Results of the WHO Meeting on the Medical Impact of the Use of Antimicrobials in Food Animals

R. Crom and K. Stöhr

BACKGROUND

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

Considerable amounts of antimicrobials are also being used in animal and plant agriculture. Some countries report more than 50 percent of all antimicrobial compounds are used in agriculture, with much of this applied in subtherapeutic doses as growth promoters in food-producing animals. Microbiological and clinical evidence suggests that resistant bacteria or resistance determinants might be passed from animals to humans. Antimicrobials have, however, proved to be important for sustainable livestock production and the control of animal diseases and infections which could be passed on to humans. Growth promoters contribute to better utilise the genetic potential for growth of pigs and poultry, improve feed conversion, and reduce waste product output from intensive livestock production.

The real magnitude of the public health consequences of the use of antimicrobials in food animals is unknown, but timely public health action is needed to control or mitigate any medical problem which might be related to such use. Given this, the World Health Organization (WHO) convened a meeting of over 60 specialists involved in developing, licensing and use of antimicrobials in livestock, as well as in microbiology, resistance monitoring, and infectious disease control. The objectives of the meeting were to: obtain an international consensus on priority medical problems that arise from antimicrobial use in livestock production, and recommend the next steps toward

the development of guidelines for control and containment of the emergence of medically-relevant antimicrobial resistance in food animals.

The first part of the meeting included presentations and discussions on antimicrobial use in food animal production, known and potential medical consequences of such use, and potentially effective corrective and preventive actions. Subsequently, three working groups discussed:

Medical impact of the use of antimicrobials in livestock production.

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

Risk management at the primary production level: prudent use of antimicrobial substances.

Reports from the working groups were discussed and adopted during a final plenary session.

CONCLUSIONS

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 and growth promotion. Bacteria and genes, including resistance genes, can each move among human, animal and other ecosystems. When resistant bacteria are themselves pathogenic, or transfer their resistance genes to another species of pathogenic bacteria, adverse health effects can result.

Related to antimicrobial use in animals, consequences of selecting resistant bacteria may include:

Increase in the prevalence of resistant bacteria in animals.

Transfer of resistant pathogens to humans via direct contact with animals, or through the consumption of contaminated food or water.

Transfer of resistance genes to human bacteria.

Increase in the incidence of human infections caused by resistant pathogens.

Potential therapeutic failures in animals and humans.

Examples of the medical consequences of resistance acquisition in bacteria of animal origin include:

- *Salmonella*

There is direct evidence that antimicrobial use in animals selects for antimicrobial resistant non-typhoid *Salmonella* serotypes. These bacteria have been transmitted to humans in food or through

direct contact with animals. A recent example is a clone of *S. typhimurium* DT104, resistant to ampicillin, tetracycline, streptomycin, chloramphenicol and sulphonamides, which has become prevalent in the United Kingdom, Germany and the United States. Following the introduction of fluoroquinolones for food-producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluoroquinolones 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.

• Enterococci

The use of avoparcin as a feed additive in animal husbandry has contributed to the reservoir of transferable resistance genes to glycopeptides, including vancomycin, in the commensal enterococci of animals. There is concern that there will be increased dissemination of glycopeptide resistance genes to *Enterococcus faecalis* and spread to other gram positive organisms, particularly to multiresistant *Staphylococcus aureus* for which vancomycin is the drug of last resort.

• *Escherichia coli*

Multiresistant *E. coli* have been selected by the use of broad-spectrum antibiotics in both livestock and humans. The development of resistance in *E. coli* creates problems due to their propensity to disseminate resistance genes. Resistance genes have been traced from *E. coli* in animals to *E. coli* in humans.

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

Information is lacking on the prevalence and spread of resistance in zoonotic bacteria or indicator agents isolated from diseased or clinically healthy animals and food of animal origin. Although some countries have established surveillance projects for key foodborne zoonotic bacteria, monitoring of antimicrobial resistance in food animals and food of animal origin 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 goal of a monitoring system for antimicrobial resistance should be to provide, analyse and disseminate descriptive data on the extent and temporal trends of resistance against relevant antimicrobials in key zoonotic and indicator bacteria isolated from livestock, food of animal origin and humans. This will ultimately: help to prolong the efficacy and thus the useful life of existing and new antimicrobial agents in humans, allow informed decision-making for the protection of public health by national regulatory institutions and other authorities, guide prescription, 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 amongst the various sectors involved.

Risk management at the primary production level: prudent use of antimicrobial substances

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 goal for risk management at the primary production level must be to: assure the efficient production of safe and wholesome food of animal origin for human consumption, reduce potential public health risks associated with farming practices, and enable the growth of the global food supply in sustainable agriculture.

Management of the resistance risks posed by the use of antimicrobials in food animals should be accomplished by actions at the local, regional, national and international levels.

International agreements are needed to reduce the risk of resistance transmission between countries.

National governments are important for instituting laws and regulations pertaining to antimicrobial licensure, prudent use and compliance.

Local and regional actions are needed to manage resistance risks in the context of the special and varying conditions of local food animal production systems.

National laws and regulations are the principal tools used to limit the usage of antimicrobials in food animals. Laws and regulations should reflect the need to protect human health while permitting the veterinary profession to effectively treat infectious diseases of food animals.

Veterinarians and food animal producers also have a role in risk management. Veterinarians should be knowledgeable in the prudent use of antimicrobials in the context of a valid

veterinarian-client-patient relationship, and with the appropriate use of diagnostic tests or procedures. Producers also have an important role in reducing the need for antimicrobials by optimising the use of good husbandry practices.

RECOMMENDATIONS

General

- The use for growth promotion in animals of any antimicrobial agent that is used in human therapeutics, and/or known to select for cross-resistance to antimicrobials used in human medicine, should be terminated.
- National authorities should define resistance levels in bacteria and circumstances where mitigation procedures should be instigated and, if such procedures are unsuccessful, when approval of a drug should be withdrawn.
- 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 risk assessment which includes the development of resistance that may impact public health; and a post-market monitoring programme to detect emergence of resistance of public health significance; if such emergence is detected, appropriate action should be taken; this may include the withdrawal of the antimicrobial in question.
- 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.

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

Countries should establish and monitor the prevalence of resistant bacteria in food-producing animal populations and animal-based food products. Specific objectives, structure and institutional framework of national programmes will depend on the local conditions. Classes of organisms to be included in national monitoring programmes should be important zoonotic foodborne bacteria, with *Salmonella* as the primary group of organisms, as well as key indicator bacteria which would allow for comparison of the same bacterial species isolated from various sources, *e.g.*, healthy and diseased animals. Antimicrobial compounds to be monitored in isolates from food 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. Quantitative data, obtained through the application of standardised laboratory methods with ongoing quality assurance, will allow for more meaningful epidemiological analyses and evaluation.

Risk management at the primary production level: prudent use of antimicrobial substances

• 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.

-- Enforcement policies should be designed to ensure compliance with laws and regulations pertaining to the authorisation, distribution, sale and the 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.

• A WHO/FAO (Food and Agriculture Organization) expert consultation should be convened to develop a code of practice for prudent use of antimicrobials in food animal production.

Research and development

Priorities for further research and development should include:

- alternative approaches for growth promotion which do not require antimicrobials,
- 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,

- studies of the resistance selection potential of antimicrobials at permitted minimum residue levels,
- determination of means to re-establish susceptible flora following antimicrobial usage,
- evaluation of the risks from the presence of resistant genes in bacteria used as probiotics.