Antimicrobial resistance in Europe: burden and successful prevention and control initiatives

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European Centre for Disease Prevention and Control
Washington (DC), 6 April 2010
What Does “Antimicrobial Resistance” Represent?

Several, inter-related compartments of healthcare, i.e. patients in primary care, hospitals, nursing homes and long-term care facilities, food animals, food, environment)

Many types of infection, i.e. respiratory tract, urinary tract, skin and soft tissue, bloodstream, surgical site, related to medical devices, etc.)

Many bacteria/microorganisms

Many antimicrobials and mechanisms of resistance

Patients with infections due to resistant bacteria!
Compartment of antimicrobial resistance

- Humans
  - HA-MRSA
  - CA-MRSA
  - LA-MRSA (mostly CC398)
- Food Animals
  - Salmonella
  - Campylobacter
- Enterobacter
  - Klebsiella pneumoniae
  - Clostridium difficile
- Pseudomonas aeruginosa
- Acinetobacter baumannii
- Strep. pneumoniae
- Strep. pyogenes
- Haem. influenzae
What is the European Union?

- 27 Member States
- 23 official languages
- > 500 million inhabitants
  (per country: 416,333 - 81.7 million)
- €25,100 GDP/capita
  (per country: 10,400 - 69,300)
- A patchwork of cultures!

1 € = 1.36 US$
Healthcare resources in the EU

- % GDP for healthcare: approx. 6 to 11%
- Physicians: 27 to 200 per 100,000 inh.
- Nurses: 327 to 1550 per 100,000 inh.
- Ratio nurses/physicians: 1.6 to 36

Source: Eurostat and WHO Health For All online database (WHO Euro, latest available year).
Europe: cultural differences, but a healthy culture of benchmarking!

Who makes fun of whom in Europe?

Adapted from: Helsingin Sanomat, Finland
Methicillin-resistant Staphylococcus aureus (MRSA), blood and CSF, 2008

Source: European Antimicrobial Resistance Surveillance System (EARSS), 2009

Country with:
- **É** Significant increase (2005-2008)
- **Í** Significant decrease (2005-2008)
Third-generation cephalosporin-resistant Escherichia coli, blood and CSF, 2008

Country with:
- Sign significant increase (2005-2008)
- Í Significant decrease (2005-2008)

Source: European Antimicrobial Resistance Surveillance System (EARSS), 2009
Population-weighted, average % resistant isolates among bacteria from bloodstream infections, EU, Iceland and Norway, 2002-2008

Gram-positive bacteria

- Methicillin-resistant S. aureus (MRSA)
- Vancomycin-resistant E. faecium
- Penicillin-resistant S. pneumoniae*

Gram-negative bacteria

- Third-gen. cephalosporin-resistant E. coli
- Third-gen. ceph.-resistant K. pneumoniae**
- Carbapenem-resistant P. aeruginosa**

*Excluding Greece, which did not report data.

**Excluding Belgium and Slovakia, which did not report data.

Methods: Burden of human infections due to 6 selected resistant bacteria

Human burden

– Extrapolations from %population coverage of EARSS in each country

– Extrapolations for 4 main types of infection (bloodstream, respiratory tract, skin and soft tissue, urinary tract)

– Extrapolations of burden parameters from literature (e.g.: attributable mortality, extra length of stay in hospital)

Economic burden

– Extra in-hospital costs

– Productivity losses due to absence from work because of illness and premature death of infected patients

# Burden of multidrug-resistant (MDR) bacteria in the EU, Iceland and Norway

## Human burden

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
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<tbody>
<tr>
<td>Infections (6 most frequent MDR bacteria, 4 main types of infection)</td>
<td>approx. 400,000 / year</td>
</tr>
<tr>
<td>Attributable deaths</td>
<td>approx. 25,000 / year</td>
</tr>
<tr>
<td>Extra hospital days</td>
<td>approx. 2.5 million / year</td>
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## Economic burden

<table>
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<tr>
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<th>Value</th>
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<tr>
<td>Extra in-hospital costs</td>
<td>approx. € 900 million / year</td>
</tr>
<tr>
<td>Productivity losses</td>
<td>approx. € 600 million / year</td>
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**Limitation:** these are underestimates.

Economic burden of multidrug-resistant (MDR) bacteria: nomogram for in-hospital costs

Burden of multidrug-resistant bacteria in the EU, Norway and Iceland (1)

Adapted from data source:
Burden of multidrug-resistant bacteria in the EU, Norway and Iceland (2)

Adapted from data source:
Probable burden of multidrug-resistant bacteria in Europe

15 novel, systemically administered antibacterial agents in the pipeline

13 agents against Gram-positive bacteria

6 agents against Gram-negative bacteria

There is a gap between the burden of infections due to MDR bacteria and the development of new antibiotics to tackle this problem.

There is a particular lack of new agents to treat infections due to MDR bacteria, in particular MDR Gram-negative bacteria.

A European and global strategy to address this gap is urgently needed.

Survey of European intensive care specialists on experience with infections due to resistant bacteria, 2009

### Gram-positive bacteria
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Vancomycin-resistant Enterococcus spp. (VRE)
- Penicillin-resistant Streptococcus pneumoniae (PRSP)
- Vancomycin-resistant/intermediate S. aureus (VRSA/VISA)

### Gram-negative bacteria
- Third-generation cephalosporin-resistant Enterobacteriaceae
- Carbapenem-resistant Pseudomonas aeruginosa
- Carbapenem-resistant Acinetobacter spp.
- Carbapenem-resistant Enterobacteriaceae

### Bacteria totally or almost totally resistant to available antibiotics

<table>
<thead>
<tr>
<th>% respondents</th>
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<tbody>
<tr>
<td>0 20 40 60 80 100</td>
</tr>
</tbody>
</table>

No. treated patients during past 6 months:
- >10 patients
- 3-10 patients
- 1-2 patients
- 0
- Do not know
- Missing

Source: Lepape A & Monnet DL, on behalf of participating members of the European Society of Intensive Care Medicine (ESICM), Eurosurveillance, November 2009
Carbapenem-resistant Klebsiella pneumoniae, blood and CSF, 2008

Source: European Antimicrobial Resistance Surveillance System (EARSS), 2009
Main actions to prevent and control antimicrobial resistance

Prudent use of antimicrobials
(only when needed, correct dose, dose intervals, duration)

Infection control
(hand hygiene, screening, isolation)

New antibiotics
(with a novel mechanism of action, research, development)
European legislation on feed additives


- New rules for the authorisation, supervision and labelling of feed additives
- Phasing out the authorisations of antibiotic feed additives as from 1 January 2006
- Completes the ban on antibiotic growth promoters in feed.
- “This Regulation shall be binding in its entirety and directly applicable in all Member States.”

Council Recommendation on the prudent use of antimicrobial agents, 2001

Council Recommendations and Conclusions, 2008-2009

Council Conclusions on Antimicrobial Resistance (AMR) (10 June 2008)

Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections (2009/C 151/01)

Council Conclusions on innovative incentives for effective antibiotics (1 December 2009)
What is ECDC?

"An independent agency, named the European Centre for Disease Prevention and Control ..."
— ECDC Founding Regulation (851/2004)

A European Union Agency which:
- is a member of the European Union (EU) family;
- covers EU 27, EEA/EFTA countries;
- reaches out to other countries beyond the EU 27 through Neighbourhood Policy and DG RELEX;
- supports and promotes global health security (role in International Health Regulations);
- is financed through EU budget;
- is based in Stockholm, Sweden.
Coordination of AMR activities, 2007-2010

Network of National AMR Focal Points
(representing national Intersectoral Coordination Mechanisms, i.e. National committees)

Meet twice a year since September 2007

Meetings in 2010:

- Stockholm, 21-22 April 2010 (together with Competent Bodies for Communication)
- Madrid, 2-4 June 2010 (followed by 5th International Conference on Patient Safety)
- Brussels, 8-10 November 2010 (followed by workshops and EU Conference on AMR & HAI)
Country visits to discuss antimicrobial resistance (AMR) issues, 2006-2010

Based on Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC)

Reports (observations, conclusions, suggestions, examples of best practice)

14 initial visits (see map)

5 follow-up visits (Czech Rep., Greece x 2 and Hungary x 2)

More visits in 2010
Implementation of National Intersectoral Coordination Mechanisms on AMR

As of 2008, 18 EU Member States and Norway had implemented an Intersectoral Coordination Mechanism.

*Adapted from: European Commission, Directorate - General Health and Consumers, 2010 (in press)*
Legal framework on prudent use of antibiotics in 10 EU countries, 2008-2009
(Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Luxembourg, Sweden, UK)

- Surveillance of antibiotic resistance
- Surveillance of antibiotic consumption
- Hospital antimicrobial stewardship
- Hospital infection control
- Assessment of implementation in hospitals (mostly infection control)

Source: Dumartin C & National AMR Focal Points (preliminary data).
Implementation of measures in Member States and Norway

Surveillance

- All countries but one participate EARSS
- All countries participate in ESAC
- Only 7 countries (and Wales) could link national antibiotic consumption and resistance data
- Links with veterinary surveillance in only 16 countries

Guidelines

- National guidelines on appropriate use of antimicrobials in all but four countries (and Wales)
- Complicance rarely assessed by the countries
- Guidelines in hospitals only reported by half of countries

Total outpatient antibiotic use (ATC J01) in 29 European countries, 1998-2005

*Total use for Bulgaria and Iceland, and for Greece (2004 & 2005 only).
**Reimbursement data, which do not include over-the-counter sales without a prescription.

Decreases in antimicrobial resistance following national media campaigns

2008

- Materials for general public
- 32 countries participated

2009

- Materials for primary care prescribers
- Website translated in all EU languages
- TV spots developed

2010

- Focus on hospital prescribers
- Will match Get Smart week in the United States

Antibiotics kill viruses. True or false?

% respondents with correct answer (i.e., "false"): 36% (range: 14 - 73%)

National hand hygiene campaigns in European countries, 2000-2009

- Survey among 30 countries (all EU Member States plus candidate countries)
- 13 countries had had national hand hygiene campaigns
- 3 countries were organizing a campaign
- 10 countries only had regional campaigns that included hospital-based activities

- Published in support of WHO campaign “SAVE LIVES: Clean Your Hands”, 5 May 2009

Looking ahead: key certainties

• Antibiotic resistance will exist as long as antibiotics are used

• New resistance mechanisms will necessarily emerge

• Antibiotics will always be misused to a certain extent

• Compliance with hand hygiene and other infection control measures will never be 100%
# Mapping the future: uncertainties and implications

## Prevention and control of AMR

<table>
<thead>
<tr>
<th>New antibiotics with a novel mechanism of action</th>
<th>Activities in only a few countries</th>
<th>Activities in many countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>• Must rely on rational use of existing antibiotics and on infection control</td>
<td>• Must rely on rational use of existing antibiotics and infection control</td>
</tr>
<tr>
<td></td>
<td>• Mitigation an achievable goal?</td>
<td>• Increase awareness among new generations</td>
</tr>
<tr>
<td>Yes</td>
<td>• New antibiotics always essential</td>
<td>• Market for new antibiotics mostly empirically for severe infections</td>
</tr>
<tr>
<td></td>
<td>• Focus on rational use of new and other antibiotics</td>
<td>• Focus on detection and control of emerging AMR</td>
</tr>
<tr>
<td></td>
<td>• Re-emphasize infection control</td>
<td>• Re-emphasize rational use of antibiotics</td>
</tr>
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</table>
The more antibacterial trade names, the more consumption of antibacterials!

Distribution of antibiotic use in healthcare compartments in 4 EU countries

a. Denmark

b. Sweden

c. Germany

d. Spain

- Other
- Imidazoles
- Quinolones
- Carbapenems
- Aminoglycosids
- Cephalosporins
- Macrolides, lincosamides & streptogramins
- Penicillins (combined)
- Penicillins & beta-lactamase inhibitors
- Penicillins
- Tetracyclines
- Sulfonamides & trimethoprim

aWHO-Defined Daily Doses except Spain, intensive care: Days of Therapy
Hypothetical compartmentation of antibiotics in healthcare

Disclaimer: The views expressed on this slide are personal and may not be understood or quoted as being made on behalf of or reflecting the position of ECDC.
5-Month moving average % imipenem-resistant/intermediate P. aeruginosa and hospital imipenem use, Hospital Vega Baja, Spain, 1991-2002

Average delay = 1 month
+1 DDD/1000 pat-days -> +0.40 % R
-1 DDD/1000 pat-days -> -0.40 % R
Antimicrobial consumption drives antimicrobial resistance in hospitals

Implementation of control programme

Antibiotic rotation and development of resistance, Surgical ICU, Utrecht (NL)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
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<tbody>
<tr>
<td>Levofloxacin</td>
<td>40</td>
<td>0</td>
<td>52</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cefpirome</td>
<td>0</td>
<td>44</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>55</td>
<td></td>
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How to... new class of antibiotic

**Class protection**
- Early patent of close chemical structures
- Life-long patent of class?

**Class compartmentalization**
- New class only patented and used in one compartment of healthcare

**Class (short!) cycling**
- "Beat the Bug Before it Bites!"
- Are there enough antibiotic classes to do this?

**Class isolation**
- Preventively isolate patients treated with new class

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Thank you!