Comparative studies with antibiotics: Why should we change the rules?

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What its all about ?

- We are in real need of novel antibiotics… but …
  - ➔ most clinical studies with new compounds aim at equivalence or non-inferiority, failing to meet clinicians' expectations and regulatory requirements for novelty.
  - ➔ In parallel, safety issues are becoming an increasingly worrying hurdle for manufacturers
  - ➔ Pricing make antibiotic unattractive
- What are the possible solutions ?

The antibiotic crisis *

* A pictorial view using 4 paintings of Van Gogh (who stayed briefly in Belgium when moving from Holland to France) and with selected Belgian and International data…

Are antibiotics following a path to madness ?

1928 - …

discovery in soil bacteria and fungi

Are antibiotics following a path to madness ?

1950 – 1980 …

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

Are antibiotics following a path to madness ?

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

1970 …

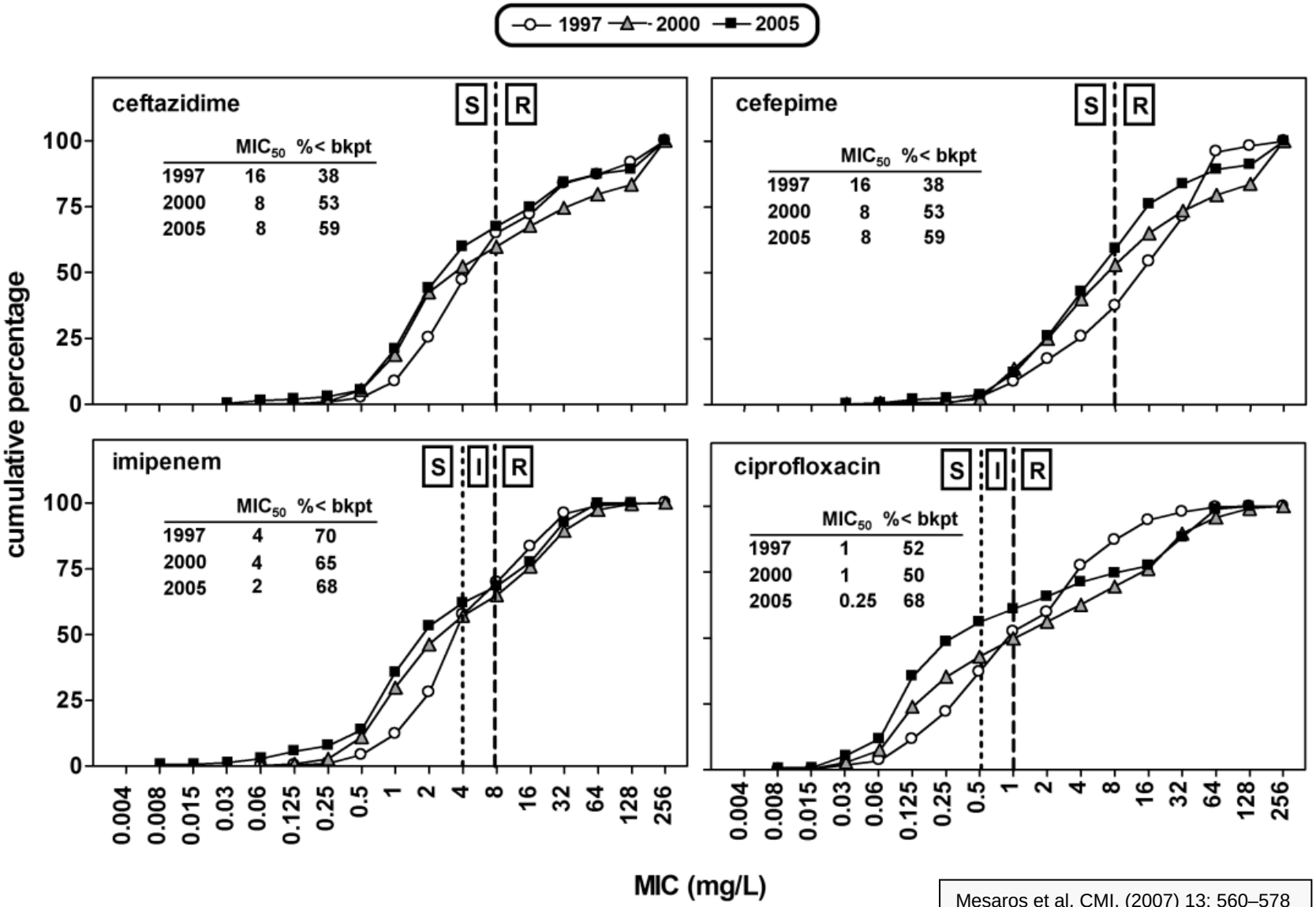
Are antibiotics following a path to madness ?

But…

2012 …

Extent of resistance of *P. aeruginosa*

(International data – EUCAST breakpoints)



Mesaros et al. CMI, (2007) 13: 560–578

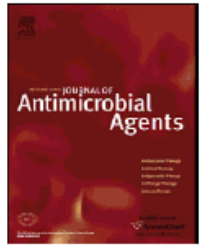
The hidden risk of therapy (at the corner of your street …)

International Journal of Antimicrobial Agents 36 (2010) 513–522

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag



In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

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[d] *Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium*
[e] *Laboratoire de Microbiologie, Cliniques Universitaires St-Luc, Brussels, Belgium*
[f] *Laboratorium voor Microbiologie, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[g] *Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium*
[h] *Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium*
[i] *Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium*

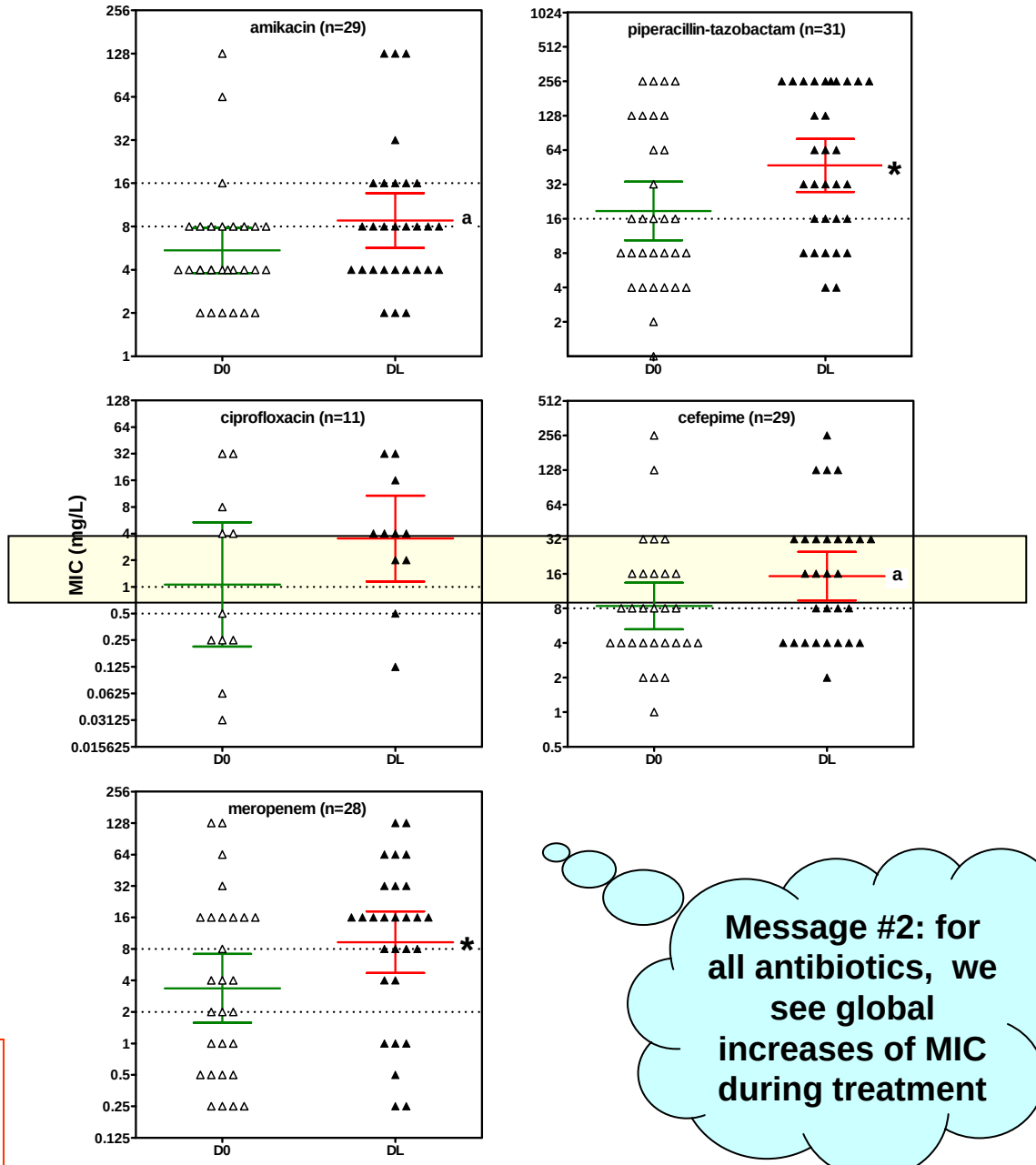
Question #1: are you effective ?

Assessment of adequateness of initial therapy

	No. of patients	No. of adequate antibiotics/total	% (no.) of patients with adequate therapy (EUCAST)
Monotherapy	26	1/1	57.7 (15)
2 antibiotics	14	2/2	71.4 (10)
3 antibiotics	13	3/3	38.5 (5)
4 antibiotics	1	3/4	100(1)

Message #1: many patients receive ineffective antibiotics

Question #2: do you remain effective while treating ?



- D0: initial isolate
  DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

[a] $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

Message #2: for all antibiotics, we see global increases of MIC during treatment

Question #3: Can you still treat patients ?

- In North-America / Western Europe", we may still work with available antibiotics but we are reaching the limit…

A well known Belgian politician…

- heart attack during his holidays (in Europe) …
- transfer to hospital Intensive Care Unit
- nosocomial pneumonia …
- dying a few days later (multi-resistant organism)

- The situation becomes hopeless in several other countries for hospitals (Russia, Vietnam, …) and, for some countries, even in the community…

Resistance IS a problem …

Journal of Antimicrobial Chemotherapy (2009) **64**, *Suppl. 1*, i29–i36
doi:10.1093/jac/dkp255

JAC

Has the era of untreatable infections arrived?

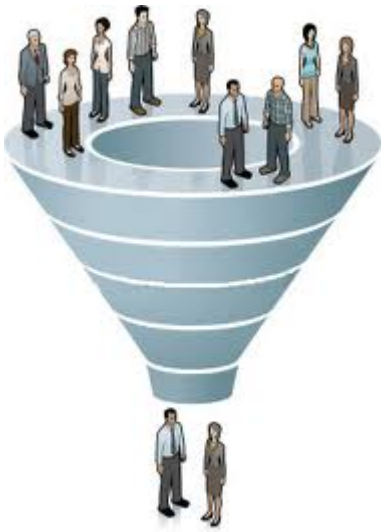
David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

- The choices of effective therapies is narrowing dangerously for several important pathogens
- Good faith people try acting by
  - Rationalizing the choice among the remaining ones
  - Optimizing those "remaining antibiotics
  - decreasing the inappropriate use of antibiotics whenever possible and improving hygiene with close follow-up of the epidemiology

The problem is the lack of new compounds…

The drying pipeline ?



research

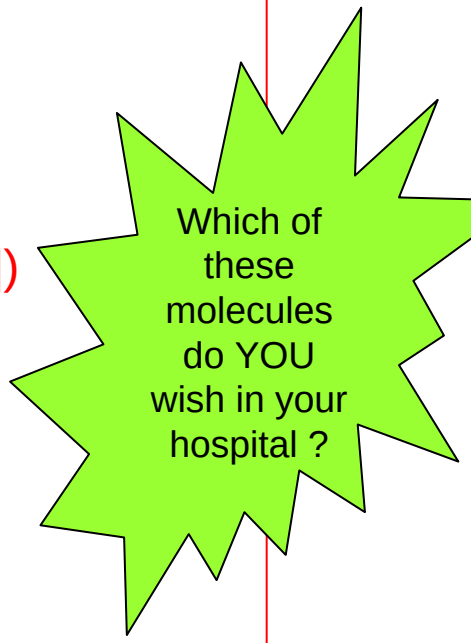
results

The drying pipeline ? (1)

- Everyone speaks about the reduction in the number of new antibiotics… What is your reality ?

New antibiotics introduced in the Belgian market since 2000 in ATC code J01

- J01A tetracyclines……1 (tigecycline [Pfizer])
- J01B phenicols ……0
- J01C β-lactams (penicillins)…….0
- J01D other β-lactams ……..1 (doripenem [Janssen-Cilag])
- J01E sulfamides/trimethoprim:... 0
- J01F macrolides/linc./streptogr.:.1 (telithromycin [Sanofi])
- J01G aminoglycosides……..0
- J01M quinolones……...1 (moxifloxacin [Bayer])
- J01R associations:……....0
- J01X others:……1 (linezolid [Pfizer])



Drying pipeline ? (2)

Antibiotics in ATC code J01 and with EMA approval but **not available** in Belgium

- J01A tetracyclines……. 0
- J01B phenicols …….. 0
- J01C β-lactams (penicillins)……. 0 (sulbactam [Pfizer])
- J01D other β-lactams ……..1 (ertapenem [MSD])
- J01E sulfamides/trimethoprim:... 0
- J01F macrolides/linc./streptogr.:.1 (quinupristin/dalfopristin)
- J01G aminoglycosides……..0
- J01M quinolones……...0
- J01R associations:……....0
- J01X others:……2 (daptomycin [Novartis])
  (telavancin [Astellas])

* in at least one EU country since 2000 and with at least some advantages/differences with comparators

Drying pipeline ? (3)

New antibiotics in ATC code J01 and in the pipeline/waiting for EMA approval *

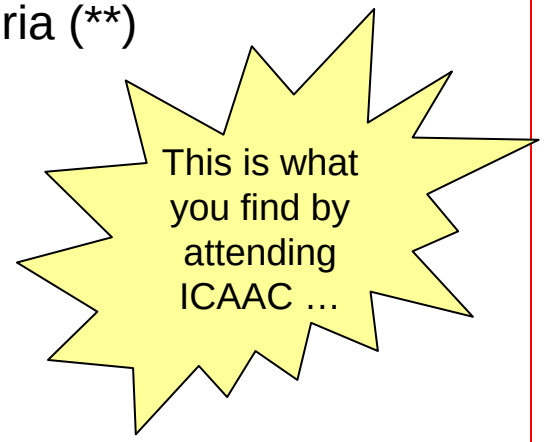
- J01A tetracyclines……. 1 → amadacycline (PTK 0796)
- J01B phenicols …….. 0
- J01C β-lactams (penicillins)……. 0
- J01D other β-lactams ……..3 → ceftobiprole, ceftaroline
- J01E sulfamides/trimethoprim:... 0 → iclaprim
- J01F macrolides/linc./streptogr.:.1 → cethromycin
- J01G aminoglycosides……..0 → plazomycin (ACHN-490)
- J01M quinolones……....0 → several…
- J01R associations:……..... 0 → avibactam (+ cephalosporins)
- J01X others:……2 → oritavancin, dalbavancin

* not an exhaustive list

Drying pipeline ? (4)

New molecules in preclinical/early clinical development *

- New oxazolidinones (tedizolid, radezolid …) active against LZD^{R} strains
- New aminoglycosides active against AMG^{R} strains (including arm) (**)
- New fluroquinolones active against MRSA (including CIP^{R} strains)
- New gyrase inhibitors active against CIP^{R} Gram(-) bacteria (**)
- New pleuromutilins (active against Gram + bacterial)
- New anti-MRSA carbapenems
- New lipopeptides (not affected by lung surfactant)
- New polymyxins derivatives (potentially less toxic)
- New dual target gyrase inhibitors (new target)
- …



* not an exhaustive list
** DOD/NIH program

So, what are the hurdles ?

- Discovery !
  - More efforts must be made with both public and private funding
- Clinical development
  - We must strive to efforts that are really meaningful (but this may command a smaller market … see hereunder)
- Registration
  - Provisional registration must be warranted for really innovative compounds (at phase II level) if helping to solve unmet medical needs
  - Safety issues must remain of paramount importance but should not deter honest efforts (no drug is harmless !)

So, what are the hurdles ?

- Discovery !
  - More efforts must be made with both public and private funding

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

But NIH (and EU…) programs are catching up…

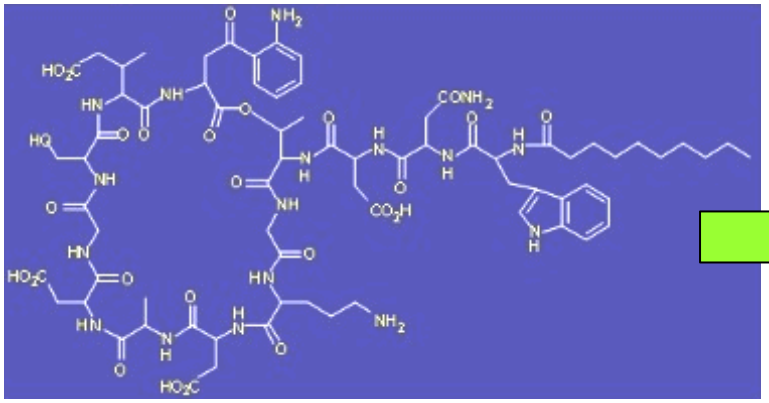
So, what are the hurdles ?

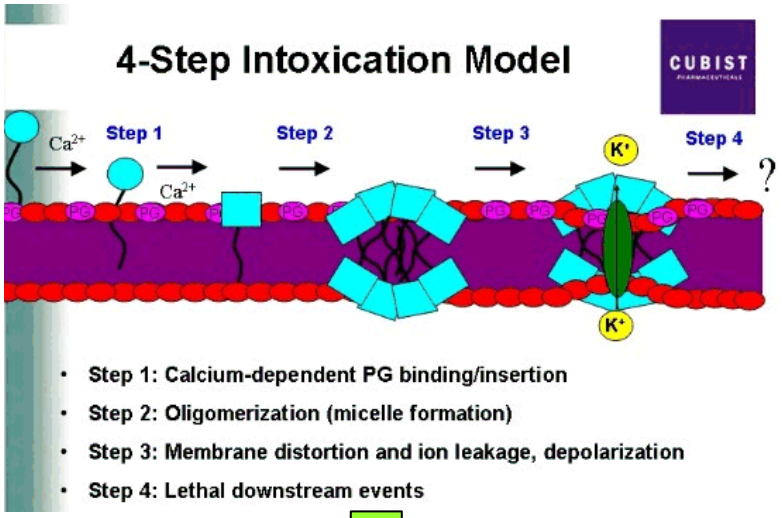
- Clinical development !
  - Phases I and phase II are reasonable
  - The major weakness is in phase III

- Currently, phase III studies are "controlled" (i.e. with a comparator) as per Regulatory Authorities requests…
- Almost all antibiotic therapies are still initiated empirically (i.e. without documentation of the causative organism)
- For ethical reasons, the comparator must be active
- Therefore, most if not all studies follow a "non-inferiority" design

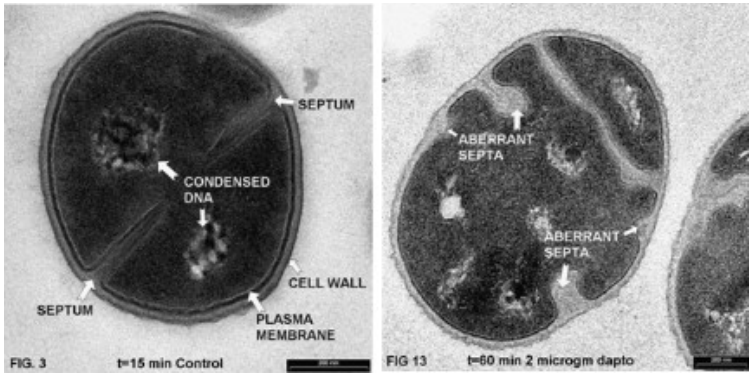
An example with daptomycin…

- Original molecule with a novel mode of action !





- **very bactericidal (membrane destabilization; no need of proteinaceous receptor !) and potent (MIC *S. aureus* = 0.5mg/L)**
- **spare eucaryotic cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes**



An example with daptomycin…

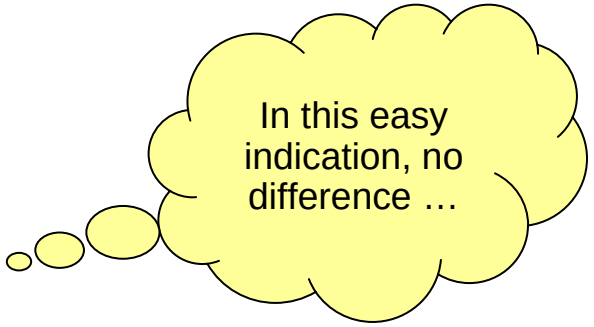
- Phase III studies : 1. skin & skin structures infections

Table 12. Clinical Success Rates by Infecting Pathogen in the cSSSI Trials (Population: Microbiologically Evaluable)

Pathogen	Success Rate n/N (%)	
	CUBICIN	Comparator*
Methicillin-susceptible *Staphylococcus aureus* (MSSA)†	170/198 (86%)	180/207 (87%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)†	21/28 (75%)	25/36 (69%)
Streptococcus pyogenes	79/84 (94%)	80/88 (91%)
Streptococcus agalactiae	23/27 (85%)	22/29 (76%)
Streptococcus dysgalactiae subsp. *equisimilis*	8/8 (100%)	9/11 (82%)
Enterococcus faecalis (vancomycin-susceptible only)	27/37 (73%)	40/53 (76%)

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

† As determined by the central laboratory.



An example with daptomycin…

- Look at the phase III studies : 2. endocarditis

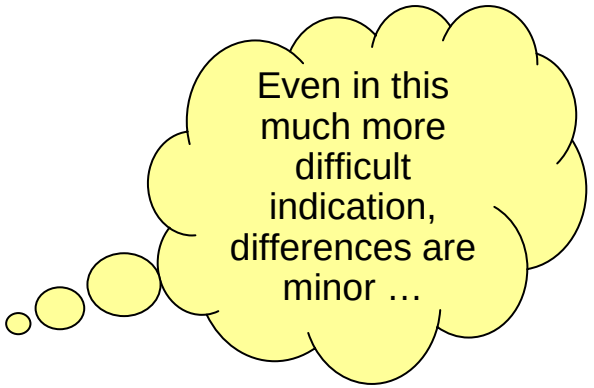
Table 13. Success Rates at Test of Cure in the *S. aureus* Bacteremia/Endocarditis (ITT)

Population	Success Rate n/N (%)		Difference: CUBICIN – Comparator (Confidence Interval)
	CUBICIN 6 mg/kg	Comparator*	
Overall	53/120 (44%)	48/115 (42%)	2.4% (–10.2, 15.1)†
Baseline Pathogen			
Methicillin-susceptible *S. aureus*	33/74 (45%)	34/70 (49%)	–4.0% (–22.6, 14.6)‡
Methicillin-resistant *S. aureus*	20/45 (44%)	14/44 (32%)	12.6% (–10.2, 35.5)‡
Entry Diagnosis§			
Definite or Possible Infective Endocarditis	41/90 (46%)	37/91 (41%)	4.9% (–11.6, 21.4)‡
Not Infective Endocarditis	12/30 (40%)	11/24 (46%)	–5.8% (–36.2, 24.5)‡
Final Diagnosis			
Uncomplicated Bacteremia	18/32 (56%)	16/29 (55%)	1.1% (–31.7, 33.9)¶
Complicated Bacteremia	26/60 (43%)	23/61 (38%)	5.6% (–17.3, 28.6)¶
Right-Sided Infective Endocarditis	8/19 (42%)	7/16 (44%)	–1.6% (–44.9, 41.6)¶
Uncomplicated Right-Sided Infective Endocarditis	3/6 (50%)	1/4 (25%)	25.0% (–51.6, 100.0)¶
Complicated Right-Sided Infective Endocarditis	5/13 (39%)	6/12 (50%)	–11.5% (–62.4, 39.4)¶
Left-Sided Infective Endocarditis	1/9 (11%)	2/9 (22%)	–11.1% (–55.9, 33.6)¶

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

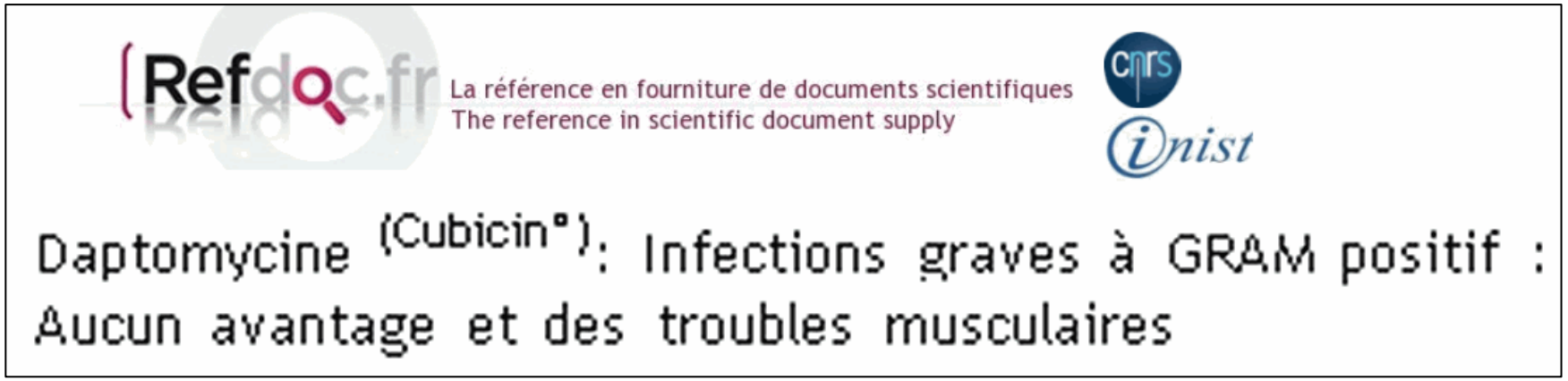
† 95% Confidence Interval ‡ 97.5% Confidence Interval (adjusted for multiplicity)

§ According to the modified Duke criteria[4] ¶ 99% Confidence Interval (adjusted for multiplicity)



An example with daptomycin…

- As a result, in a major EU country …



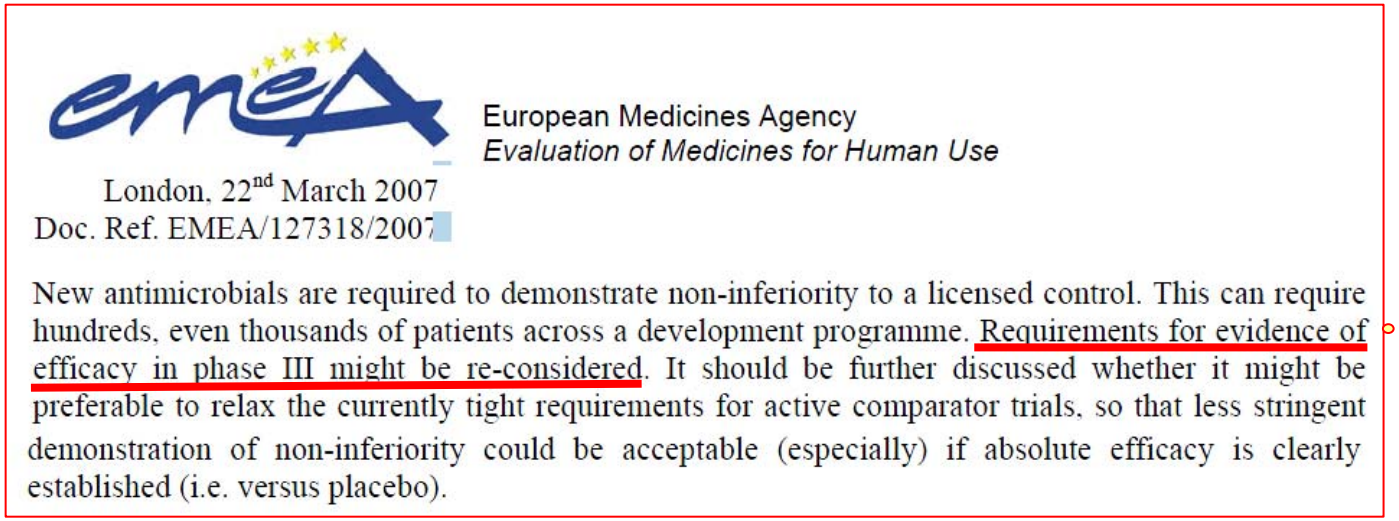
Is this what discovery was promising ?

Solving the problem of "uninteresting phase III studies" ?

- Address a real problem … and look for the **correct target** (the bacteria)
  - Look for infections caused by multi-resistant RESISTANT organisms (or organisms you cannot fight with available antibiotics)
    (infections need NOT be necessarily severe…)
- Run the study in a **non-controlled fashion**
  - By definition, you cannot have a comparator if you aim at resistant organims
- Target your study for non-inferiority against **historical controls**
  - Control = same type of infection caused by the same organisms but when it was still susceptible to the best-in-class antibiotic at that time
- By definition, **you will be superior** since the "control antibiotic" will not longer be acceptable.

Why not avoiding phase III altogether ?

- Provisional registration could be be warranted for really innovative compounds at phase II level if helping to solve unmet medical needs (and be accepted for that) !



European Medicines Agency
Evaluation of Medicines for Human Use

London, 22nd March 2007
Doc. Ref. EMEA/127318/2007

New antimicrobials are required to demonstrate non-inferiority to a licensed control. This can require hundreds, even thousands of patients across a development programme. Requirements for evidence of efficacy in phase III might be re-considered. It should be further discussed whether it might be preferable to relax the currently tight requirements for active comparator trials, so that less stringent demonstration of non-inferiority could be acceptable (especially) if absolute efficacy is clearly established (i.e. versus placebo).

2007

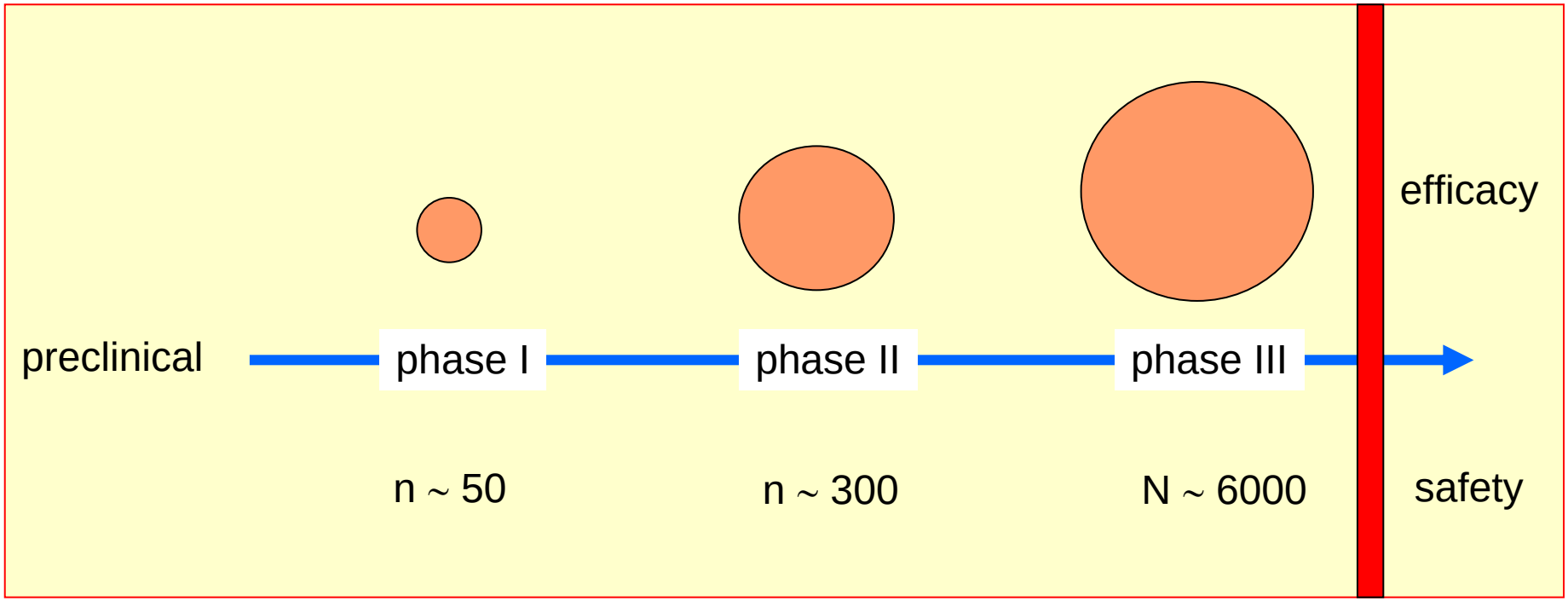
Why not avoiding phase III altogether ?

- Provisional registration could be be warranted for really innovative compounds at phase II level if helping to solve unmet medical needs (and be accepted for that) !

2011

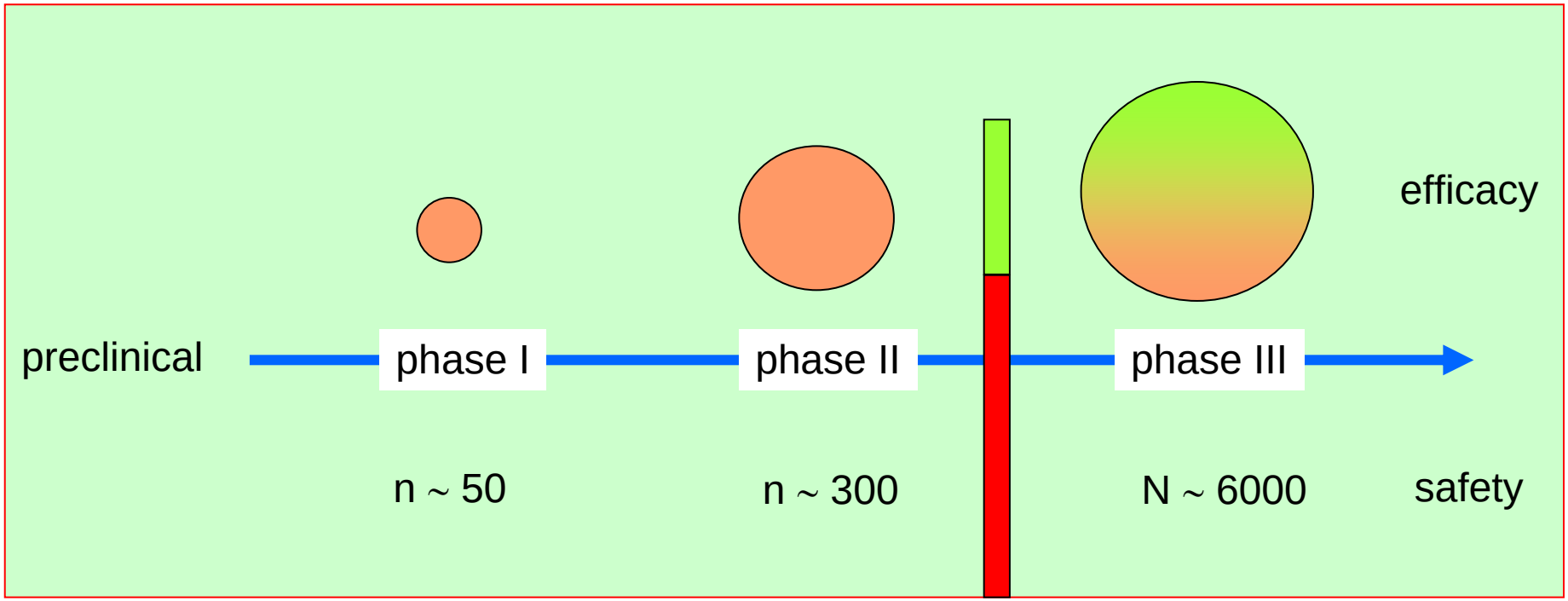
What about safety ?

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



How to combine this with 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



But there us still another problem ?

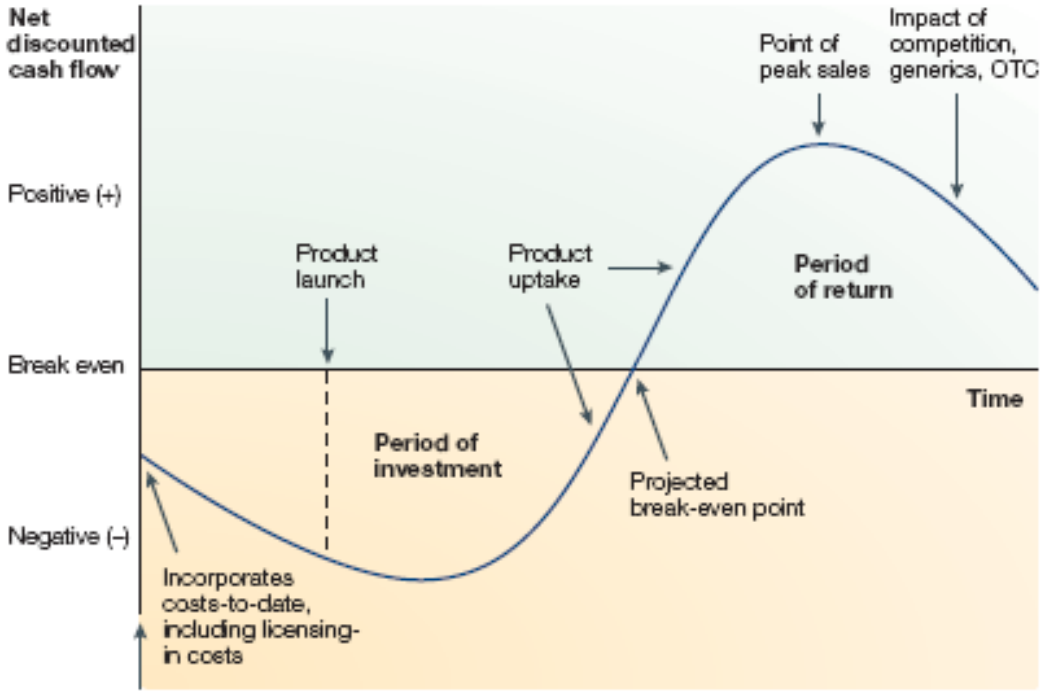
- Discovery **IS** difficult…
- Preclinical development **IS** challenging…
- Clinical development and registration are **not easy …**
- **But, will you recoup your investment ?**

This is a main part of the problem (in our current situation)

Why is economy important ?

- Can you work without support ? …
  - You need investors
  - Those will ask some return at some point…
  - And none ignores what is a ROI

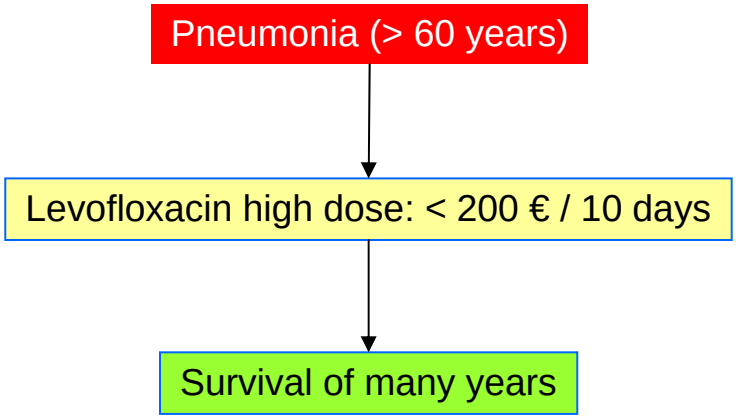
This is what every economist will tell you
(and you know it !)

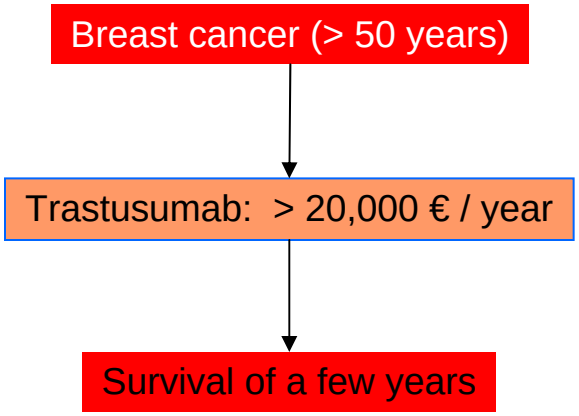


Let us take a simple comparison …

- Pricing
  - Antibiotics are cheap…
  - And now, the Belgian pharmacist must deliver the cheapest one (generic)…
  - Why would Industry make an effort ?

Allow me to take a simple example…





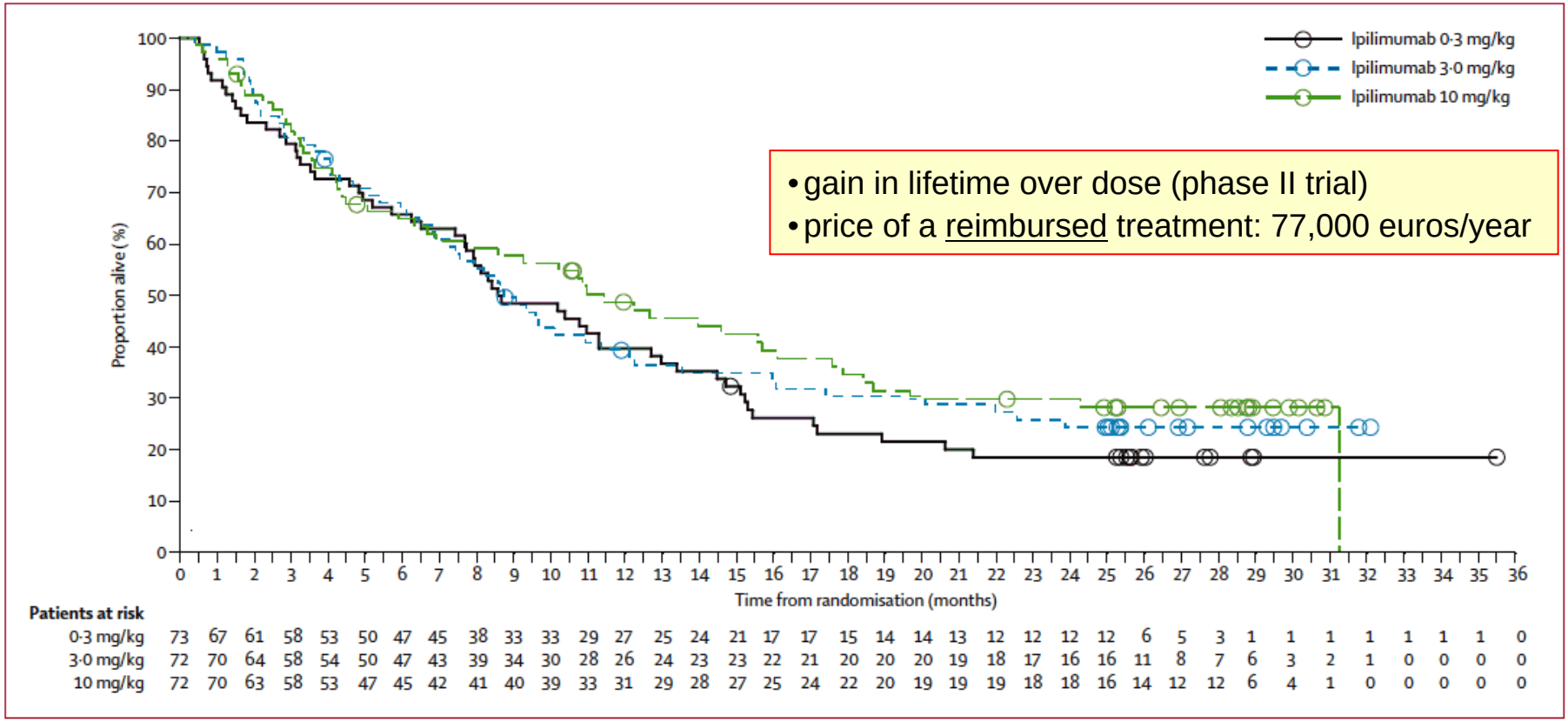
This may be saving lives … but at which price ?

Lancet Oncol. 2010 Feb;11(2):155-64. Epub 2009 Dec 8.

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study.

Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, Waterfield W, Schadendorf D, Smylie M, Guthrie T Jr, Grob JJ, Chesney J, Chin K, Chen K, Hoos A, O'Day SJ, Lebbé C.

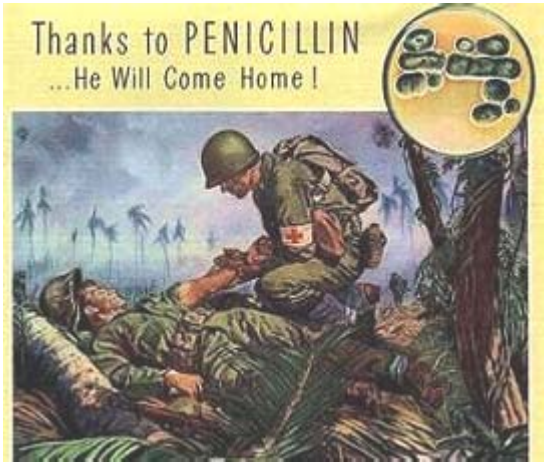
Ludwig Center for Cancer Immunotherapy, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. wolchokj@mskcc.org



- gain in lifetime over dose (phase II trial)
- price of a reimbursed treatment: 77,000 euros/year

Figure 2: **Kaplan-Meier estimate for overall survival, by treatment arm**

Do you remember having seen this ?



Penicillin saves lives (in 1944) !

It is no longer true !

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PERSPECTIVE

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

N Engl J Med 2012; 366:485-487 | February 9, 2012 | DOI: 10.1056/NEJMp1112456

Gonorrhea, which disproportionately affects marginalized populations, is the second most commonly reported communicable disease in the United States. Over the past 3 years, the gonococcus has shown decreased susceptibility to our last line of antimicrobial defense.