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TECHNICAL DOCUMENT

Antimicrobial Resistance at the Human-Animal Interface

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is a consequence of the use, particularly the misuse, of antimicrobial medicines and develops when a microorganism mutates or acquires a resistance gene. Other factors also increase the magnitude of the problem, such as the use of antibiotics in agriculture and animal health and production, and fragile programs on Infection Prevention and Control at health facilities. AMR increases mortality, morbidity, and health expenditures. Veterinary Public Health contributes to containing the alarming rise of antimicrobial-resistant infections globally by supporting innovative actions for the prudent use of existing antimicrobials in food producing animals to reverse current trends (OIE intergovernmental standards) (1). Good animal production and welfare practices can prevent the spread of infections at farm level and minimize the impact of antimicrobial resistance. Also, there is a need to continue improving our information and understanding of antimicrobial resistance burden. Significant efforts are underway to improve integrated surveillance on antimicrobial resistance, led by the work of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) and other partners to increase international cooperation with and within countries. But much remains to be done to bring this investment to completion and develop the required infrastructure and capacities. Last but not least to achieve the Sustainable Development Goals, countries need to improve the way that food is produced. Disease prevention – and so reducing the demand for antimicrobial drugs – is a necessary part of tackling the threat of drug resistance and contributing to the SDG.

BACKGROUND AND CONTEXT

Antimicrobial resistance increases mortality, morbidity, and health expenditures. Lately, the challenge has increased through the inappropriate use of antimicrobial drugs in human and veterinary medicine, through the lack of infection and control measures for health-care-associated infections, and through the failure to develop new antimicrobial drugs.

As in human medical care the introduction of antimicrobials was a significant milestone in veterinary practice. Similar to their use in humans, antimicrobial agents are used for the treatment of infectious diseases in individual companion and food animals ensuring animal welfare and global food production. The main difference between use in human and veterinary medicine is seen in food animals. In food animals, antibiotics are used extensively for disease prevention and as growth promoters, involving mass drug administration to many animals at the same time. Furthermore, antibiotics are used in greater quantities in healthy food producing animals than in the treatment of disease in human patients. Approximately 74% of antimicrobials used in USA are used in food animals (2). Such use provides favorable conditions for the emergence, spread and persistence of antimicrobial resistance (AMR) in bacteria capable of causing infections not only in animals, but also in people. The antimicrobial agents used for food animals are frequently the same or belong to the same classes as those used in human medicine. Aquaculture is known to use large quantities of antimicrobials annually to prevent and treat bacterial infection. For example, quantities of antimicrobials used to produce 1 ton of salmon may vary from 0·0008 kg to 1·4 kg. (3,4). Independently of the factors related with such differences associated with local differences on disease risks and the knowledge and awareness of the producers with respect to the harmful effects of excessive antimicrobial use, efforts should be made to prevent antimicrobial overuse in aquaculture. Actions like education of the detrimental effects on human health and the aquatic environment combined with the use of other measures of disease prevention, including vaccines, probiotics. The responsible use of antibiotics in aquaculture is crucial against the increasing problem of antimicrobial resistance in human and veterinary medicine (5).

The use of antimicrobial agents in food animals is also an important food safety issue. Foodborne diseases are a major cause of human morbidity and mortality. According to recent estimates from the WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), foodborne diseases caused 600 million illnesses, 420,000 deaths, and 33 million Disability Adjusted Life Years (DALYs) globally in 2010 (6). Foodborne diseases are particularly important in children; according to the WHO FERG estimates, although children <5 years of age represent only 9% of the global population, 40% of the foodborne disease burden is borne by children in this age group. Food animals are the predominant source of many of foodborne diseases including infections caused by non-typhoidal Salmonella, and Campylobacter (7). According to WHO FERG, non-typhoidal Salmonella caused an estimated 80 million infections and 60,000 deaths and Campylobacter caused 95 million infections and 21,000 deaths worldwide in 2010. WHO FERG estimates did not include estimates of the human health burden of antimicrobial-resistant foodborne diseases; however national surveillance and other studies have identified a significant prevalence of antimicrobial resistance among human infections caused by non-typhoidal Salmonella and Campylobacter. In studies in Asia, for example, the majority of Campylobacter isolated from ill humans have been resistant to fluoroquinolones, an antimicrobial agent commonly used to treat Campylobacter infections in adults (8). Furthermore, it is well established that pathogenic (e.g., *Salmonella*, *Campylobacter* spp.) and commensal (e.g., *Escherichia coli*, *Enterococcus* spp.) bacteria, including resistant bacteria with resistant determinants, are transmitted to humans through food or, to a lesser extent, by direct animal contact. Finally, it has also been demonstrated that infections with antimicrobial resistant bacteria, including antimicrobial resistant foodborne bacteria (such as non-typhoidal Salmonella and *Campylobacter* spp.)

can contribute to more severe human health consequences, including treatment failures, increased or longer hospitalizations, and prolonged illnesses, compared with infections with susceptible bacteria.

The latter situation has been recognized by various international organizations.

a. WHO published in 2000, the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food, which recommended that:

   i. use of antimicrobial growth promoters that belong to classes of antimicrobial agents used in humans should be terminated,
   ii. use of antimicrobial agents in food animals judged to be essential to human medicine should be restricted and justified by culture and susceptibility results, and
   iii. routine prophylactic use of antimicrobials in food animals should not be a substitute for good animal health management.

b. Also, in 2003, a joint FAO, OIE, and WHO report of the Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment recommended that the WHO appoint an expert group of clinicians to define the antimicrobial agents that are considered critically important in humans. In 2004, a joint FAO, OIE, and WHO recommended that the WHO develop a list of antimicrobial agents critically important for humans with a view to enabling specific resistance-prevention actions for these antimicrobial agents in the context of non-human use. This list is now known as “Critically Important Antimicrobial Agents for Human Medicine”

c. In 2015, the World Health Assembly adopted the Global Action Plan (WHO GAP) to combat Antimicrobial Resistance which called on Member States to:

   i. develop policies on use of antimicrobial agents in food animals including implementation of guidelines on use of antimicrobial agents critically important in humans,
   ii. phase out of use of antimicrobial agents for growth promotion in food animals, and
   iii. reduce the non-therapeutic use of antimicrobial agents in food animals.

d. During the same year FAO and OIE passed similar resolutions in their respective Governing Bodies.

e. WHO/FAO Codex Alimentarius Commission published the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance which states that foodborne antimicrobial resistance risk analysis should be considered when addressing the topic in relevant international documents.

f. PAHO is working with member states in establishing surveillance systems to address AMR and to develop control measures. The components of these programs monitor changes in susceptibility/resistance to antimicrobial agents of selected zoonotic pathogens and commensal organisms recovered from animals, retail meats and humans. These actions are part of the regional Plan of Action on Antimicrobial Resistance (9), which has been approved by PAHO’s Directing Council in 2005 (10).

WHAT IS REQUIRED?

WHO in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Animal Health Organization (OIE) are proposing options for actions to be taken by national and international authorities, mainly:

a. Global interventions aimed at reducing the use of specific classes of antimicrobial agents, especially those critically important for human clinical practice:

   i. Drug licensing: to implement restrictions on the approved usages of licensed antimicrobials. As an example, it is possible to limit off-label/extra-label use or to restrict use to individual animals. Current legislation in the Americas is insufficient to reject the approval of new antibiotic simply on the basis that it belongs to a class of antimicrobial agents of special or critical importance for human health.
   ii. Improve governance mechanisms, coordination and collaboration, between animal health, human healthcare and public health professionals and experts to advance antimicrobial stewardship.
   iii. Introduction and enforcement of norms and standards to promote the prudent use of antibiotics, and measures to improve animal health and welfare so that less antibiotic use is needed.

Data on AMR associated with animal husbandry: The extent of AMR in foodborne bacteria, and the global burden of human infections due to such bacteria, is unknown. Therefore, there is a need for data to guide evidence based policy decisions:

i. Data on quantities of antimicrobial use: data on total volumes of antimicrobials used and the indications for which they are used are also limited.
ii. Evaluation of impact: The potential impact of various interventions in different settings is still largely unknown.

Integrated surveillance, based on 'One Health', including data from agriculture and health, which provides information on antimicrobial use and consumption as well as resistance data in both humans and animals is a key component of preventing and controlling AMR. Environmental surveillance of antimicrobials on farms is also recommended.

CONCLUSIONS

The widespread use of antimicrobials in food animal production increases the risk of AMR in humans and animals with the consequent spill to the wider environment. Solutions to tackle this issue are: to reduce antimicrobial use in food production animals, to restrict the use of antibiotics critically important for humans, to develop and apply minimum standards to reduce the discharge of antimicrobial manufacturing waste into the environment, and to improve surveillance to advance the monitoring of these risks in humans, animals and the environment.

DELIVERY MECHANISMS

1. **Capacity to respond to AMR**: National capacity to respond to problems due to AMR is not uniform at either country or local level. Capacity at farm level (terrestrial or aquatic) is lacking in many countries, for reasons such as a lack of effective organizational structure, trained personnel, and sufficient knowledge about the risks involved. To improve this situation, instruments are available to guide the characterization

and evaluation of institutional and operational capabilities, measure advancement, and propose strategic actions for technical cooperation. Joint evaluations of OIE/WHO using the PVS pathway and IHR evaluation framework could be instrumental on this regard.

2. **Evaluation of impact:** The potential impact of different interventions in different settings is still largely unknown. Measuring impact on food safety of enteric and other zoonotic diseases in people, animal health, animal productivity, national economy and other indicators at the regional/national level requires standardized indicators and sustainable capacity for monitoring AMR and antimicrobial use. The impact could probably be determined by targeted research studies, and meta-analyses.

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