Antibiotics case study: How can re-studying old drugs improve existing ones?

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

What its all about ?

- Discovery of really novel antibiotic (new mode of action) is difficult due to the limited number of useful targets.
- In the past, several antibiotics of various classes were left undeveloped because of the success of blockbusters.
- Several “old antibiotics” are active against strains that have now become resistant to blockbusters.
- Revisiting these old molecules and tailoring them for use in specific situations of resistance may be much rewarding (“bacteria-personalized drugs...”) and help sparing the other ones.

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 ?

discovery in soil bacteria and fungi

1928 - …

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 …

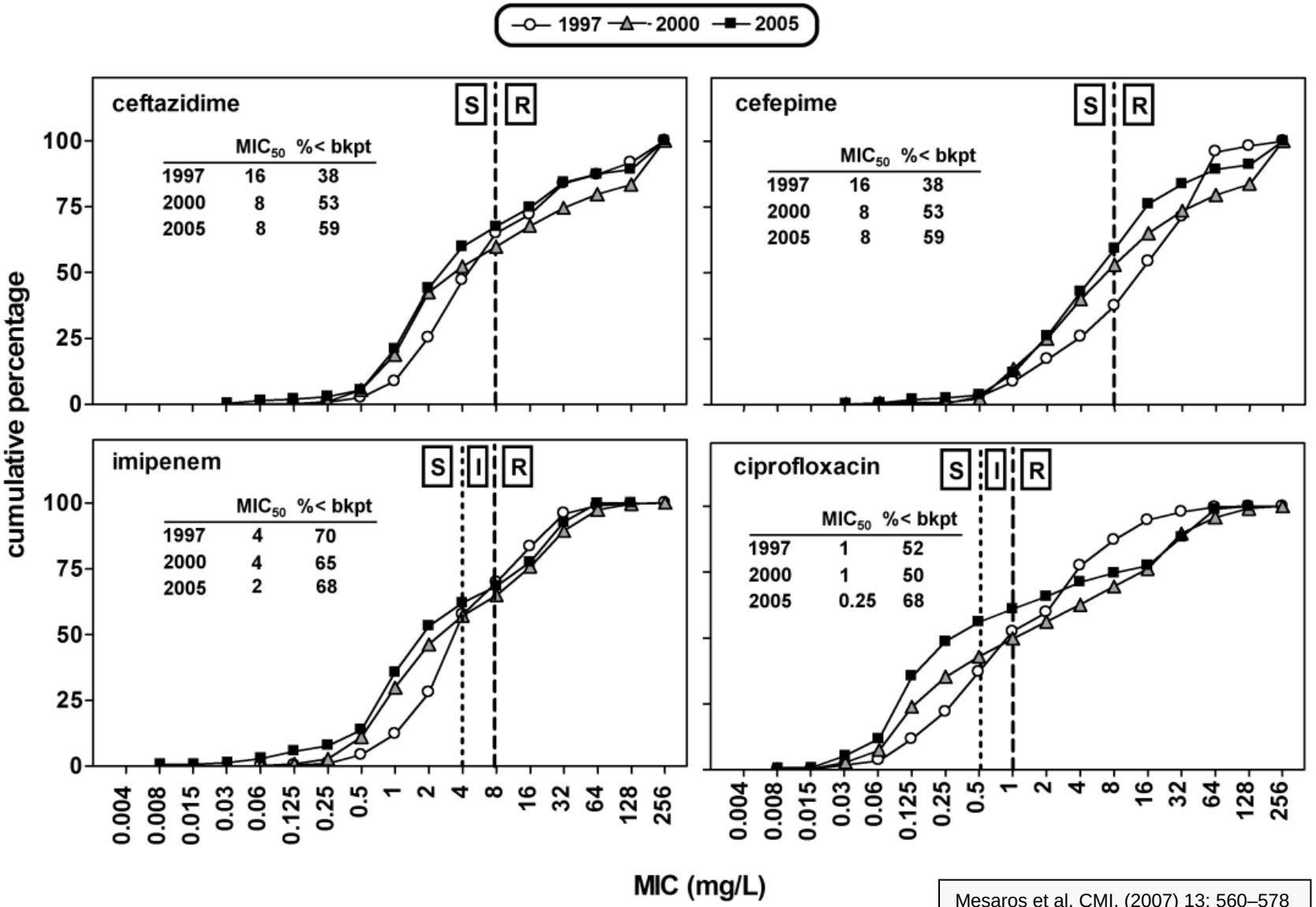
Are antibiotics following a path to madness ?

But…

2012 …

Extent of resistance of *P. aeruginosa*

(International data – EUCAST breakpoints)



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

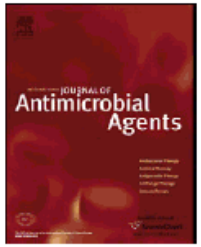
The hidden risk of therapy (at the corner of your street …)

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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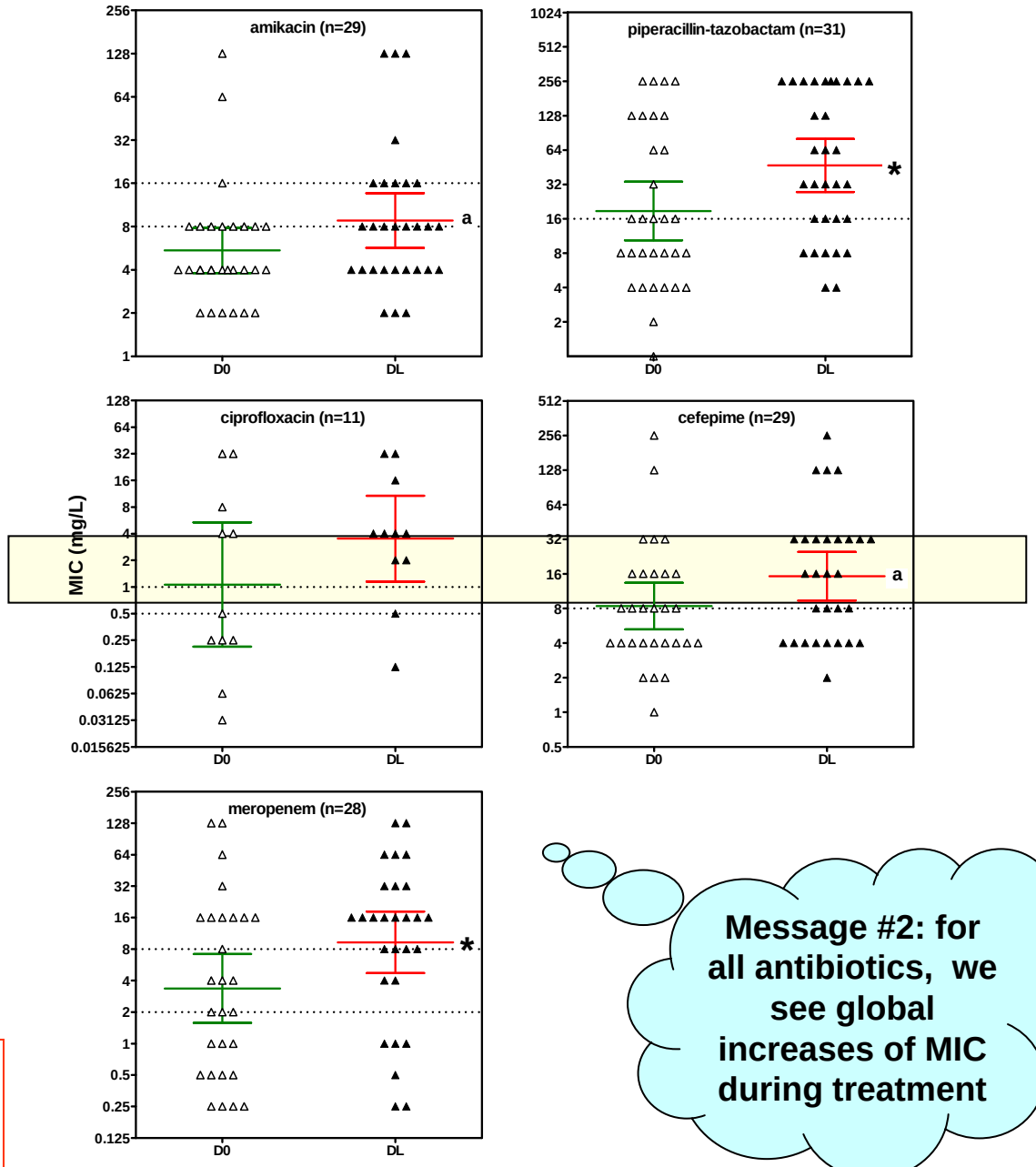
Question #1: are you effective ?

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?

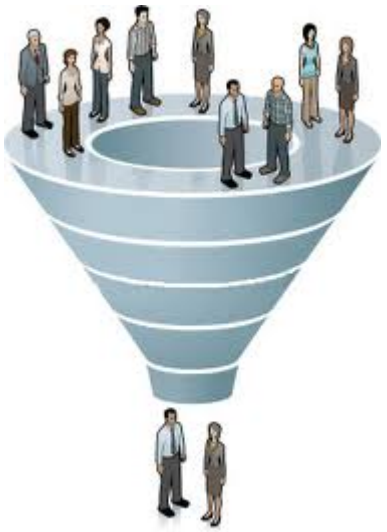
David M. Livermore*

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

So, what are the hurdles for new compounds ?

- **Discovery:**
  - Remains (very) difficult especially for Gram-negative…
- **Clinical development:**
  - Remains costly (especially for new chemical entities) and will probably command (intially) a smaller market
- **Registration of new compounds:**
  - Provisional registration of really innovative compounds (at phase II level) may, in the future, be warranted … if solving unmet medical needs
  - Safety issues will remain of paramount importance but should not deter honest efforts (no drug is harmless !)

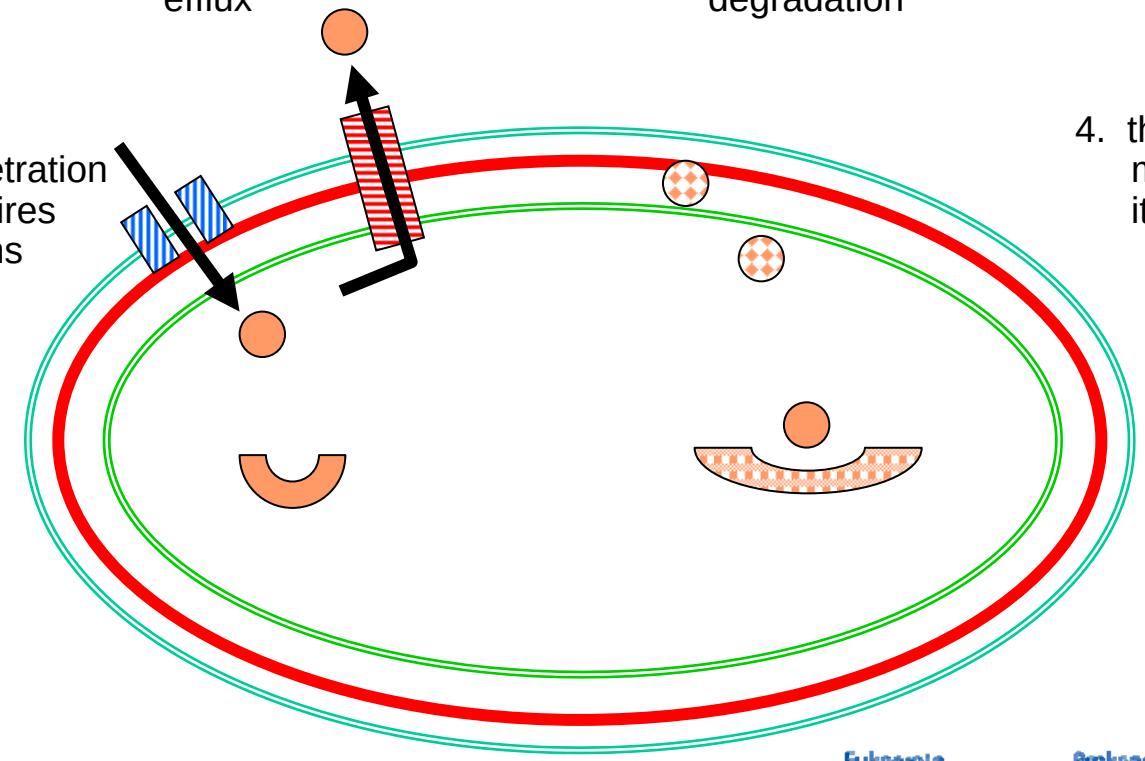
Why are Gram-negative so difficult ?

2. the drug must avoid efflux

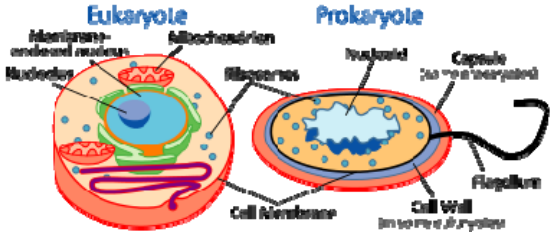
3. the drug must avoid degradation

1. drug penetration requires porins

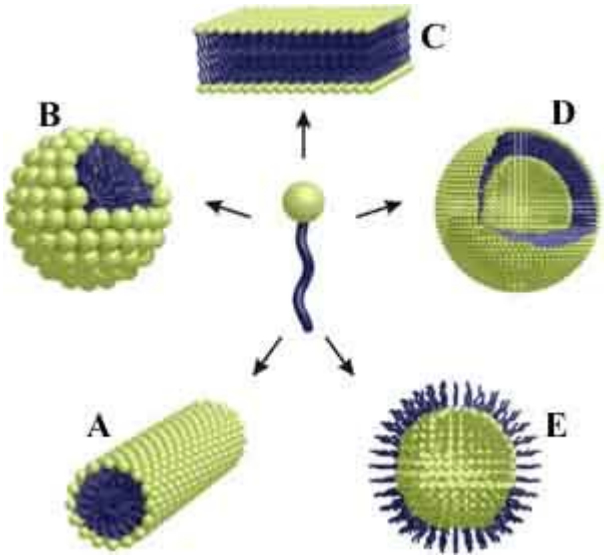
4. the drug must bind to its target



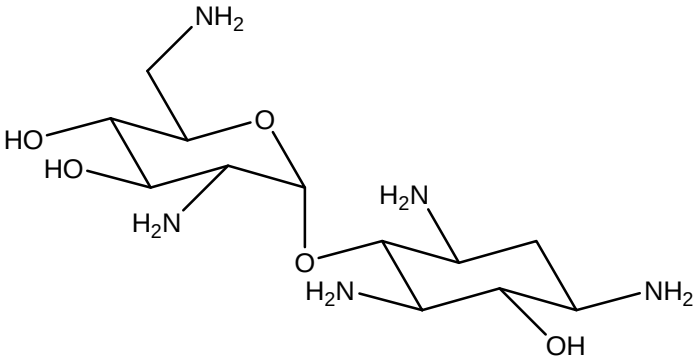
5. the drug must not harm eucaryotic cells



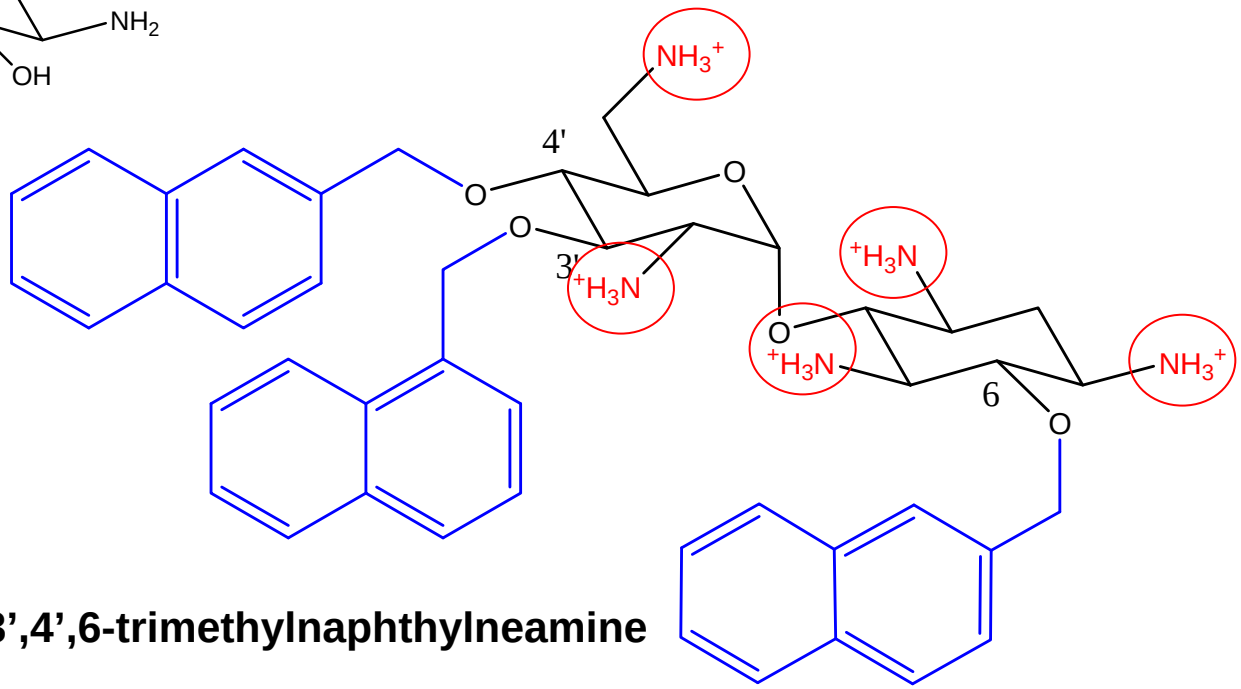
Amphiphilic aminoglycosides: an example of "dead" end ?



Amphiphilic aminoglycosides: derivatives from neamine



neamine



3’,4’,6-trimethylnaphthylneamine

Baussane et al. J. Med. Chem. 2010; 53:119–127

Amphiphilic aminoglycosides
(methylnaphthyl neamine derivatives)

Table 1. Minimum Inhibitory Concentrations against Different *Staphylococcus aureus* Strains for the Neamine Derivatives, Neomycin B, and Neamine

	MIC μg/mL							
aminoglycosides	ATCC 25923	pump NorA	pump MsrA	enzyme APH2″-AAC6′	enzyme APH3′	enzyme ANT4′	ATCC 33592 HA-MRSA	VRSA-VRS-2
neomycin B	2	1	2	1	> 128	32	> 128	128
neamine **1**	32	32	16	16	> 128	> 128	> 128	> 128
3′-mono2NM **2**	> 128	> 128	> 128	> 128	128	> 128	ND	ND
4′-mono2NM **3**	> 128	> 128	> 128	> 128	> 128	> 128	ND	ND
5-mono2NM **4**	> 128	> 128	> 128	> 128	> 128	> 128	ND	ND
6-mono2NM **5**	> 128	> 128	> 128	> 128	> 128	> 128	> 128	ND
3′,4′-di2NM **6**	4	8	8	8	4	8	8	4
3′,6-di2NM **7a**	8	8	8	8	4	8	16	16
4′,5-di2NM **8**	64	128	128	128	32	128	64	64
4′,6-di2NM **9**	32	32	32	32	16	16	64	32
3′,4′,6-tri2NM **10a**	4	4	4	4	2	4	2	4
3′,4′,5,6-tetra2NM **11**	32	64	64	64	32	64	32	64
3′,6-diBn **7b**	> 128	> 128	> 128	> 128	> 128	> 128	ND	ND
3′,6-di2PM **7c**	> 128	> 128	> 128	> 128	> 128	> 128	ND	ND
3′,6-di2QM **7d**	> 128	> 128	> 128	> 128	> 128	> 128	ND	ND
3′,4′,6-triBn **10b**	> 128	> 128	> 128	> 128	> 128	> 128	> 128	64
3′,4′,6-triPM **10c**	> 128	> 128	> 128	> 128	> 128	> 128	ND	ND
3′,4′,6-tri2QM **10d**	128	> 128	> 128	128	64	> 128	64	64

Baussane et al. J. Med. Chem. 2010; 53:119–127

Amphiphilic aminoglycosides
(methylnaphthylderivatives)

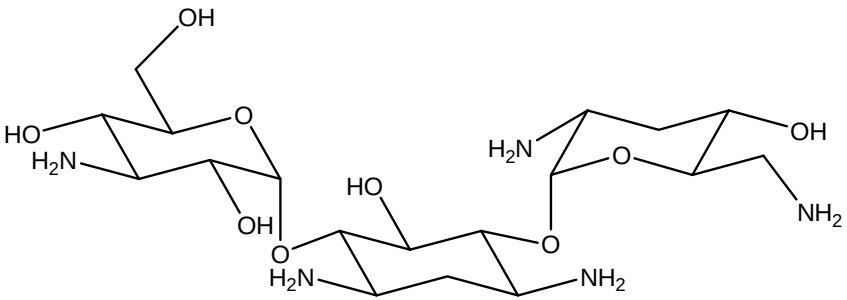
- no significant inhibition of bacterial protein synthesis at 10 x the MIC
- decreased cell thickness decreased by 50% (Atomic Force microscopy) suggestive of intra-bacterial content leakage
- depolarization of bacterial membrane (DiSC$_3$(5) probe)
- binding to LPS (displacement of BODIPY-TRcadaverine)
- permabilization of liposomes mimicking *P. aeruginosa* membranes (POPE:POPG:CL; 60:21:11) (calcein release)

BUT …

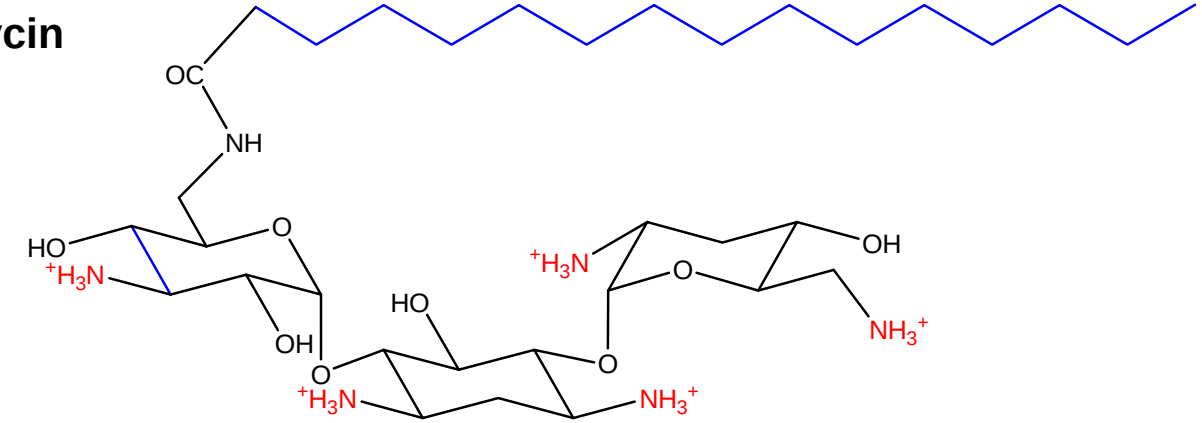
- cytotoxicity to eucaryotic cells at 2 to 10 x the MIC !

Ouberai et al. Biochimica et Biophysica Acta 1808 (2011) 1716–1727
Zimmerman et al. Journal of Medicinal Chemistry (2013) 56:7691-7705

Amphiphilic aminoglycosides
(lipid derivatives of tobramycin)



tobramycin



6'NHCO-$C_{15}H_{31}$-tobramycin

Dhondikubeer et al. Journal of Antibiotics (Tokyo) 2012 Oct;65(10):495-8.

Amphiphilic aminoglycosides
(lipid derivatives of tobramycin)

- MICs are between 4 (*Staphylococci*, *Enterococci*…) and 256 (*Acinetobacter*)
  → preferential anti-Gram + spectrum
- amphiphilicity is critical for antibacterial activity
- the pentacationic tobramycin-based headgroup appears to be optimal
  (vs. kanamycin, e.g.)
- MICs are increased (4 to 8 x) by addition of 4% albumin (binding)

BUT

- concentration-dependent hemolytic activity (37% at 100 mg/L)
  [can be reduced by replacement of the lipid tail by a fluorinated lipid tail ($C_2H_4C_8F_{17}$)
  but is still 27 % at 500 mg/L]

Dhondikubeer et al. Journal of Antibiotics (Tokyo) (2012) 2012 Oct;65(10):495-8.

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…

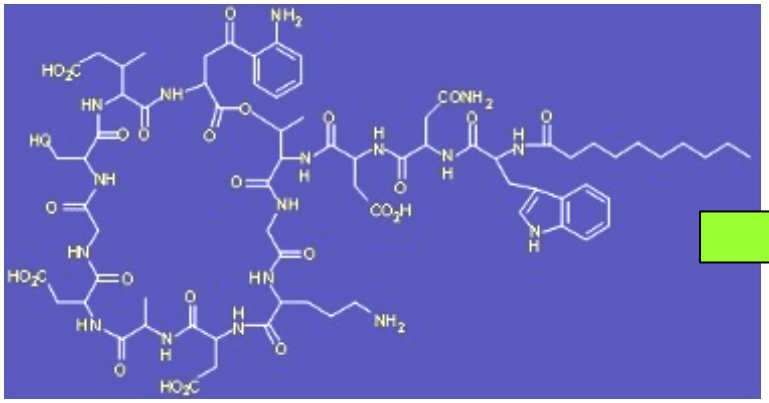
Why using "old" antibiotics ?

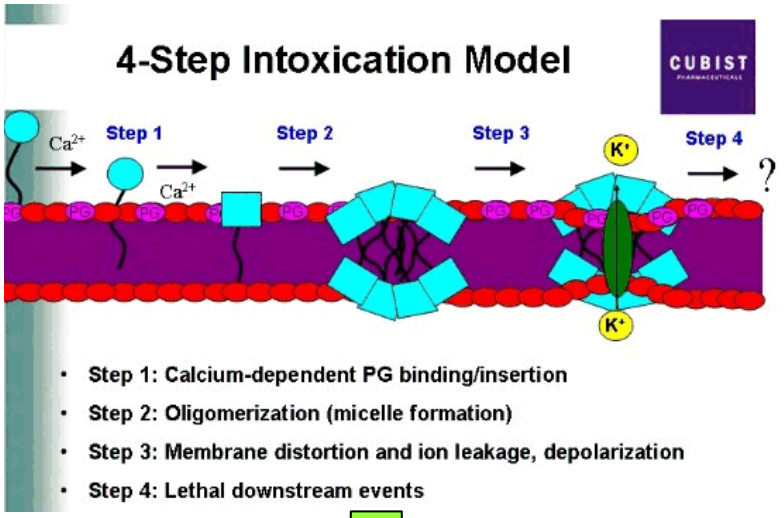
- Clinical development !
  - Preclinical data are well known
  - Phases I and phase II are reasonable fast
  - The major weakness remains is in phase III

- 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

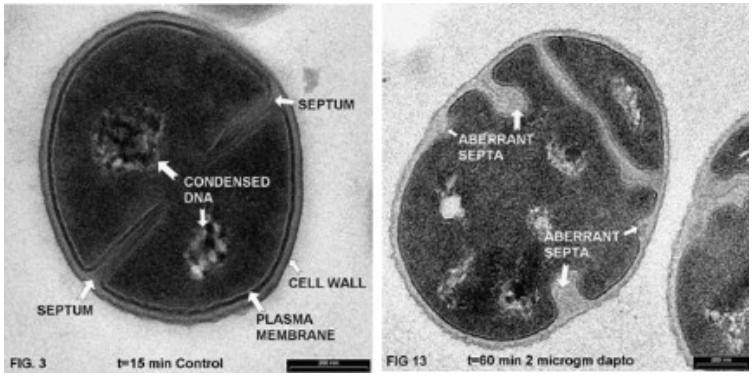
An example of success with daptomycin…

- 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**



Daptomycin: historical landmarks….

1987 1993 1997 2003-2006 2009- …

Discovery of daptomycin as a novel anti-Gram + lipopeptide

In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.
Eliopoulos *et al*, **1986** Antimicrob. Agents Chemother. 30, 532-5

Development halted

- **lack of efficacy**
- **toxicity**

*"Lilly was not satisfied with the overall clinical results observed with the **twice-daily** dosing regimen utilized in these studies"*

Taking over by CUBIST

or "pharmacodynamics in action ….."

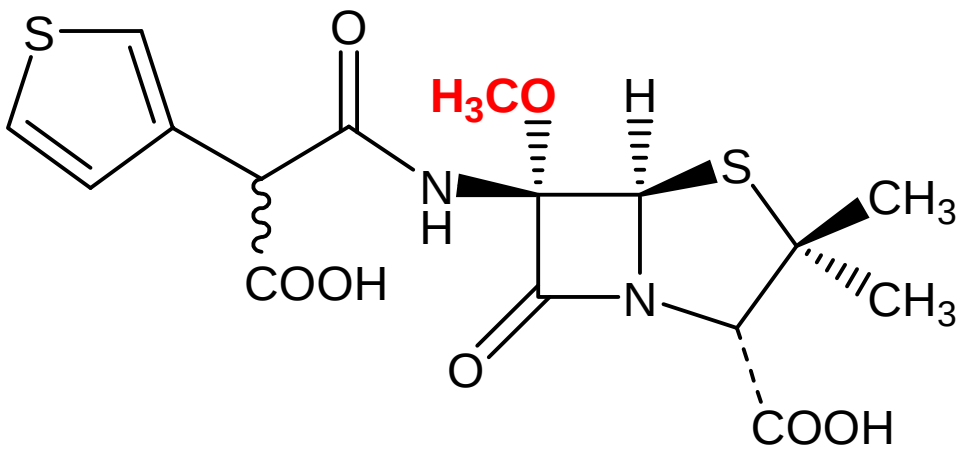
Once-daily dosing in dogs optimizes daptomycin safety.
Oleson *et al*, **2000**, AAC. 44:2948-53.

Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha *et al*, **2003,** AAC 47:1598-603

Approval at 4 mg/kg (skin) and 6 mg/kg (bacteremia, endocarditis) by FDA and EMA

- **large success in the US**
- **problematic commercialization elsewhere**

Temocillin



temocillin

Journal of Antimicrobial Chemotherapy (2009) **63**, 243–245
doi:10.1093/jac/dkn511
Advance Access publication 18 December 2008

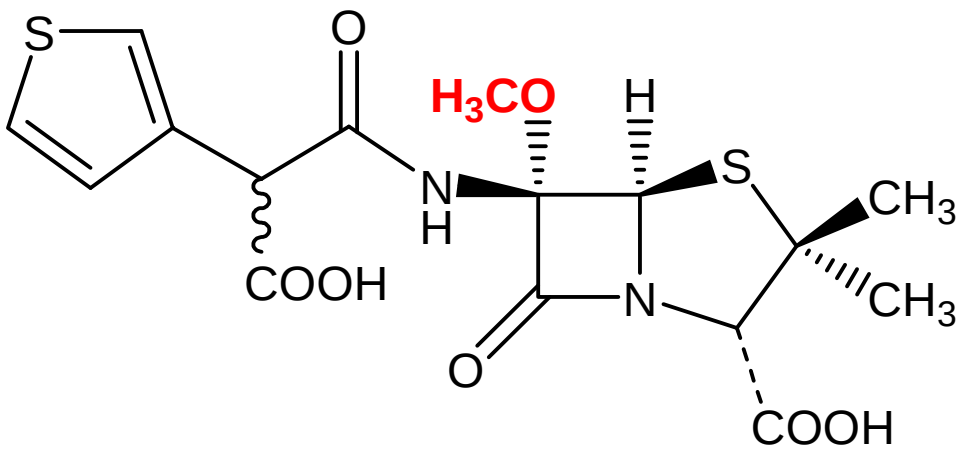
JAC

Temocillin revived

David M. Livermore[1]* and Paul M. Tulkens[2]

[1]Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK; [2]Unité de Pharmacologie Cellulaire et Moléculaire & Centre de Pharmacie Clinique, Université Catholique de Louvain, Bruxelles, Belgium

Temocillin



temocillin

Resistance in Gram-negative pathogens is an increasing concern, with carbapenems often appearing as the only acceptable treatment option in serious infections. Reviving older compounds that have fallen into disuse may help to alleviate this burden. Temocillin (6-α-methoxy-ticarcillin) is resistant to most if not all classical and extended-spectrum β-lactamases and to AmpC enzymes. It is also chemically stable, allowing administration by continuous infusion.

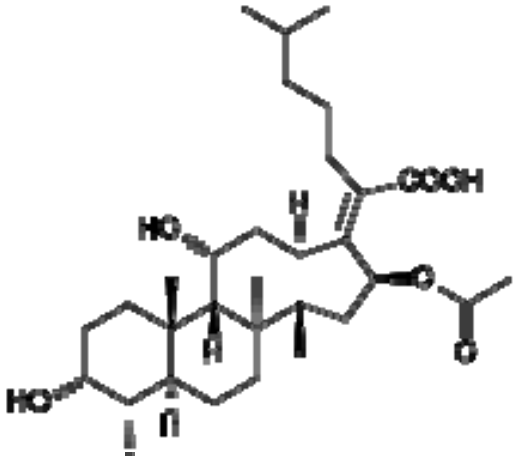
Temocillin's weaknesses, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas*.

Temocillin and efflux

Strain	Origin	Description	MIC (mg/L)			
			temocillin		ticarcillin	
			- PAβN	+ PAβN	- PAβN	+ PAβN
PAO1	ATCC		**1024**	**64**	**32**	**16**
68	**clin**		**512**	**64**	**32**	**16**
168B	**clin**		**256**	**32**	**16**	**16**
PAO1 mexAB	eng.	PAO1 Δ(*mexAB*::FRT)	**4**	**2**	**2**	**1**
PAO 200	eng.	PAO1 Δ(*mexAB-oprM*)	**4**	**0.5**	**2**	**0.5**
PAO 280	eng.	PAO1 Δ(*mexAB-oprM*, *mexXY*::FRT)	**2**	**0.25**	**2**	**1**

Buyck et al. Journal of Antimicrobial Chemotherapy (2012) 67:771-775

Fusidic acid…



Fusidic acid is bacteriostatic but may be bactericidal at high concentrations.
Although fusidic acid has been used in many countries for years, it has never been approved in the US so far. In view of the mounting epidemic of community-acquired MRSA, a clinical development of fusidic acid in the US is presently under way.

Falagas ME, Grammatikos AP, Michalopoulos A. Potential of old-generation antibiotics to address current need for new antibiotics. Expert Rev Anti Infect Ther. 2008; 6(5):593-600

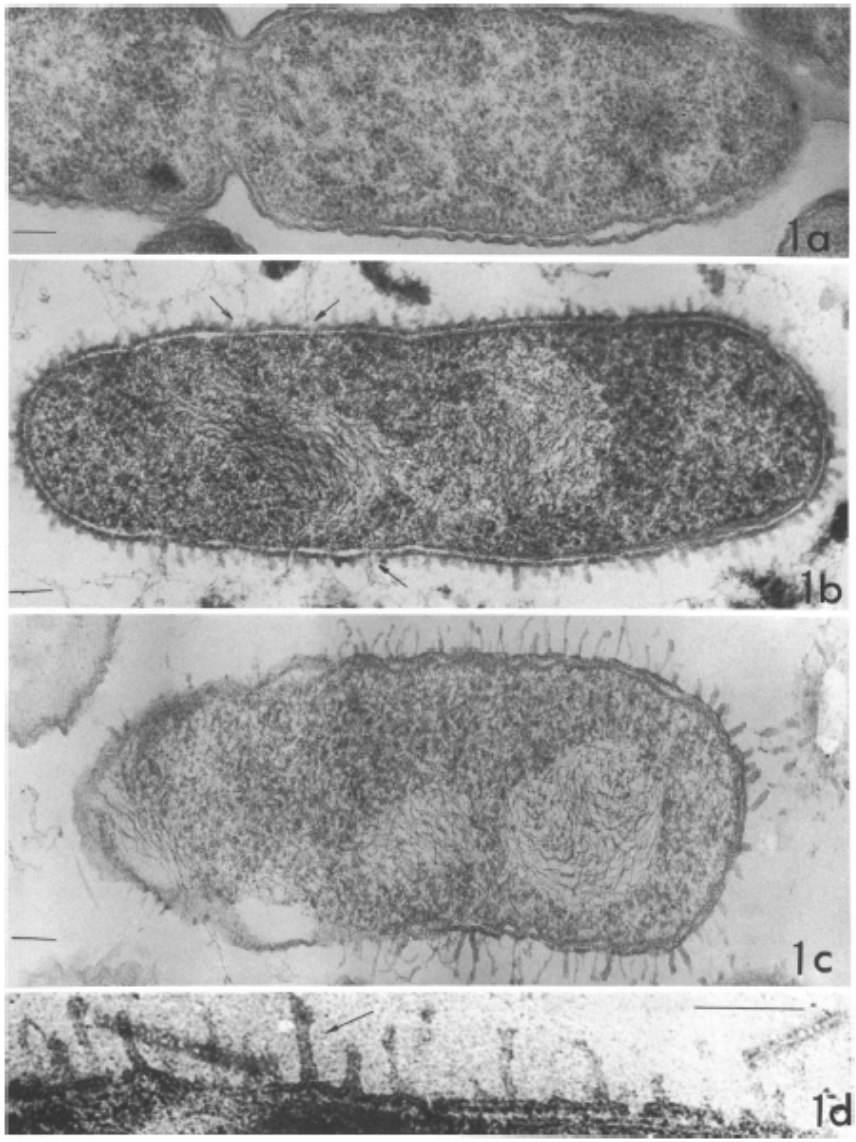
TAKSTA™ (CEM-102)

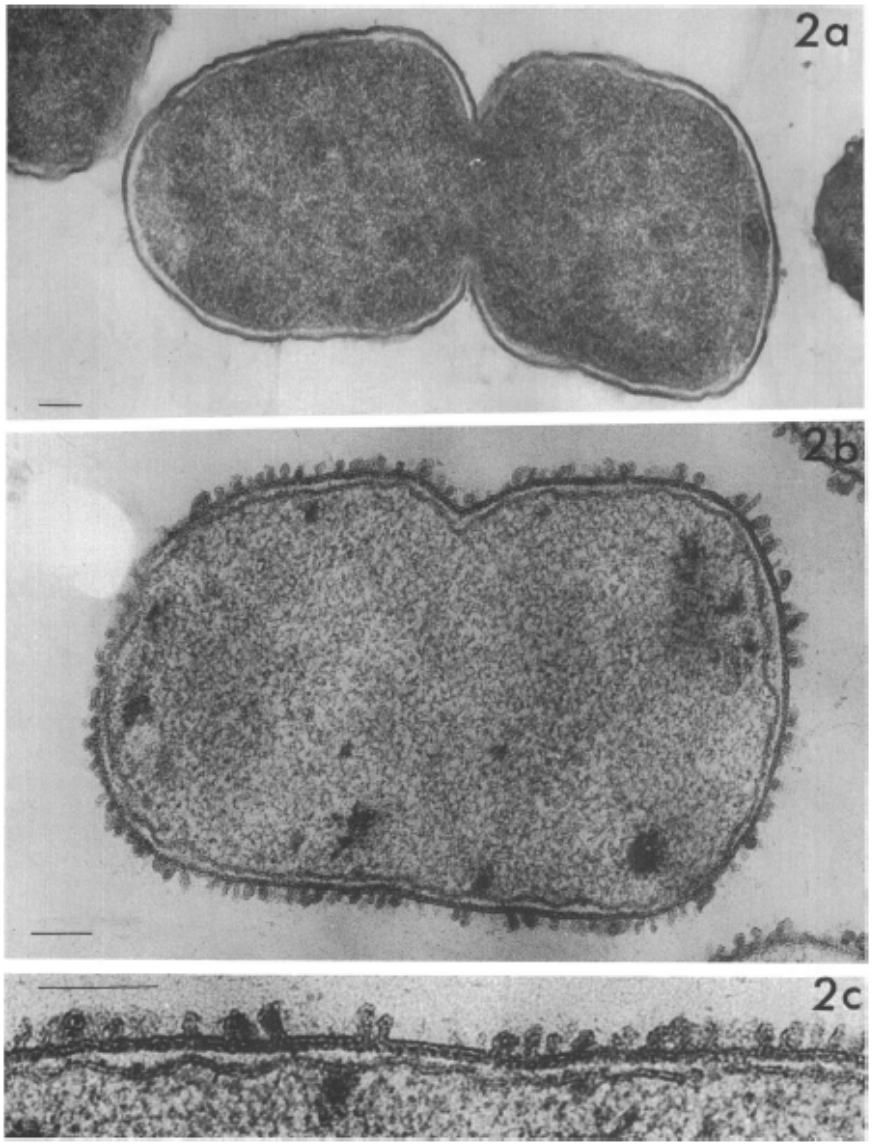
Fusidic acid (TAKSTA™, CEM-102) is an antibiotic with a long history of safety and efficacy outside the United States. Cempra has exclusive rights to the supply of the compound for the U.S. market. Fusidic acid is orally active against gram-positive bacteria, including all *S. aureus* strains such as HA-MRSA and CA-MRSA. A novel dosing regimen has been successfully evaluated in a Phase II trial in patients with acute bacterial skin and skin structure infections (aBSSSI). Cempra is conducting a Phase II trial of TAKSTA for patients with prosthetic joint infections.

Colistin: History

- Isolated in Japan in 1949 from *Bacillus polymyxa* var. *colistinus* and indentified as **polymyxin E**
  (discovered in 1947 among polymyxins A to E).
- Differs from **polymyxin B** by only one aminoacid (D-Phe replaced by D-Leu)
- Exists under at least 2 components (**E1** and **E2**, also called colistin A and colistin B) differ ring by the length of the fatty acid chain
- Supplied as the
  - methylsulfonate derivative (often called methane sulfonate and also known as **colistimethate sodium**), which is a **prodrug**
  - sulfate (**colistine sulfate**)

Colistin Microbiology: morphological aspects





Koike et al. J. Bacteriol. 1969; 97:448-452

A recent prospective clinical study

Effectiveness and safety of colistin: prospective comparative cohort study

Mical Paul[1,2*], Jihad Bishara[1,2], Ariela Levcovich[1,2], Michal Chowers[2,3], Elad Goldberg[1,2], Pierre Singer[2,4], Shaul Lev[2,4], Perla Leon[5], Maria Raskin[1,2], Dafna Yahav[2,6] and Leonard Leibovici[2,6]

[1]Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [3]Unit of Infectious Diseases, Meir Medical Center, Kfar Saba, Israel; [4]Intensive Care Unit, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [5]Department of Anesthesiology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [6]Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

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Received 6 January 2010; returned 14 January 2010; revised 9 February 2010; accepted 12 February 2010

Background: Colistin has re-entered clinical use by necessity. We aimed to assess its effectiveness and safety compared with newer antibiotics.

colistimethate: 6–9 MU (million units) divided in 3 doses/day (if hemodialysis: 1–2 MU twice daily) if Gram (-) carbapenem resistant *vs.* beta-lactams (if susceptible)

Conclusions: The need for colistin treatment is associated with poorer survival. Adjusted analyses suggest that colistin is less effective and more toxic than β-lactam antibiotics.

J Antimicrob Chemother 2010; **65**: 1019–1027
doi:10.1093/jac/dkq069 Advance publication 18 March 2010

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 at phase II for really innovative compounds or compounds that solve unlet medical needs 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 ?

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, eve
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2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

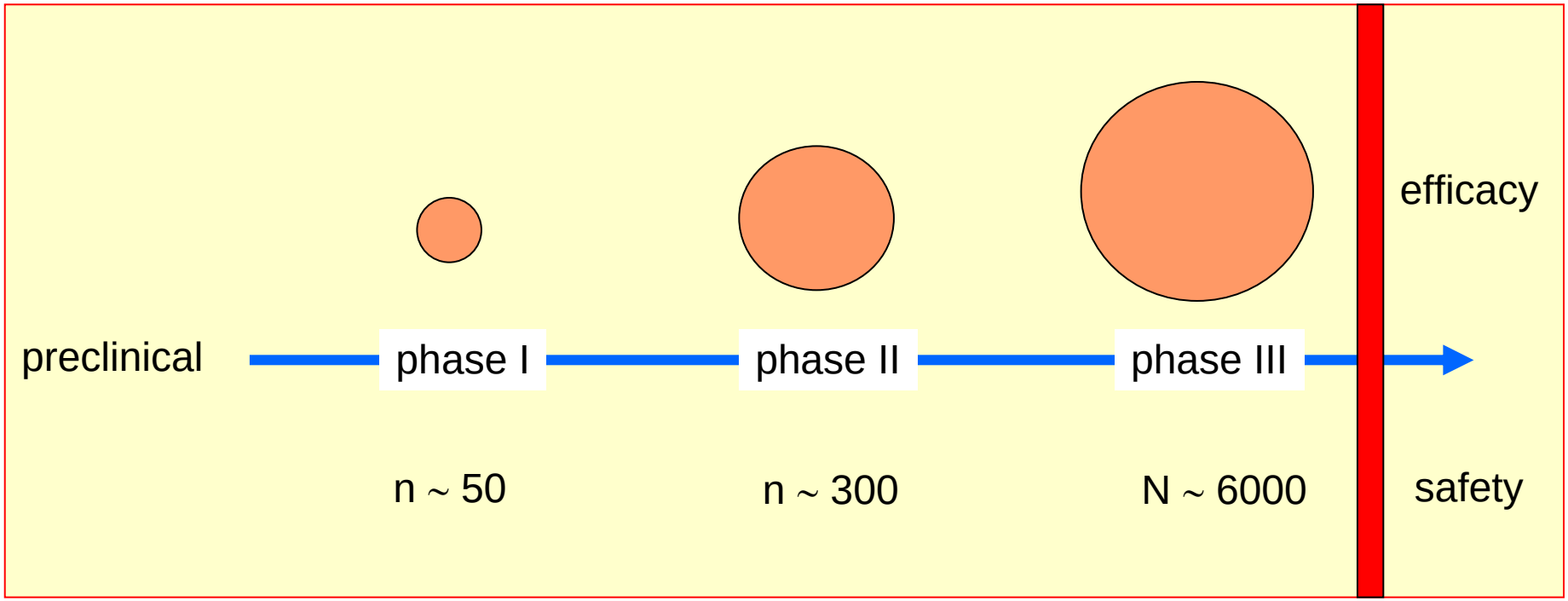
6 October 2011
EMA/MB/550544/2011 Endorsed

Exploring options for new and effective antibiotic treatments

Reviewing existing options to promote development of new antibiotics to treat multi-resistant bacteria including adaptation of clinical guidance documents, consideration of the balance between the amount of prior data needed with enhancing post-marketing surveillance, use of orphan legislation, etc.

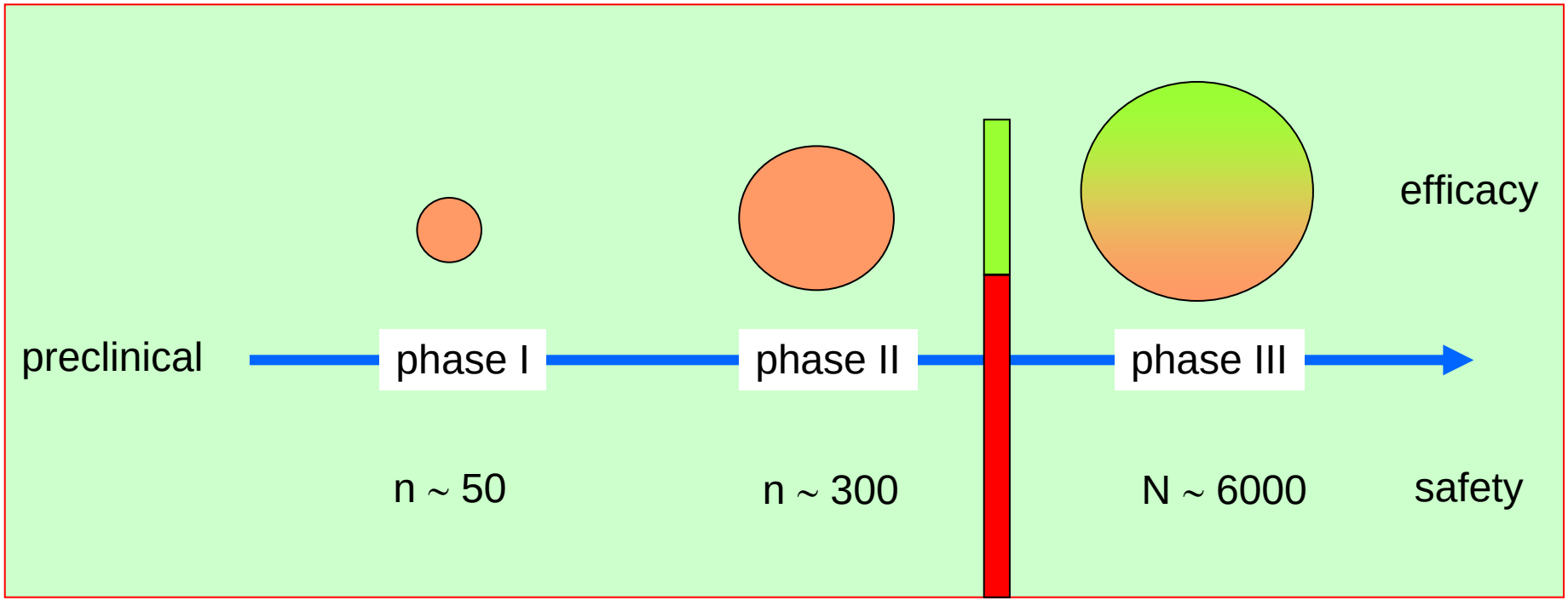
What about safety ?

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



How to combine this with safety ?

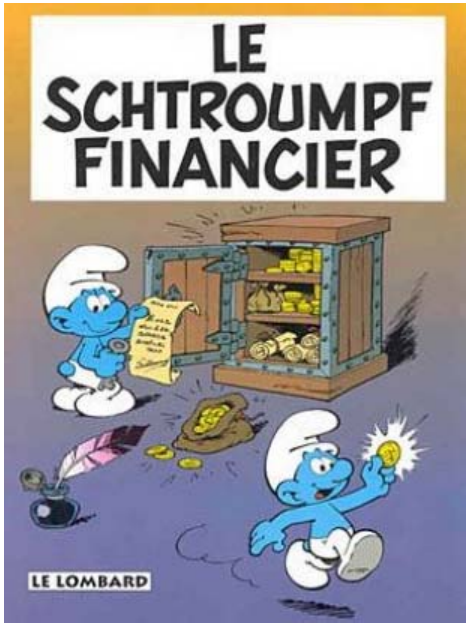
- Registration: proposed new scheme
  - Provisional registration at phase II level (solving the unmet medical need with compounds we know about …)
  - Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration



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 ?**

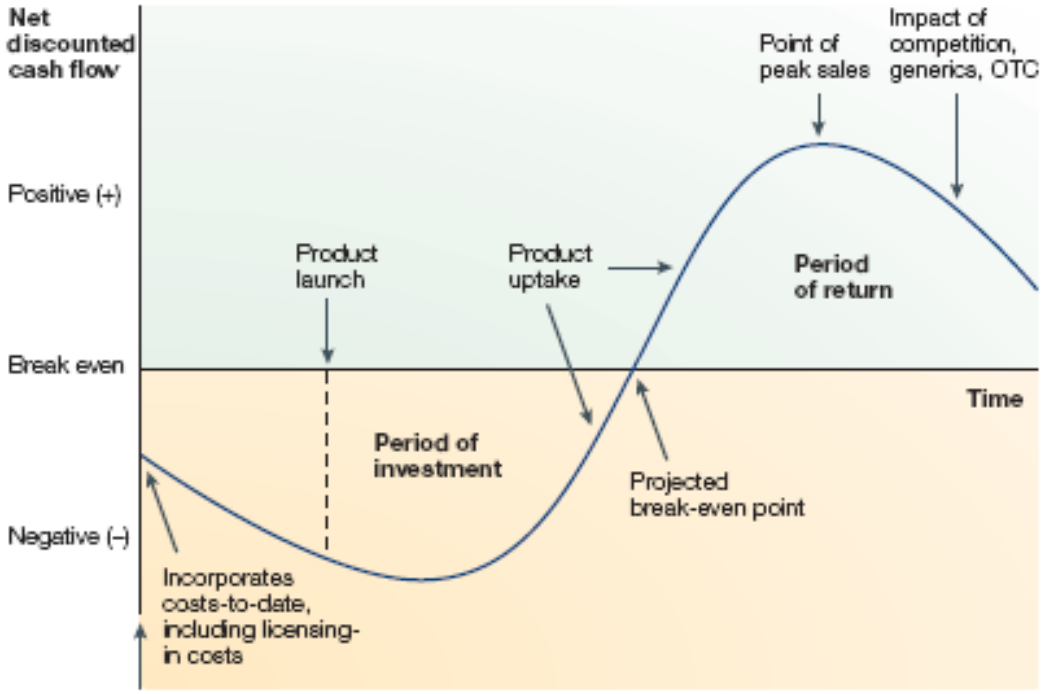
This is a main part of the problem (in our current situation)



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

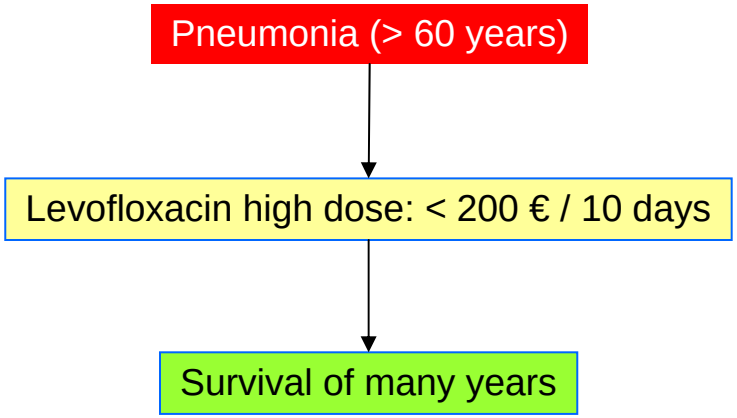
This is what every economist will tell you
(and you know it !)

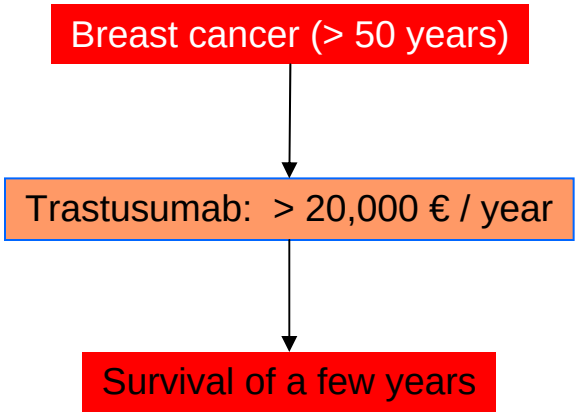


Let us take a simple comparison …

- 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…





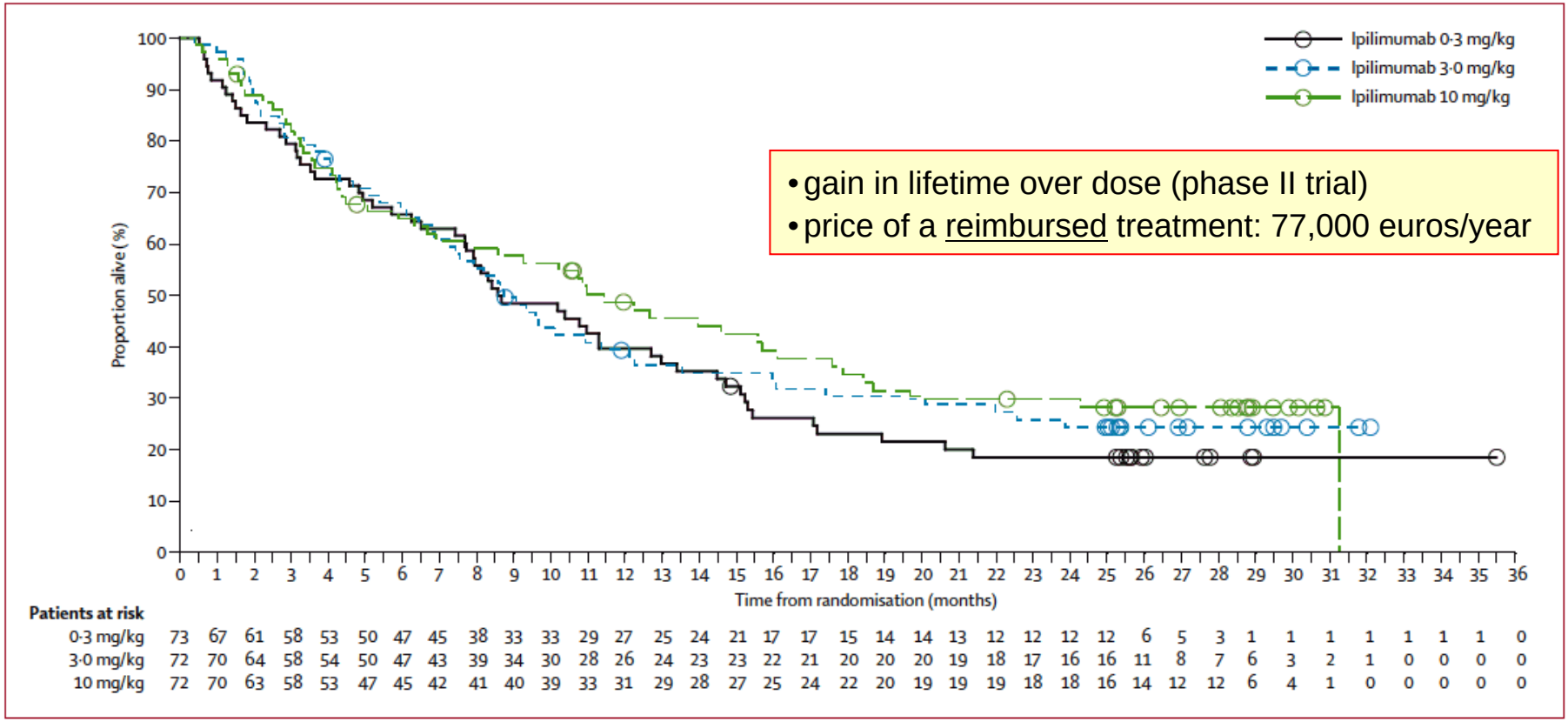
This may be saving lives … but at which price ?

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.

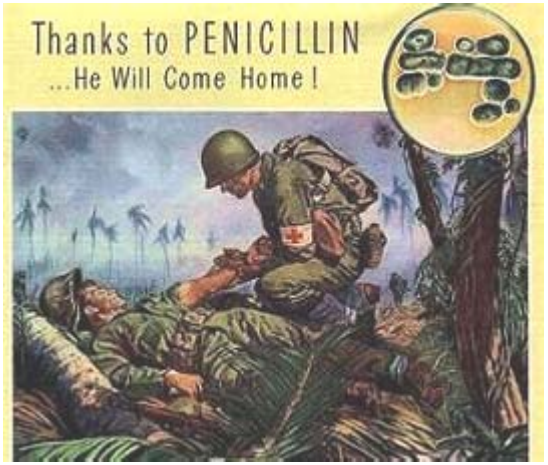
Ludwig Center for Cancer Immunotherapy, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. wolchokj@mskcc.org



- 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.

Old antibiotics may help …

REVIEWS OF ANTI-INFECTIVE AGENTS MAJOR ARTICLE

Louis D. Saravolatz, Section Editor

Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

Céline Pulcini,[1] Karen Bush,[2] William A. Craig,[3] Niels Frimodt-Møller,[4] M. Lindsay Grayson,[5] Johan W. Mouton,[6] John Turnidge,[7] Stephan Harbarth,[8] Inge C. Gyssens,[9,10] and the ESCMID Study Group for Antibiotic Policies

[1]Centre Hospitalier Universitaire de Nice, Service d'Infectiologie and Université de Nice Sophia-Antipolis, Faculté de Médecine, France; [2]Biology Department, Indiana University, Bloomington; [3]University of Wisconsin, School of Medicine and Public Health, Madison; [4]Department of Clinical Microbiology, Hvidovre Hospital, Copenhagen, Denmark; [5]Infectious Diseases Department, Austin Health and Department of Medicine, University of Melbourne, Victoria, Australia; [6]Department of Medical Microbiology, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; [7]SA Pathology, The University of Adelaide, SA, Australia; [8]Geneva University Hospitals and Medical School, Switzerland; [9]Department of Medicine, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; and [10]Hasselt University, Diepenbeek, Belgium

In view of the alarming spread of antimicrobial resistance in the absence of new antibiotics, this study aimed at assessing the availability of potentially useful older antibiotics. A survey was performed in 38 countries among experts including hospital pharmacists, microbiologists, and infectious disease specialists in Europe, the United States, Canada, and Australia. An international expert panel selected systemic antibacterial drugs for their potential to treat infections caused by resistant bacteria or their unique value for specific criteria. Twenty-two of the 33 selected antibiotics were available in fewer than 20 of 38 countries. Economic motives were the major cause for discontinuation of marketing of these antibiotics. Fourteen of 33 antibiotics are potentially active against either resistant Gram-positive or Gram-negative bacteria. Urgent measures are then needed to ensure better availability of these antibiotics on a global scale.

But you may learn how to use them properly

Drug Resistance Updates 14 (2011) 107–117

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Conserving antibiotics for the future: New ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective

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[j] *SA Pathology at the Women's and Children's Hospital, North Adelaide, SA, Australia*

Why not ?