The European road map against antimicrobial resistance…
(a changing paradigm for drug discovery and development?)

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What is the European Union?

• 28 Member States
• 24 official languages
• 508 million inhabitants (range: 429,344 – 81.2 million)
• A patchwork of
  - medico/pharmaceuticals
  - resistance patterns
  - antibiotic stewardships
  - drug reimbursement schemes

Healthcare resources in the EU

- €27,300 GDP/capita
  (range: 5,800 – 88,500)
  1 € = 1.11 US$

- %GDP for healthcare:
  <6% to approx. 12%

- Physicians:
  221 to 614 per 100,000 inh.

- Nursing professionals:
  44 to 1264 per 100,000 inh.

- Ratio nursing professionals / physicians:
  0.2 to 4.7

Source: Eurostat, 2015 (physicians and nursing professionals, 2012 or latest year available).
Council Recommendations, 2001 & 2009; Decision on serious cross-border threats to health, 2013


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

Decision of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health (L 293/1)

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

Council Conclusions on innovative incentives for effective antibiotics (1 December 2009)

Council Conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector—a “One Health” perspective (22 June 2012)
European Commission action plan to combat AMR, 2011: 12 key actions

**Human medicine**
1. Appropriate use
4. Prevention infections
6. New antibiotics
9. Surveillance

**Human + Veterinary**
8. International cooperation
11. Research & Innovation
12. Communication, education

**Veterinary medicine**
2 & 3. Appropriate use
5. Prevention infections
7. Need for new antibiotics
10. Surveillance

European Commission action plan to combat AMR, 2011: 12 key actions

Human medicine
1. Appropriate use
4. Prevention infections
6. New antibiotics
9. Surveillance

Veterinary medicine
2 & 3. Appropriate use
5. Prevention infections
7. Need for new antibiotics
10. Surveillance
8. International cooperation
11. Research & Innovation
12. Communication, education

European strategic action plan on antibiotic resistance (2011 – 2016): 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
Surveillance in human medicine

- European Surveillance system of Antimicrobial Consumption (ESAC-Net)

Surveillance in veterinary medicine

- European Surveillance system of Veterinary Antimicrobial Consumption (ESVAC)
- Monitoring on AMR in zoonotic / commensal bacteria in animals and food (Commission Decision 2013/652/EU)
- New Animal Health Law: legal basis for monitoring AMR on animal disease (other than zoonotic)
Integrated approach for surveillance, prevention and control of HAI* and AMR** in European acute care hospitals

* HAI: health care associated infections
** AMR: antimicrobial resistance

**Guidance (directory of online resources)**

**Outcome indicators**
- EARS-Net
- Limited list tbd
- Only HAI cases
- Verification and additional data from HAI-Net PPS every five years

**Structure and process indicators (incl. antimicrobial consumption)**
- Limited list tbd
- HAI-Net PPS SPIs
- ESAC-Net (hospital module)
- Verification from HAI-Net PPS (antimicrobial use)
Towards actions...
Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

2009 EU-US Summit Declaration called for the establishment of “...a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us.”

EU-US Summit – Washington 3 November 2009
What specific in Europe?

ECDC/EMEA Joint Working Group
- assigned on 28 February 2008.
- circulated for information on 20 August 2009.
- published in September 2009

Last accessed: 21-09-2015
What in Europe?

3 Analysis of the research and development pipeline of antibacterial agents

Most relevant findings

- Fifteen systemically administered antibacterial agents with a new mechanism of action or directed against a new bacterial target were identified as being under development with a potential to meet the challenge of multidrug resistance. Most of these were in early phases of development and were primarily developed against bacteria for which treatment options are already available.
- There is a particular lack of new agents with new targets or mechanisms of action against multidrug-resistant Gram-negative bacteria. Two such agents with new or possibly new targets and documented activity were identified, both in early phases of development.

The bacterial challenge: time to react

A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents

Last accessed: 9 May 2014
The reaction of the EU...

Communication from the Commission to the European Parliament and the Council

Action plan against the rising threats from Antimicrobial Resistance

COM (2011) 748

Last accessed: 21-09-2015
The reaction of the EU…

5-year Action Plan to fight against AMR based on 12 key actions:

Action n° 6:
*Promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antimicrobials to patients.*

Action n° 7:
*Promote efforts to analyse the need for new antibiotics into veterinary medicine*
Concerted actions...

HORIZON 2020

AMR RESEARCH AND INNOVATION LANDSCAPE

- European Research Council
- Marie Skłodowska-Curie actions
- Research infrastructures
- Societal challenges:
  - Health, Demographic Change And Wellbeing
  - Food, Security, Sustainable Agriculture, Marine and Maritime Research and the Bioeconomy
- Innovation in SMEs
- Access to risk finance

From van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.
Examples of direct ongoing aids to academic/industrial research (FP7)

Current activities on Diagnostic test development

**C4L** aims to develop rapid diagnostic tests to link antibiotic prescription with evidence-based diagnosis. Combining the Multiplex Ligation-dependent Probe Amplification (MLPA) and microfluidic technologies will allow determination of viral or bacterial origin, as well as bacterial resistance mechanisms.

**PARCIVAL** aims to develop an integrated and automated multi-analyte lab-on-a-disk platform for the fast and reliable sample in -> answer out diagnosis of highly infectious respiratory pathogens, resistance patterns and biomarkers for individual severity of the infection.

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Examples of direct ongoing aids to academic/industrial research (FP7)

Current activities on Diagnostic test development (INNO-2)

**ROUTINE** aims to develop a test that will integrate sample preparation, DNA amplification and a fluorescent-based read-out on one platform to allow direct detection of bacteria causing UTI and the associated antibiotic resistances within 30 min.

**RiD-RTI** aims to develop and evaluate three diagnostics products for the rapid (< 2 hrs) diagnosis of CAP, HAP/VAP and ORTIs. The diagnostics products will be ‘near patient’, reliable, cost-effective and user friendly allowing for detection, identification, and quantification (for selected targets) and molecular drug susceptibility testing of RTIs.

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Public/Private shares in Europe

Public-private partnerships

- Pooling expertise, knowledge and resources
- Developing incentives to address major unmet medical needs
- Providing a neutral trusted platform to align public and private interests

An opportunity to combine public and private resources for new antimicrobials
IMI in action …

- €2 billions euro budget…
- collaborative research projects and networks of industrial and academic experts…
- collaborative ecosystem for pharmaceutical research and development (R&D)…
- increase Europe's competitiveness globally…
- establish Europe as the most attractive place for pharmaceutical R&D
IMI ongoing projects in Infectious Diseases…

- **ADVANCE**
  Accelerated development of vaccine benefit-risk collaboration in Europe
  €10,754,061.-

- **BioVacSafe**
  Biomarkers for Enhanced Vaccine Immunosafety
  € 30,785,632.-

- **COMBACTE (*)**
  Combatting Bacterial Resistance in Europe
  € 250,476,868.-
  - **COMBACTE-CARE**
    Combatting Bacterial Resistance in Europe - Carbapenem Resistance
    € 85,519,801.-
  - **COMBACTE-MAGNET**
    Combatting bacterial resistance in Europe - molecules against Gram negative infections
    € 168,799,580.-

- **DRIVE-AB (*)**
  Driving re-investment in R&D and responsible antibiotic use
  € 10,834,464.-
Some IMI ongoing projects in Infectious Diseases…

- **ENABLE (*)**
  European Gram-negative Antibacterial Engine
  € 100,885,487.-

- **iABC (*)**
  Inhaled antibiotics in bronchiectasis and cystic fibrosis
  € 50,685,130.-

- **RAPP-ID (*)**
  Development of rapid point-of-care test platforms for infectious diseases
  € 14,448,757.-

- **TRANSLOCATION (*)**
  Molecular basis of the bacterial cell wall permeability
  € 29,328,005.-

~ 750,000,000 €
out of which about half is paid by the EU taxpayer…
= 375,000,000 €

* Grouped under the ND4BD (New Drugs for Bad Bugs) cupola
What is ND4BB?

New Drugs for Bad Bugs (ND4BB)

Cross-project communication & collaboration

**TRANSLLOCATION**
Research on penetration & efflux in Gram-negatives
Data hub & learning from R&D experience

**ENABLE**
Discovery & development of new drugs combatting Gram-negative infections

**COMBACTE**
Enabling clinical collaboration & refining clinical trial design
Clinical development of compounds for Gram-positives

**COMBACTE-CARE**
Clinical development of antibacterial agents for Gram-negative, antibiotic resistant pathogens

**COMBACTE-MAGNET**
Systemic molecules against healthcare-associated infections

**iABC**
Inhaled antibacterials in bronchiectasis and cystic fibrosis

**DRIVE-AB**
Driving reinvestment in R&D & responsible use of antibiotics

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ND4BB Information Centre
All data generated is submitted and made accessible to all partners

Last accessed: 21-09-2015
What is ND4BB?

New Drugs for Bad Bugs (ND4BB)

Cross-project communication & collaboration

- **TRANS-LOCATION**
  - Research on penetration & efflux in Gram-negatives
  - Data hub & learning from R&D experience

- **ENABLE**
  - Discovery & development of new drugs combatting Gram-negative infections

- **COMBACTE**
  - Enabling clinical collaboration & refining clinical trial design
  - Clinical development of compounds for Gram-positives

- **COMBACTE-CARE**
  - Clinical development of antibacterial agents for Gram-negative, antibiotic resistant pathogens

- **COMBACTE-MAGNET**
  - Systemic molecules against healthcare-associated infections

- **iABC**
  - Inhaled antibiotics in bronchiectasis and cystic fibrosis

- **DRIVE-AB**
  - Driving reinvestment in R&D & responsible use of antibiotics

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Last accessed: 21-09-2015
An European Road Map…

Action Plan Against the rising threats from Antimicrobial Resistance: Road Map

ROAD MAP AMR (updated 17/03/2015)

Last accessed: 21-09-2015
Summary / Discussion

• Antibiotics have been a "gold treasure" for Industry for many years until the late 90's

• The decision to "go for generics" made by many countries, the restrictive policies of health authorities, the regulatory hurdles, the rapid attrition of molecules due to emergence of resistance and the short courses of antibiotics have, altogether, discouraged Big Pharma with reorientation towards more profitable businesses even in infectious diseases (think about anti-HIV and, more, recently about the novel anti-Hepatitis C drugs)

• In face of the vacuum of new commercializations, public authorities have decided (i) to ease the registration process; (ii) to give incentives to companies for discovery; (iii) invest large amounts of money into development programmes.

• This will lead us to a new paradigm that has never been observed so far in which public and private companies cooperate, but where also a large part of the expenses are paid by the tax-payers, supplying what social security does not want to pay (thus, moving from a Bismark to a Beveridge model for health support)