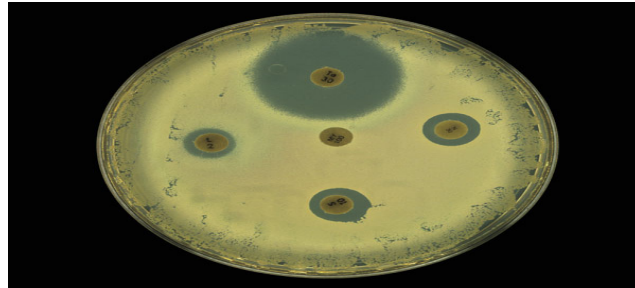


# Regulatory pathways & incentives for sustainable antibiotics- European/US Initiatives



**Broad Institute**  
**7 Cambridge Center – Auditorium**  
**Cambridge, MA**  
**7 March 2014**  
**4.00-6.00 pm**

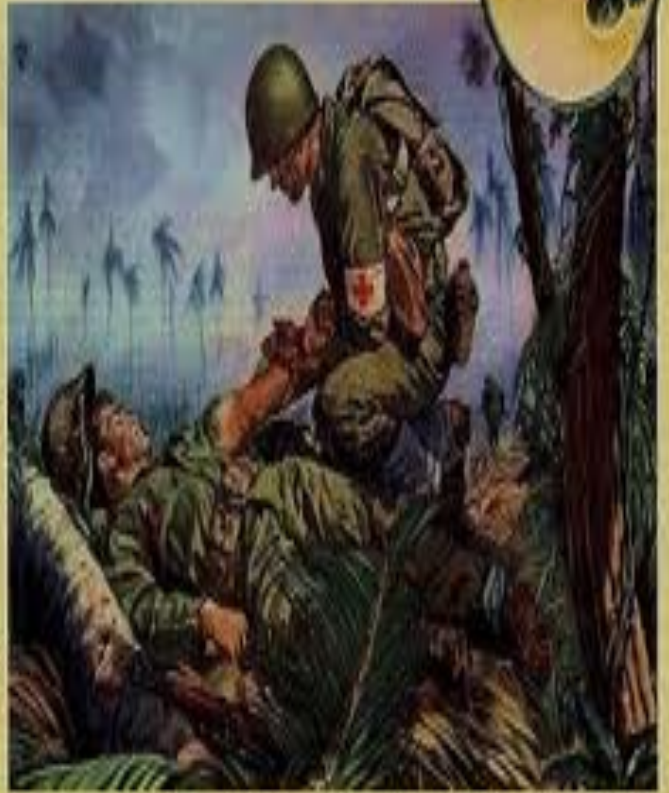
**Assoc. Prof. Dr. Timo Minssen, University of Copenhagen**  
**Guest Scholar, Harvard Law School**  
**Petrie-Flom Center**  
**for Health Law Policy, Biotechnology & Bioethics**



# AGENDA

- Problem- facts & reasons
- Potential solutions (focus here: regulatory & legal aspects)
- Recent European initiatives
- Transatlantic cooperation & US developments
- Conclusions & points for further discussion

Thanks to PENICILLIN  
...He Will Come Home!



# The problem I. (2009 EU study)

- **More infections with multidrug-resistant bacteria vs. less R&D in new Abs**
- **Resistance high among Gram-positive & -negative bacteria**
- **Up to 25% or more in several EU Member States**
- **Increasing resistance among Gram-negative bacteria (e.g. Escherichia coli)**
- **Ca. 25 000 EU patients per year die due to multidrug-resistant bacteria .**
- **Extra healthcare costs & productivity losses of at least EUR 1.5 bill. per year.**

# The problem II. (2009 EU study)

- **Only 15 AB-agents with new mechanism of action or directed against new bacteria under R&D with potential to tackle multidrug resistance.**
- **Most in early phases of R&D and primarily developed against bacteria with existing treatment options.**
- **Particular lack of new agents with new targets or mechanisms of action against multidrugresistant Gram-negative bacteria.**
- **Only 2 (!) such agents with new or possibly new targets and documented activity were identified, both in early phases of development.**
- **A European and global strategy to address this gap is urgently needed.**

# Latest data of 2013 Euro barometers on AMR

## 😊 (EU Commission Survey)

- 35% of respondents took antibiotics in the past year, a 5% decrease since the 2009 survey.
- 2% fewer people took antibiotics for the flu in 2013 compared with 2009 (18% vs. 20%).
- In 2013 more people aware that antibiotics do not kill viruses than in 2009 – 40% vs. 36%.

## ☹️ (ECDC data)

- Increasing resistance to carbapenems, a last-line class of antibiotics  
- ex: - resistant *Acinetobacter baumannii* (CRAb)
- CRAb show very large variations. Generally higher resistance percentages reported in southern Europe and lower percentages in the north of Europe.
- Infections with these multidrug-resistant bacteria are almost impossible to treat.

# US Numbers 2011-2013

- total annual cost of antibiotic resistance ca. US \$26 billion
- direct mortality from AB resistance infections : 23,000 deaths annually

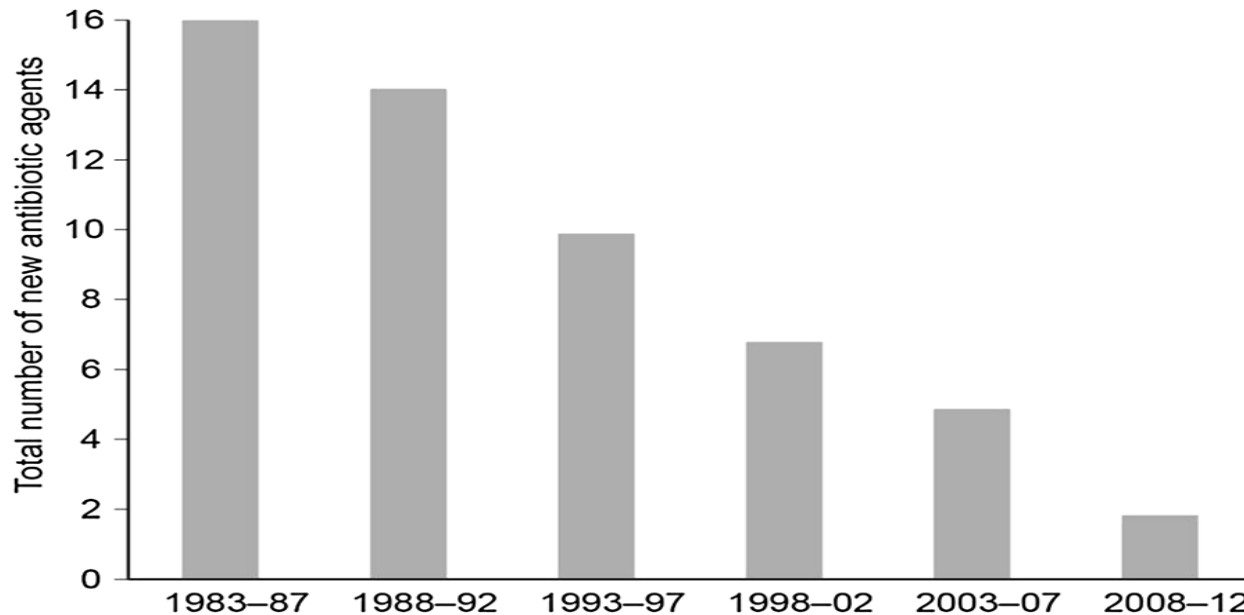


Figure 1 Number of New Molecular AB Entities Approved by the FDA per 5 year period through March 2011.  
Source: Infectious Diseases Society of America (IDSA), Spellberg B, Blaser M, et al: Combating antimicrobial resistance: policy recommendations to save lives. Clin Infect Dis 2011, 52(5):S397-428 (Oxford University Press).

# Multiple reasons for these problems I

- **Inappropriate use**
- **Insufficient precautions and lack of education**
- **Additional external factors/climate change/travel behaviour**
- **Insufficient funding of research & collaboration vs. scientific complexities**
- **Traditional pharma innovation system/incentives/business model fails**





## ***Why does the traditional pharma innovation model fail?***

**(P1) Prescription for relatively short periods**

**(P2) Most effective ABs today generic or combinations thereof**



**hard for new products to gain ground (low fruits picked)**

**(P3) Consumption intentionally kept low for fear of AMR**

**(P4) Nevertheless resistance is futile**

**(P5) High cost & efforts to find new ABs, particularly vs. Gram negative**

**(P6) Particularly complex clinical trials and unpredictable market**

# Multiple strategies to tackle the problems

- **Conservation & Prevention**
  1. Appropriate use
  2. Prevention of drug resistant infections
  3. Public awareness
- **Reactions (*Push and Pull mechanisms*)**
  1. More antibiotics R&D
  2. Legal & regulatory responses
- **Both global & local (glocal) responses necessary**



# Recent EU Initiatives



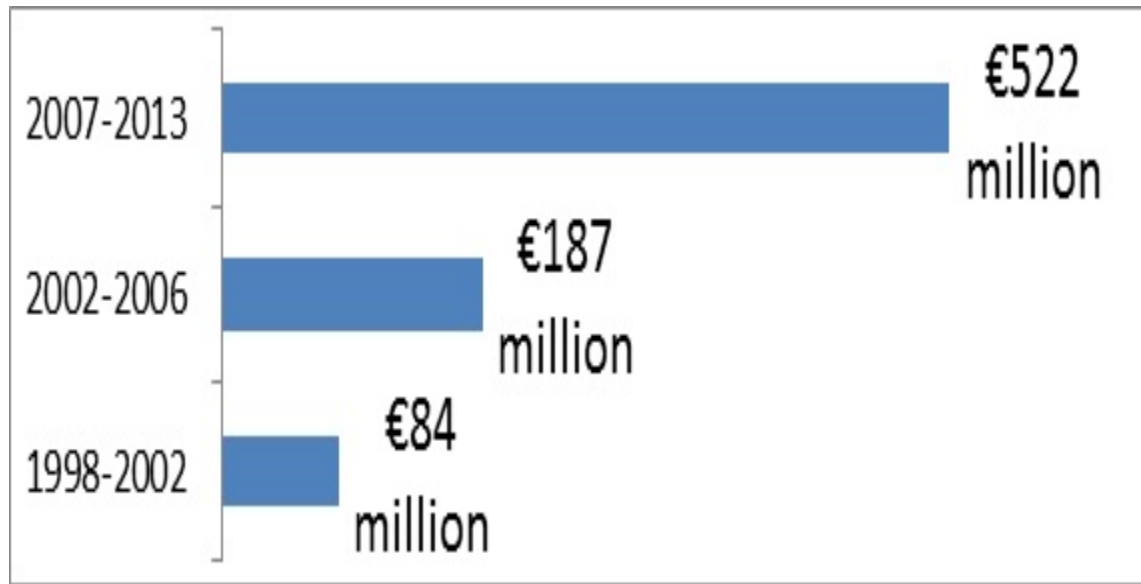
# EU Commissions Strategy AMR 2013 Roadmap

- A. Appropriate use of antimicrobials
- B. Prevent microbial infections and their spread
- C. Develop new effective antimicrobials or alternatives for treatment
- D. Global collaboration to tackle AMR spreading from trade, travel & via environment
- E. Monitoring and surveillance
- F. Additional Research and Innovation
- G. Communication, education and training

# EU Commission Memo Nov. 2013

- Six fold increase in the amount being invested, from some €84 million during the EU's 1998-2002 research programme to about €522 million for the 2007-13 period.

- 



## June 2012: EU Innovative Medicine's Initiative (IMI)

- PPP between EU & European Federation of Pharmaceutical Industries & Associations (EFPIA)
- each donate **€1 billion (\$1,23 billion)** to stimulate health innovation.
- IMI has initially dedicated **€224 million (\$275 million)** to AB initiative: NewDrugs4BadBugs.

# NewDrugs4BadBugs (ND4BB)

- total of **€600 million (\$738 million)** expected to be spent up to 2020.
- **ND4BB participants:**  
  
GlaxoSmithKline (GSK), AstraZeneca, Johnson & Johnson, Sanofi , and Basilea.
- 2 initial Subprojects:
- **COMBACTE:**
  - improving the efficiency of clinical trials on new antibiotics through better laboratory tests and better trial design.
- **TRANSLOCATION:**
  - Creation of info and data center, training & networks for researchers, facilitating and increasing the exchange of research data.

## Other important agencies on the European scene

- The European Centre for Disease Prevention and Control (ECDC).

[http://ecdc.europa.eu/en/healthtopics/antimicrobial\\_resistance/Pages/index.aspx](http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/Pages/index.aspx)

- The European Medicines Agency (EMA)

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/general/general\\_content\\_000439.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000439.jsp)

- **cf. 2013 addendum to the antibacterial guidance**

- The European Food Safety Authority (EFSA)

- National authorities



## National initiatives: Get pigs off antibiotics



28 JUNE 2012 | VOL 486 | NATURE | 465

Frank Aarestrup explains how he helped Denmark to cut the use of antibiotics in its livestock by 60%, and calls on the rest of the world to follow suit.

This website is part of the ECDC (European Centre for Disease Prevention and Control) network [See entire ECDC network](#)

FAQs Contact Sitemap Font: Accessibility View: web mobile




Home About the day Campaign materials National campaigns Contact News release


European Antibiotic Awareness Day is marked annually on 18 November.


A number of initiatives are taking place across Europe to spread the messages on the risks associated with inappropriate use of antibiotics and how to take antibiotics responsibly.

**NEWS** 2013 News release



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 Follow us on twitter!

 Tweet #EAAD

### Data and reports: Antimicrobial resistance and consumption

→ Watch EAAD video

→ Using antibiotics responsibly

→ Country activities

→ About EAAD

EXTERNAL LINKS  
→ CDC campaign "Get smart"  
→ E-Bug website  
→ Antibiotic awareness, Canada

#### ANTIBIOTIC RESISTANCE

**DATABASE**



**EARS-Net interactive database**  
Data on the occurrence and spread of antimicrobial resistance in the European countries.

**SUMMARY OF DATA**

**Summary of the latest data on antibiotic resistance in EU: 2012**  
14 May 2013  
→ Read more...

**Summary of latest data on antibiotic resistance in the European Union: 2011**  
→ Read more...

#### EARS-Net REPORT



**Antimicrobial resistance surveillance in Europe 2011**  
Scientific Publication - Nov 2012  
→ Read more...



**Antimicrobial resistance surveillance in Europe 2010. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)**  
Scientific Publication - Nov 2011  
→ Read more...



**Antimicrobial resistance surveillance in Europe 2009. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)**  
Scientific Publication - Nov 2010  
→ Read more...

#### ANTIBIOTIC CONSUMPTION

**DATABASE**



**ESAC-Net interactive database**  
European reference data on antimicrobial consumption, both in the community and the hospital sector.

**SUMMARY OF DATA**

**Summary of the latest data on antibiotic consumption in EU: 2012**  
→ Read more...

**Summary of latest data on antibiotic consumption in the European Union: 2011**  
→ Read more...

#### ESAC-Net REPORT



**Surveillance of antimicrobial consumption in Europe, 2010**  
Scientific Publication - Mar 2013  
→ Read more...

# International cooperation I.

- EU Commission, EMA, EFSA and ECDC involved in international cooperation to address AMR.
- 2009 Collaboration with US via the trans-Atlantic taskforce on AM resistance (TATFAR)-
- **Objectives : mutual activities and programmes relevant to AMR to promote information exchange, coordination and co-operation.**
- 3 key areas (2011 report)
  - 1. Monitoring and encouraging appropriate use of antibiotics in the medical and veterinary communities**
  - 2. Prevention of drug resistant infections**
  - 3. Developing strategies to enhance the antibiotic Pipeline**
- A TATFAR progress report will be published early 2014.

# International cooperation II.

- **Commission collaborates also with international organisations**
- **On-going dialogue between Commission, China & Russia.**
- **Commission also strongly supports work of WHO.**
- **WHO Expert Committee:**
- **“free market competition best mechanism to achieve affordable new products, but should be accompanied by a delinking of R&D costs and drug price”**

# Recent US Initiatives



# GAIN Act in the US (July 9<sup>th</sup> 2012)

- **Extends the exclusivity for new antibiotics**
- **Speeds development and review of new antibiotics**
- **Requires additional and/or updated clinical trial guidance**
- **Requires listing of pathogens posing threat to public health**

# Progress to date (Oct. 2013)

- **At least 16 antibiotics as qualified under GAIN**
- **Most are in early R&D stages and may not be approved.**
- **2 companies submitted market-appl. for GAIN products in late 2013.**
- **GAIN implementation is ongoing. FDA has:**
  - **Created AB Drug Development Task Force to develop guidance.**
  - **Released draft list of pathogens posing serious threats**
  - **Drafted preliminary guidance for companies developing Abs**
  - **Reviewed & updated several antibacterial drug development guidelines.**



# What's next?

- GAIN important (pull) incentive for moving antibiotics from labs to patients
- BUT: New regulatory approval pathway for limited-population AB drugs needed
- Pull incentives not always sufficient
- 3 main areas in which development incentives can be improved:
  - “Push” incentives, such as R&D tax credits
  - Reforms to streamline and make MA ptoc. more predictable
  - Reimbursement and pricing reform
- More needs to be done to incentivize antibiotic development.
- Conservation, sustainability and prevention targets?

**US ADAPT Bill. December 12th 2013 –  
(cf. EMA adaptive licensing debate & 2013 addendum to the antibacterial guidance)**

**1. New accelerated pathway:** AB drug developer may request FDA to approve drug “to treat a limited population of patients for which there is an unmet medical need.”

**2. FDA “may rely on tradition. endpoints, alt. endpoints, or combination of tradition. & altern. endpoints; datasets of limited size; pharmacologic or pathophysiologic data; data from phase 2 clinical studies; & other confirmatory evidence as [Agency] deems necessary.”**

**3. Improved monitoring & data access:** FDA required to use appropriate systems to monitor the use of antibacterial and antifungal drugs , and to monitor changes in bacterial and fungal resistance to drugs. NB: Data made public.

**4. Regular updates on break points:** FDA required to “identify upon approval and subsequently update susceptibility test interpretive criteria (“breakpoints”) for AB drugs ”, including qualified infectious disease products.”

# **(Interim) Conclusions**

- **Many EU/US initiatives starting to take effect**
- **EU Commission: much focus on push mechanism, research & awareness**
- **Pull mechanisms embedded in new EMA guidelines**
- **Gain bill (pull incentive) hudge improvement for US**
- **Important transatlantic co-operation**
- **ADAPT bill important next step**
- **Q: But which solutions are truly sustainable? Pros & Cons of different approaches?**

# How to proceed from here? Pros/Cons?

- **Antibiotic conservation: Infection control, monitoring and rational use?**
- **Supply –side incentives for new drug development?**
  - Patent term extension
  - Link to other rights
  - Orphan drug act
  - Prizes and buyout
- **Reducing drug development costs?**
- **What about an integrated approach?**
  - Value-based reimbursement
  - Conservation-based market exclusivity
  - Antibiotic delinkage?



Cf. Kesselheim & Outtersson, *Health Affairs* 29:9, 1689 (2010).

# User-generated, open activities

- BioStrike: Open Antibiotics Discovery
- See:

<http://brmlab.cz/project/biolab/biostrike>

# Further Questions

- What approach for least developed countries?
- What approach for developing countries?
- Curtailed, integrated solutions?

# Questions or Comments?

**Thank for your attention !**

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- **Training for Professionals: CPH Summer School in Pharma Law & Policy:**  
<http://copenhagensummeruniversity.ku.dk/en/courses/pharmalawpolicy>





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