

Antibiotic research and development in the age of ‘superbugs’



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- Research grants
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- Speaking fees
 - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, AstraZeneca
- Decision-making and consultation bodies
 - General Assembly (current) and steering committee (part) of the European Committee for Antibiotic Susceptibility Testing [EUCAST]
 - European Medicines Agency (external expert)
 - US National Institutes of Health (grant reviewing)
 - Belgian Antibiotic Policy Coordination Committee (BAPCOC)

Slides: <http://www.facm.ucl.ac.be> → Lectures

What shall I talk you about ?

- **What is the issue / problem we are facing?**
- **What are the implications?**
- **Why is this happening ?**
- **Is there really a drying pipeline ?**
- **What needs to be done**

Resistance: the current situation

- Bacterial resistance has now reached the point where it has become difficult to be controlled including in several European Countries
 - Witnessed by the yearly surveys from the E-CDC (EARSS network)...
 - Making the choice of antibiotics often hazardous...
 - Causing failures and/or difficult readjustments in situations where early effective therapy is essential ...

Two examples of people who should not have died...

Obituary
J.-M. Ghysen



This man discovered the mode of action of penicillin

Ann. Rev. Biochem. 1979; 48:73-101
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USE OF MODEL ENZYMES
IN THE DETERMINATION
OF THE MODE OF ACTION
OF PENICILLINS AND
 Δ^3 -CEPHALOSPORINS¹

Jean-Marie Ghysen, Jean-Marie Frère, Mélina Leyh-Bouille,
Jacques Coyette, Jean Dusart, and Martine Nguyen-Distèche

Service de Microbiologie, Faculté de Médecine, Institut de Botanique,
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In Memoriam: William A. Craig

Ursula Theuretzbacher,^a Paul G. Ambrose,^b Alasdair P. MacGowan,^c David R. Andes,^d Fritz Sörgel,^e Hartmut Derendorf,^f Johan W. Mouton,^g George L. Drusano,^h Paul M. Tulkens,ⁱ Michael N. Dudley,^j Otto Cars,^k Roger L. Nation^l

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EDITORIAL

Dr. Craig was renowned as a clinician-scholar in the fields of antimicrobial therapy and infectious disease. **His early work on quantifying the relationship between antimicrobial dosing and treatment effect led to the development of the field of antimicrobial pharmacodynamics.**

and died from invasive pneumococcal infection ... caused by a resistant bacteria

He died from infectious complications of anticancer therapy

Resistance: the problems we are facing

- Difficulties for the clinician to adjust his/her therapy
 - “Forced use” of **combination of antibiotics** (increase of the costs and the risk of toxicities)
 - Moving to older, more toxic antibiotics in order to cope with the levels of resistance to current antibiotics (creating new risks)

In some areas, including in Europe, “**last resource**” antibiotics that would never be registered for large hospital use using the so far “classical” regulatory approval system are now used on a wide scale (e.g., colistin)

Resistance: what are the implications

- increased morbidities (longer treatments...)
- Increased mortalities (failures...)
- Increased costs (more hospitalizations, multiples antibiotics, ...)
- Difficulties or even impossibility to use therapies that cause a weakening of the host defenses or to undertake many chirurgical acts...

The clinicians may largely return to **pre-antibiotic era** and/or will need to resort to other less established therapies (phage, immunotherapies, ...)

Resistance: Why is this happening ?

Antibiotic therapy will always create resistance ...
... but this is accelerated by an inappropriate use

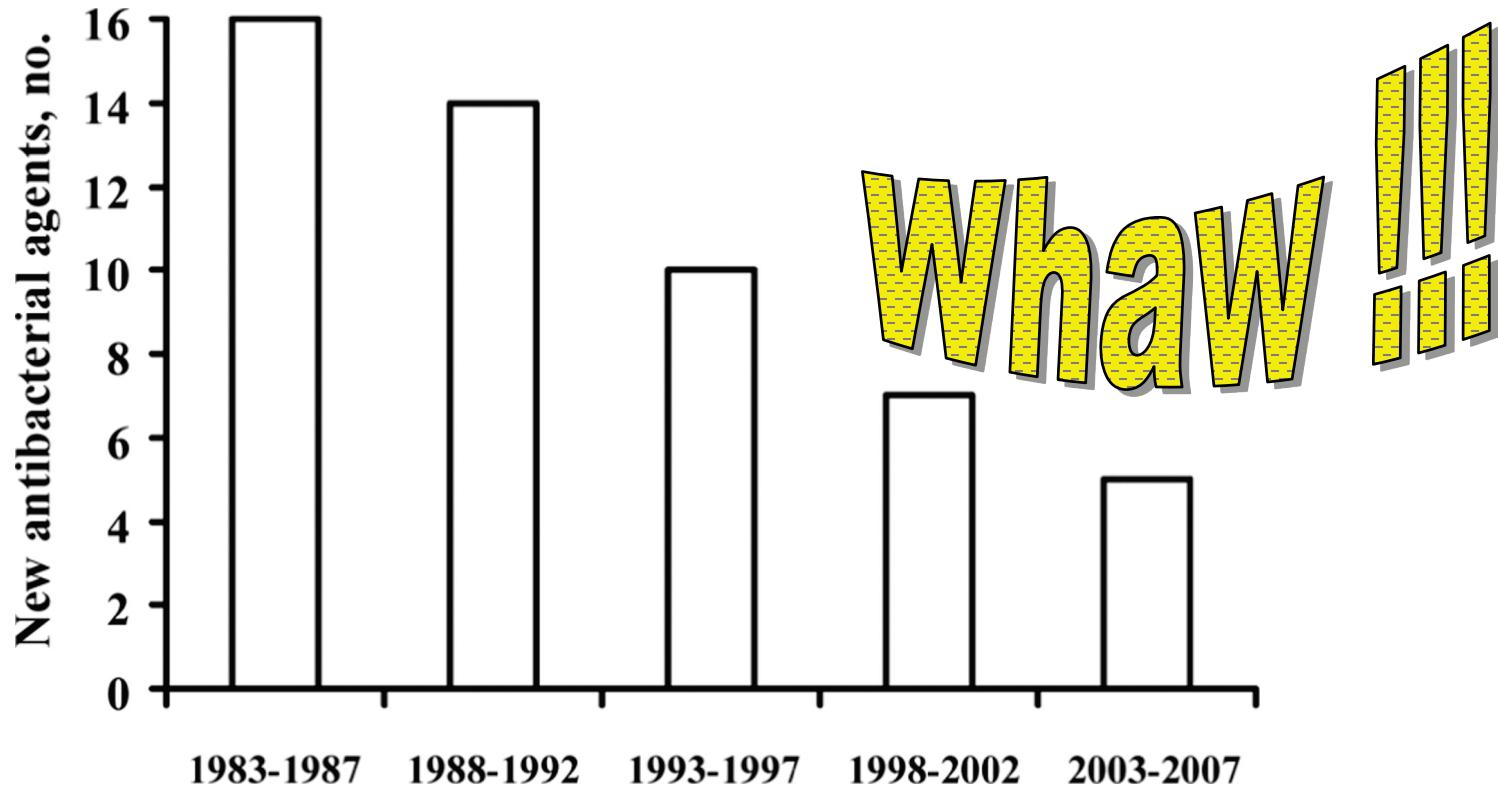
A correct use of antibiotic is essential !

But at the same time, we need to vary the environment to which bacteria are exposed...

- Reviving old but good antibiotics
- Designing new ones

A strong **discovery** and **reassessment** pipeline is essential !

But new antibiotics have long been few to reach registration



Boucher H W et al. Clin Infect Dis. 2009;48:1-12

No new antibiotics: is it true ?

- In 2013, an article in **Genetic Engineering & Biotechnology News** identified **66 companies involved in antibiotic research**, 86% of which are either small or medium-sized.
- A paper published in 2013 in **Journal of Antibiotics** (Tokyo)² lists **22 new antibiotics launched since 2000** and discusses the development status, mode of action, spectra of activity, historical discovery and origin of the drug pharmacophore (natural product, natural product derived, synthetic or protein/mammalian peptide) of **49 compounds** and **6 β-lactamase/β-lactam combinations** in active clinical development are discussed.

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1. Genetic Engineering and Biotechnology News 14 Aug 2013
<http://www.genengnews.com/insight-and-intelligenceand153/biopharmas-drive-antibiotic-development/77899874/>
Last accessed: 8 May 2014
 2. Butler *et al* Journal of Antibiotics (Tokyo) 2013;66:571–591

New antibiotics: up to phase I – II ...



THE PEW CHARITABLE TRUSTS

SEARCH



MENU

The Pew Charitable Trusts / Multimedia / Antibiotics Currently in Clinical Development

ALL VIDEO IMAGE GALLERY

DATA VISUALIZATION

SURVEY / QUIZ

DATA VISUALIZATION

Antibiotics Currently in Clinical Development

December 31, 2014 | Antibiotic Resistance Project

SHARE

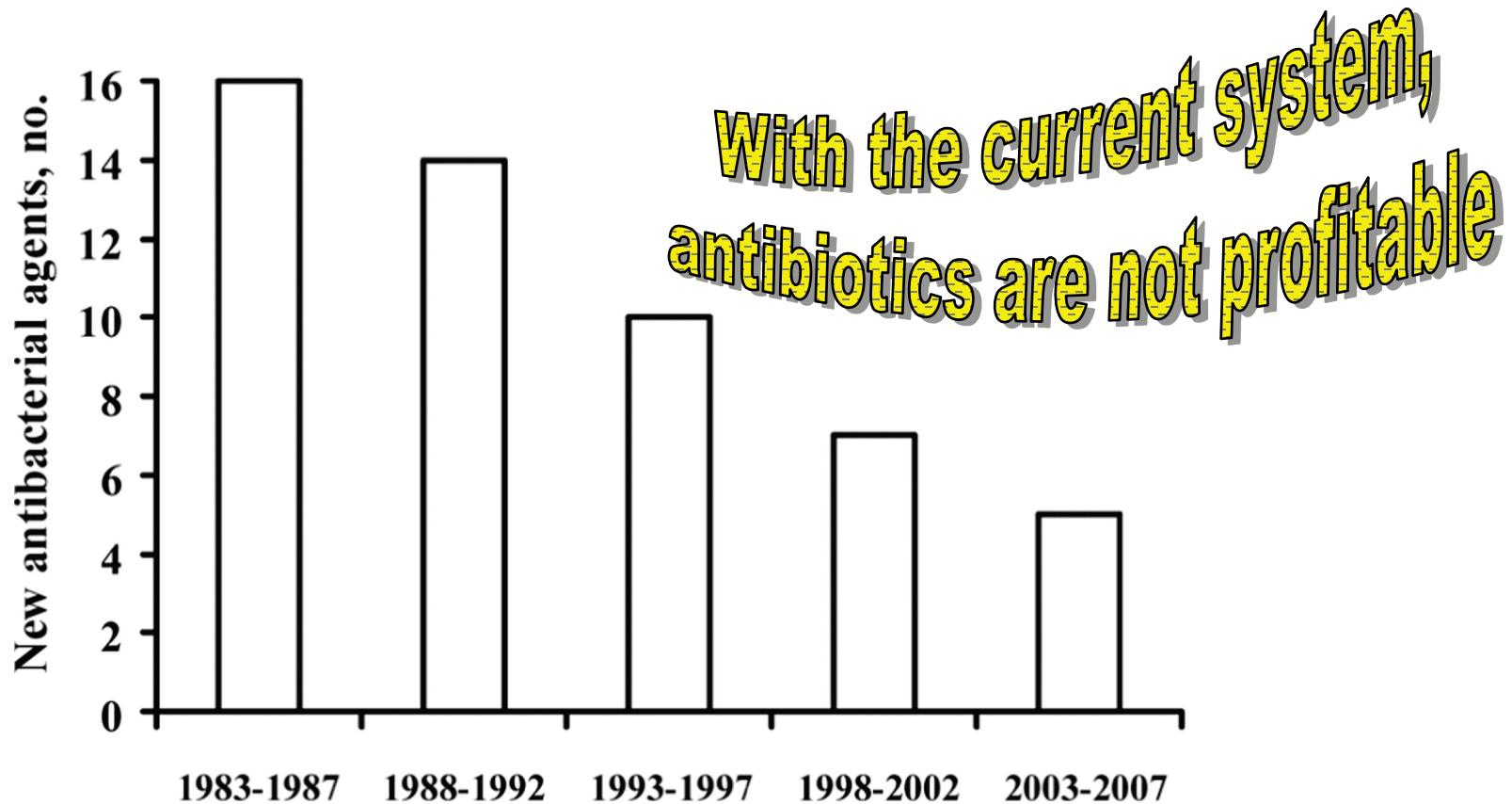
As of December 2014, an estimated 37 new antibiotics¹ that have the potential to treat serious bacterial infections are in clinical development for the U.S. market. The success rate for drug development is low; at best, only 1 in 5 candidates that enter human testing will be approved for patients.* This snapshot of the antibiotic pipeline will be updated periodically as products advance or are known to drop out of development.

The PEW Charitable Trusts (Health Initiatives)

<http://www.pewhealth.org/other-resource/antibiotics-currently-in-clinical-development-85899541594>

Last accessed: 26 May 2015

So what is the real reason ?



Boucher H W et al. Clin Infect Dis. 2009;48:1-12

The "QALY" of antibiotics ¹

- The **quality-adjusted life year (QALY)** ² is a measure of **disease burden**, including both the quality and the quantity of life lived. It is used in assessing the **value for money of a medical intervention**.
- If antibiotics **prolong your life of 2 to 10 years**, and the cost of one year of **your life is 20,000 euros**, then the value of the **"QALY" of an antibiotic treatment is 40,000 to 200,000 euros**
- But the real cost and reimbursement of an antibiotic treatment is **MUCH less**
- For comparison, the cost of an anticancer treatment for 1 year survival is.... up to 20,000 to 70,000 euros... (and the accepted "QALY" is close to that)
- Find where the problem lies...

¹ inspired by Hollis & Ahmed, Preserving Antibiotics Rationally, New Engl. J. Med. 2013; 369,26:2474-2476

² Sassi F. (2006). Calculating QALYs, comparing QALY and DALY calculations. Health Policy Plan 21(5):402-408.

(see also <http://www.eufic.org/article/en/artid/Measuring-burden-disease-concept-QALY-DALY/> - last accessed: 23 May 2015)

A too simple example from Belgium ?

- For **antibiotics** and **antifungals**, if a medical doctor or a dentist prescribes for an **acute treatment**:
 - under the name of the active compound: the rules of prescription under INN (*) are of application (delivery of the cheapest preparation available)
 - under a trade name: as from **1st Mai 2012**, the pharmacist must deliver the product available in the group of « **the cheapest drugs** ».

Official text in French available at: <http://www.inami.fgov.be/drug/fr/drugs/general-information/antibiotic/index.htm>
(last accessed: 7 November 2013)

- The drug acquisition cost for the treatment of a **community acquired pneumonia** following the **recommandations of BAPCOC (**)** (amoxicillin [3 g per day in 3 administrations for 5 to 7 days] is only **13-14 € ...** (ex-factory price: ~7 €)

Source: Belgian "Répertoire commenté des médicaments" available at http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm
(last accessed: 7 November 2013)

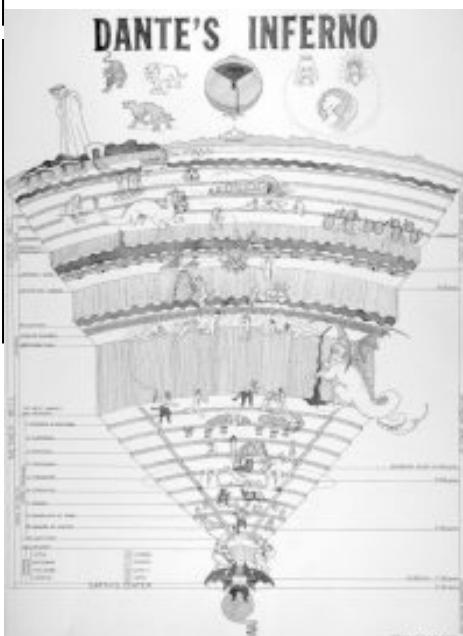
* INN: International Nonproprietary Name

** BAPCOC: Belgian Antibiotic Policy Coordination Committee

A spiral to death (in Belgium) ?

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This infernal spiral (to low prices)
make innovators to leave the field

* INN: International Nonproprietary Name

** BAPCOC: Belgian Antibiotic Policy Coordination Committee

The market is broken

- The final price of antibiotics is driven to VERY low prices, which makes new antibiotics unprofitable ... unless sold widely... **which is NOT what we would like !**
- The EU and the USA have taken useful initiatives to foster the **discovery of new antibiotics**
- But the process of **development and effective and safe availability for the public** still need to be addressed ... with **a view on low scale sales**

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

This slide 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.

EU in action ... (one example)

The screenshot shows the homepage of the Innovative Medicines Initiative (IMI) website. At the top right, there are links for Contact, Newsletter, and Links. Below the header is a banner featuring several people in professional attire, including a woman in a lab coat, smiling. A search bar is located at the bottom of the banner. To the right of the search bar are icons for download, search, YouTube, Twitter, and LinkedIn. On the left side, there is a sidebar with navigation links: Home, About IMI, Ongoing projects, Calls for proposals, News, Events & Media, and Reference documents. The main content area contains text about the IMI's mission, its support of collaborative research projects, and its joint undertaking with EFPIA. Logos for the European Union and EFPIA are present. On the right, there is a newsflash section with two entries: one for the IMI Stakeholder Forum 2015 and another for the IMI_LifeTrain case study online.

THE INNOVATIVE MEDICINES INITIATIVE

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.

IMI NEWSFLASH

26/05/2015 : Less than 3 weeks to go to the IMI Stakeholder Forum 2015
<http://t.co/oH2Ou6QtUs>
Register at <http://t.co/g6Vsujm6Iy> #IMISF2015

22/05/2015 : RT @IMI_LifeTrain: New @IMI_LifeTrain case study online: @OrionPharma's

- €2 billion 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: 26 May 2015

But additional changes have been brought in the US

- **GAIN Act** (Generating Antibiotics Incentives Now) - 2012
 - priority FDA review
 - **additional five years of market exclusivity** for breakthrough antibiotics that target serious or life-threatening pathogens
 - relaxed its criterion for non-inferiority to within 10%, making it easier to show comparability to drugs already on the market
- **BARDA:** Biomedical Advanced Research and Development Authority [within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services]
 - provides an integrated, systematic approach to the **development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools** for public health medical emergencies.

- Genetic Engineering and Biotechnology News 14 Aug 2013
<http://www.genengnews.com/insight-and-intelligenceand153/biopharmas-drive-antibiotic-development/77899874/>
Last accessed: 8 May 2014
- Biomedical Advanced Research and Development Authority
<http://www.phe.gov/about/barда/Pages/default.aspx>
Last accessed: 26 May 2015

We have to reinvent the market in Europe

The European Parliament Resolution of May 19, 2015, on Safer Healthcare in Europe (Improving Patient Safety and Fighting Antimicrobial Resistance)¹ provides some hints:

“62. Calls on the Member States and the Commission to start a reflection process to develop a new economic model, that de-links the volume of sales from the reward paid for a new antibiotic, which would reflect the societal value of a new antibiotic and allow for sufficient return on investment for the company, while the purchaser would gain the right to use the product and have full control over volumes;”

“63e: encourage the development of new revenue models whereby **economic returns for companies are de-linked from prescribed volumes of antibiotics**, while encouraging pharmaceutical innovation and balancing it with the sustainability of health systems;

¹ <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P8-TA-2015-0197+0+DOC+XML+V0//EN&language=EN>
(last accessed: 26-05-2015)

The real question is to know who will pay for the de-linking

- The **Public Authorities** (by purchasing the compounds)
- The **Industry** by obtaining a reasonable price for the efforts made and the low-scale sales