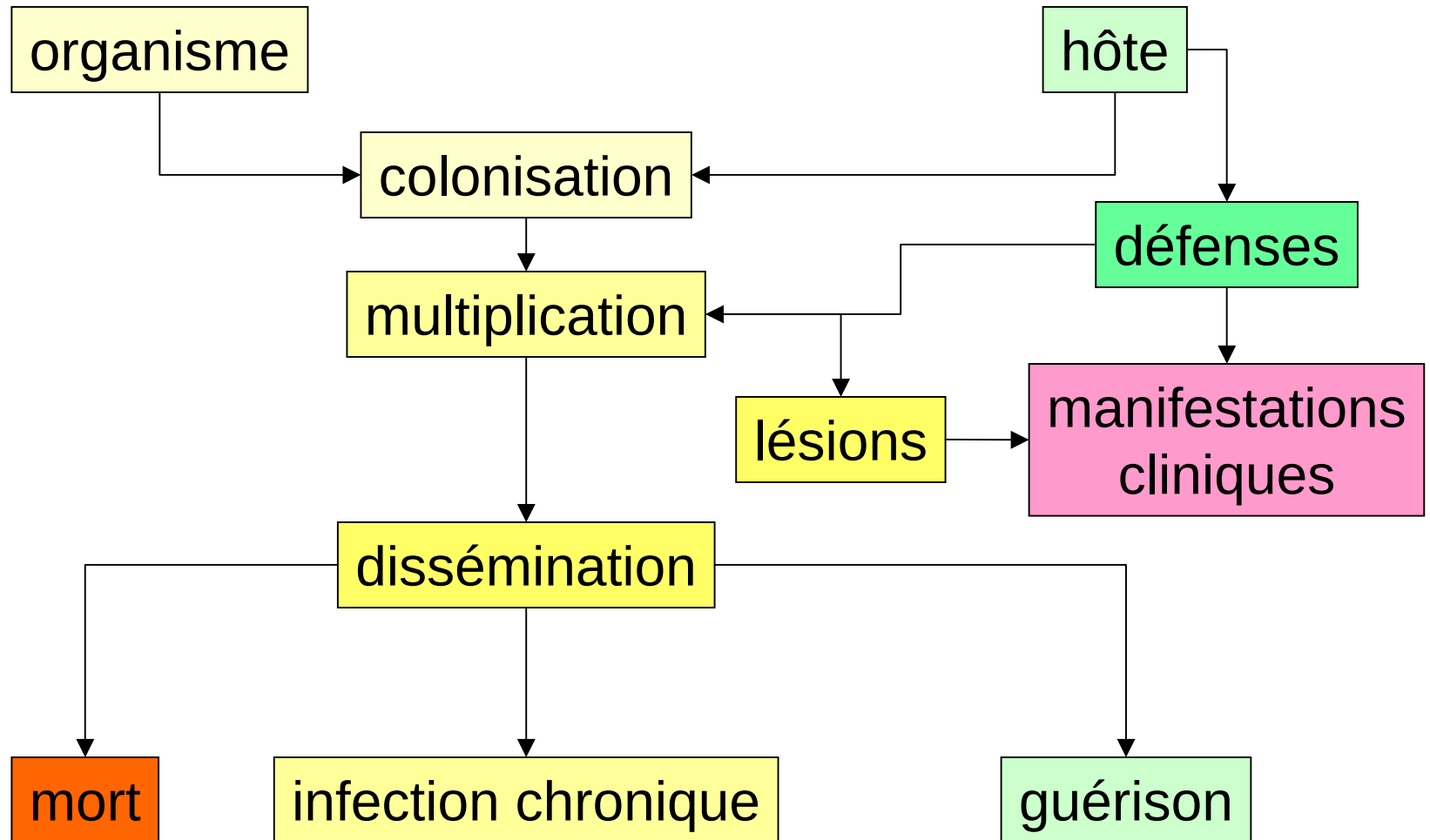


Histoire naturelle de l'infection



Capacité de dissémination d'un germe infectieux

$$D = k \frac{I \times C}{L \times D_i \times S} \times \frac{A \times F_s}{D_f}$$

où I = inoculum

C = contagiosité

L = létalité

D_i = capacité de poser un diagnostic précoce permettant un traitement

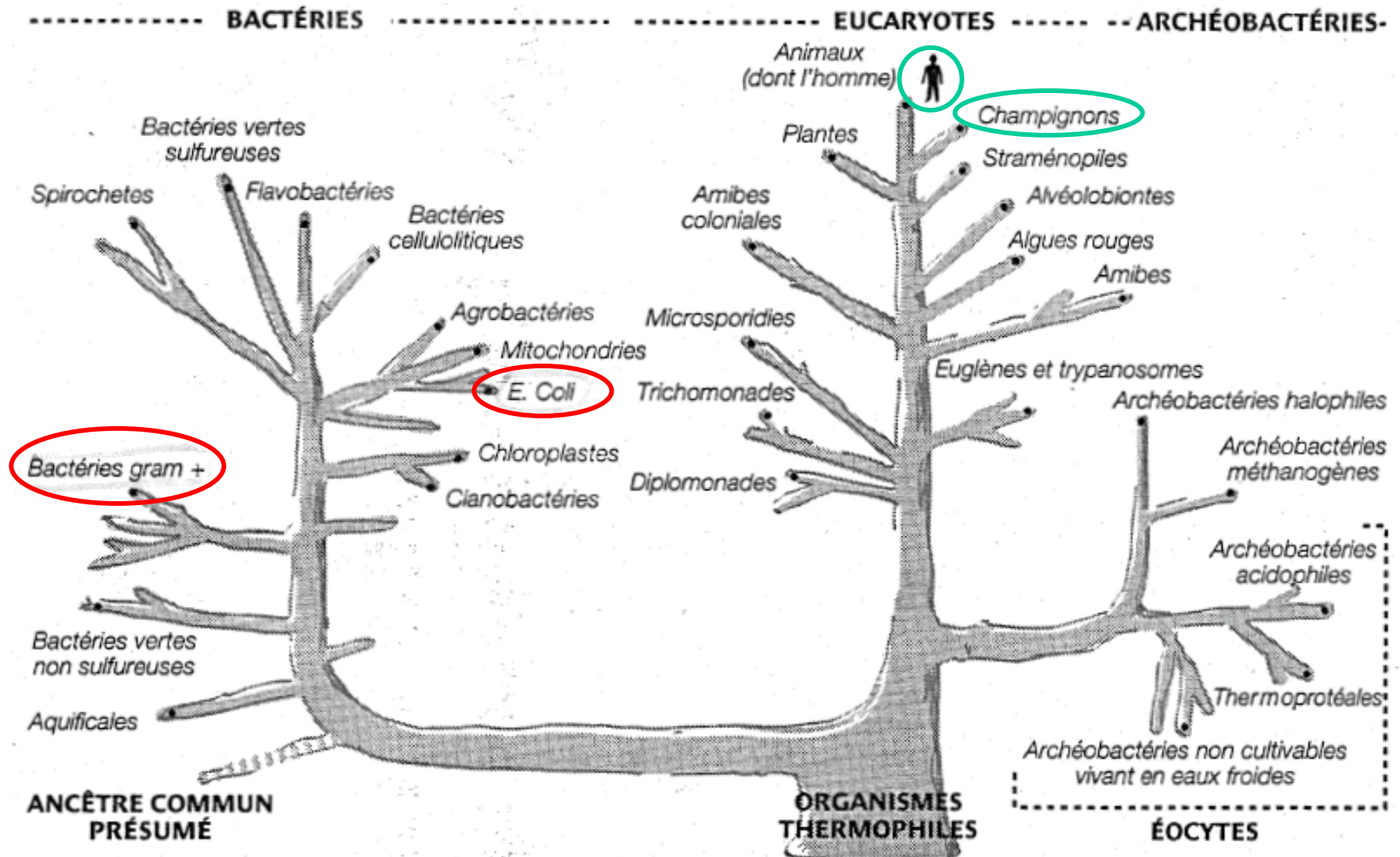
S = sensibilité à l'agent thérapeutique à l'endroit de l'infection

A = capacité d'adaptation de l'agent infectieux

F_s = facteurs de sensibilité de l'hôte

D_f = défenses de l'hôte

Le royaume du vivant ...

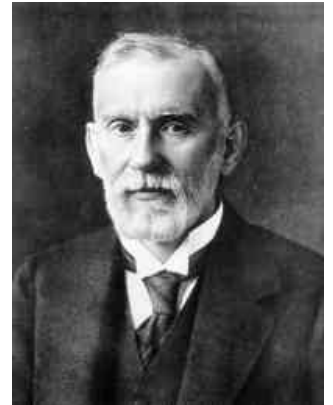


Bases moléculaires de la chimiothérapie

- être toxique pour l'organisme envahissant
- ne pas être toxique pour l'hôte
- dès lors, avoir une action sélective sur le métabolisme spécifique de l'envahisseur

Les balles magiques...

Le concept de Paul Ehrlich était que des substances chimiques pouvaient atteindre leurs cibles de façon spécifique...



Quelles sont les cibles ?

- classe I: métabolisme général
 - ➔ difficile ...
- classe II: métabolisme propre des micromolécules
 - ➔ parfois ...
- classe III: métabolisme propre des macromolécules
 - ➔ le plus fréquent ...

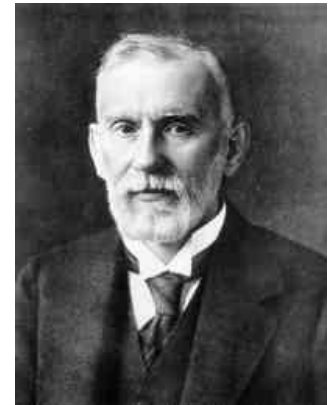
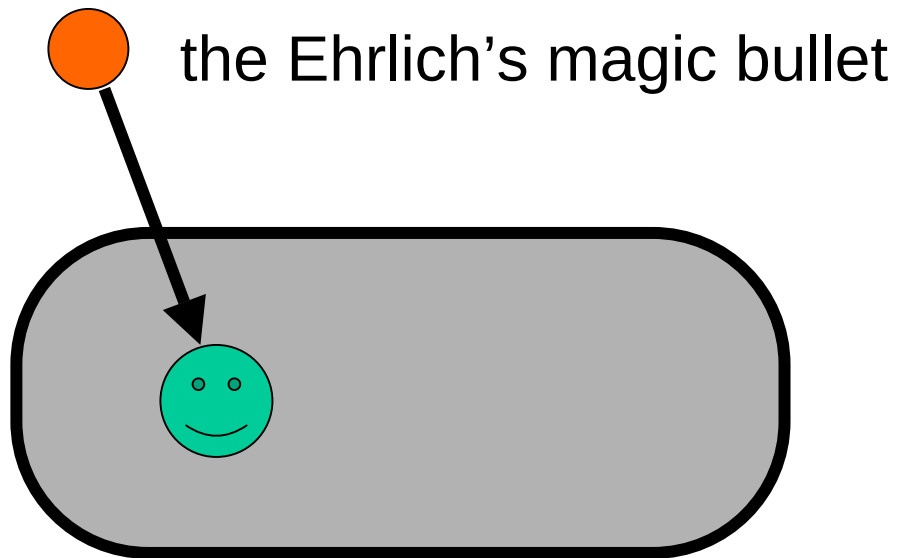
Exemple de cibles ...

- classe II
 - synthèse de l'acide folique
 - sulfamides, pyrimétamine...
 - synthèse des pyrimidines
 - fluorouracil
- classe II
 - synthèse du peptidoglycan
 - β -lactames, glycopeptides, ...
 - synthèse protéique
 - macrolides, aminoglycosides, lincosaminides, phénicolés ...
 - métabolisme des ac. nucléiques
 - fluoroquinolones, ansamycines, ...

Résistance...

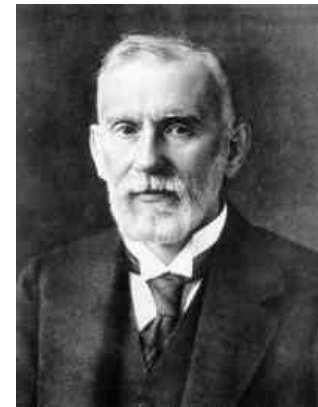
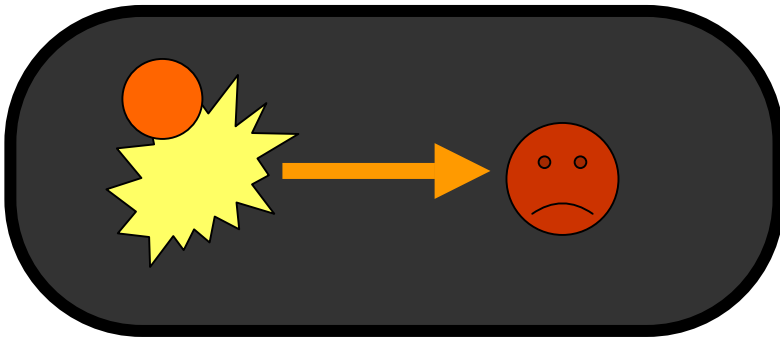
- est un phénomène naturel propre à tout ensemble d'êtres vivants soumis à une pression visant à les détruire ...
- résulte de l'acquisition de gènes (transmission / mutations) permettant, par leurs produits, d'échapper à l'agent destructeur
- se transmet facilement entre bactéries
 - plasmides
 - transposons

Bacterial resistance: the science



Bacterial resistance: the science

the Ehrlich's magic bullet has hit its target !

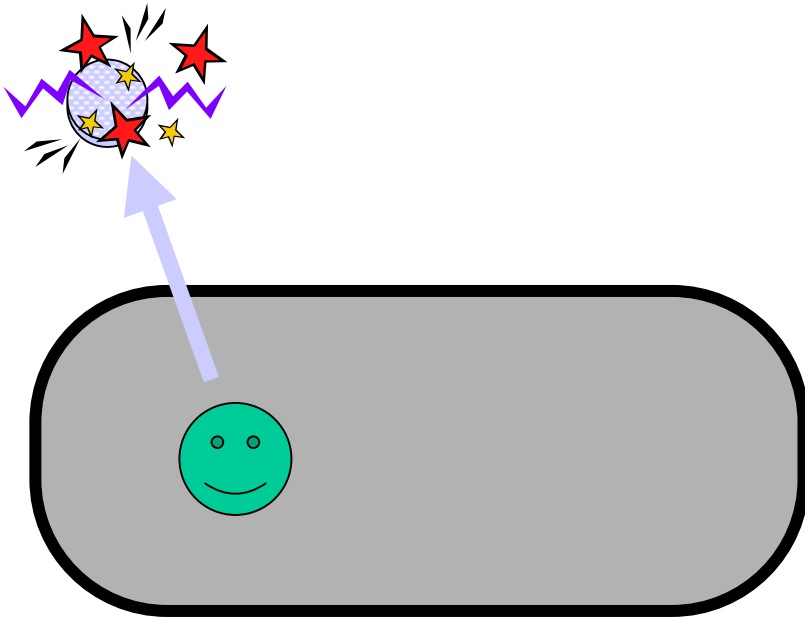


Bacterial resistance: the science



But only for a time...

Bacterial resistance: the science

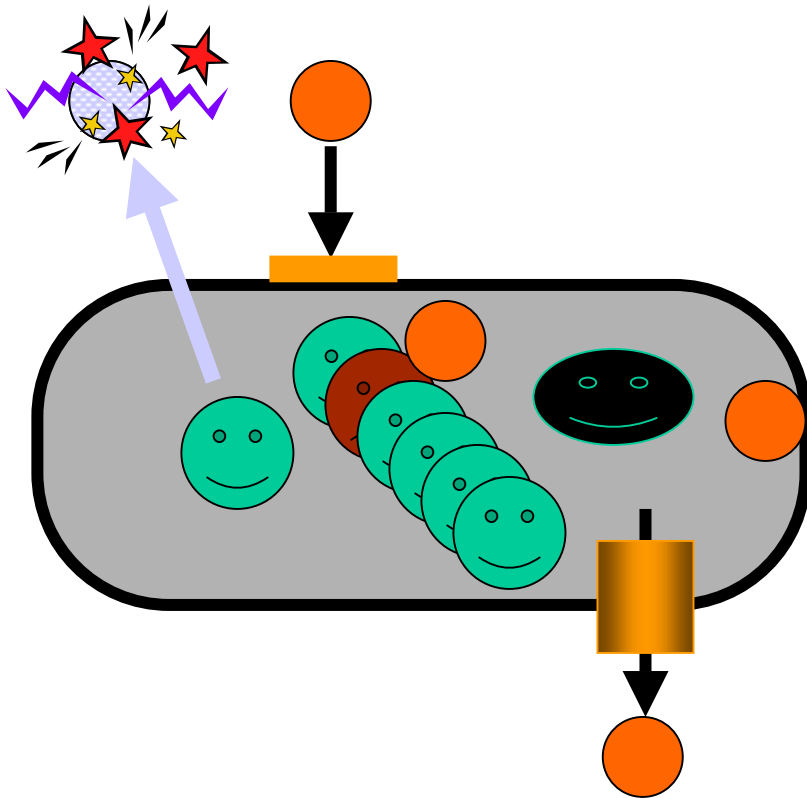


destruction of the AB

- β -lactamases,
- AG-degrading enzymes,



Bacterial resistance: the science



destruction of the AB

- β -lactamases,
- AG-degrading enzymes,

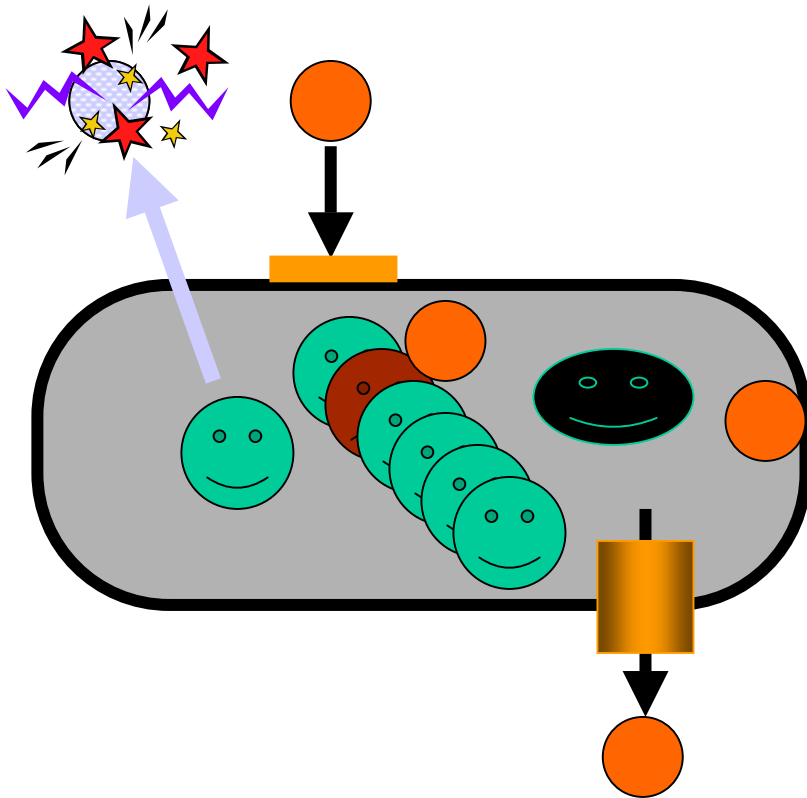
prevention of AB entry

overexpression of the target

modification of the target

efflux

Bacterial resistance: the science



development of the AB

- β -lactams
- Aminoglycosides, tetracyclines, glycopeptides, ...

prevention of entry

overproduction of the target

modification of the target

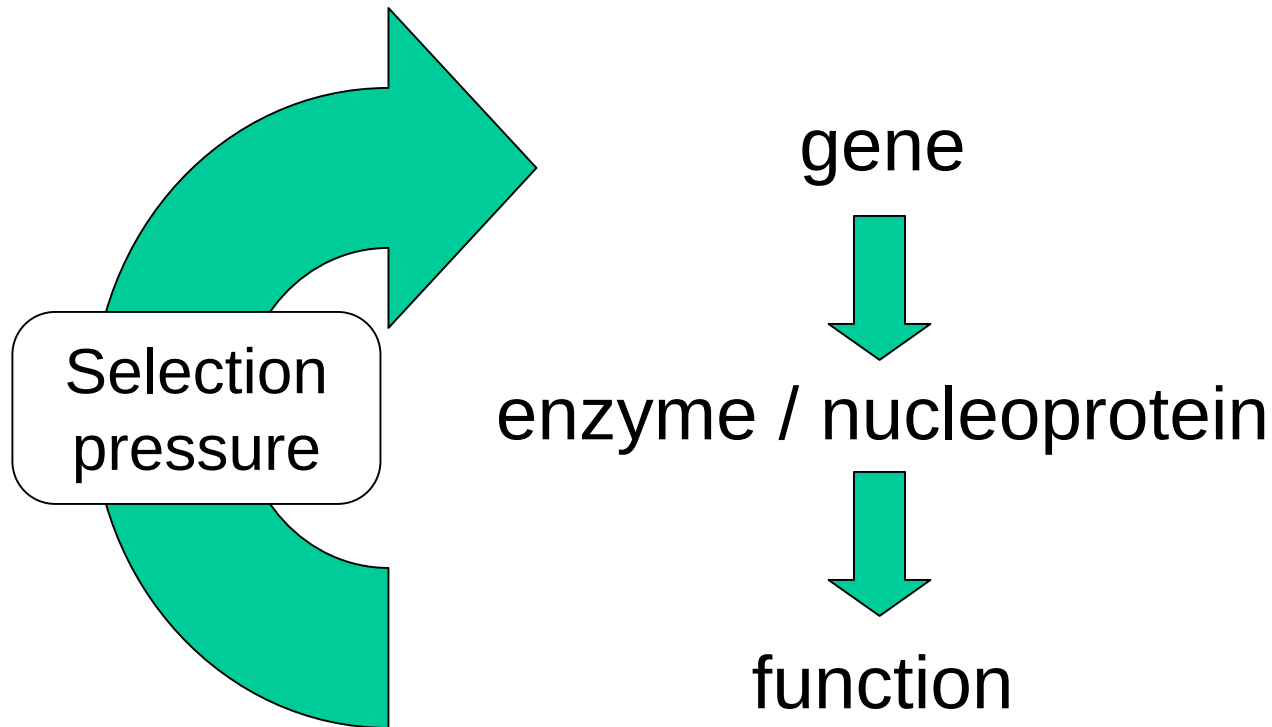
efflux



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

Bacterial resistance: why ?

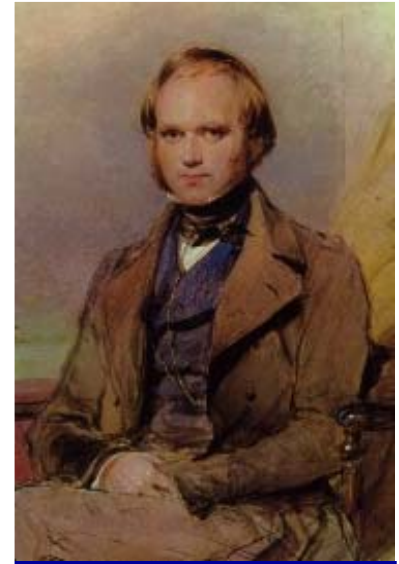
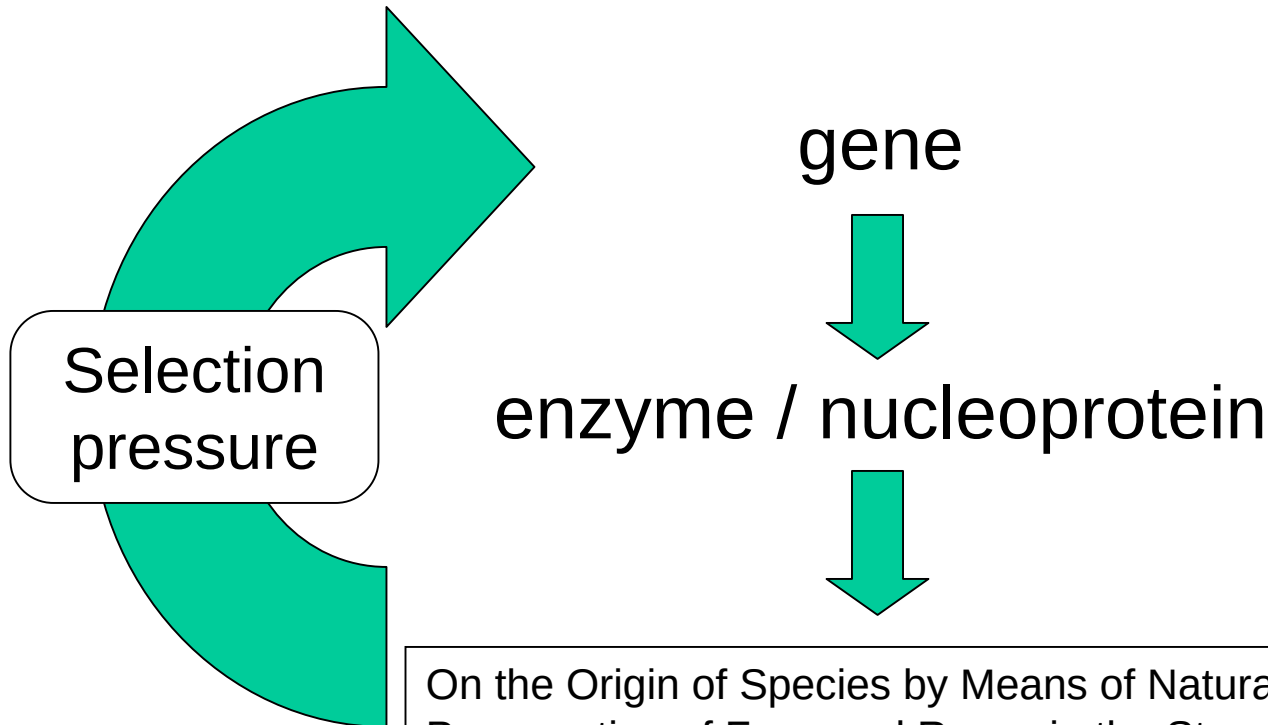
A simple application of Darwin's concepts ...



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.

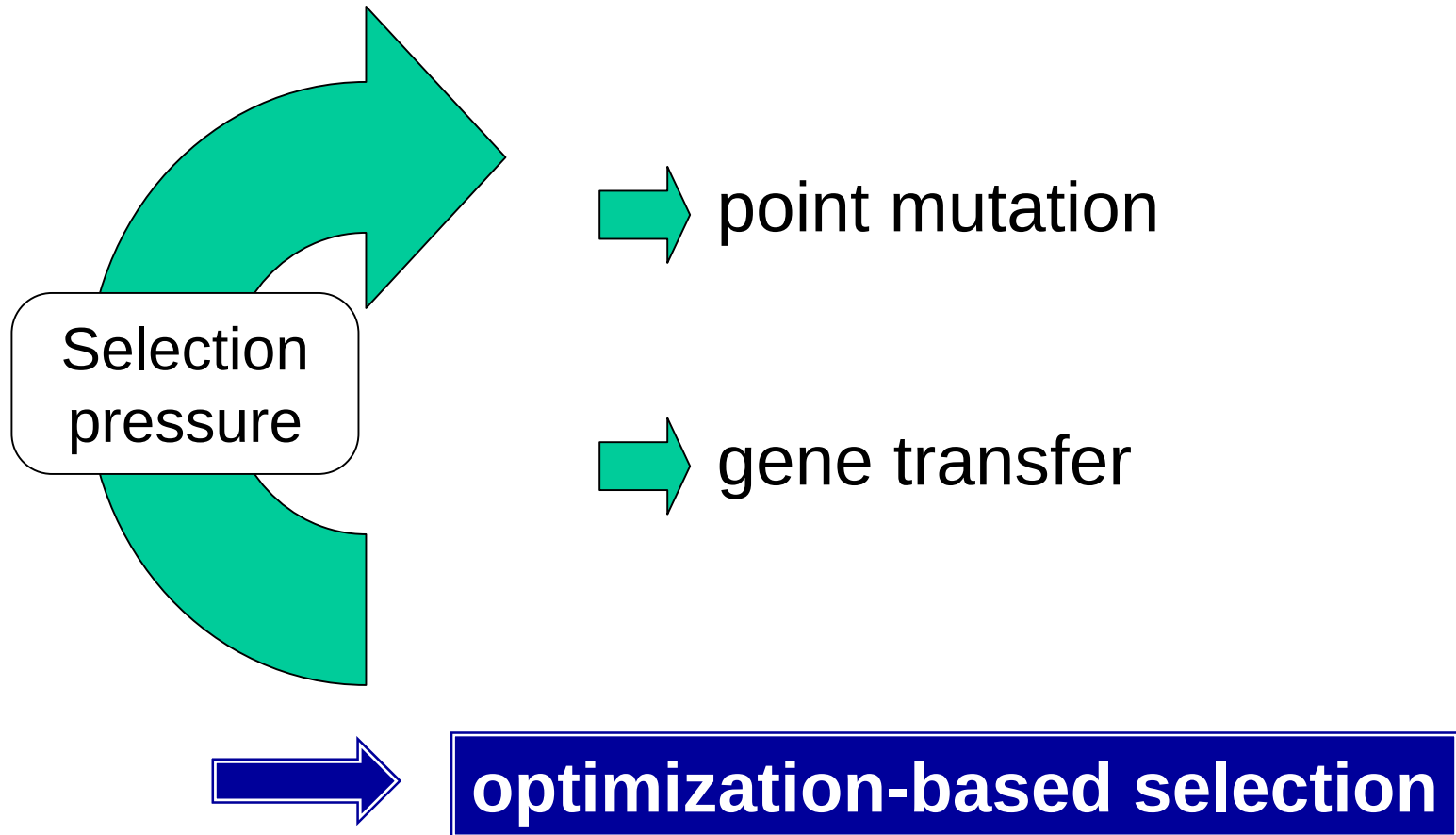
Charles Darwin, M.A.,

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>

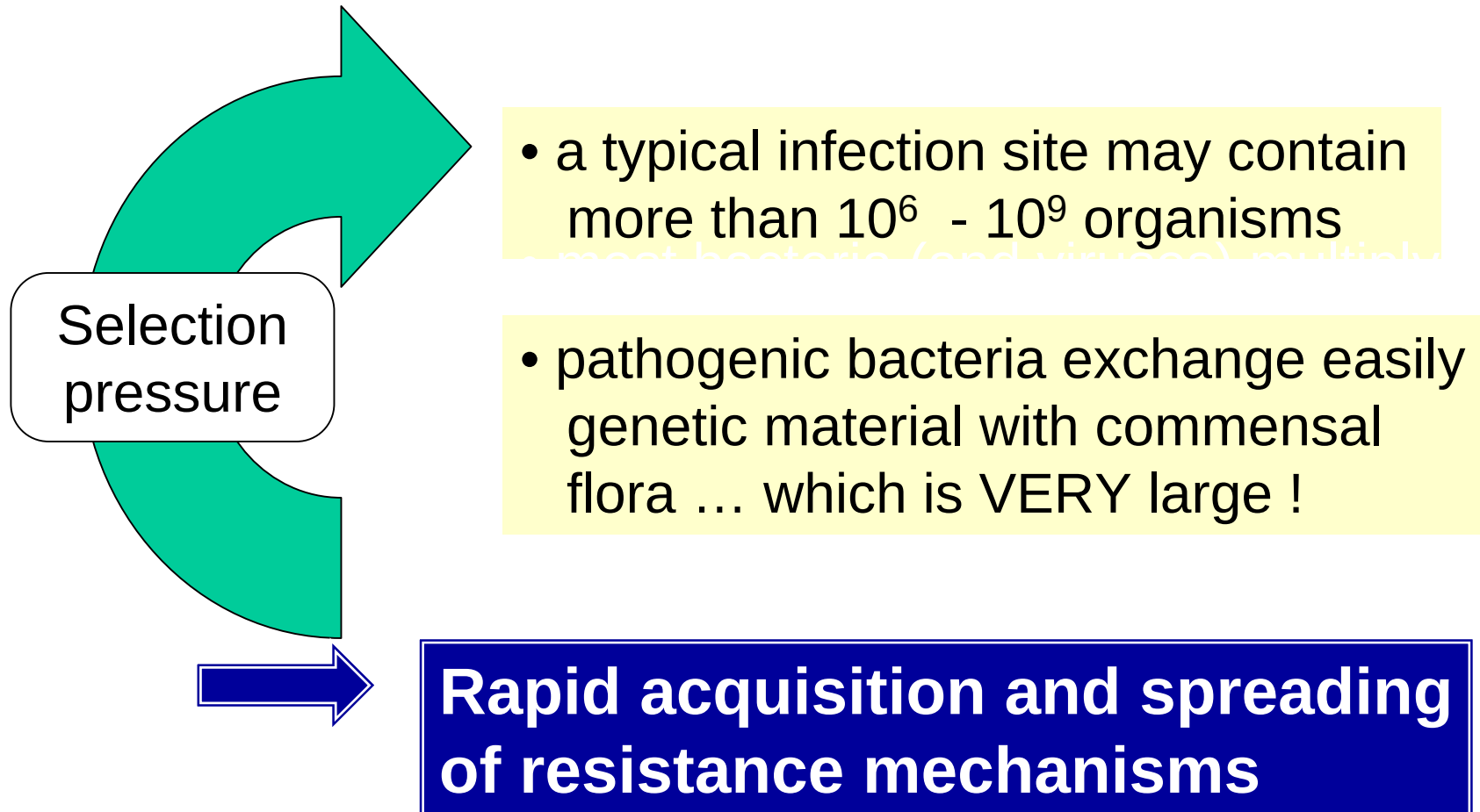
Bacterial resistance: why ?

How do bacteria apply the Darwin's principles ?.



Bacterial resistance: why ?

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



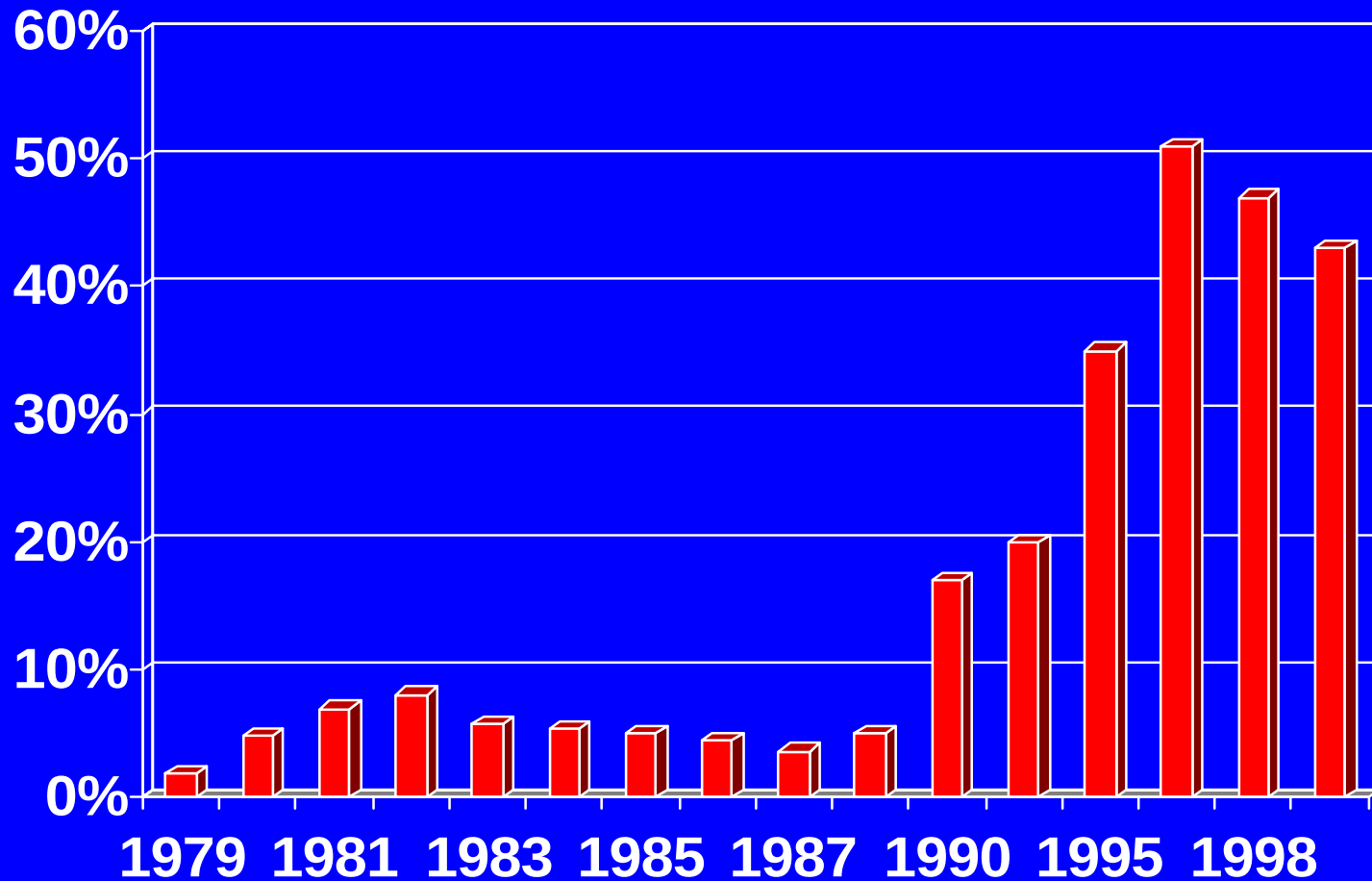
Bacterial resistance: is it important ?

- 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

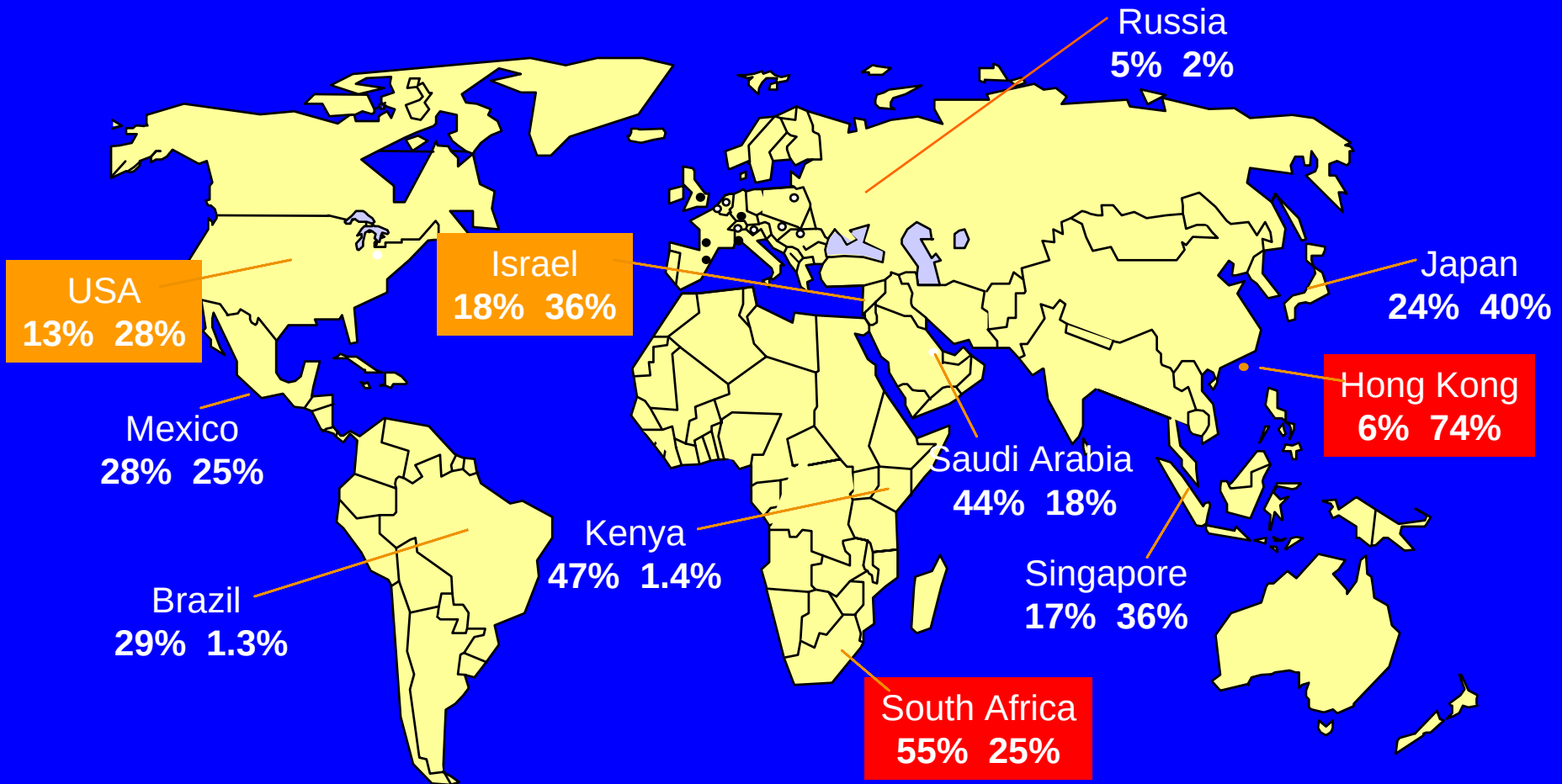
Not an exhaustive list !!

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

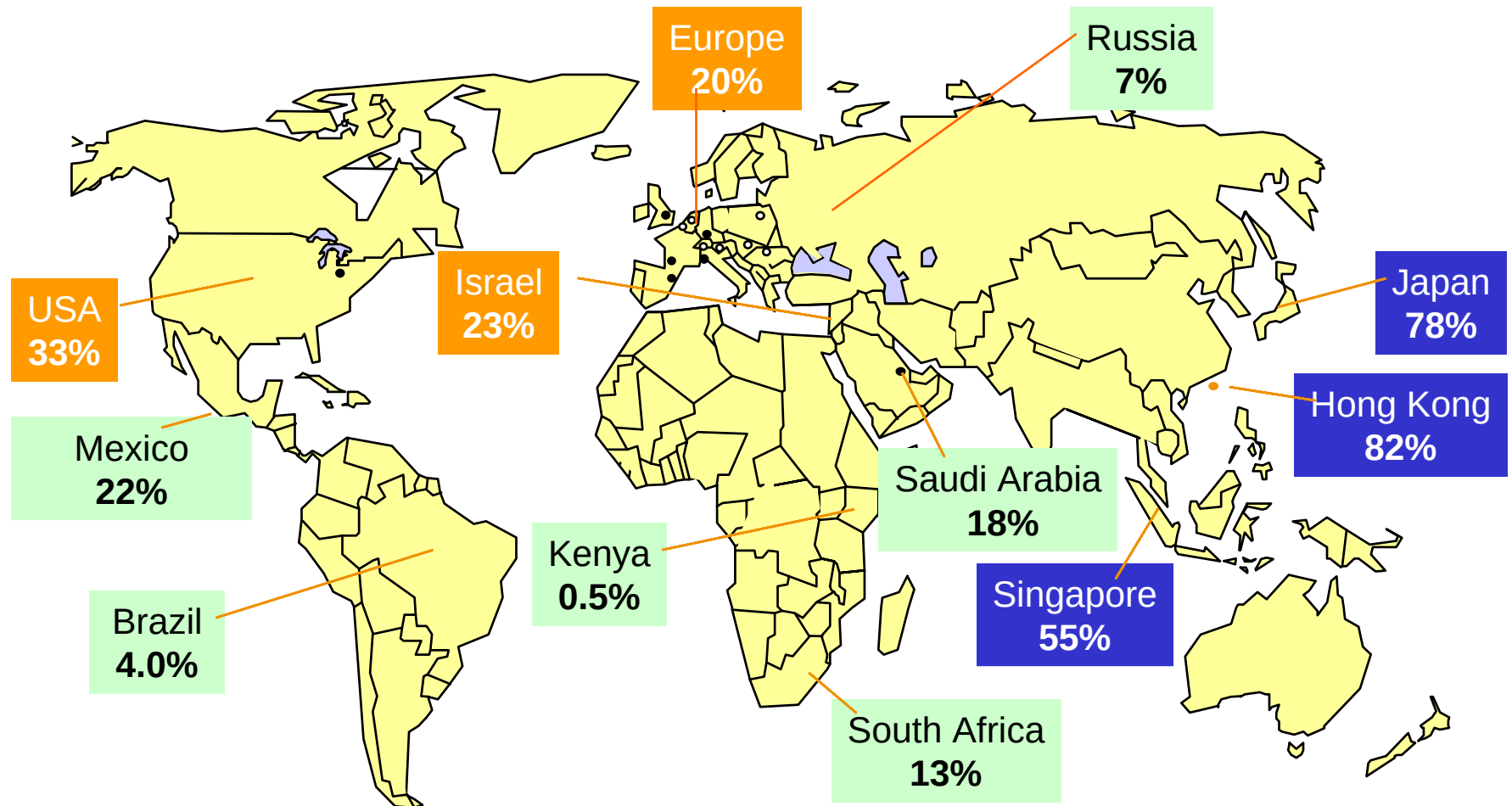
- *1st and 2d generation fluoroquinolones* *

S. aureus,
Ps. aeruginosa

- ...

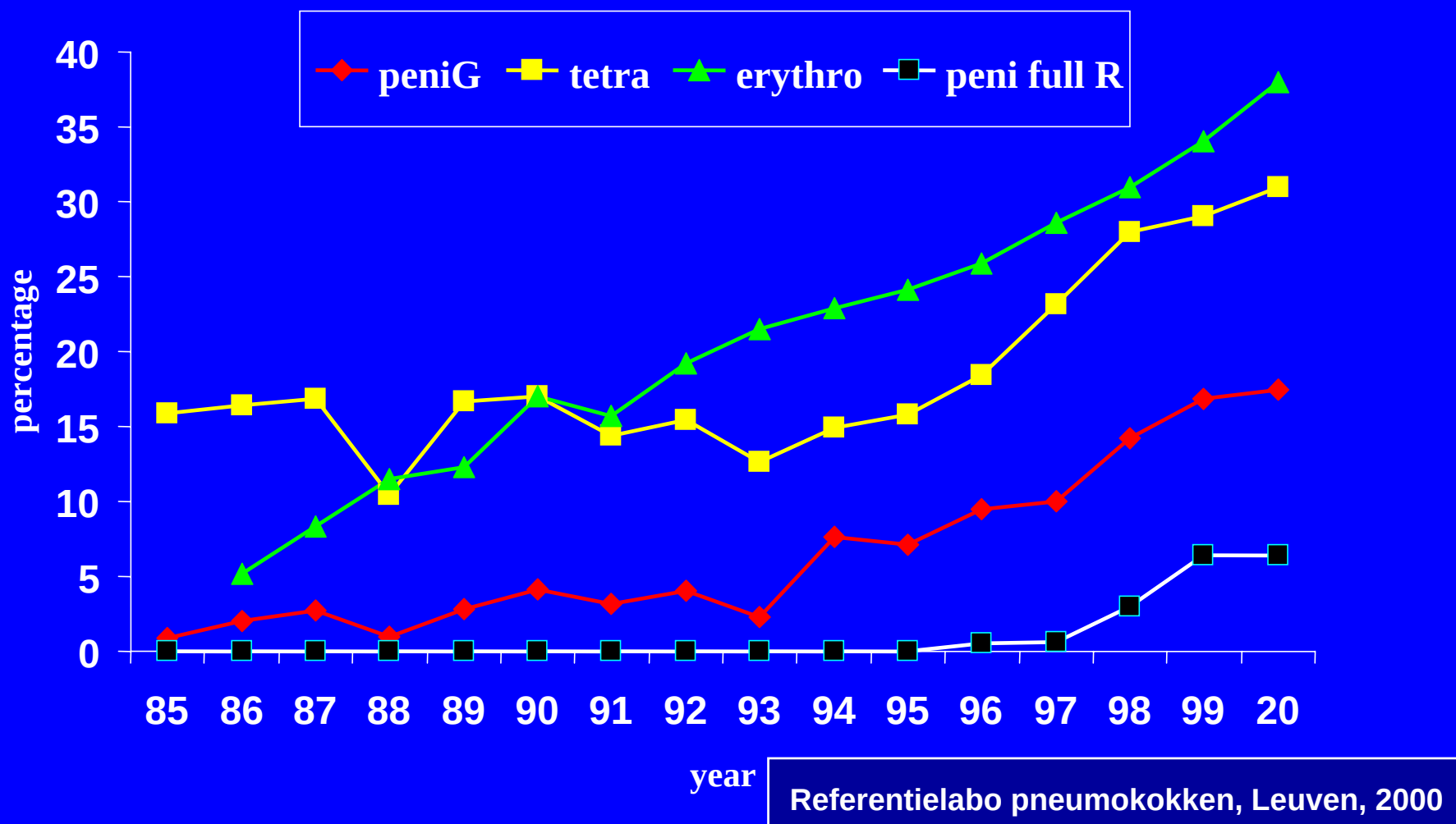
* totally synthetic molecules with new mode of action and introduced since the 80's only !!

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

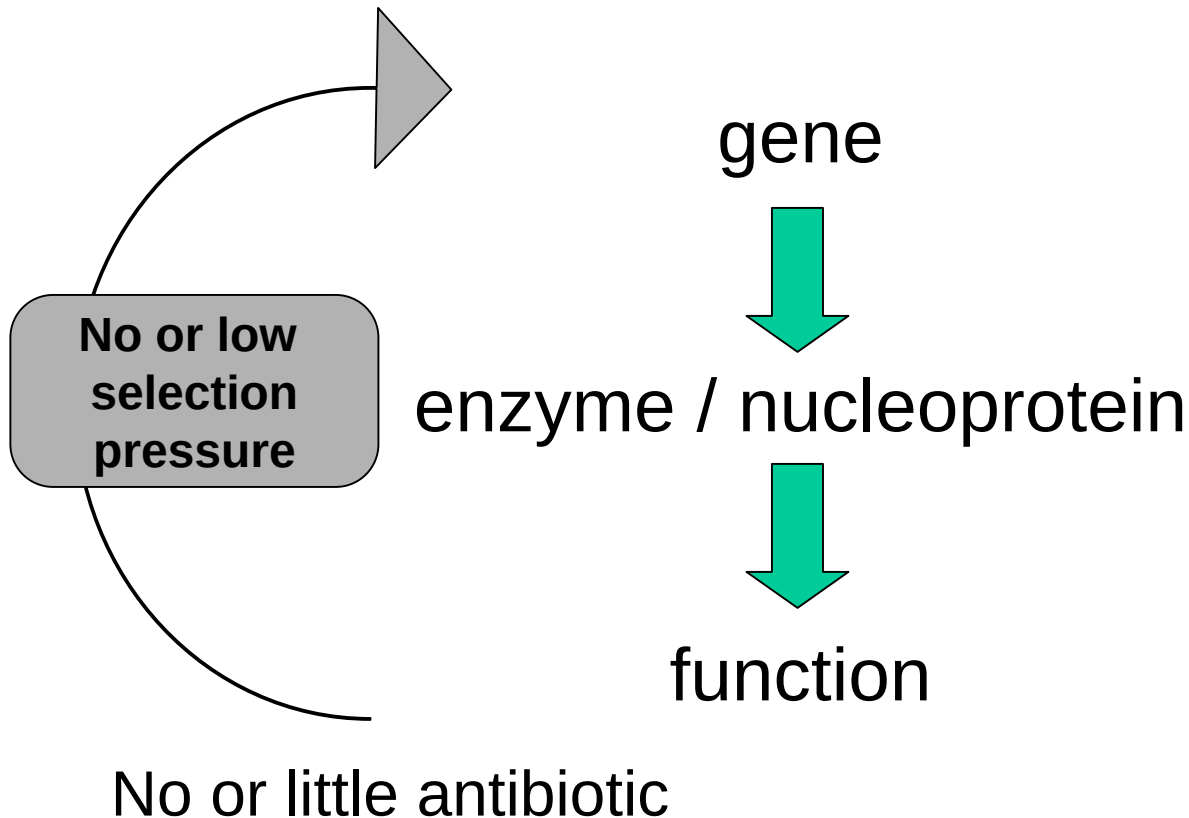


Resistance defined as erythromycin MIC $\geq 1\text{mg/L}$

Evolution of *S. pneumoniae* resistance in Belgium

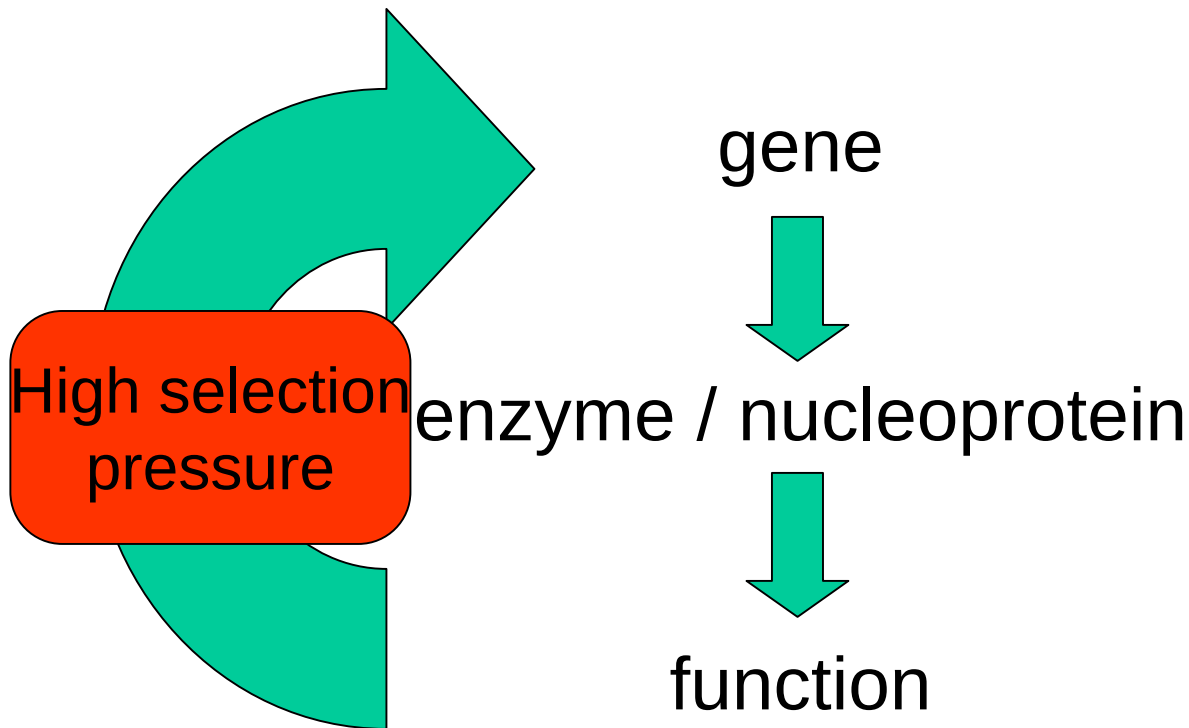


Resistance is linked to antibiotic usage and antibiotic misuse



Lowest resistance rates are seen in countries with low consumption of antibiotics and high level hygiene...

Resistance is linked to antibiotic usage and antibiotic misuse



Highest rates of resistance are seen in areas with

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

A lot of antibiotic and
a lot of non-killed bacteria

Paramètres utiles pour mesurer l'activité des antibiotiques

- CMI / CMB
- synergie / antagonisme
- effet post-antibiotique
- pharmacodynamie