Challenging AMR in low-resource settings

Building laboratory capacity to identify patterns and emergence of resistance

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Antibiotics can be bought without a prescription in many countries, and overuse of the drugs is fuelling the evolution of resistant microbes.

**PUBLIC HEALTH**

**Antibiotic resistance sweeping developing world**
In developing countries infectious diseases remain the leading cause of death.

Many sentinel hospitals have less than basic microbiology laboratory facilities:
- some institutions have all the needed microbiologic resources, while others have none;
- some hospital laboratories have instruments and reagents yet have no technical staff to use them;
- others may be able to amplify genomes yet cannot report the results of a simple Gram stain in a timely manner.

For all these reasons, the causes of many infections among inpatients in Africa, Southeast Asia, the Indian subcontinent, and parts of the Americas remain largely unknown or uncharacterized.

Antimicrobial resistance is usually not monitored in under-resourced countries because they lack surveillance networks, laboratory capacity, and appropriate diagnostics.

Why surveillance as a tool to combat AMR?

- to detect resistant microorganisms, follow their spread among people and geographic areas, and enable outbreaks of diseases caused by drug-resistant infections to be notified and investigated promptly;

- to enable correct decisions to be taken about treatment of patients, and to prevent and control the spread of infection;

- to guide policy recommendations and to monitor how well the measures taken to combat AMR are working;

- to track the use and misuse of antimicrobial medicines, so that the public health consequences can be assessed.
Challenges to overcome

• **Shortage of competent laboratories**: AMR surveillance depends on microbiology laboratories which can accurately identify resistant microorganisms. Low-income countries generally lack such laboratories, and where laboratories exist, the means to check the reliability of their work are often lacking.

• **Poor infrastructure and data management**: Poor data management prevents routine monitoring and reliable data collection to measure the extent of AMR.

• **Variation in methods**: Without standard protocols for measuring resistance, data cannot be shared and compared between laboratories and countries.
Challenges to overcome (continued)

• **Low coverage of surveillance:** A number of global databases and regional networks for specific diseases hold data related to AMR, but the data are patchy, with many gaps.

• **Lack of intersectoral cooperation:** The impact on human health of using antibiotics as growth promoters and for disease prevention in food-producing animals is unclear. It cannot be assessed without better collaboration for surveillance of AMR in bacteria from humans, food products and animals.

• **Inadequate international collaboration:** More extensive international collaboration on AMR surveillance is needed so that information can be shared to provide an early warning of new or unusual outbreaks of drug-resistant infections.
Core Actions

A) Establish AMR surveillance and monitoring systems
   Sample-based, sentinel site surveillance, standardized protocols, information system and software (e.g. WHONET)

B) Build laboratory capacity for rapid and reliable diagnostic testing
   Designation of national reference labs, establishment of quality assurance system

C) Engage in regional and global surveillance networks
   - national networks
   - regional networks – CAESAR
   - global network – GLASS
Global Action Plan on Antimicrobial Resistance

At the 68th World Health Assembly in May 2015, the World Health Assembly endorsed a global action plan to tackle antimicrobial resistance

The global action plan sets out five strategic objectives:

1) to improve awareness and understanding of antimicrobial resistance;
2) to strengthen knowledge through surveillance and research;
3) to reduce the incidence of infection;
4) to optimize the use of antimicrobial agents; and
5) develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

http://www.who.int/drugresistance/global_action_plan/en/
CAESAR
Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Joint initiative born on 30 October 2012

Network of national surveillance systems for antibiotic resistance in all countries of the WHO European Region that are not part of EARS-Net (European Antimicrobial Resistance Surveillance Network) run by ECDC (European Centre for Disease Prevention and Control).

Provide comparable and validated data on the prevalence and trends of antimicrobial resistance in a core group of invasive bacteria.

CAESAR methodology is fully compatible with EARS-Net
CAESAR
Central Asian and Eastern European Surveillance of Antimicrobial Resistance

EARS-Net (N=30)  CAESAR (N=20)

!!! CAESAR methodology is fully compatible with EARS-Net !!!
CAESAR
Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Invasive isolates (blood, CSF)
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* species
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*

AST results
- S/I/R
- class representative antimicrobials

CAESAR (N=20)

!!! CAESAR methodology is fully compatible with EARS-Net !!!
The addition of participating centers to a surveillance network increases the number of surveyed isolates in its area/region and so allows it to discriminate more trends and outbreaks sooner.

It also reduces blind spots where new resistance clones can emerge and spread unseen.

Past resistance clones, in contrast, may have spread widely in regions where laboratories are sparse before being noticed.
## World Bank List of Economies (July 2015)

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<th>Income Category</th>
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<th>No. Countries (N=215)</th>
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**GNI:** Gross national income per capita as of 2014

## Country Profiles in WHO Regional Office for Europe

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<th>EARS-Net (N=30)</th>
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Challenges to detecting, monitoring and controlling AMR infections are found in all settings and in every country.

Awareness of the problem of AMR by medical and veterinary public health officials and clinicians as well as technical capacity for detection and monitoring of these pathogens vary greatly among and within countries.

At present, the varied capacity and practices in different countries pose a serious obstacle to the usefulness of international surveillance, particularly from countries with limited resources.

A coordinated network approach will be a key element to generating AMR data of quality and comparability that would support effective control strategies across countries.

Target 1.2 Diagnostic testing guidelines

Indicator 1.24. CPE_screening
National guidelines are available to screen hospitalised patients for carbapenem-nonsusceptible/carbapenemase-producing Enterobacteriaceae.
Target 1.3 Diagnostic testing utilisation

Indicator 1.32. Blood_culture_test_rate
Average number of blood culture sets tested/1000 hospital inpatient days reported by EARS-Net participating hospitals from your country.
*The current report is based on 2012 data.

*Figure 9. EU distribution of scoring results by country for the 20 EULabCap indicators within the dimension of primary diagnostic testing*
Target 1.4 Antimicrobial drug susceptibility testing

Indicator 1.42. **EUCAST_bkpt_use**
Percentage of clinical laboratories that have used EUCAST 2013 clinical breakpoints for interpretive reporting of antibacterial drug susceptibility testing results to clinicians.
CAESAR Collaboration – Country Support

WHO EURO – Political expertise

Country support process
Country situation analysis

ESCMID ESGARS – Laboratory expertise
RIVM – IT/EPI expertise
Over-the-counter sale of antimicrobials is common
Limited number of tests for identification (mostly no full identification)
A few labs have automated systems for ID & AST – Expert competency to interpret the data is missing
Very few labs have automated blood culture instruments – The instruments are used suboptimally
Most of the laboratory equipment is quite old, but are being taken very good care of.
Paper-based record keeping is common
Patient data is recorded onto many different forms rendering the retrospective analysis of data highly difficult.
Whether standards are not being followed or the standards are outdated
Reagents are not stored accordingly, internal or external quality control studies are not being performed.
Media, antimicrobials, disk potencies are not in concordance with guidelines (EUCAST and/or CLSI)
Substantial imbalance between the capacities of laboratories, even in the same city
CAESAR Collaboration – Country Support

WHO EURO – Political expertise

Country support process

Country situation analysis

Follow up activities

National workshops
Multi country workshops
Consultancy / Mentorships
Observerships / Twinning

ESCMID ESGARS – Laboratory expertise

RIVM – IT/EPI expertise
Radu Cojocaru (CNSP) – Supravegherea rezistenței la antibiotice în Republica Moldova. Au fost prezentate exemple de sisteme naționale de supraveghere a rezistenței antimicrobiene în Olanda și Turcia.

De asemenea de către experții OMS au fost organizate exerciții încolectarea datelor și retroinformarea în acord cu metodologia CAEZAR, analiza și raportarea datelor supravegherii rezistenței la antibiotice la nivel național și de laborator.
Multicountry Training Course on Antimicrobial Resistance Surveillance and Stewardship, 9-12 November, 2015, Istanbul, Turkey
A heterogenous group of participants;

Infectious disease specialists,
- Antimicrobial stewardship

Clinical microbiologists,
- Laboratory workshop

Epidemiologists
- Data collection and analysis
Wet-lab sessions: Internal quality control, phenotypic and genotypic tests to detect resistance mechanisms
Small group tutorials according to specialty
CAESAR Collaboration – Country Support

WHO EURO – Political expertise

Country support process
- Country situation analysis

Follow up activities
- National workshops
- Multi country workshops
- Consultancy / Mentorships
- Observerships / Twinning

Focus
- Laboratory capacity building; AMR reference labs; QA, ID and AST, EUCAST
- CAESAR methodology; Standardized data collection
- PoP study; diagnostic and antibiotic stewardship

ESCMID ESGARS – Laboratory expertise

RIVM – IT/EPI expertise
**EUCAST Approach**

**Antimicrobial susceptibility testing**
- Performance of AST
- Categorization of results according to breakpoints (S/I/R)


**Detection of specific resistance mechanisms**


**Implementation of expert rules**
- Intrinsic resistances
- Unexpected phenotypes (usually resistance)
- Interpretive rules

# European Committee on Antimicrobial Susceptibility Testing

**Breakpoint tables for interpretation of MICs and zone diameters**

*Version 6.0, valid from 2016-01-01*

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EUCAST expert rules in antimicrobial susceptibility testing

R. Leclercq¹,², R. Cantón¹,²,³,⁴, D. F. J. Brown⁴, C. G. Giske²,⁴,⁵, P. Heisig²,⁶, A. P. MacGowan⁴,⁷, J. W. Mouton⁴,⁸, P. Nordmann²,⁹, A. C. Rodloff⁴,¹⁰, G. M. Rossolini²,¹¹, C.-J. Soussy⁴,¹², M. Steinbakk⁴,¹³, T. G. Winstanley²,¹⁴ and G. Kahlmeter⁴,¹⁵

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EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance

Version 1.0
December 2013

EUCAST subcommittee for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance:
Christian G. Giske (Sweden, EUCAST Steering Committee and EARS-Net Coordination Group; chairman), Luis Martinez-Martinez (Spain, EUCAST Steering Committee), Rafael Cantón (Spain, chairman of EUCAST), Stefania Stefani (Italy), Robert Skov (Denmark, EUCAST Steering Committee), Youri Glupczynski (Belgium), Patrice Nordmann (France), Mandy Wootton (UK), Vivi Miriagou (Greece), Gunnar Skov Simonsen (Norway, EARS-Net Coordination Group), Helena Zemlickova (Czech Republic, EARS-Net Coordination Group), James Cohen-Stuart (The Netherlands) and Marek Gniadkowski (Poland).
WHO Collaborating Centre for Surveillance of Antimicrobial Resistance

Welcome to the WHONET Community website. Our mission is to build and support the community needed for tracking microbial populations worldwide and to provide the information base required for effective containment and control.

On this site, you will find information on the WHONET software and on activities by our collaborators around the world.

WHONET 5.6 Documentation

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Using WHONET to identify time and space clusters of multiresistant isolates

The analysis sorts isolates by their antibiotypes, the combinations of antimicrobial agents to which each isolate tested resistant.

FIG. WHONET scatter plot of MICs of ceftriaxone (CRO) and of ceftazidime (CAZ) for all isolates of E. coli at one hospital during 1 year.

Rationale:
Surveillance needs reliable data which can only be provided by quality-assured labs.

Tool:
Laboratory Quality Stepwise Implementation (https://extranet.who.int/lqsi/)

Aim:
Implementation of Laboratory Quality Management Systems (LQMS)
Mentor Training on the Laboratory Quality Stepwise Implementation (LQSI) Tool, Copenhagen, Denmark, 23-25 February 2016
The EQA Process (UK NEQAS)

Prepare samples

Examine samples
Report results

Analyse results
Prepare report

Evaluate performance

Participants

Participants

Once a year, six strains
In 2015, 250 labs in 15 countries
Critical failures in the procedures for the performance of blood cultures.

Most of the times less than 1 mL of blood is collected and incubated.

Only a few laboratories have an automated instrument, even if they do the number of blood cultures being taken is too small.
Proof of principle study to improve sampling habits
Sepsis

• A clinical syndrome characterized by systemic inflammation due to infection.

• Over 1,650,000 cases of sepsis occur in the United States each year, with a mortality rate up to 50%.

• It is estimated that between 15% and 35% of hospitalized patients have sepsis.

Proof of Principle (PoP) to improve sampling habits

• Initiative of WHO Europe and the WHO Collaborating Centre on AMR, The National Institute of Public Health, The Netherlands

• Developed together with University Hospital Infectious Diseases in Croatia and the National Center for Disease Control & Public Health in Georgia

• To support countries with setting up routine diagnostics for AST to improve patient treatment and surveillance.
Why did we develop the PoP?

- Country Situation Analysis:
  - Low blood sampling habits
  - Blood samples are only taken after repeated treatment failure
  - Limited laboratory capacity
- Overview of the resistance problems in critically ill patients to improve treatment guidelines at local and national level
- To optimize patient treatment
Multidisciplinary approach

Clinician → Patient

Clinician → Microbiologist

Microbiologist → Reference lab

Reference lab → Microbiologist

Microbiologist → Clinician
Expected study outputs

1. Baseline AMR data for main pathogens causing BSI
2. Strengthened laboratory capacity for species ID and AST at the local laboratories and the national AMR Reference Laboratory (also including confirmatory testing)
3. Basic set-up for national AMR surveillance network and participation in CAESAR.
4. Clinicians have the capacity to take samples according to standard protocols and use microbiologic information to guide appropriate treatment decisions
5. To provide a best practice and cost estimate of blood culture sampling and routine susceptibility testing in patients with sepsis, to highlight the need for sustainable implementation
Thank you for your attention.