The value of national and international surveillance systems in the epidemiology of antimicrobial resistance.

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Santander, Spain

Bochum, Germany, September 21, 2016
1. INTRODUCTION

2. CONCEPTUAL FRAME

3. ORGANIZATIONAL ASPECTS

4. CURRENT SURVEILLANCE SYSTEMS
   Local
   National
   International
   Supranational
   Global. “One health” Surveillance

5. LIMITATIONS AND GAPS

6. CONCLUSIONS: FUTURE NEEDS
ANTIBIOTIC RESISTANCE: A MAJOR CURRENT HEALTH PROBLEM

2014. World Health Organization
“[A] Post-antibiotic era, far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century”

21 September 2016
United Nations General Assembly
High-level meeting
AIMS: To accelerate global commitments and enhance national multi-sectoral efforts to combat AMR
DEATHS ATTRIBUTABLE TO ANTIMICROBIAL RESISTANCE EVERY YEAR COMPARED TO OTHER CAUSES OF DEATH

Sources

<table>
<thead>
<tr>
<th>Disease</th>
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<td>Diabetes</td>
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© by author
NEEDS FOR SURVEILLANCE

1988. CDC:
   Guidelines for the evaluation of surveillance systems

1995. ASM Task Force:
   Recommendation for implementing surveillance measures

2000. CDC + FDA + NIH:
   Public Health Action Plan to combat Antimicrobial Resistance

... 

2005. 58th World Health Assembly urged member states…
   “To ensure the development of a coherent, comprehensive and
   integrated national approach to implementing the strategy for
   containment of antimicrobial resistance and to monitor regularly
   the use of antimicrobial agents and the level of antimicrobial
   resistance in all relevant sectors”

...
SURVEILLANCE (…of Resistance)

Ongoing generation, capture, assembly, analysis and interpretation of all information on the evolving nature, spread, and distribution of infecting microbes and their resistance to antimicrobial agents, the results of which are disseminated for public-health actions and to assess the effects of any intervention program.
NEEDS FOR SURVEILLANCE AMR

- Identifying, understanding and predicting trends in and spread of resistant microorganisms (impact in guidelines)
- Detecting new resistance mechanisms
- Identifying the need for new diagnostic tests
- Identifying outbreaks of resistant organisms and infection control
- Identifying the need for new antibiotics
- Monitoring the impact of new empirical antibiotic prescribing
- Monitoring the impact of interventions to improve antimicrobial use and control the spread of infection
- Identifying needs for sentinel laboratories in low-resources areas
- Public health and clinical guidelines
- Educating health care providers, patients and the general public
SURVEILLANCE SYSTEMS

- Local
- Regional
- National
- International
SURVEILLANCE SYSTEMS

Comprehensive surveillance:
Surveillance of a specific disease or pathogen
In the whole population at risk involves
Usually based on limited sets of data

Sentinel surveillance:
Limited to an area or population
Representative of the total population
Indicator data for the rest of the population

Continuous vs. episodic

Passive (reports are awaited) vs.
Active (reports are sought from the primary data collector)
Infrastructure to properly collect and culture [clinical] samples (routine patient care)

Laboratory facilities and trained personnel

Capacity to obtain, analyze and report surveillance data (sustainable over time)

Political support
Financial support

Cooperation between physicians, veterinarians, microbiologists, epidemiologists, soil scientists, and representatives from food production industries and government agencies responsible for risk assessment, risk management and research

Publication of findings in a timely manner (different audiences)
Guide for establishing laboratory-based surveillance for antimicrobial resistance

Disease Surveillance and Response Programme Area
Disease Prevention and Control Cluster
ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM
TECHNICAL ASPECTS

Attempting to survey all organisms from all infections for their susceptibility to all antibiotics is not practical/cost-effective

Samples:
- Humans, [food-producing] animals, retail foods
- Source (invasive vs. non-invasive), information, representativeness, collection frequency, size

Target microorganisms:
- Clinically relevant organisms
- Major foodborne pathogens
- [other bacteria]

Laboratory methodology:
- Culture methods and identification of isolates
- Standardized antimicrobial susceptibility testing and quality control
- Antimicrobials considered for surveillance
- Storage of bacterial isolates

Data analysis and reporting:
- Program description
- Data interpretation and presentation

Funding
- Public [vs.] Private
LOCAL SURVEILLANCE
GUIDELINES FOR CUMULATIVE DATA FROM ANTIBIOTICGRAM

M39-A4
Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline—Fourth Edition

This document describes methods for recording and analysis of antimicrobial susceptibility test data, consisting of cumulative and ongoing summaries of susceptibility patterns of clinically significant microorganisms.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.
## NATIONAL ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEMS

<table>
<thead>
<tr>
<th>N.</th>
<th>Surveillance of resistant bacteria from</th>
<th>Bacterial species included</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy animals</td>
<td>Diseased animals</td>
</tr>
<tr>
<td>CIPARS (7) (Canada)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Danmap (8) (Denmark)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FINRES-VET (9) (Finland)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ONERBA (10) (France)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GERM-VET (Germany)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>JVARM (11) (Japan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORM/NORMYET (12) (Norway)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ITAVARM (Italy)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NETHMAP/MARAN (13) (Netherlands)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NARMS (14) (United States)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SWEDRES/SVARM (15) (Sweden)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
OTHER NATIONAL INITIATIVES ON AMR SURVEILLANCE

RusNetc: Russian Federation, coordinated by the Institute of Antimicrobial Chemotherapy (IAC) of the Smolensk State Medical Academy, Scientific Center on Monitoring Antimicrobial Resistance. Network of 21–42 participating sites (depending on study).

ARMed: Antibiotic Resistance Surveillance and Control in the Mediterranean Region (extinguished)

AFHSC-GEIS (US Armed Forces Health Surveillance Center, AFHSC)

WHO GASP: Gonococcal Antimicrobial Surveillance Programme (established in 1992, WHO-Western Pacific Region)

The Pasteur Institute: BIRDY (Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries: an international cohort study)

Multiple Western countries are developing detailed studies on AMR, in addition to participate in supranational networks.

Other countries:
- New Zealand, Australia (AGAR,…), China (MOHNARIN), Philippines, Thailand, Vietnam, South Africa,…
INITIATIVES RELATED TO AMR SURVEILLANCE: EUROPE

Human health:
European Antimicrobial Resistance Surveillance Network (EARS-Net)
European Surveillance of Antimicrobial Consumption Network (ESAC-Net)
European Food and Waterborne Diseases and Zoonoses Network (FWD-Net)
Healthcare Associated Infection Network (HAI-Net)

[Central Asia] and European Surveillance of Antimicrobial Resistance (CAESAR)

Food-producing animals and food products:
European Centre for the Study of Animal Health (CEESA)
European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)
EFSA-Surveillance of zoonoses and disease outbreaks from food and food-producing animals

Others:
European Committee on Antimicrobial Susceptibility Testing (EUCAST)
European Society of Clinical Microbiology and Infectious Diseases (ESCMID), study groups on antimicrobial policy (ESGAP), AMR surveillance (ESGARS), veterinary microbiology (ESGVM).
EARS-Net

European Antimicrobial Resistance Surveillance Network

28 (27) EU countries plus Iceland and Norway
900 microbiological laboratories, 1500 hospitals

Coordinated by the European Centre for Disease Prevention and Control (ECDC)

Surveillance of indicator pathogens:
Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae,
Pseudomonas aeruginosa, Acinetobacter spp., Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium

Bloodstream infections and meningitis

Variations in AMR over time and place

Web-accessible database (maps, graphs,...)
Figure 5. Trends for *S. aureus* – total numbers of *S. aureus*/MRSA and percentage MRSA with 95% CIs

* Data for 2014 are provisional to the end of Q4

Figure 6. Distribution of MRSA in EARS-Net countries in 2013

Map obtained from ECDC on 28/07/2014:
EARS-NET. MRSA 1998-2014
CAESAR

Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Network of national surveillance systems for AMR

Joint initiative:
- WHO
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

Countries of the region not integrated into EARS-Net

EARS-Net methodology
Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Annual report 2014
Latin American Antimicrobial Resistance Surveillance Network

Created in 1996

Led by
WHO Regional Office for the Americas/ Pan American Health Organization (AMRO/PAHO)

Aggregated data provided by national reference laboratories (NRLs)

NRLs from 19 countries in Latin America plus Canada and the USA
720 Sentinel laboratories (2015)
Quality external control: Administración Nacional de Laboratorios e Institutos de Salud (ANLIS), "Dr. C. G. Malbrán“, Buenos Aires, Argentina

2000: 72 000 isolates
2010: >150 000 isolates
ReLAVRA

Antimicrobial Resistance (%) *K. pneumoniae*

<table>
<thead>
<tr>
<th>Country</th>
<th>Cefalosporinas 3ª generación</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>59,00</td>
<td>9,00</td>
</tr>
<tr>
<td>Bolivia</td>
<td>94,00</td>
<td>3,00</td>
</tr>
<tr>
<td>Brazil</td>
<td>44,28</td>
<td>38,20</td>
</tr>
<tr>
<td>Colombia</td>
<td>38,00</td>
<td>12,00</td>
</tr>
<tr>
<td>Cuba</td>
<td>60,00</td>
<td>2,00</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>64,00</td>
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<td>Ecuador</td>
<td>76,00</td>
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<td>El Salvador</td>
<td>53,00</td>
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<td>Guatemala</td>
<td>60,00</td>
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<td>Honduras</td>
<td>72,00</td>
<td>5,00</td>
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<tr>
<td>Nicaragua</td>
<td>79,00</td>
<td>20,00</td>
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<tr>
<td>Panama</td>
<td>40,00</td>
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<tr>
<td>Paraguay</td>
<td>49,00</td>
<td>9,00</td>
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<td>Peru</td>
<td>19,00</td>
<td>0,20</td>
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<tr>
<td>Venezuela</td>
<td>21,00</td>
<td>9,00</td>
</tr>
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SUPRANATIONAL INITIATIVES RELATED TO AMR SURVEILLANCE IN ASIA

1980s. WHO-Western Pacific Region.
Agreement of 14 Member States to share AMR data
20 pathogens (hospital --- community)
Annual reports for network participants
Interrupted in the early 2000s due to other emergencies)

2011, Jaipur Declaration on Antimicrobial resistance
Commitment to combat AMR (health ministers, 11 Member States)
6 Member States already have national surveillance systems
Regional database and consultative process

Asian Network for Surveillance of Resistant Pathogens (ANSORP)
Independent, non-profit nongovernmental international collaborative research group on AMR and infectious diseases in the Asian-Pacific region. Based in the Republic of Korea, which is a member of the Asia Pacific Foundation for Infectious Diseases (APFID)
Collaborators from 123 hospitals in 14 countries, territories and areas
INITIATIVES RELATED TO AMR SURVEILLANCE AFRICA

Limited Information

Surveillance only in a few countries.

No formal framework for collaboration among surveillance programs

No common strategy for tracking and containing the emergence of resistant organisms, and to systematically evaluate trends and resistance-containment activities

[WHO guide to facilitate the establishment of laboratory-based surveillance for priority bacterial diseases in the region]
AGISAR: WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance

Established in December 2008
Regular phone conferences and annual face-to-face meetings

Over 30 internationally experts
Transparent selection process: Web-published call

AIM: To support WHO's effort to minimize the public health impact of AMR associated with the use of antimicrobials in food animals.

- To develop harmonized schemes for monitoring AMR in zoonotic and enteric bacteria.
- To support WHO activities in Member countries for monitoring ARM and antimicrobial usage.
- To update the WHO list of Critically Important Antimicrobials for Human Medicine.
- To Provide expert advice to WHO on containment of antimicrobial resistance.
- To support and advise WHO on the selection of sentinel sites and the design of pilot projects for conducting integrated surveillance of AMR.
- To promote sharing of information on AMR.
WHO Global Strategy for Containment of Antimicrobial Resistance

In the late 1990s and 2000, WHO convened a series of consultative groups, expert workshops, and consensus meetings to assess the growing public health threat of antimicrobial resistance, to evaluate the impact of containment interventions, and to develop a series of recommendations for action. The culmination of this work was the publication in 2001 of the WHO Global Strategy for Containment of Antimicrobial Resistance and a series of supportive background materials and technical guidelines.

The WHO Global Strategy identifies 68 prioritized recommendations, for implementation targeted the following groups:

- Patients and the general community
- Prescribers and dispensers
- Hospitals
- Antimicrobials use in food-producing animals
- National governments and health systems
- Industry and research group
- International organizations
WHO GLOBAL ESTRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE

Core Documents and Summary of Recommendations

- WHO Global Strategy for Containment of Antimicrobial Resistance [pdf 529kb]
- WHO Global Strategy for Containment of Antimicrobial Resistance: Executive Summary [pdf 159kb]
- WHO Global Strategy Recommendations
- Implementation Workshop on the WHO Global Strategy
- Providing technical guidance on interventions

Background literature reviews

- Interventions and Strategies to Improve the Use of Antimicrobials in Developing Countries (319K) (2001)

Pathogen-specific issues and recommendations

- Antimicrobial Resistance in Neisseria gonorrhoeae (526K) (2001)
- Drug Resistance in Malaria (354K) (2001)
- Monitoring the Emergence of Antiretroviral Resistance (228K) (2001)
- Resistant Pneumococcal Infections (300K) (2001)

Healthcare-Associated Infections

- Infection Control Programmes to Contain Antimicrobial Resistance (361K) (2001)
ANTIMICROBIAL RESISTANCE
Global Report on Surveillance
2014

World Health Organization
# RESISTANCE TO CARBAPENEMS IN *K. pneumoniae* BY WHO REGION. 2013

<table>
<thead>
<tr>
<th>Data sources based on at least 30 tested isolates</th>
<th>Overall reported range of resistant proportion (%)</th>
<th>Reported range of resistant proportion (%) in invasive isolates (no. of reports)</th>
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<tbody>
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<td>African Region</td>
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<tr>
<td>– Publications (n=0)</td>
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<tr>
<td>Region of the Americas</td>
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<td>Eastern Mediterranean Region</td>
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<td>– Surveillance network (n=1) in 1 additional country</td>
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<td>European Region</td>
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<td>South-East Asia Region</td>
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<td>Western Pacific Region</td>
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<td>– National data (n=9 countries)</td>
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<td>– Institute surveillance (data from 2 hospitals in 1 country)</td>
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<tr>
<td>– Publications (n=2) from 2 additional countries</td>
<td>0–11</td>
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Center for Disease Dynamics, Economics & Policy (Public health organization)

Maps available at: http://resistancemap.cddep.org
**FIGURE E5-1:** Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999-2014

Source: CDEP 2015

**FIGURE 1-1:** Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA), by country (most recent year, 2011-14)

Source: CDEP 2015, WHO 2014 and PAHO, forthcoming
PRIVATE SURVEILLANCE PROGRAMS:
SENTRY
MYSTIC
TRUST
SMART
AZ Global Surveillance Program
...

PREPARATION OF LABORATORY REPORTS:
Focus Technologies TheraDoc, MedMine, Vecna, Premier (charge hospitals to extract and analyze data)
‘ONE HEALTH’ SURVEILLANCE

- Antibiotic usage/consumption PLUS Antibiotic Resistance data
- Humans, animals and the environment
- International collaboration and capacity

Quennan K et al IJAA 2016
Potential to change disease detection and surveillance capacity and organization

Possibility of Web-based data for ongoing, automated, real-time analyses with prompt alerting of responders

Genomic information can be generated viruses, bacteria, parasites

Already cost-efficiency in many countries

It will allow comparison in real-time of thousands of genomes (single strains and meta-genomic datasets)

Sharing raw data recommended by some experts

[Current major limiting factor: bioinformatic expertise]
GLOBAL SHARING AND COMPARISON OF DATA

GENOMETRAKR
2012. US Food and Drug Administration PLUS NCBI
www.fda.gov/Food/FoodScienceResearch/WholeGenomeSequencingProgramWGS
Freely available. >61,000 isolates sequenced, >100 genomes closed
Data can be uploaded into NCBI
A phylogenetic tree can be generated by NCBI with all uploaded data
Additional analysis can be performed locally

COMPARE
2014. European Commission-funded
www.compare-europe.eu
“Integrate state-of-the-art strategies, tools, technologies and methods for collecting, processing and analysing sequence-based pathogen data in combination with associated (clinical, epidemiological and other) data”
Bacteria, parasites, and viruses, single genomes and metagenomes
Support release into the public domain (temporary ‘quarantine’ allowed)
“CUSTOMERS” OF SURVEILLANCE

• Prescribers, clinicians
• Microbiologists
• Infection control practitioners
• Regulatory authorities
• Public-health authorities
• Pharmaceutical companies
• Politicians
• Public

MAJOR PURPOSE: To improve the management of infectious diseases for minimizing morbidity and mortality
SURVEILLANCE OF AMR: LIMITATIONS AND GAPS (I)

• Incomplete or erroneous species identification
• Use of different definitions for ‘resistant’
• Differences in antimicrobial agents of selected for susceptibility testing (commercial panels)
• Cascade or tier the antibiotics selected for testing (bias towards resistance)
• Need for external quality control
• Inadequate routine surveillance of new(er) antibiotics
• Limited availability of genetic data on antibiotic resistance
• Surveillance often based on samples from patients with severe infections and those in which first-line treatment has failed
• Community-acquired infections are underrepresented
• Little information on resistance in nursing homes, kindergartens, food, the veterinary sector, the environment and pets
• Data based on a small number of isolates (<30 per species)
• (Amount of) Personal data required

• Gaps in knowledge about the status of ABR surveillance capacities worldwide, particularly in resource-limited settings
• Lack of standardized methods for global surveillance
• Lack of financial resources and political support
• Some centers may withdraw from a multicenter surveys
• Surveillance is generally neither coordinated nor harmonized
• No global consensus on methodology and data collection
• Limited information on economic and societal impact of AMR
• Uncertain legal frameworks
• Ethical issues
• Ownership of surveillance data and Intellectual property
CONCLUSIONS: FUTURE NEEDS FOR AMR SURVEILLANCE

• To organize an integrated surveillance of AMR system considering humans, food-producing animals and the food chain

• To ensure collaboration between existing surveillance networks and surveillance centers towards coordinated regional and global surveillance

• To elaborate strategies for population-based surveillance of AMR

• To report data on resistance together with data on antimicrobial use in humans and animals

• To develop tools and standards for harmonized global surveillance of AMR

• To periodically evaluate both methods used and data collected to ensure their usefulness for public health purposes

• To increase the timeliness of data collection and reporting

• To collect and report subtyping data (e.g. genomic sequence) for important resistant pathogens

• To provide more extensive information on emerging and ongoing public health issues related to resistant pathogens and their health and economic impact

• To improve and continue economical-political-social support to AMR surveillance
THANK YOU!!