

**Vers des points critiques (plus) rationnels pour les antibiotiques:  
Actions de l'  
European Committee on Antimicrobial Susceptibility Testing  
(EUCAST).**

**... et quelques vues personnelles**

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Sur base de présentations de Gunnar Kahlmeter, président de l'EUCAST, et quelques dias de Johan Mouton

Conférence donnée

- au Roeulx, le 9 octobre 2007 (Groupes de Gestion de l'Antibiothérapie du Hainaut)
- à Liège, le 11 octobre 2007 (Centre hospitalier de la Citadelle)
- à Luxembourg (Gd-Duché) le 28 novembre 2007 (Groupe d'infectiologie du Luxembourg)

Note: chaque conférence n'a pas nécessairement intégré l'ensemble des données montrées ici

# Vous avez dit "point critique" ?

- Un chiffre 'magique' obtenu par le microbiologiste sur base d'un examen *in vitro* et qui a pour but de prédire si l'antibiotique sera ou non efficace *in vivo*.
- Les résultats microbiologiques sont obtenus sous forme de variable continue<sup>1</sup>, mais ces données sont traduites pour le clinicien en

– sensible ... (S)

– intermédiaire... (I)

– résistant ... (R)



qui est ce que **clinicien** recevra !

<sup>1</sup> diamètres; parfois convertis en CMI; les automates mesurent des vitesses de croissance...

Mais à quoi peuvent (bien) servir des points critiques?

Franchement, je me le suis souvent demandé ...



Bon

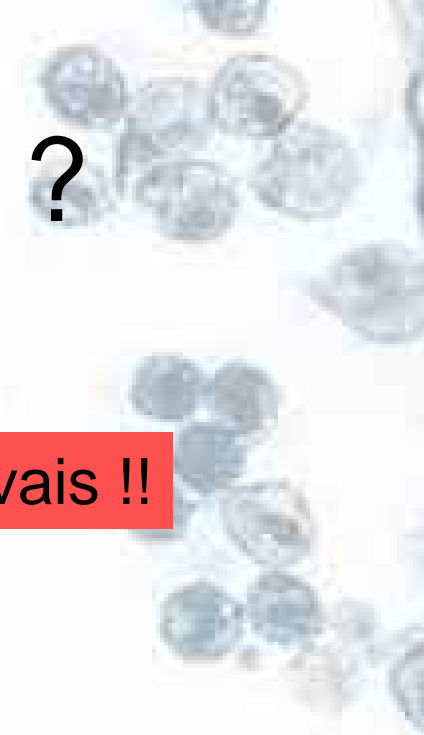
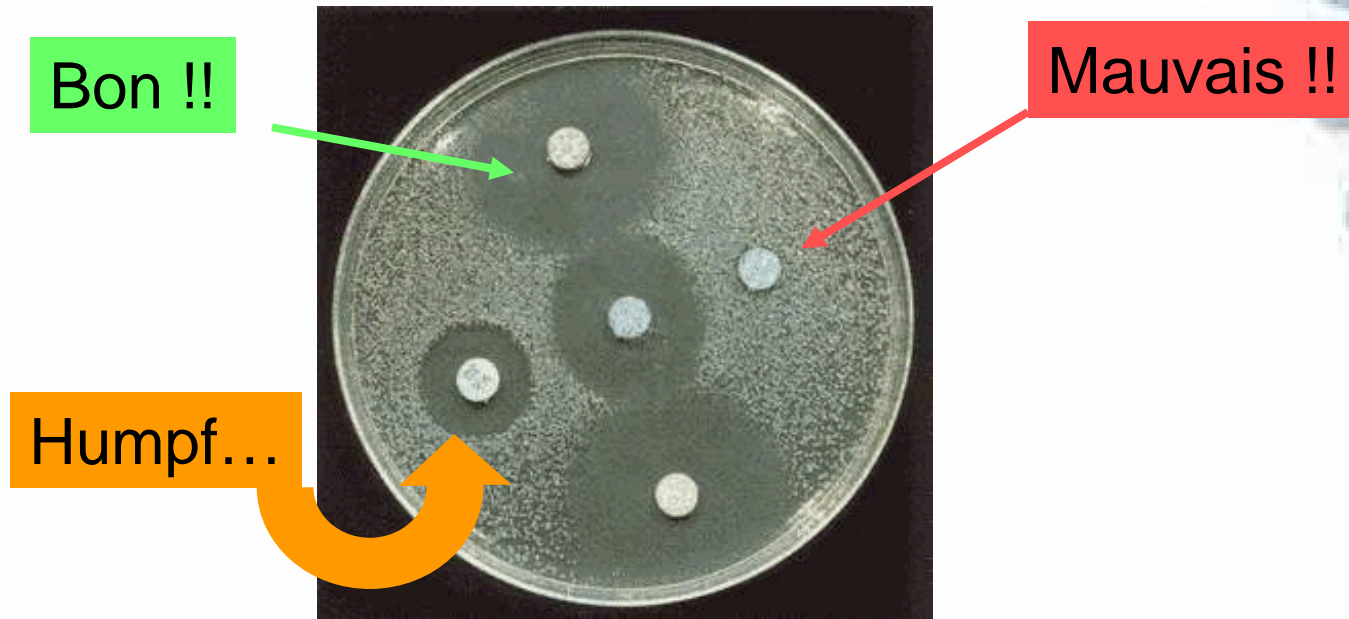
Slecht

# Pourquoi donc des points critiques?

Peut-être parce que...

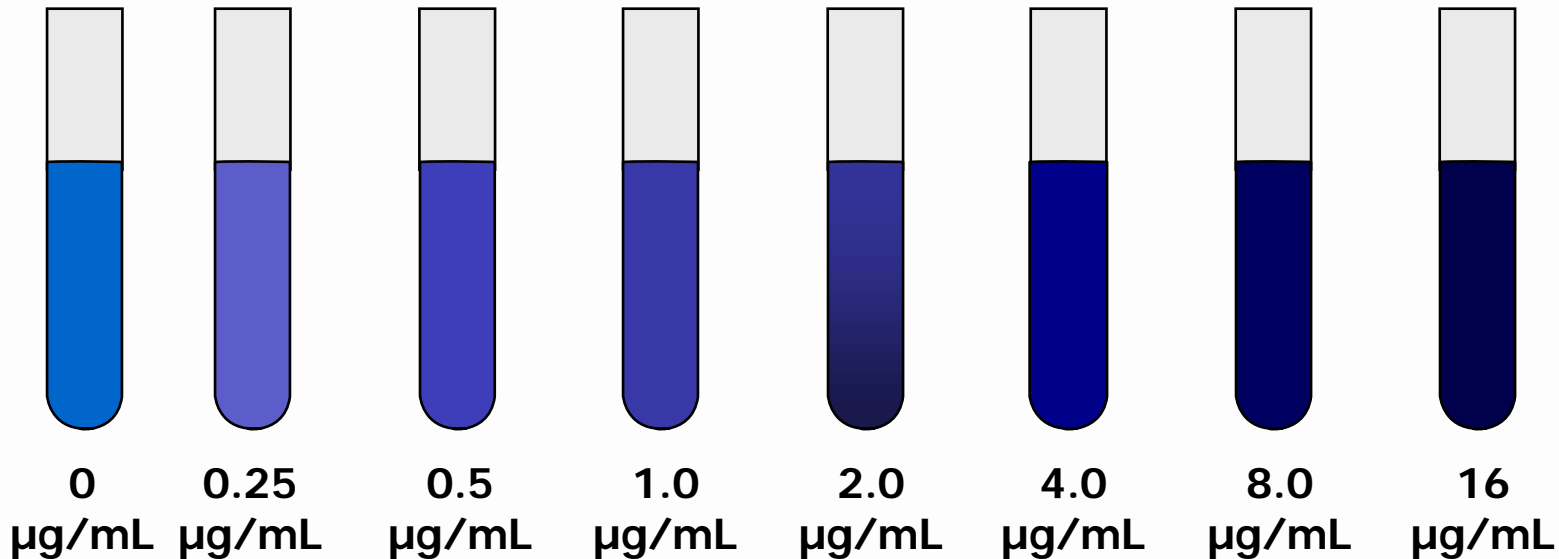
1. les médecins aiment savoir si la bactérie est **bonne** ou **mauvaise** ...
2. les Autorités aiment pouvoir dire "**Faites ceci**" et "**Ne faites pas cela**" ...
3. l'Industrie aime pouvoir dire "**Je peux**" et "**Je ne peux pas**"
4. les avocats aiment pouvoir vous déclarer **coupable** of **innocent** ...
5. les microbiologistes voudraient donner à tous des **réponses simples** ...

# Des réponses simples ?



# Commençons par le début: la CMI \* !

Quantité donnée de  
bactéries vivantes



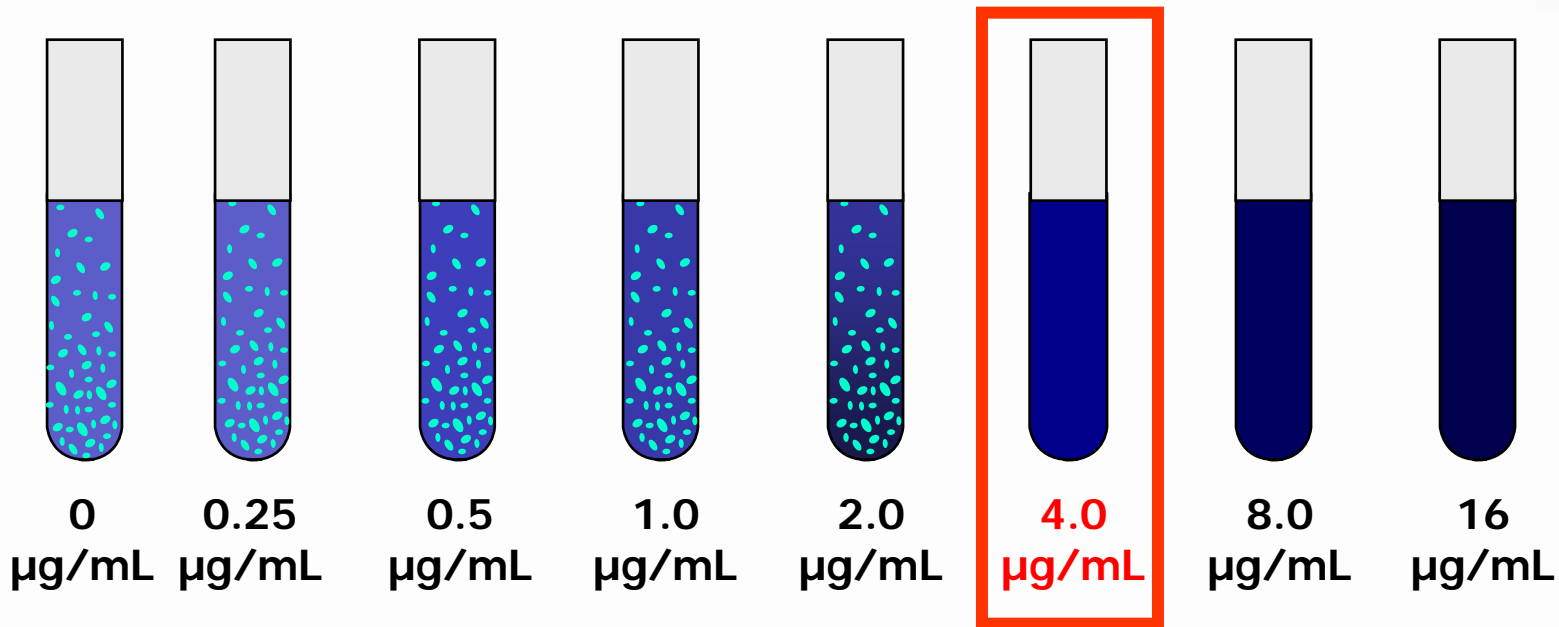
Concentrations  
croissantes  
d'antibiotique



# Et voilà la CMI \* !

24 h après ....

la concentration la plus faible à laquelle il n'y a pas de croissance bactérienne

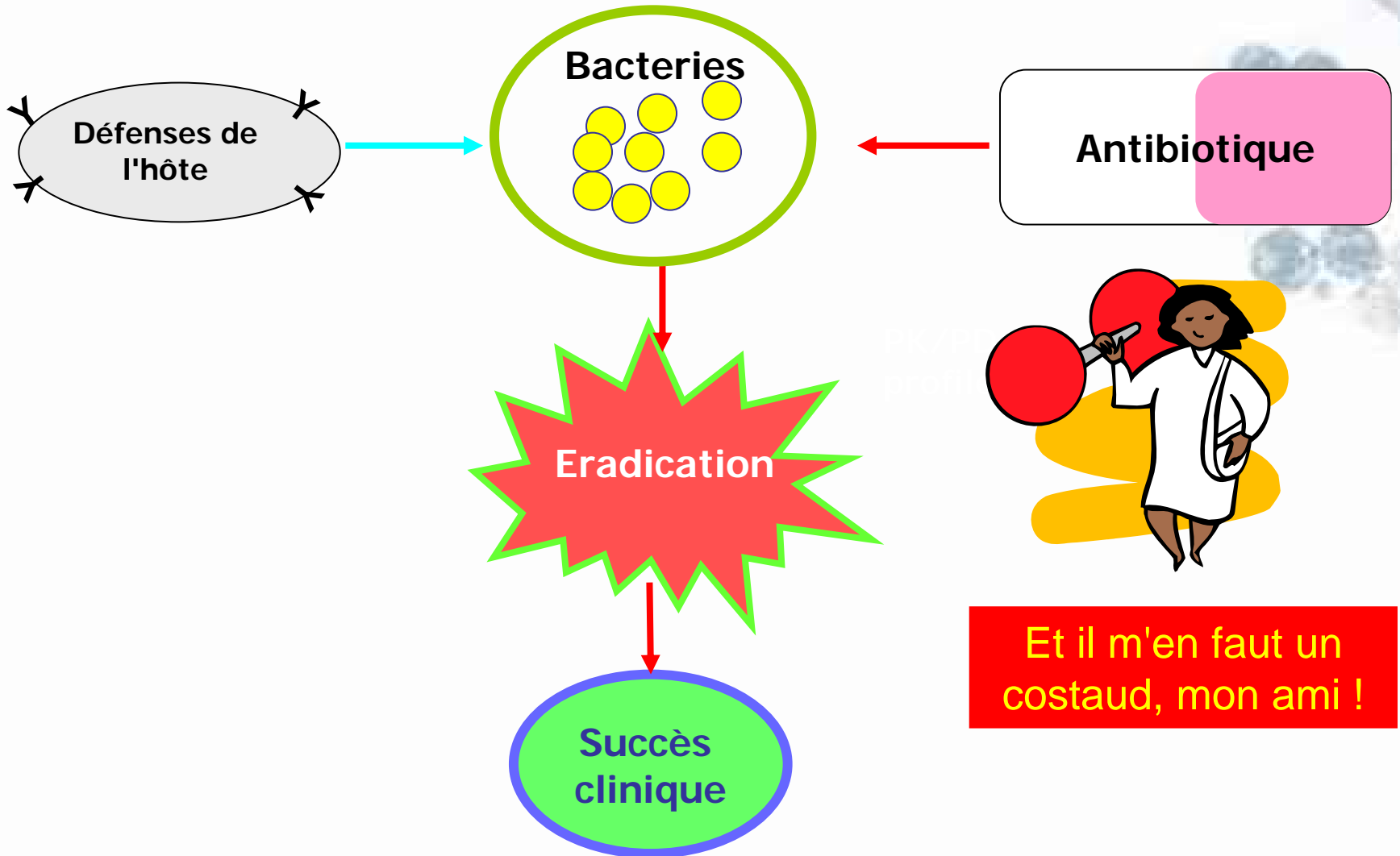


Concentrations  
croissantes  
d'antibiotique

\* CMI: concentration minimale inhibitrice  
MIC (Minimum Inhibitory Concentration)



# Mais que faites vous maintenant ?

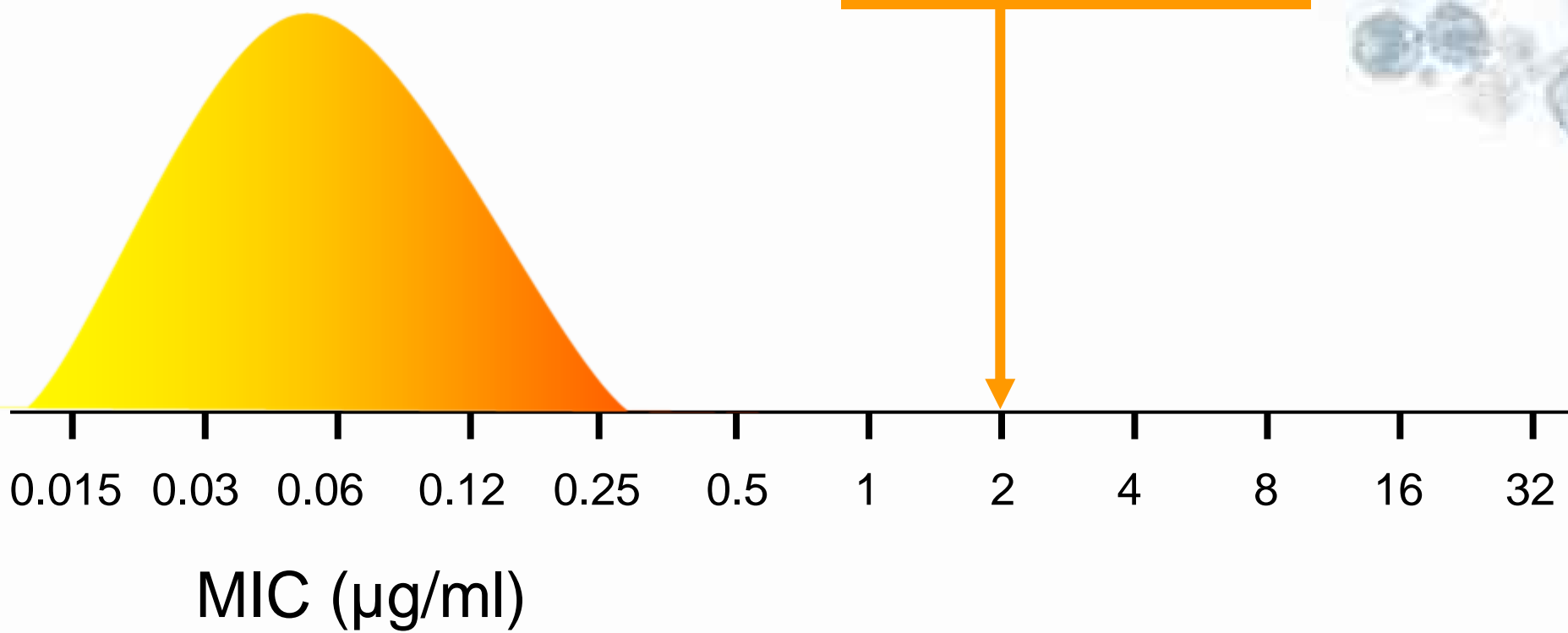


# Mais que veut dire "costaud" ?



Bon !! *Easy!!!*

concentration sérique



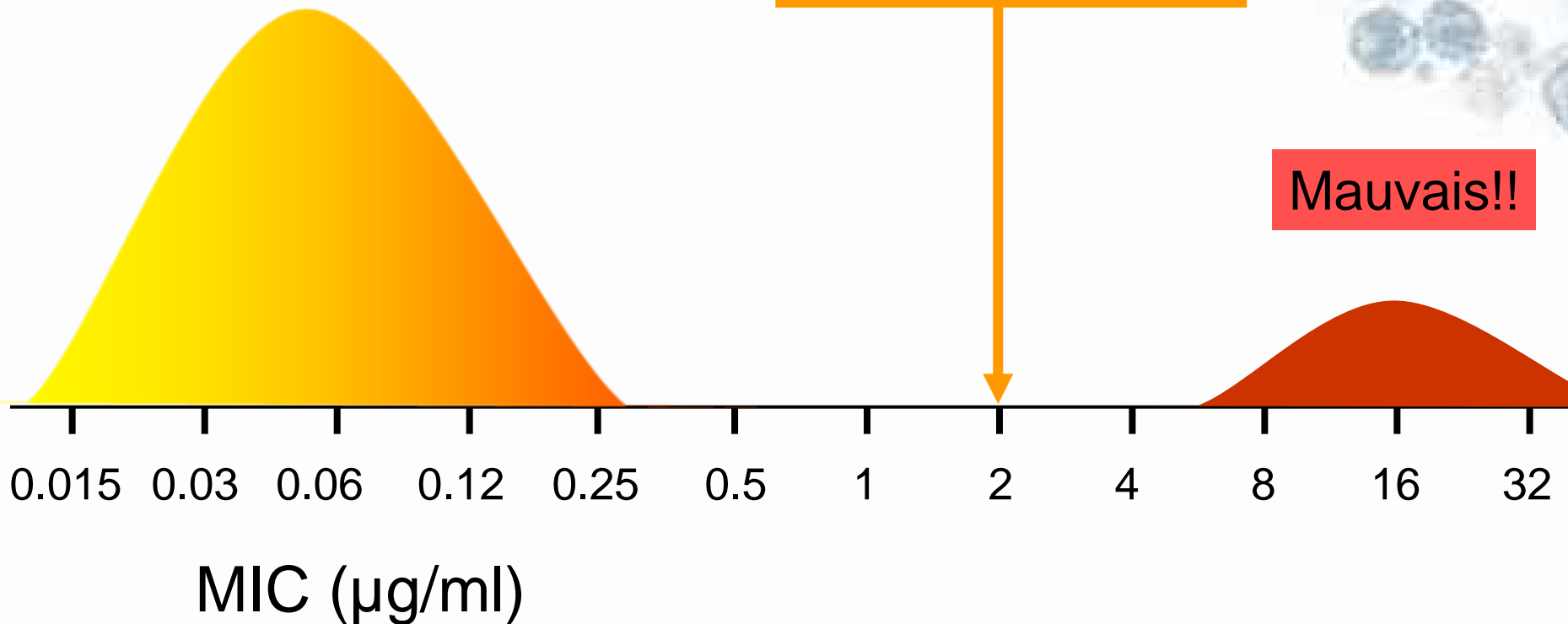
Celui-ci est-il aussi "costaud" ?

Still Easy!!!

Bon !!

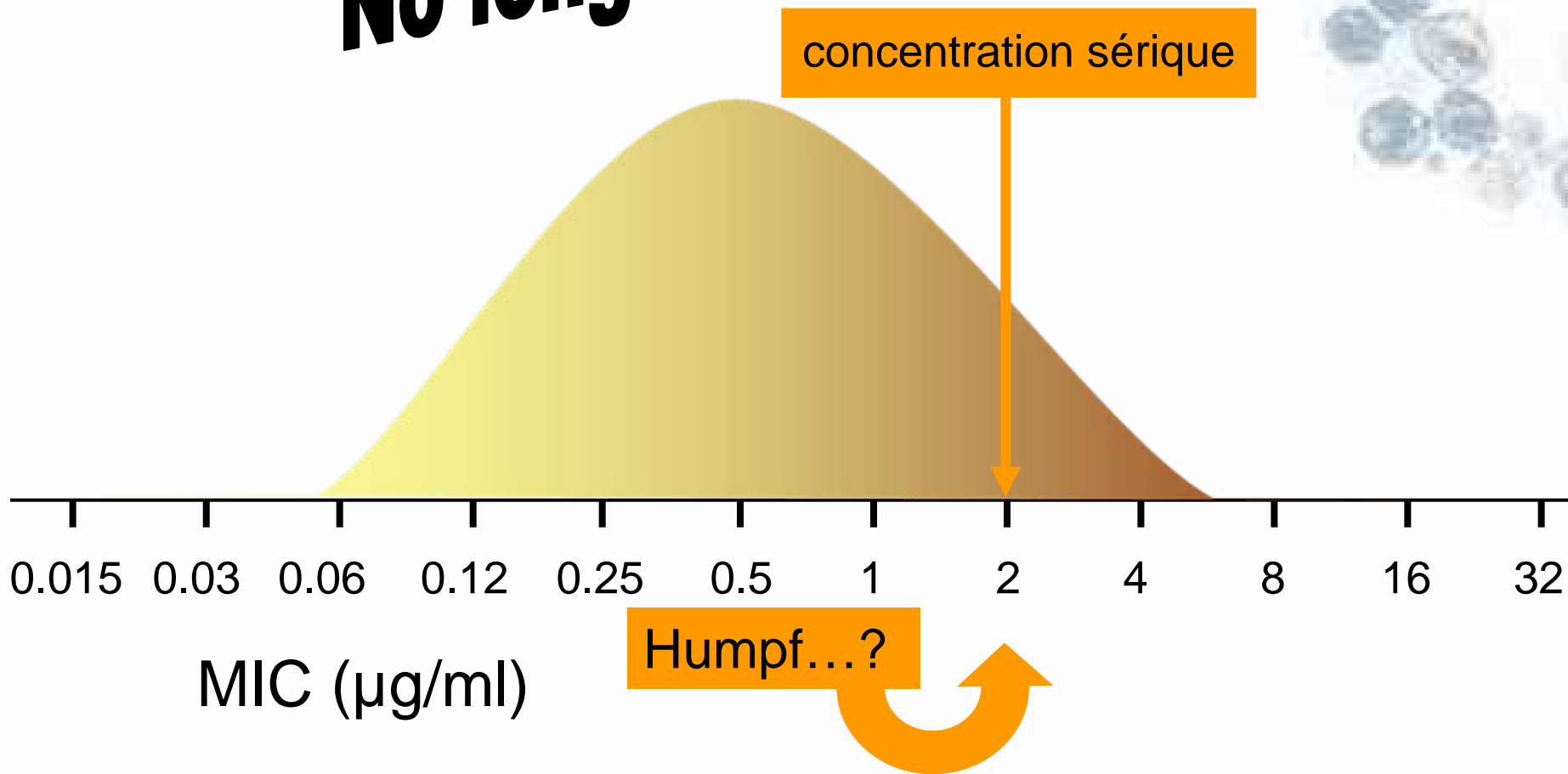
concentration sérique

Mauvais!!

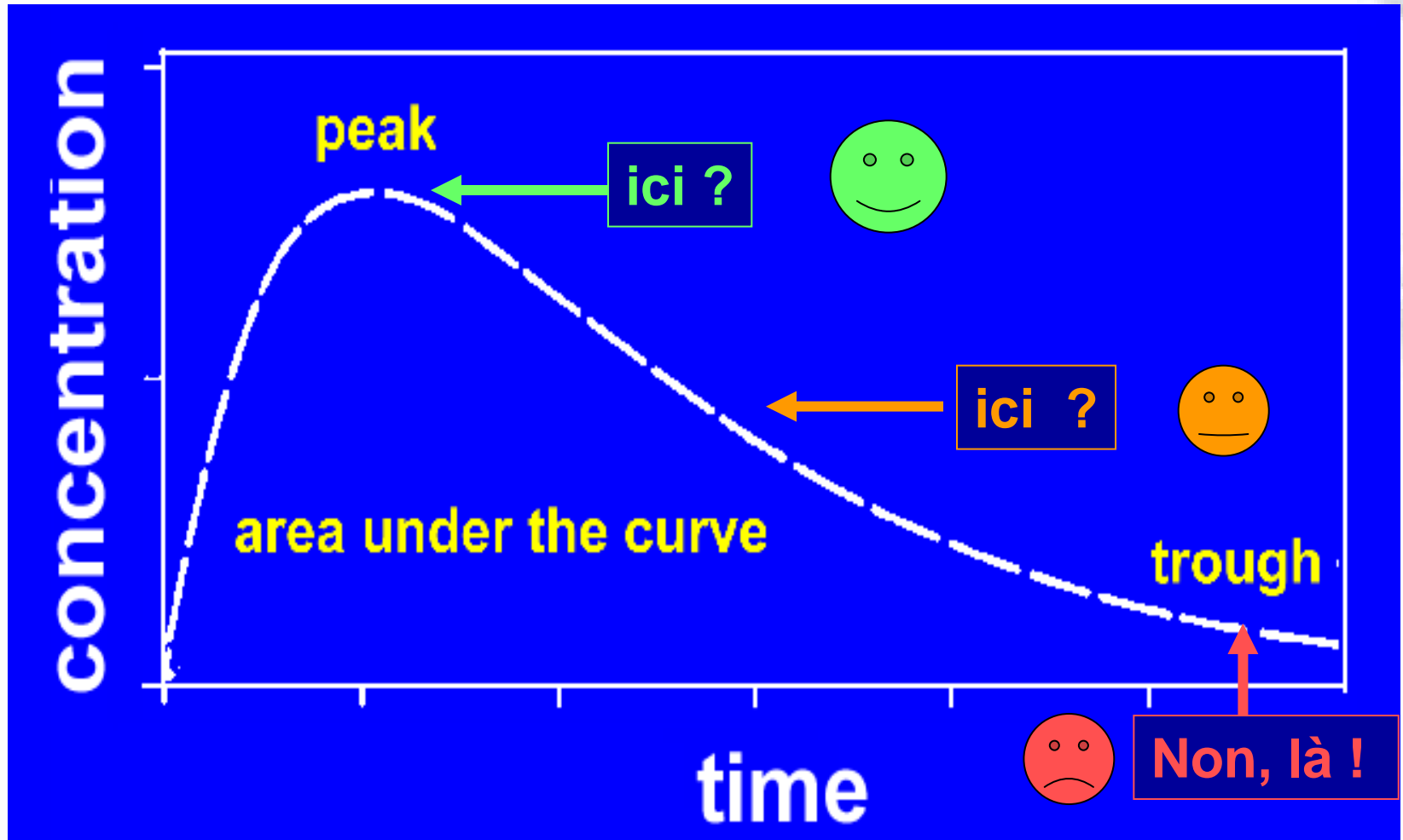


Et celui-là ?

**No longer so easy...**

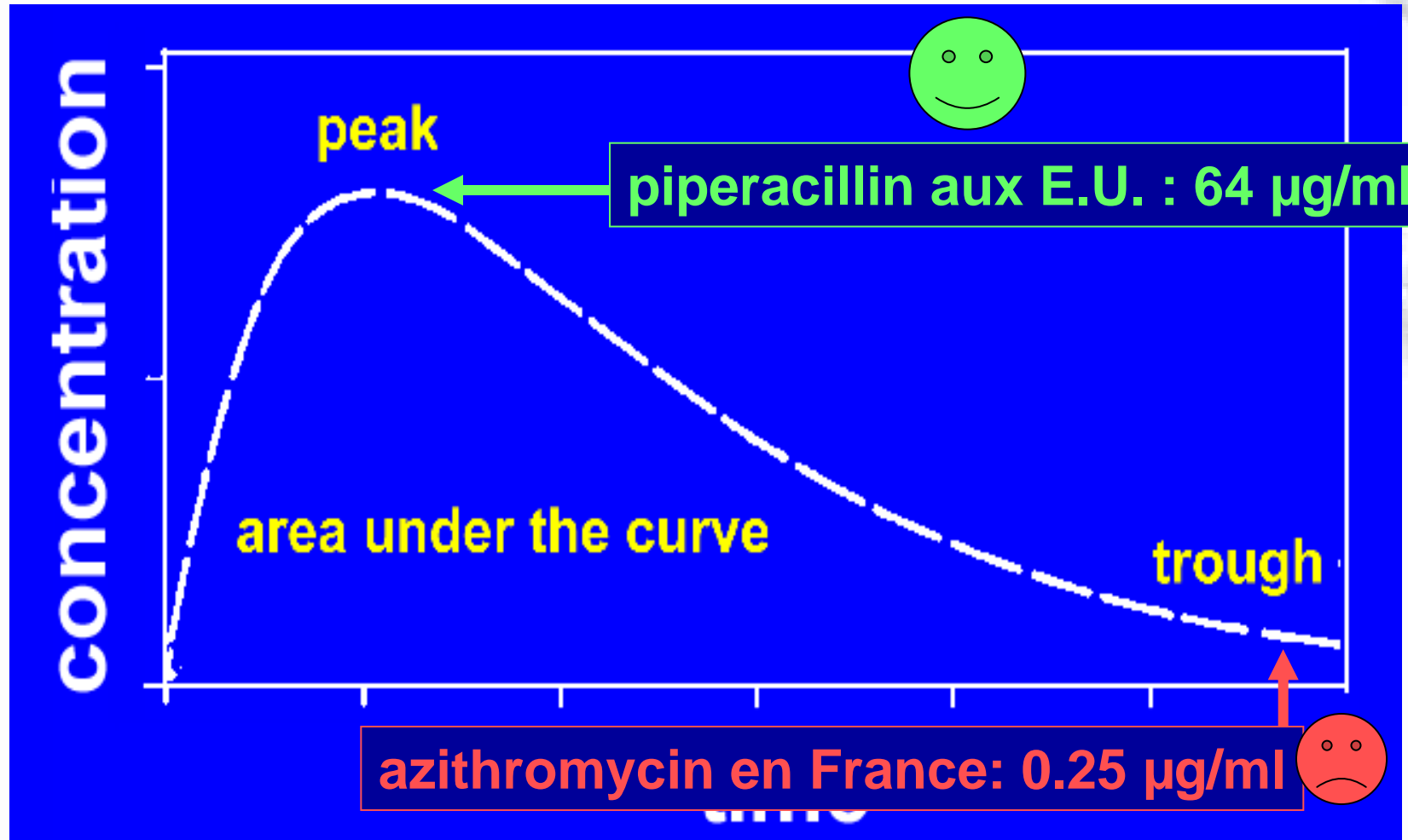


# Où devrait se trouver le point critique



# Pic ou vallée ?

un exemple de difference entre Français et Américains ...



# Mais aussi entre Européens ...



From Mouton, 8th ISAP symposium, Nijmegen, 2001

# Quelle était donc la situation ?

- L'Europe avait différentes commissions pour établir les points critiques ... et, dès lors, des points critiques différents pour **le même antibiotique**... \*
- Les points critiques américains étaient déterminés par le NCCLS\*\* ... mais ceux-ci
  - n'étaient pas (toujours) rationels ni réalistes;
  - étaient fortement influencés par la situation américaine (dosage, niveaux et type de résistance, influence de l'Industrie locale etc...
  - et ... étaient souvent différents des points critiques nationaux des pays européens

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\* In afwezigheid van een nationale commissie, gebruikten Belgische microbiologen meestal de NCCLS breekpunten ...

\*\* *National (US) Committee for Clinical Laboratory Standards*

# Un exemple simple

cefotaxime vs. <i>E.coli</i>		$S_{\leq} / R$
BSAC	Royaume-Uni	2 / $\geq 4$
CA-SFM	France	4 / $> 32$
CRG	Pays-Bas	4 / $> 16$
DIN	Allemagne	2 / $\geq 16$
NWGA	Norvège	1 / $\geq 32$
SRGA	Suède	0.5 / $\geq 2$
NCCLS	Etats-Unis	8 / $\geq 64$

Néanmoins, ces points critiques étaient utilisés quotidiennement par les **microbiologistes** pour éclairer les **cliniciens** à propos de la sensibilité des bactéries qu' **ils** devaient combattre.

# **Vous avez dit "EUCAST" ?**

## **European Committee on Antimicrobial Susceptibility Testing**



- **créé en 1997**
- **avec le soutien de**
  - **European Society for Clinical Microbiology and Infectious Diseases (ESCMID)**
  - **Les commissions nationales de détermination des points critiques en Europe (GB, F, D, NL, N, S)**
- **financé par**
  - **ESCMID**
  - **Les commissions nationales**
  - **DG-SANCO de l'Union Européenne (E-CDC vanaf 2008)**

# Buts de l'EUCAST

- **En Europe**
  - **détermination au niveau européen** de critères nécessaires pour mener les étude de surveillance de la résistance (épidémiologie)
  - détermination **de points critiques cliniques** pour les antibiotiques disponibles et pour les nouvelles molécules de façon **harmonisée**
  - **standardisation des méthodes**
  - **coopération** avec les groupes et sociétés scientifiques s'occupant de l'évaluation de la sensibilité des bactéries au niveau épidémiologique
  - **conseiller l'Union Européenne** en tout ce qui concerne l'interprétation des données provenant des études citées ci-dessus
- **Dans le monde**
  - collaborer avec les autres institutions et groupes (par ex. le CLSI [nouveau nom du NCCLS]) afin de tenter d'arriver à des consensus internationaux sur les méthodes, et si possible, sur les points critiques.



# EUCAST 1ère étape: definition d'un "cut off" épidémiologique

## (Souches sauvages)

- Un micro-organisme est considéré comme "wild type" en l'absence de mécanisme de résistance (mutation ou acquisition) vis-à-vis de l'antibiotique considéré
- La distribution des CMI des souches sauvages est établie sur base des données provenant de tous les laboratoires qui acceptent de les confier à l'EUCAST (tous les laboratoires peuvent collaborer; cette collaboration n'enlève aucun droit de publication ou autre au laboratoire)
- Ceci permet de déterminer la distribution de fréquence des souches sauvages et de définir ainsi la valeur du "cut-off" épidémiologique"
- Un isolat clinique sera catalogué "sauvage" ou "non-sauvage" en fonction de sa place dans (ou hors) de la distribution des souches sauvages

Les "cut-off" épidémiologiques sont des **constantes** pour l'espèce considérée ...

Eucast2 - Mozilla Firefox

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EUCAST Eucast2

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### Antimicrobial wild type distributions of microorganisms

Search

Method:  MIC  Disc diffusion

Antimicrobial: Antimicrobial... Species: Escherichia coli

Elements per page: 50

Species: Escherichia coli (Method: MIC)

<http://www.eucast.org>

- **Choisissez un antibiotique ou un micro-organisme... et quelques secondes plus tard, apparait une Table avec la distribution des CMI ...**

## Antimicrobial wild type distributions of microorganisms

### Search

 Method:  MIC  Disc diffusion

 Elements per page: 

 Antimicrobial:  Species: 

Species: Escherichia coli (Method: MIC)

[Show All Graphs](#)

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512
<a href="#">Amikacin</a>	0	0	0	1	0	0	0	16	129	1338	4008	1825	426	0	0	0	0	0	0
<a href="#">Aztreonam</a>	0	0	0	0	0	60	17	1	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefepime</a>	0	0	10	68	282	823	129	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefotaxime</a>	0	5	20	133	732	1857	1111	146	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefoxitin</a>	0	0	0	0	0	0	2	74	1420	4546	22698	24499	8360	2488	0	0	0	0	0
<a href="#">Cefpodoxime</a>	0	0	0	0	0	0	12	28	8	0	0	0	0	0	0	0	0	0	0
<a href="#">Ceftazidime</a>	0	0	5	26	172	1051	2672	2354	475	0	0	0	0	0	0	0	0	0	0
<a href="#">Ceftibuten</a>	0	0	0	0	0	367	756	1107	225	49	0	0	0	0	0	0	0	0	0
<a href="#">Ceftibuten</a>	0	0	0	0	0	268	224	84	19	11	0	0	0	0	0	0	0	0	0
<a href="#">Ceftiofur</a>	0	0	0	0	0	0	5	568	1920	236	0	0	0	0	0	0	0	0	0
<a href="#">Ceftriaxone</a>	0	0	5	23	51	49	4	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefuroxime</a>	0	0	1	1	1	5	88	206	1926	6448	26389	58851	18523	0	0	0	0	0	0
<a href="#">Chloramphenicol</a>	0	0	0	0	0	0	0	0	0	0	239	3962	3857	307	0	0	0	0	0
<a href="#">Ciprofloxacin</a>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Colistin</a>	0	0	0	0	0	242	35	493	1794	430	82	0	0	0	0	0	0	0	0
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32				
<a href="#">Enrofloxacin</a>	0	0	0	0	798	1689	105	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Ertapenem</a>	0	124	882	417	184	46	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Florfenicol</a>	0	0	0	0	0	0	0	0	0	1	335	4503	4260	319	0	0	0	0	0
<a href="#">Flumequine</a>	0	0	0	0	0	0	1	37	1651	446	31	0	0	0	0	0	0	0	0
<a href="#">Fosfomycin</a>	0	0	0	0	0	0	0	0	348	611	576	346	200	0	0	0	0	0	0
<a href="#">Gentamicin</a>	0	0	4	3	18	40	386	5857	16128	9077	1774	0	0	0	0	0	0	0	0
<a href="#">Imipenem</a>	0	0	3	15	64	6202	41814	10539	12263	575	0	0	0	0	0	0	0	0	0
<a href="#">Kanamycin</a>	0	0	0	0	0	0	0	126	332	365	562	465	166	0	0	0	0	0	0

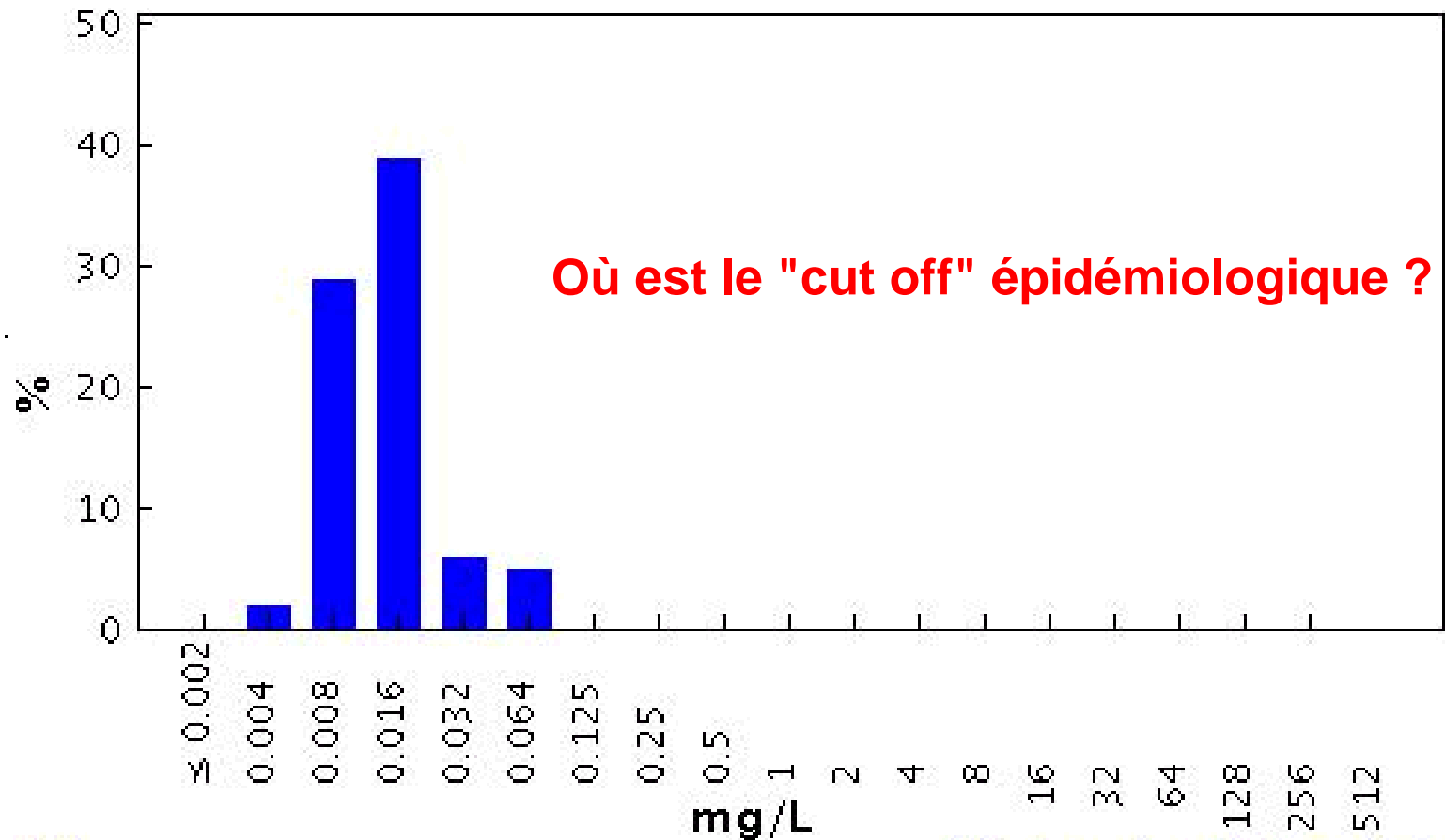
Les blocs bleus correspondent aux valeurs des souches sauvages

- Pour chaque antibiotique, vous obtenez la distribution des CMI sous forme d'histogramme

## Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

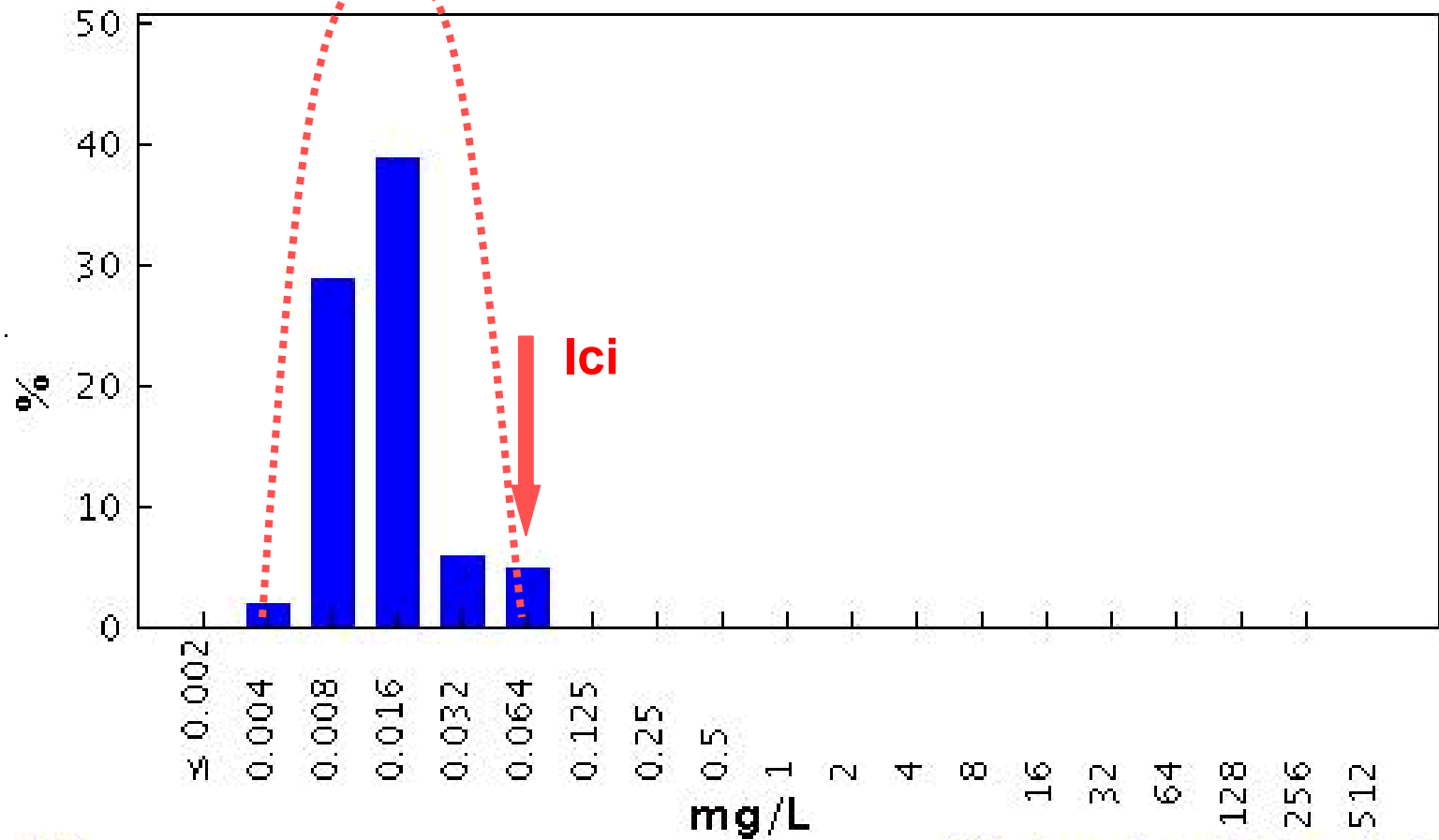
EUCAST



## Ciprofloxacin / Escherichia coli

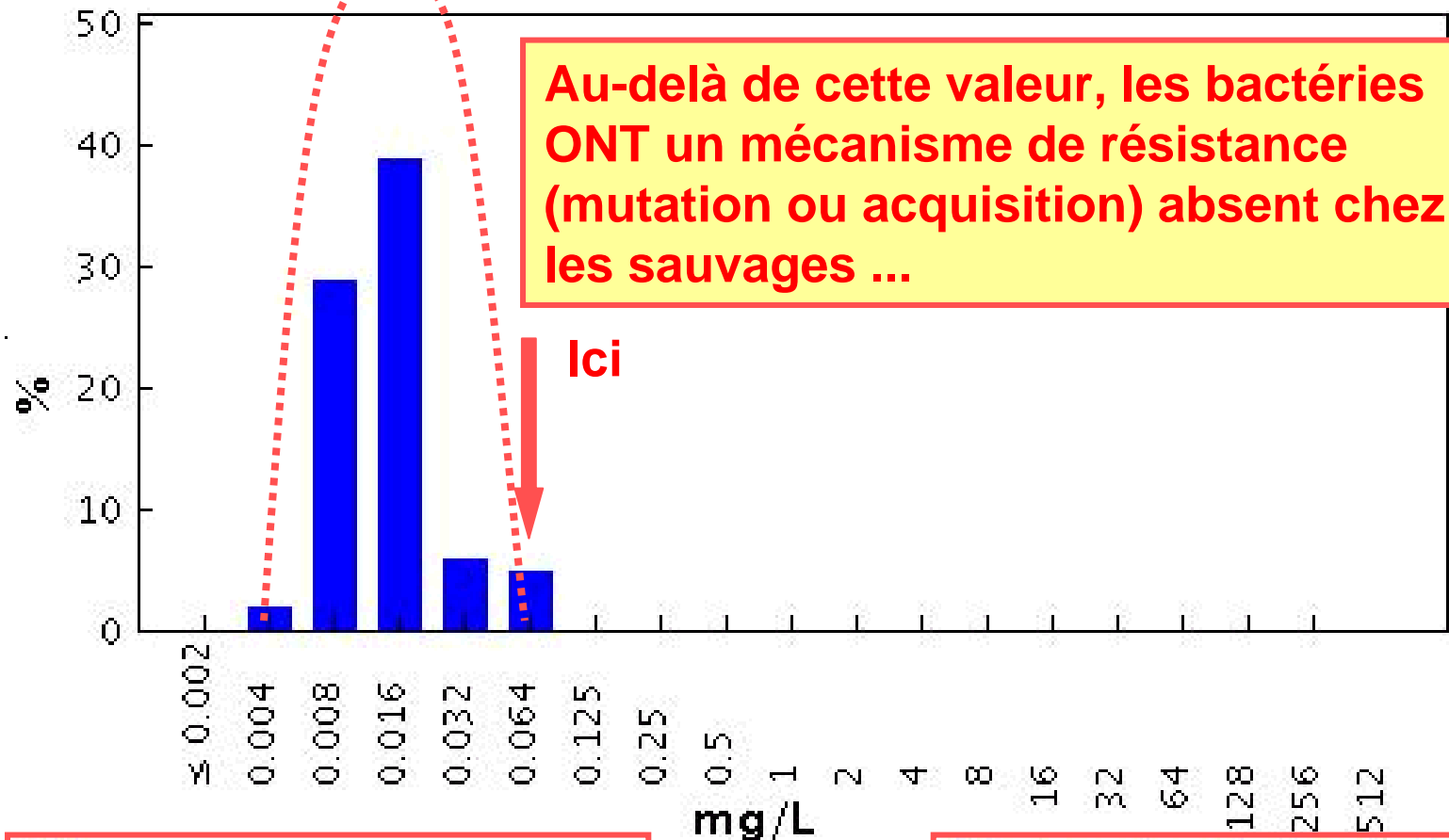
Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



## Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database  
EUCAST



Au-delà de cette valeur, les bactéries ONT un mécanisme de résistance (mutation ou acquisition) absent chez les sauvages ...

Ici

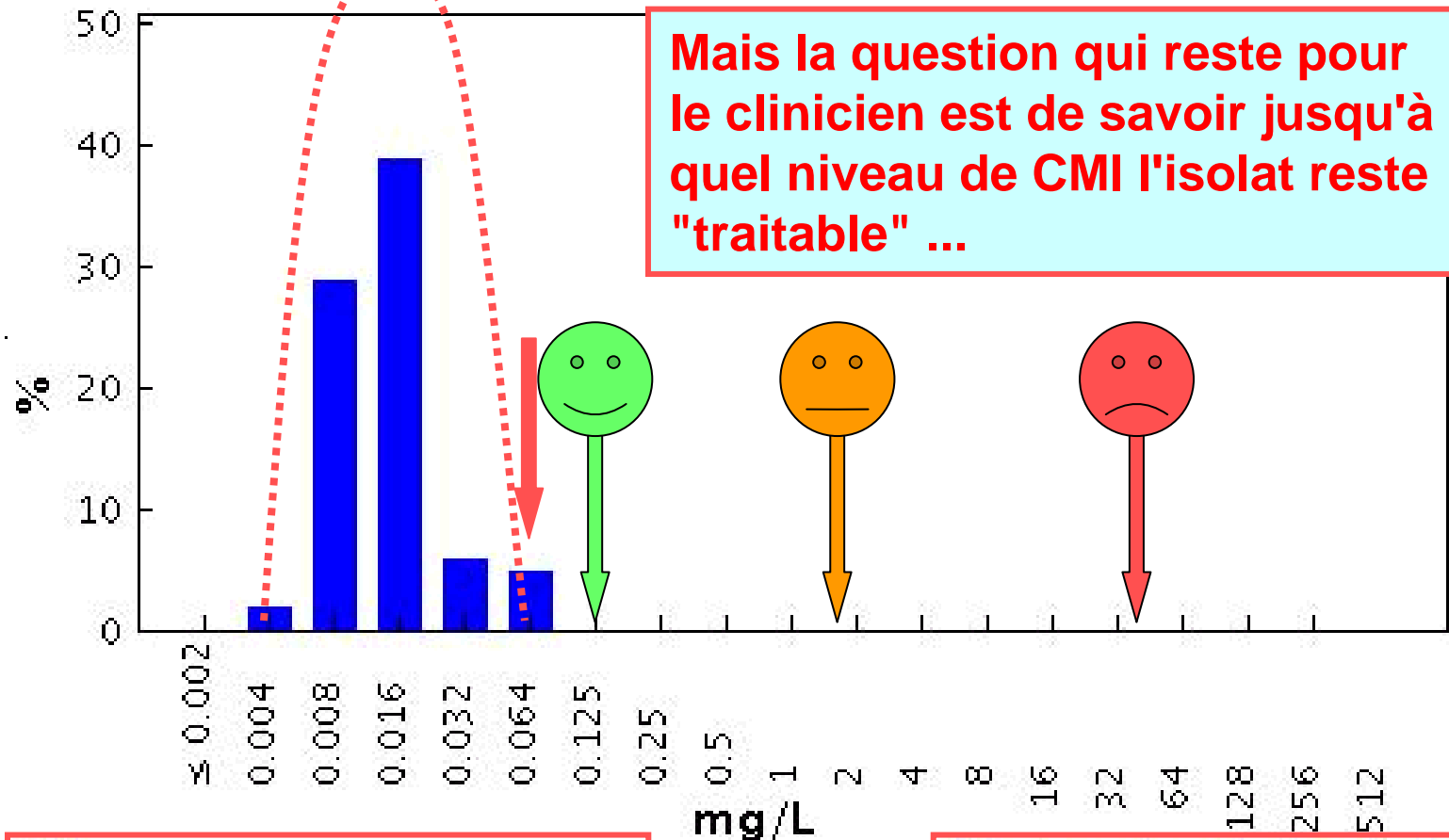
MIC  
Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

# Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



MIC  
Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

# Définition par l'EUCAST des points critiques cliniques

## Cliniquement sensible (S)

- CMI entraînant un niveau d'activité antibactérienne procurant une grande probabilité de succès thérapeutique

## Cliniquement intermédiaire (I)

- CMI entraînant un niveau d'activité antibactérienne ne donnant qu'une probabilité faible ou indéterminable de succès thérapeutique

## Cliniquement résistant (R)

- CMI entraînant un niveau d'activité antibactérienne telle que le succès thérapeutique est improbable

**Les points critiques cliniques peuvent être adaptés en fonction des circonstances (par exemple, un changement de dose)**

# Comment l'EUCAST définit-il les points critiques cliniques d'un antibiotique donné ?

- 1. Les données concernant le dosage, la formulation, les indications cliniques, et les organismes-cibles sont évalués et la pertinence des divers points critiques disponibles analysés de façon approfondie**
- 2. Un nombre élevé de distributions de CMI sont rassemblées de façon à déterminer le cut-off épidémiologique des souches sauvages ( $WT \leq X \text{ mg/L}$ )**

### 3. Les points critiques nationaux sont comparés

### 4. Les données **pharmacocinétiques** sont rassemblées et évaluées

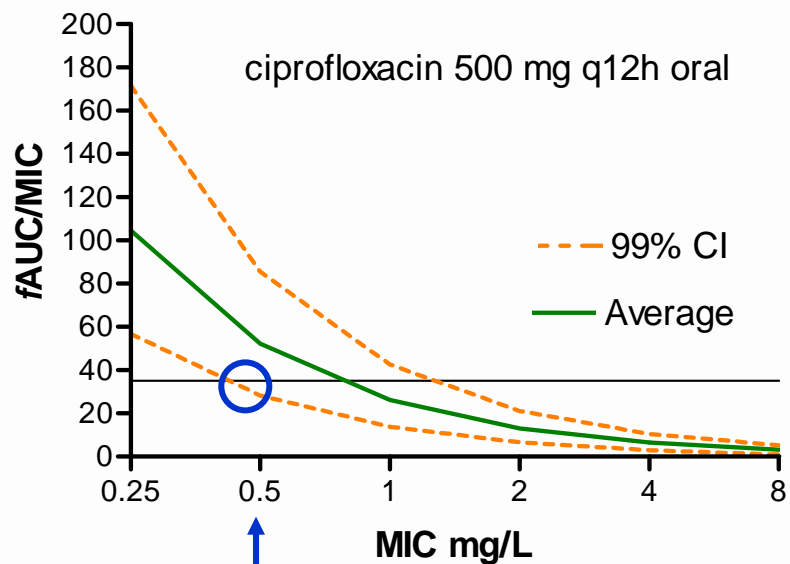
- à partir de valeurs de patients réels;
- et en utilisant des modèles de pharmacocinétique de population si nécessaire (ex.: trop peu de valeurs individuelles)

### 5. Les données **pharmacodynamiques** sont évaluées

**les paramètres PK/PD** (temps > CMI,  $AUC_{24h}/CMI$ ,  $C_{max}/CMI$ ) permettant de lier le dosage à l'efficacité sont évalués sur base:

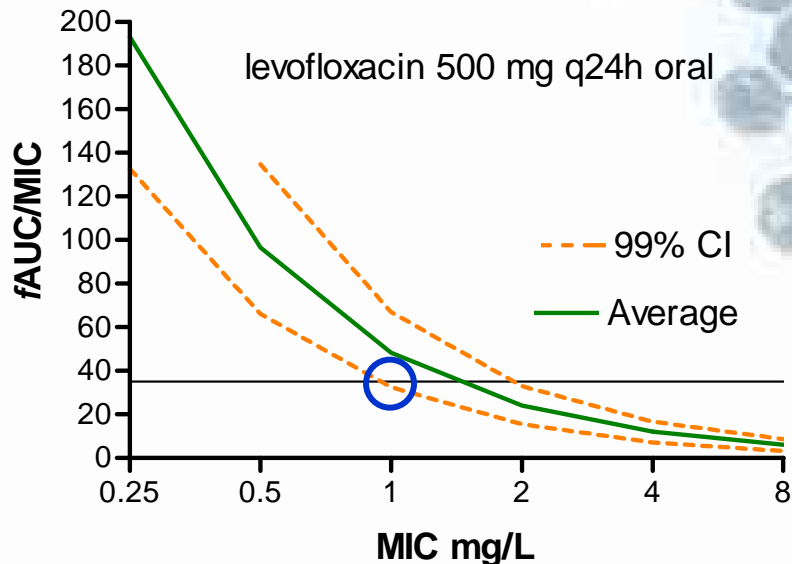
- d'études *in vitro*
- d'études animales *in vivo*
- des études cliniques pertinentes
- Le lien entre profil pharmacocinétique et le risque d'émergence de résistance est examiné

# Des simulations de Monte Carlo sont réalisées pour fixer un seuil " PK/PD" d'activité correspondant aux schémas d'administration les plus courants



S = 0.5 mg/L

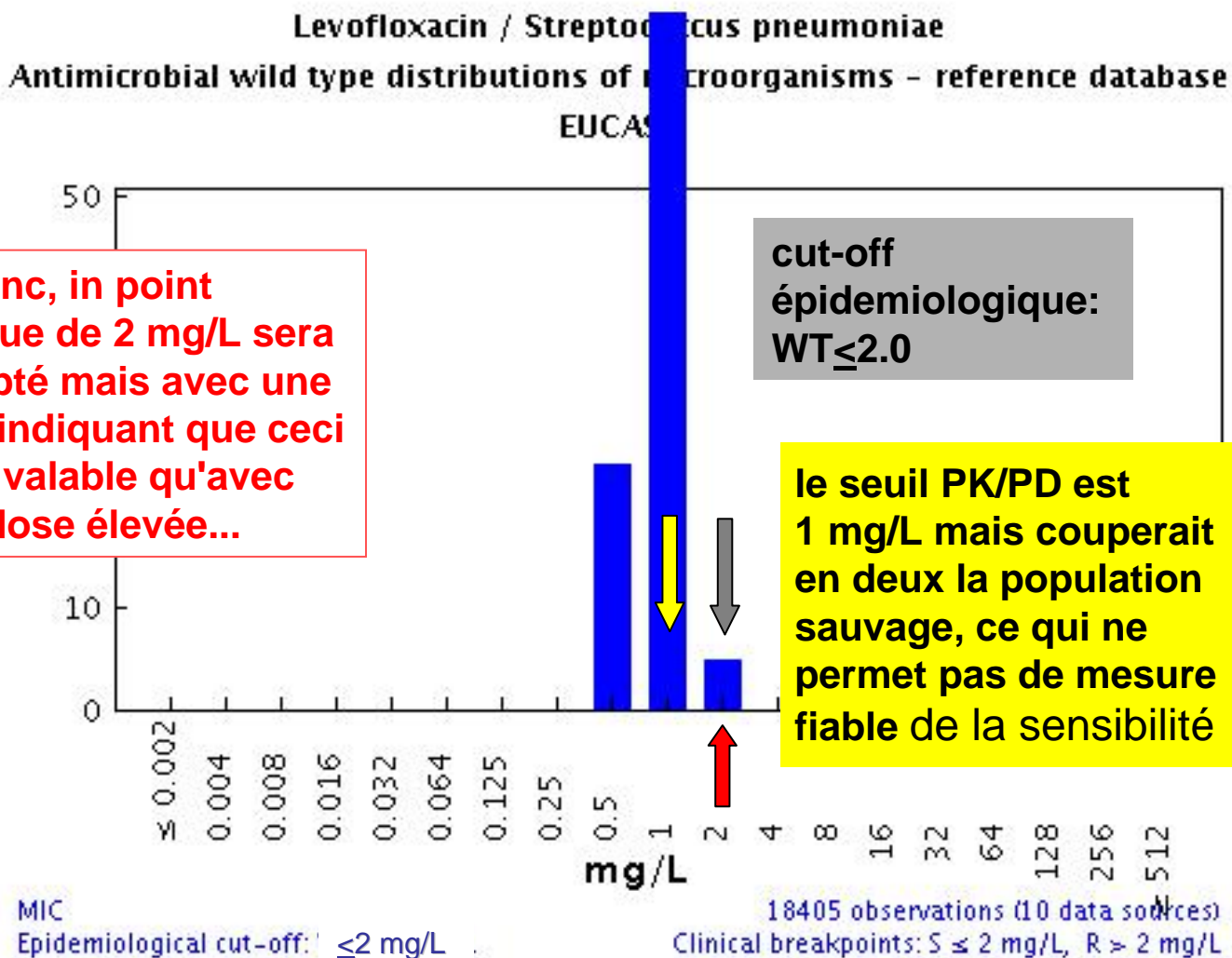
PK/PD



S = 1 mg/L

## 6. Le seuils PK/PD sont revus si nécessaire pour éviter de couper en deux la population sauvage...

Exemple: levofloxacin



**7. Les points critiques provisoires sont soumis aux commissions nationales (GB, F, NL, N, N, S) pour commentaires**

## **8. Consultation**

- **EUCAST General Committee**
- **commission d'experts si nécessaire (*Neisseria*, anaérobies, ...)**
- **Industrie pharmaceutique**
- **Fabricants de machines de diagnostic**
- **via le site WEB de l'EUCAST**

**9. Publication d'un "Rational Document" sur le site WEB de l'EUCAST**



# Et voici les résultats ...



## Fluoroquinolones - EUCAST clinical MIC breakpoints

2006-06-20 (v 2.2)

Fluoroquinolone <sup>2</sup>		Species-related breakpoints (S</R>)											Non-species related breakpoints <sup>1</sup> S</R>
		<i>Entero-bacteriaceae</i> <sup>3</sup>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i>	<i>Entero-coccus</i>	<i>Strepto-coccus A,B,C,G</i>	<i>S.pneu-moniae</i> <sup>5</sup>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.menin-gitidis</i> <sup>6</sup>	<i>Gram-negative anaerobes</i>	
<a href="#">Ciprofloxacin</a>	RD	0.5/1	0.5/1	1/1 <sup>4</sup>	1/1 <sup>5</sup>	--	--	0.125/2	0.5/0.5 <sup>7</sup>	0.03/0.06	0.03/0.06	--	0.5/1
<a href="#">Levofloxacin</a>	RD	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1 <sup>7</sup>	IE	IE	--	1/2
<a href="#">Moxifloxacin</a>	RD	0.5/1	--	--	0.5/1	--	0.5/1	0.5/0.5	0.5/0.5 <sup>7</sup>	IE	IE	IE	0.5/1
<a href="#">Norfloxacin</a>	RD	0.5/1	--	--	--	--	--	--	--	IE	--	--	0.5/1
<a href="#">Ofloxacin</a>	RD	0.5/1	--	--	1/1 <sup>3</sup>	--	--	0.125/4	0.5/0.5 <sup>7</sup>	0.12/0.25	IE	--	0.5/1

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by national breakpoint committees.
3. *Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case reports of poor response with other *Salmonella* species.
4. The S/I breakpoint has been increased from 0.5 to 1 mg/L to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Acinetobacter* species
5. *Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
6. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant. *Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae*.
8. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.  
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.  
 RD =Rationale document listing data used for setting EUCAST breakpoints.

### Clinical breakpoints

- Penicillins (2007)
- **Cephalosporins**
- **Carbapenems**
- **Monobactams**
- **Fluoroquinolones**
- **Aminoglycosides**
- **Glycopeptides**
- **Oxazolidones**
- Macrolides, ketolides & clindamycin, dalfopristine/-quinopristine (2007/08),
- Tetracyclines (2008), **Tigecycline**
- Chloramphenicol (2008),
- **Daptomycin**,
- Fusidic acid (2008),
- Rifampicin (2008)
- Trimethoprim, sulfamethoxazole, co-trimoxazole (2008),
- Nitrofurantoin (2008)
- Fosfomicin (2008).

## Pour quels antibiotiques les points critiques de l'EUCAST sont-ils disponibles ?

- **en bleu:** disponibles !
- **en noir:** points critiques prévus pour les dates indiquées ou peu après

Cephalosporins		Species-related breakpoints (S</R>)							
		Enterobacteriaceae <sup>2</sup>	Pseudo-monas <sup>3</sup>	Acineto-bacter	Staphylo-coccus <sup>4</sup>	Entero-coccus	Strepto-coccus A,B,C,G	S.pneu-moniae	H.influen M.catarrh.
<a href="#">Cefazolin</a>	RD	--	--	--	note <sup>4</sup>	--	--	--	--
<a href="#">Cefepime</a>	RD	1/8	8/8	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	1/2	0.25/0.2
<a href="#">Cefotaxime</a>	RD	1/2	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/2 <sup>6</sup>	0.12/0.1
<a href="#">Ceftazidime</a>	RD	1/8	8/8	--	--	--	--	--	--
<a href="#">Ceftriaxone</a>	RD	1/2	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/2 <sup>6</sup>	0.12/0.1
<a href="#">Cefuroxime</a>	RD	8/8 <sup>5</sup>	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/1	1/2

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriaceae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.
6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.  
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.  
 RD = rationale document listing data used by EUCAST for determining breakpoints.

Cephalosporins		Species-related breakpoints (S</R>)							
		<i>Enterobacteriaceae</i> <sup>2</sup>	<i>Pseudo-monas</i> <sup>3</sup>	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i> <sup>4</sup>	<i>Entero-coccus</i>	<i>Strepto-coccus</i> A,B,C,G	<i>S.pneu-moniae</i>	<i>H.influen</i> <i>M.catarrh.</i>
<a href="#">Cefazolin</a>	RD	--	--	--	note <sup>4</sup>	--	--	--	--
<a href="#">Cefepime</a>	RD	1/8	8/8	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	1/2	0.25/0.2
<a href="#">Cefotaxime</a>	RD	1/2	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/2 <sup>6</sup>	0.12/0.1
<a href="#">Ceftazidime</a>	RD	1/8	8/8	--	--	--	--	--	--
<a href="#">Ceftriaxone</a>	RD	1/2	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/2 <sup>6</sup>	0.12/0.1
<a href="#">Cefuroxime</a>	RD	8/8 <sup>5</sup>	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/1	1/2

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriaceae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.

**Rappelez-vous qu'un point critique clinique est TOUJOURS dépendant de la dose !**

the current resistant breakpoint (in italics) they should be reported resistant.

- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
- IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
- RD = rationale document listing data used by EUCAST for determining breakpoints.

Carbapenem Click on antibiotic name to see wild type MIC distributions	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i>	<i>Entero-coccus</i>	<i>Strepto-coccus</i> A,B,C,G	<i>S.pneu-moniae</i>	<i>H.influenzae</i> <i>M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.n</i> <i>i</i>	
<a href="#">Ertapenem</a>	RD	0.5/1	--	--	<i>note</i> <sup>3</sup>	--	0.5/0.5 <sup>4,7</sup>	0.5/0.5 <sup>4,7</sup>	0.5/0.5 <sup>4,7</sup>	IE	
<a href="#">Imipenem</a>	RD	2/8 <sup>2</sup>	4/8 <sup>6</sup>	2/8	<i>note</i> <sup>3</sup>	4/8 <sup>6</sup>	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	IE	
<a href="#">Meropenem</a>	RD	2/8	2/8	2/8	<i>note</i> <sup>3</sup>	--	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	IE	0.25

### Les points critiques du méropénème sont établis en valeur minimale et maximale

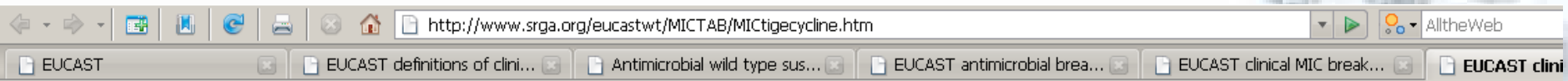
- 2 pour une dose faible (0.5 g 3 X / jour)
- max. 8 pour une dose élevée (1 g 3 X / jr).

1. Non-species related breakpoints have been established for use only for specific species. They are for use only for species where susceptibility testing is not recommended.
2. *Proteus* and *Morganella* species are considered poor targets for imipenem.
3. Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.
4. Imipenem and ertapenem are not used for meningitis. Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25/1 mg/L.
5. Meropenem breakpoints in *Neisseria meningitidis* relates to meningitis only.
6. The imipenem S/I breakpoint for *Pseudomonas* and *Enterococcus* was increased from 2 to 4 mg/L to avoid dividing the wild type MIC distribution.
7. Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
8. The ertapenem S/I breakpoint for Gramnegative anaerobes was moved from 0.5 to 1.0 to avoid dividing the wild type MIC distributions.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

# Pouvons nous juger le travail ?



## Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>
<a href="#">Tigecycline (RD)</a>	1/2 <sup>2,5</sup>	--	IE	0.5/0.5 <sup>3,6</sup>	0.25/0.5 <sup>3</sup>	0.25/0.5 <sup>3</sup>	IE	IE	IE	IE	Note <sup>4</sup>

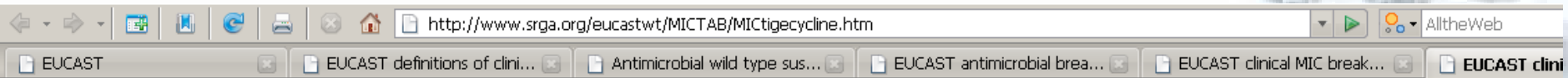
1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that have been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. Tigecycline has decreased activity against *Morganella*, *Proteus* and *Providencia*.
3. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and I/R breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

RD = Rationale document listing data used for setting EUCAST breakpoints

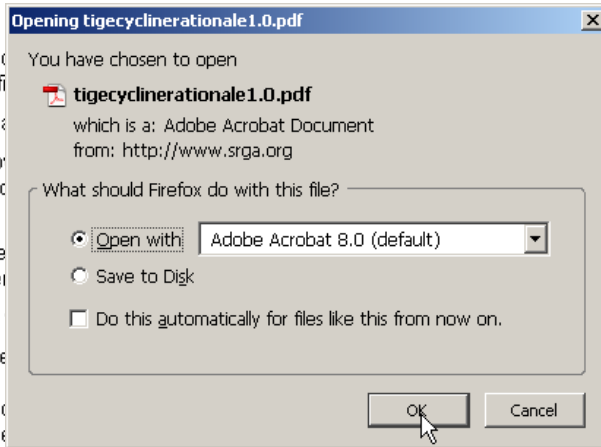
# Oui, il suffit de cliquer ...



## Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>
<a href="#">Tigecycline (RD)</a>	1/2 <sup>2,5</sup>	--	IE	0.5/0.5 <sup>3,6</sup>	0.25/0.5 <sup>3</sup>	0.25/0.5 <sup>3</sup>	IE	IE	IE	IE	Note <sup>4</sup>



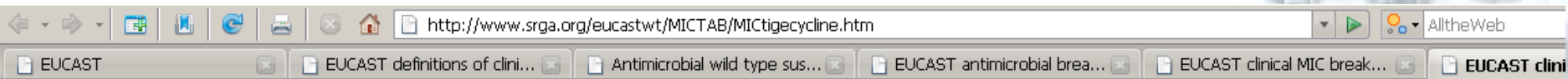
1. Non-species related breakpoints have been given a species-specific name.
2. Tigecycline has decreased MIC values for *Enterobacteriaceae*.
3. Strains with MIC values above the current breakpoint should be confirmed the isolate sent to the laboratory reported resistant.
4. For anaerobic bacteria there is no susceptibility testing is given.
5. The S/I and I/R breakpoints are not recommended.
6. The S/I breakpoint was increased.

-- = Susceptibility testing not recommended  
 IE = There is insufficient evidence  
 RD = Rationale document listing data used for setting EUCAST breakpoints

are independent of MIC distributions of specific species. They are for use only for species that have no MIC distribution. If a MIC is not recommended (marked with -- or IE in the table), the MIC value is not recommended for use. Interpretation and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is above the current resistant breakpoint (in italics) they should be reported as resistant. There is no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint is recommended for these species.

drug.

# Et vous obtenez le "Rational Document" ...



## Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline <small>Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.</small>	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>
<a href="#">Tigecycline (RD)</a>	1/2 <sup>2,5</sup>	--	IE	0.5/0.5 <sup>3,6</sup>	0.25/0.5 <sup>3</sup>	0.25/0.5 <sup>3</sup>	IE	IE	IE	IE	Note <sup>4</sup>

1. Non-species related breakpoints have been given a species-specific MIC.
  2. Tigecycline has decreased MIC values for some species.
  3. Strains with MIC values above the current breakpoint should be confirmed the isolate sent to the laboratory reported resistant.
  4. For anaerobic bacteria there is insufficient evidence for susceptibility testing is given.
  5. The S/I and I/R breakpoints are given in italics.
  6. The S/I breakpoint was increased for *Staphylococcus aureus*.
- = Susceptibility testing not recommended  
 IE = There is insufficient evidence  
 RD = Rationale document listing data used for MIC determination

Opening tigecyclinerationale1.0.pdf

You have chosen to open **tigecyclinerationale1.0.pdf** which is a: Adobe Acrobat Document from: http://www.srga.org

What should Firefox do with this file?

Open

Save

Do this later

are independent of MIC distributions of specific species. They are for use only for species that have a MIC distribution which is not recommended (marked with -- or IE in the table).

and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is not recommended (marked with -- or IE in the table) they should be repeated.

Tigecycline - EUCAST Rationale document (http://www.eucast.org) 1 (10)

<b>Tigecycline</b>	<b>Rationale for the EUCAST clinical breakpoints, version 1.0</b>	<b>30 March 2006</b>
--------------------	---	----------------------

**Introduction**

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation, and has a large volume of distribution. Nausea is the most noteworthy adverse event.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci,  $\beta$ -haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

# Et voilà la simulation de réponse PK/PD en fonction de la CMI pour le dosage clinique proposé

## 6. Monte Carlo simulations and Pk/Pd breakpoints

Figure 3 shows the probability of target attainment for *E. coli*. The target is taken from the clinical study on and complicated intra-abdominal infection. The use of this target in the Monte Carlo simulations suggests a Pk/Pd breakpoint of  $\leq 0.25\text{-}0.5\text{mg/L}$ . Similarly, for Gram-positives simulations suggest a Pk/Pd breakpoint of  $\leq 0.25\text{ mg/L}$  using the target of 12.5 obtained from the clinical CSSSI study (data not shown).

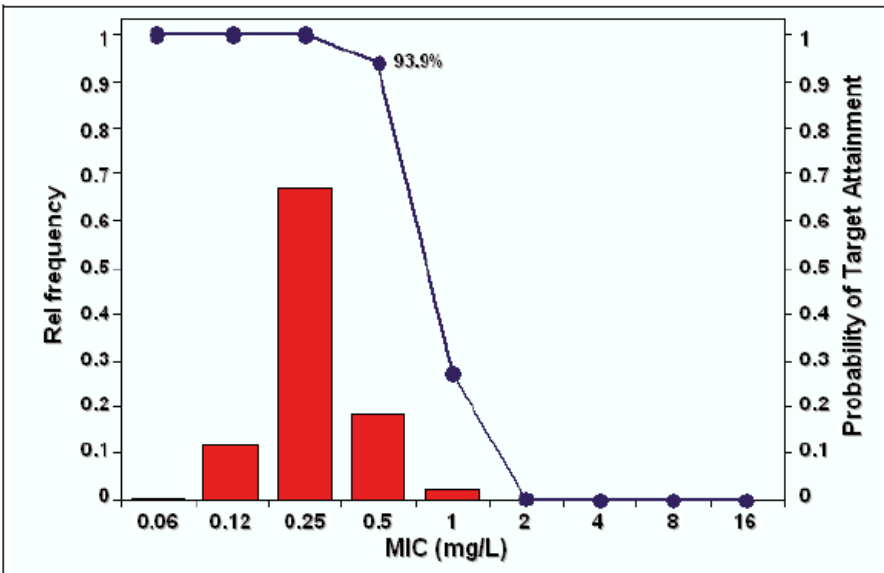


Figure 3. Probabilities of target attainment for tigecycline. Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file, Wyeth Inc.

Tigecycline

Tigecycline

Click on antibiotic name to see MIC distributions and see rationale document

Tigecycline (E)

1. Non-species have been given
2. Tigecycline
3. Strains with confirmed target reported results
4. For anaerobic susceptibility
5. The S/I and
6. The S/I break

-- = Susceptibility  
IE = There is ins  
RD = Rationale

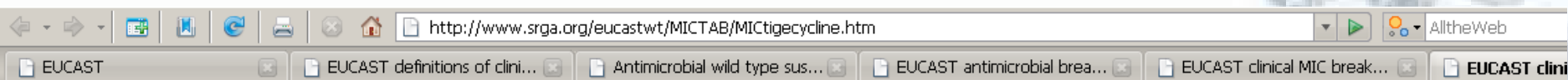
intravenous formulation, and has a large volume of distribution. Haemolysis is the most noteworthy adverse event.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci,  $\beta$ -haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

# La rationalité est importante ...



## Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline <small>Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.</small>	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i>	<i>Entero-coccus</i>	<i>Strepto-coccus A,B,C,G</i>	<i>S.pneu-moniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.mening-itidis</i>	<i>Gram-negative anaerobes</i>
<a href="#">Tigecycline (RD)</a>	1/2 <sup>2,5</sup>	--	IE	0.5/0.5 <sup>3,6</sup>	0.25/0.5 <sup>3</sup>	0.25/0.5 <sup>3</sup>	IE	IE	IE	IE	Note <sup>4</sup>

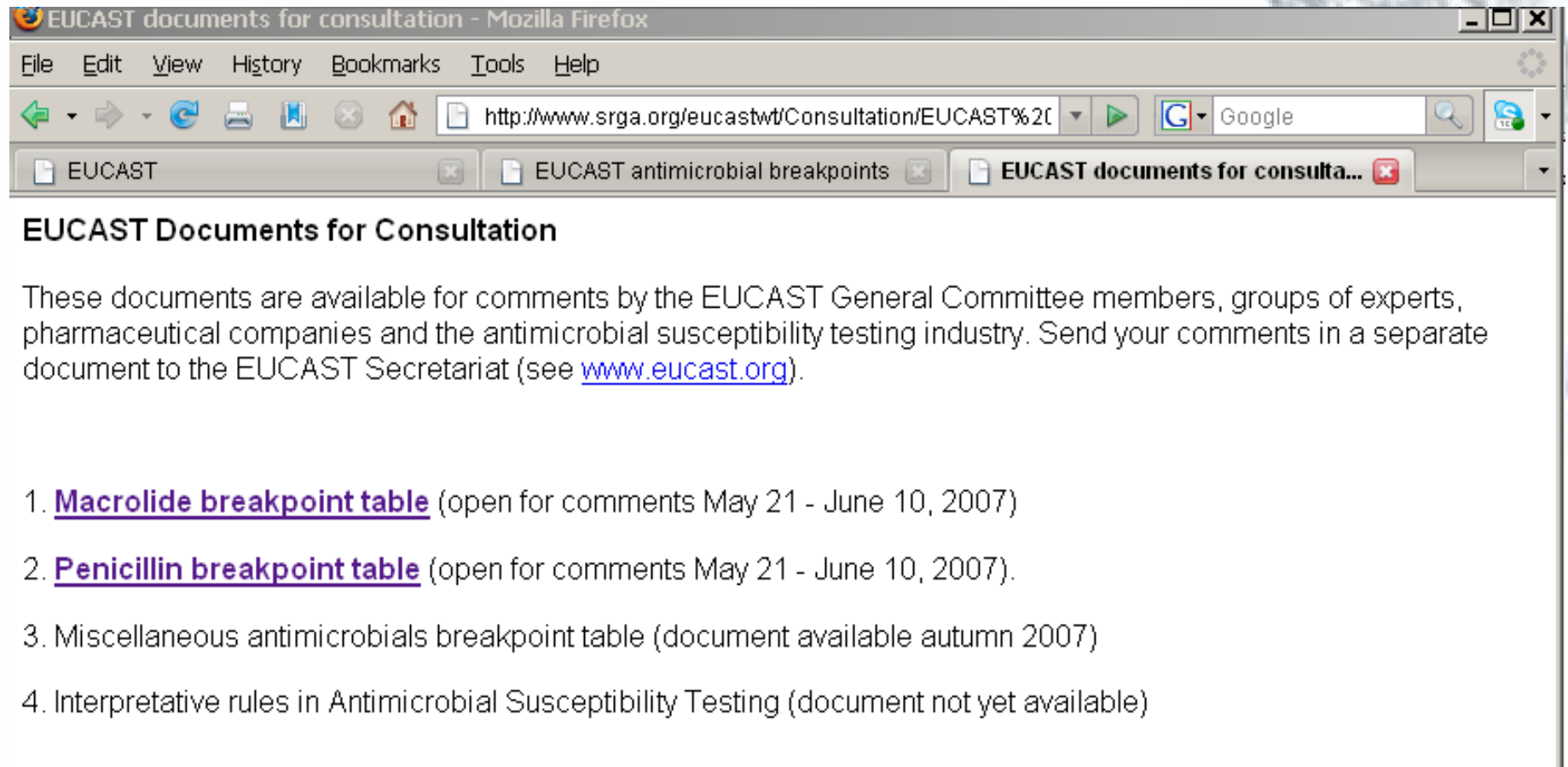
1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that have been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. Tigecycline has decreased activity against *Morganella*, *Proteus* and *Providencia*.
3. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and I/R breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.  
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.  
 RD = Rationale document listing data used for setting EUCAST breakpoints

**Le point critique clinique accepté est 1 / 2 mg/L mais le seuil PK/PD est plus bas (0.25 / 0.5 mg/L)**

**Donc: surveillance des CMI !!**

# Mais quid des points critiques non encore publiés ... ?




**EUCAST Documents for Consultation**

These documents are available for comments by the EUCAST General Committee members, groups of experts, pharmaceutical companies and the antimicrobial susceptibility testing industry. Send your comments in a separate document to the EUCAST Secretariat (see [www.eucast.org](http://www.eucast.org)).

1. [Macrolide breakpoint table](#) (open for comments May 21 - June 10, 2007)
2. [Penicillin breakpoint table](#) (open for comments May 21 - June 10, 2007).
3. Miscellaneous antimicrobials breakpoint table (document available autumn 2007)
4. Interpretative rules in Antimicrobial Susceptibility Testing (document not yet available)

# Pour bientôt ...



**EUCAST Documents for Consultation**

These documents are available for comments by the EUCAST General Committee members, groups of experts, pharmaceutical companies and the antimicrobial susceptibility testing industry. Send your comments in a separate document to the EUCAST Secretariat (see [www.eucast.org](http://www.eucast.org)).

1. [Macrolide breakpoint table](#) (open for comments May 21 - June 10, 2007)
2. [Penicillin breakpoint table](#) (open for comments May 21 - June 10, 2007).
3. Miscellaneous antimicrobials breakpoint table (open for comments May 21 - June 10, 2007)
4. Interpretative rules in Antimicrobial Susceptibility Testing (open for comments May 21 - June 10, 2007)

- **point critique probable pour la pipéracilline/tazobactame:**
  - **8/16 pour les *Enterobacteriaceae***
  - **16/16 for le *Pseudomonas***  
**(mais avec une haute dose)**

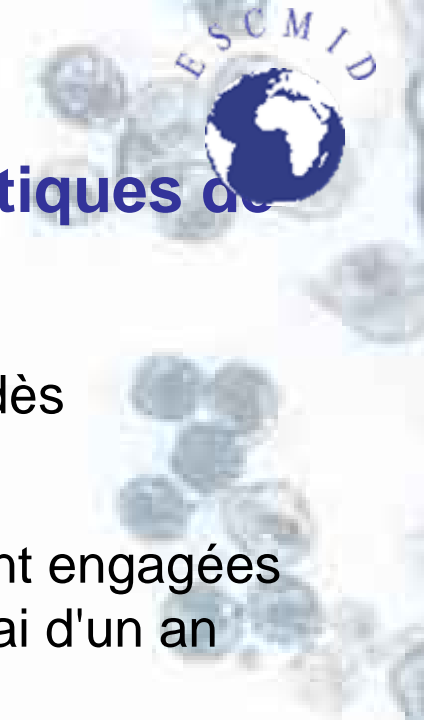
## Comment seront implémentés les points critiques de l'EUCAST en pratique ?

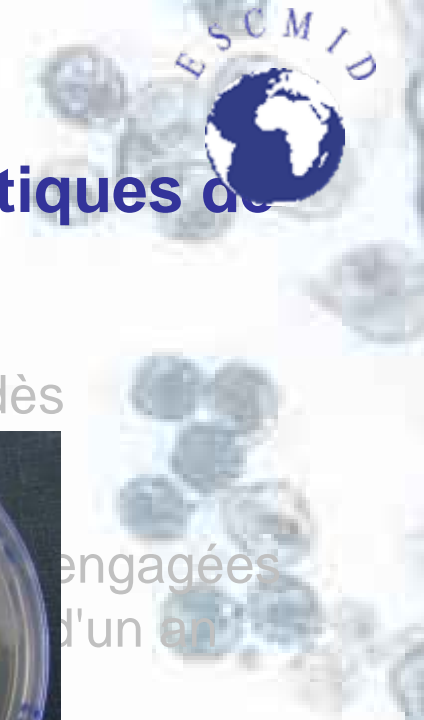
- Les points critiques de l'EUCAST peuvent être utilisés dès aujourd'hui par qui veut ...
- Les commissions nationales (GB, F, NL, D, N, S) se sont engagées à les mettre en application dans leurs pays avec un délai d'un an maximum...
- La plupart des systèmes automatiques peuvent être adaptés et les fabricants sont au travail (même si les commerciaux l'ignorent...)

**From EUCAST, October 9<sup>th</sup>, 2007:**

- **Each national committee has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision that goes down 2008 will be implemented into the systems January 2009.**
- **The manufacturers of devices (BM and BD) have both said that it is realistic that their machines will have EUCAST breakpoints January 2009.**

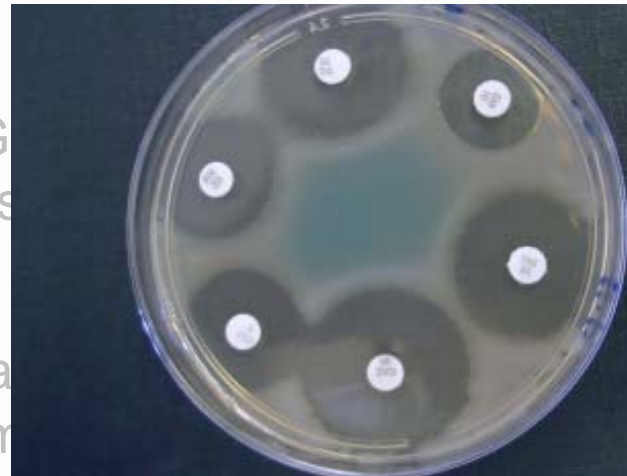
**SCOOP**





## Comment seront implémentés les points critiques de l'EUCAST en pratique ?

- Les points critiques de l'EUCAST peuvent être utilisés dès aujourd'hui ...
- Les comités de surveillance (GSC) sont engagées à les mettre en œuvre au maximum d'un an ...
- La plupart des systèmes automatisés de surveillance sont en cours de mise à jour. Dans le court terme...



- Des discussions sont en cours à propos de plusieurs aspects techniques (densité de l'inoculum, type de milieu etc... ) mais des instructions claires seront diffusées en 2008 (probablement influencées à la fois par les méthodes du CLSI et celles de la SFM)

## Comment seront implémentés les points critiques de l'EUCAST en pratique ?

- Les points critiques de l'EUCAST peuvent être utilisés dès maintenant par qui veut ...

**Des discussions actives ont cours en Belgique, et des actions de sensibilisation et de collecte d'information seront menées à partir de novembre 2007... et tout au long de l'année 2008 ...**

**Le but est d'introduire le changement en Belgique au 1 janvier 2009**

**Les francophones et les flamands sont d'accord !!**

L'Autriche, la Finlande et le Danemark bougent également...

Comment seront implémentés les points critiques de  
l'EUCAST en pratique ?

**Et les nouvelles molécules ?**





European Medicines Agency  
 Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
<b>PUBLIC</b>		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

## 1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

- **Les points critiques de TOUTES les nouvelles molécules seront fixés par l'EUCAST...**
- **Ces valeurs seront reprises dans la notice européenne et seront d'application partout ...**
- **Molécules déjà passées par cette procédure: tigécycline, daptomycine**
- **4 autres molécules à l'examen...**

# L'avenir des points critiques de l'EUCAST

- Dès aujourd'hui, l'EUCAST fixe directement ou indirectement les **points critiques officiels** pour l'Europe (U.E. et pays associés)
- Mais ces points critiques pourraient devenir des valeurs de référence mondiales...

**(see why in a moment...)**

# Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

Done...

- Cephalosporin breakpoints for Enterobacteriaceae
- Carbapenems and Monobactams (!?)

**CEN and ISO (EUCAST and CLSI) – international reference method for determination of MICs for non-fastidious bacteria.**



# EUCAST presentation at CLSI (January 2005, Tampa, Fla)



But will NCCLS (now CLSI...) still be authorized to define breakpoints ?



# L'avenir incertain des points critiques du CLSI ...



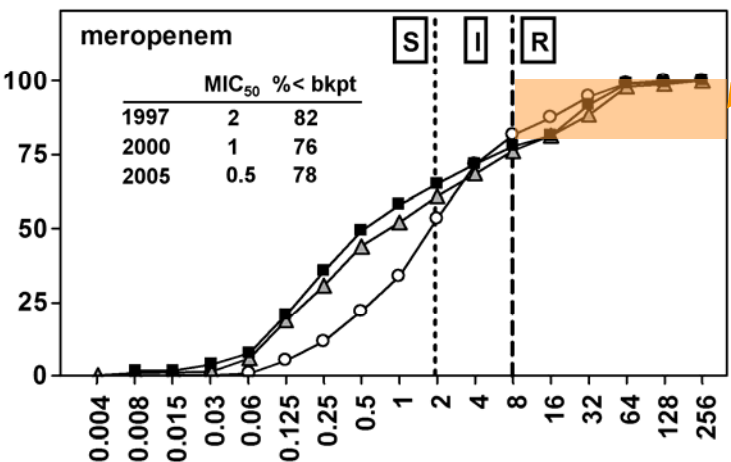
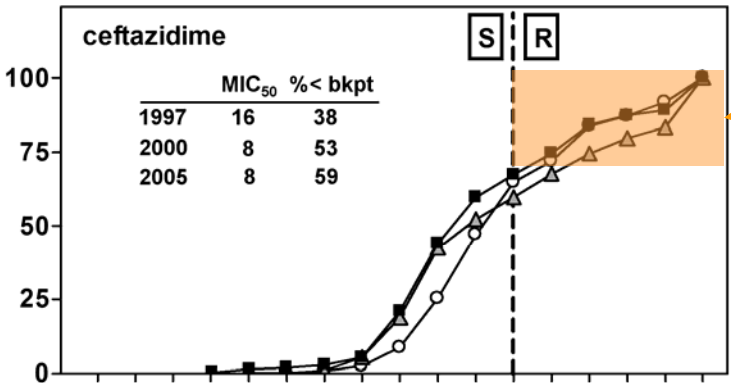
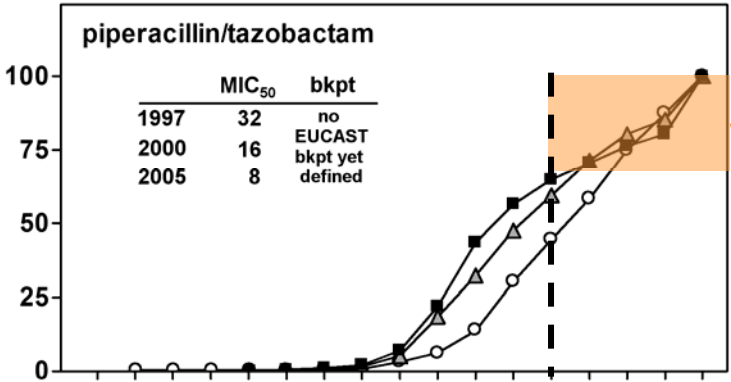
- Over the last 2 years, FDA has reasserted its legal rights to define official breakpoints (and removed it from NCCLS, hence its change of name)
- CLSI may set breakpoints **after** FDA has defined them, but will NOT publish them if they are different from those of the FDA... (CLSI may petition the FDA for breakpoint revision after 2 years...)
- CLSI will try to become the specialized committee of the FDA for setting breakpoints ... But FDA may not accept this...
- In the meantime, only FDA breakpoints will be legal ... and will be essentially geared to the protection of the American Public
- Other countries will have no direct impact on the FDA-decision process ... and may, therefore, look for another, more "non-national" body for advice and orientation ... This may be CLSI ... or EUCAST...

communicated at the General meeting of EUCAST during the 17th ECCMID & 25th ICC (Munich, Germany) by the CLSI representative

# Les points critiques résoudront-ils tous les problèmes ?

- Les points critiques ne sont que des "points de guidance" pour un traitement "général"  
(quelles sont les chances de succès pour un patient moyen)
- La connaissance des distributions de CMI (locales, regionales, nationales) demeurent essentielles pour juger de la sensibilité des germes, ... ajuster les traitement, et ... revoir les points critiques...
- Le traitement des patients "difficiles" devra toujours se faire sur une base individuelle, et en fonction des CMI.
- L'usage d'antibiotiques à action "douteuse" devra être remis en question...
- Les points critiques et la situation locale permettront de faire des choix plus rationels entre moélcules...

○ 1997    △ 2000    ■ 2005



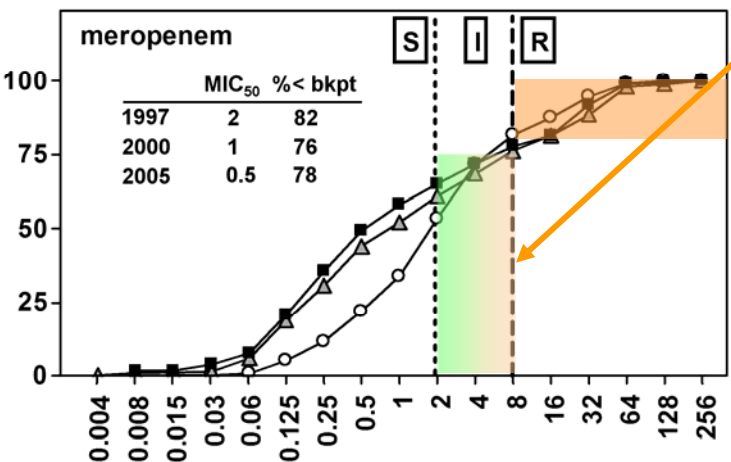
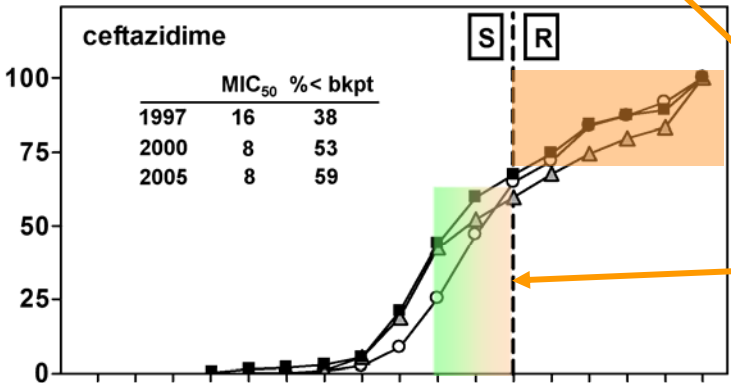
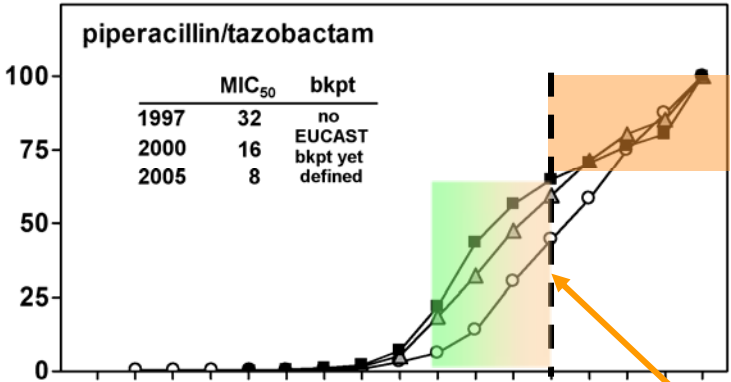
MIC (mg/L)

Exemple pour le *Pseudomonas...*

**risque élevé**  
(population > de la valeur "R")

Mesaros et al. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. Clin Microbiol Infect. 2007 Jun;13(6):560-78.

○ 1997    △ 2000    ■ 2005



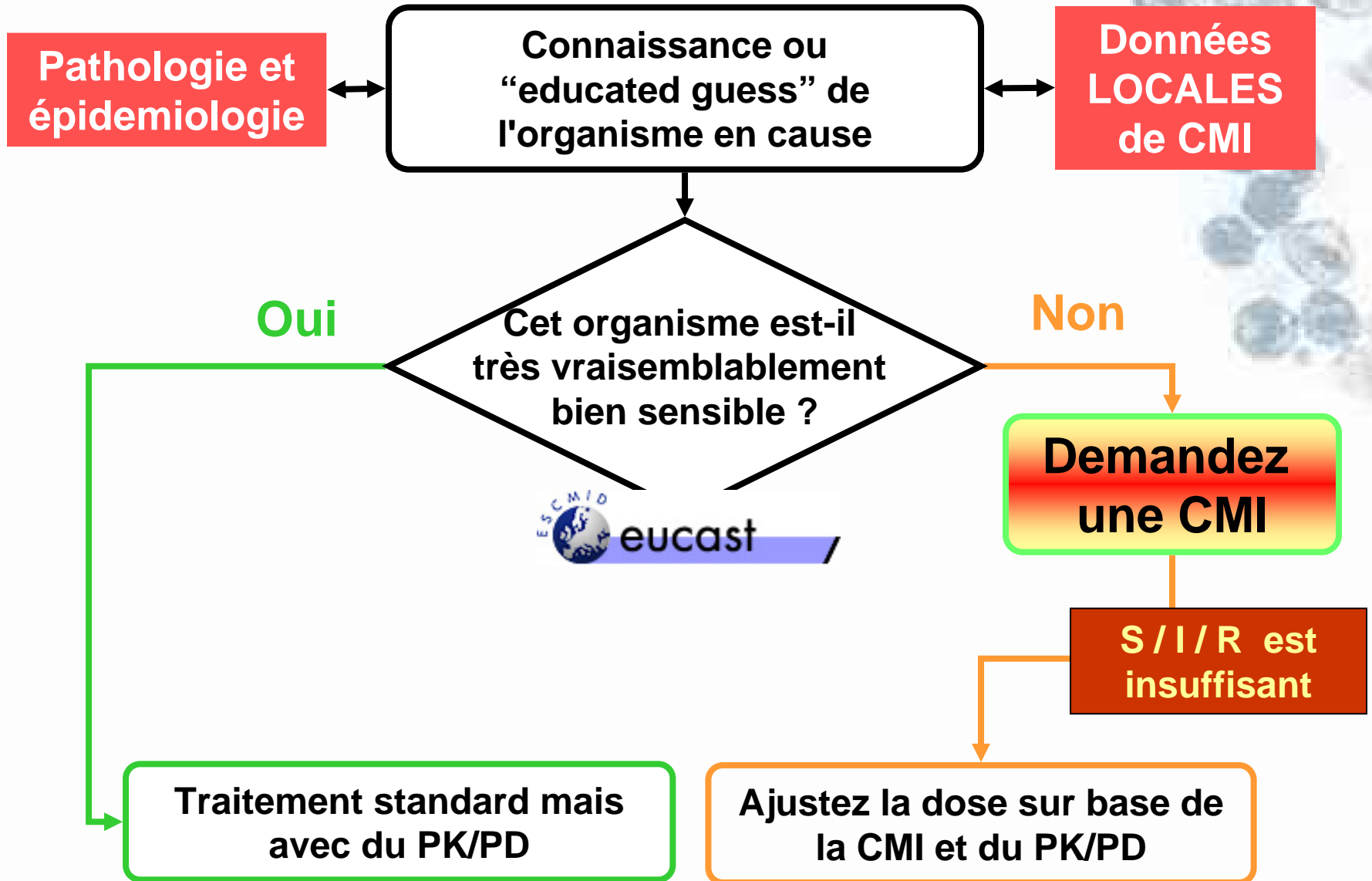
MIC (mg/L)

Application pour le *Pseudomonas*...

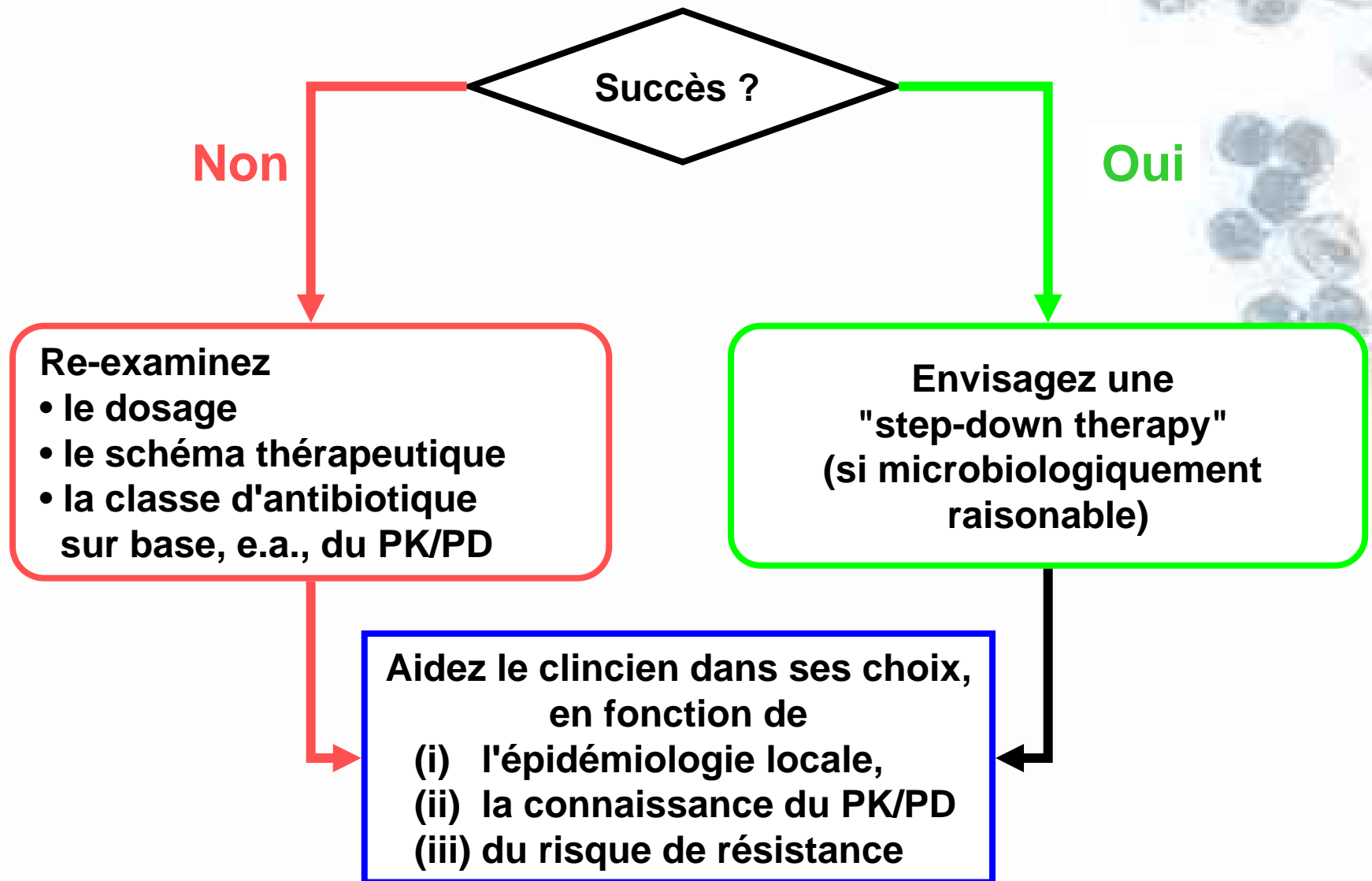
mais ces populations sont également à risque

Mesaros et al. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. Clin Microbiol Infect. 2007 Jun;13(6):560-78.

# Des clés pour le succès...

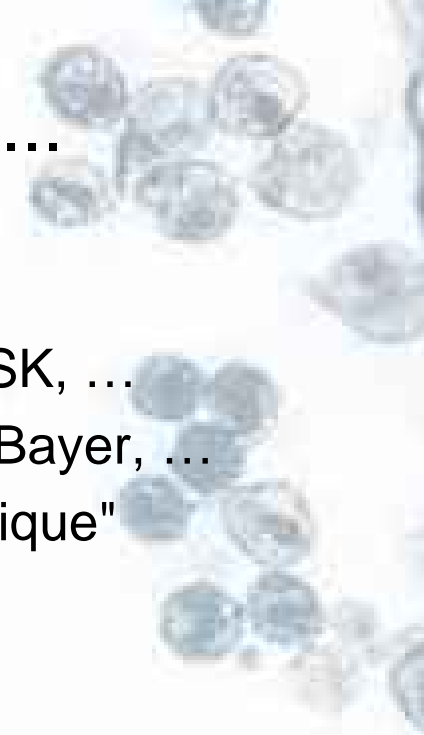


# Des clés pour le succès (suite). ..



# Conflits d'intérêt et remerciements...

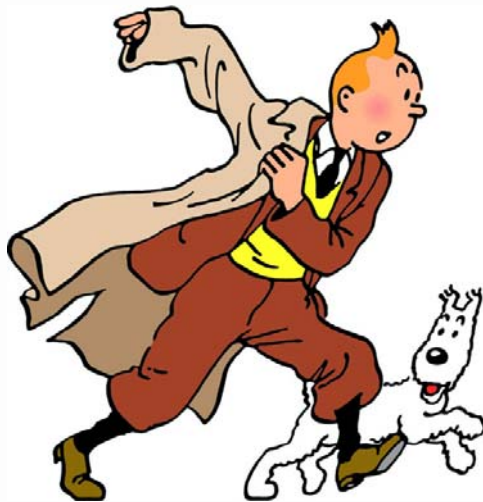
- Conflits d'intérêt
  - subventions de recherche de Bayer, Pfizer, Wyeth, GSK, ...
  - Honoraires de conférences de AstraZeneca, Aventis, Bayer, ...
  - Jetons de présence de l'INAMI et du SPF "Santé Publique"
- Remerciements
  - Gunnar Kalhlmeter (dias et discussions)
  - ISC (et JC Pechère) pour m'avoir sollicité comme représentant de l'ISC auprès de l'EUCAST
  - Johan Mouton (pour une introduction à la pharmacocinétique de population et diverses dias)
  - Els Ampe (pour des discussions et la relecture de mes dias en néerlandais)



# Et pour conclure...



Ne nions pas les difficultés...



**Mais nous pouvons dès maintenant**



**construire de vrais succès en Europe**

Il est toujours possible de découvrir ...





Et même si le chemin peut paraître dur ...

On peut y arriver...



avec ardeur...





**Les ponts sont mis en place ...**



**Et tout peut vous sourire ...**

