

Antibio - lcr

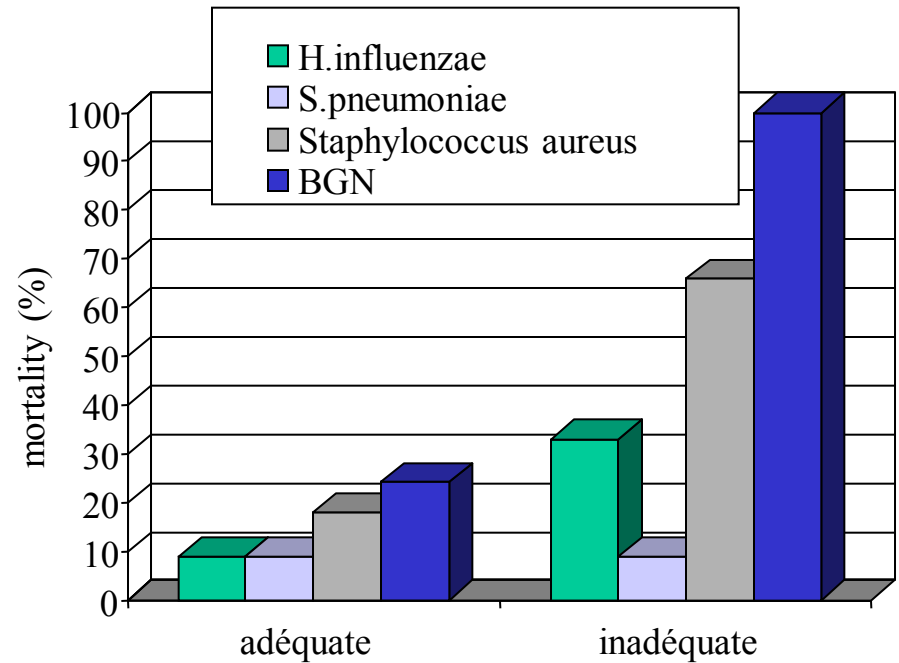
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Dijon

29 janvier 2019

Mortalité des méningites bactériennes vs antibiothérapie

**antibiothérapie
inadéquate
=> Mortalité accrue**



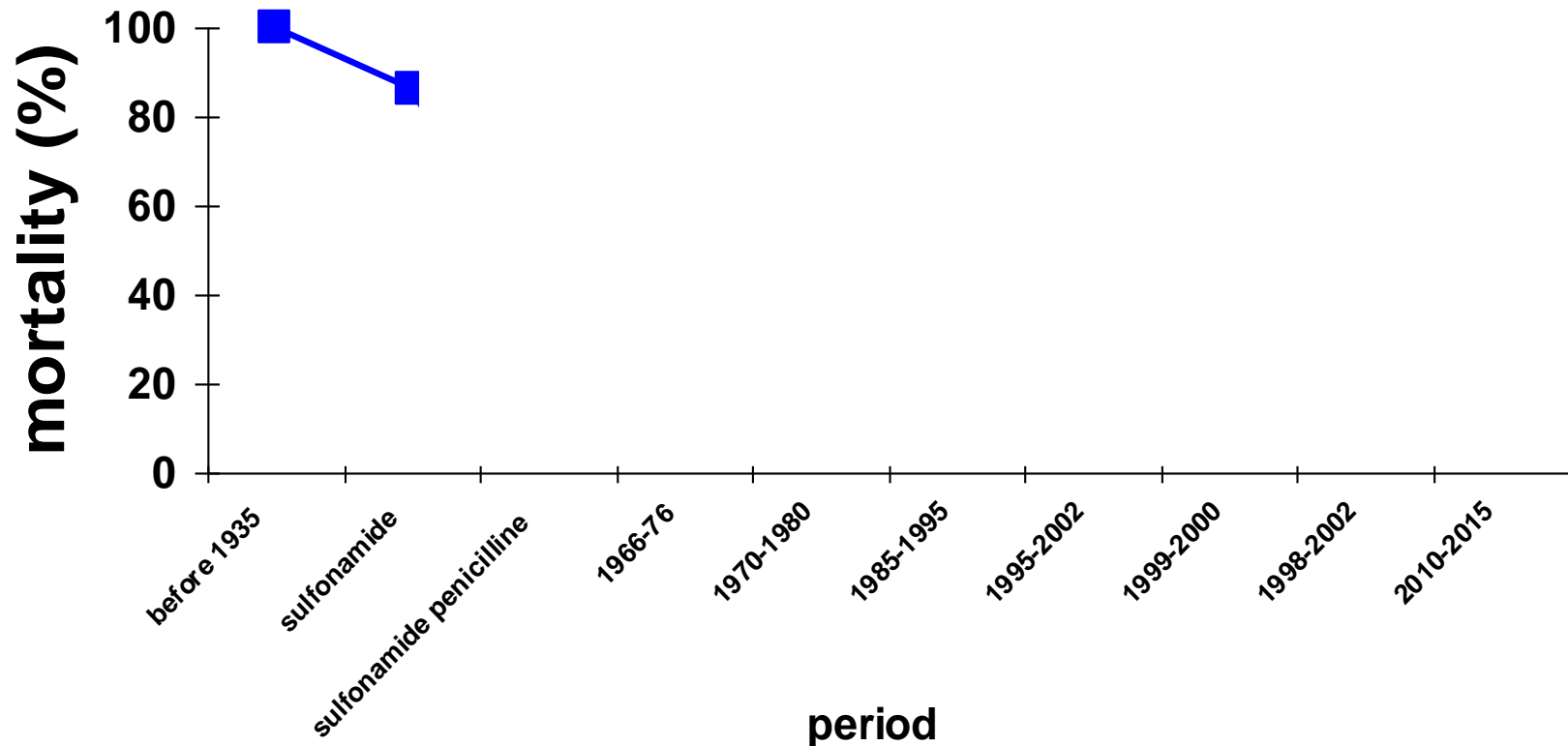
antibiothérapie

Antibiotiques vs méningite

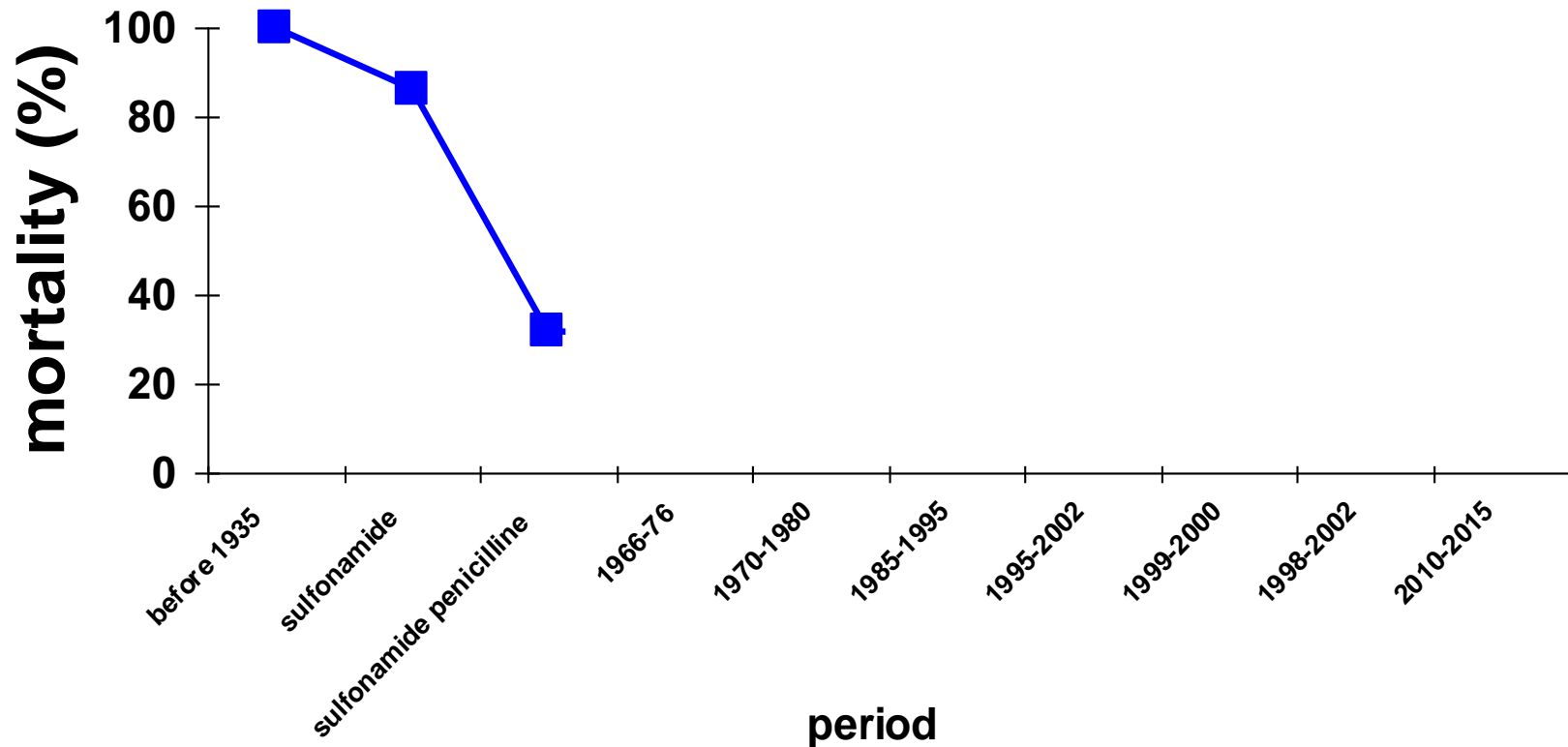
40 ans d'effort(s) pour une triste stabilité !!

	Mortalité hospitalière imputable (%)
1962-1970	21
1971-1979	18
1980-1988	17

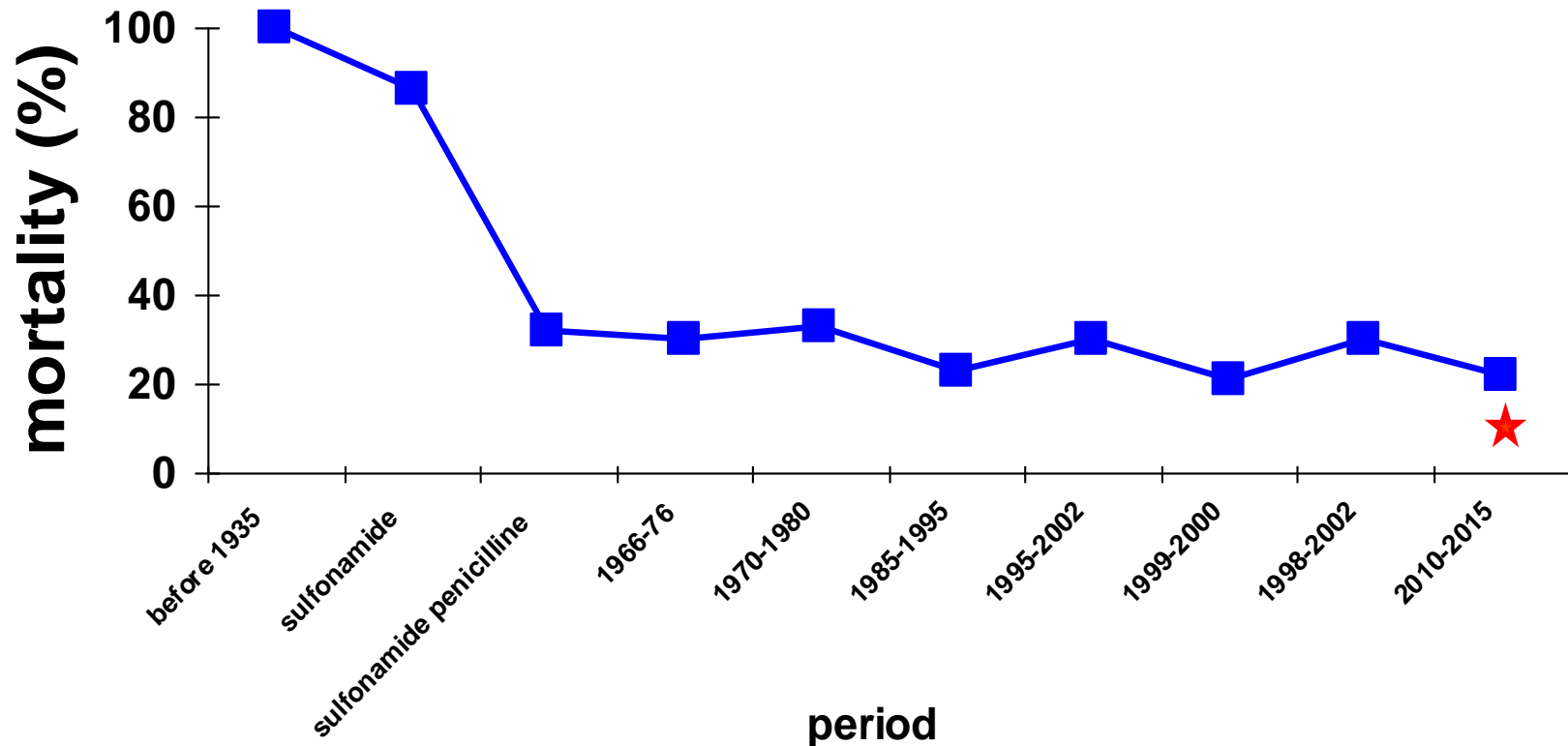
Mortalité de la méningite pneumocoque dans les pays riches vue globale



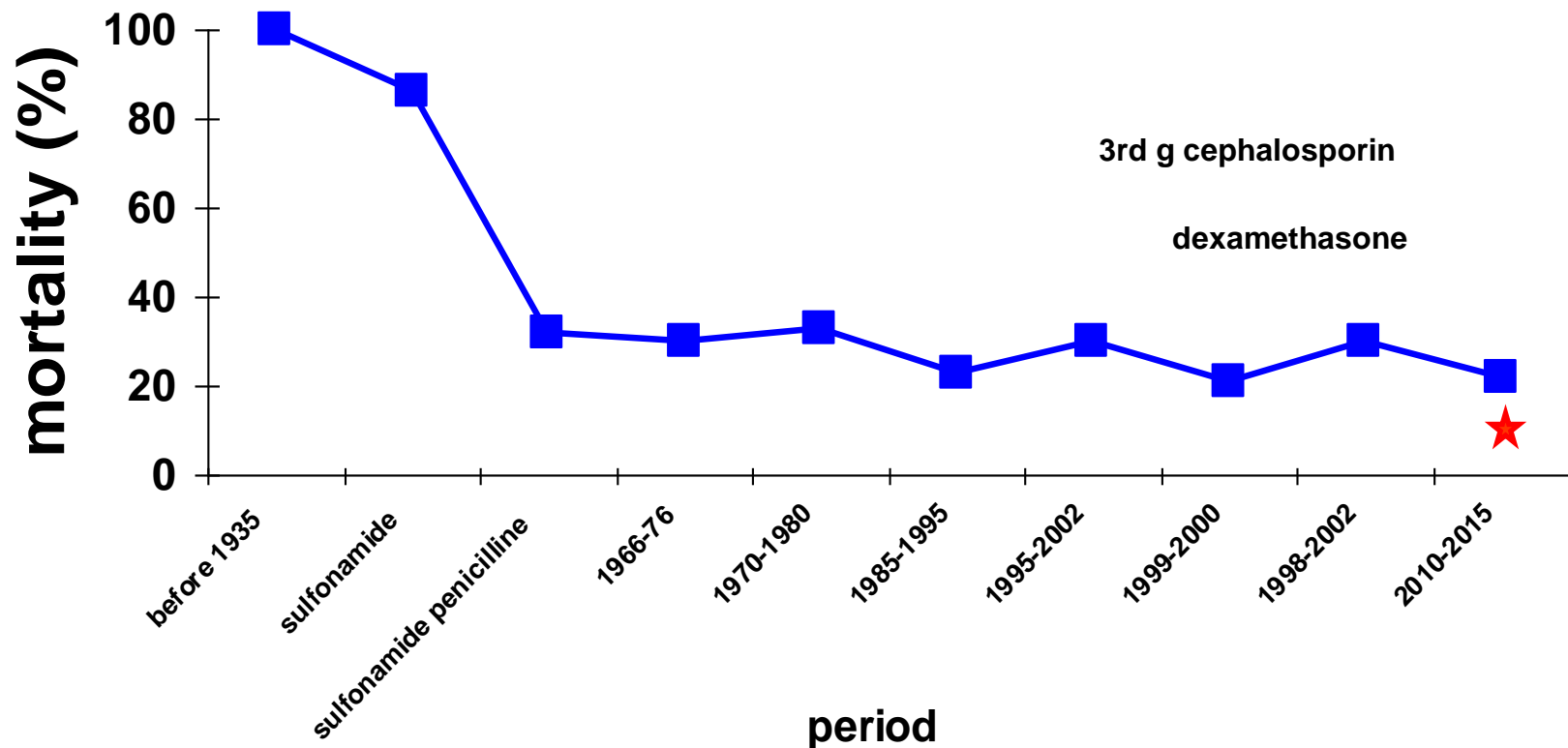
Mortalité de la méningite pneumocoque dans les pays riches vue globale



Mortalité de la méningite pneumocoque dans les pays riches vue globale

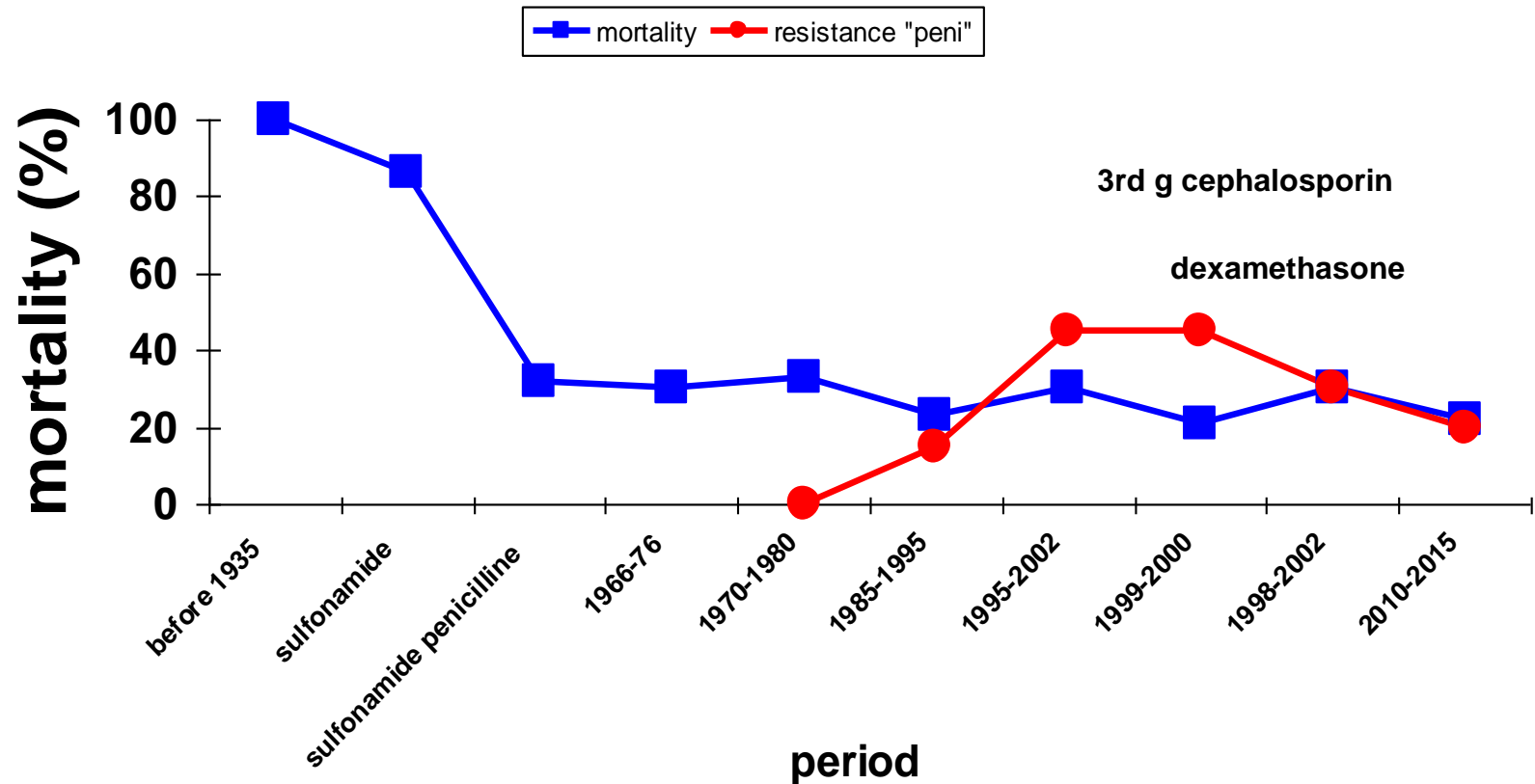


Mortalité de la méningite pneumocoque dans les pays riches vue globale

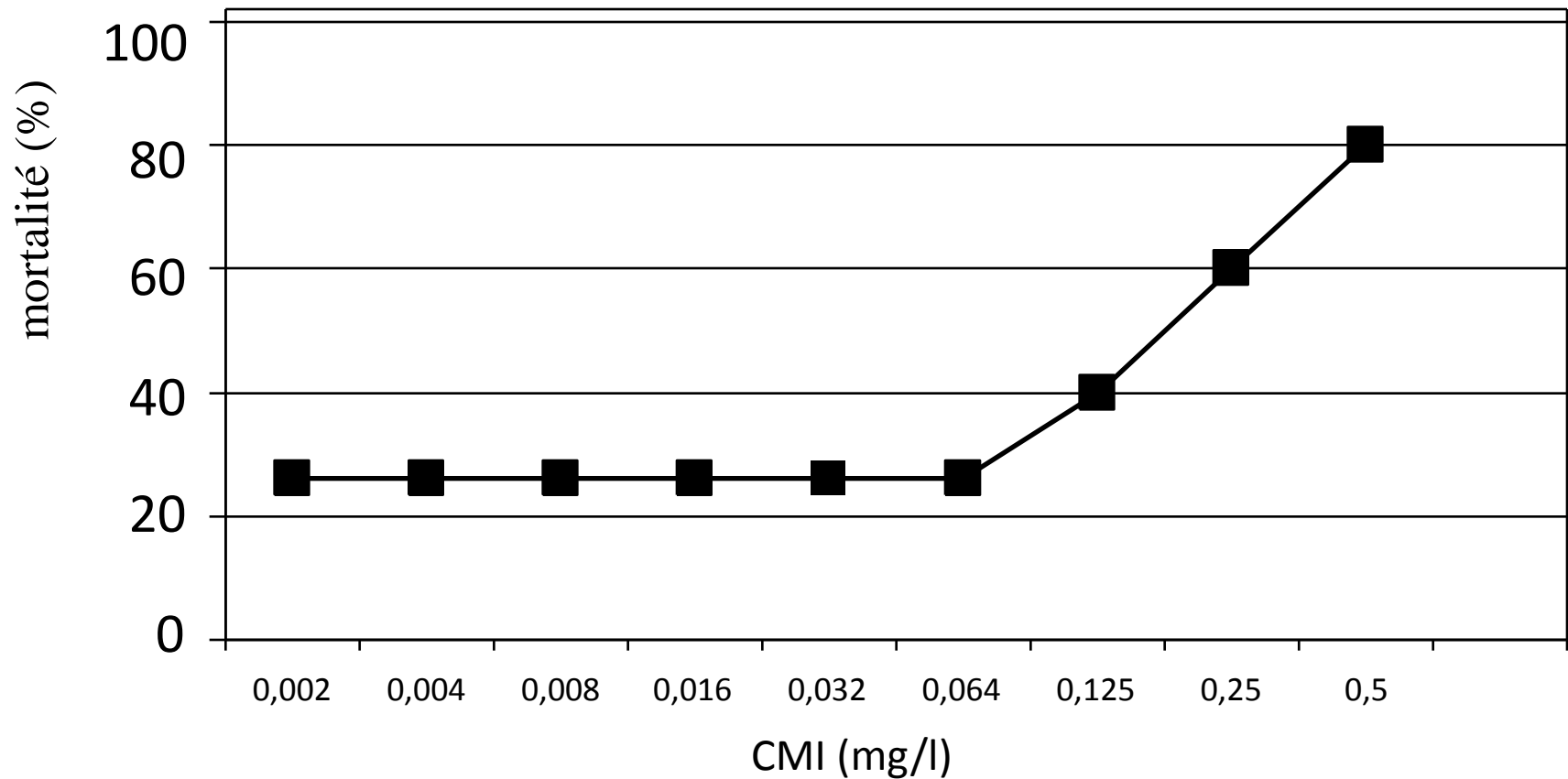


Pneumococcal meningitis mortality in high income areas

Global view



Mortalité vs CMI pneumocoque



« diffusion pneumococcique » élément pronostique

GOS=5

GOS≤4

Septicemia ≈50%^{a,b}

c

Pneumonia ≈17%^{b,d}

a) De Gans J et al NEJM 2002;347:1549; b) Østergaard, *BMC Infectious Diseases* 2005, 5:93: from 60 to 100%

c) Stefan Kastenbauer and Hans-Walter Pöster, Pneumococcal meningitis in adults Spectrum of complications and prognostic factors in a series of 87 cases, *Brain* (2003), 126, 1015±1025

d) Hoen B 1993

« diffusion pneumococcique » élément pronostique

	GOS=5	GOS≤4
Septicemia $\approx 50\%$ ^{a,b}	50%	77% ^c ± choc
Pneumonia $\approx 17\%$ ^{b,d}	11%	31%

⇒ Diffusion « générale »

⇒ Hémodynamique « parfaite »

a) De Gans J et al NEJM 2002;347:1549; b) Østergaard, *BMC Infectious Diseases* 2005, 5:93: from 60 to 100%

c) Stefan Kastenbauer and Hans-Walter Pöster, Pneumococcal meningitis in adults Spectrum of complications and prognostic factors in a series of 87 cases, *Brain* (2003), 126, 1015-1025

d) Hoen B 1993

Méningite à pneumocoque de l'adulte

- La plus fréquente des méningites bactériennes chez l'adulte (53%*)
- Mortalité hospitalière **21%** (France 2015, Combat)
- Handicap sévère **20%**
Atteintes neurologiques
— tr. auditifs > 20%

Meningite à pneumocoque - autopsie

	All patients
Meningeal inflammation	31/31 (100 %)
Inflammation of medium large arteries in meninges	30/31 (97 %)
Thrombosis of medium-large arteries in meninges	15/31 (48 %)
Thrombosis of veins in meninges	5/31 (16 %)
Ventriculitis	19/28 (68 %)

Meningite à pneumocoque - autopsie

All patients

Infarction	19/31 (61 %)
Haemorrhage	24/31 (77 %)
Abscess	6/31 (19 %)
Parenchymal infiltration of inflammatory cells	24/31 (77 %)
Inflammation of small parenchymal vessels	29/31 (94 %)
Thrombosis of small parenchymal vessels	14/31 (45 %)

De la méningite à ses complications....

Atteintes vasculaires

- **Hémodynamiques**
 - La régulation intracérébrale devient « passive »
- **Infectieuses**
 - **L'explosion, la quantité et la persistance d'éléments virulents doivent être réduites**
- **Immunologiques**
 - La réponse immune excessive doit être modulée
-

Séquelles des méningites bactériennes vs antibiothérapie

	ceftriaxone	cefuroxime	
Seq.auditives (%)	4	17	p=0.05
LCR + à J2 (%)	2	12	p=0.1

⇒ but = stérilisation précoce du LCR

⇒ Protection de la barrière hémocérébrale

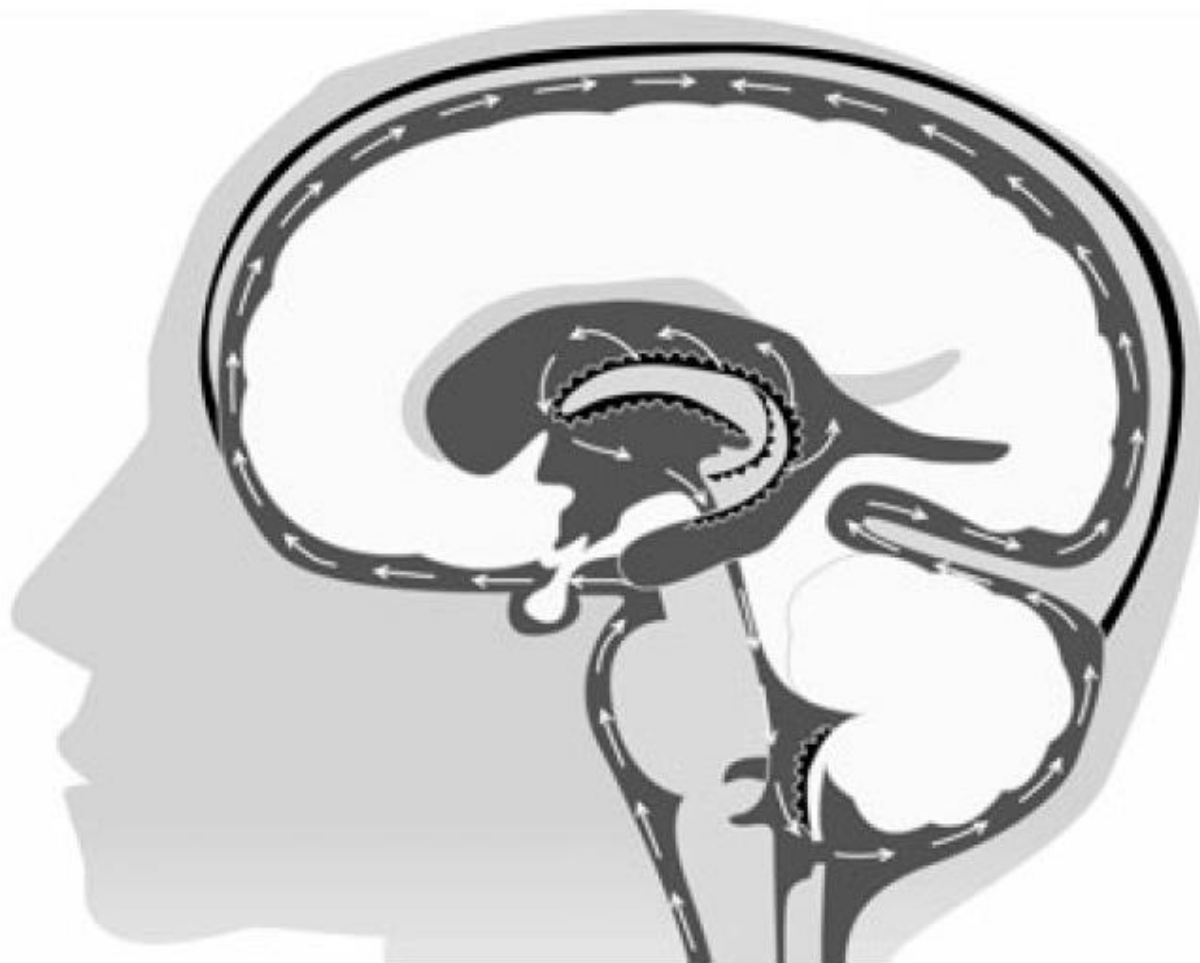
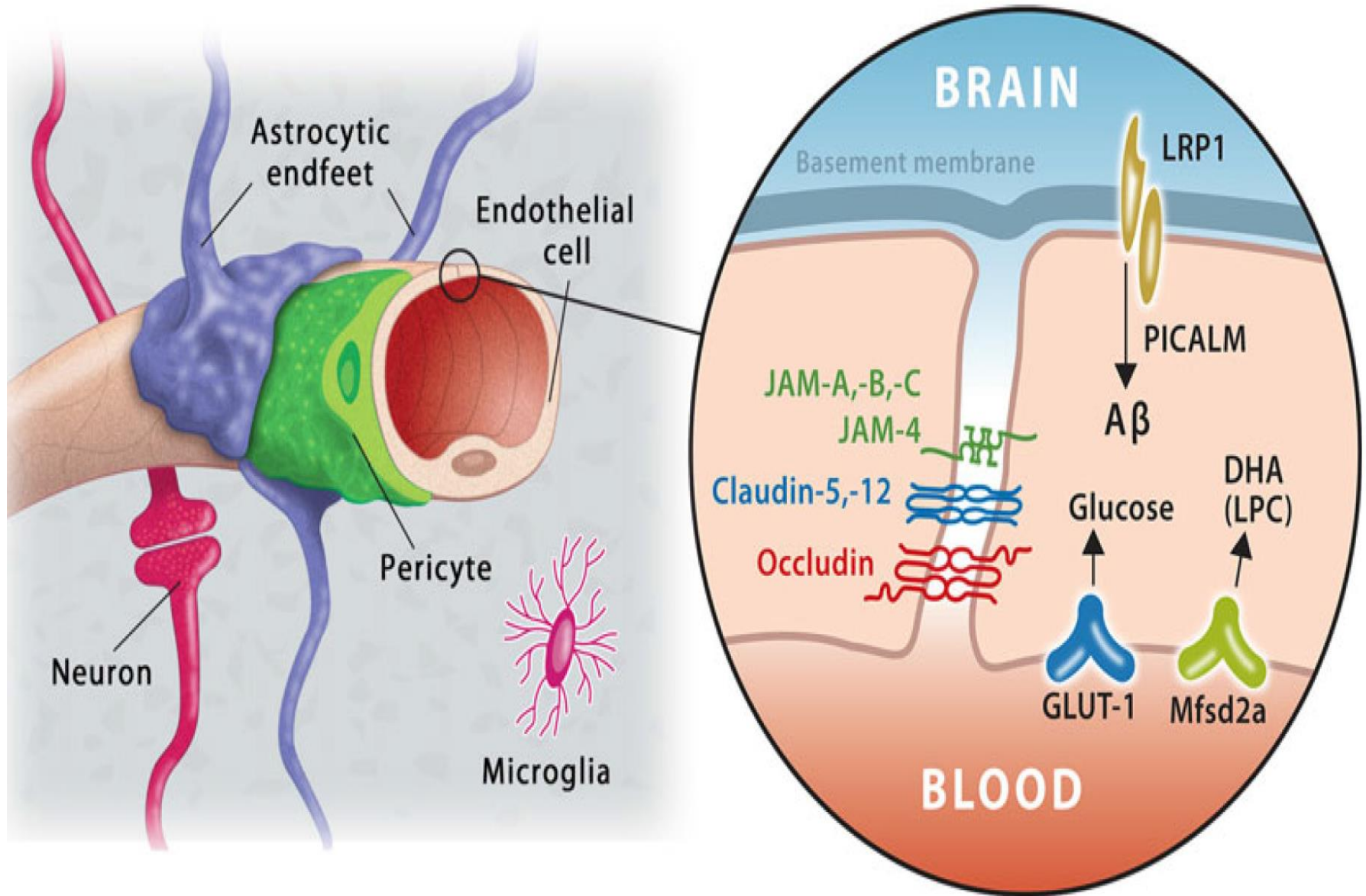
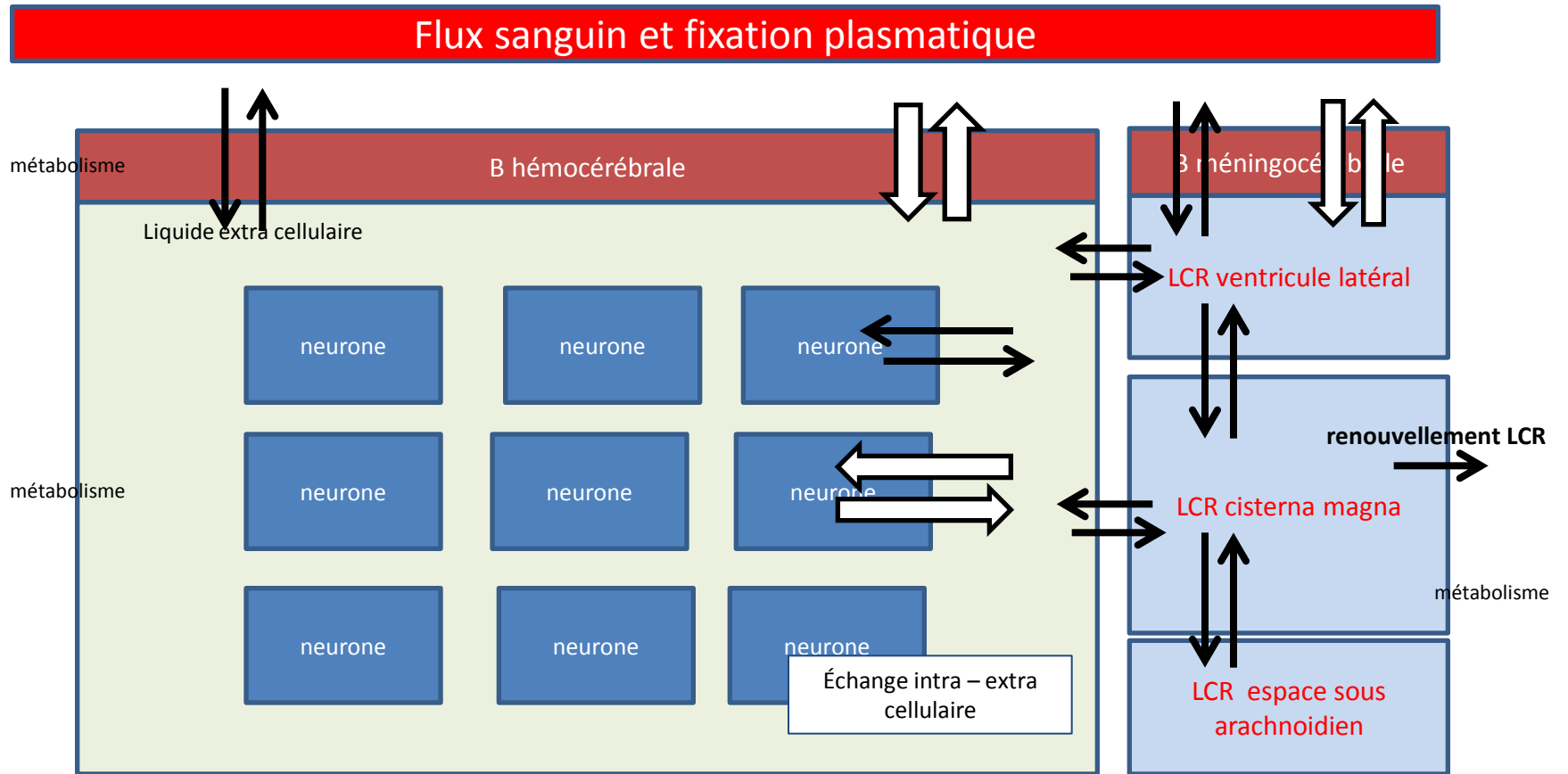


Figure 2. Schematic representation of the CSF flow path.

Vue globale des compartiments



Compartiments et circulation d'échanges possibles des médicaments

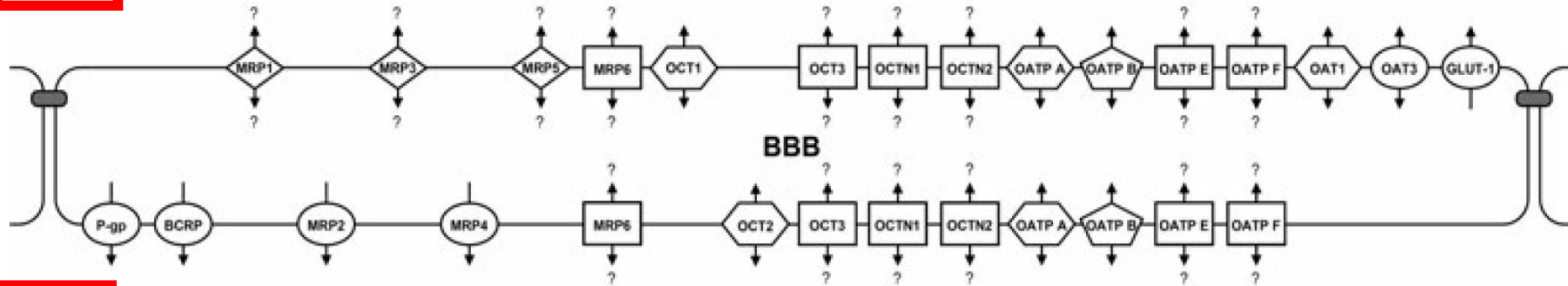


↕ Transport passif

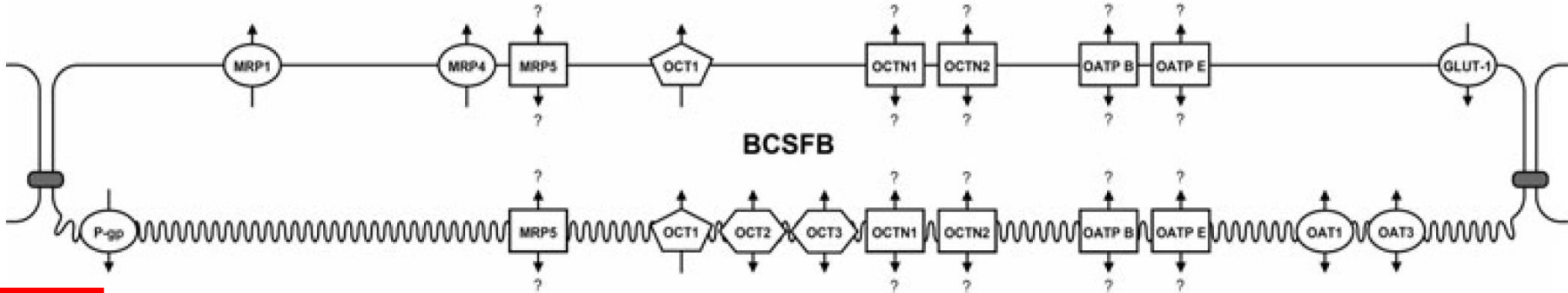
⇕ Transport actif

cartoon

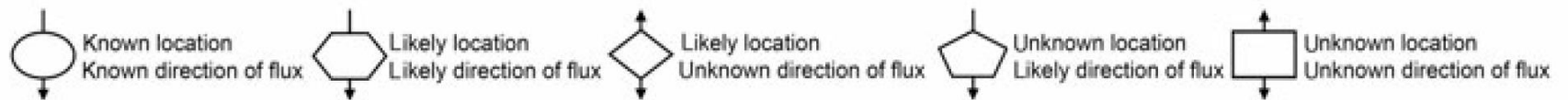
Brain

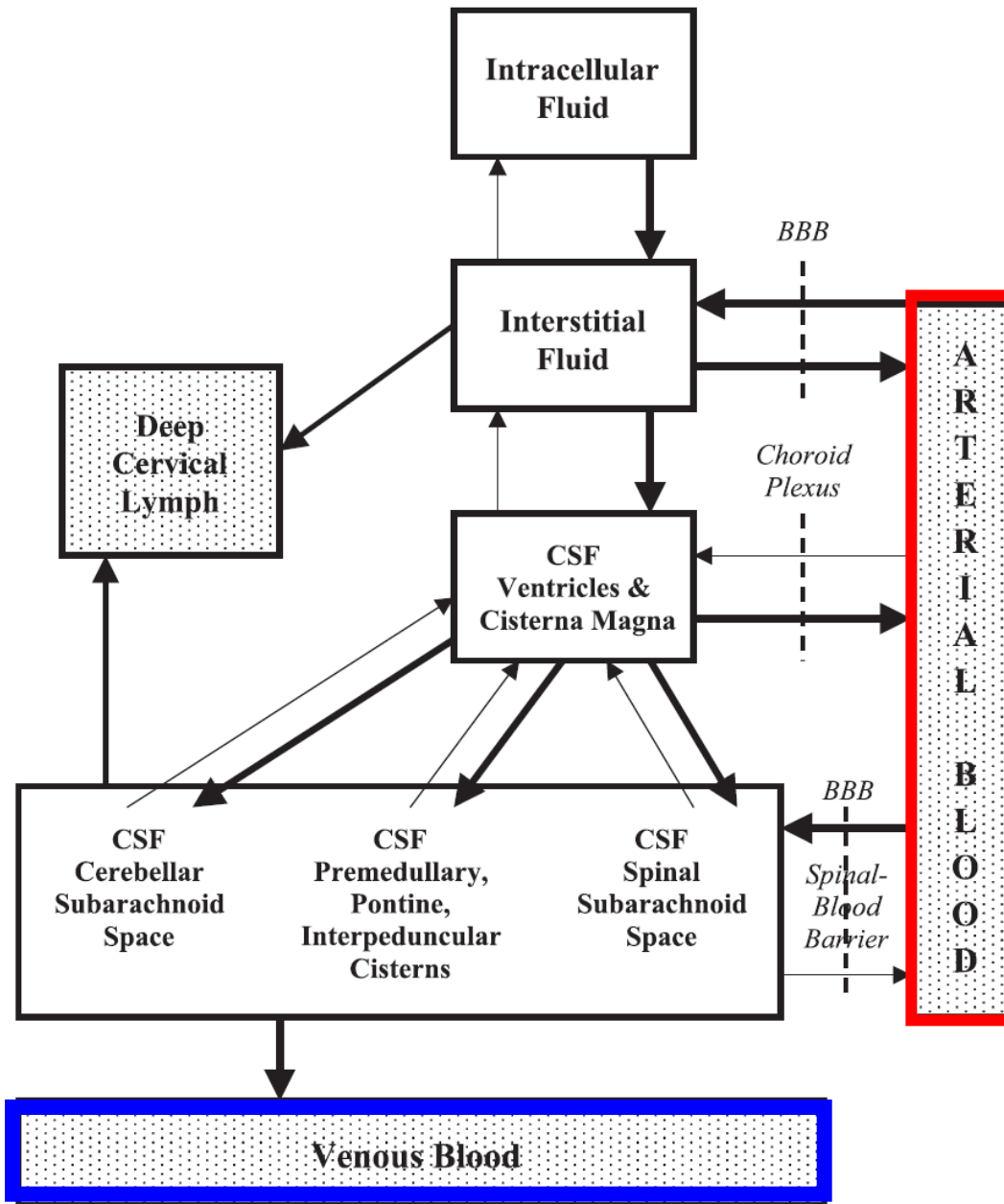


Blood

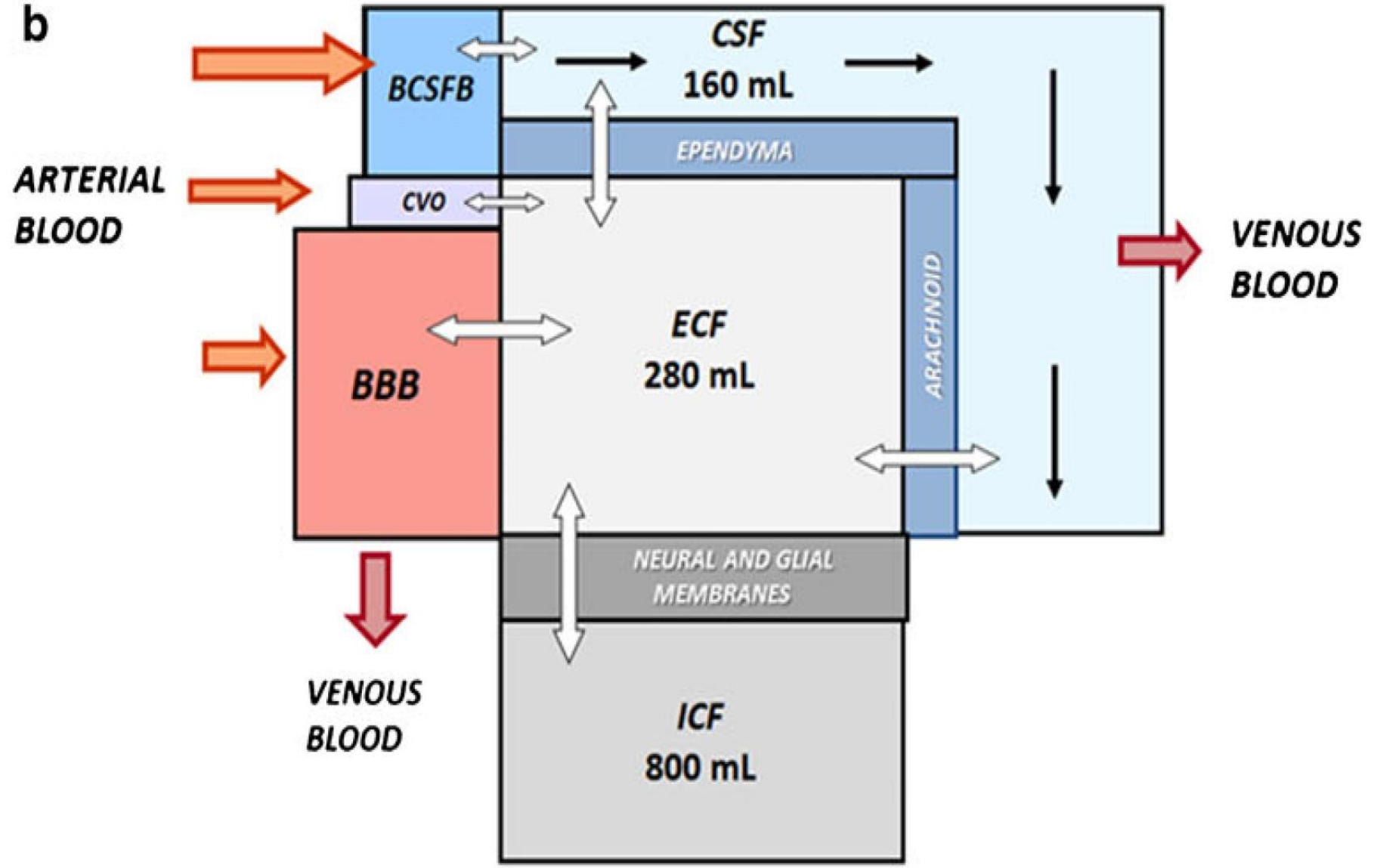


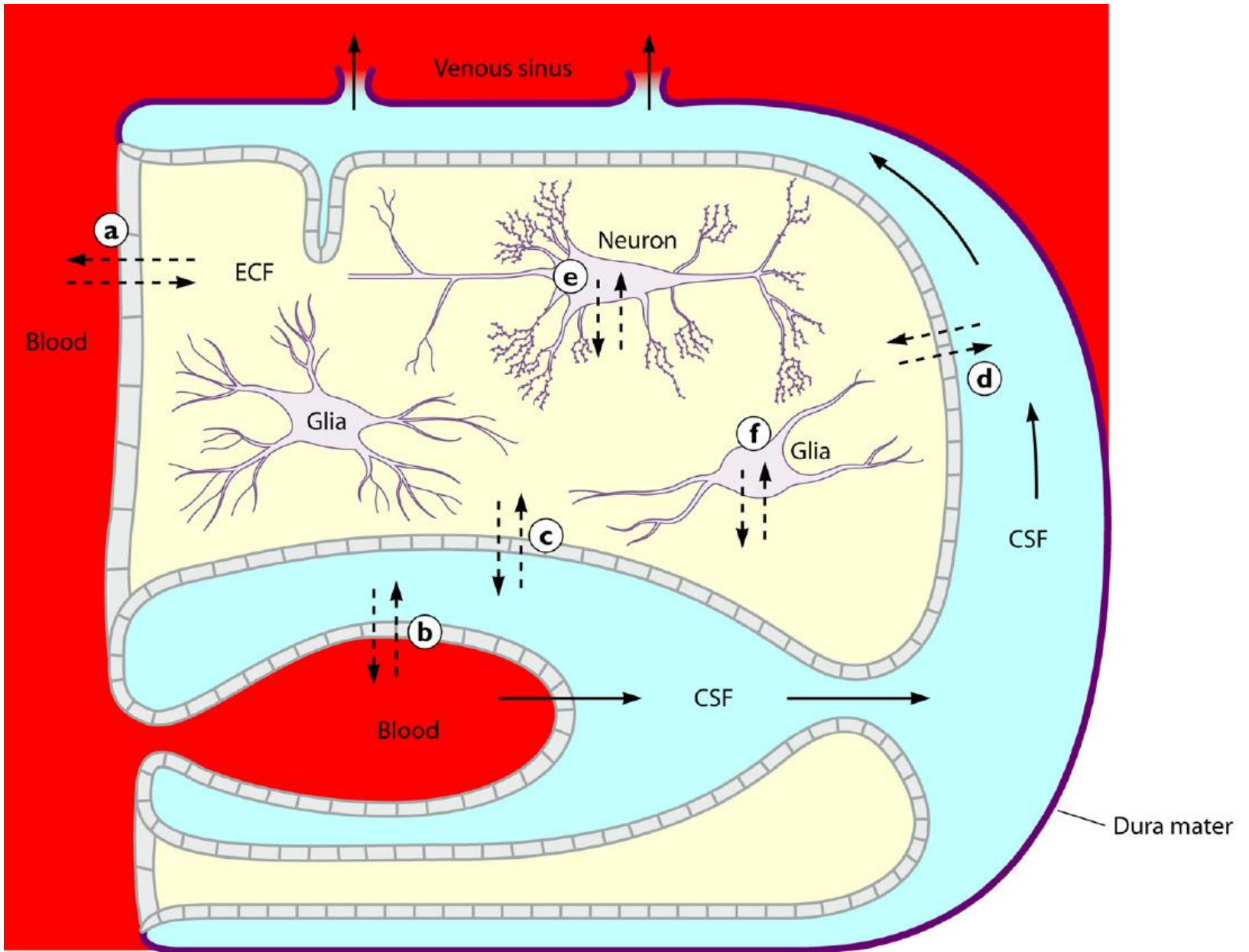
CSF

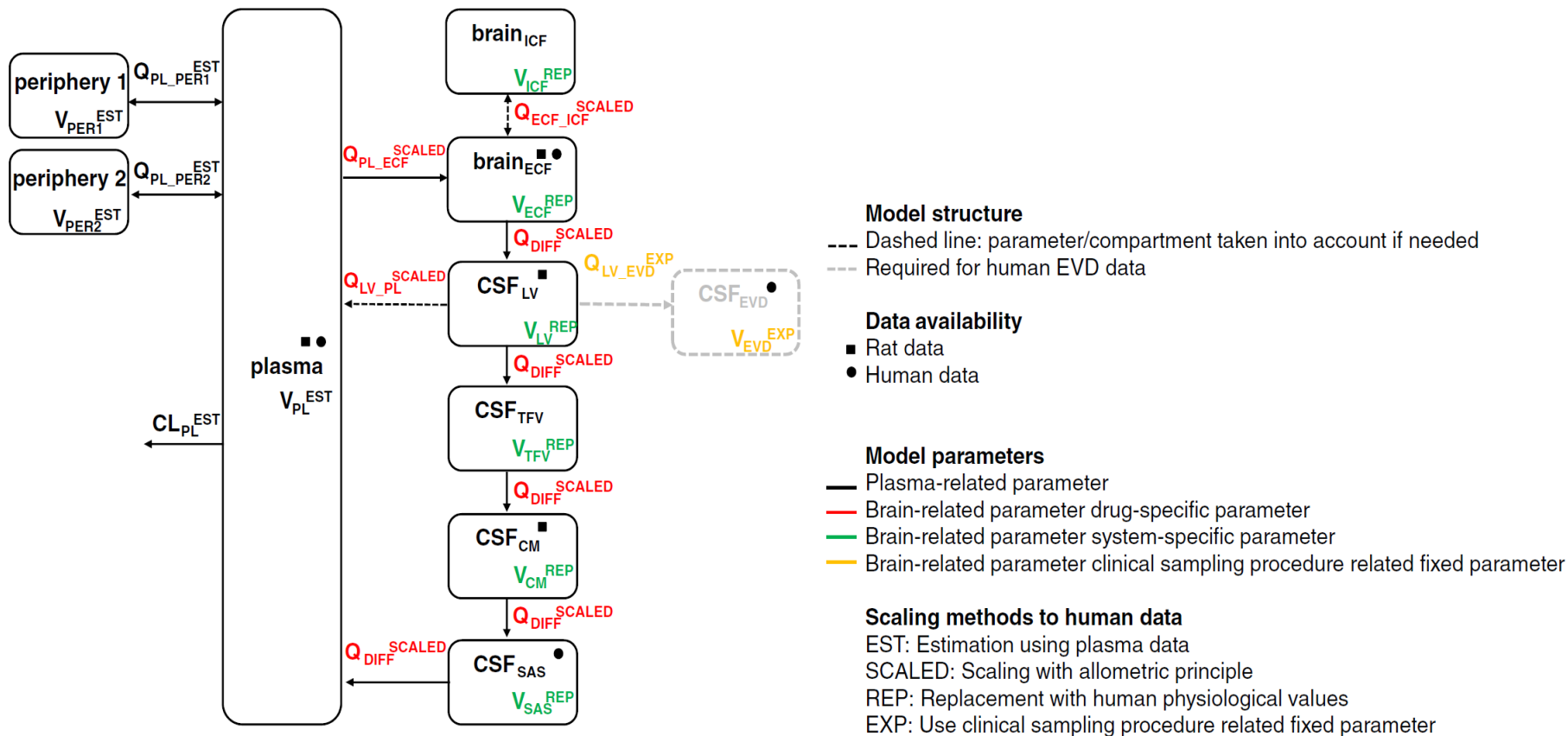




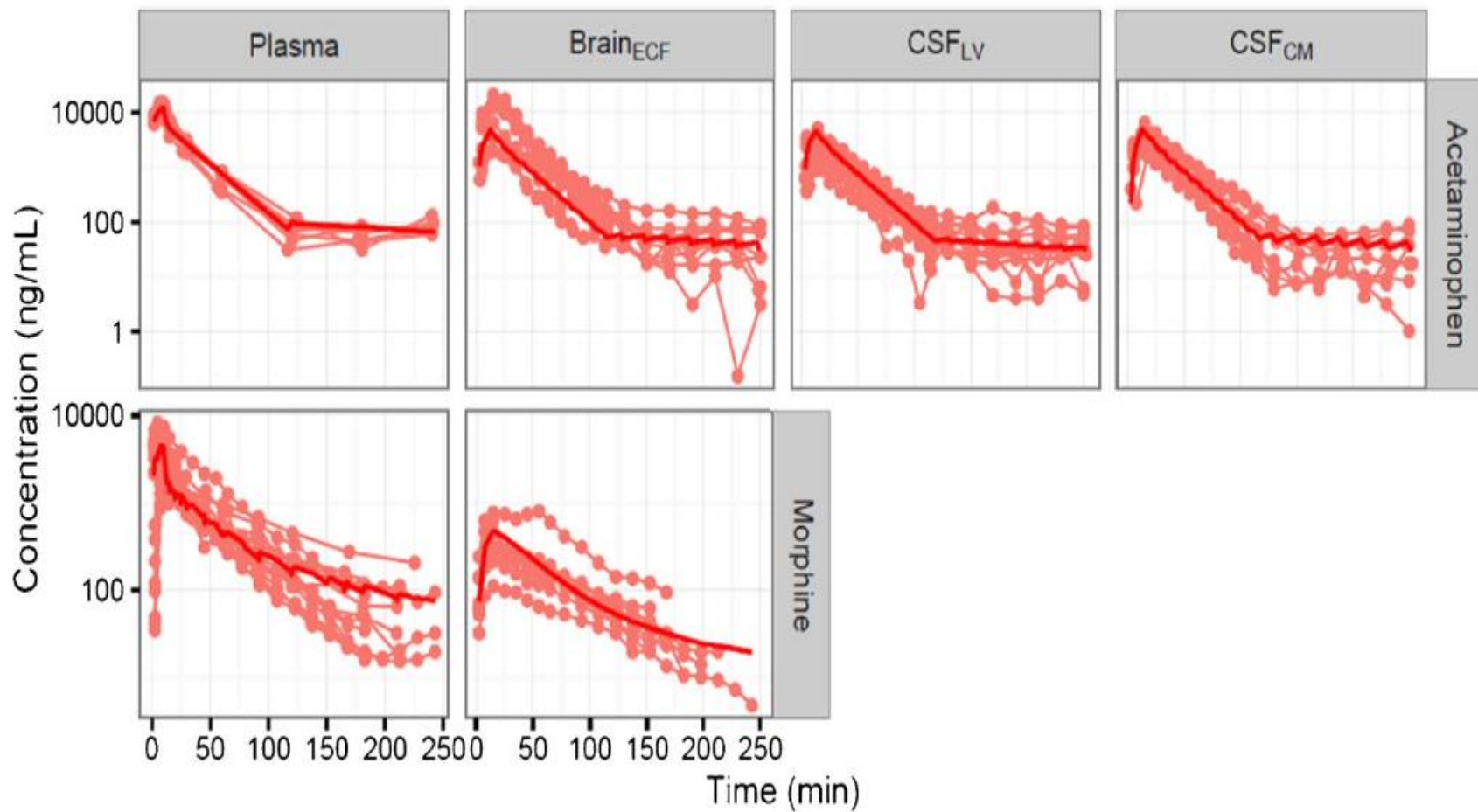
b

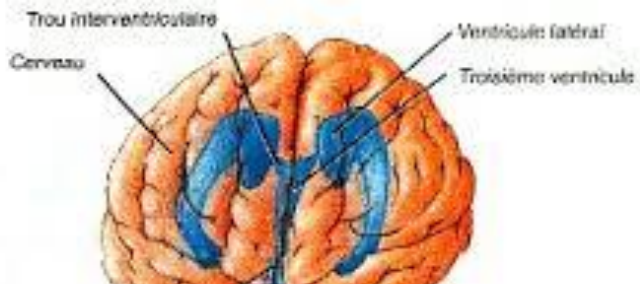




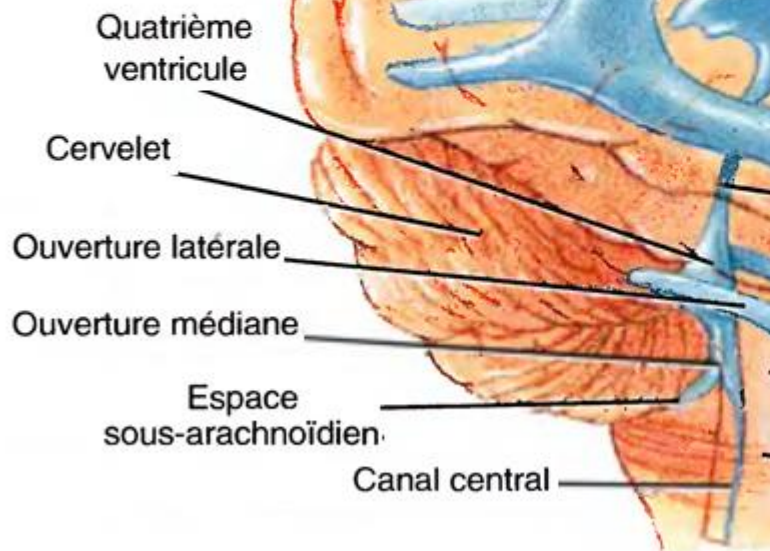


The brain PK model structure and translational methods for each parameter. The brain PK model consists of plasma, brainECF, brainICF, CSFLV, CSFTFV, CSFCM and CSFSAS, which consists of 4 different categories parameters (colors). The scaling method on each parameter is indicated with color coding.



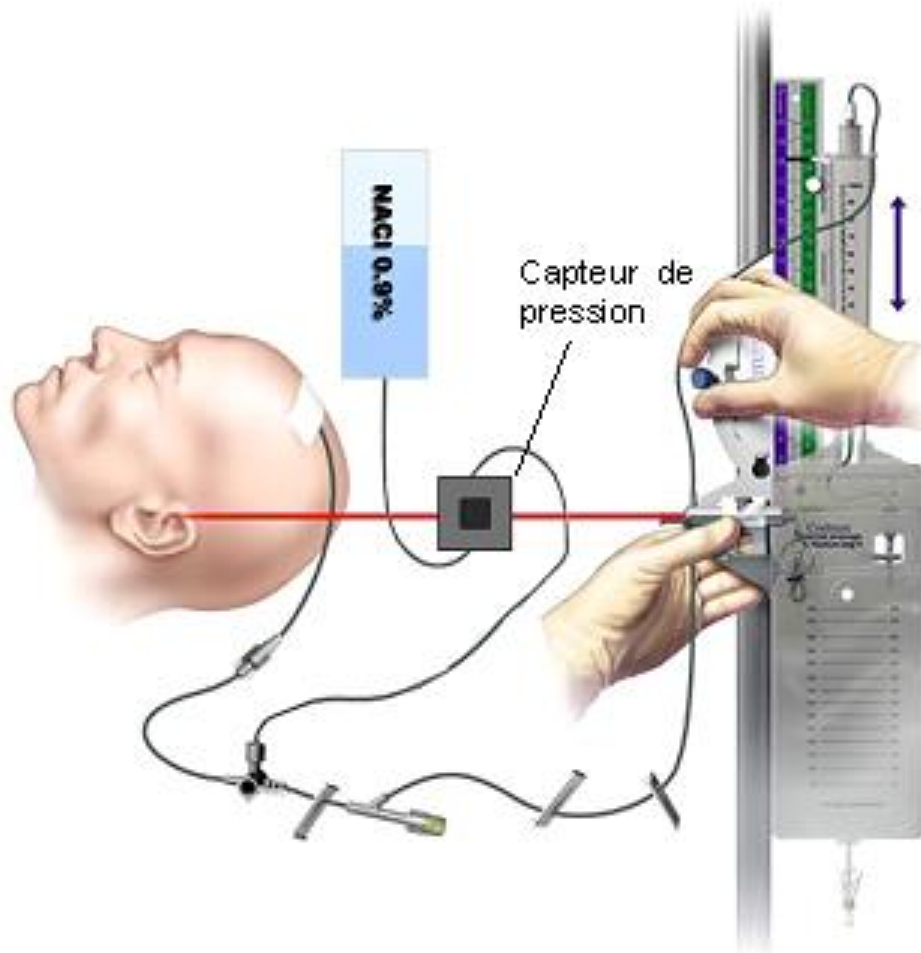


POSTÉRIEUR

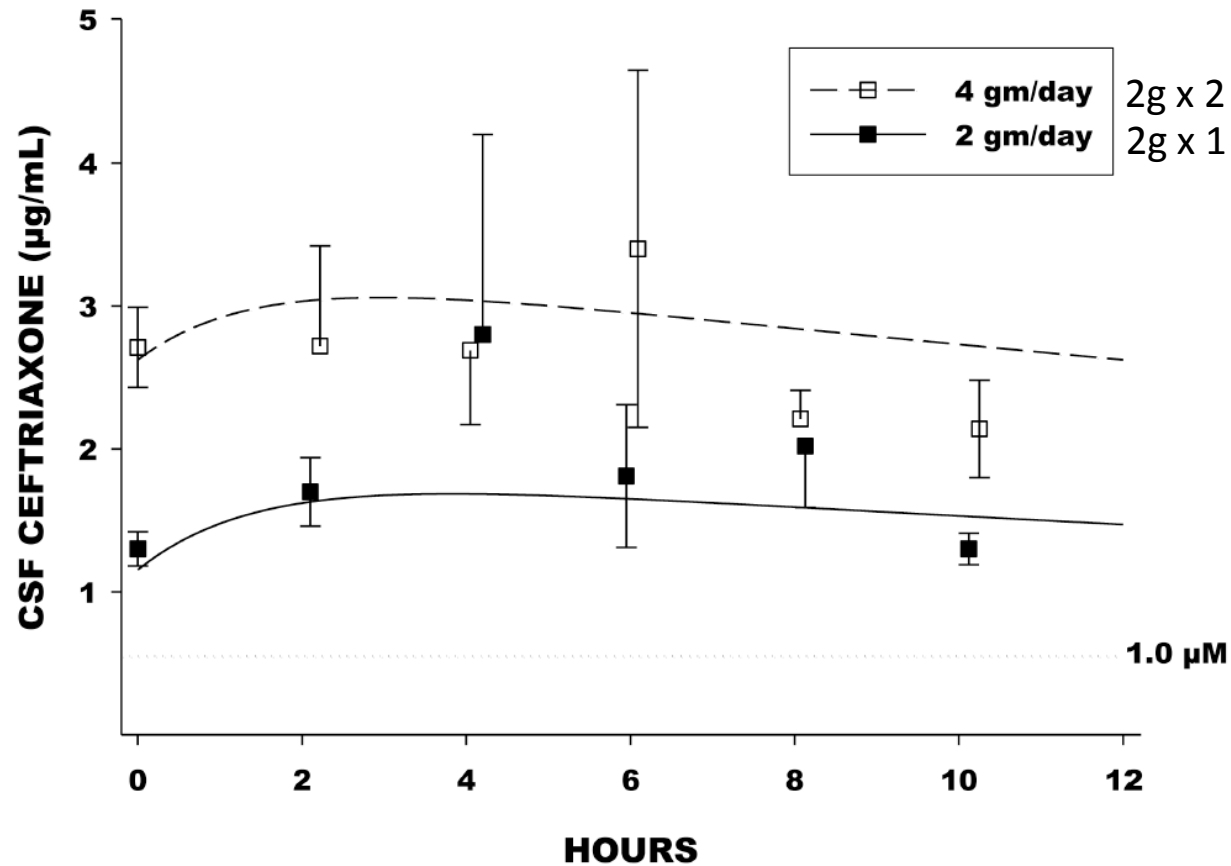


Vue latérale c

Cerveau

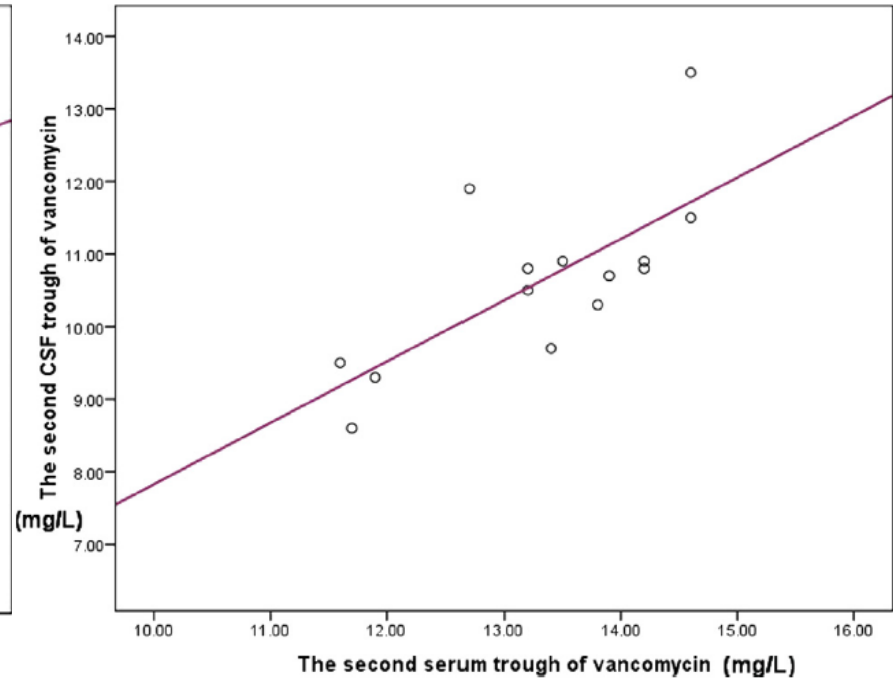
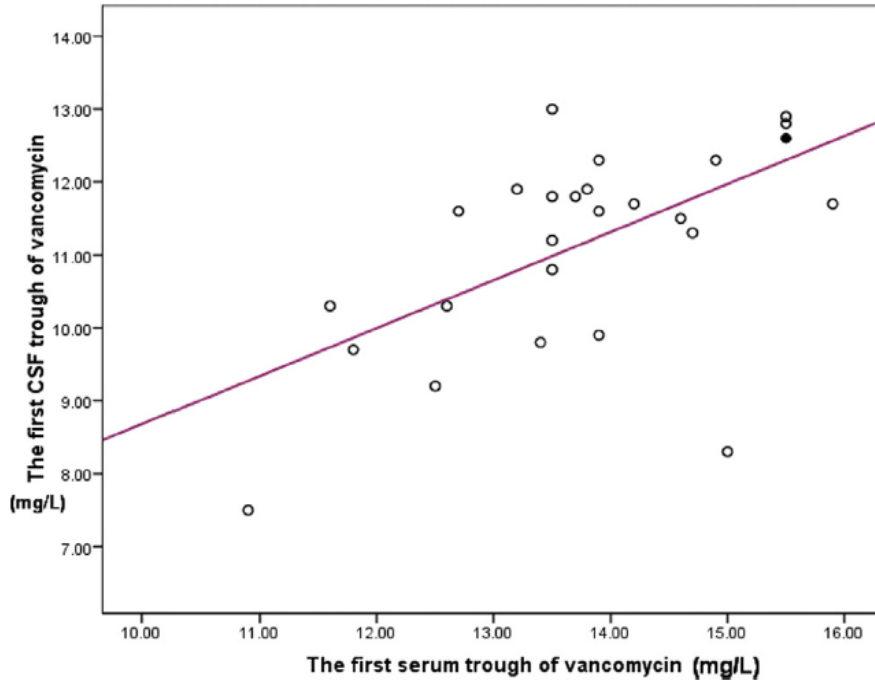


Ceftriaxone 2g vs 4g



Vanco S vs CSF

15mg/kg puis 30mg/Kg/24h en 2 perfusions



Méropénem sur 4h - ICU

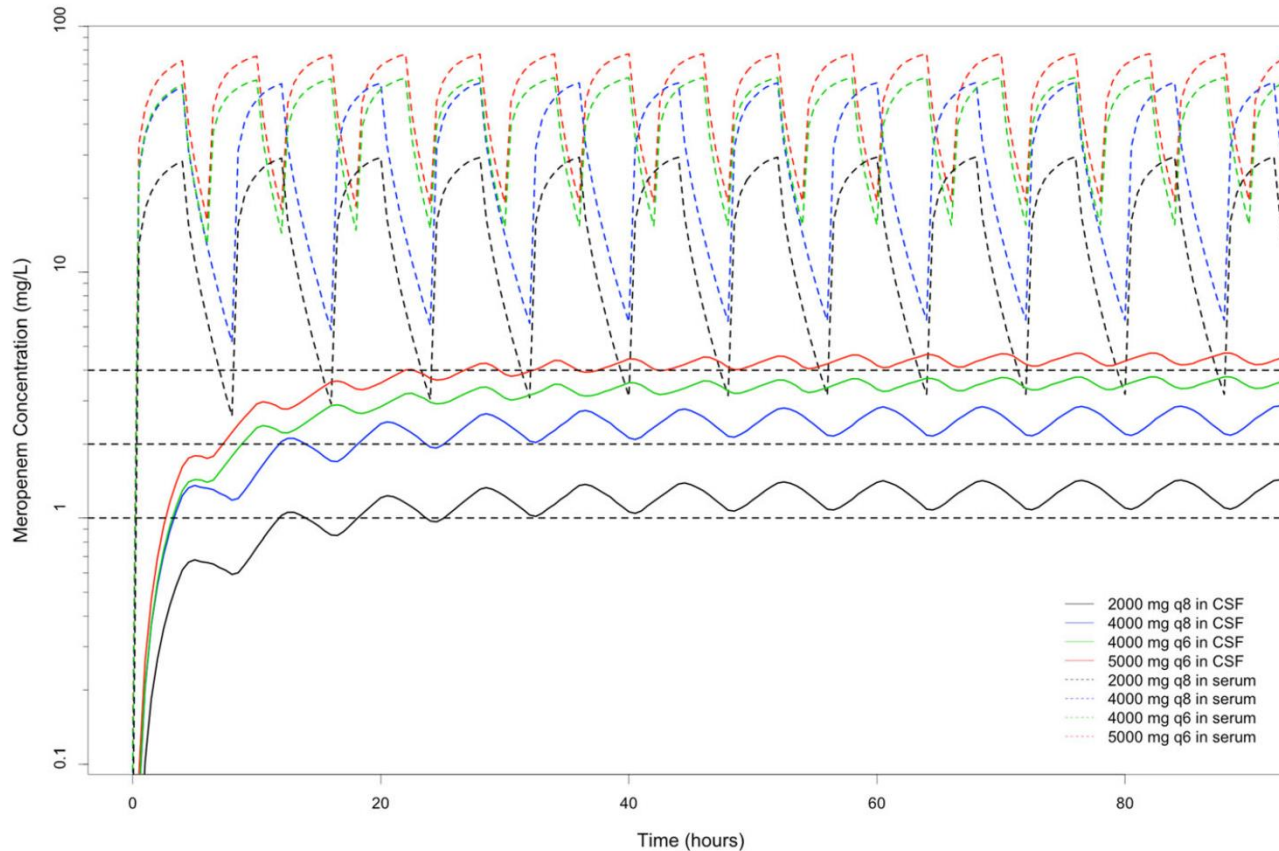
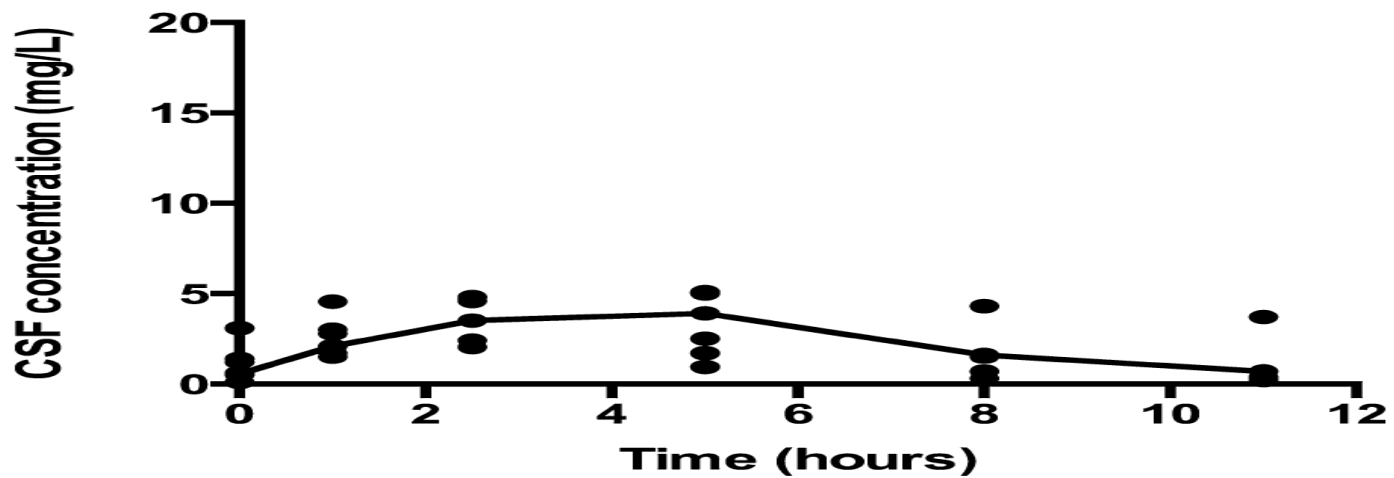
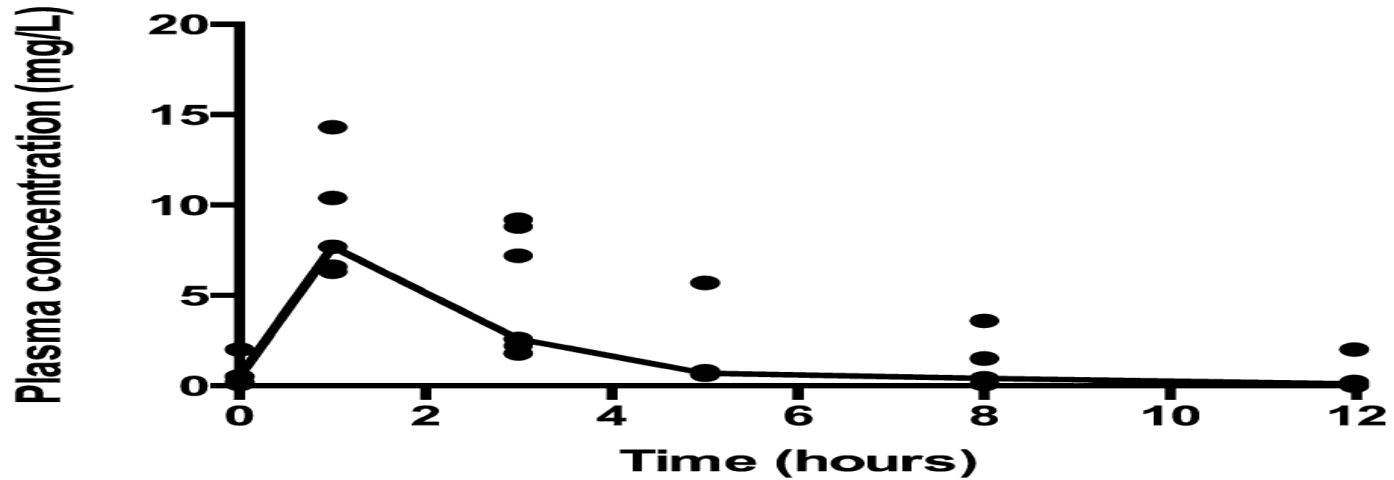
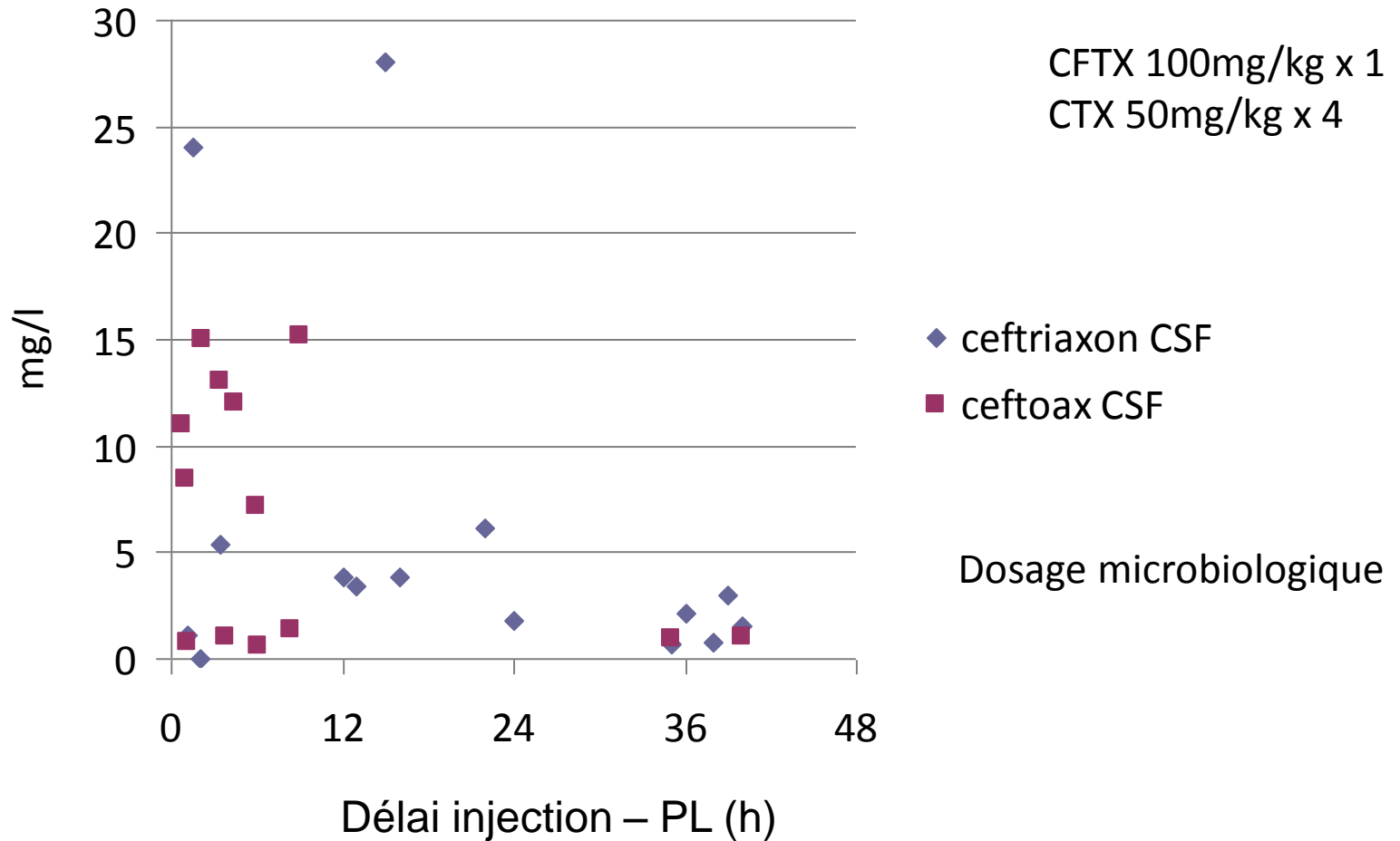


Fig. 2 Comparison of different dosing regimens as prolonged infusions over 4 h using the pharmacokinetics model. Median time course of meropenem concentrations simulated in serum and cerebrospinal fluid (CSF) over 4 days. Targeted meropenem trough concentrations in CSF were 1 mg/L, 2 mg/L and 4 mg/L

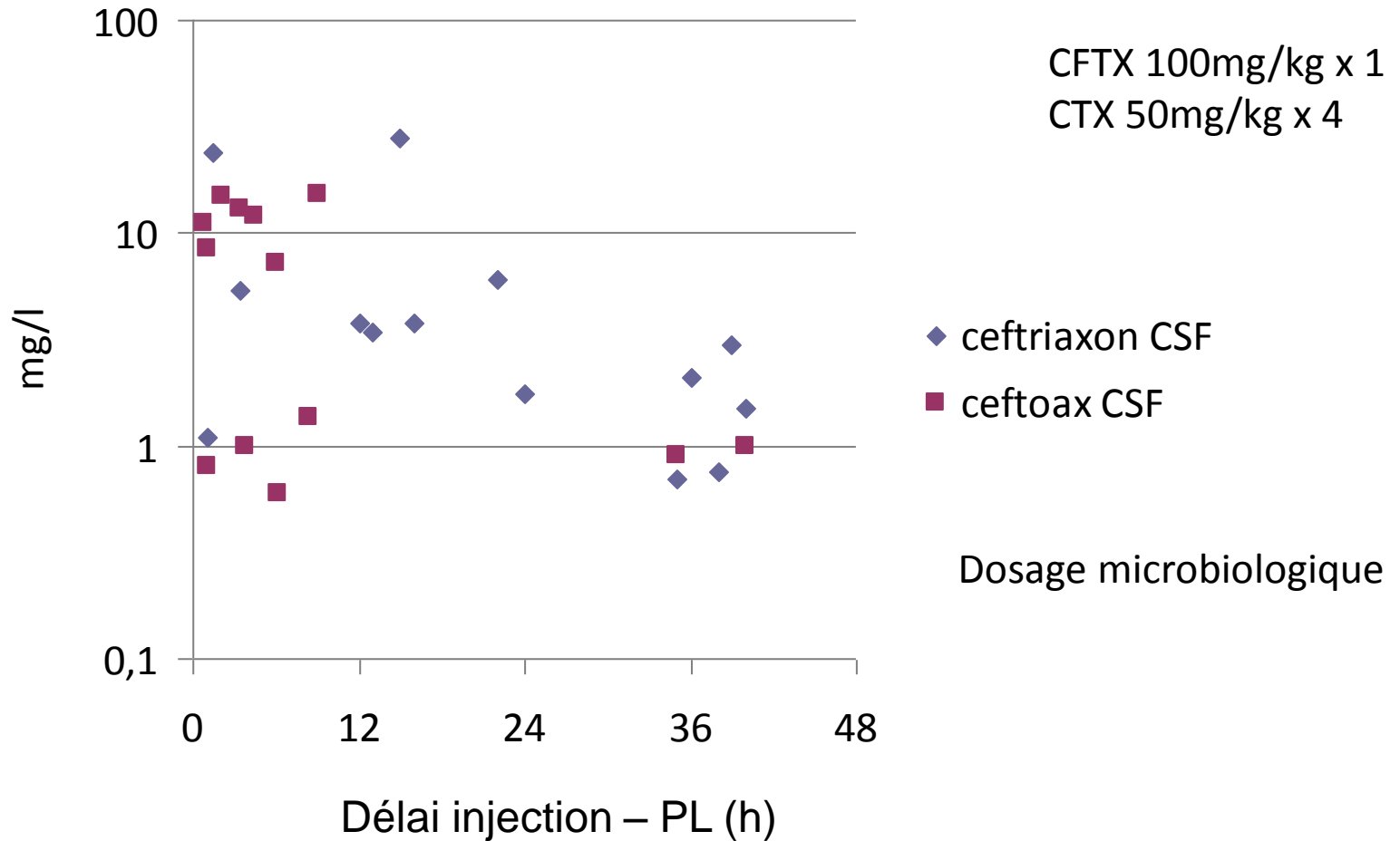
Liné « icu » 600mg x 2/j sur 1h



Ceftriaxone et cefotaxime 'PL de contrôle'

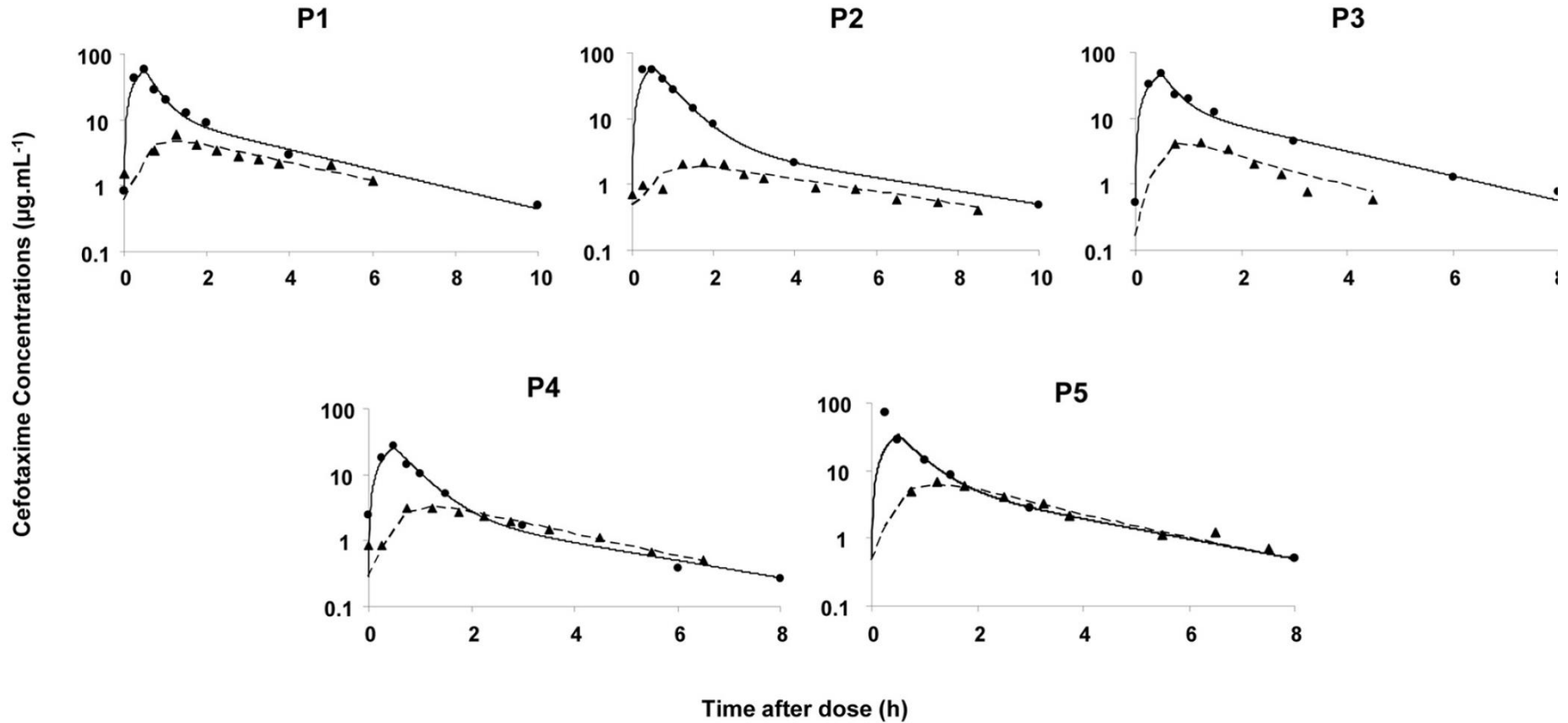


Ceftriaxone et cefotaxime 'PL de contrôle'

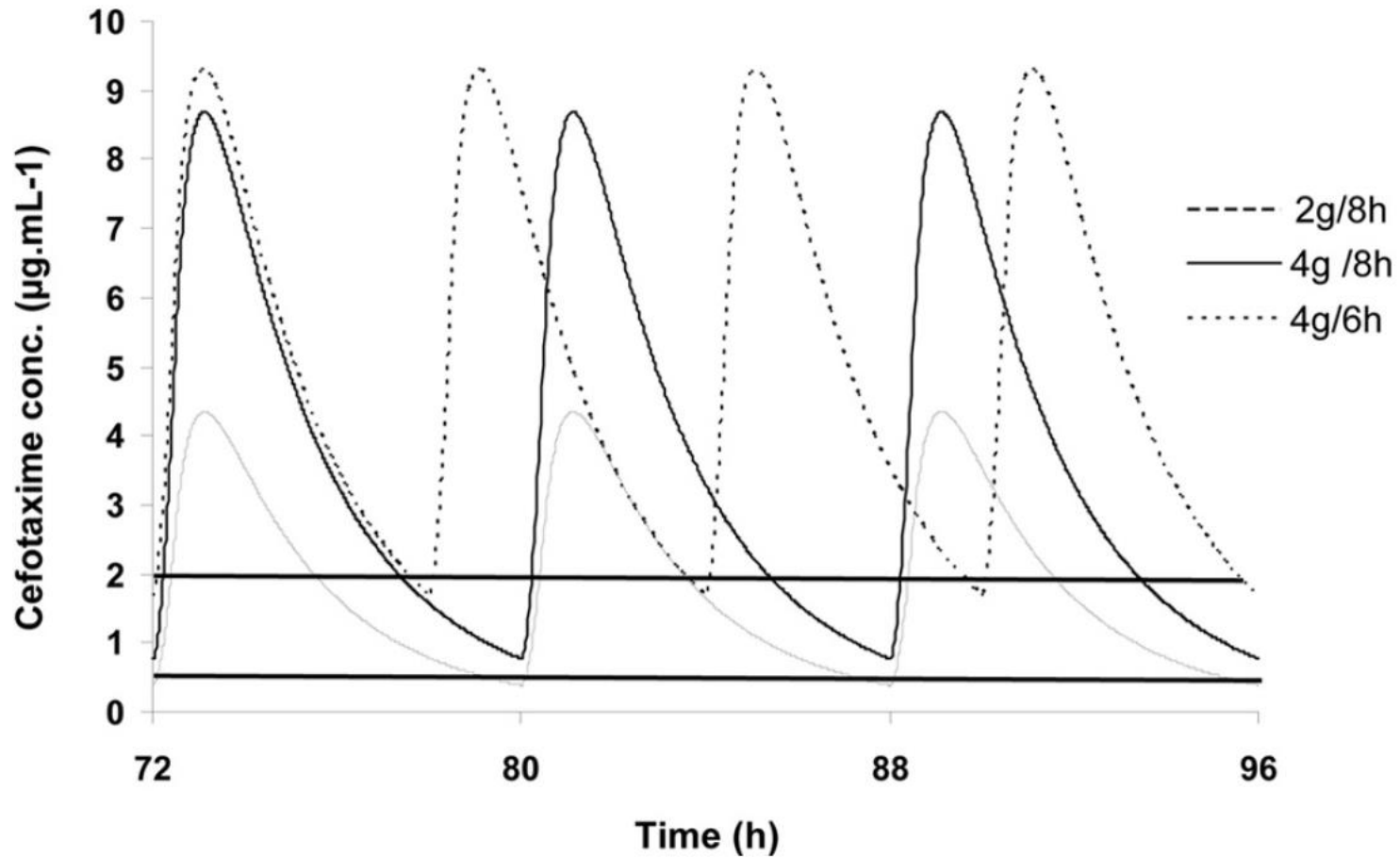


Cefotaxime

2g sur 30minutes

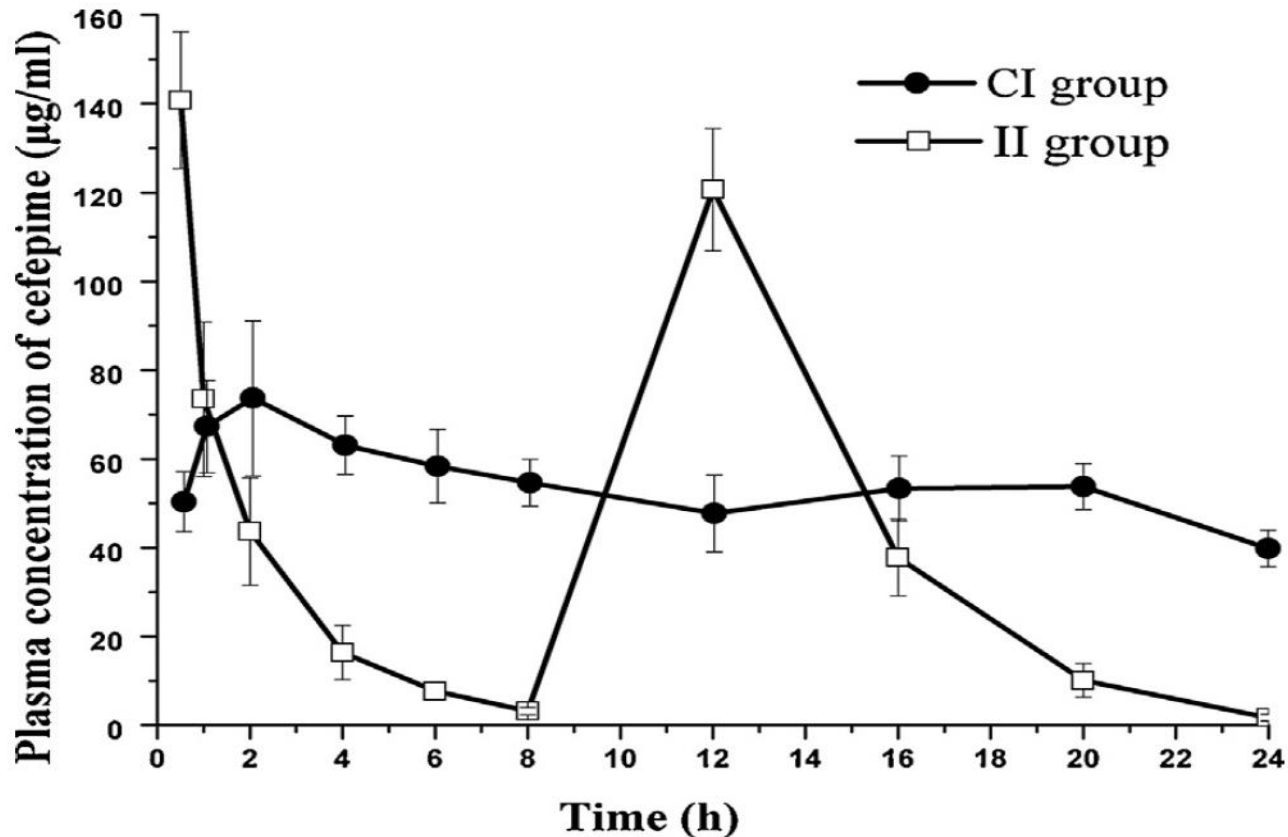


Cefotaxime simulation sur 30 minutes



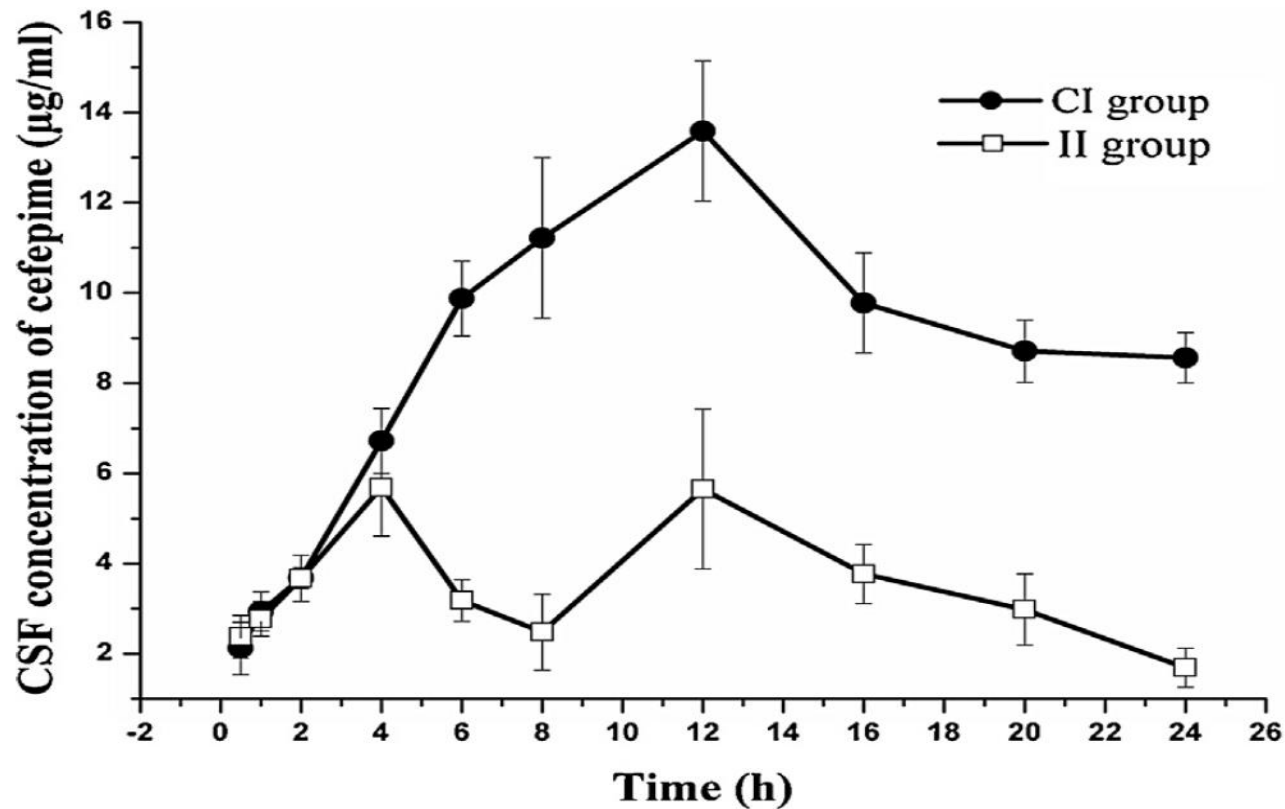
Cefepime plasma- durée de perf

- 2g sur 30 minutes toutes les 12h ou
- 4g perf continue (0,5 dose de charge)



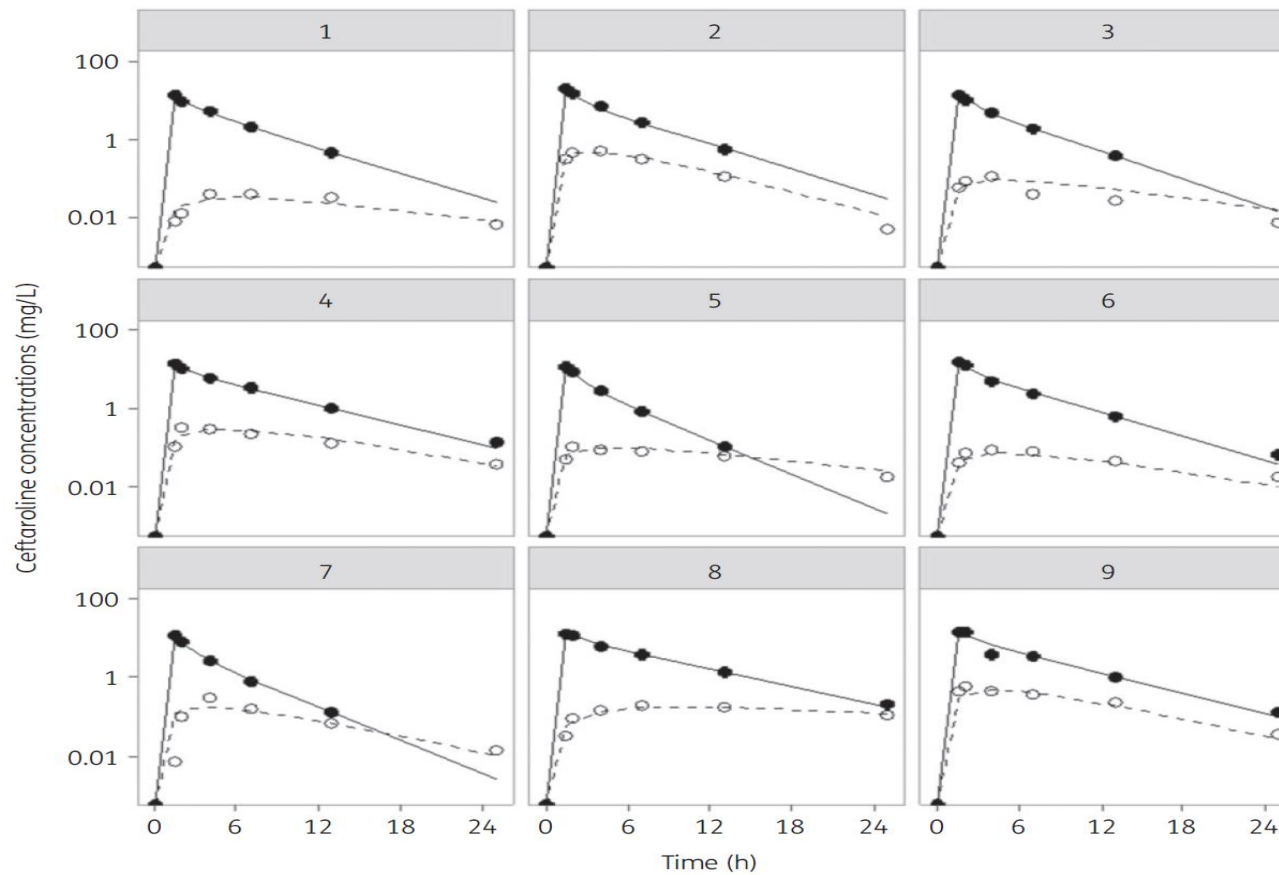
Cefepime LCR - durée de perf

- 2g sur 30 minutes toutes les 12h ou
- 4g perf continue (0,5 dose de charge)



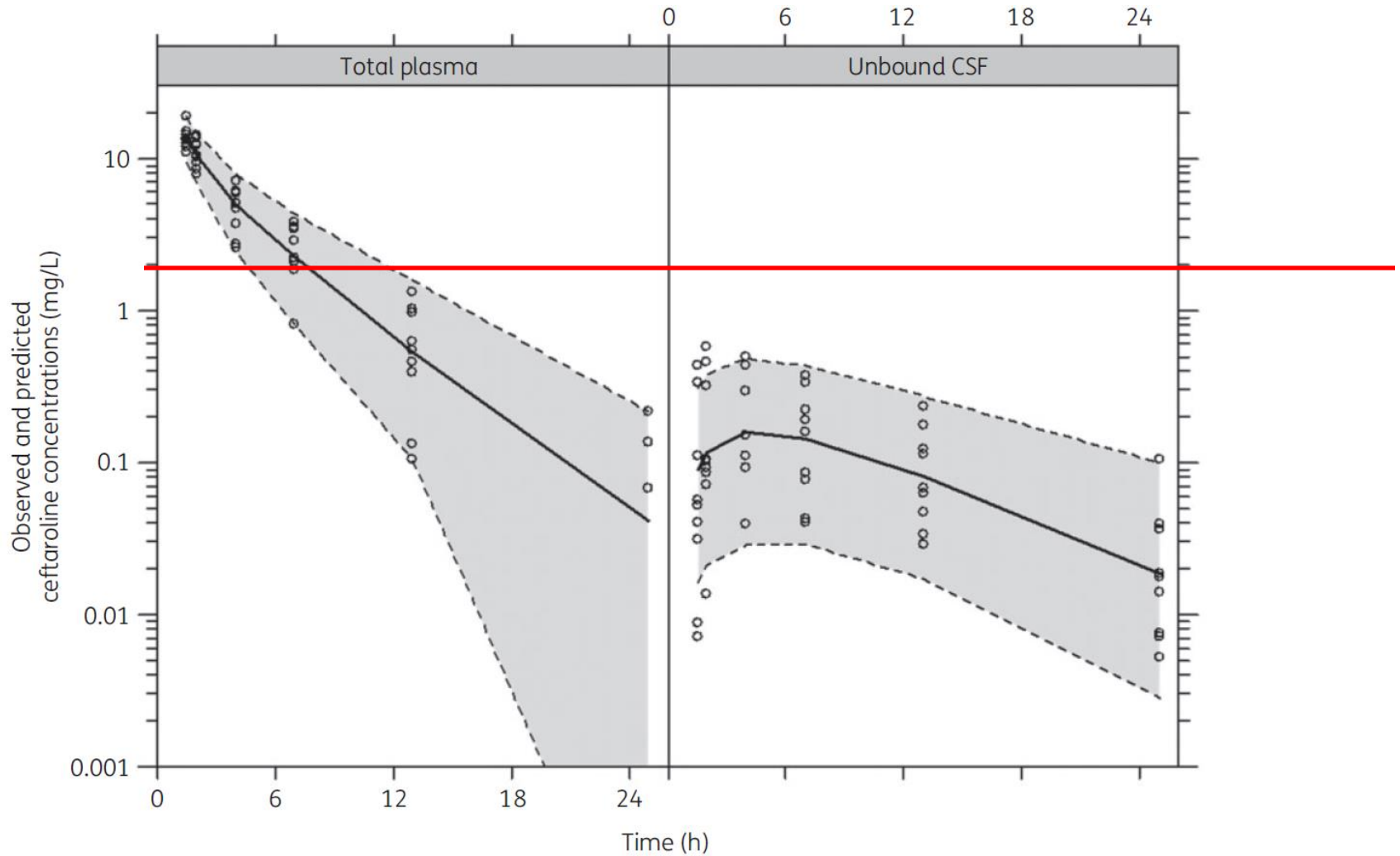
ceftaroline

- 600 mg, 1h - DVE



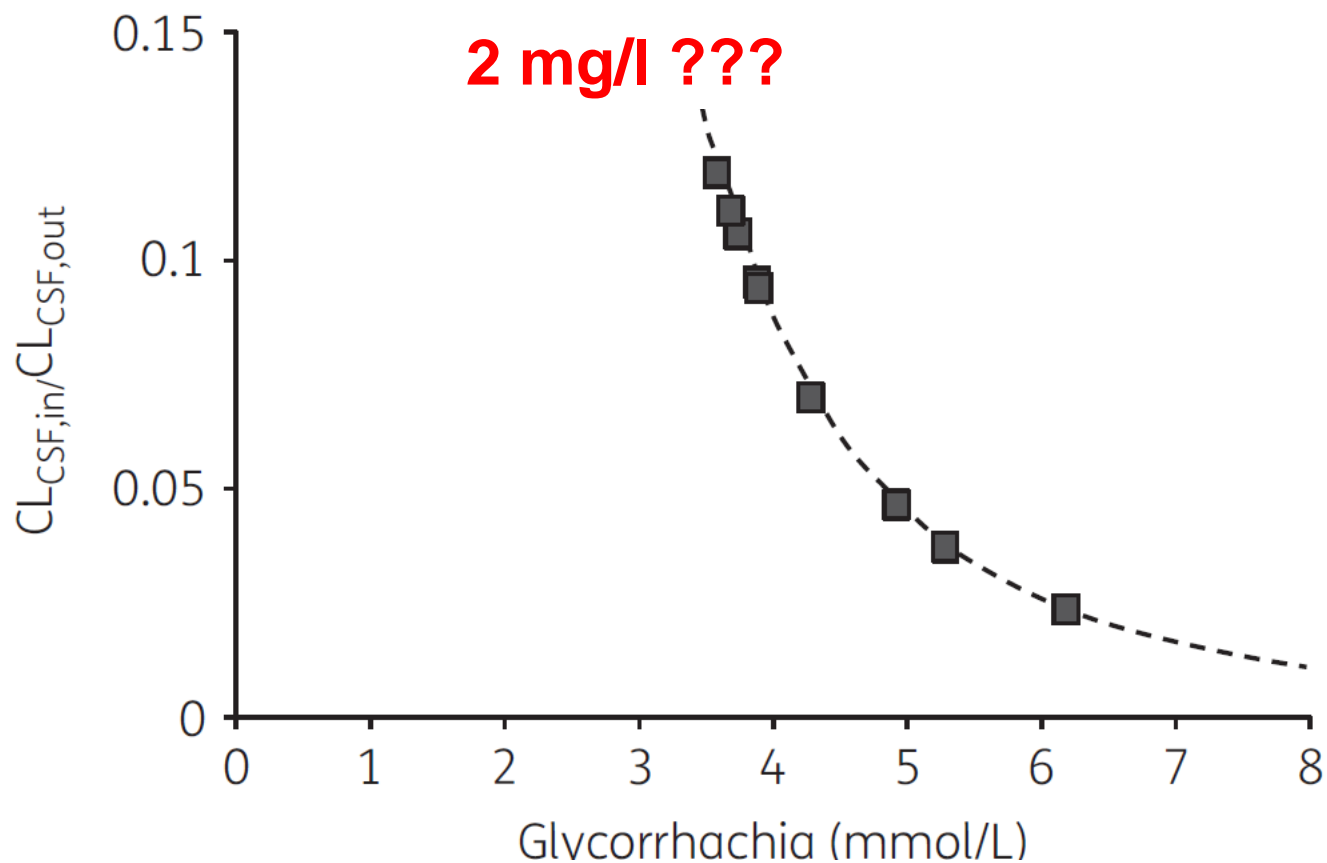
ceftaroline

- 600 mg, 1h - DVE



ceftaroline

- 600 mg, 1h - DVE



Antituberculeux chez l'enfant vietnamien avec méningite tuberculeuse pyrazinamide

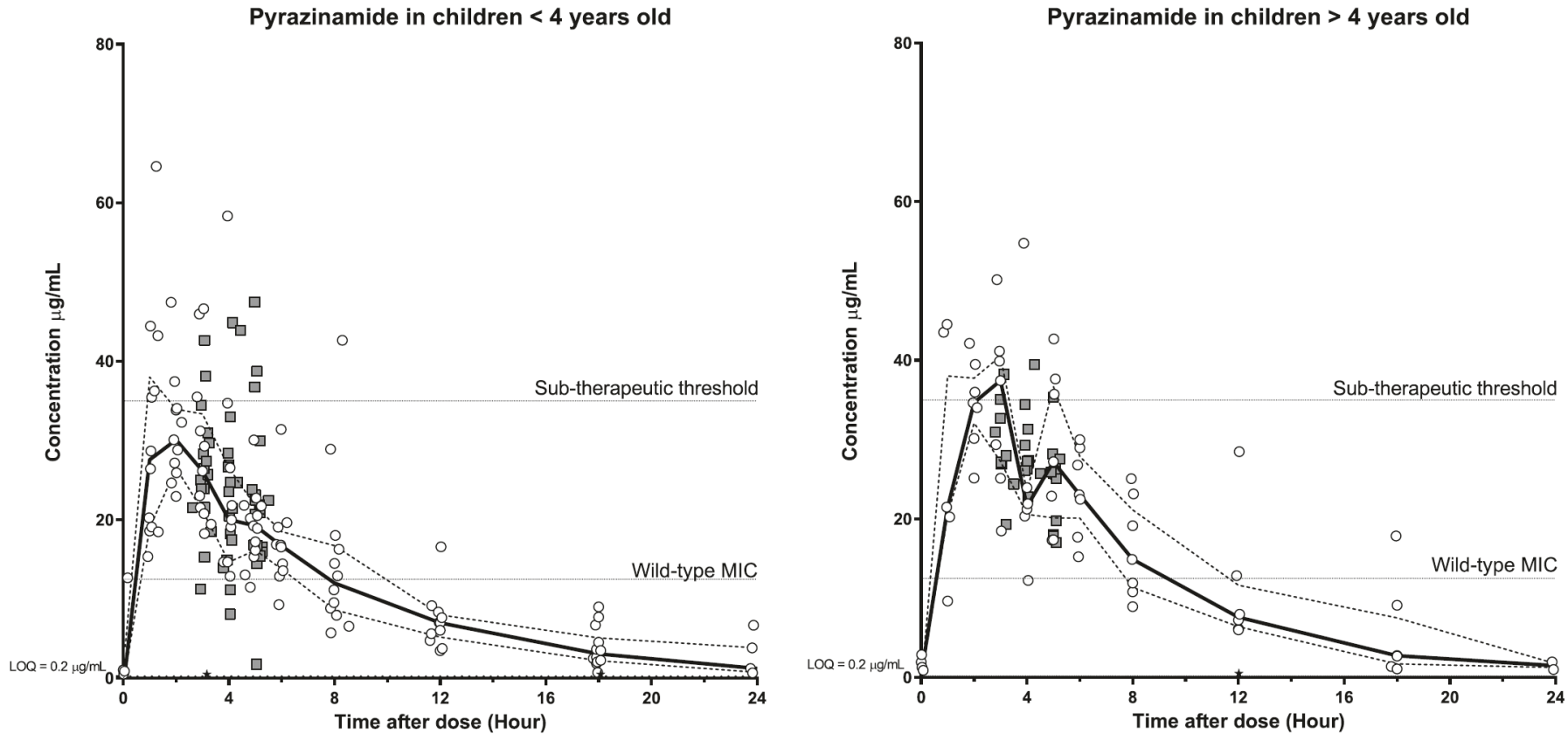


Fig. 1 Plasma (open circles) and CSF (grey squares) concentration-time profiles for pyrazinamide stratified for age (<4 years old [left] and > 4 years old [right]). Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold of 35 µg/mL; Minimum Inhibitory Concentration (MIC) of 12.5 µg/mL; and Limit of Quantification (LOQ) of 0.2 µg/mL

Antituberculeux chez l'enfant vietnamien avec méningite tuberculeuse

INH

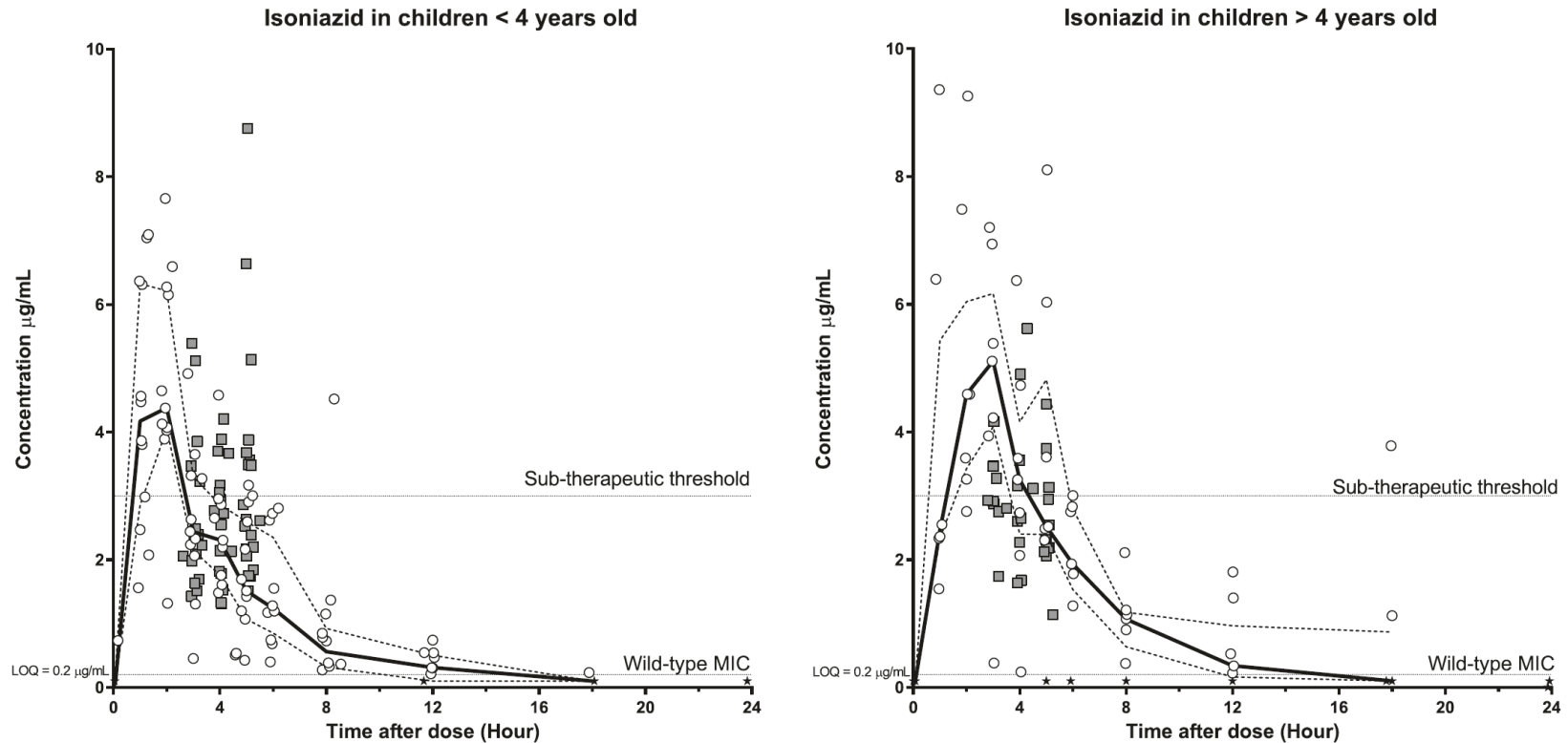


Fig. 2 Plasma (open circles) and CSF (grey squares) concentration-time profiles for isoniazid stratified for age (<4 years old [left] and > 4 years old [right]). Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold: 3 µg/mL; Minimum Inhibitory Concentration (MIC) and Limit of Quantification (LOQ): 0.2 µg/mL

Antituberculeux chez l'enfant vietnamien avec méningite tuberculeuse

RMP

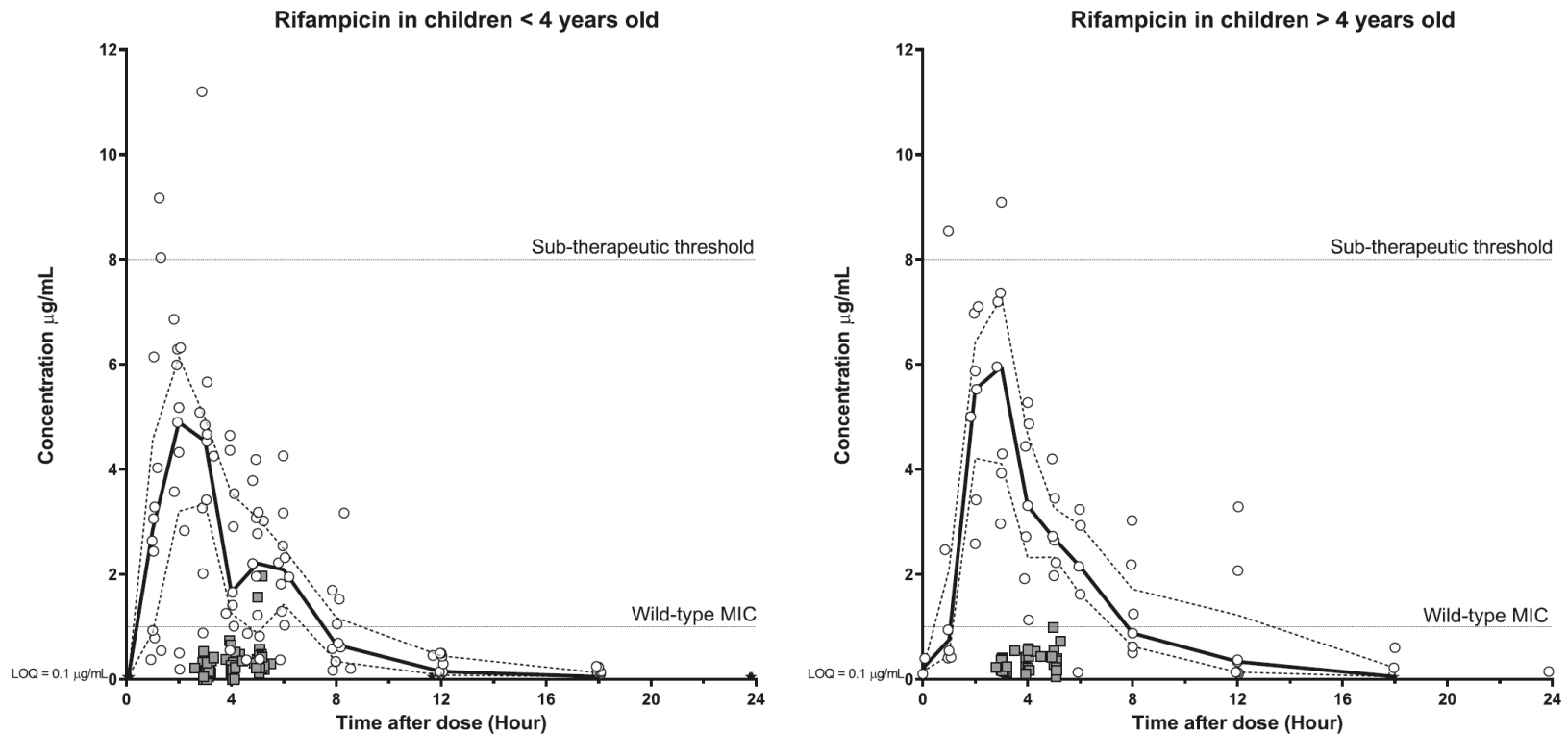


Fig. 4 Plasma (open circles) and CSF (grey squares) concentration-time profiles for rifampicin stratified for age (<4 years old [left] and > 4 years old [right]). Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold: 8 $\mu\text{g/mL}$; Minimum Inhibitory Concentration (MIC): 1.0 $\mu\text{g/mL}$; Limit of Quantification (LOQ): 0.1 $\mu\text{g/mL}$

Ordre de grandeur des concentrations des antibiotiques dans le LCR chez l'homme

concentration LCR (mg/l)

	m	CI 95
Amoxicilline	4-6	2,9 - 40
Cefotaxime	6-8	0,8 - 18
Ceftriaxone	4-8	1 - 12
Imipenem	4	0,5 - 8
Meropenem	0,6	0,3 - 4
Levofloxacin	2-4	0,5 - 6
Moxifloxacin	1-3	0,7 - 5
Rifampicine	1-2	
Vancomycine	2-4	1,4 - 13
Line	4-6	3-11
Dapto	0.4	

Concentration antibiotique libre « LCR » simulations :

perfusion continue (à l' équilibre = après dose de charge)

	C LCR, libre (mg/l, extrêmes)	C LCR, total
Cefotaxime à l' équilibre perfusion continue	7 ± 4 [1,2-18,0] 12 ± 10 17 ± 11	11 ± 7
Ceftriaxone à l' équilibre perfusion continue	1,5 ± 1,2 [0,1-4,5] 2,3 ± 2 3,6 ± 3	11 ± 6
Cefuroxime à l' équilibre perfusion continue	3,2 ± 1,8 [0,6-8,0] 5,2 ± 3,5 7,9 ± 4,7	4,7 ± 2,6
Amoxicilline à l' équilibre perfusion continue	2,4 ± 1,3 [0,5-6,0] 2,7 ± 1,5 6,0 ± 3	3 ± 1,6

CTX 300mg/kg/j <12g/j; 4 perfusions de 2 heures
 Ceftriaxone 100 mg/kg/j < 6g/j; 2 perfusions d' une heure
 Cefuroxime 240 mg/kg/j < 9g/j; 4 perfusions d' une heure
 Amoxicilline 200 mg/kg/j < 16 g/j; 4 perfusions d' une heure

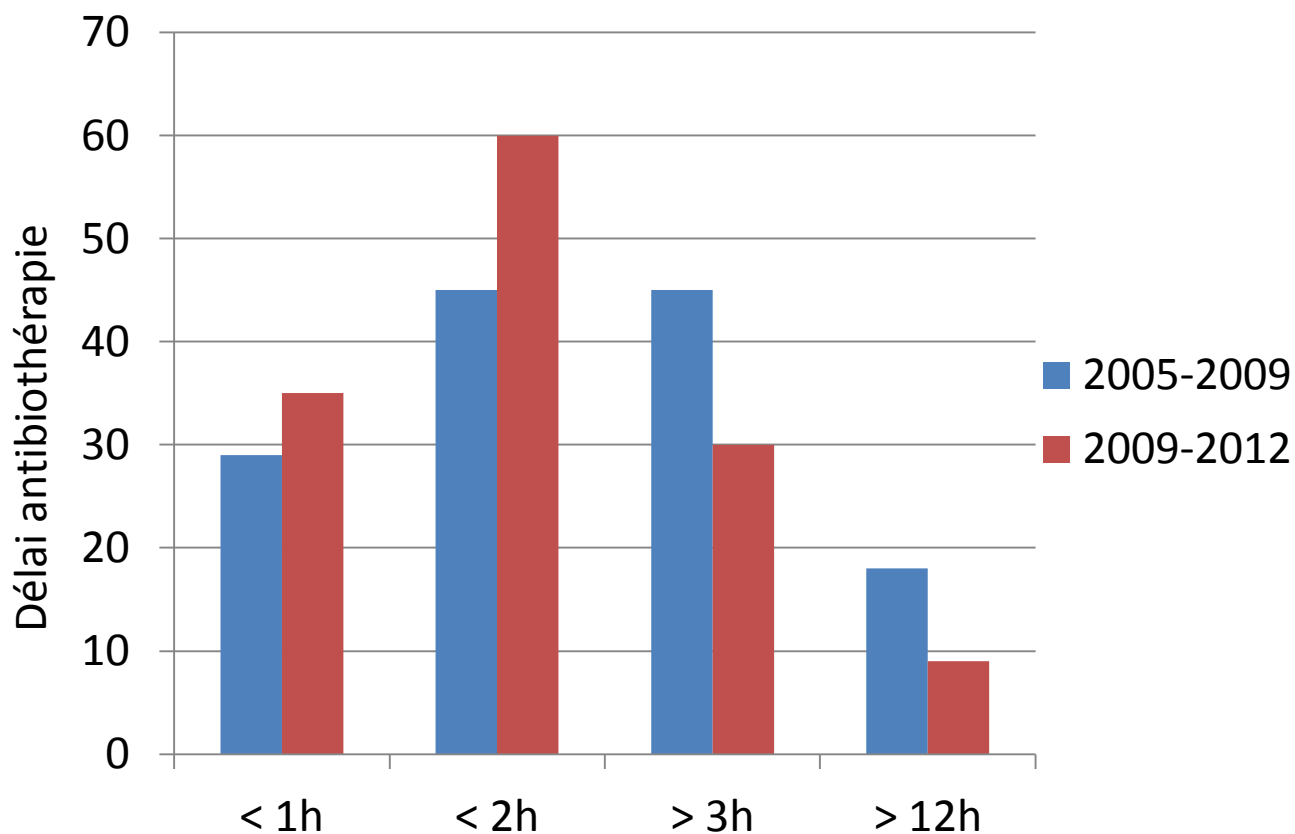
Diffusion méningée des antibiotiques

- Méconnaissance
- Variabilité
- Fortes doses
 - Dose de charge
 - Perfusion longue voire continue

Traitement antibiotique des méningites bactériennes

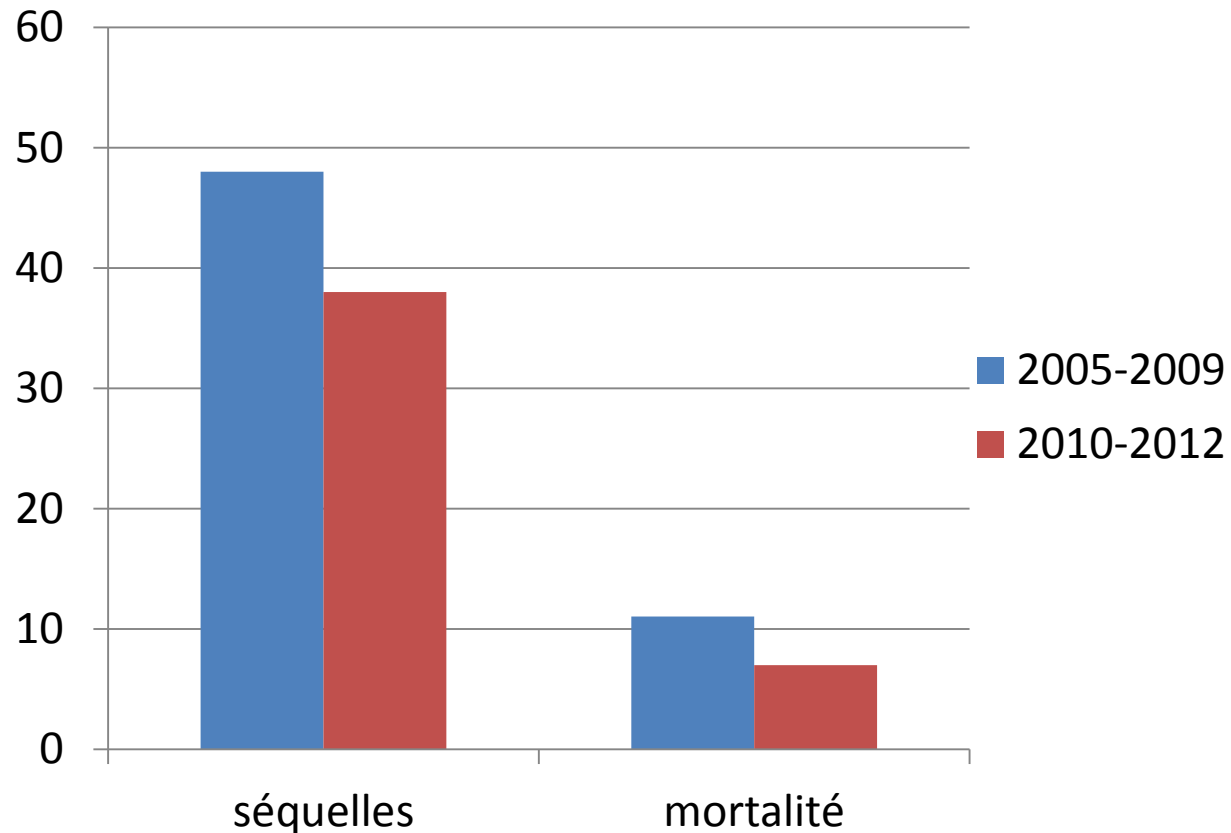
« bien faire »: impact délai antibiothérapie

« a revision of the Swedish guidelines in 2009 in which moderate to severe impairment of mental status and new onset seizures as contraindications to initial LP were deleted”



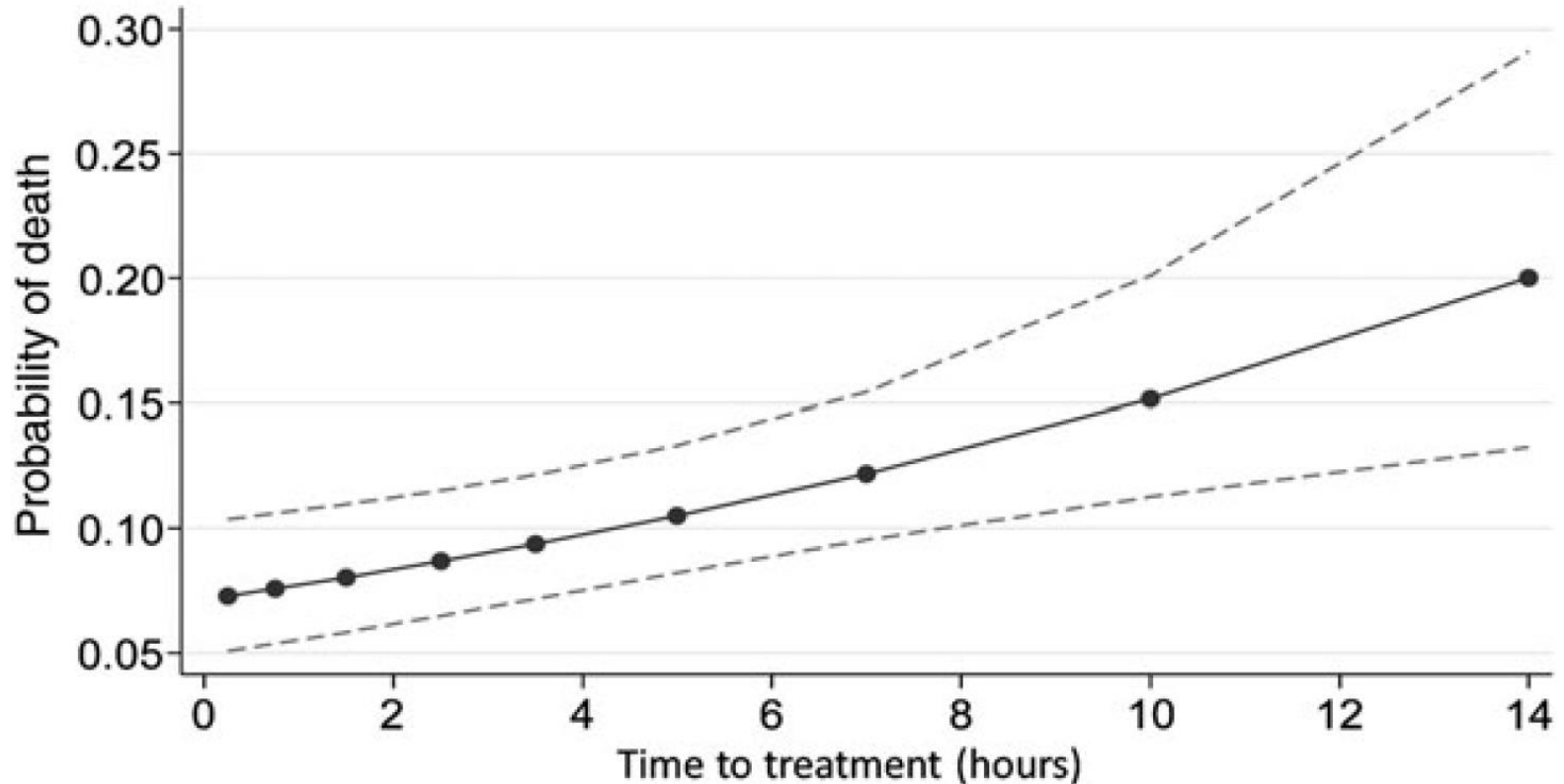
impact « délai antibiothérapie – morbi-mortalité »

« a revision of the Swedish guidelines in 2009 in which moderate to severe impairment of mental status and new onset seizures as contraindications to initial LP were deleted”



impact « délai antibiothérapie – mortalité »

increase in mortality of 12.6% per hour of delay.



Antibiotiques et méningites

- **Bien prescrire oui !**
- **Sans délai**
- **Un médicament a des chances**
 - d'être utile
 - s'il est administré !