

ANTIBIOTIC RESISTANCE STEERING GROUP REPORT TO THE ANIMAL REMEDIES BOARD

At its meeting on 23 September 1999 the Antibiotic Steering Group considered the report of the Expert Panel and the recommendations made by that Panel. The Steering Group considered that the Expert Panel Report should be made public after it is considered by the Animal Remedies Board at its meeting in October 1999. However, the Steering Group considered that there were aspects of the report that would be misleading unless the report was read in conjunction with the comments and recommendations of the Steering Group. While there was general support from the Group for the recommendations made by the Expert Panel, a number of the recommendations need modification to make them more appropriate under New Zealand conditions.

The Group was advised that research in the area of antibiotic resistance is daily adding further clarification to this problem. The Expert Panel to complete its report by 31 July 1999 had to set a cut-off date of 30 June 1999 for considering new information. Therefore, any reports available after that date have not been incorporated into the report.

The Group noted that the Expert Panel used a decision rationale as a pragmatic basis for making recommendations in the face of limited conclusive information. The Steering Group agreed that regulatory action should be based on an adequate risk assessment. They noted that the Expert Panel clearly stated in its report that there was insufficient data to carry out a risk assessment and there was no literature documenting any risk assessments that have already been carried out. The Expert Panel also considered that it was beyond its brief to carry out a risk assessment itself. Some members of the Group considered that the Expert Panel should have carried out a risk assessment before making recommendations for regulatory change. They felt that there was sufficient data to do so. Other members of the Group accepted the judgement of the Expert Panel and were comfortable with the concept of recommending prudent changes based on the decision rationale used.

The Group was also advised that the common recommendation in all the reports considered was that there were gaps in information and risk assessments should be carried out. The Steering Group considers that this should also be expressly recommended to the Animal Remedies Board as long as the conduct of an adequate risk assessment does not delay actions that are considered to be prudent for the protection of public health.

Members of the Steering Group representing the livestock production and veterinary pharmaceutical industries pointed out that the statistics on antibiotic use significantly misrepresents the use in New Zealand of antibiotics for growth promotion. They contend that in New Zealand there is virtually no use of antibiotics for growth promotion *per se*. The antibiotic products are registered for growth promotion, but they are actually used to prevent or treat specific disease conditions. The Group was also advised that precipitant withdrawal of products that are licensed for growth promotion only, but actually used for disease prevention and treatment, would have a serious detrimental effect on the welfare of the animals normally treated with those products. The precipitant withdrawal of the products would also seriously harm those industries that depend on those products to control mortality and morbidity due to the specific disease conditions.

The Steering Committee noted that the antibiotic resistance issue is greater than can be managed within the scope of the Animal Remedies Board responsibilities. Addressing the

issue will require co-operation from government department, independent authorities and interested and affected parties.

In light of these general comments the Steering Group recommends the following:

1. To ensure that it is read in the proper perspective, the report when it is made public should be prefaced with these comments and recommendations and a position statement from the Animal Remedies Board.
2. The Group supports recommendation 1 that an overarching national antibiotic resistance review committee be established with clear terms of reference and rationale for membership to maintain an overview of both the human and animal factors that may contribute to the problem. The Groups considered that there should be wide consultation on the membership and terms of reference.
3. An adequate risk assessment of antibiotic resistance in New Zealand should be carried out as soon as possible, but delays should not hinder prudent regulatory action in the mean time.
4. The Group supports recommendation 2 in regard to the establishment of a comprehensive and co-ordinated surveillance programme. However, the Group considers that there should be detailed proposals for all aspects of the programme to ensure that:
 - the objectives of the programme are clear;
 - the data that is collected is appropriate; and
 - the information that is generated is used and disseminated appropriately.
5. The Group considers that recommendation 3 should be considered in the context of the surveillance programme to ensure that Animal Remedies Board surveillance of sale and uses is the most effective and appropriate way to gather that data. The Group also considered that it should relate to all antibiotics not just those used in feed.
6. The Group supports the development of standards, guidelines, and codes of practice by the Veterinary Council and the NZVA, but considers that similar action should be taken by the livestock production and veterinary pharmaceutical industries to ensure that products are marketed and used in a responsible manner. It was considered preferable that those bodies ensure that they include the public perspective when they develop standards, guidelines and codes of practice.
7. The Group supports recommendation 5, but notes that consultation will have to occur to clarify what information should be provided in the summaries of registration information.
8. The Group supports recommendation 6 as stated above in 6, and that codes of practice should cover use as well as promotion.
9. The Group considers that producers should be encouraged to adopt quarantine procedures (recommendation 7). However, the recommendation needs clarification that it relates to widening the scope of existing quarantine practices advocated and currently implemented by livestock production sectors to ensure that they target multi-resistant organisms that could exacerbate the antibiotic resistance problem in humans.

10. The Group considers that the criteria in section 4.2 of the report are in general appropriate (recommendation 8), but they are too prescriptive in their present form. It is recommended that they be revised so that they identify aspects that must be considered rather than be conditions for exclusion. Applications for registration of an antibiotic for growth promotant use should address the following aspects:

- The implications for public health of the concurrent use of a functionally related product in human medicine in New Zealand or Australia;
- The implications for public health of the subsequent introduction of a functionally related product in human medicine in New Zealand or Australia;
- The implications for public health for products that produce resistance or cross-resistance to systemic antibiotics used in human medicine;
- Product use should be compatible with a zero withholding period;
- The impact of the product on animal welfare;
- The impact of the use of the product on the concurrent availability of the same or functionally related product as a therapeutic agent for animal disease;
- The efficacy of the product; and
- The impact of the product on international trade in primary produce.

Applications for registration of an antibiotic for prophylactic use should address the following considerations:

- The impact of the use of the drug in animals on the use of a functionally related product in human medicine for the treatment of serious disease in people for which there is no suitable alternative. Such drugs include: fluoroquinolones, glycopeptides, streptogramins and third generation cephalosporins;
- Efficacy of the drug and establishment of optimum dose and treatment duration; and
- The impact of resistance selection on animal and human health.

11. The Group supports with qualification recommendation 9 that the registration of antibiotics should be reviewed every five years in light of new scientific information. The Group considers that an antibiotic should be reviewed in less than five years if there is concern that resistance may be developing. They also consider that at five years the depth of review should be concomitant with the level of concern. A detailed review should not be necessary if there is no reason to be concerned about the registration of the product.

12. The Group consider that recommendations 10, 11 and 12 may not be practical or in accordance with New Zealand's obligations under the World Trade Organisation's principles for applying sanitary and zoosanitary measures. If the measures recommended by the Expert Panel are to be applied, there must be technically supportable arguments why the action is essential for public health and food safety reasons.

13. The Group supports recommendation 13 and would expect Government to ensure that the regulatory environment is appropriate to do what is necessary to implement these recommendations.

14. The Groups noted the use of the rationale described in 2.1 by the Expert Panel. The criteria in 4.2 as revised in 10 above serve as a pragmatic basis for considering regulatory control of specific antibiotics or groups of antibiotics. The Group also noted that the Expert Panel recommended registration changes to a number of antibiotics. However, the Group could not accept the changes to registration recommended by the Expert Panel. The Group considered that the regulatory environment under the Animal Products Act and the use of codes of practice are likely to provide control equivalent to imposing veterinary prescription. They also considered that licenses would have to be revoked for antibiotic products that are presently approved for growth promotion only but actually used for disease prevention and treatment. Some of the Group also considered that risk assessments should be carried out before any changes in registrations are made. Therefore, the Group recommends that:
- where veterinary prescription is recommended, such prescription should be imposed only in the absence of product safety programmes or risk management programmes. Such programmes should have to include monitoring the use of antibiotics in accordance with the national surveillance programme. (recommendation 4 above);
 - instead of discontinuing the growth promotion use of an antibiotic as recommended by the Expert Panel, that growth promotion use should be reassessed as soon as possible in regard to the aspects listed in the Group's recommendation 10 above; and
 - Where, after addressing all the aspects in recommendation 10, growth promotion *per se* cannot be justified by a licensee, and the withdrawal of a license is likely, consideration must be made of the use of that product for disease prevention and treatment purposes to ensure that a product, essential for the health and welfare of the animals, is not inadvertently and precipitantly removed from the market.
15. The Group support recommendation 23 that streptomycin use in horticulture should be monitored. However, it should be monitored for the development of resistant bacteria as well as violative residues.
16. The Group supports recommendation 24 with no qualification.
17. The Groups supports recommendation 25, but consider it should not be limited to rural water supplies only. It also considers that the surveillance programme should include specification for monitoring both urban and rural water supplies.
18. The Group supports recommendation 26 with no qualification.
19. The Group supports recommendation 27 with no qualification.
20. The Group considers that recommendation 28 relating to genetically modified organisms and recommendation 29 relating to the presence of DNA-encoding resistance in products should be addressed in the context of an adequate risk assessment.

The members of the Steering Group representing the livestock production and veterinary pharmaceutical industries considered that the following comments and recommendations should also be made:

21. The process of implementing changes to licence claims should be transparent and cost-effective.
22. It should be clarified that fluoroquinolones were included in the report due to there being at least one product licensed in New Zealand for use in water. That product had not been marketed in four years and no fluoroquinolones are being used as growth promotant in New Zealand.
23. Table 2 should consistently refer to licensed uses and that the figure on virginiamycin use in cattle reflects an off-label use. However, table 2 referring to licensed use seriously overstates the use of antibiotics solely for growth promotion in both the pork and poultry industries. The figures reflect prophylactic use not growth promotant use.

EXPERT PANEL REVIEW

**ANTIBIOTIC RESISTANCE AND
IN-FEED USE OF ANTIBIOTICS
IN NEW ZEALAND**

31 JULY 1999

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EXPERT PANEL REVIEW

ANTIBIOTIC RESISTANCE AND IN-FEED USE OF ANTIBIOTICS IN NEW ZEALAND

EXECUTIVE SUMMARY

Introduction

The New Zealand Ministry of Agriculture and Forestry, Te Manatu Ahuwhenua, Ngaherehere, has established a MAF Antibiotic Resistance Steering Group. The purpose of the group is to:

- provide a forum for consultation amongst key stakeholders;
- coordinate a programme of gathering and analysing information on antibiotic resistance of micro-organisms in animals associated with the use of in-feed antibiotics for enhancement of animal production (which includes growth promotion and routine prophylactic use), and the potential transfer of this resistance from animals to humans;
- assist in the development of policy for New Zealand on the use of in-feed antibiotics for enhancement of animal production (which includes growth promotion and routine prophylactic use);
- assist in the development of policy for New Zealand on animal antibiotic resistance surveillance and management strategies; and
- provide information to the public about the process and decisions.

The Steering Group is charged with providing technical information and advice to the Animal Remedies Board and MAF who will then determine and/or review regulatory controls on the use of in-feed antibiotics for enhancement of production in New Zealand.

Mandate and terms of reference

To assist the Steering Group in its work, MAF convened an Antibiotic Resistance Expert Panel (hereinafter referred to as “the Panel”). The Panel is the author of this report.

The task of the Panel was to examine the current literature and consult other relevant sources of information (including international reviews and the Ministry of Health Antibiotic Resistance Working Group) that address the issues of:

1. the extent to which feeding antibiotics to animals to enhance animal production (which includes growth promotion and routine prophylactic use) results in the development of antibiotic resistance in bacteria;
2. the possibility, likelihood and consequences of the transfer of such antibiotic resistant bacteria from animals to humans; and
3. the possibility, likelihood and consequences of the transfer of such antibiotic resistance from animals to humans in New Zealand.

On the basis of its analysis of the available information, the Panel was to report back to the Steering Group and:

1. make recommendations in relation to the current use of in-feed antibiotics for enhancement of animal production (which includes growth promotion and routine prophylactic use) in New Zealand;
2. make recommendations on appropriate criteria for assessment and registration of in-feed antibiotics used in animals for enhancement of animal production (which includes growth promotion and routine prophylactic use); and
3. make recommendations on post registration surveillance and resistance management strategies.

Summary

The Panel has:

- reviewed the issue of antibiotic resistance due to the use of antibiotics as growth promotants;
- established crucial working definitions and the New Zealand context in which to consider the issue;
- noted the limitations in the information that is available and the difficulties with comparing resistance research and statistics from one country to another and even from one research project to another.

The Panel considered that, after its review of the literature on antibiotic resistance, the information that was available was not sufficiently comprehensive and robust to carry out a meaningful risk analysis for any of the antibiotics being used for growth promotion in New Zealand. Therefore, it decided that the available information on each antibiotic (or group such as the macrolide antibiotics) would be assessed in light of a consistent rationale rather than as part of a rigorous risk analysis of that antibiotic.

The Panel reviewed:

- the mechanisms and potential for inducing antibiotic resistance to the particular antibiotics; and
- the potential for that resistance to be transferred from bacteria associated with animals to those associated with and causing disease in humans.

The Panel looked at the use of each antibiotic in human health to determine how important it was in treating human diseases. Importance was assessed in regard to effectiveness and the availability of effective alternatives. The use of the antibiotic in animal health to treat or prevent disease (therapeutic and prophylactic use, respectively) was considered, as was the availability of alternative drugs or management techniques.

The Panel's recommendations for each antibiotic were based on the following rationale:

1. If an antibiotic was important (effective and few or no alternative drugs) in the treatment of human diseases and its effectiveness must be protected, then the use of that antibiotic on animals should be carefully controlled and its use as a growth promotant should not be allowed.
2. Even if an antibiotic was not used in human medicine (or there were more effective and safer alternatives), if it was important (effective and few or no alternative drugs) in the prevention or treatment of specific animal diseases, then it should not be used as a growth promotant.
3. If an antibiotic was not used as a therapeutic or prophylactic agent in animals or humans and there was no evidence of inducing cross-resistance, then it should be allowed to be used as a growth promotant, but its use should be reviewed regularly in the light of new information.

The Panel considered the range of possible interventions from awareness and education to regulatory control. It also reviewed existing monitoring and surveillance and what surveillance should be carried out to ensure that the character and evolution of antibiotic resistance was identified as quickly as possible.

The Panel also considered a number of peripheral issues that could have an impact on the development of antibiotic resistance.

The Panel has concluded that evaluating the development of antibiotic resistance is being hampered by significant gaps in information. What data are being collected are not integrated sufficiently to conclude that the use of antibiotics in animals (in particular the use of antibiotics as growth promotants) is exacerbating the problem of antibiotic resistant bacteria causing disease in humans. Even so, the Panel considers that there is sufficient scientific information to prompt a prudent course of action to protect the effectiveness of antibiotics being used in human medicine. The Panel also considers that the same prudent course of action should be taken to prevent antibiotic resistance in micro-organisms causing animal diseases.

While the Panel has made recommendations regarding specific antibiotics, its principal recommendations relate to establishing a national antibiotic resistance review committee and a surveillance programme that:

- brings consistency to the collection and analysis of resistance data; and
- integrates human health, animal health and food production data to highlight interactions.

The Panel considers that clear surveillance objectives and a formal surveillance programme would provide timely and relevant notice of emerging resistance problems and reinforce the necessity for regulatory control of the:

- import, manufacture, sale and use of antibiotics; and
- importation of animals and food products that may contain or harbour resistant strains of human and animal pathogens.

Recommendations

The recommendations from the Panel can be divided into five areas:

- overview and ongoing assessment;
- monitoring and surveillance;
- control of antibiotics;
- use of specific antibiotics; and
- peripheral issues.

Overview and ongoing assessment

1. An overarching national antibiotic resistance review committee should be established to collect and assess information and make appropriate recommendations.

Monitoring and surveillance

2. New Zealand should implement a comprehensive and coordinated antibiotic resistance surveillance system with the following specifications:

Data collection

Isolates should be supplied and resistance monitoring data be obtained from the following bacteria:

- food borne pathogens and indicator bacteria in animals;
- food borne pathogens and indicator bacteria on carcasses and food, including fruit and fish;
- clinical isolates of animal pathogens;
- clinical isolates of human pathogens; and
- rural water supplies.

The same isolation techniques should be used for each bacterium/source combination. Standardised antibiotic susceptibility testing methods should be used for bacteria isolated from humans, animals, foodstuffs and water. A single laboratory should carry out antibiotic resistance testing of all isolates from human, veterinary and food sources. All participating microbiological laboratories should supply isolates to the resistance-testing laboratory in a regular and consistent pattern.

Data analysis

Detailed proposals should precede the establishment of the surveillance programme to set out the analyses that would be performed and the purposes for that analysis. All analyses should comply with the agreed protocols.

Dissemination of surveillance system data

Information should be generated by the surveillance programme and be published regularly in a standardised form.

3. Sale and use of antibiotics should be officially monitored by the Animal Remedies Board (or its successor).

Control of antibiotics

4. The Veterinary Council of New Zealand and the New Zealand Veterinary Association should develop and encourage the adoption of guidelines, as recommended in this report, for prudent use of antibiotics for therapeutic and prophylactic use, and for use as growth promotants.
5. MAF should establish, and make available free of charge, a database to provide summaries of registration information.
6. The animal health industry should develop a code of practice for responsible promotion of antibiotics.
7. Producers should be encouraged to adopt quarantine procedures at production units that target zoonotic pathogens as well as animal pathogens to minimise the chances of multi-resistant organisms getting into the food animal industry.
8. The Animal Remedies Board (or its successor) should adopt the recommended criteria contained in section 4.2 of this report for assessing whether or not an antibiotic should be registered for use in animals.
9. The registration of all antibiotics should be reviewed every five years in the light of new scientific discoveries.
10. MAF should carry out quarantine procedures at the border that target zoonotic pathogens as well as animal pathogens to minimise the chances of multi-resistant organisms being introduced into New Zealand.
11. Animal products imported from countries where the animals were likely to be exposed to antibiotic growth promotants should be thoroughly checked at the port of entry for bacteria resistant to a range of antibiotics.
12. Primary produce or food products derived from animals treated with a growth promotant that is not allowed to be used in New Zealand should not be allowed to be imported.

13. Urgent attention should be given to problems identified in the regulatory framework, which presents difficulties in applying some of the recommendations made in this report.

Use of specific antibiotics

14. ***Macrolides***

Tylosin, tiamulin and other similar drugs should be reserved for use in the food animal industry for prophylactic and therapeutic purposes, and only under veterinary prescription.

Macrolides should not be used for growth promotion under any circumstances.

Other methods than administering macrolides for promoting growth and disease prevention in animals should be explored and encouraged.

15. ***Bacitracin***

The use of bacitracin should be retained, but only under veterinary prescription, for the prophylaxis of clostridial disease in poultry and pigs. Bacitracin should not be used for growth promotion. Registration of bacitracin should be reassessed if surveillance shows that its use may be associated with an increase in vancomycin resistant enterococci.

16. ***Avoparcin***

The use of avoparcin for growth promotion and prophylactic use in animals should be discontinued.

17. ***Virginiamycin***

The use of virginiamycin for growth promotion and prophylactic use in animals should be discontinued.

18. ***Ionophores***

The use of ionophores should continue as “over the counter” (OTC) products as at present.

19. ***Flavophospholipol***

Flavophospholipol should be reassessed according to the registration criteria recommended by this report.

20. ***Quinoxalines***

Quinoxalines could remain available as “over the counter” (OTC) products as at present. However, it is suggested that the issues of toxicity and carcinogenicity, particularly in regard to those handling these products, be considered in any review of their continued suitability for animal use.

21. ***Fluoroquinolones***

Fluoroquinolones should be available (in injectable or tablet form) only for the treatment of serious infections in individual animals. Veterinarians should be encouraged not to use fluoroquinolones for any use where another antibacterial drug is likely to be effective.

22. ***Avilamycin***
Avilamycin should be retained as a growth promoter but its licence should be reviewed annually.

If SCH27988 progresses beyond phase 3 trials in people, then avilamycin should be withdrawn as a growth promotant.

Peripheral issues

23. Horticultural produce treated with streptomycin should be carefully monitored by food safety authorities for violative residues.
24. The national antibiotic resistance surveillance programme should include within its terms of reference a study of the effects upon antibiotic resistance patterns related to the incorporation of antibiotics in or on human foodstuffs.
25. Because of their potential impact upon human food and water consumption, the recommended national antibiotic resistance surveillance programme should include within its terms of reference a horizontal study of antibiotic resistance patterns of the bacteria in rural water supplies.
26. The recommended national antibiotic resistance surveillance programme should include within its terms of reference a study of antibiotic resistance patterns of the bacteria related to the fish farming industry.
27. The risk assessment of any importation of fish or fish product must include within its measurement, factors related to the importation of diseases or bacteria, which have the potential to increase the use of antibiotics in any current or proposed fish farming industry in New Zealand.
28. As a precautionary approach, the Panel supports avoidance of antibiotic markers in the development of genetically modified organisms that are intended for wide release.
29. Before any antibiotic preparation is registered for use as an in-feed product, data must be provided and evaluated in terms of the hazard and risk of DNA-encoding resistance causing the transfer of that resistance to gut microflora of recipients.

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1. INTRODUCTION

1.1 Background

Throughout the developed world there is public and governmental concern about the increasing prevalence of resistance to antibiotics in bacteria that cause disease. There is a worry that many antibiotics currently available to treat human diseases will no longer be effective. This ineffectiveness is expected to lead to a deterioration in human health service outcomes as well as increasing health costs. There is a parallel concern that the development of resistance among bacteria is outstripping the ability of the pharmaceutical industry to develop new antibacterial agents.

The problem of the development of antibiotic resistance in bacteria has been the subject of specially commissioned reports under the auspices of a variety of government and international bodies. To a large extent, these reports have focused on the use of antibiotics in animals and, in particular, their use as feed additives for the purpose of growth promotion. This focus is because there is a widely voiced suspicion that antibiotic resistance that develops in bacteria in animals can directly and, allegedly indirectly, have an adverse effect on human health. Direct transfer would most likely be by way of animal products such as meat. Indirect transfer would be by transfer of genetic factors coding for resistance from “animal bacteria” to “human bacteria”. Outstanding among the reports addressing this issue are the following:

- United States of America. Committee on Drug Use in Food Animals, Panel on Animal Health, Food Safety, and Public Health. *The Use of Drugs in Food Animals, Benefits and Risks* (1999). National Academy Press.
- United States of America. *Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health* GAO/RCED-99-74 (1999). United States General Accounting Office, Washington DC.
- United Kingdom. Swann M M. *Report of The Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine* (1969). Cmnd.4190: Her Majesty’s Stationery Office. London.

- United Kingdom. *A Review of Antimicrobial Resistance in the Food Chain* (1998). A Technical Report for the Ministry of Agriculture, Fisheries and Food. London.
- United Kingdom. House of Lords. *Science and Technology – Seventh Report*. 17 March 1998. Her Majesty’s Stationery Office. London.
- World Health Organization. *The Medical Impact of the Use of Antimicrobials in Food Animals* (1997). Report of a WHO Meeting, Berlin, Germany, 13-17 October 1997.
- European Commission. *Opinion of the Scientific Steering Committee on Antimicrobial Resistance*. Commission Mandate DGXXIV (1999).
- European Commission. *Opinion of the Scientific Committee for Animal Nutrition (SCAN) on the immediate and longer-term risk to the value of streptogramins in human medicine posed by the use of virginiamycin as an animal growth promoter*. (Produced at the request of the Commission in response to action taken by Denmark under a safeguard clause to ban virginiamycin as a feed additive), 19 July 1998.
- Australia. *Draft Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR)*. 8 March 1999. Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry. Canberra.
- *Emergence of a Debate: AGPs and Public Health. Human Health and Antibiotic Growth Promotants (AGPs): Reassessing the Risk*. A Bezoen, W van Heren, J C Hanekamp. The HAN (Heidelberg Appeal Nederland) Foundation, 1999*.
- * The HAN report is neither a government nor multinational report. It was sponsored from the HAN foundation by the FEFANA (Federation Europeenne des Fabricants d’Adjuvants pour la Nutrition Animal, i.e. European Federation of Feed Additive Producers), but it is stated by the authors to be a report “Reassessing the Risk”. It utilises another perspective to address much that has been stated in the other reports.

It should be noted that the whole debate on antibiotic resistance in bacteria is set against a rapidly expanding area of science and scientific debate. Concurrently, important policy decisions are being made (in precautionary mode) while efforts are being made to fill some of the more important knowledge gaps.

On 14 December 1998 the European Commission voted to ban the use of four antibiotics as growth promotants. These four antibiotics are: zinc bacitracin, spiramycin, virginiamycin and tylosin phosphate. The ban will apply from 1 July 1999 and be reviewed before 30 December 2000. By that date it is anticipated in Europe that the surveillance programme underway in the EU will determine the extent and nature of the perceived antibiotic resistance problem as it relates to antibiotic use.

It appears that the main thrust of concern in Europe has come from Scandinavia. Sweden and Finland have had a national prohibition on the use of antibiotics for growth promotion that expired on 31 December 1998. Both countries, with the support of Denmark and Germany, have been the main sponsors of the extension of the ban throughout the European Union.

In New Zealand, only zinc bacitracin, virginiamycin, and tylosin are licensed with claims for growth promotion. Spiramycin is licensed only for therapeutic use in dogs and cats. The EU had previously (from December 1998) confirmed its ban on the use of avoparcin as an antibiotic growth promotant (AGP). (See Council Resolution (EC) No2821/98 of 17 December 1998.)

The New Zealand Ministry of Agriculture and Forestry, Te Manatu Ahuwhenua, Ngaherehere, has established a MAF Antibiotic Resistance Steering Group. The purpose of the group is to:

- provide a forum for consultation amongst key stakeholders;
- coordinate a programme of gathering and analysing information on antibiotic resistance of micro-organisms in animals associated with the use of in-feed antibiotics for enhancement of animal production (which includes growth promotion and routine prophylactic use), and the potential transfer of this resistance from animals to humans;
- assist in the development of policy for New Zealand on the use of in-feed antibiotics for enhancement of animal production (which includes growth promotion and routine prophylactic use);
- assist in the development of policy for New Zealand on animal antibiotic resistance surveillance and management strategies; and
- provide information to the public about the process and decisions.

The Steering Group has been charged with providing technical information and advice to the Animal Remedies Board and MAF who will then determine and/or review regulatory controls on the use of in-feed antibiotics for enhancement of production in New Zealand.

The Steering Group is composed of representatives from the following organisations:

- MAF Regulatory Authority (Convenor)
- Agricultural Chemical and Animal Remedy Manufacturers Association (AGCARM)
- Animal Remedies and Plant Protection Association
- Animal Remedies Board
- Consumers Institute
- Environmental Risk Management Authority (ERMA)
- Federated Farmers
- Ministry of Health
- Ministry of Research, Science and Technology
- New Zealand Pork Industry Board
- New Zealand Veterinary Association
- Poultry Industry Association.

1.2 Mandate and terms of reference

To assist the Steering Group in its work MAF convened an Antibiotic Resistance Expert Panel (hereinafter referred to as “the Panel”). The Panel is the author of this report.

The task of the Panel was to examine the current literature and consult other relevant sources of information (including international reviews and the Ministry of Health Antibiotic Resistance Working Group) that address the issues of:

1. the extent to which feeding antibiotics to animals to enhance animal production (which includes growth promotion and routine prophylactic use) results in the development of antibiotic resistance in bacteria; and
2. the possibility, likelihood and consequences of the transfer of such antibiotic resistant bacteria from animals to humans; and the possibility, likelihood and consequences of the transfer of such antibiotic resistance from animals to humans in New Zealand.

On the basis of this analysis the Panel was to report back to the Steering Group and make recommendations:

1. in relation to the current use of in-feed antibiotics for enhancement of animal production (which includes growth promotion and routine prophylactic use) in New Zealand;
2. on appropriate criteria for assessment and registration of in-feed antibiotics used in animals for enhancement of animal production (which includes growth promotion and routine prophylactic use); and
3. on post-registration surveillance and resistance management strategies.

The Panel was composed of experts with expertise and experience in a broad cross-section of scientific, veterinary and medical disciplines. The Panel included:

Chairperson	Professor Bill Manktelow
Veterinary Microbiologist	Dr Roger Marshall
Epidemiologist	Dr Michael Bates
Veterinary Clinical Pharmacologist	Dr Paul Chambers
Intensive Livestock Nutritionist	Dr Julian Waters
Human Infectious Disease Specialist	Dr Tim Blackmore

Professional details on the Panel members can be found in Appendix G.

It should be noted that Dr Nick Whelan acted as secretary, on behalf of MAF, and provided additional input in the field of veterinary clinical pharmacology at the first meeting only. Dr Rod Ellis-Pegler, Clinical Director of the Infectious Diseases Department, Auckland Hospital, Auckland Healthcare Services Ltd. also participated, by electronic means, throughout the Panel’s deliberations in order to maintain appropriate liaison with parallel work on antibiotic resistance under the auspices of the Ministry of Health.

The Panel set itself a target date for completion of its report by 31 July 1999. From time to time, oral interim progress reports were made to the Steering Group by a representative of the Panel (normally the Chairperson).

The Panel concentrated its literature searches on publications appearing subsequent to the searches commissioned from the University of Newcastle (NSW) by the Australian Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). To that end, databases (Medline, Commonwealth Agricultural Bureaux, and Focus on Veterinary Science) were searched from the beginning of 1998 until the date of the Panel's search (usually April or May 1999). In addition, reliable sources on the World Wide Web (e.g. the site sponsored by the United States National Institute of Allergy and Infectious Diseases, known as ROAR – Reservoirs of Antibiotic Resistance Network) were examined. By way of personal contacts, access was sought by Panel members to unpublished work, particularly in the New Zealand context.

1.3 Context for review of antibiotic resistance

The Panel first met on 16 April 1999 and thereafter conducted formal meetings on 17 May, 8 June, 29 June, 14 July and 21 July. Between formal meetings, work was conducted by e-mail and by small group discussions.

The Panel established a New Zealand context in which to review antibiotic resistance. This included:

- definitions;
- antibiotic, in particular antibiotic growth promotant (AGP), use patterns in New Zealand; and
- basis for regulatory control.

It also reviewed a number of factors affecting antibiotic resistance.

1.3.1 Definitions

The Panel agreed that, to effectively address the issue of antibiotic resistance, it would have to extend its work to consider antibiotic resistance due to the use of AGPs within proper perspective in the general landscape of antibiotic resistance. To do this the Panel had to establish working definitions for “antibiotic”, “therapeutic use”, “prophylactic use” and “growth promotant use”. No satisfactory definitions to assist the Panel's work could be derived from other reports cited above and the overlap of effects between each use category had the potential to give rise to confusion.

Definitions of what constitutes an antibiotic can be broad or narrow. The Panel was of the opinion that the definition by JETACAR that antibiotics were “chemical agents that inhibit the growth of bacteria” was too wide and would, for example, even include

materials commonly classed as disinfectants. The Panel decided to define an antibiotic as: *A chemically complex antimicrobial substance, derived from microbial fermentations or synthetic structural derivatives thereof, that is antagonistic to microbial growth in very low concentration.*

However, the Panel also took within its wider ambit, a range of antibacterial compounds such as the ionophores (e.g. monensin) and fluoroquinolones. The Panel very briefly discussed the potential effect of increasing use of heavy metals as additives to diets in the event that more restrictions were placed on the use of AGPs. It was decided to put the issue of copper, zinc and arsenic to one side as being outside the main work of the Panel.

The distinctions between the use of antibiotics for therapeutic treatment, prophylaxis or growth promotion are not always clear. Therapeutic treatment regimes are characteristically of short duration and at high dosage. Prophylactic regimes are generally administered for defined periods. The dosage level for prophylaxis appears, at times, to be at the same level as for therapeutic treatment. However, at other times, the level is less, especially if the prophylactic effect was needed for prolonged periods.

When antibiotics are used for growth promotion they are characteristically mixed in the food at low concentration and given for very long periods. Antibiotics used in therapeutic and prophylactic modes seem to also have a growth promotant effect during the period of their administration. Use of antibiotics in growth promotant mode seems to also have a prophylactic effect against certain diseases. To clarify the overlap, suitable working definitions making the distinction between therapy, prophylaxis and growth promotion were adopted by the Panel.

Therapeutic use of antibiotics was considered to mean: *to administer antibiotics for a limited period to individual or groups of animals showing signs of disease.*

The antibiotics are usually given by injection and usually, because of the high dose rate, significant withholding times are imposed. Most antibiotics are used for a therapeutic purpose. Protecting the effectiveness of antibiotics for use as therapeutic agents is the main reason for attempting to minimise antibiotic resistance.

Prophylactic use of antibiotics was considered to mean: *to administer antibiotics for a limited period to large or small groups of healthy animals deemed to be at risk of disease caused by pathogens susceptible to the drugs.*

Antibiotics are often given orally for prophylactic purposes. They are usually absorbed by the animals treated and their use is often conditional on compliance with significant withholding times. Oxytetracycline and tilmicosin are two antibiotics that are used prophylactically.

Growth promotant (promoter) use of antibiotics was considered to mean: *to administer antibiotics orally to large numbers of healthy food animals for long periods at low concentrations, which are below the minimum inhibitory concentration (MIC) for most pathogens, to increase the rate and efficiency of growth.*

Most growth promotants are not absorbed from the gut and there is usually no withholding period. They are sometimes referred to as production enhancers, in-feed antibiotics, or feed additives. Antibiotics commonly used for this purpose are bacitracin and virginiamycin.

1.3.2 Antibiotic use patterns in New Zealand

Collection of data on antibiotic use in New Zealand was difficult, but the Panel used the best estimates that could be made in the circumstances.

Animals account for about 57% of the 92.9 tonnes of antibiotics used in New Zealand (Table 1). However, about 34% of those used in animals are ionophores, which have quite a distinct mode of action from other antibiotics. Consequently, ionophores do not pose any identified risk to human health (see section 2.6, assessment of ionophores). If they are excluded from the statistics, then animal use accounts for 47% of the remaining total of 74.9 tonnes used.

The amount of non-ionophore antibiotics used for growth promotion and prophylaxis accounts for 24% of the total 74.9 tonnes. Of that 24%, 69% is used for growth promotion and 31% for prophylaxis (Tables 1 and 2).

Ruminant livestock production is largely extensive and pastoral in New Zealand, which is why they account for only 6% of the non-ionophore use of antibiotics used in feed for growth promotion and prophylaxis. Pigs and poultry account for 19 and 74% of this use respectively. This is a higher proportion than one may expect considering the relative livestock numbers (Table 3). Of note in Table 3 is that in New Zealand sheep, beef cattle and deer are not fed a significant quantity of compounded feed that might otherwise contain a growth promotant.

Since only a very small quantity of pig and poultry products are exported, the use of antibiotic growth promotants in New Zealand does not pose a significant threat to exports of primary produce.

More antibiotics are used per head with pigs than either poultry or cattle (Table 4). However, more are used with poultry than the other two groups when use is scaled according to animal liveweight.

Table 1: Human versus animal use (kg/year)

Antibiotic group	Animal	Human	Total	Animal/Total
Penicillins	8,476	24,019	32,495	0.26
Ionophores	18,032		18,032	1.00
Polypeptides	10,905		10,905	1.00
Macrolides and Lincosamides	6,082	4,064	10,146	0.60
Sulphonamides	2,066	2,800	4,866	0.43
Miscellaneous	549	3,992	4,541	0.12
Tetracyclines	2,311	1,343	3,654	0.63
Cephalosporins	763	2,245	3,008	0.25
Aminoglycosides	2,207	35	2,242	0.98
Glycopeptides	1,060	21	1,081	0.98
Fluoroquinolones	18	984	1,002	0.02
Streptogramins	891		891	1.00
Carbopenems and Monobactams		25	25	0.00
Glycolipids				0.00
Totals	53,360	39,528	92,888	0.57
Less Ionophores	35,328	39,528	74,856	0.47

Ref for human use: IMS Health (New Zealand) Ltd New Zealand Pharmaceutical and Hospital Indices April 1999 MAT. Animal use data supplied by manufacturers and importers of antibiotic products.

Table 2: Orally administered antibiotics for growth promotion and prophylaxis (kg/year)

Group	Growth promotion			Prophylaxis			Total
	Cattle	Pigs	Poultry	Cattle	Pigs	Poultry	
Ionophores	4,708			9,391		3,933	18,032
Polypeptides	183	1,390	9,270	62			10,905
Macrolides		442			1,312	2,904	4,658
Glycopeptides						1,060	1,060
Streptogramins	851		40				891
Tetracyclines					218		218
Totals	5,742	1,832	9,310	9,453	1,530	7,897	35,764
Less ionophores	1,034	1,832	9,310	62	1,530	3,964	17,732

Table 3: New Zealand population figures*

	Population (million)	Farms (thousand)	Population /farm	Compound Feed (000t)
Human	3.87			
Sheep	46.2	12	3,850	
Dairy	4.4	14	314	90
Beef	4.2	8	525	
Deer	1.8	2	900	
Pigs	0.41	0.7	586	250
Broilers	61	0.4	30,000	240
Layers	2.4	0.15	16,000	100

*Animal data from MAF agricultural statistics 1998

Table 4: Growth promotion and prophylaxis antibiotics by population and estimated liveweight

Antibiotics	Grams per head (g)		
	Cattle	Pigs	Poultry
All Categories	1.767	4.3	0.253
Minus Ionophores	0.127	4.3	0.195
	Grams per kg liveweight (g)		
All Categories	0.004	0.052	0.127
Minus Ionophores	0.003	0.052	0.098

1.3.3 Basis for regulatory control

All antibiotics on the New Zealand market are under some form of regulatory control. The least restrictive control relates to those antibiotics that are:

- licensed with the Animal Remedies Board (Animal Remedies Act 1967) as growth promotants; or
- registered as pesticides for horticultural use (Pesticides Act 1979).

The most restrictive controls are applied to those antibiotics that can be used only under prescription by registered medical, veterinary or dental practitioners. The use of these antibiotic products is subject to special institutional and/or professional ethical considerations. (See Appendix A for an overview of the provisions of the Animal Remedies Act 1967, the Pesticides Act 1979, the Agricultural Compounds and Veterinary Medicines

Act 1997, the Hazardous Substances and New Organisms Act 1996, and the Medicines Act 1981. See also Appendix D for the Medicines Act.)

It should be noted that not all pharmaceutical substances (including antibiotics) used in the treatment of animals are necessarily registered animal remedies. Some may be human medicines used under veterinary prescription. Some may be animal remedies registered for some uses but not registered for all the uses to which they may be put. This most frequently occurs when the product is not registered for use in domestic pets or for less common species such as llama, ostrich, deer, goats, fish etc. In those cases either insufficient trial data are available to allow registration for treatment in these species or, alternatively, the company offering the product for sale to veterinarians chooses not to have the product registered for what it sees as a minor use market. Any veterinary use of a pharmaceutical for purposes not specified in the product licence is called “extra label”, “off label” or “discretionary” use. Veterinarians using any drug in such a discretionary mode are ethically required to advise animal owners of the situation. A standard form issued by the New Zealand Veterinary Association (NZVA) for use by members of the Association in this situation appears as Appendix B. The NZVA has also produced a code of practice that addresses discretionary use of pharmaceuticals (see Appendix E).

Veterinarians are also required (and subject to disciplinary sanction) by the Veterinary Council of New Zealand to adhere to the policy on all animal remedies including antibiotics (as detailed in Appendix C) as extracted from the Council’s *Guide to Professional Conduct*.

1.3.4 Antibiotic action

Antibiotics possess the characteristic of being selectively toxic to bacteria, while not unduly affecting the target species. This is because the antibiotics exploit the differences between mammalian and bacterial cells. Antibiotics kill bacteria by targeting structural components unique to bacteria that are vital for bacterial growth and metabolism. Major unique targets for antibiotic action are listed below with important examples.

Disruption of bacterial cell wall

The cell wall protects bacteria and maintains their shape. It is a complex basket-like structure, and is synthesised in several steps by unique enzyme systems. Penicillins and cephalosporins bind to several so-called penicillin-binding proteins. Glycopeptides, e.g. vancomycin and avoparcin, interfere with cross-linking, which weakens and disrupts the cell wall. Bacitracin also interferes with cross-linking of the cell wall in a similar way to that of the glycopeptides. The effect for each of these antibiotics is disruption of the bacterial cell wall, resulting in inhibited growth or death.

Disruption of ribosomal function

Ribosomes are the factories of the bacterial cell that synthesise protein that is then used for many purposes. Bacterial ribosomes are structurally different from those found in plants and animals. Antibiotics are able to selectively target bacterial ribosomes without disrupting host protein synthesis.

There are many groups of antibiotics that bind to and interfere with ribosomal function. Each group binds to a different site on the ribosome. Examples of antibiotics that act by interfering with bacterial ribosomes are shown below.

Antibiotic class	Examples
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin (human use) Spiramycin, tylosin, tiamulin, tilmicosin (animal use)
Lincosamides	Clindamycin, lincomycin (human and animal use)
Streptogramins	Dalfopristin/quinupristin (human use) Virginiamycin (animal use)
Aminoglycosides	Streptomycin (horticultural, human and animal use) Gentamicin and neomycin (human and animal use)
Tetracyclines	Doxycycline, minocycline, tetracycline (human and animal use) Oxytetracycline, chlortetracycline (animal use)

Disruption of DNA structure and function

All cell functions are encoded in the DNA. Bacterial DNA function itself may be disrupted. Examples of antibiotics that disrupt the function of bacterial DNA include the quinolone antibiotics, e.g. ciprofloxacin, and rifampicin.

Disruption of the cell membrane function

Polyether ionophores such as monensin exert their antimicrobial effects by promoting uncontrolled ion fluxes across the membrane.

1.3.5 Antibiotic resistance

Antibiotic resistance is a relative term, and describes a situation where a bacterium is not inhibited or killed by concentrations of antibiotic that would normally be lethal to that bacterium. By common usage, resistance relates to antibiotic concentrations achievable in the animal or person being treated for infection.

Antibiotic resistance in bacteria may be intrinsic or acquired. Intrinsic resistance occurs when a bacterium normally does not possess the particular target structure of the antibiotic, or does not allow the antibiotic to penetrate into the cell to produce its effects. Examples include the resistance of Gram negative organisms to glycopeptides and penicillin.

Acquired resistance occurs when a bacterial strain that is normally susceptible becomes resistant by one of the following mechanisms:

1. producing enzymes that inactivate the antibiotic, for example:
 - lactamase enzymes, which inactivate penicillins and cephalosporins
 - vancomycin ligase, which prevents glycopeptides acting on cell wall components
 - modification of aminoglycosides such as streptomycin and gentamicin;
2. altering the cellular target, for example:
 - changes to the ribosome that prevent the binding of macrolides such as tylosin and erythromycin
 - changes to the ribosome that prevent the binding of streptogramins
 - changes to the bacterial DNA gyrase, preventing the binding of quinolones;
3. actively removing the antibiotic from the bacterial cell, for example:
 - active efflux of macrolides and streptogramins
 - active efflux of tetracyclines.

A single bacterial strain will often be resistant to several different antibiotics via different mechanisms of resistance. These may be acquired either in single or multiple steps.

1.3.6 Antibiotic resistance in New Zealand

Data relating to antibiotic resistance of enteric organisms isolated from food animals are very limited in this country. This makes it difficult to assess levels of antibiotic resistance in bacteria of animal origin. Limited monitoring of some zoonotic organisms isolated from human, animal and food sources has been carried out on a regular basis at ESR, Kenepuru Science Centre. These data together with that from some hospitals are available. Some general comments can be made on these results and any trends indicated.

Measuring antibiotic resistance

Superficial comparisons between data generated by different laboratories within one country let alone different countries, are prone to error. This is because the techniques used are often different. One commonly used system uses paper discs impregnated with antibiotic that are placed on the surface of an agar plate. The plate is first inoculated with an even layer of pure culture of micro-organism to be tested and the discs are placed on the surface of the plate that is then incubated overnight. The period of incubation allows the antibiotic to diffuse into the agar and the organism to grow where it can. An area around the antibiotic disc will, if the organism is susceptible, be devoid of bacterial growth. If the bacterium is resistant, growth will occur close to the edge of the disc. The size of the zone of inhibition is indirectly related to the minimum inhibitory concentration (MIC). The MIC system uses a series of dilutions of an antibiotic in broth. Each dilution is inoculated with a standard amount of the organism to be tested. This test enables the determination of the MIC, which is the concentration of antibiotic that inhibits bacterial growth.

Susceptibility v Resistance

Different countries may employ different break points to interpret the susceptibility or resistance of organisms. A break point is the cut-off point between susceptibility and resistance. There is no international agreement as to how to set break points and these may vary from country to country. For example, the United States uses a break point of >32mg/l whereas the United Kingdom uses a break point of >8mg/l for chloramphenicol. If two different break points are applied to New Zealand chloramphenicol susceptibility data for salmonella, very different results are generated (M. Brett, unpublished). A change from 0.5% to 50% resistance occurs when the breakpoint is changed from 32mg/l to 8mg/l respectively.

The isolation technique used for gathering the bacteria may also alter the proportion of resistant to susceptible organisms. In some instances an enrichment medium containing a macrolide antibiotic is used and this may also lead to the isolation of a different proportion of resistant to susceptible organisms.

Comparison between New Zealand and United States human salmonella isolates

The comparison of resistance/susceptibility data on salmonella isolates from New Zealand and the United States is valid because both countries use the National Committee for Clinical Laboratory Standards (NCCLS) system of testing for MICs. The comparison reveals that the resistance/susceptibility ratio in New Zealand is very different from that found in the US. In 1997 New Zealand salmonella isolates with ACSSuT (ampicillin, chloramphenicol, streptomycin, sulphonamide and tetracycline) resistance were 0.3% resistant compared with the United States figure of 5.3%. It is noted that within the United States the figures vary greatly (4.2 to 58.3%). The main difference between the United States figures and those in New Zealand is that in the United States the multi-resistant DT (definitive type) 104 *Salmonella* Typhimurium constitutes a significant proportion of the isolates whereas in New Zealand it appears to be rare.

Changes with time within New Zealand

Comparisons can be made between the ESR salmonella survey results of 1997 (Brett, unpublished) and those of 1991 (Heffernan, 1991). These two surveys show that there has been little change in the level of resistance during this period. Of particular note, however, was the appearance in 1992 of serotype *S. Hadar* which gave rise to a noticeable increase in tetracycline resistant salmonella. In 1992 *S. Hadar* was the second most frequently isolated salmonella from human patients (n = 70), and a high proportion of these, over 85%, were tetracycline resistant. By 1997 only 19 *S. Hadar* isolates were recovered; four of these were tested and three were found to be tetracycline resistant.

Animals and food items are two likely sources for the introduction of *S. Hadar* and Typhimurium DT 104, as well as other strains of potentially pathogenic and antibiotic resistant organisms, into New Zealand. Serotype *Hadar* apparently came into the country with new poultry breeding stock. This experience underscores the importance of thorough quarantining of livestock before and after their introduction. The presence of zoonotic pathogens as well as animal pathogens should be targeted in that quarantine.

With respect to antibiotic resistance, the precise strain of bacterium may be as significant as the level of antibiotic usage in animals. It is important to realise that some serotypes of salmonella have much greater antibiotic resistance than others (e.g. *S. Hadar* with respect to tetracycline, and *S. Typhimurium* with respect to ACSSuT). Internationally, every effort should be made to keep these two strains under control, and we should prevent their establishment in either the animal or human population in this country.

The case for surveillance

There is an urgent need for regular and internationally recognised surveillance of both animal and human isolates. Such surveillance will enable the alarm to be raised in the event of multi-resistant DT 104 or other multi-resistant organisms becoming introduced into the intensive food-animal industries in this country. The absence of ACSSuT resistant salmonella organisms in both the animal and human populations in New Zealand suggests that the specialised use of antibiotics as growth promotants may not be affecting the development of antibiotic resistance.

As can be seen elsewhere in this report, growth promotant use is very low in ruminants. The use is more widespread in the pig and poultry industries and yet, even in those industries, antibiotic growth promotants (AGPs) may not by themselves be contributing to the level of drug resistant bacteria in humans. It appears that the development of resistance may be dependent on the presence of strains of bacteria carrying resistance genes. Early identification of these strains may prevent the development of a resistance problem. However, the Panel notes that the practice of using antibiotics as growth promotants provides the antibiotic pressure that would encourage the establishment of multi-resistant organisms should they be introduced.

Other enteric zoonoses

Data relating to other zoonoses in this country, such as *Enterococcus* spp., *Campylobacter* spp., *Yersinia* spp. and pathogenic *E. coli* also suggests that, currently, there is little acquired resistance to antimicrobial agents in New Zealand when compared with the United States, United Kingdom, and the European Union as a whole. The Panel considers that this situation does not leave room for complacency. Continued vigilance is required to ensure that, should resistant strains of these bacteria be introduced or emerge, action can be taken immediately to limit their spread.

2. ASSESSMENT OF SPECIFIC ANTIBIOTICS

2.1 Decision criteria for assessment

The Panel considered that, after its review of the literature on antibiotic resistance, the information that was available was insufficient to carry out a meaningful risk analysis for any of the antibiotics being used for growth promotion in New Zealand. Therefore, it was decided that the available information on each antibiotic (or group, such as the macrolide antibiotics) would be assessed in light of a consistent rationale rather than as part of a rigorous risk analysis of that antibiotic.

The Panel reviewed:

- the mechanisms and potential for inducing antibiotic resistance to the particular antibiotics; and
- the potential for that resistance to be transferred from bacteria associated with animals to those associated with and causing disease in humans.

The Panel looked at the use of an antibiotic in human health to determine how important it was in treating human diseases. Importance was assessed in regard to effectiveness and the availability of suitable alternatives. The use of the antibiotic in animal health to treat or prevent disease (therapeutic and prophylactic use respectively) was considered. The availability of alternative drugs for the treatment of animals was also considered.

The Panel's recommendations for each antibiotic were based on the following rationale:

1. If an antibiotic was important (effective and few or no alternative drugs available) in the treatment of human diseases and its effectiveness must be protected, then the use of the antibiotic on animals should be carefully controlled and its use as a growth promotant should not be allowed.
2. Even if an antibiotic was not used in human health (or there were more effective and safer alternatives), if it was important (effective and few or no alternative drugs) in the prevention or treatment of specific animal diseases, then it should not be used as a growth promotant.
3. If an antibiotic was not used as a therapeutic or prophylactic agent in animals or humans and there was no evidence of inducing cross-resistance, then its use as a growth promotant should be allowed.

The Panel also looked at the status of the antibiotic in other countries to determine if its assessments were consistent with the regulatory control of that antibiotic in other countries.

2.2 Macrolides (tylosin, spiramycin, tiamulin)

2.2.1 Description

Tylosin and tiamulin are used in intensive animal production. In New Zealand their use is largely confined to treatment of pigs and poultry. Most of the macrolide antibiotics are produced from *Streptomyces* spp. bacteria. The macrolide group of antibiotics includes natural members, pro-drugs and semi-synthetic derivatives. Some antibiotics in the group, including erythromycin, clarithromycin, azithromycin and roxithromycin, are used in human medicine.

Macrolides have the ability to penetrate host cells, and the therapeutic action of macrolides is, to some extent, a reflection of their intracellular concentration. Erythromycin A derivatives (e.g. roxithromycin) accumulate rapidly to a saturation point both in the cytoplasm and intracellular granules. Intracellular concentrations of derivatives with two base groups do not reach saturation because they migrate from cells. These are less effective. The macrolide group antibiotics are particularly valuable for the treatment of cell-associated pathogens such as mycoplasmas.

2.2.2 Use in human health

Erythromycin and roxithromycin are the most frequently used of the macrolide group in New Zealand. They are most commonly used empirically for lower respiratory infections suspected or occasionally proved to be due to *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. They are also used for penicillin-allergic patients.

Clarithromycin and azithromycin are newly developed relatives with restricted use in New Zealand. Clarithromycin is used as a component of multi-drug regimens for non-tuberculous mycobacterial disease and for *Helicobacter pylori* associated gastric ulcers. Azithromycin has recently been licensed solely for the single dose treatment of genital chlamydial disease, the commonest sexually transmitted disease in the world. It is important that parties do everything to maintain the efficacy of this group of antibiotics for human disease for as long as possible.

2.2.3 Use in animal health

A high proportion of starter rations, and a smaller proportion of weaner feedstuffs for pigs, have antibiotics added. Tylosin and tiamulin are certainly two of the antibiotics frequently used in either or both of these types of feeds. What proportion of veterinary antibiotic usage is applied for growth promotion and what proportion is for disease prevention is not known. Tylosin is highly favoured because of its nil withholding period and because of its effectiveness against most common pig pathogens. A particular disease of the intestinal tract of grower pigs (proliferative enteropathy) is controlled by adding antibiotic to the feed, usually tylosin. However, in a study carried out in Ontario, Canada, among pig farmers to determine the extent to which these drugs are relied upon, 29% did not use antibiotics in the finisher feed and, of these, 87% believed that they were not necessary (Dunlop *et al*, 1998).

Tylosin and tiamulin are also used in the poultry industry and, in this capacity, could conceivably confer resistance on very common zoonotic organisms such as campylobacter (Aarestrup *et al*, 1997). Tylosin is also used in layer birds for the control of mycoplasma disease although many farmers are changing to vaccination for this purpose. Those farmers that are still using antibiotics rely more on tiamulin than tylosin.

It is common practice overseas to raise cattle under intensive conditions in feedlots and to feed them tylosin to prevent liver abscesses, which cause general deterioration in health, suffering, loss of productivity and some deaths. The addition of tylosin in the feed can reduce the incidence of liver abscesses in cattle by between 40 and 70% (Nagaraja Chengappa, 1998). On a national scale, feedlot operations in New Zealand are a very small part of the total beef cattle industry.

The macrolide antibiotics are very useful drugs for both therapeutic and prophylactic use in animals and their effectiveness should be protected.

2.2.4 Evolution of resistance

The antibiotic susceptibility of the bacterium *Serpulina hyodysenteriae*, the cause of swine dysentery, is known to have been markedly reduced in some countries. This is presumed to be the result of using macrolides in the feed. However, the alteration in susceptibility is not necessarily carried over to the whole macrolide group. In Hungary, for example, tiamulin is still effective for this pathogen whereas tylosin is found to be largely ineffective. Co-resistance does, however, frequently occur as has been reported in *Campylobacter jejuni/coli* with resistance to all three macrolide antibiotics (tylosin, spiramycin and erythromycin). It has been postulated that the considerable increase in the level of tylosin resistance in *Mycoplasma hyosynoviae* isolated from pigs is best explained as having resulted from the intensive use of tylosin during many years of use for therapy, prophylaxis and growth promotion.

Under some pressure from Sweden and Denmark, the Council of the European Union decided to apply the “precautionary principle” and not allow the use of zinc bacitracin, tylosin and virginiamycin as in-feed growth promotants from 1 July 1999. This will continue until 31 December 2000 when a review of scientific literature and ongoing epidemiological investigations will have been completed by the EU Scientific Steering Committee. The political implications of such a decision cannot be ignored by New Zealand.

Methods that should be explored in order to reduce the use of these antibiotics include the development of vaccines to immunise against the pathogenic and growth limiting organisms. If these are successful, such vaccines may eliminate the need for growth promotants and their prophylactic applications. Other needs for antibiotics will probably be eliminated or reduced if improvements are made to husbandry methods and standards.

The financial impact of any restrictions on both the pig and poultry industries is difficult to foretell; however, it is known that these industries experienced a downturn in productivity in Sweden after the banning of growth promotants.

Convincing evidence that macrolides used as feed additives cause a significant risk to human health is not presently available (HAN Report, 1999). Additional research is needed to characterise resistant strains more completely and to provide methods for comparing strains present in humans and animals. Since the use of antibiotics as AGPs increases the pressure in particular on enteric bacteria and, because these bacteria are likely to enter the human gut with foods of animal origin, the Panel advises that greater control should be exercised. This control should continue until more definitive data become available indicating that controls may be relaxed.

It is important that data relevant to this problem be generated in New Zealand. This can be done by a general surveillance system and by specific sampling and strain typing of both animal pathogens and indicator organisms.

Recommendations:

Tylosin, tiamulin and other similar drugs should be reserved for use in the food animal industry for prophylactic and therapeutic purposes, and only under veterinary prescription.

Macrolides should not be used for growth promotion under any circumstances.

Methods other than administering macrolides for promoting growth and disease prevention in animals should be explored and encouraged.

Rationale:

Because of the valued nature of this class of drug in both human and animal health for treatment of respiratory infections, mycoplasma diseases and other bacterial infections, it is important to maintain the efficacy of these drugs for as long as possible. Erythromycin, lincomycin, clindamycin, pristinamycin and the new combination dalfopristin/quinupristin, which is due to be authorised as a human medicinal product in the near future, could have their efficacy put in jeopardy as a result of cross-resistance caused by tylosin phosphate. For this reason care has to be exercised in the use of these macrolides so as to prevent or slow down the development of such resistance in the bacteria against which they are used.

2.2.5 Status overseas

Tylosin

EU: banned as growth promoter at least until December 2000, available for prophylactic use in calves, pigs and poultry.

USA: pigs – for increased rate of weight gain and improved feed efficiency, for prevention of swine dysentery (vibrionic), for maintaining weight gains and feed efficiency in the presence of atrophic rhinitis;

beef cattle – for reduction of the incidence of liver abscesses caused by *Sphaerophorus necrophorus* and *Corynebacterium pyogenes*;

laying hens – for improving feed efficiency;

broiler and replacement chickens – for increased rate of weight gain and improved feed efficiency; to aid in the control of chronic respiratory disease caused by *Mycoplasma gallisepticum*.

Australia: available.

Tiamulin

EU: pigs – for treatment of swine dysentery.

USA: pigs – for treatment of swine dysentery associated with *Serpulina* (formerly *Treponema*) *hyodysenteriae* susceptible to tiamulin, for increased weight gain and improved feed efficiency from weaning to market.

Australia: available for pigs and chickens.

Erythromycin

EU: chickens – for chronic respiratory disease;
cattle, sheep and pigs – for treatment of infectious disease (injectable).

USA: cattle – for treatment of *Pasteurella pneumonia* (injectable).

Australia: injectable available.

Spiramycin

EU: cattle, pigs and chickens – banned as growth promoter at least until December 2000, available for control and treatment of bacterial infections.

USA: not available.

Australia: available.

2.3 Bacitracin

2.3.1 Description

Bacitracin is a polypeptide produced by *Bacillus subtilis* and *B. licheniformis* and first described in 1945. Its structure is unrelated to that of any other antibiotic in clinical use. Bacitracin A is the major component of commercial bacitracin. It is usually complexed with zinc to prolong its shelf life and disguise its bitter taste, although the methylene disalicylate complex is also used in the United States (note: only bacitracin zinc is banned in the European Union). Bacitracin interferes with bacterial cell wall synthesis by blocking the function of the pyrophosphate carrier that inhibits the transfer of cell wall subunits across the cell membrane. It has a number of minor actions that may or may not be relevant to antibiotic resistance. It is a protease inhibitor that has been shown to enhance uptake of some proteins from the gut. It also appears to interfere with the binding of some proteins to their receptors. Bacitracin is mainly active against Gram positive bacteria including staphylococci. *Clostridium* species are particularly sensitive. There is great variability in the sensitivity of enterococci. Some Gram negative bacteria such as *Fusobacterium necrophorum* are also sensitive, but *Salmonella* species and *E. coli* are not. Bacitracin also has some activity against some protozoa (which is enhanced by zinc). It is not absorbed from the gut. It causes severe kidney toxicity if given parenterally, so it is not used systemically. It may cause anaphylaxis in humans (Comaish and Cunliffe, 1967).

2.3.2 Use in human health

Bacitracin used to be a common component of topical antibiotic ointments, often in combination with neomycin (commercial preparations have been discontinued in New Zealand). It has also been advocated for treatment of *Clostridium difficile* associated diarrhoea (Dudley *et al*, 1986). It is licensed in Italy and Portugal (usually in combination with neomycin or neomycin and streptomycin) to treat enteritis. The EU ban was imposed so that bacitracin could be reserved for human use against VRE. This does not seem likely to happen, since many enterococci show resistance (assumed to be intrinsic) to bacitracin, and its nephrotoxicity will almost certainly preclude its use.

2.3.3 Use in animal health

Bacitracin is used as a growth promotant. It is also used prophylactically to prevent clostridial disease in poultry and pigs, and liver abscesses in feedlot cattle. It is used as a growth promotant in calf milk replacers. It is also used in a variety of topical ointments and powders. *B. subtilis* (the source of bacitracin) has also been fed to poultry (Alvarez *et al*, 1994). In some European countries, intramammary bacitracin is used for mastitis since *Lactobacillus* species and *Strep. thermophilae* are resistant to it, and residues will not interfere with cheese and yoghurt manufacture.

Bacitracin's efficacy as a growth promotant in broiler chickens has been reported as a 2.5% (Shen Jian Zhong *et al*, 1995) to zero increase (Bartov, 1992; Abdulrahim, 1995). However, it has been shown to reduce the amount of faeces and increase nitrogen retention in layers and broilers (Huyghebaert and de Groote, 1997). This effect reduces environmental costs.

Bacitracin reduces salmonella contamination of chicken carcasses by between 1 and 5% (data provided by the manufacturer). This is probably because a reduction in inflammation in the gut means that intestines are less likely to rupture during processing.

Bacitracin produces a 2% (Kirchheim *et al*, 1993) to 4% (Pacheco *et al*, 1988) increase in weight gain over controls in finisher pigs. It has also been shown to be effective against proliferative enteropathy in pigs (Tsinas *et al*, 1998), which may explain its growth promotant effects.

Most reports on the use of bacitracin in calf milk replacer have been with veal calves in Europe. However, United Kingdom experiments in conditions similar to New Zealand showed growth rate improvements of minus 3% to plus 28% with an average of about 8% (Rosen, 1972). Most calves were fed concentrates *ad libitum* and housed, which is not the usual practice in New Zealand.

Bacitracin depresses growth in fish (Vargas *et al*, 1993).

It is used therapeutically in otitis externa in dogs as a topical lotion, usually in combination with neomycin and a steroid. Otitis externa is not a life threatening disease and alternatives to bacitracin are available. It has been used experimentally in clostridial overgrowth in dogs.

2.3.4 Evolution of resistance

Resistance mechanisms have been studied in detail only in *Bacillus subtilis* (the source of bacitracin), where resistance is due to an efflux pump. Enterococci show a high level of resistance to bacitracin; there is some evidence that this resistance is inherent in some types of enterococci rather than acquired (Krogstad and Parquette, 1980). Clostridia and staphylococci are mostly sensitive, although resistance has been reported. Faecal samples from the same animals often contain resistant enterococci and sensitive clostridia, which indicates that transfer of resistance is rare under field conditions.

Before bacitracin was replaced by safer drugs for systemic use in human medicine, no clinically significant resistance occurred.

Overall resistance patterns have not changed markedly since bacitracin was introduced in the late 1940s, but clinically significant resistance in *C. perfringens* has been reported on poultry farms with a history of necrotic enteritis (Watkins *et al*, 1997). Early studies (Mahony, 1973) tended to show that more isolates were susceptible to bacitracin than later studies (Benno *et al*, 1988). In Belgium, resistance appeared to increase between 1980 and 1993 in chicken isolates but not in pig isolates (Dutta and Devriese, 1980; Devriese *et al*, 1993). Manufacturer's data indicate that resistance on one farm had disappeared after two generations of broilers that did not receive bacitracin had passed through that farm.

With the possible exception of vancomycin, bacitracin does not show cross-resistance with other antibiotics. The evidence for cross-resistance with vancomycin is conflicting. Several reports suggest that drugs that interfere with bacterial cell wall formation can induce expression of the *vanA* vancomycin resistance gene in enterococci (Allen and Hobbs, 1995; Lai and Kirsch, 1996). Vancomycin and avoparcin appear to be most potent, with novobiocin having no activity. Bacitracin and penicillin have some activity according to some authors, no activity according to others. A variety of other drugs have also been shown to induce *vanA* expression in some experiments, including flavomycin (a growth promotant), moxidectin (an anthelmintic) and robenidine (a coccidiostat) (Lai and Kirsch, 1996). The clinical relevance of this is unclear but the risk does not seem large enough to justify withdrawing bacitracin as long as there is a surveillance system in place to detect emerging problems.

There is some evidence that bacitracin reduces the transfer of resistance to other antibiotics (Pawar *et al*, 1977; Walton and Wheeler, 1987).

Recommendations:

Bacitracin should be retained, but under veterinary prescription, for the prophylaxis of clostridial disease in poultry and pigs under veterinary prescription.

Bacitracin should not be used for growth promotion.

Registration of bacitracin should be reassessed if surveillance shows that its use may be associated with an increase in vancomycin resistant enterococci.

Rationale:

Bacitracin is unlikely to ever be used for life threatening conditions in people; therefore, resistance to bacitracin is not a human health problem. Bacitracin is useful for the prevention of some serious diseases in pigs and poultry. Use as a growth promotant may compromise this usefulness, although there is no evidence of this happening so far. It is arguable that most use in chickens in New Zealand at present is for prophylaxis of necrotic enteritis.

Total withdrawal of bacitracin is likely to lead to significant animal welfare problems, particularly in poultry. Necrotic enteritis is a common and serious disease in poultry; the three drugs that can most effectively control it are bacitracin, avoparcin and virginiamycin. Of these, bacitracin carries the least risk of transfer of resistance to a clinically useful (in humans) antibiotic. If none of these are available, then large quantities of ampicillin or amoxicillin are likely to be used to treat the disease as has happened in Sweden. Knowledge of poultry and pig pathology has advanced since bacitracin was first licensed, but there are limited data on bacitracin's interactions with the causative organisms of diseases of economic importance today. The potential for bacitracin to induce resistance to vancomycin in enterococci is theoretical and probably not of clinical significance, but surveillance of human and animal enterococcal resistance patterns should reveal the importance of this. Surveillance of Gram positive organisms from pigs and poultry is essential to detect any development of vancomycin resistance.

2.3.5 Status overseas

EU: banned at least until December 2000.

USA: approved for use in poultry, cattle, pigs, pheasant and quail for increased rate of weight gain, improved feed efficiency and control of clostridial enteritis caused by *C. perfringens*.

2.4 Avoparcin

2.4.1 Description

Avoparcin is a glycopeptide antibiotic that acts by inhibiting synthesis of the cell wall of Gram positive organisms such as staphylococci, streptococci, enterococci and clostridia. Its activity against enteric Gram positive organisms is thought to account for its growth promoting effects.

Glycopeptides including avoparcin are not systemically absorbed after oral administration, and so their activity is confined to the gut bacteria.

2.4.2 Use in human health

Avoparcin is closely related to vancomycin and teicoplanin, glycopeptide antibiotics used therapeutically in humans. Vancomycin is used orally only for the treatment of *Clostridium difficile*-associated diarrhoea. Both vancomycin and teicoplanin are used

for the treatment of Gram positive infections where the patient is allergic to penicillin. Their most important use is for the treatment of Gram positive bacteria resistant to first-line agents. These include methicillin resistant *S. aureus* (MRSA), coagulase negative staphylococcal infections, amoxicillin resistant enterococcal infections, penicillin resistant pneumococcal infections and others. As these organisms are steadily increasing in prevalence, the use of vancomycin is also increasing. New Zealand is still, however, a relatively light user of glycopeptides in human medicine.

2.4.3 Use in animal health

Denmark was the first European country to ban the use of avoparcin. This provoked in 1997 a temporary withdrawal by the European Union of authorisation for its use as a growth promotant. This was followed in 1999 by a ban on the product as a growth promotant in the EU.

Avoparcin was first licensed in New Zealand in 1977, for growth promotion and improvement of feed conversion in chickens, pigs and cattle, and for the improvement of milk production in dairy cattle. It was also licensed for the prevention of necrotic enterocolitis in chickens. The New Zealand licences for growth promotion were suspended in 1997 after international concerns were raised regarding the threat of development of glycopeptide resistant enterococci in animals and humans. MAF reviewed the information on resistance to avoparcin and, in 1998, withdrew the license for use in cattle. The suspension on use of avoparcin in pigs and poultry was lifted, but use in ruminants is not allowed.

2.4.4 Evolution of resistance

There are a variety of van genes that encode ligases producing glycopeptide resistance. The most important is *vanA* that produces high level glycopeptide resistance to avoparcin, vancomycin and teicoplanin. *VanA* is usually carried on transposons, which are highly transmissible genetic elements (Arthur and Corvalin, 1993; Klare *et al*, 1995). The most clinically relevant glycopeptide resistance problems in human medicine are with *vanA* containing enterococci (VRE), especially *E. faecium* which is usually resistant to β -lactams, aminoglycosides and glycopeptides. These infections can often only be treated with streptogramins (Leclercq and Courvalin, 1997). In addition there is *in vitro* evidence that the *vanA* gene can be transferred to staphylococci, which are amongst the most prevalent and virulent human pathogens (Noble *et al*, 1992). Such organisms are already beginning to emerge in Europe and Japan (Perl, 1995).

Although there has been discussion about the scientific robustness of some reports, there is consistent evidence that the occurrence of VRE in animal faeces and food corresponds with avoparcin use (Aarestrup, 1995; Bager *et al*, 1997; Bates *et al*, 1994; Klare *et al*, 1995; van den Bogaard *et al*, 1997). Similarly, human exposure to oral glycopeptides selects for VRE (van der Auwera *et al*, 1996).

Spread of VRE from animals to humans

Enterococci are commonly found in food, especially on poultry and pig meat. There is evidence that enterococcal colonisation of the human gut by animal strains is possible,

albeit for only three weeks (unpublished finding by Bechieri, quoted by Goossens, 1998). Studies from Europe show that humans frequently carry VRE in their faeces (van der Auwera *et al*, 1996; Gordts *et al*, 1995). Although one author found a difference between meat eaters (10% carriage) and vegetarians (0%) (Schouten *et al*, 1997), this was not confirmed in a similar study (van den Braak *et al*, 1997). In contrast, a study from the USA where avoparcin has not been used as a growth promotant did not show carriage of VRE in patients admitted to the hospital from the community (Silverman *et al*, 1998).

A critical issue is whether the animal and human strains are genetically related, indicating a direct link between animal use of avoparcin and human VRE. Bates examined human and animal strains of enterococci by ribotyping, and found there were five ribotypes common to humans and animals (Bates *et al*, 1994). There have been many criticisms of this study, including the HAN and SCAN reports. The chief complaints are:

1. that ribotyping is not as discriminatory as modern typing methods; and
2. that only one strain common to humans and animals was VRE, the remainder were susceptible to vancomycin.

There is, however, evidence that VRE can spread between avoparcin-exposed broilers and their farmers. This study utilised pulsed-field gel electrophoresis (PFGE) and analysis of *vanA* structure, which are “state of the art typing methods” (Simonsen *et al*, 1998). There is also a report of human infection by VRE occurring as the result of a femoral fracture in a chicken packing factory. Using relatively non-discriminatory methods, the infection appeared to be caused by VRE of the same type as isolated from the chickens (Das *et al*, 1997).

Transfer of resistance genes from animal to human enterococci

By analysis of chromosomal DNA, human and animal enterococcal isolates are generally distinct from each other (Kirk *et al*, 1997). Studies have therefore been conducted to assess whether the resistance genes could be spread between animal and human VRE strains. This concept is tenable because the resistance genetic elements are carried on a transposon, and genetic transfer has been demonstrated in models mimicking the gut lumen (Droge *et al*, 1998). The *vanA* gene cluster can be used to type strains of VRE by examining DNA sequences occurring between genes (intergenic variation). These studies found that there were differences in subtypes between human and animal VRE isolates (Jensen, 1998; Jensen *et al*, 1998b; Simonsen *et al*, 1998; Woodford *et al*, 1998). Even strains isolated from a single patient over a period of time were of four different subtypes (Tremlett *et al*, 1998).

Spread of VRE between humans

There are many reports of spread of VRE within and between hospitals, most of which come from the United States. It appears that outbreaks are clonal in origin, and that heavy in-hospital use of third generation cephalosporins and glycopeptides are predisposing factors. Once endemic within an institution, it is very hard to control or eradicate VRE (Centers for Disease Control and Prevention, 1993). In contrast, VRE carriage in the community is much more common in Europe; yet hospital infections are rare, presumably because of less human glycopeptide use. Therefore, if human use of

vancomycin were to increase in Europe, it seems likely that the VRE problem in humans could be at least as big as in the United States.

The above data show that avoparcin use is associated with the emergence of VRE in animals. The data are suggestive but not conclusive that resistance elements from animal VRE may transfer to humans, even though transmission should be prevented by hygienic measures. A vigorous debate has occurred about the importance and risk of transfer of resistance, with both sides probably taking a stance and then quoting the same literature to justify their positions. Although the Danish group have been the main publishers in this area, and are vocal in their opposition to avoparcin use, their papers are published in refereed journals and are open to scrutiny.

Recommendation:

The use of avoparcin for growth promotion and prophylactic use in animals should be discontinued.

Rationale:

It is clear that any glycopeptide use selects for resistant organisms in the species of administration. Human infectious disease experts and microbiologists are actively discouraging excessive glycopeptide use. Many of New Zealand's meat and produce export markets have banned avoparcin. While its use in New Zealand is limited to the pig and poultry industries, which are not export industries, it may be wise not to harm market access on the basis of potentially exporting resistant bacteria. VRE are rare in New Zealand at present; therefore, a proactive approach to minimise the risk of their emergence will have greatest benefit if implemented in the near future.

Apart from growth promotion, the registered use for avoparcin is for prophylactic control of necrotic enteritis in chickens. This condition can be managed by other methods. Therefore avoparcin is not essential to New Zealand livestock industries. There did not appear to be any significant economic ill-effects nor animal welfare issues in the year when its use was suspended. There are alternative agents available.

2.4.5 Status overseas

EU: banned at least until December 2000.

USA: not available.

Australia: available.

2.5 Virginiamycin

2.5.1 Description

Virginiamycin is a streptogramin antibiotic consisting of a mixture of virginiamycin S and virginiamycin M, which together are bactericidal. It acts on the 50S bacterial ribosome at a position very close to the site of action of macrolide antibiotics.

2.5.2 Use in human health

Although virginiamycin is not used in human medicine, it is very closely related to the human antibiotic dalfopristin-quinupristin (Synercid). Whilst this antibiotic is not currently used in New Zealand, it is expected to become a very important treatment for vancomycin resistant *Enterococcus faecium* (VREF) (Leclercq, 1998). Dalfopristin-quinupristin (Synercid) was recently approved in the UK for human use.

2.5.3 Use in animal health

Virginiamycin is used for growth promotion or enhanced feed conversion in pigs and poultry. In addition to its enhancement of feed conversion, it is used in New Zealand to prevent lactic acidosis in ruminants (but not licenced for this purpose). It has also been licenced for prophylactic use in horses for laminitis. It has been, but the Panel understands not currently, used to enhance feed conversion (off-label use) in cattle.

2.5.4 Evolution of resistance

Resistance to virginiamycin confers full resistance to dalfopristin-quinipristin. The major mechanism for resistance is methylation of the target on the bacterial ribosome, encoded by the *erm* gene. In addition there are other mechanisms of resistance including membrane permeability changes, efflux mechanisms and enzymatic modification of the antibiotic. Some resistance mechanisms overlap with those of macrolides, and resistance may be encoded either on the chromosome or on plasmids (Cocito, 1997; Leclercq, 1991).

Emergence of resistant organisms in host species is a consequence of virginiamycin use. In Denmark the rates of streptogramin resistant enterococci isolated from pigs, broilers and cattle appear to correlate with virginiamycin use. Although these results have been criticised by SCAN, the main concern was that the laboratory methods used by the Danish Veterinary Laboratory to detect resistance were non-standardised. However, as trends over time have shown, using the same method, it is likely that withdrawal of virginiamycin did truly lower the rates of virginiamycin resistance (Aarestrup *et al*, 1998; Welton *et al*, 1998; Danish Veterinary Laboratory report, 1998).

Spread of virginiamycin resistant organisms from animals to man

As noted in the section on avoparcin, there are little data showing that enterococci of animal origin infect humans. However, there have been reports from the United Kingdom of human streptogramin resistant VREF (*E. faecium*), even before dalfopristin-quinupristin had been introduced for human use. Virginiamycin has been used in animals in the United Kingdom, and so the Panel questioned whether these human isolates could have arisen as the result of animal use of virginiamycin (Woodford *et al*, 1997).

Transfer of resistance genes between strains of enterococci

There are *in vitro* data showing that the genes that encode streptogramin resistance may be transferred between strains of *E. faecium* (Hammerum *et al*, 1998).

Recommendation:

The use of virginiamycin for growth promotion and prophylactic use in animals should be discontinued.

Rationale:

It is clear that virginiamycin use selects for resistant organisms in animals, even though there are no published cases of human infections caused by streptogramin-resistant VREF from animal sources. The EU has banned the use of animal use of virginiamycin because of concerns that its use may jeopardise the treatment of VRE in humans.

Virginiamycin is licenced for prophylaxis against lactic acidosis in ruminants and coccidiosis and necrotic enteritis in poultry. There are alternative agents available for the prevention of these conditions, making virginiamycin non-essential. Many of New Zealand's meat and produce export markets have banned virginiamycin, and it may be wise not to harm market access on the basis of potentially exporting resistant bacteria.

2.5.5 Status overseas

EU: banned at least until December 2000.

USA: approved for use to increase weight gain, improve feed efficiency, and reduction in the incidence of liver abscesses in cattle fed in confinement. Approved to increase weight gain and feed efficiency in broiler chickens.

2.6 Ionophores**2.6.1 Description**

Ionophores are highly lipophilic monocarboxylic acids that are toxic to many bacteria, protozoa, fungi and higher organisms. The exterior of their molecules are hydrophobic, and the interior hydrophylic, being able to bind one or more cations.

Their lipophilic nature allows them to readily penetrate lipid rich cell membranes, enabling uncontrolled influx and/or efflux of selected ions, such as potassium and sodium, from the cell. This uncontrolled ion flow interferes with the osmotic control mechanisms in cells, often leading to cell death.

2.6.2 Use in human health

Ionophores are not currently used in human or veterinary treatment. The likelihood of them being used in future may be limited as they are absorbed and can be toxic.

The different mode of action of ionophores relative to the other major antibiotic groups, and their lack of therapeutic use in human and veterinary clinical medicine, would suggest they do not represent a risk to human health through transfer of resistance to human bacteria. This concurs with the conclusion in MAFF (1998), that there is no evidence linking the use of monensin and salinomycin with problems of resistance in humans.

Legitimately, the major reviews largely ignore the ionophores, perhaps because of their markedly different mode of action (MAFF, 1998; JETACAR, 1999; EU, 1999; HAN, 1999). It has been reported that, in the current state of knowledge, ionophores do not select cross-resistance to antibiotics used in human or veterinary medicine (EC, 1998).

2.6.3 Use in animal health

There are a number of ionophores licensed for use in New Zealand (lasalocid, maduramicin, monensin, narasin, salinomycin, semduramicin). They are primarily used in broilers, layer replacements, goats, sheep and cattle for prophylactic control of coccidiosis caused by *Eimeria* spp. Salinomycin is also licensed as a growth promotant for pigs and beef cattle. Monensin is also licensed for controlling bloat and ketosis as well as improving food conversion efficiency in cattle.

The improved feed efficiency effects resulting from the use of ionophores in the rumen is due in part to a shift in the proportion of Gram negative to Gram positive bacteria, with the former increasing at the expense of the latter. However, ionophores also appear to affect Gram negative bacteria, which may either be sensitive at concentrations likely to prevail *in vivo* and subsequently become resistant, or they may be able to grow but the presence of the ionophore causes altered metabolic properties (Newbold *et al*, 1993). The net result is an increase in the molar proportion of propionate to acetate, and decrease in rumen ammonia, probably as a result of reduced hydrolysis of peptides, along with less proteolysis and deamination of amino acids in the rumen (Newbold *et al*, 1993).

Bloat is a major health issue for pastoral-based cattle, and coccidiosis of major concern to pre-ruminant and monogastric animals. The effects of coccidiosis are debilitating and can be fatal, either directly or through increased susceptibility to other diseases such as necrotic enteritis, caused by *Clostridium perfringens*, in poultry.

Other anti-bloat treatments are available; however, none are suitable for extensively grazed animals. The effect of monensin of reducing methane production and emission by ruminants, a major contributor to the greenhouse effect, could be considered beneficial to the environment.

2.6.4 Evolution of resistance

The susceptibility of Gram positive bacteria to ionophores, as measured by MICs, varies according to bacterial cell wall structure (MAFF, 1998). Gram negative bacteria are naturally more resistant to ionophores by virtue of the inability of the ionophores to penetrate the bacterial cell membrane.

The structure of the cell envelope of Gram negative bacteria appears to influence susceptibility to ionophores through differences in ionophore binding and permeability. Increased resistance to ionophores has been demonstrated by one of these strains of bacteria, *Prevotella (Bacteriodes) ruminicola* M384, which appeared to have arisen from chromosomal mutation not plasmid transfer, possibly resulting in decreased porosity of the outer membrane (Newbold *et al*, 1992).

Cross-resistance to other ionophores also appears to be a common feature of bacterial resistance to individual ionophores, which appeared to be extended to avoparcin in one *in vitro* experiment (Newbold *et al*, 1993).

Ionophores are unlike the other common antibiotics in that they do not directly affect cell wall or protein synthesis, nor do they have specific target sites. They disrupt the ionic balance in bacterial cells thus forcing them to expend energy trying to restore it.

Recommendation:

The use of ionophores should continue as “over the counter” (OTC) products as at present.

Rationale:

Ionophores are important tools in the prevention of coccidiosis, bloat and ketosis. They may benefit the environment by reducing methane production and improving food conversion efficiency.

They are not considered to provide a risk to human or veterinary treatment and the fact that they may be absorbed and toxic is likely to reduce the possibility of them being developed for clinical use in the future.

They have not been implicated in cross-resistance to therapeutically important antibiotics in human medicine.

2.6.5 Status overseas

EU: banned in Sweden since 1986 as growth promotants but available for control of coccidiosis in poultry (see page xxiv, last para JETACAR). The scientific grounds of Sweden’s case for its ban are due to be examined the Commission (EU, 1998). Monensin and salinomycin are available in the rest of EU.

USA and Canada: available.

Australia: available.

2.7 Flavophospholipol

2.7.1 Description

Flavophospholipol, also known as bambermycin, Flavomycin and moenomycin, is an antibiotic complex consisting mainly of moenomycin A, derived from *Streptomyces bambergensis*. Moenomycin A is a glycolipid unrelated to other antibiotics. Its mechanism of action is unclear, but it is probably a competitive inhibitor of the peptidoglycan polymerases. It has also been shown to inhibit penicillin binding protein’s transglycosylase activities *in vitro*. It is mainly active against Gram positive organisms, although *E. coli*

has been shown to acquire sensitivity *in vitro*. *E. faecium* and *Clostridium* species are resistant. It is not absorbed after oral administration.

2.7.2 Use in human health

None.

2.7.3 Use in animal health

Flavophospholipol is used as a growth promotant in broiler chickens, where it has been variously reported to have no effect (Dafwang *et al*, 1984), no increase in weight gain but greater breast meat weight (Izat *et al*, 1990), or a 9% increase in weight gain (Mohan *et al*, 1996). In laying hens it had no influence on energy and nutrient utilisation, and produced no significant differences in egg production over controls (Vukic Vranjes and Wenk, 1996).

In bulls fed concentrates, daily weight gains were 3.5% higher than those of the controls (Alert *et al*, 1993). In heifers, flavophospholipol did not influence dry matter intake, but significantly increased weight gain by 10.5% and reduced feed and energy required per kg weight gain by 10.6% (Richter, 1991). However, bulls fed maize silage, which is a diet closer to the average beef bull in New Zealand, showed a small insignificant improvement in daily gain and feed conversion. A control group fed a beet pulp-based diet showed significantly increased daily gain of 15.2% and feed conversion efficiency of 9.1% (De Schrijver *et al*, 1991).

In dairy cows fed flavophospholipol there were insignificant increases in milk yield, 6.5% increase in casein and significant reductions in somatic cell counts in the milk (Ruffo and Valerani, 1977).

Turkeys receiving flavophospholipol had greater body weights at 12 and 16 weeks of age than birds receiving bacitracin or the control diet (Jiraphocakul *et al*, 1990). Adding flavophospholipol increased body weights of female turkeys at 10 weeks of age and male turkeys at 6 and 10 weeks of age. No differences among treatments were noted at market weight within any of the parameters studied. No differences among treatments were noted in efficiency or mortality by the conclusion of the trial (Firman and Kim, 1989).

Flavophospholipol has been reported to have a significant effect on growth in pigs in comparison to control and tylosin groups (Hagsten *et al*, 1980), although subsequent experience has been disappointing and it is no longer considered useful in pigs.

2.7.4 Evolution of resistance

Flavophospholipol reduced chlortetracycline and carbadox resistant coliforms in gnotobiotic mice inoculated with piglet faeces (Corpet, 1984), but had no effect on salmonella shedding or resistance in broiler chicks (George *et al*, 1982).

Flavophospholipol had no synergistic activity with other antibiotics and had little effect on eliminating plasmids from host bacteria. Dependent on plasmid type, flavophospholipol

decreased or increased transfer frequency of R plasmids. Flavophospholipol also selectively inhibited growth of bacteria harboring certain R plasmids. (George and Fagerberg, 1984). Spontaneous moenomycin resistant variants of *E. coli* were isolated at a frequency of about 10^{-9} (van Heijenoort *et al*, 1987).

Flavophospholipol retained its efficacy as a growth promotant over ten generations of broiler chicks (Johnston *et al*, 1983).

Flavophospholipol has been shown to induce expression of the *vanA* resistance gene in enterococci *in vitro* with a greater potency than bacitracin (Lai and Kirsch, 1996).

Recommendation:

Flavophospholipol should be reassessed according to the registration criteria recommended by this report.

Rationale:

The potential for resistance to develop seems limited. The use of flavophospholipol is not significant to human health, unless the interaction with the *vanA* gene in enterococci is shown to be significant. There is some conflicting evidence that flavophospholipol can increase salmonella shedding by chickens (Smith and Tucker, 1975). Flavophospholipol is not used much in New Zealand, but this may change if other growth promotants were withdrawn. The efficacy data are not very impressive.

2.7.5 Status overseas

EU: licensed to improve growth rate and feed conversion efficiency in calves, fattening cattle, pigs, broiler chickens, layer hens, turkeys, rabbits and fur animals.
USA: licensed for increased rate of weight gain and improved feed efficiency in poultry, pigs, feedlot cattle and cattle at pasture receiving supplementary feeding.

2.8 Quinoxalines (Carbadox, Olaquinox)

2.8.1 Description

Carbadox and olaquinox are quinoxaline-1,4-dioxide compounds, whose mode of action is not fully understood. They inhibit bacterial DNA synthesis and denature pre-existing DNA, possibly by a free radical mechanism involving reduction of the parent drug, accounting for their antimicrobial properties (Prescott and Baggot, 1993).

2.8.2 Use in human health

Quinoxalines are not used in human medicine as they are potentially carcinogenic and toxic (WHO, 1990). The use of quinoxalines for growth promotion and prophylaxis of disease in animals do not appear to represent a significant risk to human health.

2.8.3 Use in animal health

They are used to prevent dysentery in swine, and as growth promotants in swine and broiler chickens. In New Zealand, carbadox is included in a product containing morantel citrate, a neuromuscular blocking agent in nematodes. The olaquinox licence was withdrawn by the licence holder in May 1999. Alternatives to the use of quinoxalines for the treatment and prevention of dysentery in pigs include the use of other antibiotics or vaccination.

2.8.4 Evolution of resistance

Studies, conducted during the 1980s, indicating increased resistance to both antibiotics were cited in the EU (1999) report. There do not appear to be any recent studies regarding resistance to quinoxalines (MAFF, 1998).

Recommendation:

Quinoxalines could remain available as “over the counter” (OTC) products as at present. However, it is suggested that the issues of toxicity and carcinogenicity, particularly in regard to those handling these products, be considered in any review of their continued suitability for animal use.

Rationale:

Quinoxalines are not currently used in human medicine. It is unlikely that they will be used in clinical medicine given their toxic and carcinogenic nature. However, there is insufficient evidence regarding risk to human health, arising from transfer of antibiotic resistance, to amend the current status of these products.

2.8.5 Status overseas

EU:	carbadox and olaquinox are due to be banned on 1 October 1999.
USA and Canada:	carbadox is available.
Australia:	olaquinox is available.

2.9 Fluoroquinolones

2.9.1 Description

The fluoroquinolone group of antibacterial drugs, first developed about 20 years ago, are being used increasingly and more widely. They kill bacteria by inhibiting DNA gyrase, which supercoils bacterial DNA, and topoisomerase IV. Since mammals do not supercoil their DNA, it was hoped that fluoroquinolones would not have any deleterious effects on mammals. Although this is not strictly true, they have fewer side effects than many drugs.

The fluoroquinolones are active against many Gram negative organisms, including salmonellae and campylobacter. They have some activity against strains of pseudomonas, *Staphylococcus aureus* and *Mycoplasma* spp. They are not generally effective against

streptococci in animals (although *Streptococcus pneumoniae* in people is susceptible) or anaerobes.

There is complete cross-resistance among the fluoroquinolones, and partial cross-resistance with nalidixic acid.

2.9.2 Use in human health

Norfloxacin, ciprofloxacin and ofloxacin are available in New Zealand; many others are about to be marketed. Although they are useful for a wide variety of infections, they are generally reserved for serious infections caused by Gram negative organisms including salmonellae. Nalidixic acid, from which the fluoroquinolones were developed, is still used in New Zealand for urinary tract infections.

If serious infections caused by Gram negative organisms are no longer responsive to fluoroquinolones, more expensive (third generation cephalosporins) or less safe (co-trimoxazole) drugs will have to be used, although there is already significant resistance to co-trimoxazole.

2.9.3 Use in animal health

Enrofloxacin (which is rapidly metabolised to ciprofloxacin) is used therapeutically in a wide variety of animal species in New Zealand, including cattle and pigs. Orbifloxacin is used in dogs and cats. In most countries except Australia, a variety of fluoroquinolones are used to prevent and treat disease in food animals.

2.9.4 Evolution of resistance

DNA gyrase (topoisomerase II) and topoisomerase IV are each enzymes composed of four subunits (two A and two B) encoded by *gyrA* and *gyrB*, and *parC* and *parE* respectively. Fluoroquinolone resistant isolates usually contain one or more mutations in a small section of *gyrA* or *parC*; mutation in *gyrB* and *parE* is rare (Everett and Piddock, 1997). In Gram negative bacteria where mutations have given rise to a resistant DNA gyrase, mutations then occur in the topoisomerase IV genes (and vice versa for Gram positive bacteria) to give a highly resistant bacterium. In addition, there are genes that influence the uptake of the drug into the bacterial cell and efflux pumps that can be overexpressed to enhance excretion of quinolones from the cell. This enhanced efflux in turn causes increased minimum inhibitory concentrations of several drugs, including fluoroquinolones, tetracycline, chloramphenicol, and ampicillin (Aleksun and Levy, 1997; Miller and Sulavik, 1996; Poole *et al*, 1993; Kaatz *et al*, 1993). It has been suggested that mutations enhancing efflux occur as a first step, allowing the bacteria to survive such that mutations can accumulate in genes encoding the target proteins. Plasmid mediated, transferable, fluoroquinolone resistance has recently been described (Martinez *et al*, 1998); its mechanism of resistance and epidemiology is unknown.

Salmonella Typhimurium and *Campylobacter* spp. are well known zoonoses. In Britain, *S. Typhimurium* with decreased susceptibility to fluoroquinolones and campylobacter resistant to fluoroquinolones have been isolated from animals and retail poultry (Griggs *et al*, 1994; Gaunt *et al*, 1996), from food animals (Threlfall *et al*, 1999) and from

people (Threlfall *et al*, 1998). This has been attributed to veterinary use of fluoroquinolones (Threlfall *et al*, 1999).

In Minnesota, a rise in ciprofloxacin resistant campylobacter in people has been linked to chickens by molecular biology and by the timing of the rise in resistance (Smith *et al*, 1999).

Although fluoroquinolones are safe and effective for many infections in animals, there are very few situations where another drug could not be used as successfully.

Recommendation:

Fluoroquinolones should be available (in injectable or tablet form) only for the treatment of serious infections in individual animals. Veterinarians should be encouraged not to use fluoroquinolones for any use where another antibacterial drug is likely to be effective.

Rationale:

There can be no justification for using fluoroquinolones as growth promotants; their use overseas to prevent disease has caused increases in the prevalence of resistant pathogens in both animals and people. Alternatives to their use are available. They should not be available in a form that can allow mass medication.

2.9.5 Status overseas

EU: danofloxacin, difloxacin, enrofloxacin, marbofloxacin, sarafloxacin, flumequine and oxolinic acid are used in a variety of food animals including cattle, pigs, chickens, turkeys and salmon for treatment and control of a variety of conditions.

USA: enrofloxacin and sarafloxacin are used in poultry “for the control of mortality”.

Australia: not licensed for use in food animals.

Asia and Latin America: a wide range of fluoroquinolones is available for all species.

2.10 Avilamycin

2.10.1 Description

A variety of avilamycins are produced by *Streptomyces viridochromogenes*. They are oligosaccharides and usually classified as orthosomycins. Commercial avilamycin is mainly avilamycin A; avilamycin C is also important and there are numerous less active avilamycins. There are many closely related orthosomycins, such as the evernimicins, flambamycin, curamycin and sporosuracins, none of which are used clinically in humans or animals in New Zealand at the moment.

Avilamycin binds to the bacterial 30S ribosomal subunit and inhibits the attachment of tRNA, in a similar manner to aminoglycosides (Wolf, 1973). The avilamycins are only active against Gram positive bacteria, including *Clostridium perfringens* (Devriese *et al*, 1993).

2.10.2 Use in human health

SCH27988 (Ziracin), an everninomicin that is very similar to avilamycin, has entered phase 3 clinical trials for Gram positive nosocomial infections in people. It is active against a wide range of multiresistant staphylococci, enterococci (Jones *et al*, 1999) and streptococci (Marshall *et al*, 1999). It compares favourably to vancomycin *in vitro* (Urban *et al*, 1996; Nakashio *et al*, 1995). It has not been used in New Zealand yet.

2.10.3 Use in animal health

Avilamycin is used as a growth promoter in pigs and chickens. It is also potentially useful against necrotic enteritis in chickens, although Elwinger *et al* (1998) showed that it was no better than monensin when incidence of necrotic enteritis, numbers of *C. perfringens*, mortality or bodyweight were compared. However, avilamycin produced a significantly higher carcass yield. Avilamycin may be useful against necrotic enteritis which is resistant to bacitracin (Watkins *et al*, 1997). Avilamycin did not induce salmonella colonisation in chicken guts (Hinton, 1988).

Avilamycin will increase the digestibility of pig rations (Rattay *et al*, 1998) to a similar degree as tylosin (Windisch *et al*, 1998). It produced a 2.4% increase in weight gain in pigs (Kampf *et al*, 1998), which may have been due to its partial effectiveness against proliferative enteritis (Tsinas *et al*, 1998). However, overdosage reduces growth rates (Kyriakis *et al*, 1994).

2.10.4 Evolution of resistance

There appears to be complete cross-resistance between avilamycin and SCH27988 in enterococci isolated from broiler chickens and pigs (Aarestrup, 1998). Resistance appears to develop slowly, both *in vitro* (Nakashio *et al*, 1995) and in the field (Devriese *et al*, 1993).

Recommendations:

Avilamycin should be retained as a growth promoter but its licence should be reviewed annually.

If SCH27988 progresses beyond phase 3 trials in people, then avilamycin should be withdrawn as a growth promoter.

Rationale:

Resistance to avilamycin seems to develop slowly, but this will need to be monitored by the surveillance system, particularly if avilamycin use increases because other growth promoters are withdrawn. Use of avilamycin in the UK has increased dramatically since the EU ban on most growth promoters; if problems with resistance are going to occur, they will probably be reported from the UK before they appear in New Zealand.

It seems likely that SCH27988 will progress to marketing for resistant infections in people. Since this is likely to happen in the USA or Europe several years before it reaches New Zealand, there should be time to reassess avilamycin's status and the prevalence of resistance to this group of drugs.

2.10.5 Status overseas

EU: for growth promotion in pigs and chickens.

USA: not available.

3. PERIPHERAL ISSUES

Marginal to the terms of reference of the Panel are a number of issues considered by the Panel to be peripheral, minor or insignificant players in the New Zealand landscape of antibiotic resistance. Nonetheless, the Panel wishes to call attention to them because they are often not considered or ignored in discussions that focus exclusively on the roles of antibiotic usage in humans and animals.

3.1 Use of antibiotics in horticulture

Information provided by MAF to the Panel indicates that a significantly large quantity (1.2 tonnes approximately) of streptomycin (active ingredient) is used annually in horticulture in New Zealand. Streptomycin is reportedly the only antibiotic used in the horticultural industry. Its use appears to be confined to fruit trees and tomato plants up to 60 cm tall. The Panel has been advised by MAF that there are no plans to use any other antibiotics apart from streptomycin in horticulture.

It should be noted that the range of antibiotic agents and range of horticultural usage is wider in the EU than in New Zealand. Since there is no expressed demand in New Zealand for additional antibiotics, the Panel assumes that resistance among plant pathogens in this country is not yet a problem. However, in the report of the EU Scientific Steering Committee (p51) reference is made to resistance to streptomycin occurring in phytopathogenic bacteria associated with apple and pear trees.

It is the Panel's view that, since many horticultural products are consumed in the raw state, they should be carefully monitored by food safety authorities to prevent the unsuspected consumption by individuals of unallowed (above tolerance) antibiotic residues. No firm causal association has yet been made between consumption of antibiotic treated horticultural produce and resistance of bacteria in the human gut flora but it is noted that in one study (Elder *et al*, 1993) higher levels of multi-drug resistant bacteria were detected in the intestinal microflora of vegetarians as compared to meat eaters.

The Panel applauds the conservative approach of the horticultural industry in limiting the variety of antibiotics used in horticulture to streptomycin and urges that this approach continue. However, it notes that the amount used is significant and a study of the effect of horticultural use on the development of antibiotic resistance patterns in bacteria found on horticultural product should be a strong component of the proposed national surveillance programme.

Recommendation:

Horticultural produce treated with streptomycin should be carefully monitored by food safety authorities for violative residues. Horticultural produce should also be included in the proposals for surveillance of antibiotic resistance detailed elsewhere in this report.

3.2 Direct use of antibiotics in human food

The Panel is aware that some specific antibiotics are allowed to be applied directly to food products. For example, nisin is approved in the United States to inhibit the growth of *Clostridium botulinum* (the causal organism of the potentially fatal disease botulism) in products such as pasteurised cheese. Also permitted for use in the United States (and Europe) on surfaces of cheese is the antifungal antibiotic, natamycin (see Code of Federal Regulations Title 21, Volume 3, Parts 170 to 199). Natamycin is also used in human medicine for surface treatment of fungal infections of the cornea, skin, nails etc. It should be noted that many international reports on antibiotic resistance ignore the issue of officially approved antibiotics as direct additives to human food.

Recommendation:

The national antibiotic resistance surveillance programme must include within its terms of reference a study of the effects upon antibiotic resistance patterns related to the incorporation of antibiotics in or on human foodstuffs.

3.3 Antibiotic resistant bacteria in water

Bacteria resistant to antibiotics have been recovered from water supplies in the United States (McKeon *et al*, 1995). It is not clear whether their level of occurrence is influenced by animal, human or horticultural effluent or is a reflection of the “natural” level of occurrence of resistance in the microbial flora at such sites. It should, however, be noted that the use for irrigation or washing of horticultural crops by water containing antibiotic resistant bacteria is a potential but unmeasured hazard.

Recommendation:

Because of their potential impact upon human food and water consumption, the recommended national antibiotic resistance surveillance programme should include within its terms of reference a horizontal study of antibiotic resistance patterns of the bacteria in rural water supplies.

3.4 Antibiotic use in aquaculture

The use of antibiotics in the farming of fish, particularly salmon and shrimp, has given rise to considerable concern overseas. For example, in an editorial on antimicrobial resistance which appeared in the *British Medical Journal* (5 September 1998, 317: 609-610) the following statement appears:

“What seems less controversial is the long-term risk of spraying fruit trees in some parts of the world with antibiotics and adding 50-60kg of an antimicrobial to each acre of salmon farm.”

There are no available national data that would allow the Panel to comment factually on the use of antibiotics in aquaculture in New Zealand. Such use would have to be discretionary and as prescribed by a veterinarian. No licensed animal remedy makes claims for its use on farmed fish. Because of the excellent fish health status of current stocks in this country, subjective opinion is that total use is likely to be small.

The Panel has been informed that there was use of antibiotics in New Zealand salmon in the early years of the industry, in the form of oral oxytetracycline treatment for vibriosis and /or non-specific skin lesions post grading. Reportedly there has been minimal antibiotics used for this purpose in the last 10 - 15 years. However, in the early 1990s there was limited use of oxytetracycline-medicated food for yersiniosis in salmon fingerlings in freshwater. Such use is said not to be current. It seems that improvements to husbandry have increased the resistance of farmed salmon to these bacterial conditions.

The reported exception was this year when oxytetracycline was used in the feed for newly introduced salmon in Akaroa Harbour. Seawater temperatures were unusually high during the 1998-9 summer and this may account for the reappearance of vibriosis requiring medication after an absence of 15 years. It should be noted that currently there is interest in farming of so called “new” species in New Zealand, e.g. snapper, marine flat fish, paua and crayfish. It is likely that the husbandry-related disease pattern seen in the young salmon industry will be repeated with these species. However, antibiotic use will probably be “small and confined”. New Zealand is unusual in its very limited use of antibiotics in aquaculture. Introduction of fish pathogen/s from overseas would dramatically alter the current situation.

Recommendations:

The recommended national antibiotic resistance surveillance programme should include within its terms of reference a study of antibiotic resistance patterns of the bacteria related to the fish farming industry.

The risk assessment of any importation of fish or fish product must include within its measurement, factors related to the importation of diseases or bacteria that have the potential to increase the use of antibiotics in any current or proposed fish farming industry in New Zealand.

3.5 Genetically modified organisms

It has been suggested that the common use of antibiotic resistance markers in the development of some genetically modified organisms (GMOs) might pose risks of inducing antibiotic resistance in bacteria. The hypothesis is that a GM fodder crop containing a genetic sequence for antibiotic resistance could be transferred to the resident bacterial flora of the consuming animal. An editorial appropriately entitled “Gut Reaction” in the *New Scientist* of May 6 1999 explores the issue. To quote the editorial, “While some scientists fear that these (antibiotic resistance) genes could jump into bacteria in the guts of livestock and create antibiotic resistance pathogens, others say there is no such risk

because the modified DNA breaks down quickly”.

The JETACAR Draft Report (p134) states, in the context of kanamycin resistance, that the probability of transfer of resistance from a transgenic plant to a bacterium in an animal intestine is “extremely remote”. Having examined the more recent literature, the Panel agrees with the view expressed in the JETACAR report. It should also be noted that, even if the remote possibility of transfer of antibiotic resistance genes to gut bacteria were a reality, there would have to be concurrent or subsequent selection pressure by the appropriate presence of antibiotic in the gut milieu before it could become a veterinary or human health issue. Nevertheless, as a precaution, it has been recommended by some (e.g. The Royal Society [UK] and the UK Advisory Committee on Novel Foods and Processes) that molecular biologists should try to avoid the use of antibiotic resistance markers in the development of GMOs.

Recommendation:

As a precautionary approach the Panel supports avoidance of antibiotic markers in the development of genetically modified organisms that are intended for wide release.

3.6 Antibiotic resistance sequences in unrefined antibiotic preparations

Antibiotics used as feed additives can be in the form of incompletely refined products of bacterial fermentation. There is, therefore, a potential for them to contain, as well as the antibiotic, DNA material (coding for antibiotic resistance) derived from the antibiotic resistant bacteria used in the fermentation. This has given rise to some concern (Webb and Davies, 1993).

In contrast to the hypothetical risk of transfer of resistance from GMOs this may represent a stronger theoretical case for transfer of resistance. Potentially, there are greater quantities of DNA coded for resistance likely to be present in a crude preparation. There is also the presence of the antibiotic to concurrently provide selection pressure. There is no experimental evidence known to the Panel that would allow an accurate assessment of the risk of such theoretically possible events occurring in the field. Any theoretical assessment would vary from preparation to preparation and antibiotic to antibiotic.

However, it is postulated by the Panel that sequential exposure of gut bacteria to DNA encoding for antibiotic resistance, followed by exposure to the antibiotic in question, may be a greater theoretical risk than concurrent exposure as would occur when commercial preparations are used as AGPs. It is perhaps an issue that should be the subject of more research and should be specifically addressed in any application for licencing of an antibiotic intended for oral use.

Recommendation:

Before any antibiotic preparation is registered for use as an in-feed product, data must be provided and evaluated in terms of the hazard and risk of DNA-encoding resistance causing the transfer of that resistance to gut microflora of recipients.

4. CONTROL OF IN-FEED ANTIBIOTICS AS GROWTH PROMOTANTS

The Panel considers that regulatory control by itself will not be effective in the case of antibiotic resistance. Minimising the development of resistance to antibiotics requires an integrated system that includes a combination of responsible use and regulatory control. Regulatory authorities must impose conditions on the registration and use of antibiotics to minimise the opportunities for misuse or abuse of such products. At the same time, the parties that use antibiotics must be aware of the hazards and take personal action to use antibiotics in an informed and responsible manner.

4.1 Responsible use of antibiotics

The main means of controlling the development of resistance to antibiotics must be through responsible and prudent use. This can be achieved by education but must be backed up by effective regulation. Since the development of resistance is broadly correlated with quantities of antibiotics used, most control measures will be aimed at ensuring that no more antibiotics are used than absolutely necessary, without restricting treatment of sick animals. Estimating how much is necessary will always be subjective and will depend on the current state of knowledge. This means that continuing education of those prescribing and using antibiotics is essential.

Responsible and prudent use of antibiotics requires knowledge of:

- the drugs involved;
- the animals and husbandry systems in which the drugs will be used; and
- the actual or potential threat from pathogens.

Not all infections are bacterial and therefore susceptible to antibiotics. The Panel considers that there are some general principles that should be encouraged when using antibiotics in treating animals.

Therapeutic use

To ensure that therapeutic use is as effective as possible an accurate diagnosis must be made and an appropriate treatment selected. If the treatment includes an antibiotic, then the choice of antibiotic should be based on known or predictable susceptibility. For these reasons the Panel considers that therapeutic use of all antibiotics in animals must be under the control of a veterinarian.

Prophylactic use

When antibiotics are used to prevent disease, the risks of disease must be assessed and the most appropriate measures taken to reduce those risks. This requires knowledge of the pathology and epidemiology of the disease and the ways of manipulating husbandry practices (e.g. stocking density) as well as knowledge of antibiotics and vaccines. The Panel considers that prophylactic use of antibiotics must also be under the control of a

veterinarian. The exception is the use of ionophores to prevent coccidiosis in poultry. A lack of restrictions on ionophores is justified because:

- they pose no identified risk to human health through the development of resistance; and
- coccidia are ubiquitous in chickens.

Growth promotion use

The Panel considers that the use of antibiotics for growth promotion should be allowed provided strict registration criteria (see 4.2 below) are met. The risks to public health are minimal when antibiotic growth promotants are used according to instructions. The Panel is not prepared to suggest that this use should be under veterinary control. However, if the antibiotic resistance surveillance programme reveals that problems are emerging, there must be a system in place to control and monitor that use.

4.1.1 Educating prescribers and users of antibiotics

All those who prescribe or use antibiotics need to be aware of recent developments in knowledge of antibiotics and resistant pathogens. They should know how prescribing practices, use of antibiotics, and changes to husbandry systems can reduce the development of resistance.

Antibiotic resistance is covered in veterinary pharmacology and microbiology courses, and emphasised during clinical practice. This needs continuing emphasis in the undergraduate training of veterinarians.

Education of qualified veterinarians is largely restricted to discussions at conferences, at which attendance is variable. Much more needs to be done to draw the attention of practising veterinarians to the danger of antibiotic resistance. A simple measure that could have a large effect is to develop guidelines for prudent use of antibiotics. This has already happened overseas and in the medical profession in New Zealand. The New Zealand Veterinary Association (NZVA) is in the process of developing guidelines for veterinarians. A model for this is the British Veterinary Association's (BVA) guidelines (*Veterinary Record*, 14 November 1998: 565 - 566). As set out below, these are for the prudent use of antibiotics for the prevention of disease and not to be confused with the guidelines for use of growth promotants.

1. Antimicrobial usage should always be part of, and not a replacement for, an integrated disease control programme. Such a programme is likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination etc.
2. Continued antimicrobial use in such control programmes should be regularly assessed as to effectiveness and whether their use can be reduced or stopped.
3. Protocols should be agreed between the veterinarian and the client as to when veterinary involvement is required in ongoing disease conditions. These protocols must be regularly and frequently reviewed and updated.

4. Protocols should be agreed and documented for treatment of all endemic conditions on the farm or other livestock-rearing or production premises. These protocols must be regularly reviewed and updated.
5. Use of antimicrobials for the prevention of disease can be justified only where it can be shown that a particular disease is present on the premises, or is likely to become so, and that strategic antimicrobial use will prevent clinical outbreaks of that disease.
6. Antimicrobials need to be used with care to maintain their efficacy. Alternative methods of disease control (e.g. vaccination) should be looked for to reduce antimicrobial use.
7. Should there be recurrence of disease following successful control of an outbreak, it should be investigated thoroughly to ascertain why this has occurred and the most suitable therapy to be used.

Specific and detailed evidence-based guidelines are required for individual diseases in each species. The best people to develop these are probably the special interest branches of NZVA (the BVA has adopted this approach).

4.1.2 Guidelines for the use of growth promotants

There is also an urgent need for guidelines including the following points to govern the use of antibiotics as growth promotants.

1. Antibiotic growth promotants should be used only where husbandry, feeding and disease status are optimal. They should not be used to compensate for the growth retarding effects of disease, poor nutrition or poor housing.
2. The inclusion rates and feeding instructions must be followed.
3. There should be periodic assessment of the benefits of growth promotants as prices (feed, antibiotics and products) alter, as husbandry systems (housing, disease, management, nutrition etc.) improve, and as new information becomes available.

4.1.3 Information for rational prescribing

If the registration criteria below are met, the Animal Remedies Board (or its successor) will have useful information that has been supplied by the drug companies, but which users find difficult to access. The FDA and the EMEA publish this information on their web sites as freedom of information summaries or European Public Assessment Reports. MAF should establish a similar database, giving summaries of the registration information. It should be possible to do this in such a way as to retain trade secrets where appropriate. However, if there is a conflict between trade secrets and freedom of information, then the public interest should prevail, and the information should be published.

4.1.4 Public awareness and education

The importance of good animal husbandry in preventing disease must be continually reinforced. While the Panel considers that veterinary involvement is necessary to manage the risks of antibiotic resistance, it also considers it important to make farmers, advisers and livestock producers aware of the issues and trained in the proper use of products available directly to them. They should also be made aware of the importance of quarantine measures to prevent the introduction of antibiotic resistant strains of bacteria into production units.

The general public should also be aware of the issues. The importance of good hygiene in the kitchen and cooking food properly needs to be continually stressed because it should be possible to remove most of the threat of transfer of resistance from animals to humans if this were done. The Panel considers public awareness to be a responsibility shared by all parties (private and government) that have an interest in the safety and health of the public.

4.1.5 Veterinary drug industry

The veterinary drug industry should develop a code of practice for responsible promotion of antibiotics, since this can have a major influence on prescribing habits. The National Office of Animal Health (NOAH, the United Kingdom veterinary drug industry body) has produced a Code of Practice for the Promotion of Animal Medicines, which is similar to, but much more extensive than, Part IV of the New Zealand Medicines Act 1981.

Recommendations:

The Veterinary Council of New Zealand and the NZVA should develop and encourage the adoption of guidelines, as recommended above, for prudent use of antibiotics for therapeutic and prophylactic use, and for use as growth promotants.

MAF should establish and make available free of charge a database to provide summaries of registration information.

The veterinary drug industry should develop a code of practice for responsible promotion of antibiotics.

Producers should be encouraged to adopt quarantine procedures at production units that targets zoonotic pathogens as well as animal pathogens to minimise the chances of multi-resistant organisms getting into the food animal industry.

4.2 Regulatory control of antibiotics

The non-regulatory efforts to minimise the development of antibiotic resistance must be supported by appropriate statutory control of such products. Traditionally, the manufacture and importation of products like antibiotics have been controlled by

registration / licensing products. The Panel considers that it may be necessary to also control the sale and use of antibiotics in animals. Its recommendations regarding veterinary control of antibiotics used for therapeutic and prophylactic use reflect this perspective. The Panel considers it important for the agency responsible for registering antibiotics to establish some criteria, especially in regard to registering antibiotic for growth promotion.

The following criteria should be used to assess if an antibiotic should be registered as a growth promotant in New Zealand.

1. The product, or a functionally related product, should not be registered for use as a systemic antibiotic in human medicine in New Zealand or Australia.
2. There should be no intention that the product, or a functionally related product, is to be used in the foreseeable future as a systemic antibiotic in human medicine in New Zealand or Australia.
3. There should be no evidence that the product produces resistance or cross-resistance to systemic antibiotics used in human medicine.
4. The product should be very poorly absorbed from the animal gut, such that requirements to meet a maximum residue limit in edible produce derived from any animal fed the product are met without the need to set withholding times.
5. Use of the product as a growth promotant should not pose animal welfare hazards.
6. The product is not used as a therapeutic agent for animal disease.
7. The product should have proven efficacy as a growth promotant.
8. Use of the product as a growth promotant should not jeopardise international trade in primary produce.

The information provided by an applicant must be sufficient to determine if the above criteria have been met. The Panel considers that controlled trials should be carried out to support an application for registration. Where conditions of husbandry are significantly different in New Zealand from overseas (e.g. calf rearing), the trials must be carried out in New Zealand or under conditions similar to New Zealand.

The following criteria for the registration of antibiotics for prophylactic use should be adopted. These criteria apply only to drugs formulated for mass medication, i.e. in feed or water. Drugs formulated so that they could be administered only to individual animals, i.e. parenteral preparations, should be registered in the same way as therapeutic antibiotics.

1. The antibiotic should not be a drug (or cause cross-resistance to a drug) that is used to treat serious disease in people and for which there is no suitable alternative. Such drugs would include: fluoroquinolones, glycopeptides, streptogramins and

third generation cephalosporins. The list of drugs used for this purpose would need to be constantly reviewed in the light of the WHO's list of reserved drugs and the FDA's category I drugs.

2. Controlled clinical trials of suitable power should have identified the optimal dose and duration of treatment.
3. The drug should have been shown not to give rise to significant resistance in a range of both pathogenic and marker organisms from animal and human faeces.

Although not strictly within the terms of reference, the Panel suggests that registration of antibiotics for therapeutic use in animals should continue to be based on efficacy and safety. Where such drugs are also important antibiotics to control life threatening diseases in humans, the registration should continue to be discussed with human health authorities before it is issued.

Recommendation:

The Animal Remedies Board (or its successor) should adopt the recommended criteria for assessing whether or not an antibiotic should be registered for use in animals. The registration of all antibiotics should be reviewed every five years in the light of new scientific discoveries.

4.3 Control of imported foods

There is little point taking measures to control the use of antibiotic growth promotants in New Zealand if the public is still exposed to antibiotic resistant bacteria on food products imported from countries where antibiotic growth promotant use is widespread. At the moment, this is particularly relevant to pork.

Recommendations:

Animal products imported from countries where the animals were likely to be exposed to antibiotic growth promotants should be subjected to surveillance for antibiotic resistant bacteria in a manner similar to that required for domestic product.

Primary produce or food products derived from animals treated with a growth promotant that is not allowed to be used in New Zealand should not be allowed to be imported.

4.4 Regulatory framework

Although it is not part of the Panel's terms of reference to make detailed recommendations on the mechanics of regulation, the current situation in New Zealand gives cause for concern. At present antibiotics for use in animals are regulated under the Animal Remedies

Act 1967. This allows the Animal Remedies Board to refuse a new licence on the grounds that the “remedy is a danger to public health” (s21 (2) (d)) or if “the efficacy of the animal remedy is substantially inferior to that of other available remedies of a similar type” (s21 (2) (j)). A licence for an animal remedy may also be suspended or revoked in the light of new experience or discoveries (s28 (c)), or if “the remedy is or has become a danger to public health or animal health” (s28 (g)). It should be possible to apply the criteria for registration recommended by the Panel under the Animal Remedies Act.

However, the Animal Remedies Act is to be replaced by the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 sometime soon. The ACVM Act is specific about the risks it seeks to manage; under this Act there is no provision to ban a drug because it is a danger to public health (or because it is ineffective), unless the drug happens to be a prescription drug under the Medicines Act 1981. In that case, the Director-General of Health must consent to the action. This means that antibiotics that are not prescription medicines but may cause cross-resistance would not receive any public health consideration under the ACVM Act.

When the Animal Remedies Act is repealed, the Hazardous Substances and New Organisms (HSNO) Act 1996 will be the only legislation that attempts to regulate the public health aspects of veterinary medicines that are not prescription medicines. Since most, if not all, antibiotics that induce resistance in human pathogens do not have a hazardous characteristic as specified under that Act, they will not receive public health consideration under that Act either. As products to be used on animals they will not be considered under the Medicines Act 1981 either.

Thus, after the ACVM Act comes into force, there will be no obvious means of preventing vancomycin being sold as a growth promotant, if someone is prepared to register it. The Panel is concerned that the regulatory framework may not be adequate to manage an issue as broad in its impact as antibiotic resistance in humans from the use of antibiotics in animals.

The Panel notes that other countries regulate human and animal drugs under the same legislation and by the same agency. In the United States and Europe, veterinary and human medicines are regulated under the same laws. Registration and enforcement are carried out by the FDA and EMEA, respectively. Perhaps the simplest way to regulate veterinary medicines in New Zealand effectively would be to amend the definition of medicine in the Medicines Act 1981 to include veterinary medicines. This would certainly make coordination of the response to human and animal drug resistant bacteria easier. The alternative is to ensure that the various laws are sufficiently integrated to cope with complex issues like antibiotic resistance.

The Panel has suggested the Medicines Act as a basis for control because it also legislates for greater control of advertising, which has been shown to have a large influence over prescribing habits, at least among medical general practitioners.

Recommendation:

Urgent attention should be given to problems identified in the regulatory framework, which presents difficulties in applying some of the recommendations made in this report.

5. MONITORING AND SURVEILLANCE

The Panel's recommendations on the control of antibiotic resistance in this report are based on principles rather than in-depth risk assessments. The limited information internationally and in New Zealand make it difficult to be confident there is a significant correlation between the use of antibiotics in animals and antibiotic resistance in humans. None of the reports reviewed by the Panel included sufficient and appropriate data to make conclusive statements. Management of this issue will continue to be plagued by uncertainty until appropriate information is at hand. The Panel considers that monitoring and surveillance is crucial to managing the risks of antibiotic resistance.

5.1 Antibiotic resistance surveillance

In order 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, a coordinated programme of antibiotic resistance surveillance is required. Such a programme must form a key part of an overall objective to prolong the effectiveness of existing antibiotics. At present in New Zealand, surveillance of antibiotic resistance is limited to important human pathogens. There is only limited surveillance of antibiotic resistance in food or animal isolates. There is no formal surveillance of rural water supplies to identify resistant strains of bacteria. There is no integrated surveillance protocol that would generate data that could confirm a correlation between antibiotic use in animals and developing antibiotic resistance in humans. While drug companies have been very cooperative with the Panel, there is no ongoing analysis of antibiotic use patterns in New Zealand.

Drug companies should be asked to regularly supply data on quantities of antibiotics sold as a condition of licensing, where possible with data on species and use; veterinarians writing prescriptions should supply data on quantities, use and species. A system, preferably electronic, should be established to make this reporting as simple as possible. There should be protocols for the collection and analysis of bacteria isolates from animals, humans, primary produce, human food and rural water supplies. These should be accompanied by sufficient information about associated animal production and animal health care methods to identify trends and emerging problems. The methods of analysis should be standardised and aligned to specific surveillance objectives.

Therefore, the Panel strongly recommends the implementation of a comprehensive and coordinated New Zealand antibiotic resistance surveillance programme. This recommendation is very much in line with that made by the OIE Paris report published in March 1999. The size of the New Zealand population and the willingness of two of the major antibiotic users, medical and veterinary, to work together and coordinate their efforts, puts New Zealand in an ideal position to bring this about.

The Panel has not attempted to specify the surveillance programme in detail, as it sees this as a separate exercise for which additional resources need to be allocated. However, the Panel sets out below what are the essential objectives of a comprehensive, coordinated antibiotic resistance surveillance programme:

1. to act as the national clearinghouse and repository of key data on antibiotics for human, veterinary and food uses in New Zealand, and antibiotic resistance of bacterial isolates associated with such uses;
2. to regularly collect and statistically analyse data on antibiotic use and resistance;
3. to identify emerging trends in antibiotic resistance in New Zealand and to relate these trends to patterns of antibiotic usage;
4. to regularly disseminate, in a standardised form, the results of the statistical analyses and identification of trends to policy makers, the scientific and medical communities, and other stakeholders and information suppliers; and
5. to develop and maintain appropriate standardised methods for the measurement of antibiotic resistance in bacterial isolates from veterinary, human, food and environmental sources such as rural water supplies.

Generally, all surveillance systems have three key functions:

- collecting data;
- analysing the data; and
- regularly disseminating the results of the data analysis.

These three components are discussed separately below, and proposals for their implementation outlined. The Panel considers that a detailed proposal covering all features of the surveillance system should be agreed upon prior to the establishment of the system.

5.1.1 Data collection

Although surveillance systems should strive to be comprehensive in the data they collect, it is seldom that a surveillance system is completely comprehensive, collecting all the eligible data. Of more importance is the need for the collected data to be representative and consistent over time. The representative nature of the data is concerned with avoiding bias in the data collected. Consistency is based on the need for a system that collects similar and comparable data over time. Provided such consistency is sustained, then emerging trends in data can be detected, even though the data collected may not be absolutely complete.

Freedom from bias in the data collection can largely be ensured by comprehensive (or at least representative) participation of laboratories supplying isolates and careful specification of criteria for such supply.

In general, the Panel proposes that isolates are supplied and resistance monitoring data be obtained from the following bacteria:

- food borne pathogens and indicator bacteria in animals;
- food borne pathogens and indicator bacteria on carcasses and food, including fruit and fish;
- clinical isolates of animal pathogens;
- clinical isolates of human pathogens; and
- isolates from rural water supplies.

In order to ensure consistency of data collection there are several measures that can be put in place:

Firstly, it is important to use the same isolation techniques for each bacteria/source combination. Enrichment methods for the initial isolation of bacteria have been shown to alter the number of resistant strains obtained.

Secondly, it is also important to use a common standardised antibiotic susceptibility-testing method for bacteria isolated from humans, animals, foodstuffs and water. We therefore propose that a selection of animal and human bacteria, both pathogenic and normal flora, be collected by standardised technique, and that these be tested for their susceptibility to a battery of commonly used human and veterinary antibiotics.

Thirdly, all participating microbiological laboratories must supply isolates to the susceptibility-testing laboratory in a regular and consistent pattern. This may require additional resources and this issue will need to be addressed in the detailed design of the system. At present, there is a system for antibiotic resistance surveillance of human isolates only. The Panel proposes that, in the new surveillance system, veterinary diagnostic laboratories would be required to submit isolates of prescribed groups of bacteria that are important zoonotic organisms, as well as some selected non-pathogenic enteric organisms common to both animals and humans (indicator organisms). Enteric organisms are the most important class of bacteria common to both domestic animals and humans and, therefore, the most likely bacteria to transfer resistance. Similar generic types of bacteria should be monitored from aquacultural enterprises to ensure that this industry's use of antibiotics is not responsible for the presence of drug resistant bacteria in human or animal food. Food testing laboratories would also be asked to supply organisms of the appropriate type, isolated from submitted samples. These would be subjected to the same standard antibiogram.

The Panel proposes that the organisms to be submitted to routine antibiotic resistance surveillance be:

- *Salmonella* spp. (all isolates or a random selection);
- *Campylobacter jejuni/coli* (a proportion of isolates);
- *Yersinia enterocolitica* (all isolates);
- *Enterococci* (selected examples);
- *E. coli* (selected examples).

Fourthly, the Panel proposes that a single laboratory carry out antibiotic resistance testing of all isolates, from human, veterinary and other sources. This would have major advantages in terms of ensuring consistency of data generated, as well as general efficiency in the collation of data and operation of the surveillance system. The Panel believes that, on present evidence, the most appropriate laboratory to perform this function would be the Antibiotic Reference Laboratory at ESR's Kenepuru Science Centre. This laboratory has been monitoring antimicrobial resistance in human pathogens since 1972 and, with some additional resourcing could readily encompass bacterial isolates from veterinary and food sources. The other advantage in using this laboratory would be its co-location with ESR's Epidemiology Group, which maintains a number of national surveillance systems (including the national notifiable disease surveillance system) and has probably the most extensive experience of surveillance system operation in New Zealand.

In addition to collecting and testing bacterial isolates, a system for regular collection of antibiotic use data in medicine, veterinary practice and horticulture would need to be established.

5.1.2 Data analysis

A concise definition of surveillance is "information for action". As such, a complete surveillance system will not rely on serendipity or chance for the detection of emerging trends. It will have built-in procedures for regularly and consistently analysing the collected data in a statistically robust way that will permit ready detection of incipient trends.

The Panel would expect the system proposal to set out the analyses that would be performed and their purposes. However, it suggests that an appropriate system would routinely investigate and report on at least the following:

- changes over time in the proportions of human, veterinary, and other isolates that are resistant to various antibiotics (data would be reported separately by type of isolate, by organism, and by antibiotic);
- variations between geographic areas;
- correlation's between antibiotic usage patterns and changes in resistance patterns;
- comparison with overseas trends.

5.1.3 Dissemination of surveillance system data

For the information generated by a surveillance system to be immediately useful its regular publication and feedback to data suppliers in a standardised form is essential. Such feedback also encourages the continuing and regular supply of data (or, in this case, isolates).

The means by which such data would be made available would be set out in the detailed specification for the surveillance system. However, it is noted that the ESR: Kenepuru Science Centre already produces two publications, *LabLink* and the *New Zealand Public Health Report*, through which surveillance data are fed back to interested parties. *LabLink* already includes antibiotic resistance data for human isolates. An alternative to these existing publications would be to have a new dedicated publication or to maintain the data on an internet website.

There is also a need for an expert advisory committee that would guide the development of the surveillance system and provide interpretation of the results it produced. A multidisciplinary committee of suitably experienced medical, veterinary and food microbiologists and epidemiologists should be appropriate for these purposes. This committee could perhaps have the added responsibility of evaluating applications for registration of antibiotics for animal and other agricultural/aquacultural use.

5.2 The case for surveillance

There is an urgent need for regular and internationally recognised surveillance of both animal and human isolates. Such surveillance will enable the alarm to be raised in the event of multi-resistant *S. Typhimurium* DT 104 or other multi-resistant organisms becoming introduced into the intensive food-animal industries in this country.

If animals are found to be an important source of drug resistant bacteria for humans, the Panel would expect to find ACSSuT resistant salmonella organisms in both the animal and human populations of New Zealand. There is widespread use of antibiotics within the pig and poultry industries suggesting that animal growth promotants (AGPs) may not by themselves contribute to the level of drug resistant bacteria in humans. It is important to have the bacteria carrying these resistance genes identified and under control before a problem is created. However, the antibiotics used as growth promotants provide an antibiotic pressure that will encourage the establishment of multi-resistant organisms should they be introduced. Appropriate surveillance is necessary to identify the presence of resistant strains of bacteria.

5.3 Other enteric zoonoses

Data relating to other zoonoses in this country (e.g. *Enterococcus* spp., *Campylobacter* spp., *Yersinia* spp. and pathogenic *E. coli*) also suggest that currently there is little acquired resistance to antimicrobial agents in New Zealand when compared with the United States, United Kingdom, and the European Union as a whole. This situation, however, does not leave room for complacency and continued vigilance is required to ensure so that should resistant strains of these bacteria be introduced or emerge, action can immediately be taken to limit their spread.

Recommendation:

New Zealand should implement a comprehensive and coordinated antibiotic resistance surveillance system with the following specifications:

Data collection

Isolates should be supplied and resistance monitoring data be obtained from the following bacteria: food borne pathogens and indicator bacteria in animals; food borne pathogens and indicator bacteria on carcasses and food, including fruit and fish; clinical isolates of animal pathogens; clinical isolates of human pathogens; and isolates from rural water

supplies. The same isolation techniques should be used for each bacteria/source combination. Standardised antibiotic susceptibility-testing method should be used for bacteria isolated from humans, animals, foodstuffs and water.

A single laboratory should carry out antibiotic resistance testing of all isolates, from human, veterinary and food sources. All participating microbiological laboratories should supply isolates to the resistance testing laboratory in a regular and consistent pattern.

Data analysis

Detailed proposals should precede the establishment of the surveillance system to set out the analyses that would be performed and their purposes. All analyses should comply with the agreed protocols.

Dissemination of surveillance system data

Information should be generated by the surveillance system to be regularly published in a standardised form. Both sale and use of antibiotics should be monitored by the Animal Remedies Board (or its successor).

6. CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

From the earliest days in the history of antibiotic use, it has been known that certain microorganisms were resistant to the action of some antibiotics. Resistance was first envisaged as a natural property that was intrinsic to certain bacteria. Later it was found that resistance could develop in bacterial populations as a result of selection pressure provided by the exposure to antibiotic. Then came the observation that resistance could also be transferred by transfer of genetic fragments from one bacterium to another.

As the potential consequences of this situation became more fully appreciated, concern was expressed that the evolution of resistance could soon outstrip the rate at which the pharmaceutical industry could develop new antimicrobial agents.

Although the use of antibiotics in human medicine is acknowledged as being the greatest cause of evolving antibiotic resistance in bacteria causing human disease, it is important that the role of all antibiotic use comes under scrutiny. All use, whether for treatment of human or animal disease, for growth promotion of livestock, for horticulture, or for the human food industry is part of the antibiotic landscape. Each component and its impact must be measured in the context of any emerging resistance problem.

There is a perception among many, supported by some scientific work, that the effectiveness of “lifesaving” antibiotics for human use could be prejudiced by the use of antibiotics as an additive to the feed of farm animals. There is a parallel risk that antibiotics now used by veterinarians for the treatment of important animal diseases may also become less effective and have important consequences in animal welfare. The Panel has determined that, although there is yet no evidence that either of these phenomena are happening in New Zealand, it believes that it is prudent and responsible to act before the potential problem becomes reality and it is too late for reversal.

Each of the important “in-feed” administered antibiotics has been examined by the Panel in terms of their potential to cause a problem and, where necessary, control measures have been recommended. The view was taken that attempts to make formal quantitative risk assessments as in the Australian (JETACAR) report were not justified because of the lack of good data. Nevertheless, the Panel did determine that theoretical probabilities and consequences of transfer of resistance were greater for the use of some products than others. The Panel has also specified more general criteria that should be applied before national decisions are made on the use or otherwise of any in-feed antibiotic.

The importance of education on proper use is strongly emphasised. Because changes aimed at preventing the emergence of resistance are proposed, it is vital that a comprehensive surveillance programme be instituted so that the effectiveness of change can be monitored. Policies must be continually assessed against high quality surveillance

data on resistance and appropriate recommendations made. An overarching expert committee on antibiotic resistance must be established for this purpose.

Characteristically, New Zealand raises its large population of ruminant animals at pasture. Only the intensively housed and fed poultry and pig industries are significant long-term users of in-feed antibiotics. Control measures applied to our domestic industries should also be reflected in the quality assurance provisions for any imported product. The Panel has the view that, particularly for the pig and poultry industries, quarantine measures at farm units and nationally at borders have an important role to play in preventing the introduction of multi-resistant bacteria such as certain strains of salmonella which have plagued livestock industries overseas. Continuous in-feed use of antibiotics in farm animals can easily mask suboptimal rearing practices and inadequate preventive health care. National quarantine policies have undoubtedly kept New Zealand animal industries free of some important diseases that would otherwise have triggered an increased use of in-feed antibiotics.

6.2 Recommendations

The recommendations from the Panel can be divided into five areas:

- overview and ongoing assessment;
- monitoring and surveillance;
- control of antibiotics;
- use of specific antibiotics; and
- peripheral issues.

Overview and ongoing assessment

1. An overarching national antibiotic resistance review committee should be established to collect and assess information and make appropriate recommendations.

Monitoring and surveillance

2. New Zealand should implement a comprehensive and coordinated antibiotic resistance surveillance system with the following specifications:

Data collection

Isolates should be supplied and resistance monitoring data be obtained from the following bacteria:

- food borne pathogens and indicator bacteria in animals;
- food borne pathogens and indicator bacteria on carcasses and food, including fruit and fish;
- clinical isolates of animal pathogens;
- clinical isolates of human pathogens; and
- rural water supplies.

The same isolation techniques should be used for each bacterium/source combination. Standardised antibiotic susceptibility testing methods should be used for bacteria isolated from humans, animals, foodstuffs and water. A single laboratory should carry out antibiotic resistance testing of all isolates, from human, veterinary and food sources. All participating microbiological laboratories should supply isolates to the resistance-testing laboratory in a regular and consistent pattern.

Data analysis

Detailed proposals should precede the establishment of the surveillance programme to set out the analyses that would be performed and the purposes for that analysis. All analyses should comply with the agreed protocols.

Dissemination of surveillance system data

Information should be generated by the surveillance programme and be published regularly in a standardised form.

3. Sale and use of antibiotics should be officially monitored by the Animal Remedies Board (or its successor).

Control of antibiotics

4. The Veterinary Council of New Zealand and the New Zealand Veterinary Association should develop and encourage the adoption of guidelines, as recommended in this report, for prudent use of antibiotics for therapeutic and prophylactic use, and for use as growth promotants.
5. MAF should establish and make available free of charge a database to provide summaries of registration information.
6. The veterinary drug industry should develop a code of practice for responsible promotion of antibiotics.
7. Producers should be encouraged to adopt quarantine procedures at production units that target zoonotic pathogens as well as animal pathogens to minimise the chances of multi-resistant organisms getting into the food animal industry.
8. The Animal Remedies Board (or its successor) should adopt the recommended criteria for assessing whether or not an antibiotic should be registered for use in animals.
9. The registration of all antibiotics should be reviewed every five years in the light of new scientific information.
10. MAF should carry out quarantine procedures at the border that target zoonotic pathogens as well as animal pathogens to minimise the chances of multi-resistant organisms being introduced into New Zealand.

11. Animal products imported from countries where the animals were likely to be exposed to antibiotic growth promotants should be thoroughly checked at the port of entry for bacteria resistant to a range of antibiotics.
12. Primary produce or food products derived from animals treated with a growth promotant that is not allowed to be used in New Zealand should not be allowed to be imported.
13. Urgent attention should be given to problems identified in the regulatory framework, which presents difficulties in applying some of the recommendations made in this report.

Use of specific antibiotics

14. ***Macrolides***

Tylosin, tiamulin and other similar drugs should be reserved for use in the food animal industry for prophylactic and therapeutic purposes, and only under veterinary prescription.

Macrolides should not be used for growth promotion under any circumstances.

Other methods than administering macrolides for promoting growth and disease prevention in animals should be explored and encouraged.

15. ***Bacitracin***

The use of bacitracin should be retained, but only under veterinary prescription, for the prophylaxis of clostridial disease in poultry and pigs. Bacitracin should not be used for growth promotion. Registration of bacitracin should be reassessed if surveillance shows that its use may be associated with an increase in vancomycin resistant enterococci.

16. ***Avoparcin***

The use of avoparcin for growth promotion and prophylactic use in animals should be discontinued.

17. ***Virginiamycin***

The use of virginiamycin for growth promotion and prophylactic use in animals should be discontinued.

18. ***Ionophores***

The use of ionophores should continue as “over the counter” (OTC) products as at present.

19. ***Flavophospholipol***

Flavophospholipol should be reassessed according to the registration criteria recommended by this report.

20. ***Quinoxalines***

Quinoxalines could remain available as “over the counter” (OTC) products as at present. However, it is suggested that the issues of toxicity and carcinogenicity, particularly in regard to those handling these products, be considered in any review of their continued suitability for animal use.

21. ***Fluoroquinolones***
Fluoroquinolones should be available (in injectable or tablet form) only for the treatment of serious infections in individual animals. Veterinarians should be encouraged not to use fluoroquinolones for any use where another antibacterial drug is likely to be effective.
22. ***Avilamycin***
Avilamycin should be retained as a growth promoter but its licence should be reviewed annually.

If SCH27988 progresses beyond phase 3 trials in people, then avilamycin should be withdrawn as a growth promoter.

Peripheral issues

23. Horticultural produce treated with streptomycin should be carefully monitored by food safety authorities for violative residues.
24. The national antibiotic resistance surveillance programme should include, within its terms of reference, a study of the effects upon antibiotic resistance patterns related to the incorporation of antibiotics in or on human foodstuffs.
25. Because of their potential impact upon human food and water consumption, the recommended national antibiotic resistance surveillance programme should include within its terms of reference a horizontal study of antibiotic resistance patterns of the bacteria in rural water supplies.
26. The recommended national antibiotic resistance surveillance programme should include within its terms of reference a study of antibiotic resistance patterns of the bacteria related to the fish farming industry.
27. The risk assessment of any importation of fish or fish product must include within its measurement, factors related to the importation of diseases or bacteria which have the potential to increase the use of antibiotics in any current or proposed fish farming industry in New Zealand.
28. As a precautionary approach, the Panel supports avoidance of antibiotic markers in the development of genetically modified organisms that are intended for wide release.
29. Before any antibiotic preparation is registered for use as an in-feed product, data must be provided and evaluated in terms of the hazard and risk of DNA-encoding resistance causing the transfer of that resistance to gut microflora of recipients.

7. ABBREVIATIONS

ACSSuT

Resistance to Ampicillin, Chloramphenicol, Streptomycin, Sulphonamide and Tetracycline

EMA

European Medicines Evaluation Agency

ESR

Environmental and Scientific Research Crown Research Institute

FDA

United States Food and Drug Administration

JETACAR

Joint Expert Technical Advisory Committee on Antibiotic Resistance

MIC

Minimum inhibitory concentration

NCCLS

National Committee for Clinical Laboratory Standards

OIE

Organization International des Épizooties

OTC

Over the counter

SCAN

Scientific Committee for Animal Nutrition

VRE

Vancomycin resistant enterococci

VREF

Vancomycin resistant *Enterococcus faecium*

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