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Better Training *for* Safer Food

TRAINING ON PREVENTION AND CONTROL OF ANTIMICROBIAL RESISTANCE IN THE CONTEXT OF AN OVERALL "ONE HEALTH" APPROACH TO PREVENTION AND CONTROL OF INFECTIONS AND REDUCING AMR

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PARTICIPANT'S DISSEMINATION TRAINING PACK

SYLLABUS AND ABSTRACTS

A project implemented by

AENOR with agencia española de medicamentos y productos sanitarios

CONTENTS

1. INTRODUCTION TO THE TRAINING PACK AND TRAINING MATERIALS

Dissemination of the EU legislation and best practices has been one of the key concerns of the Better Training for Safer Food Initiative. To achieve this aim, it is essential to reinforce the "train for trainer" approach, as a commitment reached by participants attending that will serve to further disseminate the information among colleagues.

To reinforce this objective, we have developed a set of materials and documents that help you in taking the knowledge gained, and share it once returning home, with other officers within your country, region, location. The more the knowledge is disseminated, the more it is known what other peers are doing in other parts of the UE and around the world, the greater the chance will be that you are all working in the same direction.

The materials produced for the training are the following:

- **Presentations made by the tutors**. These presentations are one of the basic elements for learning. They serve to make understand the situation and clarify main points to be highlighted. Sometimes they act as the skeleton of the lectures, some others as the introduction to exercises or results from brainstorming sessions. Each of them has been given a code, to serve you follow the order in which they have been delivered.
  You will be able to find the presentations in the BTSF Academy before the start of the course.

- **Working groups session's explanations**. During the different sessions that take place in a course, depending on the subject, the method used by the tutor can be working group discussions, brainstorming, case studies, etc. In those cases, an explanatory document is produced, giving the instructions of the tasks to do, and what the objective of the session is. They are also coded, for better follow the set of documents. They are, too, delivered in the BTSF Academy before the start of the course.

- **Documents produced in the group activities**: some of the outputs from the working group sessions will also be shared after the session.

- **Syllabus and abstracts of the sessions**: they both are provided in the present document. They serve as a route of the contents of the course and give you the meaning and contents of each session. They are made to serve you as guidance of each of the subjects tackled during the session.

- **Compilation of Questions and answers**: these are Q&A gathered during previous training sessions. It is a lively document, updated after each session. Some of the questions may merely repeat the contents of the session or serve to clarify concepts. It may help you to understand some of the ideas mentioned during the session. They are provided at the end of the present document.

2. RECOMMENDED ACTIONS FOR DISSEMINATION

To help you in disseminating the learnings of the training, we are listing hereby possible actions you may organise to share the information gained:

Informal Discussions: once arrived home, you may have meetings with your colleagues on specific issues or subjects linked to the project content. It could be the moment for exchanging your knowledge with them and disseminate your learning.

Distribution of learning materials received: perhaps you have an intranet in which you can upload the materials and/or latest news on audit subject.

Produced back to office notes/reports: it could be short news, articles on the key legislation and application in your country or region. It can also be detailed articles or extended notes on issues raised during the training session (i.e. best practices regarding the design, implementation and management of National Action Plans against AMR, common indicators or surveillance systems of antimicrobials in both human and veterinary sectors, etc.)

Dedicated presentations during other meetings: or organisation of short half-day courses for colleagues within your organisation or institution.

Dedicated meetings/briefings/blogs: these can be dissemination of the information in specialised forums. A web forum, specific group on the subject within your Competent Authority or linked subject to other Competent Authorities.

Workshops / Training as trainer: organisation of one-day awareness raising activities and workshops, inviting the Inspection authorities that are currently undertaking official controls, that will too in the long term understand the benefits of the training course, and what it means in the general improvement of official controls performance.

3. OBJECTIVES AND TO WHOM IT IS ADDRESSED

a. LEARNING OBJECTIVES

The general objective of the training is to provide training on the methods of prevention and control of antimicrobial resistance (AMR) in the human and veterinary sectors in order to achieve a holistic "one health" approach. The training aims to share the best practices regarding the design, implementation and management of National Action Plans in relation to the surveillance, monitoring and use of antimicrobials.

The purpose of the training will be to **provide a clear and harmonised understanding of specific objectives** of the training are to:

- Train professionals in the competent authorities to design, implement and manage adequate systems for control antimicrobial resistance;
- Promote the use of common indicators and systems to monitor and the surveillance of antimicrobials and antimicrobial resistance in both human and veterinary sectors;
- Ensure that the participants have a solid understanding of ways to collaborate and coordinate among the different national authorities as well as EU agencies involved in the fields of monitoring, surveillance, and of the use of antimicrobials and their resistances;
- Spread the knowledge about the implementation of the "one health" approach on the use of antimicrobials and AMR;
- The lectures, hands-on training, case-studies, videos and discussions shall bring the participants in a position where they are able to identify e.g. drivers, knowledge gaps and less/most efficient practices in their national systems of official control in the antimicrobial resistance field and therefore to the extent necessary be able to contribute to improve and reinforce as necessary in each of their countries.

b. AT THE END OF THE COURSE THE PARTICIPANTS WILL:

- Have the instruments and the understanding to collaborate and create communication channels to combat antimicrobial resistance among the different national authorities;
- Be aware of the legal requirements and the way to implant a "one health" approach on the use and resistance of antimicrobials;
- Be aware of the best practices to design, implement and manage National Action Plans regarding antimicrobial resistance in the human and veterinary medicine;
- Be familiar with the procedures of coordination with competent authorities in the next fields:
    - Public Health
    - Environment
    - Veterinary
    - Food production
- Be aware of how to use common indicators and systems to monitor and control AMR in all sectors;
- Be able to produce and compile comparable data for both human and veterinary sectors that can serve as basis for a better risk assessment that determines the best actions and measures for combating AMR.

c. TO WHOM THE TRAINING IS ADDRESSED

The training is mainly addressed to officials from National Competent Authorities involved, preferably at central level, in the monitoring, surveillance, reporting and control activities for the correct use of antimicrobials and the resistance to them in public health, veterinary / food and environmental sectors.

d. Pedagogical Approach

The training course consists of well-balanced theoretical and practical sessions. The training materials and contents have been specially designed to include the active participation of the attendants. The present syllabus contains the objective and summary of the subjects included in each course.

The pedagogical approach considered in the training takes into consideration:

- The goals of the courses and of the programme;
- The extension of the knowledge to deliver;
- The limiting duration of the training;
- The background knowledge and experience of the participants on the issues addressed during the training;
- The presence of the trainees during the course;
- The characteristics of the attendees.

The methodology used in the training sessions varies, depending on subject: lectures, study cases, individual thoughts working groups on best practices, brainstorming, etc. The main objective is to keep the participant attentive, interested, and participative.

To ensure that trainees are prepared prior to the training course, the programme and additional instructions are provided in advance. Besides, relevant information is published on the dedicated website: http://btsf-aenor.com

Description of the training course and structure

The course addresses the framework legislation and guidelines related, underlining those aspects of major concern from the theoretical and practical point of view.

The course has a duration of five half-days, Monday to Friday.

A variety of exercises, presentations, working groups and study cases have been put in place to ensure the exchange of experiences amongst the participants, the promotion of a holistic approach towards monitoring and surveillance systems of antimicrobial resistance, aiming the networking.

The program follows the enclosed scheme as shows the table below:

Day 1	Registration of participants Introduction of the course Pre-test **ANTIMICROBIAL RESISTANCE: GENERAL CONCEPTS and HISTORY** • Introduction to AMR: AMR occurrence factors and general concepts. The "One Health" approach. • 2017 EU AMR Action Plan • International initiatives in relation to AMR **EU LEGISLATIVE FRAMEWORK** • Overview of EU legal framework **GROUP BRAINSTORMING on the presentations of the day**

Day 2	Lectures, exercises, practical cases and questions and answers: **EU LEGISLATIVE FRAMEWORK** • Role of the EU Agencies in relation to the surveillance system on human and veterinary medicine • Joint interagency cooperation (AMEG, RONAFA, JIACRA, outcome indicators) **MONITORING AND REPORTING USE OF ANTIMICROBIALS (H/V)** • Harmonization of source of data, measure units and categories • Commission guidance documents on prudent use of antimicrobials • Practical approaches of MSs on prudent use of antimicrobials
Day 3	Lectures, exercises, practical cases and questions and answers: **MONITORING AND REPORTING OF ANTIMICROBIAL RESISTANCE (H/V)** • Monitoring and reporting of AMR in both sectors • Interpretation of results for human and animal breakpoints and cut off values • Case study of Methicillin- resistant *Staphylococcus aureus* (MRSA)
Day 4	Lectures, exercises, practical cases and questions and answers: **ROLE OF ENVIRONMENT IN SPREADING AMR** • Introduction to environmental risks and sources contributors to AMR • Relevance of AMR to environment and related regulators. Initiatives taken to address the problematic. • Identification of Knowledge gaps
Day 5	Lectures, practical cases and questions and answers: **JIACRA REPORT, COMMUNICATION PRACTICES, CONCLUSIONS AND CLOSING** • Results and conclusions of the JIACRA report • Group activity on why, how and resources to develop communication campaigns on prevention and use of antimicrobials • Summary of topics covered during the training session • Conclusions, post-test, online evaluation, and final speeches

4. SUMMARY OF PRESENTATIONS, EXERCISES

➢ OPENING AND INTRODUCTION TO THE TRAINING

Registration, Opening and Welcome:

- Opening and welcome address
- Presentation of the "Better Training for Safer Food" Programme
- Presentation of the BTSF Academy

Course Introduction:

- Course topics, objectives, and activities
- Presentation of the team of tutors

Introduction participants:

- Brief introduction of participants: participants' professional background, role, institution, expectations from the workshop etc.

➢ PRE- TRAINING TEST

Interactive online voting system

Pre-training knowledge Self-Assessment test

- Measure the participants' knowledge at the beginning of the training

Dissemination action planning

- Emphasise the importance of dissemination and discuss participant's plans for dissemination;
- Identify key topics which each delegate considers most important for dissemination.

ANTIMICROBIAL RESISTANCE: GENERAL CONCEPTS AND HISTORY

➢ S1 – INTRODUCTION TO AMR

Brief icebreaking with participants as introductory to the course – interaction with participants, making questions to the audience and providing answers at the same time on the occurrence factor of AMR:

- Biology, distribution
- Survey procedures and requirements

The resistance is a natural biological phenomenon but is amplified by a variety of factors that is accelerating and spreading resistant microorganisms:

- Inappropriate use of therapeutic antimicrobials in human and veterinary medicine
- The use of antimicrobials for non-therapeutic purposes
- The pollution of the environment by antimicrobials
- Development of resistance
- Few investments in the development of new antibiotics
- Increasing global trade and travel favours spread of antimicrobial resistance between countries and regions

The brainstorming will aim at indicating the need for a holistic approach and the need to address One Health Approach that aim at:

1. Reducing the risk of developing AMR in humans from the use of antimicrobials both in humans and animals, and the need to make cleared diagnosis to determine the need for antimicrobials;
2. Preventing microbial infections, putting in place good hygiene and manipulation practices;
3. Developing effective antimicrobial, or alternative treatments;
4. Joining forces at international level to contain the risks for spreading AMR;
5. Strengthen research to develop innovative means to fight AMR.

➢ S2 – 2017 EU AMR Action Plan

Under the Dutch presidency of the Council of the European Union in 2016, Council Conclusions on the next steps under a One Health approach to combat antimicrobial resistance were unanimously adopted by the Member States. The Council Conclusions called upon the Commission and the Member States to develop a new and comprehensive EU Action Plan on Antimicrobial Resistance, taking into account the evaluation of the current Action Plan, the outcome of the EU Ministerial One Health Conference on AMR of 10 February 2016 and the WHO Global Action Plan.

The European Commission organized an open public consultation aimed to gather detailed views and opinions from stakeholders for the new EU action plan. The consultation took place during the period 27 January 2017 - 28 April 2017. The EC received responses of 421 citizens and 163 stakeholders.

The new EU One Health Action plan against AMR was published in June 2017. The plan built up on the outcome of the evaluation, the Council Conclusions adopted in June 2016 and the outcome of the public consultation. The action plan includes key objectives built on 3 strategic pillars:

- **Making the EU a best-practice region on AMR**
- **Boosting research, development, and innovation against AMR**
- **Shaping the global agenda on AMR**

There are several actions that have been developed under the 3 pillars. A progress report is regularly updated by the European Commission and available at
https://ec.europa.eu/health/amr/sites/amr/files/amr_2018-2022_actionplan_progressreport_en.pdf

➢ S3 – Relevant international initiatives

UNGA

During a high-level meeting convened by the President of the UN General Assembly (UNGA) on the side lines of the 71st General Debate, UN Member States adopted a political declaration on antimicrobial resistance (AMR). They also called for action, and outlined initiatives carried out nationally to address AMR.

Participants highlighted several issues that need further attention in order to address AMR;

- ✓ Using antibiotics and antimicrobials “as necessary only”
- ✓ ensuring equitability of access and affordability of medicine and the use of a “One Health” approach;

- ✓ enhancing collaboration and coordination across levels and sectors;
- ✓ increasing investments in research and development;
- ✓ enacting stronger systems to monitor drug-resistant infections;
- ✓ strengthening AMR regulation;
- ✓ promoting best practices;
- ✓ fostering innovative approaches using alternatives to antimicrobials.

The resolution set up an Interagency Consultation Group (IACG). In April 2019, the IACG handed over its report to the Secretary-General of the United Nations. As part of the recommendations on accountability and governance, the IACG recommended the urgent establishment of a One Health Global Leaders Group on Antimicrobial Resistance, supported by a Joint Secretariat managed by the Tripartite agencies (FAO, OIE and WHO) to provide advocacy and advisory functions to ensure that action is taken to address the challenges of AMR:

FAO/OIE/WHO Tripartite Collaboration on AMR

The WHO, the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) speak with one voice and take collective action to minimize the emergence and spread of AMR.

The aim is to:

- ✓ Ensure that antimicrobial agents continue to be effective and useful to cure diseases in humans and animals
- ✓ Promote prudent and responsible use of antimicrobial agents
- ✓ Ensure global access to medicines of good quality

WHO

- Global Action Plan (GAP) on Antimicrobial Resistance developed by the World Health Organisation (WHO), the WHO with the active contributions of FAO and OIE in the spirit of “One Health” unanimously adopted in May 2015 by the 68th World Health Assembly, calling all Member States of the World Health Organisation to put in place national action plans against AMR by mid-2017.
- The adoption of the GAP reflects the global consensus on the need for action, emphasizing the paramount significance of achieving the five strategic objectives of the WHO GAP.

  WHO-Europe regional office: on-going bilateral contacts and join actions such as participation in workshops and training activities.
- Other activities of WHO related to AMR are:
  a. The Global Antimicrobial Resistance Surveillance System (GLASS) is being developed to support the global action plan on antimicrobial resistance. The aim is to support global surveillance and research in order to strengthen the evidence base on antimicrobial resistance (AMR) and help informing decision-making and drive national, regional, and global actions.
  b. Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was established in December 2008 to support WHO's effort to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animal.

FAO

- FAO action plan on Antimicrobial Resistance 2016-2020, and its collaboration with WHO and OIE on scientific advice on AMR.

- FAO in its Resolution on Antimicrobial Resistance adopted in June 2015 by the 39th Conference of the FAO, states that Antimicrobial medicines play a critical role in the treatment of diseases of farm animals and plants. Their use is essential to food security, to our well-being, and to animal welfare. However, the misuse of these drugs, associated with the emergence and spread of antimicrobial-resistant micro-organisms, places everyone at great risk.

- The four key areas of the action plan are:

  - Improving awareness of AMR issues among farmers and producers, veterinary professionals and authorities, policymakers, and food consumers;
  - Building national capacities for surveillance and monitoring of AMR and antimicrobial use (AMU) in food and agriculture;
  - Strengthening governance related to AMU and AMR in food and agriculture;
  - Promoting good practices in food and agricultural systems and the prudent use of antimicrobials;

OIE

- The OIE has adopted the Resolution combating Antimicrobial Resistance and promoting the prudent use of antimicrobial agents in animals in May 2015 at the World Assembly of Delegates.
- The OIE has addressed the issue of AMR in the Terrestrial Animal Health Code (Chapter 6.6, 6.7, 6.8, 6.9 and 6.10) on the health Code of Aquatic Animals.
- OIE is also working on the “Ad hoc group” on AMR that was established to monitor the consumption of antimicrobials. The OIE has also published guidance on the use of antimicrobials in the health Code of Aquatic Animals.
- The of the OIE Global Conference on the Responsible and Prudent Use of Antimicrobial Agents for Animals held in March 2013 in Paris, France; Recommended the Member States:

  - To collect harmonised quantitative data on the use of antimicrobial agents in animals with the view to establish a global database and submit them to the OIE.

  - To contribute to the OIE initiative to collect data on the antimicrobial agents used in food-producing animals (including through medicated feed) with the ultimate aim of creating a global database hosted by the OIE) and submit it to the OIE Member Countries.

  Through the unanimous adoption of Resolution No. 261 during the OIE General Session in May 2015, the OIE was officially mandated to gather data on the use of antimicrobial agents in animals worldwide and to create a global database for monitoring the use of antimicrobial agents in compliance with Chapters 6.8. of the Terrestrial Animal Health Code (Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals) and 6.3. of the Aquatic Animal Health Code (Monitoring of the quantities and usage patterns of antimicrobial agents used in aquatic animals).

- The OIE has published the first annual report on the global use of antimicrobial agents in animals in December 2016

Relevant Codex Alimentarius codes and guideline

The Codex Alimentarius has developed the following documents on Antimicrobial resistance:

- Code of Practice to Minimise and Contain Antimicrobial Resistance (CAC/RCP 61-2005);
- Guidelines on Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77-2011) have been adopted and applied;
- The 39th session of the Codex Alimentarius Commission (Rome, June 2016) agreed to:
  - Establish an Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance (TFAMR), with the purpose of revise the Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005) and proposed new work on a Guidance on integrated surveillance of Antimicrobial resistance.
  - A physical working group, open to all Members and Observers, was held in London, from 29 November to 2 December 2016 to undertake the tasks assigned to it at the 39th session of the Codex Alimentarius Commission and draft the Terms of Reference for the Task Force AMR. The next meeting of the Task Force will be in 2017.

The 40th Session of the CAC adopted the ToR and established 2 electronic working groups (EWG) to develop:

a. Revision Code of Practice to minimise and contain AMR (CAC/RCP 61/2005)
   Chair: USA and co-chairs: Kenya, UK, China
b. New Guidelines on Integrated Surveillance of AMR in the food chain
   Chair: The Netherlands and co-chairs: Chili, New Zealand and China

The 7th Meeting of the Task Force AMR took place in Korea 8 December 2019.

Global Health Security Agenda

GHSA was launched in February 2014.

GHSA acknowledges the essential need for a multilateral and multi-sectorial approach to strengthen both the global capacity and nations' capacity to prevent, detect, and respond to infectious diseases threats whether naturally occurring, deliberate, or accidental – capacity that once established would mitigate the devastating effects of Ebola, MERS, other highly pathogenic infectious diseases, and bioterrorism events.

The vision of GHSA is a world safe and secure from global health threats posed by infectious diseases – where their impact of naturally occurring outbreaks and accidental or intentional releases of dangerous pathogens can be prevented or mitigated, rapidly detect and transparently report outbreaks when they occur, and employ an interconnected global network that can respond effectively to limit the spread of infectious disease outbreaks in humans and animals, mitigate human suffering and the loss of human life, and reduce economic impact.

Within the GHSA it is foreseen 4 preventive measures, 4 actions for their detection and 3 measures to respond. The Action Package Prevent num. 1 is to fight against antimicrobial resistance, with a 5 years target, promoting three main actions: a) to confirm each country has a national plan to combat AMR; b) to strengthen the capacity of the national and international laboratories based on the use of agreed international standards, and; c) improve the conservation of the existing antimicrobials, and collaborate in the development of new ones, alternative treatments, implementing preventive measures and rapid diagnostics.

It is considered that the global health security is a shared responsibility that cannot be achieved by a single actor or sector of government. Its success depends upon collaboration among the health, security, environment, and agriculture sectors.

Since then, membership in GHSA has grown to include almost 50 countries, each committed to leading or contributing to one or more Action Packages. GHSA is coordinated by a multilateral Steering Group of 10 countries: Canada, Chile, Finland, India, Indonesia, Italy, Kenya, Kingdom of Saudi Arabia, Republic of Korea, and the United States. WHO, FAO, OIE and other international organizations serve as advisors to this Steering Group.

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)

In response to the increasing threat of antimicrobial resistance, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) between EU and US was established in 2009, with the aim to identify urgent AMR issues and propose recommendations for future cooperation. 17 measures have been identified in three key areas: 1) Appropriate therapeutic use in human and veterinary medicine 2) Prevention of drug-resistant infections; 3) Strategies for improving the pipeline of new antimicrobial drugs. Many of these measures stress the need to develop common indicators further harmonise data collection and collaboration from both veterinary and human sector.

In 2014 the taskforce decided to continue with 15 recommendations, retiring two, and created one new recommendation for collaboration from 2014-2016. In October 2015 the TATFAR held an in-person meeting in Luxembourg and extended the collaboration for an additional five years (2016-2020).

CDC currently provides the secretariat for the taskforce and publishes documents relating to the work of the taskforce on this website. The European Centre for Disease Prevention and Control (ECDC) provided the secretariat from 2009-2013.

Other multinational activities: G7, G20 and OECD work

Other EU initiatives and bilateral agreements:

- Standards and measures for tackling AMR in trade agreements;
- Bilateral relations and international Research agenda.

EU LEGISLATIVE FRAMEWORK

➢ S4 – EU LEGISLATION

This presentation aims at highlighting the main legislative framework in relation to AMR and the use of antimicrobials for both human and veterinary field. The level of development of harmonised legislation for each sector is different, being more developed in the veterinary field that in the human sector. In addition, non-binding documents exist e.g. guidelines and are recommended to be used by Member States.

The EU legislative framework in the human sector includes:

- Directive 2001/83/EC of the EP and Council (6 November 2001) on **medicinal products for human use.**
- Regulation (EC) No 726/2004 of the EP and Council (31 March 2004) laying down Community **procedures for the authorisation and supervision of medicinal products** for human and veterinary use and establishing a **European Medicines Agency** (revision on-going, provisions on vet. medicines proposed to be moved to a new Regulation).
- Decision No 1082/2013/EU of the EP and Council (22 Oct 2013) on **serious cross-border threats to health.**

EU legislation in the veterinary sector

The current legal framework for veterinary medicinal products and medicated feed (Directive 2001/82/EC, Regulation, (EC) No 726/2004 and Directive 90/167/EEC have been replaced by Regulation (EU) 2019/6 on veterinary medicinal products (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32019R0006) and Regulation (EU) 2019/4 on medicated feed. The new regulations will apply from 28 January 2022. As part of their implementation, the two Regulations require the European Commission to adopt delegated and implementing acts. This new legislation contains a comprehensive set of concrete provisions addressing the public and animal health risk of AMR. These provisions include a reinforced ban on the use of antimicrobials to promote growth or increase yield in animals; a ban on the preventive use of antibiotics in groups of animals; a ban on the preventive use of antimicrobials via medicated feed; the possibility to reserve certain antimicrobials for humans only; restrictions on metaphylactic use and compulsory collection of data on sales and use of antimicrobials. In addition, given the international dimension of AMR, the ban on using antimicrobials as growth promoters and the restrictions in using those antimicrobials designated in the EU as reserved for human use will also apply to animals or products of animal origin intended for import from Third Countries to the EU.

Other Regulations

- Regulation (EC) No 470/2009 on Community procedures for the establishment of **residue limits** of pharmacologically active substances in **foodstuffs** of animal origin

Food – Zoonotic Agents

- Directive 2003/99/EC on the **monitoring of zoonoses** and zoonotic agents
- Commission Implementing Decision 2013/652/EU on the **monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria, to be revised in 2020 for application in 2021:**
    - Mandate to EFSA for technical advice sent in 2017
    - EFSA opinion published in 2019
    - Adoption of the new legislation in 2020, to apply in 2021
- Now there is a new **decision Commission Implementing Decision (EU) 2020/1729** (repealing implementing decision 2013/652) on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria has been adopted in November 2020.

The new legal **framework on Animal Health** is based on “Prevention is better than cure”

- Animal Health Law: Regulation (EU) 2016/429 of the EP and the Council (9 March 2016) on **transmissible animal diseases** in its delegated and implementing acts

It has a p**reventive** driven **approach** by the improvement animal health and biosecurity measures, good farming practices, by establishing clear **responsibility** for all players for animal health, between the operators, that have to ensure the level of animal health and biosecurity, the veterinarians, by preventing the spreading of pathogens and raising awareness, and the Competent Authorities, by protecting the animal health, human health and environment.

The new legislation also prioritises the EU intervention, by identifying the resistant pathogens: “disease agents”, by establishing disease preventive and control measures may apply (surveillance, eradication…), and implementing legal basis to monitor AMR in animal pathogens.

The use of antimicrobials in animals needs to conform to EU and national rules and, in particular, must follow the authorised Summary of Product Characteristics (SPC).

The SPC contains information on the conditions for using a veterinary medicinal product as developed during the risk assessment process. In accordance with Article 14 of Directive 2001/82/EC and Article

31 of Regulation (EC) No 726/2004, any application for a marketing authorisation must be accompanied by the SPC which is proposed by the applicant, and assessed and, if necessary, amended by the competent authority.

Some examples of CVMP referrals and positive opinions can be found in the following articles:

Article 35

- **Lincomycin & spectinomycin combinations** administered orally to pigs and poultry / indications, dosing regimens, WPs, adopted at May meeting
- **Colistin in combination with other antimicrobials** for oral administration / follow up to AMEG advice on colistin (2013), adopted at April meeting

Article 34

- **Denagard 45% oral granules** (tiamulin)
- **Girolan-Apralan** (Apramycin)

These referrals under directive 2001/82/EC have their correspondence in the new regulation:

Directive 2001/82/EC	Regulation 2019/6
Article 33 MRP/DCP referral	Article 54 Review procedure
Article 34 SPC harmonisation	Article 69 SPC harmonisation
Article 35 Union interest referral	Article 82 Union interest referral
Article 78 Urgent Union procedure	Article 130 Suspending, revoking, or varying the terms, of MAs

S5 – EU AGENCIES AND THEIR COOPERATION

The monitoring and surveillance of AMR and antimicrobial consumption are currently coordinated by three EU agencies which operate in the areas of human health, food safety and medicinal products: European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), and the European Medicines Agency (EMA). Furthermore new agency HERA (European Health Emergency Preparedness and Response Authority) has been established recently.

The **European Centre for Disease Prevention and Control (ECDC)** has a mandate to gather and analyse data and information on emerging public health threats and developments for the purpose of protecting public health in the European Community according to Regulation 851/2004/EC. The collection of data related to antimicrobial resistance and antimicrobial consumption is included as part of the European Surveillance System (TESSy) through several networks.

Regarding the occurrence of resistance in humans, there are two surveillance networks: the European Antimicrobial Resistance Surveillance Network (EARS-Net); and the Food and Waterborne Diseases and Zoonoses Network (FWD-Net).

- **The European Antimicrobial Resistance Surveillance Network (EARS-Net)**

The European Antimicrobial Resistance Surveillance System (EARSS) project was started in 1999 and under coordination by the Dutch National Institute for Public Health and the Environment (RIVM) it grew into a network of national networks with continuous yearly data reporting. In January 2010, the coordination of this network was transferred to the European Centre for Disease Prevention and Control (ECDC) and is currently maintained as a continuous program named EARS-Net. To ensure sustainability and government support of this network Ministries of Health (MoH) of every Member state (MS) have appointed an AMR Focal Point who leads the national AMR network and collaborates with EARS-Net. EARS-Net provides guidance on AMR surveillance methodology, collects and analyses resistance data from human isolates (blood and cerebrospinal fluid samples), and provides external quality assessment for susceptibility testing.

- **Food and Waterborne Diseases and Zoonoses Network (FWD-Net)**

EU-funded dedicated surveillance network for enteric pathogens – *Salmonella, E. coli and Campylobacter* (Enter-net) was transferred to ECDC from the Health Protection Agency in the United Kingdom in 2007. Subsequently, the scope of the disease network was broadened to cover 21 food - and waterborne diseases and zoonoses, and nomination of disease experts followed the ECDC policy on Coordinating Competent Body (CCB).

FWD-Net is coordinated by ECDC with the support of a coordination committee (CC) consisting of representatives from the EU Member States. The committee advises ECDC on ways to strengthen and improve FWD surveillance and prevention in Europe and reviews technical documents relevant to the network.

Regarding consumption of antimicrobials in humans there are two surveillance networks: the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), and the Healthcare-Associated Infections Surveillance Network (HAI-Net) , coordinated by ECDC, responsible for the European point prevalence survey of HAI and antimicrobial use in acute care hospitals, the European surveillance of surgical site infections, the European surveillance of HAI in intensive care units and the repeated prevalence surveys of HAI and antimicrobial use in European long-term care facilities.

- **The European Surveillance of Antimicrobial Consumption Network (ESAC-Net)**

The European Surveillance of Antimicrobial Consumption (ESAC) project was started in 2001 and was coordinated by the University of Antwerp until July 2011 when it was transferred to the European Centre for Disease Prevention and Control (ECDC) and maintained as a continuous program named ESAC-Net. In order to ensure sustainability and government support of this network Ministries of Health (MoH) of every Member state (MS) have appointed an Antimicrobial consumption (AC) Focal Point who is responsible for national data collection and collaboration with ESAC-Net. ESAC-Net provides guidance on AC surveillance methodology, collects and analyses data on antimicrobial consumption from EU and EEA/EFTA countries, separately in the ambulatory and the hospital sector. The data sources include national sales and reimbursement data, and data are collected at national and sub-national level based on the NUTS classification. ESAC-Net provides data that can be used as indicators of rational antimicrobial prescribing.

- **The Healthcare-Associated Infections Surveillance Network (HAI-Net)**

The former ESAC subprojects that collected more detailed data on antimicrobial use in hospitals and in long-term care facilities are continued by ECDC within the activities of HAI-Net. These activities include:

- ECDC-coordinated, Europe-wide point prevalence survey of healthcare-associated infections and antimicrobial use;
- ECDC-coordinated HALT-2 project that collects data antimicrobial use in long-term care facilities.

Based on Article 33 in Regulation (EC) 178/2002, the **European Food Safety Authority (EFSA)** is responsible for examining data on zoonoses, antimicrobial resistance and food-borne outbreaks collected from the MMSS.
EFSA coordinates:

- **The Scientific Network for Zoonosis Monitoring Data**

This network collects and analysis data on antimicrobial resistance in zoonotic and commensal indicator bacteria from food, food-producing animals and food derived thereof in accordance with the Decision 2013/652/EU.

Regarding antimicrobial resistance data a specific EU Summary Report on antimicrobial resistance is produced in collaboration with ECDC on a yearly basis. It includes data related to the occurrence of antimicrobial resistance both in isolates from healthy animals and foodstuffs and in isolates from human cases of diseases, derived from the surveillance network FWD-Net coordinated by ECDC.

The **European Medicines Agency (EMA)** plays a vital role in the global response to the threat of antimicrobial resistance, by:

- supporting the development of new medicines and treatment approaches;
- promoting responsible use of existing antibiotics;
- Collecting antimicrobial consumption data to guide policy and research.

EMA supports a 'One Health' approach, promoting a close and integrated cooperation between the human and veterinary fields. As an example, the antimicrobial expert group (AMEG), where experts proposed by the Committee for Veterinary Medicinal Products (CVMP), the Committee for Human Medicinal Products (CHMP), as well as the CVMP Antimicrobials Working Party and the CHMP Infectious Diseases Working Party closely work together with other EU agencies.

EMA has also established standardised units of measurement for reporting antimicrobial consumption in specific animal species, called the ‘defined daily dose’ and ‘defined course dose’ for animals. This initiative aims to support the harmonisation and standardisation of reporting data on veterinary antimicrobial consumption collected at European level.

Ultimately, this is expected to enhance understanding of the development and occurrence of antimicrobial resistance and the impact of measures to counteract antimicrobial resistance.

The main responsibility of EMA is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. Within this body, work the following networks:

- **The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project**

ESVAC project was launched by the agency in September 2009, following a request from the European Commission (EC) to develop a harmonised approach to the collection and reporting of data on the consumption of antimicrobial agents in animals from the Member States (MSs). Thanks to coordination and voluntarily providing the sales data from EU/EEA MSs it was achieved collection of the data from 31 EU/EEA MSs.

EMA has also established standardised units of measurement for reporting antimicrobial consumption in specific animal species, called the ‘defined daily dose’ and ‘defined course dose’ for animals. This initiative aims to support the harmonisation and standardisation of reporting data on veterinary antimicrobial consumption collected at European level.

New EC legislation on Veterinary Medicine

The new Veterinary Medicine Regulations (regulation (EU) 2019/6) was published in January 2019 and there was stipulated many delegated and implementing acts related to antimicrobials. EMA, in some instances in cooperation with EFSA and ECDC was asked by the European Commission to provide scientific and technical recommendations serving as the background of setting these implementing and delegated acts, as part of the implementation of the new regulations. Further details can be found here: https://www.ema.europa.eu/en/veterinary-regulatory/overview/implementation-new-veterinary-medicines-regulation

The Agencies were asked to provide advice in items such as:

1) Article 57 of the Veterinary Medicine Regulation (VMR) states that **"Member states shall collect relevant and comparable data on the volume of sales and on the use of antimicrobial medicinal products used in animals".**

   EMA received a request to provide advice and, as a result, the Committee for Medicinal Products for Veterinary Use (CVMP) formed an expert group to prepare a scientific report. The group was composed of eight experts selected from the European network of experts, based on recommendations from the national competent authorities and two Agency staff members with expertise on collection of data on antimicrobial consumption in animals.

2) Article 37 of the VMR covers the designation of antimicrobials that should be reserved for human use to preserve the efficacy of those antimicrobials (delegated ct (definition of criteria for designation) and implementing act (list of exact antimicrobials).

   EMA received a request for advice and the CVMP formed an expert group including 8 network experts, of which 2 had expertise on human infectious disease, 1 expert nominated by EFSA, and 1 expert nominated by ECDC.

3) Article 106 covers measures rules on appropriate measures to ensure the effective and safe use of veterinary medicinal products authorised and prescribed for oral administration via routes other than medicated feed, such as mixing of water for drinking or manual mixing into feed.

4) Article 107 and implementing act defining list of antimicrobials not to be used outside of the terms of marketing authorisation or used subject to certain conditions.

Following to the information provided to participants during the session a brief explanation on the different initiatives promoted by the European Commission to produce joint reports that have produced interesting results in relation to the need to promote further the harmonization of data obtained from the different networks, EMA, ECDC and EFSA.

The presentation of the results from these reports will generate a debate by the tutors in relation to how this further harmonisation can be possible: Comparative analysis of both veterinary and human data and in between countries: Practical approaches of MMSS on the collection of data.

Interagency cooperation

The European Commission requested scientific advice from the EMA in April 2013 on the impact of the use of antibiotics in animals on public health and animal health and measures to manage the possible risk to humans.

EMA convened the **Antimicrobial Advice Ad Hoc Expert Group (AMEG)** to prepare the advice.

The AMEG is composed of representatives and experts from the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) and Committee for Medicinal Products for Human Use (CHMP) as well as the CVMP Antimicrobials Working Party and the CHMP Infectious Diseases Working Party, from the European Food Safety Authority (EFSA), the European Centre for Disease Prevention and Control

(ECDC) and the Joint Interagency Antimicrobial Consumption and Resistance Analysis Report (JIACRA).

The request had to answer four questions:

- **Question 1**: The Commission's first question concerned the use in animals of 'old' antibiotics or new antibiotics belonging to 'old' classes of antibiotics that have been re-introduced or newly used to treat multidrug-resistant infections, with a particular focus on colistin and tigecycline, two antibiotics that have become life-saving treatments for patients infected by multidrug-resistant bacteria.

In response, the AMEG concluded that maintaining the use of colistin in animals was appropriate, with additional monitoring of off-label use and restrictions on indications to therapy or metaphylaxis and removing all indications for prophylactic use to minimise any potential risk associated with a broader use. After recognising of plasmid mediated resistance: *mcr* genes, advice was updated (2016) and referral procedure was carried out to modify authorisations and restrict the condition of use (specifying indication to non-invasive *E. coli* only, max 7 days treatment); glycylcycline use in animals should remain restricted, due to evidence from human use that tigecycline resistance emerges rapidly.

- **Question 2**: Categorisation of the WHO's critically important antimicrobials according to the risk that their use in animals in the EU poses to human health.
- **Question 3**: Advice on the potential impact of authorising new antimicrobials for use in animals on the treatment of resistant bacteria in humans, if their use should be restricted.
- **Question 4**: Advice on risk management measures for the use of CIAs in animals.

Regarding these questions, EMA's advice included:

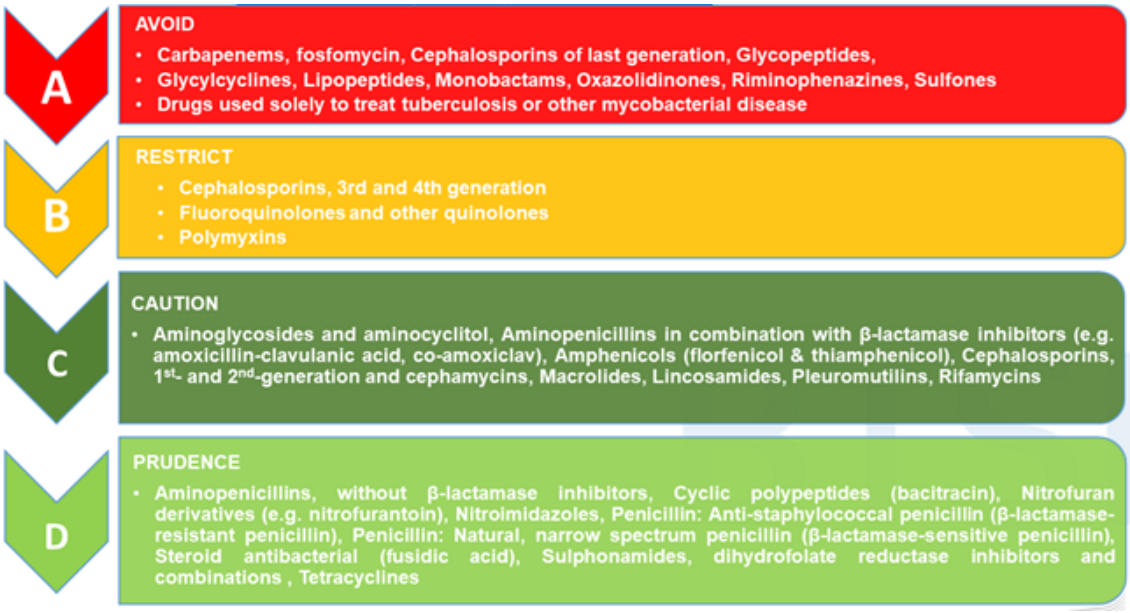
- Strengthening antimicrobial resistance risk assessment in the evaluation of marketing-authorisation applications for new antimicrobials, particularly if intended for use in food-producing animals;
- Improved reporting on "off-label" use in animals of antimicrobials authorised in humans for use against multi-drug resistant infections;
- Further risk profiling of certain classes of antibiotics with respect to their use in animals.

In 2017 AMEG based on a mandate from EC, started to update the AMEG categorisation of antimicrobials. The main differences between this and the original advice are:

- The list of antimicrobials has been expanded to include antimicrobials considered by the World Health Organisation to be considered Highly Important and Important (rather than just those considered Critically Important as in the original report)
- Categorisation is included for aminoglycosides and extended spectrum penicillin.
- As before, the antimicrobials are ranked according to importance in human medicine and the likelihood and consequences of AMR transfer from treated animals to humans. However, the criteria have been refined, with specific consideration given to mechanisms where a single gene confers multi-resistance, and the availability of alternative antimicrobials in veterinary medicine with lower AMR risk is now also considered.

Final version was published on 12th Dec 2019 and infographics in national languages published on 28th Jan 2020:
https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals

The main difference is that antimicrobials are now ranked into 4 categories (A to D) replacing categories 1 to 3. This additional "intermediate" category allows for greater distinction in raking between substances and prevents too many antimicrobials being placed in the highest category.



Category	Recommendation
A "Avoid" (not approved in veterinary medicine)	Provided no MRLs are established, these substances can only be used under the cascade in Companion Animals.
B "Restrict" (risk to public health from veterinary use need to be mitigated with specific restrictions)	Should only be used in veterinary medicine when there is no alternative from category C or D.
C "Caution" (higher AMR risk to human and/or animal health compared to category D)	Should only be used if a substance in category D would not be effective.
D "Prudence"	Responsible use principles apply unnecessary use and unnecessarily long treatment periods should be avoided and group treatments restricted to situations where individual treatment is not feasible.

Unlike category B, for both categories C and D there are alternatives available in human medicine for given indications. The main differences are category C is considered higher risk as:

- There are few or no alternatives for their given indication in veterinary medicine **and/or**
- The antimicrobial selects for resistance to a substance in category A through specific multi-resistance genes

The aim of the AMEG guidelines is to balance human and animal health needs and public health considerations. It can be used to prioritise AMR risk analysis work and as a tool for preparing local treatment guidelines and assist decision making under the cascade.

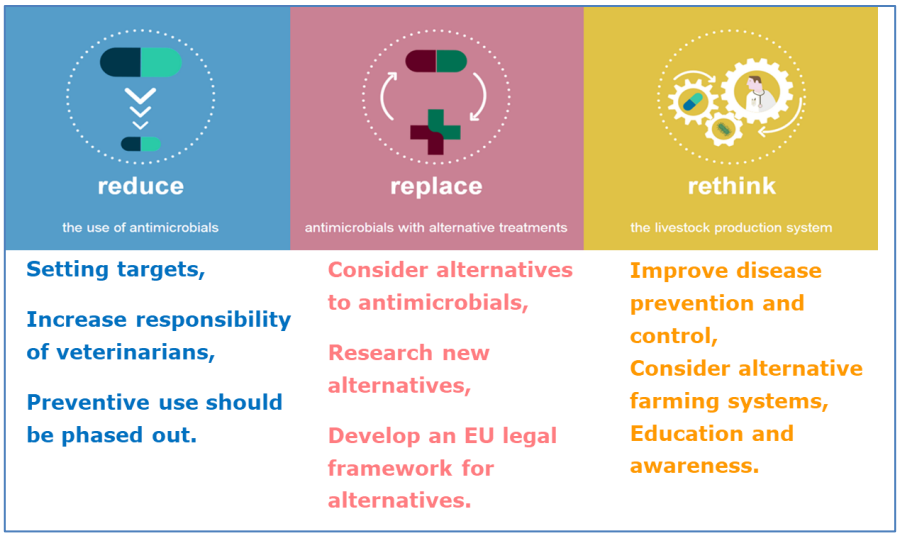
In response to a request from the Commission for an opinion on measures to reduce the need to use antimicrobials in animal husbandry in the EU, and the impacts on food safety, experts from EMA (CVMP, AWP) and EFSA (AHAW, BIOHAZ and FEEDAP panels) published the **RONAFA report**.

The report is divided into 3 main parts (terms of reference):

- Measures that have been taken to reduce the need for and use of antimicrobials in animals and the impact of those measure. This point mainly focused on measures taken in the EC's Guidelines on Prudent Use: prescribing, monitoring of use, controls on CIAs, treatment guidelines, training & education campaigns, etc.
- Possible alternatives to the use of antimicrobials; assessing the impacts of the measures and alternatives on the occurrence of AMR.
- Recommendations to reduce antimicrobial use and favour the responsible use.

The recommended conditions for use of antimicrobials in food-producing animals according to the RONAFA report are that:

- Antimicrobials remain a key tool for the treatment of infectious diseases in animals. In the treatment of livestock, there are three different circumstances for antimicrobial treatment: curative treatment, metaphylaxis and prevention;
- In all cases where administration of an antimicrobial is required, this should be prescribed following appropriate diagnosis by a veterinarian with a good knowledge of the disease epidemiology on the farm and immune status of the livestock. Approved treatment guidelines which consider the responsible use of antimicrobials that are CIAs for human health should be followed;
- Animals with clinical signs of a bacterial infection that is impacting on their health and welfare in many cases need curative treatment with antimicrobials;
- Metaphylaxis is a strategy frequently used in intensively reared animals and is appropriate when there is potential for high morbidity due to rapidly spreading disease. There should be an aim to refine and reduce the use of metaphylaxis based on identification of underlying risk factors and implementation of measures for their control;
- There should be an aim to phase out preventive use of antimicrobials, except in exceptional circumstances. This should be based on a structured review of such use in each sector.



Further on interagency cooperation, the EMA, EFSA and ECDC networks published a list of harmonised **outcome indicators** to assess progress in reduction of use and resistance. In the context of this mandate, indicators are meant to provide a simple overview to facilitate an easy evaluation of whether measures taken to reduce the use of antimicrobials and/or to improve the AMR situation are leading to progress, i.e., reduced occurrence/prevalence of AMR bacteria in animals, food, and humans, or not.

Regarding the **indicators of AMC in food-producing animals**:

- The **primary indicator** is the overall sales of veterinary antimicrobials in mg of active ingredient per kg of estimated weight at treatment of livestock and of slaughtered animals in the corresponding year, considering the import and export of animals for fattening or slaughter (mg/PCU).
- Three **secondary indicators** are proposed for critically important antimicrobials (CIA), which are considered as being most relevant for closer follow-up:
  - sales of 3rd- and 4th-generation cephalosporins (ATCvet codes QJ01DD, QJ01DE, QJ51DD and QJ51DE) in mg/PCU;
  - sales of quinolones (ATCvet codes QJ01MA + QJ01MB + QJ01RA96) in mg/PCU, specifying the proportion of fluoroquinolones (ATCvet code QJ01MA);
  - sales of polymyxins (ATCvet codes QJ01XB, QJ51XB01, QG51AG07 and QA07AA10) in mg/PCU.

		2017 Result
Primary Indicator	Overall sales (mg/PCU)	107 mg/PCU (range 3.1 – 423.1)
Secondary Indicators	Sales of 3rd/4th generation cephalosporins (mg/PCU)	0.2 mg/PCU (range <0.01 – 0.8)
	Sales of polymyxins (mg/PCU)	3.6 mg/PCU (range 0 -14.9)
	Sales of quinolones (mg/PCU) specifying % fluoroquinolones	2.8 mg/PCU (range 0.1-15.3) Fluoroquinolones = 2.4mg/PCU

When considering total sales - For the 25 countries which provided sales for all years between 2011 and 2017, an overall decline in sales (mg/PCU) of 32.5 % was observed.

Indicators of AMR in food-producing animals:

- **Primary indicator**: proportion of indicator *E. coli* from boilers, fattening turkeys, fattening pigs and calves, weighted by PCU, fully susceptible to a predefined panel of antimicrobials.
- **Secondary indicators**: the proportion of samples positive for presumptive ESBL-/AmpC-producing indicator *E. coli* from broilers, fattening turkeys, fattening pigs and calves weighted by PCU; the proportion of indicator ***E. coli*** from broilers, fattening turkeys, fattening pigs and calves, weighted by PCU, resistant to at least three antimicrobials from different classes included in a predefined panel of antimicrobials; and the proportion of indicator *E. coli* from broilers, fattening turkeys, fattening pigs and calves, weighted by PCU, resistant to ciprofloxacin.

Indicators of AMC in humans:

- **Primary indicator**: total consumption of all antimicrobials for systemic use (DDD per 1,000 inhabitants and per day).
- **Secondary indicators**:

- Ratio of consumption of broad-spectrum penicillin, cephalosporins, macrolides and fluoroquinolones to the consumption of narrow spectrum penicillin, cephalosporins and macrolides;
- And the consumption of glycopeptides, 3rd and 4th generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitors, linezolid, tedizolid and daptomycin (DDD per 1,000 inhabitants and per day, and as proportion of the total hospital use).

		2017 Result
Primary Indicator	Total consumption of all antimicrobials for systemic use (DDD per 1,000 inhabitants and per day).	21.8 DDD per 1 000 inhabitants per day (range 11-33.1)
Secondary Indicators	Community - ratio of consumption of broad-spectrum penicillin, cephalosporins, macrolides (except erythromycin) and fluoroquinolones to the consumption of narrow-spectrum penicillin, cephalosporins and erythromycin.	2.3 (range 0.1-22.2)
	Hospital sector - proportion of glycopeptides, third- and fourth generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitor, linezolid, tedizolid and daptomycin within the total hospital consumption of antibacterial for systemic use.	30% (range 16% - 59%)

Indicators of AMR in humans:

- **Primary indicator**: proportion of methicillin resistant *Staphylococcus aureus* (MRSA) and proportion of *E. coli* resistant to 3rd generation cephalosporins (3GCR E. coli).
- **Secondary indicators**:
  - Proportion of *K. pneumoniae* isolates with combined resistance to aminoglycosides, fluoroquinolones and 3rd generation cephalosporins;
  - Proportion of penicillin-resistant *S. pneumoniae* and proportion of macrolide-resistant *S. pneumonia*.
  - Proportion of carbapenem-resistant *K. pneumoniae.*

S6 – HARMONIZATION OF THE SOURCE OF DATA (MARKETING AUTHORIZATION HOLDER/WHOLESALER LEVEL, PRESCRIPTION LEVEL AND CONSUMPTION LEVEL)

The source of data – human field

Data sources used in ESAC-Net include wholesales data and reimbursement data. In some countries, wholesales data are more readily available, but they do not provide possibility of analysing data at the patient level. Reimbursement data provide excellent information in countries where all antibiotics are reimbursed as these data provide not only information on quantities of antibiotics used but also enable

patient-based analysis. These data can provide information on use of antibiotics in defined patient groups (defined by age, gender and diagnosis) which can be useful in directing interventions on optimizing antimicrobial prescribing.

The source of data – veterinary field

It is important to understand the monitoring and surveillance system of sales and use of antimicrobials to know the extent and trends that appear on the use on antimicrobials; to investigate how the use of antimicrobials correspond to the AMR; to evaluate the effectiveness of measures; to raise awareness of overuse if that is the case and to know how to benchmark.

Some definitions:

- **Monitoring** refers to a continuous, dynamic process of collecting data intended to be further analysed and used.
- **Surveillance** refers to a specific extension of the monitoring process where obtained data or information are used and allows to define what measure to take if certain threshold values are passed.
- **Sales** refer to raw data from sources close to the end user such as MAHs, wholesalers / feed mills or pharmacies / vets.
- **Use** refers to data from end-user (vets / farmers) such as data on exact use from farm level (delivery notes, prescriptions, number of packages administered, number of empty packages checked).
- **Consumption** is the calculated number of active antimicrobials which should be linked with the explanation of the data source and also with the data reflecting animal population.

ESVAC establish harmonised protocols and templates used for the data collection **on sales** from data sources (countries) like Marketing authorisation holders (FR, GR, IE, IT, NL, RO, ES, CH, UK); MAH + wholesalers (AT, DE); Wholesalers (BG, HR, CY, EE, HU, IS, LT, LV, LU, PL, PT, SK, SI); Wholesalers + Feed Mills (BE, CZ, FI, NO); Pharmacies/Veterinarians (DK, SE).

Sales data provided as number of packages of different presentations summarised and active ingredient (antimicrobials) expressed as amount of ATM, which is expressed towards the technical unit reflecting the population of food producing animals (PCU – Population Correction Unit).

Despite the fact that sales data does not allow the exact counting of sales per species, there were provided stratified estimation of the species consumption (for the purpose of JIACRA II report). The ESVAC report is not just about the data collection, it also provides data analysis (currently as an interactive database https://bi.ema.europa.eu/analyticsSOAP/saw.dll?PortalPages).

Some **special analysis performed with the sales data** paid attention to CIAs, mass medication, pharmaceutical forms, antimicrobials used in food producing animals vs. pets. Due to good stability of the system trend analysis can be performed.

More stratified and end- user data, which allows the benchmarking as well as the expression of exposure of animals to antimicrobials are data on use of antimicrobials. Existing systems are currently being described by the AACTING project, recognising governmental as well as private activities. Moreover new Regulation (EU) 2019/6 will come into force in 2022, with starting of the “USE” data collection by 1st phase for major food producing animal species/categories (of cattle, pigs, poultry (chickens + turkeys) in 2023 (with delivery of the data to EMA starting on 2024), continuing by 2nd phase: other poultry (ducks, geese), sheep, goats, finfish, horses, rabbits (food-producing) and any other food-producing animals in 2026 (delivery of the data to EMA 2027) and 3rd phase: dogs, cats fur animals (minks and foxes) in 2029 (delivery of the data to EMA 2030).

Data are gained by different systems working on survey or permanent recording systems, with partial or full coverage.

- Possible sources for use data: Health records, treatment logbooks, delivery notes /invoices; prescriptions or pharmacy records; and veterinary practice records.
  - Data on antimicrobial use collected in the form of the treatment schedule used or prescribed, including the number and weight of animals treated, VMP/ medicated feed; the number of packages per VMP presentation used for the treatment/observation; and he total quantity of a VMP (premix) mixed into medicated feed.

Rules on the methods of gathering the required data and of transferring it to the EMA enabling surveillance

Detailed rules dependent on the chosen systems for collecting/transferring/storing data on AM consumption.

The **sales and use** data to be submitted to EMA each year, by MSs for calendar year period.

The data should be validated by MS before sending to EMA (technical specifications described in relevant legislation and relevant guidance including manuals, protocols, templates and/or electronic forms)

The source of **sales** data submitted to EMA may vary per MS (marketing authorisation holders, wholesalers, feed mills, etc.) : should cover all the sales of all relevant VMP sold or placed on their market during the calendar year covering the data collection.

To collect harmonised and standardised **use** data per animal species (Article 57) MSs set up a continuous (semi)automated data collection system or other appropriate systems that enable in particular direct or indirect evaluation of the use of such products in food-producing animals at farm level.

Data provided to EMA: number of packages per presentation of the **veterinary or human** medicinal product per animal species or category used in the MSs during calendar year. The collected raw data on **use** of antimicrobials in animals should be aggregated at national level at each presentation level into the total per animal species or category.

The submission of the collected data on **sales** and on **use** of antimicrobials in animals from MSs to EMA should be carried out by **electronic means**.

Benefits of the data collection on use per species (EU level):

- Trends in use across the years for defined animal species provided;
- Exposure of animals to antimicrobials - insight into the species or animal category on
  - Identification of the sectors with highest exposure to antimicrobials
  - Possibility to identify where to focus efforts on reducing antimicrobial use
    - which species /categories consume more than others,
    - in which species more critically important antimicrobials are used
- In line with the ESVAC (overall) sales reports
  - Possibility to better understand and comment on the data, based on data sets in species (and targeted measures involved)

- Certain level of verification of the overall sales data: especially for those countries with complete (or near complete) coverage

- Verification of estimates of use in PSURs
  - Estimates in certain animal species/categories currently provided by the pharmaceutical industry
  - link to pharmacovigilance and risk/benefit re-evaluation during the life span of the VMP

- Environmental loading – data on use per species could lead to proposing mitigation measures for handling of e.g. manure according to technologies specifically for certain species of animals and certain antimicrobials;

- Identification of the areas of concern for further research in specific species.

Benefits of the data collection on use per species (national level):

- Policy makers insight into the effect of implemented measures (e.g. national responsible use and treatment GL);

- Risk managers can identify risk factors and tools for risk assessment as well as risk management at national or regional level; at the animal sector or at the pharmaceutical level depending of the data collection system in each country.

Working with the data on use per species at the national level:

- ATM use at the farm level: Data available for a (statistically valid) number of farms => insight into the variation in use among farms;
- Specific age categories of animals' data (sows/piglets, weaning pigs, finisher pigs);
- Trends monitoring;
  Calculation of the use per veterinary practice or veterinarian (e.g. responsible for several farms).

➢ S7 – STANDARDISATION OF MEASURE UNITS (DDU, PCU, ETC.)

To facilitate the ability to compare consumption information across time and geography, different technical units of **measurement can be used.**

Measure of units used in the human sector

ESAC-Net uses the WHO Anatomical Therapeutic Chemical (ATC) classification system in which most antibiotics are classified within the following groups:

- Antibacterials for systemic use (ATC group J01);
- Antimycotics for systemic use (ATC group J02);
- Antimycobacterials (ATC group J04);
- Antivirals for systemic use (ATC group J05)

ESAC-Net collects data on antimicrobial consumption at the product level. Data are expressed as number of packages per 1,000 inhabitants and per day and as a number of WHO Defined Daily Doses (DDD) per 1,000 inhabitants and per day (TID). DDD / TID data better express the ecological burden of antibiotic use while information on packages provides better understanding and interpretation of differences in antimicrobial prescribing habits observed between and within countries.

- **The Defined Daily Dose (DDD)** is the average maintenance dose per day for a drug used for its main indication in adults, and it's expressed in grams of the active substance.

- The main advantage of the DDD is that it allows comparisons with other countries, hospitals and wards. It is also independent from price and package size; and easy to calculate. **The Prescribed Daily Dose (PDD)** is defined as the average dose prescribed according to a representative sample of prescriptions. The PDD can be determined from studies of prescriptions or medical pharmacy records. It is important to relate the PDD to the diagnosis on which the dosage is based. The PDD will give the average daily amount of a drug that is actually prescribed. When there is a substantial discrepancy between the PDD and the defined daily dose (DDD), it is important to take this into consideration when evaluating and interpreting drug utilization figures, particularly in terms of morbidity.
    - The main disadvantage of the PDD is that when defined locally and does not allow inter-hospital comparisons.
- An alternative measure is the **number of days of therapy (DOT).** This measure can be used in children and is not influenced by changes in the DDD standards.
- The **number of packages** is useful when assessing the differences in antimicrobial prescribing habits or impact of awareness campaigns in countries dispensing complete packages. It does not reflect the variations in strengths.

Population data from EUROSTAT, or from national statistical reports, are used for the denominator. When consumption data do not cover the whole population, countries have to provide data on the population covered by antimicrobial consumption surveillance data.

In conclusion, there are many ways to measure antibiotic use, each with different advantages and disadvantages.

Measure of units used in the veterinary field

In order to establish a one health approach, it would be interesting to have data of antimicrobial use from humans and animals in comparable units. Although there are several documents published by the European Medicines Agency regarding DDD in human data, ESVAC data are available in mg / PCU.

Currently there are available data on sales of veterinary antimicrobials from 31 European Union/European Economic Area countries.

The sales data for antimicrobial agents (numerator) cover all food-producing species, thus the animal population ‘at risk’ of being treated with antimicrobial agents (denominator) includes all food-producing species. However, the use of antimicrobial agents in the various animal species varies considerably. Therefore, interpretation of the data should consider the stratification of the PCU value among the food producing animal species in the various countries. It should be emphasised that the PCU only represents a technical unit of measurement and not a real value for the animal population that could potentially be treated with antimicrobial agents.

As for the use data, the European Medicines Agency (EMA) has established standardised units of measurement for reporting antimicrobial consumption in specific animal species, called ‘defined daily dose’ and ‘defined course dose’ for animals. This initiative aims to support the harmonisation and standardisation of reporting data on veterinary antimicrobial consumption collected at European level.

The surveillance of antimicrobial consumption by animal species using standardised units of measurement is expected to improve the accuracy of estimation of animal exposure to veterinary antimicrobials.

Units of measurement in veterinary medicine – sales data denominator

Denominator: Population correction unit (PCU)

The amounts of veterinary antimicrobial agents sold in the different countries are linked, among others, to the animal demographics in each country. The **Population Correction Unit (PCU)** has been established as a denominator for the sales data and is used as a proxy for the size of the animal population at risk of being treated. The PCU is purely a technical unit of measurement, used only to estimate sales corrected by the animal population in individual countries; 1 PCU = 1 kg of different categories of livestock and slaughtered animals. The data sources used and the methodology for the calculation of PCU are comprehensively described in ESVAC-EMA´s reports.

Units of measurement in veterinary medicine – use data

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project established **Defined Daily Dose for animals (DDDvet) and Defined Course Dose for animals (DCDvet)** values for antimicrobials used in three major food-producing animal species: pigs, cattle and broilers (poultry). The main aim of the DDDvet and DCDvet system is to provide standardised units of measurement for the reporting of data on antimicrobial consumption by species; these units consider differences in dosing between species and substances.

DDDvet and DCDvet are technical units of measurement solely intended for the reporting of antimicrobial consumption data, and not to be assumed to reflect the daily and course doses recommended or prescribed and are not applicable for commercial use such as pricing and analyses of costs for veterinary medicinal products. The assigned DDDvet and DCDvet values are often a consensus / compromise value.

The values are based on an assumed average daily dose (DDDvet) or treatment course dose (DCDvet) of active substance. They take account of differences in dosing, pharmaceutical form and route of administration used in the different species.

The 'DDDvet' and 'DCDvet' values are based on the following units for different pharmaceutical forms or administration routes:

Administration routes/forms	Units
Oral and injectable products	Milligram per kilogram of animal
Lactating cow intramammary products	Units per teat
Dry cow intramammary products	Units per udder
Intrauterine products	Unites per animal

➢ S8 – CATEGORIES

Antimicrobial use per groups of persons based on their age, in the human sector

Reimbursement data can provide not only information on quantities of antibiotics used but also enable patient-based analysis. These data can provide information on use of antibiotics in defined patient groups (defined by age, gender, and diagnosis) which can be useful in directing interventions on optimizing antimicrobial prescribing.

It is important to note the difference between global data and specific data. Choose one of the other will depend on the question being asked.

- Global data analysis refers to the information on antimicrobial consumption and in particular the consumption of antibiotics. This is an important source for healthcare professionals and policy makers monitoring progress towards a more prudent use of antimicrobials.
- Specific data are collected from certain specific groups, such as patients hospitalised and in long-term care facilities that are collected through the Healthcare-Associated Infections Surveillance Network (HAI-Net). Other examples of data collection in specific populations are Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) or BIFAP (Spanish Farmacoepidemiological Investigation Database).

Specific data are collected from certain specific groups, such as patients hospitalised and in long-term care facilities that are collected through the Healthcare-Associated Infections Surveillance Network (HAI-Net):

- Data on the prevalence of antimicrobial use in patients from European acute care hospitals will be provided through the ECDC-coordinated, Europe-wide point prevalence survey of healthcare-associated infections and antimicrobial use;
- Data on the prevalence of antimicrobial use in residents at long-term care facilities will be collected by the ECDC-funded HALT-2 project.

Antimicrobial use per animal species in the veterinary field

The use of antimicrobials differs between animal species and production sectors in animals. Nowadays, just several countries have the information per animal species and / or production sectors, which could be useful to better understand those categories that require a higher use of antimicrobials and specially to promote prudent use where necessary.

Data collection period is one calendar year for all animal species/categories, regardless of the production cycle on individual farms.

There has not been set legal background to make the collection of the species-specific data on use of antimicrobials in animals mandatory until the approval of the Regulation (EC) 2019/6 on VMPs. New rules has been already defined in more detailed level by Commission Delegated Regulation (EU) 2021/578 of 29 January 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council with regard to requirements for the collection of data on the volume of sales and on the use of antimicrobial medicinal products in animals, for which (an advice was provided by EMA expert group (EMA/CVMP/131097/2019: Advice on implementing measures under Article 57(3) of Regulation (EU) 2019/6 on VMPs - Report on specific requirements for the collection of data on antimicrobial medicinal products used in animals) for the system of USE data collection. System will be further detailed by implementing act dealing with data format, which is currently negotiated. In this mind-set, the priority should be given to animal species/ categories in terms of antimicrobial use – especially when start to build the system. Based on the experience from some advanced countries, it can be anticipated that collecting use data by animal species is expensive**.** Therefore, Member States are allowed to choose step-wise **(phased)** approach. Some of the systems might **collect more data than** just the data on use (e.g. groups of animals, indications). So, a pragmatic approach is necessary, always taken into consideration already existing systems on collecting and utilisation of the data such as benchmarking, systems for setting measures or systems for communication etc.

The animal species and categories which should be covered in the first, starting phase, which is considered as cornerstone of the future system of USE data collection, include the priority livestock species as identified and included in the AMR monitoring as provided under the Commission Implementing Decision (CID 2013/652/EU): pigs, broilers, turkeys, bovine animals slaughters under one year of age, dairy production and beef production.

➢ S9 – EU GUIDELINES ON AMR

2015 Commission guidelines on the prudent use of antimicrobials in veterinary medicine

The purpose of these guidelines is to provide practical guidance on the development and implementation of strategies and actions by Member States in promoting and strengthening the prudent use of antimicrobials, especially antibiotics, in veterinary medicine. These measures may also contribute to and complement the control of AMR in human medicine 2017 EU guidelines on the prudent use of antimicrobials in human medicine.

These guidelines do not have legislative power. They are strong recommendations to the Member States but not legally binding.

These documents explain the principles for the prudent use of antimicrobials, providing special considerations to the use of Critical Important Antimicrobials (CIAs), which are those critical for preventing or treating life-threatening infections in humans. Special consideration is necessary to ensure the continued efficacy of such antimicrobials and to minimise the development of resistance:

- These antimicrobials should only be when there is no other non-critically important effective antimicrobial available;
- The use of these antimicrobials under off-label use (cascade) should be sufficiently justified and recorded;
- The individual treatment of the animals should be preferred;
- The antimicrobial treatment of groups of animals via feed or drinking water should only be done where there is evidence of microbial disease or infection.

The SPC needs to be complied with, both in terms of dosage and duration of treatment.

If administered in a medicated feedstuff, the homogeneity of distribution of the drug is important to ensure that each animal obtains the required therapeutic dose for treating the disease in accordance with the veterinary prescription.

Off-label (cascade) use should be limited to the necessary minimum and to exceptional occasions where no other authorised treatment options are available.

Adequate, clean storage facilities should be available on the farm to ensure proper storage of the medicated feed. Access to these facilities should be controlled.

The guidelines also indicate the different responsible actor:

The prescriber of the antimicrobial must be a veterinarian familiar with the history of the herd/flock/treated animals. It is necessary to ensure that the prescriber can make treatment decisions in an independent way and has no conflicts of interest. The position or status of the prescriber in relation to the farmer should therefore be set appropriately to ensure independent decisions, primarily based on expert knowledge.

When prescribing is necessary, it should be based on a diagnosis made following personal clinical examination of the animals and, if possible, the choice of antimicrobial should be supported by antimicrobial susceptibility testing.

The prescriber should always take account of the risk of AMR, and give serious consideration to alternative, possibly long-term solutions to prevent recurrence of disease, and implement the solutions. The prescriber is responsible for providing correct information to the person administering the antimicrobial, in the first instance based on the information from the SPC.

The **administrator** is the veterinarian, owner of the farm, the farmer or someone from the staff**.**

He needs to obtain the antimicrobials from authorised sources, always with veterinary prescription and following the prescriber's instructions. It's also essential for him to collaborate with the veterinarian who works in the farm with its animals.

The **feed business operators**, that must comply with the legal requirements for feed hygiene and implement best practices in the production of safe and nutritionally balanced feed and ensure adequate feed formulation. They must follow all legal requirements for medicated feeds and produce medicated feed only from authorised veterinary medicinal products in line with a veterinarian's prescription. Appropriate labelling and medicated feed must only be supplied to the end user on presentation of a valid veterinary prescription and other responsible actors.

2017 EU guidelines on the prudent use of antimicrobials in human medicine

In 2016, after the Council Recommendation 2002/77/EC, Council Conclusions on the next steps to follow under a One Health approach to combat antimicrobial resistance called on the Commission and the Member States to develop Guidelines on prudent use of antimicrobials in human medicine which will serve to support national guidelines of the Member States and will provide species-specific recommendations.

These guidelines are intended to be used to inform and assist activities to promote the prudent use in the public health sector, and therefore the people targeted are those who have a responsibility in administrating and prescribing antimicrobials. They include measures to be considered by Member States, and elements to be followed by healthcare professionals, like good clinical practices, good use of resources, systems and what processes could be considered implementing to have a better system in place. It proposes examples and activities that may be taken by international organisations.

There are several actors included in the guidelines:

- National, regional and local governments. They are key actors in regulating the use of antimicrobials in their countries, in educating all the levels of health professionals.
- Healthcare facilities which should focus in primary care, hospitals and long-term care facilities.
- Clinical microbiologists, prescribers, pharmacists, and nurses.
- Infectious disease specialists and infection control practitioners.
- Public / patients, professional associations and scientific societies.
- Research funders.
- Pharmaceutical and diagnostic industry.
- International collaboration.

➢ AG2 – IMPLEMENTATION OF THE EU RULES AND GUIDELINES

For this group activity, the participants will be divided in groups per sector (Public Health and Veterinary Medicine participants will not be mixed) and will be asked to, based on their practical experience of their country of origin, identify implemented practices that could be shared with the participants in their group. Participants will be able to discuss their own system and explore other practices from which they could benefit.

Plenary Session, Group results presentation, Discussion, Q&A

➢ S10 – MONITORING AND REPORTING OF AMR IN VETERINARY SECTOR

The presentation includes relevant EU rules / initiatives for monitoring and reporting of AMR data in the veterinary sector like the Commission Implementing Decision on Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria (2020/1729 EU).

Surveillance programs for antimicrobial resistance in food animals were launched in Europe in 1995, Denmark being the first European country collecting information on antimicrobial resistance in veterinary medicine. Since then, programs have been progressively harmonized, especially with the publication of the Community decision 652/2013 and upgraded with Community Decision 2020/1729. The European legislation indicates the requirements to monitor and interpret the data for antimicrobial resistance in zoonotic and commensal bacteria, including sampling, isolation, and antimicrobial susceptibility testing.

As mentioned during the course, AMR monitoring is essential to:

- Detect emergence and understand dissemination of AMR;
- Provide data relevant for risk assessment;
- Plan and implement interventions and measure their effects.

EFSA monitors and analyses the situation on antimicrobial resistance in food and animals across Europe. The Authority is assisted by the Task Force on Zoonoses Data Collection: a pan-European network of national representatives of EU Member States, other reporting countries, as well as the World Health Organisation (WHO) and World Organisation for Animal Health (OIE).

Based on data collected by the EU Member States, EFSA produces in cooperation with ECDC annual European Union Summary Reports on zoonotic infections, food-borne outbreaks and antimicrobial resistance illustrating the evolving situation in Europe. EFSA also publishes baseline survey reports on the prevalence of antimicrobial resistance in the EU in specific animal populations, for instance MRSA in pigs, and provides guidance to national authorities how to carry out their monitoring and reporting activities.

EFSA's Scientific Panels review the annual reports and make recommendations on prevention and reduction measures.

Regarding the interpretative criteria of resistance:

- The preferred susceptibility testing method is the micro-broth dilution.
- The criteria of resistance are the epidemiological cut-off values.
- To better compare with human data, dilution ranges cover both ECOFFs and clinical breakpoints.
- To create multi-drug resistance profiles, isolate-based data collection is used.

The presentation showed zoonotic and commensal bacteria which are looked for in food-producing animal populations and food together with the special requirements for the harmonised monitoring of *Salmonell*a spp., *Campylobacter coli/jejuni*, commensal *Escherichia coli. Salmonella* spp. and *E. coli* producing certain enzymes: Extended-Spectrum ß-Lactamases (ESBL); AmpC ß-Lactamases (AmpC); Carbapenameses are object of special attention given to their relationship to human health.

The analyses and testing of the antimicrobial susceptibility on the mentioned enzymes is being done in broilers, fattening turkeys, fattening pigs, bovines under one year of age and fresh meat of broilers and turkeys, pig, and bovine meat.

During the presentation, the lecturer defined values like Minimal Inhibitory Concentration (MIC) and Distributed Epidemiologic cut-off values (ECOFF).

To confirm that the Member States are coordinating and performing adequately, many audits were carried out in the Member States. The results were reported to EFSA.

A revision of the Community decision 652/2013 to monitor and report to the AMR is imperative. For this goal, EFSA has produced a supporting document about the technical specifications on harmonised monitoring of antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food, 5 June 2019 to objectively justify the changes required. New revised Community Decision 2020/1729 was published at the end of 2020. EFSA's recommended approach for the inclusion of WGS analysis in the AMR monitoring was taken to account. To solve the problem with the small number of salmonella isolates from pigs and cattle, isolation of salmonella is envisaged within the monitoring. Imports of meat from broilers, turkeys, pigs, and bovines from third countries at border control posts are included as a separate area in the monitoring.

➢ S11 – MONITORING AND REPORTING OF AMR IN HUMAN MEDICINE

To understand the monitoring of AMR, there are some concepts that need to be clear such as:

Antimicrobial susceptibility tests are used to determine if a particular bacterial isolate is *in vitro* susceptible to different antimicrobial agents. Antimicrobial susceptibility test results can guide the physician in drug choice and dosage in the infection caused for the bacteria, including difficult-to-treat infections. It is relevant to the patient, to predict the clinical success or failure of a specific antibiotic treatment (Empirical *vs.* directed).

It is relevant to the public health as the generate alerts (unexpected resistance results) are used to establish accurate treatment measures and prevention of AMR dissemination. Moreover, it is possible to know the epidemiology of antibiotic resistance mechanisms (emergence, evolution, and dispersion) and to monitor the efficacy of control measures (containment).

- MIC – minimal inhibitory concentration - The lowest concentration of an antimicrobial that inhibits the growth of a bacterial population (inoculum)
- MBC – minimal bactericidal concentration - The lowest concentration of an antimicrobial that kills a bacterial population (99.9% of the inoculum) - **[bactericidal *vs.* bacteriostatic]**

MIC (Minimal Inhibitory Concentration) values are used to **predict clinical outcome** according to previously established clinical breakpoints (EUCAST or CLSI). MIC value is associated with the presence or absence of a resistance mechanism.

The **Clinical breakpoints (EUCAST or CLSI)** are concentrations of an antibiotic that define whether a species of bacteria is S (susceptible) I (susceptible, increased exposure for EUCAST and intermediate for CLSI) or R (resistant) to the antibiotic. Parameters considered in the clinical breakpoint-setting process: Dosages, pharmacokinetics, pharmacodynamics, resistance mechanisms, MIC distributions and epidemiological cut-off values (ECOFFs). Following EUCAST criteria (www.eucast.org), the clinical interpretive categories are defined as follows:

- **S = Susceptible standard dose:** A microorganism is defined as susceptible standard dose when there is a high likelihood of therapeutic success using a standard dosing regimen of the antimicrobial agent.
- **I = Susceptible increased exposure**: A microorganism is categorized as **susceptible increased exposure** when there is a high likelihood of therapeutic success because exposure* to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

- **R = Resistant**: A microorganism is defined as resistant when there is a high likelihood of therapeutic failure even when there is increased exposure

*exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting bacteria at the site of infection.

Regarding the microbiological resistance and **the epidemiological cut off values – ECOFF**, it is important to understand the following concepts:

- **WILD TYPE (WT):** A microorganism is defined as wild type for a species by the absence of acquired resistance mechanisms to the drug in question.
- **MICROBIOLOGICAL RESISTANCE-NONWILD TYPE (NWT):** A microorganism is defined as non-wild type for a species by the presence of acquired resistance mechanisms to the drug in question.
- **EPIDEMIOLOGICAL CUT OFF VALUE (ECOFF):** MIC value identifying the upper limit of the wild type population.

Monitoring AMR means to watch closely a situation to take corrective steps while implementing a program (e.g., reduction of AMR and antimicrobial consumption). The performance and analysis of routine measurements aimed at detecting changes in the environment or health status of populations. In management, the continuous oversight of the implementation of an activity, seeking to ensure that input deliveries, work schedules, targeted outputs and other required actions are proceeding according to plan**.**

In summary, continuous measurement of the effect of an intervention on the health status of a population or environment checking whether our current progress is in line with pre-set objectives, with the aim of adjusting to meet those objectives.

The main indicators to address AMR in the human medicine are the **antimicrobial consumption** and the **antimicrobial resistance** in the community, including all ambulatory health care centres and nursing homes, and in hospitals as well as with One-Health in veterinary medicine and in the environment. The indicators are based on data already gathered through EU monitoring networks:

- **EARS-Net:** European Antimicrobial Resistance Surveillance-Network - is a publicly funded system from antimicrobial resistance surveillance in Europe, based on routine clinical antimicrobial susceptibility data of invasive isolates (blood and cerebrospinal fluid) from local and clinical laboratories reported to ECDC by appointed representatives from the Member States.

- **HAI-Net:** Healthcare-associated Infections Surveillance Network - The main priorities of HAI-Net are the coordination of the European point prevalence survey of HAI and antimicrobial use in acute care hospitals, the European surveillance of surgical site infections, the European surveillance of HAI in intensive care units and the repeated prevalence surveys of HAI and antimicrobial use in European long-term care facilities.

- **FWD-Net:** Food and waterborne diseases and zoonoses network - FWD-Net covers surveillance on human diseases acquired through consumption of food or water or contact with animals: anthrax, botulism, brucellosis, campylobacteriosis, cholera, leptospirosis, listeriosis, salmonellosis, shigellosis, tularemia, typhoid/paratyphoid fever, verocytotoxin or Shiga toxin *E. coli* (STEC) and yersiniosis. Parasitic and viral agents are included.

The session continues explaining the relevance of the surveillance and reporting AMR, identifying also the most relevant global public surveillance programmes. It ends by underlining the ecological problem of AMR and stressing the One Health approach as the unique way to combat AMR. It is impossible to

eliminate it, but it we can still use appropriately and prudently the existing antimicrobials, trying to minimise the effect.

➢ S12 – INTERPRETATION OF RESULTS FROM BREAKPOINTS

The presentation explains how the breakpoints are reached and the relevance of understanding them to be able to decide what could be the best antimicrobial depending on the case.

As mentioned before, ECOFF is the highest MIC for organisms devoid of phenotypically detectable acquired resistance mechanisms. It defines the upper end of the wild-type MIC distribution for a given microbial species and antimicrobial agent. In general, we can say that microbiological data is based in MIC values, and we can extract a clinical outcome correlation with MIC values.

It allows comparing rates of acquired resistance when clinical breakpoints differ (e.g., between organisations, between humans and animals), change over time or have not been set.

As explained in S12, WT (wild-type) is a microorganism defined by the absence of acquired resistance mechanisms to the drug in question. Wild-type MIC distribution and ECOFFs are based on phenotypic methods. However, the EUCAST/VETCAST subcommittees examine whether the presence of AMR genes in putative wild-type isolates requires adjustment of the ECOFF to correlate genotypes and phenotypes.

The role of the MIC value in surveillance programs for public health is extremely important. Some of the reasons are the following:

1. More information can be obtained with MICs than when we use clinical breakpoints only;
2. Breakpoints can be modified by different committees over time (resistance rates can be reinterpreted when MICs are available);
3. MICs explain difference between different breakpoints;
4. Clinical breakpoint might be ineffective to detect resistance mechanisms and MICs are useful for this purpose;

In this point, the tutor explains an example on the clinical response to carbapenems: most carbapenems producing *Enterobacterales* are considered resistant (R) to carbapenems but can also be considered “susceptible” (S) or “susceptible, increased exposure” (I). We see the clinical breakpoints and cut-off value for carbapenems such as meropenem, imipenem and ertapenem.

One of the ways in which bacteria can develop resistance mechanism to a certain antimicrobial is through the acceptance of a plasmid which carries the resistance gene (example of plasmid *mcr-1*).

5. MICs can simplify complex resistance mechanisms;
6. MICs are relevant when using molecular methods for surveillance.

During the presentation we see several case examples on the EUCAST website (http://eucast.org) in how to calculate the distribution of ECOFFS which allows us to study the isolates with acquired resistance mechanisms but also intrinsic resistance of a certain microorganism.

The intrinsic resistance is the innate ability of a bacterial species to resist the activity of a particular antimicrobial agent through its inherent structure or functional characteristics, which allows the bacteria tolerance of a particular drug.

➢ AG3 – CASE STUDY OF MRSA

Staphylococcus aureus is a commensal bacteria of humans and animals. However, it can cause infections from mild to severe both in humans and animals.

Methicillin resistant *S. aureus* (MRSA) in animals was firstly described as mastitis in ruminants in 1972. In companion animals, MRSA was linked with MRSA prevalence in humans, but both infections in ruminants and companion animals were considered sporadic. However, the occurrence of clinical cases in people related to the porcine sector was the first description of a reservoir of MRSA in food animals. A specific genetic lineage in pigs led to the description of a potential MRSA reservoir for humans, with the consequent risk to public health.

The occurrence of MRSA in animals and food became very relevant and mitigation measures were implemented in June 2009. Considering the reservoirs were found in pigs, veal calves and broilers, and analysing that the most important transmission route is the contact with live animals and their environments, it was encouraged to follow strict general control measures, such as GHP, HACCP and GMP, on farms, slaughterhouses and food producing areas. MRSA in healthcare settings can be managed by screening and infection control measures, and in the cases the relation between humans and their pets, the transfer of MRSA is difficult but its key the use of basic hygiene measures.

- Background of MRSA:
  - The proportion of MRSA and 3rd-generation cephalosporin-resistant *Escherichia coli* (3GCR *E. coli*), expressed as two individual numbers have been selected as primary indicator in humans. Both pathogens are of major public health importance. Though management decisions should never be based on these indicators alone but should consider the underlying data and their analysis.
  - ECDC survey on Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) among MRSA from humans across the EU/EEA, 2013
  - Funded project PILGRIM focused on one strain, the MRSA ST398, an animal-adapted, zoonotic, resistant pathogen that causes colonisation and infection in humans in community and health care settings

- Current situation in both the veterinary and in the human sectors with regards to distribution and prevalence.

- Discuss among the group: ***What are the practical approaches of Member States on measures taken to prevent and/or reduce MRSA, and the problems encountered****?* Both for the human sector and for the veterinary / food safety sectors.

Plenary Session, Group results presentation, Discussion, Q&A

ROLE OF ENVIRONMENT IN SPREADING AMR

➢ S13 – INTRODUCTION TO ENVIRONMENTAL RISKS

This brief introduction will set the scene for the rest of the sessions and introduce the fundamental issues of the occurrence and persistence of AMR in the environment consisting of a set of introductory slides.

It will introduce awareness of environmental issues on AMR, but show little engagement with the environment, considering the lack of current understanding of the issue, lack of regulatory process, despite AMR remaining a priority for the EU. The introduction will cover:

- Commission's 2011-2016 Action Plan against the rising threats from AMR was followed by a 2nd One health (that included the environment) Action Plan to support Member states in the fight against antimicrobial resistance (AMR: started 2017).
- The 7th Environment Action Programme (EAP) will be guiding European environment policy until 2020. And it sets a vision where it wants the Union to be in 2050.

- CVMP strategy on antimicrobials 2016-2020, published on 6 October 2016. The importance of the environment as a reservoir for antimicrobial resistance genes is now widely recognised…." The CVMP acknowledges that further consideration should be given to the contribution of veterinary antimicrobials use in the environmental resistome…."
- EMA and EFSA Joint Scientific opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA) published on 24th January 2017.
- The European Union "Strategic Approach to Pharmaceuticals in the Environment", identifies six action areas concerning all stages of the pharmaceutical life cycle (raise awareness and promote prudent use, improve training and risk assessment, gather monitoring data, incentivise "green design", reduce emissions from manufacturing, reduce waste and improve wastewater treatment), where improvements can be made. The text addresses pharmaceuticals for human as well as for veterinary use.
  Pharmaceuticals discarded in the environment have been shown to pose a risk to fish or other wildlife, for example by affecting their ability to reproduce, by altering their behaviour in ways jeopardising their survival, or through direct toxic effects. In addition, incorrectly disposed medicines may contribute to the serious problem of antimicrobial resistance. Increased awareness has prompted further investigation, as well as calls and proposals for action to reduce emissions to the environment, in particular to water but also to soil.
  Today's Communication places an emphasis on sharing good practices, on cooperating at international level, and on improving understanding of the risks. This is crucial in the context of addressing antimicrobial resistance, a problem that is growing at global level. Several actions in the strategic approach are intended to contribute to the objectives of the European One-Health Action Plan against Antimicrobial Resistance (AMR). The Action Plan stresses the need for a One-Health approach taking account of the interconnections between human and animal health and the environment.
  The Commission will follow up the actions set in the Communication and invites Member States and other stakeholders to take action as well.

➢ AG4 – ENVIRONMENTAL SOURCES CONTRIBUTORS TO AMR

An interactive game undertaken in the plenary session to generate questions about the sources, potential pathways, and receptors for AMR in the environment. These questions will feed into the subsequent lecture session and inform the group knowledge activity.

➢ S14 – RELEVANCE OF AMR TO THE ENVIRONMENT AND REGULATORS

A presentation will focus on the topics related to the emergence, drivers, and perpetuation of AMR in the environment. It will consider how we undertake or assess the risk and deal with the uncertainties and complexities of decision making when faced with limited evidence. The lecture will cover the following points: What is environmental AMR and what are the major concerns around AMR in the environment?

- Discussion on the global scale of the problem, causes, legislative and non-legislative options
- A review of ERA guidelines
- How do products enter the environment; which molecules are found in the environment and how do they behave?
- Assessment of the Environmental hazards, consideration of exposure
- Discussion around the role of various environmental reservoirs (e.g. surface water, soil, air) on the emergence and dissemination of AMR
- What are the drivers and complexities to understanding the environmental consequences and impacts of AMR?
- Establishing controls, e.g., EU water legislation and improvement of wastewater treatment

- What are the research's needs and frameworks for implementation and minimisation of the spread of AMR?

➢ AG5 – KNOWLEDGE GAPS

A group activity where participants are divided into smaller groups and each address a particular knowledge gap in the role of AMR in various environment compartments, reservoirs that drive the selection and transmission of AMR. There are several indicative questions provided to each group to inform discussion.

- A series of questions will be posed such as; Are the current monitoring techniques sufficient to measure relevant environmental concentrations of antimicrobials either during the assessment process or after authorisation.
- How should wastes from antibiotic treated animals be assessed for their environmental impact in the terrestrial / aquatic compartment following treatment?
- There are currently no legal requirements to monitor or prevent spreading of AMR in the environment. In this context, how could the presence of antibiotic residues be considered in a regulatory framework?

The time will be distributed in the following way: presentation of the activity and group assignment, discussions within each group, presentation of the outcomes by each group to the plenary, discussions and final Q&A.

➢ AG6 – EXERCISE ON TRANSFORMATION PROCESS

A group activity where participants are divided into smaller groups and must consider the future steps around the problem of how to achieve consistent good practice in all countries in controlling levels of AMR in the environment? A transformation map will be developed by each team during the session with opportunity for feedback and questions. This final session will confirm learning objectives and enable trainees to bring together their collective knowledge.

JIACRA REPORT and COMMUNICATION PRACTICES

➢ S15 – JIACRA REPORT

In January 2015, the first joint report on the integrated analysis of the consumption of antimicrobials agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals was published. The ECDC, the EFSA and the EMA jointly explored for the first time the associations between consumption of antimicrobials (AMC) in humans and food-producing animals using data available from their EU monitoring networks from 2011-12.

The conclusions and recommendations of the report were done in a one health perspective based of results of integrated analysis of data.

The agencies published the second JIACRA report in July 2017. It presents the data from the agencies' monitoring networks from 2013-15 and reflects an improved surveillance across Europe. JIACRA II added some changes with regards to JIACRA I such as a special section for colistin resistance, multivariate analysis or vet consumption by animal species (DDDvet).

A third JIACRA report will cover the years 2016-2018 and will be finalised by the end of 2020.

The conclusions that we can draw from the report are:

- There is indeed a link between AMC in animals and humans and the occurrence of resistance. But important differences still exist in the consumption of antimicrobials in animals and humans across the EU.
- In hospitals, resistance to 3rd generation cephalosporins in *E. coli* from humans is mainly associated with the consumption of these types of antimicrobials.

➢ AG7 – COMMUNICATION PRACTICES

This group activity will focus on why, how and the resources to develop communication campaigns on prevention and use of antimicrobials.
The participants will be organised in six groups and each group will be attributed a target as follow:

- Group 1 – Communication to education sector (schools, universities etc.)
- Group 2 – Communication to professionals (H/V)
- Group 3 – Communication to general public and/or patients and/or caregivers
- Group 4 – Communication to food chain distributors (farm to fork)
- Group 5 – Communication to long-term care facilities (for both professionals and patients)

They will then be asked three questions:

- What are their target's characteristics?
- What the message do they want to convey to this target?
- Which communication tools and/or supports they consider would be adapted for their message?

Plenary Session, Group results presentation, Discussion, Q&A

5. QUESTIONS ASKED DURING THE SESSIONS

S1 – INTRODUCTION TO AMR

S2 – 2017 EU AMR ACTION PLAN

Q1	**What is the JIACRA report? Could you give a summary?**
A1	JIACRA means Joint Interagency Antimicrobial Consumption and Resistance Analysis and is an integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. There are two JIACRA reports (2015 and 2017) produced by ECDC, EMA and EFSA. The second report addressed data obtained by the Agencies' EU-wide surveillance networks for 2013–2015. AMC in both sectors, expressed in mg/kg of estimated biomass, were compared at country and European level. Estimated data on AMC for pigs and poultry were used for the first time. Univariate and multivariate analyses were applied to study associations between AMC and AMR.
Q2	**What is meant by alternative treatments to antibiotic therapy? Does this include homeopathy?**
A2	No, it does not include homeopathy remedies. It refers to alternative treatments that target destruction or inhibition of microorganisms, such as nanoparticles or phagetherapy. So far phagetherapy is most advanced in clinical investigations as it was used in parallel with antibiotics for many decades in some parts of the world (e.g., Georgia9, it has selective effect on bacterial, not human cells and has microorganism specificity).

S3 – RELEVANT INTERNATIONAL INITIATIVES

Q1	**Is it planned to include in the Global Agenda for next time regulations/concerns about the control antimicrobials in the water (rivers, etc.)?**
A1	As we have commented before AMR is a major global threat across human, animal, plant, food, and environmental sectors and to address AMR a multifaceted strategy need to be implemented under the one health strategy. In this regards the tripartite has also engaged closely with the United Nations Environment Programme (UNEP) to strengthen the integration of environment in the work.
Q2	**Does all national actions plans have similar goals that EU action plan or WHO Global Action Plan?**
A2	Yes. The same objectives for the different countries but each country must develop a NAP adapted to the national situation.
Q3	**Can you please explain further what tripartite is?**
A3	FAO, OIE and WHO have been working together for years to address risks at the human-animal-ecosystems interface and their collaborative work was formally laid down in 2010 in the FAO/OIE/WHO Tripartite Concept Note. This Note continues to be a reference for the Tripartite on the shared responsibilities for addressing health risks through multi-sectoral collaboration. The three Organizations demonstrated that bringing together their knowledge, insights and technical capacities in food, agriculture, and human and animal health can generate strong

	synergies, which will yield more robust, effective, and cost-efficient solutions to the complex problems facing the world today. One of this problem is AMR. The WHO, the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) speak with one voice and take collective action to minimize the emergence and spread of AMR. The aim is to: - Ensure that antimicrobial agents continue to be effective and useful to cure diseases in humans and animals. - Promote prudent and responsible use of antimicrobial agents. - Ensure global access to medicines of good quality.
Q4	**Please, explain further what means that CODEX is a reference in WTO trade disputes?**
A4	The World Trade Organization (WTO) bases their sanitary measures on international standards, guidelines, and recommendations, where they exist (include CODEX, OIE AND IPPC). The Codex Alimentarius Commission is a joint body of the Food and Agriculture Organization of the United Nations (FAO) and WHO, with 187 Member States and one Member Organization (EU). Codex work to create harmonized international food standards to protect health and is the reference organization for standards relating to food standards. The OIE is the WTO reference organization for standards relating to animal health and zoonoses included in 2 codes (Terrestrial and Aquatic) and the International Plant Protection Convention (IPPC) is the WTO reference organization for standards relating to plant health.

S4 – EU LEGISLATION

Q1	**Can you please explain again the slide 15 (Comparison of legal basis under Directive 2001/82/EC)?**
A1	A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. A referral can be initiated by the European Commission, any Member State or by the company that markets or intends to market the medicine. There are several reasons why a referral may be started, ranging from concerns over the safety of a class of medicine to disagreements among Member States on the use of the medicine. EU pharmaceutical legislation on veterinary medicines (Directive 2001/82/EC, as amended) lays down a binding mechanism that can be initiated based on the different articles but the most related with the AMR issue are:
Q2	**In the new regulation there is ban of use for preventive treatment in group of animals. What does it mean with regards to Metaphylaxis?**

Article 33	Initiated because of disagreement between Member States.
Article 34	**Divergent decision referral**: initiated in order to obtain harmonisation within the EU of the conditions of authorisation for products already authorised by Member States
Article 35	**Community interest referral**: initiated in cases involving the interests of the Community or concerns relating to the protection of human or animal health or the environment

A2	In the NVR are included the definition of Metaphylaxis and prophylaxis as follow: • **Metaphylaxis** means the administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be sub-clinically infected. • **Prophylaxis** means the administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection. Antibiotic medicinal products should not be used for prophylaxis other than in exceptional cases only for the administration to an individual animal. Use AM in a MF for prophylaxis is ban. AM should be used for Metaphylaxis only when the risk of spread of an infection or of an infectious disease in a group of animals is high and where no appropriate alternatives are available.
Q3	**Why is the new Veterinary Medicines Legislation restricting "off-label" use when some national agencies are recommending that licensed dose rates for some antibiotics are too low and encouraging the use of higher than licensed dose rates?**
A3	The EMA are currently consulting on cascade use: https://www.ema.europa.eu/documents/other/open-call-data-use-antimicrobials-animals_en.pdf In the new VMD, article 107(6) makes provisions for a list of antimicrobials that may not be used under the cascade or may be used subject to certain restrictions. However, cascade use (e.g., using a medicine authorised for another species or condition) is not the same as using a product that is licensed for that species and indication but at an unlicensed dose rate.
Q4	**If I get it right, this rule for the referrals only applies for manufacturers. Or does it also apply to veterinarians?**
A4	Indeed, it only applies to manufacturers.
Q5	**Which is the difference between criteria and reserved list?**
A5	The criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans aim to define the criteria that should be used to determine those antimicrobials to be restricted to human use as foreseen under Article 37(4) of the Regulation. The reserved list will be the list of antimicrobials or groups of antimicrobials to be reserved for treatment of certain infections in humans on bases on the criteria.

S5 – EU AGENCIES AND THEIR COOPERATION

Q1	**Slide 35: Is it a specific equation to calculate these numbers?**
A1	Slide 35 is related to the indicator of antimicrobial consumption (AMC) in food-producing animals. Overall sales are calculated as a summary amount of the active substances, which were included in the VMPs sold in the respective period (expressed here as "mg"). PCU is population correction unit (technical, consensual unit) reflecting biomass of food producing animals, for which majority (or in another word biggest mass) of veterinary antimicrobials was sold. "PCU" represents "denominator", "mg" represents "numerator". Number of animals/biomass (e.g., number of heads/kg slaughtered in certain species/categories) are for each country mainly extracted from EUROSTAT, also export/import data are used from TRACES, or once not available in these databases, national statistics can be used). More deeply it is explained in the next presentation.

	Specific attention is paid to the groups of critically important antimicrobials (cef3/4th generation; sales of Q, specifying % of FQ; sales of polymyxins (practically mainly colistin) … and these amounts in mg are again compared to total PCU. On the slide 35 ranges are presented for individual indicators, and average of the overall MSs data. Data are coming from ESVAC.
Q2	**What do you mean when you talk about the mcr1 gene?**
A2	Genes of different numbering called mcr encoding for resistance to colistin and, what is of the most important, are transferable by mobile genetic elements – plasmids among different species/genera of bacteria. The gene mcr-1 was the first discovered, currently we are aware of mcr-1 to mcr-10 genes encoding colistin resistance described in different species/genera of bacteria/with slight differences among them. Discovering the mcr-1 completely changed the view on use of colistin in animals (especially those food producing), because colistin was reintroduced (despite its toxicity) in the human medicine as the last resort antimicrobial serving in some cases the last possibility to treat patients with infections caused by Gram-negative (often multidrug) resistant bacteria. Discovery of the transferable resistance enforced the need to start to use colistin more prudently in veterinary medicine, therefore AMEG-scientific advice from 2013, changed in 2016. There was also launched referral procedure with purpose to modify indications for use (including removing of prevention), to shorten duration of the use of colistin containing VMPs to the minimum necessary period as well as to improve of the information involved in the product texts (e.g., prudent use warnings, PK information etc.). It should be also mentioned that in many countries, campaigns/measures have started to reduce the use of colistin, as it is described in the colistin case study.
Q3	**What criteria have been taken into account to choose these indicators and no others to study the AMC?**
A3	T2 – Public health: For the public health sector, they are directly linked to the most important clinical problems. (Ex: KPC Klebsiella pneumoniae carbapenemase resistant, MRSA) and the most important antibiotics for the severe infections in ICUs T3 - Veterinary: Until now we have just sales data for 31 MSs of EU/EEA. So primary indicator as overall sales are appropriate (also considering that any use of antimicrobial has potential to select AMR). As for secondary indicators they were set for the groups of antimicrobials authorised in VMPs and being categorised as CIAs by WHO (so having overlap of importance to public health sector) as well as being currently included in AMEG categorisation "B" category based on more complex assessment (see the doc: AMEG 2018 - Categorisation of antibiotics (europa.eu)). The answer is not precluding existence and appropriateness of other indicators once relevant data are/will be available … you can also see some more info in e.g. recent publication Frontiers | Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes | Veterinary Science (frontiersin.org).
Q4	**About alternatives to ATM. Which alternative can be considered as most effective or more alternatives are necessary to achieve the effect?**
A4	T3 - Veterinary: According to my opinion and expertise - It depends on exact disease prevention, but generally: No single alternative seems fully equal to antimicrobial once acute microbial disease needs the treatment. Usually "alternative tools" rather than single alternative exist, and these tools should be combined … e.g., biosecurity + hygiene + care on animals + some products as probiotics, prebiotics, vitamins, phytoadditives, minerals etc. … see also doc CVMP reflection paper on alternatives to antimicrobials (europa.eu) – point 7 Appendix 1 with brief list of

	examples, as well as in the Chapter "Prevention is better than cure" (Table 6 (more details) https://link.springer.com/chapter/10.1007/978-3-030-46721-0_6 In some diseases vaccination can be powerful tool (and probably one of the most investigated and also with approved VMPs) But vaccines are usually more specific (e.g. especially monovalent vaccines against certain bacteria, with certain properties) than antimicrobial (covering different species of bacteria if, susceptible) … but there exists also vaccines combined/polyvalent containing inactivated strains, or antigens … and sometimes with antiviral/antibacterial effect – e.g. BRD vaccines for cattle).
Q5	**Q for T2: T3 was talking about mandatory collection and reporting of sale and use data in veterinary sector. It is possible also for human sector, that collection and reporting will be mandatory in the future?**
A5	T2 – Public health: I hope so but, in many countries, it is difficult to make mandatory a reporting in the health sector because many people think these information or data are personal and may be badly used for their future (employment for example).
Q6	**How is the implementation of all the organisations in Europe?**
A6	T2 – Public health: If you are talking about the organisations in charge of producing guidelines or indicators, there was an awareness of the importance of the problem in the 1990s and networks were set up on a voluntary basis from an initiative by a university team, then gradually taken over by the ECDC after its creation and the allocation of resources to run these networks and extend them to all countries. If you are aiming for implementation on the ground, the response is very different depending on the country, the kinetics of which are linked to local, political, or administrative will. Leadership is very important.
Q7	**I did not quite understand why some countries had for a few years recorded a drop in antibiotic use in humans and then again showed an average increase in their use. Could Mr. Phillippe clarify? Some of them you answered already but I am not sure which ones?**
A7	T2 – Public health: I gave the French example: a very large and excellent information has been given for 3 years (TV, radio, magazines, etc..) for reducing the AB prescription in the community. The result was excellent with a drop of 25% of AB consumption. The n all has been stopped and the consumption increased again because people forgot it and the pressure for obtaining an AB prescription increased again on the GP. Thus, the authorities decided to launch a new initiative. We do not know if we will have again a new decrease. The conclusion is: it is necessary to have a constant strategy. This was the case for hospitals with a succession of 5 strategic plans, with mandatory indicators to report and to fulfil, with an excellent result! It is necessary to maintain the pressure.
Q8	**What is the difference in the scope of EARS-Net and HAI-Net?**
A8	EARS-Net collects the data on resistance of specific microorganisms without information on the patients. HAI-net conducts point prevalence surveys with individual patient level data such as indication, age, gender, microorganism…)

S6/7/8 – SOURCE OF DATA / MEASURE UNITS / CATEGORIES

Q1	**Where do we get the data for sales?**
A1	They are communicated by the producers and the pharmaceutical laboratories.

Q2	**In some countries the big hospitals have dedicated teams able to organize the surveillance and the control of AB use. This is not the case of the smallest hospitals?**
A2	As an example, the French system for HAIs control includes at the regional level a dedicated mobile team. Its activity is to help the small hospitals with a constant mobility, part of the profile of described tasks.
Q3	**How the data on use of antimicrobials in human and in animals can be compared?**
A3	Example of the processing and comparison of the data is given e.g. in the JIACRA report. Despite the human data is calculated in DDD and currently data from veterinary part is available as mg/PCU or tonnes of antimicrobial active substances used, there were made recalculations to express weight number of antimicrobials in both areas/biomas (consensual) calculated from both areas. It is recommended reading very carefully all information and even footnotes given in the report to better understand what is behind the Figures (especially Figure 6) where comparison hum/vet in different MSs is given. Data should be interpreted with great care and understanding e.g. that not all data from human sector are “full coverage”, as some MSs reports include the community data only (and not hospitals) or have not covered whole human sector. Attention should be given also to careful comparison of hum/vet (average vs median - difference explained).
Q4	**Are ESAC-Net and EARS-Net collecting the data only from human side?**
A4	Yes, they are collecting data only from human side.
Q5	**Is EURGen only doing fentyping based surveillance or genotyping as well?**
A5	EURGen has the objective of whole genome sequencing-based surveillance.
Q6	**Are described data sources only intended for human antibiotic use or veterinary as well?**
A6	Yes, only for human antibiotic use.
Q7	**How is pharma industry involved in the efforts to decrease antibiotic consumption?**
A7	Pharmaceutical industry is getting involved in antimicrobial stewardship activities, organizing educational courses etc. However, there is no profit for industry with such approach. Research projects are being initiated that will find a solution how this problem can be overcome, such as new economic models.
Q8	**Regarding sales of antibiotics, what about informal sales by internet?**
A8	It is indeed a problem because it cannot be controlled, and it is illegal.
Q9	**Who leads harmonisation between human and animal sector regarding the AMR?**
A9	JIACRA, a collaboration between ECDC, EMA and EFSA.
Q10	**To calculate the PCU it is used the kg of different categories of livestock and also the ones which have been slaughtered. Why do you use the last ones if normally the animals which are slaughtered are not medicated?**
A10	This is about calculation of PCU as technical unit for comparison of largeness of animal population and most accurate counting of the animals. This is not linked with the period, in which animals are treated. And therefore, it is also considered that most antibiotics are used in young animals. Therefore, weight used is likely to be below final weight at slaughter. Combination of living animals number as well as slaughtered animals’ numbers as well as imported and exported animals are taken into account, when calculated PCU.
Q11	**If the DDD is not the recommended or prescribed doses, how is it reliable in measuring the use of ATM?**

A11	T2 – Public health: We do not have anything more reliable for the public health sector. T3 – Veterinary: Similarly in vet sector. But again no sole possibility exist around scientific publications, as some countries use different concept (e.g. Animal Treatment Index = treated animals x treatment days x # substances / total animal occupation etc.) ... see also Frontiers | Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes | Veterinary Science (frontiersin.org), or Figure 5 in https://link.springer.com/chapter/10.1007/978-3-030-46721-0_4
Q12	**Do you have data on where antibiotics across Europe are manufactured?**
A12	No, the ESVAC report looks at sales of antibiotics for use in a particular Member States and does not look where products are manufactured.
Q13	**What are alternatives to antibiotics e.g., what are pro-biotics and pre-biotics? And how are the alternatives authorised?**
A13	The RONAFA report provides a good summary of the different alternatives to antibiotics. These are often not "alternatives" as such (e.g., for treating clinical disease) but measures that can prevent the need to treat with antibiotics in the first place. Prebiotics are defined within RONAFA as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" whereas probiotics are "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth of or limited number of bacteria in the colon, and thus improves host health". As for authorisation, it varies. Some are licensed as Veterinary Medicinal Products, some as feed additives and some are not licensed products. RONAFA explains that, while there are numerous published papers, only a limited number provide robust scientific evidence that conclusively prove they are successful alternatives, and it was suggested that a framework at the EU level should be developed for the regulation of substances that reduce the need for antimicrobials and do not sit within the definition of a Veterinary Medicinal Product or Feed Additive.
Q14	**Can Member States send a question/mandate to EFSA or is it just the European Commission?**
A14	Yes, as shown in the diagram, questions can be raised by the European Commission, European Parliament, or individual Member States.
Q15	**Can you tell me the difference between course doses and daily doses? I do not understand course doses.**
A15	A daily dose metric takes represents the average number of days each animal is exposed to antibiotic – considering the dose given for each day and, in the case of long-acting products, the length of activity for that product. A course dose metrics, however, represents the average number of courses that each animal receives and therefore considers not just the dose given for each day but also the course length.
Q16	**Is it correct that EARS-Net only collects AMR data of invasive infections (of hospitalized patients)? How well does the suggested EARS-vet parallel it? Should the AMR data collection in humans be expanded also to other kinds of infections (in addition to food- and waterborne, zoonotic, and invasive) if the above is true?**
A16	Yes, EARS-Net collects the data on invasive isolates from blood and CSF only. The expansion of data collection could be discussed with the ECDC. It might be very difficult to collect all the data from all the Member states.
Q17	**I didn't understand if the DDDs are calculated based on consumption data, sales data, or on real administrations data…**
A17	DDDs are technical statistical units. The number of DDDs of a certain drug can be calculated regardless of the data source. We need to know what is the amount and strength of single items consumed.
Q18	**Are there any data protection issues in reporting the data?**

A18	Respecting the data protection regulation in the ESAC-Net dana are public reports present the dana only up to the 4th ATC level.
Q19	**How are AMC data collected on the "ground"?**
A19	There is a National focal point appointed in each member state and he/she is responsible for data collection. Very often it is organized by the MoH and is mandatory
Q20	**What is the difference between reimbursement data and sales data?**
A20	Reimbursement data come from health insurers. If health insurance coverage is 100% of population, the data are accurate. If not all the population is insured, the data are not complete. Sales data are obtained from wholesalers who sell drugs to hospitals and pharmacies. The drugs may be stocked in pharmacies and not consumed. Sales data may represent an overestimation of AMC.
Q21	**Please explain the term reimbursement.**
A21	Reimbursement refers to coverage of drug cost in the health insurance scheme
Q22	**Is there a uniform metric for expressing AMC in humans and animals?**
A22	Although not perfect, for the purpose of comparison AMC between sector a metric mg/kg estimated biomass is used in JIACRA.

S9 – EU GUIDELINES ON AMR

Q1	**What is being done for raising public awareness beyond the EAAD campaign?**
A1	Media contacts, Radio & TV interviews are concentrated around the EAAD but raising public awareness should be a continuous activity. Such continuous activities include school education programs like programs proposed by the e-Bug project, teaching through gaming etc. In Croatia, we have a preschool program based on a picture book that is distributed to children in kindergartens following a short education for care givers and parents on infection control and getting well without antibiotics for common cold.
Q2	**Prescription obligatory by vets only (non-EU country Q)?**
A2	In EU yes (but based on national legal provisions, in most countries only veterinarian can prescribe VMPs (including antimicrobials), in some MSs (UK, NO) also professionals defined by national legal provisions (I think e.g., licensed marine biologist) can do so.
Q3	**How to ensure incomes of vets in systems where no profit from prescription/sales is allowed?**
A3	Different experiences come from different countries – those with no profit allowed: Vets have some fixed income part + payment for service + payment for visits (weekends, holidays etc.) – decoupling from sales of VMPs. Insurance companies that can help to cover treatment and can help to vet gain money they should earn by treatment (independency on prescription/sales of VMPs). Agreements farmers/vets – with certain part of vet care linked with fixed incomes.

S10 – MONITORING AND REPORTING OF AMR IN VETERINARY MEDICINE

Q1	**Are national salmonellosis control programs in place every year and are they part of the antimicrobial resistance monitoring program?**
A1	National programs for the control of salmonellosis in birds date before to the start of the AMP monitoring program. They are conducted to minimize salmonellosis infected flocks. Salmonella isolates, which are identified to Salmonella serovar, are collected

	during their conduct and then tested with the appropriate EUVSEC and EUVSEC2 panels to determine their microbial resistance.
Q2	**You said that 170 samples were collected and tested to isolate commensal E. coli and salmonella, is that enough to characterize the situation in a given country?**
A2	In fact, we were talking about testing 170 isolates of the bacteria, E. coli in particular. In order to collect them, we are testing a lot more samples of feces or collected meat at retail. I give you an example with C. jejuni: in order to collect 85-90 isolates, we must test 400-450 fecal bird samples because most of the isolates are C. coli. Each EU Member State receives an annual decision from the EC with recorded requirements regarding the relevant reporting indicators and the maximum amount of reimbursement for monitoring expenditure.
Q3	**What do you do when you sample pig farms because you said there was a problem?**
A3	Samples shall be taken after the pigs have been slaughtered. The problem is that a farm is an epidemiological unit, which means we have to sample 300 farms, regardless of their size. This is extremely difficult and duplication of pig samples or cattle from the same farm occurs. This is against the program's sampling rules.
Q4	**About randomised sampling, how do lab-workers do it? You mentioned that you are involved in the preparation of your program, how does it work?**
A4	It is up to each EU Member State to decide who will participate in these working groups to prepare next year's monitoring plans. I set an example with myself and my involvement. In addition to my direct laboratory experience, I also have an administrative background, as well as a good knowledge of the practice, which is why I am the leader of the working groups for the preparation of the plan. In life, in principle, things are made by people who can do them. There is no prescription in this respect, each country decides how and by whom the rules are followed.
Q5	**What is better: immediately after isolation and identification of the campylobacter, to determine their sensitivity to the antimicrobials or to do so at a later stage?**
A5	My practical experience has shown me not to delay things with testing the campylobacter and immediately fill the plates with them. Campylobacteria are such sensitive microorganisms that the likelihood of revitalising them after freezing is problematic.
Q6	**Don’t you test Klebsiella pneumonie in animals?**
A6	Klebsiels are undoubtedly an important pathogen in humans, but they are not currently being tested in veterinary medicine. It is also true that through the products they can enter the human body.
Q7	**You said that you do not collect meat from administrative units with a small population. Does this not pose a risk to people and does it not change the reliability of the study?**
A7	I gave an example of how to prepare a meat sampling plan as required. As you recall, it is important that at least 80 percent of the population of the country's administrative units are included in the monitoring. In the example I gave you, we cover 94 percent of the population. And in the case of risk cannot be talked about.
Q8	**Are salmonella and E. coli isolates tested with clavulanic acid and how are beta-lactamase-producing isolates separated?**

A8	Of course, with the first panel we determine the sensitivity of the isolates to cefotaxime, ceftazidime and meropenem, and those that show resistance to even one of them are tested with the second panel, which includes clavulanic acid to demonstrate synergism and separation of the isolates into true ESBL and AmpC.
Q9	**Are these sample numbers the national target numbers for each member state?**
A9	Of course, these are the number of samples for each Member State that produce poultry and pork over 100 thousand tonnes per year and over 50 thousand tonnes of beef. In cases below these quantities, 50 percent are tested, ie. 150 samples each. This ensures the representativeness of the collected samples.
Q10	**Is it 170 isolates /bacterial species or 170 isolates for the 3 species together?**
A10	The isolates to be tested are 170 for each species of micro-organism sought. As I pointed out in the presentation, the problem has always been related to the number of salmonella isolates tested. Many Member States are unable to meet this target.
Q11	**What is the penalty if samples are unsatisfactory?**
A11	Failure to meet the indicators set in the monitoring program leads to the possible implementation of a mission by the EC, to inform the relevant Minister of Agriculture of the Member State or the head of the competent institution that the program is not implemented. In addition, it should be emphasized that the EC reimburses a large part of the costs incurred based on the volume of work done and reported data in EFSA.
Q12	**Sample processing within 48hrs from sampling, is it same all species?** **If a country has difficulty achieving sample numbers in first year 2021 are there penalties?**
A12	The rule when performing microbiological tests is to start developing the sample as soon as possible. Yes, 48 hours after the time of sampling is the general rule for starting the test. It should be borne in mind that some bacteria, such as campylobacter, are too sensitive and cause problems if we are late with the test. I should note from my practice that this problem no longer exists, colleagues in the field are trained and there are ways to send them immediately to the testing laboratory. At the beginning (2014-2015) there were unconditionally problems related to the delay of the samples. I have already answered your colleague from Ireland on the question of penalties for non-compliance with the program.
Q13	**Regarding the national programmes, the MMSS must submit the monitoring programmes to EC previously for their approval?**
A13	The annual programs are developed by a working group at the end of the year and start on January 1 of the following year. They shall be approved by the head of the relevant competent institution in the country concerned. There is no requirement for the EC to approve them. When conducting audits by EC commissions, they require them and check them for compliance with the decision to conduct monitoring of the AMR.
Q14	**Does slaughter batch definition is intended for sampling procedure or for hygiene rules too?**
A14	The adopted new definition for the epidemiological unit "slaughter batch" is applied for the needs of the decision of the EC Commission for monitoring of the AMR.
Q15	**Why was the antibiotic panel changed for amikacin?**

A15	From 2021, after a discussion of the interested organizations in the monitoring of antimicrobial resistance, it was decided to add amikacin as an aminoglycoside antibiotic. This fact is due to its undeniable usefulness and its use in practice for the treatment of a wide range of bacterial infections.
Q16	**Why is Staphylococcus aureus not included in the mandatory monitoring?**
A16	In recent years, serious attention has been paid to Staphylococcus aureus, especially its distribution in pig farms. There are several EU countries that conduct their own national monitoring and report their data to EFSA. In the last 2-3 years, an in-depth discussion has taken place at EU level whether to include it in the mandatory monitoring or to keep the current situation. To date, the EC and Member States in the talks and discussions have not reached a conclusion to include in the monitoring and this pathogenic microorganism. In our training, attention is paid to staphylococci and after a while this will be a fact.
Q17	**Can BCP samples be frozen meat?**
A17	According to EU Regulation 853/2004 the definition of “fresh meat is “1.10. ‘Fresh meat’ means meat that has not undergone any preserving process other than chilling, freezing, or quick-freezing, including meat that is vacuum-wrapped or wrapped in a controlled atmosphere”. As a result of this we can collect frozen meat and send to laboratory for testing.
Q18	**When no EUCAST breakpoints are available is it possible to refers to CLSI breakpoints?**
A18	I understand your question, but if we are talking about interpreting the results of our monitoring conducted under the EC decision last year, we do not need to resort to US standards, because the Decision has such limit values that must be used. They were in fact received from our European organization such as EUCAST and recorded in the Decision.
Q19	**If there are identified violations or discrepancies in the implementation of the Decision on monitoring of antimicrobial resistance, how is their elimination?**
A19	Very nice question. As you have seen, the EC has special groups of specialists who conduct audits in the respective countries. If problems are identified in these missions, which are described in a report, the Member State concerned must promptly rectify the irregularities found and report thereon. This is not the end of the matter, because in one of the other missions in the country concerned, an on-the-spot check may be included to find out that they have indeed been removed.
Q20	**What is the reason why salmonella isolates obtained after the slaughter of pigs and cattle, according to the requirements of Regulation 2073, are not used in the monitoring of AMP, and this was allowed in the previous Commission Decision of 2013?**
A20	The EFSA Working Party, which issued an opinion before the text of this Decision was agreed, justified the need to collect isolates from faecal samples from pigs and cattle, which better characterize the problem of Salmonella resistance. On the other hand, the number of salmonella isolates collected under Regulation 2073 was not large enough for the purposes of the monitoring program.
Q21	**You mentioned that there are changes in the antibiotic plates you use, which antibiotics are added or excluded for testing for salmonella and E. coli?**

A21	Amikacin, which belongs to the group of aminoglycosides, was added.
Q22	**How many samples have been collected from the border posts?**
A22	In the case of Bulgaria, which I can say with confidence, we do not have samples at the moment simply because we do not import pork and beef from third countries. Our market is fed with Bulgarian meat or meat imported from other EU member states.

S11 – MONITORING AND REPORTING OF AMR IN HUMAN MEDICINE

Q1	**When you define the ECOFF, you say without acquired mechanism of resistance?**
A1	An epidemiological cut-off value (ECOFF) is a concentration that separates the wild type population (population with no acquire resistance mechanisms) form those that has an acquire resistance mechanism. The ECOFFs are relevant from a microbiological point of view as they can be used to recognize isolates that might acquire a resistant mechanism, include those low-level expressed. Moreover, they are useful to calculate percentage of populations that might have resistance mechanisms irrespective of breakpoints and to compare bacterial populations regarding acquired resistance mechanisms between human and animal sectors. The ECOFF values can be found at EUCAST webpage www.eucast.org.
Q2	**When do you need to perform genome sequencing?**
A2	Whole genome sequencing is a matter of increasing interest and is being introduced in clinical microbiology laboratory. Results can be used to identify presence or absence, or resistance genes and different articles have been trying to correlate with phenotypic resistance. According to EUCAST subcommittee of whole genome sequencing, the WGS results should be compared using ECOFF values and not with breakpoints.
Q3	**How the MIC works?**
A3	This is an in vitro parameter obtain confronting a standard inoculum of a microorganisms with serial dilutions of an antimicrobial agent. The lowest antimicrobial concentration inhibiting the growth of a microorganisms defined the MIC value. Later, this value help to classify the bacteria as susceptible (S), susceptible increase exposure (I) and resistant (R) when using breakpoints stablished by EUCAST (in EU) or CLSI (in USA). The MIC value is also used to define the epidemiological cut-off value (ECOFF), which is a concentration (in fact a MIC) that separates the wild type population (population with no acquire resistance mechanisms) form those that has an acquire resistance mechanism. The ECOFFs are relevant from a microbiological point of view as they can be used to recognize isolates that might acquire a resistant mechanism, include those low-level expressed. Moreover, they are useful to calculate percentage of populations that might have resistance mechanisms irrespective of breakpoints and to compare bacterial populations regarding acquired resistance mechanisms between human and animal sectors. The ECOFF values can be found at EUCAST webpage www.eucast.org.
Q4	**Can I use disk diffusion to accurately define the susceptibility?**
A4	Yes, disk diffusion is calibrated with MIC values. In the absence of MIC values, inhibition zones obtained in disc diffusion and more importantly their interpretation (S, I or R) using breakpoints can be also use for surveillance. EUCAST web page publish disk diffusion breakpoints and the corresponding result of the calibration (www.eucast.org).

Q5	**The ECOFF (Epidemiological Cut Off): a more extensive explanation of the concept?**
A5	The in vitro parameter obtained when confronting a standard inoculum of a microorganism against a serial dilution of an antimicrobial agent is the MIC (minimum inhibitory concentration that inhibits the visible growth of a bacterial inoculum). The MIC value classifies bacteria as susceptible (S), susceptible increase exposure (I) and resistant (R) when using breakpoints established by EUCAST (in EU) or CLSI (in USA). The MIC value is also used to define the epidemiological cut-off value (ECOFF), which is a concentration (a MIC value) that separates the wild type population (population with no acquired resistance mechanisms) form that having an acquired resistance mechanism, including those of low-level expression. The ECOFF values can be found at EUCAST webpage www.eucast.org
Q6	**Can you enlarge how the ECOFFs are calculated?**
A6	This is an in vitro parameter. We first need to calculate MIC values for a specific antibiotic in collection of isolates from the same species. The epidemiological cut-off value (ECOFF) is a concentration (in fact a MIC) that separates the wild type population (population with no acquire resistance mechanisms) form those that has an acquire resistance mechanism. The ECOFFs are relevant from a microbiological point of view as they can be used to recognize isolates that might acquire a resistant mechanism, include those low-level expressed. Moreover, they are useful to calculate percentage of populations that might have resistance mechanisms irrespective of breakpoints and to compare bacterial populations regarding acquired resistance mechanisms between human and animal sectors. The ECOFF values can be found at EUCAST webpage www.eucast.org. They can be calculated visually or using a mathematical program that can be also found in the EUCAST web page. Also, a SOP (standard operation procedure) of this process.
Q7	**Why only few species and antibiotics in surveillance studies?**
A7	These can be the minimum set of microorganism and antibiotic to track antibiotic resistance trends and potential emergence of resistance mechanism. They are from blood in the EARS-net surveillance program as these isolates are normally further study and susceptibility testing performed. They are considered as sentinels. In the future data will be automatically obtained and offered in real time with machine learning and deep learning tools in the analysis. Some programs are being implemented in different countries

S12 - INTERPRETATION OF RESULTS FROM BREAKPOINTS

Q1	**Are the intrinsic resistance mechanisms covered by the ECOFF?**
A1	The ECOFF separates wild type populations from those that have acquired resistance mechanisms. If the bacteria have an intrinsic resistance mechanism (all the population are naturally resistant), the ECOFF can also define this population.
Q2	***mcr-1* positive isolates, how difficult is its detection? Are colistin ECOFF useful?**
A2	Yes, ECOFFs are useful. Isolates with colistin MIC values higher than the ECOFF have more probability to have this colistin resistant gene. A molecular test is needed to discriminate the potential presence of *mcr-1* gene or other resistance mechanism.

S13 - Introduction to environmental risks

Q1	**Where should we find environmental resistance?**
A1	Environmental resistance occurs ubiquitously in the environment; if you look for resistance genes or bacteria you will invariably find them in any environment.

S14 - Relevance of AMR to Environment and related Regulators

Q1	**What is the difference and the significance of a source and a pathway of AMR to the environment?**
A1	The sources are the main origins of AMR to the environment. Are limited and can be easily identified. The pathways are the routes that the AMR follow to reach the different environmental compartments and are very diverse and more difficult to identify. Identifying the pathways that pose greater risk for the human/animal health (higher exposure of higher hazard) we can focus of those that require greater attention to reduce the risks. If we move backwards from those pathways, we will reach the sources on which we can act to reducer the exposure and prioritize.
Q2	**How can the emission of AMR in aquaculture be controlled?**
A2	In open sea aquaculture the farmers can use tarpaulins around the cages to limit the emission to the surrounding water. In continental aquaculture the wastes can be treated (decanter, filtration, UV or O3 treatment) before the discharge to surface waters. There is also possibility of working in new administration methods that limit the total emission of a single treatment.
Q3	**How relevant is the emission from hospitals? And from manufacturing?**
A3	There is an issue of uncertainty with regards to these sources. According to unpublished data of pharma industry these two sources are almost irrelevant in the global emission of antibiotics. There are just a few of industries in the world. Nevertheless, this source can be extremely relevant locally and should not be disregarded. There is a proposal to consider the inclusion of the environment emission from production sites in the GMP. Hospitals might also not be the highest emission source, but it should be taken into account that the antibiotics used there are frequently critical antibiotics. There are ongoing research projects aiming at treating sewage produced in hospital before the emission to the mains.
Q4	**Could you tell me for example the international standards that comply with (AMR) and considered approved by WHO?**
A4	There are no recognised standards for AMR, i.e., no internationally recognised or agreed standards.
Q5	**Is there a daily concentration for animals or for humans for AMR?**
A5	Understanding the concept of extrapolation of dose between species is important when initiating new animal or human experiments. Interspecies allometric scaling for dose conversion from animal to human studies is one of the most controversial areas in pharmacology and does not apply to aspects of AMR. There is no correlation between received “dose” (exposure) and development of AMR.

Q6	**Is it true that low concentrations of AM already increase the mutation rates and genetic material transfer in bacteria?**
A6	There is dose independence between concentration of an antibiotic in the environment and the level of elicited AMR that develops.
Q7	**Relating to the land spreading of animal manure, is there any evidence of AMR transmission to the cultivated plants, or the problem remains in the soil (and in the waters)?**
A7	There is evidence of movement from manures to soils to water including ground water, certainly irrigation of plants with grey water has shown increases in contamination of leaves and surfaces of crops etc. Also, the use of antibiotics directly on plants should be stopped.
Q8	**Is there a risk of ARM appearance if milk with antibiotic residues being poured onto farmland?**
A8	In essence yes, milk from treated animals should be disposed off with consideration of the likely consequence of disposing of an antibiotic into the environment.
Q9	**Pesticides that are used to prevent plant diseases, do they produce any antimicrobial resistance?**
A9	There is little evidence that use of pesticides will drive the development of AMR. If antibiotics are used on crops, then there will be implications for the development of resistance.
Q10	**Why have we neglected the plant sector as antibiotics are essential for the control of bacterial diseases of plants, especially fire blight of pear and apple and bacterial spot of peach that May cause AMR?**
A10	The FAO are very keen to reduce the use of antibiotics on crops in order to limit the development and spread of AMR.

S15 – JIACRA REPORT

S16 – SUMMARY