The use of antibiotics in food-producing animals:

antibiotic-resistant bacteria in animals and humans

Report of the
JOINT EXPERT ADVISORY COMMITTEE
ON ANTIBIOTIC RESISTANCE
(JETACAR)

COMMONWEALTH DEPARTMENT OF HEALTH AND AGED CARE
COMMONWEALTH DEPARTMENT OF AGRICULTURE, FISHERIES AND FORESTRY — AUSTRALIA

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The Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) was established in April 1998 by the Commonwealth Department of Health and Aged Care (formerly the Department of Health and Family Services) and the Commonwealth Department of Agriculture, Fisheries and Forestry — Australia (formerly the Department of Primary Industries and Energy)

Prepared for JETACAR by Biotext, Canberra

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Dear Ministers

On behalf of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) I have pleasure in presenting to you a report responding to your request for recommendations for the appropriate future management of antibiotic use in food-producing animals.

The Committee has examined a wide range of scientific literature and consulted key stakeholders in the preparation of the report and in determining the recommendations.

JETACAR considered the whole area of the occurrence of antibiotic resistance and its importance in human and veterinary medicine. The committee agreed that there was evidence for:

- the emergence of resistant bacteria in humans and animals following antibiotic use;
- the spread of resistant animal bacteria to humans;
- the transfer of antibiotic-resistance genes from animal bacteria to human pathogens; and
- resistant strains of animal bacteria causing human disease.

The recommendations of the report provide strategies for responding to these conclusions. The committee recognised that there are funding implications for several of the recommendations and developed preliminary ideas for addressing these. I would be happy to appraise you of these after you have considered the report.

While many individuals have contributed to the outcomes of the Committee, I should particularly like to acknowledge the efforts made by Dr Janet Salisbury.

Attached is the report of the Committee for your consideration.

Given the very high level of interest in the contents and recommendations of the report among stakeholders and the public, I would like to recommend to you that the report be released at your very earliest convenience.

John Turnidge

Associate Professor John Turnidge
Chairman
Joint Expert Technical Advisory Committee on Antibiotic Resistance

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Membership of JETACAR

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Assoc. Professor John Turnidge (Chair)	Medical infectious diseases and microbiology
Dr Mary Barton	Veterinary microbiology and infectious diseases
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Executive summary

Background

The increasing prevalence of antibiotic-resistant bacteria is a public health issue of major concern. Essential, life-saving, antibiotics are becoming less effective and there are fewer alternatives available for treatment.

Antibiotics are used for treatment and prevention of infectious diseases in humans and in domestic and food-producing animals, including fish. If bacteria become resistant, the antibiotics become ineffective. In food-producing animals, some antibiotics are used for growth promotion and improving feed efficiency in situations where animals are intensively reared, including poultry, pigs, and feedlot cattle.

The use and overuse of antibiotics in human medicine is well recognised and is the major factor contributing to the development of antibiotic resistance. However, the use of antibiotics in food-producing animals, particularly as growth promotants, has recently received increasing attention as a contributory factor in the international emergence of antibiotic-resistant bacteria in humans.

In December 1997, the then Australian Minister for Health and Family Services and the then Minister for Primary Industries and Energy agreed to establish a joint expert committee with representatives from both health and agriculture to examine the issue from a scientific perspective. The Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) was appointed in April 1998 and is made up of experts from public health, human medicine, veterinary medicine, molecular biology and primary industries.

The terms of reference for the committee were broadly to review the scientific evidence on the link between the use of antibiotics in food-producing animals, the emergence and selection of antibiotic-resistant bacteria and their spread to humans; and to develop evidence-based recommendations for the appropriate future management of antibiotic use in food-producing animals.

Shortly after the committee was first convened, 52 key stakeholders were invited to provide input in the form of scientific data and practical advice. The 23 submissions received were reviewed by the committee and taken into consideration in the development of this report. When the draft report had been prepared in March 1999 it was circulated to all the key stakeholders for comments and a further 35 submissions were received. The committee considered these responses and changes were incorporated into this final report to take account of the comments.

Scientific background, regulatory controls and usage data

JETACAR reviewed the internationally available information on the nature of antibiotics, and the molecular basis of bacterial resistance. The bacteria known to be involved in transfer from food-producing animals, and those recognised as the cause of medical conditions of most concern in relation to treatment failure due to antibiotic resistance, were also identified. Priority medical problems potentially arising from, or exacerbated by, the use of antibiotics in livestock production, were identified. The benefits of antibiotic use in animals were also reviewed and alternatives canvassed.

Focusing on Australian information, the committee reviewed current regulatory controls and use patterns of antibiotics in humans and animals and antibiotic-resistance patterns in humans. Few data on antibiotic resistance were available for animal isolates in Australia.

The information collected was incomplete, as there are many gaps in the data available and in the current scientific knowledge of the mechanisms involved. The overall findings are shown below.

Antibiotics and antibiotic resistance

In the context of this report, antibiotics are chemical agents that kill or inhibit the growth of bacteria. In response to antibiotic use, resistance has emerged for all known antibiotics in use. For most antibiotics, and classes of antibiotics, antibiotic-resistance genes have also entered the bacterial population in the domains where antibiotics are used (eg hospitals, farms, aquaculture ponds). Resistant bacteria and the resistance genes they carry are selectively amplified by antibiotic exposure. This increases the prevalence of resistant bacteria in the total bacterial population and large pools of resistant bacteria and resistance genes are built up where formerly they were rare.

As the overall selection pressure is related to the total amount of antibiotics used, long-term exposure to antibiotics and treatment of large numbers of humans or animals provides greater selective pressure than short-course treatment of a single individual or a small number of individuals. The resistant bacteria are then able to spread from one host to another (human to human, animal to animal, animal to human or human to animal), either by direct contact or, in the case of bacteria of animal origin, via the food chain. Resistant bacteria and resistance genes can also be spread quite rapidly around the world, making antibiotic resistance an international issue.

Bacteria

Salmonellae and campylobacters are zoonotic bacteria that spread easily between animals and humans in contaminated food (mainly meat, eggs, milk) and water, or by direct contact (including faeces). They may be carried asymptomatically by people and animals. Nontyphoid salmonellae are an important cause of enteritis (and more generalised infections) in animals and of gastroenteritis in people. Occasionally, other more serious infections occur (eg bacteraemia, infection of internal organs). Some strains may colonise animals or humans over the longer

term but most are transient infectious agents. Overseas (United Kingdom, Europe, United States), a multiresistant strain of *Salmonella* Typhimurium DT104, which was first isolated from cattle, has become more prevalent in the last 10 years. *Campylobacter jejuni* and *C. coli* (thermophilic campylobacters) are rarely pathogenic in animals but are the most commonly notified cause of gastroenteritis ('food poisoning') in people in Western countries.

Escherichia coli and enterococci are common commensal bacteria in animals and humans. They can be transferred from animals to humans in food and water or by contact and may colonise transiently. Although usually harmless, these bacteria sometimes cause serious gastrointestinal, urinary, abdominal and bloodstream infections, especially in surgical or immunocompromised patients. Although there are strain differences between long-term colonisers of animals and humans, it is hypothesised that resistance genes might be passed from animal strains to human strains even during transient passage through the gut.

Some enterococci (which are naturally multiresistant) have now acquired resistance to the glycopeptide antibiotic vancomycin and are difficult to treat with any antibiotics. Scientific studies overseas have linked the emergence of one type of vancomycin-resistant enterococci (VRE) in humans to the routine use of a structurally related antibiotic, avoparcin, as a growth promotant in food-producing animals. In the last five years, the prevalence of VRE has increased rapidly in the United Sates, Europe and other countries. Notably, avoparcin has not been used in the United States. To date there have been over 70 strains or clusters of strains isolated from humans in Australia and the numbers are steadily increasing. However, it is unclear how VRE entered or emerged in Australia but most of the VRE identified so far are of a type not linked at this stage to avoparcin use in animals.

Regulatory controls

Australia has strict registration procedures for veterinary antibiotics that include a special evaluation requirement for information relevant to antibiotic resistance (the United States appears to be the only other country that currently has such a requirement). This conservative approach has resulted in the prohibition or severe limitation of the use of certain antibiotics in food-producing animals (eg fluoroquinolones, cephalosporins, gentamicin, chloramphenicol, nitrofurans and carbadox).

However, importers and feed-millers are not licensed (except for two licensed feed-mills in Tasmania) and there is no clear chain of audit for antibiotic substances supplied to the feed-miller or home-mixer. Also, while 'off-label' use is a desirable practice to service the animal health and welfare of minor animal species, there is a need for appropriate restrictions on antibiotic use to be enforceable in all States/Territories. Legislation relating to the use of veterinary chemical products varies considerably between States/Territories, allowing differences in application of off-label prescribing by veterinarians, which can sometimes be inappropriate. However, adherence to NRA label statements should not preclude appropriate off-label use.

At present a number of antibiotics (mainly growth promotants and prophylactics) are available as 'open sellers'; that is, purchased and used by farmers, usually without the intervention of a veterinarian.

Use patterns in humans and animals

On average, Australia imports about 700 tonnes of antibiotics each year. About one-third is for human and two-thirds for veterinary use, with most of this for addition to stockfeed for prophylactic and growth promotant purposes or for coccidiosis (protozoan) control. Some protozoan diseases, such as coccidiosis in poultry, are controlled by drugs with antibiotic activity.

Humans. In humans, most antibiotics are given for treatment of minor infectious illness, and much treatment, especially for respiratory tract infection, is unnecessary. As prescription is usually on an empirical basis (ie without a definitive diagnosis of the infecting organism), antibiotics with a broader spectrum than might otherwise be needed are frequently selected. However, rapid and effective treatment is essential in some serious infections (eg bacteraemia, heart, bone infections) as, in these cases, infection with antibiotic-resistant bacteria can be life threatening. Occasionally, antibiotics are given to groups of people as prevention against an infectious epidemic. Individual prophylactic use is also quite common, particularly in hospitals, as prevention against infection (eg before bowel cancer or hip replacement surgery). Long-term treatment and prophylaxis are less common, and apart from acne control, antibiotics are not used at subtherapeutic doses.

Animals. For extensively grazed livestock and pets, treatment is on a similar basis to humans. For most intensively farmed food-producing animals (eg chickens, pigs, feedlot cattle and some fish), however, antibiotics are more often given to groups of animals within a herd/flock in feed or water, either as treatment for an outbreak of disease or as prophylaxis against common life-threatening or production-threatening infections because it is not convenient to treat such animals individually. Antibiotic supplements at subtherapeutic doses are commonly added to feed to increase growth and reduce feed requirements (growth promotion), to prevent disease or to control protozoan diseases such as coccidiosis (see above).

Benefits of antibiotic use in animals

Veterinary requirements for the treatment of established infections are similar to those of human medicine for reasons of animal welfare and disease control. There are also a number of diseases that are prevalent in the intensive industries that pose a threat to animal health and welfare and to productivity (eg necrotic enteritis in meat poultry). Antibiotics have traditionally played an important preventive (prophylactic) role in the latter situation

The economic benefits of antibiotics that promote growth and reduce feed requirements in intensive food-producing animal production were substantial at the time of their introduction 30 years ago. With significant advances in animal husbandry, genetics, disease control and nutrition, antibiotic growth promotants are now only one of the means of improving productivity. However, even with growth promotion and feed conversion benefits of between 3 and 5% there are

environmental benefits from growth promotant use, such as reduced animal numbers, reduced pollution and reduced pressure to clear land for animal production, that have to be considered. In addition, some 'growth promotants' registered in Australia have other roles in some animal species (eg for prophylaxis or as coccidiostats) and their growth promotion benefit is less important.

International perspective

Therapeutic/prophylactic use. The use of fluoroquinolones is currently an international issue for therapeutic use of antibiotics in animals. They are widely available in most countries for food-producing and companion animals. The emergence of fluoroquinolone resistance in campylobacter isolated from human infections in The Netherlands raised the suspicion of an association with food-producing animals. In the United States, two fluoroquinolone antibiotics were recently licensed for poultry and cattle use, but a condition of licensing is that there is intensive surveillance for resistance emergence. The issue was discussed at a meeting organised by the World Health Organization (WHO) in 1998, where it was agreed that there was an urgent need to develop prudent use principles for antibiotic use in food-producing animals and to curb the indiscriminate use of fluoroquinolones. Fluoroquinolones are not registered for use in food-producing animals in Australia.

Growth promotion. With the emergence of VRE and the possible link to avoparcin use in food-producing animals, there has been intensive international debate about the role of growth promotants, culminating in a meeting organised by the WHO in Berlin in 1997, which recommended the 'termination' of growth promotants with human health implications. Sweden stopped using growth promotants in 1986 and has been seeking to maintain this status within the European Union. It claims that reduced antibiotic use in food-producing animals has resulted in long-term benefits from a reduction of the prevalence of antibiotic resistance in animal bacteria. In Europe, a two-year suspension was placed on the growth promotant use of avoparcin in 1997. In response to further lobbying and scientific assessment, the growth promotant use of four other antibiotics (virginiamycin, tylosin, spiramycin and bacitracin) has been suspended in Europe with effect from July 1999 and the avoparcin suspension has been extended. In the United States and Canada, avoparcin has never been licensed and all growth promotants are now receiving scrutiny. Avoparcin, virginiamycin, tylosin and bacitracin are all used in Australian livestock production.

Residues

Use of antibiotics in food-producing animals can result in detectable levels of antibiotic residues at slaughter or milking. The possible adverse health effects caused by the transfer of such residues to humans in food products was briefly considered because concerns have been expressed in the community that residues in animal products may cause toxicity (very rarely), allergenicity or possibly lead to the generation of antibiotic resistance in bacteria in humans.

Australia sets maximum residue limits (MRLs) permitted in food (after conducting a dietary exposure evaluation), recommends withholding periods based on good agricultural and veterinary practice, and monitors compliance through the National Residue Survey. Compliance with antibiotic MRLs in the

last five years has been excellent in cattle, sheep and poultry. A slightly higher level of non-compliance with antibiotic MRLs in pigs reflects the therapeutic and prophylactic antibiotic use patterns in this industry in order to control respiratory diseases (particularly tetracyclines). There is no evidence to confirm or refute the selection of resistant bacteria in the human gastrointestinal tract after ingestion of antibiotic residues or of increases in resistant bacteria in the food due to the presence of residues. However, the importance of residues in the generation of antibiotic resistance remains to be established but is likely to be low.

Costs of antibiotic resistance

In Australia, the costs of antibiotic resistance in human medicine, eg the need to use more expensive antibiotics, multiple courses of antibiotics, increased length of hospital stay, increased morbidity and mortality, are largely borne by the government and by patients. These costs have not been systematically investigated to date but, based on a preliminary study from the United States, would be substantial.

Assessment of evidence

In developing this report JETACAR took account of current risk analysis methodology, which includes risk assessment as one of its components. **However, it must be stressed that this report does not include a formal risk assessment because such a process is more appropriately applied to the assessment of individual antibiotics**. Rather, JETACAR attempted to provide:

- an evidence-based hazard characterisation for antibiotic use in food-producing animals;
- a framework for the future development of risk assessment methodology for individual drugs; and
- the basis for the development of an integrated antibiotic-resistance management strategy.

Hazard identification

JETACAR considered the hazard posed by the use of antibiotics in food-producing animals on the basis that antibiotic-resistant animal bacteria may infect humans directly and/or transfer their resistance genes to human pathogens, causing subsequent failure of treatment for serious infections.

Hazard characterisation

The spread of antibiotic-resistant zoonotic or commensal bacteria from animals to humans is through the food chain (meat or vegetables contaminated with animal bacteria), the environment (eg water contamination) or direct contact with animals. Humans can also acquire antibiotic-resistant bacteria by the spread of antibiotic-resistant pathogenic or commensal bacteria between humans in the community or in hospitals, through the food chain (eg contamination by food handlers), the environment (eg water contamination), direct contact between humans, or spread by health care workers.

Selection of resistant pathogenic or commensal bacteria during antibiotic treatment, prophylaxis, or other antibiotic exposure in either animals or humans can greatly amplify the number of resistant bacteria present. Transfer of antibiotic-resistance genes between different bacteria either in animals or in humans can further disseminate the resistance genes between different types and strains of bacteria.

Exposure through the food chain arises from bacterial contamination of food that is uncooked (eg salads), not adequately cooked or recontaminated following cooking. The widespread existence of antibiotic-resistant bacteria allows food from many sources to be contaminated. However, the transfer of antibiotic-resistant bacteria along the meat chain is believed to be one of the most significant sources of antibiotic-resistant bacteria from animals. Others include use of animal manure for vegetable production, contamination of water, etc.

International travel and the increasing international trade in food enable bacteria to be spread between nations and continents, and introduced into new environments. This means that there has to be international coordination as well as national action to control antibiotic resistance.

Spread of antibiotic resistance from animals to humans

An assessment of the quality of evidence for a link between antibiotic use in animals, emergence of antibiotic-resistant bacteria, and infectious diseases in humans due to spread of such antibiotic-resistant bacteria and transfer of their resistance genes to human bacteria, was necessary. JETACAR therefore commissioned an independent systematic review of the international scientific literature for four key bacterial pathogens —*Salmonella*, *Campylobacter*, *Escherichia coli* and *Enterococcus*. The evidence assessed in the literature review was rated according to a modification of the National Health and Medical Research Council (NHMRC) four-point scale (initially developed for assessment of clinical interventions).[1]

It is important to appreciate that levels of evidence higher than III-2 are unlikely ever to be possible for epidemiological studies of the emergence, spread or transfer of antibiotic resistance from animals to humans. This is because higher levels of evidence (levels I or II) require experimental studies with randomised treatment and control groups, which cannot replicate natural events occurring over many years, or which are unethical to carry out because they place participants at unacceptable risk. This situation is similar to identifying the causes of heart disease or cancer in humans, which also cannot be proved with evidence of greater than level III-2.

In the case of antibiotic resistance, however, much of the evidence is from sophisticated molecular typing methods, which, although 'observational' in nature, have the power to accurately trace antibiotic-resistant bacteria and their

[1] Levels of evidence have been modified from the NHMRC 4-point rating scale (initially developed for rating evidence for clinical interventions), where level I evidence is the highest rating (randomised controlled trials) and level IV is the lowest (professional opinion based on experience, descriptive studies, etc). The full definitions, as modified for use in this review, are given in Table 5.1 (Section 5.1).

resistance genes (these studies were designated level III-1 by the JETACAR literature review).

Overall, the JETACAR literature review found that there is qualitative evidence that antibiotics fed to animals leads to resistant bacteria and that these bacteria or their resistance genes are passed on to humans, principally via the food chain. The conclusions of the JETACAR literature review were similar to those of the MAFF and CAFA reviews. The levels of evidence were higher for some bacteria and antibiotics than for other bacteria and antibiotics. The committee accepted the findings of the JETACAR literature review, noting the degree of concurrence with other the other international reviews.

There is less information on the frequency with which resistance is passed on to humans. Such information would be valuable for formal risk assessment. Nevertheless, based on the information presented in this report, it may be possible to develop semiquantitative assessments for many bacteria and antibiotics.

Exposure assessment and risk characterisation

Overall, the risk to human health from antibiotic-resistant bacteria in food-producing animals is a dynamic process driven by such factors as the level of exposure to antibiotics, the level of infection or exposure of humans to bacteria from animals and the health status of the infected humans. The treatment and hygienic measures adopted in clinical medicine influences whether such resistant bacteria can also become established in health care settings.

The risk characterisation component of a formal risk assessment is normally based on dose–response, exposure or some other measure related to health outcomes. In the case of antibiotic use in food-producing animals and humans, three elements of exposure were identified:

- exposure of animals and humans to antibiotics (antibiotic 'load' and pattern of use [regimen]);
- exposure of animals and humans to antibiotic-resistant bacteria (bacterial 'load'); and
- exposure of bacteria to antibiotic-resistance genes (prevalence of bacteria with antibiotic-resistant genes).

Risk characterisation based on these three types of exposure would involve detailed information on, among other things, antibiotic use and the relationship between antibiotic exposure and development of resistance for different antibiotic–bacterium combinations over time; level of human exposure to bacteria from animals and the likelihood of disease and/or colonisation occurring; the prevalence of antibiotic-resistance genes in animal and human bacterial populations; and the rate of transfer of antibiotic-resistance genes between bacterial populations in different situations.

Such specific data are generally not available and at this stage it was therefore not possible for JETACAR to undertake a formal risk assessment. In addition, such an assessment would only be possible for individual antibiotic–bacterium combinations on a case-by-case basis.

It was, however, possible to identify a conceptual framework for a qualitative risk assessment method to be developed and validated in the future, including the following elements.

- *Antibiotic 'load'* — the number of resistant bacteria increases with increased use of antibiotics because, once antibiotic-resistant bacteria are present in a bacterial population, they are amplified by exposure to antibiotic(s) that select or coselect them.

- *Antibiotic regimen* — frequent exposure of bacterial populations to antibiotics increases the selection pressure for resistant bacteria. Long-term lower-dose use may increase populations of resistant bacteria more than short-term high-dose use.

- *Bacterial 'load'* — the risk of spread of antibiotic-resistant bacteria is more likely and transfer of antibiotic-resistance genes from animal bacteria to human bacteria is higher if there is a large pool of resistant bacteria infecting or colonising food-producing animals, making cross-infection common and transfer of antibiotic-resistance genes between bacterial populations more likely. Bacterial 'load' can be reduced if high standards of hygiene are maintained in the food supply.

- *Prevalence of resistant bacteria* — the risk of spread of antibiotic-resistant bacteria and/or transfer of antibiotic-resistance genes between animals and humans increases as the prevalence of resistant bacteria increases.

Uncertainties surround all these factors because of a lack of specific data (eg antibiotic exposure levels of different populations of animals and humans; host specificity of bacterial strains; prevalence of resistant bacteria and/or resistance genes in particular bacterial populations). Collection of this data must, therefore, form the cornerstone of any management plan to enable future risk assessment of antibiotics on a case-by-case basis.

Such a qualitative assessment method will also need to include assessment of the status of the antibiotic or group of antibiotics for treatment of critical human or animal conditions (ie whether the antibiotic is identical for a particular treatment or if alternative antibiotics are available). A ranking of antibiotics according to how important they are for human medicine has therefore been proposed in which category A drugs are considered critical antibiotics for human treatment. The utmost care is required not to introduce or amplify antibiotic-resistant bacteria or genes to these antibiotics into the human bacterial population. Antibiotics for which there are other alternatives for treatment of serious human conditions can be ranked as less important in terms of emergence of antibiotic-resistant bacteria (categories B and C). The same consideration can be given to antibiotics needed for treatment of serious animal diseases.

Overall conclusion

JETACAR considered the whole area of the occurrence of antibiotic resistance and its importance in human and veterinary medicine. The committee agreed that there was evidence for:

- the emergence of resistant bacteria in humans and animals following antibiotic use;
- the spread of resistant animal bacteria to humans;
- the transfer of antibiotic-resistance genes from animal bacteria to human pathogens; and
- resistant strains of animal bacteria causing human disease.

The levels of evidence were variable for the various bacteria and antibiotic combinations. The committee noted that new evidence has continued to emerge on these issues since the literature review was completed in late 1998 and that these data generally reinforce the case that antibiotic use in animal production can affect human health.

The committee agreed that it was important to report these matters to government and to make a series of recommendations about the use of antibiotics in human and veterinary medicine because remedial action taken now can reduce future adverse effects. The committee also noted that a number of other countries have taken action on the same basis.

Resistance management program and recommendations

Based on the scientific findings outlined above, and the four factors that influence emergence and spread of antibiotic-resistant bacteria (antibiotic load, antibiotic regimen, bacterial load and prevalence of resistant bacteria), JETACAR developed an antibiotic-resistance management program that focuses simultaneously on human and animal use of antibiotics in Australia. The proposed program is a coordinated multidisciplinary approach with five key elements, as follows:

- regulatory controls (Recommendations 1–9)
- monitoring and surveillance (Recommendations 10 and 11)
- infection prevention strategies and hygienic measures (Recommendations 12–14)
- education (Recommendations 15–17)
- further research (Recommendation 18)

The basics of this 'five-point plan' are equally applicable to human and veterinary medicine, as well as other areas of antibiotic use. All five elements of the program must be implemented together if there is to be any chance of reversing the trend to increasing antibiotic resistance.

In addition, further recommendations are included on communication of the issues surrounding antibiotic-resistance management to stakeholders and the general public (Recommendations 19 and 20). The overall coordination of the strategy is covered in Recommendations 21 and 22.

Regulatory controls (Recommendations 1–9)

Antibiotic 'load' and exposure in Australia can be managed in human and veterinary medicine by tightening the regulatory controls over registration (including data requirements), imports and end-use regulations (including open-selling antibiotic products and off-label uses).

It is important that the intensive animal industries are not economically disadvantaged by the sudden removal or severe limitation of veterinary chemical products that are of importance to production as a result of recommended National Registration Authority (NRA) reviews. Phasing out of in-feed antibiotics that do not fulfil recommended criteria and that fail to pass review would provide the intensive industries with time to readjust while they seek alternative measures to remain internationally competitive.

While veterinarians have the right to prescribe veterinary chemical products, including antibiotics, with due precautions, there is inconsistency in the enforcement of specific NRA label restraints, such as 'not to be used in food-producing animals' across Australia. Observance of specific NRA label restraints is mandatory in some States and Territories but not in others.

It is also important that the regulatory processes for antibiotics be identical or very similar for human and veterinary drugs and that microbial resistance safety is formally assessed as part of the evaluation of antibiotics for human as well as for animal use.

Recommendation 1

That Australia adopt a conservative approach to minimise the use of antibiotics in humans and animals and, to further this policy, that in-feed antibiotics used in food-producing animals for growth promotant purposes, or other routine uses where duration and dose level are the same, or very similar, should not be used unless they:

- **are of demonstrable efficacy in livestock production under Australian farming conditions; and**
- **are rarely or never used as systemic therapeutic agents in humans or animals, or are not considered critical therapy for human use; and**
- **are not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms.**

Recommendation 2

That the National Registration Authority (NRA) reviews the use of antibiotic growth promotants currently registered in Australia that do not appear to fulfil the criteria listed in Recommendation 1 in terms of their impact on human and animal health, using a risk analysis approach, including a cost–benefit analysis. The priority determined

should be consistent with recent international reviews and use the conditions outlined in Recommendations 1 and 4.

It is recommended that the priority of the review at this stage be:

1. **glycopeptides (avoparcin is currently under review by NRA)**
2. **streptogramins (virginiamycin)**
3. **macrolides (tylosin, kitasamycin, oleandomycin)**

This review is to be completed and outcomes acted upon within three years. Growth promotant claims of such antibiotics that do not pass the review process should be phased out of use within one year subject to consultation with relevant stakeholders.

It is also recommended that the NRA should review the prophylactic use of avoparcin and virginiamycin in animals and the possible public health impact of this use using the parameters outlined in Recommendation 4.

In order that the reviews are performed in a timely manner, it is further recommended that the federal ministers of health and agriculture ensure an adequate allocation of resources to the NRA to facilitate the rapid completion of the task and implementation of changes.

Recommendation 3

That an appropriate government authority or authorities license, or otherwise control, all importers of antibiotics (for any purpose other than individual human patient use). Licensed importers must provide import returns and distribution, and information based on amounts of active ingredient of agents intended for animal use, to the National Registration Authority, and to the Therapeutic Goods Administration for agents intended for human use.

It is also recommended that a much stronger audit trail for antibiotics from the importer to the end-user be implemented, particularly in the veterinary field, and that the aggregated information on import quantities are made available for scrutiny by relevant authorities and the results are made public.

Recommendation 4

That the National Registration Authority (NRA) evaluate all new applications, major extensions of use and any reviews of currently registered antibiotics for use in animals by applying the recently redrafted Special Data Requirements (Part 10 of the *Vet Requirements Series: Guidelines for Registering Veterinary Chemicals*, NRA 1998), which includes a risk analysis of microbial resistance safety (see Appendix 4).

Recommendation 5

That a recognised expert authority (the Working Party on Antibiotics or its successor) defines threshold (or trigger) rates of resistance for antibiotics registered for use in animals and circumstances where usage should be investigated and mitigation proceedings instigated where appropriate. In addition, resistance prevalence data should be included in the product information and this information should be updated on a five-yearly basis.

Recommendation 6

That all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only).

Recommendation 7

That the Agricultural Resource Management Council of Australia and New Zealand implement a harmonised approach by all States and Territories in Australia (including clarification of responsibilities) to the control of use of veterinary chemicals, including antibiotics.

Recommendation 8

That, following the implementation of Recommendation 7, the relevant State and Territory health/agriculture/primary industries legislation is amended to make it an offence to prescribe and/or use a veterinary chemical product contrary to a National Registration Authority (NRA) label restraint, unless authorised to do so by an NRA permit.

Recommendation 9

Similar to recommendations made in veterinary medicine, it is recommended that the Therapeutic Goods Administration (TGA) implement the following:

- **inclusion of microbial resistance safety data, including the propensity for promoting resistance and cross-resistance, as a basic requirement of the assessment of all new antibiotics by the TGA, with adoption of similar data requirements to those required in the registration of veterinary antibiotics (Recommendation 4);**
- **definition by a recognised expert authority (Working Party on Antibiotics or its successor) of the threshold rates of resistance to registered human antibiotics and circumstances where usage should be investigated and mitigation procedures instigated where appropriate; and**
- **inclusion of national human antibiotic-resistance prevalence data in the product information and updating on a five-yearly basis.**

JETACAR acknowledged that all patterns of antibiotic use, including prophylaxis, have the potential to result in further development of antibiotic resistance. JETACAR also recognised the commercial importance of the prophylactic use of antibiotics in food-producing animals for the prevention of clinical and subclinical conditions affecting productivity in livestock production systems. However, Recommendations 1 to 8 in this report have been framed on the basis that, for those antibiotics within groups of antibiotics critical to human health, growth promotion and oral prophylactic uses in food-producing animals should be reviewed and phased out.

Monitoring and surveillance (Recommendations 10 and 11)

To facilitate management of bacterial antibiotic resistance, an internationally acceptable and scientifically defensible Australian continuous surveillance program is essential to survey the prevalence of resistant bacteria in:

- human pathogens
- potential pathogens with major resistances carried by humans
- veterinary pathogens
- food-chain indicator organisms
- environmental organisms
- other areas of antibiotic usage

Systems for resistance surveillance in human bacterial isolates are well established in Australia (although funding is precarious) but there is currently no system of surveillance for bacterial isolates from animals. Standardised susceptibility testing techniques are also required for use in veterinary as well as human microbiology laboratories.

To interpret trends in antibiotic resistance, reliable data are also needed on antibiotic usage, including monitoring of import volumes and individual consultation, prescription and dispensing data for both human and animal antibiotic uses.

It has been recommended that accurate information on the amounts of antibiotics imported into Australia should be achieved through licensing of importers or similar methods (see Recommendation 3). To ensure that all areas of antibiotic use, including distribution and end-use, can be adequately monitored, a further mechanism is required to allow a full audit of antibiotic usage.

Recommendation 10

That a comprehensive surveillance system be established incorporating passive and active components measuring incidence and prevalence of antibiotic-resistant bacteria and resistance genes, covering all areas of antibiotic use. To achieve this aim, it is further recommended that a multidisciplinary taskforce of relevant experts be formed by the federal ministers of health and agriculture to design, cost and recommend funding mechanisms and management systems for reporting and analysis of antibiotic resistance data in Australia.

The overall surveillance system should include medical (including nosocomial), food-producing animal and veterinary areas, with particular emphasis on the establishment of food-chain (including imported food) and environmental connections, and include molecular studies of resistance genes. The efforts of the taskforce should be directed at adopting a uniform, systematic and synergistic approach across all areas by utilising, enhancing and extending currently available systems and organisational structures.

Recommendation 11

That a comprehensive monitoring and audit system for antibiotic usage be established that covers all areas of antibiotic use. To achieve this aim, it is recommended that the federal ministers of health and agriculture form a multidisciplinary taskforce of medical, veterinary, industry and regulatory experts (including Customs, Therapeutic Goods Administration, Department of Health and Aged Care, National Registration Authority and Department of Agriculture, Fisheries and Forestry — Australia) to refine the current antibiotic import data collection and audit process, and make recommendations to relevant authorities for developing methods of monitoring and auditing usage.

Infection prevention strategies and hygienic measures (Recommendations 12–14)

The overall bacterial 'load' to humans is reduced if high standards of hygiene are maintained in the food supply, and other precautionary measures are taken to reduce contamination of humans with animal bacteria. Microbial contamination of human foods has been the subject of much safety regulation in recent years, including HACCP ('hazard analysis critical control point') programs for safe food production, storage and preparation in the farm, wholesale, retail and home areas. In Australia this is occurring through the development of a National Food Hygiene Standard. Lowering the incidence of enteric disease in humans through such programs will have the additional benefit of reducing the transfer of antibiotic-resistant bacteria from animals to humans through the food chain, and from human to human, thus reducing the overall load of resistant bacteria.

The need for antibiotic use in food-producing animals will also be reduced if the level of disease is reduced through improved veterinary care and animal husbandry. There have been enormous improvements in the standards of veterinary care, housing, nutrition and genetics in the 40 years since antibiotics were first introduced, particularly in the intensive food-producing animal industries such as meat chicken and pig production. Owing to these improvements, the use of antibiotics for growth promotion is not as important now as it was previously. In Sweden, where growth promotants (apart from polyethers and other antiprotozoals used as coccidiostats) have not been used for the last 10 years, this requirement has largely been overcome by judicious use of therapeutic antibiotics, improvements in feed formulation and stricter hygiene measures (although a production loss of up to 1.5% has been acknowledged). However, the benefits of growth promotants in relation to disease prevention are also considered by many to be important.

A nationally coordinated system of human infection control practice and outbreak management is also required. This should include:

- hospital-acquired infection surveillance (including key resistant organisms);
- regular updates on national infection control guidelines;
- nationally agreed standards for outbreak management of infections of public health significance (including zoonotic and potentially zoonotic bacteria) with central reporting; and
- development and implementation of nationally agreed detection, screening and reporting procedures for key resistant organisms (especially multiresistant *Staphylococcus aureus* and VRE).

Recommendation 12

That 'hazard analysis critical control points' (HACCP)-based food safety procedures be implemented as a means of reducing the contamination of food products with foodborne organisms, including antibiotic-resistant organisms and that these programs also address on-farm infection control.

Recommendation 13

That where the intensive animal industries (such as meat chicken, pig, feedlot cattle and aquaculture) currently depend on the use of antibiotics to improve feed conversion and prevent and treat disease, cost-effective nonantibiotic methods to increase productivity and prevent disease should be developed by these industries. In relation to this, it is further recommended that the federal ministers of health and agriculture explore additional funding alternatives for this work, taking into account the current efforts of the animal industry research and development organisations.

Recommendation 14

That the Department of Health and Aged Care examine current surveillance activities for hospital-acquired (nosocomial) infections, particularly for antibiotic-resistant strains; and that the department work with stakeholders (including the States and Territories) to further develop a comprehensive and standardised national system for monitoring nosocomial infections that will facilitate:

- **earlier recognition of a public health problem;**
- **improvements in infection control and hygiene measures; and**
- **the timely development of national standards, guidelines and practices for both surveillance and infection control in the health care setting.**

Education (Recommendations 15–17)

To ensure the effectiveness of the prevention strategies outlined above, the stakeholders for both veterinary and medical use of antibiotics (clinicians, farmers, pharmaceutical companies, regulators) must understand the rationale and implementation of these strategies. The general public should also be fully informed about safe food handling and the efforts being made to improve the safety of food, (including that produced from animals) in order to minimise the spread of bacteria in the food chain.

Education of the medical profession has been the main approach to tackling inappropriate use of antibiotics over the last 15 years. However, these programs have not been highly successful and Australia is still the second highest per-capita user of antibiotics in human medicine, compared to seven other western countries. The most effective strategies for reducing inappropriate use have been restriction of availability through the Pharmaceutical Benefits Scheme, and prominent warning campaigns for targeted drugs. Efforts have also been made by the veterinary profession to improve prescribing practices through development of guidelines and codes of practice.

Prudent use principles need to be developed by relevant peak bodies representing key stakeholders in every area. These should be universal in nature, based on a scientific understanding of the pressures that select for, maintain and amplify antibiotic-resistant bacteria. They should be equally applicable to human and veterinary practice.

Improved guidelines for the appropriate use of antibiotics in humans and in animals are needed and will be most effective if produced with the support of the medical and veterinary professions, respectively, widely disseminated and adopted as a true 'standard of care'.

There is generally a poor community understanding of the biology of infection and infectious diseases, including among antibiotic users, patients attending their doctors with infection and farmers who have infected animals under veterinary consultation. Changing the current culture that expects almost all infections to be treated with antibiotics will require significant and targeted educational efforts at many levels.

Recommendation 15

That prudent use codes of practice for antibiotics be developed and regularly updated by medical and veterinary peak bodies, including learned societies, professional organisations, producer organisations, pharmaceutical companies and State/Territory medical and veterinary registration boards, and promulgated to their members. These codes of practice should be based on the principles articulated in this report.

Recommendation 16

That regularly updated 'antibiotic use guidelines', both human and veterinary, supported and endorsed by the appropriate professional organisations, the pharmaceutical industry and the federal and State

and Territory departments of health and agriculture, are widely disseminated and adopted as a 'standard of care' by training institutions, and established as the benchmark for undergraduate and postgraduate teaching. The effectiveness of the 'antibiotic use guidelines' in ensuring prudent prescribing of antibiotics needs to be evaluated every five years.

Recommendation 17

That, as a priority, learned (medical and veterinary) and professional societies develop continuing educational programs on the issue of antibiotic resistance, including a focus on the prudent use principles, antibiotic use guidelines and alternatives to antibiotic usage.

Further research (Recommendation 18)

Australia has a high level of expertise in the molecular biology of antibiotic resistance. However, there is no centrally coordinated antibiotic research facility and little attention has been focused on the clinical and veterinary problems of antibiotic resistance or on possible solutions. There are several important areas that require research attention. These include alternatives to antibiotic growth promotants for animal production, alternatives to other antibiotic uses in animals and humans (including vaccines), epidemiology of resistance (including molecular epidemiology and gene transfer mechanisms), effects of intervention programs (eg to reduce levels of prescribing and antibiotic use), clinical efficacy and rapid diagnostic methods.

Recommendation 18

That all relevant research funding agencies be asked to give priority to research into antibiotic resistance, including:

- **alternatives to antibiotics for growth promotion;**
- **alternatives to antibiotics for prevention and treatment of infections (including vaccines);**
- **molecular epidemiology and mechanisms of gene transfer;**
- **population dynamics of antibiotic resistance;**
- **resistance epidemiology;**
- **pharmacoepidemiology;**
- **efficacy of interventions to reduce antibiotic prescribing and use;**
- **clinical efficacy studies; and**
- **rapid diagnostic tests.**

Communication (Recommendations 19 and 20)

In addition to the five elements of antibiotic-resistance management outlined above, JETACAR recognised the importance of communication as an interactive exchange of information and opinions between regulators and stakeholders, including the general public. This should include explanation of the overall hazard that has been identified and characterised and the process for assessment of the risks for individual antibiotics on a case-by-case basis. In addition to the education measures recommended above, communication of hazard and risk to all concerned parties, especially the public, must therefore be a continuous process, much of which can be delivered by existing systems at the federal and State/Territory level.

Recommendation 19

> **That an ongoing funded education strategy be developed by the relevant federal/State/Territory departments with input from stakeholders to provide appropriately targeted information about infection, the role and benefits of prudent antibiotic use and the risks of overuse to the public, relevant professional bodies and stakeholders.**

Recommendation 20

> **That a recognised expert authority (the Working Party on Antibiotics or its successor) assume responsibility for ensuring and coordinating the communication of data on antibiotic usage and prevalence of resistant bacteria to the public and other relevant stakeholders on a regular basis, taking into account the sensitivities of trade and other international implications.**

Coordination of the resistance-management program (Recommendations 21 and 22)

The coordination of the efforts of professional, regulatory and industry bodies involved in the strategic management of this issue, and the communication of the risks involved to the wider community, will require the formation of an overarching, multidisciplinary, credible and independent authority.

The Working Party on Antibiotics (WPA) currently advises other federal government authorities, particularly the NRA and the Pharmaceutical Benefits Advisory Committee (PBAC), concerning the public health implications of antibiotic resistance and methods for controlling it. The WPA was previously convened by the National Health and Medical Research Council but now operates under the auspices of the TGA pending a more permanent home. It therefore lacks any statutory support and has only limited financial support from the TGA.

A formally constituted body that can communicate directly with both the Department of Health and Aged Care, and Agriculture, Fisheries and Forestry – Australia could extend the functions of the WPA and advise the NRA, TGA and other authorities and agencies (eg Australia New Zealand Food Authority) on antimicrobial issues. It could also advise PBAC on availability/restrictions of

antimicrobials on the PBS, oversee and refine antimicrobial resistance and usage surveillance systems, develop and disseminate national prudent use principles, and advise on the development of public education strategies in relation to infectious diseases and the role of antibiotics. Secure funding for these activities is needed. Because of the public health impact of antibiotic resistance, the preferred option would be to operate within the structure of the National Health and Medical Research Council (NHMRC).

JETACAR also recognised that further work is needed to control medical use and misuse of antibiotics and that there is an ongoing and urgent need to coordinate and supplement current efforts to reduce antibiotic-resistance selection pressure by improving medical antibiotic use in Australia.

Recommendation 21

It is recommended to the ministers of health and agriculture that:

- **the current functions and membership of the Working Party on Antibiotics (WPA) be expanded to carry out the antibiotic risk management program outlined in earlier recommendations;**
- **the administrative and reporting arrangements of the WPA (or its successor) be clarified so it can maintain its independent position and advise the Therapeutic Goods Administration (TGA) and the National Registration Authority (NRA) and other agencies/statutory bodies as required;**
- **the coordination of the antibiotic risk management program across government portfolios and industry be provided with secure recurrent funding for the additional tasks outlined in Recommendations 1 to 20;**
- **the WPA or its successor keep the regulatory framework for the use of antibiotics in human and veterinary medicine and food-producing animals under review and make appropriate recommendations to the regulatory authorities to review the uses of particular antibiotics, taking account of**
  - **the importance of the drug or class of drug in human and veterinary medicine, and**
  - **the potential for human exposure to antibiotic-resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their antibiotic-resistance genes to human pathogens;**
- **the WPA or its successor, the National Registration Authority and the Therapeutic Goods Administration develop appropriate procedures to ensure accountability and transparency of its activities, including established time-frames for reviews;**
- **the WPA (or its successor) develop a five-year strategic plan and an annual budget for its activities; and**
- **the operations of the WPA (or its successor) be subject to a five-year independent review program.**

Recommendation 22

That the Department of Health and Aged Care convene a working group to develop a fully coordinated resistance management plan for human antibiotics, incorporating the elements included in Recommendations 9, 10, 11, 14, 15, 16, 17, 18, 19 and 20. The plan so developed should be incorporated into the recommended functions of the Working Party on Antibiotics or its successor (see Recommendation 21).

Chapter 1
Introduction

1.1 Background

The ongoing emergence of antibiotic-resistant bacteria is a public health issue of increasing concern. It has led to a situation where essential, life-saving, antibiotics are becoming less effective. This means that there are fewer alternatives, and sometimes more toxic and costly antibiotics must be used.

It is well recognised that antibiotic use selects for antibiotic-resistant bacteria and that there is a direct correlation between the risk of bacteria becoming resistant to antibiotics and the level of use of antibiotics. Antibiotics are used for the treatment and prevention of infectious diseases in humans, and in both domestic and food-producing animals, including fish. Some are also used for growth promotion and improving feed efficiency in many situations where animals are intensively reared, including poultry, pigs, and feedlot cattle.

The use and overuse of antibiotics in human medicine is a well-recognised and important factor contributing to the development of antibiotic resistance. A number of strategies have been implemented in recent years in an attempt to address this issue, including the introduction of Australian therapeutic guidelines for the use of antibiotics (Therapeutic Guidelines 1998). Continued education and commitment to prudent prescribing is required by the medical community in order to curtail the development of antibiotic-resistant pathogens as a result of clinical use.

Clearly, the use of antibiotics in food-producing animals also favours development of antibiotic resistance. This use has recently received considerable attention as a contributory factor in the emergence of resistant bacteria causing human disease and there has been growing national and international concern about the use of antibiotics in animals, particularly as growth promotants. Several international reports that have examined this issue have been released over the last few years (see Appendix 1).

The overall concerns of the international community were reviewed at a recent meeting convened by the World Health Organization (WHO, Berlin, October 1997). The report from that meeting, entitled *The Medical Impact of the Use of Antimicrobials in Food Animals*, made a number of recommendations including that the use of antibiotics in food-producing animals be reduced and better regulated. The report emphasised the need for a collaborative and multidisciplinary approach to examine the issue and develop risk management strategies.

The emergence of vancomycin-resistant enterococci (VRE) in Australia and overseas is the most recent of the many examples of antibiotic resistance that has caused concern in the medical community. Vancomycin is from the class of antibiotics known as *glycopeptides* and is needed for the treatment of multiresistant *Staphylococcus aureus* (MRSA or 'golden staph') in hospital settings. It has been suggested that the emergence of one type of VRE in humans may be linked to the routine use of avoparcin (also a glycopeptide antibiotic) as a growth promotant and prophylactic agent in food-producing animals. The main

concern is that the genes responsible for resistance in VRE may be transferred to other bacteria, including MRSA, rendering them resistant to vancomycin and leaving no available treatment options for 'golden staph' infections. Such a situation could significantly compromise a patient's chance of survival.

Another example is the emergence of fluoroquinolone-resistant strains of salmonella and campylobacter, recently reported in Denmark, United Kingdom and the United States. Like vancomycin, in human medicine in Australia, the fluoroquinolone class of antibiotics is reserved for the treatment of multiresistant life-threatening infections. The concern is that human infection by salmonella strains resistant to fluoroquinolones would leave few, if any, treatment options available to the physician because multiple resistance to other previously effective antibiotics is now commonplace. The use of fluoroquinolones, which are approved for use as therapeutic medications in food-producing animals in some overseas countries, is believed to be a risk factor for the emergence of these resistant bacteria.

Australia has historically taken a relatively conservative approach to the registration of antibiotics for use in animals. The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is the regulatory body responsible for assessing and registering drugs to be used in animals. The Working Party on Antibiotics (WPA), originally established under the auspices of the National Health and Medical Research Council (NHMRC), provides advice to the NRA on human health implications of antibiotic use in animals. The WPA was formed in response to the release in 1969 of the 'Swann Report' (*The Use of Antibiotics in Animal Husbandry and Veterinary Medicine,* UK Joint Committee of Houses of Parliament; see Appendix 1), to advise on the use of antibiotics in stockfeed. It has been proactive in the area and, in conjunction with related committees, produced a number of key documents including *Antibiotics in Stockfeeds* (NHMRC 1986) and *Antibiotics in Agronomy and Horticulture* (NHMRC 1994).

In December 1997, as a result of increased concern by the scientific and medical community, the then Australian Minister for Health and Family Services and the then Minister for Primary Industries and Energy agreed that a joint expert committee be established, including representatives from both health and agriculture, to examine the issue from a scientific perspective. The Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) was appointed in April 1998 and is made up of experts from health, veterinary medicine, molecular biology and primary industry (a full list is shown on page xi). The ministers commissioned JETACAR to review the scientific evidence and develop evidence-based recommendations for the appropriate future management of antibiotic use in food-producing animals.

1.2 Scope of the report

The scope of the report is focused on the question of whether the use of antibiotics in animals could promote an increase in antibiotic resistance in animal bacteria that would subsequently infect humans and/or transfer their resistance genes to human pathogens. **This focus does not imply that restrictions on the use of antibiotics in animals would alone resolve the issue of bacterial resistance to antibiotics in humans, much of which has arisen because of clinical overuse/misuse in human medicine.** The use of antibiotics in animals, however, is one of the factors that has come to prominence in recent times, in part because it accounts for a large proportion of the total antibiotic use worldwide, especially in livestock-intensive countries. To assess this issue in an Australian context, taking account of the international perspective and concerns raised in the 1997 WHO report, JETACAR was asked to undertake, among other objectives, two important tasks:

- assess scientific evidence for the link between the use of antimicrobial growth promotants in livestock feeds and the emergence of antibiotic resistance; and
- make evidence-based recommendations on strategic management issues for animal industries and human medicine, balancing the possible benefits to livestock production against the medical risk and public health consequences arising from such applications.

However, it was recognised that in order to address these two issues a broader picture of use and resistance issues would need to be examined and recommended upon.

1.2.1 Terms of reference

To address the issues comprehensively, five specific terms of reference for JETACAR were agreed by the then Minister for Health and Family Services and the then Minister for Primary Industries and Energy.

1. Examine the status of antibiotic-resistance patterns in Australia in human and veterinary practice and in food-producing animals.
2. Examine the full range of antibiotic usage patterns and control policies in Australia in all sectors, including health, veterinary and agricultural applications.
3. Identify priority medical problems arising from the use of antibiotics in livestock production.
4. Recommend a minimum set of criteria for assessing the potential human health impact prior to licensing of antibiotics for use in animals and agriculture, taking into account the likely benefits and potential adverse outcomes (informed by models in published scientific literature and relevant measures adopted in other countries).
5. Recommend an antibiotic-resistance management strategy/strategies.

The first two terms of reference relate to the collection of baseline information against which to judge evidence for emergence of antibiotic resistance. The third term of reference provides a focus on priority medical problems that may arise as a result of antibiotic use in livestock. The last two terms of reference relate to the development of key criteria for future assessment and an overall management plan/strategy, based on currently available scientific evidence, to minimise the risks.

In order to adequately address the terms of reference, particularly number three, a quality assessment of the evidence of a link between antibiotic use in animals, development of antibiotic-resistant bacteria and development of infectious diseases in humans due to such antibiotic-resistant bacteria was necessary. This was achieved through an independent systematic literature review (see Section 1.3.2).

1.2.2 Target audience

This report was commissioned by the then Commonwealth Minister for Health and Family Services and the then Commonwealth Minister for Primary Industries and Energy to guide future policy and legislation in the area of antibiotic use. During the preparation of the report, the names and some of the areas of responsibility of the two federal ministers were changed. The new federal ministries are: the Commonwealth Department of Health and Aged Care (DHAC) and Commonwealth Department of Agriculture, Fisheries and Forestry — Australia (known as AFFA). The report will be referred to the Australian Health Ministers' Advisory Council and the Agriculture and Resource Management Council of Australia and New Zealand, who will guide any appropriate changes to legislation and regulation in this area.

The report is also intended to guide implementation of any recommended management strategies by the following professional and industry groups:

- health and agricultural and veterinary professionals, eg
  - veterinarians
  - medical practitioners
  - agricultural scientists
- health and primary industry policy and regulatory agencies
- livestock industry
- pharmaceutical industry

The report will also be of significant interest for the general community, particularly consumer health and animal welfare groups, as well as Australia's international colleagues and trading partners.

With this large target audience in mind, the report has been written as simply as possible, while assuring compatibility with the current state of scientific knowledge in this complex technical field.

1.3 Report development process

1.3.1 Information gathering

In order to complete in a timely manner the large task it had been set, JETACAR developed a work plan based on a structured set of questions arising from the terms of reference and covering risk assessment and risk management components of the issue. A summary of the work plan is shown in Appendix 2.

Baseline data and risk assessment information was compiled and submitted by individual committee members. This information was reviewed by the whole committee and the issues raised and strength of evidence were assessed. Information on current and possible future management options was also reviewed in a similar way.

The committee met on seven occasions, each over one to two days, and communicated electronically between meetings in order to complete its tasks in the limited time available.

1.3.2 Literature review

At the same time as the committee was gathering background information according to the work plan (see above), a comprehensive and independent review of the international scientific literature on the possible spread of antibiotic-resistant bacteria from animals to humans and transfer of antibiotic-resistance genes from animal to human bacteria was commissioned. The external reviewers were asked to answer four questions.

- Does the administration of antibiotics to animals result in the emergence of antibiotic-resistant bacteria?
- Do these resistant bacterial strains spread from animals to humans?
- Do these bacteria (resistant animal strains) cause clinical disease in humans?
- Do the resistance genes in these bacteria (resistant animal strains) transfer to human pathogens?

The scope of the literature review was restricted to:

- four bacterial pathogens — *Salmonella*, *Campylobacter*, *Escherichia coli* and *Enterococcus*;
- all antibiotics (but not antifungals, antivirals, anthelminthics or antiprotozoals, unless they also possess antibacterial activity); and
- scientific literature published in English since 1965 with data relevant to the four questions, by reviewing:
  - all studies published in the peer-reviewed literature,
  - studies in the non-peer-reviewed literature (where possible), and
  - unpublished material (including conference proceedings).

The purpose of the JETACAR literature review was to provide a quality assessment of the evidence for a link between the use of antibiotics in food-producing animals, the emergence of antibiotic-resistant bacteria and the development of related infectious diseases in humans. The literature review was intended to assist JETACAR address the terms of reference and inform the development of its recommendations.

Because of the limited time available for the literature review and the vast number of publications involved, the reviewers focused on areas were there was most evidence available (that is, enteroccoci and fluoroquinolone resistance in the other organisms).

To rate the evidence obtained in the literature review, JETACAR used a modification of the National Health and Medical Research Council four-point scale (NHMRC 1995). The scale (which was developed for assessment of clinical interventions) was modified to take account of the range of methodologies used to study the complex science of the emergence and spread of antibiotic-resistant bacteria or transfer of antibiotic-resistance genes, including the powerful nature of the increasing body of molecular evidence.

In the consultation process with stakeholders (see Section 1.3.3), some stakeholders claimed that the literature review did not capture all the literature available and, in particular, a number of international reviews of the literature were mentioned that were not covered in the review. However, it should be noted that the JETACAR literature review was intended to be an independent review of the primary literature and not an assessment of other reviews and that the reviews cited were published after the completion of the JETACAR literature review and draft report. Also, it proved extremely difficult to capture all of the huge primary literature on this topic in the short time available for the literature review process. In addition, the dynamic nature of this field of research has meant that many significant studies and reports have appeared in the six months since the JETACAR literature review was completed. Mindful of these restrictions, JETACAR members also reviewed many other sources of information, including newly published studies and a large number of other international reviews (see Appendix 1), in the course of their deliberations.

1.3.3 Stakeholder consultation

At the beginning of the JETACAR report process, 52 key stakeholders were advised of the terms of reference, work plan and scope of the report and invited to provide input in the form of scientific data and practical advice. The committee held the view that a collaborative effort would best serve the needs and concerns of all involved. The 23 submissions received were reviewed by the committee and taken into consideration in the development of this report.

In March 1999, the draft report of JETACAR was circulated to the 52 key stakeholders for comment. Submissions were received from 35 stakeholders and circulated to all JETACAR committee members. The points raised were summarised and discussed at a two-day JETACAR meeting in June 1999. Key points were taken into account in the finalisation of both the text of this report and the recommendations.

A list of the submissions received in both the first and second round of stakeholder consultation are shown in Appendix 3.

1.4 Report outline

To assess the issues outlined above and to develop antibiotic-resistance management strategies, JETACAR developed a framework against which the assessment would be done and recommendations made. This framework is described in Chapter 2.

In the following chapters of the report, the baseline data and risk assessment information reviewed by the committee are summarised, including:

- the scientific basis of antibiotic resistance (Chapter 3);
- bacteria of concern for spread of antibiotic resistance from animals to humans and for serious human infections (Chapter 4);
- evidence for spread of antibiotic-resistant bacteria from animals to humans or transfer of antibiotic-resistance genes from animal bacteria to human bacteria(Chapter 5);
- current controls on antibiotic use in Australia, and overseas (Chapter 6);
- the current patterns of use of antibiotics in humans and animals in Australia (Chapter 7);
- benefits for livestock production (Chapter 8); and
- antibiotic residues in food (Chapter 9).

In the last section of the report, there is a focus on management issues, including:

- an assessment of current monitoring and surveillance systems (Chapter 10);
- a discussion of alternatives to the use of antibiotics in animals (Chapter 11); and
- a risk management strategy with recommendations to guide future legislation/regulation (Chapter 12).

Chapter 2
Approach taken by JETACAR

OVERVIEW

Working within the terms of reference, JETACAR has reviewed the available data on antibiotic use, control policies and antibiotic-resistance patterns in human and veterinary practice in Australia, with particular reference to food-producing animals. Priority medical problems potentially arising from, or exacerbated by, the use of antibiotics in livestock production, have been identified. These issues were assessed in terms of an independent review of the international scientific literature for key bacterial species and an assessment of existing monitoring and surveillance programs in Australia. The benefits of antibiotic use in animals were also reviewed and alternatives canvassed. The information collected was necessarily incomplete as there are many gaps in the data available and in the current scientific knowledge of the processes involved.

In developing the report JETACAR took account of current risk analysis methodology, which includes risk assessment as one of its components. **However, it must be stressed that this report does not include a formal risk assessment because such a process was beyond the scope of JETACAR and is more appropriately applied to the assessment of individual antibiotics**. Rather, JETACAR has attempted to provide:

- an evidence-based characterisation of the hazard associated with antibiotic use in food-producing animals;
- a framework for the future development of risk assessment methodology for individual drugs; and
- the basis for the development of an integrated antibiotic-resistance management strategy.

2.1 Introduction

The issues surrounding antibiotic use in food-producing animals, and the consequences for human health, have been assessed in several international forums (see Appendix 1). However, no uniform, internationally harmonised risk analysis/ risk assessment process has been developed to date. This is because the issues involved are much more complex than normally associated with risk assessment for chemical or microbiological hazards, where the dose or exposure to an agent is related to the expected risk of an adverse health effect. By contrast, for antibiotic resistance there are several stages that need to be considered, each of which requires scientific evaluation.

These include the emergence of resistant bacteria in animals, their spread to humans, the transfer of resistance genes between commensal and pathogenic bacteria in both animals and humans and the selection and amplification of antibiotic-resistant bacteria in both animal and human populations by the use of antibiotics.

In deciding how to assess the evidence surrounding these issues, JETACAR considered currently accepted risk analysis procedures, such as the one proposed by Lammerding (1997). Similar procedures are used for the assessment of food safety issues in Australia

by the Australia New Zealand Food Authority (ANZFA 1998) and internationally by the Codex Alimentarius Commission.[2]

When fully developed to address a particular issue, risk analysis methodology allows hazards to be identified and associated risks ranked. It also allows public health administrators to select risk management options and defend their choices on scientific grounds so that scarce resources can be directed to areas of greatest risk. The approach can include qualitative or quantitative approaches, or a combination of both.

Although there is an extensive worldwide literature for risk analysis in other fields (Weingold et al 1994, Nunn 1997, Horst 1998, Sim and McNeill 1999), no such risk analysis approach has been fully developed or validated for assessing the risks associated with antibiotic use. Such a method would be inherently much more complicated than for the assessment of risks associated with toxins or pathogens where a dose-related cause and effect relationship can be determined. By contrast the emergence, spread and transfer of antibiotic-resistant bacteria is a complex multistage process, each stage of which requires careful elucidation. None of the international reports reviewed by JETACAR, including the most recent ones (see Section 5.1) have included either quantitative risk data or a structured qualitative analysis. Thus, JETACAR had no overseas expertise to draw upon. However, JETACAR decided that existing risk analysis methodologies could form a framework for consideration of the issue of antibiotic use in food-producing animals and in doing so has identified the elements required to develop a formal qualitative risk assessment method for individual antibiotics.

2.2 Definitions

Definitions of '*antibiotic*', '*antibiotic resistance*', '*growth promotant*' and other terms used in this review are given in the Glossary. '*Hazard*', '*risk'* and other risk analysis terminology is also explained below.

The term '*pathogenic bacteria*' is used to mean the bacteria that cause disease (either opportunistic infections such as wound or gastrointestinal infections, or infectious diseases such as tuberculosis). The term '*commensal bacteria*' is used to mean the bacteria that live continuously on or in certain parts of the body (eg gut, skin) without causing disease (nonpathogenic) (eg *E. coli*, enterococci), but which may cause disease if they gain access to parts of the body other than their normal habitat. '*Zoonotic bacteria'* are pathogenic organisms transferred to people by direct contact with animals or animal products (eg brucella, nontyphoid salmonella and campylobacter).

2.3 Risk analysis

In the scheme proposed by Lammerding (1997) for assessment of microbiological risks, risk analysis is described as a three-part process involving risk assessment, risk management and risk communication, as shown diagrammatically in Figure 2.1.

NOTE: Some caution is needed in using the terms 'risk assessment', 'risk management' and 'risk communication', as a review of the literature shows that they have been used differently by different groups of scientists (Nunn 1997).

[2] The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Codex Alimentarius Commission is the international organisation which sets standards for foodstuffs in international trade. The World Trade Organization *Agreement on the Application of Sanitary and Phytosanitary Measures* specifically recommends Codex standards, guidelines and recommendations for food moving in international trade.

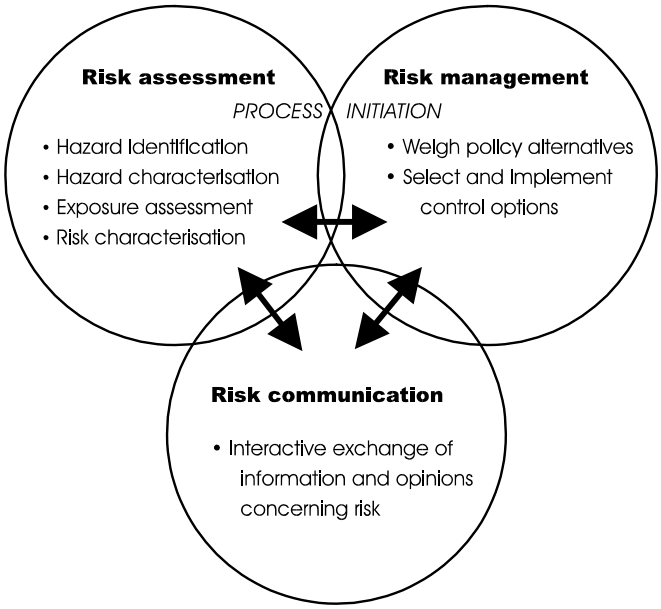

Figure 2.1 **Schematic diagram of risk analysis, a process that involves the merging of scientific assessment, practical management and ongoing monitoring and communication (from Lammerding 1997)**

For example, 'risk management' can be used instead of 'risk analysis' for the whole process, while others may use 'risk analysis' for the 'risk assessment' component shown in Figure 2.1. Despite these variations the basic principles are the same across different disciplines (Nunn 1997). The definitions used in this report are given below and in the Glossary.

JETACAR used the following definitions of hazard and risk (adapted from Codex definitions for food assessment).[3]

- *hazard* — a biological, chemical or physical agent that may have an adverse health effect;
- *risk* — the probability of an agent (hazard) causing an adverse effect and the magnitude of that effect (expressions of risk can be quantitative or qualitative, and should include consideration of any uncertainties).

2.3.1 Risk assessment

Within the scheme shown in Figure 2.1, risk assessment is the scientific evaluation of known or potential adverse health effects resulting from human exposure to hazards. The process includes the following steps:

- *hazard identification* — identification of known or potential adverse health effects associated with a particular hazard (see definition of 'hazard', above);
- *hazard characterisation* — qualitative and/or quantitative evaluation of the nature of the adverse health effects identified;
- *exposure assessment* — evaluation of the relationship between the hazard and the adverse effect (for antibiotic resistance this is very complex — see Section 2.4.2); and

[3] *Application of Risk Analysis to Food Standards Issues* . Report of the Joint FAO/WHO Expert Consultation, Geneva, Switzerland, 13–17 March 1995.

- *risk characterisation* — integration of hazard identification, hazard characterisation and exposure assessment (including any uncertainties) into an estimate of the adverse effects likely to occur in a given population.

2.3.2 Risk management

Risk management is the process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate options.

2.3.3 Risk communication

Risk communication is the process of interactive exchange of information and opinion on risk among risk assessors, risk managers, and other interested parties.

2.4 JETACAR approach

JETACAR has assessed the complex issues surrounding bacterial antibiotic resistance, especially as they relate to the use of antibiotics in food-producing animals.

2.4.1 Scope

The task set for JETACAR (see Section 1.2) was to assess the scientific evidence and make recommendations on the possible link between the use of antibiotics in food-producing animals and the emergence and spread of antibiotic-resistant bacteria to humans. **The committee acknowledged that reducing the use of antibiotics in animals would not in itself solve the problem of antibiotic-resistant bacteria in humans because the medical overuse or misuse of the drugs is a major contributor to this problem.** Nevertheless, the use of antibiotics in animals is a major concern because it accounts for a large proportion of total antibiotic use worldwide, especially in livestock-intensive countries such as Australia and those in the European Union (Australian antibiotic use patterns are shown in Section 7.1).

2.4.2 Hazard identification

Taking into account the considerations outlined in Section 2.4.1 above, and the terms of reference of the review (Section 1.2), the hazard and adverse health effects that were considered in this review were:

- *hazard* — the use of antibiotics in food-producing animals;
- *adverse health effect* — the spread of antibiotic-resistant bacteria from animals to humans, and the transfer of resistance genes from bacteria of animal origin to bacteria of human origin, with the subsequent failure of treatment for human bacterial infections.

There has also been some concern in the community about the presence of antibiotic residues in food. These concerns arise mainly from the point of view of possible allergic reactions to the residues in food. However, concern has also been expressed about the possible development of antibiotic resistance in humans due to ingested antibiotic residues (mainly because the media has frequently and erroneously cited it as the main factor involved). While this issue is considered briefly in this report (see Chapter 9), the spread of antibiotic-resistant bacteria from animals to humans and the transfer of resistance genes from bacteria of animal origin to bacteria of human origin, which are the main cause of concern in the international regulatory and scientific communities, are the focus of this report.

As outlined in Chapter 1 (Introduction) and in the JETACAR work plan (Appendix 2), the committee assessed available data on antibiotic usage patterns, control policies and the status of antibiotic-resistance patterns in human and veterinary practice in Australia, with particular reference to food-producing animals. Priority medical problems arising from the use of antibiotics in livestock production were identified and assessed in terms of a review of the scientific literature for key bacterial species.

2.4.3 Hazard characterisation

JETACAR identified the critical steps that would need to occur for the hazard (antibiotic use in animals) to result in resistant bacteria spreading from animals to humans and causing disease in humans, with possible subsequent treatment failure.

- **Step 1. Emergence of antibiotic resistant bacteria in animals:**
  - resistance emergence — antibiotic resistance arises in populations of animal bacteria by mutation or because the animal picks up a resistant bacterium;
  - antibiotic exposure — food-producing animals are exposed to antibiotics;
  - enrichment by selection — exposure to antibiotics kills susceptible bacteria and allows resistant bacteria to increase (amplification) at the expense of susceptible strains and species (enrichment); and
  - spread of resistant bacteria — spread of resistant bacteria to other animals in a herd/flock. This will be enhanced if many or all animals are exposed to the antibiotic(s) to which the bacteria are resistant.

    Plus:

    - horizontal transfer of resistance genes — some resistance genes can transfer to other bacterial species on genetic fragments (eg plasmids or transposons). Antibiotic exposure is not required for gene transfer to occur. The resistant bacteria that arise in this way are also amplified by antibiotic exposure.

- **Step 2. Spread of resistant bacteria from animals to humans:**
  - resistant bacteria spread from animals to humans indirectly via food (eg by contamination of carcases during slaughter), or less commonly by direct contact (eg in farmers, abattoir workers); and
  - resistant bacteria either take up residence (colonising commensals), attach and initiate an infection (pathogens) or stay transiently eg in passage through the human gut.

    Where:

    - human acquisition may be enhanced if the person is taking the antibiotic to which the animal bacteria are resistant; and
    - resistant bacteria are amplified and enriched in humans by exposure to the antibiotic(s) to which the acquired animal bacteria are resistant.

- **Additional Step 2. Horizontal transfer of antibiotic resistance genes from animal to human bacteria:**
  - identical processes to Step 2 followed by transfer of the antibiotic resistance gene(s) to other human pathogenic and/or commensal bacteria. Antibiotic exposure is not required for gene transfer to occur.

- **Step 3. Clinical disease in humans:**
  - humans with resistant bacteria develop illness from these bacteria

– treatment with the antibiotic(s) to which the bacteria are resistant results in adverse outcomes, eg prolonged illness, more severe illness, treatment failure and even death.

This process is shown diagramatically in Figure 2.2. In short, spread of resistant bacteria from animals to humans can occur either by the spread of the resistant bacteria themselves (bacterial spread) or spread of the resistance genes (genetic spread) to potential human pathogenic bacteria. The relevant antibiotics amplify and enrich these resistant bacteria both in animals and humans. Amplification of resistant bacteria can also occur along the food chain if food handling techniques are inadequate.

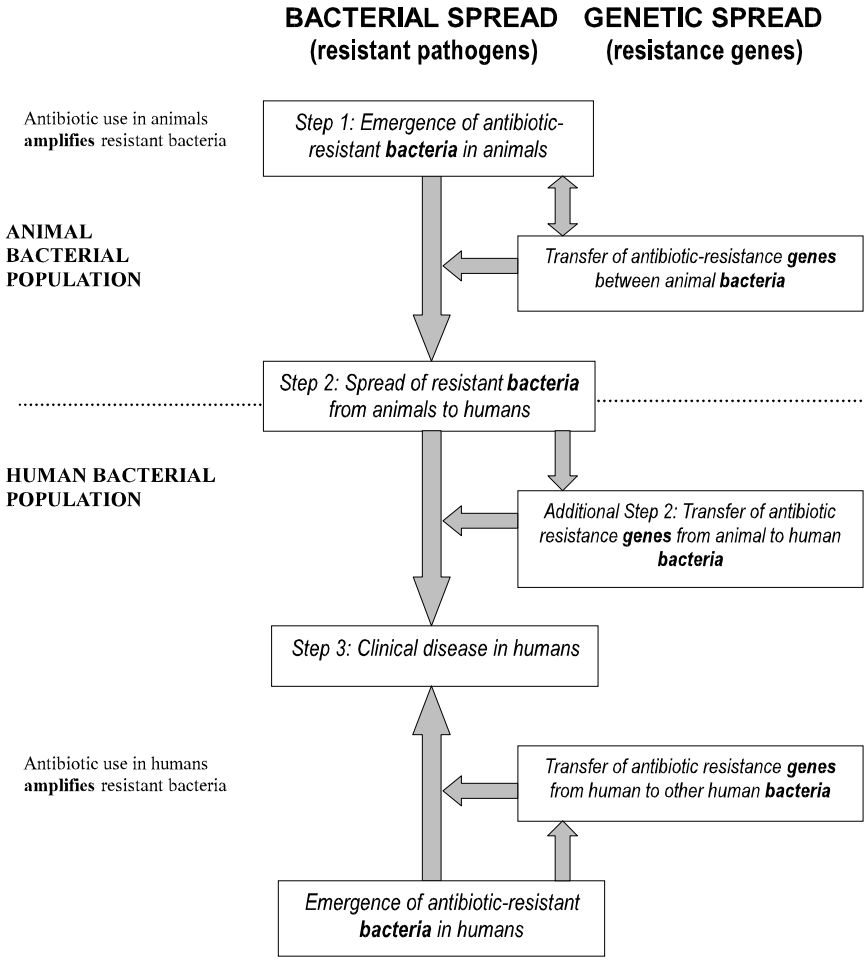

Figure 2.2 **Spread of antibiotic resistant bacteria and/or transfer of antibiotic resistance genes from animals to humans (and humans to humans) (Note: not every direction of spread is included)**

It is important to note that the animal and human bacterial populations can be considered as two separate pools. The entry of a particular antibiotic-resistant bacterium carrying a particular antibiotic-resistance gene in to the animal pool may be a rare event but antibiotic use in animals greatly amplifies the resistant bacteria/gene. The chance of the resistant bacteria transferring to humans or of a resistance gene transferring to the human bacterial population increases with any increase in the size of the pool of resistant bacteria/genes in animals. Once such transfer occurs, the establishment of a significant pool of resistant organisms in the human bacterial population requires further selection

with the same antibiotic or one that coselects for the presence of the resistance gene (see Section 3.2.2).

If animals and humans are both exposed to a particular antibiotic and there is a connection between the bacterial pools though a contact such as food, then there is potential for amplification to occur in both pools simultaneously. However, if the human population is not exposed to the same antibiotic or one that coselects for that resistance to that antibiotic, then the potential for amplification in humans is low. The reverse is also true for antibiotic spread from humans to animals.

Of course, in reality the process is more complex than that shown in Figure 2.2 because antibiotic-resistance genes can be transferred between pathogenic, zoonotic and commensal bacteria in a variety of ways and also between any other populations of bacteria that are in proximity (eg in plants, food or water). Likewise, transfer may also occur from resistant human bacteria to animal or environmental bacteria (eg if human sewage is not disposed of carefully).

Recent molecular analysis of resistant organisms and their resistance genes has provided ample evidence for the identity of many antibiotic-resistance genes from different types or strains of bacteria from both animal and human sources, indicating that genes move between these two reservoirs by horizontal gene transfer. Future surveillance must therefore also include molecular characterisation, if clear trends are to be obtained, and organisms other than those known to be directly responsible for disease in humans need to be considered.

The scientific issues surrounding antibiotic resistance, including its emergence in a few bacteria, selection by antibiotic use, transfer between bacteria by genetic means and spread between animals (including humans) by direct and indirect infection, are all global issues. In this age of international travel, bacteria are rapidly transferred from one country to another on or in their hosts. Because of these factors, the emergence of resistant bacteria anywhere in the world has significant public health implications for all other countries.

Therefore, parts of this report that deal with the science of antibiotic resistance, its spread and transfer necessarily have a global focus, based on evidence from the international literature. Other aspects of the assessment, including antibiotic use patterns and benefits in animals, regulatory controls, and antibiotic use monitoring and resistance surveillance focus more specifically on the current situation in Australia.

The JETACAR review of the international literature rated the scientific evidence for the different stages outlined in Figure 2.2 in the emergence and transfer of antibiotic-resistant bacteria from animals to humans (ie 'Does it happen?'). Assessment of this evidence and consideration of the many other reviews that have been prepared overseas (see Appendix 1), has allowed JETACAR to provide an evidence-based characterisation of the hazard associated with antibiotic use in food-producing animals.

2.4.4 Exposure assessment

Although the question 'Does it happen' was answered by evidence from the international literature review, the question of 'How often does it happen?' was harder to answer. Overall, this question is related to three forms of exposure as follows:

- exposure to antibiotics (antibiotic 'load' and pattern of use [regimen]);
- exposure of humans and animals to resistant bacteria (bacterial 'load'); and

- exposure of bacteria to antibiotic-resistance genes (prevalence of antibiotic-resistant bacteria).

JETACAR evaluated total use data and use patterns for antibiotics in Australia, discussed routes of bacterial contamination and infection and assessed existing antibiotic-resistance prevalence data. Although the data were either not available or were considered inadequate to make a complete assessment, the above three elements of exposure were taken into account by JETACAR in making recommendations for future monitoring and surveillance and for research so that an improved database will be available to inform future decision making.

2.4.5 Risk characterisation

Risk characterisation involves estimating the probability of the adverse effect happening in a given population. Overall, the risk to human health from antibiotic-resistant bacteria in food-producing animals is a dynamic process driven by factors such as the level of exposure to antibiotics (which drives secletion/coselection of antibiotic-resistant bacteria), the level of infection or contamination of humans with animal bacteria, the health status of the infected humans, and the treatment and hygienic measures adopted in animal husbandry and clinical medicine. To characterise the overall risk, it will be necessary to assess the risks (either quantitatively or qualitatively) posed by antibiotic use on a case-by-case basis, as follows:

- risk of selecting and increasing (amplifying) antibiotic-resistant populations of bacteria in animals— based on assessment of antibiotic load and regimen (and the relationship between this exposure and development of resistance for different antibiotic–bacterium combinations);
- risk of spread of resistant bacteria from animals to humans — based on bacterial load (level of contamination from environment, water, food, etc);
- risk of transfer of antibiotic-resistance genes between animal and human bacteria — based on assessment of prevalence of antibiotic-resistant bacteria and information on the rate of transfer of antibiotic-resistance genes between bacteria in different situations;
- risk of amplification of resistant bacteria in humans— through antibiotic use and poor hygiene practices; and
- risk of human disease caused by antibiotic-resistant bacteria resulting in treatment failure — based on assessment of the health status of the human population at risk and the treatment and hygienic measures adopted in clinical medicine.

Based on a similar assessment for different biological systems, it may be possible to rank the relative risks attributed to antibiotic uses in animals, humans and other biological systems.

A qualitative assessment method will also need to include assessment of the status of the antibiotic for treatment of life-threatening human conditions. If a particular antibiotic or class of antibiotics is considered critical for treatment of a life-threatening human condition (critical antibiotics[4]), the utmost care will be required not to introduce antibiotic-resistant bacteria or genes encoding resistance to this antibiotic or antibiotic class into the human bacterial population. Antibiotics for which there are other

[4] See Glossary for definition of critical antibiotics.

alternatives for treatment of serious human conditions can be ranked as less important in terms of emergence of antibiotic-resistant bacteria. The same consideration can be given to antibiotics needed for treatment of serious animal diseases.

Antibiotic use data is currently incomplete, particularly for animal antibiotic use, due to inadequacies in the audit trail for antibiotic imports and uses. The relationship between different antibiotic use regimens and the emergence of antibiotic-resistant bacteria is also not clear at this stage and requires further research.

It may be possible to assess human exposure to bacteria based on current data collection systems such as the National Disease Surveillance System but this has not been done at this stage.

The prevalence of antibiotic-resistant bacteria in food-producing animals is difficult to assess because there are so little quality data on antibiotic-resistant bacteria isolated from animals. What does exist is historical, derived using a variety of different methods, and does not include all of the bacteria of interest to medical authorities in the potential spread of antibiotic-resistant bacteria and transfer of antibiotic-resistance genes from animal bacteria to humans.

A full assessment of the prevalence of antibiotic-resistant bacteria would require surveillance of ongoing changes in specific bacterial antibiotic-resistance patterns. Such data would allow assessment of the time taken to develop resistance, prevalence of resistant bacteria in various pools (animals, humans, environment, etc), and information on the number of copies of the resistant genes in bacterial plasmids or the bacterial genome.

In the human clinical area, there has been a more systematic documentation of antibiotic resistance in medical laboratory monitoring and diagnostic isolates since 1992. The National Antimicrobial Resistance Surveillance Program (NARSP) was established through the auspices of the Working Party on Antibiotics and has been gathering data from 29 laboratories across the country annually since its inception.

The characterisation of risk could be further enhanced by monitoring the incidence of human cases of a particular disease per year, grading the human health impact of specific pathogens and measuring the number of cases where antibiotic resistance to the pathogen is a medical issue. Subsequent assessment of the human health impact of specific pathogens would then be possible.

2.4.6 Benefits of antibiotic use in livestock

The benefits of antibiotic use in livestock cannot be overlooked in risk analysis and, in any future management strategy, these benefits must be offset against the identified risks. In the terms of reference (see Section 1.2) JETACAR was asked to take account of the benefits to livestock production of antibiotic use. In the time available, JETACAR therefore assessed the evidence from the scientific literature and from representatives of the livestock industries on the benefits of using antibiotics in animals for individual or group treatment and prophylaxis of infections and diseases, or as growth promotants. In addition, alternatives to antibiotic use were canvassed, particularly for prophylactic and growth promotant uses.

Unfortunately, time and resources did not permit a critical quantitative analysis of the benefits of growth promotant antibiotics in food-producing animals. JETACAR members agreed that such an analysis would have assisted its deliberations and in formulating its recommendations.

2.5 Conclusion

JETACAR considered the use of antibiotics in food-producing animals and characterised the hazard based on evidence from the international scientific literature and other available data (including Australian data).

It also assessed the currently available data on the level of exposure of humans to the hazard in an attempt to characterise the risk in broad terms. However, the necessary data were either not available or inadequate for a quantitative risk assessment. While qualitative methods, including risk ranking, modelling and conjoint analysis are available for assessment of other types of risks (Lammerding 1997, Horst 1998), a method(s) has not been developed or validated anywhere in the world for assessment of the issues surrounding the emergence and spread of antibiotic-resistant bacteria and/or genes. It should also be noted that such a risk assessment method, if it was available, would only be applicable to the consideration of individual antibiotics.

However, in considering the stages involved in the spread of antibiotic-resistant bacteria from animals to humans and transfer of antibiotic-resistance genes from animal bacteria to human bacteria, JETACAR has provided a conceptual framework and identified the components that will be required for a qualitative risk assessment method to be developed. The detail of this method must now be worked out for the future assessment of individual antibiotics. As a result of these deliberations JETACAR developed an ongoing and integrated antibiotic-resistance management strategy, which is outlined in Chapter 12.

Chapter 3
Antibiotics and antibiotic resistance

OVERVIEW

Antibiotics are chemical agents that prevent bacterial growth by stopping the bacterial cells from dividing (*bacteriostatic*) or by killing them (*bacteriocidal*). Numerous individual antibiotics are available for the treatment of infections and diseases but they fall into a relatively few, structurally related groups. Some antibiotics are effective against only a limited range of infectious agents (*narrow spectrum*); others are effective against a wider range (*broad spectrum*).

Emergence of resistance

Antibiotic levels that would normally prevent growth or kill a particular bacterium sometimes become ineffective because of changes in the bacterium (*resistance*). If this occurs at the dose used for treatment of infection, the antibiotic is no longer effective.

There are two distinct stages in the emergence of antibiotic-resistant bacteria.

Genetic change — resistance arises either because of a mutation(s) in a bacterial gene that affects the uptake or action of the antibiotic, or because an existing antibiotic-resistance gene is transferred into the bacterium from another resistant bacterium.

Enrichment by selection — once a resistance gene or mutation is present (and is expressed), the cells containing it are able to grow in the presence of the antibiotic and therefore increase in numbers at the expense of the susceptible cells. Naturally resistant organisms are also favoured. The total amount of antibiotic used is a general indicator of the selection pressure and continuous exposure to an antibiotic provides the strongest selection pressure.

Spread of resistance

Spread of bacteria — resistant bacteria move from one ecological niche to another (eg animal to human or vice versa) by direct contact or indirectly (eg in food or water). In this case, as the bacterium itself has 'moved', when cultures from different sources are examined in the laboratory, the bacterial strain and the antibiotic-resistance determinants are identical.

Transfer of antibiotic-resistance genes (horizontal gene transfer) — all bacteria have mechanisms to share genetic material with other bacteria and antibiotic-resistance genes can move from a resistant bacterium into a sensitive one, eg on a small chromosome, plasmid or conjugative transposon. Genes can transfer from commensal to pathogenic bacteria of the same species and vice versa, and also between different species of bacteria. This occurs in the absence of selection. In this case, when cultures of bacteria from different sources are examined, the antibiotic-resistance determinant is the same but the strains or species of bacteria are different.

Coselection

Exposure to one antibiotic can select for resistance to other antibiotics.

Cross-resistance — many individual antibiotic-resistance genes are known and most confer resistance to many or all members of an antibiotic group. Some also confer cross-resistance to antibiotics from structurally unrelated groups.

Cotransfer — the fragments of genomic material that carry antibiotic-resistance determinants often carry more than one resistance gene and determine resistance to more than one antibiotic group. When this genomic material transfers between bacteria, all the resistance genes are transferred together.

3.1 Antibiotics

The term 'antibiotic' was first used to define naturally occurring chemical substances which are produced by various microorganisms and which suppress the growth of bacteria. However, modern common usage extends the term to include synthetic agents such as sulfonamides, nitrofurans and quinolones, which were formerly known as antibacterial or antimicrobial agents.

Antibiotics suppress the growth of bacteria, and hence the infections they cause, in two ways:

- by arresting growth and preventing the bacteria from dividing to produce new progeny (*bacteriostatic*); or
- by killing the bacteria (*bacteriocidal*).

There are a large number of individual antibiotics available for the treatment of bacteria that cause infections or infectious diseases (pathogens). However, they all fall into relatively few groups or families of structurally related antibiotics. The largest group, known collectively as beta-lactam (β-lactam) antibiotics, include the *penicillins, cephalosporins, carbapenems* and *monobactams*, all of which have related structures and the same mechanism of action. Individual members of this group have been tailored to be either most successful for the treatment of particular disease-causing organisms (*narrow spectrum*) or effective against many different pathogens (*broad spectrum*). Other antibiotic groups include the *aminoglycosides*, *tetracyclines*, *macrolides* and *glycopeptides* (see Chapter 7 for further details and Appendix 8 for a full list of antibiotic classes and antibiotics used in Australia).

In most cases, antibiotics from the same families are used in both human medicine and animal husbandry. Antibiotics exert their inhibitory or killing effects in a variety of ways (see Table 3.1).

Table 3.1 Mechanism of action of different groups of antibiotics

Mode of action	Antibiotic group [a]
Inhibits cell wall synthesis	β-lactams (penicillins, cephalosporins, carbapenems, monobactams), bacitracin, glycopeptides
Inhibits protein synthesis	Aminoglycosides, aminocycitols, amphenicols, macrolides, lincosamides, streptogramins, tetracyclines
Interferes with cell membrane function	Polypeptides
Interferes with DNA/RNA synthesis	Quinolones, rifamycins
Inhibits metabolism	Sulfonamides, sulfones, trimethoprim, nitrofurans, nitroimidazoles
Unknown	Polyethers

[a] This grouping does not predict cross-resistance between groups or within groups

3.2 Antibiotic resistance

3.2.1 Susceptibility and resistance

Bacteria naturally differ in their susceptibility to individual antibiotics. Natural resistance to achievable therapeutic doses can occur because the antibiotic cannot readily enter the bacterium or is pumped out (permeability); or because the target molecule for the antibiotic is not present in a particular bacterium. Thus, different antibiotics are often needed to treat infections caused by different organisms.

Antibiotic resistance occurs when a bacterium that is normally susceptible to an antibiotic becomes able to grow in the presence of antibiotic levels that would normally suppress growth or kill susceptible organisms.

Clinical resistance occurs when the bacterium can continue to divide in the presence of the antibiotic concentrations that normally occur during treatment (therapeutic doses) and the antibiotic is no longer effective for treatment.

3.2.2 Emergence of antibiotic-resistant bacterial strains

As already mentioned in Section 2.4.3, there are two stages in the emergence of antibiotic-resistant bacterial strains:

- genetic change (mutation or gene acquisition); and
- amplification and enrichment of resistant bacteria by exposure to antibiotics (*antibiotic selection*).

Genetic change

Antibiotic resistance arises as a result of genetic change. This can occur in two distinct ways (Davies 1997):

- a chance change (*mutation*) in the DNA sequence of relevant gene(s) in the bacterial chromosome; or
- the movement of an antibiotic-resistance gene(s) into one bacterium from another resistant bacterium (*gene acquisition*).

Mutation

Mutation is a natural process that occurs at a frequency of between 1 in 10^6 and 1 in 10^{12} organisms.

Sometimes, a single mutation is enough to cause resistance to a particular antibiotic, and sometimes two or more mutations are needed (eg fluoroquinolone resistance). Mutations generally alter the target of the antibiotic such that the antibiotic is no longer inhibitory, or alter the permeability of the cell, reducing the intracellular concentration of the antibiotic below that needed for inhibition of growth or killing.

While resistance to many antibiotics can arise by mutation, this mechanism is not the most important one except for certain bacteria (eg *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*).

Another type of mutation occurs when cells take up naked DNA, parts of which are incorporated into the bacterial chromosome by recombination with closely related DNA therein. In this case, the incoming DNA is generally from a related bacterial species and recombination forms mosaic genes made up of stretches of DNA from the chromosome combined with stretches of the new DNA (Maiden 1998).

This uptake of foreign DNA is referred to as 'horizontal gene transfer' but differs from horizontal gene transfer by plasmids and conjugative transposons (see below) in two important ways: (i) it does not require cell-to-cell contact, and (ii) once the new DNA is incorporated, it is not readily retransferred to other cells. So, in effect, further transmission of these 'mutations' resembles that of spontaneous mutations in that the alteration can only be passed on to progeny (vertical transmission).

Development of resistance by this mechanism is most important in genera such as neisseria and streptococcus, which readily take up DNA, and resistance to penicillins can

arise in this way. The mechanism of resistance in this case is via alteration of penicillin binding proteins such that they have a high affinity for the antibiotic and sequester it, thereby preventing its action on the inhibitory target.

Acquisition of resistance determinants

The movement of an antibiotic-resistance gene(s) from one bacterium to another can happen in many ways but most commonly occurs via transfer of a small chromosome, either a plasmid or a conjugative transposon (Figure 3.1). This type of *horizontal gene transfer* relies on contact between the cells that are exchanging DNA and can occur very efficiently under some conditions and poorly under others (Salyers et al 1995) (see Section 3.3).

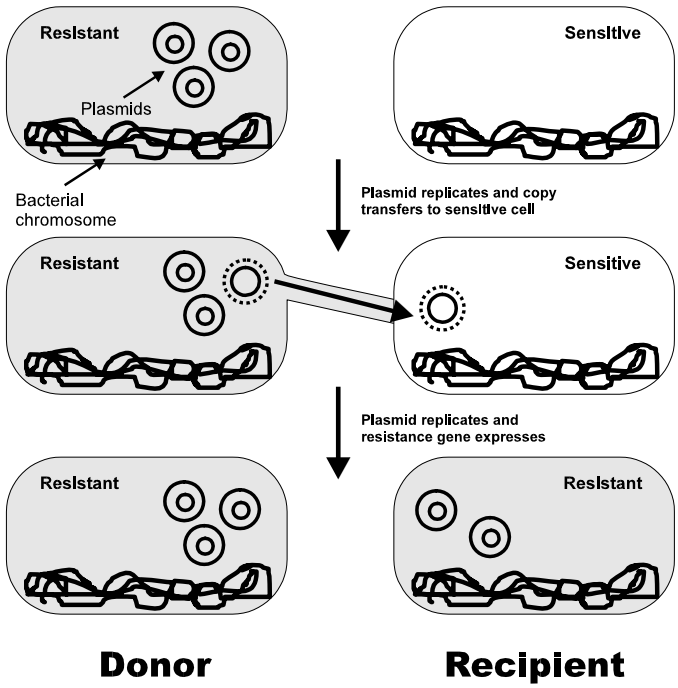

Figure 3.1 **Movement of antibiotic-resistance genes from one bacterium to another by conjugation**

Once incorporated in the bacterial cell, the antibiotic-resistance gene is 'expressed', making the bacterium resistant to the antibiotic concerned in a number of ways, including:

- reducing the amount of antibiotic that enters the bacterial cell and reaches the target by
  - pumping the antibiotic out of the cell, or
  - altering the permeability of the cell to the antibiotic;
- altering the antibiotic so that it no longer has activity (eg through enzymes such as β-lactamases);
- modifying the target of the antibiotic in the bacterial cell so that it is no longer affected; or
- replacing the target with one that is not affected by the antibiotic.

The origin of the many antibiotic-resistance genes that now circulate in bacterial populations is not currently known, but it is generally accepted that they existed in bacterial populations before the discovery and use of antibiotics in human and veterinary medicine. For example, bacteria that produce a particular antibiotic need mechanisms to

protect themselves and consequently contain genes that confer resistance. The occasional, perhaps even rare, movement of resistance genes into populations of bacteria associated with humans and animals is likely to have always occurred.

Enrichment of resistant bacteria by antibiotic selection

Selection is the process that leads to the increased prevalence of resistant bacteria in a particular niche. When an antibiotic is present, susceptible cells are unable to divide and their numbers do not increase. However, if one or more resistant cells are present, these will be able to grow and divide, thus increasing the number of resistant bacteria (*amplification*) and also the proportion of resistant organisms in the total population of that bacterium (*enrichment*).

Selection occurs at any dose of antibiotic that is higher than the concentration needed to inhibit susceptible (or sensitive) bacteria and below the concentration needed to inhibit the resistant bacteria (Levin et al 1997, Baquero et al 1998). However, the level of resistance (ie the concentration above which the resistant cells no longer grow) is a property of the particular mutation or resistance gene and its context, and is not influenced by the concentration of antibiotic to which the organism is being exposed. Exposure to low levels of antibiotics does not therefore reduce the risk of selection for bacteria that are resistant to higher doses.

Thus, exposure of mixed bacterial populations to almost any antibiotic concentrations is significant because, in the broad range of bacterial species within a particular ecological niche, there are likely to be a number that will be resistant to that concentration due to either natural resistance or resistance by mutation or an acquired resistance gene(s). These then survive and proliferate, and some may be able to pass their resistance gene(s) to other bacteria.

The extensive use of antibiotics over the last 50 years has applied a powerful selective pressure, amplifying the resistant bacteria and creating a large pool of resistant bacteria. This favours a much more extensive spread of resistant bacteria and transfer of resistance genes in and between animals and humans.

If there is a significant pool of resistant organisms in one domain (eg in an animal production facility), the probabality of resistant organisms moving into a second domain (eg hospital environment) is increased. However, once the resistant organisms have moved into into the second domain, establishment of a significant pool of resistant organisms again requires selective amplification through the use of the same antibiotic or one that coseclects for the same resistance gene.

It is widely believed that the method of drug administration (exposure) can influence the selection for antibiotic resistance. The duration of treatment is important because continuous exposure to antibiotics provides the strongest selective pressure, but there is currently little scientific evidence to clarify the importance of effect of dose level. Work has only recently begun on the population dynamics of antibiotic resistance (see Section 7.5).

Exposure to two doses of antibiotics can be important where multiple mutations are needed to achieve clinically significant levels of resistance. In this case, one mutation can lead to low-level resistance and when this population is amplified the probability that a second mutation will occur to give a higher level of resistance is increased. This effect is seen with fluoroquinolone resistance in highly susceptible bacteria such as *E.coli* (Hooper 1998).

3.3 Spread of antibiotic resistance

To assess the impact of antibiotic resistance in bacteria from one ecological niche (eg farm or hospital, animal or man) on the incidence of resistant bacteria in another, a number of different factors need to be taken into account.

3.3.1 Spread of resistant bacteria

Spread can involve the movement of resistant pathogenic bacteria themselves from one ecological niche to another (eg animal to human or vice versa). Such spread can be by direct contact (eg between animal and human) or by indirect means (eg via the food chain or water supply). The possible pathways for spread of enteric bacteria are also shown in Chapter 4 (Figure 4.1).

In this case, as it is the bacteria that have moved rather than the resistance genes, when laboratory cultures from the different sources are examined, the bacterial species/strain and the resistance determinant (mutation or gene) are exactly the same and this identity can be accurately detected using modern molecular methods. For several types of bacteria, eg specific salmonella strains, this type of spread has been well documented as these organisms are known to be zoonotic. The spread of resistant organisms globally has also been documented, and presumably occurs because of the movement of the hosts (animals or human) or contaminated products (food, water) from one location to another, even across country borders and between continents.

When resistance arises by mutation (eg fluoroquinolone resistance), this is the only type of spread that can occur.

Because of this type of movement, a particular resistant organism need only arise once at any point in the world. Furthermore, the probability of spread is increased by the use of antibiotics that favour the growth of resistant bacteria over sensitive ones, because this substantially increases the size of the pool of resistant organisms available.

3.3.2 Spread of resistance genes

For many important human pathogens, resistance develops mainly as a result of the acquisition of antibiotic-resistance genes by movement from a resistant bacterium into a formerly sensitive pathogen.

This movement of genes occurs by a process known as horizontal gene transfer (see Section 3.2.2). The resistant bacteria donate resistance genes to other bacteria in the same ecological niche (eg animal gut, human gut, pond, river) leading to the potentially rapid and extensive transfer of genes in the bacterial population. Thus, a harmless bacterium that is resistant can donate its resistance gene(s) to a pathogen.

Furthermore, the initial event need not be the establishment of an antibiotic-resistant pathogen because, if resistance due to an acquired resistance gene is established in a harmless bacterium, it can subsequently transfer into pathogens by horizontal gene transfer.

Gene transfer respects neither strain, species nor genus boundaries. The frequency of transfer depends on the particular plasmid or conjugative transposon and the relationship between the two bacteria involved. Transfer frequencies are highest when the bacteria are of the same species and strain. Under these conditions, transfer frequencies of different plasmids can be extremely high (10% per recipient or higher for some plamids) or substantially lower (10^{-6} per recipient for others). Interspecies transfer is less efficient because bacteria possess a variety of mechanisms to recognise and destroy foreign DNA.

However, once a plasmid is established in a new host, transfer frequencies to other bacteria of the new strain or species again rise, as the DNA is no longer marked as foreign.

As soon as the resistance genes become established in one bacterial strain, movement into further bacteria can occur. If the resistant bacterium is amplified by selection, the probability that this will occur increases. The likelihood that the resistance determinant will make its way into other strains and species of bacteria is thus greatly influenced by the total selective pressure of exposure to antibiotics.

Transfer of plasmids and conjugative transposons occurs in the absence of antibiotics. These small genomes existed before antibiotic use and also carry genes for other functions (eg virulence, ultraviolet (UV) resistance, resistance to heavy metals and toxins, metabolic functions). Plasmids have largely acquired resistance genes since the use of antibiotics by humans became common. The most important factor in the acquisition of antibiotic-resistance genes are small mobile genomes, transposons and gene cassettes that include antibiotic-resistance genes and are able to move from one genome (bacterial chromosome, plasmid or conjugative transposon) to another (Salyers et al 1995, Hall and Collis 1998).

The capacity of transposons and gene cassettes to move to a new location permits them to enter a cell on a plasmid that cannot be maintained (survive) in the cell, but the resistance gene(s) can nonetheless be retained by moving to the bacterial chromosome or to another plasmid already resident in that cell. This phenomenon appears to occur quite commonly and is also an important force in the transfer of resistance genes throughout the bacterial community.

In this case, because it is only the genetic determinant of resistance that is transferred, when laboratory cultures from the different sources are examined, the resistance genes are identical but they are present in different bacterial species or strains. This type of transfer was first reported over 35 years ago and has since been extensively studied and documented (Davies 1997). Furthermore, abundant recent literature documents that identical antibiotic-resistance genes are found in different human pathogens (*E. coli*, shigella, salmonella, klebsiella, enterobacteter, pseudomonas vibrio and enterococcus or enterococcus, streptococcus and staphylococcus) (Hall 1997, Roberts 1997, Salyers and Amábile-Cuevas 1997).

Identical resistance genes have also been found in animal and human pathogens and commensals and in human and plant pathogens. Because the probability that the same gene sequence (500–2000 units of information) would arise twice independently is vanishingly small, this indicates that resistance genes are moving readily from one bacterial species to another and also transferring from one niche (animal, human, plant) to another, presumably by the spread of resistant bacteria from niche to niche.

Transfer of resistance genes is thus an extremely important factor, if not the most important factor, in understanding the emergence of antibiotic-resistant pathogens.

3.4 Coselection

Two factors, which are often overlooked, are important in assessing the impact of the use of an individual antibiotic on resistance to other antibiotics. These are cross-resistance to different antibiotics conferred by a single genetic determinant, and cotransfer of multiple antibiotic-resistance genes, only one of which is selected for, due to their association on a single plasmid.

3.4.1 Cross-resistance caused by single genetic determinants

Many mutations or single transferable antibiotic-resistance genes confer resistance to many or all members of an antibiotic family (eg resistance to vancomycin and avoparcin, teicoplanin and ardacin, which are all glycopeptides, is caused by the same resistance gene clusters). Thus selection for resistance to avoparcin (used in animals as a growth promotant and/or prophylactic antibiotic) also selects for resistance to vancomycin (used in human medicine to treat staphylococcus and enterococcus infections that are resistant to other effective antibiotics) and vice versa.

A single antibiotic-resistance gene can also cause cross-resistance to structurally unrelated antibiotics (ie members of different antibiotic groups). This can occur, for example, when the antibiotic target is the same and resistance is caused by modifying the target. This is known to occur for the *erm* genes that confer resistance to macrolides, lincosamides and streptogramins B, and members of all three of these antibiotic families are used in both human medicine and animal production. Though *erm* genes confer resistance to macrolides, lincosamides and streptogramins B, these genes are normally expressed only in the presence of certain macrolides (eg erythromycin). However, mutations readily eliminate this effect.

In some bacteria, a single mutation can also cause resistance to multiple antibiotics, such as tetracycline, chloramphenicol, trimethoprim, and some penicillin family antibiotics. This resistance appears to be due to a complex set of changes that alter the permeability of the cells and, in particular, pump these antibiotics out of the cell (efflux).

3.4.2 Transfer of unselected resistance genes by cotransfer

The small chromosomes, plasmids or conjugative transposons, which carry resistance genes from bacterium to bacterium, frequently carry more than one antibiotic-resistance gene, and these are transferred together. Selection with one antibiotic thus, incidentally, selects for bacteria that are resistant to all the antibiotics affected by the set of genes involved. For example, if a plasmid carries two antibiotic-resistance genes, one determining resistance to tetracyclines and one determining resistance to aminoglycosides, selection with a tetracycline would enhance the advantage of bacteria containing that plasmid, which are resistant to both tetracyclines and aminoglycosides. In this situation, the resistance to aminoglycosides is said to be unselected.

Plasmids that carry five or more different resistance genes, each affecting a different antibiotic family, are commonly isolated from antibiotic-resistant pathogens (multiple resistance). When determinants of resistance to heavy metals (eg mercury, copper, arsenic) are carried on the same plasmid as an antibiotic-resistance gene, exposure to these metals also selects for the genetically linked but unselected resistance genes.

Although the phenomenon of cotransfer was first seen over 35 years ago, this important influence on the problem of bacterial resistance has generally been ignored in the assessment of new antibiotics for veterinary or medical use. Because of this phenomenon, it is not possible to consider the use of individual antibiotics, or of antibiotic families, and their transferable resistance genes in isolation from other antibiotics and their resistance genes. Thus, if an antibiotic from an antibiotic family that is not used in human medicine is used in animal production, it may still affect the levels of bacteria that are resistant to important human antibiotics.

In addition, genes for toxins and for determinants of virulence, which increase the severity and likelihood of infections, are also found on plasmids. When antibiotic-resistance genes are on the same plasmids, antibiotic use also selects for these factors.

Chapter 4
Bacteria of concern

OVERVIEW

Classification

Bacteria differ in their structure and staining properties (gram-negative or gram-positive), shape (rods or cocci), metabolism (aerobic or anaerobic), disease mechanism (eg entero- and exotoxins) and their responses to antibiotics. Gram-negative bacteria (including salmonella and campylobacter), which have a cell wall with an outer membrane, are intrinsically more resistant to most antibiotics than other gram-positives (eg staphylococci, streptococci). Other nontypical bacteria that do not stain with Gram stain due to an absence or modification of the cell wall include mycobacteria, mycoplasmas, chlamydia and ricksettia.

Enteric, potentially foodborne bacteria

Nontyphoid salmonellae, campylobacters, *Eschericia coli* and enterococci were selected for special study in this review because they are all enteric bacteria and are considered to be the most likely bacteria to be frequently transmitted from animals to humans in the food chain.

Salmonellae (nontyphoid) and campylobacters — zoonotic bacteria that are transferred to people by direct contact with animals or animal products. They are the two most common causes of foodborne illness (gastroenteritis) and are mainly transmitted on red meat and chicken, which are easily contaminated during slaughter by bacteria from the gastrointestinal tract of animals. These bacteria also occasionally cause more serious tissue and blood infections.

Enterococci and *Escherichia coli* — part of the normal gut flora of humans and animals (commensals) but these bacteria can cause disease if they gain access to other tissues or wounds, particularly in immunocompromised people (eg transplant or cancer patients, the very young or very old). Humans and animals have many specific strains and many other overlapping ones. Some of these strains can be transmitted from animals to humans by close contact or through food. There has been particular concern worldwide about the emergence of enterococci strains that are resistant to the antibiotic vancomycin (a glycopeptide) and its relationship to the use of avoparcin (a related glycopeptide) in animal feeds. There have been over 70 clusters of vancomycin-resistant enterococcal infections so far in Australia.

Other bacteria of concern in human medicine

The foodborne bacteria do not generally cause the most serious human diseases (although they can all cause serious, life-threatening infections in the absence of suitable antibiotic treatments. Overall, most strains of *E. coli* and enterococci are less pathogenic than bacteria such as pneumococci (*Streptococcus pneumoniae*), 'golden staph' (*Staphylococcus aureus*) and tuberculosis (*Mycobacterium tuberculosis* complex).

The latter three cause much more severe and/or serious human disease but, at present, there is no evidence that they (or the antibiotic-resistance genes that they carry) are transmitted from animals to humans, particularly via the food chain. Indeed, with many of these latter bacteria, the emergence and spread of antibiotic-resistant bacteria is due to the use (and frequently abuse) of antibiotics in humans and is not related to the use of antibiotics in animals.

4.1 Classification of bacteria

Bacteria differ in their structure and staining properties (gram-negative or gram-positive), shape (rods or cocci), metabolism (aerobic or anaerobic), disease mechanism (eg entero- and exotoxins) and their responses to antibiotics. Three major groups of bacteria can be distinguished by the properties of their cell wall.

- *Gram-positive bacteria* (rods or cocci) have a monolayered cell wall with large amounts of the polymer peptidoglycan. They retain Gram stain (crystal violet and iodine) after solvent treatment with alcohol or acetone, which makes them appear deep blue under the microscope. These bacteria may produce proteins called exotoxins that are often associated with specific disease symptoms.
- *Gram-negative bacteria* (rods or cocci) have less peptidoglycan (inner layer) than gram-positive bacteria but their cell wall has an outer membrane. This prevents them taking up and retaining Gram stain and they are decolourised by alcohol or acetone. Substances on the outer membrane of the cell wall are often toxic (endotoxins) and the outer membrane helps to protect the bacteria against the host's defences. Gram-negative bacteria are often more resistant to antibiotics because their outer membrane impedes antibiotic entry.
- *Acid-fast species* have a different type of cell wall that makes Gram staining difficult but allows them to retain certain types of red stain, such as basic fuschin, and appear red even after acid treatment.
- *Small species (eg Mycoplasma)* have no cell walls (cell membrane only).

Another important distinction between different bacteria is in the effect of oxygen on growth. Obligate aerobes use oxygen for cellular respiration and cannot grow without it. Facultative anaerobes use oxygen if it is present but can also grow by fermentation in an anaerobic environment. Obligate anaerobes cannot use oxygen and are poisoned by it. Examples of these groups of bacteria are shown in Table 4.1.

Table 4.1 Examples of the main types of bacteria involved in human infections

Stain	Shape	Respiration	Examples
Gram-negative	Rods	Aerobes/ facultative	Enteric bacteria (eg shigella, salmonella, campylobacter, *E. coli,* enterobacter), klebsiella, pseudomonas, *Haemophilus influenzae*
		Strict anaerobes	Bacteroides, fusobacterium
	Cocci	Aerobes/ facultative	*Neisseria meningitidis* (meningococcus), *N. gonorrhoeae (*gonococcus)
		Strict anaerobes	None of major clinical importance
Gram-positive	Rods	Aerobes (incl facultative)	Corynebacteria, listeria
		Strict anaerobes	Clostridia, *Propionibacterium acnes*
	Cocci	Aerobes (incl facultative)	Staphylococcus, streptococcus, enterococcus
		Strict anaerobes	None of major clinical significance
Acid fast	Rods	Aerobes	Mycobacteria (*M. tuberculosis*, *M. leprae*)
Nontypical	Small		Chlamydia, rickettsia, mycoplasma

4.2 Transmission of disease

Bacteria can be transmitted from person to person, environment to person or animal to person by physical contact, excretions (faeces, urine, respiratory droplets), contaminated food or water, or vectors (eg flies). Table 4.2 shows some examples of transmission of human bacterial infections.

Table 4.2 Examples of the transmission of bacteria involved in human infections

Bacteria	Human diseases	Principal means of transmission
Salmonella		
S. Typhi, *S.* Paratyphi	Typhoid, paratyphoid	From human to human, usually by human faecal contamination of food and water or poor hygiene by carriers.
S. Typhimurium and related strains	Gastroenteritis (salmonellosis)	Found in the intestinal tract of animals, which may not show any symptoms; shed in faeces and can contaminate water, food, etc; usually transmitted to humans on red and white meat, dairy or other food products (contaminated from animal's intestinal tract during slaughter).
Campylobacter *C. jejuni, C. coli*	Gastroenteritis (campylobacteriosis)	As for salmonella (ie food, water, etc); particularly poultry and pigs.
Escherichia coli	Enterotoxic strains cause gastroenteritis and haemorrhagic colitis. Other strains usually harmless but can cause intestinal/urinary/genital tract infections.	Food, water, faeces
Enterococcus *E. faecalis, E. faecium*	Mainly intestinal and urinary/genital tract infections, septicaemia.	Food, faeces
Staphylococcus *S. aureus*	Skin, blood, heart, bone and wound infections ('golden staph'); gastroenteritis (enterotoxins in food).	Contact, food (contamination by infected humans), respiratory droplets
Shigella		
S. flexneri and *S. sonnei*	Gastroenteritis	Food, faeces (human to human only)
S. dysenteriae	Bacterial dysentery	
Clostridia		
C. perfringens	Gastroenteritis (caused by enterotoxin), gas gangrene	Food (meat and poultry), faeces, environment
Klebsiella	Pneumonia, abscess	Faeces (incl person to person)
Neisseria		
N. meningitidis	Meningococcal meningitis, septicaemia	Respiratory droplets
N. gonorrhoeae	Gonorrhoea	Sexual contact
Pseudomonas *P. aeruginosa*	Urinary tract infections, pneumonia, meningitis	Person to person, water
Streptococcus		
Group A strep (eg *S. pyogenes)*	Wound infections, scarlet fever, rheumatic fever	Respiratory droplets
S. pneumoniae	Middle ear infection, sinusitis, bronchitis, pneumonia, meningitis, septicaemia	Respiratory droplets
Haemophilus influenzae	Respiratory infections, bacterial meningitis (children)	Respiratory droplets
Mycobacterium	Tuberculosis, pneumonia	Respiratory droplets
Chlamydia	Urethritis, pelvic inflammatory disease, respiratory infections	Sexual contact and respiratory droplets

Note: There are many other important examples not shown in the table (eg listeria, yersinia, vibrio among the foodborne infections and corynebacteria, bacteroides and mycoplasma among other infections). Those shown in the table are examples only and have been included to show the main forms of transmission.

4.3 Bacteria of concern for transmission of antibiotic resistance from animals to humans

Nontyphoid salmonellae, campylobacters, *Escherichia coli* and enterococci were selected for special study in this review because they are considered to be the bacteria that are most likely to be frequently transmitted from animals to humans, via food. This is because they are all enteric bacteria for which the predominant route of spread from animals to humans is the food chain.

Humans acquire enteric bacteria from a number of sources, primarily due to poor hygiene and sanitation, either personally or through the actions of others. The single most important principle is that the organisms are spread through animal or human faeces either directly or via objects, including food.

Gross contamination through poor personal hygiene and sanitation will result in the spread of the bacteria from object to object or from food source to food source. The potential options for transfer of enteric bacteria to humans form a complex web of possible pathways. These pathways need to be clearly understood if control of the spread of organisms is to be effectively managed. Figure 4.1 highlights the complexity of the transmission routes to be considered in dealing with the spread of antibiotic resistance from animals to humans and from humans to other humans.

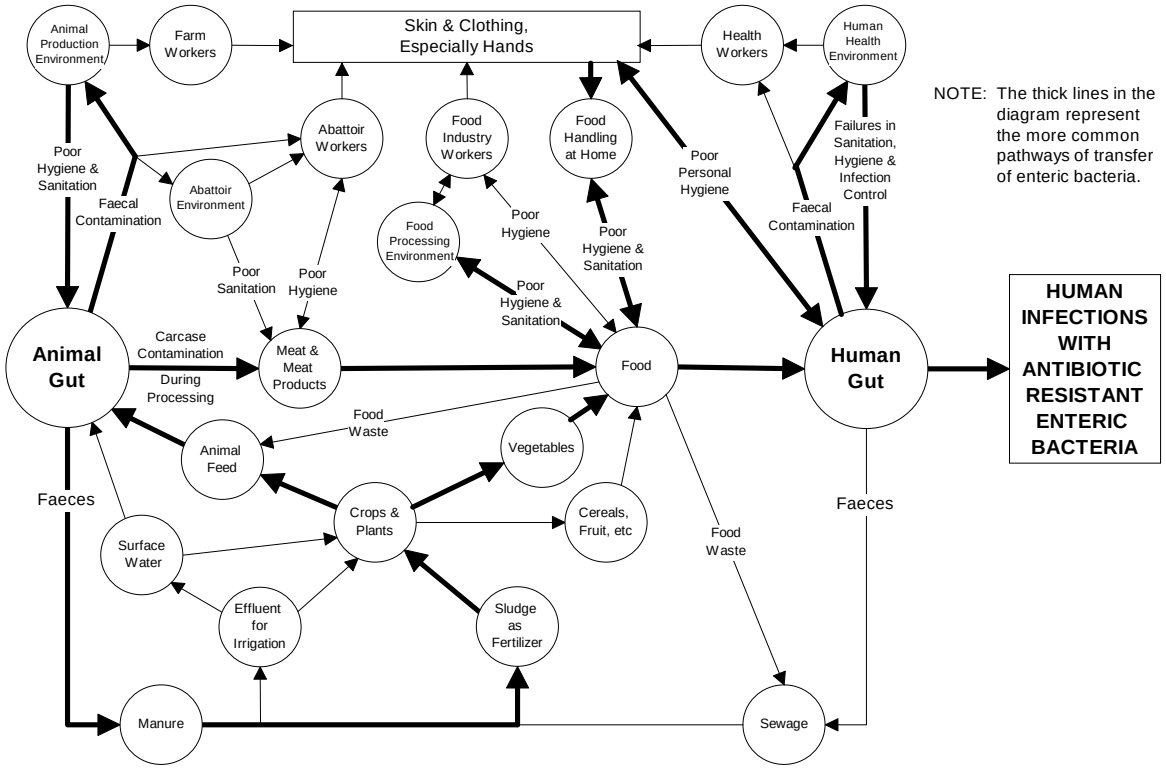

Figure 4.1 **Possible pathways for the spread of enteric bacteria, including resistance strains, with the gastrointestinal tract as the main reservoir, between animals and humans (adapted from Witte 1997)**

In the last 20 years there has been heightened worldwide concern about microbiological contamination of food along with increasing numbers of immunocompromised people (aged, transplant and AIDS patients) in the population, who are particularly vulnerable to such infections. The emergence of the enterotoxigenic *E. coli* as an important foodborne pathogen, increased consumption of raw foods and mass prepared 'fast' foods have all contributed to the reported increase in levels of enteric disease (see Section 4.3.1).

However, the foodborne bacteria do not generally cause the most serious human diseases (although they can all cause serious, life-threatening infections). Most strains of *E. coli* and enterococci are less pathogenic than bacteria such as pneumococci (*Streptococcus pneumoniae*), 'golden staph' (*Staphylococcus aureus*) and tuberculosis (*Mycobacterium tuberculosis* complex). The latter three cause much more severe and serious human disease but, at present, there is no evidence that they (or the antibiotic-resistance genes that they carry) are transmitted from animals to humans, particularly via the food chain.

In consideration of the transmission of antibiotic resistance from animals to humans, the main concern is that antibiotic-resistance genes from foodborne bacteria infecting humans may transfer into the other more virulent human pathogens, such as golden staph. To date, there is no evidence that this has occurred with *S. aureus*. A review of the international literature provides evidence that resistance genes in animal enterococci have been transferred to enterococci isolated from humans (see Chapter 5 for results of the literature review).

In the past, an antibiotic-sensitive form (*Mycobacterium bovis)* of tuberculosis (TB) was transmitted from animals to humans (eg in milk). However, eradication of TB from Australian cattle herds and pasteurisation of milk products has eliminated TB as a risk from milk products in Australia. Continued efforts to eradicate other animal diseases could similarly reduce the threat to humans, not only of infection by the bacteria concerned but also of the transfer to human bacteria of any antibiotic-resistance genes carried in those bacteria.

Most growth promotant antibiotics are only active against gram-positive bacteria. Indeed, there are currently no antibiotics with growth promotant properties that do not have this spectrum. Salmonellae and *E. coli* (gram-negatives) are therefore not sensitive to growth promotants. Campylobacters (gram-negative) are not sensitive to most growth promotant antibiotics, but are sensitive to macrolides. Enterococci (gram-positive) are sensitive to most growth promotants, including glycopeptides, macrolides, streptogramins and polyethers.

4.3.1 Salmonella and campylobacter

Nontyphoid salmonellae (see Table 4.2) and campylobacters are zoonotic bacteria (ie they are transmitted from animals to humans and cause disease in humans) and are two of the most common causes of foodborne illness. They are mainly transmitted on meat, particularly chicken, because the animal carcases can be contaminated with intestinal contents, including faeces, during slaughter, especially if handling techniques are poor. Consumption of raw or undercooked meat, or contamination of other raw food, causes the bacteria to be ingested by humans. The numbers of bacteria ingested can be very high, especially if food has not been stored or cooked correctly (eg poor refrigeration, poor hygiene, poor handling), allowing the bacteria to multiply or persist at a high level. Despite improvements in food handling, the incidence of gastroenteritis caused by these organisms has been increasing in most Western countries over the last two decades.

Salmonella

Infections

The genus *Salmonella*[5] is a group of enteric bacteria that cause a wide variety of human diseases.

In the most severe form of salmonella infection, *Salmonella* Typhi and the related strains of *S*. Paratyphi cause the clinical syndrome of typhoid fever. Untreated, this condition has a high mortality. These bacteria are purely human pathogens and the infection is usually transmitted from an infected person or carrier by faecal contamination of water or food.

Other types of salmonella (nontyphoid) are most commonly acquired from food sources and cause a variety of clinical disease, including asymptomatic infection (most common), gastroenteritis and, in rare cases, heart and blood infections, arthritis or infection at virtually any site if the bacterial infection becomes systemic. Nontyphoid salmonellae are also an important cause of enteritis in animals. Both humans and animals can be subclinical carriers of salmonella.

The most common clinical manifestation is salmonellosis (ie gastroenteritis or a form of 'food poisoning'), which includes nausea, vomiting, diarrhoea, abdominal pain, and symptoms of fever and chills. This can be mild, with only several loose bowel actions, or can be severe enough to cause hospitalisation due to profuse diarrhoea and, in rare cases (particularly in the very young and very old), death due to dehydration or blood poisoning.

In Australia, few cases of gastroenteritis have stool samples submitted to a laboratory but, of those that do, about 2% show salmonella, making it about the fourth most common identified cause of diarrhoea (after a number of gastroenteritis viruses and campylobacter). It is the second most common form of notified foodborne disease (after campylobacteriosis).

The numbers of notified cases of salmonellosis in Australia increased from 2494 in 1986 (16 per 100,000) to 6826 (37 per 100,000 population) in 1997 (National Notifiable Diseases Surveillance System annual reports). This increase is the same as seen in other Western countries. However, it is likely that only a small proportion of actual infections are ever diagnosed microbiologically because many infected people never go to the doctor and when they do faecal cultures are only performed for patients that are very ill or have a longer than usual illness. Notified cases are therefore only likely to represent a very small minority of gastroenteritis cases per year. Many other subclinical infections also occur, providing a reservoir for further transmission.

In Australia, most cases of salmonellosis are due to *Salmonella* Typhimurium. Another strain of salmonella, *S*. Enteritidis, has become the most common form in the United Kingdom, other parts of Europe and South America and other countries overseas. In these countries, eggs and egg products can be contaminated with this salmonella strain. *S*. Enteritidis is rare in Australia and is confined mainly to international tourists or travellers returning to Australia from overseas. It has not been found in Australian poultry products.

[5] Current classification groups all the salmonellae that infect vertebrates into a single species, *S. enterica,* within which there are subspecies and serovars (or strains); for simplicity these serovars are designated, for example, as *Salmonella* Typhi or *S*. Typhimurium, rather than in full as *S enterica* serovar Typhi, etc.

Antibiotic resistance

Currently, *Salmonella* Typhi can usually be treated with fluoroquinolones and chloramphenicol, and many strains still respond with trimethoprim–sulfamethoxazole (co-trimoxazole), and some β-lactams (ampicillin). Internationally, antibiotic resistance is more variable in the foodborne salmonellae but in Australia these bacteria can generally be treated with fluoroquinolones, chloramphenicol, and some β-lactams.

Most cases of gastroenteritis are self-limiting and do not require antibiotic treatment, but more virulent or invasive disease can also occur (eg septicaemia). Increasing resistance, particularly to any of the above antibiotics, would cause significant treatment problems in such cases.

A multiresistant strain of *Salmonella* Typhimurium of phage type DT104 initially emerged in cattle in the United Kingdom in 1988. It has subsequently been isolated from poultry, sheep, pigs and horses and has spread widely to humans in several overseas countries. It has not been found in Australian livestock. It causes more severe disease than other salmonella strains, with more hospitalisations and deaths. Recently, resistance to fluoroquinolones has become common in many of these strains overseas, leaving no effective antibiotics for treatment for many of these infections.

Host specificity

S. Typhi is host-specific for humans and does not infect any other species. The foodborne salmonella strains, however, are zoonotic bacteria and are capable of spreading between different animal species and from animals to humans, often causing asymptomatic infections (particularly in animals).

Campylobacter

Infections

Campylobacters (most commonly *Campylobacter jejuni* and *C. coli*) can be carried asymptomatically by humans and animals. They are rarely pathogenic in animals but commonly cause gastroenteritis in humans. About 7% of all gastroenteritis patients where samples are submitted to a laboratory have campylobacter, making it the most common cause of bacterial gastroenteritis in most areas of the world, including Australia. The most common species of campylobacter, including *C. jejuni* and *C. coli*, grow best at 42ºC and are referred to as 'thermophilic' campylobacters. The symptoms of campylobacter infection are generally nausea, vomiting, diarrhoea, abdominal pain and systemic symptoms, including fever. However, as already described for salmonella, any body site can occasionally be affected. Hospitalisation is uncommon and death is rare.

The number of notified cases of campylobacter-induced gastroenteritis (campylobacteriosis) in Australia increased from 2922 in 1986 (23 per 100,000) to 11,848 (97 per 100,000 population) in 1997 (National Notifiable Diseases Surveillance System annual reports).

Antibiotic resistance

In vitro, *C. jejuni* is susceptible to a wide variety of antimicrobial agents, including erythromycin (and other macrolides), the tetracyclines, the aminoglycosides, chloramphenicol, quinolones, nitrofurans, and clindamycin (lincosamide). Erythromycin is the most effective and commonly used antibiotic in those cases where therapy is needed. Resistance to the other effective agents (fluoroquinolones) is rapidly increasing overseas (eg The Netherlands) where these agents are used as therapeutic agents for food-producing animals. The further emergence and spread of resistance would limit the ability to treat this infection.

Host specificity

Many animals can carry or be infected with campylobacter species and show no sign of disease. Chickens are frequent carriers of the bacteria but, unlike humans, they do not show any signs of disease. Campylobacter are zoonotic bacteria and can spread easily between different animals and between animals and humans.

4.3.2 *Escherichia coli* and enterococci

Enterococci and *Escherichia coli* are commensal bacteria in both animals and humans. That is, they form part of the flora of bacteria that live continuously on or in parts of the body (in this case the gut) without causing disease. They can cause disease, however, if they gain access to parts of the body (wounds, for example) apart from their normal habitat. This can happen most easily in immunocompromised people, such as those with AIDS, transplant or cancer patients, or in the very young or very old. As for salmonella and campylobacter, however, they can also be transmitted from animals to humans through close contact or in food contaminated by animals. Once present in the hospital environment, the use of relatively large amounts of antibiotics will favour the selection and amplification of resistant bacteria (see Section 3.2.2)

Escherichia coli

Infections

E. coli continues to be a common cause of many human infections. The principal natural environment for *E. coli* is the gut, where most strains are nonpathogenic commensal organisms. Most human infections with pathogenic strains are associated with the bowel or the genital and urinary systems. When there is an infection in the abdomen (eg appendicitis, cholecystitis, perforated bowel, abdominal abscesses), *E. coli* is frequently one of the organisms involved. It is also the most common cause of infection in the urinary tract, in particular infections of the kidneys and bladder. It is also often a cause of complicating problems with the genital tract (eg infections of the prostate, ovaries and uterus) and is one of the most common causes of septicaemia. In addition, *E. coli* can cause infection at any site in the human body and is therefore also involved occasionally with problems such as pneumonia, respiratory sinus infections and intravenous catheter infections.

There are a number of strains of *E. coli* that produce toxins that can cause severe disease. Of the more serious are the shiga toxin-producing strains of *E. coli* such as O157 that cause severe bloody diarrhoea and can be associated with kidney failure and the haemolytic-uraemic syndrome (HUS). These latter strains appear to be predominantly (but not exclusively) spread through food from animals to humans (zoonotic).

Antibiotic resistance

At present, antibiotic resistance is common but, as yet, it is not a major treatment problem for *E. coli*. In Australia, *E. coli* shows widespread resistance to simpler agents, such as amoxycillin and cephalothin, but it has generally remained sensitive to the more recently introduced antibiotics (eg third-generation cephalosporins, carbapenems and fluoroquinolones) and to most aminoglycosides (eg gentamicin). However, because of the common and serious nature of *E. coli* infections, resistance to the currently used antibiotics would cause major problems for human health if it becomes widespread.

Host specificity

Pathogenic strains of *E. coli* are often restricted to specific serotypes. Serotypes that cause disease in animals are mainly different from human pathogens but there are some animal strains that that do infect humans and cause disease (eg enterohaemorrhagic *E. coli* O157, see above). The extent to which *E. coli* strains from animals can colonise human intestinal

tracts is unknown. In animals, sequential studies have shown that colonising strains (commensals and pathogens) change over time.

A study of tetracycline-resistant *E. coli* in which volunteers were given sterile food for 20 days after a control period of 21 days (Corpet 1988, 1993), showed that most tetracycline-resistant enteric *E. coli* came from food (and presumed animal sources). These foodborne strains colonised (mostly transiently) the human bowel in large numbers (Figure 4.2).

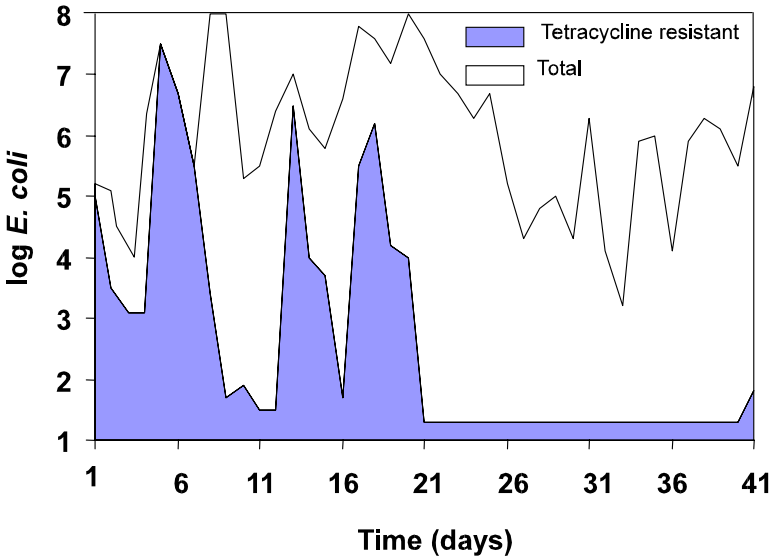

Figure 4.2 **Tetracycline-resistant and sensitive *E. coli* from a volunteer eating nonsterile food (days 1–21) and sterile food (days 21–40) (from Corpet 1993)**

Enterococci

Infections

The two most common *Enterococcus* species causing human infections are *Enterococcus faecalis* and *Enterococcus faecium*. These organisms were previously called streptococci and therefore descriptions in the literature can be confusing, as they were previously described as *Streptococcus faecalis* and *Streptococcus faecium*.

The enterococci are enteric commensal bacteria that form part of the gut flora of animals and humans and are usually harmless. However, they are becoming increasingly frequent pathogens, particularly in hospitals. They can cause infection at any site in the human body and, like *E. coli*, they are principally associated with infections in the abdomen, genital and urinary systems. They are frequently involved in the same types of infections as *E. coli*, including infections or abscesses in the abdomen (eg appendicitis, gall bladder infection) and urinary tract infections. They are less common but important causes of septicaemia and heart valve infection.

Further information about life-threatening infections that can be caused by enterococci is given in Section 4.4.1.

Antibiotic resistance

Until 20 years ago, enterococci were sensitive to many of the simpler penicillin agents (eg amoxycillin, penicillin) and were not regarded as very important human pathogens. However, since then the number of infections caused by these bacteria has risen considerably. The reasons for this are not clear, but it is thought that the widespread use of cephalosporin antibiotics (especially broad-spectrum agents such as the 3rd generation

cephalosporins, ceftriaxone and cefotaxime) has given a selective advantage to this organism, especially in hospitals, because enterococci are intrinsically resistant to cephalosporins.

Recently, the importance of enterococci has increased worldwide because of the occurrence in many countries of isolates that are resistant to all the penicillins and also to the important glycopeptide antibiotic vancomycin. These resistant bacteria, called vancomycin-resistant enterococci (VRE), have serious implications for human health as vancomycin currently represents the last defence with effective antibiotics against these bacteria. In many situations there are no other readily available and effective antibiotics to treat enterococci.

Two main genetic subtypes of acquired vancomycin resistance have been found in enterococci (French 1998):

- *vanA* — the most common form internationally with high-level resistance; it is usually plasmid-borne (but may also be transferred to the chromosome via a transposon), and has cross-resistance to teicoplanin (a related glycopeptide used in human therapeutics); and
- *vanB* — a less common form internationally with low-level resistance; resistance is usually chromosomal but may be transferred on a transposon, and usually remains sensitive to teicoplanin.

Both *vanA* and *vanB* resistance are most commonly found in *E. faecium* and, to a lesser extent, *E. faecalis*. *VanB* is more common in Australia. Some other less common intrinsic forms of resistance have also been identified in some species of enterococci (eg *vanC* in *E. flavescens*). These are not plasmid-borne and can be treated with teicoplanin (French 1998). Human infections with *vanC* enterococci are rare.

VRE was first found in Europe in the mid-1980s. A few years later, in 1989, the first strain was found in the United States in a New York hospital. VRE strains spread quickly throughout the United States and became frequent causes of hospital-acquired infection, and VRE bacteraemia is now common. In 1993, about 14% of all blood isolates of enterococci from intensive care units in the United States were vancomycin resistant (CDC 1993, quoted in Bell et al 1998ab). Because there may be no other effective antibiotics, this can be very serious for the patients, especially as infections are more likely to occur in those who are unwell for other reasons (eg following a liver transplant) and have reduced natural immunity. Mortality is approximately twice as high (over 60% compared to 30%) for patients with bacteraemia with enterococci resistant to amoxycillin and vancomycin compared to strains that remain sensitive to amoxycillin (Edmond et al 1996).

In Europe, the incidence of VRE has increased steadily since the 1980s. Large quantities of the glycopeptide antibiotic avoparcin (which is similar to vancomycin) have been used as animal growth promotants (or feed supplements) compared to the quantities of vancomycin used in human medicine, eg 20,000 kg versus 60 kg in Austria and 24,000 kg versus 24 kg in Denmark (Witte 1998). *VanA E. faecium* has been found frequently in intensively farmed pigs and poultry in Europe; in humans (normally 2–10% but in some cases over 60% of Europeans sampled) (van der Auwera et al 1996), even though they have no contact with hospitals; and in retail foods (eg on 80% of chicken meat in The Netherlands) (van den Braak et al 1998). Other surveys show a lack of VRE in animals and in the human population in areas where avoparcin is not used (eg Witte 1998). This and other circumstantial evidence strongly suggests that VRE in Europe is frequently acquired by humans through the food chain.

In the United States, avoparcin is not used in animal feeds. It has been speculated that VRE may have been introduced through foods imported from Europe or a person travelling from Europe. The VRE clone (or the gene sequence) was then probably spread and amplified by the use of vancomycin in United States hospitals. In the United States there is a five-times higher use rate of vancomycin on a population basis than in Europe (Kirst et al 1998). VRE isolates have not been found among community or animal samples in the United States (French 1998).

Currently, in Australia, over 70 separate strains or clusters of strains of VRE have been associated with infections since 1995 (Bell et al 1998ab; see Appendix 6). There have also been twice this number of sites identified where patients asymptomatically carry VRE. The implication for Australia is that these numbers will rise over the next five to ten years and may approach the level seen in the United States as Australia is a comparatively high user of cephalosporins and vancomycin in human medicine.

The occurrence of VRE in hospitals represents the first major infection involving many patients with life-threatening disease for which, for some strains, the only effective antibiotics are experimental. This is the main reason why this organism, in particular, has been responsible for focusing the medical profession's attention onto the problems of increasing antibiotic resistance.

Host specificity

E. faecalis and *E. faecium* are just two of a large number of species of enterococci. Most species are never pathogenic and there are probably more human than animal adapted strains. However, some strains may not be exclusive to one species. For example, in one study, Jensen (1998) showed that VRE isolates from pigs and chickens had distinct types of the vancomycin-resistance gene *vanX*. Almost all pig isolates were of one type and all poultry isolates were of the other type. Human isolates, however, were of both types, indicating that humans may have been infected from both sources and that the primary transmission was from animals to humans (see Section 5.3.2).

4.4 Other bacteria of concern in human medicine

Overall, for most species of bacteria, there has been a steady rise in the rate of resistance to antibiotics (see Chapter 10). There have been very few species of bacteria where there has been any improvement in the number of strains sensitive to antibiotics that are used to treat these infections and this has only occurred when the antibiotic has not been prescribed for use against the particular organism for many years. The major contributor to the development and spread of antibiotic-resistant bacteria in humans is the human use (and frequent overuse) of antibiotics. This has been a problem in both the community setting and in hospitals, where antibiotics are frequently overprescribed. Less than ideal infection control practices also help these antibiotic-resistant bacteria to spread from person to person. As discussed in Chapter 3, the rapid movement and travel of people around the world also means that resistant bacteria that develop in one area of the world can become widespread around the globe within a few years.

The rapid increase in resistant bacteria that is developing worldwide and the relative lack of new drugs have meant that older antimicrobial agents, such as colistin and polymyxin (polypeptides) and novobiocin — which were originally discontinued due to problems with toxicity — are again being looked at as possible therapeutic agents. Resistance to antibiotics, particularly multiple resistance, is developing at such a fast rate among bacterial populations that there have been suggestions that we are entering a 'post-antibiotic era' (Collignon 1997).

Some major pathogens and the antibiotics that are used to treat them are shown in Table 4.3. Table 4.4 summarises the main concerns about emerging antibiotic resistance in community and hospital-acquired bacteria.

4.4.1 Potentially life-threatening infections and diseases

Among the bacterial infections that would be most life threatening if antibiotic treatment was not available, there has been a re-emergence of gram-positive bacteria as important community and hospital-acquired infections. Such organisms include *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Enterococcus* spp. These organisms are discussed because of their importance in human health. With the first three, there is no suggestion that animals either carry the human pathogenic bacteria or transmit them to humans. Strains of *S. aureus* do infect many animals but there is no evidence at present to suggest that human strains are acquired from animals.

Table 4.3 Principal antibiotics used to treat potentially life-threatening infections and diseases in humans

Condition	Major pathogens	Principal antibiotics[a]
Bacterial meningitis (infection of brain and spinal cord membranes)	*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* type b, *Listeria monocytogenes*	Penicillin G, 3rd generation cephalosporins, co-trimoxazole (chloramphenicol)
Endocarditis (heart infection)	Streptococci, enterococci, *Staphylococcus aureus*	Penicillin G, ampicillin, flucloxacillin, gentamicin, vancomycin
Septicaemia (serious blood infection) ('blood poisoning')	*E. coli, Staphylococcus aureus* (including MRSA), *Streptococcus pneumoniae, Neisseria meningitidis*, *E. coli*, klebsiella, enterococci; many others	Aminopenicillins, 1st generation cephalosporins, 3rd generation cephalosporins, gentamicin, flucloxacillin
Severe bone, skin and muscle infections	*Staphylococcus aureus, Streptococcus pyogenes*	Flucloxacillin, penicillin, 1st generation cephalosporins
Enteric fever (eg typhoid, paratyphoid)	*Salmonella* Typhi and *S.* Paratyphi	Ciprofloxacin, ampicillin, chloramphenicol
Pneumonia	*Streptococcus pneumoniae, Legionella pneumophila*, many others	Penicillin, erythromycin, 3rd generation cephalosporins
Severe intra-abdominal infections (sepsis)	*E. coli*, klebsiella, anaerobic bacteria, enterococci	Aminopenicillins, gentamicin, metronidazole, 3rd generation cephalosporins, carbapenems
Infective gangrene	Gas gangrene (*Clostridium perfringens*) Streptococcal (*Streptococcus pyogenes)* Synergistic (mixed aerobic/ anaerobic)	Penicillin, gentamicin, metronidazole
Neutropenic sepsis (infection due to lack of white blood cells)	*E. coli, Staphylococcus aureus*, klebsiella, *Pseudomonas aeruginosa*	3rd and 4th generation cephalosporins, aminoglycosides, ß-lactamase inhibitor combinations

MRSA = multiresistant *S. aureus* (= methicillin-resistant *Staphylococcus aureus*; see Glossary)

[a] Sometimes a combination of antibiotics is needed, especially if mixed infection is present. On other occasions a single agent can be used.

Streptococci

Before the discovery of antibiotics, serious infections caused by *Streptococcus pyogenes* (Group A streptococci) were common and responsible for as many as 50% of deaths after childbirth and a major cause of deaths due to burns. After the introduction of penicillin, it seemed likely that this bacterium would be eradicated. However, since the 1980s an increasing incidence of invasive diseases involving *S. pyogenes* has been reported

from many parts of the world, including the United States, the United Kingdom and Scandinavia, coinciding with a resurgence of rheumatic fever.

This bacterium has remained sensitive to penicillin although it has become less effective in some severe cases of rheumatic fever. Resistance to other antibiotics, particularly the macrolides (eg erythromycin, which is the antibiotic of second choice for patients who are allergic to penicillin) is now also common and seen in many parts of the world, including Australia.

Pneumococcus (*Streptococcus pneumoniae*) remains one of the most common causes of life-threatening pneumonia and is also associated with many other infections related to the respiratory tract such as otitis media, sinusitis and bronchitis. As for group A streptococci, the introduction of penicillin heralded the possible eradication of this organism. However, during the 1970s penicillin resistance spread worldwide at an alarmingly fast rate, apparently based on a few clones that spread worldwide (Turnidge et al 1999). Rates of penicillin resistance were initially comparatively low in Australia but have increased over the last 10 years (Collignon and Bell 1992, Collignon and Bell 1996, Collignon 1997).

Multiple resistance also started to appear in some countries during the 1970s (eg South Africa, Papua New Guinea) and life-threatening infections such as meningitis did not respond to penicillin or chloramphenicol. In Australia, higher rates of resistance are seen for other agents than for penicillin (eg erythromycin), making it more difficult to treat patients that are allergic to penicillin.

Epidemiology

Streptococci are mainly spread by human-to-human contact, particularly in respiratory droplets (see Table 4.2). The main concern for human medicine is that resistance genes from other bacteria could transfer into these bacteria, especially via 'naked DNA' (see Section 3.2.2).

Staphylococcus aureus

In the pre-antibiotic era, *Staphylococcus aureus* septicaemia carried a mortality of approximately 80% and was identified as a leading cause of hospital-acquired wound infections in the 1880s. As streptococcal infections decreased, *S. aureus* became more common and since the 1940s it has been the most common hospital-acquired infection.

S. aureus was one of the first bacteria to develop penicillin resistance and has since developed resistance to a wide range of antibiotics. Strains that produce β-lactamase (making them resistant to penicillin) were first identified in the 1940s after which β-lactamase stable penicillins such as flucloxacillin (and methicillin) were developed and are still important for treatment of this bacterium. The first multiresistant strains of *S. aureus* (MRSA) were identified in the early 1960s and since the 1970s many more methicillin (and flucloxacillin) resistant strains have also become common. These strains are rapidly spread in hospitals throughout Australia and may represent more than 50% of *S. aureus* strains isolated in some large hospitals (Turnidge et al 1996).

At present, vancomycin remains the mainstay of treatment for multiresistant strains and has been used for more than three decades without the development of resistance. However, recently, in Japan, resistance to vancomycin has caused treatment failure (CDC 1997ab). This resistant strain has been shown to have a lower level of resistance than VRE, and the mechanism of resistance is different. It has therefore been called 'vancomycin intermediate *Staphylococcus aureus*' (VISA).

Antibiotic-resistance genes from VRE and from other strains of staphylococcus have been transferred to *S. aureus* in the laboratory. If such resistance occurs in nature, and either this or the existing Japanese strain behaves like the closely related MRSA, then spread throughout the world may occur over the next 10 years, putting treatment of some strains of *S. aureus* back where it was before antibiotics were discovered.

Epidemiology

Staphylococcus aureus lives in close, stable association with humans and is also found in many parts of the environment, including air, dust, water and environment. Many people are symptomless carriers and *S. aureus* forms part of the normal microflora of the nose, throat, perineum and skin. It is spread by direct contact between humans, in respiratory droplets and in food contaminated by infected humans (see Table 4.1). *S. aureus* is also carried by animals but animal and human strains appear to be host specific and cross-colonisation is rare (see Section 5.2.2). The main concern for human medicine is that human pathogenic strains will gain resistance genes from other bacteria, such as enteroccoci, that may transfer from animals. The possibility of the transfer of vancomycin resistance from VRE to human multiresistant *S. aureus* is a major concern. The emergence of the VISA strain in Japan has heightened the concern, although the mechanism of resistance is different from that of VRE.

Enterococci

Enterococci and, in particular, the emergence of VRE, have already been described in Section 4.3.2 above. Because of the high concentration of sick patients in hospitals, antibiotics, including cephalosporins and vancomycin, have been used in relatively large quantities, sometimes unnecessarily so. This has the effect of amplifying any enterococci that are introduced into that environment by selectively killing other bacteria (with cephalosporins) and selecting for VRE strains. It is therefore important that antibiotic-resistant strains from the community are not introduced into hospitals. Of particular concern is the fact that VRE are more commonly associated with patients who are also infected or colonised with MRSA, leading to a unique potential for transfer of resistance across species (Collignon 1997).

Epidemiology

As described in Section 4.3.2, the main reservoirs for enterococci are the gastrointestinal tracts of animals and humans. They are spread in food contaminated with faecal material and, although the majority of strains are host specific, some animal strains are able to colonise humans, although in most cases this may be only for short periods (eg days) (see Section 4.3.2).

Table 4.4 Major concerns about antibiotic resistance in human pathogenic bacteria in Australia

Organism	Concerns
Community-acquired organisms	
Streptococcus pyogenes	Fluctuating rates of resistance to macrolides
Streptococcus pneumoniae	Penicillin (ß-lactam) resistance is rapidly increasing (now ~25%)
	Cephalosporin resistance is increasing (treatment of meningitis may be compromised) (10%)
	There is a high rate of resistance to co-trimoxazole (trimethoprim + sulfamethoxazole)
	Multiple resistance (including resistance to macrolides, tetracyclines, chloramphenicol) is rapidly increasing
Staphylococcus aureus	Emerging resistance to ß-lactams in community-acquired strains with MRSA strain now spreading in the community
Haemophilus influenzae	Slowly increasing resistance to aminopenicillins
Moraxella catarrhalis	High rate of resistance to aminopenicillins
Neisseria gonorrhoeae	High rate of resistance and reduced susceptibility to penicillins
	Emergence of resistance to fluoroquinolones
Neisseria meningitidis	Emergence of strains with reduced susceptibility to penicillin
Nontyphoid salmonellae[a]	Emergence of fluoroquinolone resistance in infections acquired overseas
	Increase in prevalence of multiresistant strains in Europe and the United States (eg virulent strains such as DT104, which has not yet appeared in Australia)
Salmonella Typhi	Emergence of multiresistant strains acquired overseas, especially in Asia
Mycobacteria tuberculosis	Emergence of multiresistant strains acquired overseas, especially in Asia
Both community and hospital-acquired (nosocomial) organisms	
Escherichia coli[a]	High rate of resistance to aminopenicillins
	Increasing rate of resistance to 1st generation cephalosporins and ß-lactamase inhibitor combinations
	Emerging resistance to 3rd generation cephalosporins
	Emerging resistance to fluoroquinolones
Klebsiella spp.	Increasing resistance to 1st generation cephalosporins and ß-lactamase inhibitor combinations
	Emerging resistance to 3rd generation cephalosporins
	Emerging resistance to fluoroquinolones
Hospital-acquired organisms	
Multiresistant *Staphylococcus aureus* (MRSA)	Increasing resistance to oral antibiotics (rifampicin, ciprofloxacin and fusidic acid)
	Emergence overseas of vancomycin intermediate resistance *Staphylococcus aureus* (VISA) in hospitals (eg Japan, USA)[b]
Enterococcus spp.[a]	Emergence of resistance to glycopeptides — vancomycin and teicoplanin (few antibiotics to chose from in the first place due to natural resistances)
	Increasing resistance to high levels of aminoglycosides (heart infections now cannot be eradicated by treatment)
Acinetobacter spp.	Increasing multiresistance (few antibiotics to chose from in the first place due to natural resistances)
Pseudomonas aeruginosa	Increasing multiresistance (few antibiotics to chose from in the first place due to natural resistances)

MRSA = multiresistant *S. aureus*

[a] These are the only bacteria for which there is a documented link with food-producing animals.

[b] VISA: treatment failures occur with vancomycin but level of resistance is lower than seen in VRE and the mechanism is different.

Chapter 5
Transfer of antibiotic resistance from animals to humans

OVERVIEW

The use of antibiotics in animals or humans can result in the emergence of antibiotic-resistant bacteria. Bacteria, particularly enteric bacteria, are commonly spread from animals to humans. Resistance genes that confer antibiotic resistance on one type of bacterium can be transferred to other bacteria, including from animal to human bacteria. In particular, a bacterium can spread from an animal to human and then transfer its resistance gene to a human pathogen. The JETACAR committee examined the evidence that antibiotic-resistant bacteria emerge as a result of antibiotic use in animals, spread to humans to cause disease directly or through the transfer of resistance genes to humans pathogens, and that resistance then causes problems for treatment of human disease.

Theory

Antibiotic use in animals will select for and amplify resistant bacteria in animals. Antibiotic-resistant bacteria can spread from animals to humans and cause disease in two ways: (i) the direct spread of resistant zoonotic/pathogenic bacteria from animals to humans; and (ii) the spread of resistant commensal (such as gut flora bacteria) or pathogenic bacteria and subsequent transfer of antibiotic-resistance genes to other species or strains of bacteria.

Factors that influence the spread of bacteria include: the host specificity of bacteria and the means by which resistant bacteria spread between animal species (including humans). For transfer of resistance genes, colonisation of the human may not be essential because transfer might occur during transit through the gut or on the skin.

Molecular techniques make it possible to accurately identify individual strains of bacteria and resistance genes, allowing both the direct spread of bacteria and the transfer of resistance genes to be tracked very accurately.

The type, dose and duration of antibiotic use in animals also affect the selection of resistant bacteria. Overall, selection pressure is related to the total amount of antibiotic used but longer-term exposure of large groups of livestock to relatively low doses of antibiotics provides a stronger selection pressure than a short course to small numbers of affected animals at therapeutic (ie relatively high) doses. Broad-spectrum antibiotics affect more types of bacteria than narrow-spectrum antibiotics.

Evidence

A review of the scientific literature on whether antibiotic-resistant bacteria or resistance genes found in animals spread or transfer resistance genes to organisms that cause clinical disease in humans was commissioned by JETACAR. The literature review focused on four enteric bacteria (nontyphoid salmonellae, campylobacters, *Escherichia coli*, and enterococci) because of the exposure of people to these organisms via the food chain. The evidence from the review was combined with evidence from two other recent reviews of the literature published by the United Kingdom and Swedish ministries of agriculture.

Although the problems are complex and incompletely investigated, the JETACAR and other literature reviews showed that there is evidence for direct spread of resistant bacteria from animals to people and subsequent clinical disease. Based on the molecular evidence for some species, there is also evidence for the transfer of antibiotic-resistance genes from animal bacteria to human pathogenic bacteria. Quantitative data are insufficient at present to perform accurate risk assessment for individual antibiotic–bacterium combinations although semiquantitative assessments can be developed in future.

5.1 Evidence of the spread of antibiotic resistance from animals to humans

5.1.1 Identification of critical steps

The selection of resistance in bacteria though antibiotic use in animals and its subsequent transfer to humans through the food chain is a simple process and has been well understood for many decades for zoonotic pathogens such as salmonella. It is also recognised that resistance determinants (genes) can be transferred (by horizontal gene transfer) between bacterial species. It is possible for gene transfer to occur in animals, in the environment and in humans who have acquired animal bacteria, even if that species fails to establish itself in humans. Each animal type has its own range of bacterial flora and pathogens, some of which do not appear to spread to or colonise other animal species or humans easily. Thus, a bacterial species selected for resistance in a single animal type may not necessarily be transferred to humans. Nevertheless, it is possible that the selected resistant strain may transfer resistance genes into another bacterial species that is more easily transferred to humans.

Qualitative aspects

As outlined in Chapter 2 (Section 2.4 and Figure 2.2), three critical steps can be identified that promote the transfer of antibiotic resistance from animals to humans, and potential treatment failure. In the second step, bacteria may be spread and resistance established in humans in one of two ways.

- **Step 1. Emergence of antibiotic-resistant bacteria in animals:**
  - resistance emergence — antibiotic resistance arises in populations of animal bacteria by mutation or because the animal picks up a resistant bacterium;
  - antibiotic exposure — food-producing animals are exposed to antibiotics;
  - enrichment by selection — exposure to antibiotics kills susceptible bacteria and allows resistant bacteria to increase (amplification) at the expense of susceptible strains and species (enrichment); and
  - spread of resistant bacteria — spread of resistant bacteria to other animals in a herd/flock. This will be enhanced if many or all animals are exposed to the antibiotic(s) to which the bacteria are resistant.

  Plus:
  - horizontal transfer of resistance genes — some resistance genes can transfer to other bacterial species on genetic fragments (eg plasmids or transposons). Antibiotic exposure is not required for gene transfer to occur. The resistant bacteria that arise in this way are also amplified by antibiotic exposure.

- **Step 2. Spread of resistant bacteria from animals to humans:**
  - resistant bacteria spread from animals to humans indirectly via food (eg by contamination of carcases during slaughter), or less commonly by direct contact (eg in farmers, abattoir workers); and
  - resistant bacteria either take up residence (colonising commensals), attach and initiate an infection (pathogens) or stay transiently eg in passage through the human gut.

  Where:
  - human acquisition may be enhanced if the person is taking the antibiotic to which the animal bacteria are resistant
  - resistant bacteria are amplified and enriched in humans by exposure to the antibiotic(s) to which the acquired animal bacteria are resistant

- **Additional Step 2: Horizontal transfer of antibiotic-resistance genes from animal to human bacteria:**
  - identical processes to Step 2 followed by transfer of the antibiotic-resistance gene(s) to other human pathogenic and/or commensal bacteria. Antibiotic exposure is not required for gene transfer to occur.

- **Step 3. Clinical disease in humans:**
  - humans with resistant bacteria develop illness from these bacteria
  - treatment with the antibiotic(s) to which the bacteria are resistant results in adverse outcomes, eg prolonged illness, more severe illness, treatment failure and even death.

In short, spread of resistant bacteria from animals to humans can occur either by the spread of the resistant bacteria themselves (bacterial spread) or spread of the resistance genes (genetic spread) to potential human pathogenic bacteria. The relevant antibiotics amplify and enrich these resistant bacteria both in animals and humans. Amplification of resistant bacteria can also occur along the food chain if food handling techniques are inadequate.

Quantitative aspects

Frequencies of bacterial or genetic spread, as opposed to spread itself, will be influenced by a number of factors, such as:

- the intensity of antibiotic use in animals (with higher intensity resulting in higher numbers of resistant bacteria in animals) and in food produced from them;
- level of contamination and amplification at the various steps in the food chain through inadequate food hygiene;
- the ability of the bacteria to colonise humans (it is hypothesised that strains with higher colonisation potential are more likely to lead to disease or transfer their resistance genes due to their persistent presence);
- the ability of the resistant bacteria to transfer the resistance gene(s) to other animal or human pathogens; and
- human use of the antibiotic(s) to which the bacteria are resistant.

Frequencies of clinical disease will be influenced by:

- the pathogenic potential of the resistant bacteria;
- the immune status of the human who has acquired the resistant bacteria; and
- medical procedures which breach mechanical defences such as skin and mucosal surfaces (eg surgery, indwelling devices such as urinary or intravenous catheters).

The remainder of this chapter describes the scientific evidence for each of the three critical steps outlined under qualitative aspects above. For each stage, the findings of the independent literature review commissioned by JETACAR (see Chapter 1) are presented for each bacterium. Also included is relevant additional evidence from other literature reviews, in particular the Swedish Commission on Antimicrobial Feed Additives (CAFA 1997) and the UK Ministry of Agriculture, Fisheries and Food (MAFF 1998). A conclusion is drawn for each stage, and the levels of evidence from the JETACAR literature review are reproduced, as shown below. This is followed by a section on current Australian evidence on the three critical steps.

5.1.2 Levels of evidence

To assign a level of evidence to the findings of the literature review, JETACAR used a modification of the National Health and Medical Research Council four-point scale (NHMRC 1995). The scale (which was developed primarily for assessment of clinical interventions) was modified to take account of the range of methods used to study the complex science of the emergence and spread of antibiotic resistance. Further details of this modification are provided in the review itself, and are summarised in Table 5.1.

Although the modification has been debated, the committee agreed that the modification is a reasonable attempt to deal with the comparability of different types of evidence for the critical steps, as well as comparability to levels of evidence for causation and outcome in other areas of medicine. However, it must be stressed that for Steps 1 to 3, levels of evidence higher that III-2 are unlikely to ever be possible. This is because higher levels of evidence (levels I and II) require experimental studies with randomised treatments and control groups, which cannot replicate natural events occurring over many years, or are unethical because they place participants at unacceptable risk. Thus, double-blind controlled studies to directly determine if resistant bacteria of food-animal origin colonise humans or transfer their resistance genes to human bacteria in vivo are not possible.

Considerable evidence is now being derived from sophisticated molecular techniques of typing bacteria and their resistance genes. These techniques have the power to accurately trace resistant bacteria and their resistance genes in similar ways to those of forensic scientists identifying criminals by DNA fingerprinting. Because of this sophistication, it has been argued that such molecular evidence should attract the highest level of evidence (level I). However, for consistency with evidence for other areas of medicine, the JETACAR literature review chose to designate the best molecular evidence as level III-1.

Table 5.1 NHMRC evidence rating scale and modifications used in the JETACAR literature review

NHMRC rating	Source of evidence (NHMRC 1995)	Modification used for this literature review
I	Systematic review of all relevant randomised controlled trials	Not applicable
II	At least one properly designed randomised controlled trial	Experimental controlled studies of in vivo exposure to antibiotic agents
III-1	Evidence obtained from well-designed controlled trials without randomisation	Broad range studies showing concordance of resistance determinants or clonality among animal, food and human isolates; some experimental studies and controlled studies are also in this category
III-2	Evidence obtained from well-designed cohort or case-control analytic studies, ideally from more than one research centre	Cohort evidence of resistance development in defined populations with different exposure characteristics (eg comparisons of country-wide data or farm cohort comparisons)
III-3	Evidence obtained from multiple time-series with/without the intervention. Dramatic results in uncontrolled experiments	Development of resistance over time in the same population after change in exposure conditions or introduction of a new agent
IV	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	As described

5.1.3 JETACAR literature review — summary of findings

The Executive Summary of the literature review is presented in Box 5.1. The full review and further references can be obtained from:

(i) JETACAR literature review. *Antibiotic Resistance in Animal Enteric Bacteria and Human Disease –- A Review of the Scientific Literature*, 1998, (time frame 1965 to November 1998). This is available separately from the Department of Health and Aged Care.

(ii) United Kingdom Ministry of Agriculture, Food and Fisheries (MAFF). *A Review of Antimicrobial Resistance in the Food Chain*, 1998; (time frame 1956 to February 1998).

(iii) Swedish Commission on Antimicrobial Feed Additives (CAFA). *Antimicrobial Feed Additives*, 1997; (time frame 1972 to 1997)

After completion of the draft JETACAR report in March 1999 (which was submitted to stakeholders for their consideration), an additional scientific review was published:

- Heidelberg Appeal Nederland Foundation (HAN). *Emergence of a Debate: AGPs and Public Health.* Human health and antibiotic growth promotants (AGPs): reassessing the risk, 1999.

After consideration of this report, the committee felt that some the conclusions of this report differed somewhat from the conclusions of the other three reports, reflecting a divergence of scientific views on the available data. Nevertheless, because the evidence on which it was based was identical, the recommendations of the committee remained unaltered.

Box 5.1 Executive summary of the JETACAR literature review

Epidemiology

- The main source of infection for nontyphoid *Salmonella* spp., shiga-like toxin producing *Escherichia coli* and *Campylobacter* spp. is animals.
- The predominant route of transfer for zoonotic enteric bacteria is via the food chain.
- Transfer of other enteric commensal bacteria of animals such as enterococci to humans also occurs across the food chain.
- The efficient transfer and repassaging of bacteria among animals in intensive farming facilities and their environment has the capacity to enhance selection of resistant bacteria.

Bacterial resistance

- Generic mechanisms of resistance include intrinsic resistance, acquisition of new resistance genes or mutational change within the existing bacterial chromosome.
- There is a vast reservoir of genetic bacterial resistance factors within environmental and animal/human bacterial populations.
- The majority of antibiotic substances are derived from natural microbial products and hence are prone to the naturally developed defence mechanisms of bacteria.
- There is a great capacity for transfer of resistance to occur across bacterial genera through a variety of efficient mechanisms.
- Antibiotic exposure leads to selection and amplification of resistant bacteria in all contexts of antibiotic use.
- Antibiotic-resistance factors, once acquired, are slow to be lost and efficient mechanisms exist that enable acquisition of multiple resistance over time, often in association with virulence factors.

Transfer of resistance

Four main questions were examined in this review:

- Does administration of antibiotics to animals result in the emergence of antibiotic-resistant bacteria?
- Do these resistant bacterial strains spread from animals to humans?
- Do these bacteria (resistant animal strains) cause clinical disease in humans?
- Do the resistance genes in these bacteria transfer to human pathogens?

From a range of perspectives and specific evidence, the support for these hypotheses in the indicator bacteria is strong (Tables 1 and 2). Furthermore, it is scientifically reasonable, in the light of the principles stated above, to assume that if these hypotheses are well supported by evidence from one bacterium–organism combination, then in general (with few known exceptions) the same sequelae will follow antibiotic use in other locales or targeted against other bacteria.

The specific evidence is summarised below with the highest assessed NHMRC quality of evidence in parenthesis. The levels of evidence have been modified to accommodate the types of available evidence [see Section 5.1, above]. It should be noted that the highest attainable level of evidence from most studies in this area cannot be expected to exceed level III (ie predominantly observational studies) owing to the impossibility of performing properly designed randomised controlled trials that examine horizontal resistance transfer. To place level III in perspective, the association between lung cancer and smoking is currently supported by evidence at a III-2 level.

Box 5.1 (contd)

Conclusions of the JETACAR literature review

1. With regard to the bacteria examined in this review (enterococci, nontyphoid salmonellae, *E. coli* and campylobacters), the selective pressure provided by nonhuman use of antibiotics has been sufficient to cause development of (multiple) resistance by combinations of one or more of the three mechanisms specified above.
2. Even low amounts of therapeutic quinolone use in animals have been sufficient to select for significant levels of resistant salmonella and campylobacter strains.
3. Through extended selective pressures, sequential acquisition of resistance factors has occurred in some salmonellae, particularly *Salmonella* Typhimurium, which has resulted in stable multiple resistance in virulent clones that have had a measurable impact on human health.
4. There is strong evidence to show that the predominant direction of transfer of gastrointestinal zoonotic bacteria is from animals to humans via the food chain.
5. There is strong evidence that demonstrates dissemination of identical or genetically similar resistance determinants amongst animal and human populations. Some evidence (for streptothricin, apramycin and avoparcin) is able to directly indicate the direction of transfer.
6. There exists strong evidence (for salmonella, campylobacter and enterococci) that human disease is caused by resistant bacteria or bacteria containing resistance determinants that are present in animals.
7. The human disease caused by these resistant bacteria has been associated with increased morbidity and treatment failure.
8. The Australian situation in this area has not been well studied. However, demonstrated emergence and transfer of resistance overseas provide an important model that should inform development of Australian policy.

Executive summary of the JETACAR literature review (contd)

Table 1 Enterococci

Drug class	Animal agent(s) of concern	Human agent(s) of concern	1.Emergence of resistance following exposure?	2. Spread from animals to humans?	3. Resistant animal clones cause disease in humans?	4. Horizontal transfer of resistance into human pathogens?
Glycopeptide (*vanA*)	avoparcin ardecin	vancomycin teicoplanin	yes (III-2)	yes (III-2)	yes (IV)	yes (III-1)
Macrolide	tylosin spiramycin kitasamycin oleandomycin	erythromycin lincosamides	yes (II) (tylosin)	yes (III-2)	unknown	yes (III-1)
Streptogramin	virginiamycin	pristinamucin quinupristin/ dalfopristin	yes (III-2)	yes (IV)	unknown	unknown
Orthosomycin[a] (oligosaccharide)	avilamycin	everninomycin	yes (IV)	unknown	unknown	unknown

Table 2 Gram-negative zoonotic indicator bacteria

Streptothricin[a]	nourseothricin	no agent of this class	yes (III-2)	yes (III-3)	unknown	yes (IV)
Aminoglycoside (AAC(3)-IV)	apramycin	gentamicin tobramycin	yes (III-2)	yes (IV)	unknown	yes (IV)
Quinolone	oxolinic acid[a] enrofloxacin[a]	naladixic acid ciprofloxacin norfloxacin	yes (II)	yes (III-2)	yes (III-2)	unknown; probably rare
Multiresistance in Salmonella spp.	multiple	multiple	yes (III-3)	yes (III-3)	yes (III-3)	yes (IV)

[a] not in use in Australia

5.2 Emergence of antibiotic-resistant bacteria in animals (Step 1)

5.2.1 Factors that influence the emergence of antibiotic resistance in bacteria in food-producing animals

The following factors influence the emergence of antibiotic resistance in bacteria in food-producing animals.

- *The spectrum of activity of the antibiotic* — broad-spectrum antibiotics affect more types of bacteria than narrow-spectrum antibiotics. For example, some in-feed antibiotics with growth promotant activity such as avoparcin, virginiamycin and the polyether ionophores are only active against gram-positive bacteria (including enterococci), while others such as the macrolides are also active against some gram-negative bacteria.

- *The number of animals exposed to antibiotics* — resistance problems are more likely to occur with intensively raised livestock, where antibiotics are most often given to all animals in the group, flock or herd, usually in the feed or water.

- *The total amount of antibiotic used* — which in turn is influenced by the dose and duration. Longer-term use at low doses, often over many weeks, is the typical use pattern for prophylactic and growth promoter antibiotics in intensive animal industries

Resistance to fluoroquinolones is a special case. Unlike resistance to most other antibiotics, which occurs mainly through the acquisition of resistance genes, fluoroquinolone resistance occurs predominantly by mutation. In *E. coli* and salmonella, which are highly susceptible to fluoroquinolones, two mutations are required to express the full resistance required to overcome the effect of therapeutic doses (clinical resistance). However, each mutation alone reduces the susceptibility to fluoroquinolones (Hooper 1998), and the spread of strains with a single mutation increases the risk of selecting for full resistance when fluoroquinolones are used in humans. Single mutations can be detected by demonstrating resistance to nalidixic acid (the original, nonfluorinated quinolone with low potency), and raised minimum inhibitory concentrations to fluoroquinolones compared to strains without a mutation.

5.2.2 EVIDENCE: Does administration of antibiotics to animals result in the emergence of antibiotic-resistant bacteria?

It is universal experience that whenever antibiotics are used, resistance will emerge at some time. All literature reviews have confirmed that exposure of animals to antibiotics selects for antibiotic resistance in animal pathogens and enteric commensal bacteria.

Enterococci

Due to the scientific interest in enterococci since the emergence of vancomycin-resistant strains in human medicine, a considerable body of evidence on animal enterococci and resistance has accumulated which has been the subject of several reviews. The JETACAR review in particular focused on enterococci. Almost all recent reviews have reached essentially the same conclusions, summarised below.

Glycopeptide resistance

While early studies were difficult to interpret because of inadequacies in experimental design, later controlled studies in Europe have demonstrated significantly higher rates of resistance in *Enterococcus faecium* to avoparcin in treated animals (pigs and chickens) compared to controls. This finding has been supported by many observational studies.

The widespread nature of glycopeptide resistance in non-food producing animals has been demonstrated recently (Devriese 1996).

Macrolide resistance

There is a strong association between the use of macrolides, in particular tylosin, and resistant enterococci in animals. Evidence of a link for other macrolides used in animals such as spiramycin, kitasamycin and oleandomycin is largely lacking, although there is no reason to expect that they would have different effects from tylosin. Resistance to tylosin generally confers cross-resistance to two other drug classes — the lincosamides and the streptogramins B. Moreover, high prevalences of macrolide resistant enterococci have been reported in countries where macrolides are used (figures of 10 to 91% were quoted in the CAFA report).

Streptogramin resistance

More recent efforts have focused on the role of virginiamycin in selecting for resistant enterococci in animals. Although the number of studies is smaller than that of avoparcin, controlled studies have been performed. All studies have demonstrated emergence resistance in *E. faecium* in association with its use. A recent study in the United States demonstrated a clear-cut time-dependent increase in the prevalence of resistance strains over the life of turkeys under intensive rearing conditions (Welton 1998).

Orthosomycin resistance

Recent attention has focused on avilamycin, an orthosomycin used for growth promotion, because everninomycin, a drug from the same class that has been shown to have cross-resistance with avilamycin, is under development for human use. Limited observational data supports the view that enterococcal resistance can emerge, in chickens at least, though avilamycin use.

Salmonella

Aminoglycoside resistance

There has between a significant correlation between the use of the aminoglycoside apramycin and the isolation of resistant salmonella in food-producing animals, in especially *Salmonella* Typhimurium DT104 in calves. The resistance is due the acquisition of a single determinant coding for a unique acetylating enzyme (AAC(3)-IV) which has not been found as a consequence of human aminoglycoside use. It also confers resistance to the important human aminoglycoside, gentamicin.

Quinolone resistance

Fluoroquinolone resistance was addressed in detail in the JETACAR literature review. For *Salmonella* species, evidence was found of the emergence of decreased susceptibility in animals related to fluoroquinolone use. The most recent instance of this has been found in the already multi-resistant strains of *Salmonella* Typhimurium DT104 in the United Kingdom (see below).

Multiresistance

Resistance to multiple antibiotics in *Salmonella* species isolated from animals has been documented since the mid-1960s, particularly in *Salmonella* Typhimurium (the commonest serovar). The current problem in Europe and the United States is *Salmonella* Typhimurium DT104 that is resistant to five classes of antibiotics. Although multiresistance has been observed less frequently in some serovars, a common observation in resistant salmonella over more than 30 years has been their emergence, spread and eventual waning.

Campylobacter

Fluoroquinolone resistance

The JETACAR literature review concentrated on fluoroquinolone resistance, and this subject was also discussed at length in the MAFF report. The review concluded that there was strong evidence from several studies that use of fluoroquinolones in animals selects for resident populations of thermophilic campylobacters.

Resistance to other antibiotics

There are less data that document the prevalence of resistance to other agents in isolates of campylobacter from food-producing animals. This is not surprising as campylobacters are nonpathogenic in animals, and up to now there has been no interest in testing animal strains for resistance. However, macrolides are used extensively in some intensive industries, such as pig production, where they are used for the prevention and treatment of respiratory infections, and the macrolide erythromycin is considered the drug of choice in humans when treatment of campylobacter is required. Thus, further studies would be desirable.

Escherichia coli

Quinolone resistance

For *E. coli*, the JETACAR literature review only considered resistance to fluoroquinolones. Observational studies in Saudi Arabia have found resistance in quinolone resistance in chickens associated with the use of the older quinolones oxolinic acid and flumequine. In Sweden, where quinolone use has been low, resistance in *E. coli* has remained low (Wienpetal 1998).

Streptothricin resistance

Nourseothricin, an antibiotic that is a member of the streptothricin class, is an agent that was used extensively in eastern Europe in the past. Studies of reasonable quality have demonstrated a direct association between its use and the development of resistance in *E. coli*.

Resistance to other antibiotics

Several papers from the United Kingdom and other parts of the world have documented increasing resistance over the years to a wide range of antibiotic classes including tetracyclines, aminoglycosides, sulfonamides and penicillins. Indeed multiple resistance in isolates from livestock species is the rule rather than the exception. Sweden has been able to demonstrate steady rates of resistance in *E. coli*, from chickens and pigs over the last 10 years, in keeping with their reduction in total antibiotic use.

5.2.3 Conclusion

The few well-controlled prospective studies and a much larger volume of observational studies all support the general contention that use of antibiotic in food-producing animals leads to the emergence of resistant bacteria. Not all areas of relevance have been examined thoroughly, and thus levels of evidence vary for antibiotic classes and bacterial species. The picture is clearest for antibiotic resistance generally in salmonella and *E. coli*, and for fluoroquinolone resistance in campylobacter. European studies have also shown that glycopeptide resistance in *E. faecium* isolated from food-producing animals is correlated to avoparcin use in animal feeds.

5.2.4 Horizontal transfer of antibiotic-resistance genes between animal bacteria

Qualitative aspects

Resistance genes carried on transmissible elements such as plasmids and transposons are widely distributed through the microbial population and are spread by a variety of gene transfer mechanisms (see Chapter 3). Resistance will be amplified in animal populations through horizontal transfer of resistance genes between bacteria on or within the same host animal or its immediate environment, or because the bacterium carrying the resistance gene spreads to another animal(s) with transfer occurring on or within the new host.

Quantitative aspects (pertinent to risk assessment)

For gene transfer it may be unnecessary for the bacterium to colonise the new host, and transfer of resistance genes may occur while the bacterium is in transit through the gut or on the skin. Colonisation may provide greater opportunities for transfer than brief transit. Data are limited on the relative importance of colonisation versus transient exposure, and whether gene transfer is a common or rare occurrence in animals. Gene transfer is more frequent if there are large numbers of donor strains, the antibiotic in question is present, or there is reduced or limited gut flora. One study has shown that it is important for the recipient strain to be a good coloniser (Smith 1969).

The JETACAR literature review did not examine evidence for this phenomenon (it was not in the brief). However, other reviews, in particular the MAFF report, have expanded on this question. There is an abundance of evidence for transfer of resistance genes between related and unrelated genuses and species of bacteria (Davies 1994, Levy 1995) and between animal, human and environmental strains in simulated microenvironments such as mincemeat on a cutting board and milk from cows with mastitis on a hand towel (Kruse and Sørum 1994). Data of frequency of transfer in vivo are very limited.

5.3 Spread of antibiotic-resistant bacteria from animals to humans (Step 2)

5.3.1 Factors that influence bacterial spread from animals to humans

Animal bacteria, including resistant strains, can spread to humans by direct contact, through the food chain and by environmental contamination. Although salmonella, campylobacter and shiga-toxin producing *E. coli* are well recognised zoonotic pathogens, there are many other bacteria that are known to spread from animals to humans including other *E. coli*, *Yersinia enterocolitica* and enterococci.

Water contamination with antibiotic-resistant animal bacteria has been documented (Young 1993, Moringo et al 1990) and resistance can be spread to aquatic organisms (Marshall et al 1996). Even campylobacters have been isolated from groundwater (Stanley et al 1998). Antibiotic-resistant bacteria have been found in fish and crustacea (Hatha and Lakshmanaperumalsamy 1995) suggesting that this resistance has arisen through contamination of water with faeces and or sewage of antibiotic-treated animals.

For some bacteria, host specificity may play a role in the frequency with which bacteria, including resistant strains, spread between animals and humans. Bacterial species or strains that colonise a broad range of animals will spread to humans more frequently than those that colonise a narrow range because more foods of animal origin can be contaminated by them. This is supported in part by a Danish study of antibiotic

resistance in campylobacters from different sources: pigs, humans, cattle and chickens (Aarestrup et al 1997), which reported different patterns of resistance in different species, suggesting that each animal strain had a narrow host range.

5.3.2 EVIDENCE: Do antibiotic-resistant strains of bacteria spread from animals to humans?

Initially, evidence for the spread of antibiotic-resistant bacteria from animals to humans consisted of demonstrating concordance of strains from animals and humans by detailed strain typing and antibiotic-resistance profile. Zoonotic salmonella infections are the best example of this strategy. While these methods are still useful, recent evidence for spread of resistance has involved the detection of unique gene sequences in animal strains and human isolates. This method does not confirm the direction of flow of resistance, nor does it necessarily distinguish between transmission of resistant bacteria or resistance genes. However, if the antibiotic used or the resistance mechanism is initially unique to animals, then the direction of spread is obviously from animals to humans.

There are limited studies examining occupational exposure, based on the plausible hypothesis that farm and abattoir workers would have higher exposure to resistant bacteria from animals than others remote from the farm/abattoir. There are no well-controlled studies on this question, but there are a number of observational studies that support this hypothesis.

Finally, detection of resistant zoonotic bacteria on food for human consumption would provide reasonable evidence that these bacteria will spread to humans. There is a small amount of data of this kind.

Enterococci

Glycopeptide resistance

The JETACAR literature review presented considerable evidence for the presence of *vanA E. faecium* in the food chain. The strains have been found in meat products from countries where avoparcin has been used in animal production, but not in meat from countries where it is not used, and they have declined in Germany after avoparcin use was suspended. A number of European studies have now documented carriage of *vanA E. faecium* in a proportion healthy humans who have never been hospitalised (van de Auwera 1996), and in farm workers (van den Bogaard et al 1997). Studies on the prevalence of these strains in vegetarians versus meat eaters have been conflicting, possibly due to the use of animal manure on vegetable crops. Studies using molecular strain typing of *vanA E. faecium* from different sources generally show great diversity and infrequent concordance between animal and human strains. Nevertheless, when the *vanA* gene sequences are compared they are almost identical, consistent with gene transfer rather than strain transfer to humans (see Section 5.4.2). Apart from a single strain in Australia (Butt et al 1997), enterococci harbouring the *vanB* gene have not been isolated from food or animals.

Macrolide resistance

The JETACAR literature review noted studies that have shown virtually identical resistant determinants for macrolides in animal and human strains of enterococci. Studies of food and other vehicles for spread, looking for macrolide resistant enterococci, appear to be lacking.

Streptogramin resistance

Studies are limited but suggestive that there has been transfer of resistance genes.

Orthosomycin resistance

There are no studies on this subject.

Salmonella

Aminoglycoside resistance

As presented in the JETACAR literature review, the apramycin resistance gene (AAC(3)-IV),first noted in animals after apramycin was introduced, has been detected in human isolates of *S*. Typhimurium DT204c.

Quinolone resistance

The JETACAR literature review listed evidence for the isolation of non-typhoidal salmonella from humans that were resistant to nalidixic acid and had reduced susceptibility to fluoroquinolones following the introduction of enrofloxacin in Europe to prevent the transovarial (hen to egg) spread of *S*. Enteritidis in poultry. At present, this problem has only been well documented in single strain: *S*. Typhimurium DT104, but has significance as this strain is usually resistant to five other antibiotic classes, and confirms that is likely to emerge in other salmonella species in future.

Multiresistance

There is considerable evidence for the zoonotic spread of multi-resistant strains of salmonella. The most important recent example is *S*. Typhimurium DT104. This problem has been extensively reviewed by the United States Department of Agriculture Food Safety and Inspection Service (Hogue et al 1997). Direct spread from cattle to humans has been reported (Fone and Barker 1994, Wall et al 1995). as has suspected spread from cats to humans (Wall et al 1996).

Campylobacter

Fluoroquinolone resistance

The JETACAR literature review cited the multiple reports from the Netherlands, the United Kingdom and Spain, where there have been significant rises in the prevalence of fluoroquinolone resistant campylobacters isolated from human infections and the introduction of fluoroquinolones for treatment of food-producing animals. A very recent publication (Smith et al 1999) has shown similar temporal associations in the United States, and a high degree of relatedness between human and chicken isolates of fluoroquinolone resistant *Campylobacter jejuni*.

Resistance to other antibiotics

There is no information about animal bacteria with resistance to other antibiotic classes and their spread to humans. Differences in antibiotic-resistance patterns have been noted in one study between human, porcine and poultry strains of campylobacter (Aarestrup et al 1997)

Escherichia coli

Resistance generally

Pig farmers and abattoir workers in the Netherlands have been shown to carry more resistant *E. coli* than suburban residents (Nijsten et al 1994). Further studies by the same group showed even high rates of resistant *E. coli* in the pigs tended by the farm workers, with concordance of their plasmid patterns in some cases (Nijsten et al 1996ab)

Quinolone resistance

There are no published studies on quinolone resistant bacteria from food-producing animals and spread to humans.

Streptothricin resistance

Nourseothricin-resistant *E. coli* strains, coded by the identical gene to that detected in animal isolates, have been detected in humans. As this class of drugs has only been used in animal husbandry, and is not cross-resistant with agents used in human medicine, the evidence of spread from animals to humans is conclusive.

Aminoglycoside resistance

As for salmonella, the apramycin resistance gene (AAC(3)-IV) has been detected in human isolates of *E. coli*.

5.3.3 Conclusion

Resistant bacteria in food producing animals have spread to humans, either directly or through the food chain. For salmonella and campylobacter the evidence suggests transfer of the bacteria themselves. For *E. coli* and enterococci, most evidence indicates that transfer of resistance genes is equally or more important (see next section). The risk (rate) of transfer from animals to humans will differ between bacterial types and location of resistance genes.

5.4 Horizontal transfer of antibiotic-resistance genes from animal to human bacteria (additional Step 2)

5.4.1 Factors that influence horizontal gene transfer from animal to human bacteria

The factors outlined in Section 5.2.4 also apply to the spread of resistance genes from animal to human bacteria.

5.4.2 EVIDENCE: Do resistance genes in animal bacteria transfer to human pathogens?

Evidence for the spread of resistance genes has been used in some investigations as a tool to identify whether resistant animal bacteria have spread to humans (see above).

Enterococci

Glycopeptide resistance

As noted in Section 5.3.2, studies using molecular strain typing of *vanA E. faecium* from different sources generally show great diversity and infrequent concordance between animal and human strains. Nevertheless, when the *vanA* gene sequences are compared they are almost identical. Given the very large size and complexity of the gene sequence for *vanA* (seven genes linked together in a transposon) it must be concluded that human and animal *vanA E. faecium* share the same *vanA* gene cluster. From a Danish study, small differences have been detected in the *vanA* gene sequence (Jensen 1998). The study showed that the origin of the genes in humans strains is from both pigs and poultry, as both types are detected in humans but only one type each is detected in pigs or poultry.

Macrolide resistance

Studies on macrolide resistance in enterococci of food-producing animal and human origin have yielded similar findings to that of vancomycin resistance.

Streptogramin resistance

There is recent evidence from Europe that the *satA* resistance gene has been found in both animal and human isolates of *E. faecium*. The animals isolates predated any use of

streptogramins in humans in the country where one of the studies was conducted (Germany).

Orthosomycin resistance

At the time of the JETACAR literature review, there were no studies on this subject.

Salmonella and campylobacter

At the time of the JETACAR literature review, there were no studies on whether resistance genes from campylobacter have been transferred to human bacteria. Studies on transfer from salmonella to other bacteria were not reviewed.

Escherichia coli

Quinolone resistance

As resistance to quinolones results from chromosomal mutation rather than acquisition and transfer of resistance genes, transfer of resistance between bacteria is unlikely. So far there has been only one recorded case of fluoroquinolone resistance coded on a transmissible plasmid in an enteric gram-negative bacterium, and this was in the human setting. The origin of this resistance gene has yet to be reported.

Streptothricin resistance

As noted in Section 5.3.2, streptothricin resistance genes appear to have spread widely in the countries where this agent has been used in food producing animals. The gene has spread from animal *E. coli* to salmonella, and subsequently to human strains of *E. coli* and *Shigella sonnei*. *Shigella* species are gram-negative pathogens confined to humans and primates.

Aminoglycoside resistance

The *aacC4* gene, which codes for the aminoglycoside-modifying enzyme AAC(3)-IV, emerged as a consequence of animal use of apramycin. The enzyme confers cross-resistance to gentamicin, an important antibiotic in human medicine. Although other aminoglycoside resistance genes have developed in human medicine as a result of human aminoglycoside use, the *aacC4* was not one of them. The gene, originally detected in animal isolates of *E. coli* and salmonella, has been detected subsequently in human isolates of *E. coli* and *Klebsiella pneumoniae*.

5.4.3 Conclusion

There are several well-characterised examples of resistance gene transfer between animal and human bacteria. The frequency of these events is unclear, but they may not need to be frequent because antibiotic use in humans could subsequently amplify the resistance in human populations.

5.5 Resistant animal strains or resistance of animal origin causing human disease (Step 3)

Antibiotic-resistant zoonotic bacteria such as salmonella and campylobacter are well-documented causes of human infection. Disease caused by human bacteria with resistance genes of animal origin are also well documented.

5.5.1 EVIDENCE: Do antibiotic-resistant bacteria from animals cause disease in humans?

Enterococci

Glycopeptide resistance

E. faecium with *vanA* resistance are well established as opportunistic pathogens in humans. There have been cases in Europe, the United States, Australia, and most recently Japan. Disease is seen almost exclusively in hospitalised patients with compromised host defences and those patients who have undergone invasive procedures at hospital. Many of these infections arise in patients who have recently received or are receiving vancomycin or the related glycopeptide teicoplanin, and are thus already 'failures' of treatment. The pattern of infection with vancomycin-resistant strains is similar to that seen with vancomycin-susceptible *E. faecium*.

Resistance to other antibiotics

There were no published studies on other antibiotics and enterococci at the time of the JETACAR literature review.

Salmonella

Over more than 30 years, there have been many instances of antibiotic-resistant salmonellae that have caused human infection.

Campylobacter

Fluoroquinolone-resistant campylobacters have identified from cases of human gastroenteritis in Europe and are temporally associated with the introduction of fluoroquinolones into food-producing animal use. This is well documented in the JETACAR literature review. These findings were extended in a very recent publication from the United States (Smith et al 1999) which confirmed the same temporal association. They also showed patients with fluoroquinolone resistant strains who were treated with fluoroquinolones had diarrhoea for significantly longer periods than those with susceptible strains.

Escherichia coli

As the JETACAR literature review noted, patients with urinary tract infection caused by *E. coli* harbouring streptothricin resistance have been documented. The one *E. coli* of animal origin known to cause human infection, enterohaemorrhagic *E. coli* that produces the shiga toxin, has yet to demonstrate any resistance to antibiotics. Infections caused by *E. coli* harbouring AAC(3)-IV have not yet been documented.

5.5.2 Conclusion

There is ample evidence that antibiotic-resistant strains of several bacterial species of animal origin can cause disease in humans

5.5.3 Therapeutic implications of resistance

Enterococci

Vancomycin-resistance in enterococci has a major impact on treatment. Enterococci are naturally resistant to many antibiotics, and many *E. faecium* and vancomycin-resistant strains of enterococci were known to harbour additional resistances prior to the emergence of vancomycin resistance. As a consequence, *vanA E. faecium* must often be treated with investigational antibiotics which have unproven efficacy.

Salmonella

At present resistance in salmonella has a lower therapeutic impact. Nontyphoidal salmonella infections of the type acquired through the food chain usually resolve without antibiotic intervention. However, treatment is required in a small proportion of patients in whom the infection becomes prolonged, severe or invasive. Fluoroquinolones are now the drugs of choice for invasive salmonella infection, in part because salmonella sometimes harbour resistances to other antibiotics. Thus, multi-resistant strains that also harbour resistance to fluoroquinolones could be difficult to treat. There is limited documentation of therapeutic failures attributable to resistance derived from animals.

Campylobacter

Like salmonella infections, while most campylobacter infections resolve without antibiotic intervention, antibiotic treatment is recommended for prolonged, severe or invasive disease. When campylobacter infections do require treatment, macrolides are the drugs of choice and fluoroquinolones are second-line agents. However, fluoroquinolones are frequently preferred because treatment is usually required before the availability of faecal culture results, and fluoroquinolones cover the other bacterial causes of gastroenteritis, whereas the macrolides do not. As Smith et al (1999) has shown, fluoroquinolone resistance does have a significant negative impact on treatment.

E. coli

Because streptothricins are not used in human medicine, there are no direct implications for treatment. However, aminoglycoside resistance encoded by the animal derived gene AAC(3)-IV generates cross-resistance to gentamicin, an important antibiotic for the treatment of the more severe infections caused by *E. coli*. As *E. coli* isolated from humans are frequently resistant to multiple classes of antibiotics, and gentamicin is recommended as part of standard initial therapy for more serious *E. coli* infections in humans, increasing aminoglycoside resistance could have significant consequences.

5.6 Australian data

5.6.1 Emergence of antibiotic-resistant bacteria in animals

Enterococci

There are very few Australian studies on resistance patterns in animal enterococci. Butt et al (1997) reported the isolation of VRE from animals. Most were species of minor importance with low-level intrinsic resistance (*vanC*). Two VRE strains with acquired resistance (*vanA* and *vanB*) were detected, but due to the limited data on antibiotic exposure could not be directly related to the prior use of avoparcin.

Barton and Pratt (unpublished, 1998)[6] isolated 849 strains of vancomycin-sensitive enterococci (46% *E. faecalis* and 27% *E. faecium*) and 367 strains of enterococci classified as *vanC* (constitutively resistant to ≤ 8 μg/mL vancomycin) enterococci (made up of *E. gallinarum* 51%, *E. casseliflavus* 37% and *E. flavescens* 11%) from 1000 pigs in South Australian piggeries. No *vanA* or *vanB* VRE were detected in this study. None of the piggeries sampled had used avoparcin for some time. All enterococci isolated showed high rates of resistance to macrolides, tiamulin and virginiamycin. The vancomycin-sensitive enterococci showed higher rates of resistance to the aminoglycosides and very high rates of resistance to tetracyclines were detected in all of the enterococci tested. All

[6] Barton MD and Pratt R (1998). Antibiotic resistance in bacteria associated with pigs. Pig research report —Project USA 1/1206. Unpublished report prepared for the Pig Research and Development Corporation.

of the enterococci were resistant to monensin (a polyether ionophore) and there was some resistance to bacitracin. There were only low rates of resistance to ampicillin. It is not known how these results relate to antibiotic use in piggeries. However, the extent of resistance found suggests that there has been significant exposure to antibiotics.

Salmonella

Apart from those examined in the JETACAR literature review, Australian reports include an Animal Health Committee (AHC) Australia-wide surveillance program of cattle, pig and commercial poultry isolates carried out between 1975 and 1982 (Murray et al 1986). This study did not distinguish between the various serovars of salmonella. Resistance rates were lower than reported in more recent studies. Valcanis et al (1994) noted an increase in multi-resistant strains of *S*. Typhimurium PT44 in both Victorian (Australian) dairy cattle and humans.

A 1996 study of dairy cattle and calves (Mackie et al 1996) reported high levels of resistant bacteria in different phage types (PTs) of *Salmonella* Typhimurium. All 10 isolates of PT44 were resistant to ampicillin, chloramphenicol, kanamycin, neomycin, streptomycin, sulfonamide, tetracycline and trimethoprim; none were resistant to gentamicin or spectinomycin and 1 of 6 isolates tested was resistant to apramycin. Smaller numbers of PT170, 179 and 185 isolates were tested and gave similar results. All 10 isolates of *S*. Dublin were fully sensitive to the antibiotics tested.

Antibiotic resistance in 39 Victorian horse isolates has been reported in a study published in 1997. All isolates were resistant to streptomycin and seven showed multiple resistance (Bucknell et al 1997).

The National Enteric Pathogen Surveillance System (NEPSS) has been testing salmonella strains from humans, animals and food since 1988. Data on more than 6700 animal and food isolates examined between 1989 and 1998 have demonstrated resistance and multiple resistance to a wide range of antibiotics of potential human health significance (Appendix 7). Resistance and multi-resistance has been most prevalent in isolated from pigs and chickens. Overall resistance rates appear steady; the multi-resistant strain *S*. Typhimurium DT104 has never been documented in Australia. Resistance to fluoroquinolones has been rare in animal isolates. No fluoroquinolone is registered for use in food producing animals in Australia, although there are anecdotal reports of some illegal use, at least in pigs.

Barton and Pratt (unpublished, 1998) isolated only 15 salmonellae from 1000 pigs sampled. The five *S*. Seftenberg isolates were mostly resistant to tetracycline, trimethoprim, sulfonamide, carbadox, spectinomycin, neomycin, streptomycin and apramycin. The 10 *S*. Derby isolates were resistant to fewer antibiotics, namely tetracycline, sulfonamide, neomycin, streptomycin and apramycin, even though all the pigs would have been exposed to similar antibiotic treatments. Thus, salmonellae were uncommon in this sample but were usually multi-resistant. Fluoroquinolone resistance was not detected.

Campylobacter

There are limited published Australian data, but Korolik et al (1996) reported significant resistance to erythromycin, some resistance to doxycycline but no resistance to enrofloxacin in 79 chicken isolates. An unpublished study of 116 pig isolates (Barton and Pratt, unpublished, 1998) found significant rates of resistance to erythromycin and tylosin, lincomycin, ampicillin and tetracycline, reflecting high use of antibiotics in these animals. There was no resistance to fluoroquinolones.

E. coli

There are few published Australian results. Bucknell et al (1997) isolated resistant *E. coli* from 75% of 143 horses examined. Resistance to streptomycin was the commonest resistance found and 6.5% of isolates were resistant to at least three antibiotics. Results of testing *E. coli* isolates from Australian livestock in the AHC survey have not been published. Pig, cattle and 'isolates of miscellaneous origin were collected between 1976 and 1981. High rates of resistance to streptomycin and tetracycline were found in pig isolates, with significant resistance to furazolidone and lower rates of resistance to ampicillin, chloramphenicol and neomycin. In some years, bovine isolates showed slightly reduced rates of resistance to streptomycin and tetracycline and slightly increased rates of resistance to ampicillin and chloramphenicol (JA Craven, Attwood Research Laboratory, Department of Agriculture, Victoria, unpublished report, 1982).

Barton and Pratt (unpublished, 1998) tested 957 isolates from healthy pigs and 52 isolates from clinical specimens. Almost all the isolates were resistant to tetracyclines, streptomycin and apramycin, with high rates of resistance to neomycin, sulfonamides and nitrofurans and much lower rates of resistance to spectinomycin, gentamicin and carbadox. Ampicillin and trimethoprim resistance was quite high but there was little resistance to cephalosporins. In the absence of information on what antibiotics were used in the piggeries, it is difficult to comment on the results. Tetracycline is commonly used to prevent and control mycoplasma infections in pigs, which presumably accounts for the high levels of resistance to it. There was no resistance to fluoroquinolones.

5.6.2 Spread of antibiotic-resistant bacteria from animals to humans

Salmonella

As found by the NEPSS, fluoroquinolone resistance has not been documented in Australian endemic human isolates of salmonella, but low level resistance has been found in imported isolates (infections acquired overseas).

5.6.3 Resistant animal strains causing disease in humans

NEPSS has documented resistances in human isolates of nontyphoid salmonella since 1988. For the phage types PT9 and PT44 of *S*. Typhimurium, resistance patterns for human isolates are very similar to those of bovine origin, which is the ultimate source of most human infections. The rates of resistance for human isolates have been consistently lower than bovine isolates for these two phage types, suggesting alternative origins for some human strains.

Many of the VRE clones from humans in Australia to date have been from cases of infection (Appendix 6). The serious underlying illnesses in many of the patients from whom these bacteria have been isolated attest to the important clinical impact of these resistant bacteria. However, only about 20% of strains are *vanA E. faecium*, the type for which the link between animal and human resistance is established. Only one strain of *vanB E. faecium*, the predominant Australian clinical type of VRE, has been found in animal specimens to date. Based on present, inadequate, survey information from animals in Australia, only a proportion of human infection can so far be suspected to result from resistance transfer to human enterococci. However, further work is urgently required to clarify the epidemiology of VRE in Australia, particularly to determine whether or not there is an animal reservoir for *vanB E. faecium*.

Campylobacter resistance to quinolones is rare in Australia; cases of selection to resistance during treatment have been recorded in human immunodeficiency virus (HIV)-positive patients. Clinical infection due to resistant *E. coli* of possible animal origin has not been documented in Australia

5.7 Overall conclusions

The JETACAR literature review found that there is qualitative evidence that antibiotics fed to animals leads to resistant bacteria and that these bacteria or their resistance genes are passed on to humans, principally via the food chain. The conclusions of the JETACAR literature review were similar to those of the MAFF and CAFA reviews. The levels of evidence were higher for some bacteria and antibiotics than for other bacteria and antibiotics. The committee accepted the findings of the JETACAR literature review, noting the degree of concurrence with other the other international reviews.

There is less information on the frequency with which resistance is passed on to humans. Such information would be valuable for formal risk assessment. Nevertheless, based on the information presented in this report, it may be possible to develop semiquantitative assessments for many bacteria and antibiotics.

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Chapter 6
Current controls for antibiotic use in animals

OVERVIEW

Australian controls

Imports. Antibiotics are imported into Australia on permits from the Therapeutic Goods Administration. There is no licensing mechanism for importers and antibiotic permit holders only have to submit quantity and end-use information retrospectively. There are therefore few or no accountability mechanisms to ensure that imported antibiotics comply with registration requirements (eg approved manufacturer and formulation), and that unregistered antibiotics are not diverted to feed-millers and home-mixers (neither of which are currently licensed).

Registration. The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) registers veterinary chemicals, including antibiotics. Data submitted on chemistry and manufacture, toxicology, environmental issues, residues, genetic engineering, occupational health and safety, efficacy and target animal safety, labelling and trade issues are evaluated. There is also a special requirement for data on antibiotic resistance, which are reviewed by the Working Party on Antibiotics. After the evaluation, the NRA grants or refuses registration (specific for the product, manufacturer, formulation, directions for use and dosage regimen). Post-registration there is monitoring of adverse reactions and participation in chemical review programs.

Controls of use. Antibiotic products are classified as 'open sellers' when available for open sale to the public or as prescription animal remedies (S4) when veterinary supervision is required. Open sellers are limited to low-dose antibiotics for in-feed use, such as avoparcin, tiamulin and virginiamycin, while prescription animal remedies (S4) include all dose forms for therapeutic and most dose forms for prophylactic use (eg penicillin, tetracyclines). Further conditions of use (eg supply, registration of veterinarians) apply under State/Territory legislation, which is not uniform and in some cases off-label use allows registered products to be used in an inappropriate manner.

Overseas controls

Although most countries evaluate data for new veterinary chemicals on safety, efficacy, residues and so on, the United States is the only other country that has a special data requirement for antibiotic resistance. In the European Union, there are centralised procedures for assessment of veterinary chemicals and Member States must comply with rulings. Growth promotants are used in all countries, except Sweden, which banned their use in 1986. Due to pressure from Sweden and other countries, the European Union imposed a temporary ban on avoparcin in 1997, which has recently been extended for a further two years; virginiamycin, tylosin, spiramycin and zinc bacitracin have also recently been suspended pending further review in 2000. Avoparcin is not used in the United States or Canada.

Trade issues

As Australia is a large agricultural producer, regulations to protect public health must also take account of the economic impact on Australia's domestic and export livestock industries and must be defensible on scientific and legal grounds. Under World Trade Organization arrangements, Australia is obliged to justify any sanitary measures that are not consistent with established international standards.

6.1 Australian controls

The Australian regulatory system for veterinary antibiotics is considered to be among the best in the world and, as a result, Australia has taken a conservative approach to the registration and use of antibiotics in animals and animal feeds. Controls over the veterinary use of antibiotics in Australia cover three main areas:

- *import* — from manufacturing sites overseas;
- *registration as veterinary chemicals* — involving product evaluation; and
- *use* — in veterinary practice or as 'open sellers' (for in-feed use only) for domestic and farm animals.

6.1.1 Import of antibiotics

Antibiotic raw materials (active constituents) used in the formulation of antibiotic products are not manufactured in Australia and are therefore imported from manufacturing sites overseas.

Importers must hold a permit covering each consignment. Permits are issued by the Therapeutic Goods Administration (TGA) under the Australian Customs (Prohibited Imports) Regulations (*Customs Act 1901*) and checked by the Australian Customs Service at the point of entry. At the expiry of each permit (ie retrospectively), importers must advise the TGA of all consignments imported, including the quantities and end uses.

In addition, antibiotics of biological origin must be approved by the Australian Quarantine and Inspection Service (AQIS) with regard to quarantine requirements relating to freedom from foreign human, animal and plant diseases.

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) collects annual import figures for agricultural and veterinary chemicals to satisfy, on a commercial-in-confidence basis, Australia's Organization for Economic Co-operation and Development (OECD) obligations.

6.1.2 Evaluation and registration of veterinary antibiotics

The NRA is the independent statutory body responsible for evaluating the efficacy, safety, residues and trade criteria for *registration* of agricultural and veterinary chemicals, including antibiotics, on the basis of good science.

The NRA is also responsible, in partnership with the State/Territory departments of agriculture and primary industries, for *regulating* the use of agricultural and veterinary chemicals. The NRA is responsible for the chemicals up to and including the point of sale, and the States/Territories are responsible for the control of use of the products. The primary NRA legislation governing registration and regulation of agricultural and veterinary chemicals is the *Agricultural and Veterinary Chemicals Code Act 1994* (Agvet Code).

As for other veterinary chemicals, the evaluation of a new antibiotic for use in animals or animal feedstuff is a detailed and complex process, including various evaluating agencies who assess data supplied by the sponsors in their respective fields, as follows:

- TGA — toxicology and public health issues;
- Environment Australia — environmental issues;
- National Occupational Health and Safety Commission (NOHSC) — occupational health and safety of chemicals;

- State/Territory departments of agriculture/primary industries — efficacy and target animal safety; and
- NRA — chemistry, residues, trade and labelling issues.

These agencies evaluate and make recommendations to the NRA. All the data requirements for registration of veterinary chemicals are set out in the *Vet Requirements Series: Guidelines for Registering Veterinary Chemicals* (NRA 1998).

These procedures, including the special arrangements for antibiotics described below are summarised in Figure 6.1. '*Registration*', if granted, covers the following specific factors:

- antibiotic product;
- manufacturer;
- formulation;
- animal species;
- directions for use;
- dosage regimen; and
- precautionary and restraint statements.

Variation of any of these factors comprises a breach of the registration and requires a new application and re-evaluation of the data.

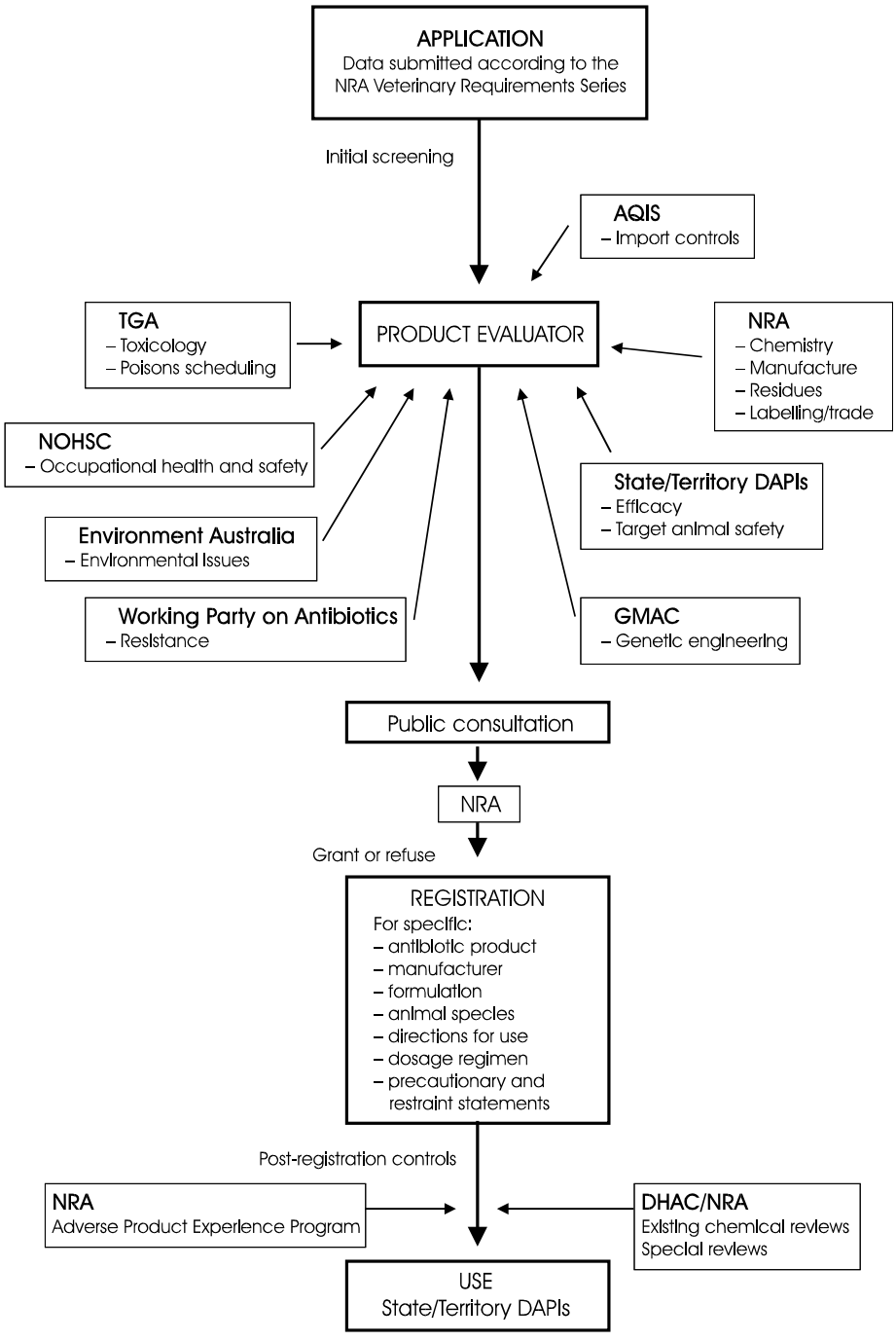
Working Party on Antibiotics

For the registration of veterinary antibiotics, an additional agency, the Working Party on Antibiotics (WPA), is also involved. The WPA was previously convened by the National Health and Medical Research Council (NHMRC) but, following a restructure in 1997, is now administered under the auspices of the TGA, pending a more permanent 'home'. This committee evaluates the likelihood of resistance developing and transferring from animal to man and the potential of human health to be affected.

The WPA (and its predecessor the Expert Panel on Antibiotics) have been evaluating new antibiotics for use in animals and animal feeds since the early 1980s. Since that time these committees have been guided by the principles first outlined in the Swann Report, which was published in 1969 by the United Kingdom Joint Committee of Houses of Parliament (see Appendix 1), as follows:

- the supply and use of drugs without prescription in animal feed should be restricted to antibiotics that:
  - are of economic value in livestock production,
  - have little or no application as therapeutic agents in man or animals,
  - will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms; and
- 'therapeutic antibiotics' should be available for use in animals only if prescribed by a veterinarian who has those animals under his care.

(In Australia, most antibiotics used for prophylaxis in animals have to be under the control of the veterinary surgeon, ie by prescription.)



Key:

TGA Therapeutic Goods Administration (DHAC)
NOHSC National Occupational Health and Safety Council
AQIS Australian Quarantine and Inspection Service
NRA National Registration Authority for Agricultural and Veterinary Chemicals
DAPIs Departments of agriculture and primary industries (State/Territory)
GMAC Genetic Manipulation Advisory Committee
DHAC Commonwealth Department of Health and Aged Care

Figure 6.1 Procedures for registration of veterinary antibiotics in Australia

The WPA's special data requirements, which are set out in the *Vet Requirements Series: Guidelines for Registering Veterinary Chemicals*, Part 10: Special Data Requirements (NRA 1998), include details of the antimicrobial spectrum, evidence of cross-resistance patterns, pharmacokinetic details, including achievable tissues levels, minimum inhibitory concentrations (MICs) for common human/animal pathogens and so on. For a growth promotant, details of the proposed antibiotic's effect on the flora of the gastrointestinal and respiratory tract must be provided. These special data requirements are currently being updated with stakeholder input.

Because of the importance for human medicine of the cephalosporin and quinolone antibiotics, WPA has developed policies for the regulatory control of these antibiotics for use in veterinary medicine. These policies are shown in Table 6.1.

After its evaluation, WPA makes recommendations to the NRA on whether to grant, refuse, restrict or amend the proposed application. Under the terms of the Agvet Code, the NRA takes the WPA's recommendations into consideration in its decision. The Australia New Zealand Food Authority (ANZFA) also requires WPA to report on the potential for the use of an antibiotic to contribute to the emergence of antibiotic-resistant human pathogens.

During 1998, the NRA, in conjunction with the chemical industry, reviewed the current protocol for data submitted with new antibiotic registration applications. New guidelines addressing the potential for antibiotic resistance to develop in animals and transfer to humans were developed (see Appendix 4). Late in 1998, the draft guidelines were amended by incorporating comments from JETACAR members. In February 1999, the revised guidelines were circulated to relevant stakeholders for additional comment. Further revisions to the guidelines were discussed at a meeting of relevant stakeholders at the NRA on 10 June 1999. The NRA is currently finalising Part 10 based on the principles shown in Appendix 4 and the stakeholder comments.

Table 6.1 WPA policies for regulatory control of the cephalosporin and quinolone antibiotics in veterinary medicine

Antibiotic	Regulatory principles
Cephalosporins	In veterinary chemicals registered by the NRA for: • selective use for treatment of disease in individual animals under direct control of veterinarians; • short-term oral or parenteral therapy in companion animals and by injection in food-producing animals; and • intramammary products for single-dose dry cow therapy and for short-term therapy (maximum 5 days) in lactating cattle. Not recommended for: • topical dose forms (any species); • oral dose forms in food-producing species including calves and pigs; • situations where animals are mass medicated other than for dry cow therapy of dairy cattle.
Quinolones (including fluoroquinolones)	For therapeutic use in nonfood-producing animals under direct control of a veterinarian, either as veterinary chemicals registered by the NRA or as human dose forms.

Amendments to guidelines

In May 1998, NRA and WPA started work to strengthen the pre-registration special data requirements relating to antibiotic resistance for new antibiotic applications.

As well as information on the antibacterial spectrum, MICs, etc, as before, these draft requirements include a risk assessment for possible contribution to antimicrobial

resistance in animal and human pathogens in order to determine a level of acceptable risk with a reasonable certainty of no harm.

For digestion enhancers (growth promotants), the likely effect on the flora of the gastrointestinal tract must be assessed, including effects on coliform-resistance patterns in animals or animal products and effects of the substance on intestinal anaerobes.

The draft guidelines also indicate the need for monitoring studies to detect major changes in susceptibility of bacterial pathogens following registration.

The draft amended special data requirements are shown at Appendix 4.

Genetic Manipulation Advisory Committee

Antibiotics that have been genetically engineered must be evaluated by the Genetic Manipulation Advisory Committee (GMAC) for assessment of safety issues relating to the use of genetically manipulated organisms before registration by the NRA.

National Drugs and Poisons Scheduling Committee

The poisons schedule classification plays an important part in the control over the use of antibiotics. During the evaluation process, each new antibiotic is classified according to its toxicological properties by the National Drugs and Poisons Scheduling Committee (NDPSC). The NDPSC is primarily concerned with the potential for a product to cause harm to humans if it is eaten, inhaled or comes in contact with the skin and/or eyes. With each poison classification, or 'schedule', comes appropriate label statements and controls (AHMAC 1997).

- *Antibiotics available as 'open sellers'*— antibiotics for use in animals that are exempt from poisons scheduling, or are classified in schedule 5 or 6 (S5 or S6), can be sold to the public for use at low-dose concentrations in animal feeds, provided they are registered by the NRA. Examples include avoparcin, virginiamycin and tiamulin.
- *Antibiotics available as prescription only* — antibiotics classified as schedule 4 (formerly called S4) are called prescription animal remedy (PAR) antibiotics and must be prescribed by a registered veterinarian for animals under their care. Persons distributing, wholesaling or retailing PARs must be licensed by the relevant State/Territory health department. All antibiotics used therapeutically in animals are classified as PARs. Examples are the penicillins, neomycin and the tetracyclines.

Taking the toxicological profile of a particular antibiotic at different concentrations into consideration, certain antibiotics, such as tylosin, are currently classified as both 'open seller' and PAR products depending upon the concentration of the antibiotic in the product.

Public consultation

A public consultation process must take place for every proposed new product, or proposed major extension of use in another food-producing animal or crop, that is made to the NRA. For this consultation process, technical evaluation reports and/or trade advice notes are made available to anyone for comment. Under the terms of the Agvet Code, the NRA must consider public consultation comments in its decision to grant or refuse an application to register an agricultural or veterinary chemical product.

6.1.3 Post-registration controls

Adverse Product Experience Program

The NRA administers the Adverse Product Experience Program. Anyone can lodge an adverse product experience report with the NRA on a voluntary basis. All registrants of veterinary chemical products must report all adverse product experiences that they receive to the NRA on a six-monthly basis for new products for the first two years after registration and once a year thereafter. The annual return must also include a summary of adverse product experiences on all other existing registered products. Serious incidents must be reported promptly by registrants on a case-by-case basis. The NRA evaluates all adverse product experience reports and takes appropriate regulatory action where required.

Chemical review

The Agvet Code 1994 also provides for ongoing review of existing chemicals under two major chemical review programs.

- *Existing Chemical Review Program* — a systematic and comprehensive review of older chemicals to ensure they meet contemporary standards of safety and performance, taking into account any new information and scientific data generated since their registration.
- *Special Review Program* — allows the NRA to immediately review chemicals if issues arise that may alter the terms of their registration. The review addresses urgent or specific concerns about chemicals that may require a quick response.

The NRA announced a special review of avoparcin in the June 1998 edition of the *Commonwealth of Australia Agricultural and Veterinary Chemicals Gazette* (NRA Gazette).

6.1.4 Controls over use of antibiotic products

State legislation

As described above, the NRA is responsible for the evaluation and registration process and for regulation of antibiotics up to and including the point of sale. State/Territory health, agriculture and primary industries departments provide further controls over the supply and use of the products, through relevant legislation, as follows:

- *health legislation* — enables registered veterinarians to prescribe PARs, licenses sellers of PARs and regulates conditions of supply of PARs, including scheduling classifications;
- *health, agriculture/primary industries legislation* — allows registered veterinarians to practise through registration by veterinary surgeons boards under veterinary surgeons legislation, which regulates professional standards and behaviour, including the responsible use of drugs; a veterinarian found guilty of a breach of the legislation may have his/her registration suspended or cancelled;
- *agriculture/primary industries legislation* — enables control of the use of registered products, off-label use, traceback and regulatory action associated with violation of permitted residue levels.

There are considerable differences between the various State and Territory health, veterinary surgeons and agricultural/primary industry legislation with regard to the control of veterinary chemicals. There is also considerable overlap of responsibilities between the health and agriculture/primary industries legislation controlling veterinary chemicals.

In most States it is not illegal for a veterinarian to prescribe an antibiotic registered for one food species to be used on another food species or to vary a dosage regimen. In some States it is also not illegal for a veterinarian to use a product registered for nonfood-producing animals off-label in a food-producing species, while some States are unable to enforce NRA label restraint statements such as 'not for use in food-producing animals'. These discrepancies can therefore be a disincentive for chemical companies to register an antibiotic in more than one species knowing that they can promote off-label use. While it may not be practical or desirable to prevent off-label use in some minor species, enforceable harmonised restrictions on the use of antibiotics in major livestock species is considered essential.

There have been discussions at State level about a harmonised approach to the supply and use of veterinary chemical products. A harmonised approach across Australia must address the situations where off-label prescription is inappropriate.

Stockfeed production

The Agvet Code 1994 allows considerable flexibility to the feed-milling and home-mixing industries, enabling the incorporation of NRA-registered products into feed without further duplication of registration of premixes as was the case under previous State registration. However, the Agvet Code requires that only the registered product itself can be incorporated into feeds for medication purposes, where 'registration' includes the source and formulation of the products.

While TGA permits are technically required for the importation of antibiotics, there are few checks on what antibiotic substance is actually imported. Once an in-feed antibiotic is registered by the NRA, there is a practice of importing a cheaper unregistered generic antibiotic under the same permit. Importers, who are supposed to only supply licensed manufacturers of veterinary chemical products, often divert unregistered in-feed antibiotics to feed-millers and home-mixers.

There is no licensing mechanism for importers of agricultural and veterinary chemicals (including antibiotic substances). There are therefore few or no accountability mechanisms to check if the importers are diverting unregistered antibiotics to feed-millers and home-mixers or if the imported antibiotic matches the approved source and registration specifications.

Stockfeed manufacturers are also not currently licensed. In 1986, the NHMRC report *Antibiotics in Stockfeeds* was released, supporting the development of a code of good manufacturing practice for feed-mixers and the licensing of manufacturers of stockfeed containing antibiotics. Although an Australian *Code of Good Manufacturing Practice for Homemixed Feeds, Feed Milling Industry and Stock Feed Premixes* was developed and published, the Standing Committee on Agriculture did not consider licensing necessary at that stage (SCA 1992).

Professional codes of practice

The Australian Veterinary Association (AVA) has professional codes of practice for use of antibiotics in each major animal species while the individual livestock industries have specific codes of practice for antibiotic use for their particular industry. These codes of practice set out guidelines for their members for the appropriate use of registered antibiotics for the particular species or industry (see Section 7.3.4).

6.2 Australian versus international controls

As indicated above, in comparison with most other countries, the Australian regulatory system for veterinary antibiotics is very conservative. Since 1970, in addition to the routine data requirements for all veterinary drugs, antibiotics for use in animals in Australia have been assessed by the WPA (or its predecessors) for potential to compromise human health. The United States is the only other country that assesses antibiotic-resistance data submitted against specific guidelines (see Section 6.3.1, below).

Because of these strict regulatory guidelines, Australia has not registered the fluoroquinolone or amphenicol classes of antibiotics, colistin or gentamicin (aminoglycoside) in food-producing animals, based on the potential risk of compromising human health through the development of antibiotic resistance. For the same reason, cephalosporin antibiotics have only recently (mid-1990s) been registered for restricted use in food-producing animals, whereas most other countries have been using them in food species for the last 15–20 years. In the late 1980s, following a health department review, the quinoxaline derivative carbadox was prohibited for use in all species in Australia based on carcinogenicity grounds. Carbadox is still registered for use in Europe, the United States and Canada.

The nitrofuran class of antibiotics was prohibited from use in food-producing animals in 1992 in Australia, several years before a similar prohibition in the European Union on carcinogenicity grounds. Penicillin is not permitted in stockfeed in Australia but it is permitted in the United States.

6.3 Overseas controls and data requirements

The data requirements and registration procedures for veterinary use of antibiotics vary from country to country. Requirements and/or procedures in the United States, United Kingdom (European Union) and Canada are briefly described below.

6.3.1 United States

The United States has a similar process for the registration of veterinary drugs to that used in Australia and is the only other country that assesses antibiotic-resistance data submitted against specific guidelines. Veterinary drug registration is administered by the Center for Veterinary Medicine (CVM) under the United States Food and Drug Administration (FDA). New animal drug applications include information on manufacture, animal safety, efficacy, human drug residue consumption safety and environmental impacts. In addition, like Australia, antibiotic use in animals is assessed against specific guidelines, which include antibiotic resistance. Under these guidelines antibiotics are assessed against the following criteria.

- *Human safety criteria* — drugs should not result in:
  - a significant adverse effect in the relative quantity, prevalence and shedding of salmonella organisms in animals;
  - a significant increase of salmonella organisms resistant to drugs used in human clinical medicine in the animals;
  - a significant increase in the resistance of coliforms to antibacterial drugs used in human clinical medicine provided this resistance is transferable to bacteria in humans;
  - enhancement of pathogenicity of bacteria; or

- adverse effect to humans due to ingestion of residues of the antibacterial drug, metabolites or degradation products.

- *Animal health safety criteria* — drugs should not result in:
  - a significant adverse effect in the relative quantity, prevalence and shedding of salmonella organisms in the animal;
  - a significant increase of salmonella organisms resistant to drugs used in clinical veterinary medicine and to drugs not authorised for use in food-producing animals;
  - disease that is more difficult to treat;
  - adverse effect on the animal due to significant increase in the resistance of coliforms to antibacterial drugs used in clinical veterinary medicine;
  - enhanced pathogenicity of bacteria;
  - continuing increase in amount of drug necessary to achieve the desired response.

In the United States, almost all antibiotic feed additives are available over the counter (open sellers), whether they are for therapeutic, prophylactic or growth promotion use.

6.3.2 United Kingdom/European Union

In the United Kingdom, antibiotics are authorised either as veterinary medicinal products or as zootechnical feed additives. Zootechnical feed additives are compounds that are used as growth promotants or to treat coccidial protozoal infections (ie coccidiostats).

Veterinary medicinal products

Veterinary products are authorised in accordance with the provisions of the European Commission (EC), which require assessment against criteria of safety, quality and efficacy. Applications under the decentralised procedure for first authorisation in the United Kingdom are made to the Veterinary Medicines Directorate under the terms of the Marketing Authorisations for Veterinary Medicinal Products Regulations 1994, which implement the EC directives. Applications under the centralised procedure are made to the European Medicines Evaluation Agency. Before an antibiotic is authorised in the United Kingdom for the treatment of a food-producing animal, an application is first considered by the independent, scientific Veterinary Products Committee (VPC), which has a statutory role to advise health and agriculture ministers on the safety, quality and efficacy of veterinary medicines. Safety and efficacy include the risk of development of resistance and/or cross-resistance. In considering the use of antibiotics, the committee has consistently followed the principles established in the Swann Report (UK Joint Committee of Houses of Parliament 1969). The VPC's policy has been that new antibiotics should not necessarily be precluded from therapeutic use in animals, but that their prophylactic use should be discouraged.

Zootechnical feed additives

Within the European Union, the use of additives in animal feed is subject to Directive 70/524/EEC, which includes a requirement that at the level permitted in animal feed it does not adversely affect human or animal health, or the environment. Authorised zootechnical additives, which are listed in Annex I and II of the directive, are permitted for use throughout the European Union. Member States must permit the use of those listed in Annex I but have the option not to permit those listed in Annex II (see Table 6.4).

The permitted antibiotics are not absorbed through the gut and thus do not enter the edible tissues of food-producing animals. Resistance and/or cross-resistance is taken into account in the authorisation process and data from salmonella-shedding studies are required. If a Member State feels that evidence has come to light that calls the safety of a zootechnical feed additive into question, that country can suspend or restrict the use of the additive (this is referred to as the 'safeguard clause'). In this situation, the EC and the other Member States must be informed immediately and scientific information supporting the action must be provided. The Standing Committee on Animal Nutrition (SCAN) reviews the evidence and makes recommendations. The EC then consults other Member States through a Standing Committee and amendments to the approval (or its revocation) are ratified by a majority of this committee, after which all Member States must comply with the decision.

Controls on distribution and use

Controls over the distribution and use of antibiotics, particularly feed additives, vary from country to country in the European Union. Like Australia, however, all antibiotics authorised for therapeutic use (veterinary medicinal products) are classified as *prescription only medicines*. That is, they can only be used on prescription from a veterinary surgeon. This requirement applies whether or not the antibiotic is incorporated into animal feeds.

6.3.3 Canada

Canada has a similar process for registration of veterinary drugs to that used in Australia but does not yet have specific data requirements addressing antibiotic resistance.

6.4 Controls on growth promotant use

6.4.1 Australia

In Australia, provided antibiotics are registered by the NRA for growth promotant uses (including avoparcin and virginiamycin), they are available for over-the-counter sale to livestock owners, feed-millers and feed-mixers (see Section 6.1). The antibiotic uses currently registered for growth promotion in Australia are shown in Table 6.2 (for further details see Table 7.4; Chapter 7).

Table 6.2 Antibiotics registered as growth promotants in Australia

Group	Antibiotic	Food species
Arsenicals	3-nitro-arsonic acid	Pigs, poultry
Glycopeptides	Avoparcin	Pigs, meat poultry, cattle
Macrolides	Kitasamycin	Pigs
	Oleandomycin	Cattle
	Tylosin	Pigs
Polyethers (ionophores)	Lasalocid	Cattle
	Monensin	Cattle
	Narasin	Cattle
	Salinomycin	Pigs, cattle
Polypeptides	Bacitracin	Meat poultry
Quinoxalines	Olaquindox	Pigs
Streptogramins	Virginiamycin	Pigs, meat poultry
Others	Flavophospholipol[a]	Pigs, poultry, cattle

[a] Also known as bambermycin
Source: NRA, November 1998

6.4.2 Overseas

Antibiotics are used for growth promotion in all countries except Sweden but controls over their use vary widely from country to country.

United States

The antibiotics registered for growth promotion to animals in the United States are shown in Table 6.3. The active ingredients in this list are usually associated with growth promotion and they are all available over the counter (ie without a veterinarian's prescription).

Table 6.3 Antibiotics registered for growth promotion to animals in the United States

Group	Antibiotic	Food species
Arsenicals	3-nitro-arsonic acid and others	Pigs, poultry
Beta-lactams	Penicillin	Pigs
Lincosamides	Lincomycin	Pigs
Macrolides	Erythromycin	Pigs
	Tylosin	Pigs, cattle
Pleuromutilins	Tiamulin	Pigs
Polyethers (ionophores)	Monensin	Cattle
Polypeptides	Bacitracin	Pigs, poultry, cattle
Quinoxalines	Carbadox	Pigs
Streptogramins	Virginiamycin	Pigs, poultry, cattle
Tetracyclines	Tetracycline	Pigs, poultry, cattle
Others	Flavophospholipol[a]	Pigs, poultry, cattle

[a] Also known as bambermycin
Note: Avoparcin is not registered for animal use in the United States
Source: Prescott and Baggott (1995)

European Union

Table 6.4 shows the antibiotics that were permitted until recently by the EC for use in animal feeds under Directive 70/524/EEC.

From 1986, Sweden banned the use of all growth promotants and claims that, as a result, the numbers of antibiotic-resistant bacteria have remained lower in Sweden than in other countries over the last 10 years. However, when Sweden joined the European Union in 1995, it was obliged to comply with EC directives. Nevertheless, under the safeguard clause (see Section 6.2.2), Sweden argued for a continuation of its ban and was granted a special dispensation until December 1998, during which time the EC assessed the scientific evidence relating to growth promotant use of antibiotics.

In 1995, Denmark (followed by Germany in 1996) also banned the growth promotant use of avoparcin within its borders. The ban was a result of concerns that use of avoparcin was leading to an increase in resistance, not only against itself, but also to a similar glycopeptide antibiotic, vancomycin, which is used in human medicine. The Danish Veterinary Laboratory considered that there was a danger of transfer of this vancomycin resistance to humans via the food chain. This would be important as vancomycin is a so-called antibiotic 'of last resort' for a number of human pathogenic bacteria that are resistant to many other alternative antibiotics.

Table 6.4 Antibiotics permitted as growth promotion in the European Union under EC Directive 70/524/EEC, 1998

Group	Antibiotic	Food species[a]
Glycopeptides	Avoparcin	Suspended (1996)
Macrolides	Tylosin#	Piglets, pigs
	Spiramycin#	Turkeys, other poultry, calves, lambs, kids, piglets, pigs
Oligosaccharides	Avilamycin	Piglets, pigs, chickens for fattening, turkeys[b]
Polyethers (ionophores)	Monensin	Cattle for fattening
	Salinomycin	Piglets, pigs
Polypeptides	Bacitracin#	Laying hens, turkeys, other poultry (chickens for fattening[b]) calves, lambs, kids, piglets, pigs[b]
Streptogramins	Virginiamycin#	Laying hens, turkeys, other poultry, calves, piglets, pigs, calves, cattle for fattening, sows[b]
Others	Flavophospholipol[c]	Laying hens, turkeys, other poultry, calves, piglets, pigs, calves, rabbits, cattle for fattening

use suspended from 1 January 1999
[a] 'Other poultry' excludes ducks, geese, pigeons; also excludes laying hens unless specifically mentioned
[b] Ban optional (Annex II)
[c] Also known as bambermycin
Source: Prescott and Baggott (1995)

Denmark and Germany both submitted reports to the EC in support of their bans. This evidence was considered by SCAN, which reported to the EC that, whilst the reports indicated that there was a possible hazard from the use of avoparcin, the evidence failed to establish a risk of transfer of resistance. The United Kingdom's VPC agreed with this finding. Nevertheless, the Standing Committee endorsed an EC proposal to ban the use of avoparcin as growth promotant feed additive within the European Union from 1 April 1997, pending further research work.

Denmark has also invoked the safeguard clause to ban virginiamycin on the grounds that it is closely related to another streptogramin antibiotic (quinupristin/dalfopristin) that is being developed for human use. Finland had bans against the use of tylosin and spiramycin when they joined the European Union.

The issue of antibiotic resistance generally was addressed at a meeting of European Union health ministers and scientists in Copenhagen in September 1998 (European Union Conference 1998). Animal antibiotic use was considered and, among other recommendations, prudent use promoted. There was unanimous agreement that the use of growth promoters should be stopped if there was clear evidence of a risk to human health.

At the end of 1998, SCAN reviewed a proposal to ban the growth promotant use of the four antibiotics virginiamycin, tylosin phosphate, spiramycin, and zinc bacitracin. The proposal did not receive the required qualified majority of votes at SCAN, as three countries abstained, and was referred to the Agriculture Council of Members, who subsequently voted in favour of the ban.

Although the ban was agreed from 1 January 1999, Member States have been given until 1 July 1999 to use up stocks, including stocks of pre-mixtures and feed of which they are an ingredient. The ban on avoparcin was also extended.

The ban is to be reviewed before 31 December 2000 on the basis of the information available from investigations, particularly from the Report of the Scientific Steering Committee, and surveillance on bacterial resistance.

6.4.3 Canada

Canada has a range of antibiotics registered for growth promotant use: bacitracin, bambermycins (flavomycin), carbadox, tylosin, virginiamycin, lasalocid, monensin, narasin and salinomycin. They are all available over the counter for addition to stockfeed. Avoparcin is not registered in Canada. Apramycin, neomycin, spectinomycin, streptomycin, erythromycin, penicillin and lincomycin are all also available over the counter in Canada (Health Canada, pers comm, November 1998).

6.4.4 Japan

The use of antibiotics in food-producing animals for growth promotion is considered an extremely sensitive issue in Japan. There are currently no antibiotics registered for growth promotion as such. However, antibiotics are permitted for use as a component of 'feed additives' but only after obtaining ministerial approval.

6.5 Current international action to address concerns over antibiotic resistance

The Berlin meeting organised by the World Health Organization (WHO) on antimicrobial use in food-producing animals (WHO 1997), the recent European Union Conference (The Microbial Threat, Copenhagen, September 1998) and the WHO Geneva meeting on use of quinolones in food-producing animals (WHO 1998) all made recommendations on the use of antibiotics in food-producing animals.

- WHO 1997 — the use of any antimicrobial agent for growth promotion in animals should be terminated if it is used in human therapeutics or known to select for cross-resistance to antimicrobials used in human medicine.
- European Union Copenhagen meeting 1998 — antimicrobial resistance is a major European and global problem; steps should be taken to develop new antimicrobials, set up surveillance systems, collect consumption data, encourage prudent use of antimicrobials, coordinate research efforts and review progress.
- WHO 1998 — recommendations for research, surveillance and prudent use in food-producing animals.

These recommendations are currently driving decision making in Europe, the United States and other countries.

6.5.1 United Kingdom

Reports relevant to antibiotic resistance have been published recently by both Houses of Parliament. A subcommittee of the House of Lords Select Committee on Science and Technology produced a report on antimicrobial resistance, whilst the House of Commons Select Committee on Agriculture reported on food safety (see Appendix 1). Although the use of antibiotics in animal production was outside the original terms of the Lords' inquiry, both reports made recommendations on this issue. The Lords' report recommended the phasing out of some antibiotic growth promotants, such as virginiamycin, whilst the Commons' report favoured a complete ban. The Advisory Committee on the Microbiological Safety of Food (ACMSF) set up a working group

specifically to look at microbial antibiotic resistance in relation to food safety and is expected to report soon.

6.5.2 European Union

Currently, a European Union/industry antibiotic-resistance monitoring program is being set up. The scheme, which was developed in response to the European Union temporary ban on avoparcin, will monitor resistance in *Enterococcus faecium* from pigs and poultry to some growth promotants in six European Union member states — Sweden, Denmark, France, Spain, The Netherlands and the United Kingdom. The scheme may be expanded in the future to include a wider range of microorganisms and antibiotics.

The Committee on Veterinary Medicinal Products (CVMP), which advises the EC on the safety, quality and efficacy of veterinary medicinal products, has also set up a working group, which is currently examining the issue of antimicrobial resistance.

6.5.3 United States

In the United States the CVM is applying a multipronged strategy, including the development of a new policy document for premarket approval for new veterinary antibiotics. There will be new additional requirements for the submission of data in support of the approval of antibiotics for veterinary use related to evaluation of resistance development and additional requirements for postmarket surveillance. The new criteria will not apply to antibiotics already approved but if a company lodges a supplemental approval application then the new criteria will apply.

The National Antimicrobial Resistance Monitoring Program (NARM) has been set up to monitor changes in resistance patterns for salmonella and other enteric bacteria. NARM is a joint project between the United States FDA, Department of Agriculture, and Centers for Disease Control. There have also been a number of other food safety initiatives involving veterinary professional organisations and industry.

6.5.4 Canada

In Canada, the health department (Health Canada) sponsored a workshop in 1997 for interested stakeholders from the medical, public health, veterinary and agricultural communities. A set of recommendations was developed to focus on professional and public efforts to reduce the development and transmission of antibiotic resistance. After the conference a multidisciplinary committee, the Canadian Coordinating Committee on Antimicrobial Resistance, was set up to coordinate information on antibiotic use in all sectors and oversee initiatives on a national scale. Medical initiatives are focused on communication and prudent use guidelines to reduce unnecessary prescribing. In the veterinary and food-producing areas, a stakeholder consultation was held in June 1998 and initiatives have started to improve data collection and potential linkage of data for disease incidence and antibiotic resistance in animals.

Antibiotic resistance has been given a top priority in Health Canada and several projects have been set up relating to antibiotic resistance, with a primary focus on multiresistant salmonella. A prevalence study of campylobacter has also been started.

6.6 Implications for trade

Australia exports about 65% of its agricultural production, including livestock products. For example, Australia is the world's largest beef exporter. Our national economic well-being is therefore readily affected by any disruption in the trade of livestock products.

Technical barriers to trade in an increasingly deregulated global economy are therefore of great importance to Australia.

As a member of the World Trade Organization (WTO), Australia is subject to a number of international treaty obligations, including the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). Two key elements of this are that sanitary and phytosanitary measures must be applied only to the extent necessary to protect human, animal or plant life or health and must be based on scientific principles and not maintained without sufficient scientific evidence. Australia is obliged by the WTO/SPS Agreement to justify any sanitary measures that are not consistent with established international standards. However, Australia can implement different systems as long as the final outcome can be shown to be equivalent to that required by an importing country. Alternatively, it must be scientifically justified in our circumstances, applied consistently and used on local products as well as imported products. The equivalence determination must be made using an acceptable scientific assessment process that is open to international scrutiny.

This means that adverse human health effects attributed to antibiotic-resistant bacteria from food-producing animals need to be clear and well documented. Regulations designed to protect public health must then take account of the potential economic impact on Australia's domestic and export-oriented livestock industries and, in particular, must be defensible on scientific and legal grounds.

Opportunities for international trade harmonisation exist through international bodies such as Codex Alimentarius, the Office International des Epizooties (OIE) and the WHO. Standards for antibiotic resistance have not yet been developed for international trade. Codex Alimentarius is an important mechanism through which Australia can promote an internationally harmonised approach.

JETACAR was aware of the realities of the potential economic impact on Australia's domestic and export-oriented livestock industries of any bans on the use of antibiotics and considered the time-course needed for implementation of any changes to the regulations.

The question of the economic and trade implications of banning the use of a particular antibiotic in agriculture can be addressed using three scenarios:

Scenario 1 A trading partner bans the use of a particular antibiotic

If a trading partner bans an antibiotic and stops imports from countries that use that antibiotic, Australian industry has two choices. It can continue to use this antibiotic in production, which would mean that access to that particular market could be lost pending any WTO challenge. For example, the European Union ban on hormone growth promotants (HGPs) was challenged at the WTO by the United States and Canada (Australia was a third party to the dispute). The dispute settlement meant the European Union is now forced to accept imports from countries allowing the use of HGPs with controls, or to pay compensation to these countries.

Alternatively, if the market in question is a major market, industry may choose to not use this antibiotic either in production specifically for that market, or for any other production. However, any decision not to use particular antibiotics in production can result in an increase in production costs, particularly in the intensive industries. A potential positive is that producers not using this antibiotic to satisfy a particular export market may also be able to obtain a market premium in Australia or in other export markets for animal products produced in an antibiotic-free/restricted environment. However, it is unlikely that more than about 10% of Australians will pay a premium for

meat from livestock fed without antibiotic growth promotants. It has not happened in the case of HGPs (Avcare submission to JETACAR).

Scenario 2 A world-wide ban is placed on a particular antibiotic

In this situation, all countries would be equal in terms of trade. Research could lead to alternative treatment methods including alternative antimicrobials, or changes in production methods to replace the banned antibiotic. A short-term increase in production costs for producers should therefore be overcome in the medium to long term. Although improvements in management practices and housing can and will reduce reliance on antibiotic use, these can only occur as part of a gradual process because of the capital costs they usually involve.

One important fact to note is that if the banned antibiotic was only used in one major commodity, increased market prices due to increased production costs could lead to consumers using other commodities.

Scenario 3 Australia unilaterally places a ban on an antibiotic

A move by Australia to unilaterally ban an antibiotic used by the intensive and semi-intensive production systems would place Australian producers at a serious commercial disadvantage in current overseas markets because our competitors in other parts of the world would have access to these production tools. In the domestic market, increased production costs could lead to increased prices for that product. In this situation, if the banned antibiotic was only used in one major commodity (eg chicken meat), this could lead to domestic consumers turning to alternative commodities, with a detrimental effect on the affected industry.

Any ban of antibiotics in Australia would have some implications in terms of trade into our country. If Australia prohibited imports from countries that use the banned antibiotic, scientific justification would be required and would be subject to challenge and scrutiny under WTO rules. It is likely that there would be some WTO/SPS Agreement appeals to such a measure from other countries. Therefore, a ban of antibiotics in Australia may not prevent Australians from consuming imported meat or other animal products produced with the assistance of antibiotic supplements.

Conclusion

Meat-producing industries face significant challenges due to the liberalisation of international trade. To remain competitive industries need access to the same production tools as those available to overseas competitors. Any strategy developed in Australia needs to be part of an integrated global approach to antibiotic resistance.

International treaties, such as the SPS Agreement, provide the basis for international trade. Therefore, in the assessment of risk, Australia needs to take into account the objective of minimising negative trade effects. While antibiotic-resistance standards have not yet been developed for international trade, a way forward would be to refer this issue to the Codex Alimentarius Commission in order to promote an internationally harmonised approach, particularly in the risk assessment process. In the meantime, Australia must ensure that regulatory controls on antibiotic use are at least as stringent as those of our key trading partners.

Chapter 7
Current antibiotic use patterns

OVERVIEW

Level of use
Antibiotics are widely used in Australia both in humans and animals. Import data show that approximately one-third of the antibiotics imported is for humans and two-thirds for animals. In human medicine, Australia uses more antibiotics than most other developed countries but over the last five years the levels of use have decreased slightly. This contrasts with most other countries where the medical use of antibiotics has increased over this time.

For extensively-raised sheep and cattle, antibiotic use is minimal. Intensive livestock producers (feedlot cattle, pigs and poultry) use antibiotics primarily for disease control and prevention but they are also used for growth promotion. Economic factors are paramount and prevention strategies other than antibiotics (eg vaccines, eradication, biosecurity) are used for control of bacterial diseases, if these disease control measures exist and are cost-effective.

Human uses
Antibiotics in humans are used to treat established infections or prevent infections (prophylaxis). There are usually a number of different antibiotics for the medical practitioner to choose from for each infection, but the treatment of some serious infections is limited to only one or two antibiotics because resistance has developed to other antibiotics.

Animal uses
Antibiotics are used to treat established infections or to prevent disease (prophylaxis) in individual or groups of animals. Lower levels of antibiotics are added to feed to improve animal growth and feed conversion (growth promotion). Although this may be a proven benefit, in many cases it is incidental to other, disease prevention uses. For example, ruminants that are fed on grain may need antibiotics to prevent lactic acidosis; in poultry meat production, polyether antibiotics are added to feed to control protozoal diseases such as coccidiosis (ionophore coccidiostats). Some antibiotics that are incorporated into feed at low levels for growth promotion are available without a veterinary prescription (open sellers).

It is not always economic for manufacturers to register antibiotics for minor purposes or rare species. 'Off-label' prescription by veterinary surgeons is therefore necessary for the health and welfare of these species. Such usage is controlled under State/Territory legislation.

Critical antibiotics
The Swann Report (1969) first recognised that important therapeutic antibiotics in humans or animals should not be incorporated into animal feeds, particularly for growth promotion. However, for various reasons, some agents have been registered in animals that are related to those currently of importance in humans. Avoparcin (a glycopeptide) is registered in Australia as a growth promotant in pigs, broiler chickens and (feedlot) cattle; it is related to the human antibiotic vancomycin. Virginiamycin (a streptogramin) was registered as a growth promotant in pigs and poultry and for some other animal uses because streptogramins were not widely used in human medicine. This situation has changed with the development of the related streptogramins (quinupristin/dalfopristin) for treatment of human multiresistant infections.

Enhancement of resistance
There is a widely held belief that the method of drug administration (dose and duration) can influence the selection of resistance, but the evidence is mostly circumstantial. There is most concern that the use pattern of growth promotion and some prophylaxis in animals, ie subtherapeutic concentrations for long periods, might provide the greatest selection pressure.

Economic impact of antibiotic resistance
Quantitative information about the economic impact of resistance is limited but experience shows that there are significant additional costs to managing resistant organisms. Modelling suggests that the increases in costs are directly proportional to the rates of resistance.

7.1 Level of antibiotic use

Trends in the level and type of antibiotic use in Australia can be assessed from import records. These records also include some information on the way in which the imported products will be used.

One of the recommendations of the National Health and Medical Research Council report *Antibiotics in Stockfeed* (NHMRC 1986) was that the then federal department of health should collect data on antibiotic imports into the country for animal and human use, including the quantity and end use of each antibiotic imported. As described in Section 6.1.1, importers of antibiotics (merchants, pharmaceutical companies and private individuals) must hold a permit. Since 1992, all importers have been required to declare in general terms the end use of the products that they have imported as: human therapeutic, veterinary therapeutic, stockfeed additives, laboratory only or special purpose. Products that are re-exported are excluded from the total.

The Commonwealth Department of Health and Aged Care through the Therapeutic Goods Administration (TGA) is responsible for the collection and tabulation of the end-use data. The TGA issues permits, and collects and maintains the end-use data in an electronic system (recently converted to a LAN-based system).

The quality of the data collected is dependent on a number of factors, such as the level of understanding of clerical staff in the importers' offices, and the quality of records kept by importers. A problem for the merchant importers is that they are not necessarily aware of the proportioning of a consignment according to the end use. For example, an importer may bring in a tonne of oxytetracycline for a buyer who manufactures both veterinary and human drugs. Once delivered, the importer will not necessarily know how the consignment is used in the factory.

Separation of veterinary usage into therapeutic and stockfeed is also difficult and there is currently no requirement to separate therapeutic/prophylactic stockfeed end use from stockfeed use for growth promotion purposes.

Despite these imperfections, the data, which have been collected in this way since 1992, are representative, in general, of overall consumption. The average yearly totals for human and veterinary uses for the main classes of antibiotics (for 1992–97) are shown in Table 7.1. More detailed data are shown in Appendix 8.

The data have been subject to only limited scrutiny to date (Turnidge and Howard 1996) but show that approximately two-thirds of all antibiotics imported are for veterinary use and only one-third is for human use. Of the veterinary imports, the majority are used for stockfeed production (ie for therapeutic, prophylactic, growth promotant and coccidiostat uses). As noted above, a breakdown of stockfeed use for growth promotant, coccidiosis control, and other prophylactic uses is not available from these data.

It should be noted that the values in Table 7.1 are in kiograms of active ingredient. These values do not accurately reflect the differences in potency between agents. Unfortunately there is not an agreed standard for potency comparisons. Furthermore, a substantial proportion of stockfeed use is represented by polyethers (ionophores) (40% of all stockfeed antibiotics and 22% of antibiotic overall), a class of agents with no human equivalent, and no as yet recognised human health implications.

Table 7.1 Australian import statistics for antibiotics 5-year average for financial years 1992–93 to 1996–97

	Nominated end use (average kg active ingredient per year)[a]			
Antibiotic group	**Human**	**Stockfeed[b]**	**Veterinary**	**Totals**
Aminoglycosides and aminocyclitols	650.2	4948.4	7030.9	12629.6
Aminoglycosides plus other agents	0.4	0.0	4.7	5.1
Amphenicols	207.9	0.0	297.5	505.4
Ansamycins	503.7	0.0	7.6	511.3
Antiprotozoals[c]	0.0	13632.1	0.0	13632.1
Antituberculars	618.6	0.0	0.0	618.6
Arsenicals	0.0	590.5	0.0	590.5
ß-lactamase inhibitors	12978.8	0.0	19.2	12997.9
Carbapenems	40.6	0.0	0.0	40.6
Cephalosporins	27289.3	0.0	324.6	27613.9
DHFR[d] inhibitors	2652.8	209.4	934.6	3796.7
DHFR inhibitors plus sulfonamides	3.2	41.2	94.8	139.2
Fusidanes	119.0	0.0	2.6	121.5
Fusidanes and others	0.0	0.0	0.6	0.6
Glycopeptides	643.1	10029.8	0.0	10672.9
Glycophospholipids	0.0	1189.0	0.0	1189.0
Lincosamides	3996.3	943.8	339.4	5279.5
Lincosamides plus aminoglycosides	0.0	0.0	247.3	247.3
Macrolides	47495.1	21360.6	831.2	69686.9
Macrolides plus polypeptides	0.1	0.0	0.0	0.1
Miscellaneous	10.6	4190.3	929.3	5130.2
Monobactams	16.3	0.0	0.0	16.3
Nitrofurans	345.3	2680.0	17.4	3042.7
Nitroimidazoles	6095.8	7491.2	2039.2	15626.2
Oxazolidinones	0.0	0.0	0.0	0.0
Penicillins	109297.6	7136.6	18316.4	134750.6
Penicillins plus ß-lactamase inhibitors	237.8	0.0	85.8	323.6
Polyethers	0.0	159359.1	8905.2	168264.3
Polypeptides	40.5	44984.7	9.3	45034.4
Quinolones	3210.5	0.0	17.8	3228.3
Quinoxalines	0.0	7336.8	0.0	7336.8
Streptogramins	2.4	23170.0	0.0	23172.4
Sulfonamides and sulfones	22331.1	17162.3	7706.9	47200.3
Sulfonamides plus steroids	0.4	0.0	0.0	0.4
Tetracyclines	12677.6	72031.6	5587.4	90296.6
Tetracyclines plus other agents	0.0	61.5	0.0	61.5
TOTALS	**251465.0**	**398548.9**	**53749.6**	**703763.5**
(Percentages)	35.7%	56.6%	7.6%	100%
TOTALS without antiprotozoals	**251465.0**	**384916.8**	**53749.6**	**690131.4**
(Percentages)	36.4%	55.8%	7.8%	100%

DHFR = dihydrofolate reductase

[a] Table does not include antineoplastic or immunosuppressive agents with antibacterial activity.

[b] Split of stockfeed and veterinary use is not precise because separation is difficult. The use is as nominated by the importer. Some stockfeed use is for short-term therapeutic use, rather than prophylactic or growth promotion purposes. In addition, some veterinary use is for longer-term prophylactic use. Some products fall into both types of use but the importer nominates only one.

[c] Although it is unclear at present, the antiprotozoal class contains four agents (amprolium, dinitolmide, nicarbazin and robenidine), which appear to have no antibacterial activity, but are included because of doubt. These agents are used almost exclusively as coccidiostats. Other agents in the table, especially some of the polyethers, DHFR inhibitors and sulfonamides, are also used primarily as coccidiostats but have known antibacterial activity as well.

Note: See Appendix 8 for full details.

7.2 Uses of antibiotics in humans

The modern era of treatment of infections started with the clinical use of sulfanilamide in 1936 but the golden age of antimicrobial therapy began with the production of penicillin in 1941. About a third of all hospitalised patients now receive one or more courses of antibiotics and millions of potentially fatal infections have been cured.

At the same time, these agents have become among the most overused of all drugs in human medicine; one result of this widespread overuse is the exacerbation of resistance in bacteria, creating a constant need for the development of new drugs.

7.2.1 Treatment of infections

Antibiotics are used in the treatment of human infections in two general ways:

- *Empirical therapy* — initial therapy pending the outcome of culture and susceptibility results or where cultures are difficult to obtain or have not yielded a pathogen, but the infection is suspected of being bacterial on clinical grounds. The antibiotic used should cover most of the likely pathogens involved in a particular type of infection. Combination therapy or treatment with a single broad-spectrum agent is usually used, but in certain circumstances narrow-spectrum agents are also suitable (eg penicillin for sore throat thought to be due to streptococcus infection).
- *Definitive therapy* — directed therapy selected on the basis of culture and susceptibility testing (laboratory culture or other molecular tests). Often, a narrow-spectrum agent specific for the organism can be used.

The goal for effectively treating bacterial infections is to choose a drug that is selectively active for the most likely infective organisms, with the least potential for toxicity or allergic reactions in the patient. Unfortunately, the frequent use of antibiotics to treat fevers and other symptoms, which are not always caused by bacterial infections, has contributed to the selection of resistant bacteria. However, doctors usually do not have the luxury of a definitive identification of bacterial infection before treatment must be started, because of the time taken to culture swabs (about two days). Antibiotics must be used if the disease is severe because withholding therapy may result in failure to manage a potentially life-threatening infection.

For empirical therapy antibiotic choices are determined by:

- the relative importance of the common pathogens in the infection syndrome (ie which bacteria are common and which are uncommon but important to cover);
- the prevalence of resistance to first-, second- and third-line antibiotics in those pathogens (knowledge of resistance to second- and third-line antibiotics is required for patients who are allergic to or intolerant of first- or second-line antibiotics);
- the seriousness of the infection being treated (ie for minor infections failed first-line treatment is not life threatening, but merely requires a change in drug, with added time to resolution, added cost and added inconvenience); for life-threatening infections, even uncommon pathogens and resistances need to be considered in selecting empirical therapy;
- the site of infection (some infection sites restrict the penetration of certain antibiotic classes and therefore reduce the range of antibiotics to choose from); and/or
- the oral bioavailability of the antibiotic (where oral therapy is the preferred mode of delivery).

For definitive therapy, antibiotic choices are determined by:

- the bacterium involved (each organism has classes of drugs that are preferred for treatment);
- the susceptibility profile (ie the profile of resistances and intermediate susceptibilities);
- the seriousness of the infection (as for empirical therapy);
- the site of infection (as for empirical therapy); and/or
- the oral bioavailability of the antibiotic (as for empirical therapy).

7.2.2 Prevention of infection

Antibiotics are also administered to prevent infection. This is termed *prophylactic* use of antibiotics and may represent a relatively large proportion of all antibiotic use in humans. Such prophylactic treatment has been used in five ways:

- to prevent infection after various surgical procedures (eg bowel tumour surgery or insertion of an artificial hip joint);
- to protect healthy people from infection with specific organisms (eg penicillin for group A streptococci in patients who have previously had rheumatic fever, or trimethoprim–sulfadiazine to prevent urinary tract infection in some women with *E. coli*);
- rarely, to prevent secondary infection in patients who are ill with other diseases (eg leukaemia, AIDS); this may however be self-defeating and impair the normal flora that play a role in the prevention of colonisation with infectious agents;
- to prevent further transmission of certain epidemic diseases (eg *Neisseria meningitidis*); and
- to control acne (when oral agents are used at subtherapeutic concentrations for many weeks).

If prophylaxis is given, it needs to be an appropriate dose and time; otherwise it can be ineffective.

7.2.3 Types of antibiotic used in humans

The choice of antibiotic for the treatment of infections in humans depends on a number of factors outlined previously. One of the main factors is the likely organisms and their resistance pattern. The main indications for use of the most common human antibiotics are shown in Table 7.2.

In some cases there are a wide range of alternative antibiotics that can be used while in others the choice is very limited. In Table 7.2, the antibiotics have been classified according to a three-point scale based on the availability of alternative drugs, as follows:

- category A: essential antibiotics for treatment of human infections where there are few or no alternatives for many infections.
- category B: other alternatives are available but less than for category C OR there are concerns that use will lead to more chance of resistance in category A drugs; and
- category C: a reasonable number of alternative agents in different classes are available to treat most infections.

Antibiotics classified as category A are those currently regarded as the most critical because for certain, possibly life-threatening, infections there are no alternative

antibiotics to use if therapy fails because of resistance. The emergence of resistance to the sole remaining antibiotic used to treat these infections would leave them untreatable.

7.2.4 Consumption and end-use statistics for humans in Australia

Medical antibiotic use in Australia was analysed by McManus et al (1997), with data gathered from four sources: prescription dispensing, sales, prescriber survey and through specific projects (including the TREND project).

TREND project

Use of antibiotics for upper respiratory tract infection/pharyngitis and influenza was examined using the database of 33,203 doctor–patient encounters recorded in August and September 1994 by the TREND project. This project was part of the development of a new practice assessment in therapeutics option within the Royal Australian College of General Practitioners (RACGP) Quality Assurance and Continuing Education Program. Participating general practitioners recorded prospectively their drug and nondrug management, including lifestyle advice, investigations and referrals, for 100 consecutive patient encounters of all types (including surgery and telephone consultations, home, hospital and nursing home visits).

Results

Between 1990 and 1995, there was little change in the level of antibiotics dispensed through Australian community pharmacies, with almost 25 defined daily doses (DDDs)/1000 population/day dispensed in each year. Pharmaceutical industry sales data also show about 25 DDDs/1000 population/day in 1989 and 1994.

Like most developed countries, Australia has a high use of oral antibiotics. In 1994, retail sales in Australia were second only to those in France, and followed closely by those in the United States (Figure 7.1). However, between 1989 and 1994 sales in Australia declined in contrast to other countries — France (up 2.8%), United States (up 2.3%), Italy (up 2.9%), West Germany (up 4.4%) and the United Kingdom (up 3%).

The type of antibiotics used in different countries varies. In 1994, Australia had the highest percentage use of tetracyclines (25.5% of total oral antibiotics), the lowest use of fluoroquinolones (2.2%) and mid-range use of penicillins, which included both narrow-spectrum (7.1%) and broad-spectrum (35%) penicillins. The overall profile of antibiotic use in Australia was similar to that in the United Kingdom.

Table 7.2 Summary of antibiotic uses in humans in Australia

Antibiotic	Cat[a]	P,T,R[b]	Human use
Narrow-spectrum penicillins			Active against gram-positives (eg streptococci, enterococci, syphilis) and some anaerobes
Benzylpenicillin (pen G) and phenoxymethylpenicillin (pen V)	C	P_2,T_3,R_1	Short acting
Procaine and benzathine penicillins	C	P_2,T_3,R_1	Long acting (intramuscular injection)
Moderate-spectrum penicillins			
Aminopenicillins (amoxycillin, ampicillin)	C	P_2,T_3,R_1	Also active against GNRs (*E. coli,* klebsiella) plus *Haemophilus influenzae*. Destroyed by staphylococcal β-lactamase enzymes.
Broad-spectrum penicillins			
Antipseudomonal penicillins Piperacillin, ticarcillin	A	P_1,T_3,R_2	Similar to amoxil but have antipseudomonal activity and some additional gram-negative activity, eg klebsiella.
β-lactamase inhibitors Clavulanate, tazobactam	B	P_1,T_3,R_2	Used for combination treatment (eg with amoxil, ticarcillin, piperacillin) to prevent β-lactamase destruction of partner compound (eg amoxil against *S. aureus*).
Other penicillins			
Antistaph penicillins Dicloxacillin, flucloxacillin, cloxacillin, methicillin	B	P_2,T_3,R_1	Essential treatment against *S. aureus*. Not destroyed by staphylococcal β-lactamase.
Cephalosporins			Widely used broad-spectrum (often in surgical prophylaxis). No activity against enterococci (unlike amoxil) or MRSA.
1st generation			Same activity as amoxil but also against staphylococci and better
Cephalexin, cefaclor, cephalothin, cephazolin	B	P_3,T_3,R_1	against GNRs (*E. coli*, klebsiella).
2nd generation			Slightly increased activity against GNRs. Some activity against
Cephamandole, cefotetan, cefoxitin	B	P_2,T_2,R_2	anaerobes.
Cefpodoxime, cefuroxime	B	P_1,T_1,R_4	
3rd generation			Slightly increased activity against GNRs, less against staph.ylococci
Cefotaxime, ceftriaxone	A	P_1,T_3,R_2	Main major advance in meningitis treatment.
Ceftazidime, cefpirome, cefepime	A	P_1,T_3,R_4	Last 3 agents also antipseudomonal (sometimes called 4th generation).
Carbapenems			
Imipenem, meropenem	A	P_0,T_3,R_4	β-lactams with broadest cover. No activity against MRSA or VRE, poor activity against xanthomonas. Others are sensitive but some (eg pseudomonas) can develop resistance. (Injection)
Monobactams			
Aztreonam	A	P_1,T_3,R_4	Little use in Australia. Only active against GNRs.
Aminoglycosides/ aminocyclitols			
Paromomycin, neomycin	C	P_1,T_2,R_1	Most predictively active against aerobic GNRs (but more toxic than
Gentamicin, tobramycin	A	P_2,T_3,R_1	some other antibiotics). No activity against strep, enterococcus or
Netilmicin, amikacin	A	P_1,T_3,R_3	anaerobes.
			Amikacin is the most stable against inactivation by bacteria.
Spectinomycin	B	P_1,T_3,R_1	Used infrequently for gonorrhoea.
Tetracyclines			
Demeclocycline, doxycycline, minocycline, tetracycline	C	P_1,T_3,R_1	Mainly 2nd line agents. Useful for atypical infections, eg mycoplasma, chlamydia, where there are few suitable substitutes (**cat A**).
Sulfonomides–trimethoprim			
Sulfadiazine	C	P_1,T_2,R_3	Mainly 2nd line agents but with serious side-effects. Many are still
Trimethoprim, trimethoprim–sulfamethoxazole (co-trimoxazole)	C	P_1,T_3,R_1	sensitive. Trimethoprim used alone to reduce side effects. Very high resistance in orgs such as pneumococci but still recommended drug for resp infections in developing countries (cheap). Drug of choice for some conditions (pneumocystis in AIDS, nocardia; **cat A)**.
Macrolides			
Azithromycin	A	P_2,T_2,R_2	Mainly for gram-positive infections (esp staph and strep) but
Clarithromycin ,	A	P_2,T_2,R_2	resistance is increasing. First choice for some conditions
Erythromycin, roxithromycin	C	P_1,T_3,R_1	(mycoplasma, chlamydia) (**cat A**). Clarithromycin and azithromycin was major advance for atypical mycobacteria (**cat A**) but value may be lost because of widespread human use for resp tract infections (especially in the United States and Europe).

Table 7.2 (contd)

Antibiotic	Cat[a]	P,T,R[b]	Human use
Lincosamides			
Clindamycin	B	P_1,T_3,R_3	Similar to macrolides.
Lincomycin		P_1,T_1,R_2	
Glycopeptides			
Teicoplanin	A	P_1,T_1,R_4	Last resort for many gram-positives including MRSA and for
Vancomycin		P_2,T_3,R_3	enterococci in allergic patients.
Nitroimidazoles			
Metronidazole, tinidazole	B	P_1,T_3,R_1	Very active against anaerobes (most predictable activity and least resistance). Also active against protozoans (eg giardia) which have few other options for therapy.
Quinolones			
Nalidixic acid	B	P_1,T_2,R_1	Active against most GNRs.
Fluoroquinolones			
Ciprofloxacin, enoxacin	A	P_1,T_3,R_3	Last major new class of human antibiotics. Very active against
Norfloxacin	A	P_1,T_3,R_2	GNRs, including some with no other oral treatments (eg
Ofloxacin	A	P_1,T_3,R_4	pseudomonas, enterobacter). May be only active agent against multiresistant klebsiella or *E. coli*. Poor activity against strep (latter agents have improved activity). Not active against anaerobes.
Streptogramins			
Quinupristin with dalfopristin	A	P_1,T_3,R_4	New class. Hopes that it will be useful for resistant gram-positive infections, eg staph. Not approved for use yet but resistance has already been detected.
Antimycobacterials			
Pyrazinamide, streptomycin, rifampicin, rifabutin, isoniazid, ethambutol	A	P_1,T_3,R_4	Effective against tuberculosis but resistance is a problem and 2nd line drugs (which are more toxic) now have to be reused in some cases (eg ciprofloxacin). TB is still a major killer in patients with multiresistant strains.
Antileprotics			
Clofazimine, rifampicin	A	P_1,T_3,R_4	Very effective against leprosy but resistance is a problem, especially
Dapsone	A	P_1,T_3,R_2	if drugs not taken correctly.
Polypeptides			
Bacitracin, capreomycin, colistin, gramicidin, polymyxin B, thiostrepton	C	P_1,T_2,R_1	Colistin useful for pseudomonas, may need to be resurrected if multiple resistance occurs (toxic).
Miscellaneous			
Chloramphenicol	B	P_1,T_2,R_1	Broad-spectrum activity for resp tract infections and useful for oral therapy of meningitis but little use in developed countries (marrow toxicity). Widespread use in developing countries (cheap).
Hexamine hippurate, nitrofurantoin	C	P_1,T_2,R_1	Only used for urinary tract infections; many other substitutes.
Sodium fusidate	A	P_1,T_3,R_2	Fusidic acid very good in combination as antistaph. One of few orals for MRSA.

GNR = gram-negative rod; MRSA = multiresistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci; further information on the groups of bacteria mentioned in this table is given in Chapter 4 (Table 4.1).

[a] **Category A:** essential antibiotics for treatment of human infections where there are few or no alternatives for many infections
Category B: other alternatives are available but fewer than for category 3; OR there are concerns that use will lead to more chance of resistance in category 1 drugs
Category C: a reasonable number of alternative agents in different classes are available to treat most infections

Note: Some antibiotics may be in more than one category (A–C). This is because for some infections there are many choices of antibiotics but for other infections this antibiotic is the only one (or one of a few) available for treatment.

[b] P = Prophylactic use (0 = not recommended for prophylactic use; 1 = rarely used or not recommended; 2 = moderate; 3 = frequent or major use);

T = Therapeutic use, ie to treat established infections (1 = little used; 2 = moderate use; 3 = used frequently to treat the infections shown). **Note**: This does not refer to the total amount of antibiotic used, which is given in Table 7.1.

R = All antibiotics require prescriptions from a medical practitioner (1 = readily available for short course; 2 = some rules for use, eg restricted benefit system in the Pharmaceutical Benefits Scheme (PBS); 3 = needs authority, ie phone or mail approval from government, for pharmaceutical benefits (authority prescription); 4 = use severely restricted (not available for prescription under PBS; only available in major hospitals with permission from microbiologist or infectious diseases consultant, or in a special clinic; eg anti-TB drugs).

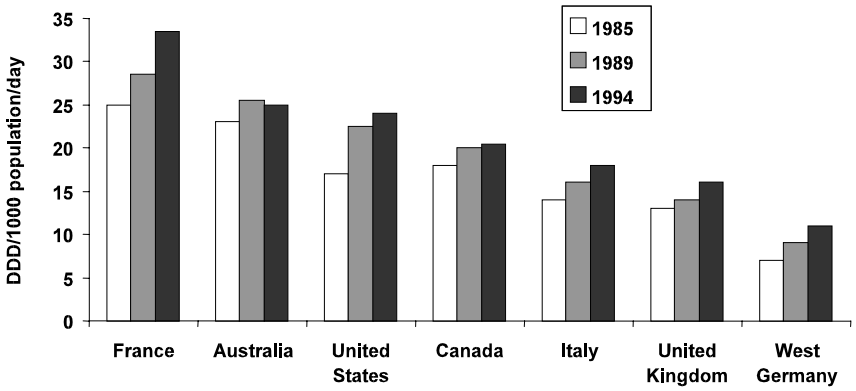


Figure 7.1 Retail sales of oral antibiotics 1985–94 (McManus et al 1997, based on data from Intercontinental Medical Statistics) (DDD = defined daily dose)

Most used antibiotics

The top 10 antibiotics, on prescription volume, dispensed through Australian community pharmacies in 1990 and 1995 are shown in Table 7.3. Amoxycillin was the most dispensed antibiotic in both 1990 and 1995 although its use declined.

Table 7.3 Top 10 antibiotics by human prescription volume, Australia 1990 and 1995, and their percentage contribution to prescriptions for common conditions in 1995

	Rank		Millions of prescriptions[a]		Percentage of prescriptions for each condition (1995)[b]					
Antibiotic	1990	1995	1990	1995	Sinusitis	Bronchitis	OM	URTI	UTI[c]	SSTI
Amoxycillin	1	1	6.6	5.5	11.6	18.1	21.0	29.5	6.9	3.9
Amoxycillin–clavulanate	5	2	2.1	3.4	18.1	13.7	20.5	9.4	17.2	8.7
Cefaclor	14	3	–	2.7	15.1	15.2	35.5	10.2	1.4	2.2
Doxycycline	2	4	3.1	2.6	20.7	9.5	0.5	5.5	0.3	8.2
Cephalexin	6	5	2.0	2.4	4.3	4.5	5.2	3.3	18.9	20.8
Roxithromycin	–	6	–	2.0	13.2	16.5	0.7	8.7	0.1	1.5
Erythromycin	3	7	2.7	1.9	2.8	8.0	3.3	8.2	0.3	11.3
Trimethoprim–sulfamethoxazole	4	8	2.5	1.2	2.5	2.5	3.7	3.3	28.5	1.9
Phenoxymethylpenicillin	8	9	1.1	1.1	0.4	0.1	0.1	7.2	0.0	1.2
Flucloxacillin	7	10	1.3	0.9	0.3	0.0	0.0	0.1	0.1	23.3
Tetracycline–nystatin	9	19	0.6	–	–	–	–	–	–	–
Tetracycline	10	12	0.4	–	1.3	1.0	0.1	0.3	0.0	1.4

OM = otitis media; URTI = upper respiratory tract infection; UTI = urinary tract infection;
SSTI = skin and soft tissue infection; – not available

[a] Defined daily doses/1000 population/day. (Source: Drug Utilisation Sub-Committee, Department of Health and Family Services).

[b] Australian Medical Index, Intercontinental Medical Statistics.

[c] 11.2% of prescriptions for urinary tract infection were for trimethoprim.

Source: McManus et al 1997

Antibiotic prescribing profiles

Table 7.3 also shows antibiotic prescribing profiles for various indications in 1995. For sinusitis, the most prescribed antibiotics were doxycycline (20.7%), amoxycillin-clavulanate (18.1%) and cefaclor (15.1%). For bronchitis, the most prescribed antibiotic was amoxycillin (18.1%), followed closely by roxithromycin (16.5%) and cefaclor (15.2%). In urinary tract infections, trimethoprim–sulfamethoxazole (28.5%) was most commonly prescribed, followed by cephalexin (18.9%) and amoxycillin–clavulanate (17.2%).

Antibiotic prescribing for upper respiratory tract infection (URTI)/pharyngitis and influenza was examined in the TREND sample; 11.6% of encounters were for URTI/pharyngitis and 1.2% for influenza. For new cases of URTI/pharyngitis, an

antibiotic prescription was recorded for 57% of urban patient encounters and for 73% of rural patient encounters. The *Therapeutic Guidelines — Antibiotic 1997–98* (Therapeutic Guidelines 1998) state that for URTI 'the cause is almost invariably viral' and 'antibiotics are not indicated'. Rural general practitioners were also more likely to prescribe antibiotics for URTI than were urban general practitioners, possibly due to concern for the greater patient travel and inconvenience in visiting the doctor, with prescriptions being supplied for use if symptoms fail to resolve after a period of time. However, it may also reflect differences in access to continuing education and in industry promotion between rural and urban general practitioners.

Antibiotic resistance

The data also provide insight into general practitioners' perceptions of antibiotic resistance among bacteria. For sinusitis, the most prescribed antibiotics were doxycycline, amoxycillin–clavulanate and cefaclor, which are recommended if resistance to amoxycillin is suspected or proven (Therapeutic Guidelines 1998). For bronchitis, amoxycillin was most prescribed, followed closely by roxithromycin and cefaclor, which are recommended if a β-lactamase producing organism is isolated or if the clinical response is slow. The results indicated that doctors think that resistant organisms are a significant clinical problem, at least for sinusitis and bronchitis. The reasons for this deserve investigation and may include previous clinical experience of slow resolution of these infections with standard therapy, or awareness of the prevalence of resistant bacteria in the local community.

Other factors

Antibiotic usage was proportional to representation of age groups in the population except for the under-20-year-olds, for which group it was higher. For specific conditions the age patterns varied. There was also a markedly seasonal pattern of antibiotic prescribing, with higher levels in winter.

7.2.5 Medical guidelines for antibiotic use

There are a number of ways in which antibiotic use in Australia has been improved and/or restricted over the last two decades.

- Clinical practice guidelines — widely accepted clinical practice guidelines for the prescription of antibiotics were first developed in Australia in 1978. The 10th edition was published in March 1998 (*Therapeutic Guidelines — Antibiotic 1997-98*). These guidelines provide state-of-the-art advice on whether antibiotics are indicated for particular conditions and also which ones should be used if they are indicated.
- Pharmaceutical Benefits Scheme (PBS) —the use of antibiotics in Australia is effectively restricted through the PBS system. Some antibiotics cannot be freely prescribed through the system and the individual practitioner must apply to the federal department of health in Canberra for permission to use them (authority prescription). This limits the use, for example, of fluoroquinolones to only specific conditions. Outside the PBS, a medical practitioner may prescribe any agent and it will be dispensed provided that the patient pays for it. As Australians are 'unused' to paying significant amounts for their drugs, they rarely take this option and thus the PBS is an effective gatekeeper for antibiotic use.
- Some antibiotics are severely restricted. They are not available through the PBS for practical or economic (cost) reasons. They are usually only available from major hospital pharmacies after approval by a microbiologist or infectious diseases consultant (eg imipenem).

7.3 Uses of antibiotics in animals

In parallel with the development of antibiotic use in human medicine from the mid-1930s, veterinary use extended to provide similar control in both farm animals and domestic pets. This contributed greatly to animal welfare and allowed large increases in livestock production but, as for human medicine, concerns quickly arose that an over-reliance on antibiotics was contributing to the development of antibiotic-resistant strains of bacteria.

Today, Australia's excellent animal health status, development of vaccines, good record in eradication of diseases and climatic differences have reduced the commercial need for medication, including antibiotics, when compared with Europe and North America.

Contagious bovine pleuropneumonia, sheepscab, bovine brucellosis and bovine tuberculosis have all been eradicated where few other countries have been successful. *Salmonella* Pullorum has been eradicated from commercial poultry flocks and classical swine fever and highly pathogenic avian influenza have also been eradicated each time they have entered Australia. Australian poultry remain free from *Salmonella* Enteritidis. National animal quarantine policy and practice support the excellent animal health status in Australia.

7.3.1 Uses of antibiotics

Antibiotics are used in animal husbandry in four ways:

- for therapy
- for disease prevention (prophylaxis)
- as growth promotants (to increase feed conversion, growth rate or yield)
- for coccidiosis control (substances with antibiotic activity are also fed to poultry and cattle to control protozoal diseases such as coccidiosis)

Most of the antibiotics used in animals are members of the same range of antibiotic families as the agents used in human therapy. Some belong to structural families where a member of the family was not initially used in human therapy or where this is still the case. However, as key human pathogens have become resistant to many or all of the available therapeutically effective antibiotics, members of families assigned to veterinary use have been developed for human therapy (eg vancomycin) or are currently in development (eg streptogramins B).

Antibiotics used for therapy and individual animal prophylaxis are administered by injection or orally in dose forms similar to human medication. Antibiotics used for group prophylaxis are usually administered in feed, or sometimes in water. Growth promotants are given at low concentrations (eg 2.5–50 mg/kg) in feed. Premixes containing antibiotics are prepared by feed-millers and home-mixers incorporating registered antibiotic products.

State/Territory drugs and poisons legislation requires veterinary practitioners to record the scripts for 'prescription animal remedies/S4' drugs supplied to clients, but use records generally do not go further than this. Orders for medicated feed for pigs, poultry, feedlot cattle and sheep are recorded by the feed-mill, and by the veterinarian supplying the prescription. Quality assurance programs such as FlockCare™ and CattleCare™ and the Australian Pork Industry Quality (APIQ) program (see Section 11.1.1) require the producer to record antibiotic use but it is difficult to access this information in a systematic way. Quantities of antibiotics used could be compiled from veterinary script records.

Choice of antibiotic

Some antibiotics are specific for a particular species/strain of bacteria (narrow spectrum) and others are less specific and can kill a range of different bacteria (broad spectrum). Ideally, if an isolate from an infection can be definitively identified, a narrow-spectrum antibiotic targeting the specific pathogen of concern is the best choice and could reduce the range of resistance that develops in the exposed population of bacteria. A combination of antibiotics can also be used.

However, animal owners bear the full cost of laboratory testing on their animals, and veterinary practitioners often need to make decisions based on a clinical diagnosis, not necessarily supported by laboratory confirmation of the responsible microorganism or antibiotic sensitivity information. If there is doubt about the specific bacteria involved, then, as in human medicine, broad-spectrum or combinations of antibiotics are used.

Broad-spectrum antibiotics, for example tetracyclines, are specifically required in some situations — for example, the control of mycoplasma infections in pigs — because there are no known narrow-spectrum agents to treat these infections.

Some combinations may not be available in future because of a lack of evidence of enhanced efficacy and also because of prolonged tissue residues with some antibiotics, such as streptomycin. This is likely to encourage greater use of broad-spectrum antibiotics.

7.3.2 Treatment and prevention of disease

The principles of treatment and prophylaxis of infection are the same for animals as those described for humans (Section 7.2.1). However, in animals, particularly food-producing animals, the prophylactic use of antibiotics is more common. For example, in some cases, when the proportion of diseased animals in a herd or group reaches a threshold value (such that there is a high probability of most, or all, of the animals becoming infected), all the animals in an infected group or shed are medicated. Prophylactic administration of antibiotics to animals can be to individuals or to groups as additives to feed or water.

Most pets, horses or extensively raised animals do not receive any therapeutic antibiotics during their lives or, at most, only one or two short-term courses for specific infections.

Food-producing animals

A summary of the registered uses of antibiotics, by antibiotic group, for treatment and prophylaxis in food-producing animals is shown in Table 7.4. The use categories (A, B, C) correspond to those described for human use (see in Section 7.2.3). Tables showing the registered used of antibiotics for horses, small animal pets and fish are included at Appendix 5.

The animal diseases currently requiring the most extensive use of therapeutic or prophylactic drugs are respiratory and enteric diseases of pigs and calves, necrotic enteritis of poultry and mastitis in dairy cattle.

In the case of certain protozoan diseases, the probability of clinical outbreaks or production losses due to subclinical disease is so high that treatment with antiprotozoals is standard practice. These diseases include coccidiosis of poultry (caused by the protozoan parasite *Eimeria* spp.) and histomoniasis of turkeys (caused by *Histomonas meleagridis*). Antimicrobial agents that are effective against these protozoan diseases are called anticoccidials (or coccidiostats) and antihistomonals (or histomonostats). In most parts of the world, including Australia, they are used as feed additives. Some

antimicrobial drugs act against a number of microorganisms and some coccidiostats also have antibacterial activity. The drugs with unknown antibacterial activity are categorised as antiprotozoals in Table 7.1.

Beef and dairy cattle

Antibiotics are used therapeutically for a wide range of infectious conditions in cattle. However, with the exception of occasional outbreaks of disease in a herd, the therapeutic use of antibiotics is on an individual animal basis and most extensively raised (pastoral) beef cattle in Australia are never exposed directly to antibiotics.

Prophylactic and therapeutic herd treatments with antibiotics typically include:

- respiratory infections in cattle (eg tetracyclines, tylosin, tilmicosin, ceftiofur, erythromycin, neomycin, trimethoprim–sulfonamide combinations);
- mastitis in dairy herds (eg beta-lactams, tetracyclines, lincomycin, trimethoprim–sulfonamide combinations);
- dry cow therapy for mastitis control in dairy herds (eg beta-lactams, cephalosporins, neomycin, tetracyclines);
- control of lactic acidosis and bloat in feedlot cattle (virginiamycin and polyethers);
- coccidiosis in young animals (eg polyethers);
- enteric infections (eg tetracyclines, neomycin);
- hoof infections such as footrot (eg penicillin, tetracyclines, ceftiofur, trimethoprim–sulfonamide combinations).

A strategy for reducing *Staphylococcus aureus* mastitis in dairy cattle, as part of a multifaceted approach to minimise this disease, is to give an intramammary infusion of specifically registered antibiotics (in a slow-release base) at therapeutic levels when cows are 'dried off' at the end of lactation. This allows release of the antibiotic in the mammary gland tissues at high concentrations for a long period.

While careful animal husbandry management practices can reduce the risk of disease outbreaks occurring, they will not be eliminated entirely. Consequently, there is a continuing need for antibiotics to be available for the health and welfare of beef and dairy cattle.

Pigs

Since 1990, there has been a reduction in the number of pig producers in Australia from 6847 to 3522, with an increase in the average herd size. Larger herds have a greater veterinary involvement in their management and as a consequence there is less, and more appropriate, use of antibiotics (approximately 70–80% of all pigs produced are under veterinary supervision).

There are some major diseases in pigs that frequently require therapeutic or prophylactic use of antibiotics. The most important are as follows, with the antibiotics most frequently used:

- enterotoxigenic *E. coli* in piglets (unweaned) and weaner pigs (first two weeks postweaning) — treated with amoxycillin, trimethoprim, spectinomycin, apramycin and neomycin;
- *Mycoplasma* pneumonia — tetracyclines, lincomycin, tylosin, tiamulin;
- pleuropneumonia (*Actinobacillus pleuropneumoniae*) — procaine penicillin, amoxycillin, tetracyclines, trimethoprim, tilmicosin;

- proliferative enteritis (*Lawsonia intracellularis)* — olaquindox, tetracyclines, lincomycin, tylosin; and
- colitis (*Serpulina* spp.*)* — dimetridazole, tiamulin, lincomycin

Prophylactic use of antibiotics at particular stages of the pig's development to prevent some of these diseases is essential in many piggeries. These diseases could not be fully controlled without prophylactic use of antibiotics, and the welfare of the pigs would be severely compromised, therapeutic use of antibiotics would be increased and profitability would be reduced.

There is an appreciable increase in the cost of production if antibiotics have to be used to control disease. As a consequence it is in the producers' interests, in consultation with their veterinary advisers, to reduce the quantity and increase the effectiveness of antibiotics used.

Sheep

Antibiotics are rarely used in commercial sheep production due to the high cost relative to the value of the livestock. They may, however, be used for footrot and in stud sheep production for prophylactic and therapeutic purposes.

Recent changes to meat production (eg fat lambs) have seen the introduction of grain feeding. This has been accompanied by the need to effectively control lactic acidosis through the use of antibiotics (virginiamycin) as a feed additive for the lambs.

Poultry

The poultry industry is very well serviced by veterinarians, who provide specialised input into the control of bacterial diseases. Bacterial diseases of poultry have been increasingly controlled in recent years by eradication of pathogens from breeding stock, biosecurity programs, upgraded hygiene procedures, improved husbandry and vaccination resulting in less dependence on antibiotics. For example, mycoplasma infections, coryza (*Haemophilus paragallinarum*) and fowl cholera (*Pasteurella multocida*) are now mainly controlled by vaccination. *Salmonella* Pullorum was eradicated from Australian commercial poultry some years ago.

Antibiotic therapy is required when alternative disease control procedures (eg vaccination) fail or for diseases for which currently there are no successful alternative disease control measures (see Table 7.4).

Antibiotic use in egg and poultry meat production is limited by the withdrawal times necessary to prevent antibiotic residues in the products. For example only two antibiotics (amoxycillin and erythromycin) used therapeutically in poultry have a withdrawal time of less than five days.

Necrotic enteritis caused by *Clostridium perfringens* interferes with the intestinal function of meat chickens, resulting in growth depression, poor feed conversion and, occasionally, death. In Australia, the only registered antibiotics that are useful in preventing this disease are avoparcin, virginiamycin and bacitracin, all of which are added to feed and are not absorbed from the intestinal tract. Neomycin or amoxycillin is used therapeutically in drinking water for 3–5 days if the preventative in-feed medication fails.

Horses

Details of antibiotic use in horses are shown in Appendix 5. In almost all cases, administration is for treatment of individual animals with symptoms of disease. The exceptions are gentamicin, which is given routinely by injection to prevent foal sepsis and for surgical prophylaxis (treatment for gram-negative bacteria), and virginiamycin, which

is given in feed to prevent laminitis. Although the long-term antibiotic treatment of animals is rare, an exception is the treatment of osteomyelitis and pneumonia in foals caused by *Rhodococcus equi*.

Small animals (pets)

Details of antibiotic use in small animal pets are also shown in Appendix 5. In this case, antibiotic use is always for treatment of individual animals showing symptoms of disease.

Some antibiotics, such as certain sulfonamides and tetracyclines, are registered for use on ornamental caged birds and aquarium fish.

Fish

The aquaculture industry is at present a minor, but increasing, user of agricultural and veterinary chemicals including antibiotics. However, some of the antibiotics used are not registered for fish and are used under veterinary supervision.

An aquaculture industry taskforce is currently completing an investigation into the use of aquacultural chemicals. The findings of this taskforce will be reviewed by the National Registration Authority for Agricultural and Veterinary Chemicals (NRA). Of the 11 current applications to the NRA for permits, three are for antibiotics (oxytetracycline, amoxycillin and trimethoprim–sulfadimidine). The Fisheries Research and Development Corporation is looking into applying for registration for several antibiotics, because it is not commercially attractive for the companies to do it. Antibiotics that are used in aquaculture are generally only used at the early stages of production. However, the microbiology of aquatic animals and their environments is complex and some concern has been expressed about antibiotic-resistant bacteria in water and environmental samples and residues in water and sediments.

Table 7.4 Summary of registered antibiotic uses for therapy and prevention of diseases in food-producing animals in Australia[a]

Antibiotic group[b]	Cat[c]	Industry[d]	Treatment (individual)	Treatment (in feed/water)	Prophylaxis (in feed/water)
Penicillins					
Amoxycillin, procaine, penicillin G	C	Beef cattle/calves	Various infections	—	—
Amoxycillin, procaine, penicillin, ampicillin, cloxacillin	A	Dairy cattle	Mastitis	—	—
Amoxycillin, procaine, penicillin G, ampicillin,	A	Pigs	Erysipelas and meningitis	Erysipelas and meningitis	—
Amoxycillin, procaine, penicillin G, benzathine, benethamine,	C	Sheep	Various infections	—	—
Amoxycillin	A	Meat poultry	—	*E. coli*, staph, cholera, necrotic enteritis	—
Amoxycillin	A	Eggs	—	*E. coli*, staph, necrotic enteritis, coryza	—
Cephalosporins					
Ceftiofur	B	Beef cattle/calves	Resp disease	—	—
Ceftiofur, cephalonium, cefuroxime	C	Dairy cattle	Resp disease, footrot, mastitis	—	—
Macrolides					
Erythromycin, tylosin, Tilmicosin	B B	Beef cattle	Resp disease, footrot	Mycoplasma, liver abscess	Liver abscess
Erythromycin, tilmicosin	B	Calves	Resp disease	—	—
Erythromycin, tylosin, oleandomycin	C	Dairy cattle	Various infections	—	—
Erythromycin, tylosin, oleandomycin, kitasamycin, tilmicosin	B	Pigs	Resp tract infections, colitis, PE	Resp tract infections, colitis, PE	Resp tract infections, colitis, PE
Erythromycin	C	Sheep	Footrot, dermatophilosis	—	—
Erythromycin, tylosin	A	Meat poultry	—	Coryza, resp disease, mycoplasma	Mycoplasma (tylosin)
Erythromycin, tylosin	A	Eggs	—	Coryza, resp disease, cholera, mycoplasma	Mycoplasma (tylosin)
Lincosamides					
Lincomycin	C	Dairy cattle	Mastitis	—	—
Lincomycin (+spectinomycin)[e]	B	Pigs	Resp tract infections, colitis	Resp tract infections, colitis	Resp tract infections, colitis
Lincomycin (+spectinomycin)[e]	B	Meat poultry	—	Mycoplasma, *E. coli*, salmonella	—
Lincomycin (+spectinomycin)[e]	B	Eggs	—	Mycoplasma	—

Table 7.4 (contd)

Antibiotic group[b]	Cat[c]	Industry[d]	Treatment (individual)	Treatment (in feed/water)	Prophylaxis (in feed/water)
Tetracyclines					
Oxytetracycline, chlortetracycline	C	Beef cattle/calves	Various infections (incl resp disease in calves)	Various infections (incl resp disease in calves)	Various infections (incl resp disease in calves)
Oxytetracycline, chlortetracycline	C	Dairy cattle	Various infections, including mastitis	—	—
Oxytetracycline, chlortetracycline	A	Pigs	Resp disease, urinary tract infections, PE	Resp disease, urinary tract infections, PE	Resp disease, urinary tract infections, PE
Oxytetracycline, chlortetracycline	C	Sheep	Pneumonia, footrot, dermatophilosis	—	—
Oxytetracycline, chlortetracycline	A	Meat poultry	—	Coryza, cholera, staph aureus, mycoplasma	—
Oxytetracycline, chlortetracycline	A	Egg	—	Staph, cholera, mycoplasma	—
Aminoglycosides					
Neomycin [streptomycin under review for calves]	C	Beef cattle/calves	Various infections	—	—
Neomycin, apramycin, streptomycin	C	Dairy cattle	Various infections	—	—
Apramycin	C	Calves	Salmonella/E.coli enteritis	—	—
Neomycin, apramycin, streptomycin, spectinomycin	A	Pigs	*E.coli* enteritis	*E. coli* enteritis	*E. coli* enteritis
Neomycin, streptomycin	C	Sheep	Footrot, dermatophilosis, colibacillosis	—	—
Neomycin	A	Meat poultry	—	Necrotic enteritis	—
Glycopeptides					
Avoparcin	A	Meat poultry	—	—	Necrotic enteritis
Nitroimidazoles					
Dimetridazole	B	Pigs	—	Colitis	Colitis
Polypeptides					
Zn bacitracin	A	Meat poultry	—	—	Necrotic enteritis
Zn bacitracin	A	Egg	—	—	Necrotic enteritis
Sulfonamides (including trimethoprim and diaveridine)					
Many agents	C	Calves	Various infections	Various infections	—
Many agents	C	Dairy cattle	Various infections	—	—
Many agents	B	Pigs	Various infections	Various infections	Various infections
Many agents	C	Sheep	Coccidiosis, scours	—	—
Many agents	A	Meat poultry	—	*E. coli*, salmonella, cholera	—
Many agents	A	Eggs	*E. coli*	*E. coli*	—

Table 7.4 (contd)

Antibiotic group[b]	Cat[c]	Industry[d]	Treatment (individual)	Treatment (in feed/water)	Prophylaxis (in feed/water)
Streptogramins					
Virginiamycin	B	Beef cattle/calves	—	Lactic acidosis	—
Virginiamycin	B	Dairy cattle	—	Lactic acidosis	—
Virginiamycin	A	Sheep	—	Lactic acidosis	—
Polyethers (ionophores)					
Monensin	B	Beef cattle/calves	Bloat	—	—
Monensin	B	Dairy cattle	Bloat	—	—
Others					
Olaquindox	B	Pigs	—	PE, colitis	PE, colitis
Novobiocin	C	Dairy cattle	Mastitis	—	—
3-Nitro-arsonic acid	C	Pigs	—	—	Colitis

PE = proliferative enteritis

[a] **REGISTERED GROWTH PROMOTANT USES ARE SHOWN IN TABLE 7.5; coccidiostat (antiprotozoal) uses are not shown**

[b] Only antibiotic groups permitted for use in Australia are listed

[c] **Category A:** essential antibiotics for treatment or prevention of animal infections where there are few or no alternatives for many infections.

Category B: other alternatives are available but fewer than for category C OR concerns that use will lead to more chance of resistance in category A drugs.

Category C: a reasonable number of alternative agents in different classes are available to treat most infections.

[d] The table covers the beef, dairy, pig, sheep, meat poultry and egg industries. If an industry is not mentioned beside a particular antibiotic it means that antibiotic is not permitted/not registered for use in that species.

[e] Spectinomycin is an aminocyclitol.

Source: NRA; and *IVS Annual* (MIMS 1998)

7.3.3 Growth promotion

Antimicrobial agents have been used as growth promotants worldwide for about 30 years (UK House of Lords 1998). These agents are added to the feed of cattle, pigs and poultry to improve the growth rate and efficiency of feed use. They are used at low concentrations (2.5–50 mg/kg [parts per million] according to the drug used). It is not fully understood how they work but it is thought to be by suppressing sensitive intestinal bacterial populations that would divert nutrition away from the animal and by maintaining a more effective and absorptive gut lining.

The antibiotics used as growth promotants in livestock industries in Australia are shown in Table 7.5. Further details of the benefits and uses of growth promotants are given in Chapter 8. Some of these agents are primarily used as coccidiostats rather than specifically for growth promotion.

Although some antibiotics used in this way are different classes from those used therapeutically in human medicine or for prophylactic or therapeutic use in animals, avoparcin (a glycopeptide antibiotic) registered in Australia for use as a growth promotant in pigs, broiler chickens and (feedlot) cattle, is chemically related to vancomycin, which is a human antibiotic.

Virginiamycin (a streptogramin antibiotic registered in Australia for growth promotant use in pigs and poultry and as a preventive treatment against founder in horses and lactic acidosis in cattle) was selected for use as a growth promotant because streptogramins were not widely used in human medicine. This situation has changed with the

development for human use of quinupristin/dalfopristin (a streptogramin) for treatment of infections caused by multiresistant gram-positive bacteria. The quinupristin/dalfopristin combination has not yet been registered for human use in Australia, although it is available under the compassionate use program, and is considered the drug of choice for the treatment of ampicillin plus vancomycin-resistant enterococcal infections.

Macrolides are also used as growth promotants (eg typlosin), in human medicine and as therapeutic agents in veterinary medicine.

7.3.4 Veterinary guidelines for antibiotic use

Registered veterinarians must comply with State/Territory legislation for veterinary surgeons and also with State/Territory legislation controlling the use of drugs. This latter legislation includes the authority of veterinarians to prescribe 'off-label', ie with drugs registered for human use or for use in other species. In most States and Territories, such off-label use of a drug in food-producing animals is only permissible if the drug is registered for use in another food-producing species. This legislation varies from State to State and there is an urgent need for harmonisation of State/Territory legislation, as discussed in Chapter 6.

The Australian Veterinary Association (AVA) has published Guidelines for Prescribing and Dispensing in Veterinary Medicine in its *Members Directory and Policy Compendium* (AVA 1997). In addition, guidelines have been published by the University of Sydney in association with the NHMRC (Cooper 1994). Specific codes of practice for the use of S4 substances in the poultry and pig industries have been developed (AVA 1997) and a similar code is currently being developed for sheep. Draft general guidelines for the use of antibacterial drugs in veterinary practice are also currently under development by the AVA (AVA Code of Practice for the Use of Antimicrobial Drugs in Veterinary Practice). 'Prudent use of antibiotics' has been defined by the World Health Organization (WHO 1997). A new set of global principles for use of antibiotics in animals was also recently jointly released by the World Veterinary Association, the International Federation of Agriculture Producers and the World Federation of Animal Health Industry (WVA et al 1999).

Table 7.5 Use of antibiotics as growth promotants in food-producing animals in Australia [a]

Antibiotic group	Antibiotic	Animal industry	Other uses
Macrolides	Tylosin	Pigs	Mycoplasma infections, colitis, PE
	Kitasamycin	Pigs	
	Oleandomycin	Calves	
Glycopeptides	Avoparcin	Beef cattle	
		Pigs	(Registered but not commonly used)
		Meat poultry[b]	Necrotic enteritis prevention
Polypeptides	Bacitracin	Meat poultry[b]	Necrotic enteritis prevention
Streptogramins	Virginiamycin	Pigs	Serpulina colitis
		Meat poultry[b]	Necrotic enteritis prevention
Polyethers (ionophores)	Monensin[c]	Beef and dairy cattle	Bloat prevention, rumen modifier, improves efficiency of ruminant digestion (increases milk production)
	Salinomycin	Beef cattle Pigs	
	Lasalocid	Beef cattle	(Registered but not commonly used)
	Narasin	Beef cattle	(Registered but not commonly used)
Quinoxaline	Olaquindox	Pigs	Proliferative enteritis prevention
Others	Flavophospholipol (flavomycin)	Beef cattle	(Registered but not commonly used)
		Pigs	
		Meat poultry[b]	
	3-Nitro-arsonic acid	Pigs	Serpulina colitis
		Meat poultry[b]	Used mainly as a coccidiostat

[a] Growth promotant uses indicated here are as reported by the industries concerned. Some antibiotics that are registered by the NRA as growth promotants are not currently in common use in the industries.
[b] No growth promotants are used in egg production.
[c] Monensin has a registered claim for improved milk production (ie not strictly a growth promotant).

Poultry meat companies have formal minimum standards for livestock production (good operating standards) that include guidelines and safeguards for chemical use to ensure safe and efficacious chemical use with no resultant food residues, as well as hygiene procedures for the farming of poultry. Standards such as these are currently being translated into 'HACCP' (hazards analysis critical control point) or process control plans as a requirement of major retail customers. The use of a HACCP approach is also a requirement of the *Australian Standard for Hygienic Production of Poultry Meat for Human Consumption*: AS 4465: 1997 (ARMCANZ 1997).

Very few antibiotics are registered for use in egg-laying poultry, and no growth promotants are used. Those that have the potential to cause food residues are controlled by orders for medicated feed under veterinary supervision.

Results of the National Residue Survey from 1995 to 1998 have indicated excellent compliance with the use of antibiotics in both the chicken meat and egg-laying industries (see Chapter 9).

The pig industry, which is served by two statutory bodies — the Pig Research and Development Corporation (PRDC) and the Australian Pork Corporation — has developed HACCP-based systems for the producer and the processor (the APIQ

program). A significant component of the APIQ program is to ensure that there is appropriate use of antibiotics under veterinary supervision, to also ensure that withholding periods are followed and to reduce the risk of contamination of carcases with intestinal bacteria.

Some large retailers and some processors now insist that their pig suppliers are enrolled in the APIQ program. At the processing stage, contamination of carcases and meat products with bacteria of faecal origin is comparable to or lower than that recorded in other countries (McCauley et al 1998).

7.4 Essential antibiotics

In 1969, the Swann Report of the United Kingdom Joint Houses of Parliament, recommended that the supply and use of an antibiotic without prescription in animal feed should be restricted to antibiotics that have little or no application as therapeutic agents in humans or animals and will not reduce the effectiveness of prescribed antibiotics through the development or transfer of resistant bacteria (see Section 12.2).

Although most countries, including Australia, have supported the principle of this recommendation, for a variety of reasons it has not been fully implemented locally. In addition, some antibiotics that were initially only used in animals have now become vitally important for human therapeutic use. It has also become apparent that the extent of cross- and multiple resistance for different antibiotics and the ease of transfer of resistance genes between bacteria is greater than previously thought.

Antibiotics classified as category A in Table 7.2 (human uses) are essential antibiotics for treatment of human infections where there are few or no alternatives for many infections. Those classified as category A in Table 7.4 are considered essential for animals for the same reason. Table 7.6 shows details of antibiotics considered to be category A for both humans and animals in Australia.

7.5 Enhancement of resistance

7.5.1 Introduction

The genetic principles by which antibiotic resistance arises and is amplified and enriched within bacterial populations have been outlined in Chapter 3. However, this knowledge does not provide insight into the factors that influence the enhancement of resistance within and between the hosts carrying the resistant bacteria. It is probable that the method, or regimen, of drug administration has a significant influence on the likelihood of resistant strains emerging in an individual host. Included in the regimen method are the route of administration, the dose and the duration of treatment. Earlier sections of this chapter described the uses in animals and humans (treatment, prophylaxis, growth promotion), but do not describe the methods of administration for these particular uses. Antibiotic spectrum can also play a role in enhancement of resistance.

7.5.2 Antibiotic administration

Route of administration

Antibiotics may be administered in a number of different ways.

- *Topically* — eg onto skin, directly onto tissues, into the conjunctival sac, into the external ear canal or intravaginally.

- *Orally* — usually in bolus form in humans and companion animals (ie capsules, tablets, suspensions); or incorporated into feed in food-producing animals. For well-absorbed antibiotics, this is the commonest method of achieving systemic levels of drug. For some antibiotics that are poorly absorbed from the gut, this method of administration is used to treat or control intraluminal bacteria.

- *Parenterally* — eg intravenously, intramuscularly — to provide systemic levels when oral administration does not provide effective systemic levels (eg poorly absorbed drug, gut disturbance), oral administration is not feasible (eg unconscious patient), or very high levels of drug are required (such as endocarditis).

- *Into body cavities* — eg intraperitoneally or intrathecally into the cerebrospinal fluid — sometimes preferred as it provides high topical levels.

Table 7.6 'Category A' antibiotics in humans and animals[a]

Antibiotic group	Antibiotic[b]	Species	Infections
Moderate-spectrum penicillins	Amoxycillin	Poultry (meat and eggs)	*Staphylococcus aureus, E.coli,* necrotic enteritis, coryza, fowl cholera
		Pigs	Erysipelas, meningitis
		Dairy cattle	Mastitis
Antipseudomonal penicillins	Piperacillin, ticarcillin	Humans	Pseudomonas, klebsiella
Cephalosporins	3rd generation (eg cefotaxime, ceftriaxone)	Humans	Meningitis, pseudomonas
Carbapenems	Imipenem, meropenem	Humans	Hospital-acquired gram-negatives
Monobactams	Aztreonam	Humans	Gram-negatives
Aminoglycosides	Gentamicin, tobramycin, netilmicin, amikacin	Humans	Gram-negatives
	Neomycin, apramycin, spectinomycin	Pigs	*E. coli* enteritis
	Neomycin	Meat poultry	Necrotic enteritis
Tetracyclines	see Table 7.2	Humans	Gram-negatives (eg brucella), atypical infections (mycoplasma, chlamydia)
	Oxy- and chlortetracycline	Pigs Poultry (meat and eggs)	Mycoplasma infections, PE Coryza, fowl cholera, mycoplasma infections
Sulfonamides + trimethoprim		Poultry (meat and eggs)	*E. coli*, salmonella, fowl cholera
Macrolides	Azithromycin, clarithromycin	Humans	Mycoplasma, chlamydia
	Erythromycin	Horses	Rhodococcal pneumonia/foals (individual treatment)
	Erythromycin, tylosin	Poultry (meat and eggs)	Coryza, fowl cholera, mycoplasma infections
Glycopeptides	Teicoplanin, vancomycin	Humans	MRSA, enterococcus in allergic patients
	Avoparcin	Poultry (meat)	Necrotic enteritis (prophylaxis)
Nitroimidazoles	Dimetridazole	Pigs	Colitis
Fluoroquinolones	Ciprofloxacin, enoxacin, norfloxacin, ofloxacin	Humans	Multiresistant klebsiella, gram-negatives (pseudomonas, enterobacter)
Antimycobacterials	Pyrazinamide, streptomycin, rifampicin, rifabutin, isoniazid, ethambutol	Humans	Tuberculosis
Rifamycins	Rifampicin, rifabutin	Humans	Tuberculosis
	Rifampicin	Horses	Rhodococcal pneumonia/foals (individual treatment)
Antileprotics	Clofazamine, rifampicin, dapsone	Humans	Leprosy
Streptogramins	Quinupristin + dalfopristin	Humans	Resistant gram-positives (eg staphylococcus)
	Virginiamycin	Horses	Laminitis prophylaxis
	Virginiamycin	Sheep	Lactic acidosis
	Virginiamycin	Poultry (meat)	Necrotic enteritis (prophylaxis)
Polypeptides	Zinc bacitracin	Poultry (meat)	Necrotic enteritis (prophylaxis)
Miscellaneous	Sodium fusidate	Humans	MRSA
	Olaquindox	Pigs	PE

MRSA = multiresistant *Staphylococcus aureus;* PE = proliferative enteritis; AIDS = autoimmune deficience syndrome

[a] Not including growth promotant uses.

[b] For humans, examples of antibiotics in each class are given; for animals, registered antibiotics for species indicated are given.

Dose and duration

Treatment courses are administered in higher dosage over short intervals (days to weeks). Prophylactic courses are either:

- higher doses for very short periods (single dose to several days); and
- lower doses for long intervals (weeks to years).

Pre-emptive treatment is given in higher doses for short to very short intervals for contacts of certain infections that may be incubating the disease. All three strategies are used in both human and veterinary medicine.

Influence of method of administration on resistance

It is widely believed that the method of drug administration (exposure) can influence the selection for resistance. Unfortunately the scientific basis for a complete understanding of how the elements of exposure (use and dosing) bring about selection is lacking. Work has only just begun on the population dynamics of antibiotic resistance (Levin et al 1997, Baquero et al 1998).

Nevertheless there are laboratory and clinical observations that give some insights into how variations in antibiotic exposure generate selective pressure for resistance, as follows.

- For some bacteria, the simplest method for selecting resistant mutants of a bacterium to an antibiotic is to expose the bacterium to increasing antibiotic concentrations by repeated subculture starting at concentrations just below or above the minimum inhibitory concentration (MIC, a standardised technique for measuring the intrinsic activity of an antibiotic against a bacterium). The resistant mutants generated in this way may or may not resemble resistant strains isolated from humans or animals.

- Some types of bacteria, such as *Pseudomonas aeruginosa*, harbour resistant mutants than can be easily selected during treatment, depending on the dosing schedule. For drugs, whose effect depends on both concentration and time of exposure (such as aminoglycosides and quinolones), the emergence of resistance during treatment can be reduced by using higher doses less frequently without compromising efficacy. Peak concentrations that are 8–10 fold that of the MIC are able to inhibit the resistant subpopulations, as well as the susceptible parent population.

- Lower doses and longer courses of antibiotics increase the likelihood that the patient will be carrying or acquire resistant bacteria in their normal flora. These resistant bacteria may later become pathogenic to the patient. This has been demonstrated definitively for at least one bacterium, *Streptococcus pneumoniae*, where carriage of penicillin-resistant strains has been demonstrated to occur significantly more often if patients have been exposed to beta-lactams for longer periods and/or lower doses (Guillemot et al 1998).

- For *Streptococcus pneumoniae* at least, isolates from superficial sites (eg respiratory specimens) harbour more resistances than invasive (blood and cerebrospinal fluid) isolates. For antibiotics administered systemically, concentrations of antibiotics at superficial sites are often negligible or low, providing greater selective pressure for colonisation or persistence in the face of treatment.

- Resistance is more likely to be selected where the concentration and the diversity of the bacterial population is high, namely at the site of infection and in some areas of normal flora such as the bowel, mouth and throat. This occurs because of the higher

likelihood of the presence of a mutation or a naturally resistant species. At normal flora sites with mixed bacterial populations there is the additional risk of selecting for resistance in potential pathogens by the transfer of resistance genes from bacteria sharing that niche.

- At selective concentrations, intermittent exposure to antibiotic results in less resistance than continuous exposure. This may relate to the ability of the susceptible parent to 'recover' between exposures and overtake resistant subpopulations.

Thus, lower concentrations (lower doses) and longer durations of exposure (courses) appear to provide the highest selective pressure for resistance; the pressure is further increased if these selection conditions prevail at sites of normal flora, and or if antibiotic exposure is continuous.

Methods of administration in animals and their potential impact

The administration of antibiotics to animals occurs in two ways:

- administration of the medication to groups of animals through feed and water; and
- treatment of individual animals by injection and oral routes.

Administration of antibiotics to groups of animals occurs in four ways:

- treatment (in the event of a disease outbreak);
- prevention of disease (prophylaxis);
- pre-emptive treatment (sometimes called metaphylaxis); and
- growth promotion.

Doses and durations vary for each type of use. Treatment of only the individual animals that actually show signs of disease reduces the population of bacteria exposed to the antibiotic. However, this is not always practical, especially in the face of a disease outbreak (eg for poultry) because of the labour requirements, expense, rapidity of disease spread in intensively reared animals and for animal welfare reasons (stress of catching and restraint). A theoretical complication of administering antibiotics in feed is the variable dose that each animal may receive. Poor feeders, especially those that are ill, may naturally limit their food intake and thus receive lower doses than intended.

Short-course therapeutic use

When antibiotics are used to treat infections in pets (cats and dogs), horses, cattle, sheep and pigs, they are generally given as a short course either by injection or by injection followed by oral treatment at a proven therapeutic dose. The precise length of treatment depends on the type of infection, the antibiotic and the formulation, but is usually five days or less. However, for intensively raised poultry, and in some other situations, antibiotics can be added to food or water. In aquaculture settings, they are added to food or to the water environment. Long-term therapeutic use in animals is unusual.

Medium to long-course prophylactic use

To prevent infections that are known to be problems for intensively raised livestock, such as poultry or pigs, levels of antibiotics lower than those used therapeutically are added to feed for varying periods. The types of infections that need to be prevented in this way include respiratory (eg mycoplasma pneumonia and bacterial pleuropneumonia) and enteric (eg clostridial necrotic enteritis, swine dysentery and coccidiosis) infections. Similar treatment regimes are used to prevent skin and systemic infections in aquaculture species.

Such medium to long-term exposure of animal bacterial populations to antibiotics at medium doses has a higher probability of leading to the development and selection of resistant populations of bacteria in the treated animals. This is because, overall, much larger volumes of antibiotics are used, for longer periods and at concentrations closer to the inhibitory concentrations of pathogens and commensals.

Long-term use of growth promotants

Subtherapeutic levels of some antibiotics are fed continuously to livestock species to improve growth rates and feed utilisation (see Section 7.3.3 and Chapter 8). Some of these agents are also used to control infections such as swine dysentery in pigs, necrotic (clostridial) enteritis in poultry and coccidiosis. The incidence of bloat and lactic acidosis in cattle can be reduced by the use of subtherapeutic levels of the antibiotic growth promotant monensin (polyether ionophore), which is used as a coccidiostat in ruminants and poultry.

In some circumstances doses that have been proven to be effective for growth promotion are the same as those proven to be effective for prophylaxis. Therefore the selective pressure for resistance will be identical because the method of administration (route, dose and duration) are identical or nearly identical.

Antibiotic spectrum

Broad-spectrum antibiotics are active against a range of different bacteria and their use is thus more likely to select for antibiotic resistance in at least one type of bacteria in a niche where the antibiotic reaches. This is of greatest concern, not at the site of infection, where the bacterial population is usually from a single species, but at normal flora sites where mixed bacterial populations are present and levels of antibiotic may be low. A narrow-spectrum antibiotic targeting the specific pathogen of concern is therefore the better choice and could reduce the range of resistance that develops in the exposed population of bacteria.

7.6 Economic impact of antibiotic resistance

Definitive studies on the economic impact of resistance are scant. Some data are available for hospital-acquired *Staphylococcus aureus* infection, showing the increased mortality and additional costs of managing methicillin-resistant as compared to methicillin-susceptible strains (Rubin et al 1999). With considerable experience of managing resistance, particularly in the hospital setting, the following are well understood:

- the antibiotics effective against resistant bacteria are usually more expensive than the ones used for susceptible bacteria;
- the antibiotics effective against resistant bacteria may have to be given intravenously rather than orally, requiring much more expensive hospitalisation or home intravenous therapy plus additional consumable costs;
- the antibiotics effective against resistant bacteria are sometimes more toxic and require monitoring (in humans at least) to minimise toxicity (monitoring has its attendant costs);
- the antibiotics effective against resistant bacteria are usually broader in spectrum and therefore increase the breadth of the selective pressure for resistance, and result in even more resistant bacteria;
- acquisition of resistant bacteria may prolong hospital stay, and never shortens it;

- hospital patients with some types of resistant bacteria require segregation from other patients — this increases nursing and consumable costs; and

- therapy that has failed because of resistance increases the cost of treatment (unless the patient dies) because
  - a new antibiotic must be given, and/or
  - additional investigations may be required, or
  - community patients may require hospitalisation.

On commonsense grounds therefore, it is easy to understand that there must be an economic impact of antibiotic resistance. Unfortunately, information is limited about the size of the impact. Decision-tree models of resistance have shown that costs are directly proportional to the prevalence of resistance; thus, doubling the rate of resistance in a particular bacterium doubles the costs of managing that infection. (Eandi and Zara 1998). Recent experiences with some bacteria (eg *Streptococcus pneumoniae*) in the Australian community have shown that resistances tend to increase 'exponentially' over time (Turnidge et al 1999). Where this 'exponential' increase is rapid, the costs of management will also increase 'exponentially' and rapidly.

In Australia, the costs of antibiotic resistance (eg use of more expensive antibiotics, in multiple courses of antibiotics, increased length of hospital stay and increased mortality) are largely borne by the government and by the patients. These costs have not been systematically investigated to date. However, figures from the United States Office of Tertiary Assessment estimate minimum costs of US$1.3 billion per annum (Congress of the United States 1995) for resistance to only one antibiotic in only six bacterial species.

Chapter 8
Benefits of growth promotants

OVERVIEW

Australian animal industries

Australia has approximately 26 million cattle, 120 million sheep and 5 million pigs; 10 million egg-laying hens and 400 million meat chickens are raised annually. The cattle industry is a mix of extensive and intensive enterprises and between 60% and 70% of production is exported. The sheep industry is predominantly extensive and about 50% of production is exported. The pig and poultry industries are mainly intensive industries supplying the Australian domestic market.

Growth promotion

For over 30 years it has been known that the addition of low concentrations (2.5–50 mg/kg, according to the antibiotic drug used) of antibiotics to the feed of cattle, pigs and poultry improves the growth rate and feed conversion efficiency (FCE) of these animals. That is, for a unit amount of feed consumed, the animals grow more than they would without the antibiotic feed additive. This effect is usually called '*growth promotion*'. The antibiotics are thought to work by reducing the numbers of some intestinal bacteria that would divert nutrition away from the animal; by maintaining a more effective and absorptive gut lining; and, in ruminants, by maintaining the composition of rumen microflora, thus aiding the digestion of grain-based high energy diets.

Disease prevention

Some antibiotics fed primarily as growth promotants can also suppress some diseases. This occurs for necrotic enteritis in chickens, which is caused by *Clostridium perfringens* infection, often after infection with coccidia (protozoa); and proliferative enteritis in pigs caused by *Lawsonia intracellularis*. On the other hand, some antibiotics used principally as prophylactic agents also have growth promotant benefits. For example, the antibiotics used to modify ruminal bacteria of cattle and sheep fed on grain to minimise bloat and lactic acidosis also have growth promotion effects. Some coccidiostats (polyether antibiotics, or ionophores) used in chickens primarily to treat the protozoan disease coccidiosis, are also registered as growth promotants in some other animal species.

Benefits

The range of benefits observed has varied widely between different studies and between different animal species raised under different conditions. Some studies have shown no benefits in either weight gain or FCE, but the majority of studies have shown benefits that average between 1% and 10% for both weight gain and FCE improvement. Larger benefits have been shown in studies where the animals were stressed or experimentally challenged with infective organisms.

Higher feed efficiency, reduced feed requirements and reduced incidence of disease all increase profitability. They can also reduce manure and nitrogen output, which has environmental benefits. However, not all studies have shown these benefits; some studies with chickens have shown increased salmonella excretion (but not confirmed in other studies); and in some studies with healthy poultry an increase in mortality has been recorded. Overall, the economic benefits to farmers must be weighed against the costs of the antibiotics themselves and other possible effects including increasing antibiotic resistance. However, as many other animal husbandry improvements have been made over the last 30 years, antibiotic growth promotants are now only one of the means of improving growth rate and FCE.

8.1 Australian animal industries

8.1.1 Cattle

The majority of the 26 million cattle in Australia are raised on open grazing land without the use of antibiotics. The Australian beef industry is highly competitive on both the domestic and overseas markets and the margins for profit are extremely low. Consumers of red meat in Australia and overseas require a consistent quality and value-added product. This has led to the use of intensive and semi-intensive systems of beef production, including grain feeding, to 'finish' or prepare cattle for slaughter.

In the intensive and semi-intensive systems of beef production, antibiotics are used for prophylactic and therapeutic purposes, and for improved growth rate and feed conversion efficiency (FCE) (growth promotion). The majority of the antibiotics used are, however, in classes of antibiotics that are not used in humans (eg polyethers such as monensin), which are primarily used for disease prevention (eg bloat, liver abscesses) but also have growth promotant effects. Virginiamycin is used for the prevention of lactic acidosis when drought-feeding grain to both cattle and sheep.

Australia's premium beef markets to Japan and South Korea are based on grain finished beef. This market requires visually identifiable fat deposition within the muscle (ie marbling of the meat). Based on industry figures about 25% of Australian prime cattle slaughtered have passed through a feedlot for 'finishing'. These animals account for approximately 30% of the meat production from prime cattle due to their higher carcase weights. Australia's manufacturing beef trade to the United States and other markets is based on a mix of lower-value cuts from lot-fed beef and grass-fed beef. Australia exports between 60% and 70% of its total beef production.

8.1.2 Sheep

There are 120 million sheep in Australia. The majority are merino or merino crosses bred for wool production, and these are produced using extensive grassland management systems. Extensive sheep management systems use minimal amounts of antibiotics, and usually only on valuable stud animals. There is a major and expanding prime lamb (meat) industry. Semi-intensive and intensive sheep meat production systems are not as common or as sophisticated as in the beef industry. Semi-intensive and intensive systems use antibiotics such as virginiamycin for prophylactic control of lactic acidosis and other antibiotics for the control of infectious diseases. Australia exports about 50% of its sheep meat production.

8.1.3 Pigs

Australia has a small intensive pig industry of 3 million animals serving mainly the domestic market. There are a relatively small number of producers (3500) and the majority of production is concentrated in larger and increasingly vertically integrated enterprises. Intensive pig production often requires therapeutic and prophylactic use of antibiotics to counter enteric and respiratory diseases, although the industry is developing and adopting management measures to minimise their use.

8.1.4 Poultry

The Australian poultry meat and egg industries are sophisticated and highly organised industries. Twelve companies produce over 90% of processed poultry meat using a combination of company-owned and contract farms. Currently, approximately 400 million meat chickens are reared annually in Australia on approximately 1500 farms located throughout Australia adjacent to major population centres. There is often

common ownership of breeding farms, processing plants and feed-mills in addition to meat-producing farms.

In the case of the egg industry, privately owned farms produce eggs or egg pulp, which are sold to retail outlets. There are approximately 10 million egg-laying hens on 1000 farms in Australia. Some egg farms have a feed-mill while others purchase feed compounded by a commercial mill. In recent years there has been some concentration of ownership of the egg industry, with eight farmers now owning a number of farms which produce more than 40% of Australia's table eggs.

A small percentage of Australia's poultry meat and eggs is produced from farms using extensive or semi-intensive farming methods.

Antibiotic use is for disease prophylaxis and treatment although vaccines, biosecurity procedures and hygienic methods are the main means of controlling bacterial diseases in the poultry industry. In the case of the poultry meat industry, antibiotics are also used for growth promotion and improvement of feed utilisation.

The poultry industry services the Australian domestic market as well as an important but small export trade. A small quantity of pasteurised egg pulp has been imported, but currently there have been no imports of cooked or raw poultry meat.

8.2 Growth promotion

8.2.1 Introduction

Antimicrobial agents have been added to animal feed at low concentrations to promote growth and feed conversion in cattle, pigs and poultry worldwide for about the last 30 years. Just how they work is not fully understood. It is thought to be by suppressing sensitive intestinal bacterial populations that would divert nutrition away from the animal, maintaining a more effective and absorptive gut lining due to reduced thickening of the intestinal wall and reduced toxin production of microbial flora (Fiems et al 1991 cited by Viaene 1997, CAFA 1997). Most growth promotants are not active against gram-negative bacteria (see Section 4.1).

The use of antibiotic feed additives results in improved meat quality (increased protein, reduced fat), and increased growth and FCE. Growth promotant use has generally been reported to improve average daily growth and FCE in the range of 1-10% (UK House of Lords 1998, US National Research Council 1998, CAFA 1997).

In some studies, the adverse effects of stress (eg heat stress) or challenge with infective organisms (eg clostridia) on growth performance have been restored by feeding antibiotics at growth promotant levels, indicating that the benefits are greatest under these conditions (CAFA 1997). Conversely, the benefits are reduced or eliminated for animals raised in pathogen-free environments, indicating that the antibiotics may work, in part, by controlling pathogens as well as by modifying commensal organisms and/or by a direct effect on the intestinal wall (CAFA 1997, Gropp and Schuhmacher 1997). Further information is needed on these mechanisms.

There are wide variations in the observed benefits both in different animal species and in the conditions under which the animals are raised. In the Swedish report (CAFA 1997) a number of previous large studies were evaluated. The average weight gain with the use of antibiotics in weaner pigs (piglets) was 6.8% and FCE improved by 4.6%. Without antibiotics there is now estimated to be an increase in mortality of 0.6%. For grower pigs the average weight gain improvement was 1.9% and FCE improved by 1.7%. For

chickens the average weight gain was 2.1% and FCE improvement 1.4%. Egg production can also be increased but this is not consistently seen in all studies (Gropp and Schuhmacher 1997); **growth promotants are not used in egg production in Australia**.

However, in some poultry studies with healthy animals an increase in mortality has been recorded for animals treated with growth promotants, compared with untreated controls (see Section 8.3.3). Antibiotic use has also been associated with increased salmonella excretion (especially in chickens) but this has not been consistently confirmed; in some studies with other species (pigs, calves), the prevalence and duration of salmonella shedding was decreased (CAFA 1997).

Overall, the benefits of growth promotants have become less marked in recent times with improving feed formulation, hygiene and disease control by vaccination and improved breeding/genetics (particularly in chickens) (Gropp and Schuhmacher 1997, CAFA 1997).

8.2.2 Prevention of disease

Although most growth promotant antibiotics are given in subtherapeutic doses (2.5-50 mg/kg or ppm [parts per million]), they also appear to suppress some diseases. This is probably because, even at these low doses, the minimum inhibitory concentration (MIC) for a number of pathogenic bacteria is exceeded in the gut of the animal. Indeed, one of the main reasons for using these agents in poultry is for the control of *Clostridium perfringens*. This bacterium frequently overgrows normal intestinal flora in chickens, causing necrotic enteritis, for example following infections with the protozoan parasite *Eimeria* spp. (coccidia). The addition of olaquindox to pig diets at low levels as a growth promotant prevents proliferative enteritis caused by *Lawsonia intracellularis*, which is an important and common disease in pigs.

On the other hand, some antibiotics used principally as prophylactic agents also have growth promotant benefits. For example, the polyether (ionophore) antibiotics, such as monensin, are primarily used to modify ruminal bacteria of cattle and sheep fed on grain to minimise bloat and lactic acidosis. They also have growth promotion effects and are registered as growth promotants (see Section 8.2.1). In poultry, polyethers are registered as coccidiostats only and are not used as growth promotants in this species. Further details of the uses of antibiotics for prophylaxis and growth promotion in animal species are shown in Chapter 7 (Tables 7.4 and 7.5).

8.2.3 Growth promotion in ruminants

In intensive and semi-intensive systems of beef production, antibiotics are used for therapeutic and prophylactic purposes to treat and prevent disease. They are also used for growth promotion and improved FCE.

Ruminants meet the majority of their energy needs through gluconeogenesis rather than from direct absorption of sugars or other forms of carbohydrate as occurs in pre-ruminant calves and lambs, and in pigs and poultry. Gluconeogenesis requires the absorption of propionate, which is produced by the rumen microbes. Rumen microbes also produce acetate and butyrate, both of which form ketones when absorbed into the bloodstream.

Grain-based feeds used in intensive ruminant animal production (cattle and sheep) are formulated to contain high levels of carbohydrate. This is necessary to achieve the high rates of growth and carcase composition required to meet market specifications (see Section 8.3.1). High carbohydrate diets can result in bloat, acidosis (a factor in the

production of liver abscesses in cattle) and death. The highest risk period for this is during the introduction of the animals to the diet.

These conditions can be controlled prophylactically by maintaining the composition of the rumen microflora using antimicrobial compounds such as monensin (a polyether ionophore) or virginiamycin (a streptogramin). Lasalocid is also used to modify the rumen microflora. Polyether ionophores also improve FCE. The use of these compounds addresses animal health and welfare concerns and they also have growth promotant benefits due to:

- increased availability of propionate for gluconeogenesis (thereby increasing FCE and the capacity of the animal to lay down fat in a way that results in a high level of marbling);
- reduced intraruminal gas production (which may cause stress to the animal and reduce growth performance in animals not showing clinical signs of bloat); and
- reduced production of lactic acid (an outcome of anaerobic glycolysis of carbohydrates present in high energy feeds, thereby wasting the metabolisable energy in animals not showing clinical signs of lactic acidosis).

Verbeke and Viaene (1996) reviewed the literature on growth promotant use in beef cattle and calves and concluded that the average improvement in daily growth was 6% and 7% for beef cattle and calves, respectively and 6% and 4%, respectively, for FCE.

8.2.4 Environmental benefits

Increased feed efficiency due to growth promotant use can lead to reduced manure and nitrogen output, which has environmental benefits, including reduced odour and pollution, which can be substantial in intensive farming situations (Gropp and Schuhmacher 1997). In his presentation to the Berlin Conference organised by the WHO, Lawrence (1997) estimated that in the 10-year period from 1980–1990 in the United Kingdom, the use of growth promotants saved nearly 2 million tonnes of feed (based on a national kill of 14 million pigs per year), 1.2 billion gallons of potable water and 1.3 billion tonnes of slurry. However, although there have been various calculations made, the overall environmental and economic significance of this effect is not known.

8.2.5 Economic analysis

The United States Animal Health Institute has estimated that without growth promotants the United States would need 23 million more cattle, 12 million more pigs, 452 million more chickens and 60 thousand more sheep to produce the same amount of meat (AHI 1998).

To date, however, there have been few detailed economic analyses of the costs–benefits of growth promotion use. The US National Research Council (1998) presented such an analysis based on estimates of production costs with and without antibiotics and retail meat costs for chicken, turkey, beef and pork.

The overall cost to the United States economy was estimated to be US$1.3–2.5 billion per year for a total population of approximately 260 million, or US$4.85–9.72 per person per year (Table 8.1). Flow-on and consequential costs and losses such as research and development effects were not included in this analysis. Converting to Australian dollars and assuming Australia has 18 million people compared to the United States' 260 million, and that animal production industries are the same, these figures convert to a cost of $A125–275 million per year to the Australian economy ($A6.90–15.28 per person per year). However, the animal industries in Australia are not the same as in the United

States. Some details of beef, pork and chicken production in Australia are given in Section 8.1 and benefits from growth promotant use in Australia are described in Section 8.3.

8.2.6 Review of benefits

It was not possible within the scope and time-frame of the JETACAR review to obtain a full independent review of the scientific literature on benefits of growth promotant use. Such a review is needed to fully assess the factors involved, with particular reference to Australian conditions, so that a full evaluation of the costs and benefits of discontinuing growth promotant use can be assessed.

8.3 Benefits of growth promotants in Australia

8.3.1 Beef cattle and sheep

Feedlot cattle destined for some key markets (eg Japan) have high energy requirements and, without antibiotics as rumen modifiers, the specifications for these markets cannot be met. Without antibiotics such as the polyethers (ionophores such as monensin) and virginiamycin, Australia would lose access to high value markets for lot-fed beef. The majority of antibiotics used in beef cattle and sheep in Australia (polyethers) are not in a class that is used in human medicine and, on current scientific knowledge, are not likely to be associated with the spread of antibiotic-resistant bacteria to humans, or to compromise the use of any antibiotics in human medicine (particularly those classified as 'last line' or category A, see Table 7.2).

Feedlot industry sources indicate that an improvement in FCE in the range 4–11% can be reasonably expected through the use of antibiotic growth promotants under normal commercial Australian feedlot conditions. The following example of the benefits of antibiotics as growth promotants under feedlot conditions is based on an improvement in FCE of 5%.

For an animal spending 100 days in a feedlot and consuming 10–12 kg (dry weight) feed per day, this represents a potential feed saving in the order of 50–60 kg (dry weight) per animal. This is a saving of about $10–12 per head in actual feed costs (assuming feed costs, including handling, are $200 per tonne on a dry weight basis). Gross margins for operations involving 100 days in the feedlot are highly variable. For an efficiently run medium-to-large-sized feedlot (greater than 1000 animals), gross margins in the order of $15–20 per head would be expected. The additional feed costs would absorb 50–66% of the expected gross margin.

There would also be costs associated with increased mortality (due to bloat and lactic acidosis). An assumed increase in the mortality rate of 1–2% would further erode the gross margin by $6–12 per head. Animals would weigh about 500 kg liveweight and have a value of $1.10 per kg; an induction cost of $7.00 per dead animal and an average feed cost of $30 per dead animal need to be included in any calculation. Animals would be expected to die in the early stages of lot feeding so an average expected survival period of 15 days has been used in the above calculations.

Similar improvements in FCE are seen in lot-fed lambs, or lambs paddock-fattened with supplementary feeding of high carbohydrate rations.

Supplementary feeding of dairy cattle using high energy rations to increase milk yield is now common practice in Australia. In-feed antibiotics are used prophylactically to

prevent lactic acidosis and bloat. They also improve FCE, which increases milk production.

In addition to the economic benefits, there are significant environmental benefits in terms of greenhouse gas emissions. The use of monensin as a growth promotant in cattle is reported to reduce rumen methane production by up to 16% (Thornton et al 1976).

8.3.2 Pigs

Antibiotic growth promotants provide a variable but significant improvement in growth rate and FCE, increasing the efficiency of pig production. In addition to this growth promoting effect, some antibiotics used in this way also prevent some diseases (eg proliferative enteritis), improving pig health and welfare.

AUSPIG is a computer-based decision-support model developed by CSIRO. It allows changes in some of the variables in pig production systems to be modelled and predicts likely profitability associated with environmental, nutritional, genetic and management changes.

The model used for this exercise was a 5000-sow commercial piggery. FCE was incrementally increased from 0–10%, the range associated with growth promotants.

Associated with the improvement in FCE, there is an increase in growth rate and a reduction in fatness of the carcase. Tables 8.1–8.3 show the substantial reduction in feed usage associated with the incremental improvement in feed efficiency, growth performance, profitability and nitrogen output expected with growth promotant usage.

The net profit per pig sold varies considerably from piggery to piggery and over time. However, it is frequently in the range of $10–20. The increases seen in Table 8.3 could therefore have a major effect on overall profitability. For example, a unit this size would be expected to produce 100,000 pigs per year so that the potential increase in profitability could be as high as $584,000.

Table 8.1 The simulated effect on the weaner-to-sale growth performance and nitrogen output of female pigs between antibiotic responses predicted to increase feed efficiency (ie lower FCR)

	Simulated feed efficiency increase (%)			
	Control	+2.5	+ 5	+10
FCR (feed:wt gain)	2.36	2.30	2.25	2.12
ADG (g/day)	670	690	709	763
Birth–sale ADG (g/day)	600	615	629	672
Backfat P2 (mm)	12.7	12.6	12.4	12.0
Total nitrogen output (kg)	2.71	2.61	2.51	2.30

FCR = food conversion ratio; ADG = average daily gain (a measure of growth rate); backfat P2 = a measure of fatness
Note: Simulation is under commercial production conditions with pigs sold at 78 kg carcase weight.

Table 8.2 The simulated effect on the weaner-to-sale growth performance and nitrogen output of entire male pigs between antibiotic responses predicted to increase feed efficiency (ie lower FCR)

	Simulated feed efficiency increase			
	Control	2.5%	5%	10%
FCR (feed:wt gain)	2.31	2.25	2.20	2.07
ADG (g/day)	712	744	766	831
Birth–sale ADG (g/day)	641	657	673	721
Backfat P2 (mm)	9.9	9.9	9.8	9.7
Total nitrogen output (kg)	2.73	2.64	2.56	2.37

FCR = food conversion ratio; ADG = average daily gain; backfat P2 = a measure of fatness
Note: Simulation is under commercial production conditions with pigs sold at 78 kg carcase weight.

Table 8.3 The effect on herd feed conversion, feed usage, daily weight gain, nitrogen output and profitability of simulated improvements in feed efficiency as a result of antibiotic use in a 5000 sow piggery

	Feed efficiency increase			
	Control	+ 2.5%	+ 5%	+ 10%
HFC	3.74	3.68	3.63	3.49
Birth–bacon ADG (g/day)	632	648	664	718
Grower feed use (tonnes/year)	22784	22209	21884	21519
Nitrogen output (tonnes/year)	276	266	257	237
Increased earning ($ per pig)	–	0.87	1.84	5.84

HFC = herd feed conversion; ADG = average daily gain
Source: CSIRO AUSPIG computer simulation modeling

Viaene (1997) reported investigations in the southeast of Sweden that suggested that pigs needed 3–5 more days to reach 25 kg liveweight without growth promotants than before the prohibition on antibiotics in feed. They consumed an additional 2 kg of feed, while mortality rose by 10–15%. Thafvelin and Olsson (1988) cited in Viaene (1997) also reported that it took seven days longer to bring pigs to 30 kg liveweight. However, the Swedish Commission on Antimicrobial Feed Additives (CAFA 1997) indicated that these initial problems after the ban was first introduced were overcome. The increase in mortality in weaner pigs (piglets) was 1.5% in the year following the ban (1986 compared to 1985) but this mortality has since fallen so that at present it is only 0.6% higher than in 1985 (see Section 11.5).

8.3.3 Poultry

Antibiotic growth promotants are used in poultry meat production because they improve the rate of weight gain or the FCE. Specific growth promotants, such as avoparcin, virginiamycin and zinc bacitracin, are also used to control necrotic enteritis caused by *Clostridium perfringens*. In its mildest form, this infection causes poor digestion of feed (and consequent growth depression, poor feed conversion and wet smelly droppings); in its most severe form, it can cause death of birds.

Table 8.4 shows estimates of the benefit of growth promotion for poultry meat production, based on information supplied by the manufacturers of virginiamycin and avoparcin. The improved FCE shown in this table would return a benefit (net of the cost of the growth promotants) of about 1.4 cents per kg of liveweight for an estimated 750,000 tonnes liveweight for 1997–98, a net saving of $10.5 million for the chicken meat industry. Increased growth rate helps improve FCE (because less feed is eaten by the chickens if they reach market weight faster). However, efficiencies in growing costs can also be achieved because more batches can be grown per year using the same

shedding and facilities (ie no increase in capital costs to produce more meat). **Growth promotants are not used in egg-laying chickens in Australia**.

According to Groves (1998) in the Pfizer Animal Health submission to JETACAR, a conservative estimate of improvement in feed efficiency after use of growth promotants in meat chickens is of the order of 1.5%, with an economic benefit of $7.3 million per year.

Additional economic benefits occur due to control of necrotic enteritis, increased carcase weight, increased carcase yield and alleviation of harmful effects of heat stress.

In a review of the literature, Verbeke and Viaene 1996 also reported improvement of daily growth and feed efficiency of 4% each in broilers and improvements in egg mass and feed efficiency of 2% and 1%, respectively, for laying hens. The scientific articles reviewed for the CAFA (1997) report indicated varying benefits of growth promotants for feed efficiency and growth rate of poultry. It was concluded that a 1–1.5% improvement in performance and feed efficiency could be expected if growth promotants were reintroduced into Sweden.

There are, however, some studies that have shown no benefits with the use of antibiotics as growth promotants (Proudfoot et al 1985). In addition, in some studies where a benefit was seen in weight gain and FCE, this was associated with increased mortality in the chickens that received antibiotics (eg in the 12 Pfizer trials analysed in Table 8.4, mean mortality rates were 4.8% in the treated groups and 3.9% in the negative control groups).

Table 8.4 Effects of antimicrobial growth promoters on feed conversion efficiency (FCE) and growth rate in meat chickens

Antibiotic	Dose (mg/kg)[a]	Improved FCE (%)	Increased growth rate (%)	Net cents/kg liveweight[b]
Avoparcin	10	2.96	2.37	1.33
Virginiamycin	17.5	3.48	3.19	1.48

[a] mg/kg = ppm (parts per million)

[b] based on improved FCE; calculations are based on the following:
- — liveweight of 2.69 kg at 49 days
- — feed consumption of 5.018 kg/chicken
- — cost of avoparcin of 0.38 c/kg of liveweight
- — cost of virginiamycin of 0.53 c/kg of liveweight
- — cost of feed of $310/tonne

Source: Dr Tom Grimes (JETACAR member and National Veterinarian, Steggles Ltd) based on data from 12 trials by Pfizer Animal Health (manufacturer of virginiamycin) and 73 trials by Roche Vitamins Australia Pty Ltd (manufacturer of avoparcin).

Both avoparcin and virginiamycin are effective against *C. perfringens,* and industry experience worldwide is that necrotic enteritis has been well controlled by these two antibiotics. Avoparcin is registered for necrotic enteritis control in Australia and virginiamycin has this claim registered overseas. Necrotic enteritis and poor digestion of feed due to malfunction of the gastrointestinal tract causes an environmental pollution problem because of wet smelly faeces and floor litter. Rotation of growth promotants has been practised with the aim of minimising antibiotic resistance and maintaining their usefulness.

8.4 Conclusion

There have been enormous improvements in the standards of animal care and hygiene in the 40 years since antibiotics were first introduced into veterinary care and animal husbandry. When growth promotants were first introduced into the intensive industries, the benefits were substantial in terms of disease prevention, feed conversion and weight gain. Current evidence, predominantly generated overseas, suggests that the benefits in feed conversion and weight gain are still cost-effective at the level of 0.5–5% (although some trials have shown no benefit in certain circumstances).

In Australia antibiotics are currently used extensively in the pig and meat chicken industries for disease prevention and their ability to improve weight gain and FCE. In cattle and sheep most animals do not receive antibiotics. However, some antibiotics are used for cattle in feedlots to prevent problems with bloat, lactic acidosis and liver abscesses. To achieve this, the lot-feeding industry can use antibiotics that are not currently used, and are not likely to be used in the future, in human medicine (ie the polyether ionophores).

The efficacy of growth promotants in relation to disease prevention is also an important factor for increased production and profitability. After the ban on growth promotants in Sweden a decade ago there was an initial increase in infectious disease, animal welfare and environmental problems in their intensive industries. However, while still allowing prophylactic use of some in-feed agents and with judicious use of other therapeutics, improvements in feed formulation and stricter hygienic measures, infection rates have been reduced to those experienced by countries where growth promotants are widely used (see Section 11.3.1). However, the overall effect of these measures on production costs in Sweden is not clear.

It is also not known, however, how the Swedish findings would relate to Australian livestock production conditions. Pastoral animals receive few antibiotics but these drugs are still important in the intensive industries, especially for prophylaxis. These industries have made a contribution to the development of alternatives to the use of antibiotics, especially through research into vaccination. As a major exporter of animal-derived foods, Australia has to consider its competitive position and production costs and to meet the food safety standards which ensure its access to world markets.

An independent evaluation of growth promotant efficacy, including economic benefits, by relevantly qualified and experienced experts would provide the basis for improved future management.

Chapter 9
Antibiotic residues and marker genes in food

OVERVIEW

Antibiotic residues in food

When food-producing animals are treated with antibiotics, some drug residues may remain in the food products eaten by humans. This has raised concerns overseas and in Australia about the possible emergence of resistant bacteria in people eating these foods. This issue is separate from the direct transfer of antibiotic-resistant bacteria from animals to humans through bacterial contamination of food.

The National Residue Survey (NRS) measures antibiotic residues in Australian commodities that are considered at highest risk of containing residues. NRS results for the last three years have shown that for beef and chicken there have been very few (beef) or no (chicken) instances of residue levels exceeding Australian maximum residue limits (MRLs). For pigs, less than 1% of samples tested had antibiotic residue levels above the Australian MRL (using the revised MRL for tetracyclines).

JETACAR believes that the low levels of antibiotic residues detected in Australian food (both in amount and frequency) make it unlikely that there would be a measurable effect on the emergence of antibiotic-resistant bacteria on, or in, people.

Antibiotic-resistance markers in transgenic plants

The use of antibiotic-resistance genes (particularly kanamycin resistance) as markers in the selection of transgenic plants that are subsequently released into the environment has also become an issue of concern. Some people fear that consumption of transgenic food plants may result in the transfer of antibiotic-resistance genes to human bacteria. A review of the biological mechanisms involved, however, indicates that, based on current knowledge, such transfer is unlikely to occur.

Conclusion

An examination of the residue levels in Australian foods indicates that the probability of antibiotic residues in food or antibiotic-resistance genes in transgenic plants causing antibiotic-resistance problems for humans in Australia is extremely remote. The most important factor for human health is the existence of resistant enteric bacteria in people from the use of these chemicals in human medicine. The transfer of antibiotic-resistant bacteria from food-producing animals where antibiotics have been used to humans via carcase contamination is an event of low probability, but has been documented overseas. The dietary consumption of antibiotic residues in food as a factor in the generation of antibiotic-resistant bacteria in humans in Australia is probably of minor importance although evidence for or against its occurrence is not available.

9.1 Antibiotic residues in food

In 1969, the Swann Committee (UK Joint Houses of Parliament Committee) concluded that antibiotic residues in animal-derived food did not pose any major hazard to the consumer. Now, 30 years on, the only health problem that has ever been identified as possibly arising from antibiotic residues in food is allergy to penicillin residues for those people who are hypersensitive to this drug (Joint Expert Committee on Food Additives (JECFA) 1990 meeting, Sundlof 1993). Penicillin is most widely used as an animal feed antibiotic in the United States but is not registered as a feed additive for food-producing animals in Australia. Despite this, concerns persist that microbiologically active residues of veterinary antibiotics in food may in some way contribute to antibiotic resistance either by modifying the bacterial flora in the human gut or by selecting for resistant bacteria in meat, which can then be transferred to humans in food.

9.1.1 National Residue Survey

The National Residue Survey (NRS), which is part of the National Office of Food Safety of the Commonwealth Department of Agriculture, Fisheries and Forestry — Australia (AFFA) (formerly the Department of Primary Industries and Energy), has been monitoring chemical residues in meat since 1961. Currently, a total of 28 primary industry commodities are monitored. Chemical residue levels are reported against Australian maximum residue limits (MRLs). These limits are set for particular commodity–chemical/tissue combinations (eg oxytetracycline levels in beef kidney) at levels consistent with good agricultural practice. The MRLs generally represent the maximum amount of a residue likely to occur in or on food under the most extreme conditions likely to be encountered in agricultural production. Although they are not directly based on any health criteria, they are established following a comprehensive risk assessment process, where the known toxicological risks are considered not to constitute an undue hazard to human health based on daily consumption patterns. In Australia, MRLs are set by the National Registration Authority (NRA) and are incorporated into the Australia New Zealand Food Authority (ANZFA) Food Standards Code (ANZFA 1992). The NRS results test the effectiveness of both the agricultural and veterinary chemical registration process and producer compliance with the advice provided on the label.

When NRS laboratories detect a sample with a level above the MRL they advise the relevant State/Territory regulatory authorities so that appropriate corrective action can be taken. The NRS also undertakes targeted surveillance programs to further characterise the nature of any residue issues identified by the monitoring program.

Commodity–chemical selection

Commodity–chemical/tissue combinations are selected on the basis of risk profiles — combinations of highest risk are included in NRS programs. In developing risk profiles for agricultural and veterinary chemicals in general, and antibiotics specifically, the main factors considered are:

- international and/or domestic perceptions of the commodity–chemical combination as a possible public health hazard;
- toxicity of the chemical or its break-down products; and
- likelihood of residues occurring in the product (potential for misuse, persistence in the crop, animal or environment, extent of use and use patterns);
- extent and results of previous monitoring for the commodity–chemical combination; and
- factors such as the availability of suitable sampling and analytical methods.

These principles are applied to antibiotic monitoring in Australia and, in addition, importing countries sometimes require analyses for particular chemicals of concern in their country. Consequently, NRS monitors for some chemicals (and some antibiotics in particular) that are not registered for use in Australia.

Methods

Screening test for antimicrobials

For most classes of antibiotics, a broad-spectrum antimicrobial screening test, or microbial inhibition test (MIT), is used. A kidney homogenate is subjected to solid-phase extraction and the extract is applied to a number of culture plates seeded with different susceptible organisms (eg *Bacillus subtilis, Micrococcus luteus* and *Bacillus megaterium).* After incubation of the culture plates, the presence of antibiotics is indicated by zones of inhibition of bacterial growth.

In addition to the antimicrobial screen, there are specific testing programs for chloramphenicol, dimetridazole and nitrofurans in some species. However, in Australia, chloramphenicol is not registered for use in food-producing animals and nitrofurans are only available for use in companion animals and have not been registered for use in food-producing animals in Australia since 1993.

Quantitative assays

When a positive result is obtained in the MIT screen test, every effort is made to identify the antibiotic concerned. There are very few screen test positive samples where the antibiotic responsible is not identified and quantified. The level of antibiotic residue in the commodity is determined using one or a combination of analytical chemistry methods such as gas chromatography, high-performance liquid chromatography, and mass spectrometry.

The antibiotics that could be specifically identified in this way for the NRS from 1995–98 are shown in Table 9.1.

Table 9.1 Antibiotics in food-producing animals that could be specifically identified in the NRS, 1995–98

Class	Specific antibiotic	Class	Specific antibiotic
Aminoglycosides	dihydrostreptomycin	Sulfonamides	sulfadiazine
	neomycin		sulfadimidine (methazine)
	streptomycin		sulfadoxine
β-lactams	amoxycillin		sulfafurazole
	ampicillin		sulfamethoxydiazine
	benzyl-G-penicillin		sulfapyridine
	cloxacillin		sulfaquinoxaline
Amphenicols	chloramphenicol		sulfathiazole
Nitroimidazoles	dimetridazole		sulfatroxazole
Macrolides	tilmicosin	Tetracyclines	chlortetracycline
	tylosin		oxytetracycline
Nitrofurans	nitrofurazone		tetracycline HCl
	nitrofurantoin		
	furazolidone		
	furaltadone		

Australian MRL for tetracyclines

After a review of the MRLs for chlortetracycline in 1996, the NRA raised the MRLs for chlortetracycline in edible offal of cattle, pig, poultry and sheep to 0.6 mg/kg. These have now been adopted by ANZFA and published in the Australian Food Standards Code. More recently the MRLs for oxytetracycline have been reviewed with a recommendation that the MRL for oxytetracycline in kidney of cattle, goats, sheep and pigs be set at 0.6 mg/kg instead of the current MRL of 0.25 mg/kg. The changes to the oxytetracycline MRLs would bring Australia's tetracycline MRLs more in line with international MRLs and those recommended by CODEX. The NRA recommendations for oxytetracycline have to be adopted and published by ANZFA before they become nationally ratified.

Survey results, 1995–98

The following results have been extracted from reports of the NRS results from 1995–98 (BRS 1997ab, 1998ab)

Cattle tissue (beef)

Table 9.2 shows the NRS results for beef and it is clear that the levels of antibiotics in cattle tissue, mainly kidney, are low. Over the 3.5-year period reported, 2442 animals were tested using the MIT screen and 1961 were tested for neomycin. Only 10 samples had detectable antibiotics. Five of these samples exceeded the MRL for dihydrostreptomycin. While one sample exceeded the current MRL for oxytetracycline (0.25 mg/kg), no samples exceeded the revised MRL (0.6 mg/kg).

Pig

In contrast to the beef results, the results for pig meat (Table 9.3) show that over same 3.5-year period, 2614 animals were tested using the MIT screen, 2415 for neomycin and tilmicosin and 2280 for sulfadimidine. Of these, 563 kidney/liver samples contained detectable levels for antibiotics and 67 exceeded the MRL. Forty-six were over the current MRL for oxytetracycline (0.25 mg/kg) but only eight were over the NRA-recommended MRL of 0.6 mg/kg. Two exceeded the MRL for dihydrostreptomycin, one exceeded the MRL for neomycin and 18 exceeded the MRL for sulfadimidine.

However, the pig antibiotic residue levels, irrespective of their relation to the MRL, reflect long-term prophylactic and therapeutic use of antibiotics (particularly tetracyclines) to control respiratory disease seen under the intensive-housing practices of the industry. Vaccines to reduce the effects of mycoplasma infection in pigs have recently been registered by the NRA, and it is anticipated that this and more strategic use of antibiotics will reduce antibiotic usage in pig production.

The significance of these observations for the emergence of antibiotic resistance of medical importance in pigs can only be resolved by monitoring antibiotic resistance in a range of microorganisms from pig populations in a systematic and ongoing manner.

Sheep meat

The extensive nature of sheep production and the low unit value of the product means that antibiotics are infrequently used. Accordingly antibiotic surveillance is at a lower level than for the pig and cattle industries. The antimicrobial residue figures from the sheep meat industry NRS programs do not indicate any major misuse or overuse of antibiotics. One sample out of 900 was above the MRL for sulfadimidine.

Chicken meat

As shown in Table 9.4, the levels of antibiotic residues in chicken meat are low, with no detections of oxytetracycline over the old or revised MRL in the last 3.5 years. However, 4 out of 799 chicken meat samples subjected to the MIT contained traces of an

inhibitory substance using the MIT. The identity of the substance could not be determined.

Eggs

In the period 1995–98, testing of eggs was limited to 251 samples of eggs that were tested for the presence of antibiotics with a broad-spectrum MIT. No antibiotic residues over the MRL were found.

Aquaculture

Chemical residue monitoring programs for aquaculture commodities for this period did not test for antibiotics.

Table 9.2 Antimicrobial residues found in beef, National Residue Survey 1995–98

Antimicrobial[a]	Number of samples	LOD mg/kg	LOR mg/kg	MRL mg/kg	<0.2 mg/kg	>0.20 <0.60 mg/kg	>0.60 <1.00 mg/kg	>1.00 mg/kg	Total over MRL	Total with residues
Oxytetracycline	2442	0.02	0.05	0.25 (0.60)[b]	1	1	-	-	1	2
Chlortetracycline	2442	0.02	0.05	0.60	1	-	-	-	-	1
Dihydrostreptomycin	2442	0.10	0.10	0.30	-	2	-	3	3	5
Neomycin	1961	0.25	0.25	0.50	1	1	-	-	-	2
Totals	-	-	-	-	-	-	-	-	4	10

LOD = limit of detection (screen and confirmatory tests); LOR = limit of reporting; MRL = maximum residue limit
[a]antibiotics from Table 9.2 that were detected as residues are listed'. [b]0.25 mg/kg is the current MRL for oxytetracycline. The NRA has recommended the MRL should be 0.60 mg/kg for kidney.

Table 9.3 Antimicrobial residues found in pigs, National Residue Survey 1995–98

Antimicrobial [a]	Number of samples	LOD mg/kg	LOR mg/kg	MRL mg/kg	<0.20 mg/kg	>0.20 <0.60 mg/kg	>0.60 <1.00 mg/kg	>1.00 mg/kg	Total over MRL	Total with residues
Penicillin G	2514	0.01	0.01	0.06	2	-	-	-	-	2
Oxytetracycline	2614	0.02	0.05	0.25 (0.60)[b]	355	59	4	4	46 (8)	422
Chlortetracycline	2614	0.02	0.05	0.60	7	65	10	-	-	82
Dihydrostreptomycin	2517	0.10	0.10	0.30		1	-	1	2	2
Neomycin	2415	0.25	0.25	0.50	5	-	-	1	1	6
Tilmicosin	2415	0.01	0.20	1.0	6	4	-	-	-	10
Sulfadimidine	2280	0.01	0.02	0.1	26	12	-	1	18	39
Totals	-	-	-	-	-	-	-	-	67	563

LOD = limit of detection (screen and confirmatory tests); LOR = limit of reporting; MRL = maximum residue limit
[a]antibiotics from Table 9.3 that were detected as residues are listed'. [b]0.25 mg/kg is the current MRL for oxytetracycline. The NRA has recommended the MRL should be 0.60 mg/kg for kidney.

Table 9.4 Antimicrobial residues found in chicken meat, National Residue Survey 1995–98

Antimicrobial [a]	Number of samples	LOD mg/kg	LOR mg/kg	MRL mg/kg	<0.20 mg/kg	>0.20 <0.60 mg/kg	>0.60 <1.00 mg/kg	>1.00 mg/kg	Total over MRL	Total with residues
Oxytetracycline	799	0.02	0.05	0.25 (0.60)[b]	2	-	-	-	-	2
Unidentified [c]	799	0.10	-	-	4	-	-	-	-	4
Totals	799	-	-	-	-	-	-	-	-	6

LOD = limit of detection (screen and confirmatory tests); LOR = limit of reporting; MRL = maximum residue limit
[a]antibiotics from Table 9.4 that were detected as residues are listed'. [b]0.25 mg/kg is the current MRL for oxytetracycline. The NRA has recommended the MRL should be 0.60 mg/kg for poultry offal.

9.1.2 Antibiotic residues and resistance in bacteria

Consumption of antibiotic residues in food

The main concern in the community appears to centre around the concept that ingestion of even the low levels of antibiotic residues in food recorded in Australia could have a measurable effect on the generation of antibiotic resistance in bacteria on, or in, people, and that these bacteria could then cause untreatable sickness. To the knowledge of JETACAR there have been no specific experiments or observations to either establish or disprove this concept.

From the NRS results considered in Section 9.1.1 the occurrence of residues above 1 mg/kg (1 ppm) is rare, less than 0.1% of samples. The very low levels of residues in food, the small proportion of the diet made up of products with any measurable residues, and other factors such as cooking and preparation processes indicate that the probability of antibiotic resistance arising from this source is remote. This low probability contrasts with the moderate probability, over, for example, a 10-year time-frame, of selecting bacteria with resistance to a specific antibiotic by veterinary and medical use. However, definitive research to confirm or refute this view has yet to be undertaken.

Development of antibiotic resistance in meat

It has also been suggested that antibiotic residues in the tissues of animals after slaughter may promote the development of antibiotic resistance in bacteria on the carcase and that these resistant bacteria could be consumed by humans in food. However, whether or not this occurs is very difficult to determine. The microbiological contamination of meat immediately after slaughter and chilling has been the subject of considerable study, but not in the context of the development of antibiotic resistance in this bacterial population.

On first principles, it would be expected that the possibility of antibiotic residues, even if present in a carcase at levels above the minimum inhibitory concentration (MIC), selecting antibiotic-resistant bacterial populations on the carcase would be exceedingly small given the number of generations of bacteria possible after slaughter and before the refrigerated storage transport and retail sale of the food for cooking and eating.

Relationship between MRLs and antibiotic resistance

While the MRLs for antibiotics are not health standards themselves, they are set after an exhaustive examination of toxicity and therapeutic studies. In addition, some countries are proposing to include microbiological endpoint studies, where the MIC of the antibiotic on a defined bacterial population is used as a means of assessing safety and toxicity to establish an acceptable daily intake (ADI). In Australia, the ADI has, historically, been more influenced by toxicity studies than by MIC levels. Recently, the approach in the European Union and the Codex Alimentarius Commission has been to move from toxicological studies to a combination approach incorporating methodologies that measure antimicrobial endpoints.

Gathering evidence to determine whether or not antibiotic residues in food can modify the antibiotic-resistance profile of human gut flora is problematic. While the ADI is the standard approach to assessing the safety of residues in food, it is based on toxicological studies in laboratory animals and such studies are inappropriate for the antibiotic-resistance safety evaluation of veterinary antimicrobial drugs (Woodward 1998). For this latter purpose, methodologies with antimicrobial endpoints are preferred. Determining the MIC for a range of bacterial species that are representative of the human gastrointestinal tract is the current approach in the European Union and is being discussed in international fora such as Codex. Some aspects pertaining to the use of in

vitro MIC values for establishing MRLs for veterinary antibiotics, and which need to be understood as they relate to antibiotic resistance, are discussed below.

There are a number of confounding issues in the interpretation of microbiological endpoint studies. First, not all food-producing animals are treated with antibiotics and, of those that are, few will have tissue residues at the MRL. Secondly, degradation of residues associated with food processing and cooking may result in lower concentrations of microbiologically active residues in the prepared food. Thirdly, in vivo absorption, metabolism and dilution of antibiotic residues in the human gut may further lower the concentration of antibiotic in the lumen of the gastrointestinal tract that is available to come in contact with the gut flora. Distribution of bacterial flora in the human bowel in relation to these processes is another consideration (for a review, see Ilett et al 1990). Against this background, attempts to compare MRLs and MICs require careful evaluation as they may grossly oversimplify the complex biology involved.

Because of these complexities, the Center for Veterinary Medicine in the United States has adopted a pragmatic approach whereby a 'maximum safe concentration' of 1 ppm in the total adult diet of 1.5 kg per day permits an intake of 1.5 mg antimicrobial drug per day (0.025 mg/kg body weight).

In summary, considering all these issues JETACAR agrees that dietary consumption of microbiologically active residues of veterinary antibiotics is unlikely to be a major factor in the development of antibiotic resistance in humans, although definitive evidence for or against this position is not currently available.

9.2 The use of antibiotic-resistance markers in genetically modified plants

Antibiotic-resistance genes have been traditionally used to select genetically modified bacteria and plants in the laboratory, and these genes remain when the transgenic organisms are commercialised and released into the environment.

The question of risks associated with the use of such antibiotic-resistance marker genes and the possibility that they could transfer horizontally to bacteria and thence to pathogenic bacteria has been reviewed in the Australian context by Pittard (1997).

The majority of transgenic organisms to be released into the environment in the next 10 years will be plants. Many of these will contain copies of a resistance gene for the antibiotic kanamycin (an aminoglycoside). This kanamycin-resistance gene has plant gene sequences on either side to enable the regulating gene to be recognised and read by the plant cell machinery.

Generally, DNA and protein are broken down by the digestive processes of the stomach and small intestine. Even if any of the DNA gene sequence or its protein product survived digestion, it is unlikely to be incorporated into bacteria. Furthermore, if it was incorporated into a bacterial genome, it is unlikely to be translated and produce the phosphorylating enzyme that confers bacterial antibiotic resistance to the aminoglycoside family (neomycin phosphotransferase) because the gene sequence would not have the necessary bacterial promoters to initiate translation.

Bacterial resistance genes exist naturally at low frequency for most families of antibiotics derived from bacteria. In addition, the use of aminoglycoside antibiotics for many years in human and veterinary medicine means that this gene is already widely distributed in the gut bacterial microflora of many people, without widespread aminoglycoside-resistance transfer to medically important pathogens. That is, in most environments there

is no extreme selection pressure and advantage for bacteria containing the kanamycin-resistance gene. So even if, improbably, kanamycin resistance was transferred to an enteric bacterium in a person or animal, it would only join the small population of already kanamycin-resistant bacteria that in most circumstances do not have any selection advantage over the normal gut flora. It would therefore be of minimal consequence to human health.

In summary, the probability of transfer of kanamycin resistance from a transgenic plant to a bacterium in an animal intestine is extremely remote. If it did occur, it is highly unlikely that the gene could be translated by the bacteria, and any kanamycin-resistant bacteria so formed would be only one of millions of kanamycin-resistant bacteria already existing in the intestine without discernible effect.

Chapter 10
Monitoring and surveillance

OVERVIEW

To allow the analysis and strategic management of antibiotic resistance of bacteria on a ongoing basis, it is essential for Australia to develop internationally acceptable and scientifically defensible monitoring and surveillance programs for antibiotic usage. This should include:

- *monitoring* of the amounts and usage patterns; and
- *surveillance* of the trends in antibiotic resistance in human, animal and environmental bacteria.

Current data collection

Monitoring antibiotic consumption — some basic information on the amounts of antibiotics imported into Australia is collected by the Therapeutic Goods Administration and human uses are recorded under the Pharmaceutical Benefits Scheme. Veterinary and agricultural usage data are only available through pharmaceutical companies and are not systematically collected by species.

Surveillance of human antibiotic resistance — antibiotic resistance of bacteria isolated from medical sources is surveyed in a series of loosely connected programs established by a variety of interested groups. There is no overall coordination of these programs, but they form a good base for an integrated national program for surveillance of antibiotic resistance in bacteria of medical importance, and could be used to integrate animal and environmental survey program data into a national program.

Surveillance of veterinary and agricultural antibiotic resistance — there is no comprehensive national, coordinated or standardised collection and collation of animal or environmental antibiotic-resistance data. Currently, resistant bacteria are selected from the veterinary and medical areas on an ad hoc basis. Environmental isolates are infrequently included.

Future requirements

The accuracy and availability of antibiotic use information needs to be upgraded, with systematic collection of data for both humans and animals.

Statistically valid sampling and surveillance programs are needed with accredited laboratories using validated methods to measure the prevalence and degree of antibiotic resistance in defined bacterial species in humans and animals (and in particular environments such as groundwater).

10.1 Introduction

Monitoring and surveillance of any of a range of activities in the Australian federal system of government is not an easy exercise. In many areas the central (federal government) agency does not have the legislative power or resources to collect or coordinate information that usually resides in State or Territory government authorities or, increasingly, in the private sector. The effects of deregulation and implementation of user-pays philosophies of governments over the past 20 years means that new cooperative approaches have to be devised to gather this information. Implementation is

usually through a cooperative program negotiated with stakeholders. Funding is usually a key issue in this process.

This chapter describes the current programs for monitoring antibiotic use and surveying resistance in Australia, highlighting basic principles and philosophies that should be considered in the design of such programs, and provides a broad conceptual overview for specific recommendations in this area.

10.2 Current data collection programs

10.2.1 Antibiotic consumption and end-use statistics

The collection of data on antibiotic consumption in Australia has been described in Chapters 6 and 7. It is made up of the two major components — medical and veterinary use — and the primary responsibility for its collection and tabulation rests with the Commonwealth Department of Health and Aged Care (formerly the Department of Health and Family Services), through the Therapeutic Goods Administration (TGA).

The data have been subject to only limited scrutiny to date (Turnidge and Howard 1996 — see Chapter 7) but, with refinement of permit and reporting protocols, will be a core element of the monitoring and surveillance programs that Australia needs for the ongoing strategic management of antibiotic resistance in bacteria.

Medical antibiotic use in Australia was analysed by McManus et al (1997). The Commonwealth Department of Health and Aged Care, Pharmaceutical Benefits Branch, collates consumption data, although the collection has not been motivated primarily by resistance issues but by the need for financial management of the Pharmaceutical Benefits Scheme (PBS). Other sources of information are sales data, prescriber survey and specific projects. In this paper, a cooperative approach was used to calculate absolute amounts of medical antibiotics used, determine national use trends and compare medical antibiotic use in Australia with other countries (see Section 7.2.4).

10.2.2 Antibiotic resistance surveillance programs and studies

Antibiotic-resistance surveillance can be either *passive* or *active*. Passive surveillance is the collection of routine analytical data from diagnostic laboratories, whereas active surveillance involves a more intensive study of resistance directed at specific pathogens using carefully designed and statistically valid sampling programs. Both types provide essential information on the rates of resistance and their trends.

Human medicine

The impact of antibiotic resistance has always been greater in human medicine than in veterinary medicine for a variety of epidemiological reasons (Swann Report 1969). As a consequence, the medical profession has monitored antibiotic resistance since 1985.

Australian Group on Antimicrobial Resistance (AGAR)

AGAR is an active, prospective program that was started in 1985 to collect data on the antibiotic susceptibility of *Staphylococcus aureus* from 19 hospital laboratories across Australia. It now collects data on a range of medically important human infections in electronic form and prepares an annual report of its findings. It is resourced by the hospitals involved; Eli Lily Australia provides funds for twice-yearly meetings of the group. AGAR now has a website, has representatives from all States/Territories and involves over 40 microbiologists.

AGAR has demonstrated significant trends in resistance in *Staphylococcus aureus* (especially methicillin-resistant strains) (Turnidge et al 1989, 1996) and *Streptococcus pneumoniae* (Collignon and Bell 1992, 1996; Turnidge et al 1999) and slowly evolving resistances in *Escherichia coli* and *Klebsiella* spp. (AGAR unpublished data).

National Antimicrobial Resistance Surveillance Program (NARSP)

This program started in 1992. Bacterial isolates from 29 teaching and community hospitals and large private medical microbiological laboratories are collected, making this a passive and retrospective survey. All susceptibility data generated on all human bacterial pathogens, plus salmonella data from the National Enteric Pathogen Surveillance System, are collected as electronic or hard copy. This service requires the input of a full-time scientist, and computing facilities funded by the National Centre for Disease Control of the Department of Health and Aged Care. An annual printed summary is produced along with a national collation and analysis of vancomycin-resistant enterococci. Ad hoc queries are also serviced.

NARSP has been responsible for documenting resistance patterns for a broad range of human pathogens. There have been three formal published reports covering 1992, 1993 and 1994 (Turnidge and Bell 1994, 1995, 1996) and later reports are in preparation. Early trend data show some important evolving resistances. The output has proved invaluable for the regular updating of the antibiotic guidelines (Therapeutic Guidelines 1998).

NARSP has also assumed the responsibility for monitoring emergence and evolution of vancomycin-resistant enterococci (VRE) around Australia, including the development of confirmatory typing methods. Although this aspect has been voluntary, virtually every new instance of VRE has been recorded and the isolates confirmed at the reference laboratory (Bell et al 1998ab). A summary of the current status of VRE in Australia is provided in Appendix 6.

National Enteric Pathogen Surveillance System

The National Enteric Pathogen Surveillance System is located in the Microbiological Diagnostic Unit (MDU) of Melbourne University. This active and prospective program began in 1994, collecting isolates from referring laboratories around Victoria and some other parts of Australia. Data are filed electronically and reviewed annually and added to the NARSP data. The program requires a part-time scientist funded through the Victorian Department of Health. MDU also supports the project and provides computing facilities.

Other studies

A few Australian laboratories are also involved in other international and minor local programs shown in Table 10.1.

Application of resistance data

The antibiotic-resistance data so far collected have proved invaluable for formulating antibiotic use guidelines at a local, regional and national level. The data have been requested and utilised by State/Territory and federal governments and the pharmaceutical industry.

Table 10.1 Australian laboratory involvement in international and other local antibiotic-resistance monitoring studies

Project	Year	Target pathogen(s)	Australian laboratories
International programs			
Artemis	1997 onwards	Common respiratory pathogens	2 laboratories
BIOMIC study	1997–98	Routine laboratory isolates	2 laboratories
Global SMART (Western Pacific region)	1998	*Staphylococcus* spp. *Streptococcus* spp. *Streptococcus pneumoniae* *Enterococcus* spp.	5 laboratories in Australia and 8 regional laboratories
SARISA	1997	*Staphylococcus aureus*	2 hospital laboratories
SENTRY (Western Pacific region plus)	1998 onwards	Selected routine laboratory isolates	5 Australian and 8 regional laboratories
National programs			
Cefepime study	1998	Routine laboratory isolates	10 laboratories
DRSP	1997	*Streptococcus pneumoniae*	11 public and private laboratories
Grepafloxacin study	1998	Common respiratory pathogens and selected other routine laboratory isolates	7 laboratories

KEY TO PROJECTS

International

Artemis (1997 onwards) — testing of common respiratory pathogens against a range of common antibiotics (supported by Pfizer International).

BIOMIC study (1997 onwards) — testing of trovafloxacin and fluconazole against common bacteria and yeasts, respectively, using disc diffusion (supported by Pfizer International).

Global SMART (1998) — targeted and limited study of the activity of quinupristin/dalfopristin (streptogramins) against staphylococci and enterococci, compared to commonly tested agents using E-test, disc diffusion and broth microdilution.

SARISA (1997) — coordinated from Stats Serum Institut, Denmark.

SENTRY (1998 onwards) — part of an ongoing global study of community and hospital acquired pathogens. Isolates are forwarded from laboratories (540 per laboratory) to a regional coordinating laboratory. A broad range of drugs are tested by broth microdilution (MIC) (supported by Bristol-Myers Squibb International).

National

Cefepime Study (1998) — testing cefepime and suitable comparators against a range of hospital pathogens using agar dilution (supported by Bristol-Myers Australia).

DRSP (1997) — study of *Streptococcus pneumoniae* ; over 1000 isolates were tested against common respiratory antibiotics using E-test (supported by SmithKline Beecham, Australia).

Grepafloxacin study 1998 — study of common bacterial pathogens against grepafloxacin and comparators, especially respiratory pathogens.

Veterinary medicine

In contrast to human medicine, there has only been minimal antibiotic-resistance surveillance of veterinary isolates. Between 1976 and 1981, the Animal Health Committee oversaw a limited program testing antibiotic resistance in *E. coli* and salmonella from livestock species and *Staphylococcus aureus* from bovine mastitis (Frost and O'Boyle 1981, Murray et al 1986). Resources were withdrawn and no further formal surveillance has been undertaken.

Apart from salmonella and very limited numbers of *E. coli* collected on a voluntary basis by the National Enteric Pathogen Surveillance System, there is no system in place in Australia to systematically collect information on antibiotic sensitivity/resistance patterns in bacterial isolates from animals. This is also the case overseas and it was clear from the meeting organised by the World Health Organization (WHO) in Berlin (WHO 1997) that

few countries had monitoring or surveillance of antibiotic resistance in animal pathogens, let alone of enteric commensal bacteria, such as enterococci in animals. Veterinary isolates of salmonella have been covered in some salmonella monitoring programs in the United Kingdom. The United States Department of Agriculture only established a system for monitoring antibiotic sensitivity in animal isolates of salmonella in 1996, but this program does not currently include vancomycin/avoparcin sensitivity.

In Australia, government veterinary laboratories, university veterinary school laboratories, private sector veterinary laboratories and medical laboratories testing veterinary specimens, all carry out antibiotic sensitivity on clinically significant isolates from diagnostic specimens. However, these results do not include commensal organisms likely to be of interest in human medicine such as campylobacter and enterococci species. Many of these laboratories do have antibiotic sensitivity/resistance information stored in their laboratory records. However, this information would be difficult (and expensive) to retrieve because antibiotic-resistance data have not been specifically identified in data storage/retrieval systems. Furthermore, the data would be of limited value because of lack of standardisation of test methodologies.

While the antibiotic test panels used in veterinary laboratories usually cover most classes of antibiotics used in human medicine, there are likely to be some gaps. For example, there may be information on the sensitivity to fluoroquinolones of small animal isolates but no livestock data, as fluoroquinolones are not registered for use in food-producing animals. In addition, information would only cover antibiotics used therapeutically, with limited information on those used preventively and next to none on those used as growth promotants.

Careful consideration of the range of antibiotics used in antibiotic-resistance surveillance programs is needed to ensure that all relevant antibiotic-resistance trends, irrespective of whether they are of medical or veterinary origin, are able to be detected.

Some recent data on antibiotic resistance in animals in Australia are presented in Appendix 7.

10.2.3 Industry programs

Salmonella surveillance of processed chickens has been voluntarily undertaken for many years by major meat (broiler) poultry companies who have established minimum standards to ensure that a high standard of hygiene is maintained. The objectives of the industry are to prevent disease from entering farms through quarantine, to prevent infection of incoming flocks through cleanout and disinfection of sheds after each batch of birds, and to prevent infection with foodborne pathogens and residues harmful to humans. Chickens are sampled from each processing plant of member companies on a weekly basis and cultured in accordance with Australian Standards Association methods. Results show that in 1997 about 20% of carcases were positive. Of the salmonella isolates obtained in the last eight years, 70–90% were *S*. Sofia, which rarely causes food poisoning. Less than 2% of carcases were positive for *S*. Typhimurium, the most common cause of salmonella food poisoning in Australia.

10.3 Antibiotic resistance testing methods

10.3.1 Routine laboratory methods

Laboratory assays for antibiotic resistance fall into two main categories.

- *Quantitative* — minimum inhibitory concentration (MIC) determination using agar or broth dilution methods that produce a range of antibiotic concentrations to

determine the MIC. The endpoint is the first concentration that inhibits bacterial growth, usually measured by absence of turbidity (ie a quantitative result). These methods are not used for routine susceptibility testing, although they may be used to quantify the level of resistance in problem isolates. Generally, they serve as a reference for qualitative tests. An agar diffusion gradient strip method commercially known as the E-test™ is a version of this test.

- *Qualitative* — routine tests, including the dilution and disc diffusion methods described below, that produce qualitative rather than quantitative results. Bacteria are reported as susceptible or resistant according to defined 'breakpoints' that take into account the intrinsic activity of the antibiotic, its pharmacokinetics, and (usually) response to treatment in prospective clinical trials. Some methods also define an 'intermediate' category of susceptibility, which implies either response will be achieved with increased dosage or at body sites where the antibiotic is concentrated.

As there is no international standard method for susceptibility testing, a variety of methods are used in Australian medical laboratories, including:

- dilution techniques — manual (agar dilution breakpoint) or semi-automated broth (Vitek™, Microscan™, ATB™); and
- disc diffusion methods
  - modified Kirby-Bauer (usually as defined by the NCCLS; see below),
  - CDS (calibrated dichotomous sensitivity) (a locally developed method),
  - Stokes and comparative methods (falling into disuse).

The methods used in veterinary laboratories are variable but the most widely used are adaptations of the disc methods shown above. Some veterinary antibiotics have not been calibrated and thus have no agreed breakpoints in qualitative tests.

Dilution techniques involve the use of a limited number of concentrations of antibiotic (usually one to three) around the breakpoints for that organism–antibiotic. Like the MIC method, the category is defined by the presence or absence of visible growth at those concentrations. In the semi-automated methods, growth is measured 'continuously' by dedicated machine readers.

Disc methods involve the use of antibiotic-impregnated filter paper discs placed on agar plates seeded with the bacterium under test. Antibiotic diffuses through the agar and inhibits the growth of bacteria in a defined and measurable zone. The zone is usually calibrated against MIC values previously determined, and the zone ranges then define the susceptibility category (susceptible, [intermediate], resistant).

The diversity of methods is further complicated by the existence of different breakpoints with different methods. The breakpoints defined by the United States National Committee for Clinical Laboratory Standards (NCCLS) are the ones most frequently selected. The CDS disc method uses different breakpoints from those used by NCCLS.

The National Enteric Pathogen Surveillance Program uses the agar dilution breakpoint method, and breakpoints specifically designed to detect emerging resistances, which are often lower than those used for routine testing.

10.3.2 Sources of bacteria

The most important source of bacteria in the strategic management of this issue is hospital isolates of human commensal bacteria and pathogens. The antibiotic-resistance profiles and gene content of these organisms will measure the success or failure of any strategic management of this issue. Current medical surveillance and monitoring

programs have been developed on an ad hoc basis by groups of concerned medical scientists. Their concern has been reinforced by the detailed dissection of the bacterial genetics involved by molecular microbiologists working in the medical and other fields. However, the international concern, serious public health implications and potential international trade impact of this issue means that Australia will have to take a concerted multiprofessional and cross-sectoral approach in the design, monitoring and surveillance programs that will allow meaningful analysis and coordinated strategic management of this issue.

Existing sources of bacterial isolates

There are a number of minimal cost opportunities that might be used in the collection of bacterial isolates for antibiotic-resistance testing.

- *Medical* — there are huge numbers of bacteria isolated for diagnostic purposes in hospitals and public and private medical laboratories around Australia. The problem in monitoring and surveillance design is gaining access to significant and representative isolates in a manner that will give statistical meaning to emerging trends on analysis.
- *Veterinary* — in veterinary medicine the number of bacterial isolates is much smaller and restricted by economic factors. However, there are still opportunities to capture, at low cost, significant bacterial isolates from both public and private National Association of Testing Authorities (NATA)-accredited veterinary pathology laboratories.
- *Commercial microbiological testing* — for example, the poultry industry conducts regular product testing during production of the chickens or eggs. Microbiological testing is also conducted during processing of chicken carcases. If, with industry cooperation, meaningful sampling plans can be designed, then one of the major expenses of monitoring and surveillance will be minimised.
- *Export abattoir microbiological testing* — AQIS runs a microbiological sampling program to meet United States meat importation requirements. A limited range of organisms (*E. coli* and *Salmonella* spp.) are isolated and counted. However, this program offers a framework for low-cost sampling of cattle, sheep and pigs.
- *Environmental* — water quality testing is commonly undertaken for industry and State/Territory and local government regulatory purposes. This infrastructure could be used in sampling program design. In addition, groundwater sampling by environmental management and geological authorities includes bacteriological culture and sensitivity testing.

10.3.3 Targeted surveillance programs and projects

For the more targeted surveillance programs, more extensive and detailed methods for susceptibility testing are used. Many use an MIC testing method, such as microbroth dilution or so-called E-test® strips, which use an antibiotic gradient in a strip to generate an MIC by diffusion. Some programs employ methods similar to those used for routine testing but on a wider range of agents than would be tested routinely. This may be combined with the use of MIC tests on specific isolates.

10.3.4 Quality assurance

There are two types of quality assurance for susceptibility testing. All good standardised methods have quality control systems included and prescribed. In addition all medical testing laboratories are obliged through laboratory accreditation to participate in external quality assurance programs. This provides reassurance that results using different

methods are comparable, at least for the common pathogens. The proficiency testing program for susceptibility testing in medical pathology laboratories is run by the Royal College of Pathologists of Australasia (RCPA) and is called the RCPA Microbiology Quality Assurance Program (QAP). The program is operated from of the Microbiology Department at Royal North Shore Hospital, Sydney, but is a separate entity. Susceptibility testing performance in NATA-accredited medical microbiology laboratories is assessed eight times per year as part of the QAP. Feedback is provided on each assessment and on an annual summary basis. The results of this proficiency testing are examined by NATA at each laboratory re-accreditation.

For the last decade, government veterinary pathology laboratories have been participating in the Australian National Quality Assurance Program (ANQAP) funded by the Standing Committee on Agriculture and Resource Management (SCARM) Subcommittee on Animal Health Laboratory Standards (SCAHLS). Both government and private veterinary pathology laboratories participate in proficiency testing as part of NATA veterinary pathology laboratory accreditation. ANQAP currently does not have a susceptibility test proficiency testing component, but this mechanism, or the RCPA program, could be used to ensure satisfactory performance of veterinary pathology laboratories undertaking antibiotic-resistance testing for any program. This would ensure that results are comparable between laboratories involved in monitoring and surveillance programs.

10.4 Overseas monitoring and surveillance programs

10.4.1 Antibiotic consumption

Many developed countries have some systems in place for measuring prescription volumes of antibiotics for human use, but there is little information on volumes and targets for veterinary and agricultural antibiotic usage internationally. Some information can be obtained from the pharmaceutical firms, but much of this information is difficult to access due to commercial-in-confidence issues. In the medical sphere, one market research firm has access to prescribing data obtained through a structured sample program in many developed countries. This data is collected under commercial contract and not usually available in the public arena.

10.4.2 Antibiotic resistance

The development of resistance surveillance systems in other countries is very variable. For human pathogens, only a small number of countries have truly national programs. However, there is currently a strong push to establish global resistance surveillance through national organisations, following the recognition of the value of surveillance in determining the dimension of the problem and providing a barometer to measure effects of intervention. It is recognised that the Australian pharmaceutical industry has responsibilities and a legitimate interest in this area, and already is providing funding support, and so needs to be actively involved in any surveillance and strategic management programs that are developed. Most countries do not have veterinary monitoring programs for antibiotic resistance. Recently, through a joint initiative of the Centers for Disease Control, the Center for Veterinary Medicine of the Food and Drug Administration and the United States Department of Agriculture, the United States has established a surveillance program (NARM) of animal bacteria of human medical importance. Isolates are obtained mainly through 'HACCP' (hazards analysis critical control points) sampling. At the meeting in 1997, organised by the World Health Organization, it was recognised that surveillance of animal isolates was vital to understanding and control of resistance transfer through the food chain.

Chapter 11
Alternatives to antibiotic use in animals

OVERVIEW

There are two ways in which antibiotic use in animals can be reduced:

- improved animal health status, including disease eradication and infection control through hygienic animal husbandry measures, quality assurance, biosecurity and vaccination; and
- developing alternatives to antibiotics for promoting healthy, profitable growth and feed utilisation efficiency.

Improved animal health

Australia's excellent animal health status has minimised the commercial need for medication when compared with many other countries. Many diseases have been eradicated and Australian animals are free of some of the infections that have caused concern overseas (eg *Salmonella* Enteritidis in poultry, and *Salmonella* Typhimurium DT104). This health status is maintained through responsible animal product import programs, hygienic animal husbandry measures and increasingly through quality assurance programs developed with the individual industries (eg chicken meat, beef cattle and pigs).

At a national level, biosecurity measures to support animal husbandry and quality assurance programs include quarantine measures and disease monitoring and preparedness arrangements established between the federal government and the State and Territory governments. At a farm level, biosecurity includes all-in-all-out methods of production and other measures to quarantine animals and prevent introduction and spread of infection.

Australia's animal industries have been innovative in supporting the development of vaccines to prevent bacterial diseases. Effective vaccines are available for food-producing animals and are particularly important in intensively farmed poultry and pigs and feedlot cattle. It is hoped that the continued expansion of vaccination programs in future will lead to further reductions in antibiotic use in farm animals.

Alternatives to antibiotics for growth promotion

Alternatives to antibiotic growth promotants need to produce improvements in intestinal function similar to those seen for antibiotics, reflected by cost-effective growth rate and feed conversion efficiency. Interest has therefore centred around three main approaches: in-feed enzymes, competitive exclusion products/probiotics administered in feed or water and hygienic animal husbandry practices.

While all these approaches have some merit, none has as yet proved successful in replacing the use of antibiotics for growth promotion and these approaches require further research. Also, as the use of probiotics and competitive exclusion products involve the use of mixtures of gut bacteria, antibiotic resistance in these cultures would need to be monitored.

11.1 Improved animal health and food safety

Australia's excellent animal health status and good record in the eradication of diseases minimise the commercial need for medication when compared with many other countries. Eradication of contagious bovine pleuropneumonia, bovine brucellosis and bovine tuberculosis has been achieved, when few other countries have been successful. *Salmonella* Pullorum has been eradicated from commercial poultry flocks and Australian poultry remain free from *Salmonella* Enteritidis, although the organism has come to Australia in humans. *Salmonella* Typhimurium DT104 has not been detected in Australia.

11.1.1 Animal husbandry/infection control measures

Quality assurance systems, usually based on HACCP (hazards analysis critical control point) principles, have been promoted by industry organisations and have started to be used in some sectors (such as chicken meat and export-licensed abattoirs). The pig (Australian Pork Industry Quality (APIQ) program), poultry, sheep (FlockCare™) and cattle (CattleCare™) industries have some programs in place and further development is expected in future. In these systems, quality control begins on the farm and continues through production and processing to the supermarket door. Such systems require correct use of chemicals (including antibiotics) and involve keeping records of usage and withholding periods.

HACCP programs include education and training of food processors and handlers in hygiene procedures and in the importance of preventing cross-contamination of cooked chicken from raw chicken (foodborne pathogens are destroyed by cooking). They also address such issues as the reduction in faecal contamination of carcases.

Pigs

All-in-all-out system of production

In the past piggeries were established as continuous flow facilities. Sheds were continuously occupied with pigs of various ages and each week the oldest group of pigs was moved out and the youngest group moved in. Groups are normally formed from all the pigs weaned in a set time interval, usually a week.

Piggeries are modifying their facilities, wherever possible, to compartmentalise production. Each compartment is isolated as far as possible from other compartments and operates on an all-in-all-out basis. Each age group is isolated, reducing the level of exposure to pathogens.

The ideal all-in-all-out system incorporates multisite production. For example: 1000 pigs weaned (at three weeks of age) in one week are moved to an isolated weaner shed built to accommodate this group. When these pigs are 10 weeks old, they are moved to an isolated, vacated and cleaned shed which will accommodate the 1000 pigs in isolation until they are sold at 24 weeks of age.

Segregated early weaning (SEW)

A source of pathogens for the young piglet is the sow. Therefore, early weaning (at about 10 days of age) is used to reduce the opportunity for the piglet to become infected from the sow. The earlier piglets are weaned, the broader the range of pathogens that are eliminated. However, some pathogens will be transferred at low levels to some groups of pigs and there will be system failures from time to time. For this reason, the SEW system is best used in conjunction with multisite production so that the adverse effect of infection is restricted to the particular group of pigs.

When associated with multisite production, SEW offers a system whereby antibiotic requirements are significantly reduced. However, some groups of pigs still require therapeutic antibiotic usage because of failures, as described previously, while some diseases (eg proliferative enteritis) are not eliminated by this management system and require antibiotic prophylaxis.

Effective use of SEW and multisite production requires a critical mass of pigs. The Pig Research and Development Corporation (PRDC) has produced a manual to facilitate adoption of this practice (Cargill et al 1997) and is encouraging smaller producers to form networks to provide an effective herd size suitable for this approach.

Specific pathogen-free (SPF) pigs

SPF pigs were originally derived by hysterectomy, hand-reared and isolated from other pigs. They are free from many of the diseases that require antibiotic intervention, most significantly the respiratory diseases.

Only about 10% of the Australian pig industry is SPF. Conversion of an established herd to SPF requires total depopulation and subsequent repopulation with SPF pigs. This is a very costly exercise because of the necessary reduced production during the changeover process. There is also the risk of re-introduction of disease to the SPF population.

SPF herds still require antibiotics to treat and/or prevent diseases not eliminated by this process. Important diseases in this category are enterotoxigenic *Escherichia coli* infections and proliferative enteritis (*Lawsonia intracellularis*).

Vaccination

Vaccines are currently used to reduce disease caused by enterotoxigenic *E. coli* in piglets by vaccinating the sow, and in weaners by immunisation before weaning. However, diarrhoea still occurs on occasions.

A vaccine is available for prevention of erysipelas (caused by *Erysipelothrix rhusiopathiae*) and is used in piggeries where erysipelas is a persistent problem.

A vaccine has recently been released in Australia for control of *Mycoplasma* infection. This vaccine reduces the requirement for therapy and prophylactic use of antibiotics. However, overseas experience indicates that it produces only partial protection. A vaccine is also available for preventing plueropneumonia (*Actinobacillus pleuropneumoniae*) but the level of protection is very variable.

Vaccine research, including for proliferative enteritis, has been actively supported by the pig industry levies through the PRDC for many years.

Poultry

Poultry production

Chicken and turkey meat production companies are usually vertically integrated. That is, the company owns feed-mills, livestock production systems, processing plants and sales/distribution networks. This gives poultry meat companies comprehensive control over all processes up to the point of sale of poultry meat products. Twelve poultry companies produce 95% of Australia's chicken meat and five companies produce almost all of Australia's turkey meat. Poultry companies employ veterinarians to develop and manage flock health programs that include the responsible use of antibiotics.

Typically, chicken meat production is an all-in all-out single-age broiler farm system, with collection of birds for processing at between five and seven weeks of age. Rations usually consist of starter feed for about 2.5 weeks, grower feed for one week, finisher feed for

one week and withdrawal feed subsequently until pick-up for processing. Coccidiostats to control coccidiosis (caused by the protozoan parasite *Eimeria*) and antibiotic growth promotants, used mainly for the control of necrotic enteritis (*Clostridium perfringens*), are usually included in the first three rations.

Industry standards

Very high standards of hygiene are already routine for chicken meat production in Australia, with poultry companies adhering to in-house minimum standards.

These standards are in the process of being translated into HACCP or process-control plans. Poultry meat is already processed in accordance with HACCP programs based on the *Australian Standard for Hygienic Production of Poultry Meat for Human Consumption:* AS 4465:1997 (ARMCANZ 1997). Retailers have recently established HACCP-based quality assurance programs in response to the Australia New Zealand Food Authority (ANZFA) initiative in promotion of National Food Hygiene Standards (ANZFA 1996).

Hygienic measures (eg shed/equipment disinfection, water sanitation, heat treatment of feed, personnel hygiene, rodent control and wild bird control) minimise infection and spread of foodborne pathogens.

Vaccination

Many successful vaccines have been developed and used in the poultry industry to minimise disease; for example, fowl cholera (*Pasteurella multocida*), poultry coryza *(Haemophilus paragallinarum),* erysipelas *(Erysipelothrix rhusiopathiae*), duck infectious serositis (*Riemerella anatipestifer*), salmonellosis (*Salmonella* Typhimurium) and chronic respiratory disease of poultry (*Mycoplasma gallisepticum*).

Salmonella vaccines developed in Australia and overseas are likely to be used for the control of salmonella infections as these vaccines become commercially available.

Control of campylobacter

To date, there is insufficient knowledge to prevent campylobacter infecting poultry. Hygienic measures in livestock production and processing are needed to limit the degree of contamination of poultry meat. The Chicken Meat Research and Development Committee of the Rural Industry Research and Development Corporation has supported a number of research projects to learn more about this infection of poultry and how it can be controlled.

Other research

Feeding regimes that influence the presence of certain bacteria in the gastrointestinal tract of animals are being researched in a number of countries. There is some evidence that modifying feed ingredients can reduce, if not eliminate, certain food poisoning bacteria from the gut of cattle and sheep.

11.1.2 Biosecurity

At a national level, animal quarantine policy and practice support the excellent animal disease status in Australia. In addition, a responsible animal and animal product import policy is maintained in Australia in accordance with rules negotiated under the General Agreement on Tariffs and Trade (GATT) Uruguay Round of Talks. In addition, disease monitoring and preparedness arrangements (the Australian Veterinary Emergency Plan, or AUSVETPLAN) have been established between the federal and State/Territory primary industries departments.

Consideration should be given in Australian quarantine policy and the Australian Quarantine and Inspection Service (AQIS) Imported Foods Program to the development of measures to prevent the entry of antibiotic-resistant exotic foodborne pathogens in animal and plant products. Currently such measures are largely directed to animal and plant diseases. Such action would require careful consideration in the context of the Sanitary and Phytosanitary Agreement of the World Trade Organization. In this context, it is worth noting that Japan and France will not allow imports of poultry meat from Thailand because of the risk of introducing vancomycin-resistant enterococci (VRE).

At the farm level, biosecurity systems are particularly important in the pig and poultry industries. Breeding animals are, in effect, in lifetime quarantine in order to prevent entry of disease organisms. Security measures are physical and procedural, such as showering and changing clothing before entry of authorised personnel. Commercial production farms for these species generally have restricted access for humans, and no access for other animals. These species are housed, and poultry facilities in particular are enclosed, so as to prevent contact with free-flying birds.

All-in-all-out systems, under which animals in a cohort group enter and leave the premises at the same time, facilitate disease control. For poultry, biosecurity standard procedures to prevent entry of disease to farms are through quarantine, and prevention of infection of incoming flocks by shed cleanout and disinfection after each batch.

To date, poultry meat has not been imported into Australia, thus protecting Australian consumers from infection by overseas antibiotic-resistant foodborne pathogens or antibiotic-resistance genes from this source. Pig meat has been imported from Canada since 1990, but there is a quarantine requirement that it be cooked in Canada or before release in Australia to prevent the entry of certain pig diseases.

11.2 Alternatives to antibiotics as growth promotants

The benefits from growth promotion result from alterations in the intestinal microflora, improving intestinal function (see Chapter 8). To reproduce these benefits, therefore, a system is required that would produce similar changes in the intestinal microflora and/or improvement in intestinal function. Interest has therefore centred around three main approaches: in-feed enzymes, competitive exclusion products/probiotics administered in feed or water and hygienic animal husbandry practices.

11.2.1 Enzymes

Enzymes are added to poultry and pig feeds to improve digestion of the chemical components of grains and meals. These chemical components include non-starch polysaccharides (eg arabinoxylans and beta-glucans), phytates and proteins. These in-feed enzymes usually have activities absent in the animals and birds and improve performance by digesting feed components that are otherwise undigested or poorly digested. Feed enzymes are produced by fermentation of fungi and bacteria and are stabilised for addition to feeds. Feed enzymes have been used routinely in broiler feeds in Australia for many years, particularly in wheat and barley-based feeds.

There is ongoing research to improve feed enzymes and to provide enzymes for a wider range of feed ingredients.

11.2.2 Probiotics (direct fed microbials)

Probiotics (or 'direct fed microbials', as they are called in the Agvet Code) are used in human and animal health and defined in various ways. Fuller (1989) defined probiotics as

a live microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance. Although probiotics have some strong supporters, in general, it appears that the animal production sector of the scientific community is sceptical about their use, reflecting the considerable and variable literature on the topic.

There is evidence of both beneficial effects (Pollmann et al 1980) and ill-effects (Cupere et al 1992) of probiotics used for growth promotion. Age at treatment (eg preweaned versus postweaned) and environmental effects may affect the outcome. There are also calls for standardisation and quality assurance in manufacture of these products (Ingkaninum 1994, Chesson 1995).

The way that probiotics work is not clearly established. Various proposals include:

- influence on intestinal metabolic activities (production of propionic acid, bacteriocins, vitamin B12, promotion of villous length and absorption);
- promoting resistance to colonisation (competitive exclusion of pathogenic microorganisms); and
- immune stimulation (Veld et al 1994).

The National Registration Authority (NRA) registers several probiotics as 'direct feed microbials', which is the official definition covering microbial-containing products administered to animals. Where specific claims are made, manufacturers have to produce evidence of efficacy, safety of use, and fitness for purpose before NRA can register the product. However, most manufacturers of probiotics do not make specific claims, although the manufacturers of several probiotics have provided information on efficacy, composition and manufacture that satisfy registration requirements. These are unrestricted products and available over the counter without prescription.

Overall, research and use in the poultry industry (including in Australia) have not provided convincing evidence of the benefits of probiotics in controlling pathogens or for economic improvement.

A variety of microorganisms are used in the formulation of probiotics, including *Enterococcus faecium,* lactobacilli and lactococci, which may be of concern with respect to antibiotic resistance (eg vancomycin resistance). The antimicrobial-resistance patterns of the flora, and the presence of resistance plasmids in probiotic preparations should perhaps be monitored as a registration requirement.

11.2.3 Competitive exclusion products

Competitive exclusion products have been developed overseas (eg Broilact™, Avigard™ and Preempt™). They include many species (up to 30) of undefined or partially defined bacteria isolated from the gastrointestinal tract of the animal species in which they are used. They are often used to colonise the gastrointestinal tracts of newborn animals and poultry with 'beneficial bacteria' which are reported to be helpful in preventing colonisation of 'harmful bacteria' such as salmonella. Competitive exclusion products have also been used overseas to repopulate the gastrointestinal tract with 'beneficial' bacteria following short-term therapeutic treatment of poultry with bacteriocidal antibiotics such as fluoroquinolones. Products examined to date have not been able to meet Australian quarantine requirements because the bacteria contained in the cultures are not fully defined.

11.3 Swedish animal production system

In 1985, the Swedish parliament passed the 'Feedingstuffs Act' imposing a ban on antibiotic growth promotants. This ban came into force on 1 January 1986. Since that time, all antibiotics fed to animals have had to be prescribed by a veterinarian and antibiotics can be incorporated into animal feed only to prevent, alleviate or cure a disease, or for similar purposes (ie not for growth promotion).

Since the ban, the total animal consumption of antibiotics in Sweden has dropped by 50%. After a transitional period, the growth promotants that were used in substantial quantities before 1986 disappeared from the market, or were registered as pharmaceutical specialties for therapeutic use. Sales of narrow-spectrum penicillins increased continuously during the years 1980–94 and they now represent the main group of substances used. As penicillin is the first choice for the treatment of mastitis in dairy cows, it is assumed that this is now the predominant use (CAFA 1997).

11.3.1 Effects of the ban on animal production

No major problems were reported after discontinuation of the use of antibiotics in the case of calves, fattening pigs and turkeys. The production of laying hens was also not affected by the ban. Problems did arise, however, in the production of meat chickens and weaner pigs.

Meat chickens

For two years after the ban, about the same quantities of antibiotics continued to be used for meat chickens as before the ban. This was mainly virginiamycin for the control of necrotic enteritis. Great efforts were made to establish new feeding practices and improve the rearing environment. During the third year, the prophylactic use of antibiotics was gradually reduced and replaced with a two-day treatment with penicillin in the drinking water in the event of an outbreak. Continued use of ionophore coccidiostats (polyether antibiotics) have also helped to prevent necrotic enteritis.

Weaner pigs

Before the ban practically all weaner pigs were given olaquindox or carbadox from weaning until 10–12 weeks. Slaughter pigs were given avoparcin and virginiamycin until slaughter. After the ban, the percentage of weaner pigs treated with antibiotics dropped in the first year from 100% to 12% but postweaning diarrhoea increased and there was a 1.5% increase in mortality, while the time to reach 25 kg increased by 5–6 days. This initially made it necessary to increase the incorporation of antibiotics at therapeutic doses in the feed. Great efforts were made to improve housing, partition livestock buildings and introduce planned batch rearing systems and improved hygiene in general. Animal feed was also modified. By 1993, the use of antibiotics was reduced by almost a half. Subsequently, there have been further reductions, mainly due to the addition of zinc oxide to feed to counteract disturbances in the pigs' intestines for up to 14 days after weaning. In 1995–96, only 11% of weaner pigs were treated with antibiotics in their feed.

Zinc oxide has a preventative effect on weaning diarrhoea equal to the effect of using olaquindox. However, the use of zinc in this way is not without problems and the long-term environmental impact, including coselection of antibiotic resistance, of its use is under debate. The Swedish Board of Agriculture is currently considering phasing out its use.

The ban stimulated the development of new rearing systems, eg weaning of piglets on deep litter in large groups, and the 'birth-to-slaughter' system, which involves production

in the same pen from birth to slaughter. As more units change over to these systems, the use of antibiotics in order to combat weaning diarrhoea is reduced.

In some cases, addition of enzymes, probiotics, mineral organic salts, oligosaccharides, fibre products and plant extracts have been reported to have helped to reduce the dependence on antibiotics.

Costs

A critical consideration of the Swedish system is the effect on the cost of production. Some alternatives will be revenue neutral and some may add to the cost of production. In Sweden, it is claimed that production costs are only slightly higher than costs in countries where growth promotants are used (Swedish Ministry of Agriculture, Food and Fisheries 1997; see Section 8.2.1).

11.3.2 Environmental aspects

An advantage of growth promotant antibiotics is that the amount of feed consumed is less and therefore excretion is also reduced, with consequent reduced nitrogen and phosphorus emissions to the environment. However, since the introduction of the ban in Sweden, the protein content of both pig and broiler feed has been reduced in an attempt to reduce intestinal disturbances. This also had the effect of lowering nitrogen excretion.

Supplementation of feed with enzymes and probiotics also aims to reduce feed consumption by increasing intestinal absorption of nutrients.

11.4 Market advantage of food produced without antibiotics

11.4.1 Introduction

A market exists for the production of organically grown commodities, such as fruit and vegetables, herbs, dairy and meat products, grains, wool and cotton. Some authorities put the market potential for organic produce at 10% of production (Lovisolo 1993). Such produce is grown using the National Standard for Organic and Biodynamic Produce formulated by the Organic Produce Advisory Committee (OPAC 1998). To be a registered organic producer, farmers must undertake to meet certain production and record keeping criteria as specified by the National Standard (OPAC 1998). This process of accreditation usually has about a three-year lag time to allow for the decay of conventional agricultural chemicals and fertilisers from the farm environment. Registered organic producers are subject to audit, and their produce is also expected to meet all the food regulations applying to 'normal' produce. Organically grown food, for example beef, is subjected to the same chemical residue, meat inspection and hygiene regulation as conventionally produced beef.

11.4.2 Background to organic food production

While the bulk of the organic foods produced are fruit, vegetables and grain, the original 'organic' produce was what was described at the time as 'free-range' eggs. The consumer perception was that 'free-range' eggs were produced without recourse to artificial chemicals, battery cages and intensive production techniques. However, the organically produced label has, since the early 1990s, been developed and refined to the point that 'organic' now has a precise and defined meaning in egg production. Consequently, not all 'free-range' eggs are organically produced, which would involve a comprehensive commitment to the organic methods for all phases of production, including housing, feed, water and animal husbandry and packaging. The production of organic eggs, like all

organic produce, requires very good management to avoid disease and production limiting problems. Usually, unit production costs are higher than conventional production methods so profit margins are not high and organic produce, as a consequence, carries a premium price. This applies to all organically produced food, and particularly to animal products.

11.4.3 Marketing of organic produce

A variety of markets exist, ranging from specialty health food shops, special sections of city fresh produce markets, supermarkets and Sunday market stalls. Marketing studies show that some consumers are prepared to pay a 30–40% premium for organically produced foods (Hudson 1996). Export markets for organic produce require certification by either AQIS or AQIS-accredited industry organisations to meet trading partner requirements, specifically the Export Control (Organic Products Certificate) Order (OPAC 1998). Volume market outlets, such as the big supermarket chains, some of which have organic food sections, require continuity of supply and demand assured quality. These are difficult to provide consistently in animals and crops raised under extensive conditions, and even more difficult using organic production methods, but the quality of organically produced food is improving due to these market forces.

11.4.4 Animal production

Extensively raised animals can be produced with minimal chemical use, particularly sheep, poultry and cattle. Some prophylaxis or treatment for parasites or infectious disease control may be required. The National Standard for Organic and Bio-Dynamic Produce lists the treatments and processes that can be used in 'organic' food production. Registered treatments, such as antibiotics, are not excluded if their use is necessary. However, the use of antibiotics must be recorded and the individual animals or groups concerned lose their organic production status and cannot be sold as organic produce. Another issue is the problem of disease and animal welfare. Modern society is acutely aware of animal welfare and the role of disease in pain and suffering in animals. Withholding effective treatments in the face of disease is seen as an animal welfare issue in the National Standard.

11.4.5 Economic surveys

The economic data are limited and dated. The economic advantages of organic production depend on the enterprise. In a 1989 study in southern Australia (Wyen 1996), no significant differences in returns between conventional and organic cereal and livestock (wheat/sheep) production systems were found. However, a second study of irrigated dairying enterprises in 1994 showed that conventional producers did better financially than their organic counterparts because of increased production (Wyen 1996).

11.4.6 Antibiotic resistance as an issue of public concern.

The general public is not currently as aware of the antibiotic resistance debate as it is of other public health matters such as childhood vaccination and the associated risks. If the public health issues of antibiotic use in animals are widely debated and antibiotic resistance in animal-derived bacteria becomes a major issue, it can be expected that, despite the price differential, consumer demand for organic food will increase, possibly exceeding the 10% demand predicted (Lovisolo 1993). For the majority of consumers, however, price remains the most important decision factor in purchase, assuming safety and quality are equal.

11.4.7 Conclusions

The key factor in the production of antibiotic-free animal produce is the market potential and support for the premium prices necessary for this type of production. Currently, this does not exist to the degree that would encourage large numbers of conventional producers to register and invest in organic production systems in dairy, beef feedlot and pig meat production. Significant and expanding markets do exist for extensively produced (grass-fed) lamb and beef where, with good management, antibiotic use is minimal or zero. It is also possible for markets wanting specifically antibiotic-free meat to be developed through conventional producers using the vendor declaration processes without the need for adherence to the National Standard for Organic and Biodynamic Produce.

Chapter 12
JETACAR assessment overview and management strategy for antibiotic use

Overview

Hazard identification and characterisation

JETACAR has reviewed the hazards of antibiotic use in food-producing animals and the potential for serious effects on human health using a broad qualitative framework of risk analysis based on internationally accepted methods. Through a process of hazard characterisation and the commissioning of a scientific literature review, JETACAR concluded that there is a hazard to food safety and human health, which must be weighed against the value of antibiotics to veterinary medicine, food productivity and animal welfare.

Resistance management program

A resistance management program is proposed that incorporates the necessarily multidisciplinary nature of antibiotic use and resistance issues. Its elements are regulatory controls (veterinary and human), monitoring and surveillance (antibiotic use and resistance), infection prevention strategies, education and research.

Communication

Measures to ensure that stakeholders and the public are actively informed and continue to participate in the resistance management program are proposed.

Coordination of the resistance management program

A recommendation is made to consolidate the Working Party on Antibiotics so that it may take on the coordinating role for management of antibiotic resistance in Australia.

12.1 Hazard identification and characterisation

As outlined in Chapter 2, JETACAR has collected relevant international and Australian information and evaluated the available evidence in order to identify and characterise the hazard posed by antibiotic use in food-producing animals. Although JETACAR was guided by a risk analysis framework, a formal risk assessment, such as that suggested for microbiological risks in food (Lammerding 1997), was not possible because of the complexities of antibiotic resistance and the absence of specific information, such as the prevalence of antibiotic-resistant bacteria and frequency of the organisms of interest in animal flora.

The JETACAR assessment involved identifying and characterising the potential adverse health effects of the use of antibiotics in food-producing animals (the hazard). This was done by reviewing the scientific evidence for the relationship between antibiotic use in

food producing animals, the emergence of antibiotic-resistant bacteria in animals, the spread of these bacteria or their antibiotic-resistance genes to human bacteria and the occurrence of clinical disease in humans involving antibiotic-resistant bacteria.

It should be noted that most risk assessment protocols have been developed to assess risks associated with individual chemical or biological agents, where the risk of an adverse effect is directly related to a dose–response relationship for a single agent. In these cases, after a hazard has been identified and characterised, the risk can be characterised by assessing the likely exposure to the agent concerned. The issue of antibiotic resistance considered in this review is fundamentally different, however, with many stages having no direct relationship between dose and resistance (eg long-term low-dose use versus short-term high-dose use). However, the main 'exposure' factors in emergence and spread/transfer of antibiotic-resistant bacteria/resistance genes have been identified (see Section 12.1.2) and these can be used for designing a qualitative risk assessment method in the future.

Also, as different antibiotics have different modes of action, therapeutic doses and resistance mechanisms, only a broad interpretation was possible in an overall review such as this. A qualitative risk assessment method, when developed, will need to be applied on a case-by-case basis for individual antibiotic–bacterium combinations.

12.1.1 Scientific background, controls and usage data

In line with JETACAR's terms of reference (see Section 1.2.1), the committee first reviewed internationally available information on the nature of antibiotics, and the molecular basis of bacterial resistance. The bacteria most likely to be involved in transfer from food-producing animals, and those recognised as the cause of the medical conditions of most concern in relation to treatment failure due to antibiotic resistance, were also identified. Focusing on Australian information, the committee then reviewed current regulatory controls and use patterns of antibiotics in humans and animals. The broad conclusions from these studies are shown in Table 12.1.

12.1.2 Hazard identification and characterisation

Humans can acquire antibiotic-resistant bacteria by:

- the spread of antibiotic-resistant pathogenic or commensal bacteria between humans in the community or in hospitals through
  - the food chain (food handlers),
  - the environment (eg water contamination),
  - direct contact between humans, or
  - spread by health care workers;

- the spread of antibiotic-resistant zoonotic or commensal bacteria from animals to humans through:
  - the food chain,
  - the environment (eg water contamination), or
  - direct contact with animals;

- the transfer of resistance genes to human commensal bacteria or pathogens from:
  - normal flora, or
  - organisms spread as shown above.

Table 12.1 Antibiotic use in food-producing animals — scientific background, regulatory controls and usage data

Issue	Findings
Antibiotics and antibiotic resistance	Antibiotics are chemical agents that kill or inhibit the growth of bacteria. In response to antibiotic use, resistance has emerged for all known antibiotics. For most antibiotics, and classes of antibiotics, antibiotic-resistance genes have also entered the bacterial population in the domains where antibiotics are used (eg hospitals, farms, poultry-rearing facilities, aquaculture ponds). Resistant bacteria and the resistance genes they carry are selectively amplified by antibiotic exposure. This increases the prevalence of resistant bacteria in the total bacterial population, and large pools of resistant bacteria and resistance genes are built up where formerly they were rare. Clearly, long-term exposure to and treatment of large numbers of humans or animals provides greater selective pressure than short-course treatment of a single individual or small number of individuals. Resistant bacteria are then able to spread from one host to another (human to human, animal to animal, animal to human), by direct contact or, in the case of bacteria of animal origin, via the food chain. Resistant bacteria and resistance genes also spread anywhere in the world, making antibiotic resistance an international issue.
Bacteria	
• Salmonellae and campylobacters	These are zoonotic bacteria that spread easily between animals and humans in contaminated food (mainly meat, eggs, milk) and water, or by direct contact (including faeces). They may be carried asymptomatically by humans or animals. Thermophilic campylobacters (*C. jejuni* and *C. coli*) are rarely pathogenic in animals but nontyphoid salmonellae are an important cause of enteritis (and more generalised infections) in animals. They are two of the most commonly notified causes of bacterial 'food poisoning' (gastroenteritis) in people in Western countries. Occasionally other more serious invasive infections or septicaemia occur. Some strains may colonise animals or humans over the longer term but most are transient infectious agents. Overseas (UK, Europe, US), a multiresistant strain of *Salmonella* Typhimurium DT104, which was first isolated from cattle, has become more prevalent in the last 10 years.
• *E. coli* and enterococci	These are common commensal bacteria in animals and humans. They can be spread from animals to humans in food and water or by contact and may colonise transiently. However, there are strain differences between long-term colonisers of animals and humans. Although usually harmless, these bacteria sometimes cause serious urinary, abdominal, bloodstream and gastrointestinal infections in surgical or immunocompromised patients. Some enterococci (which are naturally multiresistant) have acquired resistance to vancomycin (VRE) and are now difficult to treat with any antibiotics. In the last five years, the prevalence of VRE has rapidly increased in the US, Europe and other countries. To date there have been 71 strains or clusters of strains isolated from humans in Australia and the numbers are steadily increasing.
Regulatory controls	Australia has strict registration procedures for veterinary antibiotics that include a special evaluation requirement for antibiotic-resistance data. This has resulted in the prohibition or severe limitation of use of some antibiotics in food-producing animals (eg fluoroquinolones, cephalosporins, gentamicin, chloramphenicol, nitrofurans, and carbadox). However, importers, and feed-millers are not licensed and there is no clear chain of audit for antibiotics supplied to feed-millers or home-mixers as registered products. Moreover, animal health, veterinary practitioner and agriculture legislation varies between States/Territories allowing registered products in some States to be used 'off label' in different animal species, or at different doses, from those assessed for registration. At present a number of antibiotics used in animal husbandry are available as 'open sellers'. These antibiotics are purchased and used by farmers, often without the intervention of a veterinarian. Most of the antibiotics with growth promotant claims are open sellers.
Use patterns	
• Antibiotic uses and quantities	On average, Australia imports about 700 tonnes of antibiotics each year. About one-third is for human and two-thirds is for veterinary use, with the majority for addition to stockfeed for prophylactic or growth promotant purposes.
• Administration and dosage – humans	Most antibiotics are given for treatment of minor infectious illness. As prescription is usually on an empirical basis, agents with broader spectra that might otherwise be needed are frequently selected. Much treatment, especially for respiratory tract infection, is unnecessary. However, rapid and effective treatment is essential in some serious infections (eg heart, blood or bone infections). In these cases, infection with antibiotic-resistant bacteria can be life-threatening. Occasionally, antibiotics are given to groups of people as prevention against an infectious epidemic. Individual prophylactic use is also quite common, particularly in hospitals, as prevention against infection (eg after bowel cancer or hip replacement surgery). Long-term treatment at subtherapeutic doses is less common.

Table 12.1 (contd)

Issue	Findings
– animals	For extensively grazed livestock and pets, treatment is on a similar basis to humans. For most intensively farmed food-producing animals (eg chickens, pigs, feedlot cattle), however, antibiotics are more often given to groups of animals within a herd/flock in feed or water, either as treatment for an outbreak of infection or as prophylaxis against common life-threatening or production-threatening infections. Antibiotic supplements at subtherapeutic doses are commonly added to feed to increase growth and reduce feed requirements (growth promotion).
Benefits of antibiotic use in animals	
• Therapeutic/ prophylactic use	Veterinary requirements for the treatment of established infections are similar to those of human medicine for reasons of animal welfare and disease control. There are also a number of diseases that are prevalent in the intensive industries that pose a threat to animal welfare and productivity. Prophylactic antibiotics have traditionally played an important role in the latter situation.
• Growth promotion	The economic benefits of antibiotics that promote growth and reduce feed requirements in intensive food-producing production were substantial at the time of their introduction 30 years ago. With major advances in animal husbandry, genetics, disease control and nutrition, growth promotants are now only one of the means of improving productivity. Some 'growth promotants' registered in Australia have other roles (eg prophylaxis, coccidiostats) in some species and their growth promotion benefit is less important.
International perspective	
• Therapeutic/ prophylactic use	There is current international focus on the therapeutic use of fluoroquinolones in food-producing animals. They are used therapeutically in pets and food-producing animals in many countries (but are only registered for use in cats and dogs in Australia). The emergence of fluoroquinolone resistance in campylobacter isolated from human infections in The Netherlands raised the suspicion of an association with food-producing animals. In the United States, and in the light of the above information, two agents were recently licensed for poultry and cattle use and there is intensive surveillance being undertaken for resistance emergence as a condition of licensing. The issue was recently discussed at a meeting organised by WHO in 1998, where it was agreed that there was an urgent need to develop prudent use principles for antibiotic use in food-producing animals, to curb the indiscriminate use of fluoroquinolones. Fluoroquinolones are not registered for use in food-producing animals in Australia.
• Growth promotion	With the emergence of VRE and their possible link to avoparcin in food-producing animals, there has been intensive international debate about the role of growth promotants, culminating in a WHO meeting in Berlin in 1997, which recommended the 'termination' of growth promotants with human health implications. Sweden stopped using growth promotants in 1986 and has been seeking to maintain this status within the European Union. It claims that reduced antibiotic use in food-producing animals and long-term benefits have resulted from its policies. However, no data showing a positive benefit of lower levels of resistance in humans have yet been produced by Sweden. Meanwhile, in Europe, a two-year suspension was placed on avoparcin in 1997. However, in response to further lobbying and scientific assessment, four other growth promotants (virginiamycin, tylosin, spiramycin and bacitracin) have been suspended in Europe from January 1999 and the avoparcin suspension has been extended. In the United States and Canada, avoparcin has never been licensed and all growth promotants are now receiving scrutiny.

Selection of resistant pathogenic or commensal bacteria during antibiotic treatment, prophylaxis, or other antibiotic exposure in either humans or animals can greatly amplify the number of resistant bacteria present.

Exposure through the food chain arises from bacterial contamination of food that is uncooked (eg salads), is not adequately cooked or is recontaminated following cooking. The widespread nature of antibiotic-resistant bacteria allows the food from many sources to be contaminated. However, the transfer of antibiotic-resistant bacteria along the meat chain is believed to be the most significant source of antibiotic-resistant bacteria spread from animals to humans.

International travel and the increasing international trade in food enables bacteria to be spread between nations and continents, and introduced into new environments. This

feature means that there has to be international coordination as well as national action to control antibiotic resistance.

The use of antibiotics in food-producing animals may cause health problems for humans because antibiotic-resistant animal bacteria may infect humans directly and/or transfer their resistance genes to human pathogens, causing subsequent failure of treatment for serious infections.

Spread of antibiotic-resistant bacteria from animals to humans

To assess the scientific basis for the spread and transfer of antibiotic resistance from animals to humans, a review of the international scientific literature was commissioned against critical steps involved (see Section 2.4.1 and Figure 2.2). The literature review's general conclusions were shown in full in Chapter 5 (Box 5.1).The findings of the assessment for each stage are shown in Table 12.2.

Table 12.2 Summary of evidence for the spread of antibiotic resistance from animals to humans as a result of antibiotic use in food-producing animals

Stage in spread of resistance	Answers to questions by bacteria and resistances (including modified level of evidence[a])								
	Enterococci				Gram-negative zoonotic bacteria				*Median for each question*
	Glycopeptides (*vanA* but not *vanB*)	Macrolides	Streptogramins	Oligosaccharides[b] (orthosomycins)	Streptothricins[b]	Aminoglycosides (one gene – AAC(3)-IV)	Quinolones[c]	Multiple resistance in salmonellae	
1. Does resistance emerge in animal bacteria following antibiotic exposure?	yes (III-2)	yes (II)	yes (III-2)	yes (IV)	yes (III-2)	yes (III-2)	yes (II)	yes (III-3)	III-2
2. Do resistant bacteria from animals spread to humans?	yes (III-2)	yes (III-2)	yes (IV)	ns	yes (III-3)	yes (IV)	yes (III-2)	yes (III-3)	III-2
3. Do resistant animal strains cause disease in humans?	yes (IV)	ns	ns	ns	ns	ns	yes (III-2)	yes (III-3)	III-3
4. Do resistant genes from animal bacteria transfer to human pathogens?	yes (III-I)	yes (III-I)	ns	ns	yes (IV)	yes (IV)	ns ?rare	yes (IV)	IV
Median level evidence for each resistance class	III-2	III-2	–	IV	IV	IV	III-2	III-3	

ns = no studies; – = insufficient studies to reach a conclusion about the stages in spread of resistance

[a] See Section 5.1 for explanation of the levels of evidence used.

[b] The streptothricin and oligosaccharide (orthosomycins) classes of antibiotics are not used in Australia (in either animals or humans).

[c] The quinolone class of antibiotics are not used in food-producing animals in Australia.

Overall, the JETACAR literature review found that there is qualitative evidence that antibiotics fed to animals leads to resistant bacteria and that these bacteria or their resistance genes are passed on to humans, principally via the food chain. The conclusions of the JETACAR literature review were similar to those of the MAFF and CAFA reviews. The levels of evidence were higher for some bacteria and antibiotics than for other bacteria and antibiotics. The committee accepted the findings of the JETACAR literature review, noting the degree of concurrence with other the other international reviews.

There is less information on the frequency with which resistance is passed on to humans. Such information would be valuable for formal risk assessment. Nevertheless, based on the information presented in this report, it may be possible to develop semiquantitative assessments for many bacteria and antibiotics.

Exposure assessment and risk characterisation

The risk to human health from antibiotic-resistant bacteria in food-producing animals is not static. It is a dynamic process driven by factors including the level of exposure to antibiotics, the level of infection or contamination of humans with animal bacteria, the health status of the infected humans, and the treatment and hygienic measures adopted in clinical medicine.

The risk characterisation component of a formal risk assessment is normally based on dose–response, exposure or some other measure related to health outcomes identified in the hazard characterisation steps. In the case of antibiotic use in food-producing animals, such an approach would involve analysis of the antibiotic-resistance genes present in populations of animals and humans in relation to antibiotic exposure over long periods and the likely effects on antibiotic resistance of the withdrawal of a particular antibiotic from use. Such data are not available and at this stage it was only possible to make a broad qualitative characterisation.

JETACAR concluded that the risk of humans acquiring antibiotic resistance as a result of antibiotic uses in food-producing animals is broadly related to the following factors.

- *Antibiotic 'load'* — the number of resistant bacteria increases with increased use of antibiotics because once antibiotic-resistant bacteria are present in a bacterial population, they are amplified by exposure to antibiotic(s) that select or coselect them. The total antibiotic 'load' on all bacteria includes human and veterinary uses plus other minor uses such as aquaculture and laboratory use. Use data collated for the committee showed that in Australia over half of all antibiotic use is for administration to livestock in feed with a small amount for other veterinary use and one-third for human medical use.

- *Antibiotic regimen* — frequent exposure of bacterial populations to antibiotics increases the selection pressure for resistant bacteria. Long-term lower-dose use may increase populations of resistant bacteria more than short-term high-dose use. Long-term exposure of large groups of animals to antibiotics in feed or water increases the overall pool of bacterial resistance genes. Ultimately, these genes may transfer to human pathogens by a combination of infection and gene transfer between bacteria.

- *Bacterial 'load'* — the risk of spread of antibiotic-resistant bacteria is more likely and transfer of antibiotic-resistance genes from animal bacteria to human bacteria is higher if there is a large pool of resistant bacteria infecting or colonising food-producing animals, making cross-infection common and transfer of antibiotic-resistance genes between bacterial populations more likely. Bacterial 'load' can be reduced if high standards of hygiene are maintained in the food supply and other

precautionary measures are taken to prevent contamination of humans with animal bacteria.

- *Prevalence of resistant bacteria* — the risk of spread of antibiotic-resistant bacteria and/or transfer of antibiotic-resistance genes between animals and humans increases as the prevalence of resistant bacteria increases. Surveillance of resistance levels in pathogenic and commensal bacteria is therefore required so that antibiotic use can be restricted or other measures implemented if resistance becomes unacceptably high.

Uncertainties surround all these factors because of a lack of specific data (eg antibiotic exposure levels of different populations of animals and humans; exposure levels and host specificity of bacterial strains; and the prevalence of resistant bacteria and/or resistance genes in particular bacterial populations in relation to antibiotic exposure). Collection of this data must, therefore, form the cornerstone of any management plan and of future quantitative risk assessments.

Characterising the risk of feeding antibiotics to food-producing animals into four components, as outlined above, provides a framework for a future qualitative risk assessment method and also for both short and long-term risk management strategies as shown in Figure 12.1.

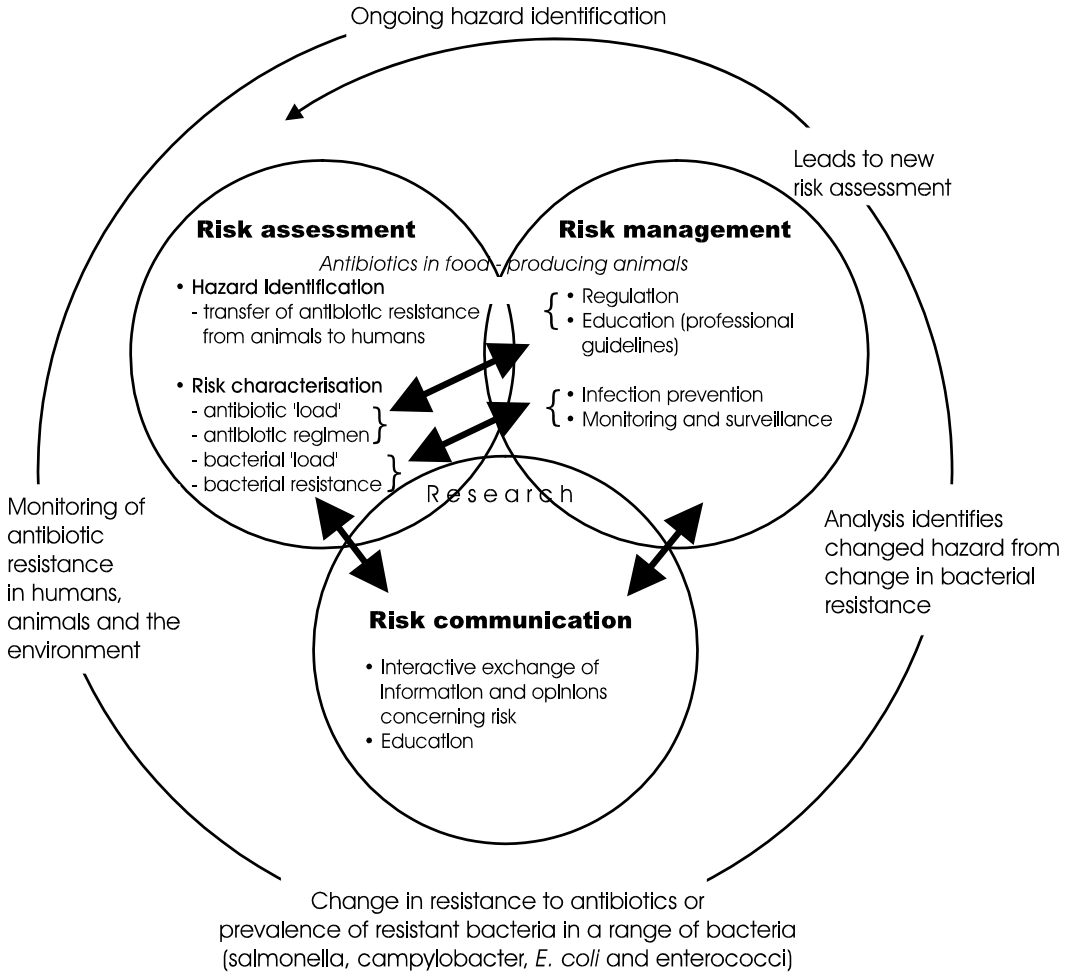


Figure 12.1 **Schematic diagram of risk analysis for antibiotic resistance with ongoing monitoring and surveillance to guide management of antibiotic use**

Residues

A further concern arising from the use of antibiotics in food-producing animals is that the transfer of low doses of antibiotics to humans in the form of residues in animal products may cause toxicity (very rarely), allergenicity or possibly antibiotic resistance. Use in food-producing animals can result in antibiotics themselves being present at detectable levels (residues) at slaughter or milking. Theoretically, antibiotic residues could select for resistant bacteria in the gut, as well as sensitise a person or cause an allergic reaction in an already allergic person. Also, residual antibiotics in food products may favour the survival of resistant bacteria in or on these products. Currently, there is no evidence to confirm or refute the selection of resistant bacteria in the human gastrointestinal tract after ingestion of detectable levels of antibiotic residues or increases in antibiotic-resistant bacteria in food due to residues. However, most adverse reactions to foodborne drug residues have been attributed primarily to penicillin hypersensitivity (Sundlof 1993). The risk of primary sensitisation resulting from consumption of foodborne residues is remote (Buck 1982, Sundlof 1989). Penicillin is most widely used as an animal feed additive in the United States and is not registered for this use in Australia.

Australia sets maximum residue limits (MRLs) using residue data and conducts a dietary exposure evaluation that takes into consideration toxicological parameters such as the acceptable daily intake (ADI) and the acute reference dose. Withholding periods are recommended based on good veterinary practice and compliance with MRLs is monitored through a structured testing program run by the National Residue Survey.

12.2 Resistance management program and recommendations

Because of the increasing international recognition that antibiotic resistance is rising rapidly and threatening human health, considerable efforts are being made in many countries to address the problem. In Europe and the United States particularly, elements of resistance management programs are being designed and implemented. These programs are focusing simultaneously on human and animal antibiotic use, recognising that they have many management principles in common. JETACAR has assessed these international activities and adapted some of them to develop a comprehensive resistance management program appropriate for the Australian context.

Antibiotic resistance is a significant issue for Australia in terms of both human public health and potential economic impact on veterinary and agricultural practice. The model of risk analysis shown in Figure 12.1 can be applied for risks from medical use of antibiotics as well as veterinary use. While emphasising the regulatory aspects of antibiotic use in food-producing animals, JETACAR has prepared this proposed antibiotic-resistance management program as an overarching strategy for all antibiotic use.

With some exceptions, antibiotic-resistance rates have not yet reached uncontrollable levels in Australia, but there is evidence of emerging resistances that are likely to have a major impact on human and veterinary medicine as well as food-animal production. Australia is therefore well placed to implement measures to keep resistances in check. With the increasing movement of humans, animals and animal products around the world, antibiotic resistance is now recognised as a global issue and has gained the attention of the World Health Organization, the European Union and several federal agencies in the United States. As a significant international player, Australia has the opportunity to show leadership by building on its current systems through the development and maintenance of a structured program for controlling resistance.

No single strategy has been found to be effective for controlling antibiotic resistance. In addition there is limited information about which interventions are most effective and current attempts use multiple strategies. The best option appears to be a coordinated

multidisciplinary approach, whose key elements are regulatory controls, monitoring and surveillance, infection prevention strategies (hygieneic measures), education and further research (Figure 12.2). The basics of this 'five-point plan' are equally applicable to human and veterinary medicine, as well as other areas on antibiotic use. The committee recognised that all five elements of the program must be implemented together if there is to be any chance of reversing the trend to increasing antibiotic resistances.

The following sections describe the management principles involved for each of the five elements of the five-point plan and gives recommendations on how they can be achieved

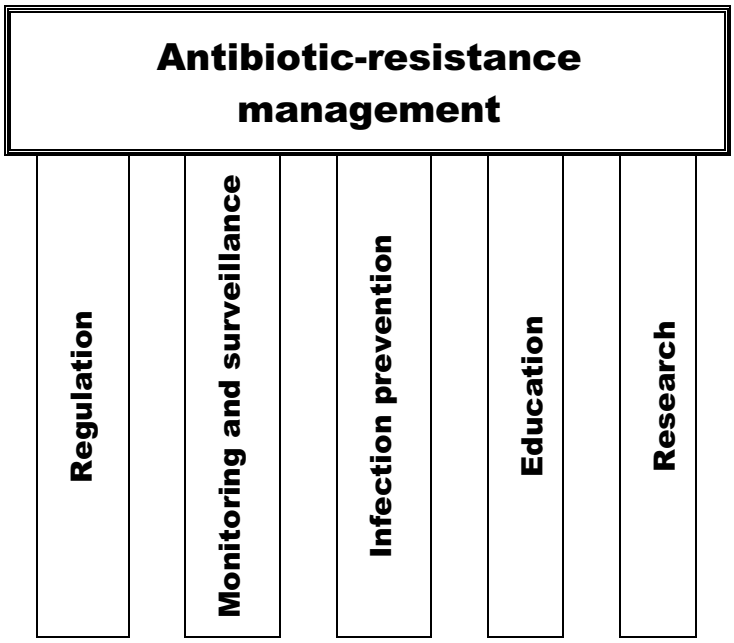


Figure 12.2 Multidisciplinary ('5-point') plan for management of antibiotic use to minimise bacterial resistance

12.2.1 Regulatory controls

Current regulatory control of veterinary antibiotic use in Australia was described in detail in Chapter 6. The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is responsible for registration and marketing approval of antibiotics after thorough evaluation of efficacy and safety.

In general, registration of antibiotics for food-producing animals in Australia has been conservative compared to most of Europe and North America. In part, this follows the recommendations of a report by the then Antibiotics Committee of the National Health and Medical Research Council (NHMRC) about the use of antibiotics in stockfeed (NHMRC 1986).

For many years new veterinary antibiotics or new veterinary indications for antibiotics have required pre-evaluation scrutiny by the Working Party on Antibiotics (WPA; formerly known as the Expert Panel on Antibiotics). The WPA is an independent group of medical and veterinary experts, including practitioners, who examine the potential for antibiotic resistance promotion and its possible impact on human health. To date, this has ensured that a number of agents, such as fluoroquinolones, which have been given open licensing in Europe and the United States for food-producing animals, have not been licensed for these animal groups in Australia. Similarly, penicillin has never been approved as a growth promotant despite its use as such in many other countries, and nitrofurans and

carbadox have been prohibited for use generally since 1993, as has chloramphenicol in food-producing animals, because of toxicity issues.

However, while the Australian approach to registration has been comparatively conservative, at present there are insufficient controls over supply and use of some antibiotics to minimise the development and transfer of antibiotic resistance from animal to animal, and from animals to humans. Of greatest importance is control over the use of antibiotics in stockfeed.

Registration of antibiotics for growth promotion and prophylactic use in stockfeed

The systematic literature review has demonstrated reasonable evidence that the use of antibiotics in stockfeed for growth promotion and/or disease prevention selects for resistant strains of zoonotic and commensal bacteria carried by food-producing animals, and that at least some of these resistant strains can be transmitted to humans and cause disease. Thus, there is a good case to be made to follow in some form the recommendations on in-feed antibiotics that were originally put forward by the Swann Committee in 1969 (UK Joint Committee of Houses of Parliament 1969; see Section 6.1.2). This position was endorsed at a meeting organised by the World Health Organization in 1997 and more recently by European Union ministers and scientists at a European Union Conference on 'The Microbial Threat' in Copenhagen in September 1998 (see Section 6.4).

At the same time, it is important that the intensive animal industries where antibiotics are commonly used in this way are not economically disadvantaged by the sudden removal or severe limitation of antibiotic applications that are of importance to animal health and welfare and to food production. Phasing out agents that do not fulfil the recommended criteria and that fail to pass review will provide the intensive industries with time to readjust while they seek alternative measures to remain internationally competitive. Alternatives are antibiotics that satisfy the recommended criteria, and animal husbandry improvements such as effective vaccination, nutritional strategies and hygiene programs.

Recommendation 1

That Australia adopt a conservative approach to minimise the use of antibiotics in humans and animals and, to further this policy, that in-feed antibiotics used in food-producing animals for growth promotant purposes, or other routine uses where duration and dose level are the same, or very similar, should not be used unless they:

- **are of demonstrable efficacy in livestock production under Australian farming conditions; and**
- **are rarely or never used as systemic therapeutic agents in humans or animals, or are not considered critical therapy for human use; and**
- **are not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms.**

Priorities for reviewing in-feed antibiotics that do not fulfil the recommended criteria have been set taking into account a number of factors. As avoparcin is already under NRA review for its possible impact on human health, its top priority is apparent. Streptogramins are second because, although the evidence is not as strong for macrolides, the product for human use is last line for the treatment of vancomycin-resistant enterococci (VRE). Macrolides are included because of their high uses in both human and animal therapeutics.

Recommendation 2

That the National Registration Authority (NRA) reviews the use of antibiotic growth promotants currently registered in Australia that do not appear to fulfil the criteria listed in Recommendation 1 in terms of their impact on human and animal health, using a risk analysis approach, including a cost–benefit analysis. The priority determined should be consistent with recent international reviews and use the conditions outlined in Recommendations 1 and 4.

It is recommended that the priority of the review at this stage be:

1. **glycopeptides (avoparcin is currently under review by NRA)**
2. **streptogramins (virginiamycin)**
3. **macrolides (tylosin, kitasamycin, oleandomycin)**

This review is to be completed and outcomes acted upon within three years. Growth promotant claims of such antibiotics that do not pass the review process should be phased out of use within one year subject to consultation with relevant stakeholders.

It is also recommended that the NRA should review the prophylactic use of avoparcin and virginiamycin in animals and the possible public health impact of this use using the parameters outlined in Recommendation 4.

In order that the reviews are performed in a timely manner, it is further recommended that the federal ministers of health and agriculture ensure an adequate allocation of resources to the NRA to facilitate the rapid completion of the task and implementation of changes.

JETACAR acknowledged that the continued prophylactic use of antibiotics in food-producing animals has the potential to result in further development of antibiotic resistance. JETACAR also recognised the commercial importance of the prophylactic use of antibiotics in food-producings for the prevention of clinical and subclinical conditions affecting productivity in livestock production systems. Recommendations 1 to 8 in this report have been framed on the basis that, for those antibiotics within groups of antibiotics critical to human health, growth promotant and oral prophylactic uses in food-producing animals should be reviewed and phased out.

Importation of antibiotics and stockfeed formulation

Advice from both the livestock industries and the NRA Quality Assurance and Compliance Section indicates that antibiotics incorporated into feeds are not always NRA-registered products. There is no licensing mechanism for importers of agricultural and veterinary chemicals (including antibiotic substances) and therefore little or no accountability mechanism to check if the importers are diverting unregistered antibiotics to feed-millers and home-mixers, or if the imported antibiotic matches the approved source and registration specifications. It would also add more rigour to the accuracy of import (likely usage) figures if annual returns for imported antibiotics were made available for relevant authorities for the purposes of risk assessment — as is already done for pesticides — to comply with United Nations Office for Economic Co-operation and Development (OECD) requirements.

The *Agricultural and Veterinary Chemicals Code Act 1994* (Agvet Code) requires the incorporation of only registered products into feeds for medication purposes. However, there appears to be a misconception amongst members of the feed-milling and home-mixing industries who consider that as long as one product is registered with an active

constituent, such as oxytetracycline, then unregistered sources of oxytetracycline or unregistered products containing oxytetracycline can be used.

Recommendation 3

That an appropriate government authority or authorities license, or otherwise control, all importers of antibiotics (for any purpose other than individual human patient use). Licensed importers must provide import returns and distribution, and information based on amounts of active ingredient of agents intended for animal use, to the National Registration Authority, and to the Therapeutic Goods Administration for agents intended for human use.

It is also recommended that a much stronger audit trail for antibiotics from the importer to the end-user be implemented, particularly in the veterinary field, and that the aggregated information on import quantities are made available for scrutiny by relevant authorities and the results are made public.

Data requirements

It has been acknowledged by both the registrants of antibiotic products and the regulators that the current data requirements for registration of antibiotics require strengthening to include specific monitoring for development of resistance both pre- and post-registration. Furthermore, at present microbial resistance safety (in terms of propensity for promoting resistance and cross-resistance) is included in the current review process for veterinary and agricultural antibiotics, in part through referral to the Working Party on Antibiotics (WPA). There have been recent moves to improve the focus on microbial resistance safety within the NRA, assisted by the WPA, by upgrading the Special Data Requirements. A similar proposal for evaluation of microbial resistance safety has been made by the Center for Veterinary Medicine of the Food and Drug Administration in the United States (the equivalent of the NRA in Australia) (http://www.fda.gov/cvm/fda/infores/vmac/antim18.htm).

Recommendation 4

That the National Registration Authority (NRA) evaluate all new applications, major extensions of use and any reviews of currently registered antibiotics for use in animals by applying the recently redrafted Special Data Requirements (Part 10 of the *Vet Requirements Series: Guidelines for Registering Veterinary Chemicals*, NRA 1998), which includes a risk analysis of microbial resistance safety (see Appendix 4).

Recommendation 5

That a recognised expert authority (the Working Party on Antibiotics or its successor) defines threshold (or trigger) rates of resistance for antibiotics registered for use in animals and circumstances where usage should be investigated and mitigation proceedings instigated where appropriate. In addition, resistance prevalence data should be included in the product information and this information should be updated on a five-yearly basis.

'Open seller' versus prescription animal remedies (PAR, or S4) antibiotics

The availability of antibiotics as 'open sellers' increases the opportunities for overuse and misuse. This type of use is also a problem in human medicine in many developing countries, and is felt to contribute to the considerable burden of resistance in those countries. In Australia, like in many other countries, all growth promotants and some

prophylactic antibiotics are available as open sellers and do not require the recommendation or prescription of a veterinarian. This is in contrast to the situation in human medicine where all antibiotics for systemic use, and many for topical use, must be prescribed by a medical practitioner. Thus, it is the (trained) medical practitioner who ultimately takes the professional responsibility for any overuse or misuse. Similarly, it is proper that the veterinary profession take responsibility for the appropriate use of antibiotics. Thus, all antibiotics used in food-producing animals, including those registered with growth promotion claims, should be classified as prescription animal remedies (S4).

Currently, no systemic antibiotics are available without medical prescription. All therapeutic antibiotics in veterinary medicine require veterinary prescription. Only low concentration feed antibiotics for growth promotion and some aquarium fish and aviary bird therapeutic use antibiotics are available without veterinary prescription. A common recommendation in the various international reports on antibiotic resistance and animal use of antibiotics since the late 1960s has been the need for professional input into the use of antibiotics including animal feed additives.

JETACAR recognises that the removal of antibiotics as open sellers has been a subject of debate in Australia for some years. It believes, however, that the principle is a vital one, and that few of the other measures recommended will be effective without this recommendation being implemented.

Recommendation 6

That all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only).

State/Territory control-of-use provisions

In its evaluation of a new use for an antibiotic in a particular animal species, the WPA considers the likely extent of use of that antibiotic in that particular species as well as any potential off-label use. Off-label use is use of a product for indications or in animals other than those for which it is formally registered. Off-label use is common practice in many settings in veterinary practice, and is permissible under legislation in all States/Territories. However, under State/Territory legislative arrangements, it is difficult to assess the extent of off-label use. There have been discussions at a State/Territory level about a harmonised approach to the supply and use of veterinary chemical products. Such a harmonised approach must address the situations where off-label prescription is inappropriate.

While veterinarians have the right to prescribe veterinary chemical products, including antibiotics, with due precautions, there is inconsistency in the enforcement of specific NRA label restraints, such as 'not to be used in food-producing species', across Australia. Observation of specific NRA label restraints are mandatory in some States and not in others.

Restraint statements such as 'not for use in food-producing species' on NRA-registered products, including the antibiotics gentamicin, chloramphenicol or the nitrofurans, must be enforceable under State/Territory legislation to provide assurance of a workable control mechanism. One major step forward would be for relevant State/Territory legislation to be amended, where necessary, to make it an offence to prescribe and/or use a veterinary chemical product contrary to an NRA label restraint. To cover exceptional circumstances, an acceptable alternative could be an NRA permit.

It should be noted, however, that adherence to NRA label statements would not preclude appropriate off-label use. For example, if the NRA restraint stated 'not for use in pigs, cattle and poultry', it would be legal for veterinarians to prescribe the antibiotic off-label

for other species such as sheep and goats. In the unlikely event of a veterinarian needing an antibiotic prohibited by a label restraint, an NRA permit may be appropriate.

Recommendation 7

That the Agricultural Resource Management Council of Australia and New Zealand implement a harmonised approach by all States and Territories in Australia (including clarification of responsibilities) to the control of use of veterinary chemicals, including antibiotics.

Recommendation 8

That, following the implementation of Recommendation 7, the relevant State and Territory health/agriculture/primary industries legislation is amended to make it an offence to prescribe and/or use a veterinary chemical product contrary to a National Registration Authority (NRA) label restraint, unless authorised to do so by an NRA permit.

Implications for human medicine

Some of the recommendations above are currently not in place in the human medicine regulatory system in Australia. As the principles of antibiotic resistance selection and spread are the same in human and veterinary medicine it is important that the regulatory processes for antibiotics be identical or very similar. Most importantly, microbial resistance safety is currently not assessed formally by the Therapeutics Goods Administration (TGA) as part of the evaluation of antibiotics for human use.

Recommendation 9

Similar to recommendations made in veterinary medicine, it is recommended that the Therapeutic Goods Administration (TGA) implement the following:

- **inclusion of microbial resistance safety data, including the propensity for promoting resistance and cross-resistance, as a basic requirement of the assessment of all new antibiotics by the TGA, with adoption of similar data requirements to those required in the registration of veterinary antibiotics (Recommendation 4);**
- **definition by a recognised expert authority (Working Party on Antibiotics or its successor) of the threshold rates of resistance to registered human antibiotics and circumstances where usage should be investigated and mitigation procedures instigated where appropriate; and**
- **inclusion of national human antibiotic-resistance prevalence data in the product information and updating on a five-yearly basis.**

12.2.2 Monitoring and surveillance

As antibiotic resistance is a problem of international significance, cutting across borders, and involving human health, tourism and trade in animals and food, there are major scientific and legal implications for Australia. The international trade in animal products from countries that are not practising a similar restraint in the use of antibiotics will mean that the Australian public will continues to be exposed to antibiotic-resistant strains of bacteria. For instance, there is a considerable risk that tourists and trade might introduce (or in some cases have introduced) resistant bacteria into Australia, eg *Salmonella* Enteritidis from Southeast Asia, VREs from the United Kingdom, Europe and the United

States, and fluoroquinolone-resistant salmonellae and campylobacters from Asia, Europe and the United States.

For these reasons many countries now have put in place or are developing systems that survey the prevalence of resistant bacteria and monitor antibiotic usage patterns, including systems specifically designed to survey resistance emergence in bacteria that can be spread from food-producing animals to humans.

The development of an internationally acceptable and scientifically defensible Australian continuous monitoring and surveillance program for resistant bacteria and usage of antibiotics in animals is essential. Such a system will benefit both the veterinary community and public health because it:

- identifies key resistance and usage problems;
- provides information for veterinarians about the likely efficacy of different antibiotics;
- records trends in resistance and usage; and
- provides the essential barometer of whether, and to what extent, resistance management interventions have been effective.

Within Australia's federal system of government, the coordination of surveillance programs can be difficult unless there is national funding, or an agreed national commonality of purpose and an agreed funding mechanism. Like the issue of antibiotic residues, antibiotic resistance has both public health and trade implications. Antibiotic residues in food commodities are seen predominantly as a trade issue and a minor public health issue in Australia. Accordingly, the funding of antibiotic residue monitoring and surveillance through statistically valid sampling programs is funded through a levy on the industries needing those programs. On the other hand, antibiotic resistance is predominantly a public health issue, with trade, at this point, a minor component. Funding responsibilities would therefore need to be negotiated and agreed for antibiotic-resistance monitoring and surveillance. In addition, monitoring and surveillance crosses two portfolios, those of agriculture and health, at both federal and State/Territory levels. Industry, including producers, processors, pharmaceutical, laboratory and health industries, also has a vested interest in resistance emergence, and therefore in monitoring and surveillance.

Resistance surveillance

Systems for resistance surveillance in human isolates are well established in Australia (especially NARSP and AGAR; see Chapter 10), although the funding base for these has been somewhat precarious over the years. By contrast, there is no surveillance system for resistant animal pathogens, or in organisms that could be transferred from animals to humans, especially via the food chain. The situation is further compromised in animals by the paucity of standardised susceptibility testing techniques for veterinary microbiology. However, there is much in common between human and veterinary medicine in terms of information needs about resistance, and laboratory methods. Thus, there is potential for synergy between any human and veterinary resistance surveillance systems, in particular the opportunity for potential veterinary and food chain systems to learn from what has been established in the human area.

As described in Chapter 10, resistance surveillance can be *passive* (collection of routine analytical data from diagnostic laboratories) or *active* (more intensive study of resistance with statistically valid sampling programs directed at specific pathogens). Both types provide essential information on the levels of resistant bacteria and their trends. Active surveillance adds indispensable insight into additional antibiotics and cross-resistance, as well as the likely utility of new agents. With modern computing and communication

facilities, passive surveillance will be possible at low cost, and limited funding resources need to be directed to active surveillance, which is inherently more resource intensive.

In the interests of public health and trade, six areas will require resistance surveillance:

- human pathogens
- potential pathogens with major resistances carried by humans
- veterinary pathogens
- food-chain indicator organisms
- environmental organisms
- other areas of antibiotic usage

The features of these six areas are listed in Table 12.3. Large numbers of bacteria are isolated for diagnostic purposes in human medicine but the number of bacterial isolates in veterinary medicine and agriculture is much smaller and restricted by economic factors. However, there are still opportunities to capture, at low cost, significant numbers of bacterial isolates of public health importance.

Recommendation 10

That a comprehensive surveillance system be established incorporating passive and active components measuring incidence and prevalence of antibiotic-resistant bacteria and resistance genes, covering all areas of antibiotic use. To achieve this aim, it is further recommended that a multidisciplinary taskforce of relevant experts be formed by the federal ministers of health and agriculture to design, cost and recommend funding mechanisms and management systems for reporting and analysis of antibiotic resistance data in Australia.

The overall surveillance system should include medical (including nosocomial), food-producing animal and veterinary areas, with particular emphasis on the establishment of food-chain (including imported food) and environmental connections, and include molecular studies of resistance genes. The efforts of the taskforce should be directed at adopting a uniform, systematic and synergistic approach across all areas by utilising, enhancing and extending currently available systems and organisational structures.

Monitoring antibiotic usage

Interpretation of resistance trends is difficult in the absence of reliable data on antibiotic usage. Some usage data, such as import volumes, are comparatively simple to collect. Other data, particularly at the level of individual consultation and prescription/dispensing, are difficult and expensive to collect. In the human medicine area, multiple data sources are accessed including antibiotic import data, prescription volumes on the Pharmaceutical Benefits Scheme (PBS), prescription volumes as determined by Pharmacy Guild surveys, and commercial data commissioned by the pharmaceutical industry. Apart from import data, few of these sources exist in veterinary medicine and livestock production.

Antibiotic usage data gathering, storage, collation, reporting and audit should utilise existing systems as much as possible if these can provide the basic information necessary for overall assessment of antibiotic use.

Table 12.3 Bacterial samples required for antibiotic-resistance surveillance

Area	Organisms	Who benefits	Current systems and potential for development
Human pathogens	All (including zoonotic pathogens and commensal organisms of potential animal origin)	Patient (routine tests) Prescriber (routine tests) Guidelines designers Infection control staff Pharmaceutical industry	Passive NARSP Active AGAR (ongoing) Other targeted programs (one-off studies)
Potential pathogens with major resistances carried by humans	MRSA VRE	Infection control staff Pharmaceutical industry	Individual hospital screening programs
Veterinary pathogens	All	Animal (routine tests) Prescriber (routine tests) Farmers/animal owners (routine tests) Guidelines designers Pharmaceutical industry	No current systems but potential to access data from veterinary diagnostic laboratories
Food-chain indicator organisms (local and imported)	*Salmonella* *E. coli* *Campylobacter* *Enterococcus*	Consumers Veterinarians Farmers/animal owners Intensive industries Pharmaceutical industry	No current systems apart from limited testing of salmonella isolates at one of the two salmonella reference laboratories. Potential to access bacterial isolates from the Australian Quarantine and Inspection Service (AQIS) microbiological surveillance of export abattoirs and imported food inspection programs as well as commercial programs (eg food and poultry processing).
Environmental indicator organisms	*Salmonella* *E. coli* *Campylobacter* *Enterococcus*	Consumer Veterinarians Farmers/animal owners Intensive industries	No current systems, but systems could be easily designed to utilise existing resources and facilities
Other areas of antibiotic use • aquaculture • apiculture • horticulture[a] • food production	Bacteria with significant potential for spread to humans	Consumer Involved industries Pharmaceutical industry	No current systems; poorly studied to date; except for aquaculture and food production, importance to human health uncertain

MRSA = multiresistant *S.aureus*; VRE = vancomycin-resistant enterococci

[a] No antibiotics are registered or permitted by the NRA for use on plants in Australia

Recommendation 11

That a comprehensive monitoring and audit system for antibiotic usage be established that covers all areas of antibiotic use. To achieve this aim, it is recommended that the federal ministers of health and agriculture form a multidisciplinary taskforce of medical, veterinary, industry and regulatory experts (including Customs, Therapeutic Goods Administration, Department of Health and Aged Care, National Registration Authority and Department of Agriculture, Fisheries and Forestry — Australia) to refine the current antibiotic import data collection and audit process, and make recommendations to relevant authorities for developing methods of monitoring and auditing usage.

12.2.3 Infection prevention strategies and hygienic measures

Food hygiene and infection control in food-producing animals

The overall bacterial load that humans are exposed to is reduced if high standards of hygiene are maintained in the food supply and other precautionary measures are taken to prevent contamination of humans with animal bacteria.

In the last 20 years there has been heightened worldwide concern about microbiological contamination of food (see Section 4.3). International publicity of a number of large-scale foodborne microbiological contamination incidents has led to government investigation and involvement in food safety regulation in the United States, United Kingdom and Australia. Terms such as 'farm to fork' or 'paddock to plate' have been used to decribe the continuum in the food chain from the point of production to the consumer. Food production, food processing and preparation procedures (on-farm quality assurance programs, abattoir hygiene, transport and storage at the wholesale and retail level) and domestic food storage, handling and preparation are all now receiving attention in an effort to reduce the transfer of pathogens to humans through the food chain. In Australia, regulatory and industry food safety and food hygiene programs are being developed for Australia by the Australia New Zealand Food Authority (ANZFA 1998b). Such programs should concurrently reduce human exposure to animal commensal and zoonotic bacteria that are resistant to antibiotics or carry antibiotic-resistance genes.

Recommendation 12

> **That 'hazard analysis critical control point' (HACCP)-based food safety procedures be implemented as a means of reducing the contamination of food products with foodborne organisms, including antibiotic-resistant organisms, and that these programs also address on-farm infection control.**

Alternatives to growth promotants

There have been enormous improvements in the standards of animal care and hygiene in the 40 years since antibiotics were first introduced into veterinary care and animal husbandry. This has been particularly noticeable in the intensive food-producing industries such as meat chicken and pig production. When growth promotants were first introduced into the intensive industries, the benefits were substantial in terms of disease prevention, feed conversion and weight gain. Current evidence, predominantly generated overseas, suggests that the benefits in feed conversion and weight gain give an economic advantage of savings of approximately 0.5–5% (although some trials have shown no benefit; see Chapter 8).

The current efficacy of growth promotants in relation to disease prevention is less clear but considered by many to be important. However, there is evidence from the Swedish experiment, where growth promotants were removed more than decade ago, that must also be considered. Following the elimination of growth promotants, Sweden experienced an initial increase in contagious disease, animal welfare and environmental problems in its intensive industries. However, judicious therapeutic use of antibiotics, improvements in feed formulation and stricter hygienic measures have reduced infection rates back to levels similar to those experienced by countries where growth promotants were widely used. While still allowing prophylactic use of some in-feed agents, and conceding that there may still be a small but measurable benefit from the reintroduction of growth promotant use, Sweden has gained acceptance in the European Union for continuation of their ban on growth promotants. How the results of the Swedish experiment apply to Australia is not known. However, it suggests that cost-effective alternatives to growth promotants may exist or could be developed. Some alternatives have been outlined in Chapter 11, but there is a great deal of work to be done if full replacement effectiveness is to be obtained.

Recommendation 13

That where the intensive animal industries (such as meat chicken, pig, feedlot cattle and aquaculture) currently depend on the use of antibiotics to improve feed conversion and prevent and treat disease, cost-effective nonantibiotic methods to increase productivity and prevent disease should be developed by these industries. In relation to this, it is further recommended that the federal ministers of health and agriculture explore additional funding alternatives for this work, taking into account the current efforts of the animal industry research and development organisations.

Infection control in humans

Infection control practices, in their broadest sense, are also vital in human public health practice to prevent transmission of resistant organisms. Resistant organisms emerging in animals and passed through to humans may do so at a very low level, but may still be amplified by poor infection control practice both in hospitals and the community. Moreover, removal of certain classes of antibiotics from animal use can not of itself eliminate already established antibiotic-resistant bacteria. For instance, VRE strains appear to be well established across Australia now, albeit at a low level, and constant high standards of infection control will be required to suppress their increase and spread.

Currently, the only nationally coordinated effort in this regard is the production of infection control guidelines. Even these are produced sporadically in the absence of a regularly planned update mechanism. Moreover, management of outbreaks of infections of public health importance is undertaken at the individual State or Territory level, with no agreed national approach, let alone central coordination.

Australia would benefit greatly from a nationally coordinated system of infection control practice and outbreak management whose elements should include:

- systematised nosocomial (hospital-acquired) infection surveillance, including a focus on key resistant organisms;
- regularly programmed updates on national infection control guidelines;
- nationally agreed standards for outbreak management of infections of public health significance, including zoonotic and potentially zoonotic bacteria, with central reporting; and
- development and implementation of nationally agreed detecting, screening and reporting procedures for key resistant organisms (especially multiresistant *Staphylococcus aureus* and VRE).

Recommendation 14

That the Department of Health and Aged Care examine current surveillance activities for hospital-acquired (nosocomial) infections, particularly for antibiotic-resistant strains; and that the department work with stakeholders (including the States and Territories) to further develop a comprehensive and standardised national system for monitoring nosocomial infections that will facilitate:

- **earlier recognition of a public health problem;**
- **improvements in infection control and hygiene measures; and**
- **the timely development of national standards, guidelines and practices for both surveillance and infection control in the health care setting.**

12.2.4 Education

Regulatory, surveillance and infection prevention strategies will not be fully effective unless the stakeholders are educated about the rationale and implementation of these strategies.

For veterinary use of antibiotics, the key stakeholders are veterinarians, farmers, pharmaceutical companies and the regulators themselves. The general public should also be fully informed about safe food handling, and the efforts being made to improve the safety of food, including that produced from animals, to minimise the spread from animals to humans of enteric bacteria generally and antibiotic-resistant bacteria in particular. In addition there is a fundamental need to ensure that veterinarians and their clients are educated about the nature of infectious diseases and the 'prudent use' principles of antibiotics in veterinary medicine.

From the human medical viewpoint, the effectiveness of education alone on antibiotic prescribing has been unclear. Education of the medical profession has been the main approach to tackling inappropriate use and consequent increased selection pressure for antibiotic resistance. Despite the fact that these educational activities, both undergraduate and postgraduate, have been going on for more than 15 years, Australia is still the second highest per-capita user of antibiotics when compared to seven other Western countries.

More recently, there have been efforts to communicate the risks of inappropriate antibiotic use to consumers through National Medicines Week. Whether these efforts have been successful in reducing human antibiotic consumption is unclear. Based on figures collected by the Drug Utilisation Subcommittee of the PBS, the most effective strategies for reducing inappropriate use have been either restriction of availability through the scheme, or prominent warning campaigns such as those for flucloxacillin and amoxycillin–clavulanate.

For these reasons, education remains a vital pillar in the suite of risk management strategies, ensuring that the stakeholders are fully informed of the risks and solutions. This is especially important in veterinary medicine because there is no PBS equivalent to intervene between the client and the prescriber.

Prudent use principles (code of practice)

The educational process requires the development and adoption of prudent use principles by the relevant peak bodies that represent the key stakeholders in every area. The prudent use principles should be universal in nature, based on a scientific understanding of the pressures that select for, maintain and amplify resistant bacteria. They should be equally applicable to human and veterinary practice. Examples of prudent use principles are listed in Box 12.1.

Recommendation 15

> **That prudent use codes of practice for antibiotics be developed and regularly updated by medical and veterinary peak bodies, including learned societies, professional organisations, producer organisations, pharmaceutical companies and State/Territory medical and veterinary registration boards, and promulgated to their members. These codes of practice should be based on the principles articulated in this report.**

Antibiotic guidelines

Guidelines for the appropriate use of antibiotics in humans were developed in the mid-1970s in Victoria and eventually became adopted across the country. These guidelines,

now called *Therapeutic Guidelines — Antibiotic* (Therapeutic Guidelines 1998), have been regularly updated biennially and are now in their 10th edition. Although the market penetration of this product has been high, and compliance with the guidelines has been frequently examined in public hospitals, their effectiveness in improving prescribing practice is unclear. In part, this results from the lack of adoption of the guidelines by the medical profession as a true 'standard of care'. It also results from the absence (until the most recent edition) of guidance about selecting which patients will and will not benefit from antibiotic treatment.

Guidelines for the broad range of veterinary antibiotic uses were published in the mid-1990s by the Veterinary Postgraduate Foundation of Sydney University, and with the support of the WPA (which was then part of the NHMRC). The market penetration has been limited, and therefore the effect on veterinary prescribing practice unclear. Other guidelines have been produced by the veterinary profession (see Section 7.3.4). There is clearly a need to develop and promulgate widely accepted standards for antibiotic prescribing in the veterinary profession.

Recommendation 16

That regularly updated 'antibiotic use guidelines', both human and veterinary, supported and endorsed by the appropriate professional organisations, the pharmaceutical industry and the federal and State and Territory departments of health and agriculture, are widely disseminated and adopted as a 'standard of care' by training institutions, and established as the benchmark for undergraduate and postgraduate teaching. The effectiveness of the 'antibiotic use guidelines' in ensuring prudent prescribing of antibiotics needs to be evaluated every five years.

Targeted education efforts

To date there have been limited efforts at educating stakeholders (other than the prescribers) in appropriate antibiotic use. It is clear from the media publicity that has surrounded antibiotic resistance in the last two years that there is generally a poor community understanding of the biology of infection and infectious diseases. This poor understanding is likely to be general among antibiotic users, including patients attending their doctors with infection and farmers who have infected animals under veterinary consultation. Ready availability of antibiotics has led to a 'culture of expectation' that almost all infections can be fixed with antibiotics, and that antibiotics are essentially harmless and can be used 'just-in-case'.

Changing this culture will require significant educational efforts at many levels. Simultaneously, it will be vital to have prescriber education and training on methods of dealing with this expectation without taking the easy option of writing a script when antibiotics are not indicated.

In the medical sphere, efforts such as National Medicines Week have at least made a start on approaching the public directly through the media with educational material. However, the impact is likely to be small unless efforts are scaled up.

Box 12.1 Prudent use principles for antibiotics

General

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

Therapy

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

Prophylaxis

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

Recommendation 17

That, as a priority, learned (medical and veterinary) and professional societies develop continuing educational programs on the issue of antibiotic resistance, including a focus on the prudent use principles, antibiotic use guidelines and alternatives to antibiotic usage.

12.2.5 Further research

Research and development are cornerstones in identifying problems and providing guidance for improvement in antibiotic usage. Experience shows that international problems are best dealt with by multiple contributions internationally.

Australia has identifiable resistance problems that are, or have the potential to be, a significant threat to public health, but by international standards it has not focused much research attention on the problems of human clinical or veterinary/agricultural antibiotic resistance and even less on seeking solutions. There is a reasonable level of expertise to tackle these problems and provide solutions, but Australia lacks any centralised or centrally coordinated antibiotic research facility.

There are several important areas that require research attention, which are described below.

Alternatives to antibiotics in growth promotion

It is important that the intensive food-producing animal industries do not suffer as a consequence of elimination of certain classes of antibiotics currently used as growth promotants, and continue to produce cost-effective, safe food. Therefore urgent attention must be directed to researching effective, safe and consumer-acceptable alternatives to antibiotics that maintain or improve on current feed conversion standards.

Alternatives to antibiotics in prevention and treatment of infections

Antibiotic load should also be reduced by seeking alternatives to antibiotics for the prevention and treatment of infection. In human medicine, new techniques for preventing infection (eg vaccines, operative strategies) and treating infection (eg supporting or enhancing immune response) must continue to be supported strongly. In veterinary practice there is an urgent need to investigate alternatives to long-term use of antibiotics to prevent common infections in the intensive industries.

Molecular epidemiology and mechanisms of gene transfer

New resistance genes are emerging all the time. At present, Australia has a fairly limited knowledge of the spectrum of resistance genes and resistance-carrying DNA in Australia. For some new resistances, such as VRE, detailed knowledge is accumulating, largely through the additional efforts of the NARSP (see Chapter 10). An intensified focus is required to characterise the types and genetic mechanisms of spread and transfer of resistance in Australia. Studies into cotransfer of resistance genes are a vital component of such studies.

Population dynamics of antibiotic resistance

Although there is a 'common understanding' of what drives antibiotic resistance and prevalence, there is little proven science to support this 'understanding'. Thus, there is an urgent need to develop basic models and undertake clinical studies that examine the relationship between antibiotic exposure (eg dose, duration) and resistance dynamics.

Resistance epidemiology

The current surveillance programs and projects for antibiotic resistance in human medicine will continue to define the extent of the problem in human antibiotic usage. However, information about the transfer and spread of resistant bacteria is largely restricted to hospital practice. Further work is required to define the mechanisms of spread of resistant bacteria in the community and the environment. In addition, there are serious gaps in our knowledge of the prevalence and transfer of resistance in animals, especially food-producing animals. Detailed baseline studies are urgently required to determine the prevalence of resistant pathogens that can be transferred from animals to humans and their rate of spread and persistence through the food chain.

Pharmacoepidemiology

Although data about consumption volumes of antibiotics are available through a variety of sources, data on prescription indications and patient demographics (including use in animal species) are very limited. Studies into these areas will provide valuable insights about how and where to target intervention strategies.

Efficacy of interventions to reduce antibiotic prescribing and use

There are a variety of strategies that can be used to attempt to reduce antibiotic prescribing and usage. Only a few have been studied, and in most circumstances their efficacy has only been evaluated in the short term. Planned longer-term studies of such interventions would provide valuable information about the relative efficacy of the different strategies, and define which are the most cost-effective.

Clinical efficacy studies

Recent experience using the evidenced-based medicine approach to the treatment of respiratory tract infections in humans has provided valuable insight into areas where the benefits of antibiotics are marginal for the majority of patients. The next phase of clinical studies has yet to be embarked upon, namely prospective studies to examine the factors that determine outcome, or even placebo-controlled studies, thereby leading to our ability to separate patients prospectively into those who are likely to benefit and those who are not. Most of these types of clinical efficacy studies involve older off-patent agents and will not be supported by the pharmaceutical industry. Indeed, in many instances it would be preferable if they were performed independently of the pharmaceutical industry.

Clinical efficacy data for minor infections in animals should also be examined in a similar manner.

Rapid diagnostic tests

Much, if not most, prescribing for treatment of infections in human and veterinary practice is empirical, done in the absence of laboratory or other diagnostic tests to confirm the pathogen(s) involved, and in particular whether it is viral or bacterial. Reliable and inexpensive 'bedside' diagnostic tests could change this prescribing pattern dramatically. Currently, almost all of the rapid microbiological diagnostic testing is laboratory based, and much is expensive. Development of affordable bedside tests, particularly ones that could exclude bacterial infection should be a prime objective. In human medicine, even tests that could provide this within a few hours from the laboratory could enable the prescriber to write the script but ask the patient not to fill it until the results confirmed bacterial infection.

Recommendation 18

That all relevant research funding agencies be asked to give priority to research into antibiotic resistance, including:

- **alternatives to antibiotics for growth promotion;**
- **alternatives to antibiotics for prevention and treatment of infections (including vaccines);**
- **molecular epidemiology and mechanisms of gene transfer;**
- **population dynamics of antibiotic resistance;**
- **resistance epidemiology;**
- **pharmacoepidemiology;**
- **efficacy of interventions to reduce antibiotic prescribing and use;**
- **clinical efficacy studies; and**
- **rapid diagnostic tests.**

12.3 Risk communication

Risk communication is a process of interactive exchange of information and opinions concerning risk between the people undertaking the risk analysis and the stakeholders, including, in this case, the general public (Nunn 1997). In addition to the education measures recommended above, which focus on the professionals and their groups, communication of risk to all concerned parties, and especially the public, must be a continuous process. There are many facets to this process, and much of it can be delivered by existing systems at the federal and State/Territory level.

Recommendation 19

That an ongoing funded education strategy be developed by the relevant federal/State/Territory departments with input from stakeholders to provide appropriately targeted information about infection, the role and benefits of prudent antibiotic use and the risks of overuse to the public, relevant professional bodies and stakeholders.

Recommendation 20

That a recognised expert authority (the Working Party on Antibiotics or its successor) assume responsibility for ensuring and coordinating the communication of data on antibiotic usage and prevalence of resistant bacteria to the public and other relevant stakeholders on a regular basis, taking into account the sensitivities of trade and other international implications.

12.4 Coordination of the resistance management program

The coordination of the efforts of the various professional, regulatory and industry bodies involved in the strategic management of this issue, and the communication of the risks involved to the wider community will require the formation of an overarching, multidisciplinary, credible and independent cross-sectional authority.

Some parts of the resistance management program outlined above currently involve the WPA, which was previously convened by the NHMRC but, following a restructuring in 1997, now operates under the auspices of the Therapeutic Goods Administration (TGA), pending a more permanent home. The WPA continues to play a significant advisory role to other federal government authorities concerning the public health implications of antibiotic resistance and methods for controlling it, including licensing and availability. In particular, it provides advice to the NRA and the Pharmaceutical Benefits Advisory Committee (PBAC). The advice is provided in the absence of any statutory support and with limited financial support from the TGA.

A formally constituted body that can communicate directly with both the Department of Health and Aged Care, and the Department of Agriculture, Fisheries and Forestry — Australia, could extend the functions of the WPA. Because of the public health impact of antibiotic resistance, JETACAR's preferred option is that this extended WPA should be realigned with the NHMRC. Potential roles of this body would include:

- advice to the NRA and TGA about guidelines for microbial resistance risk assessment for new antimicrobials (Recommendations 4, 9);
- advice to the NRA and TGA about threshold (trigger) levels and circumstances where mitigation proceedings should be instigated (Recommendation 5);

- advice to the NRA, TGA and other authorities and agencies (eg ANZFA) in relation to other matters in regard to antimicrobials;
- advice to the PBAC about availability and restrictions of antimicrobials on the PBS;
- oversight and refinement of human antimicrobial resistance surveillance systems (Recommendation 10);
- advice on development of antimicrobial resistance surveillance programs for antibiotic use in animals, and subsequent oversight and refinement (Recommendation 10);
- oversight of human antimicrobial usage monitoring (Recommendation 11);
- development of improved methods for antimicrobial usage monitoring, especially for antibiotic use in animals and subsequent oversight (Recommendation 11);
- development and dissemination of national prudent use principles (Recommendations 15–17); and
- advice on development of public education strategies in relation to infectious diseases and the role of antibiotics (Recommendations 19, 20).

It is essential that there continue to be cross-disciplinary oversight of antibiotic usage and regulation in Australia if resistance is to be adequately contained. To ensure an open and transparent process, the WPA and its successor should review applications using the NRA special requirements (based on Appendix 4) within established time-frames. It should be accountable and open to appeal.

Recommendation 21

It is recommended to the ministers of health and agriculture that:

- **the current functions and membership of the Working Party on Antibiotics (WPA) be expanded to carry out the antibiotic risk management program outlined in earlier recommendations;**
- **the administrative and reporting arrangements of the WPA (or its successor) be clarified so it can maintain its independent position and advise the Therapeutic Goods Administration (TGA) and the National Registration Authority (NRA) and other agencies/statutory bodies as required;**
- **the coordination of the antibiotic risk management program across government portfolios and industry be provided with secure recurrent funding for the additional tasks outlined in Recommendations 1 to 20;**
- **the WPA or its successor keep the regulatory framework for the use of antibiotics in human and veterinary medicine and food-producing animals under review and make appropriate recommendations to the regulatory authorities to review the uses of particular antibiotics, taking account of**
  - **the importance of the drug or class of drug in human and veterinary medicine, and**
  - **the potential for human exposure to antibiotic-resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their antibiotic-resistance genes to human pathogens;**

- **the WPA or its successor, the National Registration Authority and the Therapeutic Goods Administration develop appropriate procedures to ensure accountability and transparency of its activities, including established time-frames for reviews;**
- **the WPA (or its successor) develop a five-year strategic plan and an annual budget for its activities; and**
- **the operations of the WPA (or its successor) be subject to a five-year independent review program.**

During the course of preparing this report, JETACAR recognised that its conclusions and recommendations could lead to the incorrect impression that most antibiotic-resistance problems can be attributed to antibiotic use in animals. As noted in this report, however, human use and misuse of antibiotics is a major contributor to emerging resistance and Australia's medical use patterns are far from ideal. Considerable efforts have been made by many authorities and organisations in recent years to address medical antibiotic use. Despite this, the prescription volumes remain high and some resistances are worsening. There is an urgent need to coordinate and supplement current efforts to improve medical antibiotic use in Australia and reduce resistance selection pressure.

Recommendation 22

That the Department of Health and Aged Care convene a working group to develop a fully coordinated resistance management plan for human antibiotics, incorporating the elements included in Recommendations 9, 10, 11, 14, 15, 16, 17, 18, 19 and 20. The plan so developed should be incorporated into the recommended functions of the Working Party on Antibiotics or its successor (see Recommendation 21).

Appendix 1
International reviews

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Australian reports

NHMRC (National Health and Medical Research Council) (1986). *Antibiotics in Stockfeeds,* Australian Government Publishing Service, Canberra.

NHMRC (1994). *Antibiotics in Agronomy and Horticulture,* Australian Government Publishing Service, Canberra.

NHMRC (1996). *Emergence of Vancomycin Resistant Enterococci in Australia,* Australian Government Publishing Service, Canberra.

Appendix 2
JETACAR work plan

1. Assess the current knowledge that use of antibiotics in livestock production contributes to development of antibiotic-resistant organisms in humans
    - 1.1 Classes of antibiotics being used in animals/purpose/quantities
    - 1.2 Antibiotics in common use for animals/humans
    - 1.3 Alternatives to antibiotics in common use
      Evidence for cross-resistance
    - 1.4 Factors likely to promote development of antibiotic-resistant organisms
    - 1.5 Factors likely to promote transfer of antibiotic-resistant organisms from animals to humans
    - 1.6 How else is resistance generated/transferred
    - 1.7 Priority medical conditions in humans for which antibiotic resistance is a critical problem
    - 1.8 Theoretical basis (for transfer of antibiotic-resistant diseases from animals to humans)
    - 1.9 Evidence (for transfer of antibiotic-resistant diseases from animals to humans)
    - 1.10 Results of other expert groups
2. Determine data required to register new antibiotics for animal use in order to minimise the health impact on animals and humans
    - 2.1 Current data requirements for registration in Australia
    - 2.2 Current data requirements for registration overseas
    - 2.3 Additional data required in Australia
    - 2.4 Justification for additional data requirements
3. Determine the surveillance systems required to give early warning signals of development of new or escalating levels of antibiotic resistance in humans and animals and to monitor effectiveness of control mechanisms
    - 3.1 Systems in Australia to report on antibiotic consumption in animals/humans
    - 3.2 Systems in Australia to report on status of antibiotic-resistant organisms
    - 3.3 Do these systems constitute risk management?
    - 3.4 Further monitoring systems required
    - 3.5 Systems for better risk management in future
    - 3.6 Cost of monitoring/surveillance
    - 3.7 Cost of not having monitoring/surveillance

4. Identify studies to increase knowledge for executing better risk management strategies
    - 4.1 Work currently under way to provide new information
    - 4.2 Additional work needed to help management strategy
5. Restrictions/limitations on the usage of certain antibiotics in animals and in humans
    - 5.1 Differences between organisms in likelihood of developing resistance
    - 5.2 Critical antibiotics for treatment of disease in humans
    - 5.3 Critical antibiotics for treatment of disease in animals
    - 5.4 Antibiotics used as growth promotants
    - 5.5 Economic benefits of growth promotants
    - 5.6 Examples of economically viable livestock production practices that do not use antibiotic growth promotants
    - 5.7 Restrictions on antibiotic use in other countries
    - 5.8 Local versus international effects?
    - 5.9 International cooperation
6. Recommendations on alternative measures to overcome adverse health and economic consequences of imposed restrictions
    - 6.1 Alternatives to antibiotic growth promotants for animal production
    - 6.2 Market premium for animal products produced in antibiotic-free environment

Appendix 3
Stakeholder submissions to JETACAR

Initial consultation (June 1998)

Australian Beef and Sheepmeat Industry

Australian Dairy Industry Council

Australian Egg Industry Association

Australia New Zealand Food Authority

Australian Pharmaceutical Manufacturer Association

Australian Society for Microbiology

Australian Veterinary Association

Avcare

Consumers' Health Forum of Australia

Dairy Farmers

Department of Agriculture, Fisheries and Forestry — Australia

Elanco Animal Health

National Registration Authority for Agricultural and Veterinary Chemicals

NSW Agriculture

Pfizer Animal Health

Pig Research and Development Corporation

Public Health Division and National Centre for Disease Control, Commonwealth Department of Health and Aged Care

Roche Vitamins Australia Pty Ltd

The Woolmark Company

Thoracic Society of Australia and New Zealand

Victorian Dairy Industry Authority

Victorian Department of Human Services

Victorian Farmers' Federation, Pastoral Group

Submissions on draft report (March 1999)

ACT Department of Health and Community Care

Agriculture Western Australia

Australia New Zealand Food Authority

Australian Chicken Meat Federation

Australian Dairy Industry Council

Australian Drug Evaluation Committee

Australian Egg Industry Association

Australian Lot Feeders' Association #

Australian Meat Council

Australian Medical Association

Australian Pharmaceutical Manufacturers Association

Australian Society for Microbiology

Australian Veterinary Association

Avcare

Cattle Council of Australia #

Commonwealth Department of Health and Aged Care

Consumers' Health Forum of Australia

Department of Agriculture, Fisheries and Forestry — Australia

Elanco Animal Health

Health Department of Western Australia

Meat and Livestock Australia #

National Meat Association of Australia

National Registration Authority

Nature Vet

NSW Agriculture

Pfizer Animal Health

Pork Council of Australia

Public Health Association of Australia

Queensland Health

Ridley Agri Products

Roche Vitamins, Australia

Stock Feed Manufacturers' Association of Australia

Tasmanian Department of Health and Human Services

Therapeutic Goods Administration

Veterinary Manufacturers and Distributors Association

= Joint submission

Appendix 4
Draft amended Special Data Requirements for new antibiotic applications

(a) Detailed description of the product to be marketed (trade name, name of the drug and strengths, pharmaceutical form(s) and pack size(s). The chemical structure and class of the antibiotic(s) should also be provided. Where known, its relationship to other members of its class and related classes should be discussed.

(b) The intended clinical or other indications of the product.

(c) Is it to be administered at the recommendation and under the control of a registered veterinary surgeon? If not, please give details of how the distribution, dispensing and use of the product will be controlled and recorded.

(d) Has approval been given for the marketing of products containing the substance(s) in overseas countries for these and other indications? If so, please give an outline of the approved usage patterns and the nature of any relevant restrictions on the use of the product in the countries where it is approved. Describe any post-registration information on efficacy and safety that is available.

(e) Details of the antibacterial spectrum of the substance should be provided. Studies which have examined the minimum inhibitory concentrations (MICs) of the substance and the validity of the methods used to derive these data should be provided. MIC frequency histograms should be provided where possible. The antibacterial mechanism of action of the substance should be explained.

(f) The intended method of administration and dose regimen (dose rate(s), frequency, duration). A summary of the pharmacokinetics of the substance should include the absorption, distribution, metabolism and excretion of the substance(s). This should include the serum and tissue concentrations following dosing programs, with the likely peaks, troughs and area under curves and the achievable levels in target tissue(s) and their relationship to MICs for important pathogens. Post-antibiotic effects should be described. The tissue concentration(s) of the substance over time may be used to justify the dosing program(s) selected for the target species.

(g) A risk assessment for possible contribution to antimicrobial resistance in animal and human pathogens should be prepared. The level of acceptable risk is that with a reasonable certainty of no harm.

The risk assessment may include consideration of studies or discussion of the following areas:

i the known mechanism of resistance pathways in bacteria exposed to the substance and/or to other members of the same class of antibacterial agents.

ii the estimated rate of development of expression of resistance, such as indicated from in vitro studies of passaged bacteria in the presence of the substance as well as from field monitoring experience.

iii the MICs of field isolates collected following clinical or other use of the substance or related substances during and after field trials, the MICs of field isolates after clinical or other use of the product following its registration in other countries. Details of any microbial resistance patterns which have emerged with the use of the product, the substance or related substance(s) should be discussed.

iv evidence of any cross-resistance with other antimicrobial agents should be submitted.

v the likely effects of any resistance should be considered in terms of efficacy against target pathogens, and against organisms which may (or may not) enter the food chain. This assessment would include discussion of the levels of carriage of foodborne pathogens, such as *Salmonella* or *Campylobacter* species, in populations of the target animals and their likely exposure to the product intended for administration. The MICs of the substance against these bacteria should be indicated where exposure is considered likely.

vi the assessment may include assignment of the product to a suggested ranking with regards to the likelihood of the development of significant reductions in susceptibility of animal and human pathogens to its group of substances, and the clinical importance of the class of antibiotics for animals and humans.

Group 1 antibiotics would include clinically important drugs thought to have a high likelihood of development of reductions in susceptibility in pathogens following their use. Group 2 would include those with a moderate likelihood of reductions in susceptibility. Group 3 would include antibiotics of lesser clinical importance with a low likelihood of meaningful reductions in susceptibility, such as ionophores.

The risk stratification may need to separate the strands making up the overall risk group. These strands may include the differing importance of the antibiotic in animals and humans, the differing risks of development of resistance in target and foodborne pathogens, and the comparison of these risks to the importance of the use of the antibiotic in animals.

(h) If the substance is to be used as a digestion enhancer, or if it is likely to be present as an active substance in the lower intestinal tract, then its likely effect on the flora of the gastrointestinal tract must be discussed. While there are currently no validated tests to detect any adverse effects, studies discussed could include: evidence of likely residue concentrations of <1 ppm of the substance in the colon contents; studies of the effects of the substance or related substances on the coliform content and coliform resistance patterns in animals or animal products; studies of the effects of the substance on a range of intestinal anaerobes.

(i) As part of pharmacovigilance programs, companies wishing to register a product must give a commitment to monitoring studies designed to detect major changes in susceptibility of bacterial pathogens to the product following registration. These monitoring studies should include foodborne bacteria where appropriate. The scope and frequency of the studies should be designed to reflect the risk

ranking assessment (1 to 3) of the antibiotic group to which the substance is considered to belong.

A single laboratory capable of performing MIC studies to appropriate standard methods (such as National Consultative Committee on Laboratory Standards, document M31-T, 1997) should be chosen to receive isolates of target pathogens, and foodborne bacteria such as *Salmonella* where appropriate. At least 5 sub-clones per isolate should be evaluated in tests for MICs of the active substance(s) in each registered product.

The origin of the isolates may be samples taken from animals comparable with those used in field trials, or from food animal products taken at slaughter. MIC frequency histograms should be developed where possible, for longitudinal comparison to pre-registration data. An annual report should be submitted to the NRA in the first instance, as a condition of registration.

(j) Proposed post-registration resistance monitoring studies should indicate some threshold values of changes in the frequency of susceptibility, wherein step-wise actions could be implemented to alert veterinary associations and other authorities where appropriate. The company should indicate a set of possible action points in a step-wise manner. For example, a 10–20% reduction in the proportion of isolates showing susceptibility could lead to discussion meetings between the National Registration Authority for Agricultural and Veterinary Chemicals (NRA), Australian Veterinary Association (AVA), Working Party on Antibiotics (WPA) and the companies. All activities and actions taken as a result of monitoring studies should be subject to review.

Appendix 5
Uses of antibiotics in nonfood-producing animals and fish

The registered uses of antibiotics for treatment and prophylaxis in food producing animals and registered growth promotion uses were shown in Chapter 7 (Tables 7.4 and 7.5). Prophylactic and therapeutic uses in horses, pets and fish are shown in the following tables. Most of these products are registered by the National Registration Authority (NRA) and are restricted to use under veterinary direction. However, some are registered by the Therapeutic Goods Administration for human use and are permitted for use under veterinary supervision in nonfood animals. A few are permitted for use under an NRA permit.

Categories

Categories A, B and C, indicating the importance of a particular antibiotic for use in each species, are shown the tables. They are defined as already described in Chapter 7 for food-producing animals and human antibiotics, viz:

Category A: Essential antibiotics for treatment of animal infections where there are few or no alternatives for many infections.

Category B: Other alternatives are available but fewer alternative than category C or concerns that use will lead to more change of resistance in category A drugs.

Category C: A reasonable number of alternative agents in different classes are available to treat most infections.

Horses

Class Antibiotics	Therapeutic (individual treatment)	Therapeutic (feed/water)	Prophylactic (feed/water)	Common indications for use
Penicillins				
Amoxycillin[a]	Yes (C)	No	No	Neonatal respiratory disease, joint sepsis, surgical prophylaxis, wounds
Procaine penicillin	Yes (C)	No	No	
Ampicillin	No	No	No	
Cloxacillin	Yes (C)	No	No	Eye ointment
Cephalosporins				
Ceftiofur	Yes (B)	No	No	Respiratory disease
Cephalonium		No	No	
Cephuroxime		No	No	
Macrolides				
Erythromycin[b]	Yes (A)	No	No	Rhodococcal pneumonia in foals
Tylosin	No	No	No	
Oleandomycin	No	No	No	
Tetracyclines				
Oxytetracycline	Yes (C)	No	No	Respiratory disease
Aminoglycosides				
Neomycin	Yes (C)	No	No	Gram-negative sepsis, enteritis
Apramycin	No	No	No	
Gentamicin	Yes (B)	No	Yes(inject)(B)	Foal sepsis, surgical prophylaxis (gram negatives)
Nitrofurans				
Ntrofurazone	Yes (C)	No	No	Skin disease
Nitroimidazoles				
Metronidazole	Yes (B)	No	No	Pleuropneumonia, anaerobic sepsis, gastrointestinal surgical prophylaxis
Polypeptides				
Zn bacitracin	Yes (B)	No	No	Skin infections
Rifamycins Rifampicin	Yes (A)	No	No	Important therapeutic in rhodococcal pneumonia in foals recognised worldwide as the treatment of choice in combination with erythromycin
Sulfonamides				
Sulfadiazine plus trimethoprim	Yes (C)	No	No	Respiratory disease prophylaxis and therapy, urinary infections, joint and soft tissue infections as indicated
Sulfacetamide	Yes (C)	No	No	Eye and ear infections
Sulfadimidine	Yes (C)	No	No	Enteritis
Sulfadoxine	Yes (C)	No	No	Urinary, resp and reproductive tract infections
Sulfatroxazole	Yes (C)	No	No	Urinary, resp and reproductive tract infections
Streptogramins				
Virginiamycin[c]	No	No	Yes (A)	Laminitis prophylaxis

[a] Used off label (NRA registered for one or more animal species but not registered for horses)
[b] Human-registered product able to be used in nonfood animals under veterinary direction
[c] Open seller
Note: Categories of use (A, B, C) are shown in brackets.

Cats and dogs

Class Antibiotics	Therapeutic (individual treatment)	Common indications for use
Penicillins		
Amoxycillin	Yes (C)	Cat bite abscess, tracheobronchitis, surgical prophylaxis, urinary tract infections
Procaine	Yes (C)	Cat bite abscess
Ampicillin	Yes(rarely)(C)	Cat bite abscess
Cloxacillin/fluclox[b]	Yes (C)	Skin infections, surgical prophylaxis
Amoxycillin-clavulanate	Yes (C)	Infections of any tissue especially skin, urinary tract and respiratory
Piperacillin[b]	Yes (C)	Gram-negative ear infections
Benethamine penicillin	Yes (C)	
Benzathine penicillin	Yes (C)	
Cephalosporins		Most commonly used for skin infections
Ceftiofur	Yes (C)	
Cephalexin	Yes (C)	
Cefdroxil[b]	Yes (C)	
Macrolides		
Erythromycin[a]	Yes (B)	Respiratory tract disease in cats, skin infections, *Campylobacter jejuni*, mycoplasma and *Bartonella henselae*
Tylosin	Yes (B)	Respiratory tract disease in cats, skin infections, *Campylobacter jejuni*, mycoplasma and *Bartonella henselae*
Clarithromycin[b]	Yes(rarely)(B)	Mycobacterial infections in cats
Azithromycin[b]	Yes (rarely)	Mycobacterial infections in cats
Lincosamides		
Lincomycin	Yes (C)	Skin infections, anaerobic infections, osteomyelitis
Spectinomycin	Yes (C)	Mycoplasma infections in catteries
Clindamycin	Yes (B)	Anaerobic infections, osteomyelitis, toxoplasmosis
Spiramycin	Yes (C)	Oral infections (in combination with metronidazole)
Tetracyclines		Upper respiratory tract infections, especially cats, skin infections, atypical bacterial infections, urinary tract infections
Oxytetracycline	Yes (C)	
Chlortetracycline	Yes (C)	
Doxycycline[a]	Yes (C)	
Aminoglycosides		
Neomycin	Yes (C)	Gastrointestinal infection, hepatic encephalopathy
Gentamicin	Yes (B)	Urinary tract infection, pneumonia, septicaemia, otitis
Amikacin[b]	Yes (C)	Serious gram-negative infections
Streptomycin	Yes (C)	
Framycetin[b]	Yes (C)	Ophthalmic
Nitrofurans		
Nitrofurazone	Yes (B)	Ear and skin infections
Nitroimidazoles		
Metronidazole	Yes (C)	Oral infections, abscesses, hepatic encephalopathy, giardiasis
Polypeptides		
Zn bacitracin[a]	Yes (C)	Skin infections
Amphenicols		
Chloramphenicol	Yes (C)	Eye infections primarily, central nervous system infections
Fluoroquinolones		
Enrofloxacin	Yes (B)	Urinary tract infection, septicaemia, pneumonia, atypical bacterial infections

Cats and dogs (contd)

Class Antibiotics	Therapeutic (individual treatment)	Common indications for use
Rifamycins		
Rifampicin[b]	Yes(rarely) (C)	Deep granulomatous pyoderma
Sulfonamides		
Sulfadiazine plus trimethoprim	Yes (C)	Urinary tract infection (esp. prostate), pyoderma, tracheobronchitis
Sulfadimidine	Yes (C)	Gastrointestinal infection
Sulfadiazine	Yes (C)	Gastrointestinal infection
Sulfadoxine plus trimethoprim	Yes (C)	Urinary tract infection (esp. prostate), pyoderma, tracheobronchitis
Phthalyl sulfathiazole	Yes (C)	Gastrointestinal infections
Baquiloprim	Yes (C)	Gastrointestinal infection, coccidiosis

[a] Used off label (NRA registered for one or more animal species but not for pets)
[b] Human-registered product able to be used in nonfood animals under veterinary direction
Note: Categories of use (A, B, C) are shown in brackets

Fish (aquaculture)

Class Antibiotics [a]	Therapeutic (individual treatment)	Therapeutic (feed/water)	Prophylactic (feed/water)	Common indications for use
Penicillins				
Amoxycillin	No	Yes	No	Control of bacterial diseases in salmonids, southern bluefin tuna and other fin fish
Tetracyclines				
Oxytetracycline	No	Yes	No	Control of bacterial diseases in barramundi, native fish, prawns, eels and salmonids
Sulfonamides				
Sulfadimidine plus trimethoprim[b]	No	Yes	No	Control of bacterial diseases in barramundi and salmonids

[a] Used under NRA permit system
[b] Permit application pending

Appendix 6
Vancomycin-resistant enterococci in Australia

There have been 71 confirmed isolates or clusters of isolates of VRE from human clinical specimens in Australia up to September 1998. A number of additional isolates have been detected on patient screening. These additional isolates have not been systematically recorded or counted and therefore unbiased information on these is not available. The pattern of isolation of these organisms is in large part sporadic at the institutional, regional and national level. Only one strain has been definitely imported and two others possibly imported. The rest appear to have arisen in Australia. Unlike the United States and Europe, the predominant phenotype/genotype is *vanB Enterococcus faecium*. This genotype has not so far been associated with animal use of avoparcin.

There has been no epidemiological evidence of transfer of strains between hospitals in Australia; strains appear to have arisen de novo at each institution. Even at single institutions with repeated isolations of VRE, multiple different types have been found in most instances.

Resistance genotypes

Species	*vanA*	*vanB*	*nonABC*	Total
E. faecium	14	42	–	**56**
E. faecalis	3	9	3	**15**
Total	**17**	**51**	**3**	**71**

Evolution of clinical VRE isolates over time by institution

Institution	Year and quarter (q)																	Total for
	1994		1995				1996				1997				1998			
and city*	q3	q4	q1	q2	q3	q4	q1	q2	q3	q4	q1	q2	q3	q4	q1	q2	q3	Institution
A – Mel	1								1			3						5
B – Dar				1														1
C – New								1				2	1					4
D – Syd								1	1	4	3	2	1			1		13
E – Bri								1		1		1						3
F – Bri									1	1								2
G – Mel									1	1					2			4
H – Per									1									1
I – Bri									1	1	1	1				1	1	6
J – Syd									1							1		2
K – Mel										1								1
L – New										1		1	2	1	2			7
M – Mel												1						1
N – Syd												1						1
O – Ade													2					2
P – Mel														1				1
Q – New															1			1
R – Per															1			1
S – Mel															2		1	3
T – Vic																1		1
U – Bri																1	2	3
V – NSW																1	1	2
W – Bri																	2	2
X – Syd																	1	1
Y – NSW																	1	1
Z – Mel																	1	1
AA – Per																	1	1
Total for quarters	1	0	0	1	0	0	0	3	7	10	4	12	6	2	8	6	11	71

Appendix 7
Antibiotic resistance data in animals

Central Veterinary Diagnostic Laboratory:

IDEXX Salmonella resistance results, March 1996 — May 1998

	Positive isolates/total isolates tested					
	Ampicillin	**Amoxycillin**	**Trimethoprim**	**Sulfonamides**	**Tetracycline**	**Gentamicin**
Equine	2/8	NT	2/8	3/8	NT	1/8
Bovine	3/19	4/18	4/19	13/19	4/18	0/19
Avian	1/6	0/3	1/6	1/6	0/6	0/6
Canine	0/11	0/11	2/12	1/12	0/11	0/12
Feline	0/2	0/2	1/2	½	0/2	0/2
Reptile	1/5	0/4	1/5	1/5	0/4	0/5
Wombat	0/1	0/1	0/1	0/1	NT	0/1

Note: 4 of the bovine strains and 1 of the equine strains were resistant to 4 or more different classes of antibiotics
Source: Routine diagnostic submissions

Resistance of *E. coli* isolates from the laboratories of 3 chicken meat production companies

Amoxycillin	**Lincomycin–spectinomycin**	**Sulfonamides–trimethoprim**	**Tetracycline**	**Oxytetra-cycline**	**Neomycin**	**Chloram-phenicol**	**Gentamicin**
18/52 (35%)	–	12/52 (23%)	–	38/52 (73%)	–	–	–
26/62 (42%)	2/61 (3%)	26/61 (43%)	44/62 (71%)	32/44 (73%)	5/62 (8%)	2/44 (5%)	0/44 (0%)
3/12 (25%)	–	7/11 (64%)	–	9/12 (75%)	–	–	–

Note: gentamicin and chloramphenicol not registered for use in poultry in Australia
Source: courtesy of Dr Tom Grimes, 1998

RESISTANCE DATA ON SALMONELLA FROM THE NATIONAL ENTERIC PATHOGEN SURVEILLANCE PROGRAM – Microbiology Diagnostic Unit, University of Melbourne

Data kindly supplied by Drs Diane Lightfoot and Geoffrey Hogg.

Methods: strains are batch tested by the agar dilution breakpoint method

All strains of salmonella from all sources have been tested for their susceptibility to a range of antibiotics since 1988. Data presented here are a selection from the data available.

Table A shows the percentage of all strains tested isolated from food animals or food that were resistant to any of the antibiotics tested, according to source. The presence of resistance(s) was highest in pig isolates (>50%), followed by poultry isolates (>40%), with other sources having rates on the average less than 20%. There has been no obvious evolution of resistance.

Tables B, C and D show data on three phage types of *Salmonella* Typhimurium (PT9, PT44 and PT135). These strains were selected because there were sufficient numbers in humans and animals to make a meaningful comparison. For PT9, resistance rates in general are low for both human and animal strains. There is moderate resistance to streptomycin in bovine strains. The majority of animal isolates are from cattle, which are presumed to be the ultimate source for many human isolates. However, resistance rates in human strains have been consistently lower than bovine strains, suggesting that sources other than cattle are important for human infection with this phage type. Resistance rates for PT44 are higher, but the conclusions are otherwise similar to PT9. Again, cattle have been presumed to be the main source of human infection but resistance rates are consistently lower in human than bovine strains. There was a simultaneous rise in resistance rates in PT135 in the mid-1990s in both human and chicken isolates.

Resistance to nalidixic acid (a quinolone) is rare, in accordance with the non-use of quinolones in veterinary medicine in Australia.

A. Resistance to any antibiotics in salmonella[a] isolates of animal or food origin, Australia 1989–94

Source		1989	1990	1991	1992	1993	1994	Total
Bovine	Total	181	321	383	851	716	601	3053
	No R[b]	51	51	47	61	79	102	391
	%R[b]	28.1	15.8	12.3	7.1	11.0	17.0	12.8
Sheep	Total	7	106	22	11	16	21	183
	No R	1	4	0	1	1	4	11
	%R	14.3	3.7	0	9.1	6.3	19.0	6.0
Pig	Total	7	14	10	12	9	13	65
	No R	6	4	4	9	6	7	36
	%R	85.7	28.6	40.0	75.0	66.7	53.8	55.4
Poultry[c]	Total	184	178	541	665	207	77	1851
	No R	81	61	256	276	54	24	752
	%R	44.0	34.2	47.0	41.5	26.0	31.2	40.6
Other animals[d]	Total	44	82	91	76	126	162	581
	No R	24	24	11	17	13	24	113
	%R	54.5	29.3	12.1	22.3	10.3	14.2	19.4
Milk/Milk products	Total	50	54	49	12	26	76	267
	No R	16	3	0	0	1	6	26
	%R	32.0	5.5	0	0	3.8	7.9	9.7
Egg/Egg products	Total	35	123	45	72	16	53	344
	No R	4	11	10	22	0	0	47
	%R	11.0	8.9	22.2	30.5	0	0	13.7
Meat/Meat products	Total	32	52	27	12	11	52	186
	No R	10	2	5	2	3	12	34
	%R	31.2	3.8	18.5	16.7	27.3	23.0	18.3
Other food[e]	Total	14	52	8	18	25	55	172
	No R	7	0	0	1	2	4	14
	%R	50.0	0	0	5.5	8.0	7.3	8.1
All	Total	554	982	1176	1729	1152	1110	6702
	No R	200	160	333	389	159	183	1424
	%R	36.1	16.3	28.3	22.5	13.8	16.5	21.2

R = resistant

[a] Salmonella of all species and serovars

[b] Number and percentage of strains resistant to ANY antibiotic tested: ampicillin, streptomycin, tetracycline, chloramphenicol, sulfamethoxazole, trimethoprim, kanamycin, nalidixic acid, spectinomycin, ciprofloxacin

[c] Poultry includes chickens (meat and egg-laying), turkeys, quail and pigeons

[d] Other animals includes horses, dogs, cats, zoo animals and native animals

[e] 'Other food' includes all other types of foods, herbs and spices not listed in the other food sources

B. *Salmonella* Typhimurium Phage Type 9 — Percentage resistant to 11 antibiotics, 1988–98

Year	Source	No.	Antibiotic										
			Ampicillin	Tetracycline	Chloramphenicol	Sulfamethoxazole	Trimethoprim	Streptomycin	Kanamycin	Spectinomycin	Gentamicin	Nalidixic acid	Ciprofloxacin
1988	Human	283	1	0	0	7	0	7	0	–	–	0	–
	Bovine	47	0	0	0	4	0	13	0	–	–	0	–
	Poultry[a]	2	0	0	0	0	0	0	0	–	–	0	–
	Other	6	0	0	0	17	0	0	0	–	–	0	–
1989	Human	343	1	0.6	0	5	0.3	6	0	–	–	0	–
	Bovine	76	3	4	0	25	0	29	3	–	–	0	–
	Poultry	10	0	10	0	0	0	10	0	–	–	0	–
	Other	36	3	3	0	0	0	3	3	–	–	0	–
1990	Human	308	1	1	0	4	0.3	5	0	–	–	0	–
	Bovine	81	1	2	1	21	0	20	1	–	–	0	–
	Poultry	3	0	0	0	0	0	0	0	–	–	0	–
	Other	32	9	3	3	6	0	16	0	–	–	0	–
1991	Human	292	0.3	0.3	0	2	0	3	0	–	–	0	–
	Bovine	91	2	1	9	9	2	10	2	–	–	0	–
	Poultry	0											
	Other	24	0	0	0	4	0	4	0	–	–	0	–
1992	Human	268	1	1	0	3	0.4	4	0	–	–	0	–
	Bovine	429	2	2	0.2	3	1	3	0.5	–	–	0	–
	Poultry	0											
	Other	14	0	0	0	0	0	0	0	–	–	0	–
1993	Human	196	1	0.5	0	3	0.5	9	0.5	0	0	0	–
	Bovine	192	3	4	1	10	3	10	4	1	1	0	–
	Poultry	6	0	0	0	0	0	0	0	0	0	0	–
	Other	37	0	0	0	0.3	0	0.3	0	0	0	0	–
1994	Human	390	1	0.8	0.3	2	0.2	3	0	0.2	0	0	0
	Bovine	132	4	6	0.8	15	4	15	5	0.8	0	0	0
	Poultry	13	0	8	0	0	0	0	0	0	0	0	0
	Other	20	0	0	0	5	0	5	0	0	0	0	0
1995	Human	395	1	0.8	0	6	1	6	0.5	0.3	0	0	0
	Bovine	158	3	1	0.6	10	1	13	0.6	0.6	0	0	0
	Poultry	14	0	0	0	0	0	0	0	0	0	0	0
	Other	30	0	0	10	7	0	7	3	3	0	0	0
1996	Human	496	0.6	0.2	0	3	0.2	3	0	0	0	0	0
	Bovine	93	2	2	0	9	1	9	1	0	0	0	0
	Poultry	7	0	0	0	0	0	0	0	0	0	0	0
	Other	2	0	0	0	0	0	0	0	0	0	0	0
1997	Human	615	0.5	0.3	0	2	0.2	2	0	0	0	0	0
	Bovine	145	1	2	0	24	2	25	1	0	0	0	0
	Poultry	6	0	0	0	67	0	67	0	0	0	0	0
	Other	18	0	0	0	6	0	6	0	0	0	0	0
1998[ab]	Human	422	0.7	0.7	0.2	3	0	4	0.2	0	0	0	0
	Bovine	80	3	1	0	13	2	13	2	0	0	0	0
	Poultry	5	0	0	0	0	0	0	0	0	0	0	0
	Other	14	0	0	0	0	0	0	0	0	0	0	0

– = not tested

[a] includes chickens, turkeys, quail, pigeons

[b] up to 23 November 1998

C. *Salmonella* Typhimurium Phage Type 44 — Percentage resistant to 11 antibiotics, 1988–98

Year	Source	No.	Ampicillin	Tetracycline	Chloramphenicol	Sulfamethoxazole	Trimethoprim	Streptomycin	Kanamycin	Spectinomycin	Gentamicin	Nalidixic acid	Ciprofloxacin
1988	Human	63	2	2	2	25	2	24	0	–	–	0	–
	Bovine	31	0	0	0	13	0	13	0	–	–	0	–
	Poultry[a]	0											
	Other	3	33	33	33	33	33	33	33	–	–	0	–
1989	Human	70	6	1	0	9	1	9	0	–	–	0	–
	Bovine	16	13	19	0	38	19	38	19	–	–	0	–
	Poultry	0											
	Other	3	0	0	0	33	0	33	0	–	–	0	–
1990	Human	38	11	3	3	3	3	5	3	–	–	0	–
	Bovine	32	3	6	0	13	0	13	3	–	–	0	–
	Poultry	1	100	0	0	0	0	0	0	–	–	0	–
	Other	1	0	0	0	0	0	0	0	–	–	0	–
1991	Human	46	0	2	0	7	0	7	0	–	–	0	–
	Bovine	82	0	0	0	10	0	10	0	–	–	0	–
	Poultry	1	0	0	0	0	0	0	0	–	–	0	–
	Other	1	0	0	0	0	0	0	0	–	–	0	–
1992	Human	34	3	6	6	15	6	15	6	–	–	0	–
	Bovine	129	5	9	5	13	9	9	9	–	–	0	–
	Poultry	5	0	0	0	0	0	0	0	–	–	0	–
	Other	0											
1993	Human	106	6	5	3	9	7	13	3	0	0	0	–
	Bovine	121	17	23	15	35	23	31	22	0	0	0	–
	Poultry	1	100	100	100	100	100	100	100	0	0	100	–
	Other	13	38	54	54	54	54	38	54	0	0	0	–
1994	Human	169	8	8	7	8	6	9	2	1	0	0	0
	Bovine	78	47	55	46	56	53	47	53	0	0	0	0
	Poultry	4	0	0	0	0	0	0	0	0	0	0	0
	Other	18	44	44	39	50	50	44	39	0	0	0	0
1995	Human	98	7	10	4	8	9	8	3	0	0	1	0
	Bovine	73	22	27	7	25	26	29	21	0	0	0	0
	Poultry	2	0	0	0	0	0	0	0	0	0	0	0
	Other	11	9	9	9	9	9	9	9	0	0	9	0
1996	Human	41	7	12	7	10	12	7	10	0	0	0	0
	Bovine	59	37	42	19	39	41	39	37	0	0	15	0
	Poultry	1	0	0	0	0	0	0	0	0	0	0	0
	Other	9	67	67	67	67	67	67	67	0	0	11	0
1997	Human	55	2	5	4	5	5	2	0	4	0	0	0
	Bovine	48	15	19	4	19	19	19	19	0	0	0	0
	Poultry	0											
	Other	1	0	0	0	0	0	0	0	0	0	0	0
1998[b]	Human	57	12	12	5	12	12	11	5	0	0	0	0
	Bovine	44	32	36	7	39	32	32	14	0	0	0	0
	Poultry	1	0	0	0	0	0	0	0	0	0	0	0
	Other	1	100	100	0	100	100	100	0	0	0	0	0

– = not tested

[a] includes chickens, turkeys, quail, pigeons

[b] up to 23 November 1998

D. *Salmonella* Typhimurium Phage Type 135 – Percentage resistant to 11 antibiotics, 1988–98

Year	Source	No.	Ampicillin	Tetracycline	Chloramphenicol	Sulfamethoxazole	Trimethoprim	Streptomycin	Kanamycin	Spectinomycin	Gentamicin	Nalidixic acid	Ciprofloxacin
1988	Human	233	2	0	0	0.4	0	0.4	0	–	–	0	–
	Bovine	31	0	0	0	0	0	0	0	–	–	0	–
	Poultry[a]	3	0	0	0	33	0	0	0	–	–	0	–
	Other	5	0	0	0	0	0	0	0	–	–	0	–
1989	Human	215	3	2	0	2	0.5	2	0	–	–	0.5	–
	Bovine	17	0	6	0	0	0	0	0	–	–	0	–
	Poultry	5	0	0	0	0	0	0	0	–	–	0	–
	Other	23	0	0	0	0	0	0	0	–	–	0	–
1990	Human	237	12	2	0.4	7	2	21	0	–	–	0.4	–
	Bovine	50	2	0	0	0	0	0	0	–	–	0	–
	Poultry	4	0	0	0	0	0	0	0	–	–	0	–
	Other	11	36	9	0	9	9	9	9	–	–	0	–
1991	Human	195	2	0	0	0.5	0	0.5	0	–	–	0.5	–
	Bovine	94	0	0	0	0	0	0	0	–	–	0	–
	Poultry	11	0	0	0	0	0	9	0	–	–	0	–
	Other	4	0	0	0	0	0	0	0	–	–	0	–
1992	Human	121	4	7	4	4	0.8	5	0.8	3	–	0	–
	Bovine	56	2	4	0	4	1	4	0	2	–	0	–
	Poultry	2	0	0	0	0	0	0	0	0	–	0	–
	Other	5	0	0	0	0	0	0	0	0	–	0	–
1993	Human	182	6	3	0.5	3	2	2	0	0	0	0	–
	Bovine	81	1	3	0	3	3	3	3	0	0	0	–
	Poultry	1	0	0	0	0	0	0	0	0	0	0	–
	Other	2	0	0	0	0	0	0	0	0	0	0	–
1994	Human	361	26	3	0.6	3	1	1	0	0.8	0	0	0
	Bovine	26	4	8	0	8	4	8	4	4	0	0	0
	Poultry	12	50	0	0	0	0	0	0	0	0	0	0
	Other	14	0	0	0	0	0	0	0	0	0	0	0
1995	Human	417	22	2	0	7	4	3	0.2	0	0	0	0
	Bovine	36	17	11	0	11	0	14	11	0	0	0	0
	Poultry	6	0	0	0	0	0	0	0	0	0	0	0
	Other	33	12	0	0	0	0	0	0	0	0	0	0
1996	Human	370	10	4	0	5	0	3	0.3	1	0	0	0
	Bovine	23	4	4	0	4	4	22	4	0	0	0	0
	Poultry	7	14	0	0	14	14	29	0	0	0	0	0
	Other	20	5	0	5	5	0	5	0	0	0	0	0
1997	Human	615	8	4	0.5	11	7	2	0.3	2	0.2	0.5	0.2
	Bovine	32	0	0	0	0	0	0	0	0	0	0	0
	Poultry	2	0	0	0	50	50	0	0	0	0	0	0
	Other	17	6	6	0	12	12	0	0	0	0	0	0
1998[b]	Human	543	12	4	0	14	3	1	0.9	0.6	0	0	0
	Bovine	18	22	6	6	22	22	28	22	0	0	0	0
	Poultry	0											
	Other	4	25	0	0	25	0	0	0	0	0	0	0

– = not tested

[a] includes chickens, turkeys, quail, pigeons

[b] up to 23 November 1998

Appendix 8
Antibiotic imports to Australia, 1992–97

The tables that follow provide information on the importation volumes of antibiotics into Australia for financial years 1992–93 to 1996–97. A summary of these figures, expressed as five-year averages, is provided in Table 7.1 in the body of the report. As no antibiotics are manufactured in Australia, these figures are reasonably representative of Australian consumption. Imported antibiotics that are re-exported have been excluded from the tallies.

The following points are important in the interpretation of the figures:

- Importers are required to specify 'end-use' according to the types of use listed in the table: namely 'human', 'stockfeed', and 'veterinary'. This can oversimplify the end use. In particular, the split of stockfeed and veterinary is not precise because separation is often difficult. Some stockfeed use is for short-term therapeutic use, rather than for growth promotion or prophylactic use. In addition, some veterinary use is for long-term prophylactic use. Some products fall into both use types, of necessity, the importer nominates only one.

- For some multiple biologics the importer did not provide weights of the individual constituents. Thus, there are separate groups provided for these, rather than the individual biologics being assigned to a group.

- Although it is unclear at present to the committee, the antiprotozoals (amprolium, dinitolmide, nicarbazin and robenidine) appear to have no antibacterial activity. They are included because of doubt. These agents are used only as coccidiostats. Agents in other classes, especially the polyethers, DHFR inhibitors and sulfonamides, are also primarily used as coccidiostats, but in addition have antibacterial activity and some have growth promotion claims.

- DHFR = dihydrofolate reductase. Agents that inhibit this enzyme in the folate synthesis pathway are often combined with sulfonamides, which act on an enzyme earlier in the pathway, dihydropteroate synthetase.

Category and antibiotic	Import volume in kilograms																			
	1992-93				1993-94				1994-95				1995-96				1996-97			
	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total
Aminoglycosides and aminocyclitols																				
Amikacin	8	0	0	8	8	0	0	8	4	0	0	4	3	0	0	3	2	0	0	2
Apramycin	0	807	327	1134	0	1150	152	1302	0	986	0	986	0	3265	0	3265	0	0	412	412
Dihydrostreptomycin	5	0	6947	6952	0	5125	3607	8732	0	0	2336	2336	0	0	2700	2700	0	500	3036	3536
Framycetin	41	0	1	42	55	0	4	59	65	0	6	70	38	0	0	38	40	0	3	44
Gentamicin	202	0	155	357	447	0	391	838	261	0	92	353	431	0	334	765	510	0	3313	3823
Hygromycin b	0	1503	0	1503	0	1018	0	1018	0	980	0	980	0	792	0	792	0	508	0	508
Neomycin	74	1621	519	2214	47	2200	1787	4034	144	475	1405	2024	236	51	876	1163	89	2605	3012	5706
Netilmicin	0	0	0	0	2	0	0	2	0	0	0	0	1	0	0	1	0	0	0	0
Paromomycin	0	0	0	0	0	0	0	0	0	0	0	0	21	0	0	21	12	0	0	12
Spectinomycin	16	0	652	668	8	695	473	1176	0	232	273	505	4	100	0	104	8	28	0	36
Streptomycin	0	0	438	438	92	0	1093	1185	1	100	322	423	0	0	416	416	0	0	74	74
Tobramycin	34	0	0	34	36	0	0	36	77	0	0	77	26	0	0	26	203	0	0	203
Subtotal	380	3931	9039	13351	695	10188	7506	18389	551	2773	4433	7758	760	4208	4326	9294	865	3641	9850	14356
Aminoglycosides plus other agents																				
Neomycin / methscopolamine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12
Neomycin / novobiocin / dihydrostreptomycin	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	10	10
Neomycin/methylprednisolone	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
Subtotal	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	2	0	22	24
Amphenicols																				
Chloramphenicol	137	0	161	298	1	0	453	453	75	0	224	299	181	0	400	581	646	0	250	896
Subtotal	137	0	161	298	1	0	453	453	75	0	224	299	181	0	400	581	646	0	250	896
Ansamycins																				
Rifabutin	14	0	0	14	21	0	0	21	0	0	0	0	0	0	0	0	3	0	0	3
Rifampicin	300	0	0	300	500	0	0	500	339	0	28	367	1054	0	0	1054	287	0	10	297
Subtotal	315	0	0	315	521	0	0	521	339	0	28	367	1054	0	0	1054	290	0	10	300
Antiprotozoals																				
Amprolium	0	200	0	200	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dinitolmide (dinitro-orthotoluamide)	0	7000	0	7000	0	4050	0	4050	0	4850	0	4850	0	7750	0	7750	0	2000	0	2000
Nicarbazin	0	0	0	0	0	13228	0	13228	0	4561	0	4561	0	8619	0	8619	0	11702	0	11702
Robenidine	0	0	0	0	0	0	0	0	0	0	0	0	0	2200	0	2200	0	2000	0	2000
Subtotal	0	7200	0	7200	0	17278	0	17278	0	9411	0	9411	0	18569	0	18569	0	15702	0	15702
Antituberculars																				
Clofazimine	21	0	0	21	11	0	0	11	25	0	0	25	12	0	0	12	482	0	0	482
Cycloserine	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3	4	0	0	4
Ethambutol	200	0	0	200	350	0	0	350	453	0	0	453	0	0	0	0	405	0	0	405
Isoniazid	2	0	0	2	150	0	0	150	251	0	0	251	150	0	0	150	250	0	0	250
Pyrazinamide	1	0	0	1	24	0	0	24	297	0	0	297	2	0	0	2	1	0	0	1
Subtotal	224	0	0	224	535	0	0	535	1026	0	0	1026	166	0	0	166	1142	0	0	1142
Arsenicals																				
Roxarsone	0	1200	0	1200	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Category and antibiotic		Import volume in kilograms																			
		1992-93				1993-94				1994-95				1995-96				1996-97			
		Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total
2-nitro-4-phenyl arsonic acid		0	1750	0	1750	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4-hydroxy-3-nitrophenylarsonic		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2
	Subtotal	0	2950	0	2950	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2
ß-lactamase inhibitors																					
Potassium clavulanate		11148	0	26	11175	1275	0	11	1287	7822	0	22	7844	12144	0	36	12180	19859	0	0	19859
Tazobactam		0	0	0	0	6	0	0	6	0	0	0	0	0	0	0	0	12640	0	0	12640
	Subtotal	11148	0	26	11175	1281	0	11	1292	7822	0	22	7844	12144	0	36	12180	32499	0	0	32499
Carbapenems																					
Imipenem		4	0	0	4	61	0	0	61	2	0	0	2	47	0	0	47	66	0	0	66
Meropenem		0	0	0	0	0	0	0	0	2	0	0	2	1	0	0	1	21	0	0	21
	Subtotal	4	0	0	4	61	0	0	61	3	0	0	3	48	0	0	48	87	0	0	87
Cephalosporins																					
Cefaclor		3926	0	0	3926	6647	0	0	6647	1696	0	0	1696	11741	0	0	11741	7743	0	0	7743
Cfadroxil		0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	8	0	0	0	0
Cefepime		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	51	0	0	51
Cefotetan		618	0	0	618	693	0	0	693	810	0	0	810	433	0	0	433	520	0	0	520
Cefotaxime		16	0	0	16	51	0	0	51	141	0	0	141	0	0	0	0	0	0	0	0
Cefoxitin		32	0	0	32	21	0	0	21	1003	0	0	1003	451	0	0	451	110	0	0	110
Cefpirome		0	0	0	0	3	0	0	3	29	0	0	29	22	0	0	22	54	0	0	54
Cefpodoxime		0	0	0	0	26	0	0	26	15	0	0	15	3	0	0	3	5	0	0	5
Ceftazidime		71	0	0	71	77	0	0	77	143	0	0	143	0	0	0	0	342	0	0	342
Ceftiofur		0	0	2	2	0	0	4	4	0	0	58	58	0	0	0	0	0	0	7	7
Ceftriaxone		409	0	0	409	397	0	0	397	415	0	0	415	592	0	0	592	687	0	0	687
Cefuroxime		0	0	0	0	0	0	0	0	618	0	0	618	0	0	0	0	0	0	0	0
Cephalexin		15705	0	259	15964	16334	0	5	16339	11529	0	295	11824	13951	0	296	14247	14556	0	690	15246
Cephalothin		1307	0	0	1307	1152	0	0	1152	205	0	0	205	1553	0	0	1553	17397	0	0	17397
Cephamandole nafate		20	0	0	20	40	0	0	40	8	0	0	8	12	0	0	12	302	0	0	302
Cephazolin		238	0	0	238	288	0	0	288	252	0	0	252	221	0	0	221	591	0	0	591
Cephradine		0	0	0	0	0	0	0	0	91	0	0	91	85	0	0	85	0	0	0	0
	Subtotal	22343	0	261	22604	25729	0	9	25738	16953	0	353	17306	29064	0	304	29367	42357	0	697	43054
DHFR inhibitors																					
Diaveridine		0	0	0	0	0	0	0	0	0	0	25	25	0	0	25	25	0	0	0	0
Pyrimethamine		0	0	0	0	1	0	0	1	4	0	0	4	0	0	0	0	1	0	0	1
Trimethoprim		3655	0	666	4321	2576	0	716	3292	2775	797	834	4406	3283	250	644	4176	969	0	1763	2732
	Subtotal	3655	0	666	4321	2577	0	716	3293	2779	797	859	4435	3283	250	669	4201	970	0	1763	2733
DHFR inhibitors plus sulfonamides																					
Sulfisoxazole/trimethoprim		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Trimethoprim/sulfadiazine		0	0	0	0	0	0	0	0	0	0	100	100	0	0	0	0	0	0	0	0
Sulfadiazine/trimethoprim/clenbuterol		0	0	0	0	0	0	0	0	16	0	0	16	0	0	0	0	0	0	0	0
Sulfatroxazole/trimethoprim		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	52	52
Sulfadoxine/pyrimethamine		0	0	0	0	0	0	0	0	0	0	300	300	0	0	0	0	0	206	22	228

Category and antibiotic	Import volume in kilograms																			
	1992-93				1993-94				1994-95				1995-96				1996-97			
	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total
Subtotal	0	0	0	0	0	0	0	0	16	0	400	416	0	0	0	0	0	206	74	280
Fusidanes																				
Fusidate/ fusidic acid	0	0	3	3	4	0	3	7	87	0	4	91	289	0	3	292	215	0	0	215
Subtotal	0	0	3	3	4	0	3	7	87	0	4	91	289	0	3	292	215	0	0	215
Fusidanes & others																				
Diethanolamine fusidate/framycetin/nystatin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3
Subtotal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3
Glycopeptides																				
Avoparcin	0	11596	0	11596	0	16732	0	16732	0	600	0	600	0	13821	0	13821	0	7400	0	7400
Teicoplanin	0	0	0	0	1	0	0	1	6	0	0	6	5	0	0	5	5	0	0	5
Vancomycin	304	0	0	304	293	0	0	293	2016	0	0	2016	32	0	0	32	555	0	0	555
Subtotal	304	11596	0	11900	293	16732	0	17025	2022	600	0	2622	37	13821	0	13858	559	7400	0	7959
Glycophospholipids																				
Bambermycin	0	0	0	0	0	0	0	0	0	5625	0	5625	0	0	0	0	0	320	0	320
Subtotal	0	0	0	0	0	0	0	0	0	5625	0	5625	0	0	0	0	0	320	0	320
Lincosamides																				
Clindamycin	342	0	9	351	321	0	6	327	110	0	61	171	250	0	0	250	18753	0	4	18757
Lincomycin	79	0	399	478	51	1500	499	2050	0	1500	300	1800	76	10	160	246	0	1709	259	1968
Subtotal	421	0	408	829	372	1500	505	2376	110	1500	361	1971	326	10	160	496	18753	1709	263	20725
Lincosamides plus aminoglycosides																				
Lincomycin / neomycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1092	1092
Lincomycin / spectinomycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	145	145
Subtotal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1237	1237
Macrolides																				
Azithromycin	8	0	0	8	1	0	0	1	45	0	0	45	2	0	0	2	249	0	0	249
Clarithromycin	225	0	0	225	6	0	0	6	0	0	0	0	1	0	0	1	3	0	0	3
Erythromycin, salts and esters	66618	0	301	66919	57690	0	271	57961	6131	200	341	6672	54079	0	239	54318	37054	250	701	38005
Kitasamycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2000	0	2000
Oleandomycin	0	0	0	0	0	0	58	58	0	81	0	81	0	70	0	70	0	38064	0	38064
Roxithromycin	1412	0	0	1412	75	0	0	75	3968	0	0	3968	5292	0	0	5292	4607	0	0	4607
Spiramycin	0	0	0	0	0	625	156	781	0	0	0	0	0	0	6	6	0	0	241	241
Tilmicosin	0	0	28	28	0	0	37	37	0	0	54	54	0	0	803	803	0	10	9	19
Triacetyloleandomycin	0	0	0	0	0	0	0	0	9	0	0	9	0	0	0	0	0	0	0	0
Tylosin	0	13472	198	13670	0	25033	127	25160	0	836	233	1069	0	12951	188	13139	0	13211	165	13376
Subtotal	68263	13472	528	82263	57772	25658	649	84079	10153	1117	628	11898	59374	13021	1236	73631	41913	53535	1116	96564
Macrolides plus polypeptides																				
Erythromycin /colistin sulfomethate	0	0	0	0	0.65	0	0	0.65	0	0	0	0	0	0	0	0	0	0	0	0
Subtotal	0	0	0	0	0.65	0	0	0.65	0	0	0	0	0	0	0	0	0	0	0	0
Miscellaneous																				
Mupirocin	0	0	0	0	1	0	0	1	0	0	0	0	28	0	0	28	24	0	0	24
Novobiocin	0	0	52	52	0	0	154	154	0	0	170	170	0	0	0	0	0	0	211	211

Category and antibiotic	Import volume in kilograms																			
	1992-93				1993-94				1994-95				1995-96				1996-97			
	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total
Tiamulin	0	16750	20	16770	0	2800	5	2805	0	0	2385	2385	0	1402	0	1402	0	0	1650	1650
Subtotal	0	16750	72	16822	1	2800	159	2960	0	0	2555	2555	28	1402	0	1429	24	0	1861	1886
Monobactams																				
Aztreonam	10	0	0	10	29	0	0	29	21	0	0	21	20	0	0	20	1	0	0	1
Subtotal	10	0	0	10	29	0	0	29	21	0	0	21	20	0	0	20	1	0	0	1
Nitrofurans																				
Furaltadone	10	0	0	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Furazolidone	0	13400	0	13400	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	10
Nitrofurantoin	446	0	0	446	446	0	0	446	0	0	0	0	0	0	0	0	304	0	0	304
Nitrofurazone	0	0	0	0	0	0	20	20	520	0	0	520	0	0	35	35	0	0	22	22
Subtotal	456	13400	0	13856	446	0	20	466	520	0	0	520	0	0	35	35	304	0	32	336
Nitroimidazoles																				
Dimetridazole	0	18200	700	18900	2000	5200	0	7200	0	5047	9000	14047	0	7725	0	7725	0	1225	0	1225
Metronidazole	2844	0	1	2845	5260	0	82	5342	6880	0	0	6880	0	0	8	8	12910	0	130	13040
Ronidazole	0	0	25	25	0	0	75	75	0	0	125	125	0	0	50	50	0	59	0	59
Tinidazole	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	585	0	0	585
Subtotal	2844	18200	726	21770	7260	5200	157	12617	6880	5047	9125	21052	0	7725	58	7783	13495	1284	130	14909
Oxazolidinones																				
Linezolid	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0	0	0.1
Subtotal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0	0	0.1
Penicillins																				
Amoxycillin	61015	4744	5301	71060	89764	0	12158	101922	87310	13550	1510	102370	79889	4939	1175	86003	54494	11905	1123	67522
Ampicillin	1019	0	0	1019	994	0	17	1011	817	0	0	817	729	0	5	734	1804	0	100	1904
Benzylpenicillin & salts	4034	545	16324	20903	2357	0	12338	14695	3826	0	6172	9998	2020	0	11770	13790	368	0	11018	11386
Cloxacillin	156	0	2208	2364	207	0	141	348	2465	0	1	2466	992	0	4929	5921	103	0	5249	5352
Dicloxacillin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6003	0	0	6003
Flucloxacillin	16585	0	0	16585	21121	0	0	21121	13560	0	0	13560	9089	0	0	9089	7821	0	0	7821
Penethamate hydriodide	0	0	7	7	0	0	6	6	0	0	4	4	0	0	10	10	0	0	16	16
Phenoxymethylpenicillin	15229	0	0	15229	13075	0	0	13075	9347	0	0	9347	18047	0	0	18047	16935	0	0	16935
Piperacillin	397	0	0	397	344	0	0	344	152	0	0	152	0	0	0	0	1733	0	0	1733
Ticarcillin	94	0	0	94	1318	0	0	1318	985	0	0	985	204	0	0	204	86	0	0	86
Subtotal	98529	5289	23840	127658	129180	0	24660	153840	118462	13550	7687	139699	110970	4939	17889	133798	89347	11905	17506	118758
Penicillins plus ß-lactamase inhibitors																				
Amoxycillin/clavulanic acid	0	0	0	0	0	0	0	0	0	0	429	429	2	0	0	2	1003	0	0	1003
Piperacillin / tazobactam	0	0	0	0	0	0	0	0	27	0	0	27	0	0	0	0	0	0	0	0
Ticarcillin/clavulanic acid	0	0	0	0	0	0	0	0	0	0	0	0	157	0	0	157	0	0	0	0
Subtotal	0	0	0	0	0	0	0	0	27	0	429	456	159	0	0	159	1003	0	0	1003
Polyethers																				
Lasalocid	0	16000	0	16000	0	35000	0	35000	0	34050	0	34050	0	22350	0	22350	0	28550	0	28550
Maduramycin	0	418	0	418	0	536	0	536	0	0	0	0	0	422	0	422	0	1048	0	1048
Monensin	0	61190	0	61190	0	128387	0	128387	0	10775	0	10775	0	128431	44526	172956	0	56627	0	56627

Category and antibiotic		Import volume in kilograms																			
		1992-93				1993-94				1994-95				1995-96				1996-97			
		Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total
Narasin		0	14354	0	14354	0	26393	0	26393	0	3132	0	3132	0	28388	0	28388	0	15737	0	15737
Salinomycin		0	40517	0	40517	0	33040	0	33040	0	2037	0	2037	0	27923	0	27923	0	72810	0	72810
Semduramycin		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8680	0	8680
	Subtotal	0	132479	0	132479	0	223356	0	223356	0	49994	0	49994	0	207514	44526	252040	0	183452	0	183452
Polypeptides																					
Bacitracin		24	10560	1	10585	29	22	3	54	22	86260	0	86282	27	54608	0	54634	43	73474	4	73521
Capreomycin		0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1	0	0	1
Colistin sulfomethate		26	0	0	26	4	0	0	4	0	0	0	0	5	0	0	5	2	0	0	2
Gramicidin		1	0	0	2	2	0	0	2	1	0	0	1	4	0	0	4	5	0	0	5
Polymyxin b		1	0	2	3	1	0	2	3	2	0	1	2	2	0	1	3	2	0	2	4
Thiostrepton		0	0	0	0	0	0	0	0	0	0	30	30	0	0	0	0	0	0	0	0
	Subtotal	53	10560	3	10616	35	22	5	62	24	86260	31	86315	37	54608	1	54646	52	73474	7	73533
Quinolones																					
Ciprofloxacin		1966	0	0	1966	2348	0	0	2348	3832	0	0	3832	1372	0	0	1372	1481	0	0	1481
Enrofloxacin		0	0	0	0	0	0	0	0	0	0	9	9	0	0	31	31	0	0	49	49
Fleroxacin		1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gatifloxacin		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Lomefloxacin		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Norfloxacin		1128	0	0	1128	928	0	0	928	2122	0	0	2122	716	0	0	716	90	0	0	90
Trovafloxacin		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	67	0	0	67
	Subtotal	3095	0	0	3095	3276	0	0	3276	5954	0	9	5963	2088	0	31	2119	1639	0	49	1688
Quinoxalines																					
Olaquindox		0	3000	0	3000	0	2800	0	2800	0	8935	0	8935	0	11124	0	11124	0	10825	0	10825
	Subtotal	0	3000	0	3000	0	2800	0	2800	0	8935	0	8935	0	11124	0	11124	0	10825	0	10825
Streptogramins																					
Dalfopristin/quinupristin		0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	5	0	0	0	0
Pristinamycin		0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1	5	0	0	5
Virginiamycin		0	17000	0	17000	0	9500	0	9500	0	21500	0	21500	0	31850	0	31850	0	36000	0	36000
	Subtotal	0	17000	0	17000	0	9500	0	9500	1	21500	0	21501	6	31850	0	31856	5	36000	0	36005
Sulfonamides and sulfones																					
Acedapsone		0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Dapsone		100	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Phthalylsulfathiazole		0	0	120	120	0	0	220	220	0	0	100	100	0	0	0	0	0	0	25	25
Sulfacetamide		138	0	15	153	201	0	5	206	100	0	20	120	50	0	15	65	438	0	15	453
Sulfadiazine		16	400	2475	2891	356	4700	3859	8915	850	2075	7937	10862	328	14686	1392	16406	0	0	0	0
Sulfadoxine		650	0	650	1300	21	0	250	271	4	0	600	604	8	0	150	158	21	200	200	421
Sulfaguanidine		0	0	0	0	0	0	908	908	0	0	150	150	0	0	0	0	0	0	0	0
Sulfamerazine		0	0	150	150	0	0	700	700	0	0	50	50	0	0	200	200	0	0	50	50
Sulfamethazine		0	9525	3475	13000	0	7724	1989	9713	0	8177	4259	12436	0	24291	715	25006	0	11218	5269	16487
Sulfamethizole		0	0	0	0	900	0	0	900	2200	0	50	2250	200	0	0	200	50	0	0	50
Sulfamethoxazole		12700	0	0	12700	21528	0	0	21528	12401	0	0	12401	6650	0	0	6650	8025	0	0	8025

Category and antibiotic	Import volume in kilograms																			
	1992-93				1993-94				1994-95				1995-96				1996-97			
	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total	Human	Stock	Vet	Total
Sulfanilamide	0	0	0	0	0	0	0	0	0	0	0	0	0	0	75	75	0	0	1000	1000
Sulfapyridine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	8
Sulfaquinoxaline	0	1180	0	1180	0	610	75	685	0	75	0	75	0	200	50	250	0	750	50	800
Sulfasalazine	0	0	0	0	12158	0	0	12158	19724	0	0	19724	25	0	0	25	11805	0	0	11805
Sulfathiazole	0	0	0	0	0	0	50	50	0	0	0	0	0	0	0	0	0	0	0	0
Sulfatroxazole	0	0	200	200	0	0	183	183	0	0	0	0	0	0	245	245	0	0	154	154
Sulfisoxazole	0	0	329	329	0	0	66	66	0	0	0	0	0	0	0	0	0	0	43	43
Subtotal	13604	11105	7414	32123	35166	13034	8306	56506	35279	10327	13166	58772	7261	39177	2842	49280	20346	12168	6806	39320
Sulfonamides plus steroids																				
Sulfacetamide/prednisolone	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
Subtotal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
Tetracyclines																				
Chlorotetracycline	45	21924	100	22069	45	53792	1100	54937	18	1000	50	1068	0	7775	250	8025	0	8985	0	8985
Demeclocycline	33	0	0	33	25	0	0	25	89	0	0	89	0	0	0	0	480	0	0	480
Doxycycline	7314	0	151	7465	1970	0	178	2148	3614	0	0	3614	7735	50	6	7791	5979	0	1037	7016
Methacycline	300	0	0	300	900	0	0	900	0	0	0	0	0	0	0	0	200	0	0	200
Minocycline	600	0	0	600	1703	0	0	1703	1488	0	0	1488	70	0	0	70	1901	0	0	1901
Oxytetracycline	0	55465	2662	58127	0	71898	2283	74181	0	30560	13070	43630	111	38085	3894	42090	0	70624	2652	73276
Tetracycline	6979	0	37	7016	5716	0	137	5853	4036	0	120	4156	3605	0	105	3710	8432	0	105	8537
Subtotal	15271	77389	2950	95610	10359	125690	3698	139747	9245	31560	13240	54044	11521	45910	4255	61686	16992	79609	3794	100396
Tetracyclines plus other agents																				
Oxytetracycline/bromhexine/sulph	0	0	0	0	0	0	0	0	0	308	0	308	0	0	0	0	0	0	0	0
Subtotal	0	0	0	0	0	0	0	0	0	308	0	308	0	0	0	0	0	0	0	0
Group totals	241058	344321	46098	631476	275593	453758	46858	776209	218350	249305	53552	521207	238816	454128	76771	769714	283509	491232	45470	820211

Glossary of terms

Active constituent (of a veterinary product)

The substance(s) in a formulated veterinary product that is responsible for the primary biological effect of the product.

Amplification (of bacteria). *see* **Selection**

Antimicrobial

A chemical agent that, on application to living tissue or by systemic administration, will selectively kill or prevent or inhibit growth of susceptible organisms. This definition *includes* antibacterials (including ionophores), antiprotozoals, antifungals, antiseptics and disinfectants, but *excludes* antineoplastics antivirals, immunologicals, direct-fed microbials and enzyme substances.

Antibiotic

In this report, the term antibiotic has been used to mean a subset of antimicrobial agents (see above) that include antibacterial agents (including ionophores).

Antibiotic 'load'

The total quantity of antibiotic(s) that a particular animal/human or group of animals/humans are exposed to. It is a measure of the antibiotic selection pressure for resistant bacteria. *see also* **Selection**

Antibiotic regimen

The way in which antibiotics are used, ie the dose rate, route of administration, interval and frequency of use.

Antibiotic resistance

A property of bacteria that confers the capacity to grow in the presence of antibiotic levels that would normally suppress growth or kill susceptible bacteria. An organism is said to have become resistant to an antibiotic when the minimum inhibitory concentration (MIC) is significantly higher ($\geq$ 4 times) than the sensitive parent or than the range of MICs found in the same species not previously exposed to that antibiotic. *see also* **Clinical antibiotic resistance**

Bacterial 'load'

Level of exposure of humans to bacteria, as an indicator of potential exposure to resistant bacteria. In the context of food-producing animals the bacterial load is a measure of the level of contamination of food with commensal or zoonotic bacteria from animals. In the human hospital situation, bacterial load is related to the level of cross-infection between patients.

Breakpoint

The point at which the minimum inhibitory concentration (MIC) for an antibiotic is defined as sufficiently high to indicate clinical resistance. This level varies for different

antibiotic–bacteria combinations. *see also* **Antibiotic resistance**, **Clinical antibiotic resistance, Minimum inhibitory concentration**

Broad-spectrum antibiotic

An antibiotic effective against a large number of bacterial species; generally describes antibiotics effective against both gram-positive and gram-negative bacteria.

Chromosome

DNA structure (the major part of the bacterial genome) that is inherited by progeny of the bacterium.

Clinical antibiotic resistance

Clinical resistance occurs when the organism can continue to divide in the presence of the antibiotic concentrations that normally occur during treatment (therapeutic doses) and the antibiotic is no longer effective for treatment. The definition includes strains with abnormally elevated minimum inhibitory concentrations, which may be classified as 'susceptible' or 'intermediate' according to agreed breakpoints for standardised susceptibility testing used in diagnostic laboratories. *see also* **Antibiotic resistance, Breakpoint**

Coccidiostat

An antimicrobial agent that kills the protozoan parasites (*Eimeria* spp.) that cause the disease coccidiosis in chickens. Some coccidiostats are also antibiotics (eg the ionophore coccidiostats are also polyether antibiotics).

Commensal bacteria

Bacteria that live continuously on or in certain parts of the body (eg gut, skin) without causing disease, but which may cause disease if they gain access to parts of the body other than their normal habitat (opportunistic pathogens), eg *E. coli*, enterococci. Bacteria can be commensal in one organism (animal or human) and pathogenic in another.

Community-acquired infections

Infections acquired in the course of daily life in the community (including in the home and workplace). *see also* **Nosocomial infections**

Competitive exclusion products

Products containing many species (up to 30) of undefined or partially defined bacteria isolated from the gastrointestinal (GI) tract of animal species. They are used to attempt to colonise the GI tract of animals with beneficial bacteria and thus exclude harmful ones. *see also* **Probiotic**

Conjugation

Direct transfer of conjugative plasmids or conjugative transposons between bacteria via cell–cell contact or by a so-called sex pilus (also called conjugal transfer of genes). Genes can be transferred in this way between bacteria of the same species or sometimes between different species of bacteria. *see also* **Horizontal gene transfer, Conjugative plasmid, Conjugative transposon**

Conjugative plasmid

A conjugative plasmid is a plasmid that carries a set of genes that encode the functions required for the coupling of two bacterial cells and the conjugative transfer of the plasmid DNA to another bacterium. *see also* **Horizontal gene transfer, Conjugation**

Conjugative transposon

A discrete mobile element (normally located in the chromosome of a bacterium) that can excise and transfer by conjugation to another bacterium. In the new host it inserts into the bacterial chromosome. The mechanism of excision and reintegration is site-specific recombination. Both conjugation and site-specific recombination functions are encoded by the conjugative transposon.

Controlled studies

Studies in which the effect of an intervention (eg effect of antibiotic exposure on the development and emergence of resistance in animal populations) is studied and compared to a control population without the intervention.

Cotransfer

Simultaneous transfer of different resistance or other genes located on the same mobile element (eg plasmid).

'Critical' antibiotics (human use)

'Critical' antibiotics are those used to treat serious or life-threatening infections in humans for which there are very limited or no alternative antibiotics that can be used to treat the infections if antibiotic resistance develops. In this report, antibiotics considered critical have been deignated category A and are shown in Table 7.2.

The antibiotics that are in this critical class change from time to time and are influenced by the availability of newer antibiotics and the resistance rate of bacteria causing serious human infections. More recently, because of increasing antibiotic resistance in many human pathogens and the need for alternative antibiotics, the streptogramins (Synercid, virginiamycin) may have entered this 'critical class'. However, other antibiotics that were considered 'critical' in Australia in the past (eg choramphenicol, cloxacillin, kanamycin) are no longer considered critical because of the availablity of other agents.

Cross-resistance

Resistance to two or more antibiotics or classes of antibiotic conferred by a single resistance gene.

Definitive therapy

Directed therapy selected on the basis of culture and susceptibility testing (laboratory culture or other molecular tests) of the infectious agent. Often, a narrow-spectrum agent specific for the organism can be used.

Emergence of antibiotic resistance

In this report this term is used to mean the appearance of antibiotic-resistant bacterial strains in clinical or veterinary laboratory isolates.

Empirical therapy

Initial therapy if the infection is suspected of being bacterial on clinical grounds but pending the outcome of culture and susceptibility results, or where cultures are difficult to obtain or have not yielded a pathogen. Combination therapy or treatment with a single broad-spectrum agent is usually used, but in certain circumstances narrow-spectrum agents are also suitable (eg penicillin for sore throat thought to be due to streptococcal infection).

Enrichment (of bacteria) *see* **Selection**

Experimental study

A study in which the conditions are controlled by the investigator, for example, a study in which a population is selected for a planned trial of an intervention the effects of which are measured by comparing results of the outcome of the intervention with the results of a comparable control group without the intervention. *see also* **Observational study**

Extensive farming

Livestock rearing and production methods in which animals have free-ranging access to field/pasture conditions. *see also* **Intensive farming**

Feed-miller (stockfeed)

A person or company whose business is to compound and supply feeds for animals.

First-, second-, third generation (cephalosporins)

Structurally related subgroups of cephalosporin antibiotics that were developed sequentially in response to the development of resistance and consequently have increasingly broad spectra of activity.

Food-producing animals

Animals reared for the production of meat or other food products (eg eggs, milk).

Gene

The basic unit of inheritance; a segment of nucleic acid (usually DNA) that encodes a single cellular protein (or RNA) plus associated elements to allow transcription to occur (promoter, reading frame, etc). The gene product may contribute to specific characteristic(s) of the organism.

Gram-negative bacteria

Bacteria (rods or cocci) with a cell wall with a structurally distinct outer membrane layer and less peptidoglycan in their cell wall than gram-positive bacteria. Because of the outer layer, they do not take up and retain Gram stain and are decolourised by alcohol or acetone (eg salmonellae, campylobacters, *Escherichia coli*). Gram-negative bacteria are commonly more resistant to antibiotics because their outer membrane impedes entry of the drugs. Most growth promotant antibiotics are not active against gram-negative bacteria.

Gram-positive bacteria

Bacteria (rods or cocci) with a monolayered cell wall with large amounts of the polymer peptidoglycan. They retain Gram stain (crystal violet and iodine) after solvent treatment with alcohol or acetone, and appear deep blue under the microscope (eg enterococci, staphylococci, streptococci).

Grower pigs

Pigs during the period from the end of the weaner stage until pigs are sent for slaughter. *see also* **Weaner pigs**

Growth promotants

Substances used to increase weight gain and/or reduce feed requirements in food-producing animals (World Health Organization definition).

Growth promotion

The use of substances to increase the rate of weight gain and/or the efficiency of feed utilisation in animals by other than purely nutritional means. The term does not apply to the use of antibiotics for the purpose of inhibiting specific pathogens even when an incidental growth response may be thus obtained. (The above notwithstanding, growth promotants appear to act by virtue of their antimicrobial effect since they do not work in germ-free animals.)

Hazard

A biological, chemical or physical agent that may have an adverse health effect.

Home-mixer (stockfeed)

A person or company who compounds feeds for animals belonging to that person or company.

Horizontal gene transfer (of resistance genes)

The movement of genetic material (DNA) from one organism to another. Horizontal gene transfer can occur by transformation, transduction or conjugal transfer.
see also **Conjugation**

Hospital-acquired infections *see* **Nosocomial infections**

Incidence

The number of new cases of an event of interest that occur over a specified time period in a defined population. Incidence is usually expressed as a rate in relation to the population at risk (eg 10 new cases of VRE per 100,000 people per year).
see also **Prevalence**

Inducible resistance

The product of the resistance gene is only synthesised in the presence of the inducing substance, usually (but not always) the antimicrobial that the resistance mechanism counteracts.

In-feed antibiotic

In the Australian context, an in-feed antibiotic is an antibiotic manufactured for incorporation into the feed of animals (as distinct from administration or application of antibiotics to animals by other routes such as water medication, oral dosing, injection, dermal application or infusion). In Australia, antibiotic substances are added to animal feed for therapeutic, prophylactic, growth promotion and anticoccidial purposes.

Intensive farming

Livestock rearing and production methods in which large cohorts of animals are raised in close proximity in feedlots (cattle), or rearing sheds (pigs or poultry).
See also **Extensive farming**

Label restraint

A condition stated on the label that is a contraindication or limitation on either the effectiveness or safety of the product.

Level of resistance

The concentration above which the resistant cells no longer grow. The level of resistance is a property of the particular mutation or resistance gene and its context, and is not influenced by the concentration of antibiotic to which the organism is exposed.

Maximum residue limit (MRL)

An MRL is defined as the maximum concentration of a residue resulting from the officially authorised safe use of an agricultural or veterinary chemical that is recommended to be legally permitted or recognised as acceptable in or on a food, agricultural commodity or animal feed. The concentration is expressed in milligrams per kilogram (mg/kg) of the commodity (or milligrams per litre in the case of a liquid). Although MRLs are not directly based on any health criteria, they are only established after a comprehensive risk assessment process, where the known toxicological risks are not considered to constitute an undue hazard to human health based on dietary exposure.

Minimum inhibitory concentration (MIC)

The lowest concentration of an antibiotic that will inhibit the visible growth of a microorganism, usually after overnight incubation. MICs are determined using agar or broth dilution methods. *see also* **Antibiotic resistance**, **Breakpoint, Level of resistance**

Monitoring

In this report the term 'monitoring' is used to describe continuous routine measurement and analysis of information (in this case about antibiotic usage) to detect trends (in volume and type of use).

Multiple drug resistance

Resistance to two or more antibiotics from different classes.

Multiresistant *Staphylococcus aureus* (MRSA)

Strains of *Staphylococcus aureus* resistant to methicillin (and other β-lactams) and one or more other antibiotic classes (also called methicillin-resistant *S. aureus*).

Narrow-spectrum antibiotic

An antibiotic effective against a limited number of microorganisms; often applied to an antibiotic active against either gram-positive or gram-negative bacteria.

Nosocomial infections

Infections acquired as a result of medical intervention, eg in hospitals or in other clinical settings (also called '**hospital-acquired infections**'). *see also* **Community-acquired infections**

Observational study

A study that does not involve any experimental intervention. Changes in one characteristic are observed in relation to another characteristic, eg observe the prevalence of bacterial resistance in animal or human populations.
see also **Experimental study**

Off label (uses of veterinary antibiotics)

A use practised by, or prescribed by, a registered veterinarian where the label directions for use of an NRA-registered antibiotic product are varied. For example, use on a different species (such as use of an antibiotic registered in cattle on deer) or by varying the dose regimen (such as doubling the dose rate or increasing the frequency of dosing).

Open sellers

NRA-registered veterinary chemical products that are available for open sale to the public. An open selling antibiotic product does not require a veterinary prescription.

Pathogenic bacteria

The bacteria that cause infection. These can be either opportunistic infections, such as wound or genito-urinary tract infections, or infectious diseases such as tuberculosis.

Plasmid

A piece of extrachromosomal DNA much smaller than the bacterial chromosome, usually covalently closed circular molecules. Plasmids exists in the cytoplasm independently of the chromosome and can control their own replication. Some of them can be transferred between bacteria. *see also* **Conjugation, Conjugative plasmids**

Premix

A manufactured mixture of active ingredients(s) and carrier designed for direct inclusion into the bulk ration of animals.

Prescription animal remedy (PAR) antibiotics

Antibiotics that must be prescribed by a registered veterinarian for animals under their care (also known as poisons schedule S4). Persons distributing, wholesaling or retailing PARs (S4s) must be licensed by the relevant State/Territory health department. All antibiotics used therapeutically in animals are classified as PARs (eg penicillins, neomycin, tetracyclines). Poisons schedule definitions are given in the *Standard for the Uniform Scheduling of Drugs and Poisons* (AHMAC 1997).

Prevalence

The number of events of interest in a given population at a given point in time, usually expressed as a prevalence rate, ie as a proportion of the defined population size at that time (eg 5 VRE isolates per 100 enterococci isolates in an infectious diseases ward of a hospital at a particular time would be expressed as a 5% prevalence). *see also* **Incidence**

Probiotic (direct fed microbials)

Preparations of microbes (usually bacteria) that are included in the diet to improve health. (*see also* **Competitive exclusion products**)

Prophylaxis

The use of antibiotics (by any route of administration) to prevent infection with a pathogen(s) that is anticipated to challenge the host during the treatment period; that is, initiating treatment in advance of an actual infection or disease condition because such a condition is expected to occur if treatment is withheld.

For example, some animals may be treated on reaching a particular age because a disease condition usually occurs at that age. In humans prophylactic antibiotic treatment may be used for a patient who is about to undergo a major operation or an immunosupressed patient to prevent unwanted infections.

In intensive animal production (and some human conditions) prophylaxis is often initiated for the whole herd/flock/group when a small number have already developed the disease.

Registration (of agricultural and veterinary chemicals)

The process whereby the National Registration Authority for Agricultural and Veterinary Chemicals approves the sale and use of a formulated agricultural or veterinary chemical product after the evaluation and assessment of appropriate scientific data demonstrating that the product is effective and not unduly hazardous to human health, the environment or target plants and animals and that it will not adversely affect trade.

Residue (in food)

The remains of a chemical product persisting in or on food (including the active constituent and relevant derivatives, metabolites and degradation products).

Risk

The probability of an agent (hazard) causing an adverse effect and the magnitude of that effect (expressions of risk can be quantitative or qualitative, and should include consideration of any uncertainties).

Risk analysis

The term used to describe the three-part process involving risk assessment, risk management and risk communication.

Risk assessment

The scientific evaluation of known or potential adverse health effects resulting from human exposure to hazards. The process includes hazard identification, hazard characterisation, exposure assessment and risk characterisation.

Risk management

The process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate options.

Risk communication

The process of interactive exchange of information and opinion on risk among risk assessors, risk managers, and other interested parties.

Sanitary and phytosanitary measures

Trade measures to protect human health and animal and plant life in a country from the entry, establishment or spread of pests, diseases, disease-carrying or disease-causing organisms; and to protect humans and animals from risks arising from additives, contaminants or toxins in foods, beverages or feedstuffs. (Under this definition, 'animals' include fish and wild fauna.)

Selection (of resistant bacteria)

The process whereby exposure to an antibiotic kills or inhibits sensitive bacteria, thus allowing resistant bacteria to continue dividing and increase in number (amplify) relative to the sensitive bacteria (enrichment).

Spread (of bacteria)

The term 'spread' is used in this report to denote the movement of bacteria (particularly antibiotic-resistant bacteria) from one animal species, including humans, to another by direct contact, nosocomial spread (in hospitals or other clinical settings), or in food,

animal excreta or animal products. (As opposed to 'transfer', which is used to denote the movement of antibiotic-resistance genes from one bacterium or bacterial population to another). *see also* **Transfer (antibiotic-resistance genes)**

Stockfeed

Includes hay, straw, chaff, grain, manufactured stockfeed and byproducts, and other substances intended for feeding to animals (but not including veterinary chemical products or additives).

Surveillance

In this report the term 'surveillance' is used to describe the continuous, intensive, targeted and nonrandom collection of data on the incidence, prevalence and spread of antibiotic-resistant bacteria and antibiotic-resistance genes. Antibiotic-resistance surveillance can be either *active* or *passive:*

- *passive surveillance* is the collection of routine analytical data from diagnostic laboratories;
- *active surveillance* involves a prospective study of resistance directed at specific pathogens.

Therapeutic dose

The dose of a drug, including antibiotics, that is used in the treatment of disease.

Therapeutic use

The use of antibiotics for the purpose of inhibiting a pathogen(s) which already infects the host; that is, initiating treatment because there is a disease condition.

Thermophilic campylobacters

The most common species of campylobacter, including *C. jejuni* and *C. coli,* which grow best at 42ºC.

Transfer (antibiotic-resistance genes)

The term 'transfer' is used in this report to denote the movement of antibiotic-resistance genes from one bacterium or bacterial population to another. (As opposed to 'spread', which is used to denote movement of the bacteria themselves).
see also **Spread (of bacteria), Horizontal gene transfer**

Transposon

A small, mobile DNA element that carries one or several genes, plus genes encoding for its own transposition between various locations in the bacterial genome.

Weaner pigs

Pigs during the 6–8 week period after removal from the sow at 3–4 weeks of age.
see also **Grower pigs**

Zoonotic bacteria

Bacteria that are pathogenic to humans and are transferred to people by direct contact with animals, animal excreta or animal products (eg brucella, nontyphoid salmonella and campylobacter).

Abbreviations

ACMSF	Advisory Committee on the Microbiological Safety of Food (United Kingdom)
ADI	Acceptable daily intake
AFFA	Department of Agriculture, Fisheries and Forestry —Australia
AGAR	Australian Group for Antimicrobial Resistance
Agvet Code	*Agricultural and Veterinary Chemicals Code Act 1994* (Commonwealth)
AHC	Animal Health Committee
AIDS	Acquired immunodeficiency syndrome
ANQAP	Australian National Quality Assurance Program
ANZFA	Australia New Zealand Food Authority
APIQ	Australian Pork Industry Quality Program
AQIS	Australian Quarantine Inspection Service
AVA	Australian Veterinary Association
CAFA	Commission on Antimicrobial Feed Additives (Sweden)
CDS	Calibrated dichotomous sensitivity
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CVM	Center for Veterinary Medicine (United States)
CVMP	Committee on Veterinary Medicinal Products (European Union)
DDD	Defined daily dose
DHAC	Department of Health and Aged Care (Commonwealth)
DHFR	Dihydrofolate reductase
DNA	Deoxyribonucleic acid
DPIE	Department of Primary Industries and Energy
EC	European Commission
FAO	Food and Agriculture Organization (United Nations)
FCE	Feed conversion efficiency
FCR	Food conversion ratio
FDA	Food and Drug Administration (United States)
GATT	General Agreement on Tariffs and Trade
GMAC	Genetic Manipulation Advisory Committee
GNR	Gram-negative rods
HACCP	Hazard analysis critical control point
HGP	Hormone growth promotant
HIV	Human immunodeficiency virus
HUS	Haemolytic–uraemic syndrome
JECFA	Joint Expert Committee on Food Additives (WHO/FAO)

JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
LAN	Local area network
LOD	Limit of detection
LOR	Limit of reporting
MAFF	Ministry of Agriculture, Fisheries and Food (United Kingdom)
MDU	Microbiological Diagnostics Unit, Melbourne University
MIC	Minimum inhibitory concentration
MIT	Microbial inhibition test
MLS	Macrolide–lincosamide–streptogramin
MRL	Maximum residue limit
MRSA	Multiresistant (or methicillin resistant) *Staphylococcus aureus*
NARM	National Antimicrobial Resistance Monitoring Program (United States)
NARSP	National Antibiotic Resistance Surveillance Program
NATA	National Association of Testing Authorities
NCCLS	National Committee on Clinical Laboratory Standards (United States)
NDPSC	National Drugs and Poisons Scheduling Committee
NEPSS	National Enteric Pathogen Surveillance System
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health and Safety Commission
NRA	National Registration Authority for Agricultural and Veterinary Chemicals
NRS	National Residue Survey
OECD	Organization for Economic Co-operation and Development (United Nations)
OIE	Office International des Epizooties (World Organisation for Animal Diseases)
OM	Otitis media
OPAC	Organic Produce Advisory Committee
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PE	Proliferative enteritis
PFGE	Pulsed field gel electrophoresis
PRDC	Pig Research and Development Corporation
PT	Phage type
ppm	Parts per million
QAP	Quality assurance program
RACGP	Royal Australian College of General Practitioners
RCPA	Royal College of Pathologists of Australasia
RNA	Ribonucleic acid

SCA	Standing Committee on Agriculture (European Union)
SCAHLS	Subcommittee on Animal Health Laboratory Standards
SCAN	Standing Committee on Animal Nutrition (European Commission)
SCARM	Standing Committee on Agriculture and Resource Management
SEW	Segregated early weaning
SPF	Specific pathogen-free (pigs)
SPS	Sanitary and phytosanitary (measures)
TB	Tuberculosis
TGA	Therapeutic Goods Administration
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
UV	Ultraviolet
VISA	Vancomycin intermediate resistance *Staphylococcus aureus*
VPC	Veterinary Products Committee (United Kingdom)
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization (United Nations)
WPA	Working Party on Antibiotics
WTO	World Trade Organization (United Nations)

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