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

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AGENDA

• Problem facts & reasons

• Potential solutions (focus here: regulatory & legal aspects)

• Recent European initiatives

• Transatlantic cooperation & US developments

• Conclusions & points for further discussion
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.
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) Neverthess 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

Centre for Information & Innovation Law
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).
  

- The European Medicines Agency (EMA)
  

  - cf. 2013 addendum to the antibacterial guidance

- The European Food Safety Authority (EFSA)

- National authorities
National initiatives: Get pigs off antibiotics

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.
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.

2013 News release
Data and reports: Antimicrobial resistance and consumption

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 the European Union: 2012
14 May 2013
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 the European Union: 2011

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

EARS-Net REPORT
Antimicrobial resistance surveillance in Europe 2011
Scientific Publication - Nov 2012
Read more...

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

Scientific Publication - Nov 2011
Read more...

Scientific Publication - Nov 2010
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 9th 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 sages 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 proc. 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) huge 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 a d buyout

• Reducing drug development costs?

• What about an integrated approach?
  – Value-based reimbursement
  – Conservation-based market exclusivity
  – Antibiotic delinkage?

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