Peer review of the Report of the Expert Panel on Antibiotic Resistance, New Zealand Food Safety Authority: A review of the impact of the use of antimicrobials in animals and plants on the development of antimicrobial resistance in human bacterial pathogens

Mary D Barton, Professor of Microbiology

The report covers developments in New Zealand since the 1999 base-line report on in-feed antimicrobials and resistance and addresses in particular antibiotic use, regulation and management of use of antibiotics and surveillance.

The report provides a systematic analysis of antibiotic (but not antifungal) use in animals and plants in New Zealand and addresses in particular use of aminoglycosides, MLS_B antibiotics and cephalosporins.

The panel's task was made quite difficult because of lack of data on antibiotic resistance in animal isolates (a deficiency common to many countries). However, the recommendations they make are generally sound although evidence to back some of them is not particularly strong (see later).

The overall report is sometimes inconsistent in its approach. For example, the terms of reference seem to imply that antibiotic (antimicrobial?) use in both livestock and companion animals should be covered and some chapters do comment on both – but others focus on food producing animals only.

Chapter 3 provides a useful introduction to antibiotic resistance and summarises the current situation regarding antibiotic resistance problems in human medicine in New Zealand. It is not clear whether these results reflect sensitivity testing of clinical isolates or whether they are derived from surveillance programs. Either way, it is difficult to get a feel for the prevalence of antibiotic resistant strains as no denominators are given. The animal and plant data provided are limited as noted above and it is interesting that there is no discussion of use of antifungals in horticulture. The conclusions drawn at the end of this chapter are supported by the preceding discussion in the chapter.

Chapter 4 reports on the use of antibiotics (not antifungals) in plants and animals but not in humans. As the panel acknowledges, it is important to be able to break down antibiotic use beyond total sales figures (as in Table 4.1) but it is not clear how the information in Table 4.2 was obtained – was it derived from data collected or is it an estimation? In any event, the data is still insufficient to be of much use to the panel. The correlation of usage data with changes in animal numbers for livestock is very useful. Information about pet and horse numbers could be added in too. It is not clear how the number of prescriptions for companion animals (just cats and dogs or horses as well?) was determined. It would be interesting to compare the animal use data with human use data – is ACVM being asked to do more than is expected from the human medicine sector?

I am surprised with the statement that streptomycin is the only antimicrobial used in horticulture as I would have thought that downy mildew, powdery mildew, botrytis and other fungal infections would necessitate the use of antifungals. I am also surprised that aquaculture is excluded from consideration – off-label use is recognised as a problem in other countries where no products are registered for use in aquaculture.

The conclusions are generally in keeping with the discussion however it is not clear why use of streptomycin should be phased out by tomato growers but be allowed to continue for fireblight control in pip fruit. I think the recommendations could go further and require evidence from the pip industries that use of streptomycin is justified "especially in areas where resistance is common and persistent". Information should be sought from the aquaculture industries about antibiotic use.

Chapter 5 discusses the regulation and management of use of antibiotics in animals. The RA framework used to assess veterinary antibiotics is clearly set out. I am surprised that carbadox is listed in the "no concern" column because of issues relating to its carcinogenicity. This chapter links the New Zealand situation with WHO, OIE and FAO activities and the Codex Alimentarius proposed draft Code of Practice. The proposed classification of antimicrobials used in New Zealand is confusing. It would be much easier to follow if animal use was divided into food producing animals and pet animals and horses rather than just combining all animal use together. Note that the JETACAR categorisation of human antibiotics has been updated by the Expert Advisory Group on Antimicrobial Resistance (see the EAGAR website: http://www.nhmrc.gov.au/about/committees/expert/eagar/). This could make Table 5.2 easier to interpret too. It could also be beneficial to classify veterinary use and perhaps develop a veterinary formulary or at least categorise approach to use (first line, second line, reserve agents)... Note that this occurs already in the UK and some European countries. Some of the conclusions in this chapter relate to material that has not been discussed in this chapter but is sometimes covered in other chapters – points identified as 8,9,10, 11, and 12.

Chapter 6 provides recommendations for the regulation and use of specific antimicrobials. This chapter seems to include much material cut and pasted from the background information provided to the panel. I think this material would have benefited from more discussion by the panel. It is pleasing to see that this chapter includes consideration of the selected antibiotic classes in all animals – not just food producing animals. I think it would be helpful in this chapter to explain why these classes of antibiotics are of particular interest – for example, that of the aminoglycosides netilmicin and amikacin are reserve agents in human medicine for Gram-negative infections resistant to gentamicin or tobramycin and that gentamicin and tobramycin are important for pseudomonad infections. It would also be useful to note the fact that apramycin resistance co-selects for gentamicin resistance. No justification is given for the comment that it is appropriate to retain injectable and topical aminoglycosides but not oral preparations and the subsequent recommendation that oral use be restricted.

The discussion about bacitracin should also include discussion about the significance of heavy metal resistance as it is likely that resistance to zinc and the potential for co-location of heavy metal resistance determinants on plasmids with other antibiotic resistance genes to select for multiple resistances is an important factor here. No doubt the real issue is the quantity of zinc (or copper) fed to animals which would be much greater than the amount of zinc fed in the form of zinc bacitracin. No discussion of topical use of bacitracin in companion animals is included. The recommendation that bacitracin resistance be monitored is justified from the discussion.

The background provided (plus other references not quoted in the report) and the discussion support the conclusion that 3rd and 4th generation cephalosporins should be protected. It is difficult to think of a situation in livestock production where there is not a suitable alternative to these antibiotics. Clearly the panel were not told that the major advantage of ceftiofur is its "nil withholding time" which means that injectable formulations can be used in lactating dairy cows and in animals immediately prior to slaughter. I am not sure that this is an adequate justification for using a class of antimicrobial regarded as a reserve agent in human medicine. I could not support retrospective culture as being a justification for use of such a product and as indicated previously there are alternatives. In addition, there is no discussion of the use of ceftiofur in companion animals although there are now a number of reports in the literature of AmpC producing *E coli* from urinary tract infections in dogs. The conclusions and resultant recommendation regarding 1st and 2nd generation cephalosporins are reasonable. Fluoroquinolones are key antibiotics in human medicine and I find it very hard to justify their use in food producing animals. There is clear evidence of their use in pigs and poultry in selection for fluoroquinolone resistant -campylobacter, *E coli* and salmonella infections in humans. I do not think the discussion justifies their continuing use in food producing animals in New Zealand. In the case of non-food animals, fluoroquinolones should be reserve agents – only for use in the event of treatment failure with other products with use supported by antibiotic sensitivity tests.

Macrolides and similar drugs (MLS_B antibiotics) include some key medical antibiotics. Clearly there are a number of them that are important antibiotics in veterinary medicine. It is worth noting that azithromycin is recommended for use in treatment of *R equi* infections in foals (as well as off-label use in cats and dogs) and this is one of the key medical antibiotics. The discussion does not provide any evidence for cross-resistance between tiamulin and tilmicosin with key human products so there does not seem to be any support for removing these antibiotics from use in cattle. However, tylosin and other macrolides do cross-select for resistance to the human products and it would seem sensible to recommend restrictions on use to therapeutic rather than prophylactic use in pigs, chickens and other food-producing animals. The recommendation to include macrolides in a surveillance system is soundly based.

Streptogramins – the discussion supports the conclusions and recommendation.

Chapter 7 addresses the framework for establishing regulatory policy. The discussion is logical and addresses both food producing and companion animals and covers issues such as the hazard associated with antimicrobial use in animals, release assessment and exposure assessment. There is some useful discussion of the "polarised and politicised" debate on the importance of animals in contributing to the human antibiotic resistance problem. However, the weight of evidence in the literature does support at least the view that antibiotic resistant zoonotic organisms such as campylobacter and salmonella can spread from animals to people and that commensals such as *E coli* can spread resistance genes to human pathogens (see . Barton MD (2000) Antibiotic use in animals feed and its impact on human health. *Nut Res Rev*, 13:279-299; Stobberingh EE, van den Bogaard AE (2000) Spread of antibiotic resistance from food animals to man, Acta Vet Scand Suppl 93: 47-50.) A recent paper (Wassenaar TM (2005) Use of antimicrobial agents in veterinary medicine and implications for human health. Critical Rev Microbiol 31: 155-169) provides a balanced view. Unfortunately while it is possible to develop qualitative risk assessment models for evaluating the risks to human health associated with use of antibiotics in animals, attempts to develop quantitative models (including Cox (2005)) have foundered because of gaps in the data available. A proposed model for surveillance and monitoring of food animals is described and discussed in this part of the report. While this is a good start and the recommendations of the panel are supported by the discussion, the details of the surveillance program warrant much more discussion prior to implementation. Issues such as inclusion of campylobacter, the merits of caecal contents vs piggy backing on petrifilm samples, the numbers of cattle to be sampled (to ensure that adequate numbers of calves and cull dairy cows are included0, the antibiotics to be used (virginiamycin for enterococci) need to be further considered. The extension of the program to cover *S aureus* from cattle and enteric organisms and *S aureus* from companion animals should also be discussed.

Chapter 8 discusses the future role of an expert panel. My only comment is that thought should be given to including a veterinary microbiologist.

Overall the report reports on progress since 1999 and successfully identifies some gaps that need to be addressed if New Zealand is to meet its international obligations. The discussion of each issue is generally thorough and wide-ranging and the conclusions and recommendations for the most part supported by the discussion.

Mary D Barton
Professor of Microbiology
University of South Australia
11 September 2005

Review of Report by the Expert Panel on Antibiotic Resistance:"A Review of the Impact of the Use of Antimicrobials in Animals and Plants on the development of Antimicrobial Resistance in Human Bacterial Pathogens"

John Turnidge, FRACP, FRCPA

The Review is an extensive examination of the current status of knowledge on the use and resistance impact of antibiotics in animals and plants in the context of New Zealand's current agricultural practices. In my opinion it addresses almost all the relevant issues and makes appropriate recommendations for ongoing management of the resistance risk.

I believe the Review could be further improved by taking into account the following:

1. A recognition that the risk assessment techniques of Cox (+/- Popken) has been strongly criticised. It is referred to on page 68. The Expert Advisory Group on Antimicrobial Resistance (EAGAR) in Australia believes that the model used by Cox is seriously compromised in a number of its assumptions. Most importantly, it fails to discuss/include any potential for secondary amplification of resistance once resistance has been transmitted to humans through the food chain. Cox was also severely criticized by US Supreme Court judges about the quality of evidence he gave during a recent appeal hearing. Elsewhere in the report, the potential importance of secondary amplification is alluded to.

2. The Review uses JETACAR ratings for various antimicrobials in different places in the document. JETACAR ratings have now been superseded by EAGAR ratings and can be found at: http://www.nhmrc.gov.au/publications/_files/antirate.pdf. More importantly, the Expert Panel may not be aware of a WHO Workshop that was held in Canberra in February 2005 on "Critically Important Antibiotics for Human Health". This workshop produced an even better rating system that is likely to be adopted internationally (the US were represented at the meeting). Unfortunately, the output does not appear to have been released yet. If the Expert Panel wants further information, I recommend that it contacts Dr Awa Aidara-Kane at WHO Geneva. Her email is aidarakanea@who.int.

3. There seems to be an incomplete understanding of resistance issues in regard to streptomycin. I would make the following points:
    a. Streptomycin also has a very minor role in the treatment of streptococcal and enterococcal endocarditis. In general these conditions are managed with a combination of a cell-wall active agent (ß-lactam or glycopeptide) and gentamicin. If the isolate is high level gentamicin resistant, but susceptible to high-level streptomycin, that agent is used. This is critically important for enterococcal endocarditis where cure is unlikely without an effective combination.
    b. Usually resistance to streptomycin does not have implications for resistance to other aminoglycosides used in humans. This is because of the

slightly different structure of streptomycin (it is an aminocyclitol technically), and most resistance is due to aminoglycoside-modifying enzymes (AMEs). The common AMEs that inactivate streptomycin do not generally inactivate gentamicin, tobramycin or amikacin. The following table from Antibiotics in Laboratory Medicine, 3rd Edition; ed V L:orian, explains this:

Table 18.3.
Aminoglycoside-Aminocyclitol Enzymes and Their Substrates[a,b]

	Acetyltransferases (AAC)			Phosphotransferases (APH)					Nucleotidyltransferases (ANT)			
Antibiotic	2′	6′	3	3′	2″	3″	6	5″	2″	4′	3″	9
Kanamycin A	−	+	+	+	(+)	−	−	−	+	+	−	−
Kanamycin B	+	+	+	+	(+)	−	−	−	+	+	−	−
Kanamycin C	+	−	+	+	(+)	−	−	−	+	+	−	−
Tobramycin	+	+	+	−	(+)	−	−	−	+	+	−	−
Dideoxykanamycin B	+	+	+	−	(+)	−	−	−	+	−	−	−
Amikacin	−	+	−	(+)	(+)	−	−	−	+	+	−	−
Gentamicin C_{1a}	+	+	+	−	+	−	−	−	+	−	−	−
Gentamicin C_1	+	−	+	−	+	−	−	−	+	−	−	−
Sisomicin	+	+	+	−	+	−	−	−	+	−	−	−
Netilmicin	+	+	(+)	−	+	−	−	−	+	−	−	−
Neomycin	+	+	+	+	−	−	−	(+)	−	+	−	−
Paromomycin	+	−	+	+	−	−	−	(+)	−	+	−	−
Lividomycin	+	−	+	+	−	−	−	(+)	−	+	−	−
Ribostamycin	+	+	+	+	−	−	−	+	−	+	−	−
Butirosin	+	+	−	+	−	−	−	(+)	−	+	−	−
Streptomycin	−	−	−	−	−	+	+	−	−	−	+	−
Spectinomycin	−	−	−	−	−	−	−	−	−	−	+	+
Apramycin	−	−	+	−	−	−	−	−	−	−	−	−

[a] Symbols: + = normal substrate, (+) = substrate for some forms of the enzyme, and − = nonsubstrate for enzyme.
[b] There is one known case of a fusion protein which possesses combined AAC6′–ANT2″ activity (49).
Note: The fact that an antibiotic is a substrate for an enzyme does not necessarily mean that strains containing this enzyme are resistant to the antibiotic (see Table 18.4.).

c. There is little discussion about the persistence of aminoglycosides in the environment. Aminoglycosides are quite stable under a wide range of environmental conditions, although gradually destroyed by some soil/water bacteria.

4. There is no discussion of the strong cross-resistance relationship between apramycin and gentamicin. This has been well documented in the literature. Again it is related to AMEs.

5. Although I do not know it to be the case, I would be surprised if bacitracin were not found in New Zealand in some topical preparations for human use (e.g. Neosporin® ointment for skin infections)). This should be checked as it is relevant to “Conclusions, page 52”.

6. The Table of cephalosporin “generations” is used in a couple of places in the text. In both instances it has ceftriaxone as a “3 antipseudomonal”. It is not, it is plain “3” and should be grouped with cefotaxime.

7. The discussion on "Macrolides and similar drugs" (p 58 and Appendix 7) is less informative than it should be. The following should be taken into account:
    a. The pleuromutilins are truly a separate class and should not be included here; they should be discussed separately. They are no more related to macrolides than chloramphenicol – i.e. they have a related but different mechanism of action and are not at all affected by macrolide resistance mechanisms.
    b. The educated reader needs to know that 16-membered macrolides (used in food animals and agriculture) differ from 14- and 15-membered macrolides in a number of ways, but most importantly in their relationship to resistance mechanisms. The common macrolide resistance mechanisms in human pathogen will not necessary affect 16-membered macrolides, but resistance generated by 16-membered macrolides will affect all macrolides, ketolides, lincosamides and streptogramins B. This is important because of the widespread used of tylosin (a 16-membered agent) in food animals. The table that follows explains this:

        Common resistances and cross-resistances to the MLS_B antimicrobials in humans

Mechanism of resistance	Main species	Macrolides		Keto-lides	Lincos-amides	Streptogramins		
		14 & 15	16			A	B	A+B
Intrinsic	Enterobacter-iaceae	R	R	R	R	R	R	R
	Enterococcus faecalis	R	R	R	R	R	R	R
	Enterococcus faecium	R	R	R	R	S	R	S
Ribosomal RNA Site methylation								
erm-inducible	Staphylococci	R	S	R	Si	S	S	S
erm-constitutive	Staphylococci	R	R	R	R	S	R	r
erm-inducible	Streptococci	R	S	r	Si	S	S	S
erm-constitutive	Streptococci	R	R	r	R	S	R	r
Efflux								
mef	Streptococci	R	S	S	S	S	S	S

S = susceptible, R = resistant, r = reduced susceptibility (tests as susceptible), Si = resistance inducible by erythromycin (tests as susceptible in absence of erythromycin)

c. The most commonly used name for the group is MLS_B, – macrolides, lincosamides, streptogramins B. In this reviewer's opinion, the ketolides do not warrant a separate subclass to macrolides.
d. Resistance to macrolides is not high in *Campylobacter* as far as I know (page 57)

8. It is surprising that the deliberate non-registration of fluoroquinolones for food animal use in Australia was not mentioned under "Regulation" on page 106. This is an important point of difference across the Tasman, and should lead to a recommendation to monitor for fluoroquinolone resistance in New Zealand if the recommendation to continue with the current licensing is accepted.

Peer Reviews of the report "A Review of the Impact of the Use of Antimicrobials in Animals and Plants on the Development of Antimicrobial resistance in Human Bacterial Pathogens"

Response of the Expert Panel on Antibiotic Resistance

The Expert Panel on Antibiotic Resistance is pleased that both peer reviews of its report consider the Panel's report to be thorough and comprehensive and to make appropriate recommendations. The Panel concluded that the reviewers' comments did not warrant a revision of the report but they made important points which should be available to the ACVM Group of the New Zealand Food Safety Authority when it considers its response to the report and the views of the Antibiotic Resistance Steering Committee.

Both reviewers referred to shortcomings in published risk assessments, particularly quantitative risk assessments. This is point the Panel has made in its report. However, the international standard setting bodies are recommending that risk assessments be developed and the Panel has concluded that, while the present New Zealand management system is risk based, one prime requirement for moving from an assessment based on assumptions to one based on data is to acquire that data. Getting reliable data on the prevalence of resistance among food animal bacteria is a logical first step.

The Panel acknowledges the report's apparent bias towards antimicrobial use in food producing animals referred to by one reviewer. Our approach reflects the current international focus on antimicrobial use in farmed animals and food as a pathway for the transfer of resistant bacteria or resistant determinants from animals to humans. We have drawn attention to the need to consider other pathways such as contact with companion animals but we were unable to complete a critical analysis of these pathways. For similar reasons the report focuses on anti-bacterial antimicrobials using the proposed Codex Alimentarius definition and does not consider anti-fungal antimicrobials such as those used in horticulture.