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THE MEDICAL IMPACT OF THE USE OF ANTIMICROBIALS IN FOOD ANIMALS

Report and Proceedings of a WHO Meeting

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DIVISION OF EMERGING AND OTHER COMMUNICABLE DISEASES SURVEILLANCE AND CONTROL
WORLD HEALTH ORGANIZATION

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I. Antimicrobial Use in Livestock and the Problem of Bacterial Resistance in Humans

Antimicrobials[1] are vital medicines for the treatment[2] of bacterial infections in both humans and animals. Antimicrobials have also proved to be important for sustainable livestock production and for the control of animal infections that could be passed on to humans.

Certain antimicrobials used for treatment or growth promotion in agriculture are also used for disease control in humans. Others select for cross-resistance in bacteria to antimicrobials used in human medicine. Microbiological and clinical evidence is mounting that resistant bacteria or resistance determinants might be passed from animals to humans, resulting in infections that are more difficult to treat. With an increase in the prevalence and distribution of antimicrobial-resistant infections in hospitals and the community, the question has been raised as to how this escalation of resistance could have been influenced by the use of antimicrobials in livestock production.

Timely public health action is needed to control medical problems related to the widespread application of antimicrobials outside the medical sphere.

The magnitude of the medical and public health impact of antimicrobial use in food animal production is not known. Despite the uncertainty, however, there is enough evidence to cause concern. It is unrefuted that the use of antimicrobials leads to the selection of resistant bacteria and that the scope of the emerging problem depends, among other things, on duration of exposure to and concentration of the antimicrobial.

Timely public health action is needed to control or mitigate any medical problem that might be related to the widespread application of antimicrobials outside the medical sphere. The most desirable action is the limitation, or more prudent use[3], of antimicrobials, particularly where alternatives are available. In situations where there is evidence of a link to medical problems, appropriate control action is needed.

Reasons for the magnitude of the problem being unknown are manifold, but are related to the paucity of national and regional information on antimicrobial use and resistance trends in hospitals and the community. Scarcity of data complicates attempts to quantify the proportion of resistance problems in humans that are caused by antimicrobial use in livestock production. Data are even more limited on antimicrobial consumption, antimicrobial use in agriculture and the prevalence of antimicrobial-resistant zoonotic bacteria in food animals and food of animal origin.

Antimicrobials are used extensively in livestock, fish and plant production. Some countries report that more than 50 percent of their total output of antimicrobial compounds is used in agriculture. Most are applied to food animals in subtherapeutic doses as growth promoters[4], which boost the utilisation of the genetic potential for growth of pigs and poultry, improve feed conversion and reduce waste product output from intensive livestock production.

National policies on the use of antimicrobials in animals must balance the possible benefits to livestock production against the medical risk and public health consequences deriving from their use.

Food animal production systems, and the use of antimicrobials in those food animals, vary in different regions of the world. In some countries food animals are raised in intensive conditions with thousands of animals living under confinement on a single premises. In other countries production is less intensive, largely pasture-based and often small in scale. Similarly, the incidence and spectrum of infectious diseases of food animals – and thus the need to treat with antimicrobials – vary widely across the world.

In general, there is little doubt that treatment problems in humans due to resistant bacteria are primarily related to the prescribing practices of health workers and to medication-taking practices of patients. The liberal availability of antimicrobials in some countries also contributes to the basic problem of bacterial resistance.

In light of shrinking public resources and the increasing need to conduct scientifically-substantiated risk assessments for prioritising public health action, national policies on the use of antimicrobials in animals must balance the possible benefits to livestock production against the medical risk and public health consequences deriving from their use. This will require close cooperation between sectors involved in food hygiene, prevention and control of diseases transmitted from animals to humans, hospital infection control, resistance monitoring and prudent use of antimicrobials in humans and animals.

The animal production sector shares with other sectors the responsibility for the provision of safe and wholesome food for human consumption. Among other things, this sector must ensure that animals are healthy and are not a reservoir for antimicrobial-resistant bacteria. Food safety and the management of potential public health risks are part of a continuum of the feed-food-chain. Hazard analysis critical control point (HACCP) principles should be applied at all stages of this chain to ensure that throughout production and processing food is maintained as safe as possible.

WHO Meeting of Specialists

In October 1997, the World Health Organization convened a meeting of specialists in the areas of developing, licensing and use of antimicrobials in livestock production as well as in clinical microbiology, resistance monitoring and medical infectious disease control. The purpose of this meeting was to examine the question of whether the use of antimicrobials in livestock production contributes to the escalation of antimicrobial resistance in humans.

The objectives of the meeting were to: (1) obtain an international consensus on priority medical problems arising from the use of antimicrobials in livestock production, and (2) recommend to WHO the next steps toward the development of guidelines for control and containment of the emergence of medically-relevant antimicrobial resistance in food animals.

Thirty-nine presentations were prepared by the participants and observers[5] to this meeting. Of these papers, 31[6] were distributed electronically for discussion and comments over a four-week period prior to the meeting in Berlin, to 522 experts from at least 45 countries on all continents.

Obtaining an international consensus on priority medical problems arising from the use of antimicrobials in livestock production was a primary objective of the meeting.

Opening the meeting were Dr A. Somogyi, Director of the Federal Institute for Health Protection of Consumers and Veterinary Medicine on behalf of the Ministry of Health Germany, and Dr K. Stöhr, Division of Emerging and other Communicable Diseases Surveillance and Control, on behalf of the World Health Organization.

Presentations and discussions on the first two days of the meeting reviewed antimicrobial use in food animal production, known and potential medical consequences of the use of antimicrobials in food animal production, and known and potentially-effective corrective and preventive actions to be taken. Subsequently, three working groups drafted reports which were discussed and adopted during the final plenary session:

- Medical impact of the use of antimicrobials in livestock production;
- Monitoring of antimicrobial resistance in food animals and food of animal origin; and
- Risk management at the primary production level: prudent use of antimicrobials.

This report presents the findings of the meeting and recommendations of the Expert Committee.

II. Assessment of Antimicrobial Resistance: Scope and Evidence

Medical impact of the use of antimicrobials in livestock production

Antimicrobial use leads to the selection of resistant forms of bacteria in the ecosystem of use. This will occur with all uses including treatment, prophylaxis[7] and growth promotion. Examples of factors influencing the development of resistance include drug concentration, long-term exposure, organism type, antimicrobial type and host immune status. Low-level, long-term exposure to antimicrobials may have a greater selective potential than short-term, full-dose therapeutic use. Resistance can be selected in both target bacteria and other exposed bacteria, with resulting adverse consequences for the prevention and treatment of diseases in humans, animals and plants.

Bacteria and genes, including resistance genes, can pass between human, animal and other ecosystems.

Bacteria and genes, including resistance genes, can pass between human, animal and other ecosystems. When resistant bacteria are themselves pathogenic or can transfer their resistance genes to pathogenic bacteria, adverse health effects can result.

Antimicrobials are used in animals as growth promoters (in subtherapeutic doses), prophylactically for disease prevention (for example, after commingling of animals from different farms) or therapeutically, for treatment of infections. Adverse consequences of selecting resistant bacteria in animals include:

- an increase in the prevalence of resistant bacteria in animals; the transfer of resistant pathogens to humans via direct contact with animals, or through the consumption of contaminated food or water;
- the transfer of resistance genes to human bacteria;
- an increase in the incidence of human infections caused by resistant pathogens; and
- potential therapeutic failures in animals and humans.

Residues of antimicrobial agents in food of animal origin in excess of the agreed acceptable minimum residue levels (MRLs) may contribute to the generation of resistance in bacteria in humans. However, the current evidence suggests that the risk is low. Of more concern may be that such residues could indicate inappropriate use of antimicrobials by the producer.

The medical consequences of resistance acquisition in bacteria of animal origin are highlighted by the following examples.

Salmonella

There is direct evidence that antimicrobial use in animals selects for antimicrobial-resistant nontyphoid *Salmonella* serotypes. These bacteria have been transmitted to humans in food or through direct contact with animals. Antimicrobial resistance limits the therapeutic options available to veterinarians and physicians for the subset of clinical cases of nontyphoid *Salmonella* which require treatment. A recent example is a clone of *S. typhimurium* DT104, resistant to ampicillin, tetracycline, streptomycin, chloramphenicol and sulphonamides, which has become prevalent in many countries including the United Kingdom, Germany and the United States of America.

Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluoroquinolones in humans has become a cause for particular concern. This phenomenon has been observed in countries such as France, Germany, Ireland, the Netherlands, Russia Federation, Spain and the United Kingdom.

Following the introduction of fluoroquinolones in food-producing animals, the emergence of Salmonella *serotypes with reduced susceptibility in humans has become a cause for particular concern.*

Campylobacter

Following the introduction of fluoroquinolones for use in poultry there has been a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones. Fluoroquinolone-resistant *C. jejuni* has been associated with therapeutic failures in humans.

Enterococci

The use of avoparcin as a growth-promoting feed additive in animal husbandry has contributed to the reservoir of transferable resistance genes to glycopeptides, including vancomycin, in the commensal enterococci of animals. Glycopeptide-resistant enterococci from animals can reach humans via the food chain. Although glycopeptide resistance genes have been shown to be widely disseminated, the extent to which the gene pool in animals contributes to the prevalence of glycopeptide-resistant commensal enterococci in humans has not been quantified. Glycopeptide-resistant enterococci cause serious infections in hospitalised immune-impaired patients. In this setting they contribute to increased morbidity and mortality, in part because of limited therapeutic options. This medical impact would be greatest in countries where vancomycin is used intensively.

There is concern that there will be increased dissemination of glycopeptide resistance genes to *Enterococcus faecalis* and their spread to other gram-positive organisms, particularly to multiresistant *Staphylococcus aureus* for which vancomycin is the drug of last resort. Due to the limited number of agents available for the treatment of glycopeptide-resistant enterococci, antimicrobial agents not previously used in humans are being sought, including drugs from classes currently used as growth promoters in animals. Therefore the selection of further resistance in enterococci is undesirable, *e.g.*, streptogramin resistance due to use of virginiamycin as a feed additive in animals.

Escherichia coli

Multiresistant *Escherichia coli* have been selected by the use of broad spectrum antimicrobials in both livestock and humans. The development of antimicrobial resistance in *E. coli* creates problems due to their high propensity to disseminate antimicrobial resistance genes. Resistance genes have been traced from *E. coli* in animals to *E. coli* in humans. Certain *E. coli* are foodborne pathogens and most of these strains are currently susceptible to antimicrobials. Should therapy be required, it could be compromised by the development of resistance in these strains.

There is still a profound lack of standardised data, from both the medical and veterinary sectors in many countries, on the susceptibility of zoonotic bacteria.

Monitoring of antimicrobial resistance in food animals and food of animal origin

The need for international coordination. Although there is increased evidence of the transfer of resistant bacteria or resistance determinants from livestock to humans via food or direct contact, information is limited as to the prevalence and spread of resistance in zoonotic bacteria or indicator[8] agents. Only a few countries have established resistance surveillance projects for the most important foodborne zoonotic bacteria. Monitoring programmes in some countries are in the early stages of development; some of these are in parallel with the strengthening of resistance monitoring in hospitals and community settings. Some international programmes, such as ENTERNET[9] and the network of European zoonoses laboratories, are attempting to coordinate activities between European countries. However, monitoring of antimicrobial resistance of bacteria from food animals and food of animal origin – whether at national or international levels – is still in its infancy. International coordination is needed at early stages of national and international programme development to boost national activities and provide for data compatibility and sharing.

The need for close coordination between the human and animal fields. The problem of monitoring resistance in bacteria transmitted from animals to humans is compounded by differences in logistics, coordination, supervision and responsibility of medical versus veterinary programmes for the control of zoonotic infectious diseases. There is still a profound lack of standardised data, from both the medical and veterinary sectors in many countries, on the susceptibility of zoonotic bacteria and the presence of resistance determinants in indicator bacteria transmitted from animals to humans. While many countries have national reference laboratories for major zoonotic diseases like salmonellosis (often separated into human and animal components), isolates from various sources are commonly not tested for antimicrobial resistance with identical or comparable methods, or against the same antimicrobial compounds.

The purpose of monitoring programmes. The purpose of monitoring programmes for antimicrobial resistance in foodborne bacteria is to systematically collect and evaluate information pertinent to effective control and containment of resistant bacteria that could be transmitted from animals to humans. These programmes should contribute to: (1) the detection and prevention of transmission of resistant bacteria and resistance determinants from animals to humans, and (2) the prudent use of antimicrobials in food animals and humans.

An effective monitoring system should analyse and disseminate data on the extent and temporal trends of resistance in bacteria isolated from livestock, food and humans.

The elements of a monitoring programme. An effective monitoring system for antimicrobial resistance should provide, analyse and disseminate descriptive data on the extent and temporal trends of resistance to relevant antimicrobials in key zoonotic and indicator bacteria isolated from livestock, food and humans. This will facilitate the identification of resistance in bacteria from humans, animals and food of animal origin as it arises. It will also help to provide timely information to veterinarians and physicians, national public health and veterinary public health authorities, governmental legislative authorities, pharmaceutical companies, and to public health and veterinary laboratories.

The aim of resistance monitoring is to gather information in order to:

- *promote prudent and judicious use of antimicrobials* in livestock production to prolong the efficacy and thus the useful life of existing and new antimicrobial agents in humans;
- *enable informed decision-making* by national regulatory institutions and other authorities for the protection of public health;
- *guide prescription practice*; for example, to retain use of older compounds where possible and to improve therapy choices;
- *encourage standardisation of laboratory techniques* for resistance monitoring;
- *identify areas for more detailed investigation* and to facilitate choice of research; and
- *promote collaboration* among the various sectors involved.

Risk management at the primary production level: Prudent use of antimicrobials

Because of the growing global need for food and the potential public health consequences of the transmission of resistant bacteria through the food chain, the objectives for risk management at the animal production level are to assure the efficient production of safe and wholesome food of animal origin for human consumption and to reduce potential public health risks associated with farming practices to enable the growth of the global food supply.

Management of the resistance risks posed by the use of antimicrobials in food animals requires action at the local, regional, national and international levels. Strategies for management of risk are important at the primary production level, to decrease the public health impact of the emergence and dissemination of resistant organisms and resistance genes resulting from the use of antimicrobials in food animals.

At the local and regional level, risks are managed in the context of the special and varying conditions of local food animal production systems. Reducing the need for antimicrobials is an important means of managing resistance risk, and both veterinarians and food animal producers have a role in this. Veterinarians should be knowledgeable in the prudent use of antimicrobials in the context of a valid veterinarian-client-patient relationship, supported by the appropriate use of diagnostic tests. Producers have an important role in reducing the need for antimicrobials by optimising the use of good husbandry practices.

Reducing the need for antimicrobials is an important means of managing resistance risk.

On the national level, governments institute laws and regulations pertaining to antimicrobial licensure, prudent use and compliance. Most countries permit the use of approved antimicrobials for therapy under a veterinary prescription. Most also permit the use of antimicrobials for growth promotion and/or disease prevention or control. National laws and regulations are the principal tools used to limit the use of antimicrobials in food animals. These laws should reflect the need to protect human health while permitting the veterinary profession to effectively treat infectious diseases of food animals.

On the international level, agreements are needed to reduce the risk of transmitting resistance between countries.

III. Recommendations

General

Use of growth promoters

The recommendation made by the previous WHO advisory group (1994) is reinforced:

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.

Threshold levels

National authorities should define threshold levels of resistance in bacteria and circumstances where mitigation procedures should be instigated and, if such procedures are unsuccessful, when approval should be withdrawn.

Risk assessment

No antimicrobial should be administered to a food animal unless it has been evaluated and authorised by competent national authorities. This evaluation should include a:

- thorough risk assessment which includes the development of resistance that may impact public health; and
- post-market monitoring programme to detect emergence of resistance of public health significance.

If such emergence is detected, appropriate action should be taken, which may include the withdrawal of the antimicrobial in question.

No antimicrobial should be administered to a food animal unless it has been evaluated and authorised by competent national authorities.

Alternatives to growth promoters

Increased concerns regarding risks to public health resulting from the use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives.

Standardisation

Request the Codex Alimentarius Commission to include issues of antimicrobial resistance among the terms of reference of the Codex Committee on Residues of Veterinary Drugs in Foods.

Antimicrobial consumption

National authorities should maintain records of export/import figures of bulk chemicals with potential antimicrobial use, as such information is vital for quantitative assessments of the medical risks related to the use of antimicrobials in livestock production.

Residue standards

WHO should continue to support ongoing efforts to harmonise residue standards internationally.

National monitoring of residues

National authorities should continue to monitor and review levels of antimicrobial agent residues in food from animal sources and ensure compliance with national standards.

Monitoring of antimicrobial resistance in food animals and food of animal origin

International coordination: The role of WHO

WHO programme component

WHO should take the lead in coordinating international efforts in resistance monitoring in bacteria isolated from food of animal origin and food animals, as a part of the WHO Programme on Antimicrobial Resistance Monitoring. Training on antimicrobial resistance testing and national policy framework development activities within the medical sector should involve participation of the veterinary sector.

WHO should take the lead in coordinating international efforts in resistance monitoring in bacteria isolated from food of animal origin and food animals.

Laboratory strengthening

Strengthening of microbiological laboratories which are capable of developing national networks on resistance monitoring must be given preference, as regional and international resistance monitoring depends on reliable, quality assured and standardised susceptibility testing in individual laboratories.

Software development

The capabilities of the WHONET software (used in the WHO Programme on Antimicrobial Resistance Monitoring) should be expanded to include the peculiarities of collecting and analysing data on bacterial species isolated from animals and food of animal origin.

Collaboration with other networks

Cooperation and coordination should be sought with emerging networks, such as ENTERNET and the European zoonoses laboratories.

National activities and networks

National monitoring

Countries should ascertain and monitor the prevalence of resistant bacteria in food-producing animal populations and animal-based food products. Specific objectives, structure and the institutional framework of national programmes will depend on conditions in each country. Initial small-scale programmes based on existing resources can help to quickly obtain data on resistance of bacteria of major importance. Gradual expansion of the programmes to other bacteria, growth promoters and food products will allow time to prepare the administrative and technical ground for wider programmes and to build intersectoral cooperation. Monitoring activities should start with sentinel studies on isolates that are already collected in conjunction with other disease control programmes (*e.g.*, *Salmonella*), major therapeutic antimicrobials, and isolates from pigs and chickens.

Countries should ascertain and monitor the prevalence of resistant bacteria in food-producing animal populations and animal-based food products.

National coordination

The antimicrobial resistance monitoring programme of isolates from food animals and food of animal origin must allow for relating data obtained from animals, food and humans. Collaboration of the medical, veterinary and agricultural sectors is vitally important due to the wide variety of laboratories and logistics involved in sample procurement and transport. Joint working groups at national levels including researchers and decision-makers from all involved sites should be established, agree on a working plan and coordinate ongoing activities.

Elements of National Programmes

Bacteria to be monitored

Classes of organisms to be included in national monitoring programmes should be the important zoonotic foodborne bacteria (with *Salmonella* as the primary group of organisms) and key indicator bacteria. Indicator bacteria are included in order to allow for comparison of the same bacterial species isolated from various sources, *e.g.*, healthy and diseased animals. If feasible, programmes should include *E. coli* and *Campylobacter*. In addition, other potential veterinary and human pathogens (*e.g.*, *Enterococcus*) should be considered, based on an individual country's requirements.

Collaboration of the medical, veterinary and agricultural sectors is vitally important.

Background information should be captured on the source of the isolates, such as species or food item from which the sample was taken, as well as other data on, for example, health status, antimicrobial treatment history and exposure to antimicrobial agents.

Identification of bacteria

Bacteria should be identified to species level and phenotype as their epidemiological characteristics might differ (*e.g.*, *Salmonella enteritidis* and *Salmonella typhimurium*) as may their potential to develop resistance and their resistance mechanisms.

Additional characterisation of isolates is recommended where appropriate, including use of phage typing and molecular techniques, to assist in epidemiological studies.

Sources of isolates

Isolates should be taken from:

- livestock;
  - healthy animals (specimens collected in slaughterhouses)
  - diseased animals (samples submitted to veterinary diagnostic laboratories)
- raw food (priority: pork, chicken and beef); and
- other products (eggs, milk and milk products).

Animal species

Sampling should initially focus on the major food-producing livestock species including cattle, swine and poultry, in which the presence or potential transfer of zoonotic organisms is most likely to be significant.

> *Only quantitative data, obtained through the application of standardised laboratory methods, will allow for meaningful epidemiological analyses and evaluation.*

Antimicrobials

Antimicrobials to be monitored in isolates from animals and food of animal origin should be those that are also used as human therapeutics, and/or known or suspected to select for cross-resistance to antimicrobials used in human medicine.

Both therapeutics and growth promoting substances should be included. Human isolates should be tested against the same set of antimicrobials as those from food animals or food products or against those for which cross-resistance might occur.

Microbiological methods

Only quantitative data, obtained through the application of standardised laboratory methods ensured through ongoing quality assurance, will allow for meaningful epidemiological analyses and evaluation. Those data can be obtained through a number of methods such as microbroth dilution and disk diffusion. Isolates from various sources (animals, food, human) should be investigated using identical or comparable methods. If multiple resistance or other resistance which causes medical concern is detected, analysis to evaluate or determine the source site should be encouraged.

Data collection, processing and analysis

In general, principles established by the WHO Programme on Antimicrobial Resistance Monitoring should be followed.

Timely and comprehensive reporting of the monitoring results to all interested parties is vital.

Risk management at the primary production level: Prudent use of antimicrobials

National policies

National practices of antimicrobial use in animals should be reviewed, and antimicrobial use policies be developed to reduce the risks of selection and dissemination of antimicrobial resistance. Based on a consideration of the needs and consequences of the use of antimicrobials in both the human and animal sectors, policies should contain provisions for the establishment of surveillance, enforcement programmes, education strategies, and prescription and use.

- *Enforcement policies* should be designed to ensure compliance with laws and regulations pertaining to the authorisation, distribution, sale and the use of antimicrobials. They are intended to prevent the illicit sale and control the distribution and use of antimicrobials.
- *Education strategies* for prescribers and farmers should cover the risks of selecting resistant bacteria in food-producing animals, and the prudent use of antimicrobials in animal husbandry.
- *Prescription and practice standards* should require that antimicrobial agents for treatment of infections in animals be prescribed by authorised veterinarians, ensure that antimicrobial agents are not used as a substitute for adequate hygiene in animal husbandry, and encourage the development of production practices to reduce antimicrobial use in food animals. This may include animal health-oriented management systems to make the best possible use of the genetic potential for animal performance, and utilisation of alternatives to antimicrobial agents for infectious disease prevention and control, such as vaccines and probiotics.

Prescription and practice standards should ensure that antimicrobial agents are not used as a substitute for adequate hygiene in animal husbandry.

International practice

Convene a WHO/FAO expert consultation to develop a code of practice for prudent use of antimicrobials in food animal production.

Priorities for research and development

- Quantification of the rate of transfer of medically-relevant resistance genes and resistant bacteria from animals to humans.
- Determination of the rate of development of resistance in non-target bacteria of potential medical importance in food-producing animals.
- Determination of the effect of both duration of exposure and concentration, especially concentrations below the minimum inhibitory concentration, on the rate of resistance selection.
- Examination of the effect of cessation of use of specific antimicrobials on the prevalence and persistence of resistant bacteria in food-producing animals and their immediate environment.

- Determination of means to re-establish susceptible flora following antimicrobial usage.
- Information on the stability of important antimicrobials and their metabolites in the environment.
- Impact of the use of antimicrobials in domestic pets and birds on the development and persistence of resistant bacteria in the farm environment.
- Studies of the resistance selection potential of antimicrobials at permitted minimum residue levels.
- Alternative approaches for growth promotion that do not require antimicrobials.
- Evaluation of the risks from the presence of resistance genes in bacteria used as probiotics.

Notes

[1] Substances administered orally or systemically which kill microorganisms or inhibit their multiplication.

[2] Application of an antimicrobial to combat an established infection.

[3] Usage of antimicrobials which maximises therapeutic effects and minimises the development of antimicrobial resistance.

[4] Substances used to increase weight gain or reduce feed requirements in food-producing animals.

[5] Mainly representatives of the International Federation of Pharmaceutical Manufacturers Associations and the World Association of Animal Health Industry. Representatives of the private industry were involved in the presentation and discussion sessions. Conclusions and recommendations of this meeting were elaborated and decided upon by the participants only.

[6] Additional papers were not submitted in time for consideration by the electronic discussion group.

[7] Application of an antimicrobial to clinically healthy animals to prevent infection being either acquired or established after acquisition.

[8] Suitable indicator organisms might be those that are frequently isolated from a broad range of healthy animals, in food and humans. They are commensals in animals and humans, part of the microflora of several types of food, and often used as parameters of food hygiene, *e.g.*, *Escherichia coli*, *Enterococcus faecium* and *Enterococcus faecalis*.

[9] Formerly SALM-NET (Network for Human *Salmonella* Surveillance in Europe).

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