FAO/WHO expert meeting on foodborne antimicrobial resistance:

Role of environment, crops and biocides

Rome, 11-15 June 2018

Summary Report

1. Introduction

In recognition of the growing problem of antimicrobial resistance (AMR), its increasing threat to human, animal and plant health, and the need for a One Health approach to address this issue, the 39th Session of the Codex Alimentarius Commission (CAC) agreed it was important for the food safety community to play its part and re-established the *ad hoc* Codex Intergovernmental Task Force on Antimicrobial Resistance (TFAMR)[1] with the objectives of the Task Force revising the current *Codex Code of Practice to Minimise and Contain Antimicrobial Resistance* (CAC/RCP 61-2005)[2] and to developing new guidance on surveillance programmes relevant to foodborne AMR.

Responding to the request from the CAC and the Task Force to provide scientific advice in the areas of crops, environment and biocides,[3] the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) convened, in collaboration with the World Organisation for Animal Health (OIE), a joint "FAO/WHO expert meeting on foodborne antimicrobial resistance: role of environment, crops and biocides" on 11-15 June 2018 in Rome, Italy. The list of participants is given in Annex 1.

The primary purpose of the meeting was to synthesize the current scientific literature concerning the transmission of antimicrobial-resistant bacteria, antimicrobial residues and antimicrobial resistance genes (ARGs) from environmental sources (e.g. contaminated water, soil, manure or human wastes, fertilizers, processing and transportation facilities) to foods and feeds of plant and aquatic animal origin. As a secondary goal, given the widespread and frequent use of disinfectants in food processing plant sanitation, the potential of biocides to co-select for AMR and ARGs was also reviewed. Non-food crops (e.g. cotton, flower bulbs) were excluded from this scope.

[1] REP16/CAC
[2] CAC/RCP 61-2005
[3] REP18/AMR

The meeting therefore addressed the following priority areas: the prevalence of antimicrobial-resistant bacteria and ARGs of fruit and vegetables (Section 2.1); antimicrobial residues, antimicrobial-resistant bacteria and ARGs in the immediate food production environment, namely in soils, irrigation water, and aquaculture (Section 2.2); use of biocides in the food processing environment (Section 2.3); evidence implicating the use of frequently approved antimicrobials and copper in horticulture production and the subsequent occurrence of antimicrobial-resistant bacteria and ARGs in food (Section 2.4); and crops, aquaculture products, and their production environments in integrated surveillance of AMR (Section 2.5).

This summary report is a concise outline of the key discussion and conclusions reached at the meeting, and is meant to inform on-going Codex process in a timely manner. The content in this document is subject to modification in style and substance in the final report, which will have a formal status and will be published in future.

2. Summary of the Assessment of the Scientific Evidence

2.1. Contamination of crops with antimicrobial-resistant bacteria

Contaminated foods of plant origin (e.g. fruits, vegetables, grains) with micro-organisms are responsible for foodborne illnesses worldwide, including outbreaks of disease caused by antimicrobial-resistant bacteria. In addition to AMR pathogens, produce at retail can also be contaminated with other bacteria that are resistant to medically important antimicrobials. A scoping review of the literature identified antimicrobial-resistant bacteria on a wide range of plant origin foods recovered from all regions of the world. In those studies, approximately 25% of products were contaminated with bacteria resistant to one or more antimicrobial agents. Because fruits and vegetables are frequently eaten raw or with minimal processing, fresh produce may serve as a source of dietary exposure to antimicrobial-resistant bacteria and ARGs. Collectively, reports indicate that foods of plant origin play a role in the foodborne transmission of antimicrobial-resistant bacteria (Bezanson et al., 2008; Boehme et al., 2004; Hassan et al., 2011; Raphael et al., 2011; Rodríguez et al., 2006; Ruimy et al., 2010; Schwaiger et al., 2011; Walia et al., 2013). Reducing the contamination of foods and feeds of plant origin with antimicrobial-resistant bacteria will reduce human and animal exposure to antimicrobial-resistant bacteria and ARGs.

2.2 Antimicrobial-resistant bacteria and ARGs in the immediate plant production environment

Fruits, vegetables and other foods of plant origin can become contaminated with antimicrobial-resistant bacteria and ARGs anywhere along the food chain, from primary production to consumption. Conventionally and organically grown vegetables to be consumed raw may be vehicles of dissemination of antimicrobial-resistant bacteria and their resistance genes to humans (van Hoek et al., 2015). Important sources of microbial contamination in the pre-harvest environment include soil, organic fertilisers and irrigation water.

2.2.1 Soil

Use of antimicrobials in humans and animals selects for antimicrobial-resistant bacteria in faeces. Depending upon the species of animal and the particular drugs given, a considerable fraction (>80%) of the antimicrobial administered (as well as copper and zinc from the diet) is excreted in the faeces and urine in an active form. Thus, manure or other organic material that contains human or animal wastes used as soil amendments, as practiced worldwide, have the potential to disseminate both residues of antimicrobial agents and antimicrobial-resistant bacteria to the environment (Jechalke et al., 2013; Marti et al., 2013; Marti et al., 2014; Muurinen et al., 2017; Pourcher et al., 2014; Rahube et al., 2014; Zhou et al., 2017; Joy et al., 2013; Xie et al, 2018). Vegetables harvested from manured ground can carry an additional burden of ARGs of enteric bacterial origin.

The fate of these antimicrobial-resistant bacteria, ARGs and antimicrobial residues following application of soil amendments will vary with environmental conditions: For example the selective properties of the antimicrobial residues can last for weeks to months, and possibly more than a single growing season in humid-temperate regions (Marti et al., 2014; Chen et al., 2018). There is also evidence that bacteria carrying ARGs may not only survive, but increase during the storage of sludge, biosolids and manure (Miller et al., 2014; Muurinen et al., 2017). A greater understanding of the persistence dynamics of antimicrobial-resistant bacteria, antimicrobial residues, ARGs and the potential for exchange of ARGs in human and animal wastes and wastewater, and how these factors vary with treatment, will allow for the more precise assessment of risks associated with environmental sources of food contamination.

2.2.2 Irrigation water

Water can also be an important source of antimicrobial residues, antimicrobial-resistant bacteria and ARGs. There is a direct link between water quality used for irrigation and antimicrobial-resistant bacteria on foods. Wastewater effluent recovered from municipal sewage may contain ARGs and antimicrobial-resistant bacteria (Berendonk et al., 2015; Christou et al., 2017; Karkman et al., 2018; LaPara et al., 2011). Consequently, soils irrigated with wastewater can also become contaminated with ARGs (Pan and Chu, 2018) and with multidrug antimicrobial-resistant bacteria (Palacios et al., 2017). Comparison of fresh produce and its agricultural environment indicated that the Enterobacteriaceae population on fresh produce is a reflection of that present in the soil in which it was grown (Blaak et al., 2014). A high degree of genetic relatedness between *Escherichia coli* from irrigation water and irrigated lettuce indicated a possible common ancestry and pathway of transmission (Aijuka et al., 2015; Njage and Buys, 2015). Water found adjacent to manured fields may also be enriched in antimicrobial-resistant bacteria (Coleman et al., 2013; Pruden et al., 2006; Tang et al., 2015).

2.2.3 Aquaculture

Aquaculture products (e.g. fish, shellfish, and shrimp) at retail can carry bacteria that are resistant to medically important antimicrobials (Elbashir et al., 2018; Done et al, 2015). Data indicate that aquaculture primary food production systems that receive antimicrobials, or that are exposed to effluents containing antimicrobial residues and/or faecal material of human or animal origin, can become enriched in antimicrobial-resistant bacteria (Novais et al., 2018). Additionally, aquaculture production has the potential to contaminate water used for irrigation (Done et al, 2015). Using water contaminated with this effluent for irrigation purposes provides a direct route of contamination of fruits and vegetables, if such water is applied directly to the edible portions of the plant (Muziasari et al., 2017; Tamminen et al., 2011; Watts et al., 2017; Cabello et al., 2013). Differences between aquaculture systems are remarkable among countries and may variably impact the risk of acquiring and disseminating AMR (FAO/WHO, 2003).

2.3 Biocides in food production and AMR

Chemical disinfectants are frequently used in the food production and processing environment and are critical for food hygiene and environmental sanitation. Bacteria with increased tolerance to biocides have been recovered from food production environments. Although there is theoretical and experimental evidence that certain microbiocidal agents may co-select for AMR, there is an absence of empirical data to indicate that the use of biocides drives this co-selection under the conditions present in the food production or processing environments (Hardy et al., 2018; Bas et al., 2017).

2.4 Use of antimicrobials and copper in horticulture production

Antimicrobials, including streptomycin, kasugamycin, oxytetracycline, and oxolinic acid are vital to treat and control plant diseases (de León et al., 2008; Stockwell and Duffy, 2012). Contamination of soils with these products following crop application leads to enrichment of antimicrobial-resistant bacteria and ARGs in the environment. However, the extent to which the treatment of crops with antimicrobial agents (or copper formulations, see below) promotes AMR in bacteria found on edible portions of fresh plant produce is uncertain.

Of concern is the possibility of selection of antimicrobial-resistant bacteria and ARGs through the processes of co-resistance, cross-resistance and co-regulation with certain metal ions (Yu et al., 2017). Evidence indicates that contamination of soil with certain metal ions, such as copper ions, promotes AMR in soil bacteria. Not only are copper-containing products used to treat plant diseases, animal and human wastes often have residue levels of copper, zinc and other metals of dietary origin. Bacteria harbouring genes conferring resistance to certain metal ions (and in some cases to certain biocides) are more likely to also encode ARGs than those without such metal ion resistance traits (Pal et al., 2015). Bacteria resistant to both metal ions and antimicrobials are commonly present in diverse environments, with bacteria of plant origin having the highest relative abundance of co-resistance genes per genome, compared to bacteria from other sources such as domestic animals or wild animals and humans (Pal et al., 2015).

2.5 Crops, aquaculture products, and their production environments in integrated surveillance of AMR

Given the potential of human exposure to antimicrobial-resistant bacteria via food of plant origin (Sundin and Wang, 2018) and from aquaculture products (Elbashir et al., 2018; Done et al, 2015), there is considerable value in incorporating these products into integrated antimicrobial use (AMU) and AMR surveillance systems. In addition, including specimens collected from the immediate environment surrounding the edible products (soils where crops are grown, irrigation water, *etc*.) and aquaculture production sites should complement food surveillance systems. Surveillance programs should take into account regional specificities and circumstances when selecting suitable fruit or vegetable products, fish and crustacean species and environmental samples for inclusion in such programs (Matheu et al., 2017; Dorado-Garcia et al., 2018).

Although *E. coli* may serve as a suitable common indicator bacterium for antimicrobial-resistant bacteria in foods of animal origin, there is a need to identify additional robust indicators of antimicrobial-resistant bacteria in food of plant origin and the immediate crop production environment. Likewise, there are no universally accepted bacterial indicators of AMR in aquatic products. AMR surveillance should use classic bacteriology and antimicrobial susceptibility testing based on epidemiological cut-off values (ECOFFs) (Valsesia et al, 2015). However, this could be expanded to include methods that require more advanced technical complexity and resource requirements, for example molecular methods for ARG analysis, and antimicrobial residue chemical analyses. Antimicrobial-resistant bacteria, ARGs and AMU surveillance in fruit and vegetable production systems should capture all important meta-data for the antimicrobials such as information from manufacturers, importers, vendors, where possible.

3. Conclusions

There is clear scientific evidence that foods of plant origin may serve as a vehicle of foodborne exposure to antimicrobial-resistant bacteria. As such, concerted efforts should be made to mitigate their contamination at all stages of the food chain, from production to consumption. To achieve this goal, good agricultural practices should be employed.

- Best management practices should be adhered to with respect to the use of material of human (sewage sludge; biosolids) or animal origin (manures) in primary food production environments.
- Improved methods for infection prevention and control such as husbandry, biosecurity, diagnostics, vaccines and other alternatives should be employed to reduce the need for antimicrobial use in aquaculture, and thereby reduce the antimicrobial contamination of the primary aquaculture production environment.
- Biocides should be used according to manufacturers' recommendations.
- Antimicrobials should only be used in crop production according to label guidelines in the context of integrated pest management strategies.

At a local, regional and global scale there is insufficient knowledge about the amounts and types of antimicrobials applied to crops and those used in terrestrial and aquaculture. Research is required to fill these gaps. The development and enforcement of suitable regulatory instruments may be helpful to address potential misuse of antimicrobials, such as their application to products in the post-harvest period.

Surveillance of AMU and antimicrobial-resistant bacteria in food commodities can provide an assessment of the magnitude of the problem and a tool for measuring progress in mitigation. It is recommended that surveillance for AMR and AMU in primary food production environments be implemented in order to obtain additional data that is required for risk assessment and risk management. Terrestrial and aquatic primary food production system environments and products post-harvest should be considered for inclusion in integrated antimicrobial use and AMR surveillance programs foundational for containment of AMR.

A greater understanding of the role of food production environments in the transmission of foodborne antimicrobial-resistant bacteria and ARGs, and the role of agricultural use of antimicrobials and potential co-selective agents (e.g. copper ions, and potentially other antimicrobials) will lead to the development of additional tools and strategies to reduce foodborne AMR. Generally, more education and training concerning AMU and AMR should be made available to all stakeholders involved with the use of antimicrobials in production of plant crops and aquaculture. To address upstream contamination of water and soils from human and animal faeces and AMR pre-existing in the environment, additional training and education on AMR and AMU in terrestrial and aquatic food production systems could also be beneficial.

4. References

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