

The European road map against antimicrobial resistance...

(*a changing paradigm for drug discovery and development ?*)

Paul M. Tulkens*, MD, PhD



Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Health Science Sector
Université catholique de Louvain
Brussels, Belgium

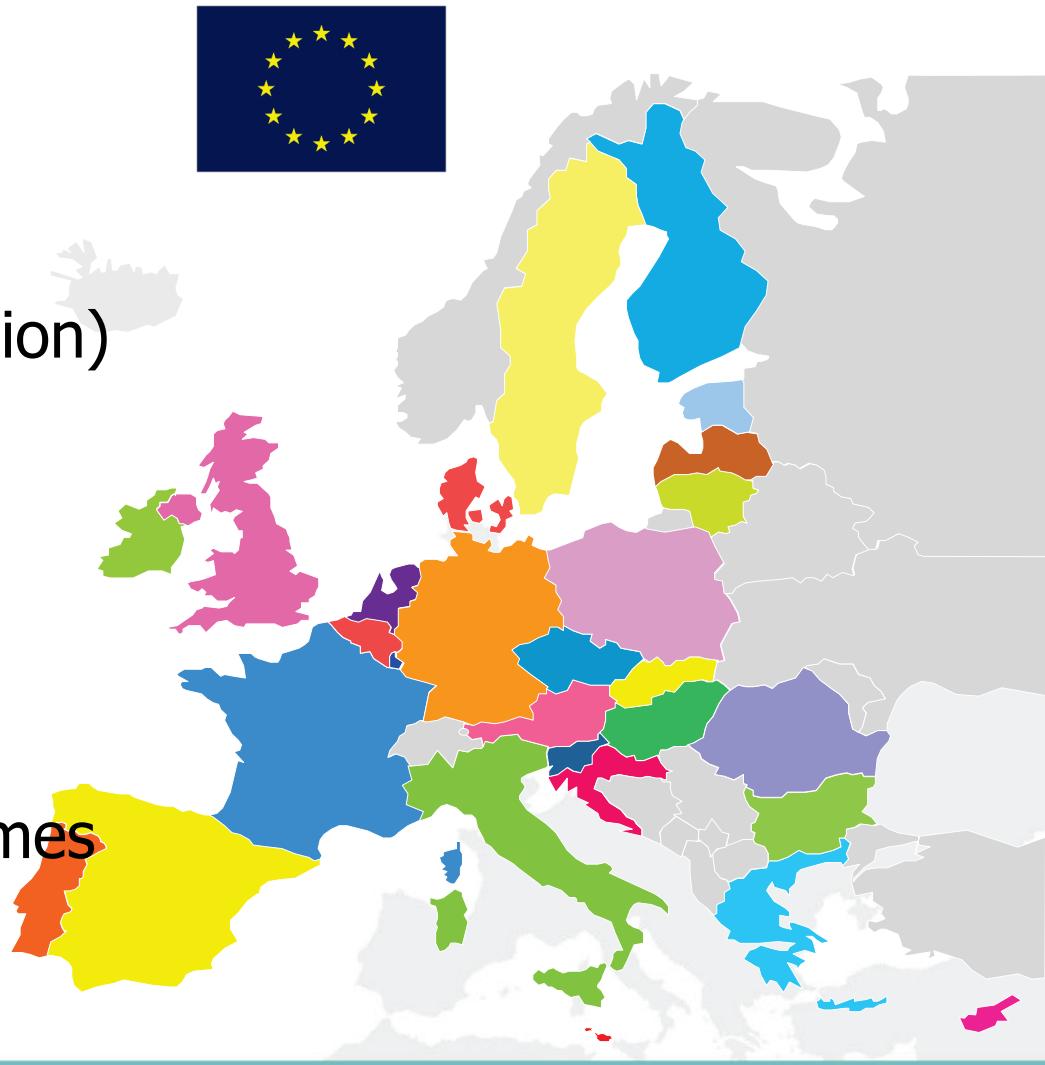


* on behalf of Otto Cars and with many slides given by Dominique Monnet



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



Council Recommendations, 2001 & 2009; Decision on serious cross-border threats to health, 2013



5.2.2002 EN Official Journal of the European Communities L 14/13

II
(Acts whose publication is not obligatory)

COUNCIL

COUNCIL RECOMMENDATION
of 15 November 2001
on the prudent use of antimicrobial agents in human medicine
(Text with EEA relevance)
(2002/77/EC)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4) thereof,

Having regard to the proposal from the Commission,

Whereas:

- (1) Antimicrobial agents are substances produced either synthetically or naturally by bacteria, fungi or plants, used to kill or inhibit the growth of micro-organisms including bacteria, viruses, fungi, and of parasites, in particular protozoa.
- (2) The use of antimicrobial agents has greatly contributed to improvements in health. Such antimicrobial agents have been introduced for decades to treat and prevent infectious diseases and infections. However, their use has been associated with the development of resistance in micro-organisms that have acquired resistance to one or more of these so-called antimicrobial resistance. Antimicrobial resistance is a threat to public health, prolonging the suffering of patients, increasing healthcare costs and has economic implications for society. The cost of combating antimicrobial resistance at the European level can be reduced by encouraging the prudent use of antimicrobial agents in human medicine and better hygiene and infection control.
- (6) To develop strategies the prevention of infections and containment of resistant pathogens, accurate surveillance systems generating valid and comparable data on incidence, prevalence and modes of spread of resistant micro-organisms, and the rational use and use of antimicrobial agents must be established through the following: That Member States must establish for an overall surveillance system to address the problem of antimicrobial resistance and is particularly important to monitor the link between the use of antimicrobial agents and the development of resistance among these pathogens.

(7) The Council of the European Union on 8 June 1999 adopted a Resolution on antibiotic resistance entitled A strategy against the microbial threat (1). The Resolution

(OJ C 195, 13.7.1999, p. 1).

3.7.2009 EN Official Journal of the European Union C 151/1

I
(Regulations, recommendations and decisions)

RECOMMENDATIONS

COUNCIL

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

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular the second subparagraph of Article 152(4) thereof;

Having regard to the proposal from the Commission;

Having regard to the opinion of the European Parliament (2),

Having regard to the opinion of the European Economic and Social Committee (3),

Having regard to the opinion of the Committee of the Regions (4),

Whereas:

- (1) Antid 152 of the Treaty provides that Community action, which shall complement national policies, shall be directed towards improving public health, preventing human illness and disease, and eliminating sources of danger to human health.
- (2) It is explained that in Member States between 8% and 12% of patients admitted to hospital suffer from adverse events while receiving healthcare (5).
- (3) The European Centre for Disease Prevention and Control (ECDC) has estimated that, on average, healthcare-associated infections occur in approximately 10% of patients in 2010, that is to say 4.1 million patients a year in the EU.

(1) Opinion of 17 April 2009 (not yet published in the Official Journal);
(2) Opinion of 25 March 2009 (not yet published in the Official Journal);
(3) Opinion of 21 April 2009 (not yet published in the Official Journal);
(4) Additional report 'Improving Patient Safety in the EU' prepared for the European Commission, published 2006 by the ECDC Co-operation.

(5) Decision No 182/2004/EC of the European Parliament and of the Council of 12 December 2004 concerning the revised framework programme of the European Community for research, technological development and demonstration activities (2005-2011) (OJ L 303, 17.10.2004, p. 1).

5.11.2013 EN Official Journal of the European Union L 293/1

I
(Legislative acts)

DECISIONS

DECISION No 1082/2013/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 22 October 2013
on serious cross-border threats to health and repealing Decision No 2119/98/EC
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 160(5) thereof;

Having regard to the proposal from the European Commission;

After examination of the draft legislative act by the national parliaments;

Having regard to the opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure (2),

Whereas:

- (1) Article 152 of the Treaty on the Functioning of the European Union (TFEU) states, inter alia, that a high level of human health protection is to be ensured in all policies of the European Union, in particular in the areas of public health, food safety and consumer protection. That Article further provides that Union action is to complement national policies, is to cover measures of general interest and is to be based on the principle of subsidiarity.
- (2) An important role in the coordination of serious crises of Union relevance has been played by an informal group of ministers of the European Union, known as the Health Council, referred to as the Health Security Committee, and established on the basis of the Presidency Conference of the European Union. The main purpose of this group is to give a formalized status to and to assign a well-defined role to specific duplicates with other Union bodies responsible for risk management.

(1) OJ C 181, 21.4.2012, p. 140.
(2) Position of the European Parliament of 1 July 2013 (not yet published in the Official Journal), and decision of the Council of 7 October 2013.

(3) OJ L 242, 3.10.2014, p. 1.

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

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, 2008, 2009 & 2012



COUNCIL OF THE EUROPEAN UNION

EN

Council Conclusions on Antimicrobial Resistance (AMR)

28th EMPLOYMENT, SOCIAL POLICY, HEALTH AND CONSUMER AFFAIRS Council meeting

Luxembourg, 10 June 2008

The Council adopted the following conclusions:

"The Council of the European Union

1. RECALLS that Article 152 of the Treaty establishing the European Community states that Community action in the field of public health is to complement national policies and be directed to ensure a high level of human health protection. This Community action shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.

2. RECALLS the Council Recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine¹.

3. NOTES that the first Report² from the Commission on the basis of Member States' reports on the implementation of the Council Recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine³ (sec(2005) 1745)

¹ doc. 14751/01
² doc. 5427/06 Report from the Commission to the Council on the basis of Member States' reports on the implementation of the Council recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine (sec(2005) 1745)

P R E S S

Rue de la Loi 175 B – 1040 BRUSSELS Tel.: +32 (0)2 281 8239 / 4318 Fax: +32 (0)2 281 8024
press.office@consilium.europa.eu <http://www.consilium.europa.eu/Newsroom>

1 EN

COUNCIL OF THE EUROPEAN UNION

EN

Council Conclusions on innovative incentives for effective antibiotics

39th EMPLOYMENT, SOCIAL POLICY, HEALTH AND CONSUMER AFFAIRS Council meeting

Brussels, 1 December 2009

The Council adopted the following conclusions:

Nota bene: In this document, the term "antibiotics" encompasses medicinal products produced either synthetically or naturally used to kill or inhibit the growth of bacteria as well as those with alternative mechanisms of action e.g. effect on bacterial virulence. In this context, alternative methods for prevention and control of infections should also be taken into account.

1. RECALLS the Community Strategy against antimicrobial resistance (COM(2001) 0333).

2. RECALLS the Council Recommendation of 13 November 2001 on the prudent use of antimicrobial agents in human medicine⁴.

3. RECALLS the Council Conclusions on antimicrobial resistance of 10 June 2008⁵.

4. RECALLS the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections⁶.

5. RECALLS the WHO report (2004) Priority Medicines for Europe and the World⁷.

¹ OJ L 34, 5.2.2002, p. 13.
² 9637/06
³ OJ C 151, 3.7.2009, p. 1.
⁴ http://webapps.who.int/bsq/2004/WHO_EDM_PAR_2004_7.pdf.

P R E S S

Rue de la Loi 175 B – 1040 BRUSSELS Tel.: +32 (0)2 281 8239 / 4318 Fax: +32 (0)2 281 8024
press.office@consilium.europa.eu <http://www.consilium.europa.eu/Newsroom>

1 EN

COUNCIL OF THE EUROPEAN UNION

EN

Council conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector – a "One Health" perspective

31st EMPLOYMENT, SOCIAL POLICY, HEALTH and CONSUMER AFFAIRS Council meeting

Luxembourg, 22 June 2012

The Council adopted the following conclusions:

"The Council of the European Union

1. RECALLS the Council conclusions of 10 June 2008 on antimicrobial resistance (AMR)¹.

2. RECALLS the Council conclusions of 23 November 2009 on innovative incentives for effective antibiotics².

3. RECALLS the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine³, including the reports of December 2005 and April 2010 from the Commission to the Council on its implementation⁴.

4. RECALLS the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections⁵.

5. ACKNOWLEDGES the Scientific Opinion of October 2009 of the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on antimicrobial resistance focused on zoonotic infections⁶.

¹ 9637/06
² OJ C 302, 12.12.2009, p. 10
³ OJ L 34, 5.2.2002, p.13
⁴ 5427/06 [COM(2005)684 final] and 8493/10 [COM(2010)141 final]
⁵ OJ C 151, 3.7.2009, p. 1.
⁶ EFSA Journal 2009, 7(11):1372,
http://ec.europa.eu/health/scientific_committees/emerging/opinions/scenahr_o_026.pdf
EMEA/CVMP/447259/2009

P R E S S

Rue de la Loi 175 B – 1040 BRUSSELS Tel.: +32 (0)2 281 8239 Fax: +32 (0)2 281 8024
press.office@consilium.europa.eu <http://www.consilium.europa.eu/Newsroom>

1 EN

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



Progress report

(26. February 2015)

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



Human + Veterinary

- 8. International cooperation
- 11. Research & Innovation
- 12. Communication, education



Progress report

(26. February 2015)

Veterinary medicine

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

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 antimicrobial resistance in human pathogens (**EARS-Net** & FWD-Net – *Salmonella spp.* & *Campylobacter spp.*)

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)

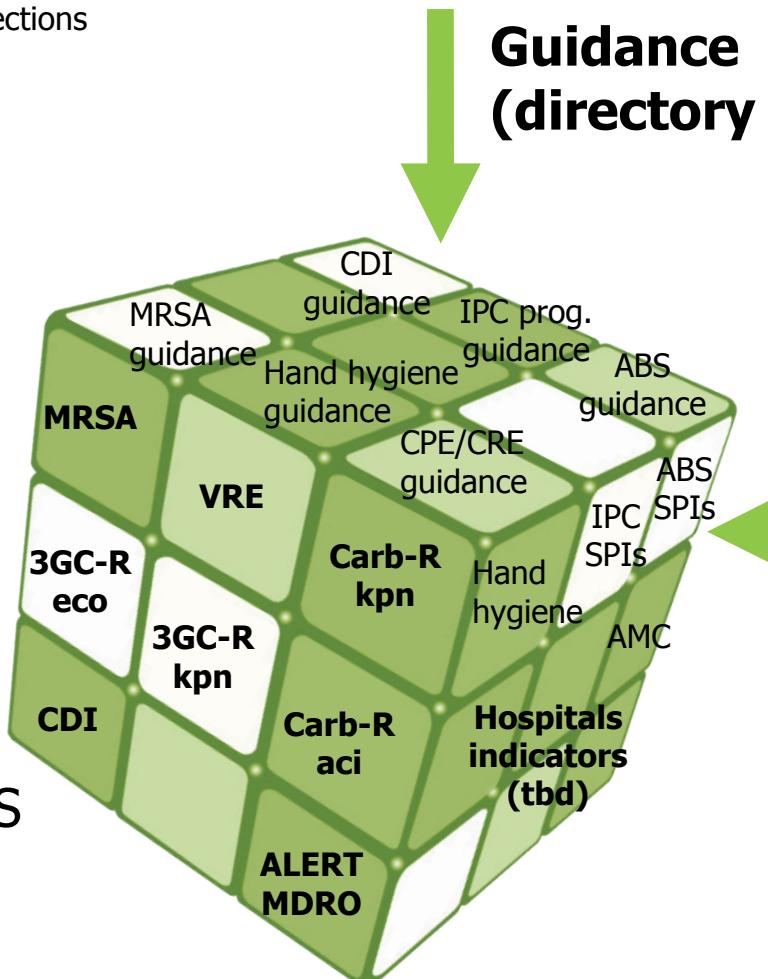
Integrated approach for surveillance, prevention and control of HAI* and AMR** in European acute care hospitals

* HAI: health care associated infections

** AMR: antimicrobial resistance

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 ?

The image shows the cover of a technical report. At the top left, there's a circular graphic featuring a white medicine bottle labeled 'Antibio' and several green and blue capsules. Below this graphic, the word 'TECHNICAL REPORT' is written in bold, capital letters. In the center, there's a logo for 'ecdc' (European Centre for Disease Prevention and Control) consisting of a globe icon and the acronym. To its right is the 'emea' logo (European Medicines Agency) with the full name 'European Medicines Agency' underneath. The main title of the report is 'The bacterial challenge: time to react'. Below the title, a subtitle reads: 'A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents'.

ECDC/EMEA Joint Working Group

- assigned on 28 February 2008.
- technical Report accepted by ECDC/EMEA on 23 July 2009
- circulated for information on 20 August 2009.
- published in September 2009

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf

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

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf

Last accessed: 9 May 2014

The reaction of the EU...



Directorate-General for
Health & Consumers

European Commission

Communication from the Commission to the European Parliament and the Council

Action plan against the rising threats from Antimicrobial Resistance

COM (2011) 748

http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

Last accessed: 21-09-2015

The reaction of the EU...



Directorate-General for
Health & Consumers

European Commission

Communication from the Commission to the European Parliament and the Council

Action plan against the rising threats from Antimicrobial Resistance

COM (2011) 748

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

....

Action n° 6:

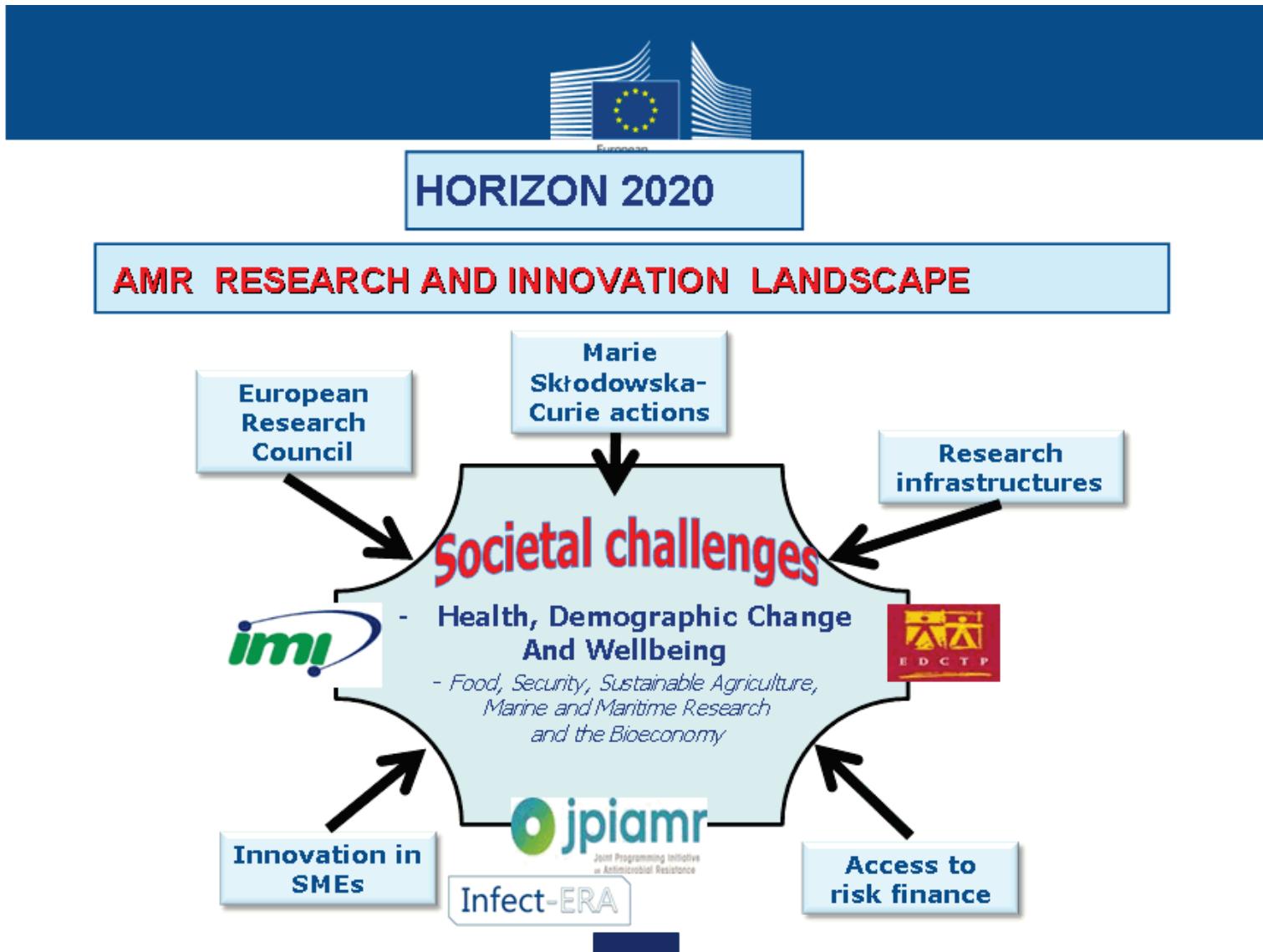
Promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antimicrobials to patients.

Action n° 7:

Promote efforts to analyse the need for new antibiotics into veterinary medicine

....

Concerted actions...



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.

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/AP 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.**

Public/Private shares in Europe



Public-private partnerships



Innovative Medicines Initiative

- ❖ 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 ...

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPia.

INTRODUCING THE NEW IMI EXECUTIVE DIRECTOR

Pierre Meulien joined IMI as **Executive Director** on 16 September and he's excited to be here!

- €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**

<http://www.imi.europa.eu/>
Last accessed: 21-09-2015

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.-

.../...

<http://www.imi.europa.eu/>
Last accessed: 21-09-2015

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						
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

ND4BB Information Centre

All data generated is submitted and made accessible to all partners

<http://www.imi.europa.eu/sites/default/files/uploads/documents/projects/ND4BBoverview.pdf>

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
 innovative medicines initiative	Drug discovery	Drug development (Gram-positives)	Drug development (Gram-negatives)	Economics & stewardship		

<http://www.imi.europa.eu/sites/default/files/uploads/documents/projects/ND4BBoverview.pdf>
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)

http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf
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)

