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USE OF ANTIMICROBIALS OUTSIDE HUMAN MEDICINE AND RESULTANT ANTIMICROBIAL RESISTANCE IN HUMANS

Antimicrobials are natural or synthetic drugs which inhibit or kill bacteria. This capability makes them unique for the control of deadly infectious diseases caused by a large variety of pathogenic bacteria.

Today, more than 15 different classes of antimicrobials are known. They differ in chemical structure and mechanism of action. Specific antimicrobials are necessary for the treatment of specific pathogens.

Following their 20th century triumph in human medicine, antimicrobials have also been used increasingly for the treatment of bacterial disease in animals, fish and plants. In addition, they became an important element of intense animal husbandry because of their observed growth-enhancing effect, when added in sub-therapeutic doses to animal feed. Antimicrobials are also used in industry, e.g. to eliminate bacterial growth on the inside of oil pipelines.

The antimicrobial resistance problem

- The widespread use of antimicrobials outside human medicine is of serious concern given the alarming emergence in humans of bacteria, which have acquired, through this use, resistance to antimicrobials.
- Most of the rising antimicrobial resistance problem in human medicine is due to the overuse and misuse of antimicrobials by doctors, other health personnel and patients.
- However, some of the newly-emerging resistant bacteria in animals are transmitted to humans; mainly via meat and other food of animal origin or through direct contact with farm animals. The best-known examples are the foodborne pathogenic bacteria *Salmonella* and *Campylobacter* and the commensal (harmless in healthy persons and animals) bacteria *Enterococcus*. Research has shown that resistance of these bacteria to classic treatment in humans is often a consequence of the use of certain antimicrobials in agriculture.
- Further study is required to investigate other possible ways of transmission of antimicrobial resistant bacteria to humans. For example, the impact on human health of the widespread distribution of non-metabolized antimicrobials through manure and other effluents from farm animals into the environment is still unknown.

Antimicrobial use in food animals

- In addition to being administered to sick food animals individually to treat them, antimicrobials are used for mass treatment against infectious diseases or continuously in feed at very low doses (parts per million) for growth promotion, particularly in pig and poultry production. Use of antimicrobials for these purposes has become an important part of intense animal husbandry.
- Some growth promoters belong to groups of antimicrobials (e.g. glycopeptides and streptogramins) which are essential drugs in human medicine for the treatment of serious, potentially life-threatening, bacterial diseases, such as *Staphylococcus* or *Enterococcus* infections.

Scale of antimicrobial use outside human medicine

- The amount of antimicrobials used in food animals is not known precisely. National statistics on the amount and pattern of use of antimicrobials in human medicine or elsewhere exist in only a few countries.
- It is estimated that about half of the total amount of antimicrobials produced globally is used in food animals.
- In Europe, all classes of antimicrobials licensed for disease therapy in humans are also registered for use in animals, a situation comparable with other regions in the world where comprehensive registration data are much more difficult to obtain.
- A recent review in Europe has shown that an average amount of 100 milligrams of antimicrobials is used in animals for the production of one kilogram of meat for human consumption.
- The increase in meat production in many developing countries is mainly due to intensified farming, which is often coupled with increased antimicrobial usage for both disease therapy and growth promotion.

Factors contributing to overuse of antimicrobials in food animals

- Education on antimicrobial resistance and prudent antimicrobial use is lacking amongst dispensers and prescribers of antimicrobials. In many countries, antimicrobials are dispensed by inadequately-trained individuals. One study reported that more than 90% of all veterinary drugs used in animals in the United States of America (USA) in 1987 were administered without professional veterinary consultation. In addition, inappropriate doses and combinations of drugs are frequently used in animals. Furthermore, administering antimicrobials to animal flocks and herds in their feed causes problems of inaccurate dosing and inevitable treatment of all animals irrespective of health status.
- Empiric treatment (based on clinical investigations, rather than isolation and typing of the causative pathogen) predominates because of the widespread lack of diagnostic services (particularly in developing countries). In many countries, submission of clinical specimens and samples from sick animals is uncommon due to costs involved, time restrictions and the limited number of laboratories.
- In many countries, including several developed countries, antimicrobials are available over-the-counter and may be purchased without prescription.
- Inefficient regulatory mechanisms or poor enforcement of regulations, with lack of quality assurance and marketing of substandard drugs, are important contributory factors. Discrepancies between regulatory requirements and prescribing/dispensing realities are often wider in veterinary medicine than in human medicine.
- Antimicrobial growth promoters are not considered as drugs and are licensed, if at all, as feed additives.
- As in human medicine, pharmaceutical industry marketing of antimicrobials influences prescribing behaviour and use patterns of veterinarians and farmers. Unlike in human

medicine, there are currently few countries with industry codes or government rules that oversee advertising practices for antimicrobials for non-human use.

- There is a significant increase in intensive animal production, particularly in countries with economies in transition, where the above-mentioned general factors are present: improper prescription and dispensing, lack of licensing and enforcement, poor drug quality, veterinary education and food safety, etc.

Examples of the consequences of the overuse of antimicrobials in food animals

- Studies in several countries, including the United Kingdom (UK) and USA, have demonstrated the association between the use of antimicrobials in food animals and antimicrobial resistance. Shortly after the licensing and use of Fluoroquinolone, a powerful new class of antimicrobials, in poultry, fluoroquinolone-resistant *Salmonella* and *Campylobacter* isolations from animals, and shortly afterward such isolations from humans, became more common. Community and family outbreaks, as well as individual cases, of salmonellosis and campylobacteriosis resistant to treatment with fluoroquinolones have since been reported from several countries. The US Food and Drug Administration (FDA) believes that each year the health of at least 5000 Americans is affected by use of these drugs in chickens. (WHO Fact Sheets on *Campylobacter* and Multi-drug Resistant *Salmonella Typhimurium* can be found at the following URLs: www.who.int/inf-fs/en/fact255.html and www.who.int/inf-fs/en/fact139.html respectively);
- With the emergence of vancomycin-resistant strains of *Enterococcus* bacteria in many hospitals around the world, the question arose if the use of vancomycin in agriculture could have compounded the worsening problem. Indeed, vancomycin-resistant enterococci were isolated in animals, food and non-treated volunteers in countries where vancomycin is also used as a growth promoter in animals;
- Because of the health threat from vancomycin-resistant enterococci, Denmark banned use of vancomycin as an animal growth promoter in 1995 and all European countries followed suit in 1997. After the ban, prevalence of resistant *Enterococcus* in animals and food, particularly in poultry meat, fell sharply.

Antimicrobial use in aquaculture

- Various antimicrobials are licensed and used in fish and shrimp production, particularly in Asia. Unfortunately, little information is available on the type and amount of antimicrobials used in aquaculture, making assessment of emerging public health risks more difficult;
- There is an urgent need to review the current usage patterns of antimicrobials in aquaculture to identify looming hazards in food safety and infectious disease control in humans. (This also applies to other uses of antimicrobials, including for plant protection and in industry);
- Because of lessons learned from antimicrobial use in species living on land, some countries have been looking for non-antimicrobial alternatives for some time. Norway, for instance, has been able to diminish antimicrobial use in aquaculture by more than 90% in a very short period of time after changing certain production practices and increasing use of vaccines.

Containment of antimicrobial resistance

1. The World Health Organization (WHO) is developing a Global Strategy for the Containment of Antimicrobial Resistance. This strategy targets all areas where antimicrobials are used in the community, hospitals and agriculture.
2. As part of this strategy, WHO, jointly with other organizations such as the United Nations Food and Agriculture Organization (FAO) and the Office International des Epizooties (OIE), developed

global principles (recommendations) for antimicrobial use in agriculture. The overall aim of this activity is to minimize the potential negative public health impact of the use of antimicrobial agents in animals used for human food, whilst at the same time providing for their safe and effective use in veterinary medicine. The global principles may be consulted on the Internet at the following address: http://www.who.int/emc/diseases/zoo/who_global_principles.html

3. Few countries have active surveillance for antimicrobial resistance in bacteria from food animals and food of animal origin. Existing programmes rarely involve all relevant zoonotic and commensal microorganisms and do not test for all the antimicrobials that may be relevant from a public health perspective. Furthermore, methods used are not sufficiently standardized to enable comparison of data between different surveillance programmes focused on animals or humans. Consequently, there is an absence of adequate data to evaluate the consequences of antimicrobial use in animals and to monitor the effect of different interventions applied to reduce antimicrobial resistance in bacteria from animals.

4. Through a concerted effort with partners from national agencies and research institutions, WHO is enhancing foodborne disease surveillance and antimicrobial resistance testing of foodborne bacteria. The laboratory strengthening focuses on salmonellosis and antimicrobial resistance surveillance in foodborne *Salmonella* and includes the following activities:

- Development of the Global Salm-Surv (<http://www.who.int/salmsurv>), a web-based, up to date databank on national and regional laboratories;
- Establishment of a network of electronically-linked national and regional reference laboratories. Currently, more than 260 scientists, microbiologists, epidemiologists and others from 109 institutions in 101 countries are participating;
- Conducting external quality assurance programmes. By the end of 2000, 80 national reference laboratories will have completed evaluation of their *Salmonella* typing and antimicrobial susceptibility testing;
- Establishment of international centres of excellence for surveillance and containment of antimicrobial resistance resulting from antimicrobial use in agriculture.

5. Containment of antimicrobial resistance will require national and local efforts to reduce use of antimicrobials. Through legislation, some countries have recently taken steps to reduce the problem of antimicrobial resistance in food animals. The European Union banned all antimicrobial animal growth promoters which are also used in human medicine in 1997. Already in 1986, Sweden banned the use of all animal growth promoters, even those which are not used in human medicine. Denmark voluntarily suspended the use of all animal growth promoters in 1999 and Switzerland did the same in 2000. Studies in Denmark have shown that voluntary suspension resulted in an overall reduction of antimicrobial use in Danish livestock of more than 60% with no significant economic impact or negative change in animal health status and food safety.

6. WHO encourages countries to use all opportunities to reduce, to the extent possible, the use of antimicrobials outside human medicine. This will minimize the risk of the emergence of antimicrobial resistance in bacteria, which can be transmitted to humans from animals or the environment. The overall aim is to ensure that infectious disease in humans can be controlled more efficiently.

Further information Journalists can contact the WHO Spokesperson's Office, Geneva, at Telephone (+41 22) 791 2599; Facsimile (+41 22) 791 4858 or E-mail: inf@who.int All WHO Press Releases, Fact Sheets (including N° 255 on *Campylobacter* and N° 139 on Multi-drug Resistant *Salmonella Typhimurium*) and Features can be obtained on Internet on the WHO home page <http://www.who.int>