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Long-term control of antibiotic resistance in livestock: a risk analysis framework

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Abstract

Antibiotic resistance in animals has been a growing problem in recent years due in part to the widespread use of antibiotics in food-producing animals, especially for prolonged periods of time to stimulate development. These antibiotic-resistant germs might eventually make their way to humans through animal products. They might also spread their antibiotic-resistance genes to germs that cause disease in humans, making it impossible to cure some potentially fatal infections. Determining the standards for risk minimization (risk management and risk communication) and the actual danger to human health from antibiotic usage in animals (risk assessment) will aid regulatory decision making. We present a new approach to risk analysis that takes into account the potential dangers posed by three interconnected agents: antibiotics (chemical agent), bacteria (microbiological agent), and antibiotic-resistance genes (genetic agent). Controlling antibiotic usage, limiting the spread of bacterial illness, and stopping the movement of resistance determinants across bacterial populations are all potential strategies for minimizing risk. Co-authored by the International Society for Chemotherapy and Elsevier Science B.V., 2002. This is a protected work.

Keywords: Food-producing animal; Antibiotic resistance; Risk analysis

1. Introduction

Inappropriate use of antibiotics promotes the spread of germs with the ability to resist treatment. When antibiotics fail to treat an illness caused by antibiotic-resistant bacteria, the results might be anything from mildly inconvenient to fatal. Although there may be additional repercussions with regard to fostering the growth of resistant bacteria, antibiotic failure has few effects on the host for mild and self-limiting bacterial illnesses.

Antibiotic failure may have lethal or life-threatening results for severe infections, leading to considerable long-term impairment and dramatically higher expenses of treatment. The threat that antibiotic-resistant bacteria (especially multiresistant strains) pose to human health has risen to the forefront as a global issue in recent years. One possible source of antibiotic-resistant microorganisms in humans is food-producing animals [1, 2]. The medical, veterinary, and regulatory communities are split on whether or not the subtherapeutic use of antibiotics in animals (for purposes like prophylaxis or growth promotion) poses a serious threat to human health and undermines the effectiveness of antibiotics for treating serious diseases [2 /4]. In order to implement regulatory measures, there must be consensus on this matter.

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implemented to reduce and manage the risk to human health without placing an unnecessary burden on the food-production industries.

In other contexts, where regulatory decisions need to take account of competing interests in an unbiased and transparent way, the agreed approach is 'risk analysis' [5 – 8]. For complex biological problems, such as the cancer risk from exposure to chemicals or the risk of introducing exotic diseases with imported food pro- ducts, 'no risk' solutions are generally either impossible or impractical. As a result, the concepts of 'acceptable risk' and 'manageable risk' have been developed [6,8,9]. The emergence of antibiotic-resistant bacteria in food- producing animals has resulted in polarised views on what should be considered an 'acceptable risk' and to what extent risks can be managed. For most of the medical profession, whose focus is usually individual patient outcome, any antibiotic resistance passed through the food chain from food-producing animals to humans may be considered 'unacceptable' [10]. On the other hand, veterinary professionals responsible for food-producing animals understand that antibiotic use can lead to resistance, but also have major concerns about animal welfare and the cost consequences of not using antibiotics. These differing views are compounded by issues such as regulatory controls (or the lack of them) and international trade obligations, which can have a profound impact on the livelihood and economic well-being of millions of people, but do not focus specifically on individuals [11].

For these reasons, there is a need for a formal and 'neutral' risk analysis framework for antibiotic use in food-producing animals. Such a framework should aim to minimise the impact on human health, while not unnecessarily disadvantaging food-production indus- tries or society in general. The need for such a model has been widely acknowledged but an agreed approach has not yet been fully developed [12].

In this paper we propose an approach to risk assessment for antibiotic resistance, within an overall risk analysis framework, for consideration by a broad range of stakeholders: the medical and veterinary professions, government policy and scientific advisers, regulators of therapeutic agents (both human and animal), pharmaceutical manufacturers, farmers and consumers.

2. Features of antibiotic resistance

The emergence of resistant bacteria was noted soon after antibiotics were first used in human and veterinary medicine in the 1940s [13]. It soon became apparent that antibiotic resistance has two forms: intrinsic and acquired. Intrinsic, or natural, resistance to a particular antibiotic or group of antibiotics is very widespread among bacteria, reflecting the evolutionary adaptation of bacteria to natural toxins in their environment. It occurs because the normal antibiotic target in the bacterial cell is not present, not susceptible, cannot be reached by the antibiotic (e.g. because the bacterial cell is impermeable to the antibiotic) or it can be due to the presence of natural degrading enzymes. Antibiotics are described as either broad spectrum (able to kill most bacteria, with only a few naturally resistant strains or species) or narrow spectrum (with many resistant strains or species).

Acquired resistance can arise either because of a random chromosomal change in one bacterial cell (mutation) involving the gene encoding the cellular target for the antibiotic, or by a bacterium acquiring a gene on a transferable (extrinsic) resistance element from another organism. In either case, in the presence of the antibiotic the resistant bacterium has a selective advantage and its numbers are amplified, while suscep- tible bacteria are inhibited or killed [14].

In bacteria, resistance genes are often found in specialised forms of DNA, such as plasmids (extrachro- mosomal, circular units of DNA), transposons or 'jumping' genes (which are found on chromosomes or plasmids) and integrons (specialised segments of DNA containing resistance determinants in packages called cassettes). Resistance determinants can also be carried by bacteriophages (viruses that infect bacteria) or on free DNA present in the environment (e.g. DNA fragments from the lysis of other cells). Acquisition of extrinsic resistance determinants can occur by conjuga- tion (cell-to-cell contact, or 'mating' with the transfer of genetic material, usually in the form of plasmids); transposition (the movement of transposons from one DNA site to another); transduction (the introduction of a resistance gene by an infecting bacteriophage); or transformation (the uptake of free DNA containing resistance genes) [14].

Human and animal skin and intestines are colonised with a diverse bacterial flora. When they are exposed to an antibiotic at sufficient concentrations, susceptible bacteria are suppressed and any resistant bacteria present in the normal flora are able to multiply (to a greater or lesser extent), greatly amplifying the numbers of resistant bacteria. The suppression of susceptible bacteria also creates the opportunity for colonisation with other resistant bacteria from external sources. Continued or repeated use of antibiotics further ampli- fies the resistant strains [15,16].

2.1. Antibiotic resistance in animal and human bacterial populations

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The first cases where disease in humans was caused by resistant bacteria of animal origin (in this instance, multiresistant strains of salmonella) were noted as early

as the mid-1960s in the United Kingdom. This led to a government investigation and recommendations in what is now referred to as the 'Swann Report' [17]. More recently, there have been concerns on both sides of the Atlantic about multiresistant *Salmonella typhimurium* DT104 [18]. A recent additional concern has been the detection of fluoroquinolone-resistant *Campylobacter* species following the licensing of fluoroquinolones for use in poultry in the United States [19]. For these and other enteric bacteria that are transferred from animals to humans via the food chain, the evidence from both observational/epidemiological and molecular studies points to a relationship between antibiotic use and the emergence of resistant bacterial strains in animals, and their spread to humans, mainly via the food chain [20 – 23].

In the late 1980s, vancomycin-resistant enterococci (VRE) were first detected in humans as specific patho- gens. This was of great concern to the medical commu- nity because enterococci are intrinsically resistant to many antibiotics and were becoming important in hospital-acquired invasive infections, especially in im- munocompromised patients. Subsequently, molecular evidence has indicated that in Europe, food-producing animals are the likely reservoir of one type of VRE, namely *Enterococcus faecium* strains with the v*anA* antibiotic-resistance gene (VREF). These particular strains are amplified in animals by the prophylactic or growth promoter use of avoparcin (a glycopeptide antibiotic, closely related to vancomycin) and trans- mitted to humans through the food chain. Other (microbiological) evidence suggests that human VREF are strains that have acquired the v*anA* resistance transposons from ingested animal enteroccoci [24]. Other strains of VRE with the v*anB* resistance gene appear to have emerged as a result of vancomycin use in human health care settings and have not been found in animals [25].

These examples highlight two mechanisms enabling antibiotic resistance to move between the bacterial populations of animals and humans:

- direct spread of antibiotic-resistant zoonotic patho- gens (e.g. salmonella) through the food chain [19 – 23], or by environmental contamination; [26] and
- transfer of genetic antibiotic-resistance determinants from host-specific animal bacteria to an opportunis- tic human pathogen that is a member of the normal human flora (e.g. v*anA* enteroccoci) [27,28].

A third scenario, which has not yet been reported in vivo but cannot be ruled out, is the possible transfer of resistance determinants from a foodborne animal bac- terium to a more pathogenic human bacterium, such as *Staphylococcus aureus* or *Streptococcus pneumoniae* [29].

3. Regulatory arrangements

Individual nations generally regulate the use of medical therapeutics and agricultural and veterinary chemicals, including antibiotics, by legislatively based registration and regulation processes. These processes are carried out by national agencies, such as the Food and Drug Administration (FDA) and FDA Center for Veterinary Medicine in the United States, and the Therapeutic Goods Administration and the National Registration Authority for Agricultural and Veterinary Chemicals in Australia.

In most developed and some developing countries, the regulatory process for agricultural and veterinary che- micals involves a rigorous scientific assessment of efficacy, toxicity and overall safety of the chemical before allowing it to be marketed (pre-registration approval). For chemicals and increasingly for biological products, this is done within a formal risk analysis framework. However, such a framework has not been fully developed for assessing the risks to human health associated with antibiotic resistance, although these concepts are now part of United States and Australian processes for registration of agricultural and veterinary chemicals.

Most nations also have registration review provisions and adverse reaction reporting arrangements in place after a product is registered for use (post-registration monitoring). If adequate monitoring programs are developed, they will ensure that further data become available that can be used to update and refine the risk assessment and assist the ongoing management of antibiotic resistance at the national and international level.

3.1. Global perspective

The scientific issues surrounding antibiotic resistance, including its emergence, selection by antibiotic use, transfer of antibiotic-resistant genes between bacteria and spread between animals (including humans) by direct and indirect mechanisms, are all global issues as has been shown, for example, with penicillin-resistant

S. pneumoniae and *S. typhimurium* DT104 [30 – 32]. In

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this age of international travel and trade, bacteria can be 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 and trade implications for all other countries, as does the uncontrolled use of antibiotics in animals and humans. Nations may, therefore, choose to impose quarantine measures to prevent the inad- vertent import of resistant/multiresistant bacteria into countries where they are not already present (in the same way as quarantine measures are applied for other

exotic diseases) [18]. This further highlights the need for a consistent approach to be taken internationally to risk assessment, regulation of antibiotic use, monitoring and surveillance of antibiotic-resistant bacteria and quaran- tine.

4. Risk analysis

There are many complex biological situations where risk analysis has been used to develop a better understanding of issues and form a framework for regulatory policy. The effect of environmental chemicals on development of human cancer is one [33]; the microbiological and chemical safety of food, and quarantine requirements for imports, are others [7,9,34,35]. Although the processes used in these situations are similar, there are differences in the approach to risk assessment and the terminology used between toxicological and food safety assessments [7,34], and quarantine assessments relating to the import and release of exotic organisms into the environment [35].

The approach that has been used most for toxicological and food safety issues is based on a method first published by the National Academy of Sciences (NAS) [36]. This approach has subsequently been used as the basis for risk analysis by the Codex Alimentarius Commission (an agency of the World Health Organization/Food and Agriculture Organization that sets standards for foodstuffs in international trade) [7] and the Australia New Zealand Food Authority [34].

The method that has been adopted by the Office International des Epizooties (OIE; the animal health equivalent of WHO) [35] for animal disease and quarantine risk analysis is based on a method first proposed by Covello and Merkhofer [37]. OIE has also recently published a draft broad outline of the risk analysis methodology to be applied to animal antimicrobial-resistance situations, based on this model [38].

The method and terms used in this paper follow the NAS/Codex approach [7,36] and build on an earlier paper on risk assessment of microbiological contamination of food [5]. However, components of the Covello—Merkhofer system [37] have also been included as appropriate, because this system is used for assessment of risks associated with the spread of animal diseases. Under both systems, risk analysis is seen as having a number of interacting components— risk assessment, risk management and risk communication.

Risk assessment provides a systematic approach for characterising the nature and magnitude of risks, in this case to human health. The ultimate aim of the process is to provide the best possible scientific information about the risks so that the best decisions are made as to what to do about them.

The results of the risk assessment allow policy makers to develop a risk management plan in order to minimise risks. However, risk management is generally separated from the neutral, scientifically based risk assessment process. Risk communication is the dialogue that must occur between the scientists or regulators who generate or assess the scientific data, the risk managers (policy/ decision makers), the stakeholders who are affected by the risk management decisions taken, and the general community that expects protection from unacceptable risks. This dialogue must occur at all stages of the risk analysis, from identification of a hazard to management of the risks and not just after management decisions are made.

4.1. Risk assessment stages

Risk assessment must be based on sound scientific principles and requires transparent consultation with all stakeholders. Under the NAS/Codex system [7,36] the process involves assessing the relationship between a hazard (a biological, chemical or physical agent that may harm human health) and the probability that it will actually cause harm (sometimes referred to as a 'risk chain'), using several well-defined steps:

- *hazard identification* to determine the potential for an adverse effect, based on toxicological, disease or other data about the activity of the hazardous agent;
- *hazard characterisation* to determine how the hazard causes the adverse effect (e.g. mechanism and dose— response);
- *exposure assessment* to determine the frequency and level of exposure of a population to the hazard; and
- *risk characterisation* to link the hazard characterisation and exposure data to provide a qualitative or quantitative estimate of risk, including the severity of the adverse effect (impact or 'consequences') overall in the population (e.g. with respect to other risks or factors affecting overall population well-being).

The Covello— Merkhofer method includes an additional stage (called 'release assessment') to describe

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the biological pathway(s) involved for the risk source to introduce risk agents (hazards) into a particular environment (and provide a qualitative or quantitative estimate of the process occurring). Under this method, 'hazard characterisation' is also replaced by 'consequence assessment', which considers the relationship between exposure (dose) and the adverse effect, but places more emphasis on the severity of the adverse health and/or economic outcome (consequences or impact). Although they reflect a different approach to risk assessment overall, these differences are not important in terms of the main theme of this paper, which is that, because of the complexity of the issue, risk assessment for antibiotic resistance can be broken down into three components (see below).

The process of risk assessment has been used for chemical, microbiological and genetic risk assessments. Chemical risk assessment has been widely used by regulatory agencies around the world for the toxicological assessment of agricultural chemicals, food additives, residues in food and environmental pollutants [7,34,36]. Microbiological risk assessment is a much less well-defined procedure that has not yet been formally adopted by most regulatory agencies because of a lack of adequate data on the relationship between the prevalence and concentration of pathogens in the environment and in various stages of the food chain, and the incidence of infectious diseases [5,39]. Genetic risk analysis is also not well defined, although the method has been discussed in connection with the assessment of horizontal gene transfer of inserted genes from genetically manipulated organisms released into the environment [40].

An important part of a risk assessment is the identification of data gaps and uncertainties in the available data. If there is a genuine indication that human health may be harmed but the level at which this occurs is uncertain, an additional safety factor may be needed to safeguard human health. This occurs for chemical risk assessment where the 'no-effect dose' may be reduced by a factor of 10 or 100 depending on the certainty about the human health impact of the chemi- cal.

5. Risk assessment model for assessing the emergence and spread of antibiotic resistance

We propose a novel approach to assessing the risks associated with antibiotic use. The method could be used to assess risks from either veterinary or medical use of antibiotics, as shown in Fig. 1, but in this paper we have considered the veterinary use of antibiotics in food- producing animals.

As with other risk chains (e.g. cancer development after exposure to an environmental carcinogen) there are numerous steps in the generation and transfer of antibiotic resistance in bacterial populations, between and within animal species and within different bacterial populations in animals, humans and the environment. This is further complicated because a number of different species of bacteria and different genetic determinants are involved, each with its own mode of action and dynamics.

In previous attempts to develop a framework for risk assessment for this issue [12,41], these multiple factors have been combined into one rather complex assessment. Instead, we propose that three separate risk assessments are needed, for three 'hazards':

1) the antibiotic;
2) the antibiotic-resistant bacteria; and
3) the genetic determinants for antibiotic resistance (antibiotic-resistance genes).

These hazards can be associated with three adverse outcomes:

1) emergence of antibiotic-resistant bacteria;
2) spread of antibiotic-resistant bacteria resulting in human exposure/infection; and
3) transfer of antibiotic-resistance genes to other bacteria.

The interrelationship between these three hazards and outcomes is shown in Fig. 1, which we have called a 'risk matrix', because it is more complex than the conven- tional 'risk chain' associated with exposure to a single hazard. This figure also indicates that the same approach can be used to assess the risks from animal or medical use of antibiotics.

As Fig. 1 shows, there are two overlapping pools of bacteria (animal and human). The emergence or entry of an antibiotic-resistant bacterium carrying a particular antibiotic-resistance gene into the animal pool may be a rare event but antibiotic use in animals will amplify the resistant bacteria or genetic determinant. The chance of the resistant bacteria spreading to humans, or of an antibiotic-resistance gene transferring to the human bacterial population, increases with any increase in the size of the pool of resistant bacteria or genetic determinants in the animal or human environment. 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 antibiotic-resistance gene.

If animals and humans are both exposed to a particular antibiotic and there is a connection between the bacterial pools through a contact such as food, then there is potential for amplification of antibiotic-resistant bacteria to occur in both pools simultaneously. How- ever, if the human population is not exposed to the same antibiotic or one that coselects for resistance to that antibiotic, then the

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potential for amplification in hu- mans is low. The reverse is also true for antibiotic spread from humans to animals.

The greatest concern at this stage is that a rare antibiotic-resistant strain of bacteria may emerge in animals as a result of antibiotic use. This resistance may not be detected immediately in animals, be spread to humans and then amplified by human use of antibiotics that occurs in the human health care environment.

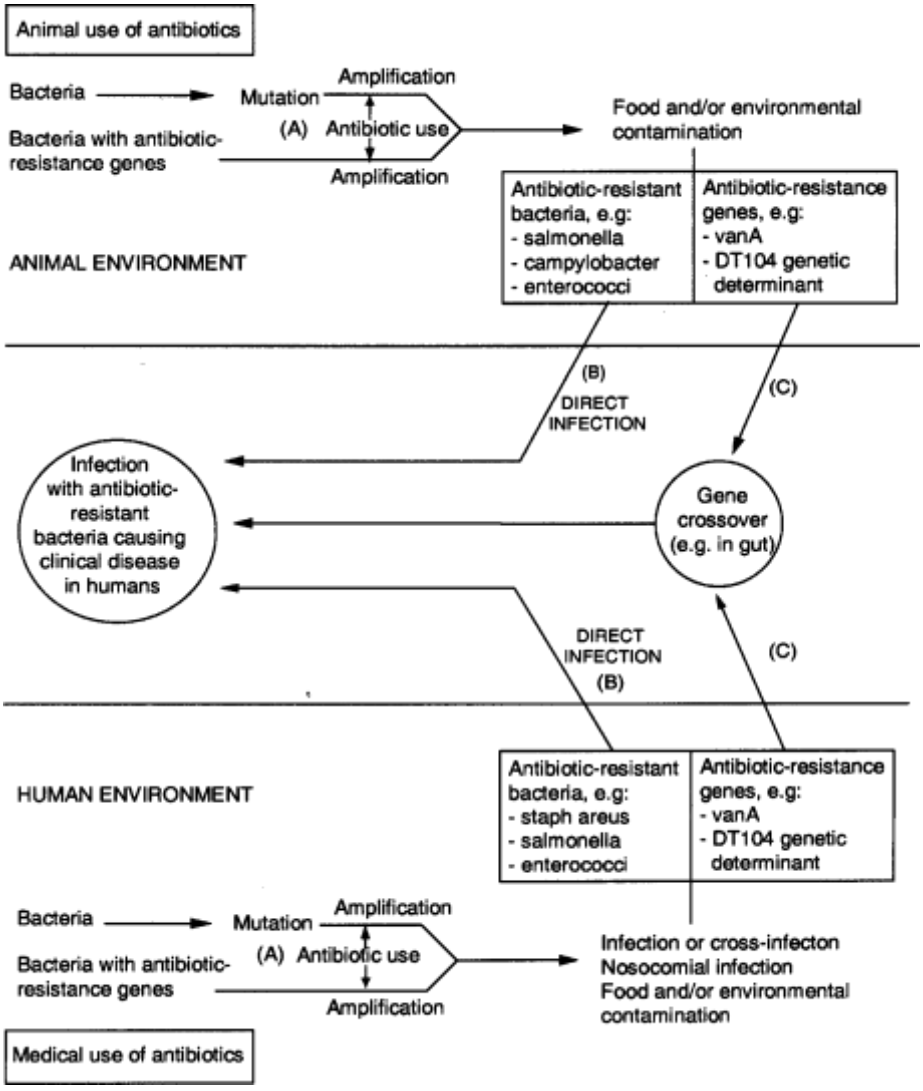

Fig. 1. Risk matrix for animal and human bacterial populations, including antibiotic use (A), spread of antibiotic-resistant bacteria (B), and/or transfer of antibiotic-resistance genes (C).

5.1. Data requirements

The risk assessment for antibiotic use is equivalent to that for chemical use in general; the risk assessment for spread of antibiotic-resistant bacteria is equivalent to microbiological risk assessment; and the risk assessment for transfer of the genetic determinants of antibiotic resistance is equivalent to a genetic risk assessment. All three risk assessments are needed before an assessment of overall risk can be made. The steps involved and data requirements for each risk assessment are shown in Table 1.

By separating the assessment into three parts, it will be possible to focus on different aspects of the assess- ment, depending on exactly what is being assessed and what data are available. One scenario is the pre- registration marketing approval of a new antibiotic for use in food-producing animals. In this case, the assess-

ment may have to focus on the antibiotic itself—the class of antibiotic, mode of action and proposed use pattern (antibiotic load) —and its relationship to human ther- apeutic antibiotics. Information may also be available on the nature of the genetic determinant responsible for the antibiotic resistance and the expected mechanism of emergence of resistant bacteria. This information should be

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available from the company application dossier, related research studies and comparison with related antibiotics. At this pre-marketing stage, however, there may be few or no data (even experimental or in vitro) available on the prevalence, spread and human disease effects of the antibiotic-resistant bacterium involved. The available data at this stage are likely to relate only to the antibiotic-sensitive strain of the bacterium: although this may be very similar to the antibiotic- resistant strain, this is an uncertainty that would need to be acknowledged.

n a different scenario, a risk assessment process may be initiated for an antibiotic already in use because of emerging concerns about its safety. In this case, assum- ing that post-registration monitoring and surveillance programs have been used (see discussion of risk manage- ment options, below), further data would be available on the actual use levels of the antibiotic, the emergence of resistant bacteria, the prevalence of resistant bacteria and their potential for spread between animal and human bacterial populations. More information may also have become available on the genetics of antibiotic resistance, as well as any coresistances (from ongoing research and molecular characterisation of human and animal isolates). Hence, in this case, the risk assessment should be able to focus more fully and quantitatively on all three components.

Finally, a risk assessment may also be required as the basis for quarantine restrictions on the import or export of certain products that may carry antibiotic-resistant bacteria (e.g. meat products). In this case, in line with other quarantine risk assessments, the OIE method, which is based on the Corvello– Merkhofer approach, could be applied for each of the three components identified in Table 1 [35,37].

Models for determining the fate and transport (dis- persal) of microbial agents released into the environment have been described [42] and could be used to determine the dispersal of antibiotic-resistant bacteria. A similar modelling approach has been used in the United States to estimate the risk of spread of resistance to the antibiotic fluoroquinolone by campylobacter bacteria, associated with a particular prevalence of resistant bacteria [43].

5.2. Overall risk characterisation (risk matrix)

After the three components (antibiotic, antibiotic-resistant bacteria, antibiotic-resistance genes) have been assessed, it will be necessary to combine the results into an overall risk characterisation, which will form the basis of risk management decisions. This will involve careful consideration of animal and human bacterial populations, as indicated by the risk matrix (see Fig. 1).

5.3. Consideration of benefits

Other considerations, such as any benefits to human health that accrue from the use of the agent, may also be useful because such benefits may offset or outweigh the risks. For antibiotic use in animals, this may include reduction of the bacterial load in the food chain. Benefits apart from those to human health (e.g. for animal health, animal production or the environment) are also important, but can only be assessed once an 'acceptable' level of human health risk has been established.

5.4. Risk management

The three-way risk assessment model outlined in Table 1 and the risk matrix illustrated in Fig. 1 show that an integrated risk management program should focus on:

- antibiotic use– the class of antibiotic with respect to human therapy, the amount of antibiotic used (anti- biotic load) and how it is used (regimen);
- the level of bacterial infection (bacterial load) and potential for spread;
- the prevalence of antibiotic-resistant bacteria; and
- molecular characteristics of the genetic determinants responsible for antibiotic resistance and their meth- ods of transfer.

To meet the ongoing data requirements of the model, continuous data collection will be needed, including data on antibiotic use (load and regimen) and spread of bacteria (e.g. incidence of foodborne infections). The model must also include molecular characterisation of the antibiotic-resistance genes from resistant bacteria, including bacteria other than those known to be directly responsible for disease in humans. Baseline data on antibiotic resistance are also urgently required for measuring trends and assessing the performance of changes implemented in the strategic management of antibiotic resistance.

Based on these principles, the Joint Expert Technical Committee on Antibiotic Resistance (JETACAR) pro- posed a management strategy for the minimisation of antibiotic resistance in a report for the Australian Government in 1999 [44]. JETACAR proposed a coordinated multidisciplinary approach to risk manage- ment based on five key elements: regulatory controls, monitoring and surveillance, infection prevention stra- tegies (hygienic measures), education, and further re- search. The basics of this five-point plan are equally applicable to human and veterinary medicine, as well as other areas of antibiotic use.

Fig. 2 has been adapted from the approach proposed by JETACAR and shows the risk analysis framework, as well as the longer-term dynamics associated with antibiotic use. A feature of this plan is the ongoing collection of data through: (a) monitoring of antibiotic use (from import and/or usage statistics); (b) monitoring the emergence of

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resistant bacteria (through a national antimicrobial-resistance monitoring program); and (c) surveillance of the prevalence of antibiotic-resistant bacteria in different bacterial populations. Within this program, targeted testing would provide data on the prevalence of resistant bacteria within specific bacterial populations, while ongoing monitoring and surveillance would indicate their prevalence in total bacterial popu- lations and their potential for spread between animal

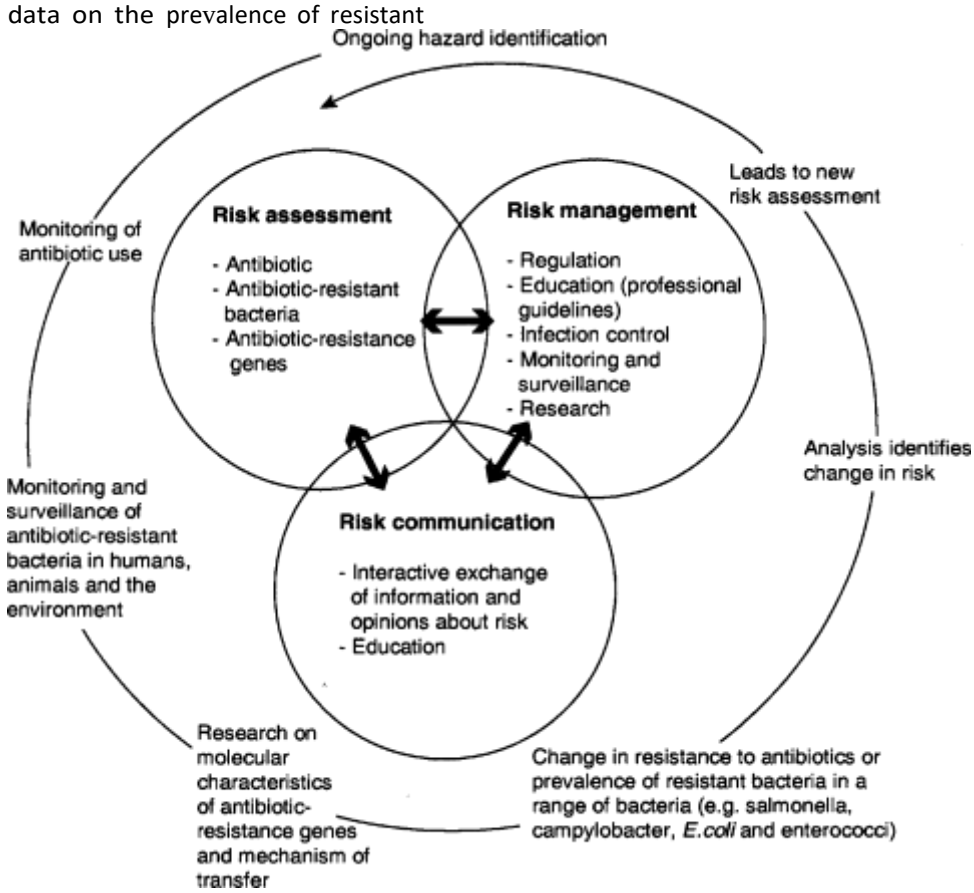

Fig. 2. Schematic diagram of risk analysis for antibiotic resistance with ongoing monitoring and surveillance to guide management of antibiotic use.

and human bacterial populations. This process will thus provide vital data for the antibiotic and bacterial components of the risk assessment that were not previously available. Ongoing research and molecular characterisation of the genetic determinants involved is also essential to improve the data available for the genetic component of the risk assessment.

Under this proposal, an independent expert body would analyse the information and make recommenda- tions for consideration by the legislative and regulatory agencies responsible for agricultural, veterinary and human antibiotics. Changes in regulations as a result of this process or new monitoring, surveillance or research will feed into the next evaluation cycle of the ongoing management strategy.

Once begun, the management of antibiotic resistance will be an ongoing process for individual nations as well as an international public health issue, affecting humans and animals (wild, food and companion) and the wider environment.

5.5. Trade and animal production

Although risk analyses, including those related to antibiotic resistance, are primarily concerned with hu- man health and safety, regulators also need to be aware

of the impact decisions made for human health reasons may have on the national and international competi- tiveness of food producers. International trade in food commodities is closely linked to public health issues. Food commodity markets and prices are rapidly and adversely affected when infectious agents from animals threaten human health, such as has occurred with bovine spongiform encephalopathy (BSE) or the enter- opathogen *Escherichia coli* O157:H7.

Any major outbreak of a zoonosis in the developed world is rapidly reported via the internet. In many cases where contamination is involved, public recall notices have to be published and media interest is high. This translates into consumer concern, with profound effects on the sales and price of particular commodities. It is also possible that administrations such as the European Commission that are concerned with antibiotic resis- tance could

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demand equivalence in monitoring and surveillance of antibiotic resistance from trading coun- tries. Such a decision could unnecessarily increase the cost of producing food.

These developments highlight the need for a trans- parent, scientific and evidence-based process to assess the real level of risk to human health, and if it is deemed to be unacceptable, to take action to reduce it to an appropriate, or 'acceptable', level. In this way, risk

management decisions will not unnecessarily disadvan- tage other areas, such as food-producing animal pro- duction, through increased costs of antibiotics or the removal of an antibiotic critical to animal health and food production [35].

5.6. Risk communication

As 'no-risk solutions' are generally impractical when dealing with antibiotic resistance (as for other public health issues), the various perceptions and perspectives of different stakeholders need to be taken into account in the development of antibiotic-resistance risk analysis and management programs.

This information sharing should aim to increase public knowledge and involvement, as well as obtain the commitment of stakeholders to the risk assessment and management processes, and particularly to the decisions made.

An example of the importance of involvement of all stakeholders can be seen from the issue of development, marketing and promotion of new antibiotics. It is clear that the current commercial environment, with high development costs and a limited time under patent to recover those costs, is counterproductive to the long- term conservation and minimisation of the emergence of antibiotic resistance, which may involve restricting the use of the drug to particular defined situations [45]. Thus, frank and open consultation is needed between government regulatory agencies, the pharmaceutical industry and other stakeholders, in the light of the risk matrix proposed in this paper.

6. Conclusions

Although antibiotic resistance is seen as an important public health issue internationally, a comprehensive method of risk analysis leading to an effective long- term management program has not yet been developed by any one nation or by any of the relevant international public health or animal health agencies.

Within the framework of risk analysis, we have broken the risk assessment for antibiotic resistance into three component parts—the antibiotic, the anti- biotic—resistant bacteria and the antibiotic-resistance genes-to guide data collection and risk assessment. These three components can then be built back into a risk matrix using ongoing monitoring, surveillance and data collection relating to antibiotic use, level of bacterial contamination and spread, emergence and prevalence of antibiotic-resistant bacteria, and molecu- lar characterisation of the genetic determinants of resistance. Development of such a matrix based on an increasing, targeted database of information—from anti- biotic usage statistics, bacterial monitoring and surveil-lance, and research—will direct the development of ongoing, long-term strategic management plans at the local, national and international levels.

It is clear that the national and international decision- making processes to husband the effectiveness and longevity of existing and new antibiotics will have to become more transparent to be acceptable to all stakeholders, whatever their perspective on this issue. The concepts presented in this paper should be con- sidered early in national and international strategic management planning processes so that informed deci- sions can be made on data requirements for marketing of new antibiotics and for ongoing monitoring and surveillance programs.

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