Finding and Developing New Antibiotics

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Affordable Quality Health Care for All:
A Belgian Experience
Ho Chi Minh City, Vietnam
March 15, 2011

The Catholic University of Louvain in brief (1 of 2)

- It was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's

Erasmus

Vesalius

The Catholic University of Louvain in brief (2 of 2)

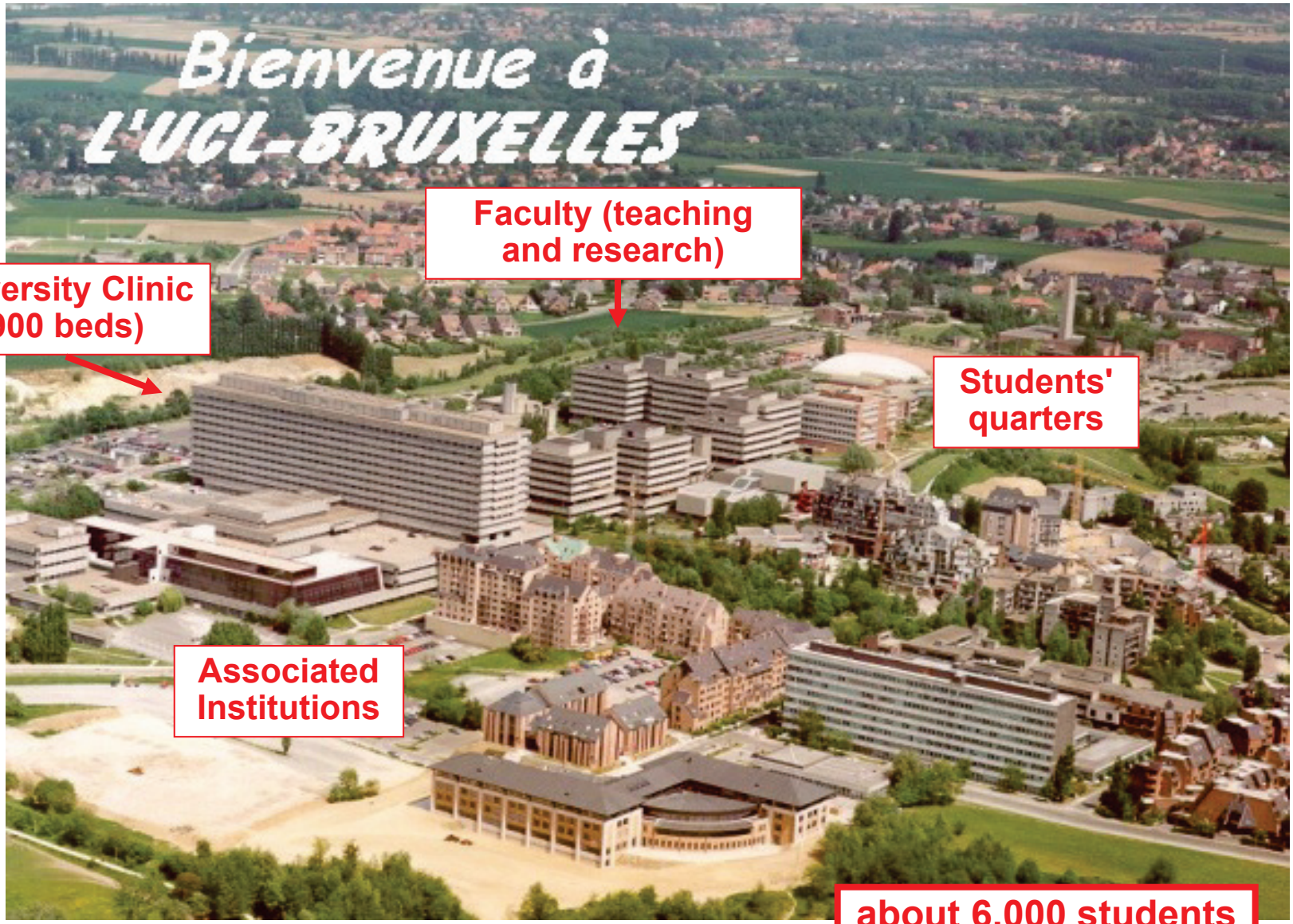
- The Flemish-speaking ***Katholieke Universiteit Leuven*** has remained in Louvain (Leuven) and is named in English "**Catholic Universiteit Leuven**".
- The French-speaking ***Université catholique de Louvain*** has moved about 25 km South in a place called "Louvain-la-Neuve, but the "Health Sciences Sector" is located in Brussels (Woluwé)

Université catholique de Louvain
http://www.uclouvain.be

Katholieke Universiteit Leuven
http://www.kuleuven.be

- Together, the two Universities have about 55,000 students

Our campus in Brussels (Health Sciences)…



The antibiotic crisis *

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

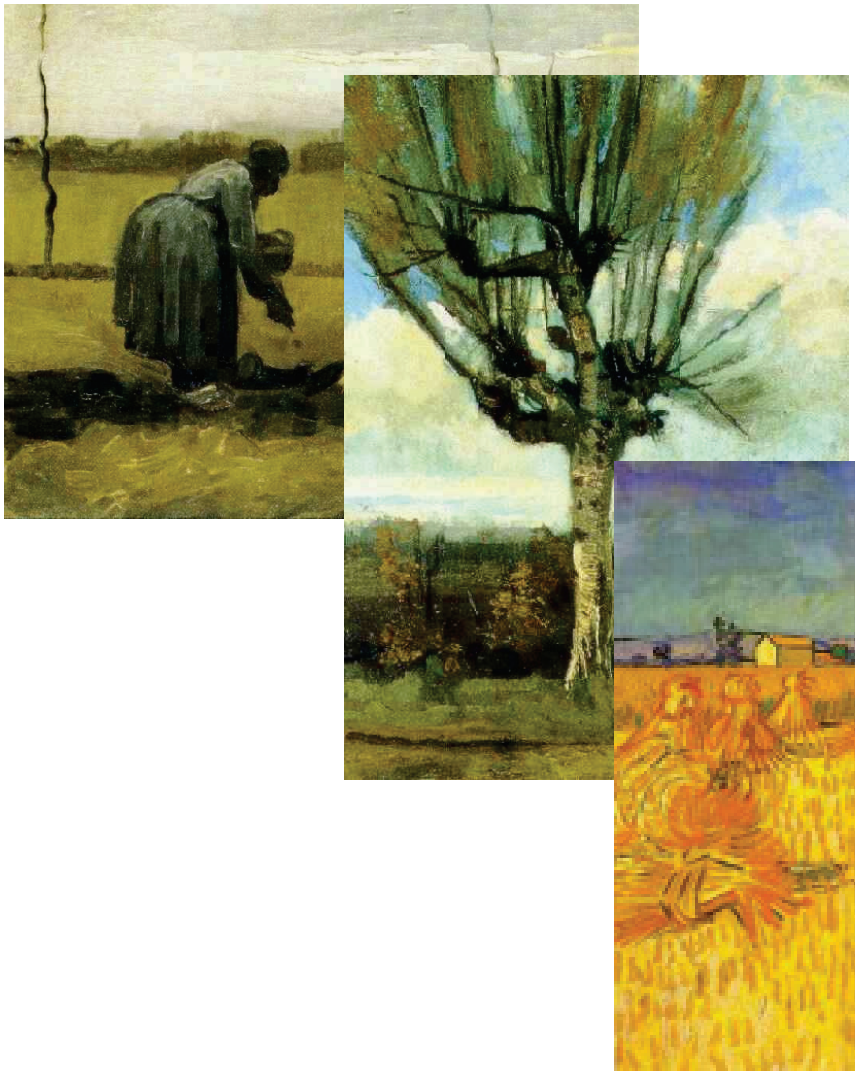
Are antibiotics following a path to madness ?

discovery in soil bacteria and fungi

Are antibiotics following a path to madness ?

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

Are antibiotics following a path to madness ?

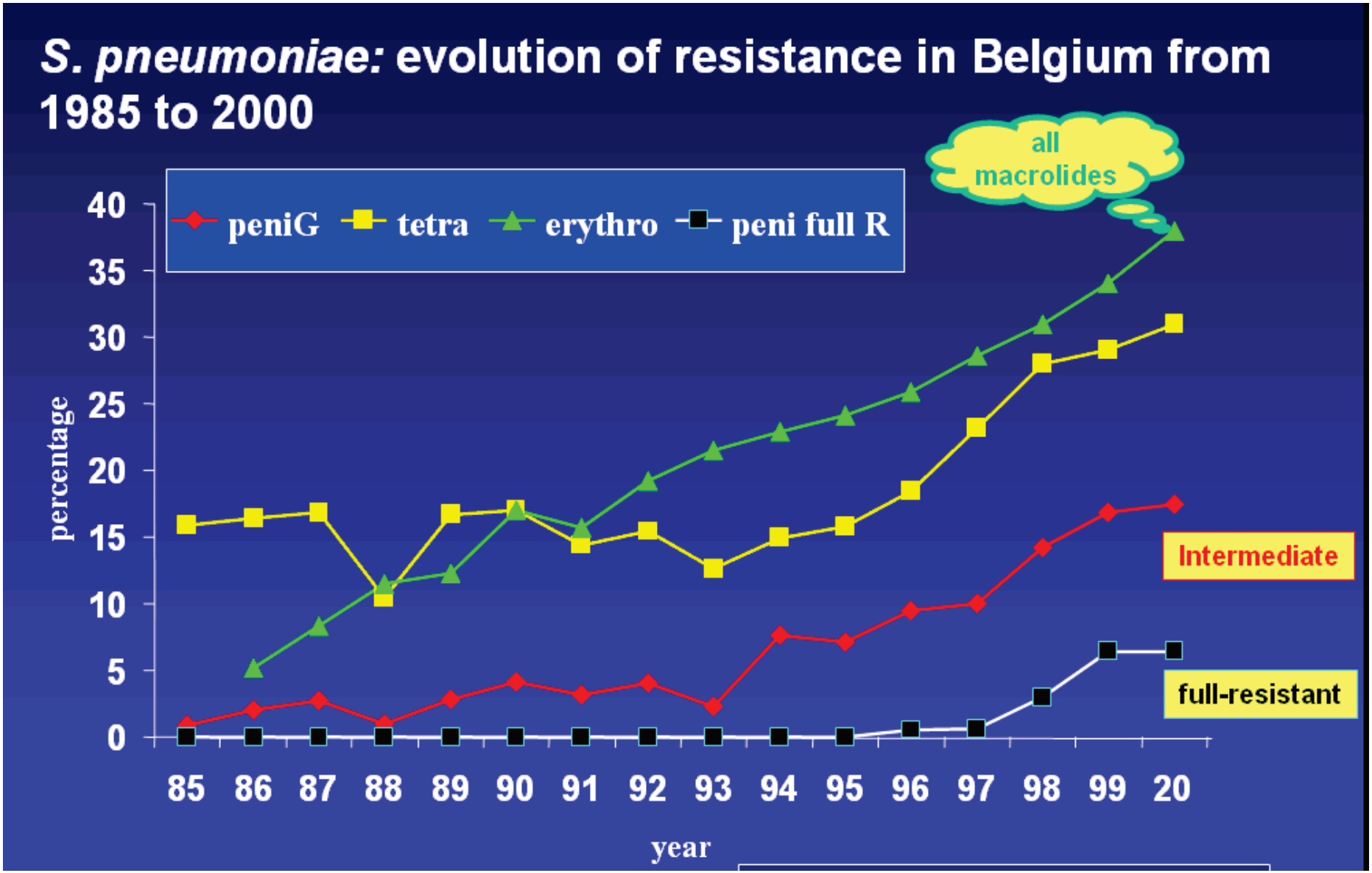


and the General Surgeon told us that the fight was over

Are antibiotics following a path to madness ?

But…

Example #1: longitudinal studies with S. *pneumoniae*



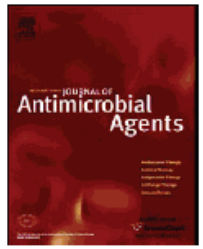
Example #2 : the hidden risk of therapy

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]

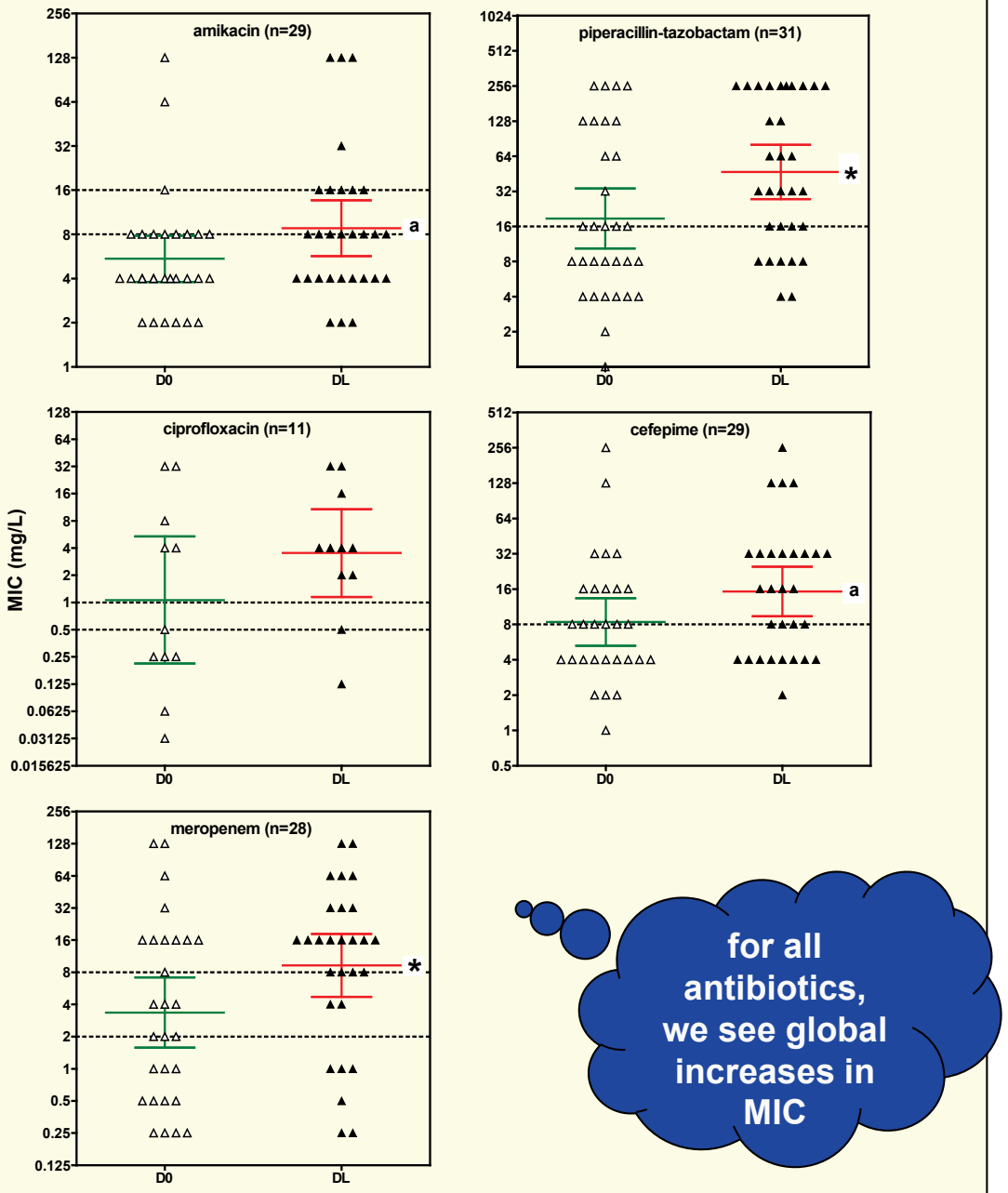
What happens during treatment ?

- 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)



Example #3 : the end of the story (*)

Diagn Microbiol Infect Dis. 2012 Mar;72(3):267-71. Epub 2012 Jan 2.

Repeated isolation of Pseudomonas aeruginosa isolates resistant to both polymyxins and carbapenems from 1 patient.

Lee JY, Lim MH, Heo ST, Ko KS.

Department of Molecular Cell Biology, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon, South Korea.

Abstract

Emergence of polymyxin resistance in carbapenem-resistant isolates is a great concern in clinical settings because it may mean the end of treatment options against Gram-negative bacterial infections. Polymyxin-nonsusceptible and -susceptible Pseudomonas aeruginosa isolates resistant to carbapenems and harboring bla(IMP-6) were alternatively isolated from a patient. In vitro antimicrobial susceptibility testing, multilocus sequence typing, and pulsed-field gel electrophoresis were performed. Metallo-β-lactamase genes such as bla(IMP), bla(VIM), bla(SPM), bla(GIM), and bla(SIM) and bla(OXA-50) were detected by polymerase chain reaction. Sequences of 2-component systems, PmrAB and PhoPQ, were also determined. All showed ST235 and the same pulsotype. Amino acid substitutions were identified in PmrB and PhoP from polymyxin-nonsusceptible isolates. **Colistin** exposure might be associated with the recovery of polymyxin-nonsusceptible isolates in this patient.

*** both in time and geographic contexts…**

Actually, triggering resistance is easy…

Exposure of *E. aerogenes* to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC détermination

Before …

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 8 April 2011

A simple experiment …

Exposure of *E. aerogenes* to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC détermination

After …

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Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 6 April 2011

Too low concentrations create resistance !

And perhaps the biggest difficulty…

Table 6: Mean European drug acquisition costs for treatments most frequently cited in the guidelines for non-hospitalized CAP [1]

Treatment	DDD (g) [a]	DDD acquisition cost (€)		Recommended daily dose (RDD) in g [d]		RDD acquisition cost (€) [e]		Treatment duration (days) [b]		Treatment acquisition cost (€)	
		min. [b]	max. [c]	min.	max.	min.	max.	min.	max.	min. [f]	max. [g]
1st line given alone											
amoxicillin	1	0.75	1.14	1.5	3	1.13	3.42	7	14	7.88	47.88
doxycycline	0.1	0.29	1.02	0.2/(0.1)*	0.3	0.58	3.05	5	10	2.89	30.45
erythromycin	1	1.33	1.33	1	4	1.33	5.32	7	7	9.31	37.24
clarithromycin	0.5	1.05	2.85	1	1	2.09	5.69	7	10	14.63	56.90
roxithromycin	3	1.94	3.16	0.3	0.6	1.94	6.32	7	10	13.59	63.18
azithromycin	3	1.96	3.36	0.5	1.5	3.26	5.60	3	3	9.78	16.80
clindamycin	1.2	5.12	6.00	0.9	0.9	3.84	4.50	7	7	26.90	31.50
2nd line or combinations											
co-amoxiclav	1	1.08	1.43	1.875	1.89	2.50	1.43	5	7	9.45	17.52
amoxicillin +azithromycin	1/0.3	2.71	4.50	3/0.5	3/0.5	5.51	9.02	10 / 3	10 / 5	32.28	62.20
amoxicillin +clarithromycin	1/0.5	1.80	3.99	3/1	3/1	4.34	9.11	10	10	43.40	91.10
telithromycin	0.8	3.30	3.65	0.8	0.8	3.30	3.65	7	10	23.07	36.48
levofloxacin	0.5	4.41	6.38	0.5	1	4.41	12.75	7	10	30.87	127.50
moxifloxacin	0.4	4.40	5.50	0.4	0.4	4.40	5.50	7	10	30.77	54.96

Carbonnelle et al. submitted

And perhaps the biggest difficulty…

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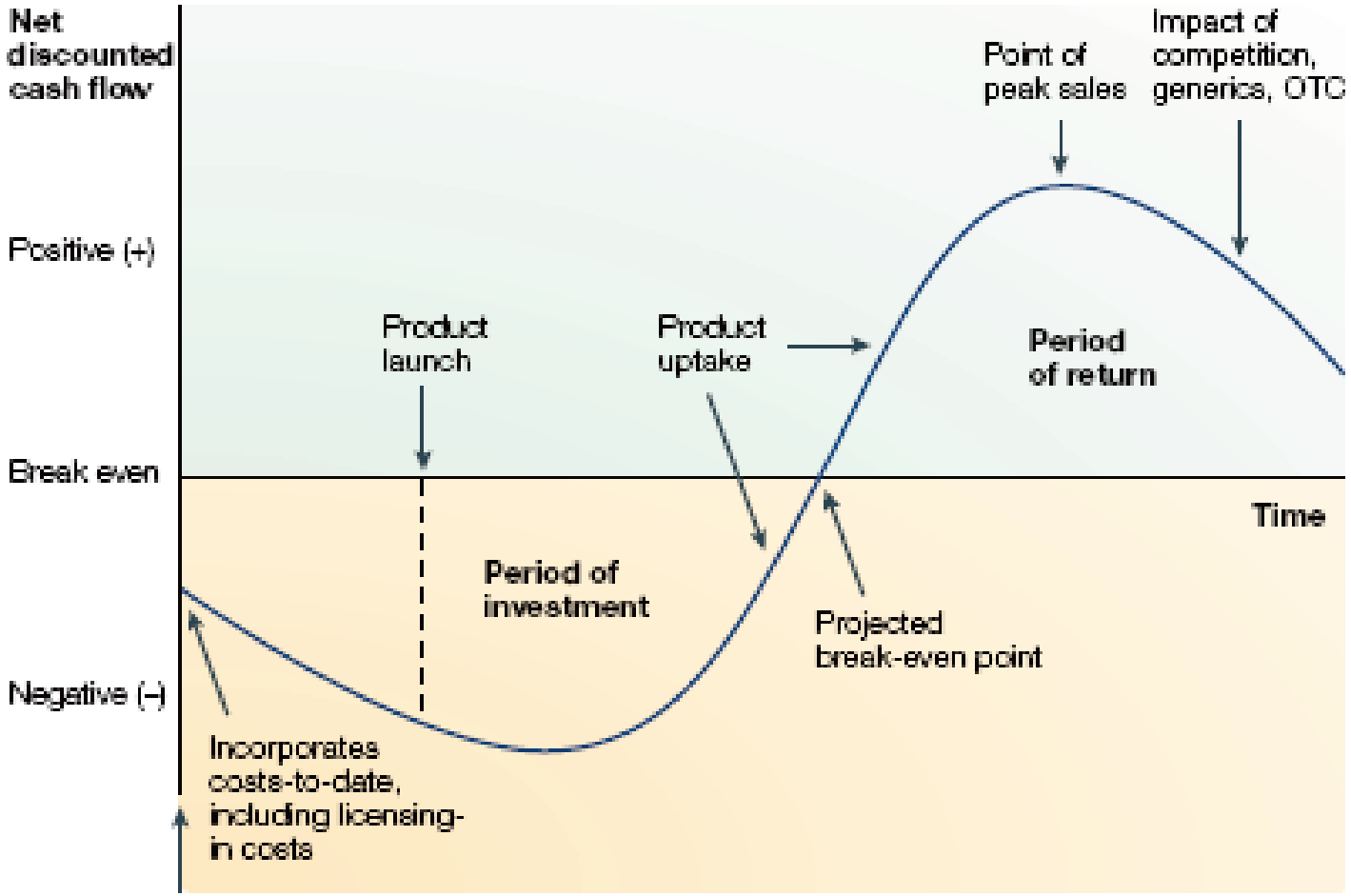
1st line given alone											
amoxicillin	1	0.75	1.14	1.5	3	1.13	3.42	7	14	7.88	47.88
doxycycline	0.1	0.29	1.02	0.2/(0.1)*	0.3	0.58	3.05	5	10	2.89	30.45
erythromycin	1	1.33	1.33	1	4	1.33	5.32	7	7	9.31	37.24
cla											
rox											
azi											
clin											
2nd li comb											
co-											
am +az											
am +cl											
telithromycin	0.8	3.30	3.65	0.8	0.8	3.30	3.65	7	10	23.07	36.48
levofloxacin	0.5	4.41	6.38	0.5	1	4.41	12.75	7	10	30.87	127.50
moxifloxacin	0.4	4.40	5.50	0.4	0.4	4.40	5.50	7	10	30.77	54.96

"Best treatment" acquisition costs

- **for CAP: < 200 euros … and long survival**
- **one year HIV treatment (in EU): 10,000 euros**
- **one year survival from cancer: up to > 20,000 euros**
- **one year of treatment of Fabry disease: 150,000 euros**

Carbonnelle et al. submitted

Can we make this graph different ?



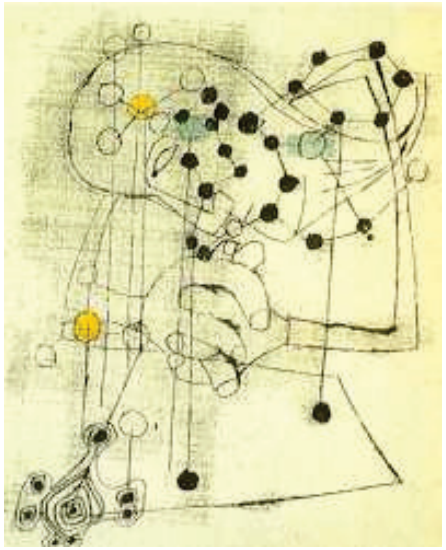
Main points of collaboration with Vietnam

cellular pharmacokinetics

cellular pharmacodynamics

antibiotic toxicity

resistance



novel bacterial targets

clinical applications

antibiotics: from molecules to man

In this context, we had 2 very active Vietnamese post-doctoral fellow … and there has been a follow-up

- supported by "Research in Brussels" of the "Région Bruxelloise"
- the Fonds de la Recherche Scientifique (F.R.S.-FNRS)
- the "Région Wallonne" (First-Post-doc)

And we now have established collaborations with the University of Pharmacy in Hanoi, and the main Hanoi Hospitals, and projects with the International University in Ho Chi Minh

Inspiration by a recently published paper

nature REVIEWS MICROBIOLOGY

ESSAY

Tackling antibiotic resistance

Karen Bush, Patrice Courvalin, Gautam Dantas, Julian Davies, Barry Eisenstein, Pentti Huovinen, George A. Jacoby, Roy Kishony, Barry N. Kreiswirth, Elizabeth Kutter, Stephen A. Lerner, Stuart Levy, Kim Lewis, Olga Lomovskaya, Jeffrey H. Miller, Shahriar Mobashery, Laura J. V. Piddock, Steven Projan, Christopher M. Thomas, Alexander Tomasz, Paul M. Tulkens, Timothy R. Walsh, James D. Watson, Jan Witkowski, Wolfgang Witte, Gerry Wright, Pamela Yeh and Helen I. Zgurskaya

Nat Rev Microbiol. 2011 Nov 2;9(12):894-6.

And here is the applied double program …

- **Public Education**
  - bringing to Vietnam part of the Belgian experience in Public Campaigns *
- **Public health, sanitation and quality of life**
  - helping to develop new methods adapted to countries of (still) limited resources *
- **Control of antibiotic use**
  - helping to develop Clinical Microbiology and Clinical Pharmacy as a means to curb antibiotic resistance in hospitals *

- **New antibiotics**
  - triggering new discoveries initiatives from local natural sources **
  - faciltating access to proof-of concept trials
- **Old Antibiotics**
  - reassessing and reintroducing wrongly "disregarded" but potentially useful molecules **

*** ongoing (with the active support of Wallonie-Bruxelles International)**

**** starting collaborations (HUP, Hanoi; IU, Ho Chi Minh) / activities in Belgium**

Wallonia