

Maintaining Antibiotic Efficacy in the Future: The Belgian Experience ...



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Presented during the visit of Prof. J.J. Schentag in Belgium
Brussels, February 3d, 2004

Bacterial resistance has become increasingly disturbing ...



β -lactamases

Bacterial resistance has become increasingly disturbing ...



Methicillin-resistance

Bacterial resistance has become increasingly disturbing ...



**Tetracyclines and Macrolides resistance
Decreased sensitivity of pneumococci**

Bacterial resistance has become increasingly disturbing ...

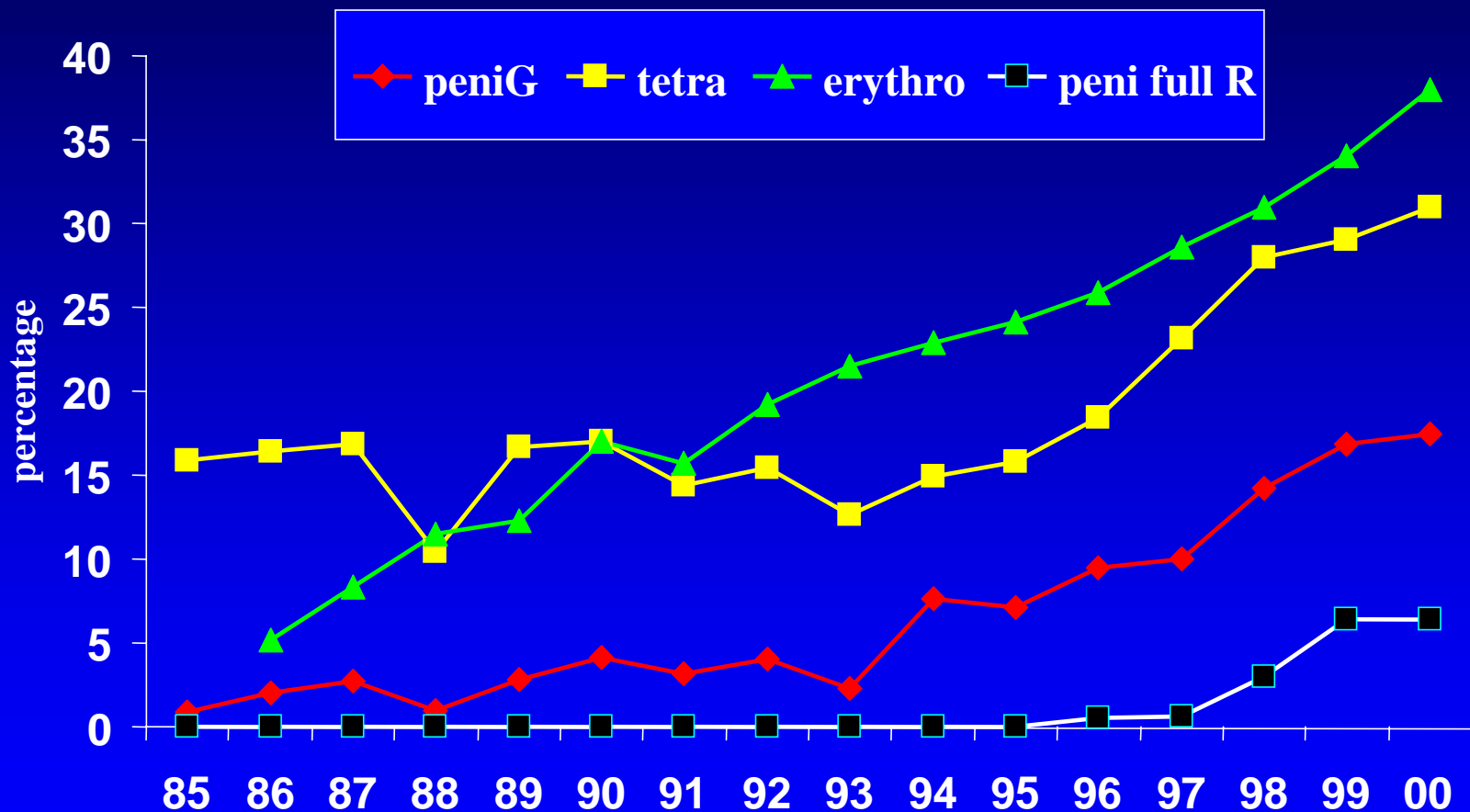
Vancomycin-resistant *S. aureus* ???



Bacterial resistance IS now disturbing in Belgium even in the Primary Care ...

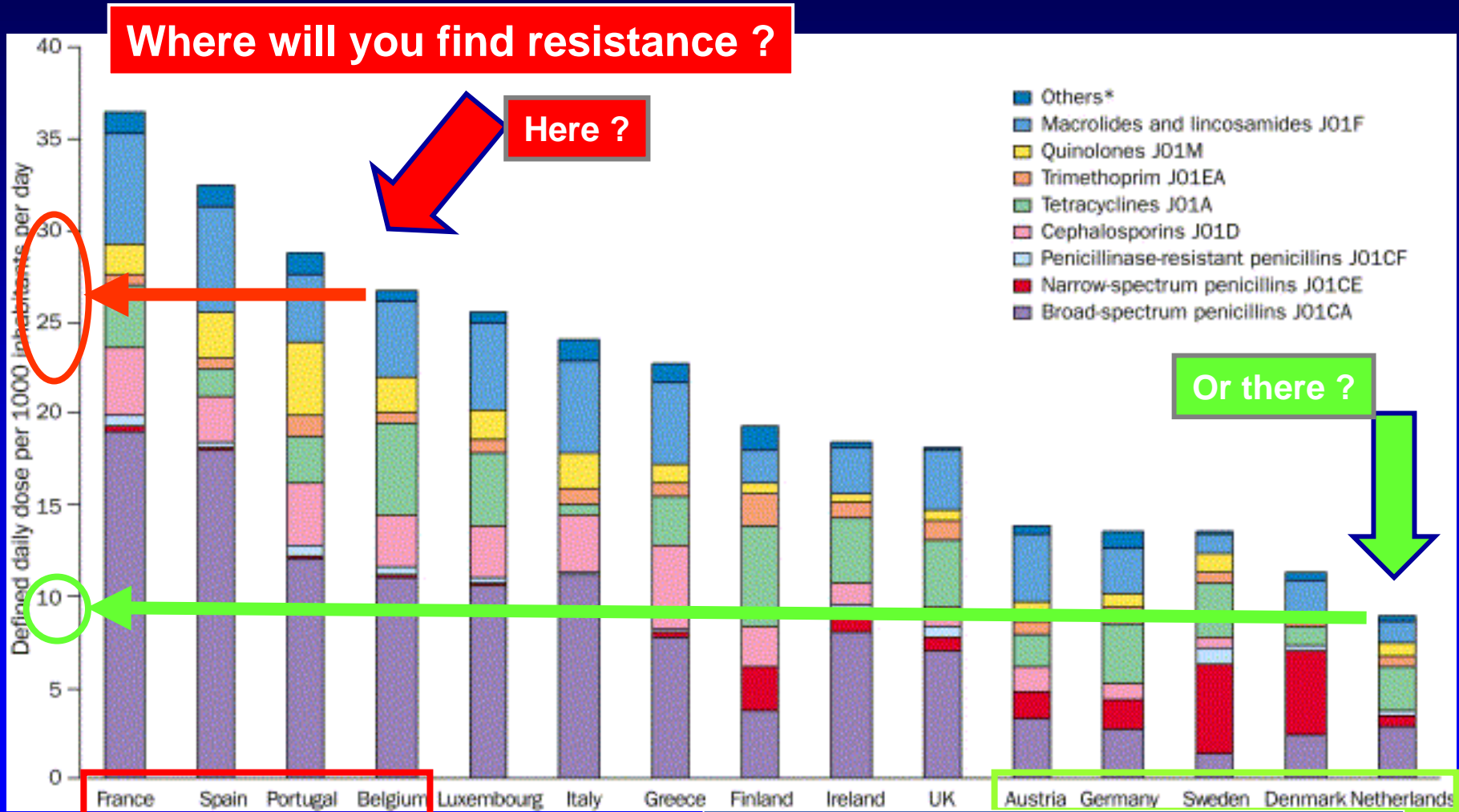


One example: the evolution of *S. pneumoniae* resistance in Belgium between 1985 and 2000



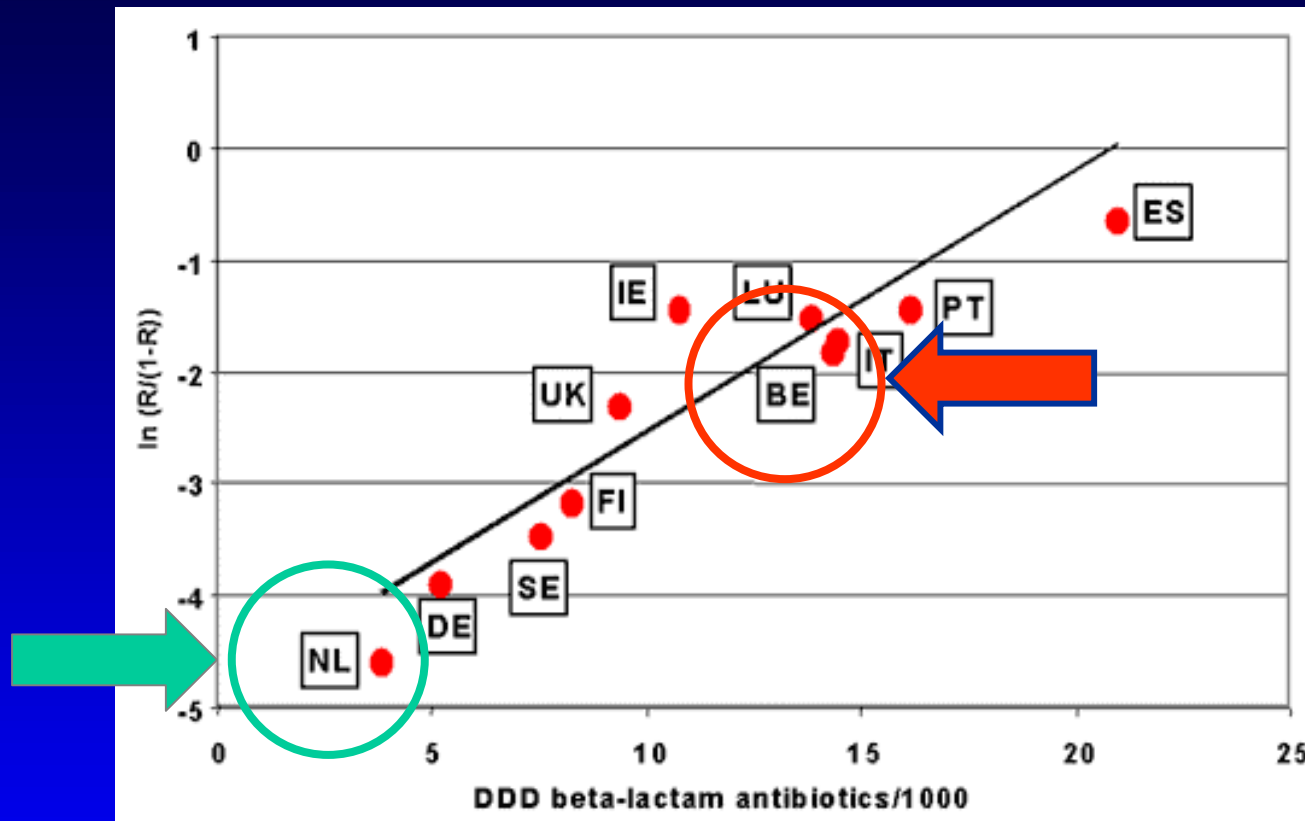
J. Verhaegen, Central Pneumococci Reference Laboratory, Louvain

A link to (over)consumption ?



Cars et al., Variation in antibiotic use in Europe
Lancet. 2001 Jun 9;357(9271):1851-3.

Relationship between use and resistance...



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

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

So, we really asked our-selves:
Are we not going to hit the wall ?



Ph. Geluck, with permission

Well, since we knew that the patient was
sick ...



We decided ...



Please, stand up
and act !!

Setting up an Antibiotic Policy ...

- Historical
- Organization
- Objectives
- Realizations
- The future

Setting up an Antibiotic Policy ...

- **Historical**
- Organization
- Objectives
- Realizations
- The future

- AB use Profiles in hospitals (with feedback)
- Global Reimbursement of Prophylaxis in Surgery
- Institute of Veterinary Expertise

- **October 1998 : « Committee for the Coordination of Antibiotic Policy »**
- **officialized by Royal Decree (M.B./Sb of 26 april 1999; pub. 31 July 1999)**

Setting up an Antibiotic Policy ...

- Historical
- **Organization**
- Objectives
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- **Multidisciplinary**
- **Scientists AND Representatives of Health Institutions**
- **Experts in the following domains**
 - microbiology, pharmacology
 - resistance mechanisms
 - drug policy and consumption evaluation
 - hospital hygiene
 - veterinary medicine
- **Representative of the Ministry of Health and Social Affairs**

Setting up an Antibiotic Policy ...

- Historical
- Organization
- **Objectives (1)**
- Realizations
- The future

- Setting up a scientific platform
- Building an information exchange procedure
- Decrease the selection pressure of antibiotics at the national level
- Decrease, on a equilibrated fashion, the total amount of antibiotics used in the country at all levels

Setting up an Antibiotic Policy ...

- Historical
- Organization
- **Objectives (2)**
- Realizations
- The future

- 1. Collect informations on AB consumption and resistance and publish the corresponding data**
- 2. Inform the public as well as the professionals and and make them both aware of the situation and of the actions taken**
- 3. Make specific recommendations on antibiotic appropriate use for both the professional and the political personnel**

Setting up an Antibiotic Policy ...

- Historical
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1. Veterinary projects
2. Awareness of the public
3. Community-based medicine
4. Hospital-based medicine
5. Data analysis
6. Reimbursement policies

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Why targeting the public ?

- Antibiotic sales in the community represent > 70 % of all systemic antibiotic sales and is, therefore, an important component in the selection pressure
- Most of these AB are prescribed to patients with minor respiratory tract infections that are often self-limiting and self-healing and in which AB real usefulness is doubtful
 - pharyngitis
 - bronchitis
 - flu-like syndrome
 - acute sinusitis
- Doctors believe they **must** prescribe, and pharmacist they must deliver antibiotics because of the demand of the patient



Aims of the campaign

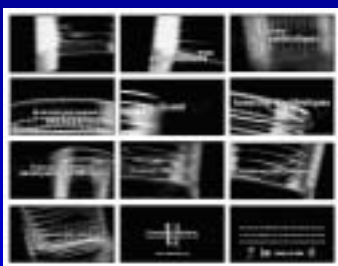
- provide the public with a better understanding of the natural course of an infection
- explain which are the real benefits of antibiotic treatment
- underline the risks associated with the rapid emergence of resistance to antibiotics
- foster discussion of the patient with his/her doctor and his/her pharmacist

The campaigns in a nutshell

Two successive 2-months national **multimedia** educational campaigns were launched in Nov. 2000 and in Nov 2001 to inform the public about the risks associated with the overconsumption and misuse of antibiotics

- **position paper** in a monthly professional official periodical (*Folia Pharmacotherapeutica*)
- **letter** to GPs and pharmacists,
- **booklets** and **leaflets**
- **prime time 30sec TV spots** and **radio broadcasts**,
- **press conferences**
- **WEB sites** (French, Dutch and German)

Budget :
370,000 / year
(1 is approx. 1 US \$)



All materials are still available at <http://www.antibiotiques.org>

The message ...



*Een initiatief van de Federale Overheidsdienst
"Volksgezondheid, Veiligheid Voedselketen en Leefmilieu"*

antibiotica
minder vaak
en
beter
gebruiken

Less often ... and better

Launching the campaign



Letter to the health professionals

Brochures and folders

TV spot



Web sites



Post-campaign evaluations:

Objective assessment of the impact of the campaigns on

- the awareness of the public
(1st campaign only);
- the appreciation of this effort by the GPs
(both campaigns);
- AB prescription at the community level
(both campaigns).

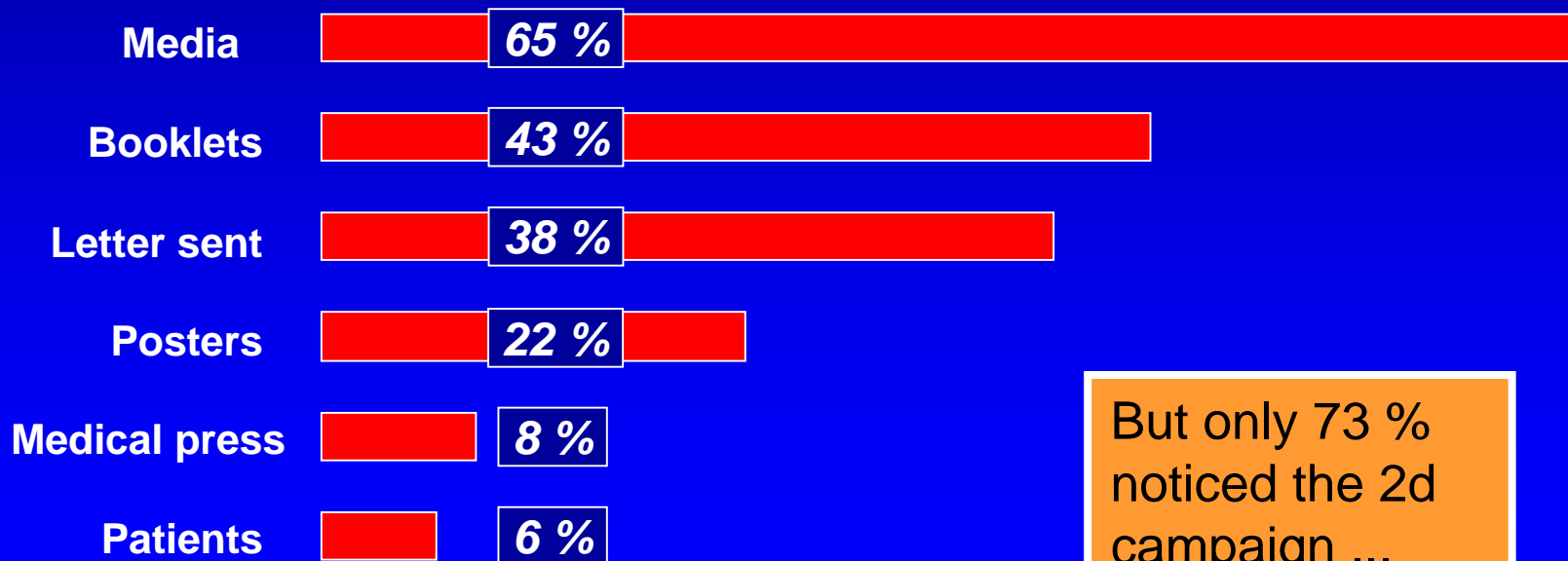
Appreciation by the General Practitioners

Method :

- telephone interviews (n=400; geographically representative)
- 3 months after end of each campaign



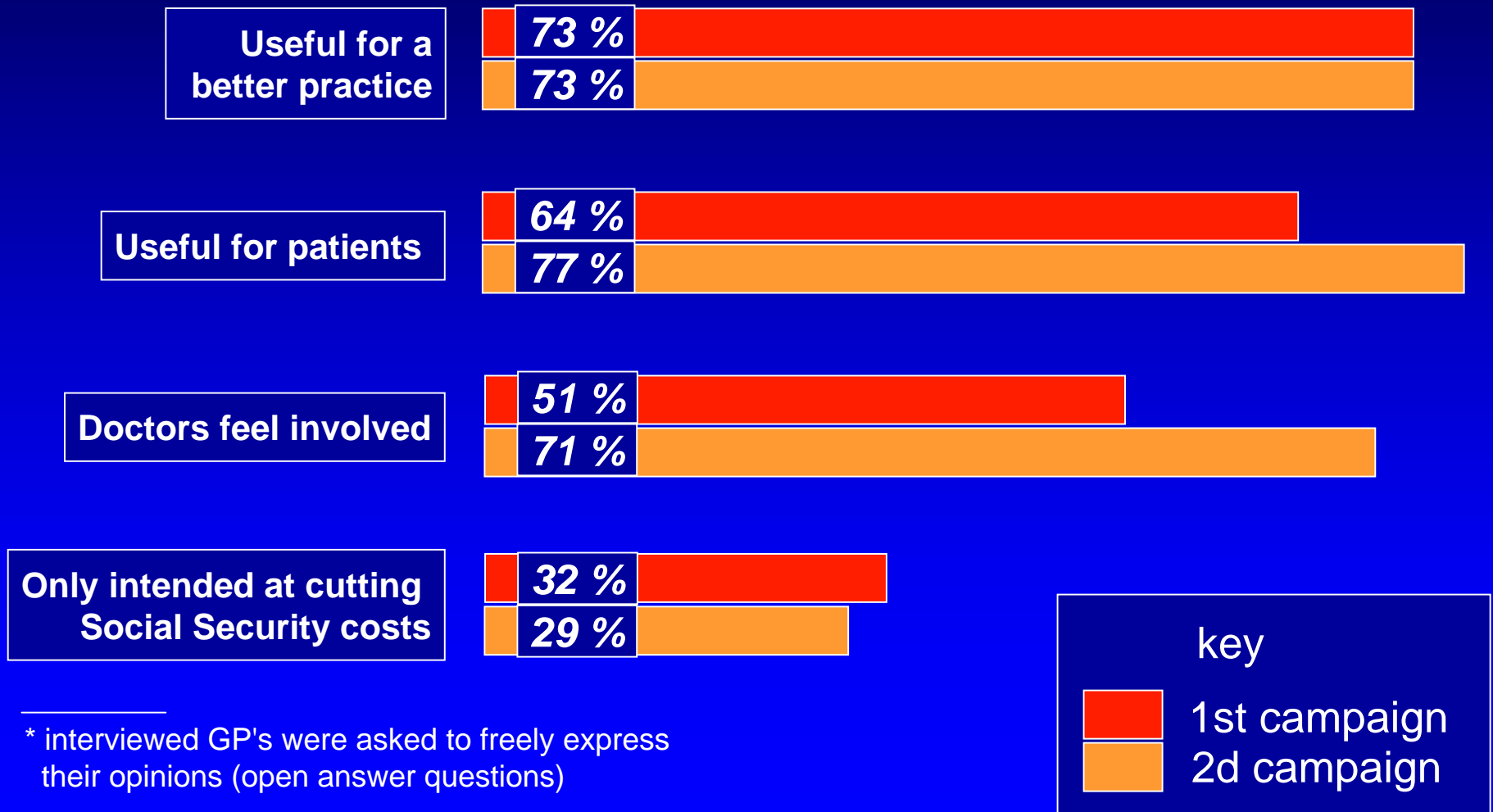
Impact : 100 % GPs remember the 1st campaign ...
... and have noticed it through:



But only 73 %
noticed the 2d
campaign ...

Appreciation by the General Practitioners

What do they think about the two campaigns * ...



Appreciation by the General Practitioners (3 of 6)

What do they remember from the two campaigns * ...

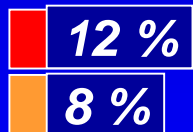
We urgently should
use less AB



Doctors should
prescribe less AB

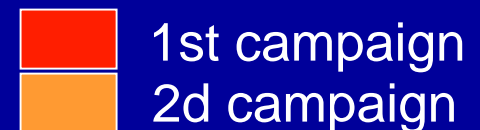


Bugs become
resistant



* interviewed GP's were asked to freely express their opinions (open answer questions)

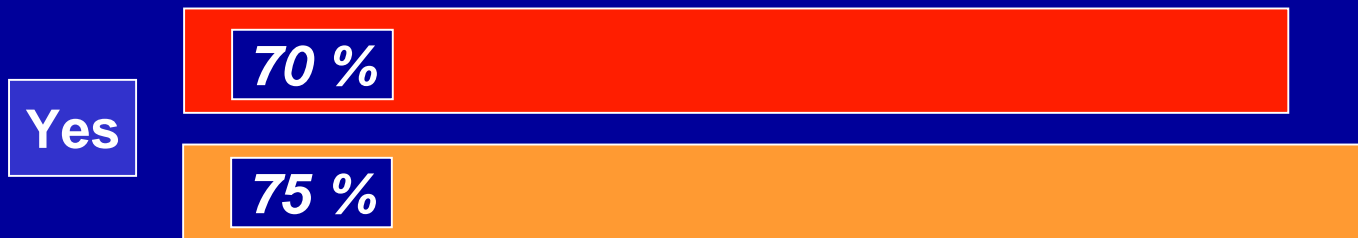
key



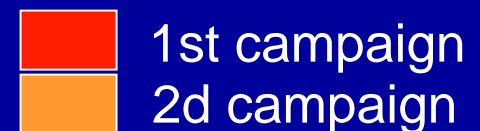
Appreciation by the General Practitioners (6 of 6)

Would you buy this car again ?

Should the campaign be repeated next year ? ...



key

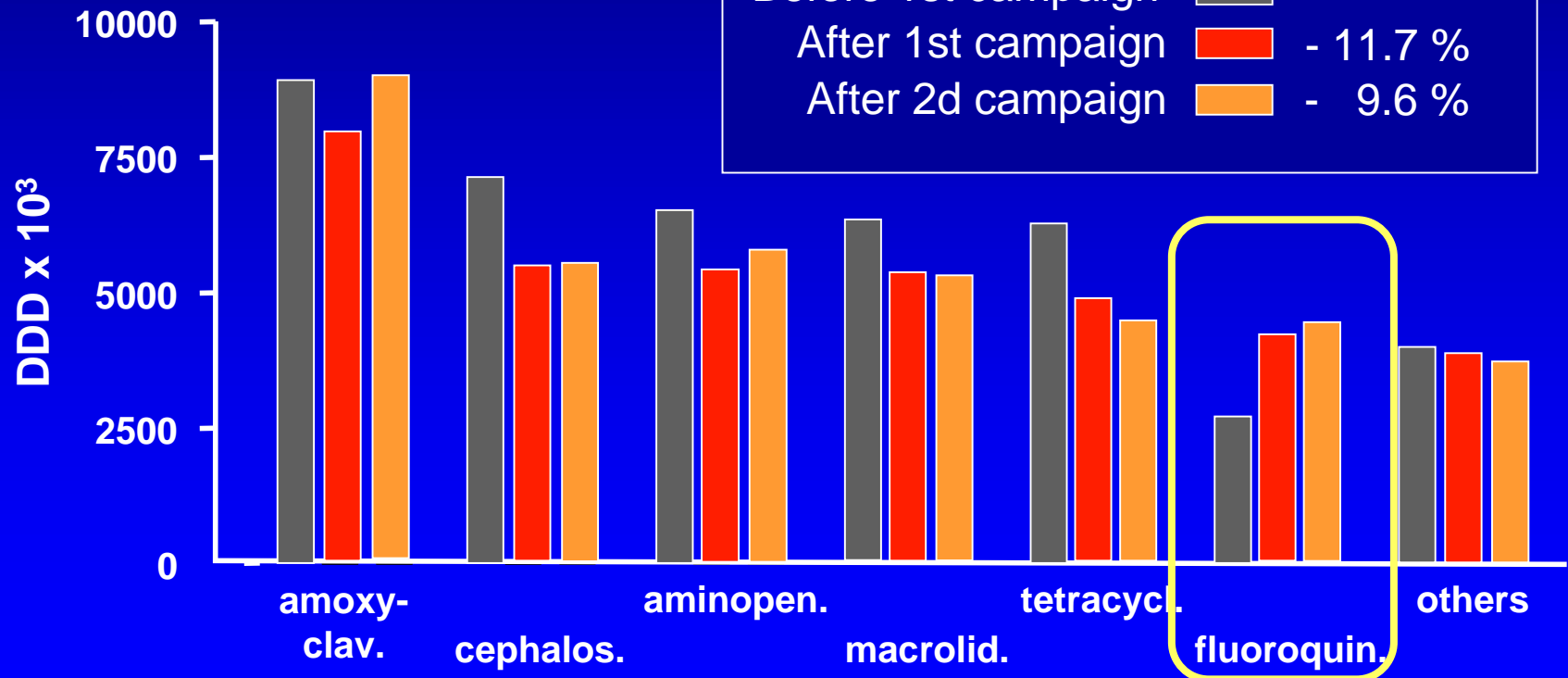


Changes of AB sales in the community (1 of 3)

1st method (descriptive approach) :

- record of AB sales (DDD; class ATC J01) in retail pharmacies* from Dec. 1999 through Mar. 2000 (baseline)
- comparison with the same periods in 2000-2001 (1st campaign) and 2001-2002 (2d campaign)

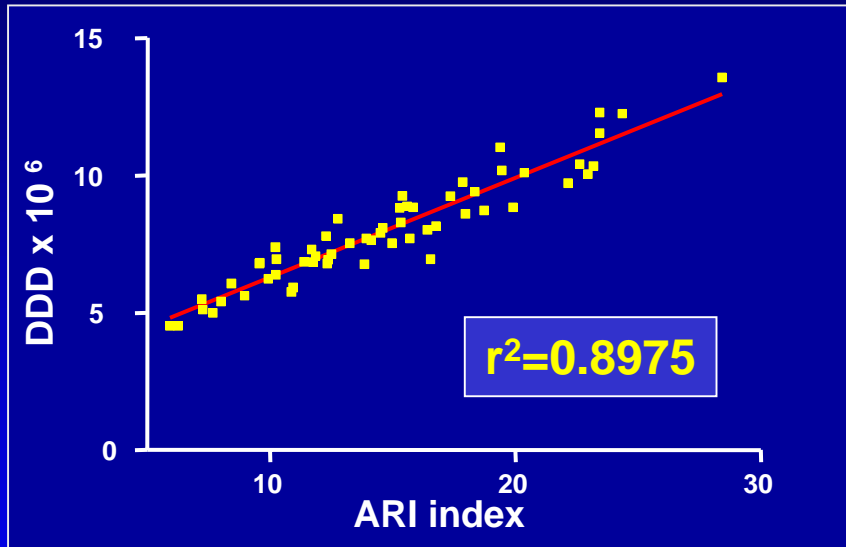
Results :



* data from a population of 8,950,476 to 9,107,039 insured persons; exhaustivity: 76.7 to 77.5 %

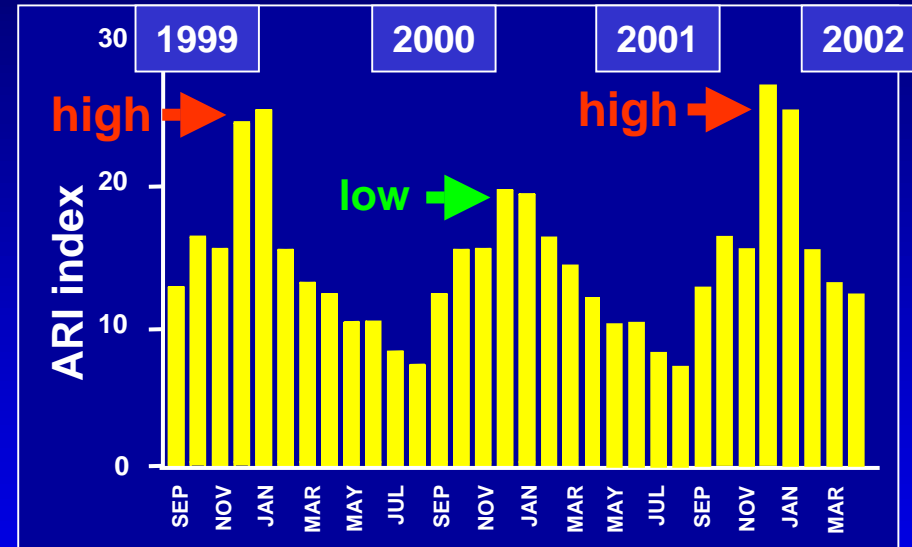
Changes of AB sales in the community (2 of 3)

Correlation between monthly DDD and ARI index (1996- nov. 2000)



➔ Each variation of 1 ARI unit causes an increase of 342,035 DDD [280,083-405,807]

Variation of ARI index during the Sep 1999 - Apr 2002 period



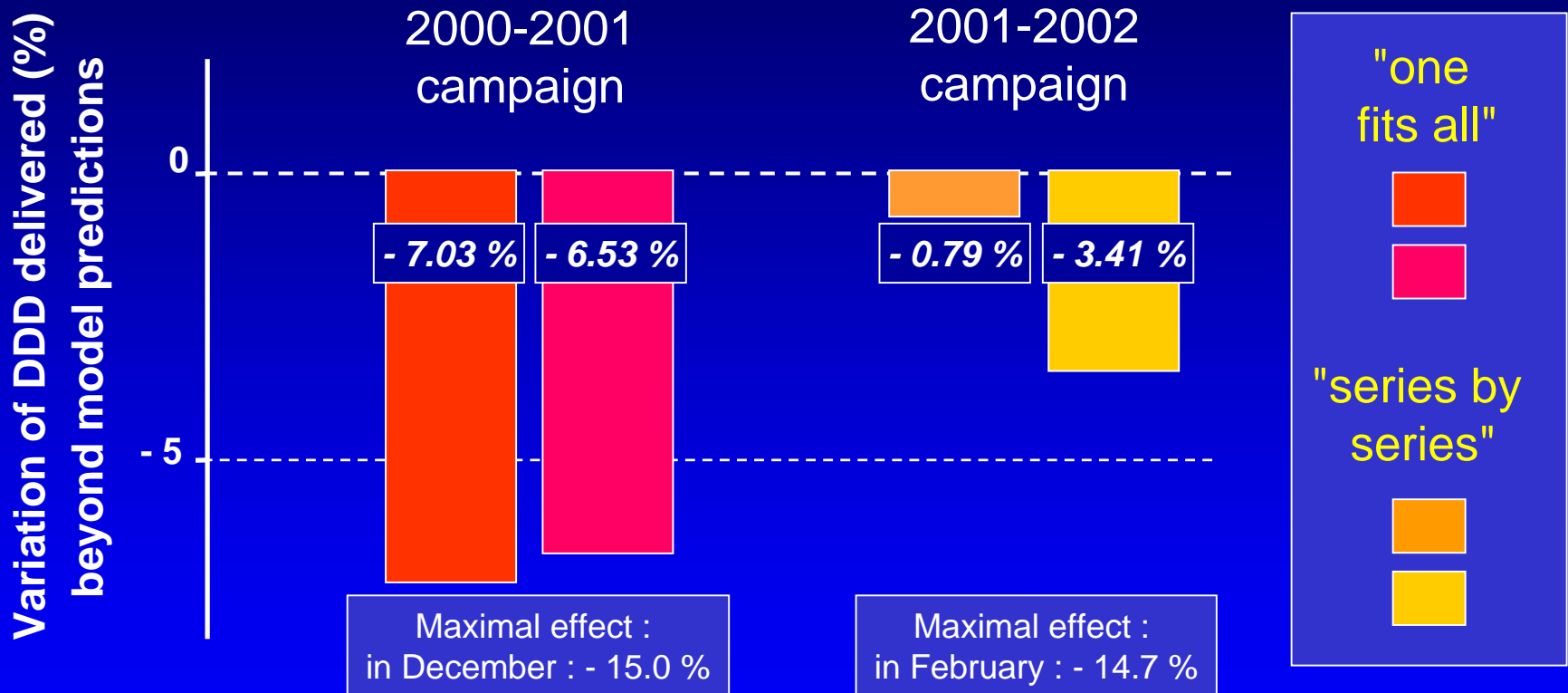
➔ Changes in ARI during the campaign periods will modulate AB consumption



Deviations from predicted values will assess the effectiveness of the campaign

Changes of AB sales in the community (3 of 3)

Results : deviations of AB sales from predicted values during each campaign period and the next two months



Global decrease over model prediction: 5.01 % $p = 0.012$

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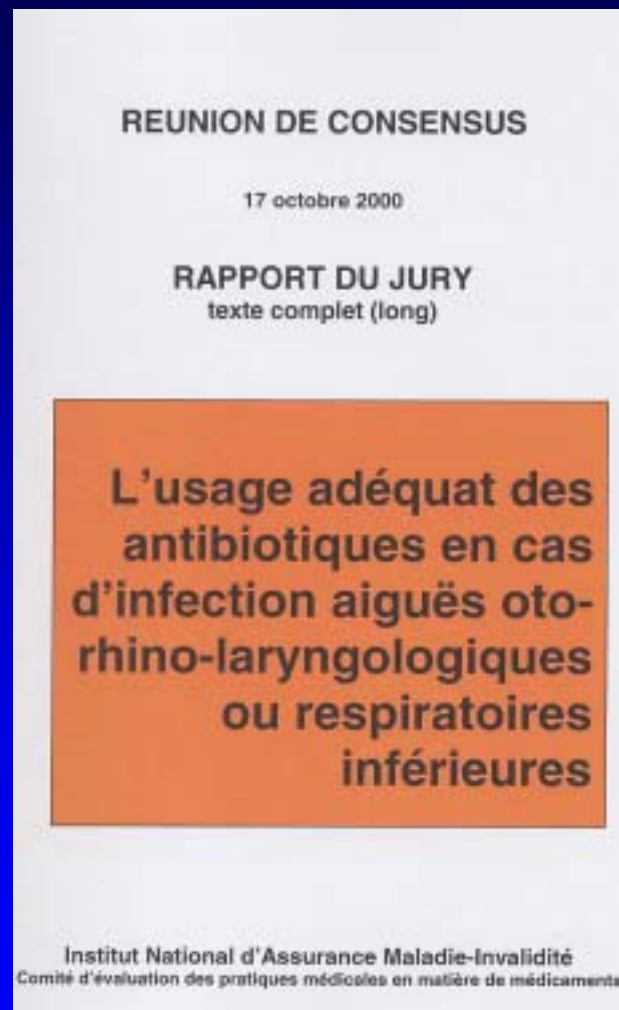
1. Veterinary projects
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4. Hospital-based medicine
5. Data analysis
6. Reimbursement policies

Community-based Medicine ...

- Setting up guidelines for community-based treatment of the following infections
 - Acute sore throat (pub. Dec. 2001)
 - Acute otitis media (pub. Dec. 2001)
 - Cystitis in women (pub. Dec. 2001)
 - Rhino-sinusitis (pub. Dec. 2002)
 - Acute bronchitis (pub. Dec. 2002)
 - CAP
 - COPD and acute exacerbations of COPD
 - Gastro-enteritis

How do we make guidelines ?

- Multidisciplinary working group
- Participation of the Scientific Societies
- Strict methodology
 - Evidence Based Medicine (including PK/PD)
 - Scientific committee
 - Consensus meetings



<http://www.inami.fgov.be>

“Prestataires de soins -> Pharmanet -> Réunions de consensus”

Beyond the guidelines ...

- Starting from 2003, all GP's have received THEIR own antibiotic prescription profile (for the year 2000) in comparison with the "mean profile" of THEIR region
- GP's are invited to discuss their antibiotic prescriptions habits in LOCAL steering groups
- Industry has launched "guidelines - PK / PD" meetings ...

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Setting up an Antibiotic Policy ...

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4. Hospital-based medicine

- surveillance of resistance
- setting up of guidelines
- « **Antibiotic Policy and Management Groups** » in each **Hospital**
- Additional tasks for the Hygiene Committee in each Hospital

Hospital-based Medicine ...

Setting up a

« **Antibiotic Policy and Management Team** » in each Hospital ...



- Origin: people interested in nosocomial infections (GDEPIH / GOSPIZ)
- Lengthy ministerial and administrative trail...
- So far, only a pilot trial (but successful ...)
- And, eventually, defined tasks:
 - Formulary recommendations
 - Direct interventions in AB prescriptions (based in part on PK/PD considerations)
 - Continuous education
 - Surveillance of consumption AND resistance
 - Direct reporting to the authorities

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- 6. Registration and reimbursement policies**

Registration: our problems ...

Belgian registration:

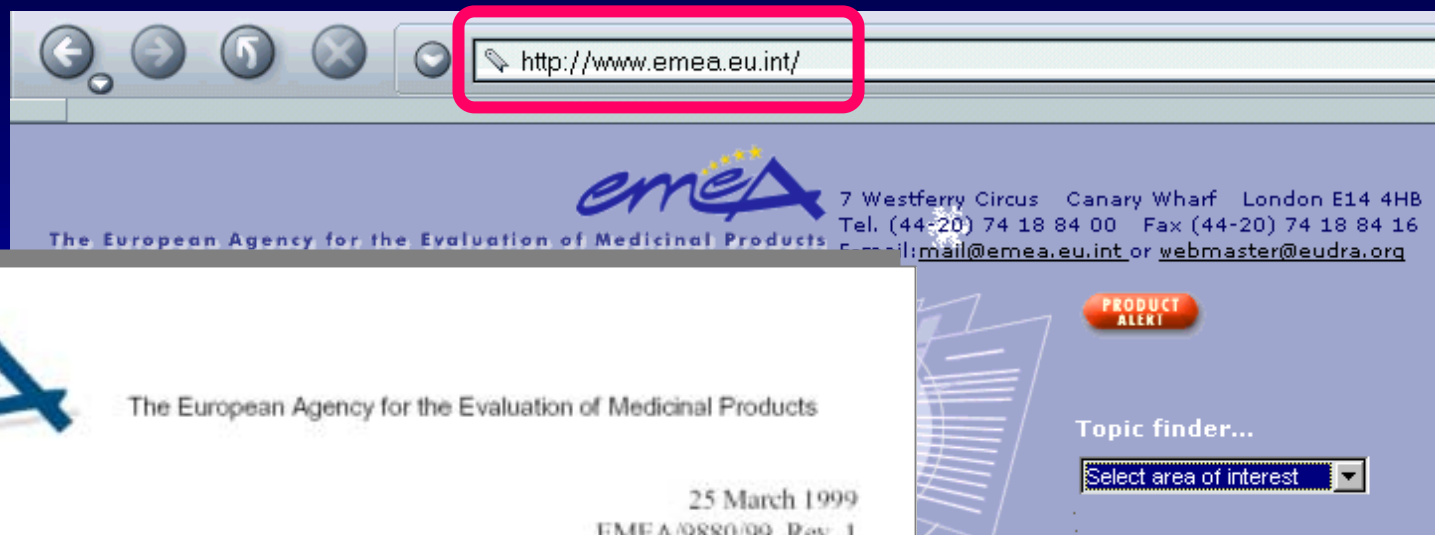
- old molecules
- generics (and not all !!)



- Bioequivalence...
- Usefulness of generics ??
- Who will do the surveillance and look at appropriate dosing ?

**Do you like ciprofloxacin @ 2 x 750 mg/day
for respiratory tract infections ...**

European Registration ...



EMEA Discussion Paper on Antimicrobial Resistance

London, 27 July 2000
CPMP/EWP/2655/99

**POINTS TO CONSIDER ON PHARMACOKINETICS AND
PHARMACODYNAMICS IN THE DEVELOPMENT OF
ANTIBACTERIAL MEDICINAL PRODUCTS**

Reimbursement:

What does Belgium now try to require from drug companies

- Defining correctly the drug true potential *
 - ➔ for antiinfective drugs, the susceptibilities towards the antibiotic under question need to be presented based on Belgian data under the form of MIC distributions ...
 - ➔ for all drugs, the rationale of the dosage should be given (... thus we expect PK/PD-based approaches for optimization of efficacy and minimization of dose-related toxicities)

Free translation and adaptation from the "Instructions and Guidance to Industry" for submitting a dossier to the Commission for Drug Reimbursement (CRM/CTG)

What do we say (when we can...) ?

*" The prescriber needs to inform him/her-self about the posologies that, at the present time, are recommended for this class of antibiotics. Studies ... show indeed very clearly that a **ratio "24-h Area Under the Curve / Minimal Inhibitory Concentration" (24h-AUC/MIC)** is one of the main parameters predicting efficacy for XXX in serious infections (nosocomial pneumonia). This ratio must be 125 or higher. "*

Free translation of an Official statement ("Definitive Opinion") of the Belgian "Transparency Commission" made on April 17th 2000, concerning antibiotic XXX, for the which the Manufacturer was seeking reimbursement by the Social Security



daily dose (mg)	max. MIC (mg/L)
200	0.060
400	0.125
600	1.180
800	0.250
1200	0.400

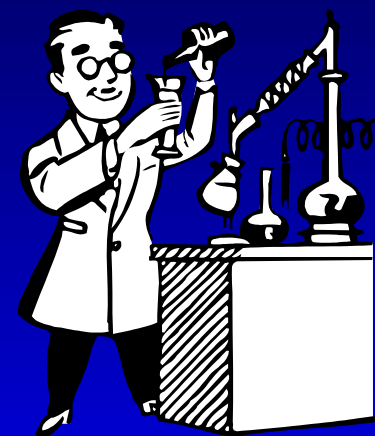
Our problem, however ...



Adapted from "Le Monde"

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Education and research

Setting up an Antibiotic Policy ...

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**Education of the students and
the doctors**

Education of the students ... and many others in PK/PD...

Antibiotiques home page - Netscape

File Edit View Go Bookmarks Tools Window Help

http://www.antiinfectieux.org/antiinfectieux/home.html

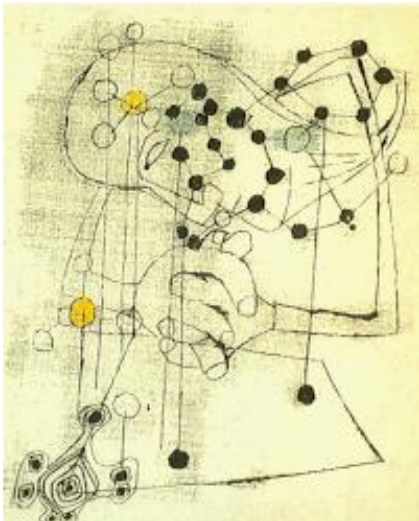


Université catholique de Louvain

Pharmacologie et pharmacothérapie des anti-infectieux

Y. Glupczynski (1), D. Lambert (2), A. Spinewine (3), P. M. Tulkens (3), F. Van Bambeke (3), Y. Van Laethem (4),
H. Van Landuyt (5)

(1) Service de microbiologie, Cliniques universitaires de l'UCL à Mont-Godinne; (2) Unité de chimie pharmaceutique; (3) Unité de pharmacologie cellulaire et moléculaire; (4) Service des maladies infectieuses, C.H.U. St Pierre, Bruxelles; (5) Dienst voor microbiologie, A.Z. St Jan, Brugge



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 - ▶ [Pharmacologie générale](#)
 - ▶ [Pharmacologie spéciale](#)
- **Pharmacothérapie**
 - ▶ [Pharmacothérapie générale](#)
 - ▶ [Pharmacothérapie spéciale](#)
- [Liens utiles](#)

Image reprise du Schorderet, avec permission

<http://www.antiinfectieux.org>

Research in PK / PD ...

Research

- Historical
- Organization
- Objectives
- Realizations
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GOVERNMENT OF THE BRUSSELS-CAPITAL REGION
FRANCOIS-XAVIER DE DONNEA, MINISTER-PRESIDENT

"PROSPECTIVE RESEARCH FOR BRUSSELS"
2003

3. RESEARCH PROJECT

Title: Improving antibacterial therapy and controlling the emergence of resistance in Brussels hospitals: a combined clinical, microbiological and pharmacodynamic/pharmacokinetic study.

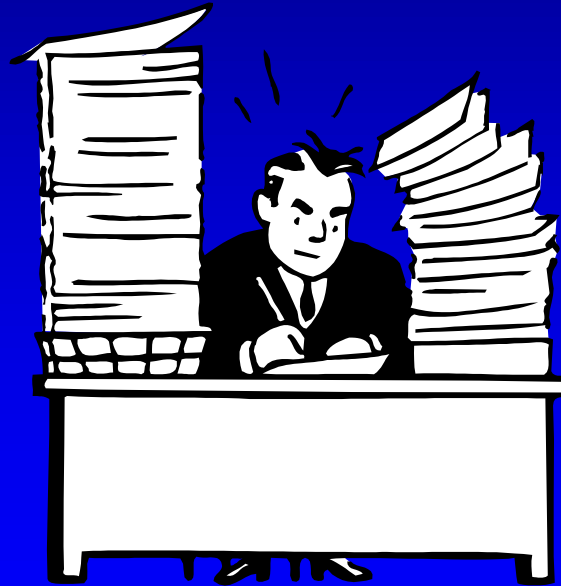
Collaborating centers:

- - the *Service des Maladies Infectieuses (CHU Saint-Pierre)*;
- - the *Dienst voor Microbiologie* of the *AZ-VUB*;
- - the *Service de microbiologie et des Maladies Infectieuses et du Voyageur* of the *Hôpital Erasme*;
- - the *Unité de Microbiologie* of the *Université catholique de Louvain*

Education in PK / PD ...

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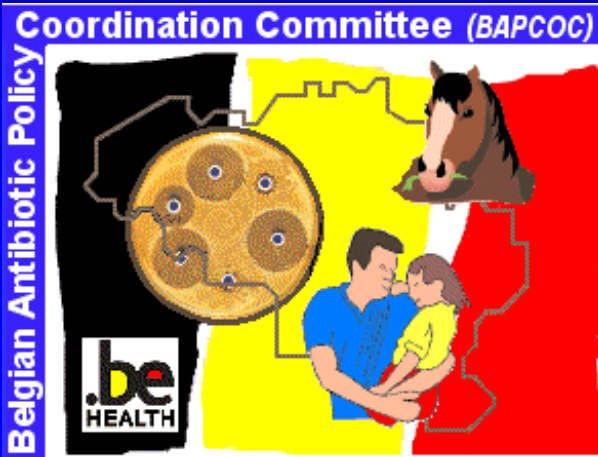
Education of the Ministeries....



Shall PK/PD lead to less resistance ?



But if we do nothing, we
are at high risk ...



Acknowledgments:

- The Federal Public Services of Public Health and Social Affairs
- The Belgian Antibiotic Policy Coordination Committee (BAPCOC)
- My co-workers at the *Université catholique de Louvain*
- Many Belgian colleagues...