Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections

# Deliverable 7.5:

# Design, roadmap and feasibility of an integrated surveillance network of antimicrobial resistance in bacteria from diseased animals in Europe (EARS-Vet)

WP7.4.2 I Surveillance of AMR in diseased animals
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# Acronyms

AMC: antimicrobial consumption

AMR: antimicrobial resistance

AMS: antimicrobial stewardship

AMU: antimicrobial use

ANSES: French Agency for Food, Environmental and Occupational Health & Safety

AST: antimicrobial susceptibility testing

CEESA: European Animal Health Study Centre

CLSI: Clinical and Laboratory Standards Institute

COST: European Cooperation in Science and Technology

EARS-Net: European Antimicrobial Resistance Surveillance network

EARS-Vet: European Antimicrobial Resistance Surveillance network in Veterinary medicine

ECDC: European Centre for Disease Prevention and Control

ECOFF: epidemiological cut-off value

EEA: European Economic Area

EFSA: European Food Safety Authority

EMA: European Medicines Agency

ESVAC: European Surveillance of Veterinary Antimicrobial Consumption

EU: European Union

EUCAST: European Committee on Antimicrobial Susceptibility Testing

EU-JAMRAI: European Union Joint Action on AMR and Healthcare Associated Infections

FAO: Food and Agriculture Organization of the United Nations

FWD-Net: Food- and Waterborne Diseases and Zoonoses Network

JIACRA: Joint Interagency Antimicrobial Consumption and Resistance Analysis

JPIAMR: Joint Programming Initiative on Antimicrobial Resistance

CLSI: Clinical and Laboratory Standards Institute

MDR: Multidrug-Resistant

MRSA: Methicillin-Resistant *Staphylococcus Aureus*

MRSP: Methicillin-Resistant *Staphylococcus Pseudintermedius*

MS: Member States

NAP: National Action Plan

Vetcast: Veterinary Committee on Antimicrobial Susceptibility Testing

SWOT: Strengths, Weaknesses, Threats and Opportunities

WHO: World Health Organization

# Introduction

Antimicrobial resistance (AMR) has been widely recognized as a major One Health and global health issue. In the European Union (EU) and European Economic Area (EEA), the European Centre for Disease Prevention and Control (ECDC) estimates that multidrug-resistant bacteria cause approximately 33 000 deaths and 672 000 infections every year (Cassini et al. 2019) in humans. AMR also has a significant impact on animal health in both companion animals and livestock. For example, methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) frequently causes treatment failures and can lead to euthanasia in companion animals. Similarly, antimicrobial-resistant *Escherichia coli* and udder pathogens lead to significant economic losses in poultry and dairy cattle, respectively. These infections drive a high antimicrobial use (AMU) in animals, including with critically-important antimicrobials for human and veterinary medicine (WHO 2019; OIE 2018a). Additionally, some of the bacterial pathogens of animals are zoonotic (*e.g. Salmonella* spp., *Staphylococcus aureus*) or broadly shared between animals and humans (*E. coli*), so AMR acquisition in these bacteria could lead to more severe or complicated human infections.

To address this issue, strong AMR surveillance systems should be developed. Among others, they have to support the detection of AMR emergence, trends and patterns, the risk analysis and evidence-based AMR control interventions, the formulation of prescription guidelines, and the assessment of the impact of local, national, and global strategies for AMR control (OIE 2018b).

Three specific European surveillance programmes of AMR already exist. In the animal sector, the European Food Safety Authority (EFSA) coordinates an active monitoring of AMR in commensal and zoonotic bacteria from healthy food-producing animals (cattle <1 year, chicken broilers and fattening turkeys, pigs) at slaughterhouse and food thereof, in accordance with the Directive 2003/99/CE of the European Parliament and the Council and the Commission Implementing Decision 2013/652/EU (EFSA and ECDC 2020). In the human sector, the ECDC coordinates the European Antimicrobial Resistance Surveillance Network (EARS-Net), which monitors AMR in invasive bacteria isolated from blood and cerebrospinal fluid of hospitalised patients (ECDC 2019), as well as the Food- and Waterborne Diseases and Zoonoses Network (FWD-Net), which monitors AMR in *Salmonella* spp. and *Campylobacter* spp. (ECDC 2016). AMR data collected by these programmes are analysed together with antimicrobial consumption (AMC) data from both humans and food-producing animals as part of the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) (ECDC, EFSA and EMA 2017). Overall, these programmes provide valuable insights into the public health impact of AMR and the spread to humans through the food chain, and support evidence-based risk management of AMR in food.

Importantly, and whereas most AMR data in the human sector originate from diseased individuals, these surveillance systems lack AMR data from clinical isolates of animals. They are therefore of little help to assist veterinary practitioners in antimicrobial choices and policy makers to regulate veterinary antimicrobial use, with the dual goal of reducing AMR while ensuring optimal treatment of animal infections. Of note, some programmes (VetPath, ComPath and MycoPath) managed by the European Animal Health Study Centre (CEESA) on behalf of a consortium of pharmaceutical companies, produce harmonized AMR data in diseased food-producing and companion animals across Europe (de Jong et al. 2013). However, these programmes, which were designed to meet regulatory requirements for marketing authorizations of antimicrobials, provide limited and intermittent data per country, and have low timeliness (results published at least five years after data collection). Therefore, they cannot be considered as a substitute for a European surveillance programme of AMR in diseased animals.

**To fill this important gap in AMR surveillance in Europe, we have explored in EU-JAMRAI Task 7.4.2 the possibility to build a European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet).**

# Objectives of Task 7.4.2

The specific objectives of Task 7.4.2 were to:

1. Describe and assess the surveillance systems in place on AMR in animal pathogens in participating member states (MS).
2. Identify the main gaps and appropriate strategies for AMR surveillance in diseased animals in Europe, taking into consideration MS specificities and diversity in animal species and diseases.
3. Define the EARS-Vet surveillance scope, i.e. the combinations of animal species, bacterial species and antimicrobials which would be the most relevant and feasible to monitor at EU level. In the One Health approach, the feasibility of inclusion of carbapenemase-producing Enterobacterales, extended spectrum ß-lactamase-producing (ESBL) *Escherichia coli*, ESBL *Klebsiella pneumoniae*, multidrug resistant (MDR) *Pseudomonas aeruginosa*, MDR *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), colistin-resistant Enterobacterales, vancomycin resistant enterococci (*E. faecalis* and *E. faecium*) in the EARS-Vet surveillance scope will be investigated.
4. Identify laboratory and technical capacities in MS for potential establishment of a molecular-based AMR national surveillance of relevant resistant pathogens, to be further compared with human counterparts.
5. Assess the opportunities and challenges to combine MS surveillance systems into a pilot EARS-Vet network.
6. Draw guidelines for uploading, validation and management of the data, with particular emphasis on accuracy and types of the data (per animal species, pathogen and disease) under each national coordinator's responsibility.
7. Provide general and specific recommendations to the European Commission to build EARS-Vet, including interface with AMR surveillance in human medicine.

With the aim to develop synergies between European initiatives, a collaboration was set up between the EU-JAMRAI and the ARCH (bridging the gap between humAn and animal suRveillance data, antibiotic poliCy, and stewardsHip) network of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). This collaboration aimed to provide guidance regarding the production and use of AMR and AMC data to plan and implement antimicrobial stewardship (AMS) programmes in different veterinary contexts and in line with the One Health approach.

# Description and assessment of existing surveillance systems in participating Member States

## Review and analysis of existing national surveillance systems

EU-JAMRAI partners were contacted in 27 EU/EEA countries (Austria, Belgium, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Ireland, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) and asked if a national surveillance system for AMR in diseased animals was in place in their country.

In the countries with an existing surveillance system for AMR in diseased animals, the system was described using a semi-structured questionnaire covering the following key areas: (i) political and financial support, (ii) objectives, (iii) central institutional organization, (iv) laboratory network, (v) monitoring procedures, (vi) laboratory techniques, (vii) data management and analysis, (viii) communication and (ix) evaluation. In addition, an analysis of the strengths, weaknesses, threats and opportunities (SWOTs) of the surveillance systems was performed. The SWOT analyses and questionnaire were completed during country visits (France visiting other countries) where physical meetings with national experts coordinating and/or involved in AMR surveillance in diseased animals were organised. An exception was made for Estonia where two virtual meetings were organised instead, due to travel restrictions linked to the COVID-19 pandemic.

Detailed results of this survey will be published in an international peer-reviewed scientific publication. Briefly, twelve countries have a system: Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Netherlands, Norway, Spain, Sweden and the United Kingdom. Important gaps in AMR data generation in Europe and a high diversity in the existing surveillance systems were identified. Systems in place do not always monitor the same animal species, bacterial species and antimicrobials, and do not always use the same AST methodologies and interpretative criteria. Most systems share common weaknesses (e.g. data management) and common threats (e.g. data access, economic sustainability), which could be addressed collectively under EARS-Vet.

## Evaluation of the French surveillance system – RESAPATH

The content of this section is based on the following publication:

> Mader R, Jarrige N, Haenni M, Bourély C, Madec JY, Amat JP on behalf of EU-JAMRAI. OASIS evaluation of the French surveillance network for antimicrobial resistance in diseased animals (RESAPATH): success factors at the basis of a well-performing volunteer system. *BioRxiv*, April 2021, https://doi.org/10.1101/2021.04.07.438805

France volunteered for a thorough evaluation of its national surveillance system called RESAPATH (https://resapath.anses.fr/). Briefly, RESAPATH is coordinated by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) and has a long-term (>30 years) history of AMR surveillance in diseased companion and livestock animal species, including ruminants, swine, poultry, rabbits, fish, horses, dogs, cats and exotic animals. In 2017, RESAPATH was composed of 71 volunteer public or private veterinary diagnostic laboratories collecting resistance data for >50,000 isolates from diverse specimens. Over the years, RESAPATH has become an important component of the French National Action Plan (NAP) to tackle AMR in the animal sector, so-called ECOANTIBIO 1 (2012-2017) and ECOANTIBIO 2 (2017-2021).

RESAPATH was evaluated with the OASIS evaluation framework (Hendrikx et al. 2011). Briefly, this semi-quantitative method enables to perform standardized, detailed and comprehensive evaluation of the organization and operations of surveillance systems. First, a questionnaire is fulfilled using available literature and interviews with key stakeholders of the surveillance system. Subsequently, an Excel-based evaluation grid composed of 78 criteria which are marked from 0 (lowest possible score) to 3 (highest possible score) is completed, with the support of a scoring guide. Scores and their justifications are later evaluated during a 1-day meeting with key stakeholders and end-users of the system. Results are displayed using three figures that give a complementary view on the system's strengths and weaknesses.

Results of the evaluation are presented in the below figures.

| Functional section | Graphical result | Score |
|---|---|---|
| 1. Objectives and scope of the surveillance |  | 83% |
| 2. Central institutional organization |  | 93% |
| 3. Field institutional organization |  | 67% |
| 4. Laboratory |  | 78% |
| 5. Surveillance tools |  | 67% |
| 6. Surveillance procedures |  | 89% |
| 7. Data management |  | 81% |
| 8. Training |  | 89% |
| 9. Communication |  | 67% |
| 10. Evaluation and performance indicators |  | 92% |

*Figure 1 Scores of RESAPATH obtained for the ten OASIS functional sections (indicated in proportions of the maximum possible score) in 2018.*

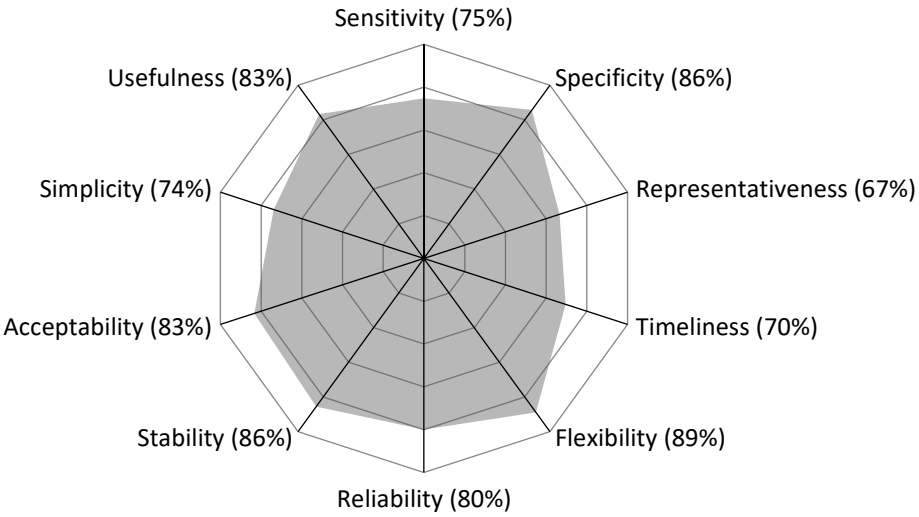


*Figure 2 Scores of RESAPATH obtained for the ten OASIS attributes (indicated in proportions of the maximum possible score) in 2018.*

Overall, RESAPATH exhibited good evaluation scores, proving that a well-performing participative surveillance system of AMR in diseased animals is a realistic option to be included in the frame of a NAP. Major strengths of the RESAPATH included (i) a strong and inclusive central institutional organization defining clear and well accepted surveillance objectives, scope and procedures, (ii) strong skills in epidemiology and microbiology and (iii) a win-win approach encouraging the voluntary participation of 71 field laboratories and where an annual proficiency testing organized and financially supported by ANSES plays a pivotal role.

The OASIS evaluation also identified areas for improvement and provided a series of recommendations. Among others, it was recommended to increase resources and improve tools that would enable RESAPATH to include more laboratories, *e.g.* via the development of an automated IT tool to facilitate data transfer and centralization from field laboratories to ANSES, which is a time-consuming task. Solutions were also proposed to address sampling bias, *e.g.* by asking veterinarians to report whether animals were treated with an antimicrobial prior to AMR sampling.

Overall, the evaluation of RESAPATH provided valuable information to countries aiming to set up a national AMR surveillance system in diseased animals using a passive surveillance approach or to those wishing to improve their current system.

# Identification of the main gaps and appropriate strategies for AMR surveillance in diseased animals in Europe

The content of this section is based on the following publication:

- Mader R, Damborg P, Amat J-P, Bengtsson B, Bourély C, Broens EM, Busani L, Crespo P, Filippitzi M-E, Fitzgerald W, Kaspar H, Munoz C, Norström M, Nykäsenoja S, Pedersen K, Pokludova L, Urdahl AM, Vatopoulos A, Zafeiridis C, Madec J-Y on behalf of EU-JAMRAI. Time to build the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet). *Eurosurveillance* 2021; 26(4):pii=2001359. https://doi.org/10.2807/1560-7917.ES.2021.26.4.2001359

## Gaps and opportunities for AMR surveillance in diseased animals in Europe

The descriptive analysis and the evaluation of national surveillance systems performed among EU/EEA countries as part of EU-JAMRAI Task 7.4.2 showed that many EU/EEA countries (at least 12) already have a national surveillance system for AMR in bacterial pathogens of animals, but that they are heterogeneous. On the other hand, many countries do not have such a surveillance system of AMR in diseased animals, even though research-based information may be provided occasionally. However, the number of European countries implementing an AMR surveillance system in veterinary medicine is expected to rise in the near future. Some countries (e.g. Spain) are currently developing their system, while the National Action Plan (NAP) of others (e.g. Italy or Belgium) highlights the need and willingness to improve AMR surveillance in the veterinary domain.

These numerous initiatives represent a great opportunity to launch a coordinated surveillance at European level. They also highlight the urgency to develop a common European surveillance framework to address the lack of harmonisation between national surveillance systems. Such a network could be usefully integrated with EARS-Net, FWD-Net, the EFSA monitoring and the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). This initiative would be in line with Regulation (EU) 2016/429 on transmissible animal diseases ("Animal Health Law"), which states that "effective collection and management of surveillance data should be established at Union level […] when relevant, for emerging diseases or antimicrobial-resistant pathogens"; Regulation (EU) 2019/6 on veterinary medicinal products, which points out the need for AMR data; and the Council Conclusions of 14 June 2019 on the next steps towards making the EU a best practice region in combatting antimicrobial resistance.

## Expected benefits from EARS-Vet

*Surveillance objectives at European level*

EARS-Vet should report on the current AMR situation, follow trends and detect emerging AMR in bacterial pathogens of animals in Europe. With the aim to trigger tangible and sustainable results in the fight against AMR, this information could be used for:

- Policy advising. More targeted and efficient interventions could be devised thanks to a better understanding of the AMR situation and evolution, as well as of the links between AMC and AMR in animals and humans. Currently, those links are investigated in the Joint Inter-Agency Antimicrobial Consumption and Resistance Analysis (JIACRA) reports (ECDC, EFSA and EMA 2017), but analysed AMR data from the animal sector currently come from healthy animals only. Those links could be better explored using EARS-Vet data, which are closer to the animal point-of-care, i.e. where antimicrobials are used. From 2024, it will become mandatory for EU Member States to provide AMU data by animal species (in a stepwise approach, starting with the main food-producing animal species) in the framework of EU Regulation 2019/6. This makes EARS-Vet even more relevant, as resistance patterns in bacterial pathogens may then be linked to AMU at the animal species level.
- Monitoring the impact of European efforts to tackle AMR in the animal sector, such as the EU One Health Action Plan and the Animal Health Law.
- Supporting AMS initiatives, especially the development of veterinary antimicrobial treatment guidelines, which need accurate resistance data in animal pathogens. However, due to differences between countries in terms of animal populations, production systems, bacterial diseases, AMR situation and available authorised antimicrobials, such recommendations would need to be tailored to each country and only general indications could be defined at European level.
- Evaluating or revising marketing authorisations of antimicrobials, in the framework of Regulation (EU) 2019/6.
- Generating epidemiological cut-off values and then clinical breakpoints. Such interpretative criteria for AST are currently missing for many common combinations of animal species / bacterial species / infection site, thereby challenging the interpretation of AST results in the veterinary field. The distributions of AST results collected by EARS-Vet would be useful to breakpoint-setting organisations, such as the Veterinary Committee on Antimicrobial Susceptibility Testing (VetCAST) to define these interpretative criteria.
- Assessing the risk of AMR transmission from animals to humans via non-food related routes, e.g. by direct contact with companion or food animals. This

would enable to complement the risk assessments performed by EFSA for the foodborne pathway.
- Estimating the burden of AMR in animal health, e.g. attributable deaths caused by infections with antimicrobial-resistant bacteria. Such an estimation could be similar to the burden assessments performed in the human sector thanks to EARS-Net data (Cassini et al. 2019), which are particularly useful to raise awareness on the need to tackle AMR.
- Raising research questions and promoting research collaborations on AMR in Europe.

*Fostering harmonisation and synergies in Europe*

EARS-Vet would provide the necessary coordination to collectively define common microbiological and epidemiological standards for the surveillance of AMR in animal bacterial pathogens in Europe, as well as a strategy to reach an effective harmonisation. More broadly, EARS-Vet represents a unique opportunity to build a European scientific community and knowledge hub to support the establishment, improvement and harmonisation of surveillance systems, a sound interpretation of surveillance outputs and their translation into interventions.

This EARS-Vet community could also prove critically useful in urgent contexts, for example when an emerging resistance type is discovered and its spread across Europe needs to be quickly evaluated, as experienced in 2015 upon the discovery of plasmid-mediated colistin resistance (Liu et al. 2016).

## A pragmatic strategy to design EARS-Vet

One of the first steps in designing EARS-Vet would be the definition of a surveillance framework, including its surveillance scope (i.e. the animal species, production types, age categories, bacterial species, diseases and antimicrobials to be covered), the antimicrobial susceptibility testing standards, the metadata to be collected (including minimum and desirable variables), the data governance, the frequency of data reporting, the general data management system and procedures (including data cleaning and validation) and how data would be analysed and communicated.

This framework should ensure that EARS-Vet can meet the above-mentioned surveillance objectives and facilitate a wide country participation. It should also address two major challenges for EARS-Vet: the current lack of method harmonisation and possible sampling biases.

To reach harmonisation, we recommend defining EARS-Vet standards in an inclusive and bottom-up approach, i.e. according to what is considered relevant and feasible within countries. In the beginning, we recommend that EARS-Vet accepts different standards over a transition period, as originally done by EARS-Net, which collected AMR data obtained using diverse standards during two decades before accepting only

those complying with the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

The possible sampling biases are linked to the fact that national surveillance systems usually collect AST results routinely produced in veterinary diagnostic laboratories. As ASTs are often performed after treatment failure, AMR levels tend to be overestimated. Such biased estimates can have important consequences, including wrongly recommending the use of critically important antimicrobials as first line treatments when other antimicrobials will actually be effective in the majority of cases. In order to ensure comparability of AMR data between countries, the representativeness of AMR data would need to be assessed before interpreting results. As in EARS-Net, a series of indicators of national geographic coverage and representativeness should be defined and regularly calculated to understand the validity of surveillance data. Besides, pragmatic solutions need to be explored collectively to address sampling biases. Of note, some countries have decided to subsidise ASTs (e.g. Czech Republic) to collect more representative AMR data comprising a broader range of cases (i.e. not only those during treatment failure).

# Definition of the EARS-Vet surveillance scope

The content of this section is based on the following publication:

> Mader R on behalf of EU-JAMRAI, Bourély C, Amat J-P, Broens EM, Busani L, Callens B, Crespo P, Damborg P, Filippitzi M-E, Fitzgerald W, Grönthal T, Haenni M, Heuvelink A, van Hout J, Kaspar H, Munoz C, Norström M, Pedersen K, Pokludova L, Dal Pozzo F, Slowey R, Teixeira C, Urdahl AM, Vatopoulos A, Zafeiridis C, Madec J-Y. Defining the scope of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet): a bottom-up and One Health approach. *BioRxiv*, March 2021 https://doi.org/10.1101/2021.03.09.434124

A major step in the proposed design of EARS-Vet consisted in defining its surveillance scope, i.e. the combinations of animal species, production types, age categories, bacterial species, specimens and antimicrobials to be monitored in EARS-Vet. In this deliverable, we only provide a summary of our approach as well as the tables describing the proposed combinations of the EARS-Vet scope. For more detailed information, readers may refer to the bioRxiv pre-print (above).

The combinations of the EARS-Vet scope were determined in a bottom-up and One Health approach, i.e. by taking into account the combinations which are relevant and feasible to be monitored in national surveillance systems, as well as considering both animal health and human health perspectives, and the need for EARS-Vet to be complementary to EARS-Net and the EFSA monitoring. In practice, the EARS-Vet scope was defined by consensus among 26 experts from 14 European countries which met at six teleconferences.

The proposed EARS-Vet scope is summarised in Table 1 in terms of animal species, production types, specimens and bacterial species. Appendix 2 summarises the EARS-Vet scope at antimicrobial level respectively for cattle, swine, poultry (chicken and turkey) and companion animals (cat and dog).

Regarding initially proposed combinations in specific objective 3, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus faecalis* and *Enterococcus faecium* were not included in the EARS-Vet scope, as only few countries would be able to provide AMR surveillance information. However, carbapenemase-producing *Escherichia coli*, ESBL *E. coli*, methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *S. pseudintermedius* and colistin-resistant *E. coli* would be covered in the proposed scope. However, as carbapenems are not authorised as veterinary medicines in the EU, most laboratories will not include this class of antimicrobials routinely in their test panels and only few countries would be able to report resistance data to carbapenems.

*Table 1: Animal species, production types, specimens and bacterial species to be covered by the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet)*

| Animal species | Production type | Specimens | Bacterial species |
|---|---|---|---|
| **Cattle** | Any | Faeces | *Escherichia coli* |
| | | Blood and inner organs | *Escherichia coli* |
| | | Milk | *Escherichia coli* |
| | | | *Klebsiella pneumoniae* |
| | | | *Staphylococcus aureus* |
| | | | *Streptococcus uberis* |
| | | | *Steptococcus dysgalactiae* |
| | | Lungs and other samples from the lower or upper respiratory tract | *Mannheimia haemolytica* |
| | | | *Pasteurella multocida* |
| **Swine** | Any | Faeces | *Escherichia coli** |
| | | Inner organs (including lungs, spleen, joints etc.) | *Staphylococcus hyicus* |
| | | | *Streptococcus suis* |
| | | Lungs and inner organs | *Pasteurella multocida* |
| | | | *Actinobacillus pleuropneumoniae* |
| **Chicken** | Broilers | Inner organs (including spleen, bone marrow, joints etc.) | *Escherichia coli* |
| | Laying hen | Inner organs (including spleen, bone marrow, joints etc.) | *Escherichia coli* |
| | Broilers | Inner organs (including spleen, bone marrow, joints etc.) | *Staphylococcus aureus* |
| | Laying hen | Inner organs (including spleen, bone marrow, joints etc.) | *Staphylococcus aureus* |
| **Turkey** | - | Inner organs (including spleen, bone marrow, joints etc.) | *Escherichia coli* |
| **Dog** | - | Urine | *Escherichia coli* |
| | | Skin and ear | *Staphylococcus pseudintermedius* |
| | | | *Staphylococcus aureus* |
| **Cat** | - | Urine | *Escherichia coli* |
| | | Skin and ear | *Staphylococcus pseudintermedius* |
| | | | *Staphylococcus aureus* |

*Information on the virulence profile would be collected in EARS-Vet.

# Identification of laboratory and technical capacities in Member States

Molecular analyses of strains collected via surveillance activities are routinely performed in eight countries, either to confirm AST results, or to explore the molecular basis of uncommon AST profiles. However, the national experts met in all country visits reported that they had the technical capacity to perform molecular analyses, including Polymerase Chain Reactions (PCRs) or whole-genome sequencing (WGS), at least at a central level. The main limitation for performing more molecular analyses is currently the cost of these analyses.

For a future pilot phase of EARS-Vet, we recommend to only include a limited number of molecular surveillance data:

- PCR *mecA* results for *S. aureus* and *S. pseudintermerdius*
- Serotypes of *E. coli* (determined by any method, to be specified).

# Assessment of opportunities and challenges to combine Member States surveillance systems into a pilot EARS-Vet network

## Opportunities

We have carried out an internal survey within the 14 countries that have participated in the development of EARS-Vet so far. Among them, 11 have a national surveillance system in place and 10 of them have expressed their interest in participating in a pilot phase, representing a major opportunity to launch an EARS-Vet pilot phase. One country did not wish to participate in the pilot phase, as existing surveillance systems are not yet harmonised. The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) is ready to coordinate such a pilot phase.

## Challenges

*Country comparability*

As explained above, data comparability between countries would be a major challenge for an EARS-Vet pilot phase, as national surveillance systems are not harmonised. However, we believe that we need to start a pilot phase to progress collectively towards harmonisation and stronger comparability and that it is not realistic to ask countries to change their practices in the short-term. In the beginning, we recommend that EARS-Vet accepts different standards over a transition period, as originally done by EARS-Net, which collected AMR data obtained using diverse standards during two decades before accepting only those complying with the EUCAST. In addition, the representativeness of AMR data would need to be assessed before interpreting results. As in EARS-Net, a series of indicators of national geographic coverage and representativeness should be defined and regularly calculated to understand the validity of surveillance data. Besides, pragmatic solutions need to be explored collectively to address sampling biases. These criteria and solutions could be devised in parallel of an EARS-Vet pilot phase.

*Funding*

Participating in an EARS-Vet pilot phase requires funding. Indeed, each country needs to dedicate time for participating and as highlighted above, human and financial resources are frequent limitations of national surveillance systems. However, as EARS-Vet would rely on data routinely produced from each national surveillance system, no material costs would be needed for initiating an EARS-Vet pilot phase.

# Definition of an EARS-Vet data management plan

In preparation of the EARS-Vet pilot study, a template to be used for future data collection was developed and is provided in Appendix 3.

Prior to data collection, a data sharing agreement would need to be prepared among EARS-Vet participants. It will address important aspects such as:

- Period of agreement
- Intended use of the data, including how the data will be analysed and communicated (e.g. which level of aggregation)
- Any constraints on use of the data, e.g. limitations on data comparability
- Data ownership
- Data confidentiality
- Data security
- Methods of data-sharing and data management

Due to different national legislations regarding data ownership and sharing, the development of an EARS-Vet data sharing agreement should be addressed with caution.

# Provide general and specific recommendations to EU to build EARS-Vet

Building on the major achievements of the EU-JAMRAI, the next steps that are needed to continue the development of EARS-Vet will consist of the following:

On the short-term (2021-2023):

- To launch a pilot phase where participating countries will start sharing data and produce a first EARS-Vet report;
- To address important methodological aspects of EARS-Vet, including the assessment of the data representativeness and comparability across countries;
- To further work towards harmonization of methods and standards for AMR monitoring in diseased animals;
- To assist countries with no surveillance system of AMR in veterinary medicine in their efforts and initiatives to develop one, hence contributing to expand the preliminary network with additional countries;
- To further explore synergies with non-European regions and bring lessons and experiences from other parts of the world with similar initiatives.

On the mid-to long term (2023-2025):

- To prepare for inclusion of other AMR hazards of interest, such as those to be identified as priorities in the EFSA scientific opinion on the listing and categorisation of transmissible animal diseases caused by bacteria resistant to antimicrobials (expected by March 2022);
- To prepare for future integration of molecular data, including genomics data that are complementing conventional techniques for routine AMR monitoring.

To achieve these next steps, and more generally to ensure the sustainability of EARS-Vet, strong political commitment from EU and national policy makers is needed. A policy brief was produced to bring their attention on this important topic (see Appendix 4) and ask them to support the development of national surveillance systems of AMR in diseased animals and foster the participation of national agencies in the EARS-Vet initiative.

The economic sustainability of EARS-Vet is also a major issue. As a first attempt in this direction, a proposal was submitted to the November 2020 open call of the European Cooperation in Science and Technology (COST), in order to fund some of the upcoming EARS-Vet networking activities and expand the network beyond EU-JAMRAI countries. Results of the COST open call are expected in May 2021. However, long-term funding has to be secured.

Additionally, the EARS-Vet activities should continue to be conducted in close collaboration with relevant EU and international stakeholders. Applying from April 2021, the Animal Health Law opens for the possibility to regulate AMR surveillance in bacterial pathogens of animals in the EU. Thus, EARS-Vet could potentially be taken over by EU bodies (e.g. EFSA, ECDC, EMA), should they receive the mandate to coordinate this surveillance. This would ensure the integration of EARS-Vet within the European landscape of AMR surveillance and related initiatives, and contribute to achieving a stronger, truly One-Health surveillance of AMR in Europe.

# Bridging the gap between surveillance data and antimicrobial stewardship in the animal sector

The content of this section is based on the following publication:

> Compri M, Mader R, Mazzolini E, D Angelis J, Mutters NT, Babu Rajendran N, Galia L, Tacconelli E, Schrijver R on behalf of the ARCH working group. White Paper: Bridging the gap between surveillance data and antimicrobial stewardship in the animal sector - practical guidance from the JPIAMR-ARCH and COMBACTE-MAGNET EPI-Net Networks, *Journal of Antimicrobial Chemotherapy*, vol. 75, suppl 2: ii52-ii66. https://doi.org/10.1093/jac/dkaa429.

The JPIAMR-ARCH network (in which EU-JAMRAI is represented) and the COMBACTE-MAGNET EPI-Net network joined forces for the shared goal of implementing a framework of actions to facilitate antimicrobial stewardship interventions and foster use of surveillance data on AMR and AMU and implementation of AMS activities in human and animal health.

In this regard, the ARCH and COMBACTE-MAGNET EPI-Net international expert panel developed four White Papers corresponding to the hospital, outpatient, long-term care facility and veterinary settings. Each White Paper contains a series of target actions focused on three areas: 1) AMS leadership and accountability; 2) AMU and AMS; 3) AMR and AMS, all considering the feasibility of the actions and the One Health approach.

To define these target actions, a review of the literature was first carried out addressing research questions in those three areas. Then, consensus on target actions was reached through a RAND-modified Delphi involving over 40 experts in infectious diseases, clinical microbiology, AMS, veterinary medicine and public health, from 18 countries.

As a result, 46 target actions were developed and qualified as essential or desirable (Tables 2-4). Essential actions included the setup of AMS teams in all veterinary settings, building government-supported AMS programmes and following specific requirements on the production, collection and communication of AMU and AMR data. Activities of AMS teams should be tailored to the local situation and capacities, and be linked to local or national surveillance systems and infection control programmes. Several research priorities were also identified, such as the need to develop more clinical breakpoints in veterinary medicine (Table 5).

In conclusion, this White Paper offers a practical tool to veterinary practitioners and policy makers to improve AMS in the One Health approach, thanks to surveillance data generated in the veterinary setting, and provides complementary information to the work carried out as part of EU-JAMRAI Task 7.3. This work may also be useful

to medical doctors wishing to better understand the specificities of the veterinary setting and facilitate cross-sectoral collaborations.

*Table 2. Leadership commitment, accountability and antimicrobial stewardship team*

| **Antimicrobial stewardship programme and team** |
|---|
| 1.1) Essential<br><br>Antimicrobial stewardship programmes should be in place in every setting where antimicrobials are used to treat food-producing or companion animals, with targets and interventions tailored to the local situation and linked to local and national surveillance systems and infection control programmes. |
| 1.2) Essential<br><br>Antimicrobial stewardship programmes should be defined, planned, implemented and evaluated by a dedicated and competent team. This team should be tailored, depending on the animal species and production type, to the local context and availability of resources and personnel. |
| 1.3) Desirable<br><br>The team should include a veterinarian competent in antimicrobial stewardship and representatives of all professionals involved in animal care (para-veterinarians, veterinary nurses, farmers, veterinary pharmacists, microbiologists from diagnostic laboratories, etc.) in a collaborative approach, under the leadership of the veterinarian. This team should seek professional advice from additional experts when needed to adequately fulfil their antimicrobial stewardship activities. |
| **Institutional support for organisation and management of antimicrobial stewardship programmes** |
| 1.4) Essential<br><br>Antimicrobial stewardship programmes should be supported at the governmental level through frameworks such as the National Action Plan in line with relevant international standards. The National Action Plan should include regulatory decisions to restrict the usage of antimicrobials in food-producing and companion animals, set specific reduction targets for antimicrobial usage and establish monitoring systems for antimicrobial usage and antimicrobial resistance. |
| 1.5) Desirable<br><br>Surveillance data on antimicrobial usage and antimicrobial resistance should be made freely available to local antimicrobial stewardship teams, as well as to all other professionals working in animal, human or environmental health. |
| 1.6) Desirable<br><br>Voluntary approaches to improve antimicrobial stewardship and surveillance in the animal sector should be encouraged, e.g. when the farming industry adopts its own measures to increase biosecurity, infection control and reduce antimicrobial usage. |

*Table 3. Antimicrobial usage and antimicrobial stewardship*

| **Which type of antimicrobial usage, animal species and antimicrobials should be monitored** |
|---|
| 2.1) Essential<br><br>Antimicrobial usage should be monitored whatever the purpose of antimicrobial administration. This includes growth promotion, a practice that should be discouraged. |
| 2.2) Essential<br><br>Antimicrobial usage should be monitored in food-producing (including aquatic) and companion animals. |
| 2.3) Desirable<br><br>Antimicrobial usage should be monitored for all animals for which antimicrobials are authorised in a country. |
| 2.4) Essential<br><br>If national monitoring of antimicrobial usage including all antimicrobials is not feasible, a risk-based approach should be promoted to target monitoring to the most relevant antibiotics for animal and/or human health and only within the most important animal species in a country or region. |
| 2.5) Essential<br><br>The choice of antimicrobials to be monitored should be guided by the World Health Organization (WHO) ranking of critically important antimicrobials, by the World Organisation for Animal Health (OIE) list of antimicrobial agents of veterinary importance and by specific rankings of risk to public health from antimicrobial resistance due to the use of antimicrobials in veterinary medicine (example in Table 5). |
| **Which metrics should be employed** |
| 2.6) Essential<br><br>Antimicrobial usage should be monitored at least at the country level, for all or selected combinations of animal species and antimicrobials. |
| 2.7) Desirable<br><br>Antimicrobial usage should be monitored at the level of each prescription, sale or animal administration, such as veterinary clinics, pharmacies and farms, for all or selected combinations of animal species and antimicrobials. |
| 2.8) Essential<br><br>Sales data are the minimal that should be provided for all or selected combinations of animal species and antimicrobials, in kilograms of active ingredient for all animals and in mg/PCU (Population Correction Unit) for food-producing animals. |
| 2.9) Desirable<br><br>When data are available on prescriptions, sales and animal administration, the amount of overall usage should be standardised according to animal production and antimicrobial daily doses or antimicrobial treatment course. |
| **Which data and stratification criteria should be adopted** |

| |
|---|
| 2.10) Desirable<br><br>Additional data should be collected as part of an antimicrobial usage monitoring such as age, production type, route of administration or treatment type (therapy, metaphylaxis, prophylaxis or growth promotion). The data analysis should be stratified according to these additional data. |
| **Which criteria for time interval and reporting should be used** |
| 2.11) Essential<br><br>Antimicrobial usage data should be reported annually. |
| 2.12) Essential<br><br>Surveillance data on antimicrobial usage should be reported at the national level. |
| 2.13) Desirable<br><br>Surveillance data on antimicrobial usage should be reported at the local level. |
| 2.14) Essential<br><br>All methods used to provide antimicrobial usage data should be clearly described. |
| 2.15) Desirable<br><br>Antimicrobial usage and antimicrobial resistance data in the animal sector should be analysed, interpreted and reported in the same report. In the One Health approach, this report should also include data on antimicrobial usage and antimicrobial resistance from the human sector. |
| 2.16) Desirable<br><br>The report should include an English version to foster easier sharing of information between countries. |
| **Who should be the end user of the report** |
| 2.17) Essential<br><br>The end users of reports on antimicrobial usage should be antimicrobial stewardship teams and all other stakeholders in animal, human and environmental health at the local, institutional or industry level. |
| 2.18) Desirable<br><br>The report should be freely available online to anyone and include a summary that is understandable for the general public. |

*Table 4. Antimicrobial resistance and antimicrobial stewardship*

| **Which animal species and resistant bacteria should be targeted** |
|---|
| 3.1) Essential<br><br>Antimicrobial resistance should be monitored in food-producing (including aquatic) and companion animals. |
| 3.2) Essential<br><br>Target resistant bacteria should be animal pathogens, but also zoonotic pathogens and commensals in the One Health approach. |
| 3.3) Essential<br><br>OIE criteria should be followed for the choice of animal pathogenic bacteria to monitor (Table 6). Examples from OIE in terrestrial food-producing animals are provided in Table 7. |
| 3.4) Desirable<br><br>In companion animals, target pathogenic bacteria may include methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) from skin samples and *Escherichia coli* from urine samples, considering their importance for animal health and the zoonotic potential of MRSA. |
| 3.5) Essential<br><br>Selection criteria for the foodborne zoonotic and commensal bacteria to include in an antimicrobial resistance integrated surveillance programme, should depend on public health priorities, antimicrobial use practices, and the estimates of the burden of foodborne illnesses, as stated by WHO (Table 8). |
| 3.6) Essential<br><br>The choice of antimicrobials to monitor should be guided by the WHO ranking of critically important antimicrobials, by the OIE list of antimicrobial agents of veterinary importance and by specific rankings of risk to public health from antimicrobial resistance due to the use of antimicrobials in veterinary medicine (example in Table 5). |
| **How should resistance be monitored** |
| 3.7) Essential<br><br>For animal pathogenic bacteria, samples should originate from diseased or dead animals. |
| 3.8) Essential<br><br>For indicator and zoonotic bacteria from food-producing animals, samples should be taken from healthy animals of defined age. |
| 3.9) Essential<br><br>Standardised and internationally recognised antimicrobial susceptibility testing methods should be used. |
| 3.10) Desirable<br><br>To support field antimicrobial stewardship teams and provide recommendations for antimicrobial therapy in veterinary setting, clinical breakpoints should be used to interpret antimicrobial susceptibility testing results. |

| |
|---|
| If not available, epidemiological cut-off values may be used. When the objective is to detect decreased susceptibility (*i.e.* to display a microbiological resistance), epidemiological cut-offs should be used. |
| 3.11) Desirable<br><br>Quantitative data (minimum inhibitory concentrations or inhibition zone diameters) should be collected rather than interpreted data (susceptible/intermediate/resistance or wild type/non-wild type). |
| 3.12) Desirable<br><br>Specific monitoring schemes may be performed in healthy animals and food thereof using selective media, e.g. to detect the presence ESBL/AmpC, carbapenemase-producing, colistin-resistant Enterobacterales, MRSA or vancomycin-resistant enterococci to assess public health risk. |
| 3.13) Desirable<br><br>Resistance mechanisms should be characterised at the molecular level, e.g. using polymerase chain reaction, sequencing or whole genome sequencing for ESBL/AmpC, colistin-resistant and carbapenemase-producing Enterobacterales. |
| **Which data and stratification criteria should be adopted** |
| 3.14) Desirable<br><br>Additional data should be collected as part of antimicrobial resistance monitoring such as age, production type, specimen and if the antimicrobial susceptibility testing was requested due to a previous antimicrobial treatment failure. The analysis should be stratified according to these additional data. |
| **Which criteria for time interval and reporting should be used** |
| 3.15) Essential<br><br>The time interval for reporting resistance data should be annual, but emerging resistances should be reported as timely as possible. |
| 3.16) Essential<br><br>Surveillance data on antimicrobial resistance should be reported at the national level. |
| 3.17) Desirable<br><br>Surveillance data on antimicrobial resistance should be reported at the local level. |
| 3.18) Essential<br><br>All standards and guidance documents used for bacterial isolation, bacterial identification and antimicrobial susceptibility testing should be clearly described. |
| 3.19) Desirable<br><br>Antimicrobial usage and antimicrobial resistance data in the animal sector should be analysed, interpreted and reported in the same report. In the One Health approach, this report should also include data on antimicrobial usage and antimicrobial resistance from the human sector. |
| 3.20) Desirable<br><br>The report should include an English version to foster easier sharing of information between countries. |

| **Who should be the end users of the report** |
| --- |
| 3.21) Essential<br><br>The end users of reports on antimicrobial resistance should be antimicrobial stewardship teams and all other stakeholders in animal, human and environmental health at the local, institutional or industry level. |
| 3.22) Desirable<br><br>The report should be freely available online to anyone and include a summary that is understandable for the general public. |

# Conclusion

Antimicrobial resistance in animal bacterial pathogens represents a major gap in the European One Health strategy for AMR surveillance. To fill this gap, EU-JAMRAI Task 7.4.2 has made substantial progress by setting up the basis for a European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet). A pragmatic, inclusive and One Health strategy was adopted to define key areas of the EARS-Vet surveillance framework, including its objectives, surveillance scope and data collection template. This work is very timely, as more and more countries are expected to build their national surveillance system in the absence of European guidance and such a situation is at risk of increasing the current lack of harmonisation in Europe. Most countries that have participated in this work are willing to continue the development of EARS-Vet and launch a pilot phase to test its implementation in routine and refine the model. However, strong political and financial support will be necessary to sustain the development of EARS-Vet, as highlighted in the EARS-Vet policy brief (Appendix 4).

# Acknowledgements

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# Appendix 1: List of participants to EU-JAMRAI Task 7.4.2

| Country | Affiliation | Contact persons |
|---|---|---|
| Belgium | Antimicrobial Consumption and Resistance in Animals (AMCRA) | Bénédicte Callens<br>Fabiana Dal Pozzo |
| Belgium | Sciensano | Marilena Filippitzi<br>Mickael Cargnel |
| Czech Republic | Institute for State Control of Veterinary Biologicals and Medicines (ISCVBM) | Lucie Pokludová |
| Denmark | University of Copenhagen, Department of Veterinary and Animal Sciences | Peter Damborg |
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| Finland | Finnish Food Authority, Laboratory and Research Division, Microbiology Unit | Tarja Pohjanvirta<br>Suvi Nykäsenoja |
| Finland | University of Helsinki | Thomas Grönthal |
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| Germany | Federal Office of Consumer Protection and Food Safety | Heike Kaskar |
| Greece | University of West Attica | Alkiviadis Vatopoulos<br>Marietta Kontarini<br>Mixalis Polemis |
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| Greece | Hellenic Pasteur Institute | Maria Linou |
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| Sweden | National Veterinary Institute | Karl Pedersen<br>Björn Bengtsson |

# Appendix 2: Animal species, bacterial species and antimicrobial combinations included in the EARS-Vet scope

*Table 1: Bacterium-antimicrobial combinations included in the EARS-Vet scope for cattle*

| Bacterium | Antimicrobial group* | Antimicrobial agents |
|---|---|---|
| ***Escherichia coli*** **(faeces or inner organs)** | Aminopenicillins | Amoxicillin, Ampicillin |
| | Amoxicillin + Clavulanic acid | Amoxicillin + Clavulanic acid |
| | Third-generation cephalosporins | Cefotaxime, Ceftiofur |
| | Fourth-generation cephalosporins | Cefquinome, Cefepime |
| | Quinolones | Flumequine, Nalidixic acid |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Tetracyclines | Tetracycline |
| | Colistin | Colistin |
| | Gentamicin | Gentamicin |
| | Neomycin | Neomycin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Piperacillin-tazobactam | Piperacillin-tazobactam |
| | Carbapenems | Imipenem, Meropenem, Ertapenem |
| | Tigecycline | Tigecycline |
| ***Escherichia coli*** **(milk)** | Aminopenicillins | Amoxicillin, Ampicillin |
| | Amoxicillin + Clavulanic acid | Amoxicillin + Clavulanic acid |
| | Second-generation cephalosporins | Cefoxitin |
| | Third-generation cephalosporins | Cefotaxim, Ceftiofur |
| | Fourth-generation cephalosporins | Cefquinome, Cefepime |
| | Quinolones | Flumequine, Nalidixic acid |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin, Ciprofloxacin |
| | Tetracyclines | Tetracycline |
| | Colistin | Colistin |
| | Gentamicin | Gentamicin |
| | Neomycin | Neomycin |
| | Streptomycin | Streptomycin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Piperacillin-tazobactam | Piperacillin-tazobactam |
| | Carbapenems | Imipenem, Meropenem, Ertapenem |
| | Tigecycline | Tigecycline |
| ***Klebsiella pneumoniae*** | Amoxicillin + Clavulanic acid | Amoxicillin + Clavulanic acid |
| | Third-generation cephalosporins | Cefotaxim, Ceftiofur |
| | Fourth-generation cephalosporins | Cefquinome |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin, Ciprofloxacin |
| | Tetracyclines | Tetracycline |
| | Colistin | Colistin |
| | Gentamicin | Gentamicin |
| | Neomycin | Neomycin |
| | Streptomycin | Streptomycin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Piperacillin-tazobactam | Piperacillin-tazobactam |
| | Carbapenems | Imipenem, Meropenem, Ertapenem |
| | Tigecycline | Tigecycline |
| ***Staphylococcus aureus*** | Penicillin | Penicillin |
| | Methicillin resistance | Oxacillin, Cefoxitin |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Lincomycin | Lincomycin |
| | Erythromycin | Erythromycin |
| | Tetracyclines | Tetracycline |

| | | |
|---|---|---|
| | Gentamicin | Gentamicin |
| | Streptomycin | Streptomycin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Vancomycin | Vancomycin |
| | Rifampin | Rifampin |
| | Linezolid | Linezolid |
| | Daptomycin | Daptomycin |
| ***Streptococcus uberis* and *Streptococcus dysgalactiae*** | Penicillin | Penicillin |
| | Oxacillin | Oxacillin |
| | Third-generation cephalosporins | Cefotaxime, Ceftiofur |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin, Ciprofloxacin, Moxifloxacin |
| | Lincomycin | Lincomycin |
| | Erythromycin | Erythromycin |
| | Tetracyclines | Tetracycline |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| ***Mannheimia haemolytica* and *Pasteurella multocida*** | Penicillin | Penicillin |
| | Aminopenicillins | Amoxicillin, Ampicillin |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin |
| | Tulathromycin | Tulathromycin |
| | Tilmicosin | Tilmicosin |
| | Phenicols | Florfenicol |
| | Tetracyclines | Tetracycline, Oxytetracycline |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |

* An antimicrobial group corresponds to a single antimicrobial agent, an antimicrobial class, or several antimicrobials (used as indicators of methicillin resistance). For the last two categories, EARS-Vet would collect and collate resistance data for different antimicrobials agents, similarly to the procedures followed by EARS-Net (ECDC 2019).

*Table 2: Bacterium-antimicrobial combinations included in the EARS-Vet scope for swine*

| Bacterium | Antimicrobial group* | Antimicrobial agents |
|---|---|---|
| ***Escherichia coli* (virulent strains)** | Aminopenicillins | Amoxicillin, Ampicillin |
| | Amoxicillin + Clavulanic acid | Amoxicillin + Clavulanic acid |
| | Third-generation cephalosporins | Cefotaxim, Ceftiofur |
| | Fourth-generation cephalosporins | Cefquinome, Cefepime |
| | Quinolones | Flumequine, Nalidixic acid |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Tetracyclines | Tetracycline |
| | Colistin | Colistin |
| | Gentamicin | Gentamicin |
| | Neomycin | Neomycin |
| | Streptomycin | Streptomycin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Piperacillin-tazobactam | Piperacillin-tazobactam |
| | Carbapenems | Imipenem, Meropenem, Ertapenem |
| | Tigecycline | Tigecycline |
| ***Staphylococcus hyicus*** | Penicillin | Penicillin |
| | Methicillin | Oxacillin, Cefoxitin |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Erythromycin | Erythromycin |
| | Tetracyclines | Tetracycline |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| ***Streptococcus suis*** | Penicillin | Penicillin |
| | Third-generation cephalosporins | Ceftiofur |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Erythromycin | Erythromycin |
| | Phenicols | Florfenicol, Chloramphenicol |
| | Tetracyclines | Tetracycline |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| ***Pasteurella multocida* and *Actinobacillus pleuropneumoniae*** | Penicillin (only for *A. pleuropneumoniae)* | Penicillin |
| | Aminopenicillins | Amoxicillin, Ampicillin |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin, Ciprofloxacin |
| | Tulathromycin | Tulathromycin |
| | Tilmicosin | Tilmicosin |
| | Phenicols | Florfenicol, Chloramphenicol |
| | Tetracyclines | Tetracycline, Oxytetracycline, Doxycycline |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Tiamulin | Tiamulin |

* An antimicrobial group corresponds to a single antimicrobial agent, an antimicrobial class, or several antimicrobials (used as indicators of methicillin resistance). For the last two categories, EARS-Vet would collect and collate resistance data for different antimicrobials agents, similarly to the procedures followed by EARS-Net (ECDC 2019).

*Table 3: Bacterium-antimicrobial combinations included in the EARS-Vet scope for chicken and turkey*

| Bacterium | Antimicrobial group* | Antimicrobial agents |
|---|---|---|
| ***Escherichia coli*** **(chicken and turkey)** | Aminopenicillins | Amoxicillin, Ampicillin |
| | Amoxicillin + Clavulanic acid | Amoxicillin + Clavulanic acid |
| | Third-generation cephalosporins | Cefotaxime, Ceftiofur |
| | Fourth-generation cephalosporins | Cefquinome, cefepime |
| | Quinolones | Flumequine, Nalidixic acid |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Tetracyclines | Tetracycline, Doxycycline |
| | Colistin | Colistin |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Piperacillin-tazobactam | Piperacillin-tazobactam |
| | Carbapenems | Imipenem, Meropenem, Ertapenem |
| | Tigecycline | Tigecycline |
| | Penicillin | Penicillin |
| ***Staphylococcus aureus*** **(only for chicken)** | Methicillin | Oxacillin, Cefoxitin |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Lincomycin | Lincomycin |
| | Erythromycin | Erythromycin |
| | Tetracyclines | Tetracycline, Doxycycline |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Vancomycin | Vancomycin |
| | Rifampin | Rifampin |
| | Linezolid | Linezolid |
| | Daptomycin | Daptomycin |
| | | |

* An antimicrobial group corresponds to a single antimicrobial agent, an antimicrobial class, or several antimicrobials (used as indicators of methicillin resistance). For the last two categories, EARS-Vet would collect and collate resistance data for different antimicrobials agents, similarly to the procedures followed by EARS-Net (ECDC 2019).

*Table 4: Bacterium-antimicrobial combinations included in the EARS-Vet scope for cats and dogs*

| Bacterium | Antimicrobial group* | Antimicrobial agents |
|---|---|---|
| ***Escherichia coli*** | Aminopenicillins | Amoxicillin, Ampicillin |
| | Amoxicillin + Clavulanic acid | Amoxicillin + Clavulanic acid |
| | First-generation cephalosporins | Cefalexin, Cefalotin, Cefazolin |
| | Third-generation cephalosporins | Cefotaxime, Ceftiofur, Cefopodoxime, Cefovecin |
| | Fourth-generation cephalosporins | Cefquinome, Cefepime |
| | Fluoroquinolones | Enrofloxacin, Ciprofloxacin |
| | Tetracyclines | Tetracycline, doxycycline |
| | Colistin | Colistin |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Piperacillin-tazobactam | Piperacillin-tazobactam |
| | Carbapenems | Imipenem, Meropenem, Ertapenem |
| | Tigecycline | Tigecycline |
| ***Staphylococcus pseudintermedius*** | Penicillin | Penicillin |
| | Methicillin | Oxacillin, Cefovecin |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin, Ciprofloxacin |
| | Lincomycin | Lincomycin |
| | Erythromycin | Erythromycin |
| | Tetracyclines | Tetracycline, Doxycycline |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| ***Staphylococcus aureus*** | Penicillin | Penicillin |
| | Methicillin | Oxacillin, Cefoxitin |
| | Fluoroquinolones | Enrofloxacin, Marbofloxacin, Ciprofloxacin |
| | Lincomycin | Lincomycin |
| | Erythromycin | Erythromycin |
| | Tetracyclines | Tetracycline, Doxycycline |
| | Gentamicin | Gentamicin |
| | Sulfamethoxazole-trimethoprim | Sulfamethoxazole-trimethoprim |
| | Vancomycin | Vancomycin |
| | Rifampin | Rifampin |
| | Linezolid | Linezolid |
| | Daptomycin | Daptomycin |

* An antimicrobial group corresponds to a single antimicrobial agent, an antimicrobial class, or several antimicrobials (used as indicators of methicillin resistance). For the last two categories, EARS-Vet would collect and collate resistance data for different antimicrobials agents, similarly to the procedures followed by EARS-Net (ECDC 2019).

# Appendix 3: EARS-Vet data collection template

| Name of the variable | Possible values |
|---|---|
| **Isolate ID** | |
| **Country** | |
| **Year of sampling** | |
| **Animal species** | swine / cattle / chicken / turkey / dog / cat |
| **Production type** (only for chicken) | broiler / laying / empty |
| **Specimen** (only for *E. coli* in cattle, as only one specimen type is accepted for all other combinations) | milk / faeces / inner organs |
| **Bacterial species** | *E. coli / K. pneumoniae / S. dysgalactiae / S. uberis / S. aureus / P. multocida / M. haemolytica / A. pleuropneumoniae / S. hyicus / S. suis / S. pseudintermedius* |
| **Virulent strain identified by PCR on virulence factors?** (Only for *E. coli)* | Yes / No / empty |
| **Virulence factor(s) identified** (if any) | |
| **Virulent serotype identified** (Only for *E. coli*) | Yes / No / empty |
| **Serotype identified** (if any) | |
| **Serotyping method** (if serotyping performed) | |
| **Haemolytic strain?** (Only for *E. coli*) | Yes / No / empty |
| **AST technique** | Microdilution / disk diffusion |
| **Standard** | CLSI or EUCAST or CA-SFM or another one |
| **Antimicrobial compound 1** | diameter / MIC / empty |
| **Antimicrobial compound 2** | diameter / MIC / empty |
| **Antimicrobial compound 3** | diameter / MIC / empty |
| **ESBL phenotypic profile?** | Yes / No / empty |
| **AmpC phenotypic profile?** | Yes / No / empty |
| **PCR mecA positive?** | Yes / No / empty |

# Appendix 4: EARS-Vet policy brief

## Policy brief:
## European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet)

## Context and rationale behind EARS-Vet

Antimicrobial resistance (AMR) should be tackled through a One Health approach, as stated in the EU One Health Action Plan. In the human sector, the ECDC monitors AMR in invasive bacteria from hospitalised patients (European Antimicrobial Resistance Surveillance Network, EARS-Net) and in *Salmonella* spp. and *Campylobacter* spp. (European Food- and Waterborne Diseases and Zoonoses Network, FWD-Net). In the animal sector, the EFSA coordinates an active monitoring of AMR in commensal and zoonotic bacteria from healthy food-producing animals at slaughter and food thereof, according to Directive 2003/99/CE of the European Parliament and the Council and the Commission Implementing the Decision 2013/652/EU. Since 2011, EU agencies deliver their findings in joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) reports. The JIACRA II report concluded that monitoring of AMR should also include animal pathogens.

While the EFSA monitoring provides valuable insights into the potential for AMR spread to humans through the food chain, it also has limitations: i) it does not inform on AMR occurrence in specific animal pathogens; this information is needed to rationalize antimicrobial use and improve antimicrobial stewardship in the veterinary sector, ii) it focuses exclusively on foodborne AMR transmission, while AMR transmission from animals to humans can occur *via* multiple other routes and iii) it targets healthy animals that have either never been treated with an antimicrobial, or been treated a long time before sampling for AMR testing, thereby limiting the sensitivity of the surveillance system, *i.e.* its ability to detect AMR, and the possibility to study direct associations between AMR and antimicrobial consumption. **Hence, an important gap that remains is a European coordinated programme on surveillance of AMR in bacterial pathogens of animals, i.e. in diseased animals.**

There is currently no EU regulation on AMR surveillance in bacterial pathogens of animals. However, the EU Regulation 2016/429 (Animal Health Law) opens for the possibility to regulate AMR surveillance in veterinary medicine. As a first step in this direction, EFSA received a mandate from the European Commission to provide, by March 2022, "a scientific opinion for the listing and categorisation of transmissible animal diseases caused by bacteria resistant to antimicrobials" (excluding those already covered by Directive 2003/99/CE). However, the way surveillance should be implemented is not part of this mandate.

Of note, a number of EU countries (at least 12) already have a national surveillance system of AMR in bacterial pathogens of animals. However, these systems are fragmented, do not all monitor the same animal species, bacterial species and antimicrobials, and do not all use the same methodologies and interpretative criteria. In addition, other countries are currently developing their surveillance system, without European guidance. **There is an urgent need for a harmonized and coordinated approach for AMR surveillance in bacterial pathogens of animals across Europe.**

**Hence, time has come to build the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet), which should be set up and designed so that it can complement and integrate with existing ECDC and EFSA monitoring systems. EARS-Vet would represent a major step towards a stronger and truly One-Health strategy for surveillance of AMR, interlinked with the monitoring of antimicrobial consumption in Europe.**

This conclusion, as well as the following technical information, results from a collective agreement within a multidisciplinary group of 30 experts from 14 European countries in consultation with relevant EU bodies (ECDC, EFSA, EMA), built as part of the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) 2018-2021 co-funded by the EU Health Programme.

## EARS-Vet objectives

EARS-Vet would be in charge of reporting on the current AMR situation, following AMR trends and detecting emerging AMR in bacterial pathogens of animals in Europe in order to:

i. Inform on AMR occurrence in specific animal pathogens;
ii. Contribute to the development of evidence-based guidelines for antimicrobial prescription in animals, thereby supporting antimicrobial stewardship in the veterinary sector;
iii. Investigate direct links between antimicrobial consumption and AMR in both animals and humans, by providing AMR data collected close to animal point-of-care; as such, EARS-Vet could complement the current pool of data covered by the JIACRA reports;
iv. Support risk assessment of human exposure to AMR from animal reservoirs via non-food related routes (e.g. direct contact with companion or food animals);
v. Provide timely information for policy makers and allow exploring the benefits of interventions at European level;
vi. Provide relevant information that could be of use to medicines agencies in the evaluation or revision of marketing authorisations;
vii. Contribute to estimate the burden of AMR in the animal sector.

## EARS-Vet design and standards

EARS-Vet would operate as a network of national surveillance systems of AMR in diseased animals, similarly to EARS-Net in the human sector. All these national surveillance systems perform passive data collection, although a few countries complement their passive scheme with an active sampling. Using a bottom-up approach that takes into account what national surveillance systems currently monitor, as well as what EFSA and ECDC already cover, EU-JAMRAI partner countries agreed on a tentative EARS-Vet scope including 220 combinations of animal species - sample types - bacterial species - antimicrobials of interest. EARS-Vet standards for antimicrobial susceptibility testing were also defined: both microdilution and disk diffusion would be accepted, and EUCAST epidemiological cut-offs would be used for interpretation (although many of them still remain to be defined). Quantitative data would be collected in EARS-Vet.

## Future steps to build EARS-Vet

Building on EU-JAMRAI achievements, the next steps will consist in launching an EARS-Vet pilot phase where participating countries will start to share and jointly analyse their data, and finally produce a first EARS-Vet surveillance report. The level of representativeness and comparability of AMR data across national surveillance systems will also be assessed. Future EARS-Vet developments also include the integration of molecular (WGS) data for AMR bacterial clones and genes surveillance, as well as the inclusion of other AMR hazards of interest, such as those to be identified as priorities in the EFSA scientific opinion on the listing and categorisation of transmissible animal diseases caused by bacteria resistant to antimicrobials.

To achieve these next steps, and more generally to ensure the sustainability of EARS-Vet, strong political commitment from EU and national decision makers is needed. On the short term, we urge them i) to provide financial support to EARS-Vet, e.g. by funding an EARS-Vet pilot phase and ii) to provide political support to EARS-Vet, by encouraging Member States to promote surveillance of AMR in bacterial pathogens of animals in their country and to invite relevant national contact points to join the EARS-Vet initiative.

On the long-term, EARS-Vet could potentially be taken over by EU bodies (e.g. EFSA), should they receive the mandate to coordinate AMR surveillance in bacterial pathogens of animals (e.g. under the umbrella of the Animal Health Law). This would ensure the integration of EARS-Vet within the European landscape of AMR surveillance and related initiatives, and contribute to achieving a stronger One-Health surveillance of AMR in Europe.

# Appendix 5: List of publications produced as part of EU-JAMRAI Task 7.4.2

The WP7.4.2 activities led and will lead to several publications in international peer-reviewed journals, which are listed below with their current status (as per April 12th, 2021):

Published:

Compri M, Mader R, Mazzolini E, D Angelis J, MUTTERS NT, Babu Rajendran N, Galia L, Tacconelli E, Schrijver R on behalf of the ARCH working group. White Paper: Bridging the gap between surveillance data and antimicrobial stewardship in the animal sector - practical guidance from the JPIAMR-ARCH and COMBACTE-MAGNET EPI-Net Networks, *Journal of Antimicrobial Chemotherapy*, vol. 75, suppl 2: ii52-ii66. https://doi.org/10.1093/jac/dkaa429

Mader R, Damborg P, Amat J-P, Bengtsson B, Bourély C, Broens EM, Busani L, Crespo P, Filippitzi M-E, Fitzgerald W, Kaspar H, Munoz C, Norström M, Nykäsenoja S, Pedersen K, Pokludova L, Urdahl AM, Vatopoulos A, Zafeiridis C, Madec J-Y on behalf of EU-JAMRAI. Time to build the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet). *Eurosurveillance*. 2021;26(4):pii=2001359. https://doi.org/10.2807/1560-7917.ES.2021.26.4.2001359

Preprints:

Mader R, Jarrige N, Haenni M, Bourély C, Madec JY, Amat JP on behalf of EU-JAMRAI. OASIS evaluation of the French surveillance network for antimicrobial resistance in diseased animals (RESAPATH): success factors at the basis of a well-performing volunteer system. *BioRxiv*, April 2021, https://doi.org/10.1101/2021.04.07.438805

Mader R on behalf of EU-JAMRAI, Bourély C, Amat J-P, Broens EM, Busani L, Callens B, Crespo P, Damborg P, Filippitzi M-E, Fitzgerald W, Grönthal T, Haenni M, Heuvelink A, van Hout J, Kaspar H, Munoz C, Norström M, Pedersen K, Pokludova L, Dal Pozzo F, Slowey R, Teixeira C, Urdahl AM, Vatopoulos A, Zafeiridis C, Madec J-Y. Defining the scope of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet): a bottom-up and One Health approach. *BioRxiv*, March 2021 https://doi.org/10.1101/2021.03.09.434124

In preparation:

Mader R on behalf of EU-JAMRAI, Munoz C, Aasmäe B, Bourély C, Broens EM, Busani L, Callens B, collineau L, Crespo-Robledo P, Damborg P, Filippitzi M-E, Fitzgerald W, Heuvelink A, van Hout J, Kaspar H, , Norström M, Pedersen K, Pohjanvirta T, Pokludova L, Dal Pozzo F, Slowey R, Teixeira Justo C, Urdahl AM, Vatopoulos A, Zafeiridis C, Madec J-Y and Amat J-P. Review and analysis of national monitoring systems for antimicrobial resistance in animal bacterial pathogens in Europe: a basis for the development of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet).

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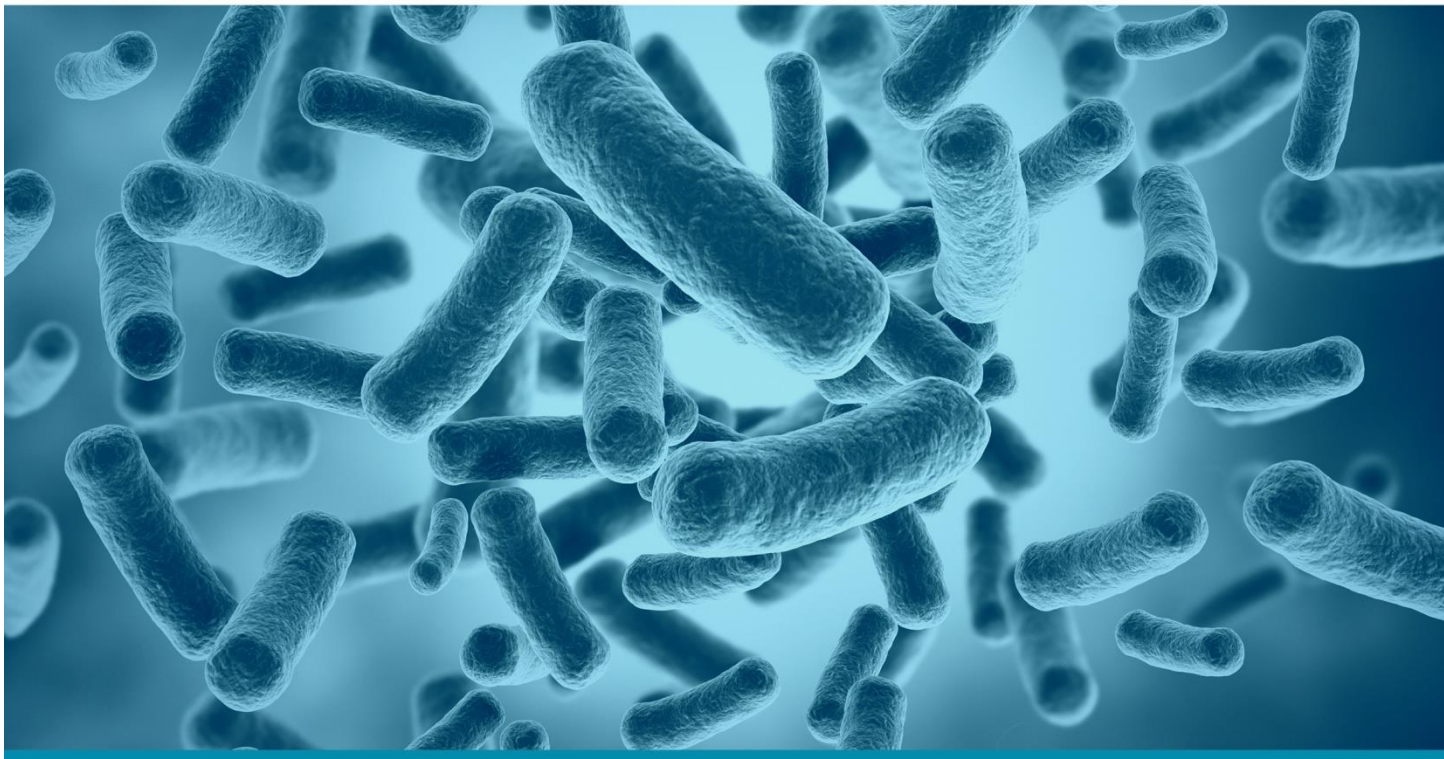
Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections



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