CODEX ALIMENTARIUS COMMISSION

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Food and Agriculture Organization of the United Nations

World Health Organization

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CODEX ALIMENTARIUS COMMISSION

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FAO/WHO SCIENTIFIC SUPPORT TO CODEX: UPDATE ON ANTIMICROBIAL RESISTANCE

(Prepared by FAO and WHO in collaboration with OIE)

Introduction

1. This paper aims to provide an overview of the global level activities on the prevention and management of antimicrobial resistance (AMR) since the 39th Session of the CAC. In particular, it provides an update on the scientific knowledge relevant to foodborne AMR in response to the request for scientific advice on AMR from Codex. While it mainly focuses on FAO and WHO activities, it also includes reference to OIE activities relevant to the Codex work and the request for scientific advice on foodborne AMR.

2. AMR has remained a high profile issue over the past year. At the 71st Session of the United Nations General Assembly in September 2016 in New York, Heads of states and governments of 193 Member States convened to address issues including AMR and to collectively address this challenge to health, food security and development. This resulted in a UN General Assembly Political Declaration A/RES/71/3[1] which reaffirmed the Global Action Plan (GAP) on antimicrobial resistance[2] as the blueprint for tackling AMR, emphasized, among other issues, the importance of National Action Plans (NAPs) and requested WHO, FAO, OIE and others to support countries in their development and implementation. In addition it requested the establishment of an *ad hoc* Inter-Agency Coordination Group (IACG), to provide practical guidance for approaches needed to ensure sustained effective global action to address AMR. The group held its first meeting on 1-3 May 2017[3].

3. FAO and WHO have actively engaged in supporting countries in the development of their NAPs over the past year. WHO, FAO and OIE issued a tripartite manual for developing NAPs[4] as well as a self-assessment questionnaire to all countries at the end of 2016 on the status of NAPs. The results are published in an online database[5] and are being presented to the governing body meetings of the three organizations in May and July 2017.

4. WHO, in collaboration with FAO and OIE, are developing a monitoring framework for implementation of the GAP. An expert consultation on appropriate indicators was convened in Geneva on 8 – 9 June 2017 and a public consultation on the monitoring framework and proposed indicators, in which all sectors, including the food sector, are strongly encouraged to participate, will be initiated during the third quarter of 2017.

5. The Rome Declaration of the Second International Conference on Nutrition (ICN2) in 2014, recognized that food systems need to contribute to preventing and addressing infectious diseases, including zoonotic diseases, and tackling AMR. Recommendations 56 and 57 of the related Framework for Action specifically

[1] Available at http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/71/3

[2] Available at http://www.who.int/antimicrobial-resistance/global-action-plan/en/

[3] The report of the first meeting of the IACG is available at http://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG-firstMtgReport.pdf

[4] Available at http://www.who.int/antimicrobial-resistance/national-action-plans/manual/en/

[5] Database available at https://extranet.who.int/sree/Reports?op=vs&path=%2FWHO_HQ_Reports/G45/PROD/EXT/amrcsat_Menu

address AMR[6]. In April 2016, the UN General Assembly endorsed the ICN2 outcome documents and proclaimed the UN Decade of Action on Nutrition (2016-2025), providing a clearly defined, time-bound cohesive framework to implement the ICN2 commitments, along with the Sustainable Development Goals (SDGs). FAO, WHO, WFP, IFAD and UNICEF, as the agencies responsible for convening the Decade of Action, are supporting countries in their efforts to meet the commitments. One initiative is this regard is the development of guidance notes for countries on how to address each of the recommendations and establish smart indicators for their achievement, including those related to AMR. These will be presented to countries in the second half of 2017.

6. WHO, in collaboration with FAO and OIE, is currently developing a global stewardship framework on AMR. The three organizations have published a draft Roadmap[7] which describes the current state of play and the way forward with respect to the establishment of a global framework for development and stewardship to combat AMR. This will be further developed over the coming months.

Technical/scientific advice related activities

7. At its upcoming meeting, the Commission will deliberate on the new work proposals to be addressed by the Codex *ad hoc* Task force on AMR (TFAMR). FAO and WHO recognize the urgency of the work to be undertaken by Codex and the significant breadth and depth of the scientific advice that is expected. FAO and WHO have therefore already launched a series of preparatory activities on data collection and collation, taking into account existing and ongoing work, as well as the gaps and the priority areas for advise identified by the Codex Alimentarius.

8. The following provides an overview of relevant past, ongoing and future FAO and WHO work on AMR, with reference to the activities of and collaboration with OIE where relevant.

a) Overview of data relevant to the development and transmission of foodborne AMR

9. Recognizing the importance of basing decisions related to the management of antimicrobial resistance on the best available scientific evidence, FAO, and WHO in collaboration with OIE have convened a number of expert meetings and consultations on this issue[8]. Recent efforts continue to collate and analyse the available scientific information to make it more accessible to member countries.

10. WHO has commissioned two independent systematic reviews on the impact of the restriction in the use of antibiotics in food producing animals on the development of antibiotic resistance in food-producing animals and humans. WHO also commissioned literature reviews on molecular mechanisms of the global emergence and dissemination of antimicrobial resistance in food production and agriculture, as well as on the potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals. Publication of these findings is planned for the last quarter of 2017.

11. FAO has commissioned and published a review of the 'Drivers, dynamics and epidemiology of antimicrobial resistance in animal production' which is now available online.[9].

12. FAO is developing a publication on Responsible Management of Bacterial Diseases in Aquaculture as a key reference in the work on antimicrobial use (AMU) and AMR in aquaculture and as a resource for countries in the development of the aquaculture component of NAPs on AMR. A series of workshops to support some of the major aquaculture producing countries in Asia to use this guidance and address aquaculture in the context of AMR NAP development is underway. A first workshop was held in Mangalore, India in April 2017 with a follow-up workshop planned for August 2017 in Putrajaya. The latter will also address aspects of implementation, such as good practices.

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[6] Recommendations 56 and 57 on AMR are available in the Framework for Action which can be accessed at http://www.fao.org/3/a-mm215e.pdf

[7] Available at http://www.who.int/phi/implementation/research/WHA_BackgroundPaper-AGlobalFrameworkDevelopmentStewardship-Version2.pdf?ua=1

[8] Links to the reports of previous FAO/WHO/OIE expert consultations on AMR can be found at http://www.fao.org/antimicrobial-resistance/key-sectors/food-safety/en/ and

http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/en/

[9] Drivers, dynamics and epidemiology of antimicrobial resistance in animal production is available to download from www.fao.org/3/a-i6209e.pdf.

13. A review is underway in FAO to collate available information on the use of antimicrobials in crop production. A short overview of the situation and the data gaps was developed and presented to the Codex Committee on Pesticide Residues in April 2017[10].

14. The Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) will continue to evaluate the safety of residues of veterinary drugs in foods including for antimicrobials and their potential contribution to AMR, by considering the impact on human gut microflora.

15. FAO and WHO in their preparatory work, recognized that a number of data gaps remain in our understanding of the development and transmission of foodborne AMR. Realizing the urgency of the matter, FAO and WHO are developing a "Call for data relevant to the development, transmission, assessment and management of foodborne AMR" which will be made available online as soon as possible[11]. Member countries are requested to respond to this data call, in particular bringing to the attention of the secretariat information which is not readily accessible in the public domain. Submitted data and the aforementioned documents will be considered through an expert consultation process. This is expected to address part one of the request for scientific advice to support the work of the TFAMR.

b) WHO and OIE critically important lists of antimicrobials

16. The development of the WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA List) was initiated almost 15 years ago following the recommendation of a 2004 expert workshop on 'Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options', jointly convened by FAO, OIE and WHO[12]. The process for defining and prioritizing which antimicrobial agents were important for human medicine was developed by an expert committee in 2005, which established the criteria for classifying antimicrobials used in humans as either critically important, highly important, or important for human medicine. These criteria were then utilized to establish the first WHO CIA List, which is updated regularly. In addition, the criteria are regularly reviewed to ensure that they remain relevant and optimized for prioritizing antimicrobials of importance to human health.

17. The list was most recently updated in 2016 for the 5th time, when experts met at the 7th AGISAR meeting in Raleigh, USA. Changes were made to the prioritization criteria to better describe usage of antimicrobials, and Polymyxins were newly classified as "highest priority critically important antimicrobials" because of the increasing usage of colistin to treat serious infections in humans in many parts of the world. The current list and the process/criteria used to establish the list were published in April 2017 and are available online[13].

18. The 2004 FAO/OIE/WHO Expert Workshop on 'Non-Human Antimicrobial Usage and Antimicrobial Resistance'[12] also recommended that the OIE should develop a list of critically important antimicrobial agents in veterinary medicine taking into account animal health needs. The OIE list of antimicrobial agents of veterinary importance is available on the OIE website[14]. The List was adopted as a preliminary list in May 2006 by the World Assembly of Delegates. A refined list was adopted in May 2007. This List was further updated in May 2013 and May 2015. The next update of the List will be on the agenda of the OIE *ad hoc* Group on Antimicrobial Resistance that will meet in August 2017.

19. A process to revisit the discussions of the 2007 expert consultation[15] on the WHO and OIE lists of critically important antimicrobials will only be scheduled once the next update to the OIE list has been completed.

WHO Guideline for use in food animals of critically important antimicrobials for human medicine

20. For preserving the long-term effectiveness of antimicrobial agents listed in the WHO CIA list for humans, a number of groups, including Member States, requested a WHO guideline which includes formal recommendations on use in food producing animals of antimicrobials important for human medicine.

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[10] Update on FAO work on Antimicrobial Resistance with a focus on Antimicrobial Use in Horticulture is available at: http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-718-49%252FWD%252Fpr49_03_add1e.pdf

[11] This will be posted on the FAO (http://www.fao.org/food/food-safety-quality/scientific-advice/calls-data-experts/en/) and the WHO (http://www.who.int/foodsafety/call-data-expert/en/) calls for data webpages[12] Available at: http://apps.who.int/iris/bitstream/10665/68701/1/WHO_CDS_CPE_ZFK_2004.8.pdf?ua=1

[12] Available at: http://apps.who.int/iris/bitstream/10665/68701/1/WHO_CDS_CPE_ZFK_2004.8.pdf?ua=1

[13] The WHO CIA list 5th revision is available at: http://apps.who.int/iris/bitstream/10665/255027/1/9789241512220-eng.pdf?ua=1

[14] The OIE list of Critically Important antimicrobials for veterinary use are available at: http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf

[15] ftp://ftp.fao.org/docrep/fao/010/i0204e/i0204e00.pdf

21. A WHO guideline on use in food animals of antimicrobials important for human medicine is being developed, based on the outcome of the above mentioned WHO systematic and literature reviews. The development of this guideline is guided by standard operating procedures in accordance with the principles and instructions provided in the WHO Handbook for Guideline Development[16]. FAO and OIE were invited as "special Members" of the Steering Group.

22. A Guideline Development Group (GDG) was formed to develop evidence-based recommendations as a basis for the guideline. The GDG was composed of independent experts from multisectoral (human, food, animal and agriculture) and multidisciplinary (i.e. human medicine, veterinary medicine, microbiology, epidemiology, animal welfare, economics) backgrounds. They met twice, in October 2016 in Raleigh, USA and March 2017 in Geneva, Switzerland. The publication of the guideline is anticipated in the last quarter of 2017.

c) Alternatives to antimicrobials in food production systems

23. Changing practices to minimize the need for antimicrobials in production systems is recognized as a key part to addressing antimicrobial use in the food and agriculture sector. It also requires consideration of a wide range of practices and contexts and the need to tailor alternative or improved approaches to the local situation. Some of the aspects identified in the request for scientific advice are already been addressed in the systematic reviews mentioned in section (a) of this document. With regard to other practices, as part of its capacity development work on AMR and in line with the FAO Action Plan on AMR[17], FAO has recently issued a survey to collate all existing good practices as of the first step in a process to identify risk management options that help minimize the use of antimicrobials, which will then be further evaluated before recommendation to member countries. FAO is collaborating with several private sector partners to produce guidance on good practices to minimize the use of antimicrobials in animal production (e.g. it is producing a guidance addressing the dairy sector with the International Dairy Federation). FAO is also preparing a publication to provide information on possible animal nutrition strategies and options that would support reducing or eliminating antibiotics for growth promotion purposes, while still ensuring adequate growth and production efficiency.

24. The OIE, in partnership with the USDA Agricultural Research Service, hosted the 2nd International Symposium on Alternatives to Antibiotics at OIE Headquarters from 12 to 15 December 2016. The meeting included sessions on vaccines, microbial-derived products, phytochemicals, immune-related products, and innovative drugs, chemicals and enzymes, and regulatory pathways. In April 2015, the OIE organised an *ad hoc* Group on Prioritisation of Diseases for which Vaccines could reduce Antimicrobial Use in Animals focussing as a first step on poultry, swine and fish diseases.

d) Antimicrobial resistance and antimicrobial use monitoring and surveillance

25. WHO established the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)[18] in 2008. AGISAR supports the efforts of WHO and its Member States to minimize the public health impact of AMR associated with the use of antimicrobials in food producing animals.

26. In 2013, after a consultative process of four years, WHO published the first version of the '*Integrated Surveillance of Antimicrobial Resistance: Guidance from a WHO Advisory Group'*[19]. The AGISAR guidance has been revised in 2017 in support of the implementation of the GAP, with the participation of FAO and OIE[20]. Similar to the 2013 guidance, the revised guidance describes a step-by-step approach to designing a programme of integrated surveillance of antimicrobial resistance in foodborne bacteria and includes recommended standardized and validated antimicrobial susceptibility testing methods, harmonized interpretive criteria, and approaches to the collection and reporting of antimicrobial consumption and use data.

27. WHO AGISAR is currently developing a global protocol on surveillance of extended spectrum beta-lactamase (ESBL*)* producing *Escherichia coli* using a "One Health" approach. The so-called "Tricycle *ESBL E. coli* surveillance project" will monitor the prevalence of *ESBL E.coli* in humans, the food chain and the environment.

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[16] http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf

[17] Available at : http://www.fao.org/3/a-i5996e.pdf

[18] For more information on AGISAR see: http://who.int/foodsafety/areas_work/antimicrobial-resistance/agisar/en/

[19] Available at: http://apps.who.int/iris/bitstream/10665/91778/1/9789241506311_eng.pdf?ua=1

[20] Details of the revised integrated surveillance guidance will be provided on http://who.int/foodsafety/publications/agisar_guidance2017/en/

28. Both the new AGISAR guidance and the Tricycle *ESBL E. coli* surveillance protocol will be disseminated and implemented through global workshops. Preparation for upcoming workshops are underway in August 2017 in the Netherlands, and in September 2017 in Sapporo, Japan.

29. AGISAR's capacity building projects are also underway to strengthen the integrated surveillance of AMR in 16 countries and territories[21].

30. Recognizing the need to foster the establishment of national antimicrobial resistance surveillance systems, WHO has developed the Global Antimicrobial Resistance Surveillance System (GLASS)[22]. The aim of the WHO GLASS is to provide a platform to report and analyse standardized, comparable and validated data on antimicrobial resistance in order to: (1) inform decision-making; (2) drive local, national and regional action; and (3) provide the evidence base for action and advocacy. The early implementation phase of WHO GLASS focuses on the assessment and reporting of resistance of selected priority human bacterial pathogens to selected priority antimicrobials. These priority antimicrobial-pathogen combinations include the following foodborne bacteria: fluoroquinolone-resistant *Salmonella spp.*, third-generation cephalosporin-resistant *Salmonella spp.*, and carbapenem-resistant *Salmonella spp*..

31. To support the food and agriculture sectors in understanding their capacities in relation to AMR susceptibility testing and surveillance, FAO have developed a tool for the assessment of AMR laboratory capacity and surveillance (ATLASS). This tool has already supported assessments in six countries with further assessments scheduled for later this year. The outcomes are used as the basis for national level discussions on the establishment of AMR surveillance programmes in the food and agriculture sector in these countries with the objective of building on existing capacities to the extent possible to facilitate sustainability. Links between GLASS and ATLASS are foreseen.

32. A regional workshop on AMR surveillance in the food and agriculture in south East Asia was convened in Bangkok, Thailand in December 2016 to support the establishment of feasible surveillance programmes for participating countries. A report of the meeting is available online[23].

33. FAO is in the process of identifying a number of reference centres on AMR as a basis for increasing their capacity to deal with requests from the food and agriculture sectors in member countries to develop testing and surveillance programmes for AMR in food, agriculture and the environment[24].

34. FAO is currently incorporating the issue of AMR surveillance in an update to its guidance on risk-based fish inspection and in the development of guidance on risk-based meat inspection.

35. The OIE is working in close collaboration with its Collaborating Centres in particular the OIE Collaborating centres for Veterinary Medicinal Products [ANSES, France], for Veterinary Drug Regulatory Programmes [FDA, USA], and for Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia [NIAH/NVLA, Japan] to organise regular training of National Focal Points on Veterinary Products in all regions.

36. The World Assembly of Delegates, during the 83rd OIE General Session in May 2015, adopted Resolution No. 26: Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals[25]. Taking forward this Resolution, and based on the chapters on Monitoring of the quantities and usage patterns of antimicrobial agents in animals of the *Terrestrial* and *Aquatic Animal Health Codes*, the OIE launched an annual collection of data on the use of antimicrobial agents in animals in the 180 OIE Member Countries in the last trimester of 2015. The first phase of this new OIE activity has been completed in line with the Global Action Plan on AMR developed by WHO with strong contribution from FAO and the OIE. From mid-December 2015 to mid-May 2016, 72% (130/180) of OIE Member Countries submitted the completed template to the OIE Headquarters and nearly 90 of those Member Countries provided detailed quantitative data. The aim of the data collection is to publish an annual report on the worldwide distribution and use of antimicrobial agents in animals establishing baseline information and measuring trends over

[21] Countries and territories supported by WHO include: Albania, Argentina, Bhutan, Chad, Ecuador, Ethiopia, Islamic Republic of Iran, Japan, Philippines, South Africa, Suriname, , Thailand, Zambia, United Republic of Tanzania, Zimbabwe and West Bank and Gaza Strip.

[22] http://www.who.int/antimicrobial-resistance/global-action-plan/surveillance/glass/en/

[23] Available at http://aphca.org/index.php?option=com_docman&task=cat_view&gid=63&Itemid=120

[24] Available at http://www.fao.org/3/a-br399e.pdf

[25] Available at http://www.oie.int/fileadmin/Home/eng/About_us/docs/pdf/Session/A_RESO_2015_public.pdf

time. The report and analysis of this first year of data collection was published at the end of 2016[26], with information currently being reported at the continental level. For the second year of data collection, a refined template was sent to OIE Member Countries at the end of September 2016 and as of 16 May 2017, 141 Member Countries and 3 non-Member Countries have responded.

37. During the 84th OIE General Session in May 2016, the World Assembly adopted Resolution No. 36: Combating Antimicrobial Resistance through a 'One Health' Approach: Actions and OIE Strategy. The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials to tackle the antimicrobial resistance threat, based on the GAP and published in November 2016, compiles actions and achievements including raising awareness, surveillance and research, supporting good governance and capacity building, and implementing standards and guidelines[27].

38. An OIE *ad hoc* Group on AMR is instrumental on OIEs activities on AMR including the update and revision of the standards and recommendations related to AMR for terrestrial and aquatic animals[28]. Both FAO and WHO participate in this Group.

[26] Available at http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/Survey_on_monitoring_antimicrobial_agents_Dec2016.pdf

[27] Available at http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/PortailAMR/EN_OIE-AMRstrategy.pdf

[28] Further details can be found at: http://www.oie.int/en/our-scientific-expertise/veterinary-products/antimicrobials/