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Ad Hoc Codex Intergovernmental Task Force on Antimicrobial resistance (6th Session)

Busan, Republic of Korea, 10-14 December 2018

European Union comments on

Agenda Item 6:

Proposed draft Guidelines on Integrated Surveillance of Antimicrobial Resistance

(CX/AMR 18/6/6)

Mixed Competence
European Union Vote

The European Union and its Member States (EUMS) would like to commend the Netherlands, Chile, China and New Zealand for leading the work on surveillance of antimicrobial resistance. The EUMS would like make the following comments on the draft text.

General comments

The guidance reads well and should serve the purpose, amongst other, to encourage countries to set up surveillance systems for antimicrobial resistance or to improve surveillance in those countries that already have systems in place.

The EUMS support the options for a stepwise development of integrated monitoring and surveillance of foodborne AMR and AMU programs, as they provide a useful tool for countries to set up surveillance in a progressive and organised manner.

The definitions in the guidance should be aligned with the definitions in the revised *Code of Practice to Minimize and Contain Foodborne AMR*.

Specific comments

1. Introduction and purpose of the Guidelines

The 3rd paragraph should be modified as follows:

An integrated monitoring and surveillance system includes the coordinated and systematic collection of samples at appropriated stages along the food chain and the testing, analysis and reporting of AMR and AMU, including the alignment and harmonization of sampling, testing, analysis and reporting methodologies and practices and the integrated analysis of

relevant epidemiological information from in humans, animals, foods, crops and environment to the greatest extent ~~practical~~ **possible.**

Rationale: editorial

The 3rd sentence of the 4th paragraph should be modified as follows:

It provides information to risk managers **and policy makers** about AMR and AMU trends and for the planning, implementation and evaluation of risk mitigation measures to minimize any public health risk due to resistance microorganisms and resistance determinants.

The 5th paragraph should be modified as follows:

It also contributes to the promotion and protection of public health by providing information to risk managers about, how ~~resistant infections differ from susceptible~~ infections **caused by resistant bacteria differ from infections caused by susceptible bacteria**, and the impact of interventions designed to limit the emergence spread of AMR.

Rationale: editorial

The 2nd sentence of the 6th paragraph should be modified as follows:

Such programs are a fundamental part of national strategies and plans to minimize foodborne AMR and an ~~important~~ **pivotal** component of a comprehensive national food safety system.

Rationale: editorial

The 7th paragraph should be modified as follows:

Each country should design and implement a system for monitoring and surveillance of foodborne AMR and AMU along the food chain that is ~~appropriate~~ **adapted** to national circumstances. This should be informed by all available knowledge on ~~priority~~ foodborne risks due to AMR while taking into consideration the international dimension of AMR and the need for data comparability between countries and sectors.

Rationale: The restriction to "priority" foodborne risks is quite unclear and not necessary. All risks should be considered.

The 1st sentence of the 8th paragraph should be modified as follows:

New scientific knowledge should be ~~incorporated into~~ **regularly accounted by** integrated monitoring and surveillance programs as it becomes available to improve the design of the programs and to enhance analysis and ~~utility~~ **use** of existing information and data.

Rationale: editorial, it is unclear how new information will increase the "utility of existing information and data".

The 10th paragraph should be modified as follows:

These guidelines will contribute to the development and implementation of National Action Plans (NAP) on AMR that make the best use of available resources at the national level, ~~**with the goal**~~ **based on the objective principle** of continuous enhancement as ~~**more**~~ **better** scientific knowledge, technical capability, data and funding becomes available.

Rationale: editorial

The last paragraph should be modified as follows:

While these guidelines ~~**are aimed**~~ **primarily aim** at action at **the** national level, countries may **also** consider creating multi-national or regional monitoring and surveillance systems to share **costs of** laboratory, data management and other **necessary** resources.

Rationale: editorial

3. Definitions

Introduce the same definition for "food chain" and "antimicrobial resistance determinant" as in the revised Code of Practice:

Food chain: Production to consumption continuum including, primary production (food-producing animals, plants/crops), harvest/slaughter, packing, processing, storage, transport, and retail distribution to the point of consumption.

Antimicrobial resistance determinant: The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial agent. They are located either chromosomally or extra-chromosomally and may be associated with mobile genetic elements such as plasmids, integrons or transposons, thereby enabling horizontal transmission from resistant to susceptible strains.

Introduce the same definition for "plants/crops" as in the revised Code of Practice

Crops: A cultivated plant that is grown as food or feed, especially a grain, fruit or vegetable, including all edible parts.

Rationale: The definitions in the guidance should be aligned with the definitions in the revised Code of Practice to Minimize and Contain Foodborne AMR.

Delete the definition for "Risk-based approach to surveillance and monitoring of foodborne AMR".

Rationale: The risk based approach to surveillance and monitoring is sufficiently explained in section 5. The suggested definition should be moved as the first paragraph in section 5.

4. Principles

The principles should be numbered for coherence with the revised *Code of Practice to Minimize and Contain Foodborne AMR.*

The 1st principle should be modified as follows:

An integrated monitoring and surveillance system for AMR should ~~***incorporate***~~ ***follow*** *an "One Health" approach;*

Rationale: editorial.

The 6th principle should be modified as follows:

In using a stepwise approach, priority should be given to the most relevant elements **to be analyzed** from a public health perspective (e.g. defined combinations of the food commodities, the ~~AMR~~ microorganisms and resistance determinants and the antimicrobial agent(s) to which resistance is expressed) ~~to be analyzed~~.

Rationale: editorial.

5. Risk based approach

Introduce the current definition of a risk-based approach as a first paragraph in this section:

For the purpose of these guidelines, a risk-based approach is the development and implementation of a monitoring and surveillance system along the food chain that is informed by data and scientific knowledge on the likely occurrence of AMR hazards at a step (or steps) in the food chain and their relationship with risks to human health.

Modify the 5th paragraph as follows:

As countries improve their AMR systems over time, a stepwise approach to monitoring and surveillance should **lead to an increased use of generated data for risk assessment** ~~increasingly incorporate risk assessment factors as an important element in design of the program and analysis of data~~.

Rationale: The wording is unclear. In the stepwise approach, the monitoring and surveillance activities should feed into risk assessments.

6.2. Other activities

The 1st paragraph should be modified as follows:

Stakeholders other than the competent authority, such as veterinarians, plant health professionals, farmers, consumer organizations, civil society, pharmaceutical industry or food and feed industry, retail and others may carry out **complementary or additional** monitoring activities e.g. monitoring of AMU on a voluntary basis.

Rationale: to clarify that monitoring carried out by stakeholders is complementary.

The 2nd paragraph should be modified as follows:

Competent authorities responsible for food safety ~~may~~ **should** ~~consider~~ play~~ing~~ an active role in design, analysis and reporting of these activities as part of an integrated "One Health"

approach in collaboration with other relevant authorities from the human, animal, plant and environmental sectors.

Rationale: The design of an integrated surveillance system is part of the role of competent authorities, as outlined in section 7.1.

7.1.1. Establishing the monitoring and surveillance objectives

The establishment of monitoring and surveillance objectives is an important initial step in the design and implementation of activities. This should be done in a consultative manner by the competent authorities and stakeholders, should take into consideration national action plans, consider knowledge on the AMR and AMU situation and any existing ~~AMR~~ activities **to mitigate risks related to AMR** in the different sectors (**environmental,** animal, plant and human health sectors). Countries should identify the challenges that they currently face in the implementation of the activities. The following aspects should be defined:

The 1st bullet should be modified as follows:

The primary reasons for the data collection (e.g., to ~~**evaluate**~~ **assess** trends **in AMR** over time and space, to provide data useful for risk assessments and risk management, to obtain baseline information on AMR and AMU, to provide harmonized data that can be easily compared, exchanged, used or aggregated locally, nationally or internationally**, to detect new and emerging resistant clones or resistance determinants**);

The 2nd bullet should be modified as follows:

The comprehensiveness of the surveillance and monitoring program (e.g., data representative of the national situation versus data representative of a regional situation, or data ~~**of**~~ **derived from** convenience sampling);

7.2. Initiating monitoring and surveillance activities

The 1st bullet under "Antimicrobial resistance" should be modified as follows:

Targeting the highest priority microorganisms **and resistance determinants**, panels of antimicrobials and ~~commodities~~ **sample sources** (see section ~~10~~ **8** of these guidelines) based on country data or international recommendations;

The last paragraph should be modified as follows:

The ~~phases~~ three gradual phases of implementation described below are **examples of** guidelines for **incremental** development and enhancement of integrated monitoring and surveillance activities. **Those three phases correspond respectively to start-up program, follow-on program and advanced program of integrated monitoring / surveillance of food-borne AMR**. These guidelines are intended to provide flexibility of options for stages of implementation and expansion, considering resources, infrastructure, capacities, and priorities of countries. They are not intended to provide prescriptive restrictive categories or steps, but rather a continuum of options for implementation. **The data obtained from the start-up, follow-on and advanced programs may be not directly comparable.**

*Rationale***:** The guidance should be clearer and explicit about the progression in quality of the three steps. The three phases should be labelled respectively as start-up program, follow-on program and advanced program of integrated monitoring / surveillance of food-borne AMR. It is worth noting that the data obtained from the start-up, follow-on and advanced programs may be not directly comparable.

7.3. Options for stepwise development of integrated monitoring and surveillance of foodborne AMR and AMU programs

Row: General Considerations

Program B and C:

- *epidemiology of antimicrobial-resistant bacteria in* ***humans*** ~~***people***~~

Row: Sampling sources

Modify the text in brackets as follows:

animal/plant species**,** ~~**or**~~ food commodity **or environmental**

Program A:

Sampling of a limited selection of animal~~s~~ **species**, food **commodities** and crop **species** at limited specific stages along the food chain

Program B:

Sampling of a broader number of animal~~s~~ **species**, food **commodities** and crop **species** at **a** higher number of stages along the food chain

Row: Sampling plans

Program A:

Passive monitoring/surveillance. Limited **number of** samples collected from the animal/crops/food (e.g., caecal contents vs. carcass swabs) at specific points in the food chain

Program B:

Active monitoring/surveillance. Sampling broaden to be more representative of the ~~**national population**~~ **domestic animal species** of interest (e.g., **monitoring/**surveillance of abattoirs according **to annual throughput of** slaughter ~~**volume**~~)

Program C:

Active monitoring/surveillance. Sampling broaden to be fully representative of the ~~**national population**~~ **domestic populations** of interest (e.g., **monitoring/**surveillance of abattoirs according to **annual throughput of** slaughter ~~**volume**~~) with stratification within animal species (e.g. broilers, layers, turkeys)

Row: Target microorganisms, bacteria isolated

Program A:

Phenotypic testing of **AMR in** representative zoonotic/pathogen**sic** (e.g., Salmonella spp. and Campylobacter spp.) and indicator bacteria (e.g., E. coli and Enterococcus spp.) for resistance

Program B:

Phenotypic testing of a broader range of **zoonotic/** pathogen**sic** and indicator bacteria for resistance

Program C:

Phenotypic testing of a broader range of ~~**pathogens**~~ **zoonotic/** pathogen**sic** and indicator bacteria for resistance

In this row, there is a mixture of information about the bacteria to be monitored and the AST methods to be used. It would be better to slip into two different rows.

Row: Source of antimicrobial use data

Program C:

End-user source: Collection of use data from veterinarian prescription, farmers use data, pharmacies and other ~~sales~~ data **sources**

Rationale: Some of those data might be from sales but also from use of antimicrobials.

7.4. Evaluation, review and adjustment or expansion of the monitoring and surveillance program

Modify the 1st bullet of the 2nd paragraph as follows:

Definition of indicators to effectively track the progress of the **national action plans based on the data resulting from** monitoring and surveillance program;

Modify the 2nd bullet of the 2nd paragraph as follows:

Periodically evaluate the monitoring and surveillance program to ensure quality and that the results are a robust and reliable indicator of AMR or AMU; **indicators also need to be reviewed periodically**;

Modify the 4th bullet of the 2nd paragraph as follows:

Use the data generated from the evaluation of activities and risk profiling to adjust the monitoring and surveillance program if required or to expand to a wider scope of ~~pathogens~~

micro-organisms, ~~foods~~ **sample sources** and antimicrobials, taking into consideration resource allocation**, capacities** and priorities (refer back to preliminary actions);

Modify the 5th bullet of the 2nd paragraph as follows:

Development and inclusion of new monitoring and surveillance tools (**e.g. Next Generation Sequencing (NGS) based technologies such as Whole Genome Sequencing (WGS) or metagenomics** ~~**whole genome sequence to facilitate genomic characterization of bacteria**~~).

8.1. Elements of an integrated monitoring and surveillance programs for AMR

The chapeau paragraph should be modified as follows:

To ensure that the monitoring and surveillance objectives are met, whatever the stage of implementation, an integrated program for monitoring and surveillance of foodborne AMR should strive to include ~~and systematic~~ **a periodical** review **(e.g. every two years) of** the following design elements and technical characteristics:

8.2. Types of design ~~or sampling plans~~

Modify the 1st bullet as follows:

~~**Simple**~~ cross-sectional point prevalence surveys that can be used to collect basic information and compare between various populations at particular point of time;

Modify the 2nd bullet as follows:

Longitudinal monitoring to routinely and continuously collect data over time. The limitations of longitudinal studies are related to their greater complexity and cost compared with point prevalence surveys, but provides valuable information on **temporal** trends. ~~**Many longitudinal studies**~~ **Longitudinal monitoring may be** ~~**are**~~ carried out by conducting repeated cross-sectorial surveys at fixed intervals;

8.3. Sample sources for the collection of isolates for AMR testing

Modify the 1st paragraph as follows:

Sources of samples for the collection of the isolates for AMR testing will be ~~**based on**~~ **determined according to** the objectives, the stage of implementation and the design of the monitoring and surveillance programs and will be determin~~ate~~**ed** by the available resources and the national infrastructure. ~~Data from the samples can be integrated with data from other sources (e.g. human isolates).~~

Rationale: The last sentence should be moved under 10.4, as it relates to the analysis level.

Delete the last sentence of the 4th paragraph:

Although samples from both healthy animals and sick animals are useful for monitoring and surveillance, samples from healthy animals should be the primary focus because such

samples can provide better measure of AMR in animals entering the human food supply chain. ~~Isolates from sick animals are useful for detecting novel resistance patterns.~~

Rationale: The last sentence should be deleted as it is not clear. If the novel resistance traits are a result of spill over from the human compartment this statement would not be true.

8.4. Sampling plans for AMR data collection

Modify the 2nd bullet of the 2nd paragraph as follows:

Target populations: animal/food/crops **or environmental** and target ~~bacterial populations~~ **micro-organisms** and resistance determinants;

8.5. Target microorganisms and resistance determinants

Modify the 1st paragraph as follows:

Bacterial species should be chosen considering public health ~~**aspects**~~ **relevance**, including the epidemiology of foodborne diseases, and should include both foodborne pathogens and indicator organisms of commensal bacteria.

Rationale: editorial

Modify the 5th paragraph as follows:

Tests for virulence factors, **sequencing of** AMR genes **and genetic environment (transposons, integrons, plasmids) and molecular typing** ~~gene transferability and gene sequencing can~~ also be applied as resources and capacity permit~~s~~.

Rationale: editorial.

8.6. Laboratories

After the third bullet point to insert a new bullet point:

Perform bacterial isolation, identification, typing, phenotypic and genotypic characterization using standardized and validated methods.

Modify the 5th bullet as follows:

Store isolates ~~for a period of time~~ using methods that ensure viability and absence of change in strain properties;

Rationale: The time period is not specified and gives no extra value to the text.

8.7.5. Molecular testing

Modify this section as follows:

The use of molecular testing such as polymerase chain reaction (PCR), **micro and nano arrays**, sanger-sequencing, pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST) or Whole Genome Sequencing (WGS), may contribute to the monitoring of AMR, the detection of resistance ~~genes~~ **determinant**s and epidemiological analysis.

The use of molecular characterization such as WGS is also an important tool for the rapid **identification** of **clusters** ~~detection of outbreaks, risk factors and epidemic source~~, **outbreak** investigation, **determination of epidemic source and** of transmission chains, detection of emergence **and investigation of the** ~~and~~ spread of new ~~drug~~ resistant strains**/resistance determinants**; source attribution by linking to molecular monitoring of pathogens**/resistant micro-organsims** in humans, animals, food and environment**al** reservoirs.

For example ~~of~~ the use of molecular testing could be useful for the enhanced surveillance and early warning of resistant ~~pathogens~~ **micro-organisms** of high public health impact such as **ESBL/AmpC/** carbapenemase-producing Enterobacteriaceae.

The application of molecular methods and the interpretation of the information derived from them **is by nature** ~~will require~~ multidisciplinary. **It is necessary to reach** ~~**interpretation**~~, global agreement **on methods and analytical pipelines.** ~~analytical and interpretational approaches,~~ **L**aboratory and technical capacity, data management **and sharing** and analytical platform to link epidemiological and microbiological information at national and international level **are also important considerations**. For appropriate and successful use of molecular surveillance data, national, international and cross-sector agreements on quality standards, analytical schemes and genomic type nomenclature for the ~~bacterial pathogen~~ **micro-organism** or resistance determinants under monitoring **or surveillance** should be established in collaboration with national and international reference laboratories.

Basic training and professional development in bioinformatics and genomic epidemiology should be carried out for public health microbiologists, **risk assessors,** epidemiologists and risk managers **to facilitate the typing, interpretation** ~~about analysis~~, reporting, ~~interpretation~~ and use of integrated genomic epidemiology data.

In some countries, using WGS costs less than using conventional microbiology~~, including isolation, detection and molecular typing~~ **(including isolation, susceptibility testing and typing)**. Countries without current AMR **monitoring or** surveillance programs may consider focusing on WGS in developing **monitoring or** surveillance programs. Countries taking this approach should do some **monitoring or** surveillance using conventional microbiology to monitor for previously undetected resistance genes. WGS approaches to **monitoring or** surveillance are particularly suited to **compare molecular** data and there are several international initiatives to collect and share WGS data.

Insert the following new paragraph under this section:

There is substantial scientific knowledge that indicates that predicting of the resistance phenotype from WGS data is now possible with a high level of accuracy. New approaches are also coming through with the application of machine learning techniques for the prediction of the level of MIC. Once sequence data are generated and stored (with appropriate metadata) these data can be easily used for retrospective surveillance (e.g. in the case of newly discovered resistance determinants). The use of

WGS allows also the integration of resistance data with other relevant data for public health such as virulence determinants etc.

9.1. Key aspects to consider when developing monitoring and surveillance of antimicrobial sales/use data in animals and crops

Modify the last bullet as follows:

The reporting of antimicrobial **sales or** use data may be further organized by crop type, animal species, **animal categories, age groups,** by route of administration (e.g. in-feed, in-water, injectable, oral, intramammary, intra-uterine, topical), by type of use (therapeutic vs non-therapeutic, pest-control in crops), etc.

9.2.2. Antimicrobial quantities (numerator)

Extensive guidelines for these topics are available from OIE and WHO. Therefore, succinct recommendations under these sections are sufficient for the purpose of the guidance document and there is no need to further develop them.

9.2.3 Animal population (denominator)

Extensive guidelines for these topics are available from OIE and WHO. Therefore, succinct recommendations under these sections are sufficient for the purpose of the guidance document and there is no need to further develop them.

The last bullet should be modified as follows:

The total number of food-producing animals by species, type of production and their weight in kilograms for food production per year (as relevant to the country of production) is ~~essential basic information~~ **important information that should be collected where possible**.

Rationale: This type of information is important, but might be difficult to obtain.

10.2. Collection and reporting of resistance data

The 3rd bullet of the 3rd paragraph should be modified as follows:

Specific information about the origin of the sample: food producing animal, plant/crop**, environmental** or food category, country of origin, type of sample, stage of sampling in the food chain, place, sampling, and isolation date, etc.

10.3. Management of data

The 4th paragraph should be modified as follows:

A description of sampling designs, stratification and randomization procedures per animal populations and **crop/plant,** food **or environmental** categories should be provided with the data.

The last paragraph should be modified as follows:

Ideally, ~~isolate-level~~ data should be collected and stored. at isolate. level (report **to the database** separately each bacterial species and ~~animal population/food combination~~ **sample source**)

10.6. Integrated analysis of results

The 2nd paragraph should be modified as follows:

The data may originate from different **monitoring and** surveillance systems, and comparability is an important factor to consider in the design of the **monitoring and** surveillance programs. The analytical approach chosen should allow the investigation of the relationship between consumption and resistance within the animal, plant/crops and human populations, as well as additional associations between equivalent data within all relevant populations**, provided that AMR and AMC data are representative.**