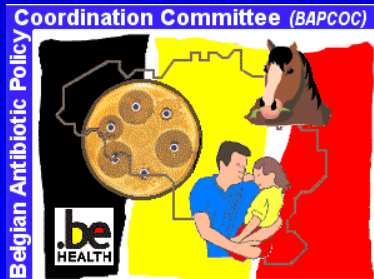


Designing, Carrying out , and Assessing the efficacy of a Public Campaign for a Better Use of Antibiotics in Belgium



P. M. Tulkens *

on behalf of the
Belgian Committee for Coordination of Antibiotic Policy,
Federal Ministry of Social Affairs, Public Health and Environment

* Cellular and Molecular Pharmacology Unit
Catholic University of Louvain, Brussels

What this presentation is about...

- The problem : bacterial resistance
 - the science
 - importance and clinical significance
 - relation with antibiotic consumption
- Actions that have been undertaken
 - at the European level
 - at the Belgian level
 - Coordination of Antibiotic Policy
 - **Sensibilization of the public**
 - » design of the campaign
 - » carrying it out
 - » assessment

Why
have we
done it ?

The
general
framework

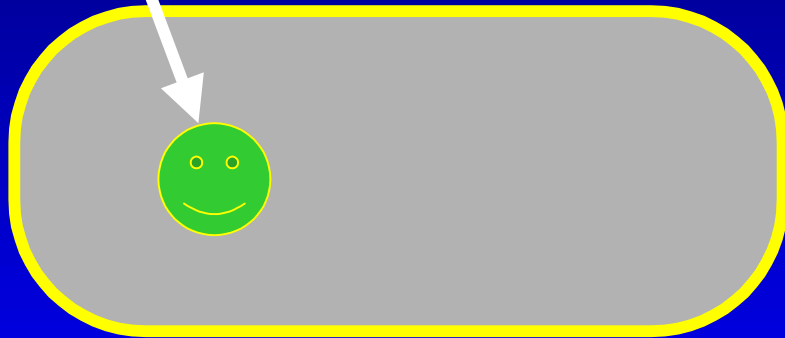
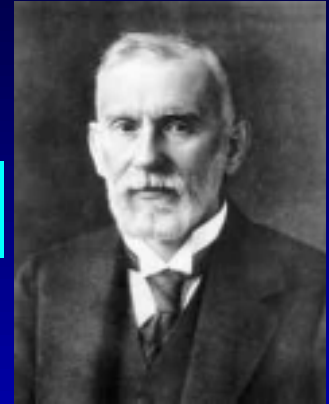
What has
been done

What are
the results

Bacterial resistance: the science



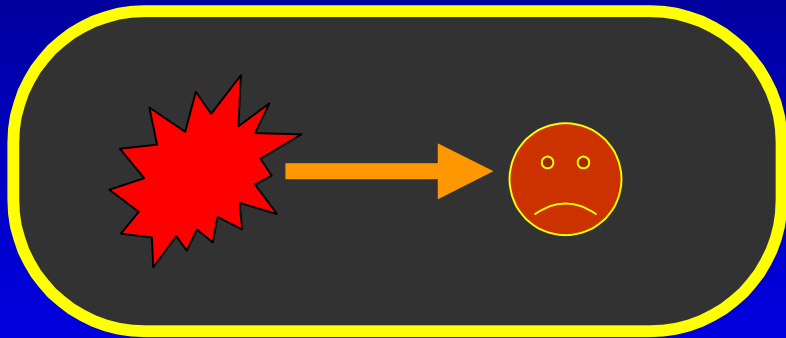
and then came the Ehrlich's magic bullet



Once upon a time,
there was an
happy bacteria ...

Bacterial resistance: the science

the Ehrlich's magic bullet has hit its target !



And Ehrlich won ...
for a time...

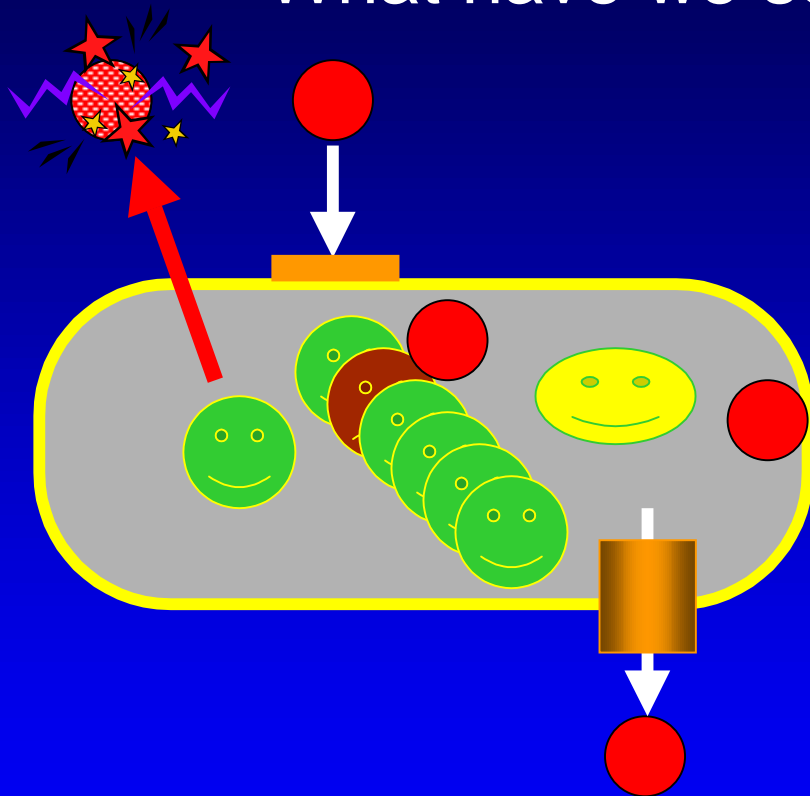
Bacterial resistance: the science

But only for a time...



Bacterial resistance: the science

What have we seen in less than 100 years ...



destruction of the AB

- β -lactamases,
- AG-degrading enzymes,

prevention of AB entry

overexpression of the target

modification of the target

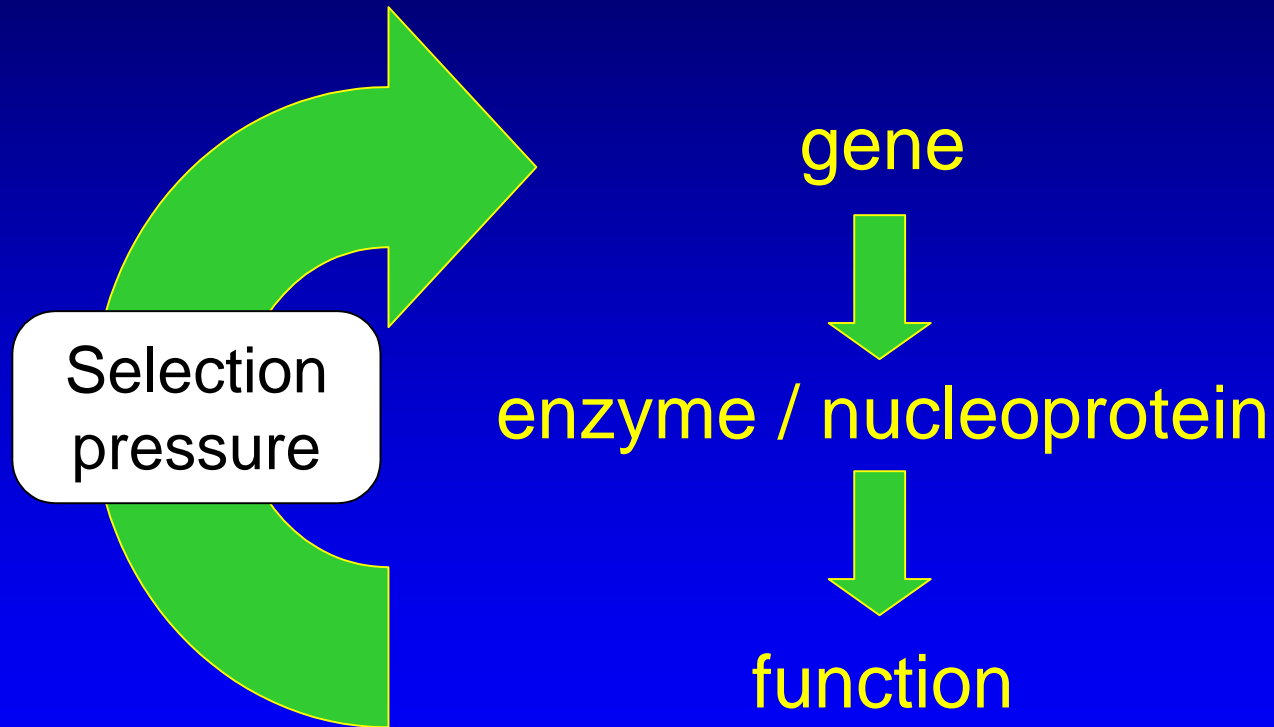
efflux



A multitude of different mechanisms
which ALL lead to resistance ...

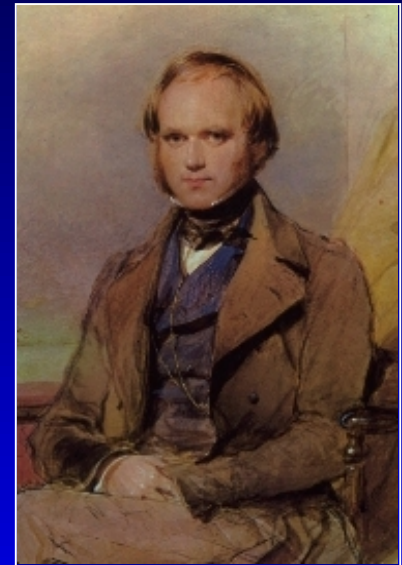
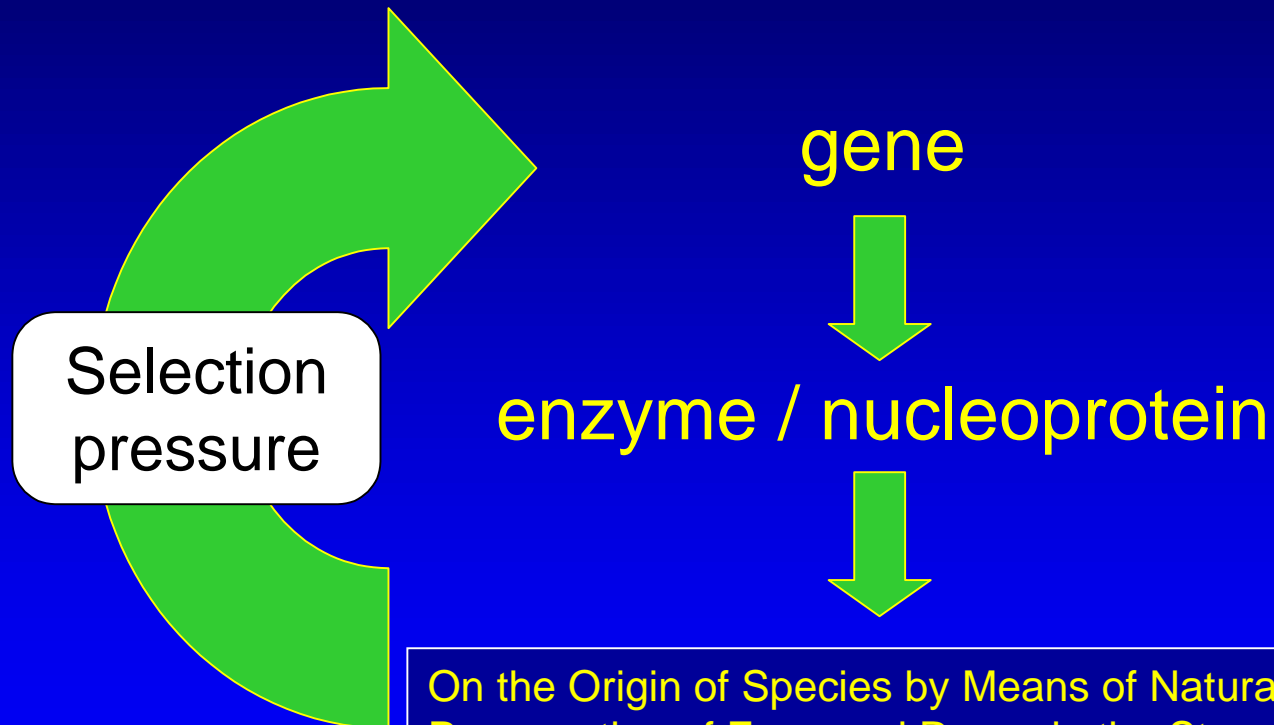
Bacterial resistance: why ?

A simple application of Darwin's concepts ...



Bacterial resistance: why ?

A simple application of Darwin's concepts ...



Detail of watercolor by George Richmond, 1840. Darwin Museum at Down House

On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life.

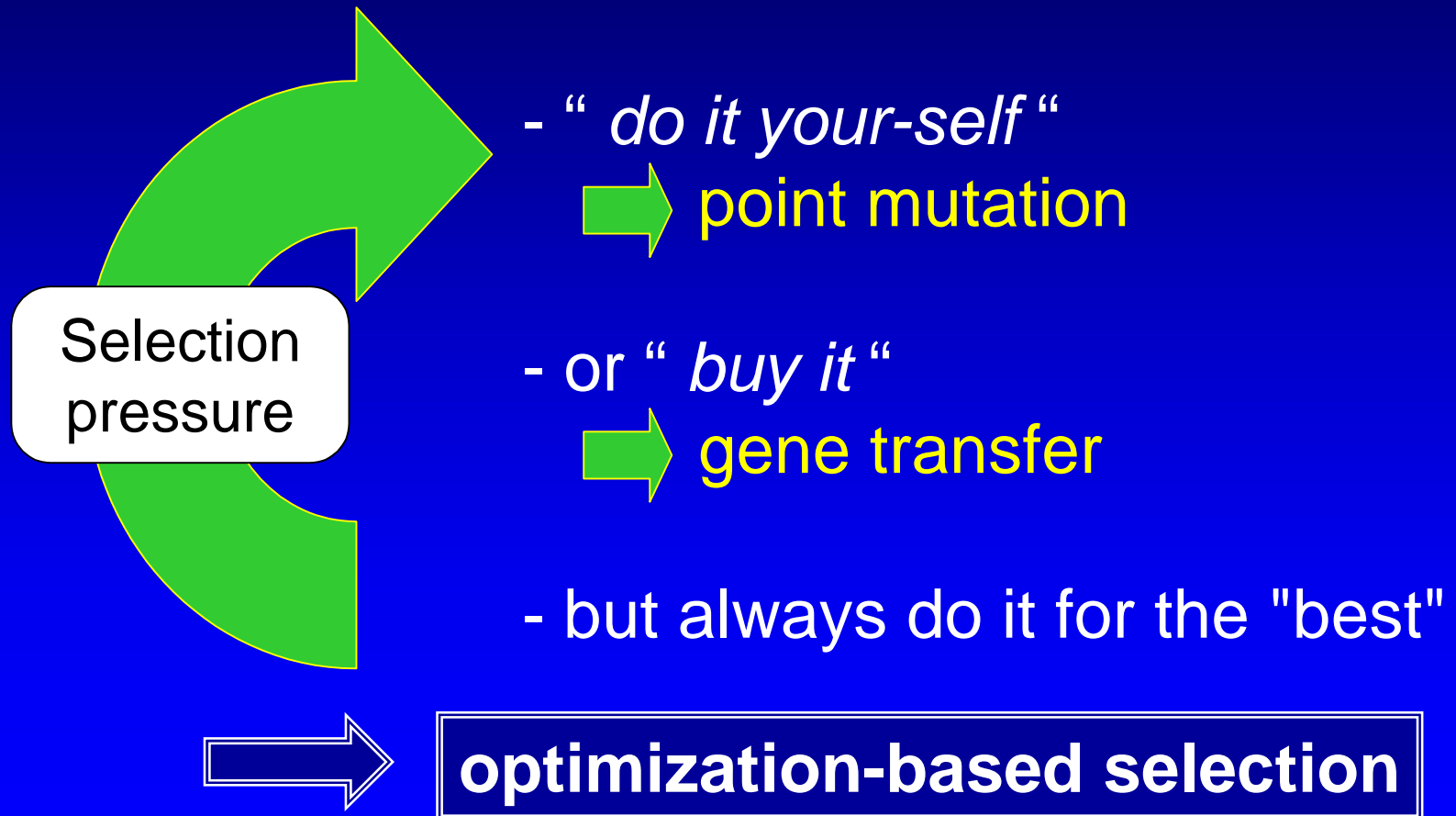
Charles Darwin, M.A.,

Fellow of the Royal, Geological, Linnæan, etc. societies; Author of Journal of researches during H. M. S. Beagle's Voyage round the world. London: John Murray, Albemarle Street, 1859

<http://www.literature.org/authors/darwin-charles/the-origin-of-species/index.html>

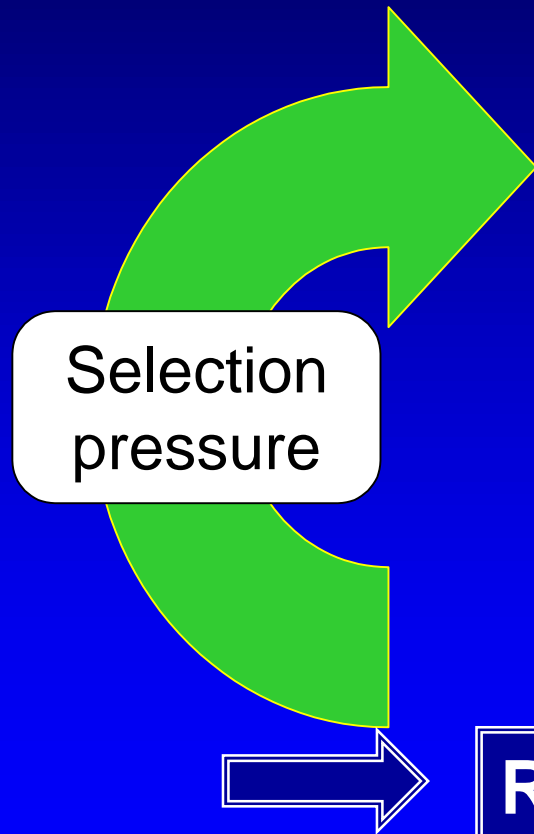
Bacterial resistance: why ?

How do bacteria apply the Darwin's principles ?.



Bacterial resistance: why ?

A simple application of Darwin's concepts ...
to a highly plastic material



- a typical infection site may contain more than 10^6 - 10^9 organisms
- most bacteria (and viruses) multiply VERY fast (20 min...) ... and spread
- pathogenic bacteria exchange easily genetic material with commensal flora ... which is VERY large !

**Rapid acquisition and spreading
of resistance mechanisms**

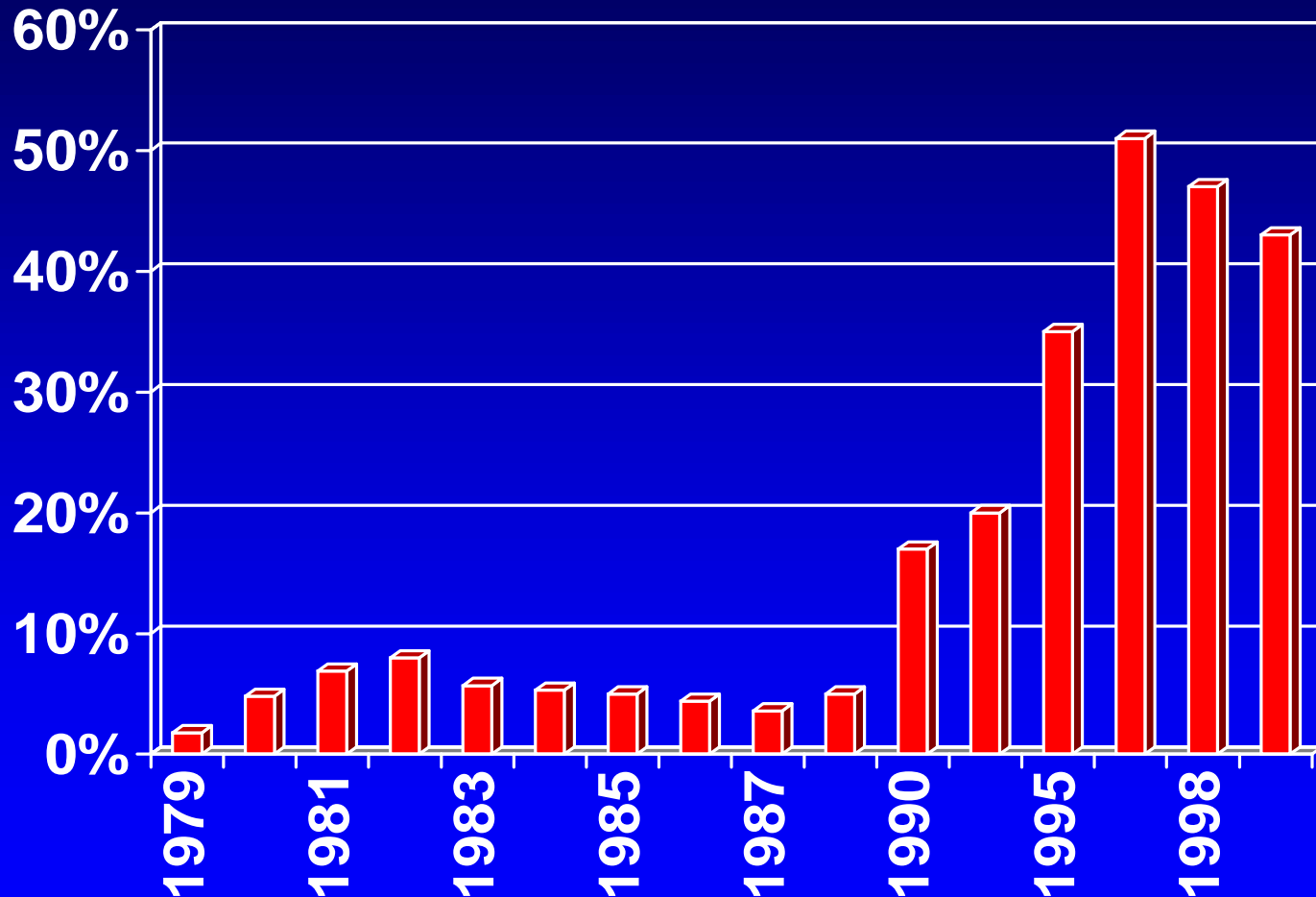
Bacterial resistance: is it important ?

- Several major **pathogens** have become “difficult” organisms because choosing empirically an active antibiotic is now more and more a challenge

- *S. aureus* β-lactamases PBP mutations target overexpression
- *S. pneumoniae* PBP and gyrase/topoisomerase mutations efflux
- *Ps. aeruginosa* AG-degrading enzymes lack of penetration efflux
- *Enterobacteriaceae* extended spectrum β-lactamases
- *Enterococci* co-resistance target modifications

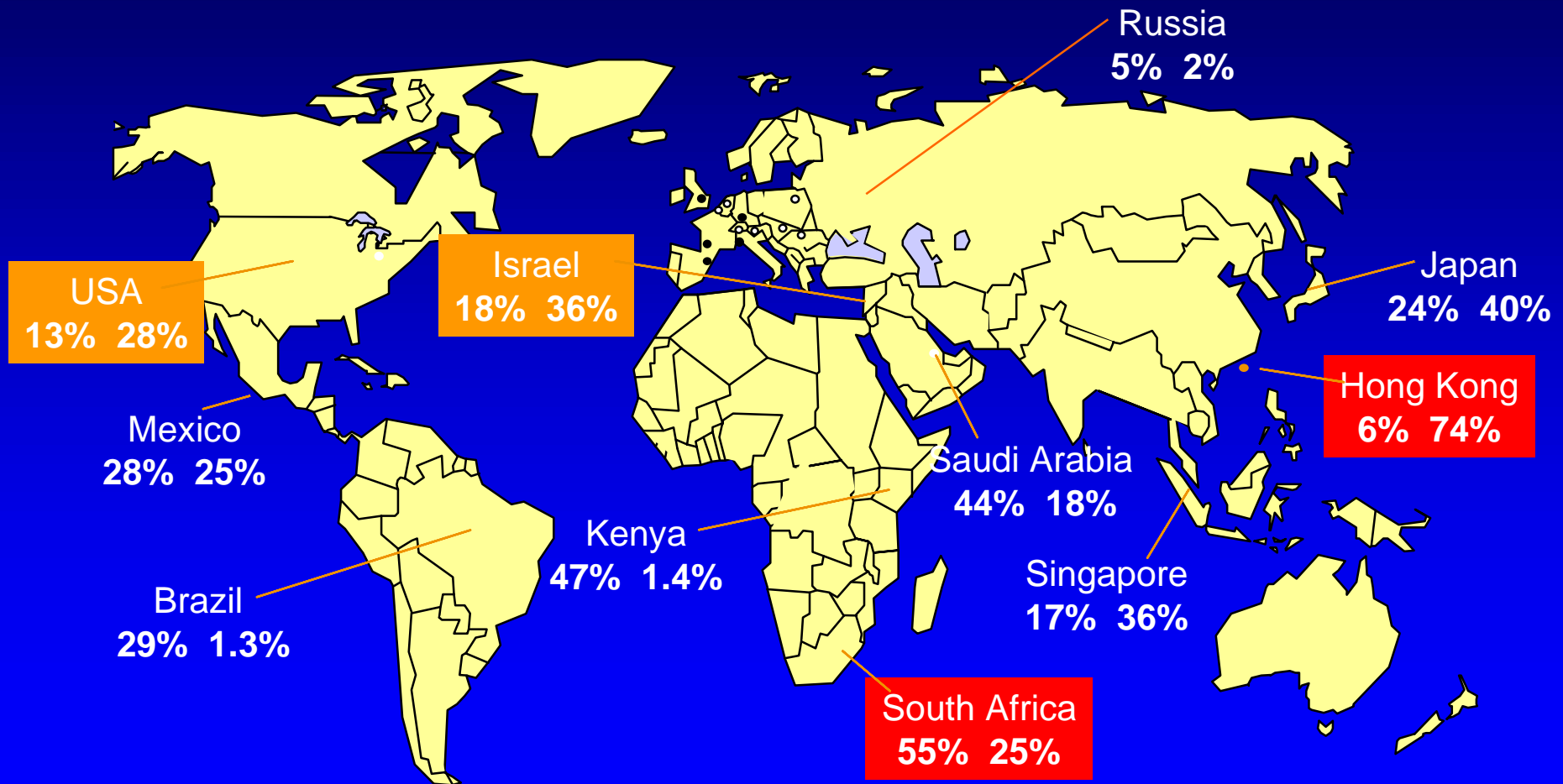
Not an exhaustive list !!

The Emergence of Penicillin Non-Susceptible Pneumococci in the US



The Alexander Project 1999

S. pneumoniae: resistance to penicillin (Pen-I / Pen-R)



Bacterial resistance: is it important ?

- Several major classes of antibiotics have lost their usefulness in empirical therapy

- *tetracyclines*

most respiratory pathogens

- *aminopenicillins and 1st gen. cephalosporins*

all β -lactamase producers

- *macrolides*

S. pneumoniae

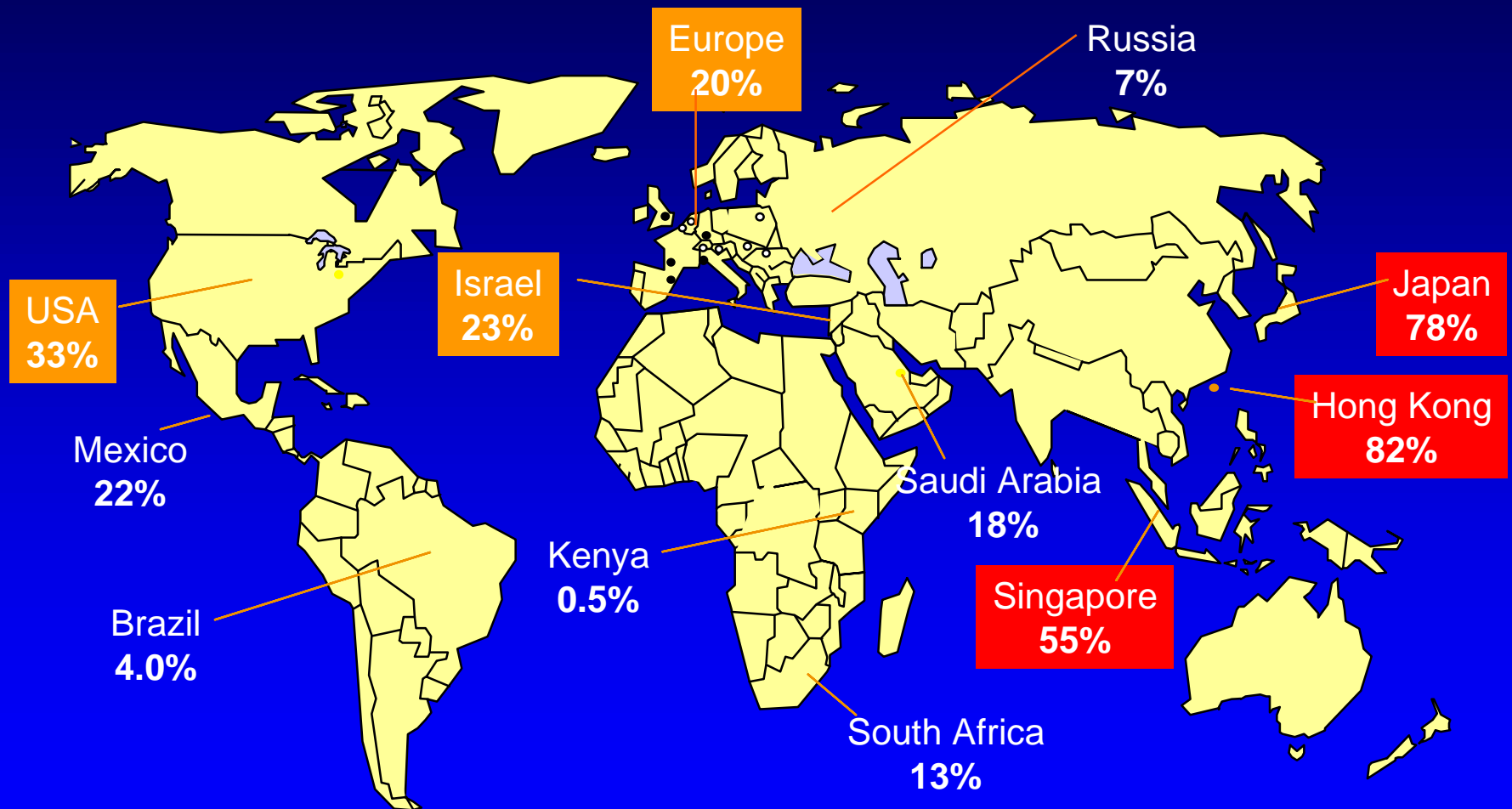
- *1st and 2d generation fluoroquinolones* *

S. aureus,
Ps. aeruginosa

- ...

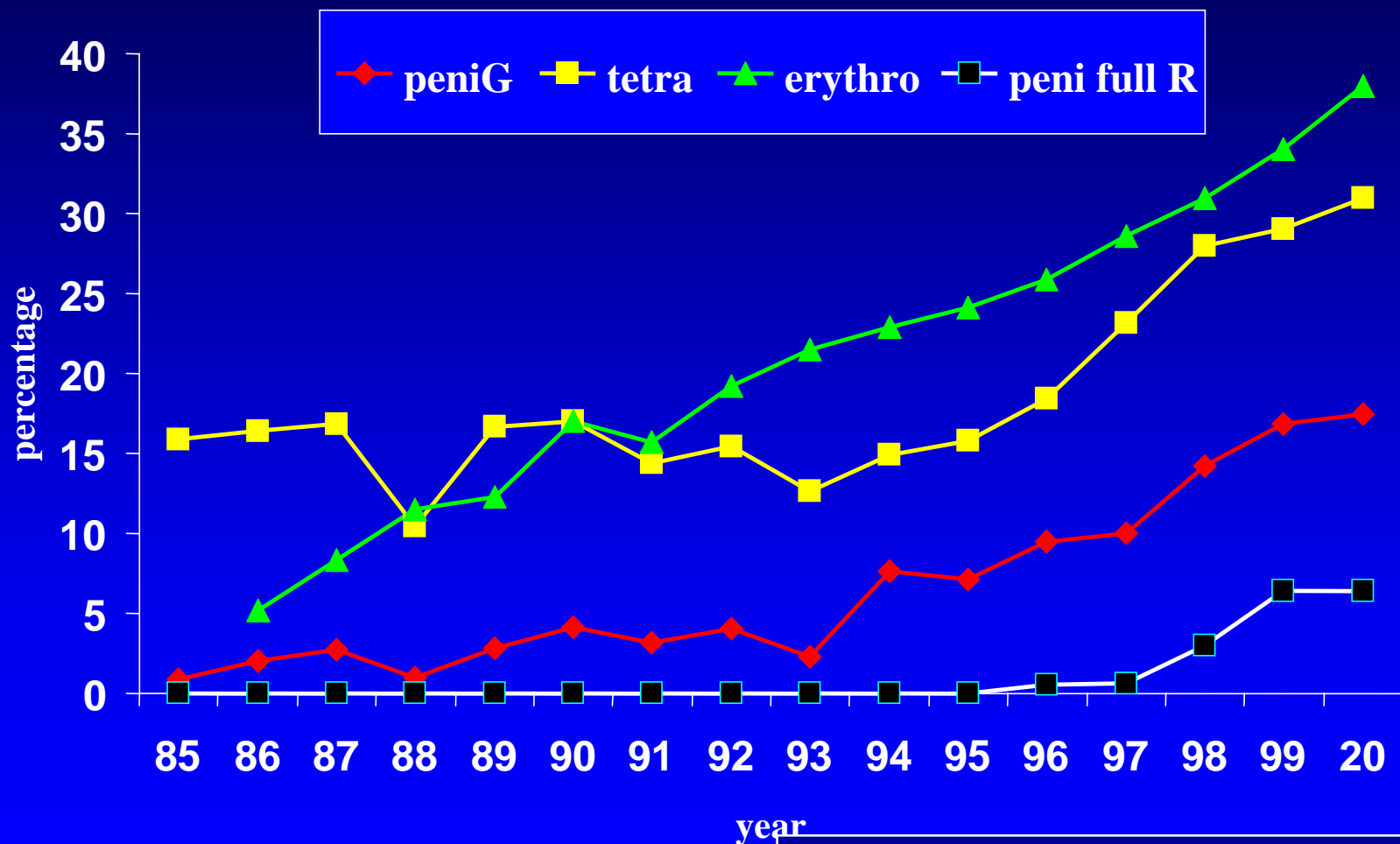
* totally synthetic molecules with new mode of action and introduced since the 80's only !!

The Alexander Project 1999: *S. pneumoniae*: Macrolide Resistance



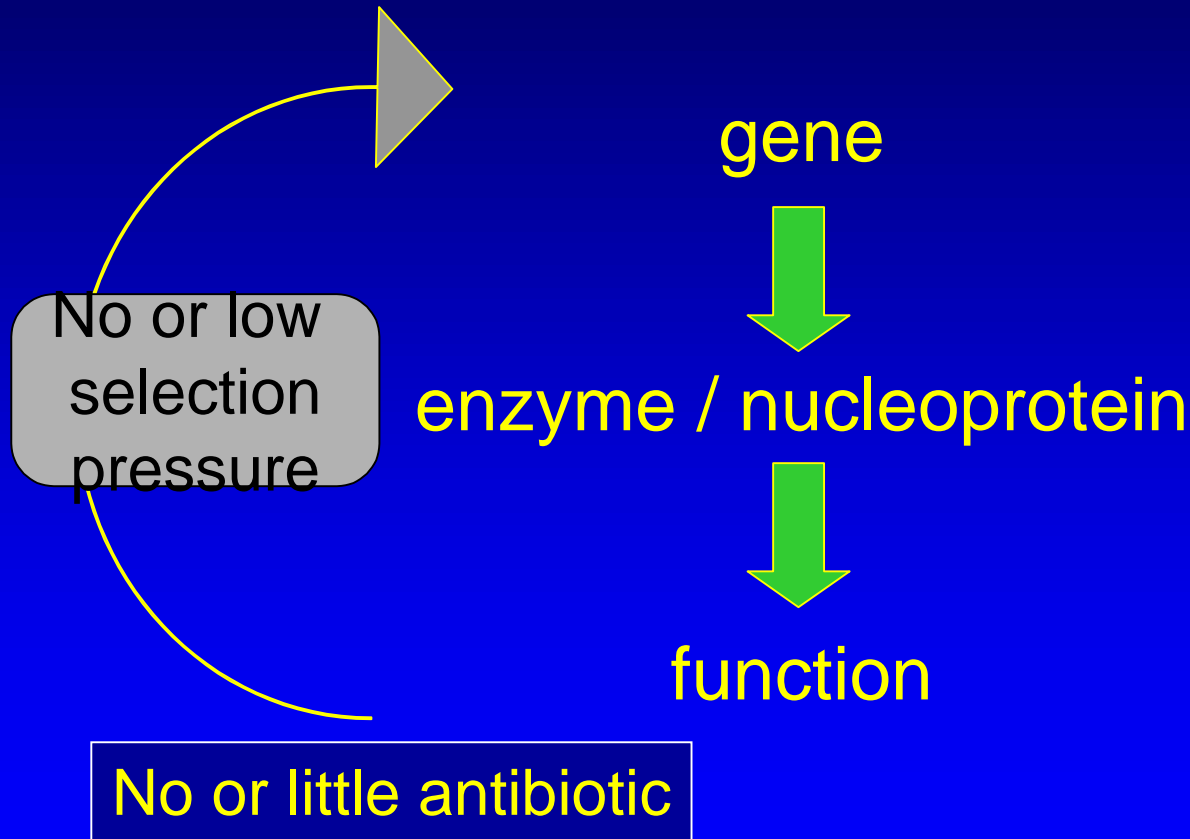
Resistance defined as erythromycin MIC ≥ 1 mg/L

Evolution of *S. pneumoniae* resistance in Belgium



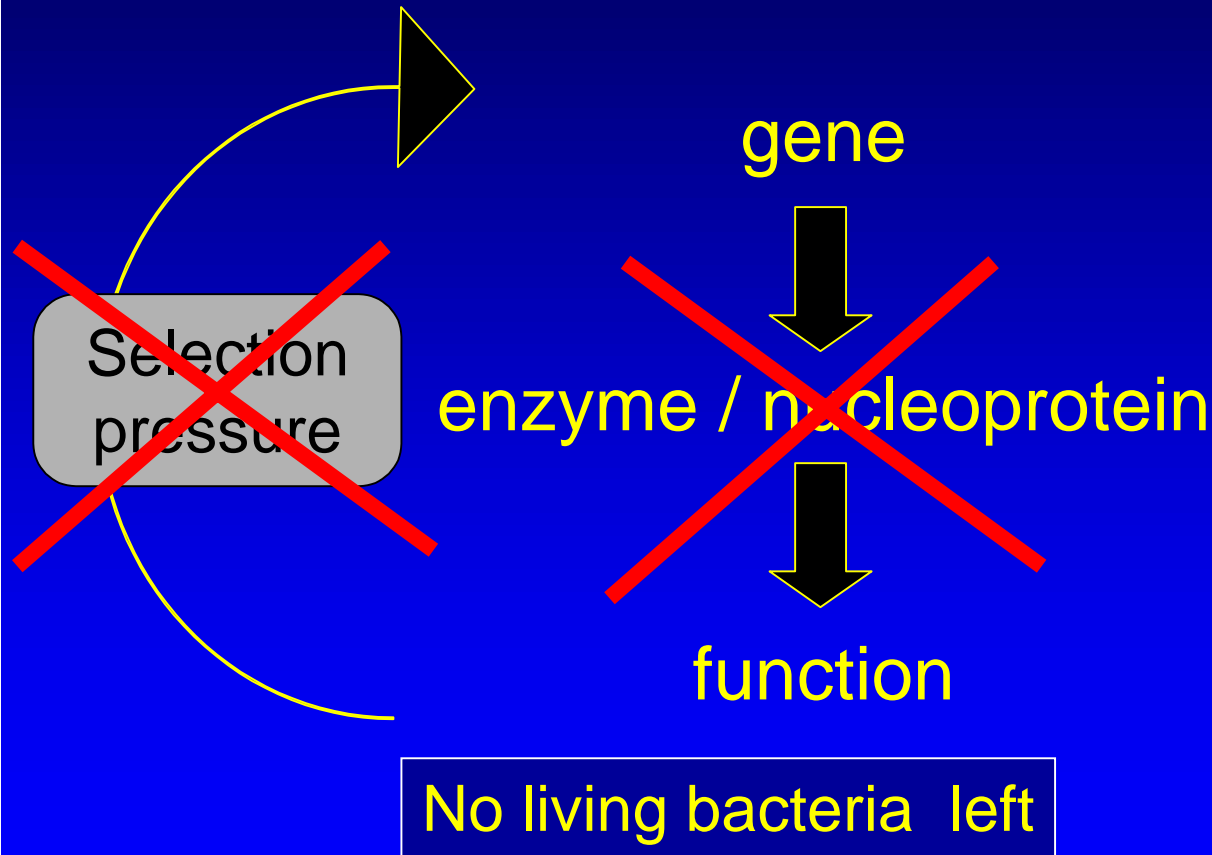
Referentielabo pneumokokken, Leuven, 2000

Resistance is linked to antibiotic usage and antibiotic misuse



- Highest rates of resistance are seen in areas or periods with
- high consumption **and**
 - poor antibiotic usage guidelines

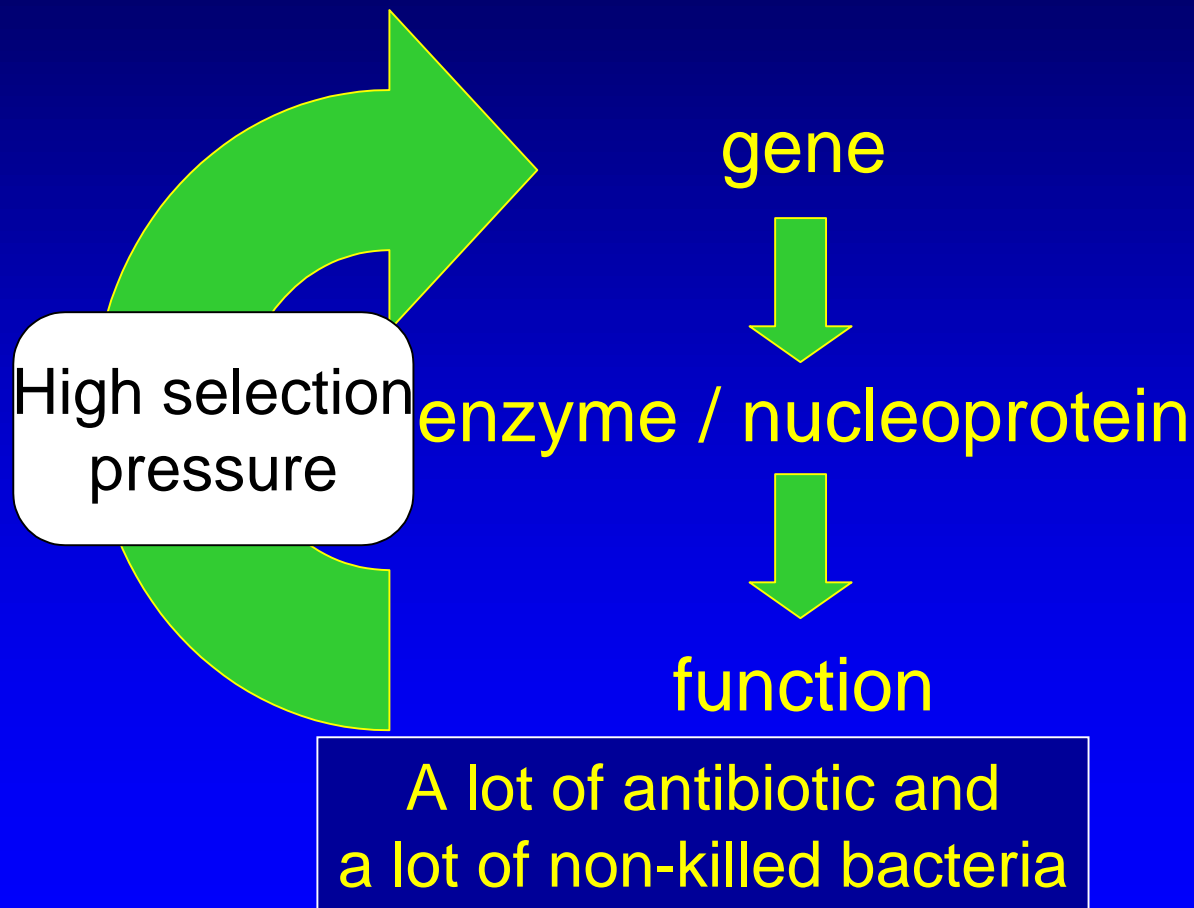
Resistance is linked to antibiotic usage and antibiotic misuse



Highest rates of resistance are seen in areas with

- high consumption **and**
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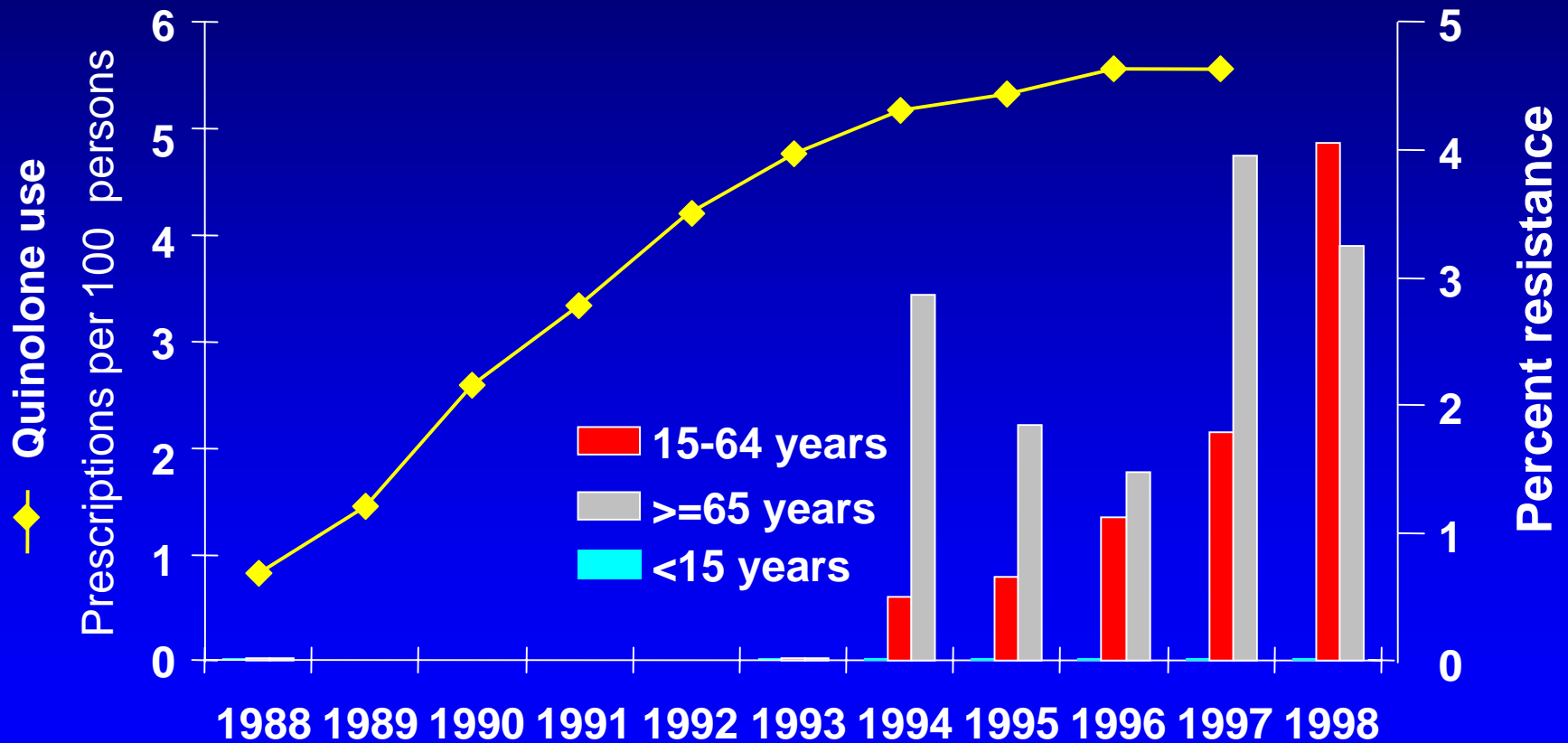
Resistance is linked to antibiotic usage and antibiotic misuse



Highest rates of resistance are seen in areas with

- high consumption **and**
- poor antibiotic usage guidelines

Fluoroquinolone use and emergence of *S. pneumoniae* with reduced susceptibility to fluoroquinolones: The Canadian (bad) experience (1988-1998)



Chen et al., 1999 NEJM

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What are
the results

Some actions at the European Level



- **At the governmental level: Knowledge dissemination, Sensibilization and Decision making**
 - 1998 : Copenhagen Scientific Conference
“The Microbial Threat”
 - ➔ The EU governments are asked to promote a more rational use of antibiotics and to set up specific actions
 - 2001 : Brussels Conference on
“Antibiotic Use in Europe”
 - ➔ The Council of the EU adopts a Resolution on a Community Strategy against antimicrobial resistance

Some actions at the European Level



- At specialized agencies level:
Regulations and promotion of better antibiotics and better antibiotic use **in relation to resistance**
 - 1997 :
Note for guidance on the pharmacodynamic section of the SPC for antibacterial medicinal products
 - 2000 :
Points to consider on Pharmacokinetics and Pharmacodynamics in the development of antibacterial products
 - 2001 :
ESAC/EMA workshop “Towards an European Consensus Indications for Major Antibiotic Classes: an Exercise with the Macrolides”

Some actions at the Belgian level



Belgian Committee for the Coordination of the Antibiotic Policy: Aims and Duties

- collection and organization of all available information on antibiotic use and resistance
- publication of reports on antibiotic use and resistance in all therapeutic and non-therapeutic fields
- making recommendations on relevant points such as detection of resistance, cross-resistance mechanisms, use and consumption of antibiotics in both man and animal, etc ...
- making recommendations for research on antibiotic resistance and on the transfer of resistance among bacteria and among ecosystems
- information and increase of public awareness on antibiotic resistance and the risks associated with the irrational use of antibiotics



Translated and adapted from the Royal Decree of April 26th, 1999

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Public campaign : Why did we do it ?

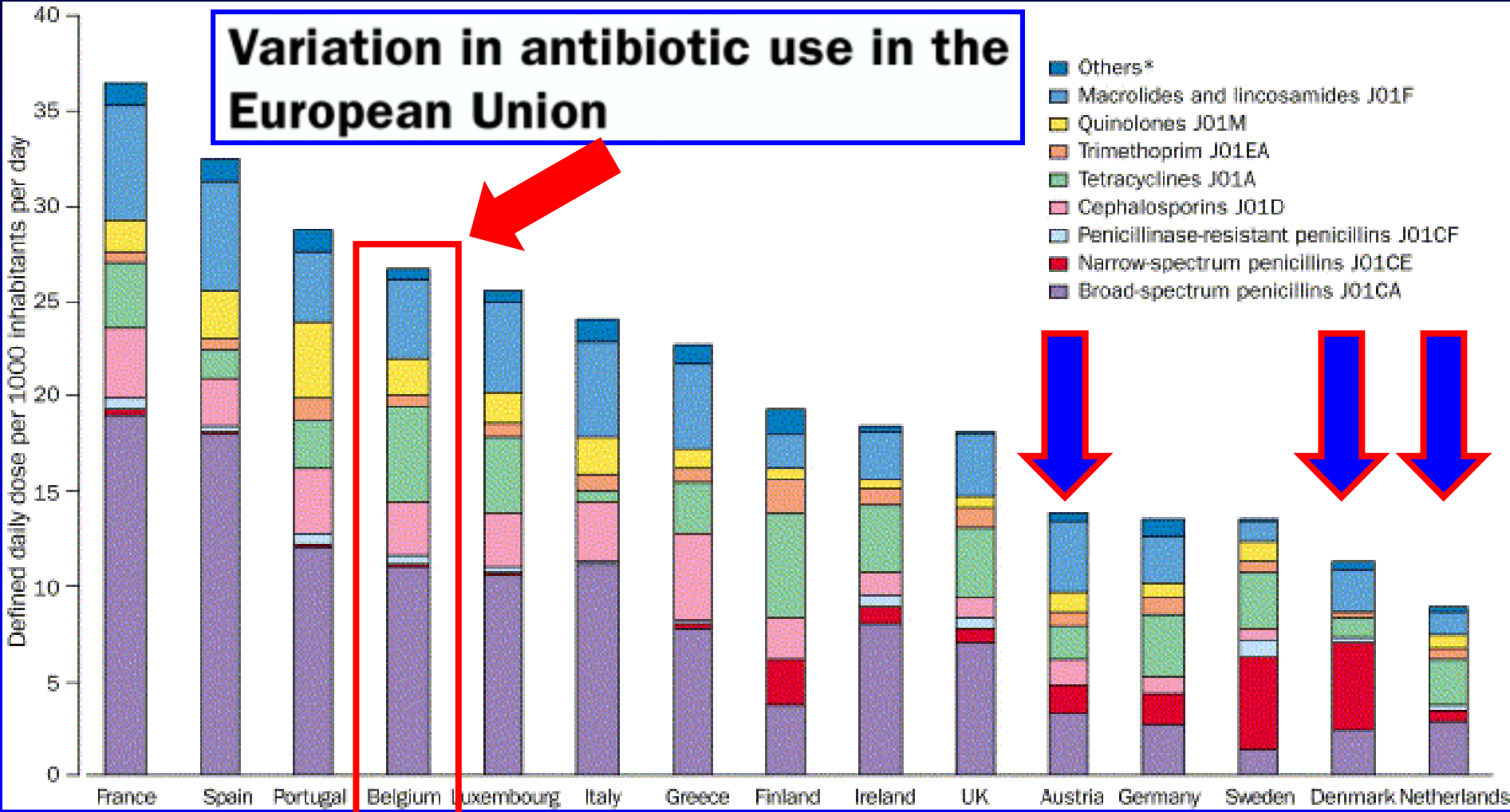
Comparative data on antibiotic consumption¹

Belgium	EU states (range)
<i>Total non-hospital antibiotic sales in 1997:</i>	
26.7	9 - 36.5
<i>Total non-hospital β-lactams sales in 1997:</i>	
14	4 - 21

¹ DDD per 100,000 inhab. calculated from IMS figures (O. Cars, Lancet, 357, 2001)

Know who you are ...

Variation in antibiotic use in the European Union



Cars & Mølsted, Lancet, 357, 2001

Why the public ?

- Antibiotic sales in the community represent > 70 % of all antibiotic sales and is, therefore, an important component in the selection pressure
- The largest use of these AB is towards minor respiratory tract infections which are often self-limiting and self-healing and for which AB real usefulness is dubious
 - 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, especially if minor and with a high rate of spontaneous resilience such as otitis media or uncomplicated bronchitis
- explain which are the real benefits of antibiotic treatment, i.e. the cure of serious bacterial infections, as opposed to their inappropriate uses such as in minor infections or infections of viral origin
- underline the risks associated with the rapid emergence of resistance to antibiotics
- foster a useful discussion of the patient with his/her doctor and his/her pharmacist on the need to use antibiotics appropriately.

The Commission “Sensibilization”

- Dr. Ludo VERBIST (microbiologist, KU-Leuven)
- Dr. P. Demol (microbiologist, Ulg)
- Dr. P. Trefois (MD, “Question Santé” [non-profit])
- Ph. Mouchet (Media Communication officer, “Question santé”)
- P. Geerts (Director “Omtrent Gezondheid” [non-profit])
- Dr. M. De Meyere (General Practice, UG)
- Dr. P. Tulkens (pharmacology, UCL)
- R. Deschepper (anthropology, UG)
- Representatives of the Community Ministeries in charge of Public Health
 - Dr. D. Wildemeersch (Vlaamse Gemeenschap)
 - Dr. J. Morel (Communauté française)
- Dr. I. Bauraind et I. Vanden Bremt (Federal Ministry of Health)



Public campaign : Budget and Support...

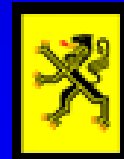
Budget

- **300,000 Euros** from Federal Funds to cover the main costs of the campaign.




Additional support

- the Flemish and French-speaking Communities (*Vlaamse Gemeenschap & Communauté française de Belgique*)
 - ➡ public Radio and TV broadcasts on public channels (free access to the French-speaking channels and direct support (approx. 50,000 Euros) for broadcasts on the Flemish-speaking channels
- the French-speaking Community
 - ➡ collaboration of a non-profit organization specialized in developing Public Communications in health-related topics (*Question Santé*).



Pre-campaign study

- **N = 1,000 persons,**
- **specialized agency,** 
- **appropriate distribution concerning sex, ages, socio-economic status and geographical distribution.**

Pre-campaign study: main results

- ➡ large misunderstanding or lack of information about the real conditions for usefulness of antibiotics in current infections
- ➡ belief that antibiotics will allow a faster cure for even minor infections
- ➡ great confidence of the public in MD's and pharmacists
- ➡ MD's tend to overestimate the "patient's pressure" for antibiotics

Public campaign : pre-information of health professionals

- "Summary and position paper" underlining the general and medical significance of the resistance to antibiotics ("*Folia Pharmacotherapeutica*"; distributed free of charge to all registered MD's and Pharmacists).
- Direct pre-information of MD's representatives at the "ad-hoc" Working Party and through two pre-campaign meetings.
- Package sent to all GP's, Pediatricians, and "Respiratory Tract" specialists, and all public Pharmacies with
 - a letter in which the campaign and its aims were explained, and its significance in terms of Public Health underlined, and
 - 20 copies of the booklets and one poster for display in their waiting room or pharmacy sent to all GP's, pneumologists, ORL, pediatricians and pharmacists in the country

Carrying out the campaign



Bruxelles, le 20 novembre 2000.

Aux médecins et aux pharmaciens

Objet: Campagne de sensibilisation de la population sur les problèmes de l'utilisation rationnelle des antibiotiques et l'antibiorésistance

Cher Docteur, Madame, Monsieur ,

La Commission de coordination de la politique antibiotique a été créée suite à une conférence européenne sur le problème de l'antibiorésistance à Copenhague en septembre 1998 ("The Microbial Threat"). Un des principaux objectifs de cette commission scientifique est d'obtenir une utilisation rationnelle des antibiotiques dans les différents domaines : en agriculture (utilisation d'antibiotiques comme promoteurs de croissance), en médecine vétérinaire et bien sûr en médecine humaine, ceci afin d'enrayer l'augmentation inquiétante de l'antibiorésistance.

Letter sent to

- all GP's
- all pharmacists
- all pediatricians
- all "respiratory diseases" specialists

(excerpt)

All documents exist in both French and Flemish
(a German version is under preparation)

Carrying out the campaign

.be
HEALTH

Objet: Campagne de sensibilisation rationnelle des antibiotiques

Cher Docteur, Madame, Monsieur

La Commission de coordination conférence européenne sur le pro 1998 ("The Microbial Threat") scientifique est d'obtenir une utilisation dans les domaines : en agriculture (utilisation en médecine vétérinaire et biologie) l'augmentation inquiétante de l'antibiotique

les antibiotiques:
à utiliser
moins souvent
et **mieux**

.be HEALTH
Une initiative du Ministère Royal des Affaires sociales, de la Santé publique et de l'Environnement

Avec le soutien de la Commission Européenne et de la Commission Flandre

Brochure sent to

- all GP's
- all pharmacists
- all pediatricians
- all "respiratory diseases" specialists

(1st page)

All documents exist in both French and Flemish
(a German version is under preparation)

Carrying out the campaign

HE

Objet:

Cher D

La Cor confère 1998 (scientif domain en mé l'augme

TV spot
(30 sec)

All documents exist in both French and Flemish
(a German version is under preparation)

Launching the campaign

Objet: Campagne rationnelle

Cher Docteur, Mac

La Commission d

conférence europée

1998 ("The Micr

scientifique est d'o

domaines : en agri

en médecine véte

l'augmentation inq

l.be HEALTH

les antibiotiques:
à utiliser
moins souvent
et **mieux**

accès brochure

pour en savoir plus

spot TV

GRAPHIC DESIGN : A.S.B.L. QUESTION SANTE
Web site sponsored by the Fédération belge d'Endocrinologie et de microbiologie clinique (ZODMO)

<http://www.antibiotiques.org> (French)

<http://www.red-antibiotica.org> (Flemish)

Web site

All documents exist in both French and Flemish
(a German version is under preparation)

Public campaign : what has been done

	number	target	channel		
Booklets	600,000	patients	MD's / Pharmac. Soc. Organizat. ¹ MD's. / Pharmc.		
Folders	400,000				
Posters	40,000				
TV-spots	French 461 ² Flemish 36 ³	general public	prime time 30 sec broadcasts		
Radio-spots	French 708 ² Flem. 44 ³				
Direct Press & Media communications				general public MD's/Pharm.	newspapers medical press
Web sites	general ⁴ scientific ⁵			general public MD's	University server Ministry server

¹ Social Security and Reimbursement Organizations (Mutuelles), etc...

² free access; ³ paying access;

⁴ www.antibiotiques.org -- www.red-antibiotica.org; ⁵ www.health.fgov.be

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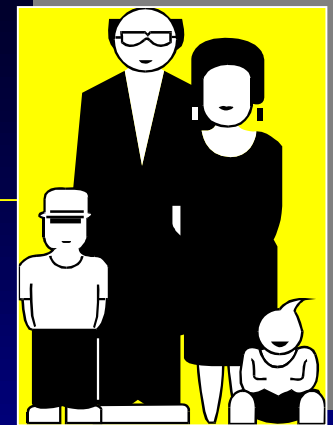
Why
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Awareness of the public



Method :

- face-to-face interviews
- n=1,015
- representative of population > 14 y.
- analysis by regions
 - Flanders (West-Fl., East-Fl., Kempen)
 - Brussels & Brabant (Fl. + Wall.)
 - Wallonia
- 1 month after end of the campaign



Awareness of the public: results (1 of 4)

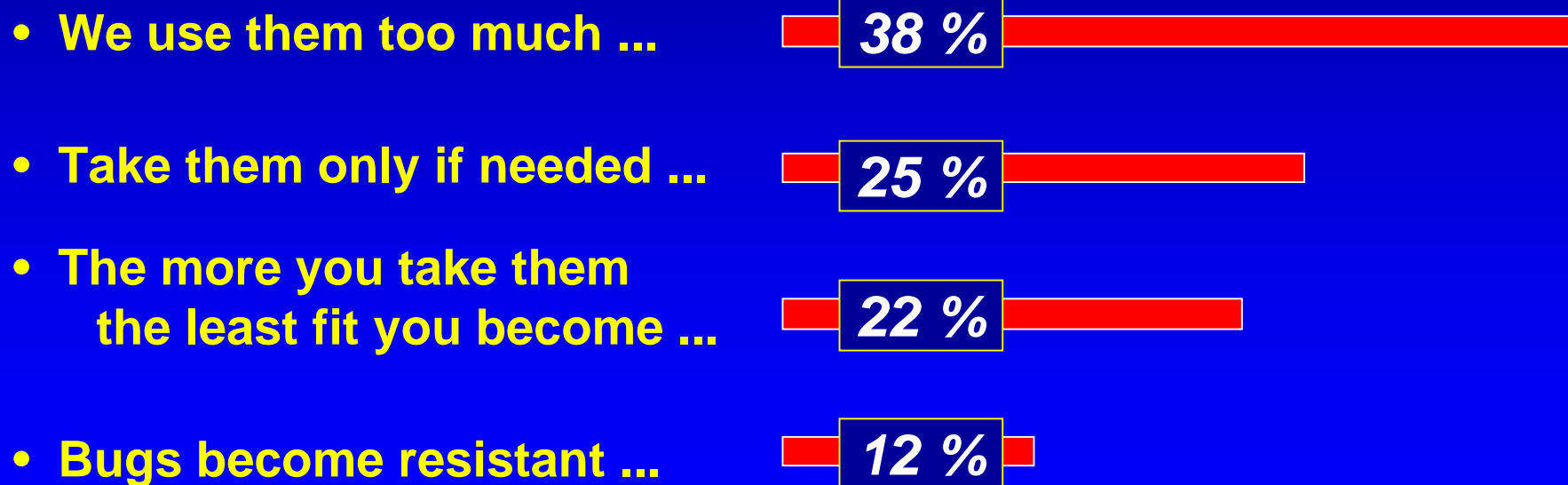
Main and most salient results concerning the **direct impact** at the national level:

➔ "Do you remember the campaign ? ..."



Main and most salient results concerning the **perception of the message** (national) :

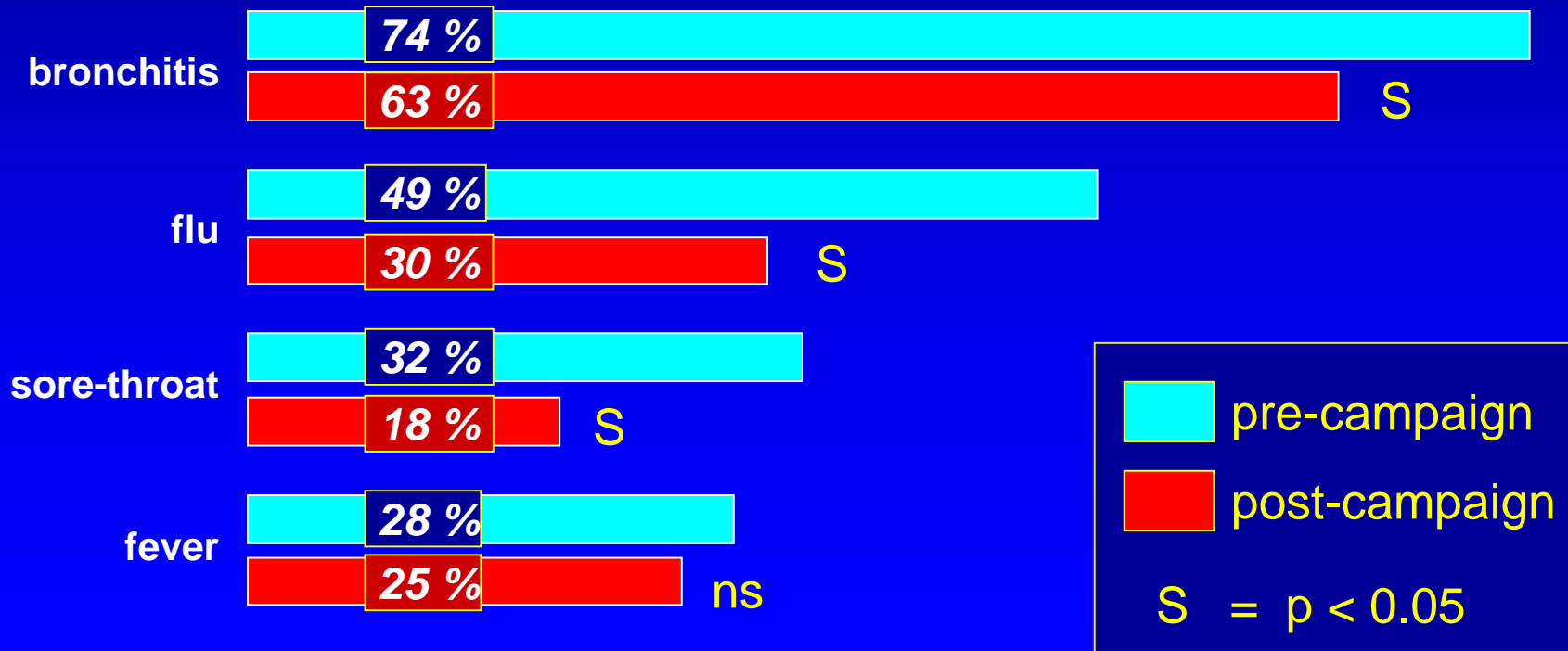
➔ What was the main message ?



Awareness of the public : results (3 of 4)

Main and most salient results concerning changes in antibiotic expectations (national) :

➔ Do you expect / ask for an antibiotic in case of ...



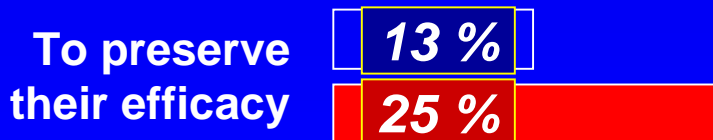
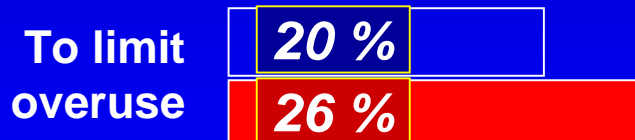
Awareness of the public : results (4 of 4)

Main and most salient results concerning individual AB use (national):

➔ Would you use less AB in agreement with your GP?



Why ?



pre-campaign
post-campaign

S = $p < 0.05$

Appreciation by the General Practitioners



Method :

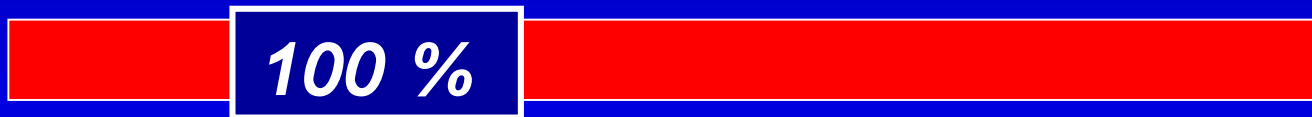
- telephone interviews
- n=400
- representative of all 3 regions
- 3 months after end of the campaign



Appreciation by the General Practitioners : results (1 of 5)

Direct impact:

How many GPs remembered the campaign ?

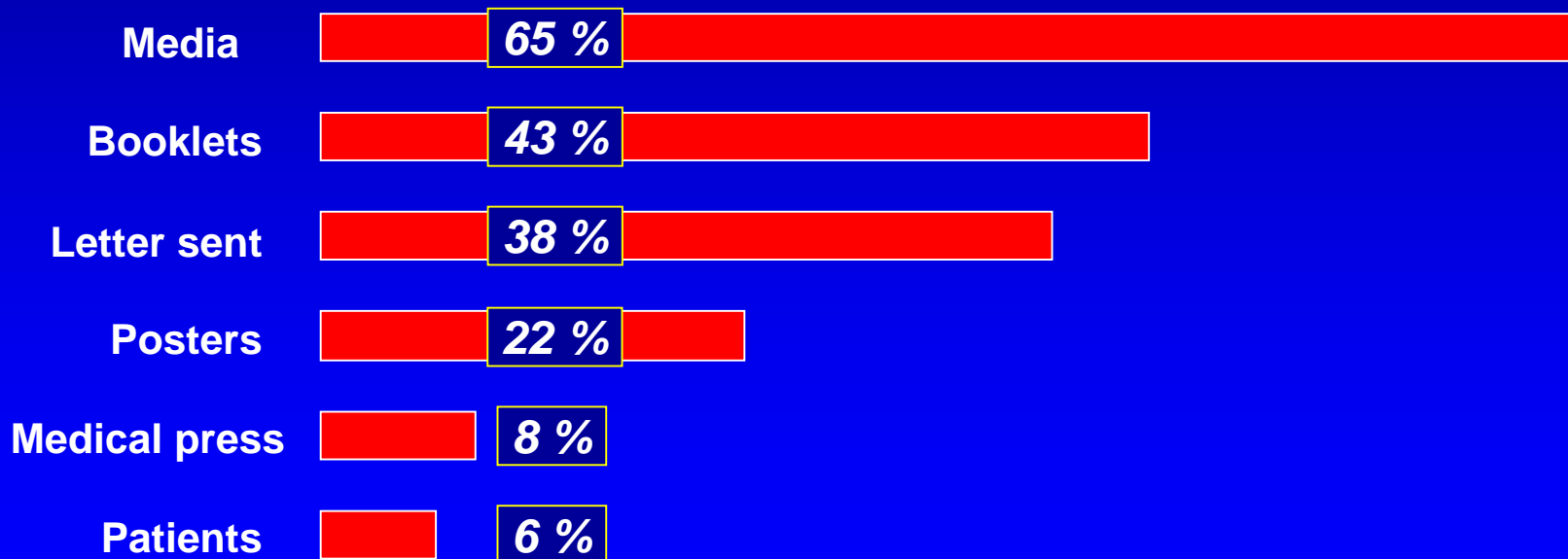


Appreciation by the General Practitioners : results (2 of 5)

Importance of the source ...

What made you to notice it ?

(several answers possible)



Appreciation by the General Practitioners : results (3 of 5)

What do **YOU** think about the campaign ...
(several answers possible)

Useful

73 %

Doctors feel involved

51 %

Only intended at money
saving by Social Security

32 %

Appreciation by the General Practitioners : results (4 of 5)

The perception of the message ...

“ What do you remember ? “

We urgently must use less AB

39 %

Doctors should prescribe less AB

36 %

Bugs become resistant

12 %

Appreciation by the General Practitioners: results (5 of 6)

Has the contact with patients
and YOUR practice been changed ?

patients accept more
easily a “no AB” prescription



I have prescribed less AB



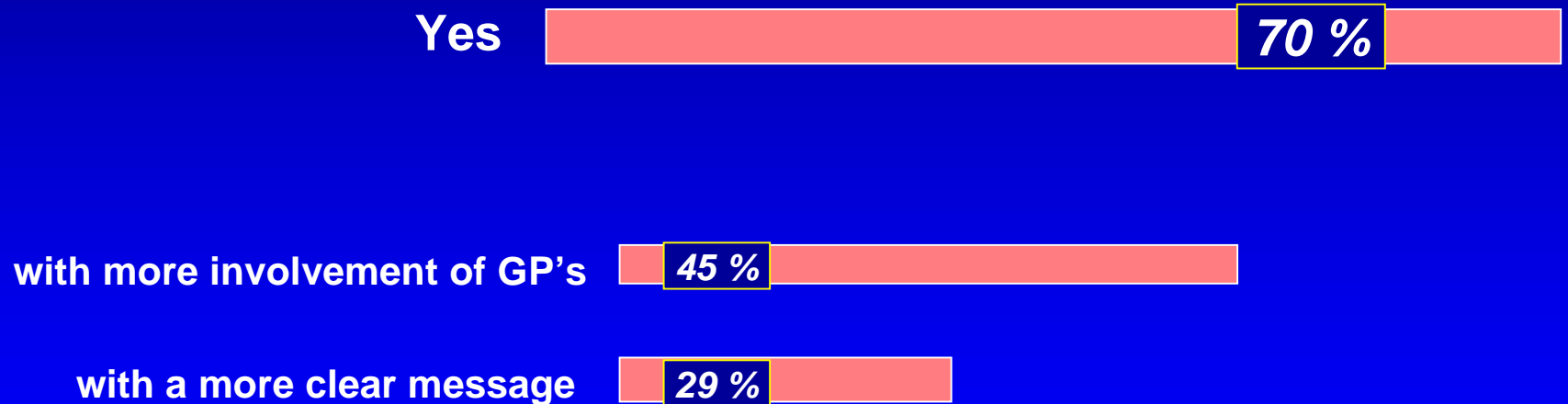
Patients spontaneously
speak about resistance



30 % of the GPs say they have changed their practice ...

Appreciation by the General Practitioners : results (6 of 6)

Should the campaign be repeated next year ?



Changes of AB sales in the community



Methods

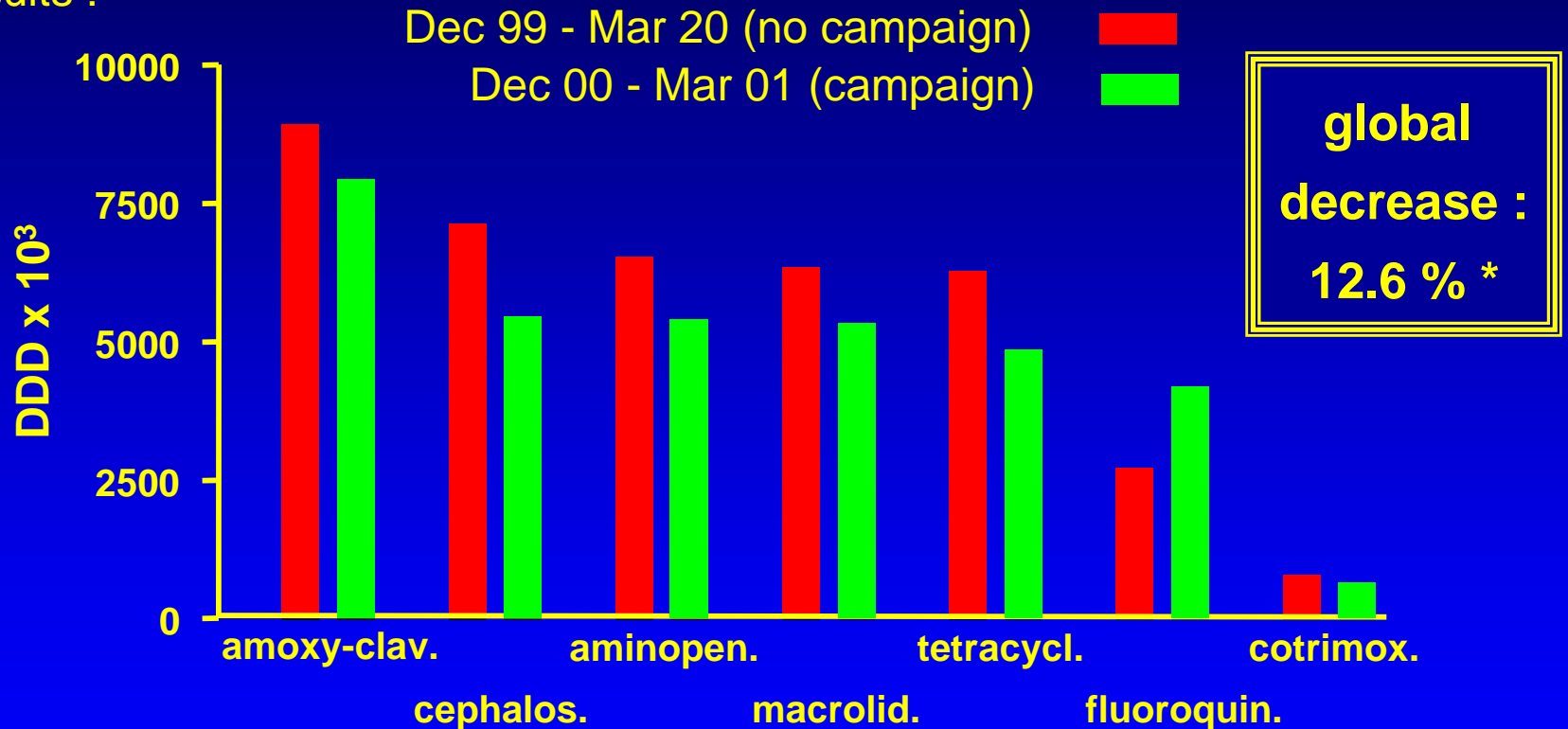
- first, **descriptive** approach :
 - record of AB sales* (DDD; class ATC J01) in retail pharmacies from Dec. 2000 through Mar. 2001 (IPhEB-IFEB; 77 % exhaustivity)
 - comparison with sales* in the same period for 1999-2000

* data purchased from the
Belgian Pharmaceutical Association



Changes of AB sales in the community: results of the descriptive approach (1 of 2)

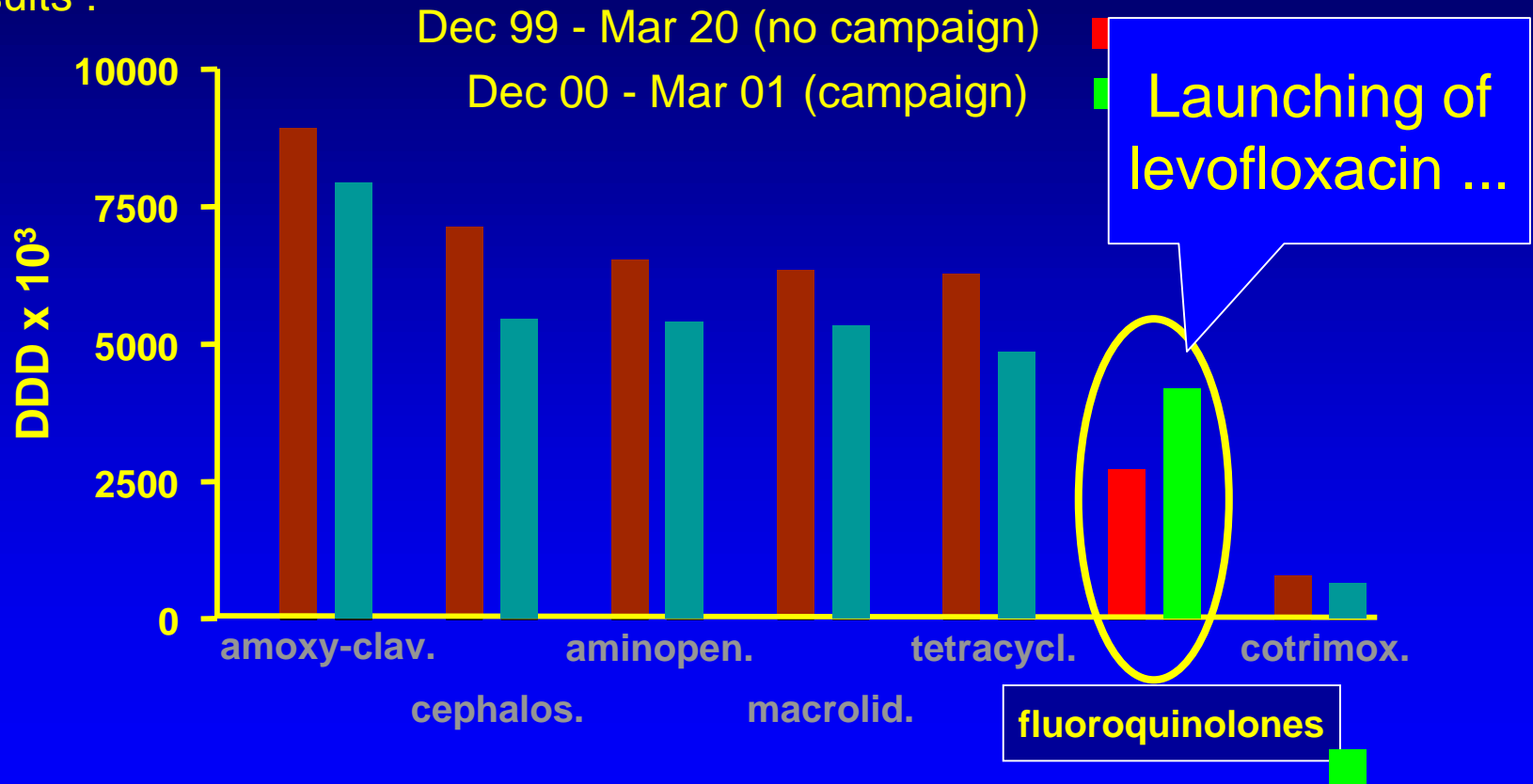
Results :



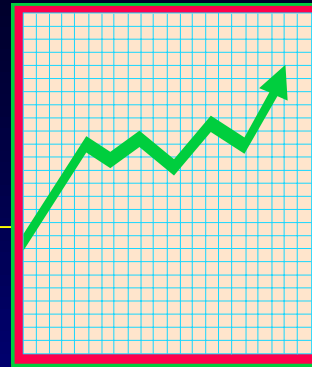
* accounting for 97.9 % of total antibiotic outpatient sales

Changes of AB sales in the community: results of the descriptive approach (2 of 2)

Results :



Changes of AB sales in the community



Methods

- 2d: **AutoRegressive Integrated Moving Average Model (ARIMA)**

Why ?

- to examine the influence of the seasonal variations in incidence of **Acute Respiratory Infections (ARI)** on antibiotic use

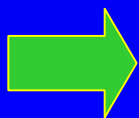
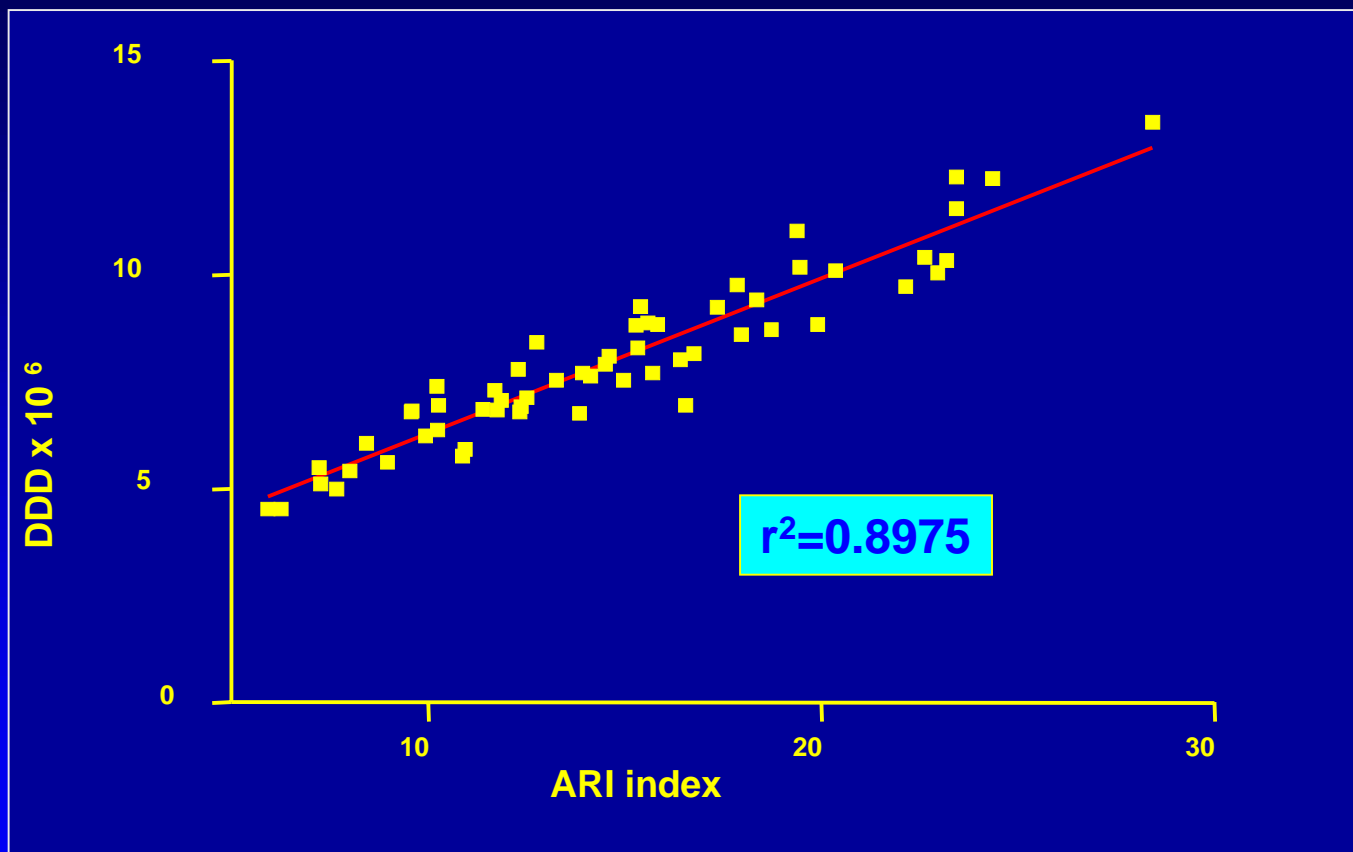
How ?

- Use AB sales and ARI incidence data for the period 1996 through Nov 2000 to predict the potential use of AB in Dec 2000 - Mar 2001 (campaign period) based on actual ARI incidence during this period
- **Deviations from predicted values will assess the role of an additional factor (i.e., the campaign ...)**

In collaboration with the Belgian
Institute of Pharmacoepidemiology

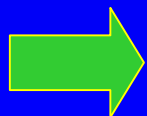
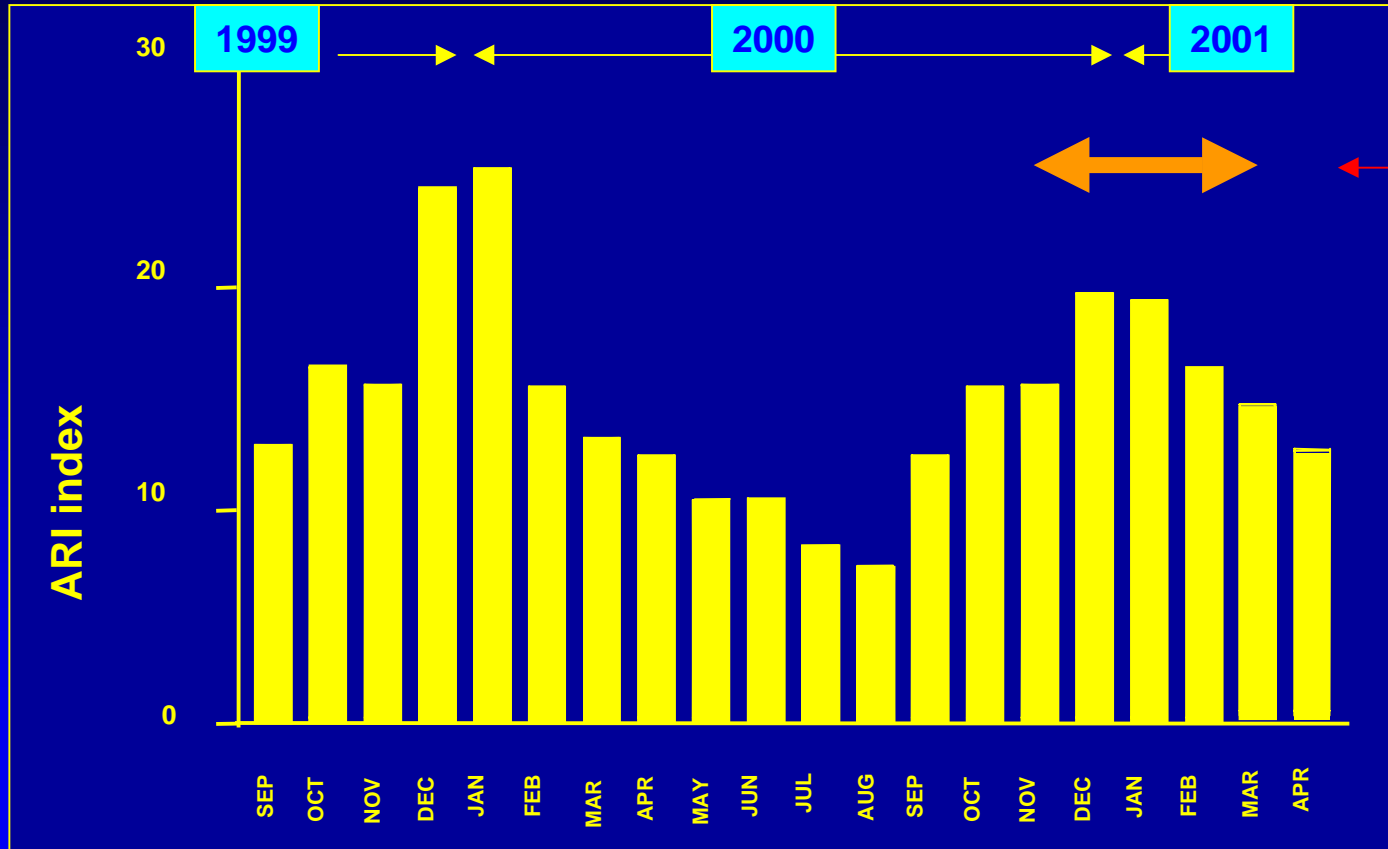


Correlation between monthly AB consumption (DDD) and ARI index (1996 through nov. 2000)



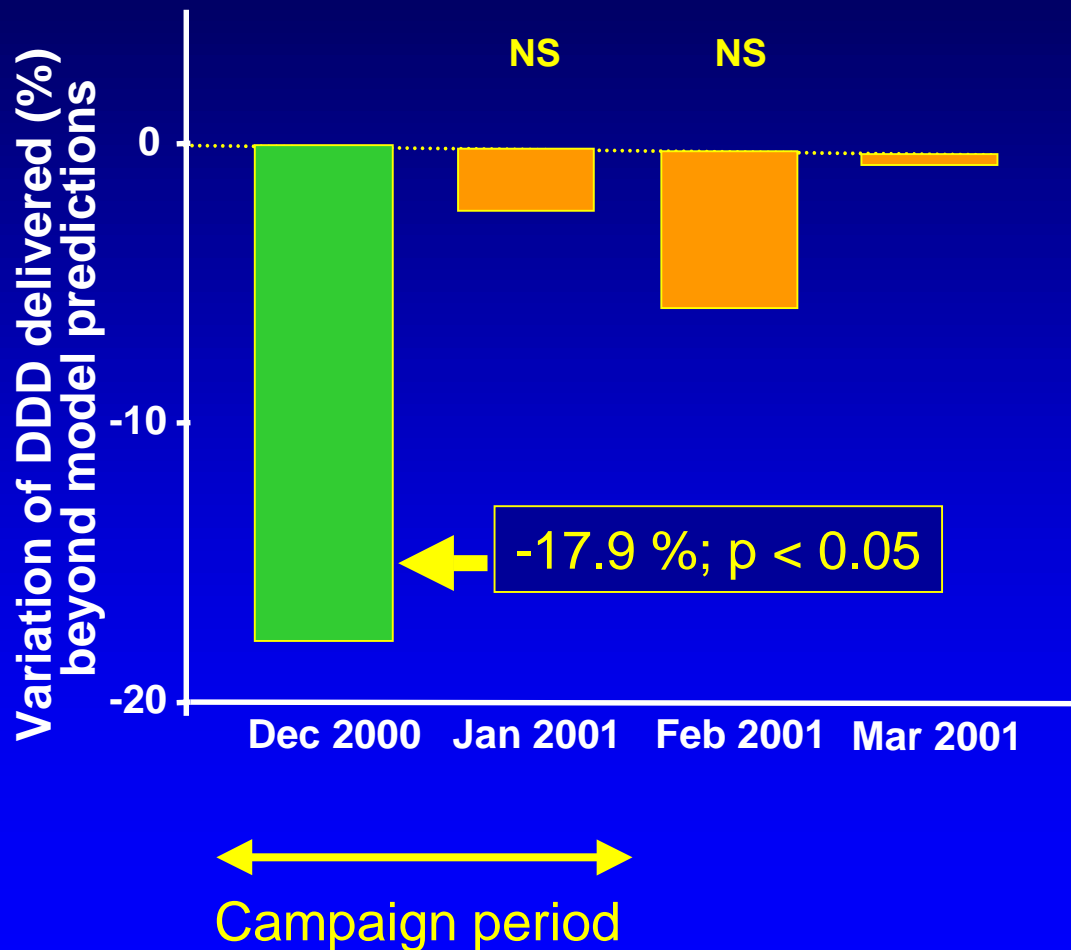
Each variation of 1 ARI unit causes an increase of AB use of 364,035 DDD [298,202-429,868]

Differences in ARI indices during the winter 1999-2000 (no campaign) and the winter 2000-2001 (campaign)



There were less ARI during the campaign than during the previous winter

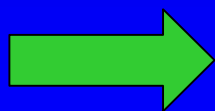
Monthly deviations of AB sales from predicted values during the campaign period and the next two months



- the campaign caused an immediate and highly significant decrease of AB sales
- this decrease
 - cannot be explained by the lower incidence of ARI in 2000-2001
 - is very transient
- the overall 4-month decrease remains significant ($p = 0.039$)

Conclusions

- The campaign
 - improved the awareness of the public, made it alert to the problem of bacterial resistance, and reduced requests for antibiotics
 - was judged globally positive by GPs
 - reduced transiently AB prescribing
- Media (mostly TV) were the most instrumental mean in attracting attention of both the public and GPs
- GPs' awareness of AB resistance in their daily practice remains low



The campaign should be repeated
(and extended /improved).

Has this been submitted to peer-review ?

- **A public campaign for a more rational use of antibiotics**

I. Bauraind, H. Goossens, P.M. Tulkens, M. De Meyere, P. De Mol, and Ludo Verbist.

11th European Conference on Clinical Microbiology and Infectious Diseases (ECCMID), Istanbul, Turkey, 2001, poster # 410

- **Evaluation of the Impact of a Public Campaign for a More Rational Use of Antibiotics in Belgium**

I. Bauraind, I. Vanden Bremt, M. Bogaert, H. Goossens, P. Mouchet, P. Trefois, J.-L. Marchal, B. Seys, P.M. Tulkens, and L. Verbist

41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, Ill. Dec 16th-19th, 2001, oral session LB # 023£

- **Researchers describe latest strategies to combat Antibiotic-Resistant Microbes**

J. Stephenson,

JAMA, May 9, 2001 –Vol 285, N°18

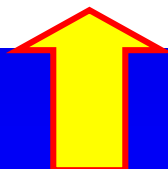
Are we the only country (with high AB consumption) to think along these lines ?

archives.lemonde.fr

Le Monde.fr

5. [La moitié des prescriptions d'antibiotiques sont injustifiées](#)    [ajouter au panier](#)

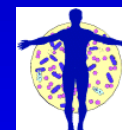
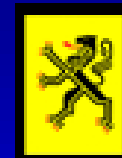
Un rapport souligne les risques de résistance bactérienne liés à la surconsommation et au mauvais usage de ces médicaments. Bernard Kouchner a annoncé un plan pluriannuel qui vise à préserver leur efficacité en sensibilisant médecins et malades
21 Novembre 2001 - SANDRINE BLANCHARD -



Acknowledgments

All the authors of the publications, and

- Mr F. Vandenbroucke and Mrs M. Aelvoet (Federal Ministers of Social Affairs, Public Health and Environment) and their cabinet members
- Mr C. Decoster, Chief Medical Officer, Federal Ministry of Health
- The French-speaking Community of Belgium*
- The Flemish-speaking Community of Belgium*
- Scientific Institute of Public Health “Louis Pasteur”
- *Société Belge d’Infectiologie et de Microbiologie Clinique / Belgische Vereniging voor Infectiologie en Klinische Microbiologie*
- *Université catholique de Louvain* (for WEB facilities)



* responsible for preventive medicine activities at the community level

All campaign materials, this set of slides, and additional information is available for download at
<http://www.antibiotiques.org/english> or <http://www.red-antibiotica.org/english>