

# Report of the 6<sup>th</sup> Meeting

## WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance

with

AGISAR 5-Year Strategic Framework to Support  
Implementation of the Global Action Plan  
on Antimicrobial Resistance (2015-2019)

10-12 June 2015  
Seoul, Republic of Korea



World Health  
Organization

AGISAR 6



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## **Declarations of interest**

All experts and resource advisers invited to participate in the expert consultations completed the WHO standard form for declaration of interests prior to the meeting. Each Declaration received from meeting participants was reviewed in the context of the objectives of the meeting. No conflicts affecting the outcomes of the meeting were identified for these experts.





## List of Abbreviations

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AGP	Antimicrobial growth promoter
AMR	Antimicrobial resistance
AMU	Antimicrobial usage
AFLP	Amplified fragment length polymorphism
CIA	Critically important antimicrobials
CLSI	Clinical and Laboratory Standards Institute
DANMAP	Danish programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
EMA	European Medicine Agency
ESVAC	European surveillance of veterinary antimicrobials consumption
ESBL	Extended spectrum beta-lactamase
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization of the United Nations
GAP	Global action plan
GFN	WHO Global Foodborne Disease Network
ISO	International Organization for Standardization
JIACRA	Joint Interagency Antimicrobial Consumption and Resistance Analysis
KCDC	Korea Centers for Disease Control
KEMRI	Kenya Medical Research Institute
MDR	Multidrug-resistant bacteria (defined by ECDC as “acquired non-susceptibility to at least one agent in three or more antimicrobial categories”)
MIC	Minimum inhibitory concentration
MFDS	Ministry of Food and Drug Safety (of Korea)
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MS	Member States
NARMS	National antimicrobial resistance monitoring system (of the USA)
OIE	World Organisation for Animal Health
PFGE	Pulsed-field gel electrophoresis
PI	Principle investigator
RELVRA	Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (Latin American Surveillance Network of Antimicrobial Resistance)
STEC	Shiga-toxin producing <i>E. coli</i>
USA	United States of America
WHO	World Health Organization
WGS	Whole genome sequencing



## Executive Summary

Antimicrobial resistance (AMR) increases mortality, morbidity, and health expenditure. It is a global concern that has worsened in recent decades through the inappropriate use of antimicrobial drugs in human and veterinary medicine. Some of the antimicrobial drugs important in human medicine are also used in animals, which increases the risk of emergence and spread of bacteria resistant to these antimicrobials, impacting public health. The spread of resistant bacteria (and genes conferring resistance) from animals to humans through food and direct contact is well documented in the literature. These concerns are increasing regionally and worldwide, leading to a growing awareness of the urgent need to take cross-sectoral action.

In 2008, the World Health Organization (WHO) established the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) to advise and support WHO to minimize the public health impact of AMR associated with the use of antimicrobials in the food chain. AGISAR is comprised of over 30 international experts from a broad range of disciplines relevant to AMR. AGISAR's advisory role includes advocating for improved control of antimicrobial use in the food chain using a cross-sectoral, multidisciplinary 'One Health' approach, promoting and facilitating integrated AMR surveillance through the development of guidance and national capacity-building projects, and maintaining the *WHO List of Critically Important Antimicrobials* (CIA List). In May 2015, the 68<sup>th</sup> World Health Assembly adopted a global action plan (GAP) on antimicrobial resistance ([http://www.who.int/drugresistance/global\\_action\\_plan/en/](http://www.who.int/drugresistance/global_action_plan/en/)). The GAP specifically mentions strengthening integrated surveillance for AMR through implementing the AGISAR recommendations on the surveillance of foodborne pathogens, thus providing the framework for the work of AGISAR into the future.

The sixth AGISAR meeting, held in June 2015 (AGISAR6), was hosted by the Korea Centers for Disease Control (KCDC), with funding provided by the Korean Ministry of Food and Drug Safety (MFDS). The specific meeting objectives of AGISAR6 were to:

- Develop a five-year strategic framework, based on the GAP
- Review progress and lessons learned from AGISAR capacity-building projects

Modified AGISAR terms of reference that directly address the strategic objectives of the GAP were developed, and the following five themes were identified as part of a new AGISAR five-year strategic framework for 2015-2019:

- Knowledge management and communication
- Critically important antimicrobials list
- Optimal use of antimicrobial agents in food production
- Laboratory methods in antimicrobial susceptibility testing
- Data integration and analysis

Thematic working group leads and members were identified for each of these five themes, and activities and outcomes aligned with the GAP objectives were discussed and agreed. The updating of the *AGISAR Guidance on Integrated Surveillance of AMR* and the development of a WHO guideline based on an updated version of the *WHO List of Critically Important Antimicrobials* will be the two priority outcomes for the coming years.



## I. Meeting Report

### 1. Background and context: alignment of AGISAR with the global action plan on antimicrobial resistance

***The World Health Organization (WHO) Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)*** was established in 2008 to support WHO to minimize the public health impact of antimicrobial resistance (AMR) associated with the use of antimicrobials in food-producing animals. The AGISAR consists of over 30 international experts, who cover a broad range of disciplines relevant to antimicrobial resistance, including physicians, microbiologists, veterinarians, and epidemiologists. Members are selected through a transparent selection process, including a web-published call for applications. In 2014, both the 2009-2014 terms of reference and the membership terms of the previous group of members expired and, through the established official process, an approximately even mix of former and new experts was appointed. AGISAR members maintain communication through regular teleconferences, email exchanges and face-to-face meetings. AGISAR advises WHO in aspects of AMR related to the food chain, including: advocating for improved control of antimicrobial use in the food chain using the 'One Health' approach; promoting and facilitating integrated surveillance for AMR through development of guidance and national capacity-building projects; and maintaining the *WHO List of Critically Important Antimicrobials* (CIA List).

***This sixth face-to-face meeting of the AGISAR*** was hosted by the Korea Centers for Disease Control (KCDC), with funding provided by the Korean Ministry of Food and Drug Safety (MFDS). Approximately 35 AGISAR members, resource persons, technical advisers, and observers attended (see annexes A and B). Dr Young Joo Hur, Director of the KCDC Center for Infectious Disease Control, welcomed participants on behalf of KCDC Director Dr Byung-Guk Yang. Dr Jinhee Hwang, Deputy Director of MFDS, gave her welcome on behalf of Dr Dongmi Choi. Appreciation was given to WHO and the AGISAR experts for choosing Korea for this year's meeting, and the importance of AMR as a major global concern and the importance of controlling foodborne diseases were emphasized. A high-level cross-sectoral meeting on AMR will be held in Korea in September 2015 to ensure that AMR will be addressed by public and private organizations in all sectors, such as agriculture and food. Korea's work on its comprehensive national plan for the control of AMR to align with the global action plan on AMR (GAP) was noted.

Dr Awa Aidara-Kane, Coordinator of the Foodborne and Zoonotic Diseases unit at the Department of Food Safety and Zoonoses of the WHO, welcomed meeting participants, stating that AMR is a growing concern in public health that challenges the control of infectious diseases and that AMR has an impact on health outcomes and the disease burden. She mentioned that, although the debate would continue on the extent to which antibiotic usage in animals is responsible for drug resistance, there was already evidence that human consumption of food carrying resistant bacteria might result in the indirect and direct acquisition of AMR infections in humans. She emphasized WHO's commitment to leadership in the global objective of reducing the burden of AMR on human health, including the development and adoption of the GAP.

**The GAP** ([http://www.who.int/drugresistance/global\\_action\\_plan/en/](http://www.who.int/drugresistance/global_action_plan/en/)) was developed based on a request by WHO Member States put forth during the WHO World Health Assembly in 2014. Development of the GAP by WHO included a broad multisectoral consultative process, including the engagement of regional committees, Member State consultations, web-based consultations, direct bilateral engagement with partners such as the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), and meetings of a WHO strategic advisory group (STAG). The STAG was convened specifically for AMR, ensuring broad support by member countries and other partners globally. The GAP was adopted by the 68<sup>th</sup> World Health Assembly in May 2015. Member States have agreed to develop, within two years, national plans based on the GAP framework, and to report back to WHO on their implementation progress every two years. The GAP is not a WHO plan, but rather a global plan; it is applicable to all Member States and partners who have agreed to engage.

Within the GAP, there are proposed actions for the WHO secretariat, Member States, and other partners. The GAP specifically mentions strengthening integrated surveillance for AMR through the implementation of the AGISAR recommendations for surveillance of foodborne pathogens and application of other international standards. The GAP thus provides a framework for the ongoing and future work of AGISAR, and this AGISAR6 was aimed at developing a new AGISAR strategic framework aligned within the five strategic objectives of the GAP, namely to:

1. Improve awareness and understanding
2. Strengthen the knowledge and evidence base
3. Reduce the incidence of infection
4. Optimize the use of antimicrobial medicines
5. Develop the business case for sustainable investment

## 2. Objectives of the meeting

Given the new AGISAR membership, the expiration of the previous terms of reference, and most importantly, the adoption of the GAP, this meeting came at a crucial time. In this context, the specific meeting objectives were to:

- Develop a five-year strategic framework based on the GAP
- Review progress and lessons learned from AGISAR capacity-building projects

### 3. The WHO-OIE-FAO collaboration in AMR

**Through long-established established tripartite collaboration,** FAO and OIE have been working with WHO on health concerns arising at the human-animal interface, including AMR along the food chain to ensure human health, animal health, and animal welfare. The AMR focal points from FAO and OIE are members of AGISAR, and the tripartite AMR focal points also meet regularly under the tripartite umbrella to develop work plans defining short-, medium- and long-term actions, identify areas for cooperation, develop common messages, and discuss common country and sub-regional approaches and projects. The focal points contribute to each other's regular and ad hoc groups, meetings, and trainings. FAO and OIE have been major contributors to and supporters of the GAP during its development, and are committed to supporting its implementation. Two important aspects of the tripartite work are to increase awareness on the need to combat antimicrobial resistance in food-producing animals and to provide guidance and options for risk management.

**During AGISAR6, OIE noted** the importance of antimicrobials for animal health and welfare, as well as food security, and noted that there are differences in AMR challenges in the animal health sector compared to the public health sector. They stressed the importance of now focusing on supporting the implementation of existing intergovernmental standards, tools, guidance and advice, and that national multidisciplinary task forces have been shown to improve effectiveness and sustainability of AMR activities in countries. OIE regularly convenes an ad hoc group on AMR, in which WHO and FAO participate, and has developed a list of antimicrobials critical for use in animals (see annex C1).

**FAO noted** that antimicrobials are important for the treatment of sick animals, and that the use of antimicrobials in crops and other plants has been increasing. FAO strongly promotes a 'One Health' approach and interdepartmental engagement through an internal AMR working group where departments and divisions responsible for the *Codex Alimentarius*, animal health, animal production, food safety, fisheries, and plants convene for internal discussions and action (see annex C2).

### 4. Policy advances

**Globally, the most significant AMR policy development** since the last AGISAR meeting was the adoption of the GAP. In another particularly important historic step, WHO, FAO, and OIE all adopted resolutions addressing AMR in their 2015 general assemblies. Although these resolutions are each different, all three align around the principles and actions of the GAP.

**Regional activity** on AMR has also been moving forward strongly. In the European Union (EU) an action plan has been developed based on seven equally-important areas for action (see annex C3): promotion of the appropriate use of antimicrobial agents in human and veterinary medicine; prevention of microbial infections and their spread; development of new antimicrobials, alternatives for treatment, or diagnostic tools; harmonization of surveillance systems; collaboration with international partners to contain the risk of antimicrobial resistance; research and innovation; and communication, education and training. The EU has harmonized surveillance of AMR in the food chain using a rotating system, including the most relevant combinations of bacterial species, food-producing animal species, and food products to be tested.

In Latin America (see annex D), the Latin American Surveillance Network of Antimicrobial Resistance (RELAVRA), PulseNet, and the WHO Global Foodborne Disease Network (GFN) have been routinely

and consistently used during national capacity building, allowing for data alignment and analysis within the regional networks despite vast differences among countries in the capacity for AMR testing. Data from bacterial isolates from humans, food, animals, environment, and feed are included in these analyses.

**Ensuring implementation of the WHO, OIE, and FAO resolutions and the GAP** is the next crucial step. Countries will need support to develop their national plans under the GAP and regional initiatives, and to establish and enforce their own legislation, for example to ensure the availability of quality medicines.

## 5. Technical updates

**Evidence continues to be generated on AMR in the food chain** (see annex C4). More evidence associating antimicrobial usage with resistance is coming available. Assessment of the effect of interventions can be used to support potential causality in these associations. For example, the Netherlands has found reduced levels of resistance in *E. coli* temporally associated with a reduction of sales of antibiotics for animals. Similarly, a reduction in resistance was noted after a reduction in use of antibiotics in commensal *E. coli*. Evidence also increasingly suggests the exchange of bacteria and genes among hosts, for example the transfer of *E. coli* with similar AMR patterns among animals, food, humans, and the environment. Associations are usually based on finding similar isolates or genes in different sectors.

An increase in the dissemination of resistance to carbapenems, the last line of broad spectrum beta lactam antibiotics, has been noted. Although carbapenem-resistant *E. coli* have not been detected in food, they have been detected in food animals; thus, more active surveillance and monitoring for carbapenem-resistant bacteria in non-human sources, including the food chain, is needed. Important actions would include continuing to prohibit carbapenem use in the food chain, and increasing surveillance and monitoring of fruits and vegetables including assessing their potential contamination with carbapenem-resistant bacteria.

There have been some improvements in antibiotic consumption and species-specific antimicrobial use surveillance in the food production chain in selected regions. In areas with good surveillance, there is notable regional variability and significant trends in consumption over time. In specific instances, surveillance data have been robust enough to demonstrate reductions in AMR in animals/food isolates associated with reductions in consumption and the success of targeted use reduction interventions. However, antibiotic consumption data are still lacking in much of the world, and consumption data tend to lack granularity, in particular the stratification of consumption by class of antibiotic. Important data are lost when distribution of consumption by class is not included. However, existing data already underscore the need for intense efforts to improve antibiotic stewardship globally.

Increasingly, ethics, in addition to scientific evidence, are influencing both technical and policy discussions and approaches. The consuming public and the private sector are, in some locations, being influenced by and are therefore influencing policy with positive effects. The CIA List is seen as an important common reference for private and public policy and risk management.



**Whole genome sequencing (WGS) and bioinformatics tools are being increasingly used** to identify AMR in organisms. These techniques reliably predict resistance, but require training for both the sequencing and interpretation, and may be more useful for surveillance than for clinical applications. Despite the huge decrease in the cost of WGS in recent years, these techniques might still be too expensive for use as routine diagnostics in most less-developed countries. Another constraint in using WGS to detect AMR is that, currently, minimum inhibitory concentrations (MICs) can not be predicted (see annex C5).

A study was published by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Agency (EFSA), and the European Medicines Agency (EMA) in the *Joint Interagency Antimicrobial Consumption and Resistance Analysis* (JIACRA) report. This study incorporates consumption and resistance data from humans and animals (not broken down by species) via five networks. The results show an association between usage and resistance in both humans and animals at the regional level. (<http://www.efsa.europa.eu/fr/efsajournal/doc/4006.pdf>)

**Important issues raised during discussions** included:

- **Finding an appropriate balance between ensuring scientific evidence for actions and implementing activities based on the precautionary principle** is required for rational implementation of the GAP. It is clear that there may not be evidence for resistance in every drug/microorganism combination; however, the development of resistance must be anticipated and prevented. It was noted that decisions could be made based on the ‘best available evidence’.
- **Including all relevant sectors in integrated surveillance** is required to understand the full picture. The role of water, sewage, and soil in maintaining resistant bacteria as a source for animals and people, as well as allowing for contact between different populations of resistant bacteria and possible transfer of genes, was repeatedly noted. Microorganisms from these sources need to be monitored, and contamination controlled. Similarly, antibiotic usage in crops and resistance in plant-derived foods would have to be included in any comprehensive, integrated surveillance plan.
- **Breaking down usage and resistance data by species and sector** will allow more precise associations to be drawn and risk management to be better directed.

## 6. Lessons learned from national capacity-building projects

**National capacity-building projects completed or in process** were presented and discussed (see annex D). These projects are reviewed, accepted and funded by AGISAR and partners (e.g. countries, other government agencies, mentors' institutions), based on a formal proposal system overseen by the WHO AGISAR secretariat. In 2014, mentors from among AGISAR members were assigned to each ongoing and new project to provide direct technical support and expertise. At AGISAR6, representatives from projects in the Americas, Bangladesh, Cameroon, Ghana, India, Kenya/Rwanda/United Republic of Tanzania, Lebanon, and Uganda presented their project objectives, results to date, and constraints. For Latin America, the benefits of implementing a regional approach for capacity strengthening for AMR, including the use of standard regional tools, was emphasized.

Overall, lessons learned included:

- Countries vary widely in their existing capacity and priorities, yet there needs to be some national capacity to apply basic international standard protocols (e.g. the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI)) in order to be able to implement even a simple project.
- The need for stricter planning for and closer oversight of funding.
- The need to revise the AGISAR process for evaluating and selecting projects. The objectives, activities, scope and sustainability of proposals need to be more critically assessed for practical applicability in the country context prior to approval.
- The possibility of supporting two types of projects: (1) implementation of AGISAR integrated surveillance approaches for national systems and (2) institutional projects on a focused AMR-specific issue.
- Although projects should use common, standard tools and methods (especially for comparability among projects), there should always be an option to fund innovative or country-specific projects in which methods may deviate from the standards, but which are justified by the principle investigator (e.g. laboratory capacity, funding, equipment or staffing-based justifications).
- Procurement is a major constraint and supply/delivery mechanisms should be ensured prior to project initiation. If samples are to be shipped, arrangements must also be ensured in advance. A system for long-term storage of isolates must also be considered.
- The importance of mentoring the projects.
- A monitoring and evaluation system should allow successful aspects of projects to be repeated and mistakes avoided in the future. This would require development of some measures of success/metrics for capacity building.

It was agreed that examples of standard methodologies and protocols for country capacity-building projects and systems would be included in the revised *AGISAR Guidance on Integrated Surveillance of AMR*.

## 7. AGISAR terms of reference

As noted above, the WHO AGISAR assists WHO on matters related to the integrated surveillance of AMR and the containment of food-related AMR. Prior to and during the AGISAR6, members identified the main achievements and strengths of AGISAR as: maintaining the CIA List; supporting capacity building (especially through pilot projects); overall advocacy for AMR; specific engagement in work of the *Codex Alimentarius*; and engagement within the tripartite collaboration. Having an experienced, established, permanent expert group working on AMR globally under the WHO umbrella was also noted as a benefit of AGISAR.

The terms of reference (ToR) governing AGISAR, originally based on a detailed analysis by the Secretariat, were agreed at the first AGISAR meeting in 2009. Before the 2015 AGISAR6 meeting, the AGISAR Secretariat requested suggestions from AGISAR members for changes to the ToR through an online questionnaire; proposed changes were discussed during the meeting. There was discussion on expanding the scope beyond the food chain; however, there was overall agreement that the AGISAR scope should remain food-chain focused. No other substantive changes to nor deletion of any of the ToR were proposed. That said, improvements to the wording were suggested and suggestions were made to better align the ToR with actual AGISAR objectives and activities, and to better align with the wording of the GAP. It was agreed that the ToR should reflect only what was possible to achieve. The ToR were thus revised and circulated for comment among the AGISAR members. The revised ToR for the period 2015-2019 are as follows:

In the context of supporting WHO and countries in the implementation of the global action plan on Antimicrobial Resistance (GAP), AGISAR shall:

1. Support WHO activities on the containment of antimicrobial resistance from the food chain (GAP objective 2)
  - Assist WHO in building its global repository for sharing antimicrobial resistance and usage data (GAP objective 2)
  - Support the collection of antimicrobial resistance and usage data on animals and the food chain, including updating and maintaining the *AGISAR Guidance on Integrated Surveillance of AMR* (GAP objective 2)
  - Develop indicators/metrics to assess antimicrobial resistance and usage from the food chain in different countries (GAP objective 2)
2. Provide advice and support to WHO capacity-building activities related to integrated surveillance of antimicrobial resistance and collection of antimicrobial usage data (GAP objectives 1, 2 and 4)
  - Develop and review antimicrobial resistance training modules and laboratory protocols (GAP objectives 2 and 4)
  - Provide training courses and technical support to WHO Member States on integrated surveillance of antimicrobial resistance and usage (GAP objectives 2 and 4)
  - Provide protocols for capacity-building projects on integrated surveillance of antimicrobial resistance and usage in countries and regions (GAP objectives 2 and 4)
  - Promote awareness and use of AGISAR and WHO advice and guidance on antimicrobial resistance (GAP objectives 1 and 2)

3. Review and maintain the WHO list of critically important antimicrobials (CIA List) for human medicine (GAP objectives 2 and 4)
4. Support WHO in the implementation of FAO/OIE/WHO tripartite activities and activities of *Codex Alimentarius* on antimicrobial resistance (GAP objectives 1, 2, 3, 4, and 5)

## II. AGISAR Five-year Strategic Framework (2015-2019)

### 1. Thematic Working Groups

***Through the pre-meeting online questionnaire, facilitated plenary discussions, and small working groups,*** participants shared perspectives and experiences to identify key priority areas where AGISAR is poised to support implementation of the GAP, both at the WHO Secretariat level and at the country level through the implementation of national-capacity building projects. In general, priorities for the next five years included: supporting implementation of the GAP; continuing advocacy in AMR (particularly integrated surveillance and prudent use); continuing capacity-building projects with an increased focus on sustainability; and developing guidance and advice, in particular, keeping the CIA List and the *AGISAR Guidance on Integrated Surveillance of AMR* up to date.

Based on the priorities discussed, five AGISAR thematic working groups and associated objectives/tasks were identified to include in the AGISAR strategic framework for the next five years. The participants separated into five working groups for further discussion and development of a framework for each theme. Each working group presented their strategic framework in plenary and further input was collected from other experts. This information was then integrated into the frameworks. AGISAR members who were unable to participate in the meeting have been asked to identify working group(s) to join based on their interest and expertise.

The new AGISAR themes are:

- **Knowledge management and communication**
- **Critically important antimicrobials list**
- **Optimal use of antimicrobial agents in food production**
- **Laboratory methods in antimicrobial susceptibility testing**
- **Data Integration and analysis**

The Knowledge Management, Laboratory Methods in Antimicrobial Susceptibility Testing, and Data Integration and Analysis thematic working groups will work together to update the relevant sections of the *AGISAR Guidance on Integrated Surveillance of AMR*, with support from the Secretariat.

## 2. Thematic working groups: objectives and linking to the GAP

### Knowledge management and communication

AGISAR produces expert guidance and support on AMR, including advocacy for prevention and control, to WHO and to countries, although sometimes AGISAR information and support are not easily accessible to those who need them. This thematic component of the AGISAR action plan supports the implementation of GAP strategic objective 1, although activities also link with GAP strategic objectives 2, 3, and 4.

The two AGISAR actions within this theme and specific tasks identified are:

#### GAP strategic objective 1:

##### Improve awareness and understanding of antimicrobial resistance through effective communication, education and training

- Steps need to be taken immediately in order to raise awareness of antimicrobial resistance and promote behavioral change, through public communication programmes that target different audiences in human health, animal health and agricultural practice as well as consumers. Inclusion of the use of antimicrobial agents and resistance in school curricula will promote better understanding and awareness from an early age.
- Making antimicrobial resistance a core component of professional education, training, certification, continuing education and development in the health and veterinary sectors and agricultural practice will help to ensure proper understanding and awareness among professionals.

#### 1.1 Communication strategy and 'One Health' dimension of AMR

1. Update chapter 7 of the *AGISAR Guidance on Integrated Surveillance of AMR* and seek ways to communicate the information to stakeholders
2. Increase the visibility of AMR, including the cross-sectoral 'One Health' dimension of AMR and AGISAR's technical contributions to AMR prevention and control
3. Develop a communication strategy for AGISAR

#### 1.2 Knowledge transfer (products to be available via websites or other appropriate communication platforms, as identified through the communication strategy)

1. Build a platform to provide qualitative and quantitative data and information and expert advice, based on the virtual retrieval of data from linked databases globally
2. Propose training at the educational level
3. Propose materials at the technical level

### Critically important antimicrobials (CIA) List

The CIA List is intended for public health and animal health authorities, practicing physicians and veterinarians, and policymakers to be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing AMR resulting from human and non-human antimicrobial use. Appropriate application of the CIA List supports the implementation of GAP strategic objective 1 to improve awareness and understanding of AMR, as the CIA List is an important component for the responsible use of antibiotics and for controlling the potential spread of resistant microbes through the food chain. Application of the CIA List supports GAP strategic objective 2 by strengthening the knowledge and evidence base through surveillance and research, and by helping

to prioritize relevant research gaps related to new or existing classes of antibiotics. It also supports GAP strategic objective 4, where there is a direct reference to the CIA List, by optimizing the use of antimicrobial medicines in human and animal health. The associated text of objective 4 recommends that any new classes of antimicrobials developed need to be classified immediately as ‘critically important’ and not used in food animals.

## **GAP strategic objective 2:**

### **Strengthen the knowledge and evidence base through surveillance and research**

Actions and investments to tackle antimicrobial resistance should be supported by clear rationales of their benefit and cost–effectiveness. National governments, intergovernmental organizations, agencies, professional organizations, nongovernmental organizations, industry and academia have important roles in generating such knowledge and translating it into practice. Particularly important gaps in knowledge that need to be filled include the following:

- The incidence, prevalence, range across pathogens and geographical patterns related to antimicrobial resistance are all information that is needed to be made accessible in a timely manner in order to guide the treatment of patients; to inform local, national and regional actions; and to monitor the effectiveness of interventions.
- Understanding of how resistance develops and spreads, including how resistance circulates within and between humans and animals and through food, water and the environment, is important for the development of new tools, policies and regulations to counter antimicrobial resistance
- The ability rapidly to characterize newly emerged resistance in microorganisms and elucidate the underlying mechanisms; this knowledge is necessary to ensure that surveillance and diagnostic tools and methods remain current.
- Understanding of social science and behaviour, and other research needed to support the achievement of objectives 1, 3 and 4, including studies to support effective antimicrobial stewardship programmes in human and animal health and agriculture.
- Research, including clinical studies conducted in accordance with relevant national and international governance arrangements, on treatments and prevention for common bacterial infections, especially in low resource settings.
- Basic research and translational studies to support the development of new treatments, diagnostic tools, vaccines and other interventions.
- Research to identify alternatives to nontherapeutic uses of antimicrobial agents in agriculture and aquaculture, including their use for growth promotion and crop protection
- Economic research, including the development of models to assess the cost of antimicrobial resistance and the costs and benefits of this action plan.

In addition, the CIA List is important for developing risk management strategies to prevent resistance developing and spreading to antibiotic classes listed as ‘critically important’. It will also be an essential tool for WHO Member States to implement their action plans.

The two AGISAR actions identified within this theme are:

1. Update the CIA List
2. Develop an official WHO guideline for the CIA according to WHO processes

## Optimal use of antimicrobial agents in food production

The WHO, FAO and OIE believe that addressing the rising threat of AMR requires a holistic and multisectoral approach. The three organizations are committed to working collaboratively on raising awareness, strengthening national capacities to address AMR (including policy and regulatory framework), supporting harmonized AMR surveillance and global monitoring of usage of antimicrobials, promoting research and development of new antimicrobial agents, diagnostics and vaccines and new approaches to AMR prevention and control, supporting efforts to fight against circulation of poor quality or counterfeit products, and promoting improved infection prevention and control measures, thereby progressively reducing the usage of antimicrobial agents.

This thematic component of the AGISAR action plan supports the implementation of GAP strategic objectives 1, 2, 3, and 4.

### **GAP strategic objective 3:**

#### **Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures**

Many of the most serious and difficult-to-treat antibiotic-resistant infections occur in health care facilities, not only because that is where patients with serious infections are admitted but also because of the intensive use therein of antibiotics. Although the development of resistance in such situations may be a natural consequence of necessary antimicrobial use, inadequate measures to prevent and control infection may contribute to the spread of microorganisms resistant to antimicrobial medicines.

Better hygiene and infection prevention measures are essential to limit the development and spread of antimicrobial-resistant infections and multidrug-resistant bacteria. Effective prevention of infections transmitted through sex or drug injection as well as better sanitation, hand washing, and food and water safety must also be core components of infectious disease prevention.

Vaccination, where appropriate as an infection prevention measure, should be encouraged. Immunization can reduce antimicrobial resistance in three ways:

- existing vaccines can prevent infectious diseases whose treatment would require antimicrobial medicines.
- existing vaccines can reduce the prevalence of primary viral infections, which are often inappropriately treated with antibiotics, and which can also give rise to secondary infections that require antibiotic treatment.
- development and use of new or improved vaccines can prevent diseases that are becoming difficult to treat or are untreatable owing to antimicrobial resistance.

Much antibiotic use is linked to animal production. Antibiotics are sometimes used to prevent infections, to prevent the spread of diseases within a herd when infection occurs, and as a growth stimulant, and are often administered through feed and water. Sustainable husbandry practices, including the use of vaccines, can reduce infection rates and dependence on antibiotics as well as the risk that antibiotic-resistant organisms will develop and spread through the food chain.



The five AGISAR actions identified within this theme are:

1. Ensure compliance with OIE and *Codex Alimentarius* standards in the optimal use of antimicrobials in animals and biosecurity, good husbandry and hygienic practices
2. At the regulatory level, promote a conducive regulatory environment to ensure improved implementation and compliance, including on a voluntary basis
3. Support the sustainable collection of antimicrobial consumption in animals and support the OIE database to allow monitoring of the efficiency of measures taken to implement prudent use
4. Propose guidance to develop treatment protocols for first, second, and third choice of antibiotics use in animal health, based on WHO and OIE CIA Lists
5. Propose guidance to support the definition and strengthening of veterinary stewardship in the optimal use of antimicrobial medicines in animal health to safeguard the efficacy of antimicrobial agents, taking into account OIE and *Codex* standards

**GAP strategic objective 4:**

**Optimize the use of antimicrobial medicines in humans and animal health**

- Evidence that antimicrobial resistance is driven by the volume of use of antimicrobial agents is compelling. High antibiotic use may reflect over-prescription, easy access through over-the-counter sales, and more recently sales via the Internet which are widespread in many countries. Despite measures taken by some Member States, antibiotic use in humans, animals and agriculture is still increasing globally. The projected increase in demand for animal food products may lead to yet further increases in antibiotic use.
- Data on antibiotic use are collected and analysed in many high- and middle-income countries and OIE is developing a database on antibiotic use in animals. However, data are lacking on antibiotic use in human beings at the point of care and from lower-income countries.
- More widespread recognition of antimicrobial medicines as a public good is needed in order to strengthen regulation of their distribution, quality and use, and encourage investment in research and development. In some cases, industry's spending on promoting products is greater than governmental investment in promoting rational use of antimicrobial medicines or providing objective information.
- Decisions to prescribe antibiotics are rarely based on definitive diagnoses. Effective, rapid, low-cost diagnostic tools are needed for guiding optimal use of antibiotics in human and animal medicine, and such tools should be easily integrated into clinical, pharmacy and veterinary practices. Evidence-based prescribing and dispensing should be the standard of care.
- Regulation of the use of antimicrobial agents is inadequate or poorly enforced in many areas, such as over-the-counter and Internet sales. Related weaknesses that contribute to development of antimicrobial resistance include poor patient and health care provider compliance, the prevalence of substandard medicines for both human and veterinary use, and inappropriate or unregulated use of antimicrobial agents in agriculture.

## Laboratory methods in antimicrobial susceptibility testing

A sound surveillance programme should include access to laboratories capable of conducting quality-assured antimicrobial susceptibility testing on animal, food and clinical samples, and which participate in an external quality-assurance programme. The standards for such testing need to be clearly laid out, science based, and practical for implementation at all levels of capacity, such as those of CLSI, EUCAST, or ISO. This thematic component of the AGISAR action plan supports the implementation of GAP strategic objective 2.

The four AGISAR actions identified within this theme are:

1. Keep updated the list of priority monitored foodborne bacteria isolated from human clinical cases, food animals, and animal-derived food products
2. Keep updated the list of priority antimicrobials to be tested (for the *AGISAR Guidance on Integrated Surveillance of AMR*)
3. Propose steps to incorporate quality assurance into antimicrobial susceptibility testing and monitoring
4. Propose steps to incorporate WGS into monitoring

## Data integration and analysis

There are a number of ways to document antimicrobial resistance and usage. There is also a wide range of potentially useful additional information relevant to understanding the decision to use a particular antimicrobial, such as clinical diagnosis, supportive diagnostic test results, patient expectations, and financial considerations. Consequently, database design and needs for data management, analysis, and presentation require guidance. This thematic component of the AGISAR action plan supports the implementation of GAP strategic objectives 2, 4, and 5. In particular, this theme will develop and design guidance on data-collection methods on usage (human and animal) to support data management in the integrated surveillance of antimicrobial resistance and antimicrobial consumption and how to integrate surveillance data from the food chain into economic models.

The four AGISAR actions and specific tasks identified within this theme are:

1. Revise/update the *AGISAR Guidance on Integrated Surveillance of AMR* (usage and data-management sections)
2. Develop integration, analysis and reporting chapter in the surveillance guidance document, based on appropriate methods
3. Provide guidance as a chapter for conducting country and regional capacity-building studies on integrated usage and resistance surveillance
4. Provide guidance for informing economic and risk analyses, based on data arising from integrated surveillance systems

**GAP strategic objective 5:**

**Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions**

- The economic case must reflect the need for capacity development, including training in low-resource settings, and the need for the evidence-based use of interventions across human and animal health care systems including medicines, diagnostic tools and vaccines.
- Economic impact assessments are needed on the health and broader socioeconomic burden of antimicrobial resistance, and should compare the cost of doing nothing against the cost and benefit of action. Lack of such data hindered implementation of the 2001 global strategy for containment of antimicrobial resistance. The few studies on the economic cost of antimicrobial resistance are limited chiefly to developed countries.
- Investment in the development of new antimicrobial medicines, as well as in diagnostic tools and vaccines, is needed urgently. Lack of such investment reflects, in part, fears that resistance will develop rapidly and that returns on investment will be limited because of restrictions in use. Thus research and development of new antibiotics is seen as a less attractive business investment than that of medicines for chronic diseases. Currently most major pharmaceutical companies have stopped research in this area, a situation described by WHO's Consultative Expert Working Group on Research and Development: Financing and Coordination as "a serious market failure" and "a particular cause for concern". New processes are needed both to facilitate renewed investment in research and development of new antibiotics, and to ensure that use of new products is governed by a public health framework of stewardship that conserves the effectiveness and longevity of such products. The cost of investment in research and development may need to be de-linked from price and the volume of sales to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results from research and development in all countries. Many forums have been created in recent years to discuss these issues.
- Antibiotics must also be supplemented by affordable, point-of-care diagnostic tools to inform health practitioners and veterinarians of the susceptibility of the pathogens to available antibiotics. The applicability and affordability of these techniques in low- and middle-income countries must be considered.



### III. Annex

#### a. Agenda

Time	Wednesday 10 June 2015	Chair/ Presenter
08:30-09:00	Registration	
09:00-09:30	Opening Remarks <ul style="list-style-type: none"> <li>• Dr Byung-Guk Yang, Director General, Korea Centers of Diseases Control and Prevention (KCDC)</li> <li>• Dr Dong-mi Choi, Director General of Food Nutrition and Dietary Safety Bureau, Ministry of Food and Drug Safety (MFDS)</li> <li>• Dr Awa Aidara-Kane, Coordinator, Department of Food Safety and Zoonoses, World Health Organization (WHO)</li> </ul>	
09:30-9:45	Group photo	
09:45-10:10	Administrative matters <ul style="list-style-type: none"> <li>• Adoption of the agenda</li> <li>• Election of Chair</li> <li>• Introductions</li> <li>• Declarations of Interest</li> </ul>	A. Aidara-Kane
10:10-11:00	Promoting multisectoral “One Health” approach to AMR: global actions <ol style="list-style-type: none"> <li>1. WHO Global Action Plan and AGISAR (15 min)</li> <li>2. Latest developments in FAO’s approach to AMR (10 min)</li> <li>3. Tripartite Collaboration on AMR and OIE actions (15 min)</li> <li>4. Discussion (10 min)</li> </ol>	A. Aidara-Kane P. Otto/ H. Ormel E. Erlacher-Vindel
11:00-11:30	Coffee break	
11:30-12:00	Promoting multisectoral “One Health” approach to AMR: EU actions <ol style="list-style-type: none"> <li>1. EU Action Plan against the rising threats from AMR (10 min)</li> <li>2. The ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals (10 min)</li> <li>3. Discussion (10 min)</li> </ol>	R. Peran  A. Muller
12:00-13:00	AMR updates and tools <ul style="list-style-type: none"> <li>• AMR and the food chain : Recent developments, gaps and challenges (25 min) (A Andremont, P Collignon, S McEwen, P McDermott, HM Scott, JA Wagenaar)</li> <li>• Use of Whole Genome Sequencing for integrated surveillance on AMR: Opportunities and challenges (15 min) (R Hendriksen, P McDermott)</li> <li>• 4-way linking project (10 min)</li> <li>• Questions (10 min)</li> </ul>	A. Andremont  R. Hendriksen  L. Mumford
13:00-14:00	Lunch	

14:00-14:30	<p>Introduction: AGISAR five-year strategic framework to support WHO in the implementation of Global Action Plan (GAP) on AMR from the food chain</p> <ul style="list-style-type: none"> <li>• The AGISAR Terms of Reference in the context of GAP.</li> <li>• Objectives, strategic framework, and governance structure</li> <li>• Intro to Working Groups (WGs)</li> </ul>	<p><u>Facilitators</u></p> <p>E. Perez (Lead)</p> <p>A. Aidara-Kane</p> <p>L. Mumford</p>
14:30-16:00	Break-out into WGs on AGISAR five-year strategic framework	
16:00-16:30	Coffee break	
16:30-18:00	<p>Plenary:</p> <ol style="list-style-type: none"> <li>1. Reporting back by WGs</li> <li>2. Discussion based on reports from the WGs</li> <li>3. Intro to the new subcommittees/task forces' tasks for Day 2 (build objectives, work plan and assign responsibilities)</li> </ol>	
18:00	Day 1 adjourns	

Time	Thursday 11 June 2015	Chair/ Presenter
09:00-10:00	<p>Update on AGISAR pilot projects (10 min each)</p> <ol style="list-style-type: none"> <li>1. Ghana</li> <li>2. Uganda</li> <li>3. India</li> <li>4. Latin America</li> <li>5. General discussion</li> </ol>	<ol style="list-style-type: none"> <li>1. R. Irwin</li> <li>2. P. Cray</li> <li>3. P. McDermott</li> <li>4. M. Galas/E. Perez</li> </ol>
10:00-10:30	Intro to subcommittee/task force WGs	E. Perez
10:30-11:00	Coffee break	
11:00-13:00	Break out session: Subcommittee/task force WGs	
13:00-14:00	Lunch	
14:00-18:00	Continued Subcommittee/task force WGs (Coffee break: 16.00)	
18:00	Day 2 adjourns	
19:00-21:30	Reception dinner hosted by KCDC	

Time	Friday 12 June 2015	Chair/ Presenter
09:00-10:00	<p>(Continued) Update on AGISAR pilot projects (10 min each)</p> <ol style="list-style-type: none"> <li>1. Lebanon</li> <li>2. Kenya, Tanzania, Rwanda</li> <li>3. Bangladesh</li> <li>4. Cameroon</li> <li>5. General discussion</li> </ol>	<ol style="list-style-type: none"> <li>1. G. Matar</li> <li>2. S. Kariuki</li> <li>3. M. A. Islam</li> <li>4. A. Ngandjio</li> </ol>
10:00-10:30	Reports of Day 2 discussion from WGs	
10:30-11:00	Coffee break	
11:00-13:00	Finalize and adopt the AGISAR 6 report / 5 year strategic plan	
13:00-14:00	Lunch	
	Meeting adjourns after lunch	
14:30-16:30	(Optional) Seoul City Tour organized by KCDC -Gyeongbokgung Palace Tour	Participants

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## c. Summaries of presentations

### Annex C1: Tripartite collaboration on AMR and OIE actions

Elisabeth Erlacher-Vindel,<sup>1</sup> Awa Aidara-Kane,<sup>2</sup> Patrick Otto<sup>3</sup>

1. World Organisation for Animal Health; 2. World Health Organization; 3. Food and Agriculture Organization

Antimicrobial resistance (AMR) is one of the three priority topics of the “Tripartite” (FAO, OIE, WHO) Agreement. The tripartite provides a platform for collaborative activities on AMR at the global level across the human, animal health and agriculture sectors. A tripartite AMR work plan defining short-, medium- and long-term actions has been defined and agreed by the three organizations. The areas of collaboration strengthened in 2014 include collection of data on use of antimicrobials in food-producing animals, integrated surveillance of antimicrobial resistance, capacity building through training workshops and national pilot projects, and development of joint advocacy material.

The following issues and challenges should be addressed for the containment of AMR, using the “One Health” approach:

- Implementation of harmonized protocols and methodologies to monitor AMR and antimicrobial usage, based on international standards;
- Limited surveillance data on AMR and on usage of antimicrobial agents in both human and animal sectors to support AMR risk analysis and to determine effectiveness of AMR mitigation strategies;
- Lack of technical capacity, in particular in developing countries, to undertake monitoring and surveillance of AMR and antimicrobial usage, and conduct AMR risk analysis;
- Lack of new drugs and need to support research and development. Lack of legislation to ensure access to quality drugs and to restrict use;
- Need for good governance and good regulatory framework covering all sectors related to authorization and use of antimicrobials in both animal and human sectors.

Both FAO and OIE have actively participated in the development by WHO of the GAP for AMR and proposed resolutions on AMR to their Member Countries that make reference to the GAP.

At its 83<sup>rd</sup> General Session in May 2015, the OIE adopted a new standard on risk analysis for AMR arising from the use of antimicrobial agents in aquatic animals, and updated versions of the standards in the terrestrial code on harmonization of national AMR surveillance and monitoring programmes, and on risk assessment for AMR arising from the use of antimicrobials in animals. The OIE *ad hoc* group that has met twice a year since 2010 has now completed the cycle of updates of the OIE standards and the list of veterinary important antimicrobial agents. Representatives from WHO and FAO are invited to all meetings of the *ad hoc* group and also regularly participate in regional training workshops organized by the OIE for national focal points on veterinary products.

As a follow-up from the global conference on the responsible and prudent use of antimicrobial agents for animals, the meeting ‘International Solidarity to Fight against Antimicrobial Resistance’ was organized by the OIE in Paris, France, on 13-15 March 2013. The *ad hoc* group, supported by FAO and WHO, is now working on the collection of quantities of antimicrobial agents used in animals with the aim of developing a global database in line with the tripartite agreement and the GAP (Conference recommendations available at [www.oie.int/eng/A\\_AMR2013/Recommendations.htm](http://www.oie.int/eng/A_AMR2013/Recommendations.htm)).

This approach is part of the Resolution No. 26 on ‘Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals’ adopted by OIE Member Countries at the general session in May 2015 in support of the global efforts to control AMR.

## Annex C2. Latest developments in FAO's approach to AMR

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Antimicrobial resistance is a major global public and animal health issue of increasing concern. The risk appears to be particularly high in countries where legislation, regulatory surveillance and monitoring systems regarding the use of antimicrobials and the prevention and control of antimicrobial resistance are weak or inadequate. Not only governments and veterinary services, but also producers, traders and other stakeholders need to be aware of the risks and be willing to adopt measures to minimize the use of antimicrobials and to prevent the development of antimicrobial resistance. This is why FAO, with its global network from field to government levels, can play an active role in implementing the GAP by supporting countries to develop their own national action plans on AMR and to improve their capacities to combat this global threat.

FAO calls for a 'One Health' and 'food chain' approach and is addressing AMR as a cross-sectoral issue because antimicrobials:

1. can spread through the food-chain
2. are widely used in aquaculture and livestock production
3. are used in crop culture – more specifically antifungicides

To guard against AMR and as part of overall efforts to reduce hunger, FAO helps countries develop and promote:

1. good hygiene practices to control the spread of resistant pathogens through food;
2. attention to AMR risks through the *Codex Alimentarius*;
3. efficient livestock husbandry for healthier, more productive animals;
4. guidelines for prudent use of antimicrobials in aquaculture;
5. good animal health and management practices, including improved biosecurity and use of vaccines instead of antimicrobial drugs;
6. policies and capacities for responsible use of antimicrobials
7. health management approaches that recognize the links between animals, humans and ecosystems

These measures help slow down the development and expansion of resistance to critically important antimicrobials for veterinary use.

The prudent use of antimicrobials in the livestock and aquaculture sectors is essential in light of the increased demand for animal proteins from a rapidly growing world population expected to exceed 9.6 billion by 2050. Intensifying production means additional challenges in disease management and even higher potential for increased AMR.

AMR can be tackled by working closely with veterinarians, farmers, feed and food producers, and food safety professionals to support the best animal health and production practices which underpin the prudent use of antimicrobials.

### Latest developments

#### FAO resolution on AMR

The 150<sup>th</sup> Session of Council (December 2014) requested for its 151<sup>st</sup> Session a document outlining the role of FAO and its partners in relation to AMR. It also requested a related draft resolution to be submitted to the 39<sup>th</sup> Conference on 6-13 June 2015.

## Rome declaration on nutrition

The second international conference on nutrition (ICN2), organized by WHO and FAO, held in Rome on 19-21 November 2014, mentioned AMR in the conference outcome document, the Rome declaration on nutrition, as follows:

### 14. We recognize that:

*1) food systems need to contribute to preventing and addressing infectious diseases, including zoonotic diseases, and tackling antimicrobial resistance.*

## AMR working group

This inter-departmental FAO group meets on a regular basis, chaired by Chief Veterinary Officer Dr Juan Lubroth, and brings together FAO officers from animal health, animal production, *Codex Alimentarius*, fisheries, food safety and plants.

## Website

The website [www.fao.org/antimicrobial-resistance](http://www.fao.org/antimicrobial-resistance) is specifically dedicated to AMR issues and available in Arabic, Chinese, English, French, Russian and Spanish.

## Codex Alimentarius texts on foodborne antimicrobial resistance

This special publication has been prepared to support the GAP. The publication compiles the two Codex-specific texts on foodborne AMR: *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CAC/GL 77-2011) and *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CAC/RCP 61-2005).

## Annex C3: European Commission action plan against the rising threats from AMR

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In November 2011, the European Commission launched a five-year action plan against the rising threats from AMR.<sup>1</sup> The plan is based on a holistic approach in line with the 'One Health' initiative. The plan aims at strengthening the prevention and control of AMR across all sectors and at securing the availability of new antimicrobial agents. The plan describes 12 detailed concrete key actions in 7 different attention areas, both in the human and veterinary fields.

Actions put forward in the plan include the promotion of the appropriate use of antimicrobial agents in human and veterinary medicine, the prevention of microbial infections and their spread, the development of new antimicrobials, alternatives for treatment or diagnostic tools, and the harmonization of surveillance systems. Other fields for action included in the plan are collaboration with international partners to contain the risk of antimicrobial resistance, research and innovation, communication, education, and training.

In order to strengthen and harmonize AMR surveillance systems in the EU, the European Commission requested that the European Food Safety Authority (EFSA) publish a scientific report revising the existing technical specifications on the monitoring of and reporting on AMR in *Salmonella* spp., *Campylobacter* spp., indicator commensal *E. coli* and *Enterococcus* spp. transmitted through the food production system.

This report, as well as other scientific opinions of EFSA, such as the scientific opinion on extended spectrum beta-lactamases (ESBL) and the scientific opinion on carbapenem resistance in food animal ecosystems, have all been considered in the recently adopted Commission's implementing decision

on 12<sup>th</sup> November 2013 on the monitoring and reporting of AMR in zoonotic and commensal bacteria<sup>2</sup> (Decision 2013/652/EU) that entered into force in 2014.

The legislation lays down detailed rules for all Member States (MS) implementing the harmonized monitoring of AMR, including the most relevant combinations of bacterial species, food-producing animal species and food products to be tested; detailed rules for the sampling (origin of isolates, sampling frequency, sampling size, randomized sampling design); analysis of isolates (antimicrobials, epidemiological cut-off values and concentration ranges to be used for antimicrobial susceptibility testing of isolates); interpretation of results and reporting of AMR data. In order to minimize the burden of each MS, EU monitoring is based on the biological samples or isolates collected by the competent authority according to the compliance of Regulation (EC) No. 2073/2005 on microbiological criteria for foodstuffs and in the framework of already established national control programmes (e.g. for *Salmonella* spp.). Additionally, the legislation includes specific requirements for the harmonized monitoring and reporting of ESBL, AmpC  $\beta$ -Lactamases (AmpC) and carbapenemase-producing bacteria in certain food-producing animal populations and in certain food types.

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- 2 <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1403185603748&uri=CELEX:32013D0652>

## Annex C4: AMR and the food chain: recent developments, gaps and challenges

### Carbapenem-resistant bacteria and the food chain

*Antoine Andreumont*

Carbapenems are the last line beta-lactam antibiotics to treat bacterial infections due to gram negative bacteria, such as *Salmonella* spp. or *E. coli*, that are resistant to third-generation cephalosporins. Due to the fact that these bacteria are increasingly prevalent, the usage of carbapenems has also increased. These facts are being observed worldwide, but particularly in developing countries (1)(2). They lead to the emergence and spread of carbapenem-resistant bacteria (3). Questions have arisen about the possible role of the food chain in this dissemination. Usage of carbapenems is not permitted in food-chain animals; until now, carbapenemase-producers have not been detected in food (4). However, they might be escaping detection (5). By contrast, there are a number of anecdotic reports on the detection of carbapenem-resistant bacteria in zoonotic bacteria such as *Salmonella* spp. (6)(7). This stresses the potential they have to transmit carbapenem resistance through the food chain. The issue of how to monitor these bacteria in food-chain products is emerging. A report from the United Kingdom of Great Britain and Northern Ireland (United Kingdom) and Germany supports the idea that active surveillance and monitoring for carbapenem-resistant bacteria in the food chain and other non-human sources is urgently needed, as well as an enhanced and rigorous follow up of all positive results (8). The European Food Safety Authority (EFSA) has published a scientific opinion piece recommending (i) to continue to prohibit carbapenem in the food chain; (ii) to decrease the frequency of use of antimicrobials in animals; (iii) to monitor on a regular basis food-producing animals and food for carbapenemase-producing bacteria through targeted surveys; and (iv) to assess fruit and vegetables, particularly those which are more prone to bacterial contamination and are usually consumed raw, for contamination with bacteria with acquired carbapenemases (9).

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## Association between use and resistance

*Jaap Wagenaar*

The association between antimicrobial use and resistance at the ‘general level’ is known. However, the quantitative associations between antimicrobial usage (AMU) and AMR in animals, and AMU in animals and AMR in humans are not very well described.

Associations can be identified, but a causative association can be determined when interventions are implemented.

A collaborative report of the European Medicines Agency (EMA), ECDC, and EFSA showed an association between AMU in humans and AMR in humans, AMU in animals and AMR in animals, and an association between AMU in animals and AMR in humans for incidental combinations (1)(see also *Animal to human transmission of antimicrobial resistance* section below).

A comparative study in seven European countries showed a very strong association between specific antimicrobials and resistance against these substances (2).

Intervention studies have been performed in Denmark for antimicrobial growth promoters (AGPs), showing a reduction in resistance against these AGPs (3), and the reduction of (already low usage levels) of cephalosporines (4). An intervention in ceftiofur use in hatcheries in Canada showed a reduction of ESBL-producing *E. coli* and *Salmonella Heidelberg* (5). This has been confirmed in the Netherlands (personal communication, Dik Mevius).

An overall reduction of 65% of AMU in food-production animals in the Netherlands (2007-2014) has resulted in a reduction in resistance against different classes of antimicrobials (6)(7). Parallel to this reduction, there has been a slight decrease observed in MRSA in pig herds (8).

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### **Animal to human transmission of antimicrobial resistance: what genes or clones of bacteria are the same in people and food animals? (Recent studies and publications after 2013)**

*Peter Collignon*

A recent study (1) reviewed the evidence on whether human infections with extra-intestinal *E. coli* resistant to expanded-spectrum cephalosporins originate from food-producing animals. The authors found evidence that a proportion of these infections originate from food-producing animals. Poultry, in particular, is probably a source; however, the quantitative and geographical extent of the problem is unclear and requires further investigation.

Another review (2) asked the question on whether extended-spectrum cephalosporin-resistant gram-negative organisms (ESCs) in livestock were an emerging problem for human health. They concluded that robust studies which prove unquestionable links of food animal-to-human transmission are limited, and that clones resistant to ESCs (especially *E. coli*) have thus far been mostly different in the humans compared to the animals. However, there are strong indications that the same plasmids are simultaneously present in the two settings. There is also evidence suggesting there is bacterial inter-/intra-species exchange and horizontal transmission between human and animal hosts.

Another review (3) looked at multi-drug resistance genes in staphylococci from animals and whether these confer resistance to 'critically' and 'highly important' antimicrobial agents in human medicine. MDR genes of staphylococci from animals include *erm*, *vga*, *isa(E)*, and *cfr* genes; MDR genes confer resistance by target-site methylation or efflux via ATP-binding cassette (ABC) transporters. These genes are of importance to human health because MDR genes are often located on plasmids and transferred across species and genus borders. In addition, MDR genes are often co-located with other resistance genes, allowing for co-selection.

A recent review (4) looked at livestock-associated *Staphylococcus aureus* CC398 and the effect of animal reservoirs on human infections. Whole genome sequencing and other genetic analyses have shown that livestock-associated strains are distinct from human-derived strains. However, there is



also an exchange of strains between the reservoirs. Livestock-associated and human-associated strains of CC398 share some virulence factors, but there are also distinct virulence factors that appear to be important in host adaptation. Exchange of genes encoding these virulence factors between strains may expand the host range and thereby threaten public health.

#### Transfer of Bacteria

A study in Thailand (5) looked at extended-spectrum  $\beta$ -lactamase producing *E. coli* isolates. These ESBL isolates were prevalent amongst healthy individuals, foods along the food-production chain from farms to consumers, and in the environment. The study concluded that there was evidence for similar antibiotic-resistant bacteria in healthy adults, foods, food animals, and the environment.

In the Netherlands (6), extended-spectrum and AmpC  $\beta$ -lactamase-producing *E. coli* in broilers and people living and/or working on broiler farms were examined for prevalence, risk factors and molecular characteristics. It involved 50 randomly selected Dutch broiler farms. Cloacal swabs were taken from 20 broilers and faecal swabs from 141 individuals from 47 farms. Despite the small size of this study, five pairs of human-broiler isolates had identical genes, plasmid families and *E. coli* sequence types, showing clonal transmission. Furthermore, similar ESBL/AmpC genes on the same plasmid families in different *E. coli* sequence types in humans and broilers suggested horizontal gene transfer.

In another study (7) in the Netherlands, 145 extended-spectrum  $\beta$ -lactamase-producing *E. coli* strains from retail chicken meat and humans were examined for the comparison of strains, plasmids, resistance genes, and virulence factors. A prediction model based on the combined data classified 40% of the human isolates as chicken meat isolates. Amplified fragment length polymorphism (AFLP) and pulsed-field gel electrophoresis (PFGE) methodology showed that the isolates from humans and chicken meat could not be segregated, and identified 1 perfect match between humans and chicken meat. Significant genetic similarities among ESBL-EC isolates from chicken meat and humans according to mobile resistance elements, virulence genes, and genomic backbone were found. They concluded that chicken meat is a likely contributor to the recent emergence of ESBL-EC in human infections in the study region. This raises serious food safety questions regarding the abundant presence of ESBL-EC in chicken meat.

In Belgium (8), *Clostridium difficile* strains isolated from retail meat and humans were studied. Meat strains were indistinguishable from the human isolates by multi-locus sequence typing (MLST), with clusters in the same lineage. This study reveals the presence of toxigenic *C. difficile* in retail meat in Belgium with the predominance PCR-ribotypes 078 and 014, which are among the four most prevalent ribotypes of *C. difficile* isolated from humans in Europe.

#### Metagenomics

A study (9) looked at metagenomic insights into the human gut resistome and the forces that shape it. They described metagenomic analysis of the human gut antibiotic resistome and compared these across large populations and against environmental or agricultural resistomes. Their findings suggested a strong anthropogenic cause behind increasing antibiotic resistance in bacteria.

#### Transfer of genes

A Hong Kong SAR study (10) looked at IncX4 plasmids carrying blaCTX-M in *E. coli* from humans and food animals. It involved 225 *E. coli* isolates from multiple sources (47 chickens, 41 pigs, 30 cattle and 107 humans) and tested for the presence of IncX1 to IncX5. Overall, the prevalence of IncX plasmids in chicken, pig, cattle and human isolates were 21.2% (10/47), 19.5% (8/41), 3.3% (1/30) and 4.8% (5/107) respectively. Conjugation experiments demonstrated that the IncX4 plasmids could be efficiently transferred at 30-42°C, at rates which were generally 102-105 times higher than those for the epidemic IncFII plasmid carrying blaCTX-M (pHK01). The IncX plasmids were more common than previously recognized. The efficient transfer of IncX4 plasmid at different temperatures and the lack

of fitness burden on bacterial hosts highlight the ability of this plasmid replicon to be an important vehicle for AMR dissemination.

A study (11) looked at the nucleotide sequences of 16 transmissible plasmids identified in nine multi-drug-resistant *E. coli* isolates, expressing an ESBL phenotype isolated from food-producing animals and healthy humans. Nine extended-spectrum  $\beta$ -lactamase (ESBL)-producing *E. coli* isolated from healthy humans and food-producing animals were found to transfer their cefotaxime resistance marker at a high frequency in laboratory conjugation experiments. Sixteen of these transmissible plasmids were completely characterized. Eight plasmids contained blaCTX-M-1 genes that were associated with either ISEcp1 or IS26 insertion sequence elements. Six plasmids isolated from humans and chickens were identical or closely related to the IncI1 reference plasmid R64. These data, based on comparative sequence analysis, highlight the successful spread of blaESBL-harbouring plasmids of different Inc types among isolates of human and food-producing animal origin, and provide further evidence for potential dissemination routes.

In another study (12), ESBL-producing *E. coli* from two longitudinal and four cross-sectional studies in broiler, swine and cattle farms, a cross-sectional and a case-control study in humans and diagnostic isolates from humans and animals were used to look at the sub-grouping of ESBL-producing *E. coli* from animal and human sources. This was used to quantify the distribution of ESBL types between different reservoirs. Most ESBL genes were found in both human and non-human populations, but quantitative differences for distinct ESBL-types were detectable. The enzymes CTX-M-1 (63.3% of all animal isolates, 29.3% of all human isolates), CTX-M-15 (17.7% vs 48.0%) and CTX-M-14 (5.3% vs 8.7%) were the most common ones. More than 70% of the animal isolates and more than 50% of the human isolates contained the broadly distributed ESBL genes bla(CTX-M-1), bla(CTX-M-15), or the combinations bla(SHV-12)+bla(TEM) or bla(CTX-M-1)+bla(TEM). Proportions of the same subtypes were detected in isolates from the human and livestock and companion animal populations which suggests exchange of bacteria or bacterial genes between these populations or a common reservoir.

## Reports

The first ECDC/EFSA/EMA joint report (13) on the integrated analysis of the consumption of antimicrobial agents and occurrence of AMR in bacteria from humans and food-producing animals was recently released. For both cephalosporins and fluoroquinolones, positive associations were found between the occurrence of resistance in indicator *E. coli* originating from food-producing animals and the occurrence of resistance in *E. coli* from humans. Positive associations were noted for the consumption of macrolides in food-producing animals and the occurrence of resistance in *Campylobacter* spp. from cases of human infection, as well as for the consumption of tetracyclines and the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp.

The report looked at the hypothesis that the consumption of antimicrobials in food-producing animals and resistance in bacteria from humans. It was addressed by using available data on the consumption of antimicrobials in food-producing animals and the occurrence of resistance in humans. The results showed that the occurrence of resistance in *E. coli* causing BSIs in humans could be correlated with the consumption of antimicrobials in food-producing animals and in humans. For cephalosporins use in humans, a positive association between consumption and resistance was observed. A positive association between consumption in food-producing animals and resistance was also observed. Moreover, resistance in the isolates from humans correlated positively with resistance in isolates from some animal species, and vice versa. For fluoroquinolones, similar positive correlations were observed, except that resistance was correlated with consumption in the community and not with consumption in hospitals.

The occurrence of cephalosporin resistance in bacteria originating from food-producing animals and the occurrence of resistance in humans was examined. The occurrence of cephalosporin-resistant *E. coli* from BSIs were analysed and compared with the occurrence of cephalosporin resistance in *E. coli* from cattle (six countries), pigs (six countries) and poultry (nine countries). A significant positive correlation (Spearman's rank correlation coefficient) was discerned when compared with resistance

in poultry (p-value = 0.0261) and resistance in the three animal species considered together (p-value = 0.0153) (summary indicator of resistance). No significant association was observed for cattle and pigs.

Fluoroquinolone resistance was found in bacteria originating from food-producing animals as was fluoroquinolone resistance in bacteria originating from humans; however, the number of countries reporting data on both fluoroquinolone resistance in humans and food-producing animals was very limited. For *E. coli*, a correlation of resistance in humans and resistance in cattle, pigs, poultry and the summary indicator of resistance, considering an average between animal species, was significant (Spearman's rank correlation coefficient) when compared with the resistance in pigs (p-value = 0.0016), poultry (p-value = 0.0199) and the average of all animal species (p-value = 0.0065).

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## Consumption (usage) of antimicrobials in food production

Scott McEwen

Surveillance of antimicrobial consumption in animals continues to be most advanced in Europe, where some countries (e.g. Denmark, the Netherlands) routinely collect, publish and take action on antimicrobial usage data at the species/farm/veterinarian level (e.g. benchmarking veterinary antimicrobial prescriptions (1)). Some other European countries (e.g. Austria) have developed approaches to collect farm-level data that take advantage of the mandatory recording of treatment information by veterinarians (2). At the EU level, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project monitors national-level antimicrobial consumption data from member states. ESVAC has developed and is testing protocols for the collection and reporting of national-level data by species, and is advancing the methodology and application of technical units for measurement and standardized reporting (e.g. defined daily dose for animals) (3). Outside of Europe, several countries (e.g. Canada, Japan, South Africa, United States of America/USA) monitor national-level aggregated data (i.e. not stratified to species level) and have identified the need for improvements in antimicrobial use surveillance in national action plans (4-7). The USA has recently proposed a requirement for pharmaceutical companies to provide antimicrobial consumption data at the species level (8). For much of the world, however, publicly available antimicrobial consumption data continue to be very sparse. Two recent reports have drawn attention to the further intensification of farming operations in highly populated parts of the world and its likely impact on antimicrobial consumption. Krishnasamy and co-workers (9) used indirect methods to estimate that 38.5 million kilogrammes of in-feed antimicrobial (mainly tetracycline and coccidiostats) were used in 2012 in China for swine and poultry production (70% of which they suggest was produced in concentrated animal feeding operations, rather than traditional small farms). Van Boeckel and co-workers (10) estimated global antimicrobial consumption in livestock production using Bayesian statistical models. They combined information on livestock density, projected meat demand, shifts in animal-production practices and made extrapolations from antimicrobial consumption patterns in high-income countries. They estimated that, by 2030, consumption will increase by 67%, from 63,151 tonnes to 105,596 tonnes; much of the increase was attributed to shifting from extensive to intensive livestock production, where antimicrobial consumption tends to be higher.

While there are some improvements in antimicrobial consumption surveillance in selected regions, there is still very limited publicly available antimicrobial consumption information for most of the world. Such data that do exist underscore the need for intense efforts to improve antimicrobial stewardship globally.

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## **AMR global policy: regulatory and voluntary initiatives**

*Morgan Scott*

Over the past 5 years worldwide many have continued the call for a wholesale reduction in the use of antimicrobials, citing evidence that there is either overuse or misuse of these products. In some jurisdictions, regulatory approaches to reduce ‘overuse’ or ‘misuse’ have proceeded on the basis of defining what is not considered judicious use [1], pointed to scientific data supporting a prohibition order for a specified product [2] (which, earlier, resulted in a change in new drug-approval processes [3]), or invoked the use of the precautionary principle to protect the efficacy of a product in the absence of firm scientific evidence (such as occurred with colistin in European agriculture in 2013) [4]. Recently, a series of policy-centred articles were published in a special issue of the peer-reviewed journal *Zoonoses and Public Health* entitled *Reducing antimicrobial usage in agriculture and aquaculture: beyond regulatory policy* [5-7]. The theme of this Organisation for Economic Co-operation and Development-sponsored special issue emerged out of the recognition that, in addition to the need for a strong regulatory framework on approval, sales, and use of antimicrobials, there exists the need for voluntary efforts to protect the efficacy of these precious resources into the future [5].



In human medical settings, such as hospitals, infectious disease specialists have long advocated for stewardship programmes to formalize restrictions on antimicrobial use and to establish codes of ethical practice for their use [8]. These codes of practice have evolved over time to be widely accepted in settings where decisions regarding necessary diagnostic procedures and compliance with formulary rules for specific therapeutic indications are centrally controlled. Rampant problems with nosocomial infections in intensive care units of hospitals have necessitated formalized stewardship programmes along the lines of those developed and promoted by the Infectious Diseases Society of America (IDSA) [9, 10]. Further, in the GAP, the WHO has proposed strengthening stewardship as a hallmark of judicious use practices in keeping with the moral imperative of protecting the effectiveness of antimicrobials into the future [11], and of extending the concept of stewardship of antimicrobials to animal agriculture.

Aligned with its classification of antimicrobials into critically important, highly important, and important for human medicine, the WHO strongly advocates the prioritization of protection for certain classes of drugs, such as 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins and the macrolides [12], as well as the invocation of an effective suite of risk-mitigation strategies to be implemented by its Member States. It is important to note that, while there has been some qualitative discussion of the need for stewardship guidelines in animal agriculture, including a vision of such by McDonald's Corporation and released in March 2015 [13], no formal guidelines for 'antimicrobial stewardship' exist for food-animal production. In examining the aspects of antimicrobial stewardship that can readily translate from human medicine to the production of animal medicine it seems likely that new ways of thinking are required to deal with major differences in prevention and control indications, and with moral imperatives to avoid animal illness from preventable bacterial conditions. Perhaps, most importantly, the risk posed by AMR bacteria to public health by spread through either the food supply or the environment adds a metric to agricultural stewardship that is not commonly considered in human medicine.

In the USA, several recent Food and Drug Administration (FDA) documents of note, the major purpose of which is to ensure the prudent approval and use of antimicrobials in veterinary medicine and animal agriculture, have been published (e.g., *Guidance for Industry (GFI) #152, #159, #209, and #213*; to a major extent, these consist of non-binding recommendations [1, 3, 14, 15]). Around the world, there exists a wide range of policies that governs the use of antimicrobials. Those factors that affect agricultural use range from legislative restrictions and the constraining economics of animal health and production to social norms and a sense of moral duty and trust [16, 17]. These additional factors can help explain varying usage patterns within any given set of regulations or economic conditions. Adding to this complexity are the various economies (monetary, political, and moral), as well as the various interests and concerns of a wide range of individuals and groups ranging from the pharmaceutical and agricultural production side, through to the consumer and health care advocacy sides [16, 18, 19]. Setting boundaries on the limits of discussion by framing the issue either as a strictly scientific one or else as an entirely economic one will alienate and marginalize persons and groups with legitimate moral and ethical concerns [19-22].

Less inclusive policy-decision processes are unlikely to result in sustainable and defensible long-term solutions. A blend of regulatory and voluntary approaches seems most likely to foster major advances in antimicrobial use policy in the coming decades, i.e. the need for rapid policy adoption and implementation may preclude a slower, more cumbersome consultative regulatory process from providing the necessary framework for an effective and timely response. Private sector partners, in the form of global food supply chain companies, can provide purchasing power pressures that can result in more rapid changes in agricultural antimicrobial use practices. Other voluntary approaches which engage multiple stakeholders and are suited to all areas of the world must be fully explored.

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## **Annex C5: Whole genome sequencing and antibiotic resistance surveillance: the power and the promise**

*Frank Aarestrup, Danish Technical Institute*

*Patrick McDermott, USA Food and Drug Administration*

In March 2015 the White House published its national strategy to combat antimicrobial resistant bacteria (1). In May 2015 the World Health Organization endorsed a global action plan to address antimicrobial resistance (2). Both list a number of important and urgent initiatives. Among the priorities of both initiatives is to strengthen national 'One Health' surveillance efforts and to increase the exchange of data between countries to identify emergent and novel resistance trends.

Since the advent of the antibiotic age, resistance has been identified in the laboratory based on the *in vitro* growth response of bacteria exposed to a range of drug concentrations. Much effort has been invested in standardizing these procedures. As commonplace as these methods are, they have many well-recognized limitations. In addition, efforts to implement the same standards for susceptibility testing and interpretation in different regions of the world have not been fully successful; different laboratories often test different antimicrobials. When systems are needed for 'One Health' approaches to surveillance, comparison between human clinical and veterinary laboratories is impeded further by the fact that different pathogens are under surveillance.

The high capacity and low costs of modern DNA sequencing technology has made it affordable to routinely determine the complete DNA sequence of a microorganism in a short amount of time. Along with an expanding set of options in bioinformatics software, it is becoming easier to analyse comprehensive genetic information from a single microorganism or a complex biological specimen. This represents a revolution in public health microbiology and the science of infectious diseases. In outbreak investigations, whole genome sequencing (WGS) is redefining cases and identifying sources with unprecedented precision, separating strains that previously could not be distinguished by traditional methods, while also capturing the range of resistance determinants, virulence factors and other pathogen traits (3). As comparable or superior information can be extracted from the genomic sequence, many traditional laboratory diagnostic and subtyping methods (serotyping, pulsed-field gel electrophoresis, PCR for resistance genes, etc.) that require dedicated reagents and specialized training are becoming obsolete.

For integrated AMR monitoring systems, such as DANMAP and NARMS, that are designed to understand resistant zoonotic bacteria in the farm-to-fork food supply, WGS is permitting, for the first time, the real-time monitoring of resistance alleles as they cross ecological boundaries. This includes genes conferring resistance to antimicrobials (including disinfectants) not tested phenotypically. In clinical medicine, the growing body of resistome data indicates that the presence of known resistance genes reliably identifies strains less likely to respond to anti-infective therapy, and that can be used to guide drug selection with a precision that is similar or even superior to that of traditional testing in some cases (4)(5)(6). In addition, as WGS data rapidly accumulate, WGS promises to aid drug discovery by identifying candidate strains for assaying new compounds and by providing a comprehensive catalog of genes as a reference for new cellular drug targets.

A promising feature of WGS is that it provides a single microbiological assay that can be readily applied to all organisms, resulting in uniform information that can be shared rapidly. This avoids the need to translate the results of different methods when evaluating resistant microbial hazards in different environments. The ability to quickly analyse and share microbiological surveillance information globally will become more automated. For global 'One Health' AMR surveillance to succeed, the development of international open-source and well-curated databases is needed to empower WGS data sharing on a global scale (7).

Lastly, WGS technologies applied to the metagenomic analysis of complex biological samples is on the horizon. As culture-independent diagnostics gain ascendancy in the market (8)(9), there will be fewer isolates available for direct characterization. Clinical and public health decision making will

become based more and more on genomic data extracted from complex mixtures of biological material. When long-read sequencing technologies become more accurate and affordable, meta-genomic surveillance will enable the effective quantification of resistance genes in all reservoirs examined.

Some form of phenotypic testing will always be needed as new mechanisms arise and the science of anti-infective pharmacology evolves. At the same time, there is a need for interpretive criteria for resistome profiling. This includes parameters for interpreting partial sequences from fragmented genomes, what thresholds to set for amino acid similarity among different gene families, how to evaluate multiple-copy genes, how to report multiple alleles conferring resistance to the same antimicrobial class, and what to make of silent genes.

Some of these questions can only be answered with research to evaluate the potency of agents against the range of genetic backgrounds in different pathogens. With the expectation that millions of microbial genomes will be published annually within the next few years, the diversity of genotypes in antibiotic-resistant strains will quickly become apparent. The availability of affordable WGS platforms, along with the pressing global threat of AMR, provides impetus for sharing real-time and comprehensive data on infectious agents and their resistance traits. This will lead to better patient management and improved global surveillance and control.

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## d. Capacity-building project update summaries

### The Americas

Title: Regional experience (presented by Enrique Perez, WHO AMRO)

In the Americas there is active participation in regional networking among countries on AMR. Critical information and technology are exchanged through these networks, common methodologies and protocols are developed, good practices are shared, regional markets are created for laboratory reagents, and resources (financial, human and material) are mobilized. Information and experiences regarding risk management have been shared. Peer learning and interaction is occurring within these collaborative networks, creating a regional network of practitioners who are in regular communication with one another. The three networks, Pulsenet Latin-American and Caribbean, GFN, and the Latin American Surveillance Network of Antimicrobial Resistance (RELVRA – the acronym is from the Spanish), cover all countries. Different sets of pathogens are under surveillance in health facilities and at the community level.

In the region, there has been WHO-GFN training in integrated surveillance systems in all countries, and integrated surveillance pilot projects and research projects for AMR in seven countries, including two active research projects in Peru and Costa Rica. The region has developed workshops to implement national programmes in three countries (Mexico, Brazil and Chile) and a workshop for six Caribbean countries. The WHONet information system is used, and the goal is to introduce WGS in the near future (there is currently a WGS pilot project in Argentina).

The objective of the Peruvian project has been to determine the AMR profile of *Enterobacteriaceae* isolated from faecal samples from children under two years of age and *E. coli* isolated from reservoirs (water, food and animal faeces) in a peri-urban community in Lima. In Costa Rica, the project is to determine the prevalence and characteristics of *Salmonella* in pigs for human consumption, through a cross-sectional study to generate information which will be useful in the design of strategies for the prevention and control of infections by this agent in both human and veterinary public health. Data from 2012-2013 are being collected from the region via a RELVRA-GFN call for data. There is an attempt being made to increase networking regarding animals and food.

### Bangladesh

Title: Do foodborne pathogens *Shigella* and *Salmonella* spp. share transferring antibiotic resistance with commensal *E. coli* in patients with diarrhea in Bangladesh?

PI: M. Aminul Islam, PhD, International Centre for Diarrhoeal Disease Research, Bangladesh

Mentor: A. Andremont

In Bangladesh, *Shigella* spp. and *Salmonella* spp. are the 2<sup>nd</sup> and 4<sup>th</sup> leading cause of bacterial diarrhoea respectively and are becoming more resistant to antimicrobials. There is also a lack of information on whether and how frequently there is horizontal transfer of resistance genes between commensal and enteropathogenic bacteria. The objectives of this project are to (1) estimate the burden of antibiotic-resistant commensal flora in stool samples of patients infected with *Shigella* spp. or *Salmonella* spp. and (2) determine if the same antibiotic resistance profiles/genes are shared by both commensal and pathogenic organisms, with a focus on ESBL and carbapenemase producers. The study site is at the International Centre for Diarrhoeal Disease Research (icddr,b) in Dhaka. This is the largest hospital in the country, serving over 200,000 patients per year and has state-of-the-art laboratories and research facilities. Stool samples included will be collected through hospital surveillance initiated on 15<sup>th</sup> May 2015 or be frozen samples from another recent study. *E. coli*, *Shigella* spp. and *Salmonella* spp. isolates will be tested for AMR by disc diffusion. The expected outcome is that *Shigella* spp. and *Salmonella* spp. will have the same resistance patterns as the *E. coli* from the same sources. To date, 12 *E. coli*-like organisms resistant to 3GC have been isolated from

stool samples positive for *Shigella* or *Salmonella* spp. If a significant proportion of *Shigella* or *Salmonella* spp. have AMR (and genes) similar with commensal *E. coli* are identified, a follow-up study to further clarify the *in vivo* transmission of resistance traits and the underlying mechanisms involved will be planned.

## Cameroon

Title: Molecular characterization of multiple-antimicrobial-resistant *Salmonella* from chickens and humans in Yaounde

PI: Antoinette Ngandjio, PhD, Head Service Hygiene and Environment (Microbiology), Centre Pasteur - Cameroon

This project took place in the context of increasing AMR work in Centre Pasteur in Cameroon (the National Reference Laboratory and Public Health Centre), such as GFN and other workshops. Between 2009-2012, laboratory-based surveillance of AMR in enteric bacteria allowed detection of multidrug-resistant (MDR) *Salmonella* *Stanleyville* in children, a *Salmonella* serotype commonly isolated in the environment.

The objective of the project was to study the phenotypic and genotypic characteristics of multiple-antimicrobial resistance in *Salmonella* spp. isolated from chickens and humans in Yaounde and to determine the genetic relationships among isolates. The results showed various *Salmonella* spp. serotypes in both chickens and humans, with a circulation of MDR strains. MDR *S. hadar*, mainly isolated in chickens, were simultaneously resistant to streptomycin, tetracycline and nalidixic acid. Human strains were mostly resistant to amoxicillin and cotrimoxazole, which are commonly used in clinics. Two *S. typhimurium* isolates from humans had a DT 104 phenotype. Resistance genes, such as *tetA*, *aadA1*, *strA*, *strB*, *sul1*, *sul2*, *dhfrA1*, and *blaTEM-1* were detected in MDR isolates. An atypical Class I integron with no *sul1* gene was detected, especially in *S. hadar*. PFGE of *S. enteritidis* revealed a close relationship between isolates from chicken and human origins. *S. hadar* isolates presented high diversity, as did *S. typhimurium*.

## Ghana

Title: Characterization and antibiotic susceptibility of *E. coli* (STEC) from street foods and raw beef in the Tamale metropolis of Ghana

PI: Courage Kosi Setsoafia Saba, PhD, Biotechnology Department, Faculty of Agriculture, University for Development Studies, Tamale, Ghana

Mentors: R. Irwin, J. Stelling

There is an overall lack of hygienic measures in street food stalls and during food transportation in this region. The goal of this project is to contribute data on resistance patterns of *E. coli* from selected street food and raw beef in Tamale, Ghana, and also to strengthen laboratory capacity on integrated surveillance of foodborne AMR. The objectives are (1) to isolate and identify *E. coli* and Shiga-Toxin-producing *E. coli* (STEC) from raw beef, macaroni and salad from street-food vendors and (2) to perform antibiotic susceptibility testing for all the isolated *E. coli* and STEC isolates from raw beef, macaroni and salad.

At the start of the project (April 2015), the methodology for sample collection and laboratory analyses were established and consumables and equipment sourced. Samples of raw beef, salad, and macaroni (n=100 for each) from enclosed, semi-enclosed, and open street-vendor stalls are being collected and tested by established STEC and AMR (disc diffusion) methods. Of the 30 samples so far collected from each sample type, 100% of raw beef was contaminated with *E. coli* (one STEC confirmed), 83% of salad, and 33% of macaroni, with some variability based on vendor enclosure type. In addition, 60% of the salad and macaroni vendors, and 100% of the meat vendors used their

bare hands. Resistance ranged from 2-21 of 30 beef samples, 0-19 of 25 salad samples, and 1-8 of 10 macaroni samples, depending on the antibiotic tested; multiple resistance was identified in 53%, 28%, and 20% of samples respectively. The next steps are to collect and test the rest of the samples.

## India

Title: Monitoring the Antimicrobial Resistance (AMR) profile of bacterial foodborne pathogens in humans, food animals and retail meat in India

PI: Sid Thacker, North Carolina State University College of Veterinary Medicine, USA

Mentor: P. McDermott

The main objective of this project is to conduct a field-based study to determine the prevalence and AMR profile of *Salmonella* spp., *Campylobacter* spp, *E. coli*, and *Enterococcus* spp. in humans, food animals, and retail meat in India, with the following specific objectives: (1) perform systematic review of existing data and information relevant to the project, collected by national agencies and researchers in India; (2) establish the prevalence of *Salmonella* spp., *Campylobacter* spp, *E. coli*, and *Enterococcus* spp. in humans, food animals, and retail meats in four distinct metropolitan regions of India; (3) determine the antimicrobial susceptibility testing of the above pathogens against a panel of different classes of antimicrobials; (4) conduct analysis to determine the attribution of antimicrobial use in humans and food animals on AMR development in the above pathogens. Representative human faecal samples will be collected from human hospitals in Chandigarh (Postgraduate Institute of Medical Education and Research) and Haldwani (Sushila Tiwari Government Medical College, Uttarakh) as part of the regular sampling done in hospitals in cases of diarrhoea due to potential enteric infections. Food animal and retail meat samples from adjoining regions will be collected by collaborators in the Indian Veterinary Research Institute in Izatnagar and the GB Pant University of Agriculture and Technology in Uttarakh.

In Year 1, percent positivity for *Campylobacter* or *Salmonella* spp. in goat, pig and chicken faecal and meat samples from Chandigarh in 2014 ranged from 0 (chicken meat-*Salmonella*) to 58% (chicken faecal sample-*Campylobacter*). In Pantnagar, *Campylobacter* spp. was predominantly isolated from chicken meat (13%) and goat meat (7.6%). No *Salmonella* spp.-positive samples were detected in goat meat, fish, carabeef, or human faecal samples, as well as minimal positivity in pork (1.5%) and chicken meat (2.4%). Similar numbers of total samples were tested in the two locations.

## East Africa: Kenya, Rwanda, and the United Republic of Tanzania

- United Republic of Tanzania: Occurrence of extended spectrum  $\beta$ -lactamases (ESBL) producing *Escherichia coli* in animals at slaughter-houses, Tanzania (PI: Ofred Jonas Mhongole, Mentors: S. Kariuki, J. Wagenaar)
- Rwanda: Extended spectrum Beta-Lactamase producing *E. coli* in patients from Rwanda (PI: Fidele Mahirane, Mentors: S. Kariuki, A. Andremont)
- Kenya: Training and mentorship in ESBL *E. coli* isolation, detection and characterization (co-PI: Sam Kariuki, R. Onsare)

The specific aims of these pilot projects are: (1) to conduct training on standardized microbiological methods for sample collection and on isolation and characterization of ESBL-producing *E. coli* from patient and animal samples; (2) to determine the prevalence of ESBL-producing *E. coli* from patients treated for diarrhoea and urinary tract infections, and animals slaughtered at abattoirs in selected representative sites; (3) to determine WGS of ESBL-producing *E. coli* and describe their variation.

In the United Republic of Tanzania, multidrug resistant *E. coli* has been identified as a problem in hospitals. The focus of current work is on aim (2), comparing human isolates to ESBL-producing *E. coli* in faecal swabs from the colon of carcasses after evisceration, on surfaces, and in raw meat at slaughter houses in Morogoro, Dodoma, and Dar es Salaam. In Rwanda, *E. coli* was isolated from 56 clinical samples from Kigali University Teaching Hospital, resistance was found in *E. coli*, particularly high to ampicillin. Sampling has been extended to six other sites. Rwanda and the United Republic of Tanzania participated in WHO-GFN-sponsored on-site laboratory and epidemiological training at the Kenya Medical Research Institute (KEMRI) in August 2014, and there is ongoing consultation and exchange of protocols among the PIs. In Kenya, a total of 22 ESBL *E. coli* from patients and four from chicken rectal swabs that were resistant to ceftriaxone were identified, and MICs determined. Steps are being taken to achieve aim (3) through training on molecular techniques.

## Lebanon

Title: Nationwide laboratory network in Lebanon for the surveillance, characterization and determination of phenotypic and genotypic antimicrobial resistance profiles of foodborne-diseases pathogens

PI: Ghassan M. Matar, PhD, Professor, Department of Experimental Pathology, Immunology and Microbiology, Laboratory Director of the Center for Infectious Diseases Research, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

Lebanon is taking major steps in food safety, but surveillance is lacking; therefore, there is insufficient information on foodborne pathogens in the diets of the population. The aim of this project is to establish a nationwide laboratory network in Lebanon for the characterization of foodborne diseases. This joint PulseNet and WHO-AGISAR project is aimed at (1) implementing a laboratory-based surveillance system for foodborne disease outbreaks in local laboratories across Lebanon, allowing for the detection of pathogens in a timely fashion; (2) identifying pathogens causing foodborne disease by time, place, type, subtype, and AMR patterns (to support and guide physicians in selecting appropriate treatment regimens); (3) directing the Ministry of Health to take the right preventive measures for foodborne diseases. In this project, bacteria isolated from clinical samples from hospitals and bacteria isolated at the LARI food laboratory are tested at the American University of Beirut's laboratory. Food has been found positive for *Campylobacter* spp., *Salmonella* spp., *Listeria* spp., and *E. coli*, and some isolates found resistant to common antimicrobials. For example, *Listeria* spp. cultured from seafood, cheese, and meats carried ampicillin, penicillin, oxacillin, and clindomycin resistance and *E. coli* carried resistance to ciprofloxacin. Clinical samples have been positive for *Salmonella* spp., *Shigella* spp., *Klebsiella pneumoniae*, and *E. coli*, and some isolates were found to be resistant to common antimicrobials, such as *E. coli* for ciprofloxacin and other third-generation cephalosporins. Some of the same sero/PFGE/antimicrobial-resistant types of *E. coli* and *Salmonella* spp. have been found in both clinical samples and food; the investigation of outbreaks has also identified similar organisms in clinical samples and food items. Key recommendations from this work include stricter application of existing laws for rational antimicrobial use, more laws related to antimicrobial use in animals, alternative treatments for sick animals, the treatment and control of drinking and utility water, and the decontamination of sewage.

## Uganda

Title: Movement pathways of antimicrobial agents and occurrence of Antimicrobial Resistance in humans, food producing animals and retail foods in Uganda

PI: Dr Francis Ejobi, Department of Biosecurity, Ecosystems and Veterinary Public Health, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda

Mentor: P. Fedorka-Cray



This two-year project's inception took place in March 2015. This is a country-level pilot farm-to-fork project focusing primarily on cattle and chickens, and includes samples from humans. The target foodborne pathogens and indicator organisms are *Salmonella* spp., *Campylobacter* spp., *E. coli* and *Enterococcus* spp. from each sample. This is a much-needed project, as current facilities are lacking in several areas of biosecurity and capacity support. This project will also elucidate the quantities of antimicrobial agents for both human and animal use imported over a five-year period (2009-13), and track their major movement pathways and geographic destinations in the country. The overall objective of this project is to determine the occurrence of AMR in bacterial isolates from humans, select food-producing animals, and retail animal-source foods in Uganda. The specific objectives are (1) to establish the trends in quantities of antimicrobial agents imported to Uganda in the period 2009-13; (2) to identify the major distribution pathways and geographic destinations of antimicrobial agents imported to Uganda; (3) to isolate *Salmonella* spp., *Campylobacter* spp., *E. coli* and *Enterococcus* spp. organisms in samples from: a) humans, b) cattle and broiler chicken, and c) retail chicken meat and beef in Uganda; and (4) to test the antimicrobial susceptibility of bacterial isolates stated in (3) above. Media and equipment procurement is challenging. To date, an assessment of antimicrobial imports is ongoing. The human sector is easy to track; however, the animal sector is proving to be challenging. A number of butcher shops were visited and whole muscle (beef) was procured and cultured for *Salmonella* spp., *E. coli* and *Enterococcus* spp. Presumptive positives have been identified for *E. coli*, *Enterococcus* spp. and *Salmonella* spp. Further characterization is ongoing.

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