Better Training for Safer Food

Initiative

Antimicrobial Resistance One Health approach

MONITORING AND REPORTING OF AMR IN HUMAN MEDICINE

BTSF

This presentation is delivered under contract with the Consumers, Health, Agriculture and Food Executive Agency CHAFEA (http://ec.europa.eu/chafea). The content of this presentation is the sole responsibility of AENOR and can in no way be taken to reflect the views of CHAFEA or any other body of the European Union. CHAFEA or any other body of the European Union will not be responsible under any circumstances for the contents of communication items prepared by the contractor.

Food safety

Malaga, Spain – 25-28 November 2019

Key objectives

1. Making the EU a **best practice region**:

   …better evidence, better coordination and **surveillance**, and better control measures.

   …establishing, implementing and **monitoring a national One Health action plans on AMR**

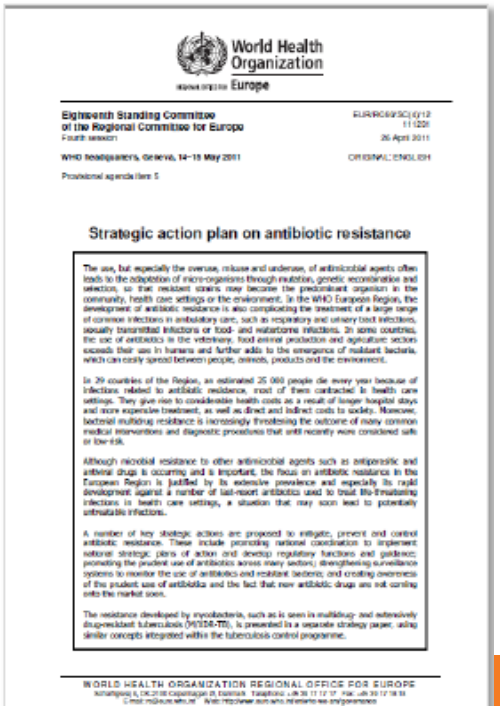
2. Boosting research, development and innovation…, providing **novel solutions** and tools to prevent and treat infectious diseases, and **improving diagnosis** in order to control the spread of AMR

3. **Intensifying EU efforts worldwide to shape the global agenda on AMR** and the related risks in an increasingly interconnected world

https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf

European strategic action plan on antibiotic resistance (2011 – 2016)

- WHO European action plan adopted by all 53 Member States
- Recognizing
  - AMR neglected in many countries of the region
  - No systematic AMR surveillance in large part of the Region
  - Need for intersectoral coordination
  - International spread through travel and trade
  - Need for international standards and data sharing



World Health Organization
Europe

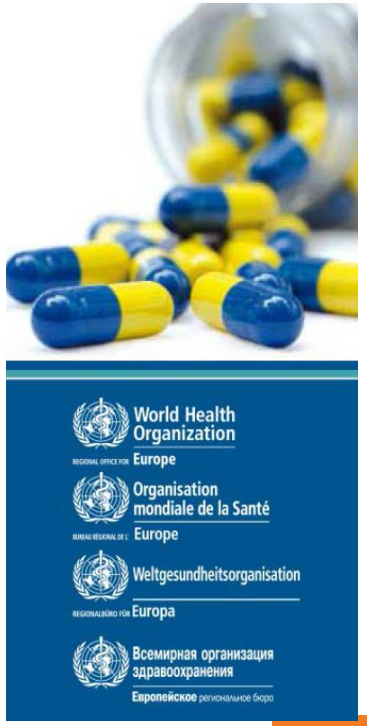
Eighteenth Standing Committee of the Regional Committee for Europe

Strategic action plan on antibiotic resistance

European Commission

Action Plan Strategic Objectives

1. Strengthen intersectoral coordination
2. Strengthen surveillance of antibiotic resistance
3. Promote rational use and strengthen surveillance of antibiotic consumption
4. Strengthen infection prevention and control and surveillance in health care settings
5. Prevent emerging resistance in veterinary and food sectors
6. Promote innovation and research on new drugs
7. Improve awareness, patient safety, and partnership



1. **AMR in human medicine:**

   - Definitions and concepts

2. **Surveillance and monitoring AMR**

   - routine laboratory skills
   - reporting of AMR

3. **The real land scape of AMR**

First concept: Antimicrobial susceptibility testing

To evaluate the *in vitro* response of a bacterial population to the action of one or several antibiotics (antibiogram)

- To **predict the clinical success or failure** of an specific antibiotic treatment (empirical *vs.* directed/targeted)

Relevant for the patient

- To **generate alerts** (unexpected results, …), to establish accurate accurate treatment measures and prevention of AMR dissemination
- To know the **epidemiology of antibiotic resistance mechanisms** (emergence, evolution and dispersion) and to establish control measures (containment)

Relevant for Public Health

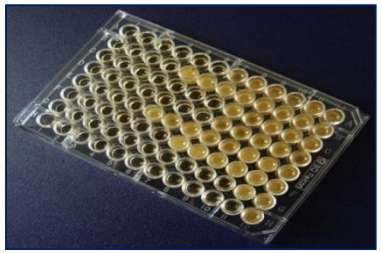
Second concept: MIC

- **MIC** (*minimal inhibitory concentration*)

  The lowest concentration of an antimicrobial that **in vitro inhibits** the growth of a bacterial population (inoculum)

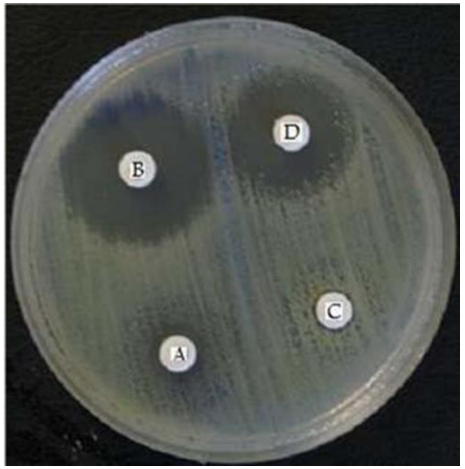
  ISO 20776-1, 2006

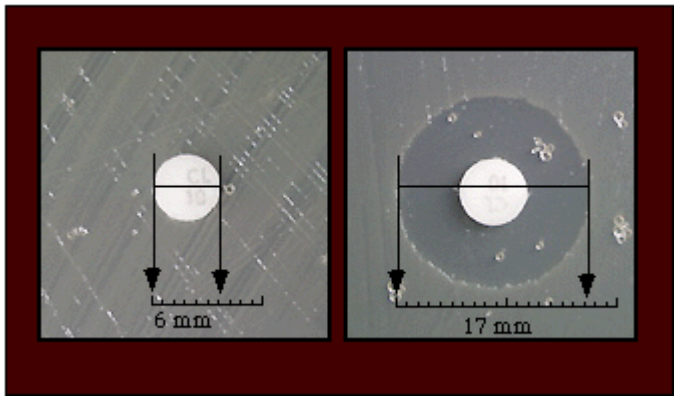
- **MIC** values are used to **predict clinical outcome** according to previously established **clinical breakpoints**
- **MIC** value is associated with the **presence or absence of a resistance mechanism**



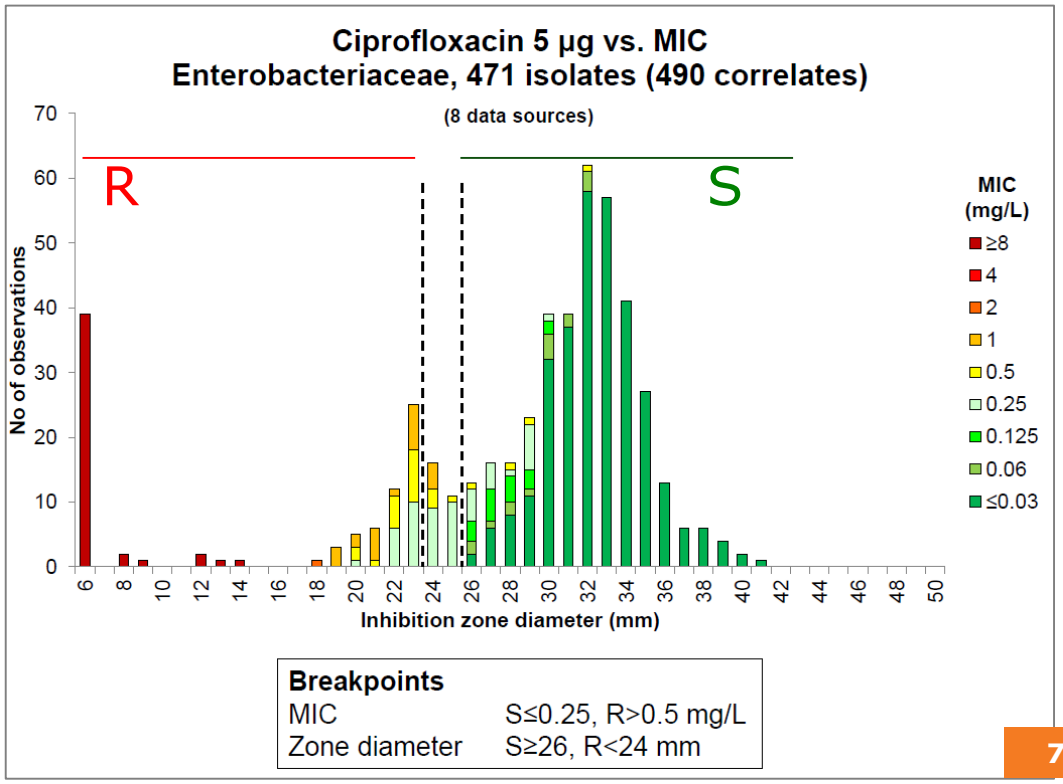


Antimicrobial susceptibility testing: disk diffusion





MIC and inhibition zone correlation



http://www.eucast.org/ast_of_bacteria/calibration_and_validation/

Third concept: Clinical breakpoints

CLINICAL BREAKPOINTS: concentration of an antibiotic that define whether a species of bacteria is **clinically susceptible (S), susceptible, increased exposure (I)** or **resistant (R)** to the antibiotic

www.eucast.org

New EUCAST definitions (2019)

S - *Susceptible, standard dosing regimen*: A micro-organism is categorised as *Susceptible, standard dosing regimen,* when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.

I - *Susceptible, increased exposure*: A microorganism is categorised 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 categorised 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 organism at the site of infection.

European Commission

CLINICAL AND LABORATORY STANDARDS INSTITUTE ™ (Formerly NCCLS)

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

CLSI (NCCLS)

✓ **CLINICAL BREAKPOINTS**

EUCAST

✓ **CLINICAL BREAKPOINTS**
✓ **EPIDEMIOLOGICAL CUT-OFF**

Breakpoints are defined for **clinical purposes** (to treat patients) and not with the specific aim to detect resistance mechanisms

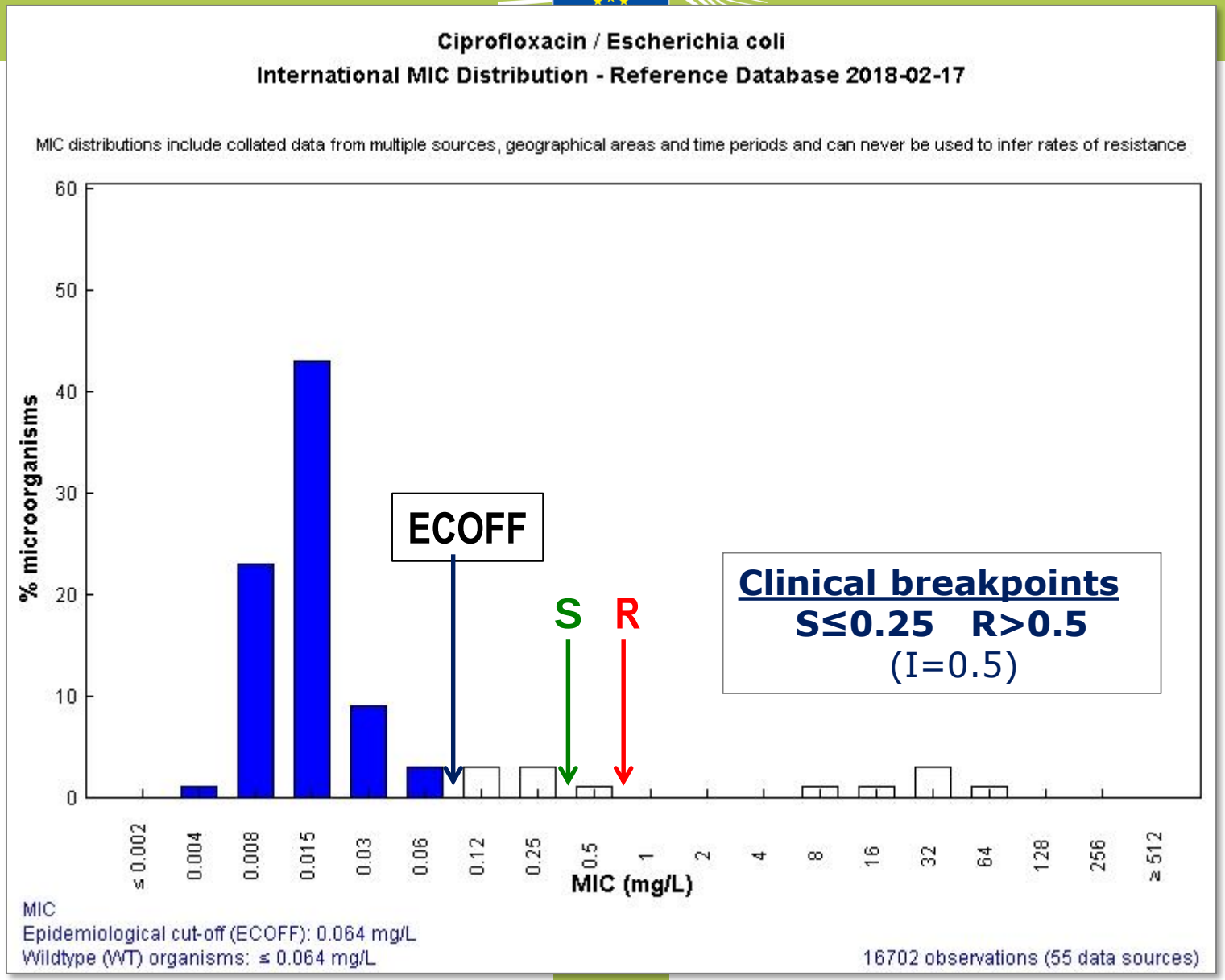
Epidemiological cut-off values can be used to detect resistance mechanisms

Fourth concept: epidemiological cut off value

- The **epidemiological cut-off value (ECOFF)** is a MIC value that separates microorganisms **without (wild type)** and **with acquired resistance mechanisms (non-wild type)** to the agent in question

https://mic.eucast.org/Eucast2/

- Not used to define clinical susceptibility (S) or resistance (R)
- Used to define the absence or presence of a resistance mechanisms (including those conferring low level resistance) and **monitoring of antimicrobial resistance**



https://mic.eucast.org/Eucast2/

Routine clinical microbiology laboratories

Bacterial identification
and
antimicrobial susceptibility testing (MIC)

↓

Clinical interpretation using clinical breakpoints

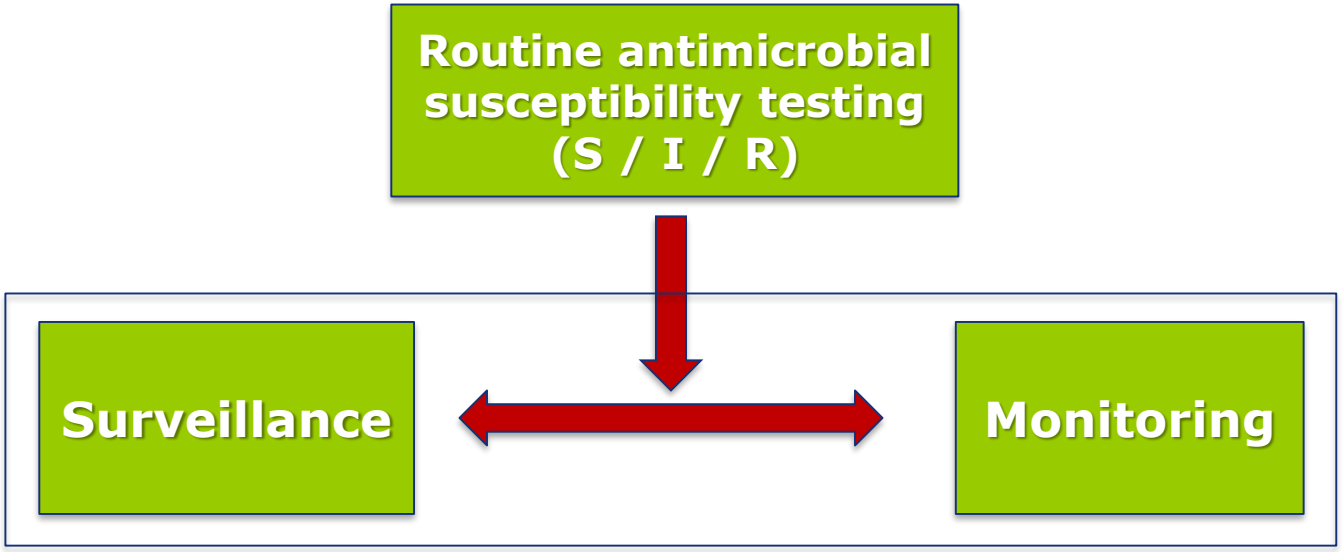
↓

S / I / R

Other competences associated with **AMR**

- Detection of AMR mechanisms
  - phenotypic detection (*interpretive reading of the antibiograms*)
  - molecular detection
- Typing of isolates
- Participation in stewardship programs
- Guidelines

Can we take advantages of routine work and integrate data on surveillance and monitoring programs of AMR?



1. **AMR in human medicine:**

   - Definitions and concepts

2. **Surveillance and monitoring AMR**

   - routine laboratory skills
   - reporting of AMR

3. **The real landscape of AMR**

29 June 2017

https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf

Clinical microbiologists should:

- Ensure that susceptibility testing and reporting are in accordance with treatment guidelines (selective reporting) and European (i.e. EUCAST) and national standards. Ensure timely diagnosis and communication of critical results (e.g. blood cultures).
- Provide facility-specific cumulative susceptibility reports for common bacterial pathogens against antibiotics that are recommended in the guidelines.
- Be available to clinicians for counselling on diagnostics of infectious diseases, including correct sampling and interpretation of test results, difficult-to-treat pathogens and complicated infections.
- As full members of the antimicrobial stewardship team, take on responsibilities that include coordination, planning, post-prescription review and feedback.

(Public Health) Surveillance, definition and OUS

"… **continuous, systematic collection, analysis and interpretation of health-related data** needed for the planning, implementation and evaluation of public health practice".

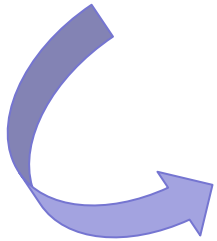
Thacker SB. Surveillance. In: Gregg, MB, ed. Filed Epidemiology. Oxford University Press, 1996; 16-32

Surveillance serve as an early **warning system** for impending public health emergencies; document the **impact of an intervention**, or track progress towards **specified goals**; and **monitor** and clarify the epidemiology of health problems, to allow priorities to be set and to inform public health **policy and strategies**.

AMR

(Public Health) Surveillance, definition and OUS

Surveillance is restricted by its objective i.e. the **operational unit of surveillance (OUS)** which represents the quantifiable subject under surveillance



OUS

- Antimicrobial Resistance (AMR)
- Infectious diseases
- Antibiotic consumption

Aims of AMR surveillances (*…from professional associations*)

"to assist the preparation of **cumulative antimicrobial susceptibility reports** that would prove to be useful to clinicians in **the selection of** the most **appropriate agents** for empirical antimicrobial therapy"

AMERICAN SOCIETY FOR MICROBIOLOGY

ASM Task Force. Report of the ASM Task Force on Antibiotic Resistance. Washington, DC: ASM Press, 1995

"…collect data from all countries in a defined geographical region, encompass the highly clinical important bacteria representing a current health problem, and aim at **an early warning of emerging resistant trends**…"

ESGARS ESCMID STUDY GROUP FOR ANTIMICROBIAL RESISTANCE SURVEILLANCE
European Society of Clinical Microbiology and Infectious Diseases

Giske & Cornaglia (ESCMID Study Group on Antimicrobial Resistance Surveillance, ESGARS). Drug Resist Update. 2010;13:93-8

AMR Surveillance: main features

- **AMR surveillance** is an ongoing observation (**NOT an intervention**) of a system, restricted by its objective, i.e. the **operational unit of surveillance (OUS)** which represents the quantifiable subject under scrutiny, e.g. **AMR.**

- **Systematic collecting data** through which AMR threats (known or emerging) are detected. A preliminary diagnose of problems or bottlenecks can be done.

- Once AMR surveillance results are collected, analysed and reported, **intervention strategies** will be delineated and actions will be taken by the corresponding Public Health Agencies. Corrective and timely measures will be taken through multipronged strategies.

Monitoring of AMR

Monitoring: Close watch on a situation in order to take corrective steps while implementing a program **(i.e. *reduction of AMR and antimicrobial consumption*)**

Objective of the performance and analysis of routine measurements (of AMR) to detect 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 making adjustments so as to meet those objectives

Global Public Surveillance Programs on AMR

- EARS-Net
- CAESAR
- ESAC-Net
- EuSCAPE
- NARMS
- WHONET
- GLASS
- Others

Surveillance programs are part of **AMR monitoring**

Private Surveillance Initiatives on AMR

- TEST (Tigecycline Evaluation and Surveillance Trial)
- ATLAS (Antimicrobial Testing Leadership And Surveillance; comprising TEST, AWARE, INFORM databases)
- SENTRY … … …

EU monitoring networks

(Focused on human medicine)

- **EARS-Net:** *European Antimicrobial Resistance Surveillance-Network*

EARS-Net is a public 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

https://ecdc.europa.eu/en/about...networks/...networks/ears-net

EARS-Objectives

1) Collect comparable, representative and accurate AMR data
2) Analyse temporal and spatial trends of AMR in Europe
3) Provide timely AMR data for policy decisions
4) Encourage the implementation, maintenance and improvement of national* AMR surveillance programmes
5) Support national* systems in their efforts to improve diagnostic accuracy by offering annual external quality assessments (EQA)

https://ecdc.europa.eu/en/about...networks/...networks/ears-net

*Spain: Health Institute Carlos III; www.isciii.es

EARS, cont.

Data reported at national level

'Indicator' bacterial species: commonly causing bacterial infections in humans

ONLY INVASIVE ISOLATES (Blood and cerebrospinal fluid)

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.
- *Staphylococcus aureus*
- Enterococci: *E. faecalis, E. faecium*
- *Streptococcus pneumoniae*

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Tacconelli and Magrini, 25 Feb 2017

- Previous global priority pathogen list (PPL) issued by the CDC[1] and the Public Health Agency of Canada[2]
- Also guided by pharma companies according to perceived/ unmet medical need, pressure of investors, market size, scientific discovery potential, and availability of specific technologies
- WHO global PPL issued to guide prioritization of incentives and funding, help aling R&D priorities with public held need and coordination in the fight against antimicrobial resistant bacteria

[1]CDC, Antibiotic Resistance Threats in the United States, 2013; http://www.cdc.gov/drugresistance/threat-report-2013/)
[2]Public Health Agency of Canada. PLoS One. 2015;10:1-11

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

Other sites: ECDC | European Antibiotic Awareness Day | ESCAIDE - Scientific conference | Eurosurveillance journal

European Centre for Disease Prevention and Control
An agency of the European Union

Infectious diseases & public health | News & events | Publications & data | About us

Home > About us > Partnerships and networks > Disease and laboratory networks > European Antimicrobial Resistance Surveillance Network (EARS-Net)

- Disease and laboratory networks
- Emerging Viral Diseases-Expert Laboratory Network (EVD-LabNet)
- **European Antimicrobial Resistance Surveillance Network (EARS-Net)**
  - About the network
  - Data collection and analysis
- European Creutzfeldt-Jakob Disease Surveillance Network (EuroCJD)
- European Diphtheria Surveillance Network (EDSN)
- European Food- and Waterborne Diseases and Zoonoses Network (FWD-Net)

European Antimicrobial Resistance Surveillance Network (EARS-Net)

about us | networks and partnerships

About the network

The European Antimicrobial Resistance Surveillance Network (EARS-Net) is the largest publicly funded system for antimicrobial resistance (AMR) surveillance in Europe.

Data collection and analysis

EARS-Net is based on routine clinical antimicrobial susceptibility data from local and clinical laboratories reported to ECDC by appointed representatives from the Member States.

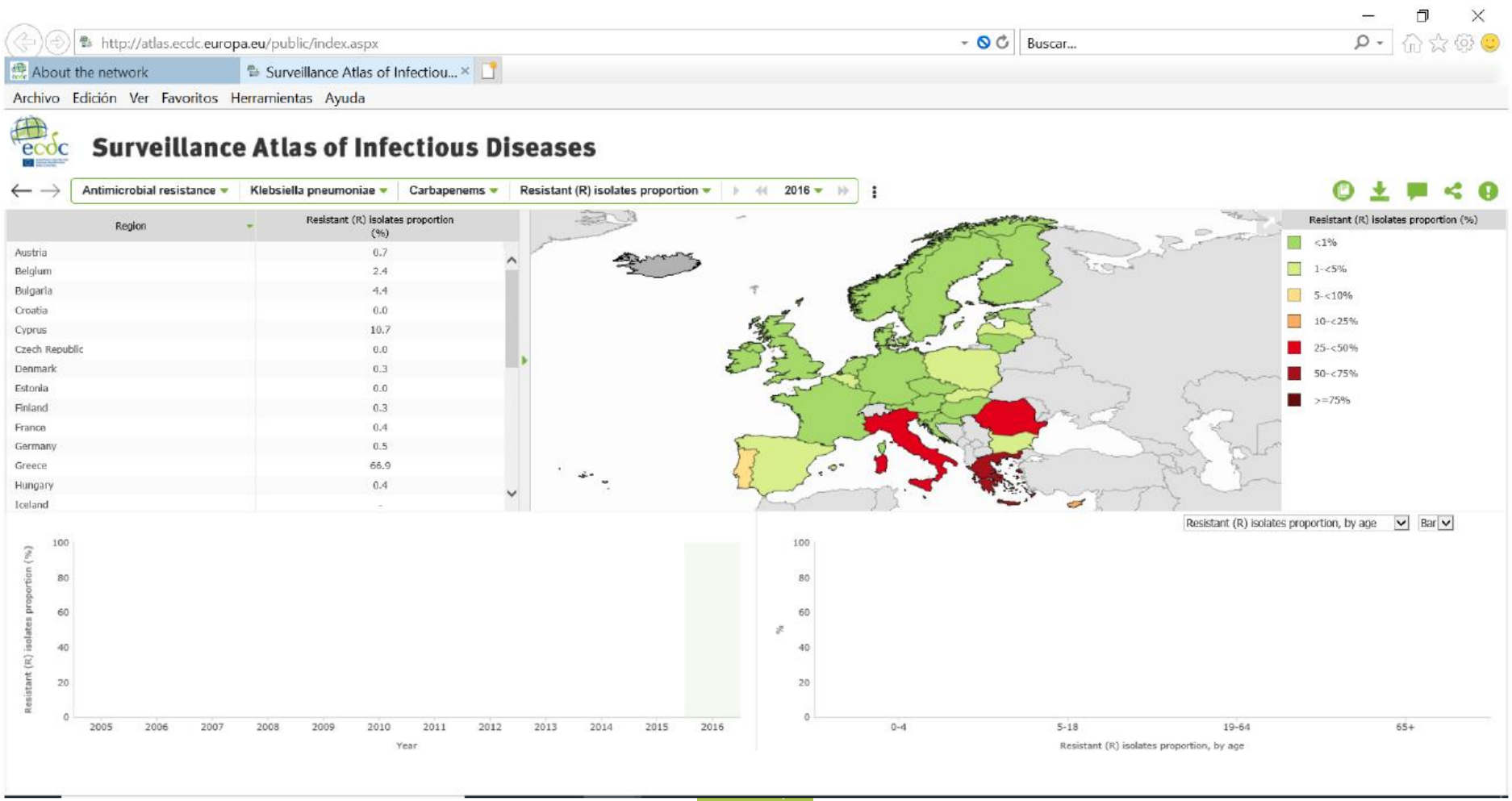
https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net

EARS-Net: Publication of results

The **ECDC Surveillance Atlas of Infectious Diseases** provides user-friendly access to data in various downloadable formats (tables, figures and maps).

Data also available in **annual reports** and related **publications** (current and historical trends in the occurrence of AMR across Europe

http://atlas.ecdc.europa.eu/public/index.aspx



EARS-Net: *European Antimicrobial Resistance Surveillance-Network*

Gram-negative microorganisms	Aminopenicillins	Piperacillin—tazobactam	3er gen. ceph.	Carbapenem	Fluoroquinolones	Aminoglycosides	MDR (≥3)
E. coli	X		X	X		X	X
K. pneumoniae			X	X	X	X	X
Acinetobacter spp.				X	X	X	X
P. aeruginosa		X	X	X	X	X	X

MDR: resistant to at least 3 antimicrobials

Reporting AST results: S, I+R, R
No reporting resistance mechanisms

EARS-Net: *European Antimicrobial Resistance Surveillance-Network*

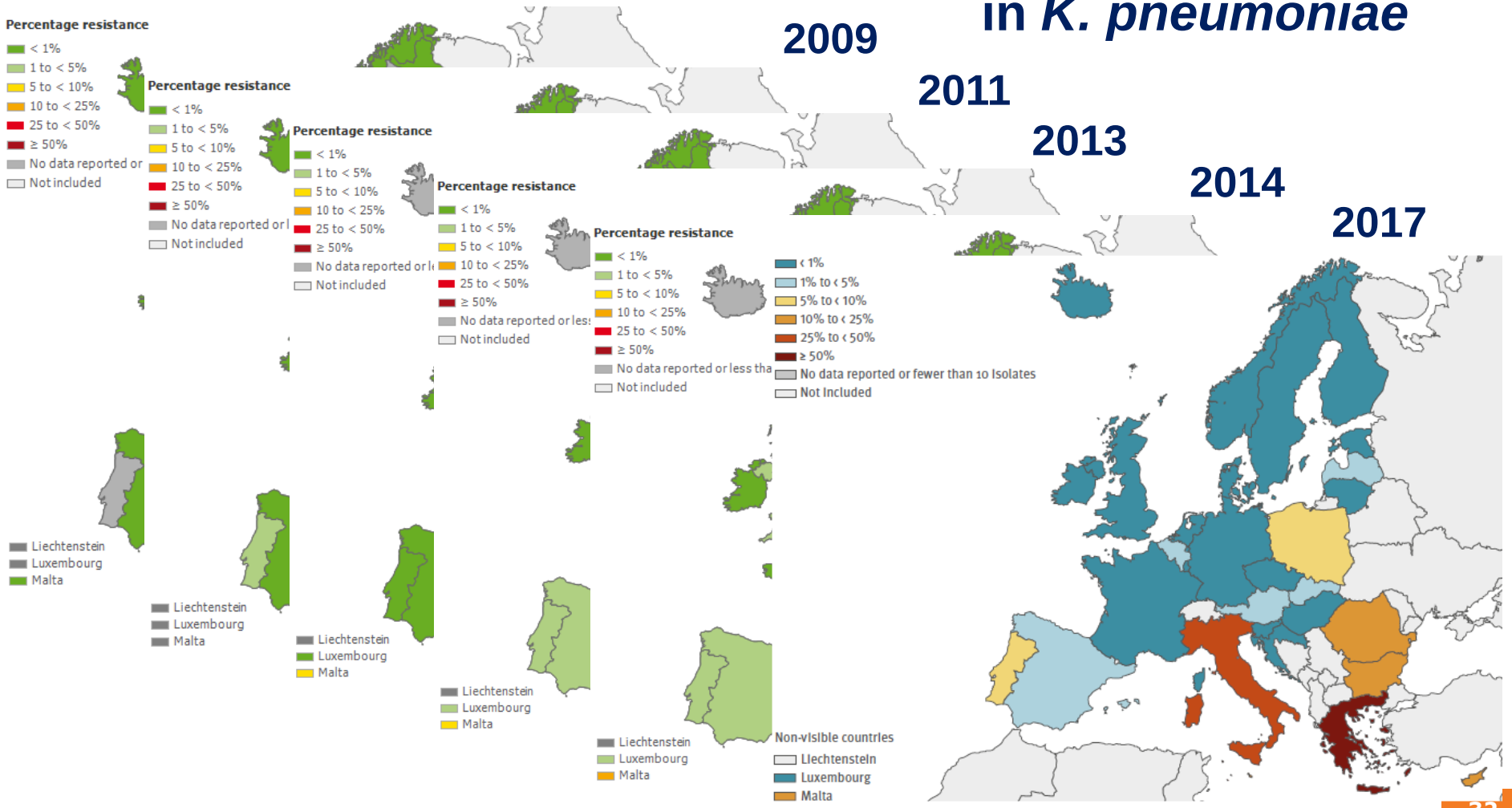
Gram-positive microorganisms	Penicillin	Aminopenicillins	Meticillin	Vancomycin	Hihg-level gentamicin	Macrolides	MDR
S. aureus			X				
E. faecalis		X		X	X		
E. faecium		X		X	X		
S. pneumoniae	X					X	X

MDR: resistant to at least 2 antimicrobials

Reporting AST results: S, I+R, R
No reporting resistance mechanisms

EARS-Net database

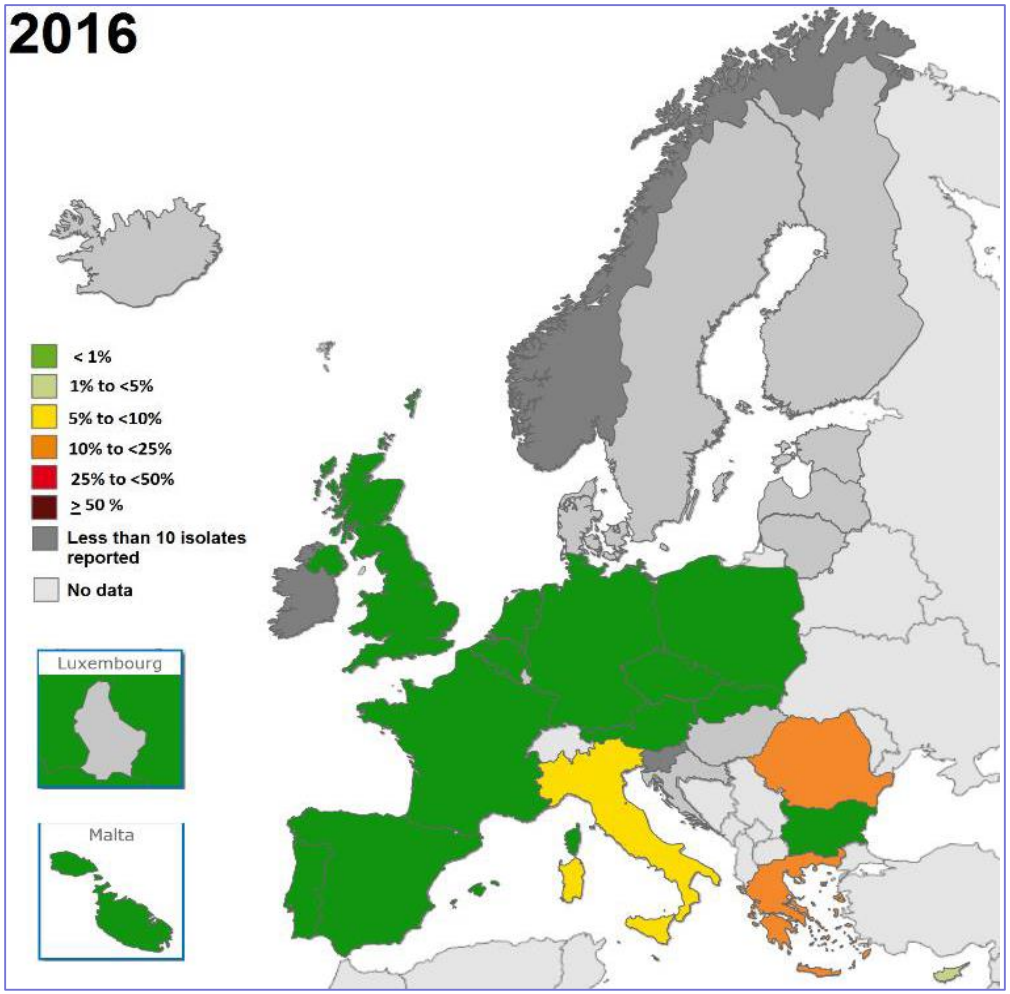
Carbapenem resistance in *K. pneumoniae*



http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/map_reports.aspx

K. pneumoniae: combined resistance to carbapenems and colistin

New antibiotics



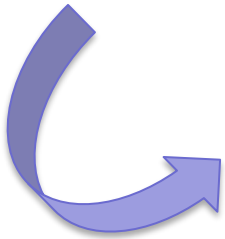
ECDC, Summary of the latest data on antibiotic resistance in the EU EARS-Net surveillance data. Nov 2017

Laboratories' skills for susceptibility testing and data reporting

Homogeneous reporting of results (adopting **EUCAST guidelines)**.

Interpretation of AST results with minimal variations at least for resistance mechanisms resulting in minimum inhibitory concentrations (MICs) close to the breakpoints.

As **quantitative data** (i.e. disk diffusion zone diameters or MIC values) are not provided by all participating laboratories, **only the reported S, I, and R results are considered for the analyses**



external quality assessments (EQA) of AST in collaboration with the ***United National External Quality Assessment Service*-UK NEQAS**.

Laboratories' skills for susceptibility testing and data reporting

The **ability to identify the microorganism and its associated antimicrobial susceptibility pattern** may differ among laboratories.

All laboratories providing data for EARS-Net are offered participation in an **annual external quality assessment (EQA)** to assess the reliability of the laboratory test results.

EARS-Net have organised **external quality assessments (EQA)** of antimicrobial susceptibility testing in collaboration with the ***United National External Quality Assessment Service*-UK NEQAS**.

UK NEQAS is based at Public Health England in London and is a non-profit organisation.

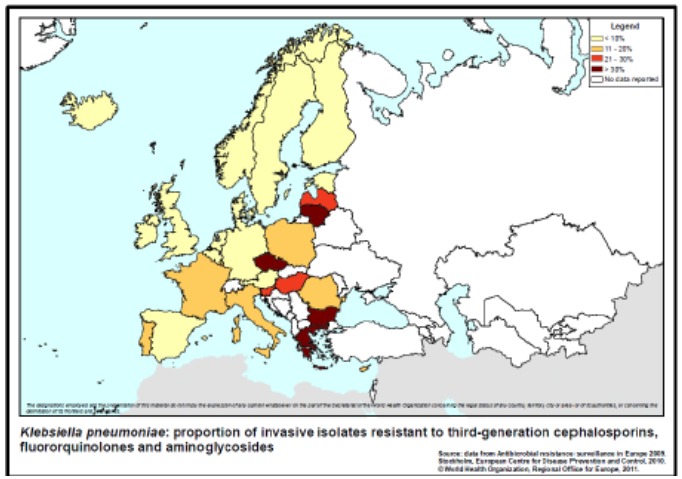
CAESAR Network

(Central **A**sian and eastern **E**uropean **S**urveillance of **A**ntimicrobial **R**esistance**)**

- Network of national surveillance networks in non-EU Member States

- Joint initiative
  - European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
  - Dutch National Institute of Public Health (RIVM)

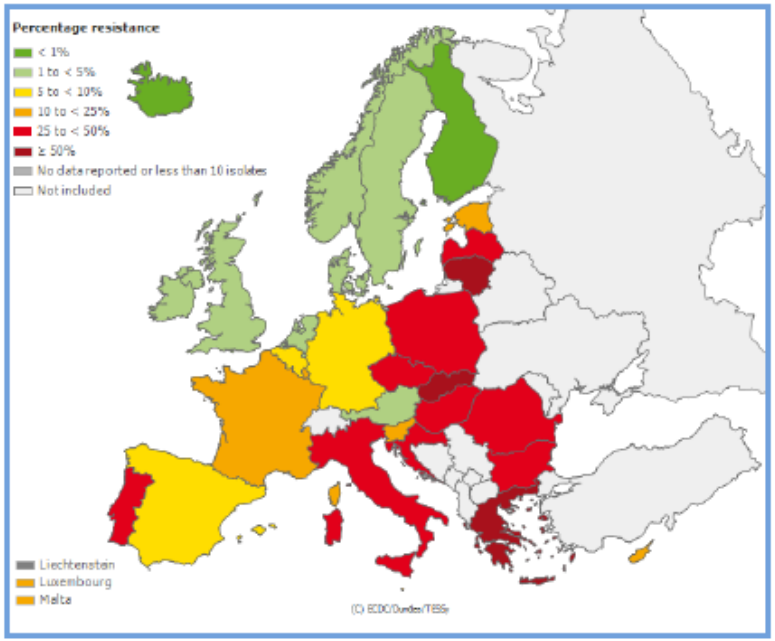
- Close collaboration with ECDC
  - Using methodology comparable with EARS-Net



***Klebsiella pneumoniae*: proportion of invasive isolates resistant to third-generation cephalosporins, fluororquinolones and aminoglycosides**

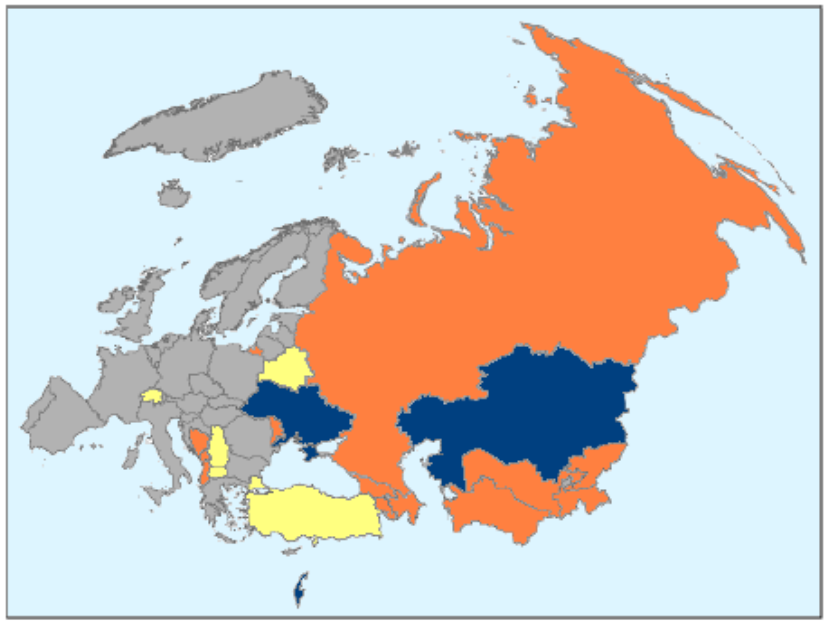
Expanding AMR surveillance throughout Europe

European Antimicrobial Resistance Surveillance Network (EARS-Net)



European Centre for Disease Prevention and Control

Central Asian and eastern European Surveillance of Antimicrobial Resistance (CAESAR)



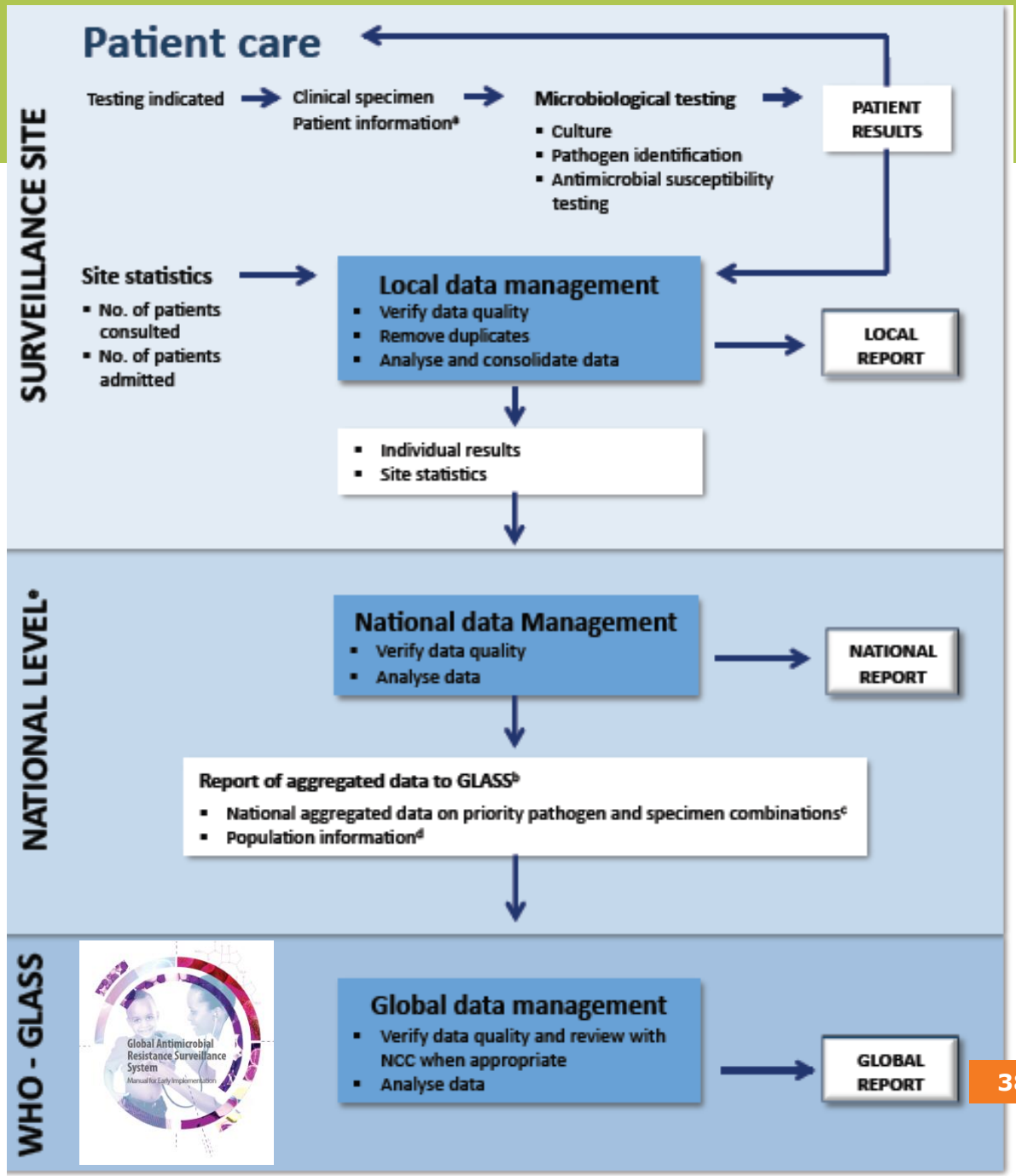
World Health Organization Regional Office for Europe

World Health Organization
REGIONAL OFFICE FOR Europe

- Countries submitting data to CAESAR
- Countries visited for CAESAR participation
- Countries to be visited for CAESAR participation
- Countries participating in EARS-Net

WHO-GLASS

Schematic view of information flow
(An example)



http://www.who.int/glass/en/

- **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**

Coordination: ECDC

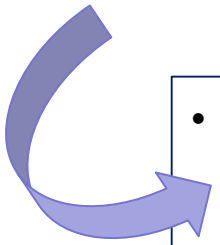
Spain: ENVIN: Hospital Vall d'Hebron, Barcelona (UCIs)
SSI surveillance by Carlos III Institute of Health, Madrid

Activities of HAI-Net (Summary of core surveillances)

- **Surgical site infections**: epidemiology and interhospital comparison of risk-adjusted rates
- Infections acquired in **ICUs**
- Infections acquired in **long term care facilities (HALT Project)**
- Infections due to ***Clostridioides difficile*,** establishing a European ribotyping nomenclature and a comprehensive reference collection of strains (including a web-based database) and by developing a European CDI surveillance protocol

- **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.



- **AMR** data are **collected** particularly **for salmonellosis**, **campylobacteriosis** and partly also for **cyto- or Shiga toxin-*E. coli***.

Communicable diseases

1. **AMR in human medicine:**

   - Definitions and concepts

2. **Surveillance and monitoring AMR**

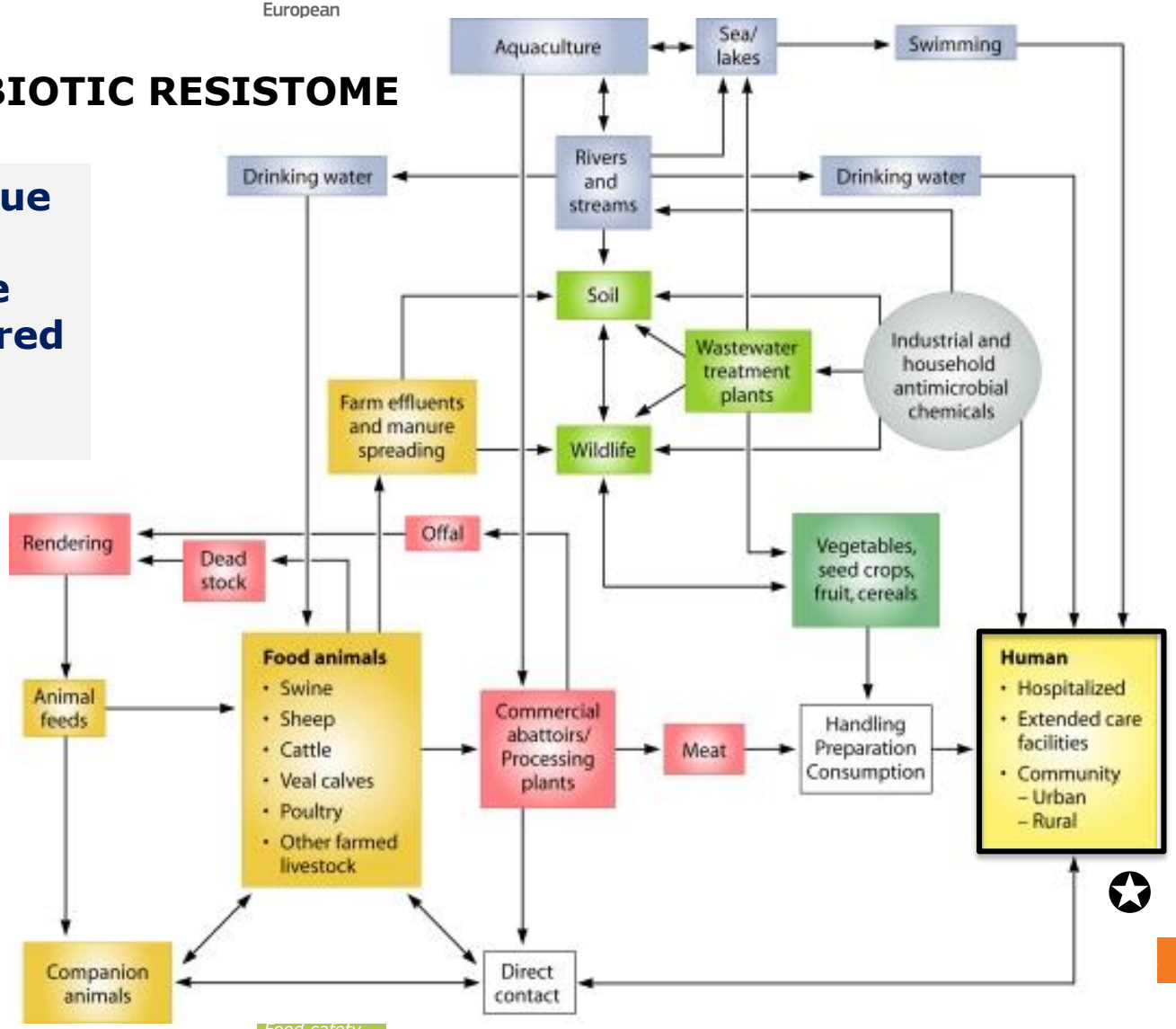
   - routine laboratory skills
   - reporting of AMR

3. **The real landscape of AMR**

European

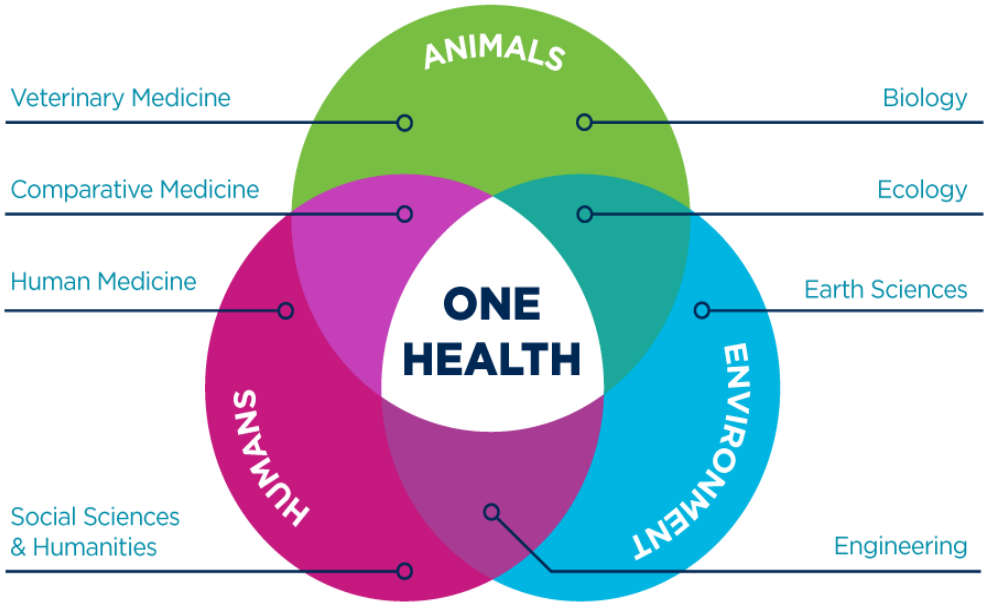
ENVIRONMENTAL ANTIBIOTIC RESISTOME

Pool of AMR genes due to "anthropogenic activities" with the potential to be captured and expressed by different bacteria



Davies & Davies. Microbiol Mol Biol Rev. 2010;74:417-33

One Health approach for Combating AMR



www.ucdavis.edu. University of California, Davis-USA

One health: To improve health and well-being through the prevention of risks and the mitigation of effects of crises that originate at the interface between humans, animals and their various environments

What is needed in future AMR surveillance and monitoring?

Objectives

- Real-time occurrences of ALL pathogens
- Rapid detection of emerging threats and related clusters in time and space
- Trends (species, clones, genes or other markers)
- Ability to compare

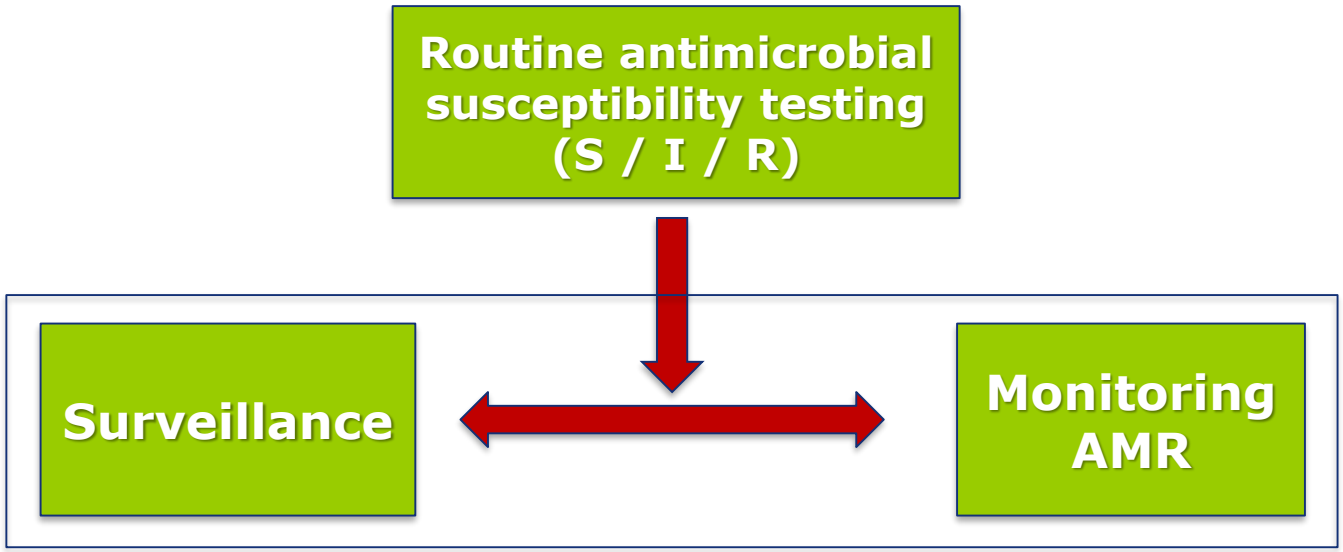
Real time surveillance, real time sharing

Epidemic preparedness research

European Union-supported efforts

- **Prediction**
  - Emergence, surveillance, modelling
- **Early recognition and containment**
  - Surveillance, clinical awareness, infection control
- **Data infrastructure**
  - Data repositories, sharing
- **Clinical research**
  - Pathogen and disease characterization
  - Prevention and treatment
- **Funding**
  - Rapid responses

PREDEMICS / antigone / Emperie	2009-2016 € 36 M
Compare	2015-2020 € 21 M
elixir	2013-? € >100 M
Platform foR European Preparedness Against (Re-)emerging Epidemics PREPARE	2014-2019 € 24 M
GloPID-R	2015-2020 € 3 M



Control of antimicrobial use

This presentation is delivered under contract with the Consumers, Health, Agriculture and Food Executive Agency CHAFEA (http://ec.europa.eu/chafea). The content of this presentation is the sole responsibility of AENOR and can in no way be taken to reflect the views of CHAFEA or any other body of the European Union. CHAFEA or any other body of the European Union will not be responsible under any circumstances for the contents of communication items prepared by the contractor.

AENOR INTERNACIONAL

6, Genova street. 28004. Madrid, SPAIN
Tel: +34 91 432 61 25
Mail: 20169607_amr@aenor.com
www.btsf-aenor.com

AENOR agencia española de medicamentos y productos sanitarios

---

Better Training for Safer Food
BTSF

European Commission
Consumers, Health, Agriculture and Food Executive Agency
DRB A3/042
L-2920 Luxembourg

Food safety