

Antimicrobial Resistance Review – A New Zealand Perspective

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INTRODUCTION

Throughout the developed world there is public and governmental concern about the increasing prevalence of antimicrobial resistance in bacteria that cause diseases in humans. There is a parallel concern that the development of resistance among bacteria is being outstripped by the ability of the pharmaceutical industry to develop new antibacterial agents.

The problem of the development of antimicrobial resistance has been the subject of specially commissioned reports under the auspices of a variety of government and international bodies. Much of the focus of these reports has been upon the use of antimicrobials in animals and, in particular, their use as feed additives for the purpose of growth promotion.

The European Commission voted to ban the use of four antimicrobials as growth promotants. These four antimicrobials were zinc bacitracin, spiramycin, virginiamycin and tylosin phosphate. Europe also instigated a surveillance programme to determine the extent and nature of the perceived antimicrobial resistance problem as it relates to antimicrobial use in animals.

The impact of antimicrobial-resistant bacteria or resistance genes found in animal isolates on the increasing antimicrobial resistance of human pathogenic bacteria have been reviewed and reported on in a number of countries. Some of the reports are listed in the references in section 7 of this paper. Two notable reports were the Australian Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR, 1999), the United Kingdom Ministry of Agriculture, Food and Fisheries (MAFF, 1998) and the Swedish Commission on Antimicrobial Feed Additives (CAFA, 1997). All these reviews showed that there is evidence for direct spread of resistant food-borne pathogens from animals to humans and also the possibility, *in vitro*, for transfer of antimicrobial resistance genes from animal commensals to human pathogenic bacteria.

Existing antimicrobial resistance surveillance programmes in most countries are not able to provide comprehensive data on antimicrobial usage and the prevalence of antimicrobial resistance among human and veterinary bacteria isolates. Nevertheless, what data is available indicate that the total use of antimicrobials is a contributing factor in the development of antimicrobial resistance. It is known that the use of antimicrobials in humans is a significant cause of antimicrobial resistance in humans. What is not known is whether or not the use of antimicrobials in feed animals is a significant factor.

Experiences in certain European countries has shown that precipitous action to prohibit the use of certain antimicrobials in livestock feed may result in serious negative animal health consequences that required immediate action to rectify, paradoxically resulting in increases in antimicrobials to control disease. This experience has highlighted the need to ensure that any action taken protects both human and animal health.

ANTIMICROBIAL RESISTANCE

Use of antimicrobials in food producing animals in New Zealand

New Zealand has not imposed general bans on the use of antimicrobials. Of the antimicrobials that have been banned in Europe, only zinc bacitracin and tylosin are licensed in New Zealand with claims for growth promotion, and these are currently under review.

Spiramycin is only licensed for therapeutic use in dogs and cats. Avoparcin is no longer registered in New Zealand. Virginiamycin, is no longer used for growth promotion, but has been reclassified for use under prescription only.

Due to the pastoral farming system used in this country, the use of antimicrobials in cattle and sheep is low, compared to some other countries. The industries that use significant volumes of antimicrobials are the pig and poultry industries.

Antimicrobial Resistance Surveillance

New Zealand's surveillance systems like those in the other countries mentioned were not designed to provide the appropriate information to establish whether the use of antimicrobials in animals is having any effect on the development of antimicrobial resistance. The Ministry of Health has monitored the prevalence of antimicrobial resistance among important human pathogens since 1972. Among human pathogens, there has been an increase in the prevalence of methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and antimicrobial-resistant gram-negative bacilli. There has also been a small increase in the number of vancomycin-resistant enterococci (VRE) confirmed in New Zealand. To date, nine VRE have been confirmed. The first VRE was isolated in 1996, the second in 1998 and, in the period 1999 till January 2000, seven VRE were confirmed. There is no evidence that use of antimicrobials in animals (either in feed or parenteral) has prompted the resistance in these cases.

The only zoonotic species that has been monitored through this surveillance programme has been *Salmonella* spp. Between 1972 and 1982, every salmonella isolate that was received at ESR was tested for susceptibilities. From 1982, five yearly surveys of the antimicrobial susceptibilities of salmonella from human and non-human sources were carried out. The data from this surveillance has shown a low level of antimicrobial resistance among salmonella from human and non-human sources. Multi-resistant *Salmonella Typhimurium* DT104 has been isolated, albeit infrequently, in New Zealand.

There are international concerns about the possible association of antimicrobials used in animals (in particular the use of antimicrobials as growth promotants in animals) and human antimicrobial resistance problems. In response, the Animal Remedies Board, which is responsible for licensing animal remedies, commissioned an expert panel report to review not only the international situation but also the implications for New Zealand.

After its review of the literature, the expert panel considered that the information that was available was not sufficiently comprehensive and robust to carry out a meaningful quantitative risk analysis for any of the antimicrobials being used for growth promotion in New Zealand. Therefore, the panel decided that the available information on each antimicrobial (or group such as the macrolide antibiotics) should be assessed in light of a consistent rationale. The panel's rationale was used as the basis for the one to be used in a review of all antimicrobial products used in animals. The rationale is based on the principles that:

- important human uses of antimicrobials must be protected; and

- animal health care uses that are not relevant to the antimicrobial resistance problem should not be hindered.

In amending licences the purpose is to:

- ensure that their use, particularly in food-producing livestock, will not prompt resistance in bacteria that cause diseases in humans, reducing the effectiveness of these antimicrobials when used to treat disease;
- retard the development of antimicrobial resistance in bacteria that cause diseases in animals; and
- foster the prudent use of the full range of animal health antimicrobial products.

The Board accepted in principle all the recommendations of the expert panel with the qualification that, rather than taking immediate action and applying general bans, the rationale should be applied to each trade name product in turn, starting with those that contain the antimicrobials of greatest human health significance. The Board considered a prudent response as appropriate to ensure public health was protected and, at the same time, animal welfare problems were not exacerbated unnecessarily.

The Board considered that the following matters must be addressed in the licensing of new antimicrobial products for growth promotion and re-assessment of existing products:

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

Factors in the review of antimicrobial products

To be comprehensive and appropriate the review of antimicrobial products has to recognise that:

- there are different aspects to antimicrobial resistance that must be considered separately;
- not all antimicrobials are the same in the way they inhibit bacteria or their potential to lose effectiveness due to bacterial resistance;
- not all antimicrobials are used for the same purposes;
- there may not be common opportunities for humans to be exposed to resistant bacteria; and
- not all antimicrobials are equally important to human health.

Nature of antimicrobial resistance

Evolution of antimicrobial resistance

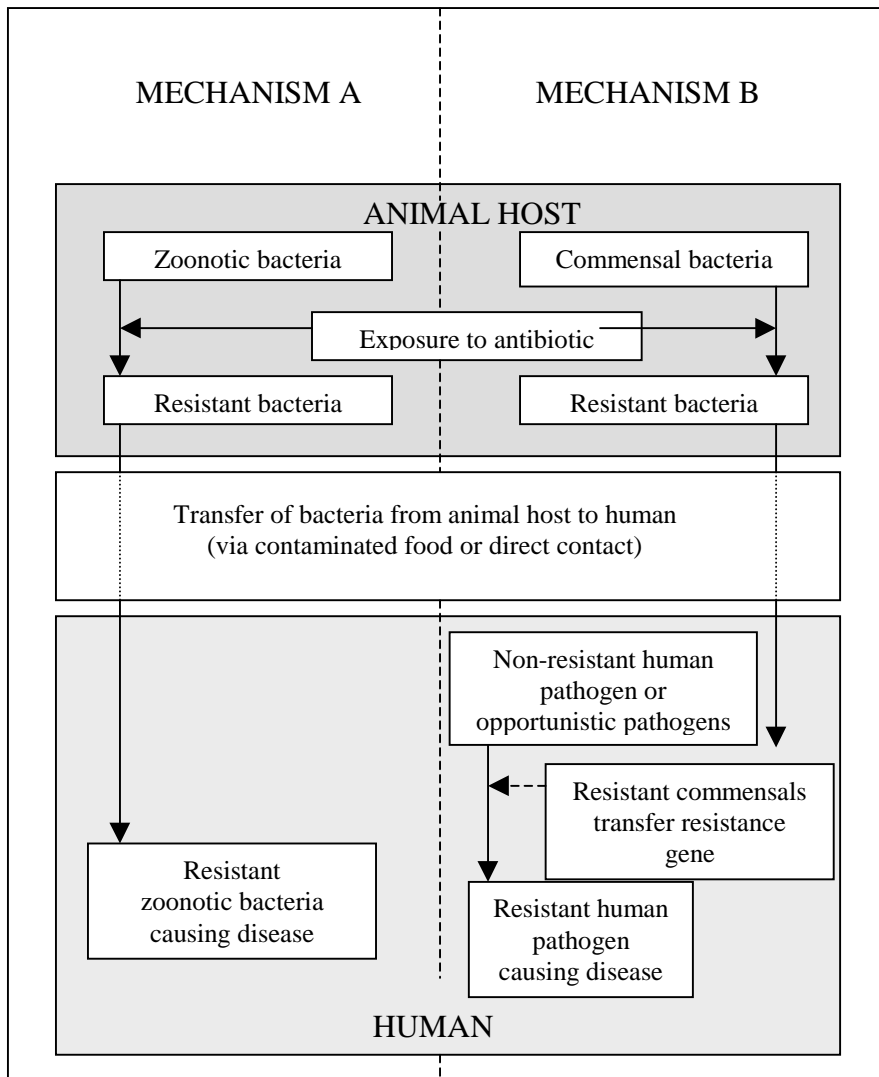
Antimicrobial resistance arises as a result of genetic change, which can occur through mutation or by the acquisition of an antimicrobial resistance gene. The antimicrobial-resistant bacteria are subsequently able to grow in the presence of the antimicrobial that is preventing the growth of non-resistant strains. The resistant strain replaces the non-resistant strain and the antimicrobial loses its effectiveness.

Spread of antimicrobial-resistant bacteria and genes

Spread of antimicrobial resistance can occur by two mechanisms:

- A. transfer of resistant disease-causing bacteria (pathogenic bacteria) from one host to another; and
- B. transfer of antimicrobial resistant bacteria that do not cause disease (commensal bacteria) and subsequent transfer of resistance genes from the animal host commensal bacteria to pathogenic (to humans) bacteria or commensal bacteria that can become pathogenic under certain circumstances.

Resistant bacteria can be transferred from one person to another, from animals to people, or even from people to animals. However, this paper is concerned with the transfer of antimicrobial resistant bacteria from animals to people. The following figure shows the difference between mechanisms A and B.



Development of antimicrobial resistance in zoonotic bacteria

While resistance mechanism B can be involved, mechanism A is usually the cause of resistance in zoonotic bacteria. The bacteria are exposed to the antimicrobial while they are in the animal. The bacteria are already resistant when they are transferred to people. The most common diseases involved are the food-borne gastro-intestinal diseases caused by *Salmonella* and *Campylobacter* but can involve other pathogenic bacteria. It is unknown how much the use of antimicrobials in animals contributes to the development of antimicrobial resistance in humans. However, the development of multi-resistant *Salmonella Typhimurium* DT104 suggests a link between antimicrobials used in animals and resistance patterns emerging in zoonotic pathogens.

Transfer of resistance genes

The development of resistance via mechanism B is more complicated. Commensal bacteria in animals exposed to an antimicrobial can develop resistance to that antimicrobial. The bacteria can be transferred to a person via either direct contact or contaminated food. The commensal bacteria do not cause disease in that person but, they may be able to transfer the antimicrobial resistance gene to pathogenic bacteria that are already present in that person.

Resistance genes are often carried on genetic elements, which frequently carry more than one resistance gene. Genetic transfer of the genetic elements frequently results in the transfer of all the different resistance genes.

Mechanisms A and B are distinctly different. The significance of mechanism A is fairly well known as a result of existing surveillance programmes, but the significance of mechanism B is still uncertain.

Mechanism A is dependent on:

- the presence of the zoonotic bacteria in animals;
- exposure of the bacteria to the antimicrobial and mutation to a resistant strain;
- exposure of people to the resistant strain; and
- susceptibility of people to the zoonotic bacteria.

Mechanism B is dependent on:

- the presence of commensal bacteria in animals;
- exposure of the bacteria to the antimicrobial and mutation to a resistant strain;
- exposure of people to the resistant strain of commensal bacteria;
- the presence at the same time of a non-resistant strain of pathogenic bacteria in people;
- the opportunity and mechanism for transferring resistance genes from the commensal bacteria to the pathogenic bacteria; and
- susceptibility of people to the pathogenic bacteria.

Cross-resistance

Many antimicrobial resistance genes confer resistance to many or all members of an antimicrobial group (e.g. the *erm* genes confer resistance to macrolides, lincosamides and streptogramins B).

Antimicrobial product differences

Differences in antimicrobials

The antimicrobial families differ chemically and in the way they inhibit bacteria. Different species of bacteria respond differently to different types of antimicrobials. Not all bacteria develop the same level and type of resistance to all the antimicrobial families. Some oral antimicrobials stay in the digestive tract and inhibit only GIT bacteria, while others are absorbed and act on bacteria in other

parts of the body. Some antimicrobials are sufficiently similar to other types of antimicrobials that resistance to one may result in resistance to others. Consequently, general statements and, in particular, precipitous and non-specific bans on antimicrobial use, are seldom appropriate and often result in serious negative animal health consequences.

Differences in uses

Some antimicrobials are used in human and animal health, while others are used only in animal health. Particular antimicrobial families are the preferred choice for treating specific bacterial infections in humans. The relative importance of a particular antimicrobial in human medicines is a primary consideration in this review. The development of resistance to an antimicrobial that has no use in human medicines (and does not contribute to cross-resistance to any antimicrobial that does have a use in human medicines) is not significant. Conversely, the development of resistance to an antimicrobial that is essential in human medicines requires immediate and effective regulatory action to protect that use. However, since circumstances can change, it is essential to be prepared to reassess the relative significance of an antimicrobial.

Antimicrobials are also used for different purposes in animals and humans. In humans they are most often used therapeutically to treat clinical cases of bacterial infection. They may also be used for prophylaxis where apparently healthy people have been exposed (or are likely to be exposed) to diseases such as bacterial meningitis. Human antimicrobial products, with the exception of a few skin preparations, can be obtained only under the prescription of a medical practitioner.

In animals, antimicrobials are primarily used therapeutically to treat clinical cases of bacterial infection. They are usually given by injection to individual animals rather than mass medication. Protecting the effectiveness of antimicrobials for use as therapeutic agents for both human and animal use is the primary driver for minimising antimicrobial resistance.

Antimicrobials may also be used in animals prophylactically (ie to prevent disease). For this purpose they are usually given orally in feed or water to livestock and usually on a flock/herd basis. Some diseases (such as necrotic enteritis or coccidiosis in chickens) are so common that the antimicrobial is included in the feed for the whole production period. Other diseases occur at a particular stage of production, such as at weaning in pigs. For these diseases the antimicrobial is added to the feed just before or at the time when the disease challenge is most likely to occur. However, in all cases, administration is closely tied to a diagnosis or clinical history of the disease and use is limited to what is necessary and sufficient to prevent the disease.

The effectiveness of antimicrobials used either therapeutically or prophylactically is measured on the farm by the elimination or absence of clinical signs of the particular disease. In the laboratory, effectiveness is measured by testing the minimum inhibitory concentration (MIC), which is the smallest amount of the antimicrobial that inhibits the disease-causing bacteria. The antimicrobial is always used at dosages that exceed the MIC to ensure maximum biocidal effect.

Antimicrobials may also be administered to animals for a growth promotant purpose (ie increased production). They are always given orally (mixed into feed or water). While they modify the mix of bacteria in the digestive tract, their effectiveness is measured in production gains (increase weight, growth, milk or egg production, etc) rather than by the effect on the bacteria. Since biocidal effect is not the specific outcome, dosages may be less than is required to maintain the MIC for that antimicrobial. This may mean that disease-causing bacteria are exposed to growth promotant antimicrobials for long periods of time at concentrations too low to inhibit them but at sufficiently high concentrations to prompt the selection of strains of bacteria that are progressively more resistant to the bacteria. It is this long-term exposure that brings the use of antimicrobials solely for growth promotion into question.

Internationally, the use of certain antimicrobials for growth or performance enhancement has in the past been common practice in intensively reared livestock operations. This was the case in New Zealand in the formative years of intensive livestock farming. In the past decade antimicrobial use in

feed for poultry and pigs was common practice, but the purpose was to prevent specific diseases. Growth or performance gains are secondary benefits. Nevertheless, antimicrobial products are still licensed solely for growth promotion and information was not provided at the time the products were licensed that specified the most appropriate use of the product to prevent specific diseases. Recommendations for disease prevention have subsequently been developed by the livestock industries using the products for this purpose.

All therapeutic animal health antimicrobial products that are licensed in New Zealand can be obtained only under the prescription of a registered veterinarian. Products registered for growth promotion can be purchased by anyone without a prescription. This is seen as a lack of control by the public that may encourage the development of antimicrobial resistance. However, the only two livestock industries (pig and poultry industries) that use in-feed antimicrobials depend for the most part on specialist veterinarians rather than general practitioners for advice on disease prevention. Nevertheless, unrestricted access may not provide sufficient control to prevent or stop imprudent use of the antimicrobials, or ensure that emerging resistance problems would be identified in a timely manner.

Potential for exposure to resistant bacteria

Antimicrobial resistance due to use of antimicrobial in animals can occur only if people become exposed to the resistant bacteria. Most therapeutic uses of antimicrobials in animals do not result in situations in which people would come into contact with the resistant bacteria. However, the situations in which significant human exposure can occur (e.g. food-borne diseases and direct contact with animals, particularly with air and fluid discharges) will have to be kept in mind during the review.

Significance of antimicrobials to human health

Not all veterinary antimicrobials are used on humans. Some antimicrobials are sufficiently toxic to humans to ensure that they will never have any practical use in human medicine, e.g. the ionophores. Bacitracin was used topically in humans in New Zealand, but due to its toxicity is no longer used locally in human medicine. Despite this limited use, bacitracin, as a growth promotant, was banned in Europe so that it could be saved for use against bacteria resistant to vancomycin. This is unlikely because some of the bacteria that it might be used against are inherently resistant to bacitracin.

In New Zealand the most commonly used in-feed antibiotics are ionophores and bacitracin. The former is used to prevent coccidiosis and the latter to prevent necrotic enteritis. Neither antibiotic poses a significant threat in regard to antibiotic resistance.

There are antimicrobials of significant importance in human health care used in animal health care, but there is no evidence that their use in animals is contributing to the antimicrobial resistance problem in human health. Nevertheless, their use should be allowed when that use is essential to the health and welfare of the animals, and the risks of developing antimicrobial resistance can be managed adequately.

Some antimicrobials are essential for treating specific human diseases, and for a number of these there are no practical alternatives. The fluoroquinolone family of antimicrobials is a good example. Two other important families of antibiotics are the glycopeptides such as vancomycin and macrolides, such as tylosin. The use of these families of antibiotics in human health must be protected.

The expert panel report noted that, in New Zealand, erythromycin and roxithromycin are the most frequently used antibiotics from the macrolide family, used to treat lower respiratory infections suspected due to *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. In addition, clarithromycin and azithromycin are new antibiotics from the macrolide family used in the treatment of *Helicobacter pylori* and chlamydial disease respectively. The expert group noted the importance of ensuring that the efficacy of these drugs be maintained for the treatment of human disease for as long as possible (Expert Panel Report, 1999, p23).

PROCESS OF REVIEW

Review rationale

Given the previous description of the matters that have to be considered, the review of animal antimicrobial products has to be based on a line of inquiry that can put the findings into proper perspective. The first step in the review is to categorise the antimicrobial or antimicrobial family in regard to its significance to human health and the likelihood that antimicrobial resistance will develop. This assessment will be done in a generic fashion because the categorisation is not affected by the animal health use of the antimicrobial. Expert parties will be asked to comment on the use of the antimicrobial in human health. They will also be asked for information on whether or not and why they consider that use is likely to be in jeopardy. It is expected that proprietors of both human and animal health products as well as human health specialists would participate in the categorisation.

Once an antimicrobial or antimicrobial family has been categorised as significant to human health, individual trade name products that contain that antimicrobial or any antimicrobial that might cause cross-resistance will be reviewed in regard to the particular antimicrobial resistance hazards they pose. If those hazards are significant then the conditions on their licence will be amended to manage the risks by either reducing the magnitude of the hazards or reducing the exposure to the hazards.

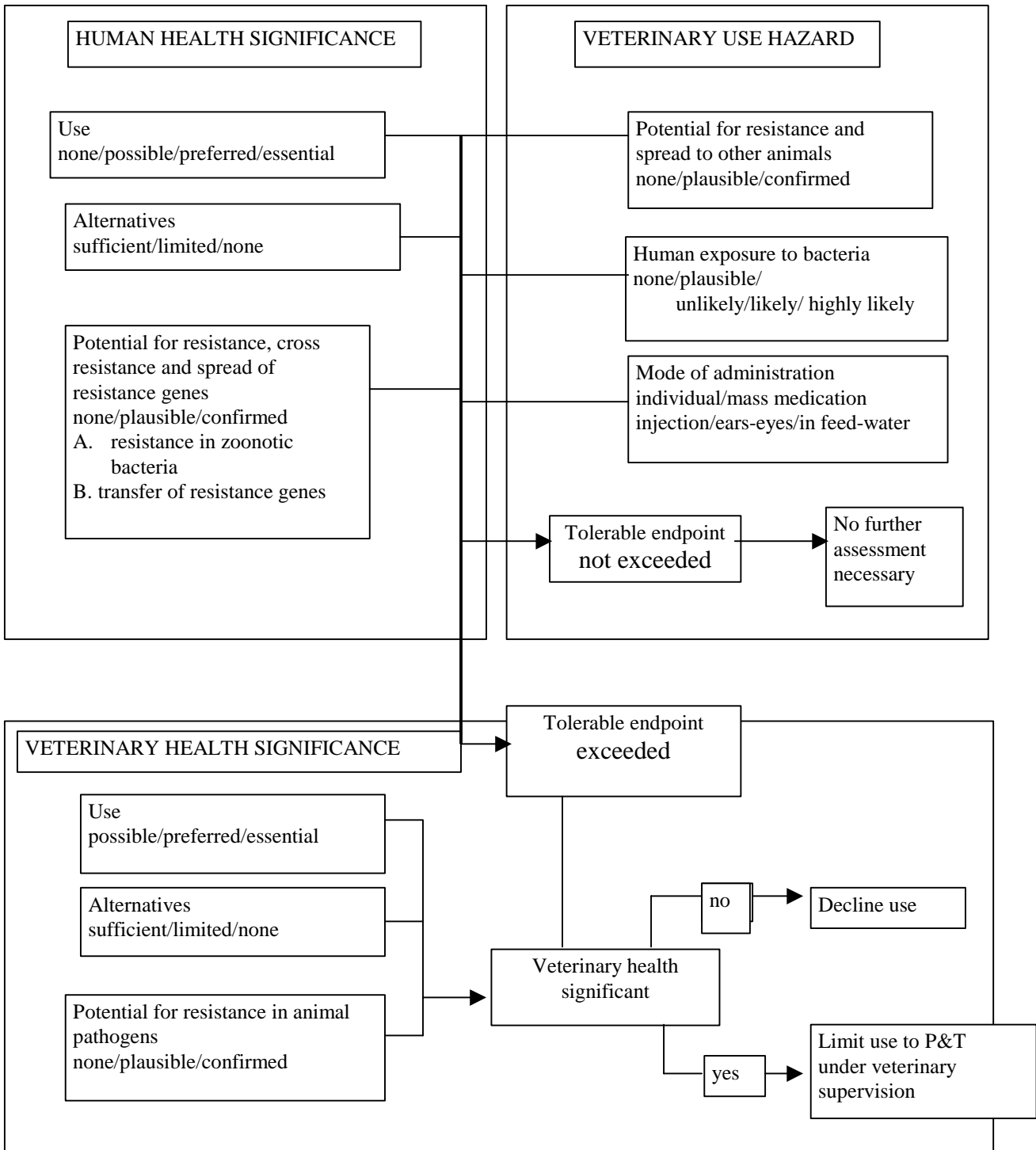
This rationale creates the following order of priority for the areas of interest.

1. human health significance and potential for resistance;
2. veterinary use and exposure hazards; and
3. veterinary use significance.

Obviously the highest priority matter is to establish how important the antimicrobial is to human health. Products will be subjected to the full line of inquiry to develop a comprehensive picture. However, if the antimicrobial in a product is not important to human health and it does not cause cross-resistance with any antimicrobial that is important in human health, then antimicrobial resistance in the context of this review is irrelevant.

The following figure shows the factors in each area of interest that will be reviewed. The line of inquiry begins with the categorisation of the antimicrobial (or family) then reviews the hazards posed by animal health trade name products containing that antimicrobial. If licences must be amended, then the significance of the product to animal health will be reviewed to ensure that antimicrobial resistance is managed without compromising the health and welfare of animals that would suffer if an essential product was precipitously withdrawn from the market.

ANTIBIOTIC RESISTANCE REVIEW RATIONALE



The criteria of significance in human health are:

- use and importance of the antimicrobial;
- whether or not there are alternative antimicrobial products; and
- the potential for resistance, cross-resistance and spread of resistance genes from resistant bacteria.

The second area of interest is the veterinary use and exposure hazards. The factors that will be reviewed are:

- potential for resistance to develop in the bacteria in the animals treated and spread to other animals;
- the potential for human exposure to the bacteria that may be resistant; and
- the mode of administration of the antimicrobial.

Veterinary use will highlight how prevalent a resistant strain might be and how much human exposure might occur as a result of the veterinary use. It will also address those few cases in which a non-feed use of an antimicrobial may result significant opportunities for human exposure.

The third area of interest will highlight the significance of an antimicrobial in maintaining animal health. This should expose any negative animal health consequences that might occur as a result of altering present regulatory controls.

The combination of human health significance and veterinary use and exposure hazards establishes a tolerable endpoint (estimate of significance in regard to antimicrobial resistance) at which a decision must be made whether or not a particular antimicrobial/use combination should be allowed. The antimicrobial resistance tolerable endpoint that is likely to prompt regulatory action in regard to the licensing of animal health antimicrobial products to prevent resistance may include the following:

- the use of the antimicrobial or a related antimicrobial in human medicine is important for the treatment of human disease;
- there are limited alternatives for use in human medicine;
- there is a plausible potential for the development of resistance in zoonotic bacteria or the transfer of resistance genes, or the exposure of humans to the resistant bacteria is likely;
- the mode of administration of the antimicrobial to animals is such that it would increase the probability of resistance developing in a critical mass of the animal population (ie mass medication in feed or water exposing whole flocks/herds to the antimicrobial, or unusually high risk of personal exposure to infected material), thus increasing the likelihood of human exposure to resistant bacteria.

If the tolerable endpoint does not apply, then trade name products containing that antimicrobial will not be reviewed further and no action will be taken to amend product licences.

If it is decided that the tolerable endpoint does apply, then regulatory action in regard to the licensing of trade name products containing that antimicrobial will be reassessed and amended accordingly. The types of action that will be taken may be any one or a combination of the following:

- prohibit all uses of that antimicrobial in animal health (veterinary) products;
 - prohibit a particular practice (i.e. mass-administration orally to food producing animals);
 - prohibit a particular use (i.e. use as a growth promotant);
- restrict access to particular persons (i.e. use only under registered veterinarian's prescription).

All new antimicrobial products will be subject to the same rationale as applications are received. Conditions on licensing for new antimicrobial products will be consistent with the new conditions proposed for existing licensed products.

CHANGE IN LEGISLATION

The Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 may be implemented while this review is in progress. Under the ACVM Act 1997, the licensing of animal health antimicrobials will become the responsibility of the MAF Food Assurance Authority, rather than the Animal Remedies Board. While the change will cause some disruption, the Animal Remedies Board's intended outcome for the review will still be appropriate under the ACVM Act. MAF considers that the review can progress even with a change in governing legislation.

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