Antibiotic (accelerated) discovery and (more) rational use: a change in (accepted) paradigms based on economics ?

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DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

DRIVE-AB 2015 General Assembly Meeting, October 15-16, 2015

Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
- 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)
- Past competing interest
  - applicant to IMI call for “ND4BB TOPIC 4: DRIVING RE-INVESTMENT IN R&D AND RESPONSIBLE USE OF ANTIBIOTICS” (application: NEM4AB (New Economic Model for AntiBiotics)).

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

What shall I talk you about ? (*)

- Do we all know about the issues ?
- What is true and not true in antibiotic crisis ?
- Money available for discovery ?
- Where is the real problem for developed countries ?
- The situation in developing countries …
- A bunch of proposals

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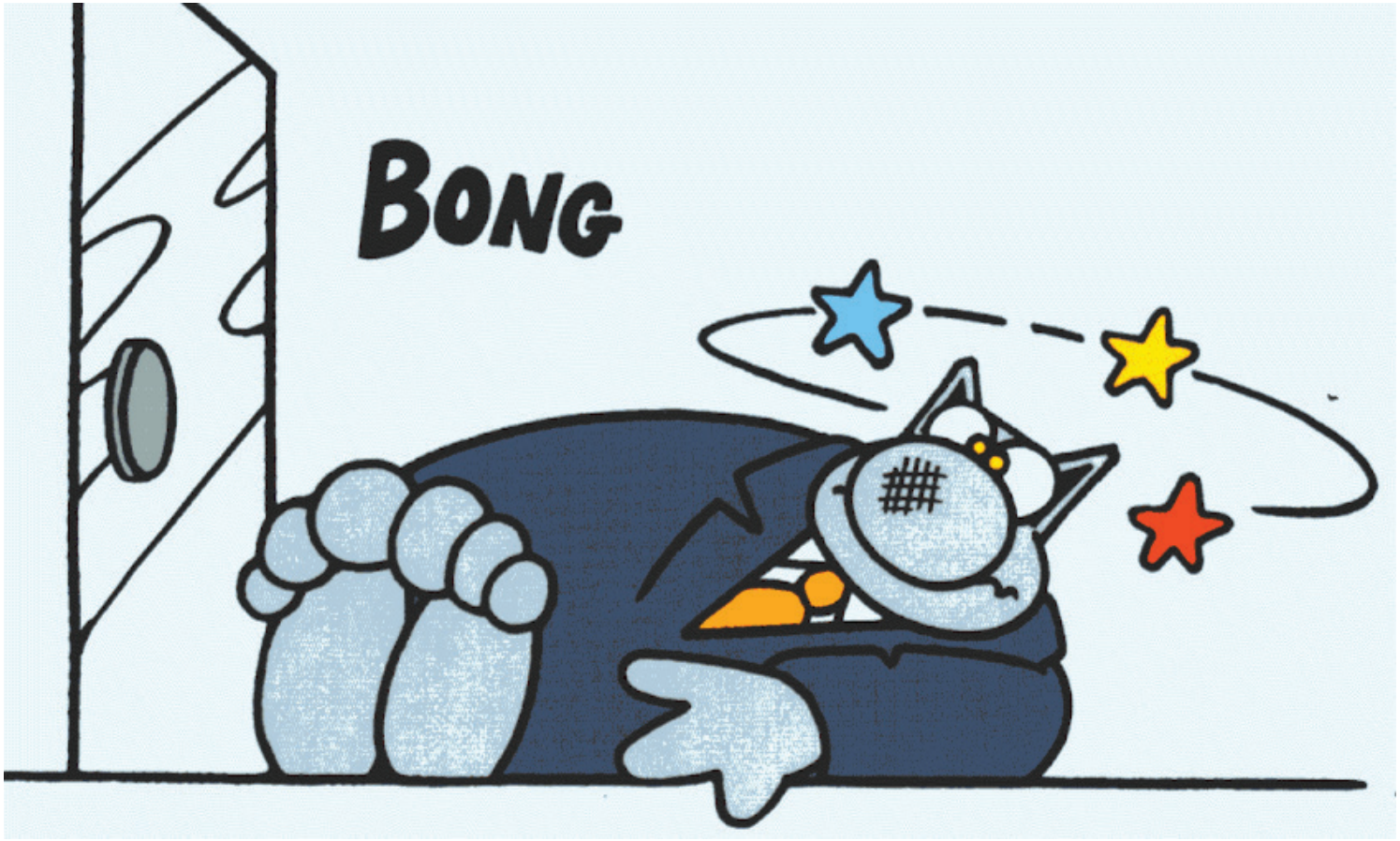
* not necessarily in that order…

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 …

Are we going to hit the wall ? (*)



Ph. Geluck, with permission

* taken from a slide presented at ECCMID in 2002

Two examples of people who should not have died…

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillin

Ann. Rev. Biochem. 1979. 48:73-101

USE OF MODEL ENZYMES IN THE DETERMINATION OF THE MODE OF ACTION OF PENICILLINS AND Δ^3-CEPHALOSPORINS[1]

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

Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

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

AAC Journals.ASM.org

EDITORIAL

In Memoriam: William A. Craig

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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.**

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 of the risk of toxicities)
  - need to develop sophisticated PK-PD-based therapeutic monitoring methods to make sure that we do not undertreat patients
  - Moving to older, more toxic antibiotics in order to cope with the levels of resistance to current antibiotics
    (creating new risks)

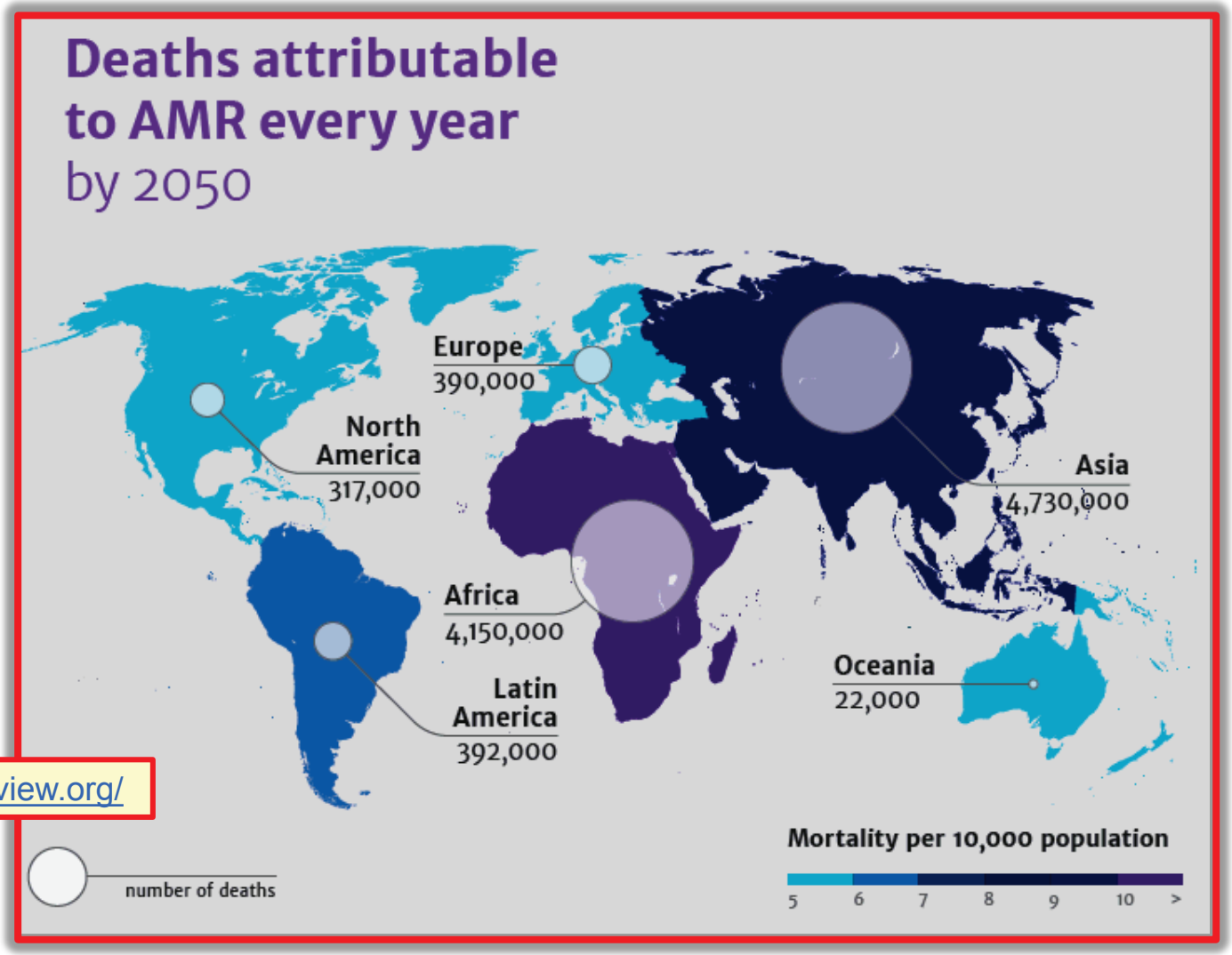
In some areas, including in Europe, **"last resource" antibiotics** that would never be registered for large hospital use using the so far "classical" regulatory approval system are **now used on a wide scale** (e.g., colistin)

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, …)

For developing countries, the situation may become dramatic



http://amr-review.org/

Resistance in Vietnam: Hospital

Pediatrics International (2008) **50**, 514–518 doi: 10.1111/j.1442-200X.2008.02616.x

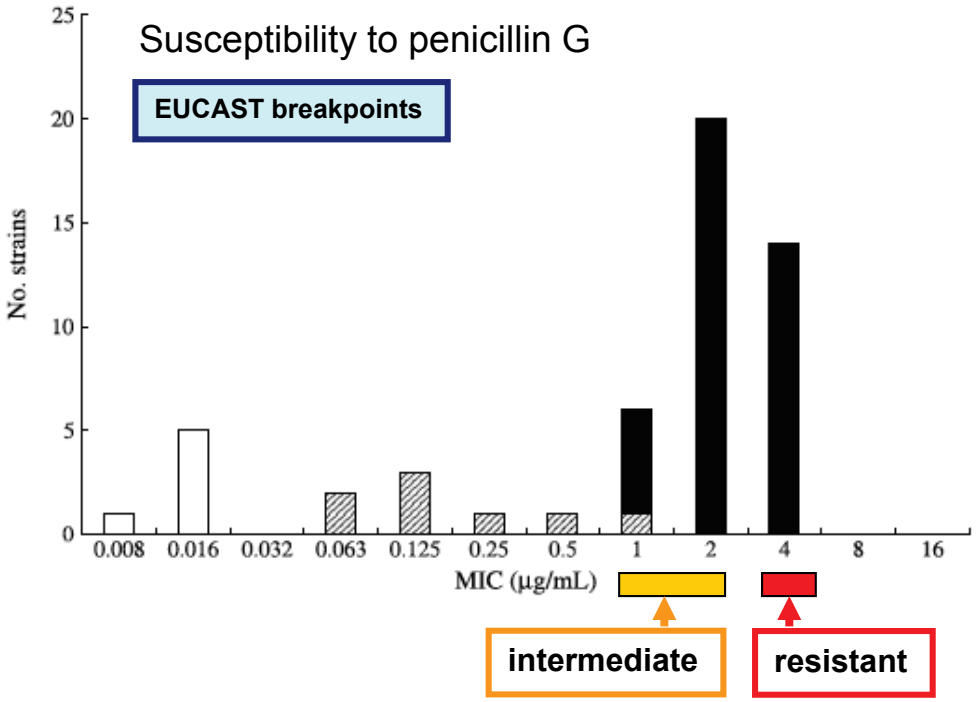
Original Article

Drug-resistant pneumococci in children with acute lower respiratory infections in Vietnam

Kiwao Watanabe,[1] Dang Duc Anh,[2] Phan Le Thanh Huong,[2] Nguyen Thu Nguyet,[3] Nguyen Thu Hien Anh,[2] Ngo Thi Thi,[3] Nguyen Tien Dung,[4] Doan Mai Phuong,[4] Olivia S. Rusizoka,[1] Tsuyoshi Nagatake,[1] Hiroshi Watanabe[1,†] and Kazunori Oishi[1,5]

Departments of [1]Internal Medicine and [5]Special Pathogen, International Research Center for Infectious Diseases, Institute of Microbial Diseases, Osaka University, Japan and [2]National Institute of Hygiene and Epidemiology, [3]Department of Laboratory, National Pediatric Hospital and [4]Department of Laboratory, Bach Mai Hospital, Hanoi, Vietnam

Resistance for *S. pneumoniae* at Bach Mai, Hanoi, Vietnam



Watanabe *et al*. Ped. Int. 2008; 50:514-518

Isolates from sputum and endotracheal fluid

unpublished data from Bach Mai hospital, 2014

TT	Vi khuẩn	n	%
1	*Acinetobacter baumannii*	333	33.1
2	*Pseudomonas aeruginosa*	240	23.8
3	*Klebsiella pneumoniae*	130	12.9
4	*Stenotrophomonas maltophilia*	62	6.2
5	*Haemophilus influenzae*	33	3.3
6	*Staphylococcus aureus*	37	3.7
7	*Escherichia coli*	29	2.9
8	*Enterobacter cloacae*	23	2.3
9	*Burkholderia cepacia*	12	1.2
10	*Streptococcus pneumoniae*	11	1.1
11	Khác	97	9.6
12	Tổng	1007	100.0

Pham Hong Nhung, MD, PhD Dept. Microbiology, Hanoi Medical University and Bach Mai hospital

Resistance to 11 antimicrobial drugs of *bla*$_{NDM-1}$–positive *Klebsiella pneumoniae* isolates from the Kim Nguu River, Hanoi, Vietnam

Antimicrobial drug	MIC, mg/L		
	EUCAST brakpoint	Site X	Site Y
Piperacillin/tazobactam	R > 16	64–>256	64–>256
Ceftazidime	R > 4	>256	>256
Ceftriaxone	R > 2	96–>256	128–>256
Meropenem	R > 8	8–>32	12–>32
Imipenem	R > 8	6–>32	>32
Fosfomycin	R >	3–8	8
Gentamicin	R > 4	>1,024	>1,024
Tobramycin	R > 4	384–>1,024	256–384
Ciprofloxacin	R > 1	0.064–1.5	0.064
Colistin	R > 2	0.19–2	0.125–0.38
Tigecycline	R > 2	1.5–3	0.5–1.5

Emerg Infect Dis. 2012 August; 18(8): 1383–1385

Resistance: Why is this happening ?

Antibiotic therapy will always create resistance …

… but this is accelerated by an inappropriate use

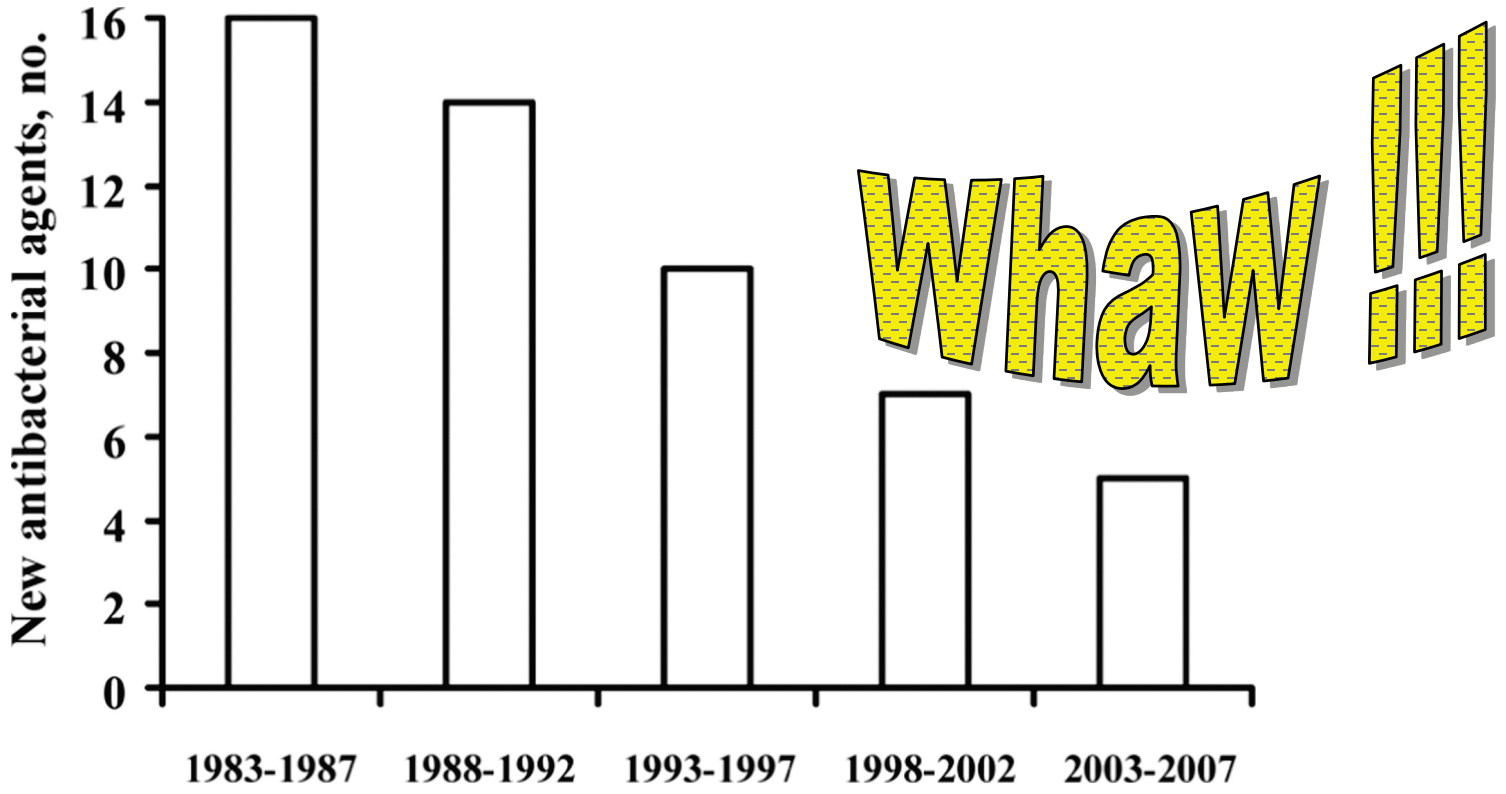
A correct use of antibiotic is essential !

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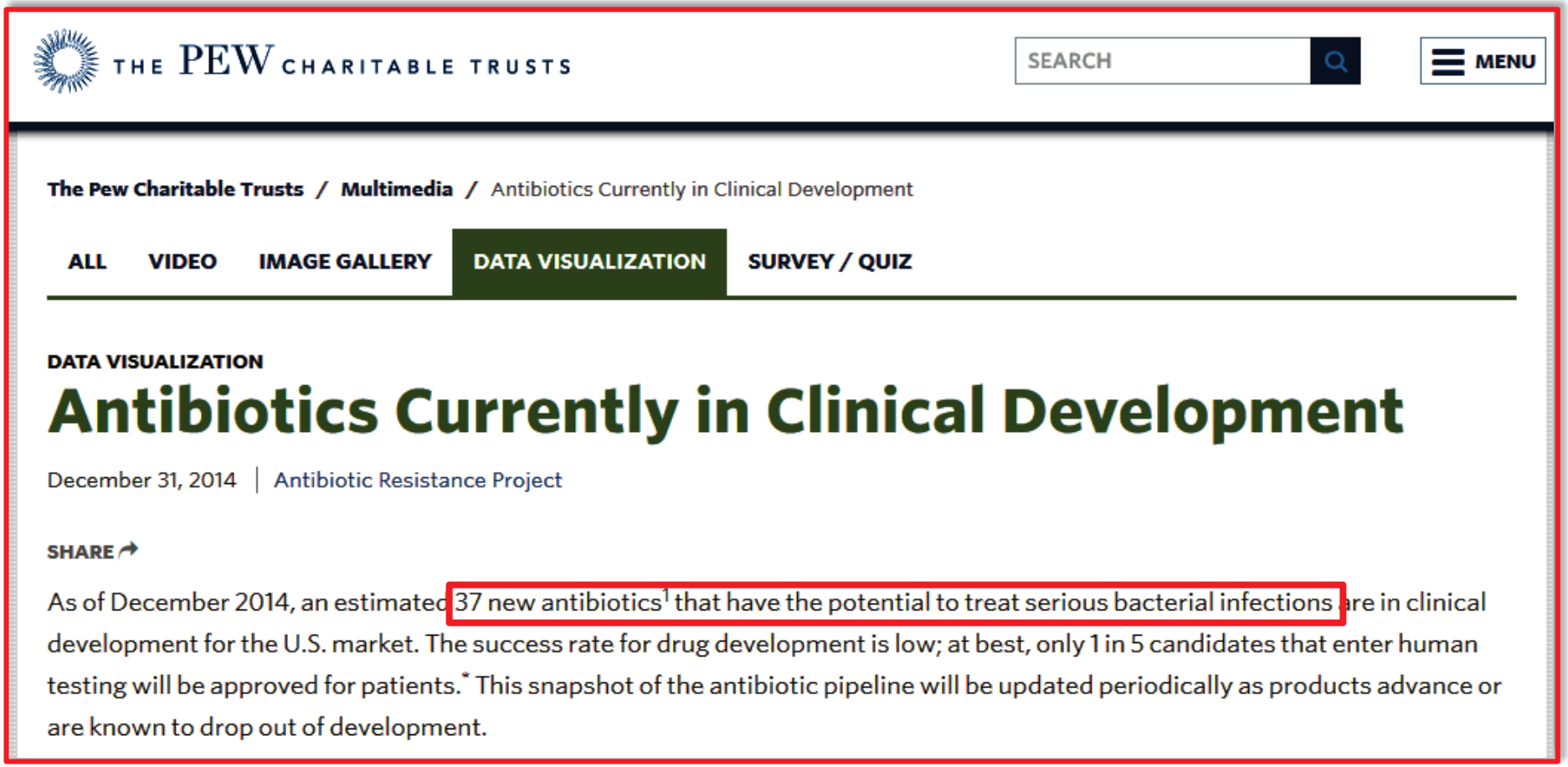
1. Genetic Engineering and Biotechnology News 14 Aug 2013
   http://www.genengnews.com/insight-and-intelligenceand153/biopharmas-drive-antibiotic-development/77899874/
   Last accessed: 8 May 2014
2. Butler *et al* Journal of Antibiotics (Tokyo) 2013;66:571–591

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 antibiotics[1] 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

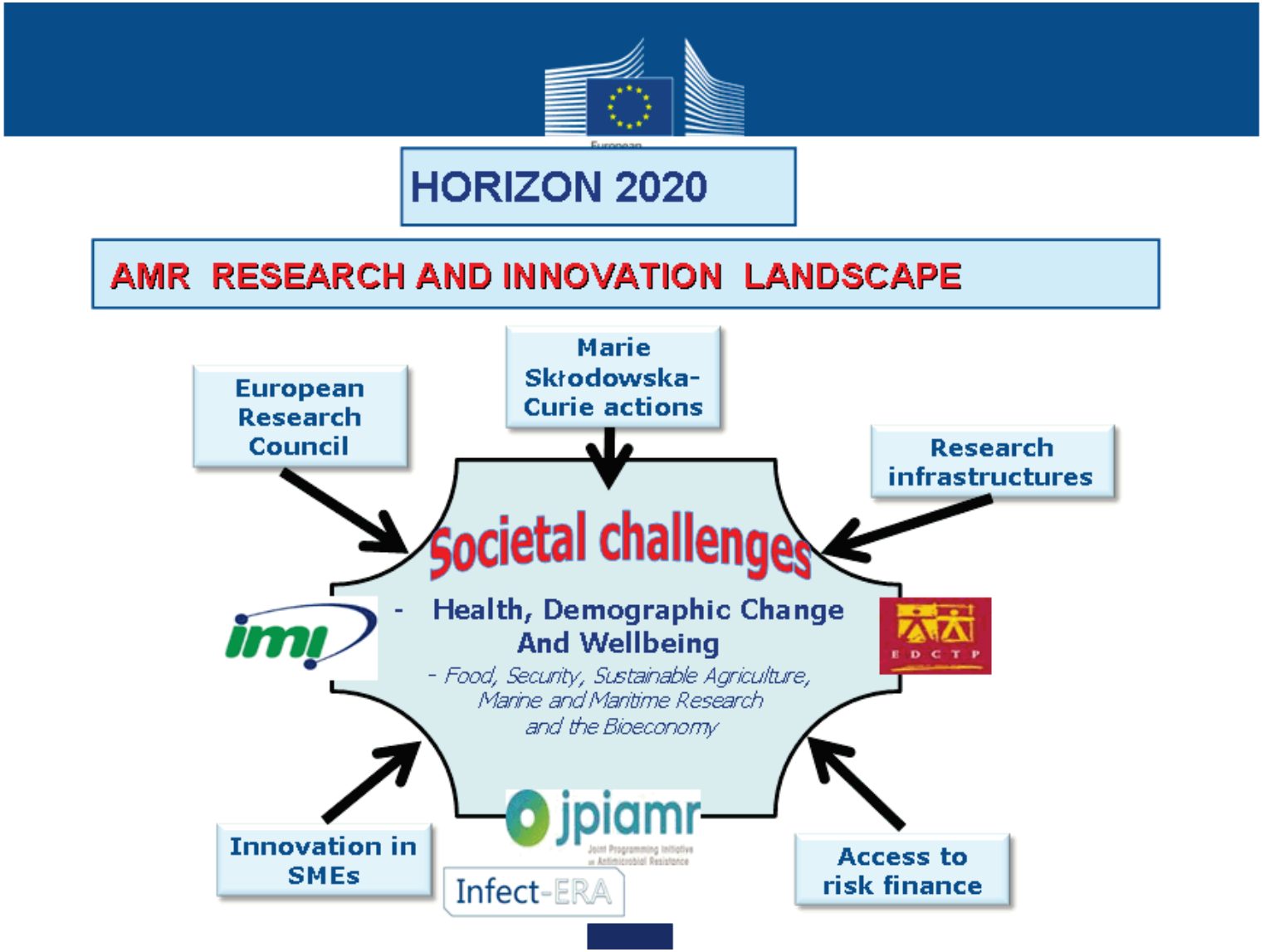
Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

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.

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.

EU in action … (one example)

- €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: 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/barda/Pages/default.aspx
  Last accessed: 26 May 2015

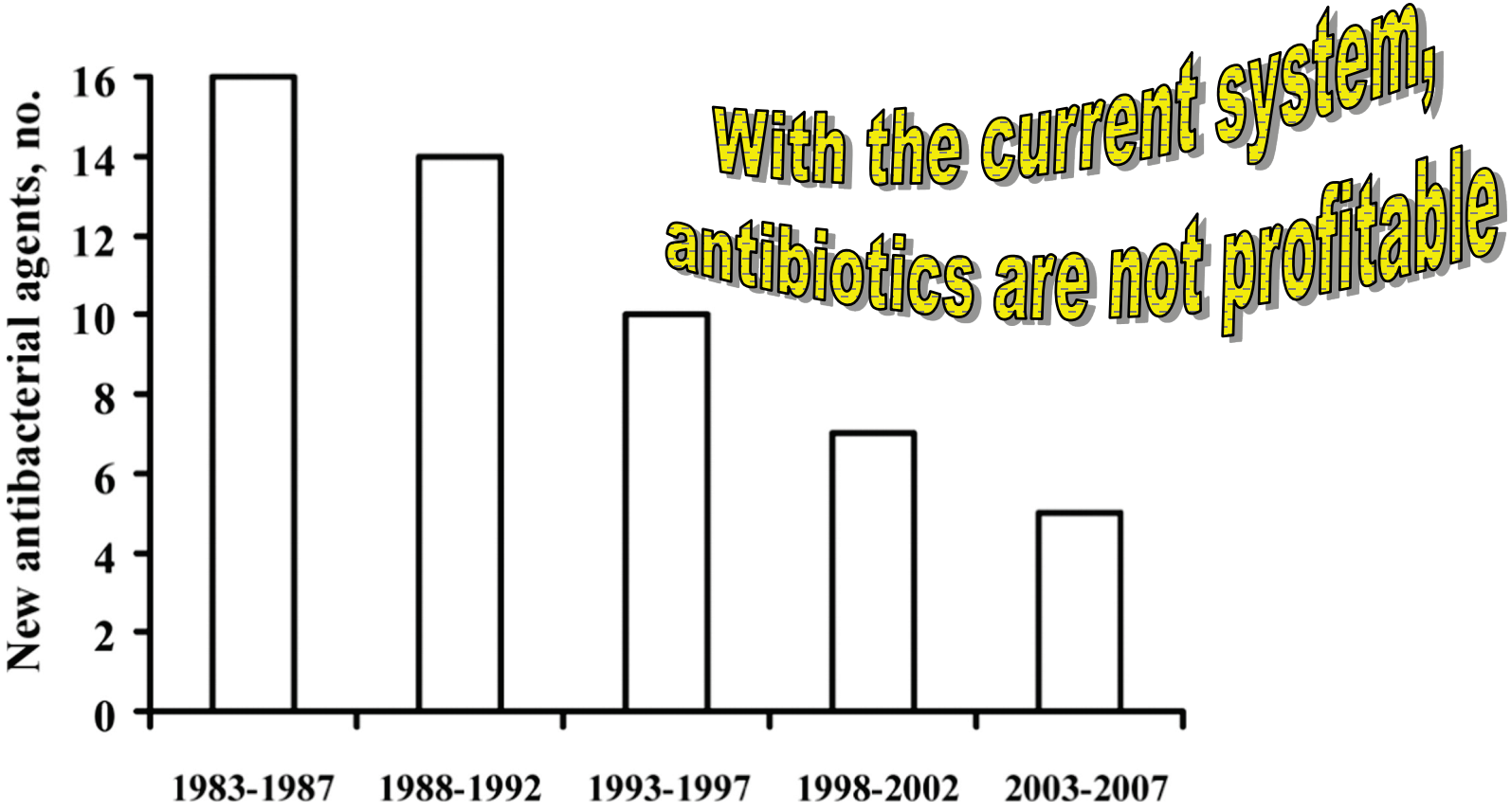
New antibiotics: newly approved (or close to) *

- anti-Gram-positive
  - lipoglycopeptides: telavancin, oritavancin, dalbavancin
  - oxazolidinones: tedizolid, …
  - anti-MRSA cephalosoprins: ceftaroline, ceftobiprole
  - kétolides: solithromycin
  - tetracyclines: omadacycline, saracycline
  - fluroquinolones: ozenoxacin, delafloxacin, …
  - …

- anti-Gram-negative
  - ceftozolane (+ tazobactam)
  - new β-lactamase inhibitors: avibactam, RPX7009, relebactam, …
  - aminoglycosides: plazomycin, …
  - …

* not an exhaustive list

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 should be 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 is …

[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 to7 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) ?

- 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)
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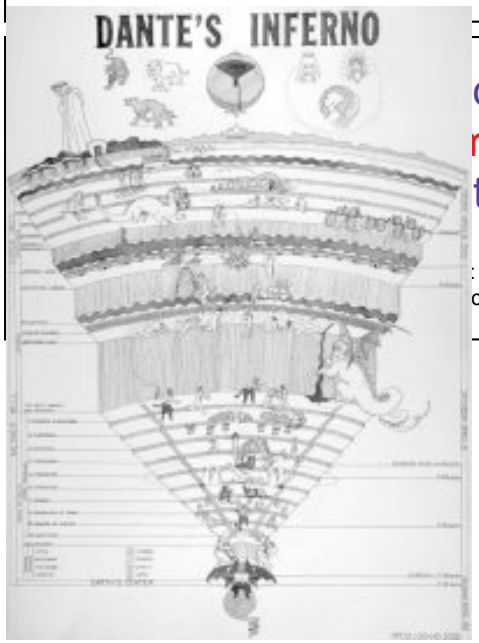

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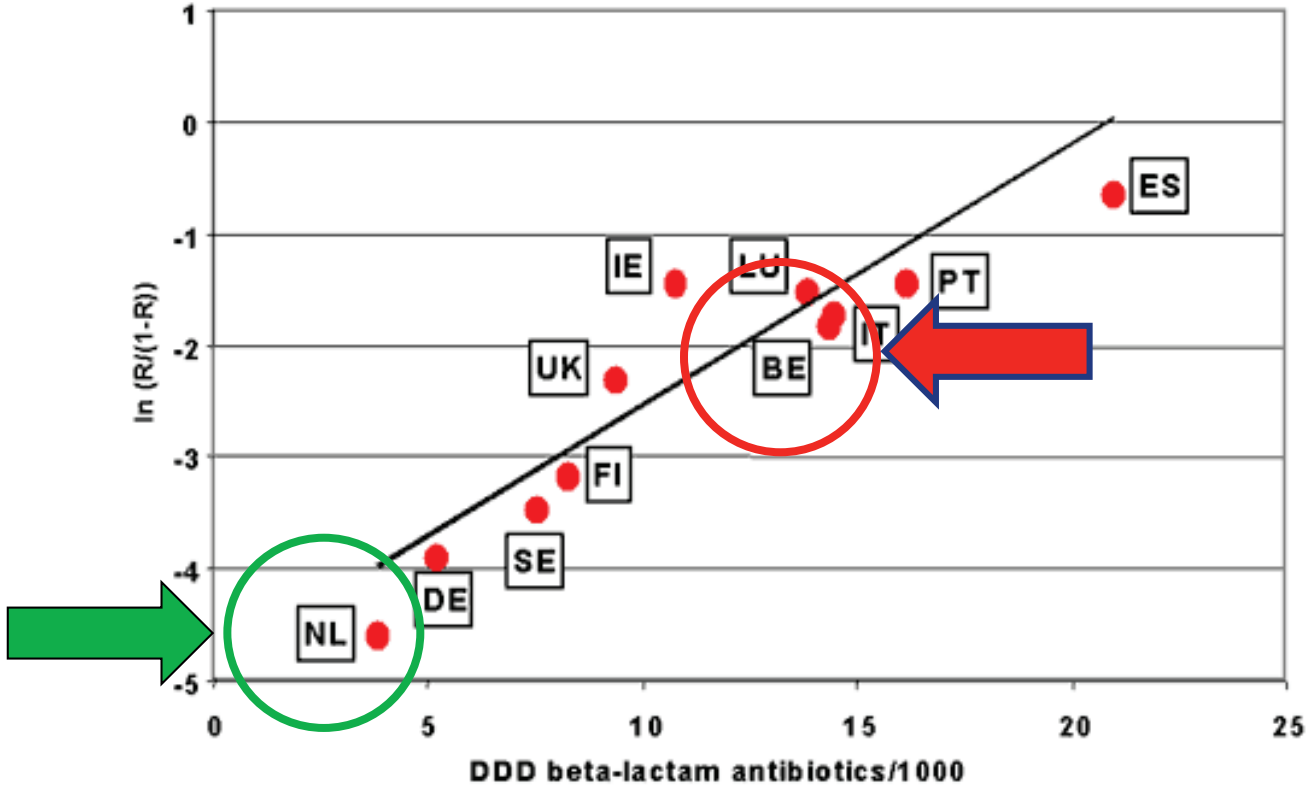
cessed: 7 November 2013)

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

* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee

But what about the consumption of antibiotics

- we all wish to reduce the overconsumption of antibiotics because we know it creates resistance…

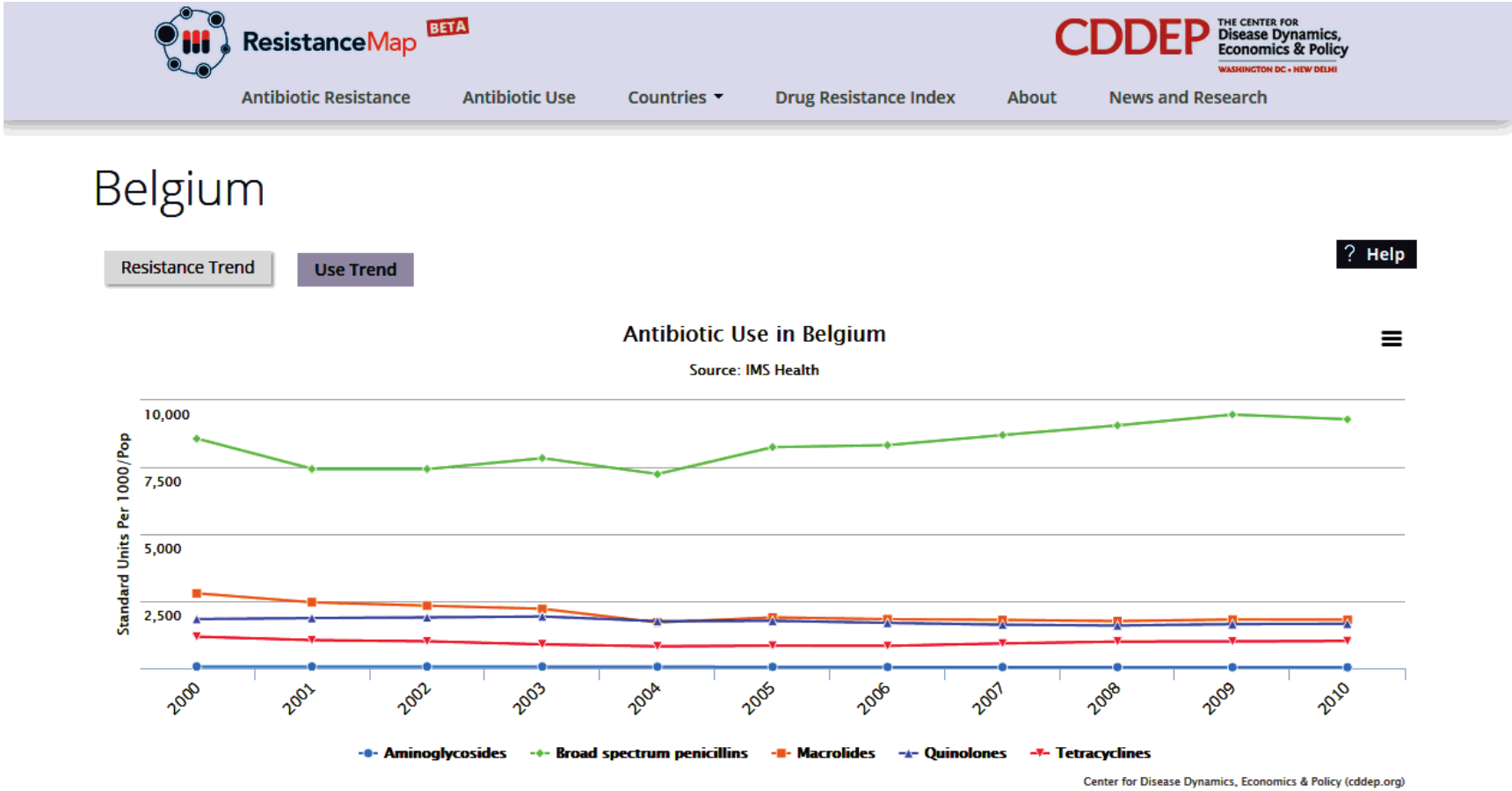


Logodds of resistance to penicillin among invasive isolates of Streptoccus pneumoniae regressed against outpatient sales of beta-lactam antibiotics in 11 European countries; (resistance data are from 1998 to 1999; antibiotic sales data 1997. DDD = defined daily dose)

Bronzwaer SL, Cars O, et al. Emerg Infect Dis 2002 Mar;8(3):278-82

But what about the consumption of antibiotics

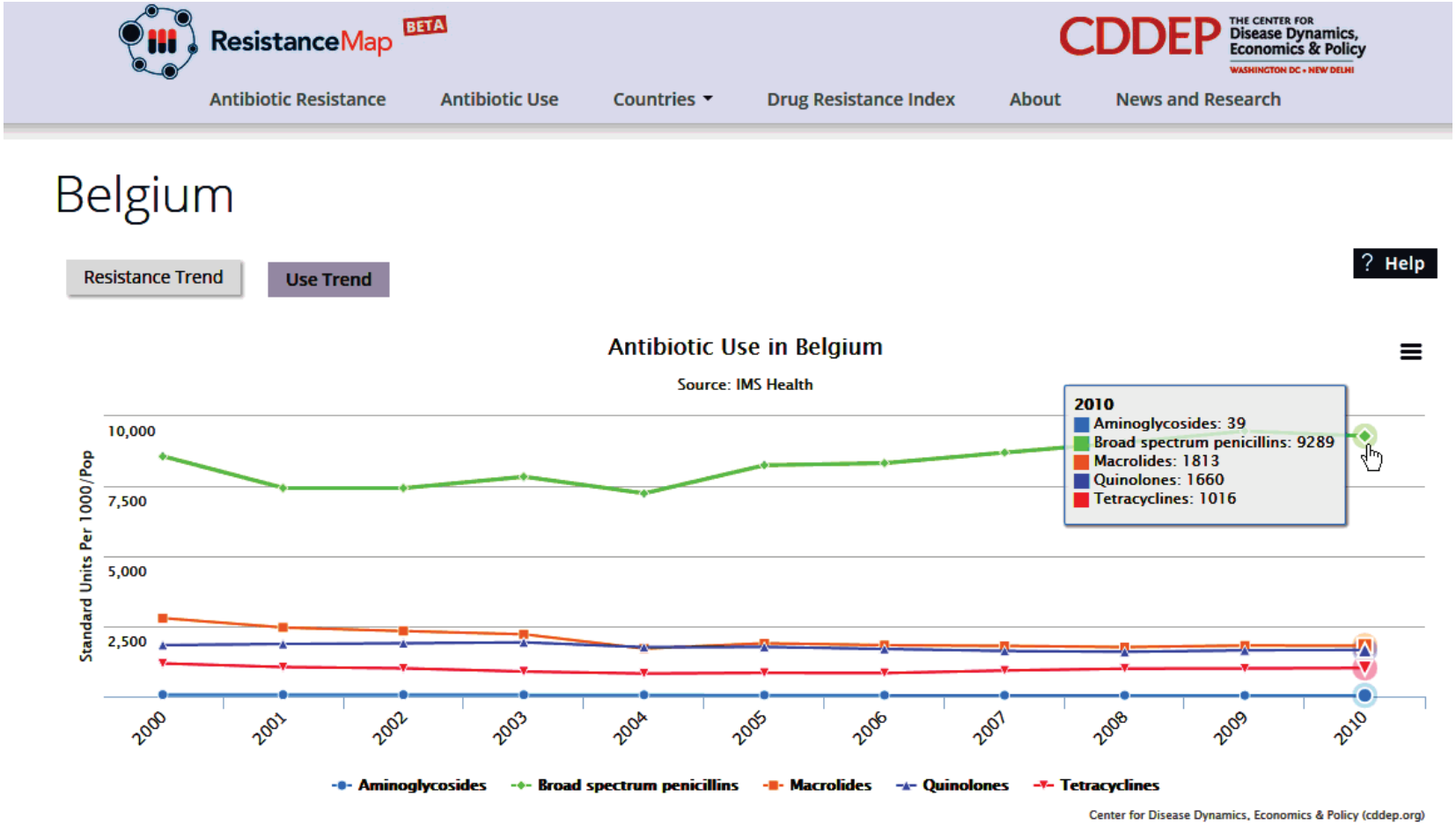
- and we launch campaigns at all levels… (*)



** yearly public campaigns were launched in Belgium since 2001 together with other activities directed to the professionals*

But what about the consumption of antibiotics

- and we launch campaigns at all levels… (*)



** quinolones were especially targeted especially for actions directed towards professionals*

Actually, low prices favor consumption

A sour Danish experience

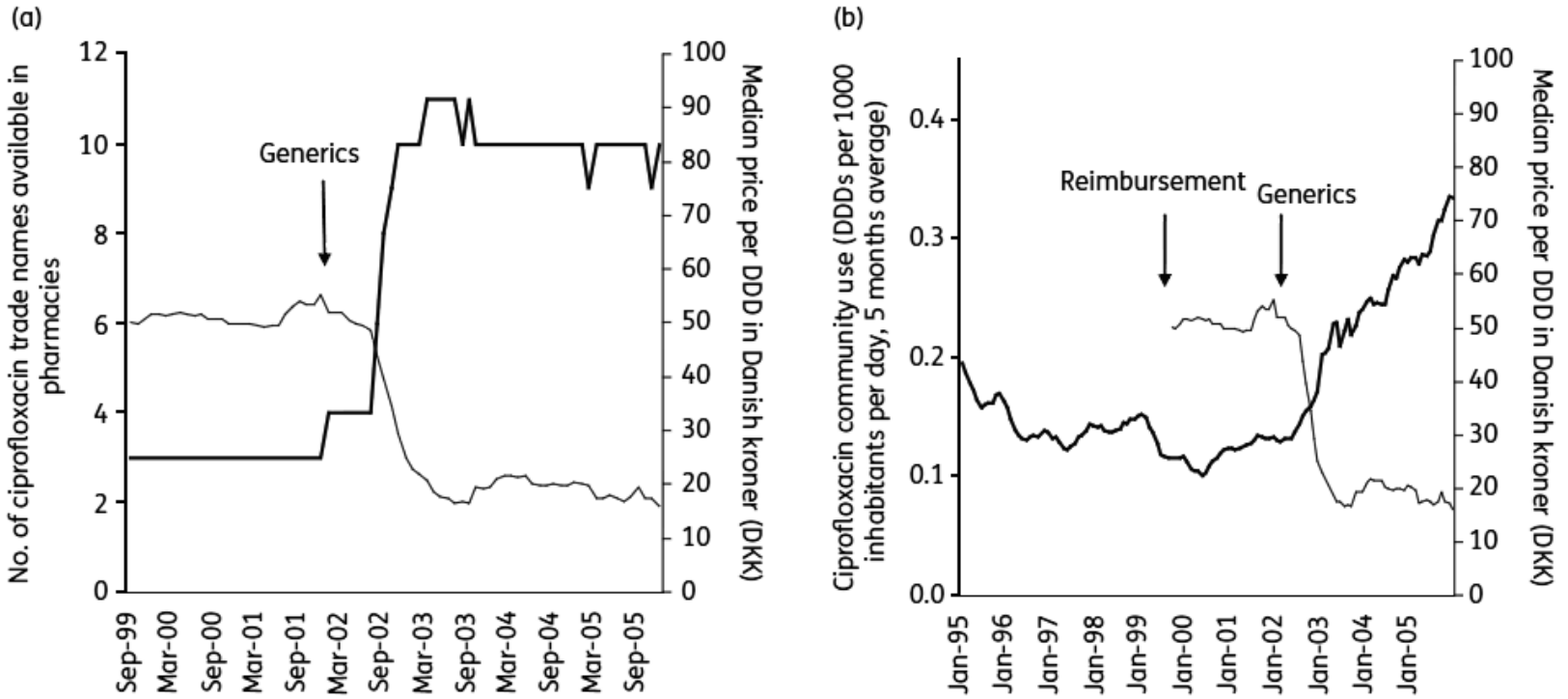


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (b) The influence of removal of 50% reimbursement and of the introduction of generics on the total use of ciprofloxacin and median price per DDD registered monthly in PHC in Denmark (thin line). Consumption (thick line) is expressed in terms of DDDs per 1000 inhabitants per day. The arrows mark the times of removal of reimbursement of ciprofloxacin and the introduction of generic versions, respectively. 100 DDK≈13 EUR.

Jensen *et al.* J Antimicrob Chemother 2010; 65:1286–1291

And generic producers only think about sales

Something you should not have seen … (*)

Find the errors …

** quinolones were especially targeted (for consumption reduction) by the authorities with "direct" actions towards professionals*

Is the market 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 to see (but what generic producers do) !**

- In parallel, the EU and the USA have taken useful initiatives to foster the **discovery of new antibiotics,** which is now **gaining momentum**

- 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**

Towards proposals ?

1. **Dissociate the discovery/development process from the commercialization**

   – Private/public partnership (PPP) on a competitive basis ("grant application" type)

   – After approval (EMA), select only the best and most needed candidates for actual commercialization

   – Keep the other ones on the shelf but rewards the discoverers/developers

PPP empowers the public authority

Towards proposals ?

2. **For new antibiotics** allowed for commercialization, define selected and limited indications and allow for **"life-saving" drugs prices** with

   – reversion of part of the profits to the discovery process, and

   – control by the Public Services in an ethical way

Towards proposals ?

3. **For "older" antibiotics**, propose a **tender to best offering** for **linked**

   – **responsible and prudent use** (accepted limits in volume and active participation to public initiatives limiting the inappropriate use)

   – **price** (but this will not be the only consideration) and respect of antibiotic "value" as a important public health commodity

Towards proposals ?

None of these proposals are for all situations !

Each of them (and others) must be tested in the appropriate environment

But others may have similar ideas…

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

Summary / Discussion / Food for thought

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

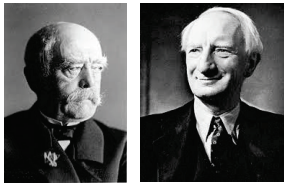
- The decision to "**go for generics**" made by many countries, the **restrictive policies** of health authorities, the **regulatory hurdles**, the **rapid attrition of molecules** due to emergence of resistance and the **short courses** of antibiotics have, altogether, **discouraged Big Pharma** with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

Summary / Discussion / Food for thought

- In face of the vacuum of renewed commercialization, 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

- But we also **DO need** to secure a **limited use of antibiotics** while **rewarding** those who find and develop them (empowering the pubic service)

- 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 covered 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)



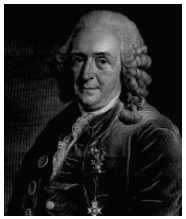
So, it a nutshell…

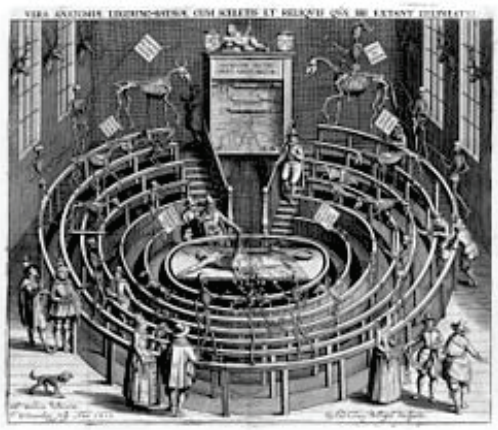
While strolling through Rotterdam
and seeing the building of a Dutch High School …

But the equilibrium may be difficult to reach, although the Dutch may have suggestions….

While continuing my stroll through Rotterdam….

To conclude…





We are here to change the world of antibiotics
by dissecting out its parts (science and economy)
to find how they can work together…

but we are in good company or can get
help in Uppsala !

Back-up

Public/Private shares in Europe

European Commission

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

efpia European Federation of Pharmaceutical Industries and Associations

TATFAR Recommendations

- **Issue:** Investigators should consider funding sources and research resources on both sides of the Atlantic to support antimicrobial research and antibacterial product development efforts
- **Recommendation 14:** Publicise funding opportunities to the EU and US research communities

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.

DMID Resources for Researchers

Resources for Researchers

Share this:

Microbiology and Infectious Diseases Resources

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV.

Funding Opportunities

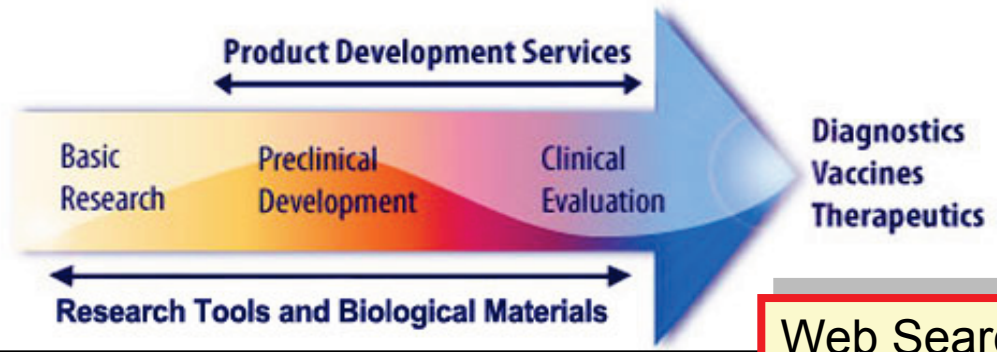
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- NIH-Wide Funding Opportunity Announcements
- NIAID Funding Opportunity Announcements and Requests for Proposals

Product Development Services and Research Tools and Biological Materials

Request development by DMID-funded contractors of critical information needed to move a product through the product development pathway. Note: Services are contingent upon availability of required preliminary data.

Click on labels below to view information on services.



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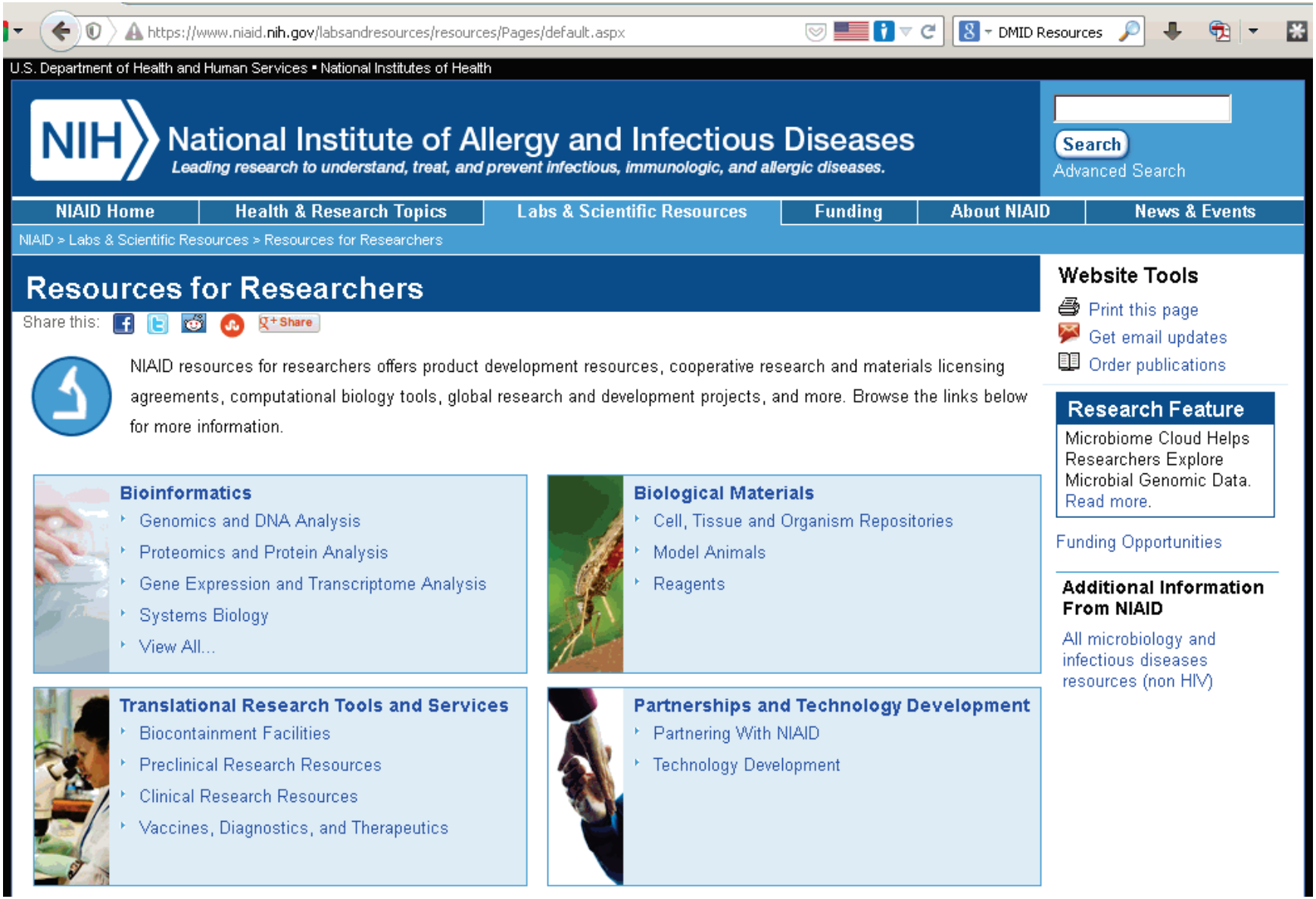
This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

DMID Resources for Researchers



Monnies from "Big Bother"

U.S. Department of Health & Human Services

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Public Health Emergency

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PHE Home > PHE Newsroom > MCM Procurements and Grants

MCM Procurements and Grants

Medical Countermeasures Advanced Research, Development and Acquisition Contract and Grant Awards

October 21, 2013: New blood test would provide fast results for medical care after anthrax attack

September 26, 2013: BARDA boosts global ability to respond to pandemics

September 20, 2013: HHS funds development of freeze-dried platelets for disaster response

September 19, 2013: BARDA funds development of device to aid burn patients in disasters

September 19, 2013: HHS replenishes nation's supply of anthrax antitoxin

September 18, 2013: HHS explores new emergency response use for approved steroid

September 17, 2013: BARDA funds study of therapy for thermal burns

September 16, 2013: BARDA evaluates burn dressing for radiation, sulfur mustard burns

August 23, 2013: BARDA Contract Supports Evaluation of Therapy for Severe Thermal Burns

August 22, 2013: BARDA Supports Proof-Of-Concept Studies for Small Molecule Development

July 30, 2013: BARDA contract supports the development of a more effective skin graft to help burn patients after a rad/nuke event

June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

April 3, 2013: HHS awards contract to create test to identify resistant influenza viruses

About BARDA

- BARDA Strategic Plan
- Procurement and Grant Awards
- Program Divisions
- Making Progress, End to End, in Medical Countermeasures
- Project BioShield Annual Reports
- Leadership Biographies

This page last reviewed: January 03, 2014

http://www.phe.gov/newsroom/Pages/mcm-procurements.aspx
Last accessed: 8 May 2014

When Big Brother helps Big Pharma…

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

Date: May 22, 2013

Company: GlaxoSmithKline of North Carolina

GlaxoSmithKline US

40 to 200 x 10^6 US$

Contract amount: This agreement is not a contract; other transactional authority was used to create a strategic alliance. BARDA will contribute $40 million over 18-months. The agreement can be extended up to five years and up to a total of $200 million

About the contract: The agreement is the first in which BARDA has taken a portfolio approach with a private sector company instead of contracting to develop a single medical countermeasure. The agreement is flexible, allowing drug candidates to be moved in or out of the portfolio, based on advanced development stage and technical considerations, during joint semi-annual portfolio reviews. Under the agreement, GSK researchers will conduct safety and toxicology testing, clinical pharmacology studies, clinical studies, and non-clinical studies to support approval to treat illnesses caused by bioterrorism agents like anthrax, plague and tularemia, as well as address antibiotic resistance. One of the antibiotics to be further developed under this agreement is GSK'944, the first in class of drugs that targets bacterial DNA replication in a unique fashion. GSK has conducted studies in which GSK'944 protected or successfully treated animals suffering from anthrax, plague, or tularemia.

Additional information: The partnership with GSK is funded by BARDA's Broad Spectrum Antimicrobials Program. BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illness due to biological threat agents. Proposals are accepted through the Broad Agency Announcement BARDA-BAA-12-100-SOL-00011 at www.fbo.gov.

Anthrax, plague, tularemia … and resistance

Press Release: HHS forms strategic alliance to develop new antibiotics

PHE.GOV - Leading a Nation Prepared HHS/ASPR
http://www.piersystem.com/go/doc/3803/1863406/
Last accessed: 8 May 2014

and also helps small pharma for a new ketolide …

May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tulermia

Date: May 24, 2013

Company: Cempra Pharmaceuticals of Chapel Hill, N.C.

Contract amount: $17.7 million for two years

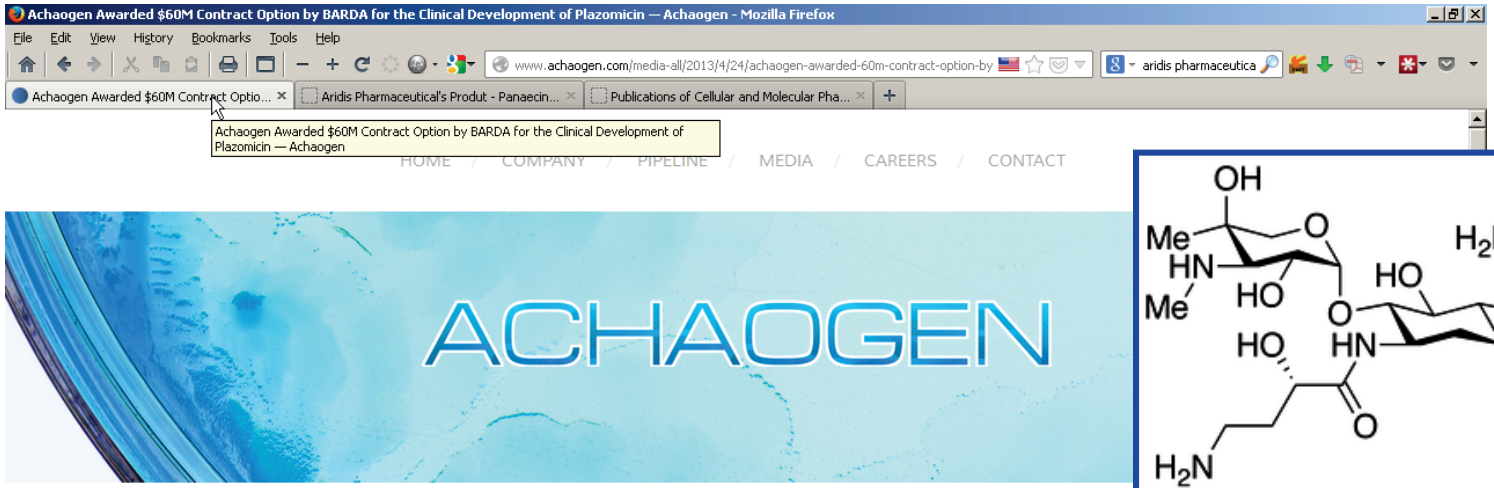
About the contract: The contract supports studies needed to request FDA approval of a drug called solithromycin to treat adults and children infected with anthrax, tularemia or community-acquired bacterial pneumonia. If approved, the drug would be the first orally administrated antibiotic approved in decades to treat children who develop community acquired bacterial pneumonia. Studies of the drug's use in treating anthrax or tularemia will be conducted under the FDA's Animal Efficacy Rule.

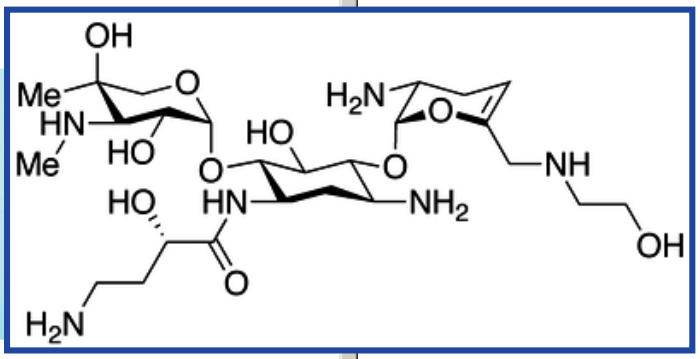
Additional information: BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illness due to biological threat agents. Proposals are accepted through a Broad Agency Announcement BARDA-BAA-12-100-SOL-00011 at www.fbo.gov

Press Release: HHS funds drug development for bioterror infections

PHE.GOV - Leading a Nation Prepared HHS/ASPR
http://www.piersystem.com/go/doc/3803/1863410/
Last accessed: 8 May 2014

And even for an aminoglycoside …





Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin

April 24, 2013

- Contract to fund Phase 3 superiority study of plazomicin in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections -

South San Francisco, CA, April 24, 2013 – Achaogen, Inc. today announced the award of a $60M contract option from the Biomedical Advanced Research and Development Authority (BARDA). The option supports the conduct of a global Phase 3 superiority study that will evaluate the efficacy and safety of plazomicin in treating patients with serious gram-negative bacterial infections due to CRE. This pathogen-specific clinical study represents a new development approach to address unmet medical needs for multi-drug resistant bacterial infections. The study is expected to start in fourth quarter of 2013.

"We are excited and honored to continue the development of plazomicin in partnership with BARDA," said Kenneth J. Hillan, M.B. Ch.B., Chief Executive Officer and Chief Medical Officer of Achaogen. "The growing prevalence of CRE infections poses a substantial public health threat, given the high mortality rates associated with CRE infections. Plazomicin's strong potential to address this public health issue and to contribute to the global effort to guard against bacterial biothreats makes it a critically important agent in the antibacterial pipeline."

Achaogen Inc
http://www.achaogen.com/media-all/2013/4/24/achaogen-awarded-60m-contract-option-by-barda-for-the-clinical-development-of-plazomicin
Last accessed: 8 May 2014

Big Brother in Switzerland…

June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

Date: June 25, 2013

Company: Basilea Pharmaceutica International Ltd., Basel, Switzerland

Contract amount: BARDA will provide $16.8 million in the first phase of the contract. The contract can be extended up to a total of six years with BARDA contributing up to a total of $89 million

About the contract: This contract is a cost-sharing public-private partnership. The partnership supports Basilea in conducting studies to evaluate the safety and efficacy of the antibiotic BAL30072 to treat Gram-negative infections including melioidosis, glanders, hospital-acquired pneumonia, and complicated urinary tract infections. Results from these studies will support the eventual filing of a new drug application with the FDA. In addition to showing promise in treating melioidosis and glanders, early studies of BAL30072 have demonstrated the drug's potential in treating a broad range of multidrug-resistant Gram-negative bacteria commonly found in hospitals.

Additional information: BARDA is seeking additional proposals for broad-spectrum antimicrobials that potentially could treat or prevent diseases caused by bacterial and viral threat agents, and clinically relevant emerging and drug resistant pathogens that through the Broad Agency Announcement BARDA CBRN BAA-12-100-SOL-00011 at www.fbo.gov.

Press Release: BARDA supports new broad-spectrum antibiotic

PHE.GOV - Leading a Nation Prepared HHS/ASPR
http://www.piersystem.com/go/doc/3803/1863402/
Last accessed: 8 May 2014