Future design of (comparative) clinical trials…

or how to bring antibiotics to the bed side

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Ceftaroline Fosamil (ZINFORO™) Speaker Summit

The Role of Ceftaroline in our Antibiotic Armamentarium

7–8 March 2013

London Heathrow, UK

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  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, Vetoquinol
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - Belgian Transparency and Reimbursement Committees
  - Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones

Are antibiotics following a path to madness ? *

1928 - …

discovery in soil bacteria and fungi

* a pictorial story based on Van Goch's paintings from grey Belgium to sunny Provence

Are antibiotics following a path to madness ?

1950 – 1980 …

and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics

* a pictorial story based on Van Goch's paintings from grey Belgium to sunny Provence

Are antibiotics following a path to madness ?

and the US General Surgeon told us that the fight was over

1970 …

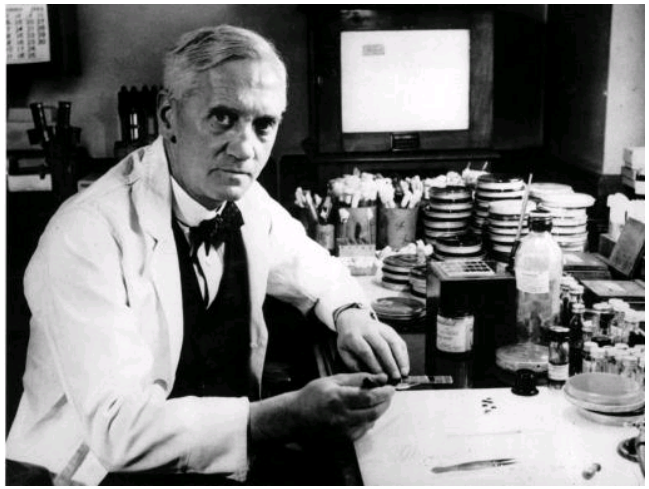
* a pictorial story based on Van Goch's paintings from grey Belgium to sunny Provence

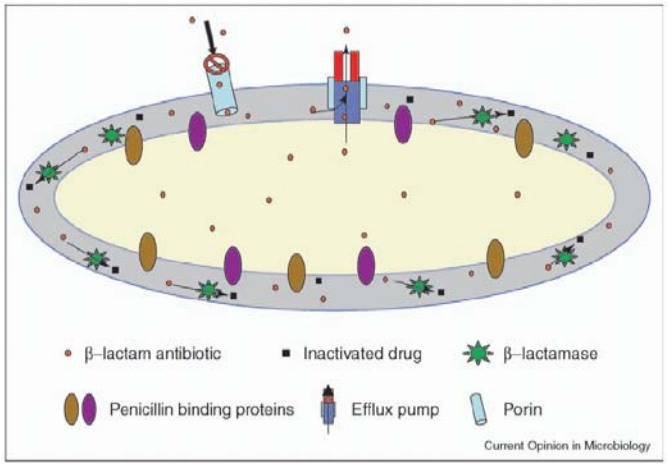
Are antibiotics following a path to madness ?

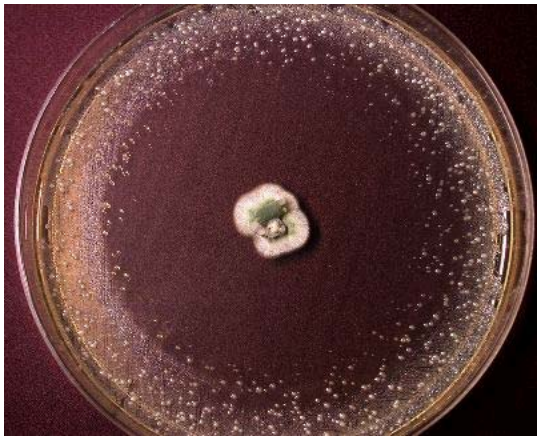
But…

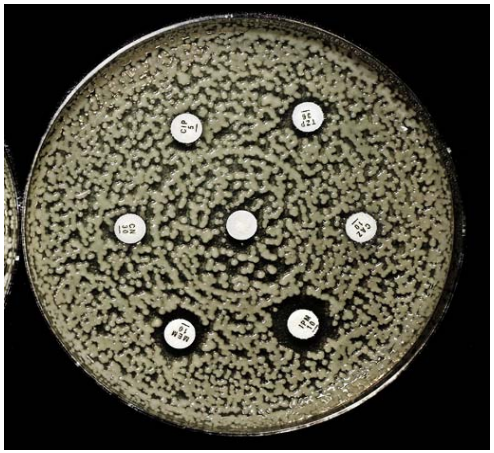
2012 …

Our first problem: antibiotics from discovery to demise

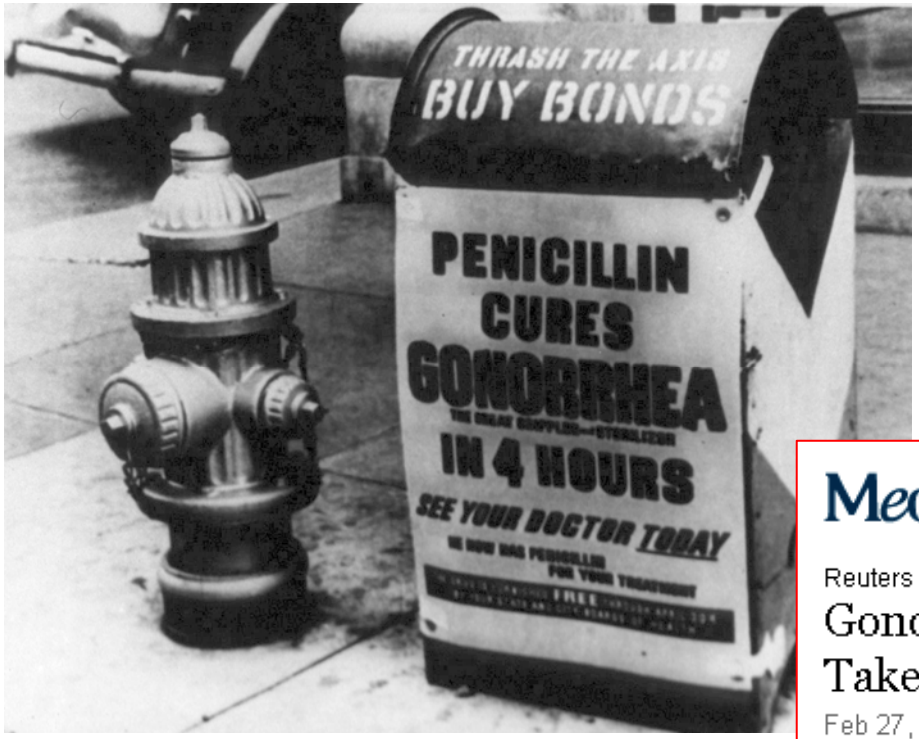








If you do not believe me …



London, UK, 1944 *,[1]

* see the top ad

Medscape Infectious Diseases NEWS

News

Reuters Health Information

Gonorrhea Cases Soar 25% in England as Superbugs Take Hold

Feb 27, 2013

LONDON (Reuters) Feb 27 - Gonorrhea cases have soared by 25% in the past year in England as drug-resistant strains of the sexually transmitted infection (STI) take hold worldwide, British health officials said on Wednesday.

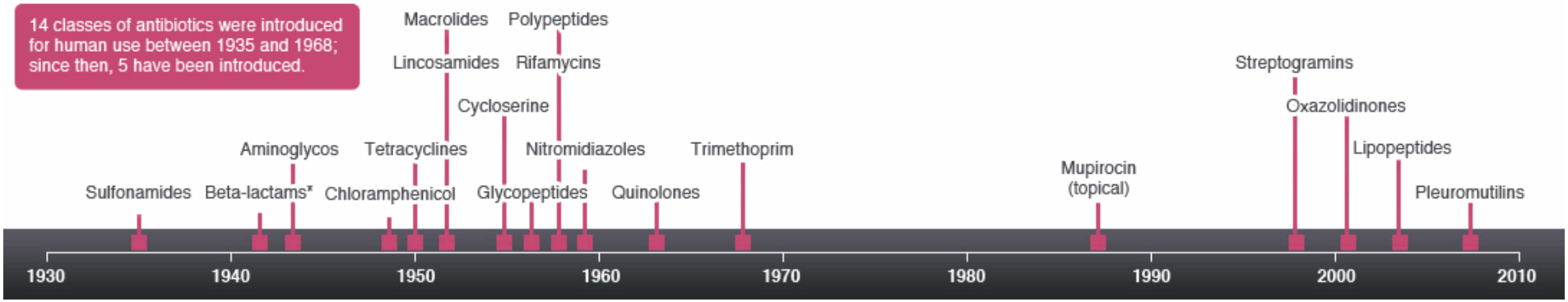
REUTERS HEALTH INFORMATION

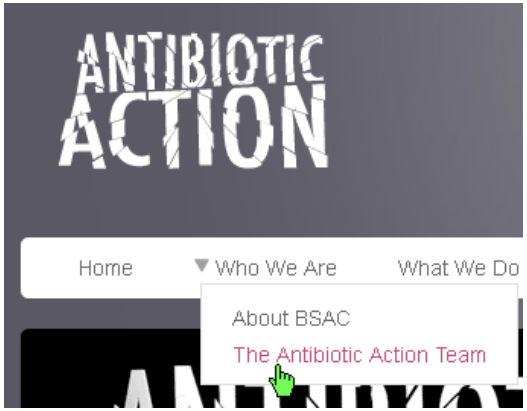
London, UK, 2013 [2]

[1] http://ihm.nlm.nih.gov/images/A20824

[2] http://www.medscape.com/viewarticle/779972?nlid=28961_804&src=wnl_edit_medp_infd&uac=83243PZ&spon=3

Our second problem: a drying pipeline [1]





About BSAC

Founded in 1971, and with 700 members worldwide, the British Society for Antimicrobial Chemotherapy exists to facilitate the acquisition and dissemination of knowledge in the field of antimicrobial chemotherapy.

1. World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010;

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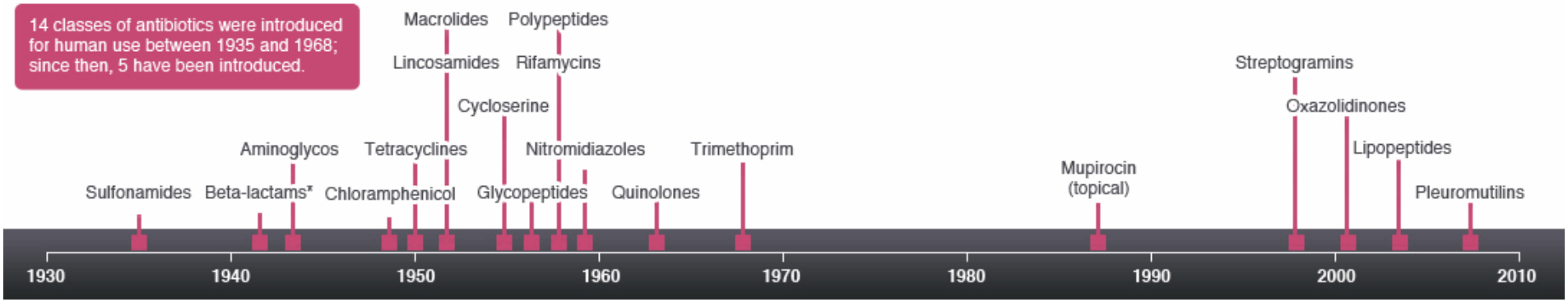

- Antibiotics made up only 1.6% of drugs in development in 2004[2]
- Currently the industry pipeline contains few late-stage antibiotics that can effectively combat the emergence and spread of resistant strains[1]

Chemotherapy exists to facilitate the acquisition and dissemination of knowledge in the field of antimicrobial chemotherapy.

1. World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010;
2. Spellberg et al. Clin Infect Dis 2004;38:1279–86.

Key factors contributing to underinvestment in antibiotic R&D

- Availability of inexpensive, generic antibiotics

INAMI

Communiqué de presse

Bruxelles, 24 avril 2012

Prescription et délivrance de médicaments : Nouveautés

Deux nouvelles mesures ont pour objectif de réaliser des économies et sont donc favorables pour l'assurance soins de santé et pour le patient qui paiera moins cher ses médicaments.

- **Le pharmacien devra délivrer un des antibiotiques ou antimycosiques les moins chers, à partir du 1er mai 2012.**

http://www.inami.be/news/fr/press/pdf/press2012042401.pdf

The pharmacist must deliver one of the cheapest antibiotic as from 1 May 2012 …

Key factors contributing to underinvestment in antibiotic R&D

- Availability of inexpensive, generic antibiotics
- Antibiotics are not considered profitable compared with drugs for chronic conditions
  - Relatively short treatment duration
  - Antibiotics effective against severe infection need to be used carefully
    - Impression of treatment of last resort only
    - Small patient population eligible to receive treatment with new antibiotics
  - May have short clinical lifetime if resistance develops rapidly
  - Current pricing and reimbursement policies
    - Do not prioritise drugs according to their ability to reduce morbidity or mortality

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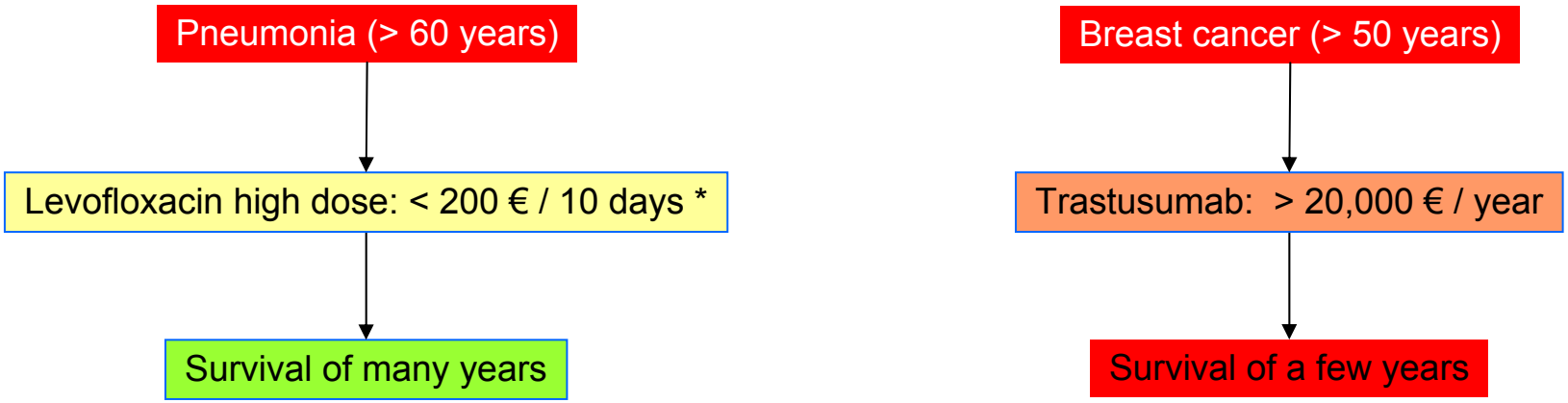
Allow me to take a simple example (drug acquisition costs)…



* can be as low as 20 € with a generic amoxiclin (as recommended by local guidelines)

World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010.

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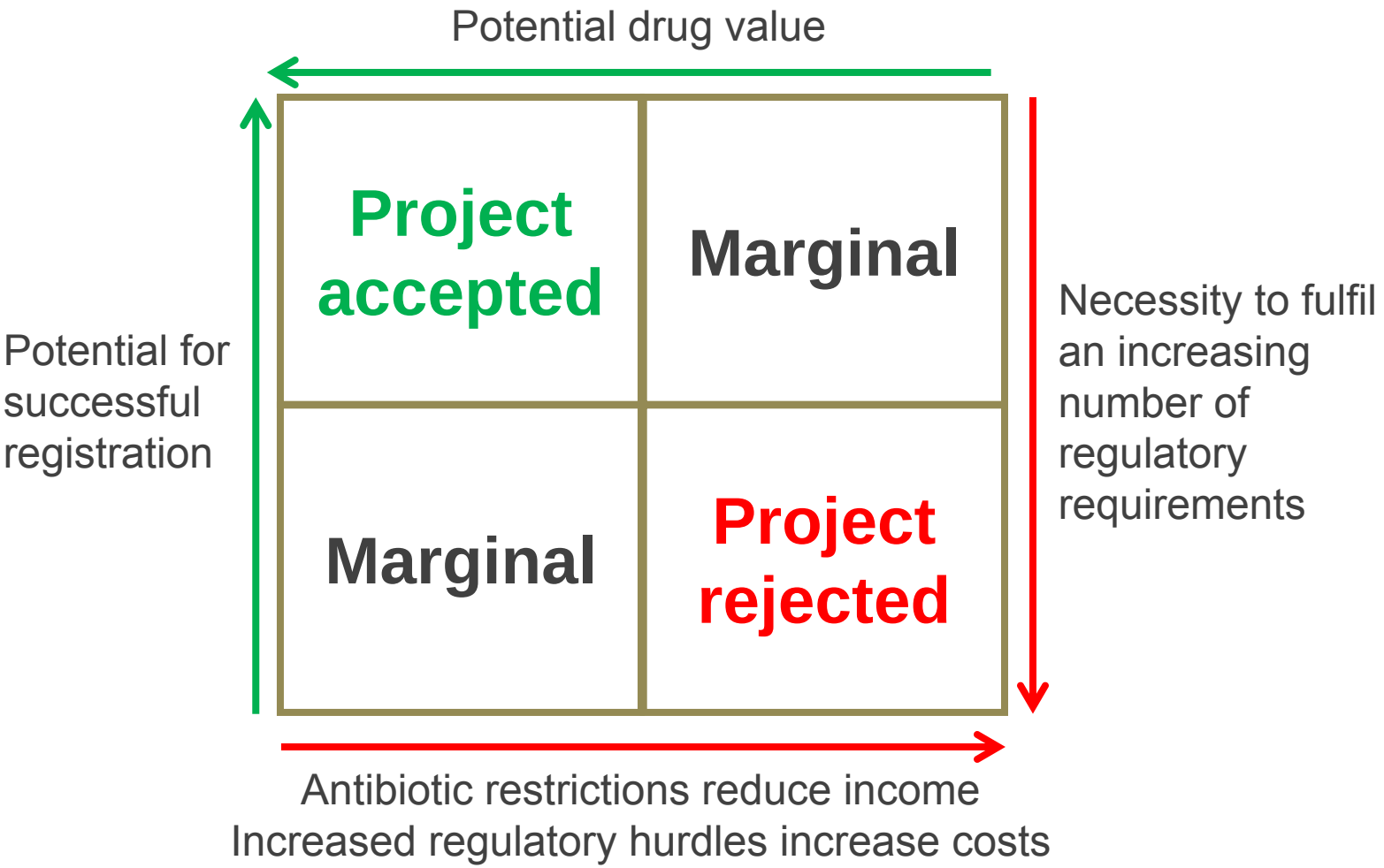
    - Do not prioritise drugs according to their ability to reduce morbidity or mortality
- Regulatory constraints and uncertainty regarding appropriate clinical trial design?

World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010.

Decisions when considering the development of an antibiotic



Adapted from: World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010.

The pipeline identified by EMA in 2008

Figure 7. New systemic antibacterial agents with new target or new mechanism of action and *in vitro* activity against selected bacteria based on actual data (●) or assumed activity based on known class properties or mechanisms of action (●), by phase of development (n=15, as of 14 March 2008). Total represents the number of agents active against each of the selected bacteria in a best-case scenario.

Name of agent	Gram-positive bacteria				Gram-negative bacteria			Phase of development
	MRSA	VISA/VRSA	PRSP	VRE	3rd Gen Cep. R ENB	Carb. R ENB	Carb. R NF GNB	
WAP 8294A2	●							I
PZ-601*	●	●	●	●	●			I
ME 1036*	●	●	●		●			I
NXL 101	●	●	●	●				I
Friulimicin B	●	●	●	●				I
Oritavancin	●	●	●	●				Filed
Telavancin	●	●	●	●				Filed
Ceftobiprole medocaril†	●	●	●					Filed
Ceftaroline fosamil †	●	●	●					III
Tomopenem‡	●	●	●		●	●	●	II
hLF1-11	●	●			●	●	●	II
Lactoferrin	●	●			●	●	●	I
Talactoferrin-alfa	●	●			●	●	●	II
Opebacan					●	●	●	III
NXL 104/ceftazidime§					●	●	●	I

The pipeline indentified by EMA in 2008

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NXL 101	●	●	●	●				I
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Ceftobiprole medocaril†	●	●	●					Filed
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Tomopenem‡	●	●	●		●	●	●	II
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Lactoferrin	●	●			●	●	●	I
Talactoferrin-alfa	●	●			●	●	●	II
Opebacan					●	●	●	III
NXL 104/ceftazidime§					●	●	●	I

Only 2 have been registered in 2013…

A 3d problem:
regulatory hurdles and the clinical trial design saga

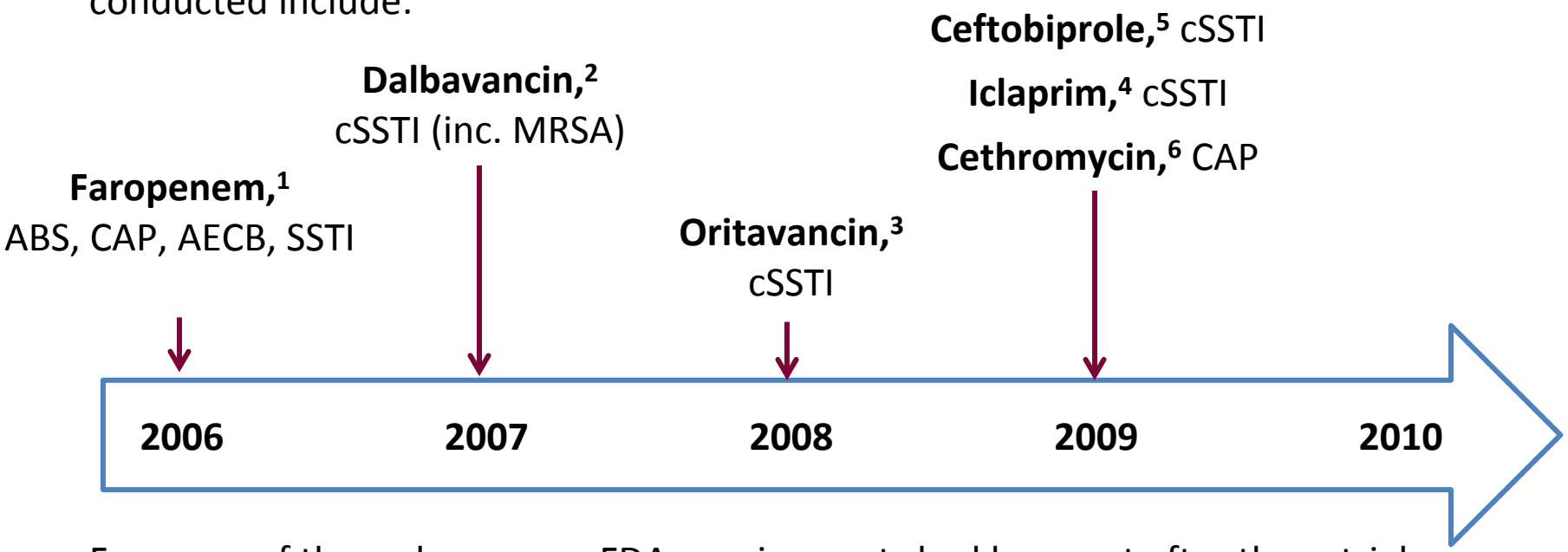
Is this really true ?
Or is it not
(sometimes) the
opposite
(drugs killed by the
FDA; see next
slide…)

"The FDA has even gone out of its way to **ignore critical evidence about dangerous drugs** in order to appease its Big Pharma clients and keep those high-profit drugs selling while people are dying."

(statement made by David Icke at
http://foodfreedomgroup.com/2013/02/01/death-by-doctors-the-shocking-figures/)

FDA non-approvals of antibiotics for severe bacterial infections

- Recent antibiotic submissions for which the FDA have required further trials to be conducted include:



- For some of these drugs, new FDA requirements had been set after these trials commenced and the study design agreed[2,6]

ABS, acute bacterial sinusitis; AECB, acute exacerbation of chronic bronchitis; CAP, community-acquired pneumonia; cSSTI, complicated skin and soft tissue infection; FDA, Food and Drug Administration; SSTI, skin and soft tissue infection

1. No author. Drugs R&D 2008;9:115–24; 2. Press release, 21-12-2007 Available at: http://www.reuters.com/article/2007/12/24/idUSN2127847620071224; 3. Press release 9-12-2008. Available at: http://www.fiercebiotech.com/press-releases/fda-issues-complete-response-letter-oritavancin; 4. Press release 20-01-2009. Available at: http://www.medicalnewstoday.com/releases/135981.php; 5. Basilea Pharmaceutica. 02-07-2009. http://www.basilea.com/News-and-Media/FDA-issues-ceftobiprole-Complete-Response-Letter/317; 6. Press release 31-07-2009. Available at: http://www.drugs.com/nda/restanza_090806.html.

A 3d problem:
regulatory hurdles and the clinical trial design saga

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

As for all other medicinal products, the size of the safety database that would be required before initial approval of an antibacterial agent or before approval of additional indications and alternative dose regimens must always take into account the demonstrated and anticipated benefits and risks.

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) - http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003417

Regulatory requirements contribute to the risk of antibiotic development

- Strict regulatory constraints are definitely necessary to protect patients

- Typically, the phase III studies used for registration are expected to have enough patients to detect at least the **uncommon effects**

Frequency categories: *

- very common: ≥ 1/10
- common: ≥ 1/100 to < 1/10
- Uncommon: ≥ 1/1000 to < 1/100
- Rare: ≥ 1/10000 to < 1/1000

- The data base must, therefore, contain at least 1,000-2,000 patients treated with the drug and a similar number of comparators **
- This results in a major difficulty in recruitment if concentrating on "interesting cases" and **favours non-inferiority design studies**

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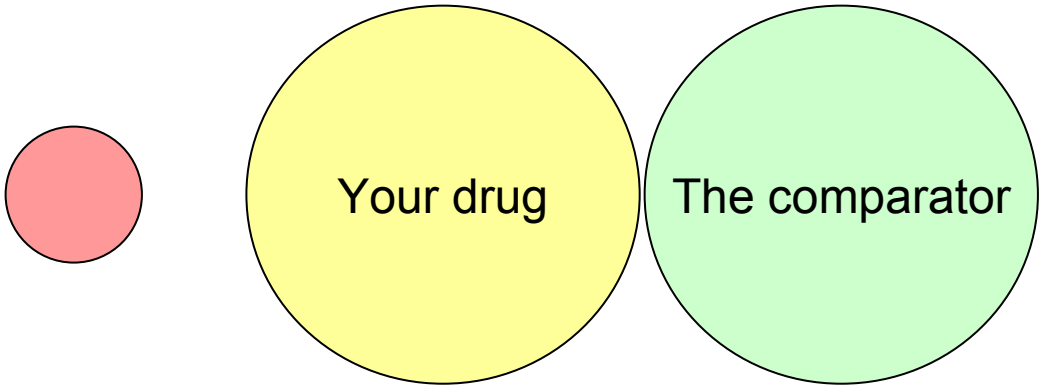
* As per current EMA SmPCs

** 1306 for ZINFORO™ at registration

Why non-inferiority trials and why they are disappointing …

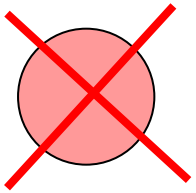
START: The trial must be "controlled"



By definition, you will only include patient with organisms susceptible to both antibiotics

Patients with documented resistant organisms

The population needed for safety



You cannot knowingly include resistant organisms

END: both drugs will be effective !

Non-inferiority trials at EMA in 2012 …

When a placebo cannot be used and if

- confidence of superior efficacy to placebo
- study design minimising false conclusion of non-inferiority.

Indications (and delta):

- Skin and soft tissue infections (-10%)
- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than ≤ -12.5%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)

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The phase III studies of ceftaroline

Phase 3 studies			
Study	**No. randomised**	**Treatment**	**Primary objective**
P903-06	Patients with cSSTI Ceftaroline: 353 Vancomycin / aztreonam: 349	Vancomycin 1 g q12h plus 1g aztreonam q12h Ceftaroline 600 mg q12h 5 to 14 days	Non-inferiority in clinical cure rate of ceftaroline vs. comparator at TOC visit in CE and MITT populations
P903-07	Patients with cSSTI Ceftaroline: 348 Vancomycin / aztreonam: 346	Vancomycin 1 g q12h plus 1g aztreonam q12h Ceftaroline 600 mg q12h 5 to 14 days	Non-inferiority in clinical cure rate of ceftaroline vs. comparator at TOC visit in CE and MITT populations
P903-08	Patients with CAP Ceftaroline: 305 Ceftriaxone: 309	Ceftriaxone 1 g q24h Ceftaroline 600 mg q12h Each + oral clarithromycin 500 mg q12h on Day 1 only 5-7 days	Non-inferiority in clinical cure rate of ceftaroline vs. ceftriaxone at TOC visit in CE and MITTE populations
P903-09	Patients with CAP Ceftaroline: 317 Ceftriaxone: 310	Ceftriaxone 1 g q24h Ceftaroline 600 mg q12h 5-7 days	Non-inferiority in clinical cure rate of ceftaroline vs. ceftriaxone at TOC visit in CE and MITTE populations

Non-inferiority trials ?

- Most clinical trials of antibiotics are designed to demonstrate non-inferiority vs standard of care
  - Intend to demonstrate that a new drug is not worse than an active comparator by more than a specified amount (delta value)

- Non-inferiority trials have many associated difficulties
  - New drug only seen as 'non-inferior' to the comparator[1]
  - Comparator drug should be known to be superior to placebo[2–4]
    - For most severe bacterial infections no placebo-controlled trials have been conducted
  - Susceptibility to operational biases (non-adherence, missing data etc)[5]
  - Limit innovation – need to maintain the conditions of previous studies[5]
  - Difficulties in specifying delta value needed for non-inferiority margin[1–3]

1. World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010;
2. Tillotson & Echols. Clin Infect Dis 2008:42(Suppl 3);S237–40; 3. Spellberg et al. Clin Investig 2011;1:19–32; 4. Spellberg et al. Clin Infect Dis 2009;49:383–91;
5. Fleming & Powers. Clin Infect Dis 2008;47:S108–20.

Should we not make superiority trials ?

- Several strengths[1]
  - Intended to detect a difference between two drugs
  - If successful will demonstrate that study drug is better than those on the market
  - Allow innovative trial designs[2]
  - May require fewer patients than non-inferiority trials (and hence lower costs)

- Disadvantages
  - Problematic for more serious infections, e.g. community-acquired pneumonia[3]
  - Active-controlled superiority trials are impractical[4]
  - Placebo-controlled superiority trials are unethical[4]

1. World Health Organization and European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010;
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Superiority trials at EMA in 2012 …

In situations where antibiotics have not consistently demonstrated superiority versus placebo (infections associated with high spontaneous resolution rates or limited populations)

- if ethically acceptable and with clinical judgment
- if expected to lead to superiority against placebo (95% 2-sided CI)
- with preferably a 3-arms design (drug – placebo - active comparator) or sequential design (test vs. placebo replaced by comparator > 3 days).

Indications :

- acute otitis media (with sustained effect at 14-21 days)
- acute bacterial sinusitis (difficulties in causality assessment)
- Inhalational antibacterial regimens in non cystic fibrosis patients (clinical criteria)
- superficial skin infections (stratify according to underlying diagnosis)

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) - http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003417
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Weaknesses of the EMA approach to superiority

- Strict exclusion criteria may limit generalisability of study results
- Important and frequent indications will never be covered
  - CAP of sufficient severity
  - HAP/VAP
  - Severe skin and skin structure infections
  - bacteremia
- Oral antibiotic compounds for CAP cannot be tested

Response of EMA to weaknesses in superiority

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Acceptable approaches

- strong prediction of efficacy in the intended use(s) from PK/PD analyses
- limit to one randomized and active controlled study in a specific type of infection where resistant organisms are frequent
- evidence of efficacy through non-controlled studies in situations where resistance is very problematic *(retrospective comparison)*
- use of flexible (adaptive) study design

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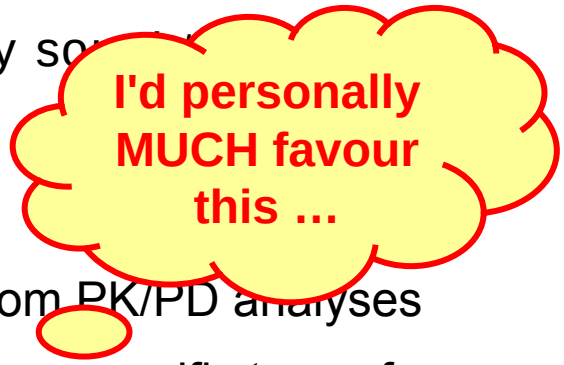

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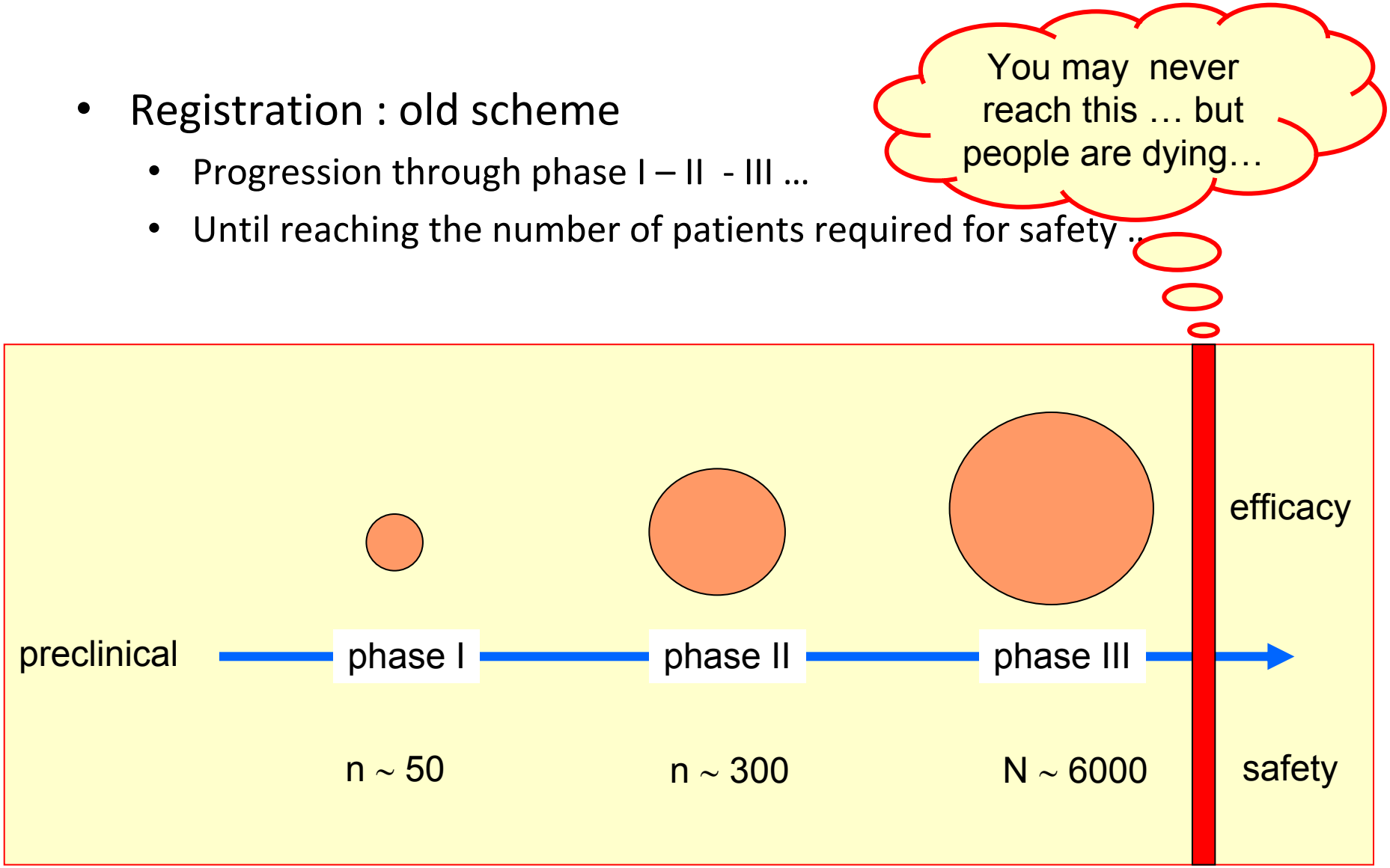
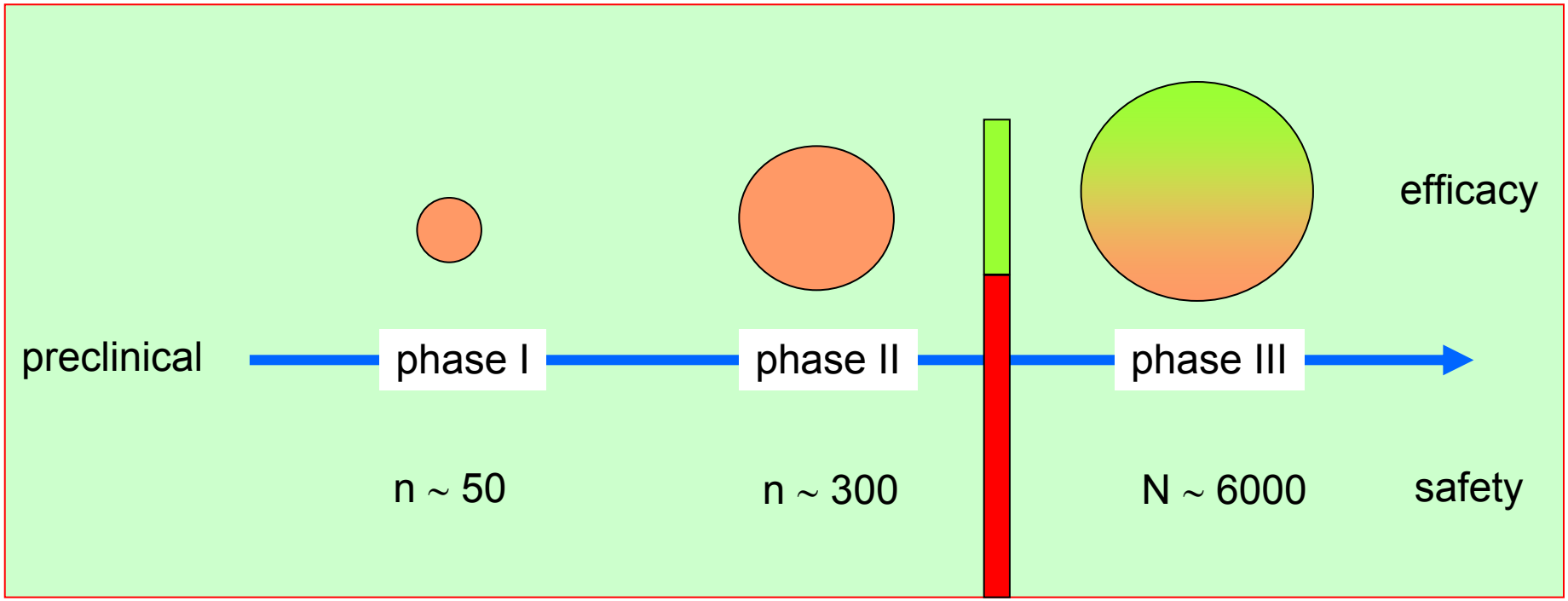
What about safety if you have few patients ?

- Registration : old scheme
  - Progression through phase I – II - III …
  - Until reaching the number of patients required for safety …



Registering for efficacy while not compromising safety…

- Registration: proposed new scheme
  - Provisional registration at phase II level (solving the unmet medical need)
  - Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration



What EMA has in store…

- A test agent expected or shown to be clinically active against multi-resistant Gram-negative pathogens could be indicated for studied infections without qualification by pathogen.
- Details of the actual organisms treated would be reflected in the "Pharmacodynamic" section of the SmPC along with mention of the evidence supporting activity (specific multi-resistant organisms).
- A pathogen-specific indication is a possibility.
- The label could included a restriction to use when other commonly used agents are not suitable for the individual patient.

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Are we approaching the most appropriate endpoint?

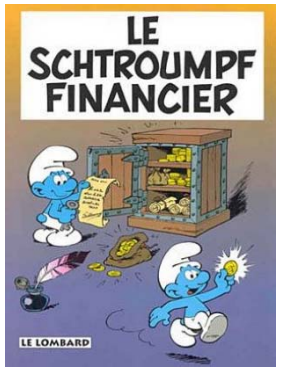
- Clinical response endpoint at test of cure[1]
  - Limitations of historical data
  - Lack of clear evidence for a treatment effect based on resolution of signs and symptoms attributable to the disease being studied
- Historical data support an all-cause mortality endpoint for CAP[1]
  - Non-inferiority trial with this primary endpoint would require a very large patient population
  - Evaluation of less important endpoints may bias estimates of effect if all-cause mortality not taken into account2
- Patients and physicians expect a cure for infection[1]
  - Early time points cannot answer this question (therefore may not be acceptable primary endpoints)
  - However, early time points are often indicative of efficacy and are important in the clinic

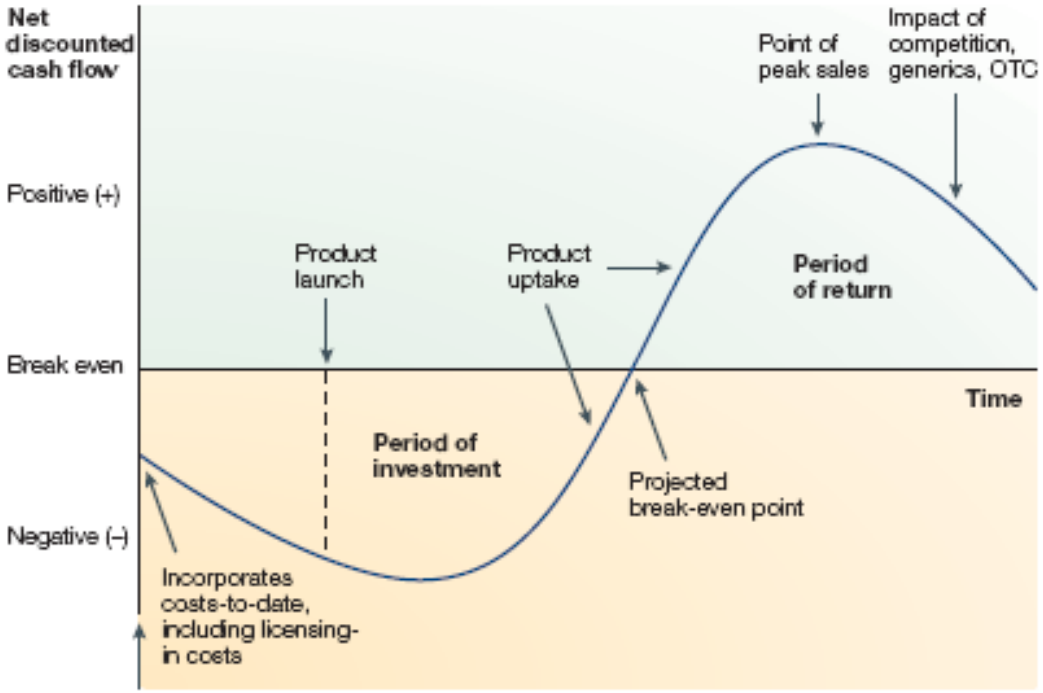
Endpoints aimed to meet regulatory criteria may not be the most relevant to clinical practice

1. FDA briefing document. Endpoints and Clinical Trial Issues in Community-Acquired Bacterial Pneumonia. Anti-Infective Drugs Advisory Committee. November 3, 2011; 2. Fleming & Powers. Clin Infect Dis 2008;47:S108–20.

An additional caveat …

Part of the problem is this





Today, several new antibiotic programs are financed by the US DOD …

But EU monnies are also used

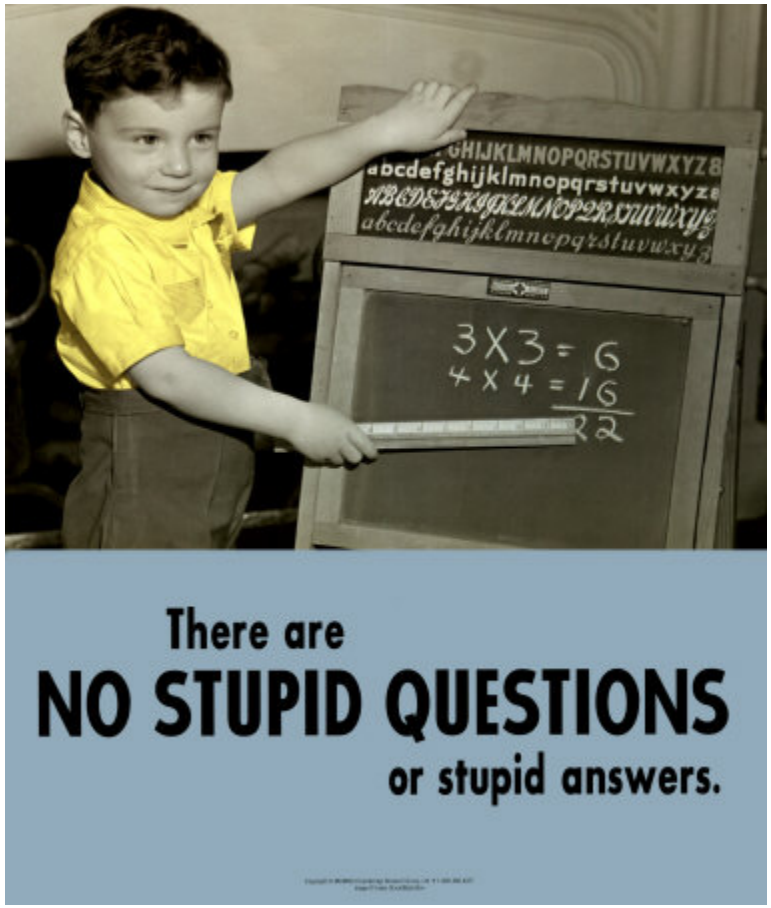
Innovative Medicines Initiative

http://www.imi.europa.eu

Summary

- Bacterial resistance to currently available antibiotics is becoming increasingly frequent
- There is an unmet need for new antibiotics that are effective against resistant pathogens
  - Despite the need, few antibiotics are being developed
- R&D for antibiotics with novel mechanisms of action should be actively promoted
- Balance between regulatory requirements and study feasibility is essential
- Innovative trial designs should be encouraged

Questions ?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22
There are
NO STUPID QUESTIONS
or stupid answers.