then be tempting to extend the use of oxytetracycline for control of AFB that could lead to strains of the AFB pathogen becoming resistant to oxytetracycline.

Antimicrobial use in aquaculture

There are no antimicrobial products registered for use in aquaculture at present and no off-label use known to the Expert Panel.

Antibiotic resistance marker genes (ARMGs)

During genetic modification marker genes are generally used to facilitate the selection and identification of the few genetically modified cells among the large number of untransformed cells. Antibiotic resistance genes are the most prevalent markers.

Antibiotic resistance genes are used at two stages during the genetic modification of eukaryotes. These are:

1. in bacteria during development of the gene construct containing the genes to be introduced into the eukaryote; and
2. in selection of transformed eukaryotic cells following introduction of the gene construct.

They remain in the final genetically modified organism (GMO) although they serve no purpose. Alternative strategies are under development and include use of alternative markers, and inactivation or removal of the marker gene (Read, 2000).

Although there is no evidence that the use of antibiotic resistance genes in GMOs contributes to the development of resistant pathogens, there is a theoretical possibility that they could add to the problem. Horizontal gene transfer has been reported between distantly related bacteria, and from bacteria to yeast, mammalian cells and plant cells. The few examples of transfer from plants to bacteria demonstrated by DNA sequence comparisons and the lack of experimental evidence, albeit from a small number of studies, suggest that the occurrence of successful gene transfer from plants to bacteria is extremely low. However, rare transfer events can be amplified quickly under selective pressure. If gene transfer occurred the gene must be expressed before there could be any potential impact, the significance of which would in turn depend on the clinical importance of the antimicrobial to which the gene confers resistance.

In the case of GM bacteria containing ARMGs, the probability that transfer occurs is likely to be the same as between non-GM bacteria and gut bacteria.

The European Food Safety Authority has categorised ARMGs into three groups based on the extent of distribution of the antibiotic resistance genes in bacteria in the environment (soil, plant, water and mammalian gut) and clinical importance of specific antibiotics to human and veterinary medicine. This has resulted in the recommendation that some resistance genes e.g. those conferring resistance to tetracyclines should not be present in GM plants to be placed on the market or in plants used for experimental field trials (Opinion of the Scientific Panel on GMOs, 2004).

In New Zealand the Environmental Risk Management Authority expects ARMGs to be removed or inactivated in GMOs that are food or feed crops for commercial release or viable

GM food micro-organisms for release. If the ARMG in the GMO for conditional or full release into the environment is active, the Authority assesses the risk on a case-by-case basis taking into account the nature of the resistance gene, the organism that is genetically modified and the circumstances in which the GMO will be used (ERMA New Zealand, 2004).

Conclusions

The raw data on sales of antimicrobials for animal use are not helpful in getting an understanding of how and why they are used. This understanding is critical for undertaking risk assessments and, in particular, for estimating the public health costs versus the animal health and welfare benefits of their use and understanding the consequences of withdrawing antimicrobials from use in animals.

The total sales of antimicrobials excluding the ionophores have increased by 60% from 1999 to 2003 with the largest increases in the penicillins (60%) and bacitracin (150%). In the other groups, sales appear to be relatively static. In the same period, the numbers of dairy cows, pigs and poultry have increased substantially. The increase in the use of the penicillins appears to be attributable mainly to intramammary use whereas bacitracin is used almost exclusively in poultry production.

Intramammary antimicrobial products account for about 90% of the total amount of antimicrobials used in cattle. The very strong financial incentive to achieve low somatic cell counts in raw milk is a significant driver of this use. There is an equally strong financial disincentive to supply raw milk that contains antimicrobial residues. There are no particular short-term incentives to avoid the development of antimicrobial resistance.

The anecdotal evidence available to the Expert Panel indicates a high degree of awareness of the consequences of using antimicrobials among veterinarians and industry organisations, particularly in the intensive industries. The Panel has been told of the efforts being made to ensure that the use of antimicrobials is not a panacea for poor husbandry practices. The Panel was given examples of husbandry programmes designed to achieve high health status and the performance benefits of doing so.

The Expert Panel believes there is considerable value to be obtained by developing and documenting 'best practice' guidelines on the use of antimicrobials by veterinarians. This is discussed in Chapter 5.

The horticultural industries that use streptomycin appear to do so responsibly. The amount used is reducing as the industries adopt management strategies to limit its use. Sales of streptomycin in 2003 were less than half that sold in 1999. Notwithstanding the apparently reduced threat of bacterial diseases to these industries, there is no satisfactory alternative to streptomycin in those situations where outbreaks of bacterial disease occur.

Because of the timing of applications, the fruit produced from treated trees or plants presents a low risk to humans of the transfer of streptomycin residues, resistant pathogens or resistance determinants. Streptomycin applications in orchards may contribute selection pressure for resistance to plant-associated and soil organisms but the significance of this is unknown. It is not considered to be a significant pathway for human exposure. The Expert

Panel endorses ERMA New Zealand's policy on the release of genetically modified organisms that include antibiotic resistance marker genes.

Recommendations

1. The development of animal disease management and good husbandry practices that minimise the routine prophylactic use of antimicrobials should be actively promoted by NZFSA, NZVA, animal industry organisations and the pharmaceutical industry.
2. The use of streptomycin in the pipfruit and summerfruit industries should continue to be permitted under present controls.
3. The use of streptomycin for the treatment of tomato seedlings should be phased out.
4. The horticultural industries should be encouraged to continue to seek alternative strategies to control bacterial diseases so that the use of streptomycin can be phased out in the future.
5. Ongoing monitoring of resistance in the plant pathogens that are targets for streptomycin treatment should be undertaken.

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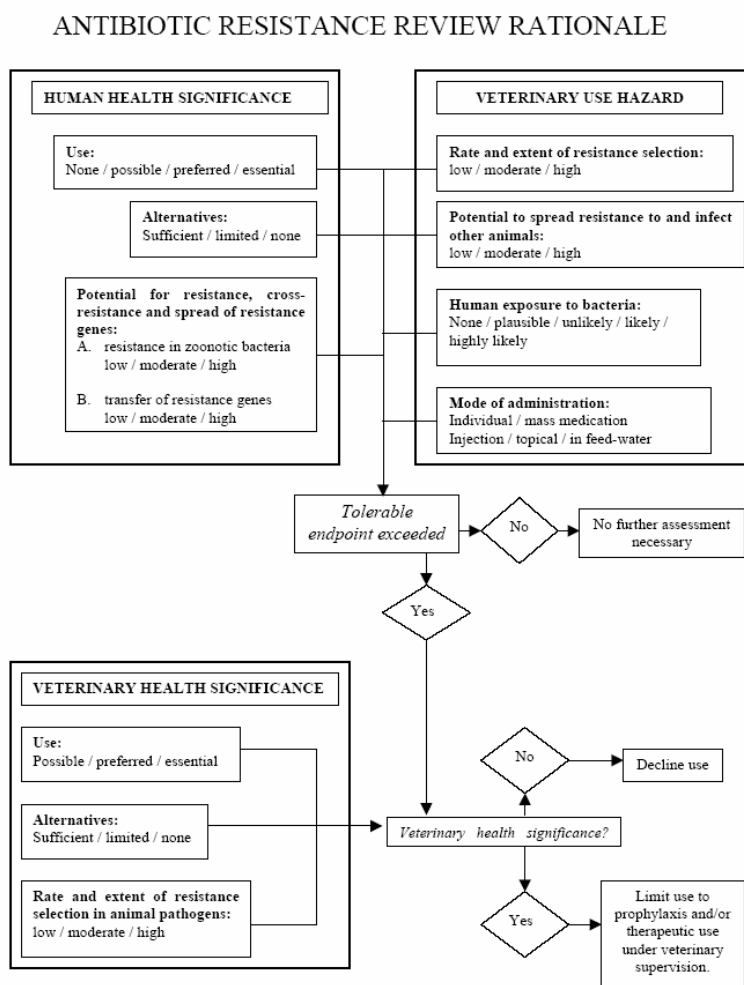
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CHAPTER 5: REGULATION AND MANAGEMENT OF THE USE OF ANTIMICROBIALS IN ANIMALS

The Regulatory System

Following the 1999 Expert Panel report, the ACVM Group, in consultation with Medsafe and ERMA, undertook a complete review of all registered antimicrobial products from the perspective of their potential to contribute to the evolution of antimicrobial resistance in human pathogens. A standard qualitative risk assessment framework was adopted and the actives were classified as having high, medium, low or no concern to public health. The assessment framework is illustrated in Figure 5.1.

Figure 5.1: Risk assessment framework used by the ACVM Group to assess the public health risks of the use of antimicrobials in animals



The results of this assessment are set out in Table 5.1. The categorisations of the antimicrobials, their assignment to prescription classes and the summary of the conditions of use are generalisations. Each registered product has specific conditions of use.

Table 5.1: Classification of antimicrobials used in animals according to their concern to public health and a summary of the conditions applying to their use

Greatest concern	Medium concern	Low concern	No concern
avoparcin (cross-resistance to vancomycin)	Macrolides and lincosamides	Penicillin	Avilamycin
Cephalosporins (newer generations)	Tetracyclines	Amoxicillin	Carbadox
Aminoglycosides		Ampicillin	Flavophospholipols
Fluoroquinolones		Flucloxacillin	ionophores
Penicillins (newer generation virginiamycin)		Polymyxin	
		Nitro-imadazoles	
		Nitrofurans	
		Tiamulin	
		Sulphonamides	
		Trimethoprim	
		Chloramphenicols	
		Fusidic acid	
		Zinc bacitracin	
Summary of conditions of registration			
Antimicrobials of greatest and medium concern		Antimicrobials of low concern	Antimicrobials of no concern
Use limited to therapeutic purposes – use essential for health and welfare		Veterinary diagnostic and therapy competency	MoH confirms no concern
Veterinary diagnosis and selection of the active as the only effective treatment		Veterinary prescription	No prescription required
Label statements relating to the resistance risk from indiscriminate use and use in food-producing animals requires bacteriological confirmation and susceptibility testing where appropriate		Reference to management of resistance not required	May be sold over the counter
Prophylactic use permitted where the infection challenge warrants it		May be administered by anyone	Growth promotion claim may be permitted if resistance unlikely
For some actives, use is limited to that specified on the label, no discretion is allowed and the prescribing veterinarian must notify the ACVM Group in each case of its use			

In evaluating the effectiveness of the regulatory regime administered by the ACVM Group and the complementary regulatory and management procedures put in place by the Veterinary Council of New Zealand (VCNZ) and NZVA, the Expert Panel compared the New Zealand practices with those recommended by the international standard setting bodies.

Since 2000 WHO, OIE and FAO have collaborated to bring together guidelines for the management of the use of antimicrobials in food-producing animals. Several sets of international guidelines that recommend interventions by national governments to manage the use of antimicrobials for the purpose of containing the evolution of antimicrobial resistance in bacteria and resistance determinants that may be transferred to human pathogens have been developed (or are under development). They are:

1. WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food, 2002 (WHO/CDS/csr/drs/2001.2).
2. OIE Guidelines for the Harmonisation of Antimicrobial Resistance Surveillance and Monitoring Programmes. Terrestrial Animal Health Code, 2004, Appendix 3.9.1.
3. OIE Guidelines for Monitoring the Quantities of Antimicrobials used in Animal Husbandry. Terrestrial Animal Health Code, 2004, Appendix 3.9.2.
4. OIE Draft Guidelines for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine. Terrestrial Animal Health Code, Appendix 3.9.3.
5. OIE Draft Guidelines for Risk Assessment for Antimicrobial Resistance arising from the Use of Antimicrobials in Animals. Terrestrial Animal Health Code, Appendix 3.9.4.
6. Laboratory Methodologies for Bacterial Antimicrobial Susceptibility Testing. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, 2004, Chapter 1.1.10.
7. Codex Alimentarius Proposed Draft Code of Practice to Minimise and Contain Antimicrobial Resistance. Alinorm 05/28/31, Appendix VIII.

It is expected that the Codex Alimentarius Draft Code of Practice will be adopted at the meeting of the Codex Alimentarius Commission in July 2005. The OIE draft Guidelines were considered at the meeting of the International Commission in May 2005, but the outcome had not been made public at the time of writing this report.

These documents have or will have recognition under WTO rules as international best practice. Countries may choose to follow these guidelines in full or select those parts that are relevant to their circumstances. However, if they choose to adopt more stringent standards, they must be able to demonstrate a scientific basis for their decisions. A precautionary approach may be acceptable provisionally to justify a more stringent standard but it carries an obligation to undertake a more objective risk analysis within a reasonable period of time.

The Expert Panel benchmarked the New Zealand systems for the management of antimicrobial use in animals against these guidelines. The Panel also noted that the *New Zealand Veterinary Code of Professional Conduct*, issued by the VCNZ, was amended in 2004 to incorporate new responsibilities under the stratified system of control of the use of veterinary antimicrobials. The Code also includes three appendices related to the use of antimicrobials:

1. Code of practice for the discretionary use of human and animal medicines by registered veterinarians (approved as a code of practice under section 28 of the ACVM Act);
2. Standard relating to sufficient information (relates to the right to prescribe drugs for the control of dry cow therapy);
3. Code of practice for registered veterinarians writing prescriptions for prescription medicines and prescription animal remedies (prescription writing standard) (approved as a code of practice under section 28 of the ACVM Act).

The conclusions of the benchmarking are set out below.

Antimicrobials Used in New Zealand: A Proposed Classification

A wide variety of antimicrobials is used in humans and animals in New Zealand. Some are of greater concern than others as far as development of resistance and the public health significance of resistance is concerned. The JETACAR Report (1999) divided antimicrobials into four categories, based on these concerns:

- Category A:** essential antibiotics for treatment of human infections where there are few or no alternatives for many infections
- Category B:** other alternatives are available but fewer than for category C, or there are concerns that use will lead to a greater risk of resistance in category A drugs
- Category C:** a reasonable number of alternative agents in different classes are available to treat most infections
- Category D:** drugs with no equivalent in human medicine.

Category A drugs include anti-pseudomonal penicillins, third generation and fourth generation cephalosporins, carbapenems, monobactams, some aminoglycosides including streptomycin, some macrolides, glycopeptides, fluoroquinolones, streptogramins, most drugs used to treat mycobacterial infections and fusidate. Some category A drugs, such as carbapenems, monobactams, glycopeptides and fusidate, are not used in animals. Others, such as anti-pseudomonal penicillins, are used only very rarely in individual companion animals. These will not be discussed further.

A proposed classification using the JETACAR criteria listed above is set out in Table 5.2. It differs from the original JETACAR table by including newer antimicrobials and antimicrobials in use in New Zealand but not in Australia. The column headed 'Animal Health Importance' is a judgement of the relative importance of the antimicrobial in veterinary medicine and is also based on the JETACAR criteria.

Table 5.2: A proposed classification of the antimicrobials used in New Zealand based on the JETACAR classification

ANTIBIOTIC		HUMAN USE		ANIMAL USE		Animal Health Importance
	JETACAR Category.	Treatment	Prophylactic use	Treatment	Prophylactic use	
narrow spectrum penicillins						
benzyl penicillin	C	G+ infections, some anaerobes	yes	all species by injection, intramammary	Dry cow Intra-mammary	high
phenoxymethyl penicillin	C	G+ infections, some anaerobes	yes	very rare (off-label)	no	low
moderate spectrum penicillins						
ampicillin, amoxycillin	C	G+ and G- infections	yes	all species by injection, intramammary, oral	Dry cow therapy	high
anti-pseudomonal penicillins						
piperacillin, ticarcillin	A	<i>Pseudomonas</i> infections	no	very rare (off-label)	no	low
β lactamase inhibitors						
clavulanate, tazobactam	B	with amoxycillin / ticarcillin for β lactamase producing bacteria	no	all species by oral, injection intramammary	no	high
β lactamase resistant penicillins						
cloxacillin, flucloxacillin, dicloxacillin, (methicillin)	B	<i>S. aureus</i> infections (not MRSA)	yes	Cows by intramammary	dry cow intramammary	high
1st generation cephalosporins						
cephalexin, cephalothin, etc	B	mainly G+ infections	yes	all species by oral, injection intramammary	dry cow therapy, dog	med
2nd generation cephalosporins and cephamycins						
cefuroxime, cefaclor, cefoxitin etc	B	broad spectrum	yes	Cows by intramammary	no	low
3rd generation cephalosporins						
cefotaxime, ceftiofur?	A	serious G- infections	no	cattle and pigs by injection	no	low
3rd generation anti-pseudomonal cephalosporins						
ceftazidime, ceftriaxone, etc	A	<i>Pseudomonas</i> infections	no	very rare (off-label)	no	low
4th generation cephalosporins						
cefpirome, cefquinome, etc	A	serious G- infections	no	cattle and pigs by injection intramammary	no	low
carbapenems and monobactams						
imipenem, aztreonam, etc	A	serious G- (G+) infections	no	none	no	low
aminoglycosides						
(dihydro)streptomycin	A	2nd line TB treatment combinations	no	all species by injection,	dry cow	low

ANTIBIOTIC		HUMAN USE		ANIMAL USE		Animal Health Importance
	JETACAR Category.	Treatment	Prophylactic use	Treatment	Prophylactic use	
				intramammary	therapy	
gentamicin	A	G- infections	no	all species by injection	no	high
tobramycin, amikacin	A	G- infections	no	very rare (off-label)	no	low
neomycin	C	G- infections	no	all species by intramammary topical	dry cow intramam.	low
spectinomycin, apramycin	B	G- infections	no	pigs and poultry by oral	yes	med
tetracyclines						
oxytetracycline, doxycycline, minocycline, etc.	C	mycoplasma, <i>Chlamydia</i>	no	all species by oral, injection intramammary, topical	yes	med
(potentiated) sulphonamides						
sulphonamides	C	rarely used	no	calves and poultry by oral	yes	low
co-trimoxazole, co-trimazine	C	2nd line broad spectrum	no	all species by injection, oral	no	high
trimethoprim, bacquiloprim	C	urinary tract infections	yes	Only with sulphonamides	no	high
macrolides, lincosamides and similar drugs						
azithromycin, clarithromycin	A	respiratory tract infections	no	cats and horses, off-label, oral	no	med
erythromycin, roxithromycin	C	G+ infections	no	pigs, poultry, cattle, dogs by intramammary	no	med
tylosin, tilmicosin	C	none	no	pigs, poultry by oral, cattle by injection.	yes	med
lincomycin, clindamycin	B	G+ infections	no	pigs and poultry by oral	yes	med
tiamulin, valnemulin	D	none	no	Pigs by oral	yes	high
telithromycin	A	respiratory tract infections	yes	none	no	low
streptogramins						
quinupristin and dalfopristin	A	MRSA infections	no	none	no	low
virginiamycin	A	none	no	horses, poultry by oral	yes	low
glycopeptides						
vancomycin, teicoplanin	A	MRSA infections	no	none (avoparcin withdrawn)	no	low
nitroimidazoles						
metronidazole, tinidazole, dimetridazole	B	anaerobic infections	no	all species by injection, oral	yes	med
quinolones						
ciprofloxacin, enrofloxacin, norfloxacin, etc	A	serious G- infections	no	cattle and pigs by injection, dogs and cats by injection,	no	med
levofloxacin, moxifloxacin,	A	serious G- infections, (G+ infections,	no	none	no	low

ANTIBIOTIC		HUMAN USE		ANIMAL USE		Animal Health Importance
	JETACAR Category.	Treatment	Prophy-lactic use	Treatment	Prophy-lactic use	
anti-mycobacterials						
isoniazid, pyrazinamide, ethambutol, ethiononamide, etc	A	TB (in combination)	no	none	no	low
clofazimine	A	leprosy	no	cats, very rare (off-label)	no	low
rifampicin	A	TB and leprosy (in combination)	no	horses, rare (off-label)	no	low
dapsone	A	leprosy	no	none	no	low
amphenicols						
chloramphenicol	B	broad spectrum	no	dogs and cats, eye drops	no	low
florfenicol	B	none	no	cattle and pigs by injection	no	med
oxazolidinones						
linezolid	A	MRSA infections	no	none	no	low
polypeptides						
bacitracin	D	topical, rare		pigs and poultry by oral; dogs topical	yes	high
colistin, polymixin B	C	topical, <i>Pseudomonas</i> infections	no	dogs, topical	yes	med
nitrofurans						
nitrofurantoin	C	urinary tract infections (rare)	no	dogs, oral, very rare (off-label)	no	low
nitrofurazone	C	none	no	all species by topical	yes	low
furazolidone	C	none	no	pigs and poultry, oral; all species by topical	yes	med
ionophores						
monensin, salinomycin, etc	D	none	no	poultry and pigs, cattle by oral	yes	high
orthosomycins						
avilamycin	D	none	no	poultry by oral	yes	med
quinoxalines						
carbadox (olaquinox)	D	none	no	pigs and poultry by oral	yes	high
dinitro-o-toluamide, nicarbazin	D	none	no	pigs and poultry by oral	yes	med
others						
flavophospholipol	D	none	no	no longer registered (poultry oral)	yes	low
fusidate	A	MRSA infections	yes	none	no	low
mupirocin	B	MRSA infections	yes	none	no	low

Conclusions

The Panel concluded that the regulatory system as represented by:

- the ACVM Act;
 - the administrative procedures operated by the ACVM Group, including collaboration with MoH and ERMA New Zealand; and
 - the New Zealand Veterinary Code of Professional Conduct meets the recommendations of the international guidelines in most respects but noted the following:
1. The ACVM Act does not currently provide for conditions of registration to be applied to antimicrobial veterinary medicines in furtherance of public health objectives. A Bill to amend the Act is being drafted to provide the statutory basis for what is currently done administratively.
 2. The surveillance and monitoring systems do not meet the recommended standards because no surveillance or monitoring of antimicrobial resistance in animal bacteria is undertaken.
 3. The regulation of antimicrobials does not comply with the draft OIE Guidelines for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine, which recommend that “all the antimicrobial agents used in animals are prescribed by a veterinarian or other authorised person” (Article 3.9.3.3 Paragraph 12). However, the Expert Panel does not consider that antimicrobials that are of no concern to human antimicrobial resistance (e.g. ionophores, carbadox) should be subject to veterinary prescription.
 4. Statistical data on antimicrobial sales have been collected since 2000 but the methodology of collection and analysis has been evolving. Comparisons between years are problematic. It is noted that the supply of sales statistics became compulsory from 2003 and a method of presentation settled on. Sales data do not provide an adequate picture of the use of these medicines and are of little value on their own.
 5. While risk analysis methodology has been applied on a case-by-case basis, there has not been an adequate examination of the pathways by which human exposure to resistant animal bacteria or resistance determinants could occur. The Expert Panel considers that if these assessments were done and adopted by the MoH and the ACVM Group, decisions relating to the registration of antimicrobial products would be facilitated.
 6. Unlike their medical counterparts, veterinarians have few resources to turn to in obtaining guidance on the prudent use of antimicrobials. There is an unfulfilled need for development and documentation of ‘best practice’ that offers advice on the choice of treatments that are designed to achieve the intended clinical result while preserving the efficacy of veterinary antimicrobial products in the long term and reducing the risk of resistance transfer. The Panel has been informed of how this is done in the medical sphere and has formed the view that more could be done to assist veterinarians in matters of prudent use. Such an approach could preserve veterinarians’ right to access the spectrum of available antimicrobials and may be as effective in achieving some of the objectives of management of antimicrobial resistance as regulation of use. This approach would require a collaborative effort involving the expertise that resides within NZFSA, NZVA and its membership, the pharmaceutical industry and elsewhere. The Panel notes that NZVA has an established ‘best practice’ vehicle.

Recommendations

6. The ACVM Act amendment to give statutory authority for applying conditions of registration to antimicrobial veterinary medicines in furtherance of public health objectives should be passed as soon as possible.
7. The ACVM Group should continue its present policy of classification of antimicrobial veterinary medicines for the purpose of registration (Stratification of Class I Prescription Animal Remedies, 2001) notwithstanding the potential non-compliance of the policy with the OIE Guideline (as presently drafted).
8. A programme of surveillance and monitoring of antimicrobial resistance of animal bacteria as described in Chapter 7 should be implemented as soon as practical.
9. The annual summary of statistics on sales of antimicrobial veterinary medicines should be accompanied by an analysis that shows how the medicines are used. Information on use should be obtained from industry sources and veterinarians who service the various industries. Consideration should be given to commissioning selected veterinarians to undertake periodic sentinel quantitative surveys of use within species/industries.
10. The ACVM Group and MoH should commission the development and documentation of generic risk analyses of pathways by which humans are exposed to resistant zoonotic bacteria and human pathogens may acquire resistance determinants of animal origin as a basis for future decisions on the registration and classification of antimicrobial veterinary medicines.
11. The development and documentation of 'best practice' guidelines for veterinarians in the prudent use of antimicrobials drawing on the expertise within NZFSA, NZVA and its membership, the pharmaceutical industry and elsewhere should be given high priority.
12. The proposed classification of antimicrobials used in New Zealand set out in Table 5.2 should be adopted as a resource.

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CHAPTER 6: RECOMMENDATIONS FOR THE REGULATION OF THE USE OF SPECIFIC ANTIMICROBIALS IN ANIMALS

The ACVM Group's technical brief to the Expert Panel sought the Panel's views and recommendations on a number of specific antimicrobials and antimicrobial classes. The Panel's analysis and recommendations follow. Further detail is provided in the related appendices. Most of the reviewed literature on which the recommendations are based was from overseas because there is very little published New Zealand data, particularly on the prevalence of resistance. The literature references relating to specific antimicrobials are included in the appendices.

The recommendations are intended to encourage prudent use of the antimicrobials in animals while ensuring that conditions of access to the antimicrobial products do not impinge on the health and welfare of animals. The Panel has taken account of the fact that any change in use patterns can have detrimental as well as beneficial effects. For example, swine dysentery in pigs is usually kept under control using tiamulin. The only other drug that is reliably effective is carbadox. If carbadox is withdrawn because of concerns about its carcinogenicity (as seems likely) then the alternatives are:

- tylosin or lincomycin - resistance has developed overseas (including Australia);
- copper or arsenic compounds - can cause environmental problems with slurry disposal;
- some ionophores - relatively toxic to mammals, including pigs.

This situation has prompted research into alternatives, but nothing as effective as tiamulin has yet been found. Biosecurity and good husbandry are the basis of preventing swine dysentery, but these are not always enough. As wild birds can carry several species of *Brachyspira*, possibly including *B. hyodysenteriae* (Janssen *et al*, 2004), protecting against re-infection would be difficult. *Brachyspira hyodysenteriae* infection provokes antibody production, but vaccines have not been very effective at preventing infection (La *et al*, 2004). The pigs' diet can have a small effect (Hampson and Pluske, 2004) and anti-inflammatory fatty acids in food may help (Hontecillas *et al*, 2002). A variety of 'natural' products, such as citrus extracts may have some effect (Lobova and Cizek, 2004). Less toxic metals such as zinc (Zhang Peng *et al*, 2001) may also be useful.

In the final analysis, sick pigs have to be treated and any antibiotic used to treat them, such as doxycycline, clarithromycin or a fluoroquinolone, is likely to engender more concern about resistance than tiamulin. Casewell *et al* (2003) have drawn attention to both good and bad consequences of the withdrawal of growth promoters in Europe.

Aminoglycosides

See Appendix 3

The aminoglycosides are bactericidal, narrow spectrum (mostly Gram negative) antimicrobials. They have been in use since the 1940s but have significant drawbacks in clinical use: they are relatively toxic and do not penetrate tissues well. If given orally they will have only a local effect on the gut flora. For systemic effects, they must be injected. Systemic use in food animals is reducing because of residue concerns. The more modern

aminoglycosides are less likely to be inactivated by resistant bacteria, but are too expensive for most veterinary use. The older drugs are still widely used.

Actives in this group

Aminoglycosides used clinically include amikacin, dihydrostreptomycin, framycetin (neomycin B), gentamicin, kanamycin, neomycin (a mixture of neomycin A, B and C), netilmicin, paromomycin, streptomycin and tobramycin. Spectinomycin and apramycin are closely related but are usually classified as aminocyclitols. They are similar in most respects to aminoglycosides.

Spectrum of action

Aminoglycosides are mainly effective against aerobic gram-negative organisms. They can also be effective against some gram-positive organisms, such as *S. aureus*, some mycobacteria, some strains of mycoplasma and some spirochetes. They are inactive against anaerobes and streptococci. Some aminoglycosides are active against *Pseudomonas aeruginosa*.

They are sometimes given with other antimicrobials, particularly β lactams, particularly in oral and intramammary products, to achieve a synergistic effect. In most cases there is no evidence that synergism actually occurs (Whittem and Hanlon, 1997a and b).

Resistance

Resistance can arise from mutations in the bacterial ribosome, production of metabolising enzymes (probably most important), or reduced transport of the drugs into bacterial cells. A single plasmid may code for cross-resistance to several different aminoglycosides (Blackburn *et al*, 1984; Chaslus-Dancla *et al*, 1986; Platt and Smith, 1991) and also other antimicrobials (Johnson *et al*, 1994).

Uses in animals

Uses for which there is good evidence of efficacy and for which there are limited alternatives include:

- gentamicin and amikacin for bone and joint infections and septicaemia in cats, dogs and horses; and
- gentamicin for *Pseudomonas* infections.

Uses for which there is some evidence of efficacy and where alternatives exist:

- (dihydro)streptomycin for leptospirosis in food animals, actinobacillosis, gut infections
- neomycin - gut infections, otitis externa.

Uses for which there is limited or no evidence of efficacy:

- mastitis in cattle and pigs
- metritis when given by the intrauterine route
- pneumonia in cattle.

Conclusions

There are good animal health and welfare reasons to retain injectable and topical aminoglycosides as prescription veterinary medicines, but the benefits of oral and

intramammary formulations are questionable. Oral formulations for the treatment of diarrhoea in young animals have the potential to be used indiscriminately for uncomplicated diarrhoea where fluid therapy is the treatment of choice. Intramammary formulations, usually in combination with penicillin, became popular as *S. aureus* emerged as an important pathogen in bovine mastitis, but the synergy of the combination has not been established and there are more effective antimicrobials available. Combinations of β -lactams and aminoglycosides can be synergistic, neutral or antagonistic, depending on concentration, site of infection and causative organism.

Requiring evidence of synergistic effect and efficacy would bring the registered products into line with the ACVM *Standard and Guideline: Efficacy of Intramammary Antimicrobials*, which states (s2.1.5): “In the case of fixed combination products, it must be demonstrated that all active ingredients produce their expected effect(s).”

Recommendations

13. Evidence of synergistic effect and enhanced efficacy of mixtures of β lactam and aminoglycoside should be required at the time of their next registration.
14. Oral aminoglycosides, alone or in combinations, should not be used to treat non-specific enteric infections in groups of food-producing animals. If used to treat gut infections, their selection should be confirmed by bacteriology and susceptibility tests.

Bacitracin

See Appendix 4

Bacitracin is the only drug in this class. The producing organism, *Bacillus licheniformis*, has been fed to pigs overseas as a probiotic. Bacitracin requires divalent cations to be effective, and is usually combined with zinc.

Resistance

The main mechanism of resistance is thought to be increased expression of an efflux pump. Resistance in *Bacillus licheniformis* is mediated by *bcrABC* genes, which code for an efflux pump (Neumueller *et al*, 2001); the same genes seem to be involved in enterococci (Manson, Keis *et al*, 2004).

Resistance in *C. perfringens* can occur, but does not appear to persist in a flock. As long as other drugs are available to treat it in the short term, it is not regarded as a problem. A recent survey of *C. perfringens* in Scandinavian poultry showed no resistant isolates in Norway, 3% of isolates resistant in Sweden and 15% resistant in Denmark (Johansson *et al*, 2004). All were susceptible to ampicillin, which was used in large quantities to control necrotic enteritis when bacitracin was banned in Sweden and Denmark. *Clostridium aminophilum*, from cattle, can become resistant to ionophores, and this also causes bacitracin resistance (Houlihan and Russell, 2003).

There is some evidence that bacitracin can induce *vanA* expression in enterococci. However, the epidemiological evidence suggests that bacitracin use does not select for VRE.

Uses in animals

Bacitracin is used almost exclusively in the poultry industry to control necrotic enteritis caused by *Clostridium perfringens* Type A. Limited quantities are used in pigs to control a similar condition.

Conclusions

The 1999 report recommended that bacitracin be retained but be subject to veterinary prescription, and growth promotion claims should be removed. Since then its classification has been changed to Prescription Animal Remedy (PAR) 1. Bacitracin resistance in human pathogens or commensals would have no impact on human health because the drug is not used in human medicine. Bacitracin-induced expression of vancomycin resistance would be important, but seems not to occur outside the laboratory. If it were withdrawn from use in animals, other more valuable antibiotics would have to be used to treat necrotic enteritis. For example, in Scandinavia large quantities of ampicillin were used when bacitracin was banned.

Recommendation

15. Bacitracin resistance should be monitored as part of the surveillance system to investigate any correlation of bacitracin and vancomycin resistance trends. If no correlation is seen, this surveillance could safely be stopped.

Cephalosporins

See Appendix 5

The cephalosporins are β lactams, similar to penicillins, but the β lactam ring is protected from some β lactamase enzymes produced by bacteria by the shape of the adjoining ring. This means that cephalosporins are effective against some penicillin-resistant bacteria. The spectrum of activity varies with the different members of the group (see below).

Actives in this group

There are several different ways of classifying cephalosporins; the generation classification (below) is commonest. None of the classification systems are particularly useful with the newer drugs.

Generation	Spectrum	Veterinary drugs in NZ	Human drugs in NZ
1 oral	good G+, moderate G-, not <i>Pseudomonas</i>	cephalexin, cefadroxil	cephalexin, cefadroxil,
1 parenteral	very good G+, moderate G-, not <i>Pseudomonas</i>	cephalothin, cephaloridine, cefapirin, cephalonium	cephradine cephalozin, cephradine
2 oral	fair G+, good G-, not <i>Pseudomonas</i>		cefaclor
2 parenteral	fair G+, good G-, not <i>Pseudomonas</i>	cefuroxime	cefuroxime, cephmandole
3	moderate G+, very good G-, some activity against <i>Pseudomonas</i> and <i>Bacteroides</i>	ceftiofur	cefotaxime
3 antipseudomonal	moderate G+, very good G-, good <i>Pseudomonas</i>		ceftazidime, ceftriaxone

4	very good G ⁺ , very good G ⁻ , good <i>Pseudomonas</i> , <i>Bacteroides</i> , <i>E. faecalis</i>	cefquinome	cefpirome, cefepime
cephamycins	moderate G ⁺ , good G ⁻ , not <i>Pseudomonas</i> , good <i>Bacteroides</i>		latamoxef, cefotetan, cefoxitin

Resistance

The main mechanisms of resistance are through production of a range of β lactamases, which break down the drugs. These include *ampC* and extended spectrum β lactamases (ESBLs). Exposure to any cephalosporin could select for ESBL producing *E. coli*, MRSA and other resistant organisms. Fourth generation cephalosporins have greater stability to β lactamases produced by Gram negative organisms. As such, they are generally restricted in human health to treat infections proven or suspected to be caused by resistant Gram negative bacteria. ESBL genes have been isolated from *Salmonellae* and *E. coli* from chicken and beef in the USA (Zhao *et al*, 2001). Emergence of resistance to third generation cephalosporins in human pathogens has been linked to the use of fluoroquinolones, as well as third generation cephalosporins themselves (Talon *et al*, 2000).

Uses in animals

First and second generation cephalosporins are widely used in companion animals, particularly for β lactamase producing *S. intermedius* skin infections. They are also commonly used for β lactamase producing *S. aureus* mastitis in lactating cows, where their rapid elimination allows short withholding times.

The only third generation veterinary cephalosporin, ceftiofur, behaves in many ways more like a second generation cephalosporin. It is registered for use in *Pasteurella pneumonia* (rare in cattle in New Zealand, and is normally susceptible to penicillin) and foot rot (usually a trivial disease that can be cured by most antibiotics and antiseptics).

The only veterinary fourth generation cephalosporin, cefquinome, is used for similar infections to ceftiofur, and also acute *E. coli* mastitis with systemic involvement (also rare in New Zealand). It is used in pigs for respiratory infections and mastitis-metritis-agalactia syndrome. It is also available for intramammary use, where it is effective against β lactamase producing *S. aureus* and most of the *Streptococcus* spp. that can cause mastitis.

Conclusions

Animal welfare would be compromised if it were no longer possible to use these drugs in serious infections in individual animals. Use in trivial infections should be discouraged. The use of first and second generation cephalosporins in cows is mainly to treat *S. aureus* and streptococcal infections. There is an adequate selection of alternative treatments, so reduced use for this indication should not affect animal welfare. The short withholding periods of cephalosporins are valuable in lactating cows but are not critical in dry cow therapy.

As noted above, third and fourth generation cephalosporins are regarded in human medicine as both major drivers of antibiotic resistance and of critical clinical importance. Their use in terms of who can prescribe them, what they are used for and how they are used is controlled. In contrast, the constraints that apply to veterinary use are much more liberal. While the chances of bacteria or determinants resistant to third and fourth generation cephalosporins

being passed on to humans via the food chain are small, other pathways cannot be discounted and the consequences of transfer would be severe.

Recommendations

16. Third and fourth generation cephalosporins should be registered for use in animals with a condition that they are for use only in life-threatening conditions in individual animals where culture and susceptibility testing provides evidence of their unique clinical value.
17. Registration of current third and fourth generation cephalosporins for intramammary use and any new applications for registration should be reconsidered.
18. A condition of the use of first and second generation cephalosporins in dry cow therapy should be that the criteria of Appendix 2 of the *New Zealand Veterinary Code of Professional Conduct* be applied and that they are the treatment of choice based on herd culture and susceptibility tests.

Fluoroquinolones

See Appendix 6

Actives in this group

Enrofloxacin, marbofloxacin and orbifloxacin are used in animals in New Zealand. Sarafloxacin and danofloxacin are in veterinary use overseas. Norfloxacin and enrofloxacin's main metabolite, ciprofloxacin, is in human use in New Zealand. The newer generation fluoroquinolones (8-methoxyfluoroquinolones), such as levofloxacin, moxifloxacin and gatifloxacin, have recently reached New Zealand for human use.

Spectrum of action

Ciprofloxacin and enrofloxacin are mainly active against aerobic Gram negative organisms, but are not very active against Gram positive aerobes (except for reasonable activity against some *Staphylococcus* spp.) or anaerobic organisms. They are reasonably active against *Mycoplasma* and *Campylobacter*. Some activity is reported against *Pseudomonas*, *Rickettsia*, *Chlamydia*, and *Mycobacteria*. Newer drugs (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin, and trovafloxacin) have more activity against Gram positives, especially *Streptococcus* spp. and *Mycobacteria*.

Resistance

There are four recorded resistance mechanisms for fluoroquinolones. These include modification of DNA gyrase and/or topoisomerase IV, active efflux and altered membrane permeability. A protein from *Mycobacterium tuberculosis* has recently been shown to mimic bacterial DNA and confer some resistance to fluoroquinolones (Hegde *et al*, 2005)

Fluoroquinolone resistant isolates usually contain one or more mutations in a small section of GyrA or ParC; mutation in GyrB and ParE is rare, but getting commoner. In Gram negative bacteria, where mutations have given rise to a resistant DNA gyrase (low level resistant), mutations then occur in the topoisomerase IV genes (and vice versa for Gram positive bacteria) to give a highly resistant bacterium. Newer drugs that inhibit both enzymes give rise to less resistance. A single point mutation in *gyr A* in *Campylobacter* can cause a high level resistance (Luo *et al*, 2003).

Efflux pumps are an important mechanism of resistance in many bacteria (reviewed by Pool, 2000). In *Campylobacter*, the CmeABC efflux pump may even be necessary for a *gyrA* mutation to give rise to clinical resistance (Luo *et al*, 2003).

Clinically significant resistance occurs in *Pseudomonas*, *S. aureus* and *Campylobacter*.

Uses in animals

Enrofloxacin registered indications:

- Bacterial infections of bones in cats, dogs, pigs and cattle
- Mastitis in cows where the causative organisms have been established to be either *E.coli* or *Pseudomonas*. Appropriate intramammary treatment with another antibiotic should be used in combination with systemic treatment (other than oral).
- Ear and skin infections caused by *Pseudomonas* in dogs and cats.
- Urinary tract infection in dogs and cats.
- Infection of the (male) reproductive tract (prostatitis, vesiculitis, orchitis) in the bull and dog.
- Certain infections of cattle, pigs, dogs and cats in locations where poor tissue penetration by other antimicrobial drugs can be expected and where the condition is caused by a susceptible organism that does not respond readily to other antibiotics.

Orbifloxacin registered indications:

- Dogs and cats: For treatment of skin and associated soft tissue infections (wounds and abscesses) caused by susceptible strains of *S. intermedius*, *E. coli*, *Enterobacter* spp., *Pasteurella multocida*, *Klebsiella pneumoniae*, *Pseudomonas* spp., *Acinetobacter* spp., and *Streptococcus* - hemolytic group G.
- Dogs: For treatment of urinary tract infections caused by susceptible strains of *E. coli*, *Proteus mirabilis*, *S. intermedius* and *Enterococcus faecalis*.

Marbofloxacin registered indications:

- In cattle: the treatment of respiratory and other infections caused by susceptible strains of organisms.
- In sows: the treatment of metritis-mastitis-agalactia syndrome (MMAS) and other infections caused by susceptible strains of organisms.
- In neonatal calves: treatment of gastroenteritis caused by sensitive strains of *E. coli*.

Regulation

Marbofloxacin boluses have the following conditions of use.

1. “Indiscriminate use of the product could contribute to the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic.”
2. “The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivities tests have shown that it is the only alternative that is likely to be effective.”
3. “The prescribing veterinarian must notify the ACVM Group of every case the antibiotic is prescribed, giving date, species prescribed for and condition treated.”

Conclusions

Animal health and welfare would be compromised if it were no longer possible to use these drugs in serious infections in individual animals. Fluoroquinolones should be reserved for serious infections, and treatment of trivial infections with fluoroquinolones should be actively discouraged. Indiscriminate use of these actives could contribute to the development of antibiotic resistance. They should not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and susceptibility tests have shown that they are the only alternative that is likely to be effective.

Recommendations

19. The first two conditions applied to marbofloxacin boluses should be applied to all use of fluoroquinolones in food animals.
20. The first condition should be applied to all fluoroquinolone use in non-food animals, and any registered indication for use that does not meet this criterion should be re-considered.

Macrolides and similar drugs

See Appendix 7

These drugs have different chemical structures but are clinically very similar in their pharmacokinetics and spectrum of action (although differences in resistance patterns are starting to emerge). They are all bacteriostatic.

Actives in this group

Macrolides include erythromycin, tylosin, tilmicosin and spiramycin (less active), which are commonly used in animals; oleandomycin is no longer used in people and is used for intramammary treatment of *S. aureus* mastitis. Roxithromycin (a derivative of erythromycin), clarithromycin and azithromycin are new human drugs that have more suitable pharmacokinetics. Kitsamycin is used in animals in Australia. Aivlosin is a tylosin derivative under development.

Streptogramin Bs are also macrolides.

Lincosamides are chemically different but clinically identical to macrolides. Lincomycin and pirlimycin are used in animals, clindamycin in people.

Pleuromutilins are also very similar. Tiamulin is the only drug used in New Zealand, but valnemulin is used in Europe. This class of drugs is not used in people.

Ketolides are macrolide derivatives with a slightly different mechanism of action. Telithromycin is licensed for people in the USA and Europe, but not yet in New Zealand.

Spectrum of action

These drugs have a narrow spectrum, mainly confined to Gram positive bacteria, including penicillinase producing staphylococci, but not enterococci. They are also active against *Pasteurella* and *Bacteroides* spp., *Mycoplasma* spp. and *Rickettsia* spp. Tylosin and roxithromycin are used clinically against *Mycoplasma*, *Chlamydia* and some spirochaetes

(*Treponema* and *Moraxella*). Tilmicosin has a slightly broader spectrum. Tiamulin is effective in swine dysentery (*Brachyspira hyodysenteriae*). Most strains are now resistant to tylosin. Tiamulin is also effective against *Actinobacillus pleuropneumoniae*. Erythromycin is effective against *Rhodococcus equi* in foals.

Macrolides (especially erythromycin) are used in people for severe *Campylobacter* infections, but resistance is high and increasing. Roxithromycin and azithromycin have some activity against protozoa such as *Toxoplasma gondii*. Lincosamides, particularly clindamycin, have useful activity against anaerobes

Resistance

Chromosomal resistance occurs readily. Plasmid mediated resistance is also common. Resistance usually involves point mutations in the 23S rRNA of the 50S ribosomal unit, which prevent drug binding. This occurs very quickly with lincosamides but more slowly with tiamulin. The sites of mutation are different for lincosamides (Karlsson *et al*, 1999) and tiamulin (Bosling *et al*, 2003; Pringle *et al*, 2004). Telithromycin binds to domains II and V of 23S rRNA of the 50S ribosomal subunit. Mutations at both of these sites are thought to be necessary for resistance.

Cross-resistance amongst the groups

Cross-resistance is common but not complete among macrolides, lincosamides and streptogramin Bs, mainly mediated by the *ermB* and *mefA* genes. Pleuromutilins and ketolides have different resistance patterns, but these have not been directly compared. If the patterns are similar, tiamulin use could cause problems when telithromycin is approved for people in New Zealand.

Seventy-six *Brachyspira hyodysenteriae* field isolates from Australia had MIC(90)s (mg/l) of: tiamulin, 1; valnemulin, 0.5; tylosin>256; erythromycin>256; lincomycin, 64 and clindamycin, 16. (Karlsson *et al*, 2002). There was no significant change over three years. Thirty-seven isolates from Japan were all susceptible to tiamulin and valnemulin, but most were resistant to lincomycin and macrolides (Uezato *et al*, 2004). Resistance to tiamulin in *B. hyodysenteriae* can increase dramatically in a short time (Lobova *et al*, 2004). In northern Germany, resistance to tiamulin and valnemulin gradually increased up to 2001 (MIC50 2µg/mL) but decreased in 2002 (Rohde *et al*, 2004)

There appears to be complete cross-resistance between tiamulin and valnemulin in *B. hyodysenteriae* (Karlsson *et al*, 2001). Sixty percent of macrolide and lincosamide resistant *Brachyspira pilosicoli* from field isolates in Sweden had a point mutation in the 23S rRNA gene, which rendered them completely resistant to tylosin and erythromycin, but not tiamulin (Karlsson *et al*, 2004). Some tiamulin resistant isolates were also found.

Spirochaete isolates from Japanese dogs, which were resistant to erythromycin, but not tylosin, lincomycin or tiamulin, became resistant to tylosin by a point mutation of the 23S rRNA gene (Prapasarakul *et al*, 2003).

Mycoplasma bovis from Belgian cattle were susceptible to tiamulin but not lincomycin or tylosin (Thomas *et al*, 2003). A study in Japan showed similar results, with all field isolates resistant to erythromycin but susceptible to tiamulin (Hirose *et al*, 2003). *In vitro*, resistance in *Mycoplasma* species from chickens developed quickly for erythromycin and tylosin, but

much more slowly, if at all, for tiamulin (Gautier-Bouchardon *et al*, 2002). Strains with induced tylosin resistance were also always resistant to erythromycin, but not vice versa.

Seventy-one per cent of *S. suis* isolates from Belgian pigs possessed the *ermB* gene and were resistant to macrolides and lincosamides. Only one was resistant to tiamulin. The *ermB* gene in most of the isolates tested was 100% homologous with *ermB* genes from some isolates of *S. pneumoniae* and *S. pyogenes* from people (Martel *et al*, 2001). Telithromycin has been shown to be effective against macrolide resistant *Strep. pneumoniae* containing *mefA* and *ermB* genes in vitro (Zhanel *et al*, 2004).

Uses in animals

- cattle - *Pasteurella pneumonia* (rare in New Zealand although almost ubiquitous in feedlots in the USA) (mainly tilmicosin). Intramammary use of oleandomycin for *S. aureus*.
- pigs - treating and preventing respiratory infections (pleuropneumonia and enzootic pneumonia) and dysentery (especially tiamulin).
- chickens - chronic respiratory disease caused by *Mycoplasma*
- small animals - skin infections, osteomyelitis, anaerobic infections, rickettsial and chlamydial infections, (toxoplasmosis) (azithromycin)
- horses - *Rhodococcus pneumonia* in foals (erythromycin)

Conclusions

The risk of in-feed tiamulin use to control swine dysentery to public health is very small. This could change if pleuromutilins start to be used in human medicine. Some *Brachyspira* species colonise people, but they are usually regarded as commensals.

Singer *et al* (2004) conducted a risk assessment of the use of in-feed or in-water tylosin and concluded that if tylosin were not used in chickens:

- the number of human cases of campylobacteriosis in the USA caused by eating chicken would increase an estimated 11,000 to 70,000 cases per year;
- the number of human illness days would increase an estimated 50,000 to 500,000 days per year; and
- for every illness day prevented by removing tylosin from chicken production, an estimated additional 3 to 30 illness days are caused by the increased *Campylobacter* contamination.

The choice of drugs for treatment of pigs with respiratory disease due to *Mycoplasma* and ileitis due to *Lawsonia intracellularis* is limited. The public health risks are probably low and do not justify reducing the use in pigs.

The use in cattle could be discouraged without seriously affecting animal health and welfare.

If veterinary macrolides/lincosamides in tablet form were not available, it would likely lead to greater discretionary use of human drugs for infections where nothing else is likely to work. The public health risk is small and does not justify increased control.

Recommendations

21. The use of macrolides and similar drugs in cattle should be discouraged.

22. Macrolide resistance should be included in the surveillance system screens.

Antimicrobials used for mycobacterial diseases

See Appendix 8

Isoniazid, streptomycin, rifampicin, rifabutin, pyrazinamide, ethionamide, prothionamide and ethambutol are used for tuberculosis; clofazimine and dapsone are used for leprosy. Clarithromycin and azithromycin (macrolides) and some of the newer fluoroquinolones are also occasionally used to treat tuberculosis.

Mycobacterial infections in food animals are not treated and infected animals are likely to be slaughtered. Rarely, human drugs may be used to treat feline leprosy. The current situation in animals does not give rise to concern. Indiscriminate or widespread use would be likely to lead to increased resistance in the environment. It may be that the current rare discretionary use of human drugs is the preferred arrangement.

Recommendation

23. None of these drugs should be registered for use in animals without a condition that they are for use only in life-threatening conditions where a culture and susceptibility has shown that no other drug is likely to work or where there are sound clinical grounds to believe they are the drug of choice.

Streptogramins

See Appendix 9

Actives in this group

The streptogramins used are virginiamycin in animals and dalfopristin and quinupristin (in combination as Synercid®, QD) are used in people.

Spectrum of action

They are effective against Gram positive bacteria, including MRSA and vancomycin resistant *E. faecium*, but not usually *E. faecalis*.

Resistance

E. faecalis is intrinsically resistant to streptogramins. *E. faecium* and staphylococci can acquire resistance genes which can cause inactivation of the antibiotic (streptogramins A and B), increase the number of efflux pumps (streptogramins A and B) or alter the binding site (streptogramin B).

Uses in animals

- Horses - prevention of laminitis
- Chickens - prevention and treatment of necrotic enteritis (*Clostridium perfringens*)

Conclusions

The Australian Pesticides and Veterinary Medicines Authority (APVMA) concluded that virginiamycin should be retained for use in animals but should not be used for growth

promotion, which is the current situation in New Zealand. Labelling specifies conditions of use (APVMA, 2004).

The principal hazard is considered to be the selection of resistance genes to virginiamycin in *Enterococcus faecium* in animals. In characterising the hazard it was noted that:

- Use of virginiamycin in food-producing animals can select for *E. faecium* possessing either the *vat(D)* or *vat(E)* genes, which encode for production of a streptogramin A acetyltransferase (an inactivating enzyme), resulting in virginiamycin-resistant *E. faecium*.
- Production of streptogramin A acetyltransferases confers resistance to the dalfopristin component of QD. Resistance to virginiamycin requires resistance to both streptogramin A and B.
- Virginiamycin-resistant *E. faecium* found in food-producing animals and their commercial products can be co-resistant to other antimicrobials, including vancomycin.

In assessing the above steps, the following were taken into account:

- conclusive evidence of human infection with animal-derived streptogramin-resistant *E. faecium* or transfer of resistance genes is lacking;
- vancomycin-resistant enterococci have a high propensity to cause outbreaks in hospitals;
- while the number of infections resulting from colonisation with vancomycin-resistant enterococci is low, these strains spread easily to other patients, resulting in significant numbers of infections;
- the *vanB* gene complex encodes the more common form of vancomycin-resistant enterococci in Australia. With a single exception, this form of resistance has not been found in animals;
- recent Australian studies have demonstrated no resistance to QD in human clinical isolates;
- septicemia from *vanA*-type vancomycin-resistant *E. faecium* mostly occurs in highly vulnerable patients who have multiple medical problems. Failure of therapy in these patients would result in significant mortality or prolonged treatment. Currently these patients are treated with QD, a streptogramin, or the newer antibiotic linezolid;
- the impact of antibiotic failure on relatively minor infections such as wound infections and urinary tract infections is small.

The probability of disease due to infection in susceptible humans due to exposure to streptogramin-resistant *E. faecium* of animal origin is low, but the severity of impact in susceptible humans would be high. Regarding the risk to the general population, the probability of disease due to infection due to exposure to streptogramin-resistant *E. faecium* of animal origin is low, and the severity of impact in the general population is low.

New Zealand has already taken reasonable steps to prevent significant streptogramin resistance developing, but there are no New Zealand data on the prevalence of such resistance in animals

The FDA Center for Veterinary Medicine has also carried out a risk assessment on the use of virginiamycin in animals (November 2004). They concluded that the risk of acquiring a

streptogramin-resistant enterococcal infection (assuming that all resistant enterococci came from animals) was 60 to 1,200 chances in 100 million per person per year among the hospitalised population and 7 to 140 chances in 100 million per person per year for the general US population (FDA, 2004).

New Zealand has already taken reasonable steps to prevent significant streptogramin resistance developing, but there are no data on the prevalence of such resistance in animals.

Recommendation

24. Streptogramin resistance should be monitored as part of the surveillance system.

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CHAPTER 7: INFORMING REGULATORY POLICY

The international guidelines referred to in Chapter 5 propose that regulatory policies should be based on improved risk analysis employing data derived from surveillance and monitoring of antimicrobial resistance among animal (and plant) bacteria, which contribute to the prudent use of antimicrobials. Current policy settings internationally vary from the European precautionary approach to the ‘principle of proof’ approach adopted by the FDA in the USA (Turnidge, 2004). As discussed in Chapter 5, the New Zealand policy is based on risk but in the absence of hard data, conservative risk assumptions had to be used.

This chapter outlines a framework for the assessment of the risks of using antimicrobials in animals and plants and a proposed surveillance programme that will yield some of the data needed to make better-informed risk assessments

A Framework for Assessment of the Risks of Antimicrobial Use in Animals and Plants in New Zealand

The following framework for the assessment of the risks of development of resistance, transfer of resistant bacteria to humans and/or transfer of resistance determinants to human pathogens in New Zealand as the result of the use of antimicrobials in animals and plants is based on the findings and conclusions of a number of recent papers that review the international literature on antimicrobial resistance. Attention is given to those findings and conclusions that are relevant to New Zealand.

Hazards

The potential antimicrobial resistance hazards faced by New Zealanders as the result of the use of antimicrobials in plants and animals are similar to those faced by human populations in many other countries. They are:

- infection with zoonotic bacteria exhibiting antimicrobial resistance e.g. non-typhoid *Salmonella enterica* serotypes, *Campylobacter jejuni* and *C. coli*, *Yersinia enterocolitica*, *E.coli*, *Enterococcus faecalis* and *E. faecium*;
- transfer of resistance genes, acquired through exposure to antimicrobials, from animal or plant bacterial pathogens or commensals to human pathogens; and
- expansion of the pool of transferable resistance genes within bacterial populations, notably genes that confer cross-resistance or co-resistance.

While the incidence of *Campylobacter* and non-typhoid *Salmonella* infection in New Zealand is significantly higher than in most developed countries (see Table 7.1), the prevalence of antimicrobial resistance in zoonotic bacteria is low by international standards (Table 7.2).

Table 7.1: The incidence of some bacterial zoonoses in New Zealand

Species	Incidence (cases per 100 000)		
	2002	2003	2004
<i>Campylobacter</i>	334.3	395.6	326.8
Non-typhoid <i>Salmonella</i>	37.5	37.5	28.9
<i>E. coli</i>	2.0	2.8	2.4

VTEC/STEC

Yersinia

12.7

11.7

11.2

Source: ESR: Notifiable and Other Diseases in New Zealand, Annual Report 2004

Table 7.2: Susceptibility/resistance of *Salmonella* to 10 (2003) or 12 (2004) antimicrobials

Origin	Number tested		% fully susceptible		% resistant to one or more antimicrobials		% resistant to 3 or more antimicrobials	
	2003	2004	2003	2004	2003	2004	2003	2004
Human	348	247						6.1
Animal/environment	265	242						1.7
Total	613	489	94.5	92.6	5.5	7.4	3.0	3.9

Source: esr.cri.nz

There were no significant differences in the resistance patterns of human and non-human *Salmonella* isolates in 2003 except for chloramphenicol where 1.4% of human isolates but none of the non-human isolates were resistant. In 2004, resistance of human isolates to 7 antimicrobials was significantly higher than those from non-human sources.

Campylobacter resistance to erythromycin declined from 3.4% of isolates to 1.3% over the period 1999 to 2003. Fluoroquinolone resistant isolates increased from 2 to 3.4% from 2000 to 2001 and decreased to 2.5% in 2003.

The fragmentary nature of the information on resistance in animal and plant bacteria in New Zealand does not permit any firm conclusions on hazards posed by other organisms.

Release assessment

It is generally assumed that the prevalence of antimicrobial resistance in animal bacteria is proportional to the amounts of antimicrobials used. On this basis, it could be expected that the following antimicrobial resistance patterns might be found in New Zealand:

1. multiply resistant *Salmonellae*;
2. macrolide resistant *Campylobacter* (fluoroquinolone resistance probably rare given the small amounts used);
3. vancomycin-resistant *Enterococcus* spp. (use of avoparcin in poultry discontinued in 2000);
4. resistant streptococci and staphylococci associated with the bovine udder and milk;
5. multiply resistant *E. coli*;
6. commensals, notably those in the gut of pigs and chickens and the bovine udder with transferable resistance genes.

While the available evidence suggests low levels of resistance among animal bacteria that parallels the low levels found in the comparable human pathogens, the sampling of animal bacteria has been *ad hoc* and the isolates cannot be considered representative of those to which the human population is exposed through food. However, they may be representative of exposures through direct contact with farm and companion animals.

The genetic mechanisms by which antimicrobial resistance in bacteria develops and may be transferred among bacteria are well understood (see Chapter 3). Transmission of resistant bacteria from animals to humans can occur either by transmission of the resistant bacteria or horizontal transfer of the resistance genes from animal to human bacteria. Transmission is affected by factors such as bacterial host specificity and mechanisms by which bacteria are transmitted between species.

In recent years food animals have been identified as the putative source of antimicrobial resistance transferred from animals to humans, but the connection has often been inferred on ecological grounds without supporting temporal or spatial epidemiological evidence (Phillips *et al*, 2003). For example, the European Union adopted a ban on the use of growth promotion antimicrobials as a precautionary measure in spite of the advice of its Scientific Committee on Animal Nutrition that there was not enough data to support such a ban (SCAN, 1998). In contrast, the FDA has tended to adopt a ‘principle of proof’ approach (Turnbridge, 2004) and has applied quantitative risk analysis to determine its policy (see below).

Prior to 2000, the potential of an antimicrobial to induce resistance through its use in animals or plants was not a factor in determining its suitability for registration as an agricultural compound or veterinary medicine in New Zealand. Products could be registered as having growth promotion, improved weight gain and/or improved food efficiency functions. As the result of a policy review in 2000, claims of growth promotion or food conversion efficiency are no longer permitted for those antimicrobials that have public health significance and only flavomycin, carbadox, avilamycin and the ionophores may be sold with such claims and without veterinary prescription. All other antimicrobials are required to meet claimed treatment or infection prevention needs, require a veterinary prescription and have conditions of use imposed commensurate with their assessed risk.

The consequences in food-producing animals of the introduction of stricter controls over the use of antimicrobials in animals are:

1. With the exception of the penicillins and bacitracin, sales of antimicrobials appear to have remained relatively static since 1999.
2. Over the period 2000-2003, only small amounts of the fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin, difloxacin) were sold.
3. Virginiamycin is largely restricted to the prevention of laminitis (founder) in horses known to be susceptible.
4. The use of tylosin and zinc bacitracin in pigs and poultry is now restricted to the control and treatment of specific infections although a coincidental growth promotion effect can be expected. Advice on current practices in these industries indicates a more strategic approach to the use of antimicrobials and a greater dependence on administration at therapeutic doses. It is notable that the amounts used have not increased at a rate commensurate with the rate of growth of the pork and, particularly, the poultry industries.
5. The increases in the use of oxytetracycline and the sulphonamides in 2003 may reflect increased therapeutic and pro-(meta)phylactic use following reduced use of tylosin and bacitracin.
6. Apart from intramammary preparations, the use of antimicrobials in pastoral animals is believed to be largely therapeutic or pro-(meta)phylactic.

- Intramammary use consumes more than 60% of the penicillins, 40% of the cephalosporins and 27% of the aminoglycosides used. There is no recent examination of resistance patterns among bacteria causing mastitis.

Based on current use, the animal bacteria exposed to the highest levels of antimicrobials are:

- pathogens and commensals associated with the bovine udder;
- enteric organisms in the gut of pigs, poultry and hand-reared calves (which may be exposed to milk containing antimicrobial residues as well as veterinary medicines).

A wider range of bacteria may be exposed to antimicrobials in companion animals undergoing treatment.

Exposure assessment

The possible pathways by which humans might be exposed to resistant bacteria or resistance determinants of animal origin are shown in Figure 7.1

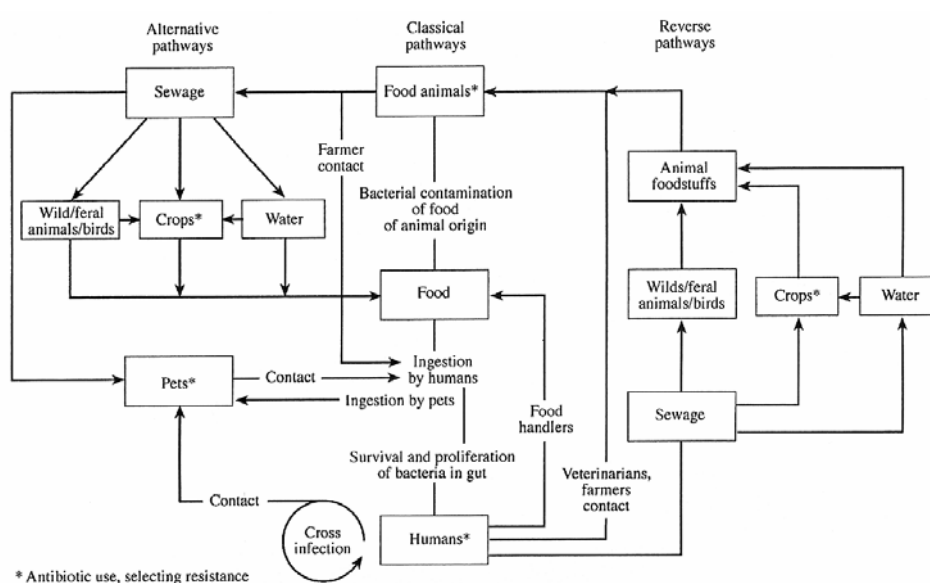


Figure 7.1: Possible pathways through which human exposure to resistant zoonotic pathogens or bacteria carrying resistance determinants might occur

Source: Phillips *et al* (2003)

In New Zealand, the most important potential sources of exposure to resistant organisms of animal or plant origin appear to be:

1. the food chain notably from fresh meat products and raw milk – the high incidence of food-borne infections illustrate the importance of this pathway;
2. direct contact e.g. between farm animals and those who handle them (it is estimated that 10 000 families might be exposed in this way);
3. direct contact between companion animals treated with antimicrobials and their owners; and
4. contamination of food and water with bacteria in the environment.

The Expert Panel have been unable to identify any New Zealand data that suggest that any of these pathways are significant in human medicine. We lack the data that would allow the

ranking of the pathways in terms of their importance but we can draw some general inferences. With respect to the food pathway:

1. The incidence of human campylobacteriosis and non-typhoidal salmonellosis is high by world standards. While cooking could be expected to block the food exposure pathway, under-cooked chicken is a known source of *Campylobacter* (Ikram *et al*, 1994; Eberhart-Phillips *et al*, 1997) and it must be assumed that food is an important exposure pathway for food-borne enterococci, *E. coli* and other organisms.
2. On present evidence, exposure to resistant *Salmonella* and *Campylobacter* is low because the prevalence of resistant strains is low.
3. The relatively large amounts of antimicrobials used to treat and control bovine mastitis suggest milk as a possible food pathway. However, the strict measures adopted by the dairy industry to regulate the quality of raw milk and routine pasteurisation militate against milk as a pathway for transfer of resistant organisms. People who drink raw milk may have a higher risk profile but there are no data to support this.

There is a major international debate around exposure assessments that is becoming increasingly polarised and politicised. Phillips *et al* (2004), in an extensive review of the literature on the risk to human health of the use of antimicrobials in food animals, draw attention to:

- the range of pathways by which humans may be exposed to animal bacteria, including resistant ones;
- the lack of evidence that humans have acquired resistant bacteria such as *Salmonella* and *Campylobacter* through exposure to resistant animal bacteria in the food chain – acquisition could be via other pathways. Cross-infection of humans by *Salmonella* is common;
- the fact that, even if resistant zoonotic pathogens do reach humans, the clinical consequences of resistance may be small;
- the evidence of two examples only of a human and animals sharing the same resistant enterococci is circumstantial and not necessarily a causal relationship;
- evidence that *E. coli* and enterococci exhibit host specificity, making it unlikely that an animal strain will colonise the human gut even though they may persist in the human gut for up to two weeks (raising the question whether sufficient mixing occurs to allow horizontal gene transfer to occur). They conclude that “the truth about gene transfer from animal isolates of indicator organisms to human isolates in the human intestine (or even in other relevant sites) remains beyond our grasp”;
- the benefits of a ban on growth promoters are small and the risks to human and animal health may be larger than believed.

Notwithstanding the authors’ claims to independence, critics see the review as justifying the position of the Animal Health Institute (AHI), which seeks proof that food animals and the food chain is a source of resistant human pathogens let alone a significant source to justify a ban on growth promoters. The review has been criticised by several authors for alleged misuse of references, including their data (Chiller, Barrett and Angulo, 2004; Jensen *et al*, 2004; Karp and Engberg, 2004; Tollefson, 2004).

A review of human diseases caused by food-borne pathogens of animal origin (Swartz, 2002) traverses a similar body of published literature on human infections with non-typhoidal *Salmonella*, *Campylobacter*, *E. coli*, enterococci, *Listeria* and *Yersinia* to attempt to establish

connections between the use of antimicrobials in animals and human infections with resistant organisms. In almost all the examples cited, the connection is inferred without an adequate examination of alternative explanations. Where a close connection appears to exist, the examples are best explained by exposure through direct contact between the animals and the human subjects. The evidence that food is a pathway is not well established. This review can be criticised on the same grounds as the Phillips *et al* review because it was published as part of a series of papers prepared by the Scientific Panel for the Facts about Antimicrobials in Animals and the Impact on Resistance (FAAIR) report sponsored by the Alliance for the Prudent Use of Antimicrobials.

The Expert Panel has concluded:

- There are many references in the international literature to human infection by *Salmonella* and *Campylobacter*, some of which were resistant to antimicrobials, and it is a reasonable assumption that some resistant strains had their origin in antimicrobial use in animals.
- The evidence for human infections by resistant enterococci (VRE) of animal origin is much less convincing.
- The potential for horizontal transfer of resistant determinants from animal gut commensals to human bacteria is recognised but the evidence that it happens is hard to find. However, the possible amplification of resistant strains once established through antimicrobial use, as suggested by Turnidge (2004), means it would not have to happen very often to be significant.
- The focus on antimicrobial use in food animals and the food chain as the pathway for transfer of resistant organisms or determinants fails to give other pathways, such as direct contact between humans and both farm and companion animals, appropriate attention.
- The epidemiological tools needed to answer these questions may be lacking at this time.

Risk estimation

The lack of data on the nature and prevalence of antimicrobial resistance among animal bacteria in New Zealand makes it impossible to attempt even a qualitative estimation of the risk of the transfer of resistance determinants from animal to human bacteria. We can conclude that at the present time, the available data indicates the risk of human infection with resistant zoonotic bacteria (VRE, *Salmonellae*, *Campylobacter*) is very low. *Salmonella* and *Campylobacter* remain valuable indicator organisms for resistance development even though antibiotic therapy is not required or recommended for the majority of human clinical infections. The frequency of transfer resistance genes from commensal bacteria to potential human pathogens cannot be estimated and may be very difficult to measure if the rate of transfer is low, as is believed to be the case.

Risk assessment studies

Most of the studies published to date have considered the risks associated with the use of a particular antimicrobial group on a specific bacterium, e.g. virginiamycin use in animals (FDA Center for Veterinary Medicine, 2004) or the use of the macrolides, tylosin and tilmicosin in cattle pigs and poultry (Hurd *et al*, 2004). Phillips *et al* (2003) have critiqued a number of these studies and have concluded that they are potentially flawed because of the unsupported assumptions that are involved. In the absence of complete data sets, stochastic and deterministic risk assessment models must rely on assumptions. How these assumptions

are dealt with and the susceptibility tests applied to them are crucial to the outcome of the assessment.

Cox (2005) has proposed an alternative to the ‘farm to fork’ model of risk assessment. He has developed the Rapid Risk Rating Technique, which relies on working backwards from an observed data point, e.g. the number of VRE cases per year, and estimates fractions that when multiplied compare the number of adverse consequences attributable to the use of antimicrobials in animals with the number of adverse consequences prevented through their use. The estimates of risk obtained by the studies conducted so far suggest that the adverse consequences of using the antimicrobials studied have very low frequencies.

A Proposed Surveillance and Monitoring Programme of Food Animals

Introduction

The 1999 Expert Committee report recommended that surveillance systems should be established to monitor antibiotic resistance (AR) in food-producing animals: “to provide up-to-date information on the extent to which antibiotic resistance is occurring and to facilitate a rational and evidence-based policy response to such resistance”. This Expert Panel concurs with this recommendation.

Such surveillance should be integrated with surveillance of antimicrobial resistance in pathogens isolated from humans, as currently provided by ESR.

As discussed in Chapters 3 and 4, rates of antimicrobial resistance in New Zealand human isolates are relatively low when compared to other countries but data from animal isolates are scant. It is important to obtain an accurate, integrated picture of antimicrobial resistance. If initial surveys show a low prevalence of antimicrobial resistance in animals, it is especially important to preserve this situation and prevent the ‘horse from bolting’. The loss of the effectiveness of antibiotics due to resistance has been identified as a major issue for both human and animal health, and so any increase in resistance rates should result in action. In addition, surveillance provides a unique opportunity to examine the impact of antimicrobial resistance in the food chain of a country with low prevalence of resistance in human pathogens. Only surveillance and directed research will provide information that directs one of only several control options:

- infection control on the farm, hospital, home or other environment
- altered food handling practices
- altered antibiotic control and use in medical or agricultural practice.

Rationale for setting up a surveillance and monitoring programme

The intention is that the data gathered would inform decisions on antimicrobial control and enable control measures to be applied in the correct place. It would also inform policy makers and the public of the extent of risk, if any, of antibiotic resistance from the food chain.

While the international guidelines referred to in Chapter 9 all call for the establishment of national surveillance and monitoring programmes, this alone is not sufficient reason to incur

the costs of establishing and operating a surveillance and monitoring programme in New Zealand. Nevertheless, a New Zealand national programme is likely to become an important contribution to the global surveillance and monitoring, which is developing at present.

The present classification of antimicrobials and the controls over the use of antimicrobial products are based on the qualitative risk assessment discussed in Chapter 9. The risk assessment model depends on a number of significant assumptions such as:

- the extent of human exposure
- the frequency of resistance in zoonotic bacteria
- the rate and extent of resistance selection in pathogens and commensals
- identification of a 'tolerable' end-point.

All of these criteria used in the risk assessment suffer from a lack of quantitative data that could inform or replace the assumptions used. In the absence of appropriate data, the assumptions are likely to adopt a conservative precautionary view.

The proposed surveillance programme can be expected to have objectives similar to those of the UK programme, which are to:

- provide information on the prevalence, patterns and trends of antimicrobial resistant micro-organisms in animals and their environment and their spread;
- produce this information so that it can be related to patterns detected in similar micro-organisms in foodstuffs and humans;
- investigate any relationship that might exist between the prevalence of resistance to antimicrobials in animals, the pattern of use and the amounts of antimicrobials sold for use in animals;
- investigate any relationship that might exist between the prevalence of resistance to antimicrobials in animals and husbandry methods, non-antimicrobial constituents of animal feed, vaccination or hygiene procedures;
- use the data generated to guide and encourage the responsible, prudent and judicious use of antimicrobials by the veterinary profession and producers and thus prolong the efficacy of these valuable drugs;
- address the issue of cross-correlation with parallel human antimicrobial resistance surveillance schemes; and
- use the data generated to identify areas for further research and investigation.

New Zealand's agricultural practices are sufficiently different from those of other countries that assumptions based on overseas data and experience may be irrelevant and are potentially misleading. Equally important is the evidence of changing practices that are likely to alter the rates of exposure of animal and plant bacteria to antimicrobials.

For these reasons the Expert Panel considers a surveillance and monitoring programme to be essential to ensure that policies for the management of the use of antimicrobials are founded on sound risk assessments. The Panel proposes a pragmatic approach that employs existing sampling systems to the greatest extent possible. The Panel considers that the management of the programme must involve careful analysis of the value of the data produced so that timely changes are made or the programme amended if it is not producing useful data. Evaluation must take account of whether improved risk assessments can be made and that, in turn, policy settings can be re-examined.

Programme design

In order to be effective a surveillance system must be:

- sustainable
- consistent
- supported by the relevant industries and participants
- scientifically robust
- comparable with other surveillance programmes, in this case linking human resistance rates with those in food-producing animals
- affordable.

Denominator data

Ideally, denominator-based frequencies of AR should be described, not just numbers of resistant organisms. This is the normal practice when collating AR in human pathogens, and it is possible to overemphasise resistance as a problem unless susceptible isolates are also described.

The corollary is that sampling should allow the growth and identification of bacteria both resistant and susceptible to the antibiotic in question.

Sampling different points in production will provide information that will require careful interpretation. Farm-based surveillance will provide the greatest information about impacts of animal husbandry, and surveillance of dressed carcasses will provide greatest information about food close to entry into the retail system. The cost of sampling will be least for abattoir or processing options, particularly if the AR surveillance programme ‘piggybacks’ off existing surveillance programmes, such as the National Microbiological Database (NMD) testing scheme (Appendix 12).

A number of approaches were considered at the level of AR at the herd, animal, bacteria and gene levels (see Appendix 11). It was considered that the surveillance objectives would best be served by sampling at the level of the bacterial population, preferably in faecal material from animals at slaughter.

Site of sampling

The main purpose of this surveillance programme is to establish the degree of risk to human health arising from animal AR. On the balance of practicality, cost and sustainability the Panel recommends sampling at the time of slaughter.

The advantages of this approach are that sampling is carried out near to the consumer end of the food chain, and therefore likely to be representative of human exposure. The scheme is also relatively cheap compared to bespoke systems that require additional sampling and microbiology.

Disadvantages of this approach include the possibility that isolates may not be representative of carriage and shedding on-farms. Moreover, cross-contamination in slaughterhouse and selection of particular isolates may result in a biased sample. These biases could be important if an attempt is made to relate antimicrobial usage on farms to antimicrobial resistance in animal populations. There may be large between-abattoir variations in the proportion of

positive carcasses. This could result in more samples being submitted from abattoirs with poorer hygiene practices.

Although carcasses are randomly sampled from lines, it is possible that carcasses of species such as sheep sampled on a given day come from the same farm. This lack of independence would reduce the precision of prevalence estimates.

Animals to be sampled

The proposed approach explicitly intends to utilise the existing NMD scheme, which includes mandatory sampling of adult cattle, bobby calves, sheep, poultry and ostrich, and voluntary sampling of deer. Currently the scheme does not include pigs, although it is hoped that a programme will be implemented during 2006. Given that pigs and broiler chickens are the species most likely to receive antimicrobials in feed and water it is important that they are included in the surveillance scheme.

'Incident' testing

An important feature of a human and animal health integrated surveillance programme would be to have the ability to investigate particular situations that may be identified from routine surveillance or clinical testing. It will be necessary from time to time to establish whether a particular phenotype is related to an individual or multiple clones. This information is important when assessing the relative importance of pathways of exposure, effects of widespread or local antibiotic use, and infection control at multiple levels.

The key components of such reference testing would include an ability to perform molecular strain typing to establish whether human and animal bacterial isolates are related or indistinguishable. Valuable techniques would involve macrorestriction and pulsed field gel electrophoresis (PFGE), multilocus sequence typing (MLST) and potentially other more automated methods such as ribotyping. In addition, it would be important to be able to examine and characterise resistance genes in molecular detail by polymerase chain reaction (PCR) and sequencing.

Participation of the food-producing industry

Recent research into AR in bacteria from food-producing animals has been associated with some difficulties. These relate to funding and support of research that may produce results that can have significant impact on the reputation of the industry. It is explicitly understood that the results of any surveillance programme should be made available first to steering groups and industry representatives to enable them to comment on the findings and to take any necessary action.

Aims

The overall aims of the surveillance programme would be to provide:

1. baseline data on the frequency of antimicrobial resistance of human relevance in livestock bacterial populations;
2. an ongoing system for detecting changes in the frequency of resistance in these populations;
3. a mechanism for identifying the determinants of any adverse trends;
4. a system for monitoring the response to interventions / control measures.

Methods

Sampling strategy: organisms

We recommend focussing on:

- *E. coli*
- *Salmonella* spp.
- *Enterococcus* spp.

These bacteria have zoonotic potential, or have resistance genes that are capable of transferring from animal to human strains. They occur with sufficient frequency to allow meaningful statistical analysis. Other important food-borne zoonotic pathogens such as *Campylobacter* spp. and *Yersinia* spp. should also be considered, although they are not currently part of the NMD programme. Isolation procedures for *Yersinia* spp. from pork meat have to date been inadequate, although an NZFSA-sponsored project at ESR is expected to provide a reliable method.

Testing strategy: antibiotics

Isolates should be screened primarily for antimicrobial agents of relevance to human health, rather than focussing on those currently used in livestock production. They should include:

- 1st and 3rd generation cephalosporins, including ampC and ESBL
- sulphamethoxazole
- amoxicillin
- gentamicin
- fluoroquinolones
- erythromycin
- vancomycin (enterococci only).

The methods used should be consistent with the NCCLS methods used in diagnostic microbiology laboratories processing samples from humans. The specific techniques to be used are not described here, but would include one or more of the following methods: Kirby-Bauer disc diffusion, E-test (ABI), agar dilution.

Testing strategy: storage and strain typing

It is important that representative resistant, and a subsample of susceptible, isolates of human and animal origin are stored to form a repository that might be used to answer specific questions. Many isolates of human origin are stored in diagnostic medical laboratories, but there is no systematic storage of isolates from non-human animals. Standardised typing methods should include:

- Pulsed field gel electrophoresis (PFGE)
- Multilocus sequence typing (MLST)
- Phage typing
- Riboprinter/ribotyping
- PCR and DNA sequence analysis.

The equipment and training for this aspect of the work should be concentrated in one laboratory or a small network to ensure consistency of results and avoidance of duplication.

PFGE and MLST profiles may best be deposited in the National Typing Database (a.k.a. PulseNet Aotearoa) administered by ESR.

Sampling strategy: source of isolates

E. coli

Randomly sample isolates from positive samples identified by standard NMD testing (see Appendix 12 for further details). The samples most likely to be representative of faecal contamination are those taken from the flank and rump of fresh carcasses, although this would require confirmation with a pilot study. This would require participating laboratories to submit a defined number of isolates per year (see below for indication of numbers). Isolates would either be randomly selected from positive Petrifilms or entire Petrifilms submitted to the testing laboratory.

***Salmonella* spp.**

All salmonellae identified through the NMD scheme, albeit low in number, are currently submitted to ESR for serotyping. Currently less than 20% are tested for antimicrobial resistance. We recommend that all are tested for AR because this organism has direct zoonotic potential and resistance rates from human and animal sources are particularly informative. The relatively small number of animal isolates limits statistical analysis, but it should be possible to have a complete data set.

While *Salmonella* analyses under the poultry NMD programme are carried out on all sampling days, those for other species are carried out only for the initial six weeks of the processing season. Fortunately, this period corresponds with the previously identified period of greatest prevalence of *Salmonella* detection on carcasses. Unfortunately, mandatory *Salmonella* testing for ovine species has already been removed for carcasses from domestic only premises and will be removed for export premises on agreement with the United States (likely early 2006).

***Enterococcus* spp.**

The vancomycin resistance phenotype (VRE) is the antibiotic of most interest, and there is already reasonably complete collection and analysis of human isolates through diagnostic laboratories and ESR. Systematic surveillance, particularly of enterococci from broilers, is a particularly important facet of the proposed surveillance programme. It is likely that *Enterococcus* spp. will be present on plates used for aerobic plate counts (APCs) as part of NMD testing. A suitable method of identifying and sampling *Enterococcus* spp. from NMD samples will need to be devised.

Sampling strategy: sample size estimation

The following table gives an indication of the precision for a range of prevalence estimates, for sample sizes of 100, 200, 300, 400, 500 isolates. This assumes that the selection of single individual colonies from positive petrifilms represents a simple random sample of all isolates carried in the faeces of the particular livestock species at slaughter. More complex sampling schemes are considered in Appendix 12.

Exact binomial 95% confidence intervals						
Sample size	Prevalence	Prevalence	Prevalence	Prevalence	Prevalence	Prevalence

	1%	5%	10%	20%	50%	80%
100	0.03-5.4	1.6-11.3	4.9-17.6	12.6-29.1	39.8-60.2	70.8-87.3
200	0.12-3.6	2.4-9.0	6.2-15.0	14.7-26.2	42.9-57.1	73.8-85.3
300	0.21-2.9	2.8-8.1	6.8-14.0	15.6-25.0	44.2-55.8	75.0-84.4
400	0.27-2.5	3.1-7.6	7.2-13.4	16.2-24.3	45.0-55.0	75.7-83.8
500	0.33-2.31	3.3-7.3	7.5-13.0	16.6-23.8	45.5-54.5	76.2-83.4

We recommend sampling **400 isolates per year per livestock species**. This provides an estimate of 50% with 95% confidence limits of $\pm 5\%$ and reasonably precise estimates for lower and higher prevalence estimates. If we require greater power to detect trends on a finer temporal scale (e.g. quarterly rather than annually), this number should be increased. However, unless multiple colonies per Petrifilm/agar plate are sampled, this would be limited by the number of positive samples and the strong seasonal variation in some livestock species (see Appendix 12). If multiple colonies per Petrifilm/agar plate are sampled, then the precision of estimates of prevalence would need to be adjusted to allow for the lack of independence of isolates taken from the same animal.

Analysis of data

The data will need to be summarised, analysed and presented to risk managers in a format that is consistent with current ongoing human antimicrobial surveillance schemes and reporting mechanisms. This will include annual reviews of both livestock and human prevalence data. The data will be used to inform risk assessments and will provide trend data of sufficient temporal resolution to identify emerging phenotypes and trigger appropriate responses. It can be used to identify the need for interventions, and assess the impact of particular control measures – a process that will require initial setting of appropriate targets and the definition of acceptable limits. As such it will inform policy recommendations and priority-setting for human and animal health, and provide evidence to support programmes aimed at promoting the prudent use antimicrobials in livestock.

The following analytical approaches should be considered for both scanning and targeted surveillance:

- Simple, target-oriented time-series monitoring
- Early Aberration Reporting Systems (EARS)
- Model-based approaches (e.g. temporal, geostatistical)
- Online, web-based real-time monitoring
- Trace-back and network analysis.

Governance and funding

It is important to have clearly established funding streams and involvement of the relevant parties. The results of surveillance may have political or economic consequences, and it is important that participants have confidence in the programme. We propose that:

- funding is established between the Ministries of Health and MAF and the relevant industries;
- the programme utilises and does not duplicate existing laboratory structures;
- there is an oversight committee with a clear brief, to ensure that all aspects of the programme are handled scientifically. In Chapter 12 we suggest that this could be a function of an ongoing Expert Panel.

Pilot studies

We recommend commissioning studies to address the following questions:

1. *How representative of faecal carriage are isolates sampled from fresh carcasses?*
This will involve sampling at various points in the abattoir, and enumerating and genotyping isolates.
2. *What are the primary sources of variation in prevalence of antimicrobial resistant organisms?*
This will inform the sampling strategy. For example, an analysis of variance will inform where to focus sampling effort, the value of ‘clustered sampling’ and the number of primary and secondary sampling units. Such a study would enumerate resistant organisms and provide data for calculating intra-class correlation coefficients and variance estimates at the following levels: between farms, between animals within farms, within animals over time, within samples, between replicates in the laboratory.
3. *What is the relationship between antimicrobial use on New Zealand farms and the prevalence and relative frequency of antimicrobial resistant organisms?*
Such studies have not been conducted on the relevant livestock systems in New Zealand. For example, what are the effects of the ‘routinely’ used mass-medicated antimicrobials, such as zinc bacitracin in poultry flocks and carbadox in pig production, on the selection of resistant organisms? What would be the immediate and long-term effects of removing these products? (Here the effects on production and welfare and the use of alternative therapies would need to be considered.)

Conclusions

- Obtaining data on the existence and prevalence of antimicrobial resistance in animal bacteria is critical to being able to make an estimation of the risks of exposure of humans to zoonotic bacteria or the transfer of resistance determinants to human pathogens. In turn, a better estimation of the risks is essential to determining whether current policy settings are appropriate.
- Current policy settings have been based on a qualitative assessment of the risks and, while they are consistent with guidelines on prudent use, they represent a precautionary approach. This is appropriate in the present state of knowledge, but the application of a precautionary approach assumes that risk assessments will be carried out as scientific data come to hand.
- The application of risk analysis to the issue of antimicrobial resistance is in its infancy and will require more research before it can be used with confidence as a tool to inform policy decisions.
- Considering the possible pathways by which humans and their pathogens might be exposed (see Figure 7.1), some periodic surveys of the animal bacteria that are most exposed to antimicrobials will give better information to assist the design of future surveillance and monitoring programmes. The possible candidates are:
 - *Salmonellae*
 - *Campylobacter* spp.
 - *E. coli*
 - enterococci

- *Staphylococcus aureus*
- *Streptococcus uberis* (most prevalent ‘environmental’ pathogen in mastitis)
- The development of a surveillance programme as detailed above employing existing sampling systems is an appropriate first step in acquiring better information about antimicrobial resistance in *Salmonella*, enterococci and *E. coli* associated with meat. It is hoped that *Campylobacter* can be added. Adjustments can be made to the programme in the light of results obtained.

Recommendations

25. The present policy settings are prudent and conservative. No further general restriction on the use of antimicrobials in animals seems justified. Some specific adjustments are proposed in Chapter 6.
26. Risk assessment protocols acceptable to both the ACVM Group and Medsafe should be developed hand in hand with the surveillance and monitoring programme proposed above. These protocols must reflect New Zealand practices because they differ from practices in other countries.
27. A surveillance programme, as outlined in this chapter (Chapter 7), utilising existing/proposed microbiological sampling in the food animal industries and existing laboratory resources should be established forthwith.
28. Funding should be negotiated between NZFSA, MOH and the industries concerned.
29. The programme should be managed by an oversight committee made up of persons with the requisite expertise, nominated by the funding parties.
30. The pilot studies described in this chapter should be initiated to run in parallel with the surveillance programme.

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CHAPTER 8: THE FUTURE ROLE OF AN EXPERT PANEL

One of the terms of reference for the Expert Panel is to:

“develop a framework for the ongoing provision of technical advice to the ACVM Group and Medsafe for the approval of antibiotic products under the ACVM Act”.

Appointment

Because a future expert advisory group is intended to be a resource for the ACVM Group and Medsafe, the members of the Panel should be appointed through consultation between these two bodies. It should not be appointed by the Antibiotic Steering Committee as is the present practice, but the ACVM Group and Medsafe may choose to consult the Steering Committee on appointments, terms of reference or other matters. The Steering Committee should have the right to raise matters through the ACVM Group or Medsafe to be considered by the Expert Panel.

The advisory group should be as few in number as is consistent with core expertise in the areas of:

- pharmacology
- medical/clinical microbiology
- epidemiology
- food animal production
- veterinary practice.

An independent chairperson is desirable but that person is likely to act as a convenor rather than simply as a chairperson. The group should have the authority to co-opt relevant expertise in consultation with the ACVM Group and Medsafe to assist it with specific matters.

Purpose

The purpose of a future advisory group is to give advice to the ACVM Group and Medsafe on any matters related to the use of antimicrobials in animal and plant species that bear on the evolution of antimicrobial resistance and the transfer of antimicrobial-resistant pathogens or resistance determinants to human pathogens.

Role

The role of an advisory group is to give advice to the ACVM Group and Medsafe on the consequences related to antimicrobial resistance including:

1. advice on any application for registration of a veterinary antimicrobial medicine that:
 - is a new antimicrobial active proposed for use in veterinary medicine
 - is a proposed use of a new or existing active in a new species not covered by current registrations
 - is a proposed new formulation/route of administration/use in a new age group of animals of a new or existing active, or
 - has a changed risk profile as the result of changed use patterns, altered resistance patterns or other factors that may effect the efficacy of the antimicrobial, the evolution of resistance or the transfer of resistance;

2. advice on any adverse consequences of current use or changes in the overall patterns of use of antimicrobials in animals and plants as revealed by the annual analysis of sales and use information;
3. advice on regulation of the use of antimicrobials in animals and plants in the light of new research, emerging issues or analysis of current trends;
4. advice or peer review of the results of surveillance and monitoring programmes, including recommendations on changes to surveillance and monitoring programmes to reflect changes in information needs;
5. advice or peer review of risk assessments;
6. advice on relevant research and education topics;
7. advice on domestic or international trends that may:
 - impact on the regulation of the use of antimicrobials in animals and plants
 - alter the design of surveillance and monitoring programmes, or
 - require research in New Zealand.

The advisory group should also review the registration of antimicrobial products and their conditions of use on a schedule to be determined by the ACVM Group and Medsafe. Those antimicrobials of high concern to public health should be reviewed every five years.

In developing its advice, the advisory group will balance the risks to human health and the risk to animal health and welfare from lack of efficacy due to the development of resistance against the risks to animal health and welfare from not having drugs available to treat disease.

Review of registration applications

Documentation of applications for registration referred to the advisory group should adhere to the guidelines provided by VICH (http://vich.eudra.org/pdf/01_2004/gl27_st7f.pdf) as far as possible and, where the information is absent, the applicant should explicitly state how this information is to be collected or why it is not relevant for the particular antibiotic/indication/species combination. New Zealand data should be provided where possible; otherwise an explanation of how relevant the overseas data are to New Zealand must be given.

The advisory group should review every application that may alter the risks of development of resistance. Applications for a change of formulation that is unlikely to result in a change of use need not be reviewed by the Panel. The review process should involve a formal examination of the submitted documentation as well as a review of any other relevant literature and surveillance results.

The advisory group will balance the risks to human health and the risks to animal welfare from lack of efficacy from the development of resistance against the risks to animal welfare from not having drugs available to treat disease. The advisory group should consider (among other things) the probability and likely rate of development of resistance in animal or environmental bacteria, and the probability and possible consequences of resistance genes spreading to bacteria of concern in people. Likely patterns of use, whether approved by the manufacturers or off-label, should also be considered. Where the evidence is incomplete, the advisory group should adopt a conservative approach. The evidence required to approve JETACAR category A drugs (see Appendix 2) will need to be much more complete and convincing than for category D drugs.

The Panel will recommend that:

- the application should be approved, if necessary, with conditions on use, or
- the application should be declined until more information is provided, or
- the application should be declined as the risks are unacceptable.

Operation of the advisory group

The frequency of meeting of the advisory group will depend on the number of new applications. However, assessment of applications may start by experts soon after receipt before the next meeting. The process must allow enough time for a thorough review. The application may be sent to a recognised expert(s) not normally on the Panel for an assessment if felt appropriate.

The group will need to meet at least once per year.

Group members' time and the time of any experts used in assessing applications needs to be remunerated appropriately.

Recommendation

32. The ACVM Group and Medsafe should appoint a standing advisory group comprising expertise in medical microbiology, epidemiology, veterinary pharmacology, animal nutrition and veterinary practice to advise them on any matters related to the use of antimicrobials in animals and plants that influence the evolution of antimicrobial resistance and on the design and interpretation of the surveillance programme.

GLOSSARY OF ABBREVIATIONS USED

ACVM	Agricultural Compounds and Veterinary Medicines
AHI	Animal Health Institute
AFB	American foulbrood
APC	Aerobic plate counts
APVMA	Australian Pesticides and Veterinary Medicines Authority
AR	Antimicrobial (antibiotic) resistance
ARMG	Antibiotic resistance marker gene
Codex	Codex Alimentarius (joint FAO/WHO Food Standards Programme)
EARS	Early Aberration Reporting Systems
EFB	European foulbrood
ERMA New Zealand	Environmental Risk Management Authority New Zealand
ESBL	Extended-spectrum beta-lactamase
ESR	Institute of Environmental Science and Research Ltd
FAAIR	Facts about Antimicrobials in Animals and the Impact on Resistance
FAO	Food and Agriculture Organization
FDA	US Food and Drug Administration
GMO	Genetically modified organism
HSNO	Hazardous Substances and New Organisms Act 1996
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
MAF	Ministry of Agriculture and Forestry
Medsafe	New Zealand Medicines and Medical Devices Safety Authority
MIC	Minimum inhibitory concentration
MLST	Multilocus sequence typing
MoH	Ministry of Health
MRL	Maximum residue limits
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NCCLS	Clinical Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards)
NMB	National Microbial Database
NZFSA	New Zealand Food Safety Authority
NZVA	New Zealand Veterinary Association
OIE	Office International des Epizooties
PAR	Prescription animal remedy
PCR	Polymerase chain reaction
PFGE	Pulsed field gel electrophoresis
POM	Prescription only medicine
SCAN	Scientific Committee for Animal Nutrition
VCNZ	Veterinary Council of New Zealand
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization
WTO	World Trade Organization

APPENDIX 1: THE EXPERT PANEL

The Expert Panel was comprised of professionals with expertise and experience in a broad range of scientific, veterinary and medical disciplines.

Chair

Peter O'Hara, BVSc (Hons), PhD, DipACVP

Members

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Julian Waters, BSc Hons, MSc, PhD, CBiol, MIBiol, RNutr, CPAg
Consultant nutritionist

APPENDIX 2: TECHNICAL BRIEF FOR THE ANTIBIOTIC RESISTANCE EXPERT PANEL

(Prepared by the ACVM Group, NZFSA)

Overview

This brief summarises the issues requiring consideration that have arisen following the completion of the last Expert Panel report. The issues have primarily arisen following consultation with the Ministry of Health (MoH) during registration or update of products to the ACVM Act. New information has also been supplied by registrants in the form of risk analyses or expert argument supported by literature. New Zealand-based microbiologists have also raised the possibility of the maintenance of resistant genes due to co-selection via the continued use of unrelated antibiotics.

Following the initial review it was recognised that more precise management than provided for within prescription conditions was required. This has resulted in the introduction of levels of management that arose from translating the outcome of the initial review and subsequent MoH input into registration conditions and label content.

The outcome for registrations so far is provided in *A summary of risk management of currently registered antibiotics*.

Aminoglycosides

The aminoglycosides were not considered in the initial review. Subsequently, the majority of actives have been updated to the ACVM Act. With the exception of streptomycin/dihydrostreptomycin and spectinomycin, any additional risk management proposed has not conflicted with currently approved use patterns.

Streptomycin/dihydrostreptomycin

These actives have historically been used in combination with other actives (such as penicillin) in a range of injectable, oral and intramammary preparations as well as in horticulture.

The MoH has provided an opinion that covers the following points:

- Streptomycin is essential human medicine and a Jetacar Category A medicine.
- Use is not supported in intramammary preparations as alternatives that contain actives not regarded as essential human medicines exist.
- The preference is to restrict use to injectable products limited to situations where bacterial sensitivities indicate no other antibiotic would be appropriate (equivalent to 2nd or 3rd level prescription animal remedy [PAR] management).
- Risks associated with use in horticulture are ill-defined but potentially considerable.
- Theoretical risks include streptomycin in the soil resulting in resistance in soil mycobacteria and transfer of resistance to pathogenic mycobacteria. Residue on fruit is a potential pathway for resistance.
- The importance to horticulture is recognised, as is the need for an expert review.

Streptomycin use has been restricted in Australia due to residue concerns associated with injectable products. Combinations with penicillin have been withdrawn in the US as the synergism between the active is challenged, resulting in the lack of a rationale for the active.

Subsequently, the ACVM Group has not imposed changes to the registrations or additional label statements on streptomycin products. Affected products have limited period registration enabling changes to be made, if required, following a review by the Expert Panel.

If a risk assessment indicates there is a risk of antimicrobial resistance that is of significance to humans developing, then the rationale for combination products should also be considered.

Other aminoglycosides

Spectinomycin is regarded as an essential human antibiotic used in the treatment of venereal disease in humans. Products are approved for water and feed medication of poultry and pigs and for individual treatment of neonatal lambs. The MoH requirement is for level 2 PAR management consistent with that required for lincocin, which is used in combination with spectinomycin.

Apramycin has not been specifically considered. Its use is now limited and confined to imports of the registered product for treatment of clinical salmonellosis in poultry breeding stock. The possibility of apramycin use contributing to the emergence of multi-resistant bacteria has been raised as an issue.

Topical preparations of aminoglycosides have label warnings to manage the transfer of potentially resistant organisms to humans.

Gentamycin use has not been considered when used off-label in food-producing animals such as cattle.

A review of streptomycin should also provide a rationale for comparative risk for all aminoglycosides and the potential for cross-resistance. Currently the actives in this group have been considered in isolation, primarily on the status in human medicine.

Macrolides/Lincosamides

The mass medication use of macrolides was considered in the initial review, resulting in a recommendation for restriction to PAR status with no growth promotion claims. Subsequent to this, additional label statements have been required after consultation with the MoH.

When considering the wider group of actives and indications not considered in the initial review, there is a need to consider not only risks associated with individual use patterns but also the relative risks associated with the use of actives in the entire group.

Tylosin

As a result of the initial review, products containing tylosin were updated to the ACVM Act without growth promotion claims.

In considering the update to the ACVM Act, the MoH made the following points:

- There is evidence resistance to tylosin is widespread amongst enterococci and that spread of resistance from animals to humans has occurred. Bacterial resistance to tylosin may confer cross-resistance to other macrolides and to lincosamides and streptogramins. This is a major concern.
- The preservation of the macrolide group in human medicine is important.
- In human medicine access to lincosamides and streptogramins is tightly controlled.
- The MoH preferred use should be under direct veterinary supervision for the treatment of significant infections that are insensitive or unresponsive to other antibiotics but recognised the need for access for animal health.

Subsequently, the products were updated with label statements advising of the risk of antibiotic resistance but not restricting use to unresponsive infections.

The first three points were reiterated in the consideration of lincomycin, oleandomycin and erythromycin.

Recently a semi-quantitative risk analysis on the resistance potential for tylosin and tilmicosin in feed medication has been published. This should be considered as new information when considering the risk management of tylosin and macrolides in general.

Lincomycin

The MoH opinion made the following points:

- Lincomycin is not used in humans in New Zealand.
- There is little or no evidence on resistance to lincomycin. There is no reason to believe it will behave differently to clindamycin and other macrolides.
- PAR level 2 label statements are requested.

The registrant for the intramammary product has subsequently submitted a case for reconsidering this decision. As a result, the ACVM Group has not imposed additional label statements on lincomycin products. Affected products have limited period registration enabling changes to be made if required following a review of the submitted information and required risk management by the Expert Panel.

Oleandomycin and erythromycin

Current veterinary use is in milking cow preparations.

The MoH opinion made the following points:

- Similar spectrum of activity to erythromycin.
- There is little or no antibiotic resistance data available for oleandomycin.
- It is accepted that there is little absorption from intramammary use.
- Erythromycin (the most similar antibiotic) is not regarded as essential in human medicine.
- PAR 1 conditions with no further requirements are acceptable. This is in the context of a therapeutic stepladder with actives such as tylosin viewed as a higher risk.

When this consideration was given, it was not recognised that erythromycin is also used as an oral medication in poultry. Subsequently this has been considered with the same management as the intramammary use proposed with the claims for 'treatment of stress' removed.

Clindamycin

Current use is oral in dogs and cats. The MoH has recognised the potential for multi-resistant bacteria due to complete cross-resistance between clindamycin and lincosamide. Risk management additional to PAR 1 has not been required, recognising use is in companion animals and off-label use in food-producing species is unlikely.

Tiamulin

In the initial review this active was considered as a macrolide with the same risk potential as tylosin. Subsequent to this, information has been provided that has led the MoH and the ACVM Group to conclude the pleuromutilin group does not confer cross-resistance to macrolides. As a result there has been no additional risk management proposed.

Neomycin (and framycetin)

The MoH opinion made the following points:

- Neomycin is primarily used as a topical antibiotic in humans though it may be used for enteric infections.
- Low levels of resistance are known. There is evidence of resistance to aminoglycosides emerging in animal enteric pathogens.
- It is classified as a category C antibiotic.
- Adequate instructions minimising the risk of transfer of resistant bacteria from topical infections are required.

Cephalosporins

Cephalosporins have been considered by the MoH in the context of the currently approved products and during the registration of cefquinome. These actives are regarded as Jetacar category B with the third and fourth generation products regarded as essential human antibiotics. Bacterial cross-resistance is regarded as well recorded between cephalosporins and penicillins. There are concerns with widespread use of first and second generation drugs, which may increase resistance rates to later generation products. The MoH has requested cefuroxime, as a second generation product, be restricted to a greater extent. Use in dry cow intramammary products would not be supported.

Cefaquinome was approved as an injectable product and a lactating cow intramammary with level 2 label statements. The intramammary product was viewed as providing a higher risk, which resulted in a reporting requirement on the prescribing veterinarian.

The risk management of cephalosporins in general needs further review. The current opinion is based primarily on the use of actives within medicine. Further consideration of risk pathways is required and a firm basis for considering future applications with new use patterns and actives is needed. A review should consider the degree of cross-resistance likely to occur within the group and the extent that risk management can be split based on the categorisation of a cephalosporin.

Intramammary products

A consistent concern that has been repeated in the consideration of actives such as cephalosporins and lincomycin and streptomycin is the risk associated with the use of antibiotics in intramammary products.

This is exacerbated by the use of dry cow products in appreciable percentage of a herd or as whole herd treatment. The use pattern may include a degree of prophylaxis as well as treating subclinical infections.

The submission on the resistance potential of lincomycin in a lactating cow product contains argument that is in part based on the risk of an intramammary product.

Consideration of the relative risk of intramammary use in both lactating and dry cow products compared with other dosage forms, such as injectable products, is required as a basis for consistent decision making on future applications as well as existing products.

A risk analysis should include consideration of the normal flora and pathogens found in the mammary gland and risk pathways other than the ingestion of antibiotic residue or resistant bacteria in milk.

Summary

The following issues in relation to the management of antibiotic resistance have arisen during the registration and updating of products to the ACVM Act:

- The current use of streptomycin and dihydrostreptomycin in veterinary medicine and horticulture potentially conflicts with the use in human medicine. The risk of agricultural use to human medicine requires assessment in order to make informed decisions about changes to use if required.
- Additional to the consideration of streptomycin, the aminoglycoside group should be considered relating to the potential for cross-resistance between the actives. This provides a basis for existing risk management and future decisions about new use patterns.
- The macrolide/lincosamide group should be considered including the degree of cross-resistance to provide a basis for considering the relative risk for each active ingredient.
- New information is available in the form of a risk analysis of the antibiotic resistance associated with the use of tylosin and tiamulin. The outcomes of the last antibiotic resistance review and the subsequent management of registrations should be reviewed considering the risk analysis and any other new information available.
- There has been a specific challenge to the label statements required for the intramammary Lincocin Forte S to manage resistance arising from the use of lincocin. This information needs to be considered in relation to this product but also has relevance for macrolides and lincosamides in general and the risk associated with intramammary use.
- The cephalosporin group needs consideration to provide a basis for comparative risk management between actives.
- Consideration of the risk associated with intramammary use of antibiotics in lactating and dry cow therapy is needed to provide as basis for current and future decisions about this use pattern.

APPENDIX 3: AMINOGLYCOSIDES

Introduction

The aminoglycosides are bactericidal, narrow spectrum (mostly Gram negative) antimicrobials. They have been in use since the 1940s but have significant drawbacks in clinical use: they are relatively toxic and do not penetrate tissues well. If given orally they will have only a local effect on the gut flora. For systemic effects, they must be injected. Systemic use in food animals is reducing because of residue concerns. The more modern aminoglycosides are less likely to be inactivated by resistant bacteria, but are too expensive for most veterinary use. The older drugs are still widely used, often without good evidence of efficacy.

Drugs

Aminoglycosides used clinically include amikacin, dihydrostreptomycin, framycetin (neomycin B), gentamicin, kanamycin, neomycin (a mixture of neomycin A, B and C), netilmicin, paromomycin, streptomycin and tobramycin. Spectinomycin and apramycin are closely related but are usually classified as aminocyclitols. They are similar in most respects to aminoglycosides.

Aminoglycosides consist of aminocyclitol groups with a variable number of amino-sugars attached. They are natural or semisynthetic substances derived from various soil fungi, mainly *Streptomyces* species, except for gentamicin and netilmicin, which come from *Micromonospora* species.

JETACAR category

Amikacin, gentamicin, netilmicin, tobramycin, streptomycin - A
Spectinomycin - B
Neomycin, paromomycin - C

Pharmacology

Aminoglycosides are rapidly bactericidal by blocking protein synthesis. The effect is concentration dependent. They bind tightly to the bacterial 30S ribosomal subunit, and block peptide synthesis by preventing tRNA attachment, blocking normal initiation, and distorting the codon arm to cause mismatching of the codon-anticodon couples resulting in the production of so-called 'nonsense peptides'.

Aminoglycosides diffuse through aqueous channels in the outer membrane of Gram negative bacteria, but are transported across the inner membrane by an active process. This process can be blocked by lack of oxygen, divalent cations, low pH and hyperosmolarity.

Aminoglycosides are very polar molecules: they are not well absorbed from the gut and do not penetrate most tissues very well. Penetration of the cell (and thus activity) can be greatly aided by drugs that interfere with cell wall synthesis such as β -lactams.

Aminoglycosides are relatively toxic. They are concentrated in the inner ear and proximal tubule cells of the kidney, where they may cause deafness, loss of balance or kidney failure.

Spectrum of action

Aminoglycosides are mainly effective against aerobic gram-negative organisms. They can also be effective against some gram-positive organisms, such as *S. aureus*, some mycobacteria, some strains of mycoplasma and some spirochetes. They are inactive against anaerobes and streptococci. Some aminoglycosides are active against *Pseudomonas aeruginosa*.

They are sometimes given with other antibacterials, particularly β lactams, to achieve a synergistic effect. In most cases there is no evidence that synergism actually occurs (Whittem and Hanlon, 1997a and b). For instance, neomycin added to penicillin was shown to produce the same rate of cure (by a variety of different measures) as penicillin alone in cows with mastitis in a blinded study (Taponen *et al*, 2003).

In vitro susceptibility does not always correspond with clinical usefulness because the drugs often do not penetrate to the site of infection. This may be particularly important with *S. aureus* mastitis.

Evolution of resistance

Resistance can arise from mutations in the bacterial ribosome, production of metabolising enzymes (probably most important), or reduced transport of the drugs into bacterial cells.

Once the drug diffuses into the periplasmic space, it may be acetylated, adenylated or phosphorylated by at least 20 different enzymes (Chambers and Sand, 1996). The genes coding for these enzymes are usually on plasmids (Pohl *et al*, 1993), which are widely distributed. A single plasmid may code for cross-resistance to several different aminoglycosides (Blackburn *et al*, 1984; Chaslus-Dancla *et al*, 1986; Platt and Smith, 1991) and also other antimicrobials (Johnson *et al*, 1994). These enzymes have different efficacies against the different drugs: amikacin is less easily inactivated as side groups on the molecule protect some of the enzyme binding sites (Chambers and Sand, 1996). However, in some cases, a single acetylase can inactivate gentamicin, tobramycin, amikacin, kanamycin and netilmicin (Murray, 1991).

Failure of the drug to move across the bacterial cytoplasmic membrane can also cause resistance. This is an oxygen dependent process, so anaerobes are resistant, as are facultative anaerobes grown in anaerobic conditions (such as the middle of an abscess) (Chambers and Sand, 1996).

Alterations in the ribosome, which stop the drugs binding, are rarer although they can occur in *E. coli* by a single mutation (Stoffler and Tischendorf, 1975). This type of resistance is usually specific to streptomycin. Resistance has been recorded in most animal and human pathogens.

Resistance to streptomycin has been recorded for *Erwinia amylovora*, the fire blight pathogen in the USA (California, Idaho, Michigan, Missouri, Oregon and Washington) and in Israel; for *Pseudomonas syringae* in the USA (Michigan, New York, Oklahoma, Oregon); for *Pseudomonas cichorii* in Florida and for *Xanthomonas campestris* in Argentina, Brazil, Taiwan, and the USA (California, Florida, Georgia and Pennsylvania) (see Chapter 4, Antimicrobial Use in Horticulture).

Fate in the environment

Streptomycin has been shown to lose about 30% of its potency after five days in activated sludge (Halling-Sorensen *et al*, 2003). It also breaks down slowly in light. No information on the other aminoglycosides could be found.

New Zealand data

New Zealand data are very limited. Penethamate (penicillin prodrug) given intramuscularly has been shown to be as effective as penicillin and dihydrostreptomycin given by the intramammary route for mastitis in cows, with the exception of mastitis caused by coagulase negative staphylococci (McDougall, 1998).

The prevalence of streptomycin resistance in *S. aureus* from mastitic cows remained just below 10% from 1976 - 1995 (Carman and Gardner, 1997), or declined from 18% in 1978 to 8% in 1989 (Belton, 1991).

Use in people in New Zealand

amikacin and netilmicin - serious Gram negative infections, particularly those resistant to other aminoglycosides; as second line treatment as an adjunct to other antibiotics for MRSA

gentamicin and tobramycin - serious Gram negative infections

neomycin (and Framycetin) - topical use for superficial eye and ear infections

streptomycin - second line treatment for multi-resistant TB in combination with other antibiotics (prescribed under s25 of the Medicines Act 1981).

Use in animals in New Zealand

Uses for which there is good evidence of efficacy and for which there are limited alternatives:

gentamicin, amikacin - bone and joint infections, septicaemia in cats, dogs and horses

gentamicin - *Pseudomonas* infections

Uses for which there is some evidence of efficacy and where alternatives exist:

(dihydro)streptomycin - leptospirosis in food animals, actinobacillosis, gut infections

neomycin - gut infections, otitis externa

Uses for which there is no evidence of efficacy:

mastitis in cattle and pigs

metritis when given by the intrauterine route

pneumonia in cattle

Use overseas

Penicillin and streptomycin mixtures were withdrawn in the USA in 1993.

UK - see Appendix 13

Australia - similar to New Zealand, although injectable streptomycin is not used in food animals for residue reasons.

Use on plants overseas

From this year, streptomycin is not allowed in Europe for the treatment of plant bacterial diseases. Israel withdrew registration for this antibiotic in 1997, following the emergence of streptomycin resistant bacteria. In the USA streptomycin is allowed for control of diseases on fruits, vegetables, tobacco and ornamentals. The pathogens targeted for each of these crops are: fire blight caused by *Erwinia amylovora* on apple and pear, soft rots due to *Pectobacterium* sp. (ex soft rot *Erwinia*) on cut flowers and potato seed pieces, bacterial blight of celery caused by *Pseudomonas cichorii*, fruit spotting or blossom blast symptoms on apple, pear and other trees caused by *Pseudomonas syringae* of different pathovars, bacterial spot of pepper and tomato caused by *Xanthomonas campestris vesicatoria*, crown gall of roses caused by *Agrobacterium tumefaciens*, and on tobacco wildfire caused by *Pseudomonas syringae tabaci* and blue mold caused by *Peronospora tabacina*.

In Mexico and Latin America, gentamicin is used alone or in combination with oxytetracycline for control of fire blight on apple and pear and for the control of soft rot caused by *Erwinia* and *Pectobacterium* and the control of diseases caused by *Pseudomonas*, *Ralstonia* and *Xanthomonas* on vegetables.

Regulation

New Zealand: most are Prescription Animal Remedies class 1

UK: all are Prescription Only Medicines (POM)

Prospectus

Systemic use of the older drugs in animals is limited by toxicity and poor pharmacokinetics, which make the drugs inconvenient to use and result in long withholding periods in food animals. Use of the newer drugs is severely limited by cost. These limitations are likely to increase in importance in the future.

There are no new drugs of this class likely to enter the clinics soon: most research is aimed at developing new drugs with a similar mechanism of action but a different structure. Any new drug would have to be much less toxic and preferably more effective to be commercially viable.

If the incidence of multidrug resistant TB increases in New Zealand, streptomycin may well have to be brought back as part of a treatment combination. It would be desirable to have as few resistance genes in the environment as possible.

Risk - benefit analysis

Injectable aminoglycosides

Hazard

Use of these drugs has been shown to lead to resistance in pathogens in people and animals given the drugs.

Exposure

The toxicity of these drugs means that they are likely to be used only in individual sick animals where nothing safer would work. These animals are unlikely to enter the food chain.

Impact

Aminoglycosides, particularly the newer ones, are important for treating serious diseases in people but are not used routinely because of toxicity. Alternative drugs are available for people.

Benefits

These drugs can be life saving in individual animals.

Conclusion

Veterinary use under prescription should continue or animal welfare would be seriously compromised.

Intramammary aminoglycosides

Hazard

These drugs have been used for many years without significant resistance developing, but data are scarce. Streptococci, collectively the major mastitis pathogens, are intrinsically resistant.

Exposure

Most milk in New Zealand is pasteurised, so most people will not be exposed to resistant bacteria. However, the Panel estimates that up to 10,000 rural families drink unpasteurised milk, and could be exposed.

Impact

Aminoglycosides, particularly the newer ones, are important for treating serious diseases in people but are not used routinely because of toxicity. Alternative drugs are available.

Benefits

Gram negative bacteria are a very rare cause of mastitis in New Zealand. Aminoglycosides are usually combined with penicillin, but there is no evidence that the combination is more effective in treating mastitis than penicillin alone.

Conclusions

Requiring evidence of synergistic effect and efficacy would bring the registered products into line with the ACVM *Standard and Guideline: Efficacy of Intramammary Antimicrobials*, which states (s2.1.5): “In the case of fixed combination products, it must be demonstrated that all active ingredients produce their expected effect(s)”.

Oral formulations

Hazard

Resistance in pathogens is relatively common, resistance in commensals is likely.

Exposure

These are usually used in neonatal animals, which are unlikely to enter the food chain (although there have been problems with bobby calves in the past). Persistence of resistant bacteria in the gut after treatment is unknown. Some resistant bacteria can persist in the environment for months. If an animal with resistant gut bacteria entered the food chain, a large number of people could be exposed to the bacteria.

Impact

Aminoglycosides, particularly the newer ones, are important for treating serious diseases in people but are not used routinely because of toxicity. Alternative drugs are available.

Benefits

Aminoglycosides can be of benefit, but are not the treatment of choice in uncomplicated diarrhoea. Antibiotics are really indicated only when bacteria have invaded the mucosa.

Conclusions

Aminoglycosides should be used only where there is good evidence of infection and mucosal invasion by susceptible bacteria. They should not be used to treat non-specific enteric infections in groups of food-producing animals.

The risks are low, but so are the benefits of indiscriminate use. There is a danger that these drugs could be used instead of fluids, which are likely to be more effective, if more time consuming to administer. If oral formulations were withdrawn, animals could be given injectable formulations if indicated.

Topical formulations

Hazard

These are mostly used in companion animals, particularly in dogs for otitis. Resistance has been shown to develop, particularly multi-resistant *Pseudomonas*. Otitis in dogs is usually a sign of atopy, and tends to recur, so dogs are often given repeated long courses of treatment.

Exposure

Very little data on transfer of bacteria from dogs' ears, but most dog owners practise minimal infection control and are probably exposed to resistant bacteria. Family members, particularly children, are also likely to be exposed.

Impact

Aminoglycosides, particularly the newer ones, are important for treating serious diseases in people but are not used routinely because of toxicity. Alternative drugs are available.

Benefits

Aminoglycosides are useful topically, but in many cases antiseptics could be used as effectively.

Conclusions

Many topical aminoglycosides are overused, but withdrawal would compromise animal welfare.

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APPENDIX 4: BACITRACIN

Drugs

Bacitracin is the only drug in this class. The producing organism, *Bacillus licheniformis*, has been fed to pigs overseas as a probiotic. Bacitracin requires divalent cations to be effective, and is usually combined with zinc.

JETACAR category

D

Pharmacology

Much more is known about the pharmacology of bacitracin than in 1999. It has become clear that it has a wide variety of actions, some of which may be relevant to its use in animals. It can act as a protease; it can enhance uptake of small proteins across the intestinal wall and it blocks breakdown of leucine enkephalin, which has an antidepressant effect in people.

Spectrum of action

Bacitracin mainly affects Gram positive organisms. Susceptibility is variable among enterococci, and varies with host species. Only enterococci (both *E. faecalis* and *E. faecium*) from chickens in Belgium were resistant; enterococci from pigs, ruminants and pets were susceptible (Butaye *et al*, 2001). It has some effect against *Brachyspira hyodysenteriae*, but can also increase infection with *B. pilosicoli* in chickens (Stephens and Hampson, 2002). It may also have some effect against *Lawsonia intracellularis*, although it is unlikely to penetrate cells.

Evolution of resistance

The main mechanism of resistance is thought to be increased expression of an efflux pump. Resistance in *Bacillus licheniformis* is mediated by *bcrABC* genes, which code for an efflux pump (Neumueller *et al*, 2001); the same genes seem to be involved in enterococci (Manson, Keis *et al*, 2004).

Resistance in *Cl. perfringens* can occur, but does not appear to persist in a flock. As long as other drugs are available to treat it in the short term, it is not regarded as a problem. A recent survey of *Cl. perfringens* in Scandinavian poultry showed no resistant isolates in Norway, 3% of isolates resistant in Sweden and 15% resistant in Denmark (Johansson *et al*, 2004). All were susceptible to ampicillin, which was used in large quantities to control necrotic enteritis when bacitracin was banned in Sweden and Denmark. *Clostridium aminophilum*, from cattle, can become resistant to ionophores, and this also causes bacitracin resistance (Houlihan and Russell, 2003).

There is some evidence that bacitracin can induce *vanA* expression in enterococci. However, the epidemiological evidence suggests that bacitracin use does not select for VRE.

Subclinical levels of bacitracin can prevent *E. coli* from transferring resistance genes (Mathers *et al*, 2004).

New Zealand data

From 213 faecal samples from chickens from all over New Zealand, 98.7% of enterococci were resistant to bacitracin (Manson, Smith and Cook, 2004).

Use in people in New Zealand

Not used at present. It used to be used as a topical ointment or drops for superficial infections but this use has given rise to a large number of allergic reactions. It seems unlikely that bacitracin will be used in this way again.

Bacitracin has been advocated as a means of eliminating VRE carriage in people, but the published evidence shows that the efficacy is low and that recolonisation takes place quickly. It has also been advocated as a means of eradicating MRSA carriage, but its efficacy was approximately half that of mupirocin (Soto *et al*, 1999).

Bacitracin has been shown to potentiate the effects of clarithromycin in resistant mycobacteria (Bosne-David *et al*, 2000). However, ethambutol had the same effect, and is already approved for use in tuberculosis in New Zealand, so it seems unlikely that bacitracin would be used in this way.

Use in animals in New Zealand

Pigs and poultry - prevention of clostridial enteritis

Use overseas

UK -	banned
USA -	poultry - growth promotion, prevention of necrotic enteritis
	pigs - growth promotion, prevention of clostridial enteritis and swine dysentery
	cattle - prevention of liver abscesses
Australia -	poultry - growth promotion and prevention of necrotic enteritis
Canada -	poultry - growth promotion, prevention of necrotic enteritis, reduction in early mortality
	pigs - growth promotion, prevention and treatment of bacterial enteritis

Regulation

PAR 1

Prospectus

There are no new drugs with the same mechanism of action likely to arrive in the near future.

Risk - benefit analysis

Hazard

Bacitracin resistance genes could be transferred to human *S. aureus* or *enterococci*.

Exposure

People are likely to be exposed by eating or handling undercooked chicken.

Impact

Bacitracin resistance in human pathogens or commensals would have no impact on human health. Bacitracin-induced expression of vancomycin resistance would be important, but seems not to occur outside the laboratory.

Benefits

Bacitracin is effective in preventing necrotic enteritis in chickens. If it were withdrawn, other, more valuable, antibiotics would have to be used to treat necrotic enteritis. In Scandinavia, large quantities of ampicillin were used when bacitracin was banned.

Conclusion

Bacitracin poses a very low risk to human health, but its withdrawal would seriously compromise animal welfare.

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APPENDIX 5: CEPHALOSPORINS

The cephalosporins are β lactams, similar to penicillins, but the β lactam ring is protected from some β lactamase enzymes produced by bacteria by the shape of the adjoining ring. This means that cephalosporins are effective against some penicillin-resistant bacteria. The spectrum of activity varies with the different members of the group (see below).

Drugs

There are several different ways of classifying cephalosporins; the generation classification (below) is commonest. None of the classification systems are particularly useful with the newer drugs.

Generation	Spectrum	Veterinary drugs in NZ	Human drugs in NZ
1 oral	Good G+, moderate G-, not <i>Pseudomonas</i>	cephalexin, cefadroxil	cephalexin, cefadroxil, cephradine
1 parenteral	very good G+, moderate G-, not <i>Pseudomonas</i>	cephalothin, cephaloridine, cefapirin, cephalonium	cephazolin, cephradine
2 oral	fair G+, good G-, not <i>Pseudomonas</i>		cefaclor
2 parenteral	fair G+, good G-, not <i>Pseudomonas</i>	cefuroxime	cefuroxime, cephmandole
3	moderate G+, very good G-, some activity against <i>Pseudomonas</i> and <i>Bacteroides</i>	ceftiofur	cefotaxime
3 antipseudomonal	moderate G+, very good G-, good <i>Pseudomonas</i>		ceftazidime, ceftriaxone
4	very good G+, very good G-, good <i>Pseudomonas</i> , <i>Bacteroides</i> , <i>E. faecalis</i>	cefquinome	cefpirome, cefepime
cephamycins	moderate G+, good G-, not <i>Pseudomonas</i> , good <i>Bacteroides</i>		latamoxef, cefotetan, cefoxitin

The clinically used drugs are semi-synthetic derivatives of natural metabolites from various *Cephalosporium* species.

JETACAR category

Third generation (including antipseudomonals) and fourth generation - A
Others - B

Pharmacology

Cephalosporins are bactericidal by inhibiting cell wall synthesis in the same way as penicillins. They also bind to penicillin binding proteins.

Most third and fourth generation cephalosporins are broken down in acid and are not effective by mouth. Most, with the exception of third generation drugs, do not penetrate the blood brain barrier. Most cephalosporins, particularly the later generations, are cleared rapidly by the kidneys, although cephalothin, cephapirin, cefotaxime and probably ceftiofur are metabolised in the liver. These processes tend to be faster in animals than people, making third and fourth generation cephalosporins too short acting to be much use in most circumstances in animals. However, this rapid clearance allows short withholding times in food animals.

Cephalosporins' penetration into tissue is generally similar to that of penicillins, although this has not been studied in detail and there are likely to be differences between individual drugs. Ziv *et al* (1973) compared two cephalosporins which are now obsolete with a variety of penicillins which are still used to treat mastitis in cows and found that pharmacokinetic parameters used to indicate tissue penetration were similar to ampicillin and cloxacillin for one of the cephalosporins and slightly better for the other. Similar data for modern cephalosporins have not been published. Similarly, cephalosporins showed no better activity against *S. aureus* inside bovine macrophages *in vitro* than cloxacillin (Sanchez *et al*, 1988), implying a similar degree of penetration into the cells.

Intramammary administration of cephalosporins is likely to lead to some systemic uptake (Wilson and Gilbert, 1986) and consequent exposure of gut bacteria to low concentrations. This area has not been well studied.

Cephalosporins can cause allergic reactions in animals as in people, but this is extremely rare.

Spectrum of action

This varies (see table above). While classifying the spectrum of action by generation is clinically useful, there can be differences between individual drugs in the same group, for example, cephalothin and cephazolin (Yeh and Chi, 2001). Third and fourth generation drugs are mainly used for Gram negative (including *Pseudomonas*) infections in people. First generation drugs are effective against many Gram positives, but not MRSA. *Enterococci* and *Campylobacter* are resistant. Some strains of *S. pneumoniae* are also resistant.

Evolution of resistance

The main mechanisms of resistance are through production of a range of β lactamases, which break down the drugs. These include *ampC* and extended spectrum β lactamases (ESBLs). Exposure to any cephalosporin could select for ESBL producing *E. coli*, MRSA and other resistant organisms. Fourth generation cephalosporins have greater stability to β lactamases produced by Gram negative organisms. As such, they are generally restricted in human health to treat infections proven or suspected to be caused by resistant Gram negative bacteria. ESBL genes have been isolated from *Salmonellae* and *E. coli* from chicken and beef in the USA (Zhao *et al*, 2001). Emergence of resistance to third generation cephalosporins in human pathogens has been linked to the use of fluoroquinolones, as well as third generation cephalosporins themselves (Talon *et al*, 2000).

Fate in the environment

Ceftiofur in cattle faeces or urine is rapidly broken down by ESBL-producing bacteria (Hornish and Kotarski, 2002). It has a half-life in soil of about three hours (Smolenski *et al*, 2002). Other cephalosporins are assumed to be similar.

New Zealand data

ESBL producing enterobacteria have increased from 16 isolates from people in 1998 to 389 in 2004 (ESR, 2005), mainly in Hawke's Bay and Auckland. These were mostly *E.coli* and mostly from urine.

Dry cow treatment with cephalonium was not as effective against *S. aureus* as a penicillin, novobiocin and neomycin combination (Buddle and Cooper, 1980). Intrauterine infusion of cephapirin reduced reproductive problems in cows that had had infections the previous season (McDougall, 2001). Cephalonium dry cow treatment was as effective at preventing *Strep. uberis* infection in the following season as teat sealing (Woolford *et al*, 1998). Dry cow treatment with cephalonium reduced new *Streptococcus uberis* infections from 12.3% to 1.2% (Williamson *et al*, 1995).

MRSA has been isolated from cows in the Waikato (Gibson, 2005), and there is some indication that this contains the same resistance genes as the common human strain in New Zealand, EMRSA 15 (Alex Grinberg, personal communication). EMRSA 15 is resistant to cephalosporins, and also the penicillins used to treat mastitis.

Use in people in New Zealand

Third and fourth generation cephalosporins are used for serious Gram negative infections, including meningitis. They are restricted to hospital specialists.

Use in animals in New Zealand

First and second generation cephalosporins are widely used in small animals, particularly for β lactamase producing *S. intermedius* skin infections. They are also commonly used for β lactamase producing *S. aureus* mastitis in lactating cows, where their rapid elimination allows short withholding times.

The only third generation veterinary cephalosporin, ceftiofur, behaves in many ways more like a second generation cephalosporin. It is registered for use in *Pasteurella pneumonia* (rare in cattle in New Zealand) and foot rot (usually a trivial disease that can be cured by most antibiotics and antiseptics).

Similarly, the only veterinary fourth generation cephalosporin, cefquinome, is used for similar infections to ceftiofur, and also acute *E.coli* mastitis with systemic involvement (also rare in New Zealand). It is used in pigs for respiratory infections and mastitis-metritis-agalactia syndrome. It is also available for intramammary use, where it is effective against β lactamase producing *S. aureus* and most of the *Streptococci* that can cause mastitis.

Use overseas

UK - see Appendix 13

USA - all generations used for mastitis, in both dry and milking cows, ceftiofur for respiratory infections in many species, ceftiofur for coliform infections in chickens and turkeys, cefquinome as in New Zealand.

Australia: cefquinome not registered; ceftiofur used for respiratory infections in horses and cattle, and urinary tract infections in dogs, use for mastitis in cows banned; cephalexin used in cats and dogs only; cefuroxime used for mastitis in milking cows; cephalonium used for mastitis protection in dry cows and eye infections; cephapirin used for intra-uterine treatment of metritis in cows.

Regulation

New Zealand: PAR 1

UK: POM

Prospectus

Many other cephalosporins have been developed. Most of these have not made it into clinical use because of side effects, particularly kidney failure. It is conceivable that some of these may be developed for veterinary use. In the longer term, the main thrust of research seems to be aimed at drugs without the β lactam structure (and so not susceptible to β lactamases) but which act in the same way.

Risk - benefit analysis

Intramammary use

Hazard

Use of these drugs is likely to lead to resistant bacteria in milk and in faeces (although many faecal bacteria are intrinsically resistant).

Exposure

Fonterra test all bulk milk for inhibitory substances, so milk containing cephalosporins is very unlikely to enter the food chain. Milk sold commercially is pasteurised, so no viable resistant bacteria should enter the food chain. However, up to 10,000 families in New Zealand may drink unpasteurised milk and be exposed to resistant bacteria. Farmers and milkers will also be exposed through direct contact with cows. Faeces from treated cows, or calves that have been fed milk from treated cows within the withholding time, are a possible pathway of unknown importance.

Impact

There is only one alternative group of drugs to treat serious resistant Gram negative infections in people, the fluoroquinolones.

Benefits

Effective against penicillin resistant *S. aureus*, but alternatives are available, e.g. cloxacillin. Short withholding times are useful in milking cows.

Injectable use

Hazard

Use of these drugs is likely to lead to resistant bacteria in milk and in faeces (although many faecal bacteria are intrinsically resistant).

Exposure

This use is likely only in sick animals that will not enter the food chain, so only the animal handler will be exposed.

Impact

There is only one alternative group of drugs to treat serious resistant Gram negative infections in people, the fluoroquinolones.

Benefits

Use of these drugs can be life saving in individual animals.

Oral use

Hazard

Use of these drugs is likely to lead to resistant bacteria in faeces (although many faecal bacteria are intrinsically resistant).

Exposure

This use is likely only in sick animals, particularly companion animals, so only the people in the same household as the animal will be exposed. However, dermatitis attributed to *S. intermedius* is common in dogs, and the number of households affected is unknown.

Impact

There is only one alternative group of drugs to treat serious resistant Gram negative infections in people, the fluoroquinolones.

Benefits

Use of these drugs can be life saving in individual animals, but they are also effective in trivial infections.

Conclusions

Animal welfare would be compromised if it were no longer possible to use these drugs in serious infections in individual animals. Use in trivial infections should be discouraged.

First and second generation cephalosporins are mainly used in cows to treat *S. aureus* and streptococcal infections. There is an adequate selection of alternative treatments, so reduced use for this indication should not affect animal welfare. The short withholding periods of cephalosporins are not critical in dry cow therapy.

Third and fourth generation cephalosporins are regarded in human medicine as both major drivers of antibiotic resistance and of critical clinical importance. Their use is controlled as to who can prescribe them, what they used for and how they are used. In contrast, the

constraints that apply to veterinary use are much more liberal. While the chances are small of bacteria or determinants resistant to third and fourth generation cephalosporins being passed on to humans via the food chain, other pathways cannot be discounted and the consequences of transfer would be severe.

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APPENDIX 6: FLUOROQUINOLONES

Fluoroquinolones were covered in the 1999 report and are only updated here.

Drugs

Enrofloxacin, marbofloxacin and orbifloxacin are used in animals in New Zealand; sarafloxacin and danofloxacin are in veterinary use overseas. Norfloxacin and enrofloxacin's main metabolite, ciprofloxacin, is in human use in New Zealand. The newer generation fluoroquinolones (8-methoxyfluoroquinolones), such as levofloxacin, moxifloxacin and gatifloxacin, have recently reached New Zealand for human use.

Pharmacology

Fluoroquinolones bind to DNA-gyrase (most important in Gram negatives) and topoisomerase IV (most important in Gram positives), which are responsible for supercoiling the bacterial DNA. The fluoroquinolones cause the enzyme complex to bind irreversibly to the bacterial DNA. This usually kills the bacteria.

Fluoroquinolones have been shown to cause a marked post-antibiotic effect, i.e. a continued bacterial growth inhibition in those bacteria surviving after the removal of the drug from the bacterial media.

Fluoroquinolones are partially metabolised in the liver and are excreted as both active and inactive metabolites (ciprofloxacin is the major active metabolite of enrofloxacin), and as parent drug. They may be found in both the bile and urine at 20 times the plasma concentration. They are concentrated in macrophages and are able to kill some intracellular bacteria.

Spectrum of activity

Ciprofloxacin and enrofloxacin are mainly active against aerobic Gram negative organisms, but are not very active against Gram positive aerobes (except for reasonable activity against some *Staphs*) or anaerobic organisms. They are reasonably active against *Mycoplasma* and *Campylobacter*. Some activity is reported against *Pseudomonas*, *Rickettsia*, *Chlamydia*, and *Mycobacteria*. Newer drugs (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin, and trovafloxacin) have more activity against Gram positives, especially *Streps* and also *Mycobacteria*.

Evolution of resistance

There are four recorded resistance mechanisms for fluoroquinolones. These include modification of DNA gyrase and/or topoisomerase IV, active efflux and altered membrane permeability. A protein from *Mycobacterium tuberculosis* has recently been shown to mimic bacterial DNA and confer some resistance to fluoroquinolones (Hegde *et al*, 2005)

Fluoroquinolone resistant isolates usually contain one or more mutations in a small section of GyrA or ParC; mutation in GyrB and ParE is rare, but getting commoner. In Gram negative bacteria, where mutations have given rise to a resistant DNA gyrase (low level resistant), mutations then occur in the topoisomerase IV genes (and vice versa for Gram positive bacteria) to give a highly resistant bacterium. Newer drugs that inhibit both enzymes give

rise to less resistance. A single point mutation in *gyr A* in *Campylobacter* can cause a high level resistance (Luo *et al*, 2003).

Efflux pumps are an important mechanism of resistance in many bacteria (reviewed by Pool, 2000). In *Campylobacter*, the CmeABC efflux pump may even be necessary for a *gyrA* mutation to give rise to clinical resistance (Luo *et al*, 2003).

Clinically significant resistance occurs in *Pseudomonas*, *S. aureus* and *Campylobacter*.

Fate in the environment

Unknown

New Zealand data

ESR data for 2002 (the last year for which animal data are available) show fluoroquinolone resistance in *E. coli* in dogs was 2% (comparable to human isolates in 2002) and that most of the resistant isolates from dogs were reported from Auckland (Heffernan, 2003). Fluoroquinolone resistance in *S. aureus* has varied from 0% of animal isolates in 1999 to 12.5% in 2001 and back to 1.8% in 2002 (Heffernan, 2002, 2003).

Use in people in New Zealand

The fluoroquinolones (and the third generation cephalosporins) are the main group of drugs used for serious Gram negative infections in people, although they are also sometimes used for more trivial infections such as urinary tract infections. The second generation fluoroquinolones moxifloxacin, levofloxacin and gatifloxacin are approved in New Zealand, mainly for community-acquired pneumonia. The newer fluoroquinolones may have to be used as part of a multi-resistant TB treatment protocol soon.

Use in animals in New Zealand

Enrofloxacin registered indications:

Bacterial infections of bones in cats, dogs, pigs and cattle

Mastitis in cows where the causative organisms have been established to be either *E. coli* or *Pseudomonas*. Appropriate intramammary treatment with another antibiotic should be used in combination with systemic treatment (other than oral).

Ear and skin infections caused by *Pseudomonas* in dogs and cats.

Urinary tract infection in dogs and cats.

Infection of the (male) reproductive tract (prostatitis, vesiculitis, orchitis) in the bull and dog.

Certain infections of cattle, pigs, dogs and cats in locations where poor tissue penetration by other antimicrobial drugs can be expected and where the condition is caused by a susceptible organism that does not respond readily to other antibiotics.

Orbifloxacin registered indications:

Dogs and cats: For treatment of skin and associated soft tissue infections (wounds and abscesses) caused by susceptible strains of *S. intermedius*, *E. coli*, *Enterobacter* spp., *Pasteurella multocida*, *Klebsiella pneumoniae*, *Pseudomonas* spp., *Acinetobacter* spp., and *Streptococcus* - hemolytic group G.

Dogs: For treatment of urinary tract infections caused by susceptible strains of *E. coli*, *Proteus mirabilis*, *S. intermedius* and *Enterococcus faecalis*.

Marbofloxacin registered indications:

In cattle: treatment of respiratory and other infections caused by susceptible strains of organisms.

In sows: treatment of metritis mastitis agalactia syndrome (MMAS) and other infections caused by susceptible strains of organisms.

In neonatal calves: treatment of gastroenteritis caused by sensitive strains of *E. coli*.

Use overseas

UK - similar to New Zealand plus:

danofloxacin injection used in cattle and pigs; difloxacin tablets used in dogs, oral solution in chickens and turkeys; enrofloxacin used in poultry and sarafloxacin used in fish (Appendix 13).

USA - sarafloxacin and enrofloxacin have been withdrawn from use in poultry.

Regulation

New Zealand - PAR 1. Marboflxacin boluses also have the conditions:

- Indiscriminate use of the product could contribute to the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic.
- The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivities tests have shown that it is the only alternative that is likely to be effective.
- The prescribing veterinarian must notify the ACVM Group of every case the antibiotic is prescribed, giving date, species prescribed for and condition treated.

UK - all POM

Prospectus

After a rush of new 8-methoxyfluoroquinolones onto the market, development of new drugs has paused because some of the newer drugs have caused serious cardiovascular side effects in people.

Risk - benefit analysis

Hazard

Use of these drugs in food animals has been shown to lead to resistant bacteria in food. Fluoroquinolone-resistant *E. coli* isolates from dogs in New Zealand are increasing in prevalence.

Exposure

Resistant faecal organisms are almost certain (chickens) or likely (other species) to get onto meat, despite precautions at killing. Resistant faecal organisms are very likely to be transferred between companion animals and their owners.

Impact

There are very limited treatment options (usually only third generation cephalosporins) for serious fluoroquinolone-resistant infections in people.

Benefits

These drugs can be life saving in individual animals. They can compensate for poor husbandry in intensive farming situations.

Conclusions

Animal health and welfare would be compromised if it were no longer possible to use these drugs in serious infections in individual animals. There are many other ways of treating trivial infections, and fluoroquinolones should be reserved for serious infections.

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APPENDIX 7: MACROLIDES AND SIMILAR DRUGS

These drugs have different chemical structures but are clinically very similar in their pharmacokinetics and spectrum of action (although differences in resistance patterns are starting to emerge). They are all bacteriostatic.

They were reviewed in the 1999 report.

Drugs

Macrolides include erythromycin (originally derived from *Streptomyces erythreus*), tylosin (originally derived from *Streptomyces fradiae*), tilmicosin and spiramycin (less active), which are commonly used in animals; oleandomycin is used in animals but no longer used in people. Roxithromycin (a derivative of erythromycin), clarithromycin and azithromycin are new human drugs that have more suitable pharmacokinetics. Kitsamycin is used in animals in Australia. Aivlosin is a tylosin derivative under development.

Streptogramin Bs are also macrolides.

Lincosamides are chemically different but clinically identical to macrolides. Lincomycin (originally derived from *Streptomyces lincolnensis*) and pirlimycin are used in animals, clindamycin in people.

Pleuromutilins are also very similar. Tiamulin is the only drug used in New Zealand, but valnemulin is used in Europe. This class of drugs is not used in people. Pleuromutilins were originally derived from the basidiomycete *Pleurotus mutilus* (now called *Clitopilus scyphoides*).

Ketolides are macrolide derivatives with a slightly different mechanism of action. Telithromycin is licensed for people in the USA and Europe, but not yet in New Zealand. Most ketolides are derivatives of clarithromycin.

JETACAR category

azithromycin, clarithromycin - A
erythromycin, roxithromycin - C
clindamycin, lincomycin - B
tiamulin, tilmicosin - not classified
telithromycin - not yet classified

Pharmacology

These drugs inhibit bacterial protein synthesis by binding to the 23S rRNA of the 50S bacterial ribosomal subunit and inhibiting peptide chain elongation by blocking translocation and movement along the mRNA. The exact binding site varies among the drug classes, which probably accounts for much of the difference in resistance. The ketolides are thought to bind to two sites.

Several of these drugs have other effects that may be clinically useful. The macrolides have recently been shown to have some anti-inflammatory effect, preventing superoxide and

cytokine production and stabilising macrophages and T cells. This may be a useful side effect in respiratory and skin infections.

Erythromycin acts as a prokinetic in the bowel by several mechanisms. This makes it unpopular in some species because it makes them vomit.

Absorption after oral administration varies with the different drugs from poor (erythromycin) to almost complete (clindamycin). They are extensively metabolised.

Spectrum of activity

These drugs have a narrow spectrum, mainly confined to Gram positive bacteria, including penicillinase producing staphylococci, but not enterococci. They are also active against *Pasteurella* and *Bacteroides* spp., *Mycoplasma* spp. and *Rickettsia* spp. Tylosin and roxithromycin are used clinically against *Mycoplasma*, *Chlamydia* and some spirochaetes (*Treponema* and *Moraxella*). Tilmicosin has a slightly broader spectrum. Tiamulin is effective in swine dysentery (*Brachyspira hyodysenteriae*)(most strains are now resistant to tylosin). Tiamulin is also effective against *Actinobacillus pleuropneumoniae*. Erythromycin is effective against *Rhodococcus equi* in foals. Macrolides (especially erythromycin) are used in people for severe *Campylobacter* infections, but resistance is high and increasing (particularly around Auckland). Roxithromycin and azithromycin have some activity against protozoa such as *Toxoplasma gondii*. Lincosamides, particularly clindamycin, have useful activity against anaerobes.

Evolution of resistance

Chromosomal resistance occurs readily. Plasmid mediated resistance is also common. Resistance usually involves point mutations in the 23S rRNA of the 50S ribosomal unit, which prevent drug binding. This occurs very quickly with lincosamides but more slowly with tiamulin. The sites of mutation are different for lincosamides (Karlsson *et al*, 1999) and tiamulin (Bosling *et al*, 2003; Pringle *et al*, 2004).

Telithromycin binds to domains II and V of 23S rRNA of the 50S ribosomal subunit. Mutations at both of these sites are thought to be necessary for resistance.

Cross-resistance amongst the groups

Cross-resistance is common but not complete among macrolides, lincosamides and streptogramin Bs, mainly mediated by the *ermB* and *mefA* genes. Pleuromutilins and ketolides have different resistance patterns, but these have not been directly compared. If the patterns are similar, tiamulin use could cause problems when telithromycin is approved for people in New Zealand.

Seventy-six *Brachyspira hyodysenteriae* field isolates from Australia had MIC(90)s (mg/l) of: tiamulin, 1; valnemulin, 0.5; tylosin>256; erythromycin>256; lincomycin, 64 and clindamycin, 16. (Karlsson *et al*, 2002). There was no significant change over three years. Thirty-seven isolates from Japan were all susceptible to tiamulin and valnemulin, but most were resistant to lincomycin and macrolides (Uezato *et al*, 2004). Resistance to tiamulin in *B. hyodysenteriae* can increase dramatically in a short time (Lobova *et al*, 2004). In northern Germany, resistance to tiamulin and valnemulin gradually increased up to 2001 (MIC50 2µg/mL) but decreased in 2002 (Rohde *et al*, 2004)

There appears to be complete cross-resistance between tiamulin and valnemulin in *B. hyodysenteriae* (Karlsson *et al*, 2001). 60% of macrolide and lincosamide resistant *Brachyspira pilosicoli* from field isolates in Sweden had a point mutation in the 23S rRNA gene, which rendered them completely resistant to tylosin and erythromycin, but not tiamulin (Karlsson *et al*, 2004). Some tiamulin resistant isolates were also found.

Spirochaete isolates from Japanese dogs, which were resistant to erythromycin, but not tylosin, lincomycin or tiamulin, became resistant to tylosin by a point mutation of the 23S rRNA gene (Prapasarakul *et al*, 2003).

Mycoplasma bovis from Belgian cattle were susceptible to tiamulin but not lincomycin or tylosin (Thomas *et al*, 2003). A study in Japan showed similar results, with all field isolates resistant to erythromycin but susceptible to tiamulin (Hirose *et al*, 2003). *In vitro*, resistance in *Mycoplasma* species from chickens developed quickly for erythromycin and tylosin, but much more slowly, if at all, for tiamulin (Gautier-Bouchardon *et al*, 2002). Strains with induced tylosin resistance were also always resistant to erythromycin, but not vice versa.

Seventy-one per cent of *S. suis* isolates from Belgian pigs possessed the *ermB* gene and were resistant to macrolides and lincosamides. Only one was resistant to tiamulin. The *ermB* gene in most of the isolates tested was 100% homologous with *ermB* genes from some isolates of *S. pneumoniae* and *S. pyogenes* from people (Martel *et al*, 2001). Telithromycin has been shown to be effective against macrolide resistant *S. pneumoniae* containing *mefA* and *ermB* genes in vitro (Zhanel *et al*, 2004).

Use in animals

cattle - *Pasteurella pneumonia* (rare in New Zealand although almost ubiquitous in feedlots in the USA) (mainly tilmicosin). Oleandomycin is used to treat *S. aureus* mastitis

pigs - treating and preventing respiratory infections (pleuropneumonia and enzootic pneumonia) and dysentery (especially tiamulin).

chickens - chronic respiratory disease caused by *Mycoplasma*

small animals - skin infections, osteomyelitis, anaerobic infections, rickettsial and chlamydial infections, (toxoplasmosis) (azithromycin)

horses - *Rhodococcus pneumonia* in foals (erythromycin and azithromycin)

Human use

Erythromycin has traditionally been used as a substitute for penicillin in people who are allergic to penicillin. It was also used to treat *Campylobacter*, but overuse as part of a protocol for *Helicobacter* means that many strains of *Campylobacter* in New Zealand are now resistant. *Campylobacter* infection is not usually treated with antibiotics in otherwise healthy people.

Azithromycin is usually reserved for chlamydial infections, but has been used in antimalarial combinations with chloroquine. Clarithromycin has some effect against tuberculosis, and is included in some protocols for multi-resistant tuberculosis.

Telithromycin has been licensed for human use overseas and appears effective against macrolide resistant *S. pneumoniae*.

Prospectus

All these drugs have large, complicated molecules with many side groups that can be substituted. There is plenty of scope for developing huge numbers of derivatives.

Most of the large drug companies are developing new ketolides, particularly for treatment of macrolide-resistant *S. pneumoniae*. They appear effective against *S. pneumoniae* containing *mefA* and *ermB* genes, but not those with ribosomal mutations (Abbanat *et al*, 2005).

Bicyclic ketolides have also been investigated. They appear effective and have a different resistance pattern again.

New, semi-synthetic pleuromutilins are also under development. If these become established in human medicine, the use of tiamulin in pigs may become untenable.

Risk - benefit analysis

In-feed tiamulin

Hazard

Human pathogens or commensals could become resistant to tiamulin.

Exposure

Faecal contamination of pork, which is then undercooked, could allow exposure through the food chain. Food handlers who do not wash their hands could be exposed. Pig farmers are likely to be exposed directly.

Impact

As pleuromutilins are not used in people, and do not appear to cause cross-resistance to drugs that are, the impact of resistance developing would be zero.

Benefit

Swine dysentery is likely to compromise animal welfare seriously. The alternative means of prevention are not very effective and involve antibacterials of more concern.

Conclusions

The risk of tiamulin use is very small. This could change if pleuromutilins start to be used in human medicine. Some *Brachyspira* species colonise people, but they are usually regarded as commensals, as enterococci were until recently.

In-feed / water tylosin / lincomycin

A risk analysis of tylosin in chickens (Singer *et al*, 2004). concluded that if tylosin were not used in chickens:

- The number of human cases of campylobacteriosis, a foodborne illness, caused by eating chicken increases an estimated 11,000 to 70,000 cases per year.
- The number of human illness days increases an estimated 50,000 to 500,000 days per year.

- For every illness day prevented by removing tylosin from chicken production, an estimated additional 3 to 30 illness days are caused by the increased *Campylobacter* contamination.

Hazard

Macrolide resistant organisms could be passed to people.

Exposure

Chicken meat is likely to be contaminated by faecal pathogens/commensals. This is also possible for pork.

Impact

Macrolides are used to treat serious infections in people. Other drugs would have to be used if there was widespread macrolide resistance.

Benefit

Chickens are healthier and may excrete fewer *Campylobacter*, reducing the risk of infection in people. *Mycoplasma pneumonia* seriously compromises pig welfare and cannot be left untreated -- other antibiotics would have to be used.

Conclusions

Pigs with respiratory disease or ileitis must be treated; the choice of drugs for *Mycoplasma* and *Lawsonia intracellularis* is limited.

Injectable macrolides / lincosamides

Hazard

Macrolide resistant organisms could be passed to people.

Exposure

These drugs are given to individual sick animals, so the main group exposed are farmers. It is possible that resistant organisms may still be present when the pigs or cattle have recovered and are killed for meat, and could enter the food chain.

Impact

Macrolides are used to treat serious infections in people. Other drugs would have to be used if there was widespread macrolide resistance.

Benefit

These drugs are very effective for respiratory disease and *Mycoplasma* arthritis in pigs, where the range of alternatives is very limited. The conditions macrolides/lincosamides are used to treat in cattle are either rare in New Zealand, such as *Pasteurella pneumonia*, or have many alternative drugs available, such as foot rot and mastitis.

Conclusions

The risks to humans are probably low, and do not justify reducing use in pigs. Use in cattle could be discouraged without seriously affecting animal welfare.

Tablet macrolides / lincosamides

Hazard

Macrolide resistant organisms could be passed to people.

Exposure

As these drugs are used exclusively in dogs and cats, only the owners will be exposed.

Impact

Macrolides are used to treat serious infections in people. Other drugs would have to be used if there was widespread macrolide resistance.

Benefit

These drugs can be life saving in individual animals.

Conclusions

Withdrawing registration of veterinary macrolides/lincosamides would lead to greater discretionary use of human drugs for infections where nothing else is likely to work. The risk to people is small and does not justify increased control.

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APPENDIX 8: ANTIBIOTICS USED FOR MYCOBACTERIAL DISEASES

The only one of these drugs registered for use in animals in New Zealand is streptomycin, which is covered under the aminoglycosides. The others are very rarely used in animals, and all such use at present is discretionary use of human drugs.

Drugs

Isoniazid, streptomycin, rifampicin, rifabutin, pyrazinamide, ethionamide, prothionamide and ethambutol are used for tuberculosis; clofazimine and dapsone are used for leprosy. Clarithromycin and azithromycin (macrolides) and some of the newer fluoroquinolones are also occasionally used to treat tuberculosis.

JETACAR category

All these drugs are category A.

Ethionamide and prothionamide, also used in New Zealand, are not classified.

Pharmacology

These drugs have a variety of mechanisms of action. They are nearly always used as combinations because they have to be given for long periods, and resistance can develop to single drugs relatively quickly. Most penetrate tissues and cells readily, and are sometimes used in other infections for this property.

Spectrum of action

streptomycin - Gram negative aerobes, staphylococci *in vitro*

rifampicin and rifabutin - *Mycobacterium tuberculosis* and *M. leprae*; many Gram positives; *Neisseria meningitidis* and *N. gonorrhoeae*, *Haemophilus influenzae*, some *Chlamydia* species and some anaerobes

ethambutol, isoniazid and pyrazinamide - *M. tuberculosis*

ethionamide and prothionamide - *M. tuberculosis* and *M. leprae*

clofazimine - some effect against *M. leprae* and some other *Mycobacteria*

dapsone - many bacteria, also *Plasmodium* and *Pneumocystis*

Evolution of resistance

Resistance develops quickly to all these drugs when used alone, but the precise mechanisms are not clear in most cases.

New Zealand data

Multi-resistant TB is widespread in people overseas, but is still rare in New Zealand (ESR, 2004).

Use in people in New Zealand

In combination to treat tuberculosis and leprosy. Multi-resistant tuberculosis imported from overseas means that combinations often have to be tailored to the patient.

Use in animals in New Zealand

Mycobacterial infections are not treated in animals, with the exception of feline leprosy which is very rare (clofazimine). Food animals with tuberculosis are slaughtered. Very rarely, zoo animals develop tuberculosis and are treated.

Rifampicin in particular is able to penetrate cells better than most antibiotics and is sometimes used for a variety of Gram positive intracellular pathogens, such as *S. aureus* and *Rhodococcus equi*.

Use overseas

UK - similar to New Zealand; see Appendix 13.

In some European countries, other rifamycins are used to treat *S. aureus* mastitis in cows.

Regulation

New Zealand - human prescription medicines, used off-label in animals.

UK - human POM, used off-label in animals.

Prospectus

Most of the current drugs are very old and have significant side effects. Although the global threat from tuberculosis is growing (WHO calculates that 30% of the world's population is infected), there are very few new drugs in development. Newer fluoroquinolones, ofloxacin, moxifloxacin, gatifloxacin and levofloxacin have shown good efficacy and are now in phase 3 trials for tuberculosis. Quinolizines and pyridones are still under development and are in phase 1 trials. Longer-acting rifamycins and nitroimidazole derivatives are in preclinical trials. However, most work is concentrated on vaccines and manipulation of the immune system.

Risk - benefit analysis

Hazard

Use of these drugs quickly leads to resistance in mycobacteria.

Exposure

These drugs are currently used only in a very small number of horses or companion animals. They are not used in food animals, so the number of people exposed is very low. This could change if rifamycins were ever registered to treat *S. aureus* mastitis.

Impact

Resistance to these drugs could make TB untreatable in people.

Benefits

These drugs can be life saving in individual animals.

Conclusion

The current situation in animals does not give rise to concern. Indiscriminate or widespread use is likely to lead to increased resistance in the environment.

Reference

<http://w3.whosea.org/tb/basicF.htm>

APPENDIX 9: STREPTOGRAMINS

Streptogramins were covered in the 1999 report. Since then, additional conditions have been put on their use and use in poultry has declined markedly.

Drugs

Viginiamycin (derived from *Streptomyces virginiae*) is used in animals; dalfopristin and quinupristin (Synercid®) is used in people.

JETACAR category

A

Pharmacology

Streptogramins are mixtures of streptogramins A and B. Streptogramin Bs are macrolides and show cross-resistance with other macrolides, but the combination is still usually effective against macrolide resistant bacteria. Both components bind to the bacterial 50S ribosome (at different sites) in a similar way to macrolides.

Streptogramins penetrate tissues poorly: when given orally, they stay in the gut.

Spectrum of action

Gram positive bacteria, including MRSA and vancomycin resistant *E. faecium*, but not usually *E. faecalis*.

Evolution of resistance

E. faecalis is intrinsically resistant to streptogramins. *E. faecium* and staphylococci can acquire resistance genes which can cause inactivation of the antibiotic (streptogramins A and B), increase the number of efflux pumps (streptogramins A and B) or alter the binding site (streptogramin B).

Fate in the environment

Streptogramins can be broken down by *Lactobacillus* in animals' guts (Dutta and Devriese, 1981). They are unlikely to persist in the environment.

New Zealand Data

none

Use in people in New Zealand

Treatment of MRSA and VRE infections requiring intravenous therapy in beta-lactam, quinolone or glycopeptide allergic or intolerant patients or where other antibiotics are inappropriate.

Use in animals in New Zealand

Horses - prevention of laminitis

Chickens - prevention and treatment of necrotic enteritis

Use overseas

UK - withdrawn

USA - growth promotion in chickens and pigs, prevention of necrotic enteritis in chickens, increased feed conversion and prevention of lactic acidosis and abscesses in feedlot cattle, treatment and control of swine dysentery.

Australia - prevention of laminitis in horses, use for growth promotion being phased out and time limits placed on treatment.

Canada - growth promotion in chickens and pigs, treatment and control of swine dysentery, prevention of necrotic enteritis in chickens.

Regulation

PAR 1; when used in chickens, subject to conditions: culture and susceptibility testing is required before use and every use must be reported to the ACVM Group.

Prospectus

Although other streptogramins are known, none are in clinical trials at the moment.

Risk - benefit analysis

A risk assessment was recently carried out by APVMA (2004). In summary:

Hazard

The hazard considered was the selection of resistance genes to virginiamycin in *Enterococcus faecium* in animals. In characterising the hazard it was noted that:

- Use of virginiamycin in food-producing animals can select for *E. faecium* possessing either the *vat(D)* or *vat(E)* genes, which encode for production of a streptogramin A acetyltransferase (an inactivating enzyme), resulting in virginiamycin-resistant *E. faecium*.
- Production of streptogramin A acetyltransferases confers resistance to the dalfopristin component of QD, which is another streptogramin class of antibiotic. Resistance to virginiamycin and QD requires resistance to both streptogramin A and B.
- virginiamycin-resistant *E. faecium* found in food-producing animals and their commercial products can be co-resistant to other antimicrobials, including vancomycin.

Exposure

The main exposure to the hazard was considered to be the transfer of streptogramin-resistant *E. faecium* to humans. Based on overseas findings, the following factors were considered:

- Virginiamycin-resistant enterococci, which are also resistant to vancomycin, have been cultured from food animals, their environment and their meat products.
- Colonisation of humans by animal-derived *E. faecium* and/or transfer of resistance to human strains of *E. faecium* may occur, although transfer of resistance has not yet been observed.
- Virginiamycin-resistant *E. faecium* of animal origin given to human volunteers can survive gastric passage, multiply, and be cultured for up to 14 days from the volunteers' stools. Intestinal transit did not result in disease.

Impact

The impact was defined as disease due to infection in susceptible humans. Susceptible humans are those most likely to succumb to an infection with a relevant micro-organism. Factors considered included:

- infection of humans with streptogramin-resistant *E. faecium*;
- infection with vancomycin-resistant *E. faecium*;
- disease due to infection with *E. faecium* resistant to both vancomycin and streptogramins; and
- treatment failure attributable to acquisition of streptogramin-resistant *E. faecium* from animals.

In assessing the above steps, the following were taken into account:

- conclusive evidence of human infection with animal-derived streptogramin-resistant *E. faecium* is lacking;
- vancomycin-resistant enterococci have a high propensity to cause outbreaks in hospitals;
- while the number of infections resulting from colonisation with vancomycin-resistant enterococci is low, these strains spread easily to other patients, resulting in significant numbers of infections;
- the *vanB* gene complex encodes the more common form of vancomycin-resistant Enterococci in Australia. With a single exception, this form of resistance has not been found in animals;
- recent Australian studies have demonstrated no resistance to QD in human clinical isolates;
- septicaemia from vanA-type vancomycin-resistant *E. faecium* mostly occurs in highly vulnerable patients who have multiple medical problems. Failure of therapy in these patients would result in significant mortality or prolonged treatment. Currently these patients are treated with QD, a streptogramin, or the newer antibiotic linezolid;
- the impact of antibiotic failure on relatively minor infections such as wound infections and urinary tract infections is small.

The quality of the data available was also taken into account, including uncertainty due to inherent variability and measurement error, as well as uncertainty due to lack of information. Data on the prevalence of virginiamycin-resistant and vancomycin-resistant *E. faecium* in food animals and the incidence of human infections in Australia are lacking. There are limited data on the importance of virginiamycin in the selection of enterococci co-resistant to both virginiamycin and vancomycin in food animals.

Benefits

APVMA considered that there is data to support the use of virginiamycin to prevent lactic acidosis in grain fed cattle and sheep, and to prevent necrotic enteritis in chickens, but not growth promotion in chickens and pigs.

Conclusion

The findings are that the probability of disease due to infection in susceptible humans due to exposure to streptogramin-resistant *E. faecium* of animal origin is low, but the severity of impact in susceptible humans is high. Regarding the risk to the general population, the

probability of disease due to infection due to exposure to streptogramin-resistant *E. faecium* of animal origin is low, and the severity of impact in the general population is low.

APVMA (2004) also recommended that virginiamycin should not be used for growth promotion, which is the current situation in New Zealand.

The FDA (2004) has also carried out a risk assessment on the use of virginiamycin in animals. They concluded that the risk of acquiring a streptogramin resistant enterococcal infection (assuming that all resistant enterococci came from animals) was 60 to 1,200 chances in 100 million per person per year among the hospitalised population and 7 to 140 chances in 100 million per person per year for the general US population.

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APPENDIX 10: ALTERNATIVE SAMPLING SCHEMES: CONSIDERING OUTCOMES AT THE LEVEL OF THE HERD, ANIMAL, BACTERIA OR GENE

The recommended surveillance scheme builds upon existing surveillance systems rather than creating new ones. The system is focussed on *bacteria-level sampling* of isolates from carcasses at slaughter. For completeness other schemes are considered, although all require additional resources and are likely to be more costly than the proposed scheme.

Two recent papers that address antimicrobial resistance sampling issues are Davison, Low *et al* (2000) and Humphry, Blake *et al* (2002). The following describes alternative examples of sampling schemes that could be employed at each level.

Bacteria-level: Rather than using isolates cultured from carcase swabs, faecal or caecal contents may be collected from a simple random sample of animals at slaughter and individual colonies submitted for antimicrobial resistance testing (e.g. direct plating and random selection of one or more colonies). The outcome would be estimate of proportion of bacteria shed in faeces by livestock at slaughter that have particular phenotypic traits (e.g. minimum inhibitory concentrations [MICs], multi-drug resistant).

Herd-level sampling: This could be carried out on a simple random sample of herds. The number of animals sampled would be proportional to the size of the herd, and based on statistically defined limits of detection of at least one positive animal. Samples could be pooled and selective media used to identify the presence of resistant bacteria. The outcome would be estimate of the proportion of herds in which at least one animal is shedding at least one resistant bacteria. Such a scheme could be done as cross-sectional or longitudinal study (e.g. using ‘sentinel’ herds).

Animal-level sampling: This could employ multistage sampling of herds and animals and be carried out either on-farm or at the slaughterhouse. Herds could be sampled using simple random sampling, and the number of animals within each herd sampled proportional to the size of the herd. Selective media could be used to identify the presence of resistant bacteria and the outcome would be an estimate of proportion of animals shedding at least one resistant organism.

Gene-level sampling: Simple random samples of faeces could be taken from livestock at slaughter. Molecular techniques such as real time PCR could then be used to detect the presence and number of copies antimicrobial resistance genes in the microbial population for example gyrase gene mutants associated with fluoroquinolone resistance.

Relating antimicrobial usage to trends in antimicrobial resistance in livestock (and humans)

If this is a major requirement of the surveillance scheme, then it can be achieved by sampling at more than one level. Both of the following schemes would address this objective:

1. Monitor trends in the proportion of food-producing livestock (e.g. lactating cows, meat-animals pre-slaughter) shedding resistant bacteria.
2. Monitor trends in the proportion of isolates shed by food-producing animals that have particular resistance phenotypes.

Where to sample in the food chain?

The further along the food chain, the less likely the bacterial populations sampled will be an unbiased representation of those exposed to antimicrobials on the farm of origin. Selection of phenotypes associated with, for example, heat and acid tolerance, combined with cross-contamination (e.g. in scald tanks, de-hairing machines and cold storage) will progressively bias the sample. However, isolates from further along chain are more likely to be representative of the population of bacteria humans are exposed to via food pathways. For example:

- On-farm, rectal faecal samples: would be representative of carriage/shedding on farms but are less likely to represent human exposure. However such samples would be good indicator of response to antimicrobial usage.
- At the slaughterhouse, caecal contents at evisceration: could be representative of carriage /shedding on farms and are more likely to represent human exposure. Again, they could be good indicator of response to antimicrobial usage.
- At the slaughterhouse, carcase swabs: could be representative of carriage /shedding on farms and are likely to represent human exposure. However, they are less likely to be good indicator of response to antimicrobial usage.

References

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Humphry RW, Blake D *et al* (2002). The quantitative measurement of antimicrobial resistance in *Escherichia coli* at the meta-population level (meta-population analysis). *Letters In Applied Microbiology* 35(4): 326-330.

APPENDIX 11: DETAILS OF RELEVANT MICROBIOLOGICAL SURVEILLANCE IN NEW ZEALAND AND OTHER COUNTRIES

We have recommended utilising existing surveillance activities rather than developing new ones. This required a detailed examination of current, relevant schemes and an assessment of the likely success of piggybacking antimicrobial resistance (AR) testing within them. Here we outline these schemes and describe the feasibility analysis.

Current surveillance of animal-derived microbes in New Zealand

Currently there is no structured, nationwide microbiological testing of animals on-farm in New Zealand; therefore this is not a potential source of isolates for antimicrobial surveillance. There is limited, passive surveillance of animal pathogens from samples submitted for diagnostic testing to private veterinary laboratories, but this is likely to be a biased, non-standardised and potentially unreliable source of surveillance data. In dairy production, raw milk quality checks are carried out, but there is limited microbiological testing of the raw product and hence this would not be a good source of isolates for AR testing. There have been a number of ad hoc surveys, undertaken by Crown Research Institutes and university researchers, of microbes isolated from environmental matrices contaminated with livestock faeces and retail food. Again, although these are highly informative, they could not form the basis of ongoing surveillance.

The only extensive, ongoing microbiological testing occurs in the abattoir. There is mandatory testing of carcasses of cattle, sheep, goats, poultry, ostrich, and voluntary testing of deer. The microbes isolated are likely to be predominately faecal in origin.

Scanning abattoir surveillance in New Zealand and the National Microbiological Database (NMD)

E. coli, *Salmonella* and Aerobic plate counts

Key features

Scanning surveillance. A combination of mandatory and voluntary testing of meat from all export plants and some plants producing meat solely for domestic consumption.

Scope

Mandatory testing: Adult beef, bobby calves, sheep (lamb and adult), goats, poultry and ostrich

Voluntary testing: farmed deer

Current exclusions: pork

Sampling scheme

Frequency: all plants once weekly. The number of weekly samples will depend on the number of weeks the livestock species are slaughtered and for some species this is highly seasonal (e.g. bobby calves).

Samples on the NMD represent all export plants from which domestic meat is also derived (with meat export [ME] licence numbers) some domestic-only abattoirs (with abattoir [AB]

licence numbers) and pack-only houses (with PH reference numbers where there is no slaughter and dressing, just boning of chilled carcasses).

Numbers from beef and sheep: Swabs from 5 fresh carcasses, 5 chilled carcasses (6 weeks only) and 5 primal cuts and 5 whole tissue samples of bulked meat from beef and sheep per week (see table below). Carcasses and meat samples are randomly selected (see technical operating procedures manual for details <http://www.nzfsa.govt.nz/animalproducts/publications/manualsguides/nmd/index.htm>) and swabs taken from areas likely to have greatest faecal/gut contents contamination. Carcasses are sampled at three sites (forequarter, flank, hindquarter).

Note that the ovine NMD programme now only requires testing of the forequarter of fresh carcasses in domestic premises for aerobic plate count (APC), and this requirement will be expanded to export premises on agreement with the United States.

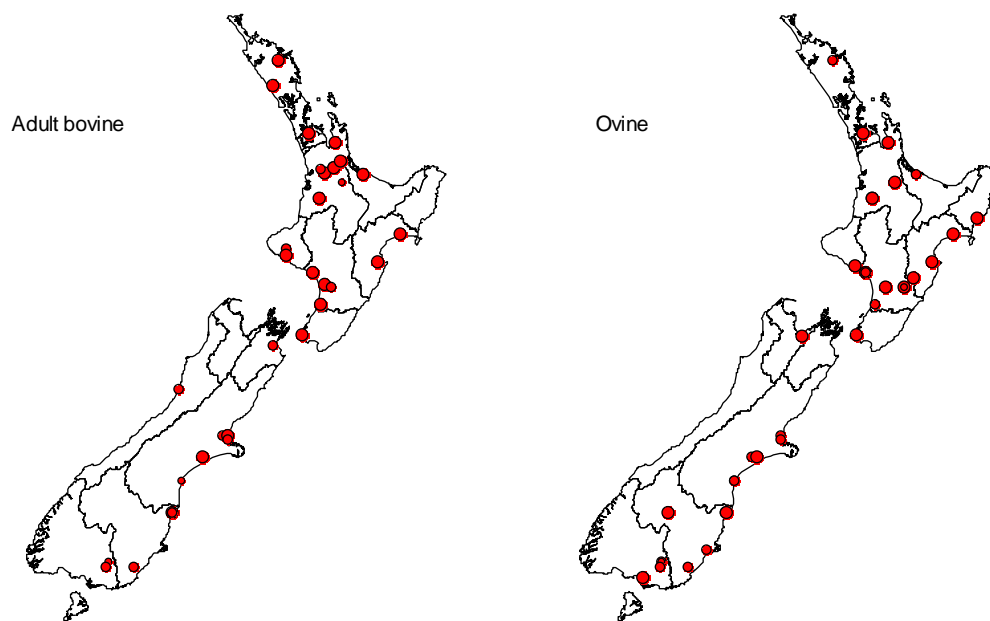
Species	Product type	Technique	Domestic and non EU and non US listed	EU and US listed standard throughput	EU and US listed VLT
Bovine	Carcass	Multiple Swab Technique	1 per week	5 per week	1 per week
	Primal Cuts	Multiple Swab Technique	Not required	5 per week	1 per week
	Bulk Meat Product	Whole Tissue Composite Sampling	Not required	5 per week	1 per week
	Post Chill Carcass	Multiple Swab Technique	Not required	5 per week for 6 weeks	1 per week for 6 weeks
Ovine	Carcass	Multiple swab technique	5 per week	5 per week	Not applicable
Bobby Calf, and Caprine	Carcass	Multiple Swab Technique	Not required	5 per week	1 per week
	Primal Cuts	Multiple Swab Technique	Not required	5 per week	1 per week
	Bulk Meat Product	Whole Tissue Composite Sampling	Not required	5 per week	1 per week
	Post Chill Carcass	Multiple Swab Technique	Not required	5 per week for 6 weeks	1 per week for 6 weeks
Cervine	Carcass	Multiple Swab Technique	3 per week VLT: 1 per week	3 per week	1 per week
	Primal Cuts	Multiple Swab Technique	2 per week VLT: 1 per week	2 per week	1 per week
Ostrich/Emu	Carcass	Multiple Swab Technique	1 per week	2 per week	Not applicable
Poultry	Carcass	Whole Carcass Rinse Method	2 per day VLT: 1 per week	Not applicable	Not applicable

Number of samples collected and analysed for the NMD

These figures are estimated from data provided by the NZFSA restricted website: <http://www.nzfsa.govt.nz/animalproducts/publications/manualsguides/nmd/natprofiles>) and refer to 2003.

- 37 plants collected approx 36,000 adult bovine samples
- 46 plants collected approx 41,000 ovine samples
- 24 plants collected approx 10,000 bobby calves samples
- 9 plants collected approx 3,000 caprine samples
- 18 plants collected approx 2,000 cervine samples
- 2 plants collected approx 120 ostrich samples
- 12 plants collected approx 3,230 poultry samples

The distribution of plants providing bovine, ovine, bobby calf and caprine samples are shown in Figure 11A.1 below.



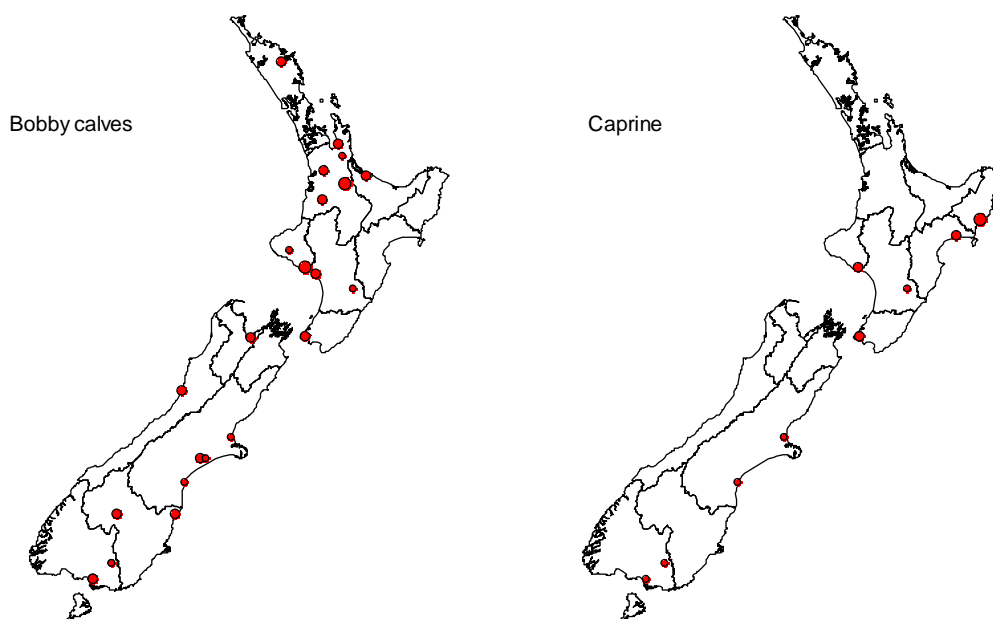


Figure 11A.1 Distribution of export meat plants conducting microbiological testing of carcasses for the NMD in 2003 (red circles). The size of the circle is proportional to the number of weekly samples submitted (maximum 255).

***E. coli* isolation**

a) Total numbers

The number of samples positive for *E. coli* in 2003, and therefore potentially able to contribute to surveillance were:

Species	Number of positive samples
Adult bovine	2,400
Ovine	13,000
Bobby calf	6,000
Caprine	680
Cervine	600
Poultry	3,000

b) Numbers taken from sites more likely to be representative of individual animal faecal flora

The following table gives an indication of the number of *E. coli* isolated from samples collected from fresh carcasses at meat plants over the last 2 years. The samples were taken from the hindquarter, flank/flap and forequarter (Source: NMD from NZFSA website <http://www.nzfsa.govt.nz/animalproducts/publications/manualsguides/nmd/natprofiles>)

Species	Number of samples positive for <i>E. coli</i> (number tested) post slaughter						
	2003				2004		
	1 QTR	2 QTR	3 QTR	4 QTR	1 QTR	2 QTR	3 QTR
					QTR	QTR	

Adult cattle	377 (5828)	391 (5821)	240 (3952)	462 (4768)*	471 (6015)	453 (6044)	270 (4014)
Sheep	3068 (6187)	2569 (5438)	1910 (4495)	2550 (5396)	3151 (6610)	2348 (5783)	1694 (4784)
Bobby calves	24 (60)	226 (464)	2081 (3250)	758 (1220)	19 (45)	149 (359)	1741 (2984)
Goats	32 (225)	234 (855)	144 (495)	145 (465)	127 (420)	214 (930)	219 (705)
Deer	54 (546)	157 (504)	183 (552)	174 (522)	138 (534)	147 (519)	127 (510)
Poultry	<i>Not available from NZFSA website</i>						

* calculated due to error on website

Notes

Much higher proportion of ovine and calf carcasses contaminated

Seasonal killing of bobby calves

High flank contamination in bobby calves

Rump and flank isolation generally 2-3 x brisket, but high on forequarter opening Y-cut line in ovines.

c) Distribution by meat plant

The prevalence of positive carcasses, prime cuts and bulk meat showed some variation between plants. For example, the proportion of positive flank samples from adult bovine fresh carcasses varied from 0.4% to 29% and the proportion of positive 'flap' samples from ovine fresh carcasses varied from 29% to 89%. There is evidence that this variation in reported carcass contamination may be spatially dependent and care is therefore needed to avoid biasing the sampling towards particular geographical regions. In contrast, the proportion of positive poultry carcass samples showed little variation between plants, ranging from 87% to 100%.

Salmonella isolation

Currently, *Salmonella* testing is highly seasonal. All products (excluding chilled carcasses) from the following red meat species (bovine, bobby calf, caprine, cervine, ostrich, and poultry) are tested for *Salmonella* under the NMD programme. *Salmonella* testing is no longer carried out on ovine species from domestic-only premises. Bovine, bobby calf, caprine and cervine samples are tested for *Salmonella* during an initial 'primary sampling window' (PSW) of 16 consecutive weeks, within a processing season (1st October – 30th September). If all samples are negative, sampling is reduced to a six weeks in the subsequent season. Ostrich are sampled for *Salmonella* sampling during each processing week. Poultry premises are recommended to monitor their performance according to the PR/HACCP *Salmonella* Performance Standards.

The number of samples positive for *Salmonella* is generally very low. The number of positive samples from fresh carcass swabs is shown in the following table. For example, in 2003, 0.8% of fresh ovine carcasses (N=20) were positive for *Salmonella* and these were found in just three plants.

Species	Number	of	Proportion	of	samples	Number of meat plants
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	carcasses positive for <i>Salmonella</i> in 2003	carcasses testing positive for <i>Salmonella</i> in 2003	with positive samples in 2003
Bovine	5	0.36%	1
Ovine	20	1.3%	3
Bobby calves	30	2.4%	6
Caprine	5	1.6%	1
Poultry	38	2.0%	4

Aerobic plate counts

Most samples are positive on APCs and the numbers of samples are roughly the same as above for *E. coli*. These samples would be suitable for the isolation and testing of *Enterococcus* spp.

Laboratory testing

Microbiological testing is carried out at NZFSA-approved laboratories accredited to ISO 17025. These can be in-house or external private labs. The Petrifilm™ *E. coli* method is the only method for *E. coli* analysis approved for the NMD red meat, and poultry NMD Programmes. Detailed technical operating procedures available on website: <http://www.nzfsa.govt.nz/animalproducts/publications/manualsguides/nmd/index.htm>

Current follow-up of isolates

All *E. coli* Petrifilm plates are currently disposed of locally. Representative colonies are not purified. Salmonellae are sent to ESR, Wellington for serotyping. Some of these will be selected for antimicrobial resistance testing as part of the routine testing done by ESR.

Other more targeted surveillance activities in New Zealand that could provide additional baseline data

i) Bovine / bobby calf meat E. coli O157 testing

Mandatory testing of meat of bovine origin for *E. coli* O157 from all meat plants exporting to the United States has been carried out since 1998. Adult bovine and bobby calf bulk meat samples in export meat plants are tested for *E. coli* O157 using immunomagnetic separation techniques at NZFSA-approved laboratories. All plants are sampled every day and 5 bulk meat samples are taken. All *E. coli* O157 isolates sent to ESR, Wellington for typing and inclusion in national typing database. Some of these will be selected for antimicrobial resistance testing as part of the routine testing done by ESR.

ii) Microbiological survey of uncooked retail meat products This NZFSA funded countrywide survey (2003-2005) was carried out by ESR. Prevalence and levels of *Salmonella*, shiga-toxin producing *E. coli* (STECs), *Campylobacter* spp. and *E. coli* O157:H7 were tested in retail beef, sheep, veal, poultry and pork meat products. All isolates were sent to ESR, Wellington for typing and inclusion in the National Typing Database. Some of these will be selected for antimicrobial resistance testing as part of the routine testing done by ESR.

iii) Microbiological survey of imported and domestic pork (ESR Food, 2004-2005)

The goal of this project is to carry out a pilot survey of uncooked imported and domestic pig meat prior to secondary processing for the presence of *Salmonella* and *E. coli* O157:H7, and presence/numbers of generic *E. coli*.

Current relevant livestock surveillance in other countries

There are many schemes in operation internationally and details for some can be found on the following websites:

Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) <http://www.vetinst.dk>

European Antimicrobial Resistance Surveillance System (EARSS) <http://www.earss.rivm.nl/>

Foodborne Diseases Active Surveillance Network (FoodNet) <http://www.cdc.gov/foodnet/surveillance.htm>

National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria <http://www.cdc.gov/narms/>

Norway: Antimicrobial resistance in bacteria from animals, feed, and food <http://www.zoonose.no/Zoonosis-centre.htm>

Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) <http://www.sva.se/dokument/stdmall.html?id=341&lang=e>

WHONET <http://www.who.int/emc/WHONET/WHONET.html>

For comparison, we provide further details of the Australian and UK AR surveillance schemes below:

Australian government scheme

In 2003 the Australian Government released *Strategy for Antimicrobial Resistance Surveillance in Australia* (www.health.gov.au/pubhlth/strateg/jetacar/pdf/armstrategy.pdf). This followed the 1999 JETACAR report (www.health.gov.au/pubs/jetacar.pdf) and the Australian Government response in 2000 (www.health.gov.au/pubhlth/publicat/document/jetacar.pdf). The response recommended the “development of a comprehensive surveillance system for antimicrobial resistant bacteria and resistance genes in humans and animals”.

After the release of the strategy document, an action plan for AR in animals was developed by the Australian Department of Agriculture, Fisheries and Forestry (DAFF). A major element of this plan was a pilot programme to be carried out in Queensland, New South Wales, Victoria and South Australia. The surveillance goals were to:

- develop and implement a pilot surveillance programme for AR in animals that has a public health focus;
- develop electronic capture of data from laboratories to a central database; and
- review the operation of the programme with a view to making amendments for incorporation into the development of an ongoing programme.

The intended outcomes were:

1. A snapshot of AR in bacteria from animals that are of human health importance.
2. Establishing the most efficient mechanisms for the implementation of a full surveillance programme. These encompassed sampling strategies, sample collection and transport, standardisation of laboratory procedures, cost-effective quality assurance programmes and data management.
3. Guidelines for the analysis, interpretation and reporting of AR data to address public health concerns.
4. Background data and experience to inform future AR surveillance needs.

The pilot scheme started in November 2003 and sampled cattle (feedlot, grass-fed and dairy), slaughter pigs and broiler chickens at abattoirs (7-10 slaughter establishments per commodity). This ensured a focus on species fed the greatest amount of in-feed and in-water antimicrobials. The target organisms were *E. coli*, *Enterococci* spp. and *Campylobacter* spp., and the antimicrobials chosen were those of greatest public health importance. Although the focus of the pilot scheme was on cattle, pigs and poultry, the Technical Reference Group (TRG) also recommended that future surveillance should include bobby calves, aquaculture and companion animals.

The pilot scheme aimed to obtain approximately 140 isolates per livestock species per bacteria per year from 200 caecal samples taken at slaughter. The taking of caecal samples requires additional sampling and is not nested within existing microbial surveillance at the abattoir (e.g. *E. coli*, *Salmonella* Monitoring Programme, ESAM). Assuming the isolates represented approximately one per farm of livestock group this would provide 95% confidence intervals of approximately +/- 5% for an expected prevalence of 10%. Inherent seasonal patterns were captured by the sampling scheme.

Laboratories testing for AR used the NCCLS method for determining MICs using agar or broth serial dilution. The sampling utilised the National Residue Survey (NRS) courier system for transporting samples to laboratories, and data were stored on the NRS database prior to interpretation by the TRG. These were then discussed with stakeholders before being forwarded to the Expert Advisory Group on Antimicrobial Resistance (EAGAR) for reporting as part of the national AR surveillance.

UK government schemes and proposed surveillance of AR

Details of the current and proposed surveillance scheme for antimicrobial resistance in England and Wales are given in the strategy document available at: http://www.vmd.gov.uk/general/publications/Defra_AMR_Surveillance_Strategy_webpage.htm.

In summary the document outlines a number of existing schemes for AR resistance in food animals in the UK. These include regular monitoring of patterns of resistance in *Salmonella* isolates and, more recently, testing of clinical veterinary pathogens and commensals (including *E. coli*). Seven programmes providing data for informing surveillance are identified in the document. In 2002 and 2003 abattoir surveys were conducted on zoonotic, commensal and indicator bacteria in cattle, sheep and pigs. Caecal samples were taken at slaughter and the results are available at: <http://www.defra.gov.uk/animalh/diseases/zoonoses/conference/amrdsstrat.htm>.

The proposed new surveillance scheme will focus on food-producing animals (cattle, pigs, poultry, fish and game), although consideration at a later stage will be given to companion and wild animals. The bacteria to be examined include animal pathogens, zoonotic organisms and commensals considered to be important as reservoirs of resistance genes. The zoonotic pathogens identified are *Salmonella* spp., *Campylobacter coli* and *C. jejuni*, *Yersinia* spp. VTEC O157 and other VTEC spp. Commensals are *Enterococcus faecium* and *E. coli*. An extensive list of antimicrobial agents to be considered for each organism is provided in the strategy document.

Agents will be included in either routine and enhanced surveillance programmes, prioritisation will depend on whether antimicrobials are currently authorised as veterinary medicines and of therapeutic importance to animals and man. Other factors such as developments in the medical field and emerging trends in resistance will also be considered. Presently the precise source of samples (e.g. sick animals, healthy animals on-farm, healthy animals at slaughter) has not been identified.

The recommendation of the Advisory Committee on the Microbiological Safety of Food (ACMSF) is that the proposed scheme will provide data to estimate and identify:

- the total number or percentage of sensitive/resistant organisms in the population sampled;
- the percentage of resistance for the most frequently isolated organisms from sick and healthy animals;
- how the above relate to factors such as husbandry and treatment history; and
- the occurrence of co-resistance and multiple resistance (to four or more unrelated antimicrobials).

The data should also allow comparison with other EU countries and be presented in a way that allows joint reporting of human and animal surveillance.

The proposed schemes identified to implement the strategy include extending the current surveillance of cattle, sheep, poultry and pigs at slaughter and linking the data with the new DEFRA surveillance initiative 'RADAR'.

APPENDIX 12: PRECISION OF PREVALENCE ESTIMATES

Our recommendation is to sample individual colonies from positive plates or Petrifilms. This assumes that the samples represent a simple random sample of the population of bacteria in animals at slaughter and we recommend testing this assumption in pilot studies. For completeness we have considered other sampling schemes based on selecting multiple colonies from fewer samples. Figure 12A.1 shows the estimated 95% confidence intervals for different sampling schemes. Figure 12A.2 shows the difference between the upper and lower 95% confidence intervals for each scheme.

Both simple random and clustered sampling are considered. For simple random sampling, the exact binomial distribution is used to provide estimates of 95% confidence intervals. For clustered sampling, an intra-class correlation coefficient, ρ , of 0.2 is assumed (i.e 20% of the variation in the proportion of isolates positive is at the level of the sample) and the variance correction factor, C , calculated using the formula (Donald and Donner, 1987):

$$C = 1 + (n-1)\rho$$

Where n is the number of isolates examined for each sample – the cluster size. The value of the intra-class correlation coefficient is unknown, but from unpublished poultry data for ampicillin resistant *E. coli* the value of 0.2 is not unreasonable.

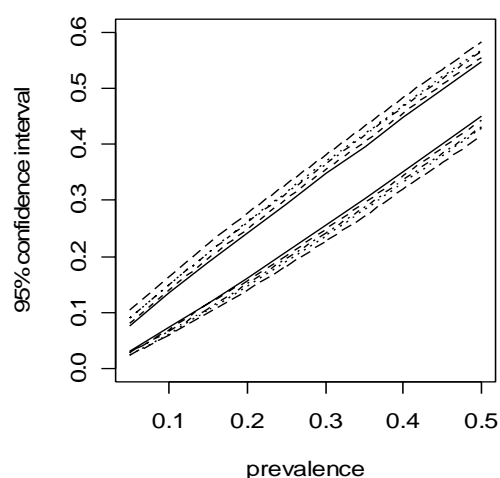


Figure 12A.1

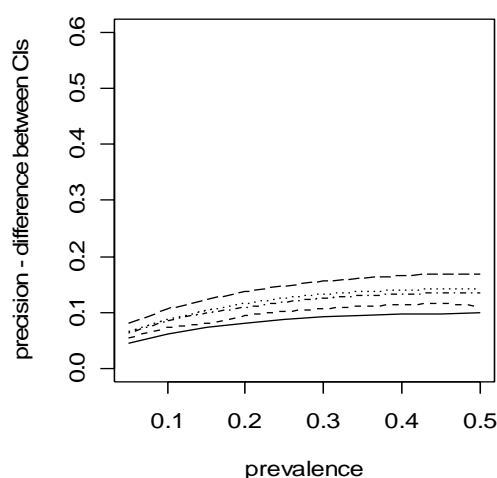


Figure 12A.2

The relationship between sample size and precision for a range of sampling schemes. The solid line is the most precise and the long dash line the least precise. The lines represent:

Simple random sample of 400 isolates

Simple random sample of 300 isolates

Clustered sampling of 400 isolates, cluster size = 5 (i.e. 80 carcasses, 5 isolates per carcass)

Simple random sample of 200 isolates

Clustered sampling of 400 isolates, cluster size = 10 (i.e. 40 carcasses, 10 isolates per carcass).

Reference

Donald A and Donner A (1987). Adjustments to the mantel-haenszel chi-square statistic and odds ratio variance estimator when the data are clustered. *Statistics in Medicine* 6: 491-499.

APPENDIX 13: VETERINARY MEDICINES DIRECTORATE LISTING OF ANTIMICROBIALS USED IN THE UK

Separate PDF file

APPENDIX 14: CONSULTATION

There was a general call for submissions. Letters were written to the following companies requesting technical information they wished to bring to the notice of the Expert Panel.

Alpharma (New Zealand) Limited
C/-KPMG Legal
Private Bag 92101, Auckland

Ancare New Zealand Limited
PO Box 36 240, Northcote, Auckland

Animal Health Centre
PO Box 21, Morrinsville

Apex Laboratories NZ Ltd
PO Box 97 110, South Auckland Mail Centre, Wiri, Auckland

Asia Pacific Speciality Chemicals (NZ) Limited
PO Box 62 005, Auckland 6

Ausrichter (NZ) Ltd
PO Box 74 036, Auckland

Bayer New Zealand Ltd
CPO Box 2825, Auckland

Bimeda (NZ) Ltd
C/-Curran Sole & Tuck
PO Box 76 261, Manukau City

Bomac Laboratories Limited
PO Box 76 369, Manukau City

Brooklands Aquarium Ltd
21 McGiven Drive, New Plymouth

Ceva Animal Health (New Zealand) Ltd
PO Box 76 261, Manukau City

Douglas Pharmaceuticals Ltd
PO Box 45 234, Auckland

Elanco Animal Health
PO Box 97 046, South Auckland Mail Centre, Manukau City

Ethical Agents Ltd
PO Box 97 110, South Auckland Mail Centre, South Auckland

Fort Dodge New Zealand Limited
Private Bag 92 903, Onehunga, Auckland

Image Holdings Limited
PO Box 45 175, Te Atatu Peninsula

Intervet Ltd
PO Box 4079, Auckland

Jurox New Zealand Ltd
PO Box 72529, Papakura, South Auckland

Merial NZ Ltd
PO Box 76 211, Manukau City

Nature Vet Pty Ltd
PO Box 147, Glenorie
NSW 2157, Australia

Norbrook NZ Ltd
C/-PharmVet Solutions
PO Box 46 153, Herne Bay, Auckland

Novartis NZ Ltd
Private Bag 19 980, Auckland

NRM New Zealand
Private Bag 99 927, Newmarket, Auckland

Parnell Laboratories NZ Ltd
PO Box 58 502, Greenmount, Auckland

PCL Industries Limited
PO Box 79 048, Royal Heights, Auckland

Pfizer New Zealand Limited
PO Box 3998, Mt Eden, Auckland

Phoenix Pharm Distributors Ltd
PO Box 31 363, Milford, Auckland

Racing Pigeon Research
PO Box 31, Upper Moutere, Nelson

Schering-Plough Animal Health Ltd
Private Bag 908, Upper Hutt

South & Mid Canterbury Veterinary
35 King Street, Temuka

Stockguard Laboratories NZ Ltd
PO Box 10 305, Hamilton

Technik Products
PO Box 79048, Royal Heights, Auckland

The Australian Pigeon Company Pty Ltd
11 Henry Street, Wantirna South, VIC 3152, Australia

Virbac Laboratories (NZ) Ltd
30-32 Stonedon Drive, East Tamaki, Auckland

Submissions were received from Alparma (zinc bacitracin) and Stockguard Laboratories (*E. coli*).

A general call for submissions was posted in the New Zealand Institute of Food Science and Technology newsletter in December 2004. No submissions were received in response to this.

Letters were sent to individuals requesting any technical information they wished to bring to the attention of the Panel.

Mike Butcher
Technical Manager, Pipfruit NZ Inc
PO Box 11094, Hastings

Roger Morris
EpiCentre, Massey University
Private Bag 11-222, Palmerston North

David Lawton
45 Kentucky Way, Palmerston North

Selwyn Dobbison
Freshpork Farms
PO Box 6258, Upper Riccarton, Christchurch

Bruce Welch
PIC NZ
PO Box 348, Christchurch

David Marks
Private Bag 99927, Newmarket, Auckland

Brian Jones
30A Burwood Road, Matamata

Leslie With
3-7A Seaside Avenue, Waterview, Auckland

Neil Christenson
39 Hillcrest Road, RD 10, Palmerston North

Peter Collignon
Professor of Infectious Diseases and Microbiology
Canberra Clinical School, Australian National University
PO Box 11, Woden, ACT, Australia 2607

A submission was received from Mr Butcher and a letter was received from Mr Christenson. A submission on virginiamycin was received from Phibro Animal Health. A late submission was received from Dr Collignon.

Letters were sent to the following individuals advising that the Panel was aware of their interest in the area of antibiotic resistance and asking if there was any information that they wished to make available to the Panel and/or if they wished to meet with the Panel to discuss their work.

Greg Cook
Department of Microbiology
University of Otago, PO Box 56, Dunedin

Mark Jones
Clinical Microbiologist
Southern Community Laboratories
472 George St, Dunedin

John Aitken
Microbiologist
Southern Community Laboratories
444 Durham Street North, Christchurch

Letters were received from Dr Jones and Mr Aitken. No meetings were arranged.

Correspondence was entered into with Dr Cook and an attempt was made to arrange a meeting. However, in the end this was not possible and Dr Cook did not respond to final offers of a teleconference or making a written submission before he left for overseas.

Letters were sent to organisations regarding the specific issue of streptomycin use in horticulture.

Mike Butcher
Technical Manager, Pipfruit NZ Inc
PO Box 11094, Hastings

Marie Dawkins
Summerfruit New Zealand Inc.
PO Box 2175, Wellington

Chris Hale
Summerfruit New Zealand Inc.
83 Edmonton Road, Henderson

Ken Robertson
Vegfed Fresh Tomato Sector
PO Box 10232, Wellington

Submissions were received from Mr Butcher, Dr Hale and Mr Robertson.

Field visits

During the Panel's deliberations it was opined that 'field trips' to see how antibiotics were utilised in industry would be of value, especially for those Panel members with a human medicine background. Visits to a broiler farm, feed mill and pig farm were organised. A visit was also arranged to a meat plant to view sampling, which assisted in the development of a surveillance programme.

The visits were very successful and provided much useful information. The Panel wish to express thanks to the following people for making the visits possible and for providing the opportunity for open and robust analysis:

- Michael Brooks, Poultry Industry Association
- Frances Clement, NZ Pork Industry Board
- Deanne Hockley, PPCS Richmond
- David Lawton, Veterinarian
- Andrew Managh, Ratanui Development Company, Feilding
- David Marks, Tegel
- Neil Smith, PPCS Richmond
- Chris Trengrove, Chairman, NZ Pork Industry Board