Metaphylaxis vs. curative treatment for antibiotics : why we need different dosage regimen

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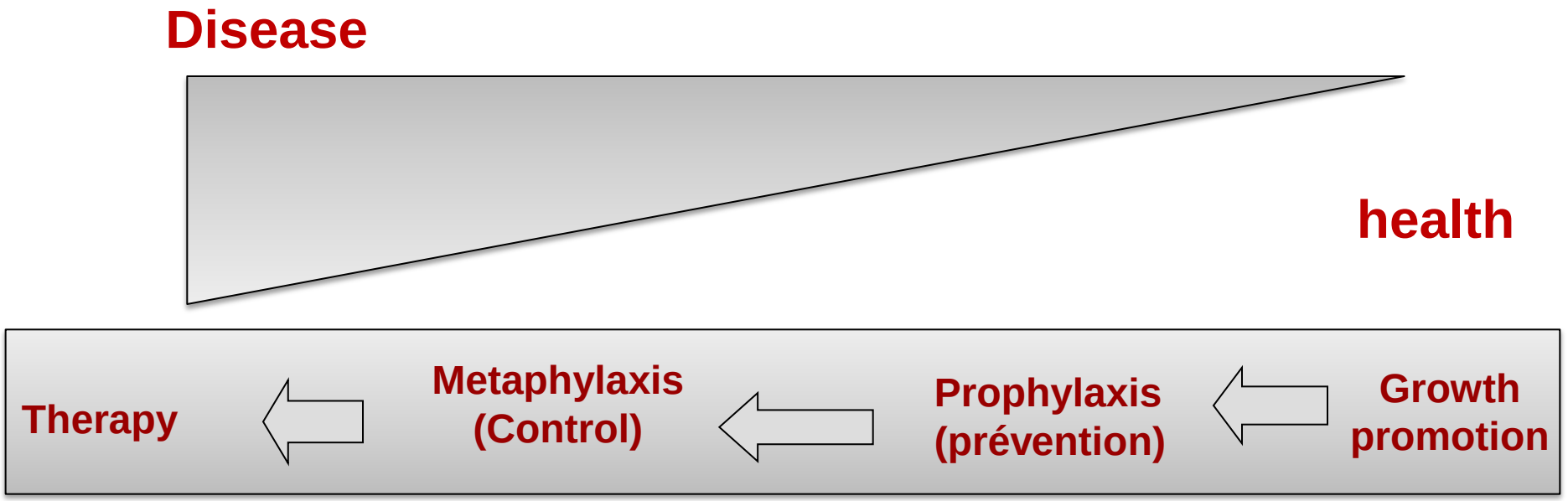
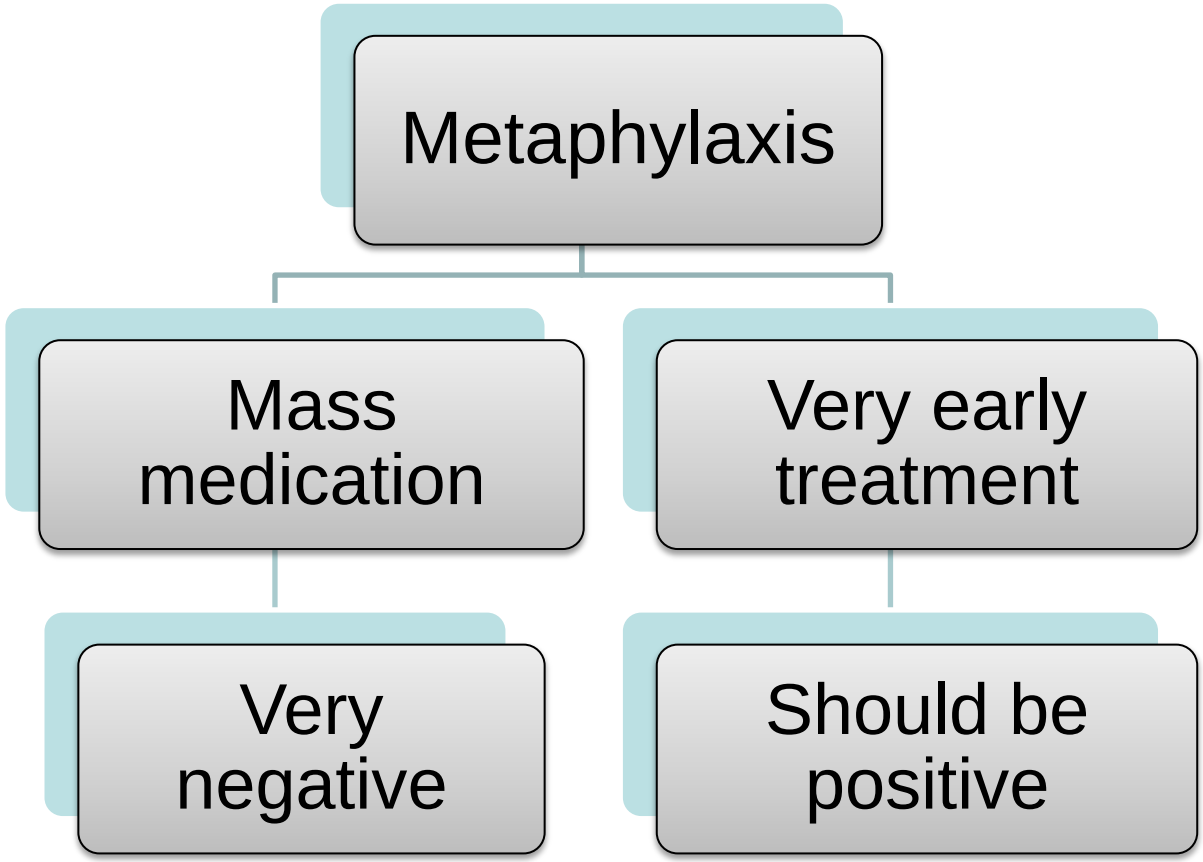
Wuhan 09/10/2015

Terms to describe herd or flock antibiotic use



Terminology and risk communication

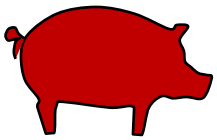


2-Why metaphylaxis

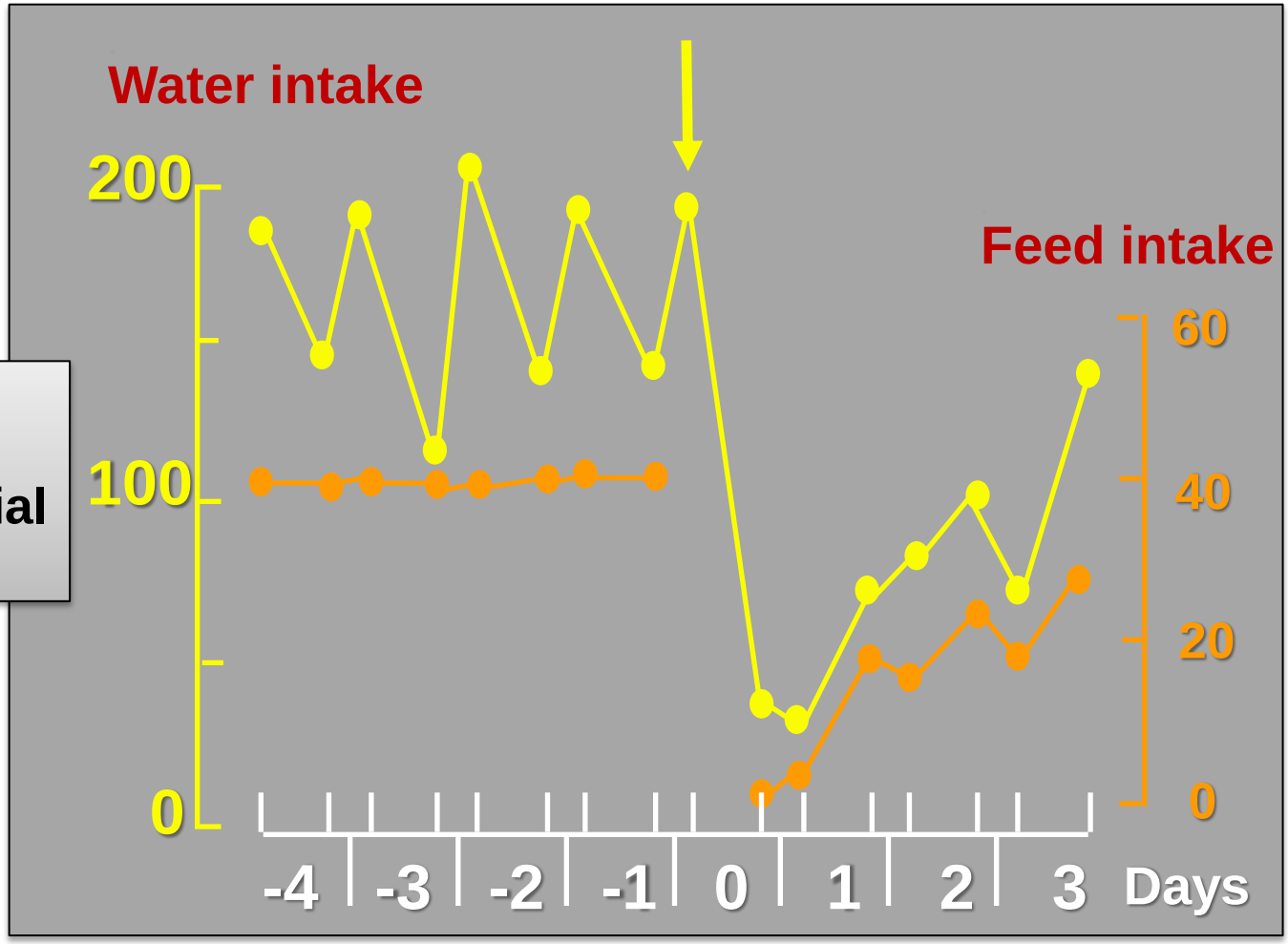
The pro

- **Convenience**
  - Possible administration by the oral route to a group of animals (pen, herd…) i.e. collective treatments
- **Medical reasons**
  - No alteration of physiological function
  - No or minimal depression of natural mechanisms of defense
  - Prevent possible alteration of the disposition of the AMD
  - Better cure rate
- **Animal welfare**
  - all animals determined to be at an inacceptable high risk of developing a bacterial disease
  - No subsequent lesion (lungs…)
- **Economical reasons**
  - increase the average daily gain (ADG)

Fever: water vs feed intake

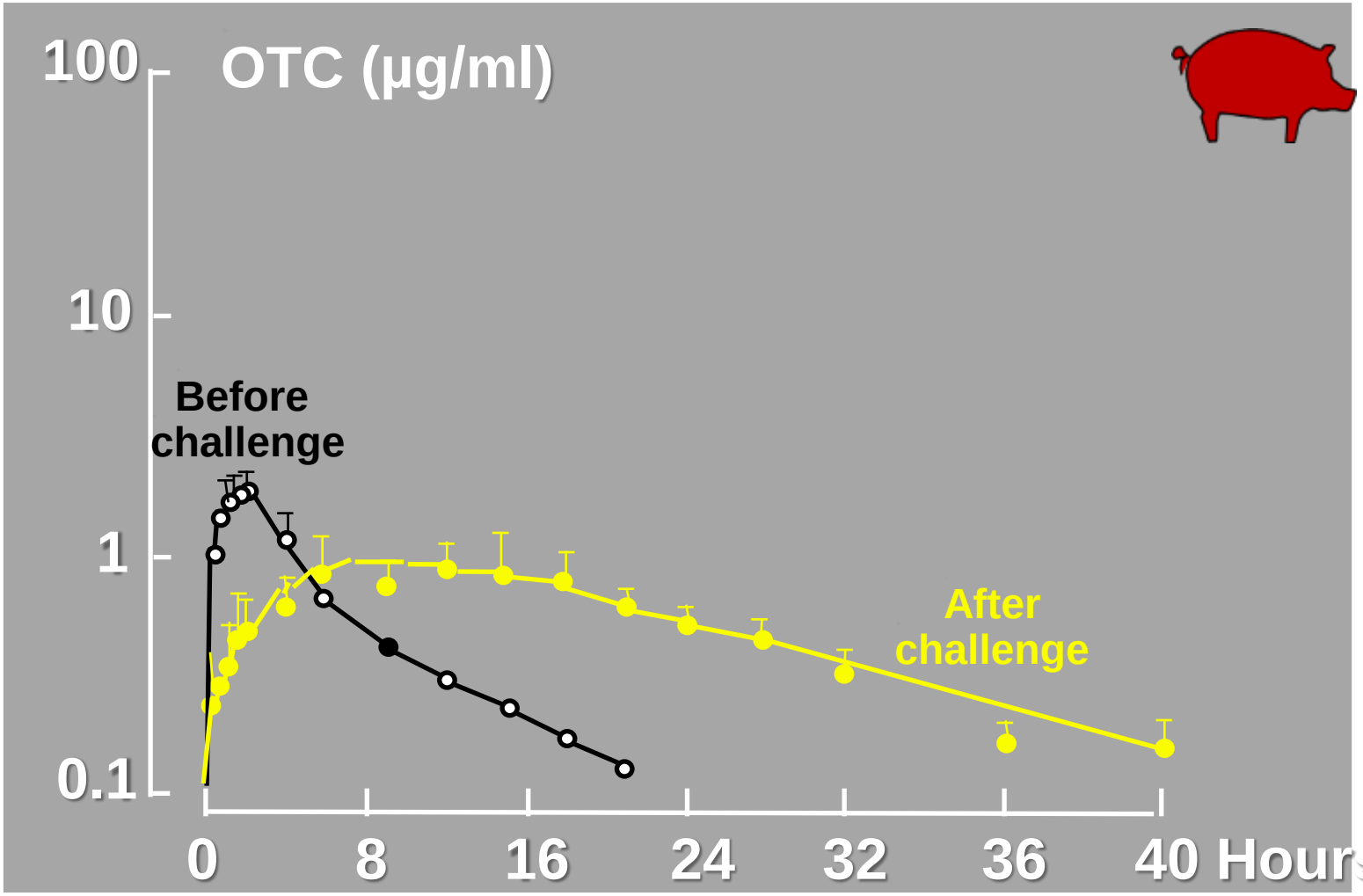


Challenge with Actinobacillus Pleuropneumonial Toxins



Pijpers et al. J.Anim. Sci. 1991,69 : 2947

Influence of disease on PK of orally administered OTC (50 mg/kg)



The cons

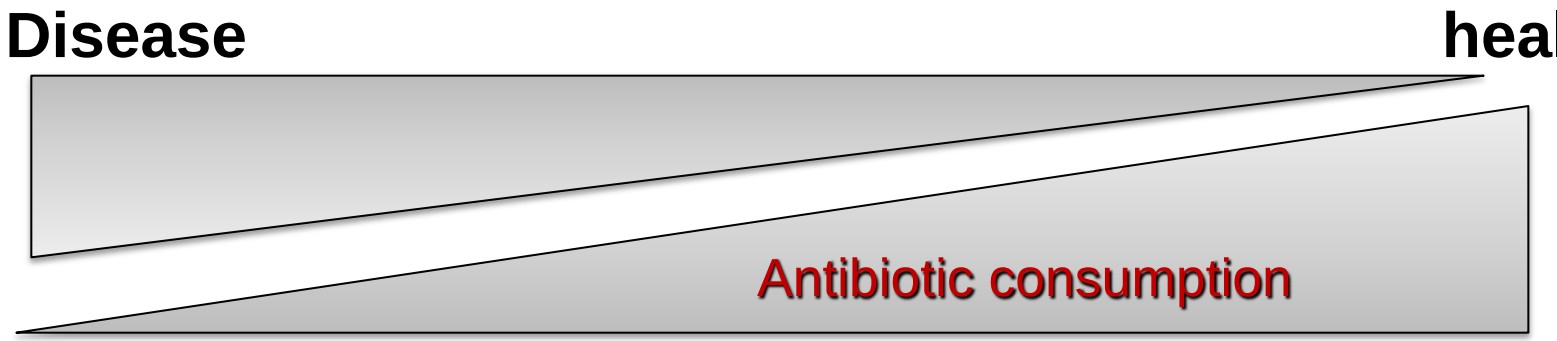
- Public health issues
- Overuse of antimicrobial drugs favouring the selection of resistant bacteria
  - Actually never demonstrated
  - Not a relevant endpoint that is the impact on gut microbiota

The most relevant endpoint is not the AMD consumption but the collective impact on commensal microbiota

- Further studies should now investigate, at group level, the impact on the overall consumption of antibiotic vs. the impact (the selection of resistance) on the gut microbiota (both treated and not treated)

Metaphylaxis: the point of view of the microbiologist

The point of view of the microbiologist

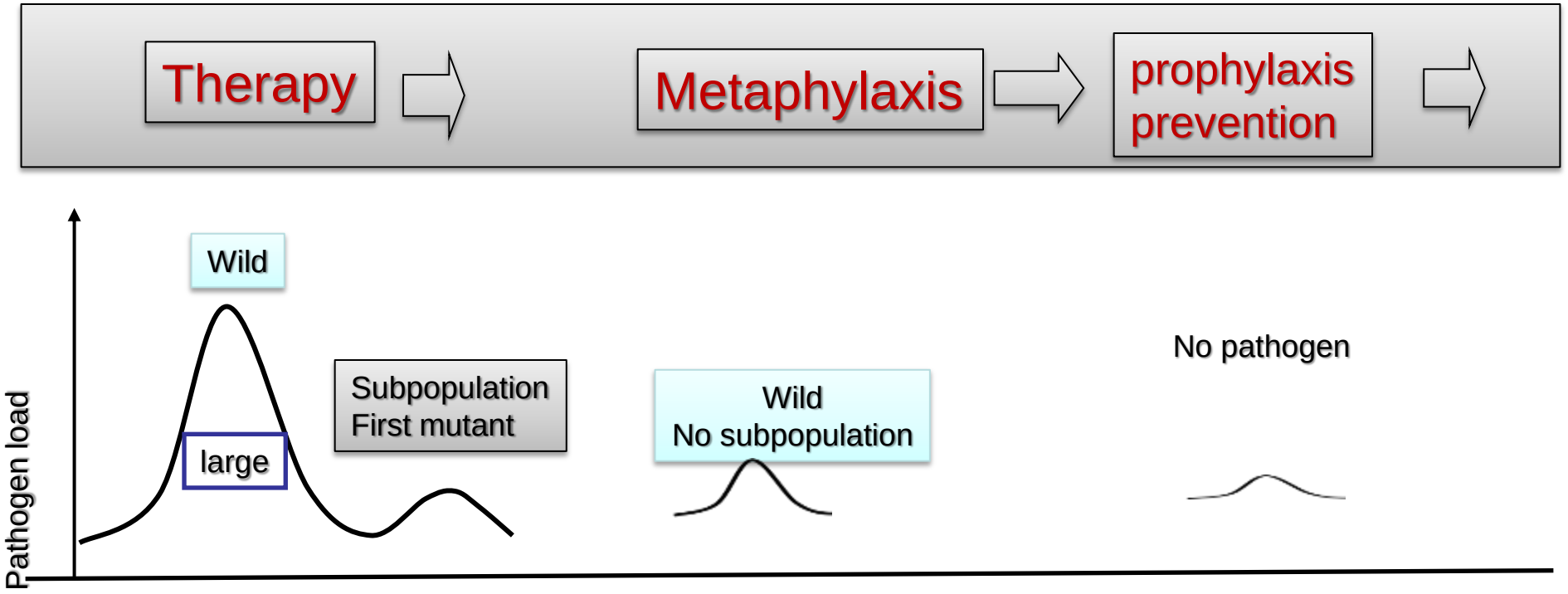


Therapy ⇐ Metaphylaxis (Control) ⇐ Prophylaxis (prévention) ⇐ Growth promotion

Pathogen load

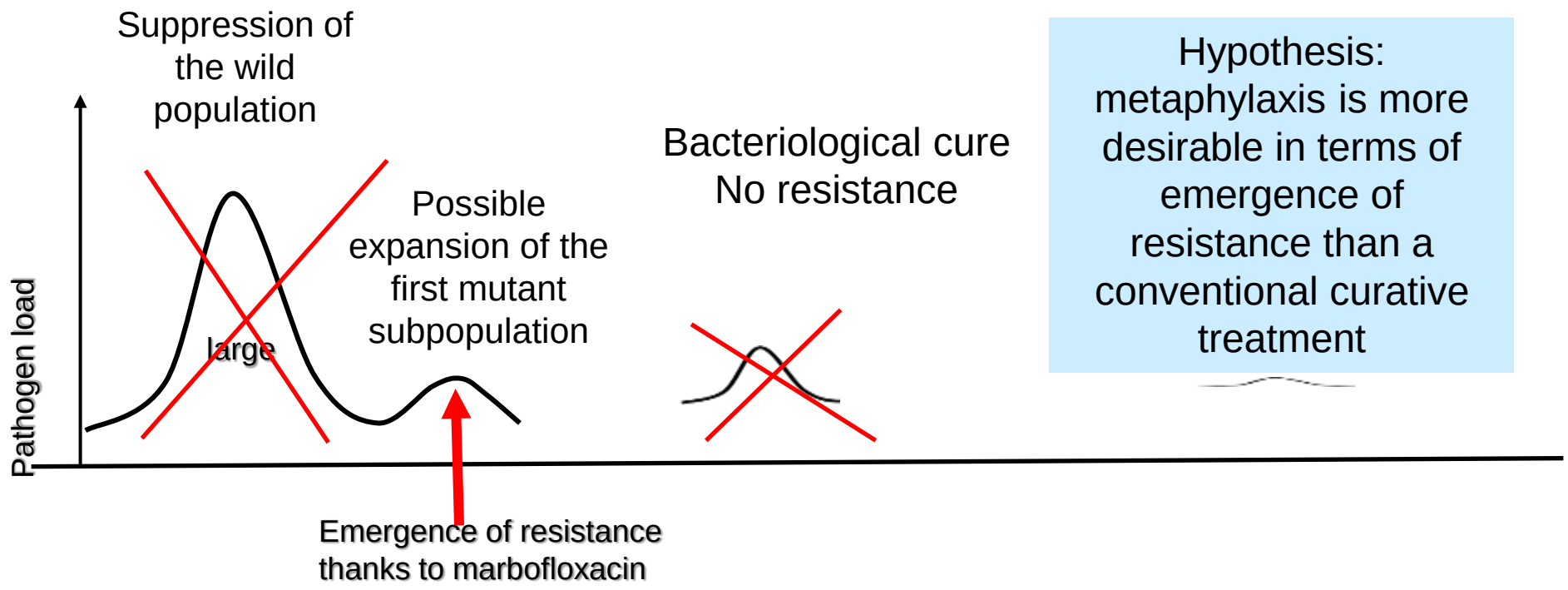
High ⇐ Small ⇐ No ⇐ NA

Pathogen load:
Wild and mutant subpopulations



Our Hypothesis on the influence of FQ on the emergence of resistance in the target flora

Therapy ⇨ Metaphylaxis ⇨ prophylaxis prevention ⇨



Bacteriological cure
No resistance

Hypothesis: metaphylaxis is more desirable in terms of emergence of resistance than a conventional curative treatment

Our set of working hypothesis

- Efficacious dosage regimen is different when the pathogen load is large, low or null: the so-called inoculum effect
- The likelihood of resistance is less with metaphylaxis than with those associated to therapeutic treatment
- The appropriate dose should be different

The inoculum effect: in vitro evidences

MICs estimated with different inoculmum densities, relative to that MIC at $2x10^5$

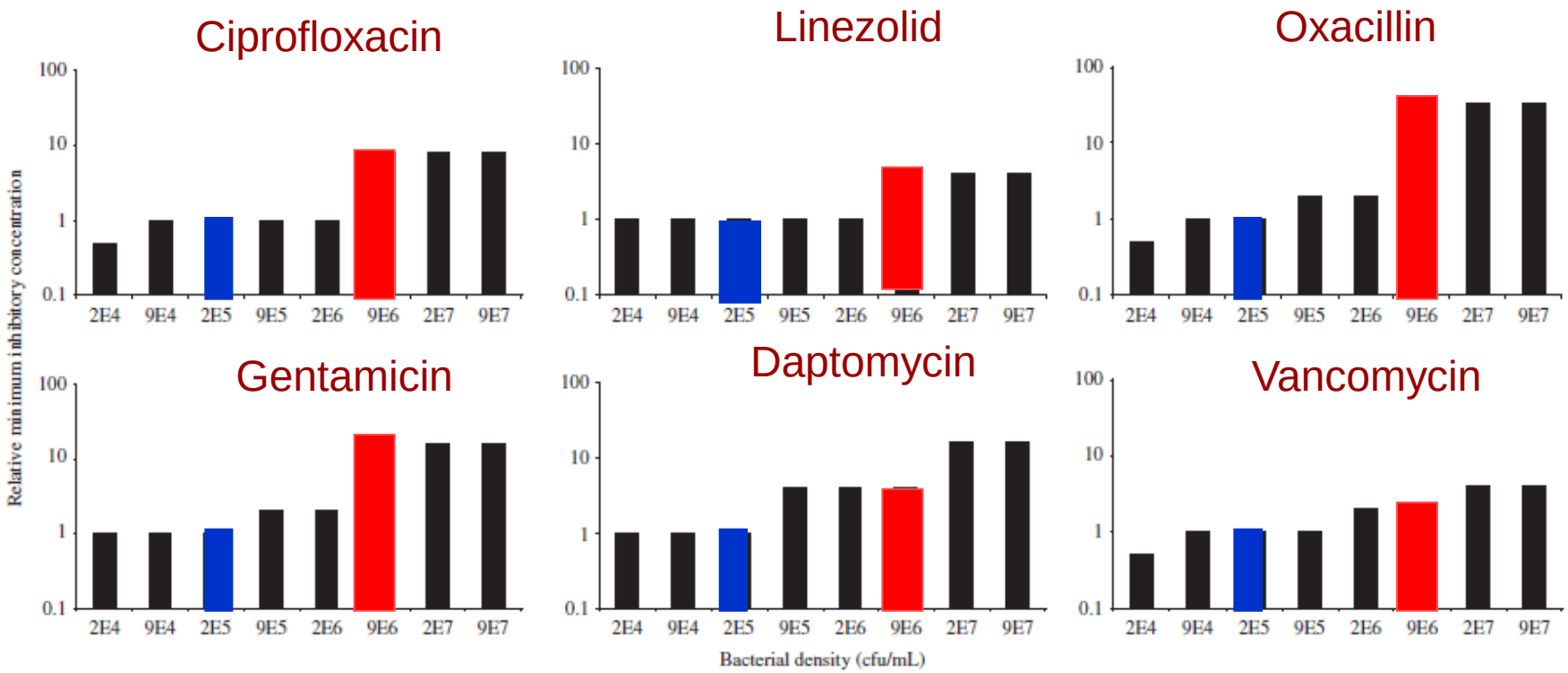


Figure 3. MICs estimated with different inoculum densities, relative to that MIC at 2×10^5. These estimates were obtained from cfu data; when the viable cell density at 18 h was approximately equal to that in the initial inoculum.

Journal of Antimicrobial Chemotherapy Advance Access published February 13, 2009

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkn554

JAC

Functional relationship between bacterial cell density and the efficacy of antibiotics

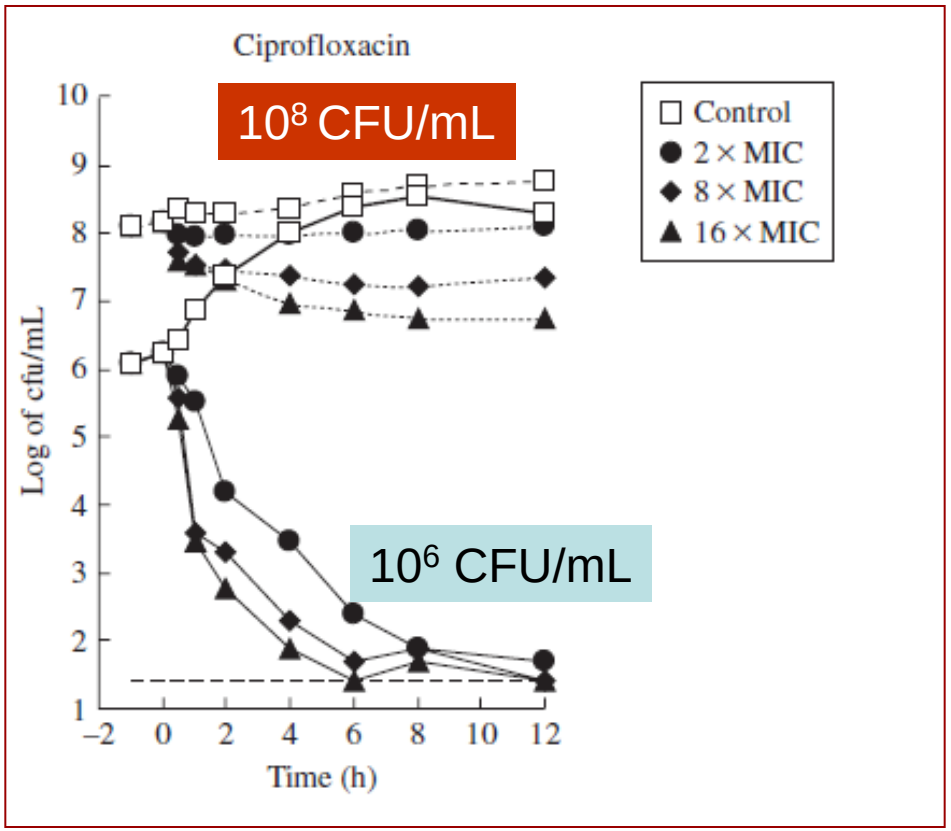
Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dki163

2005

JAC

Influence of inoculum size of *Staphylococcus aureus* and *Pseudomonas aeruginosa* on *in vitro* activities and *in vivo* efficacy of fluoroquinolones and carbapenems

Shingo Mizunaga*, Tomoko Kamiyama, Yoshiko Fukuda, Masahiro Takahata and Junichi Mitsuyama



Inoculum at 10^6 cfu/mL

- 99.9% killing after 2 h, at the concentration of 16 · MIC.

Inoculum at 10^8 cfu/mL

- No bactericidal activity at 2–16 · MIC

Similar results with different penems

- **The case of marbofloxacine**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2007, p. 4163–4166 Vol. 51, No. 11
0066-4804/07/$08.00+0 doi:10.1128/AAC.00156-07

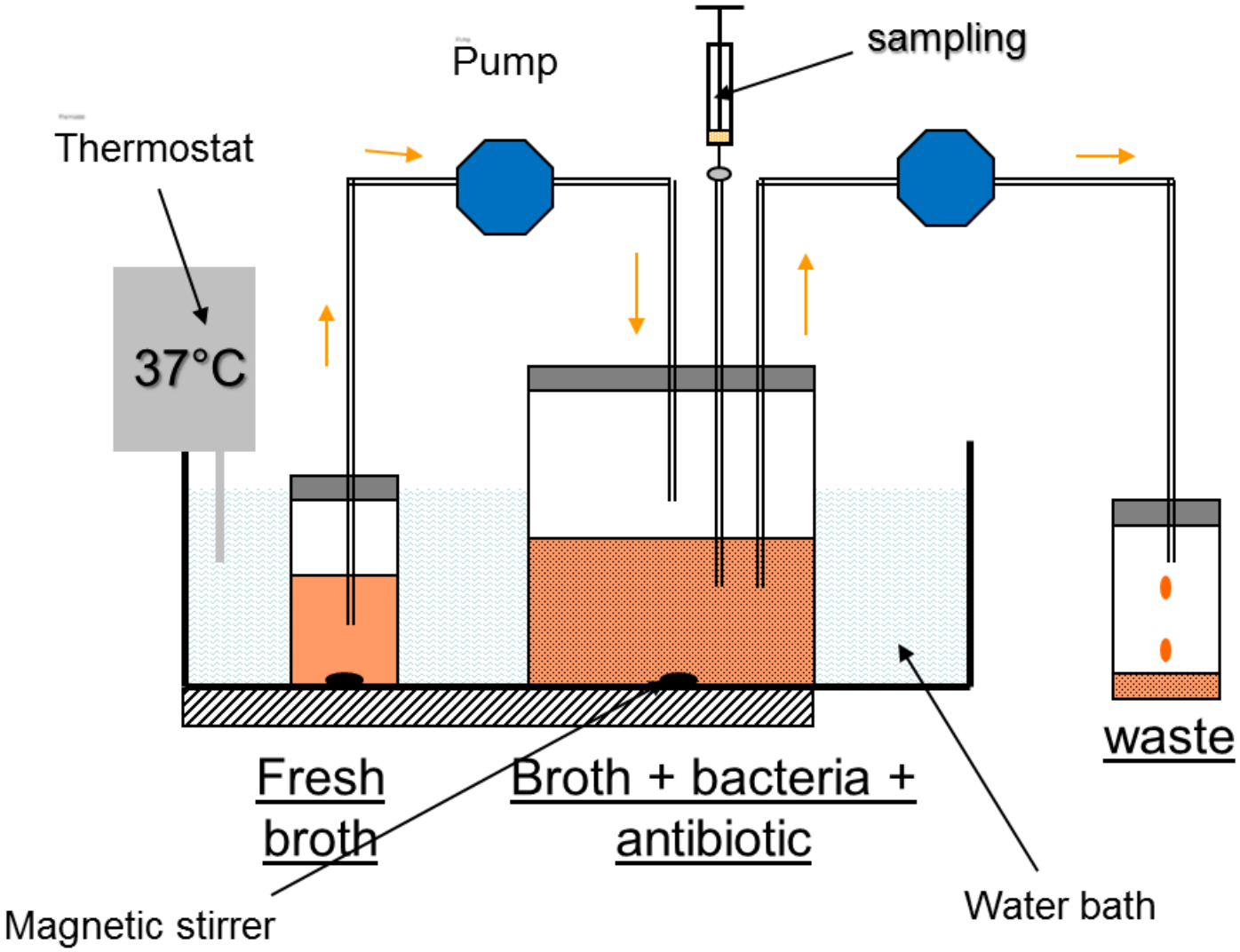
Influence of Inoculum Size on the Selection of Resistant Mutants of *Escherichia coli* in Relation to Mutant Prevention Concentrations of Marbofloxacin[▽]

Aude Ferran, Véronique Dupouy, Pierre-Louis Toutain, and Alain Bousquet-Mélou*

UMR181 Physiopathologie et Toxicologie Expérimentales, INRA, ENVT, Ecole Nationale Vétérinaire de Toulouse, 23 chemin des Capelles, BP 87 614, 31076 Toulouse Cedex 3, France

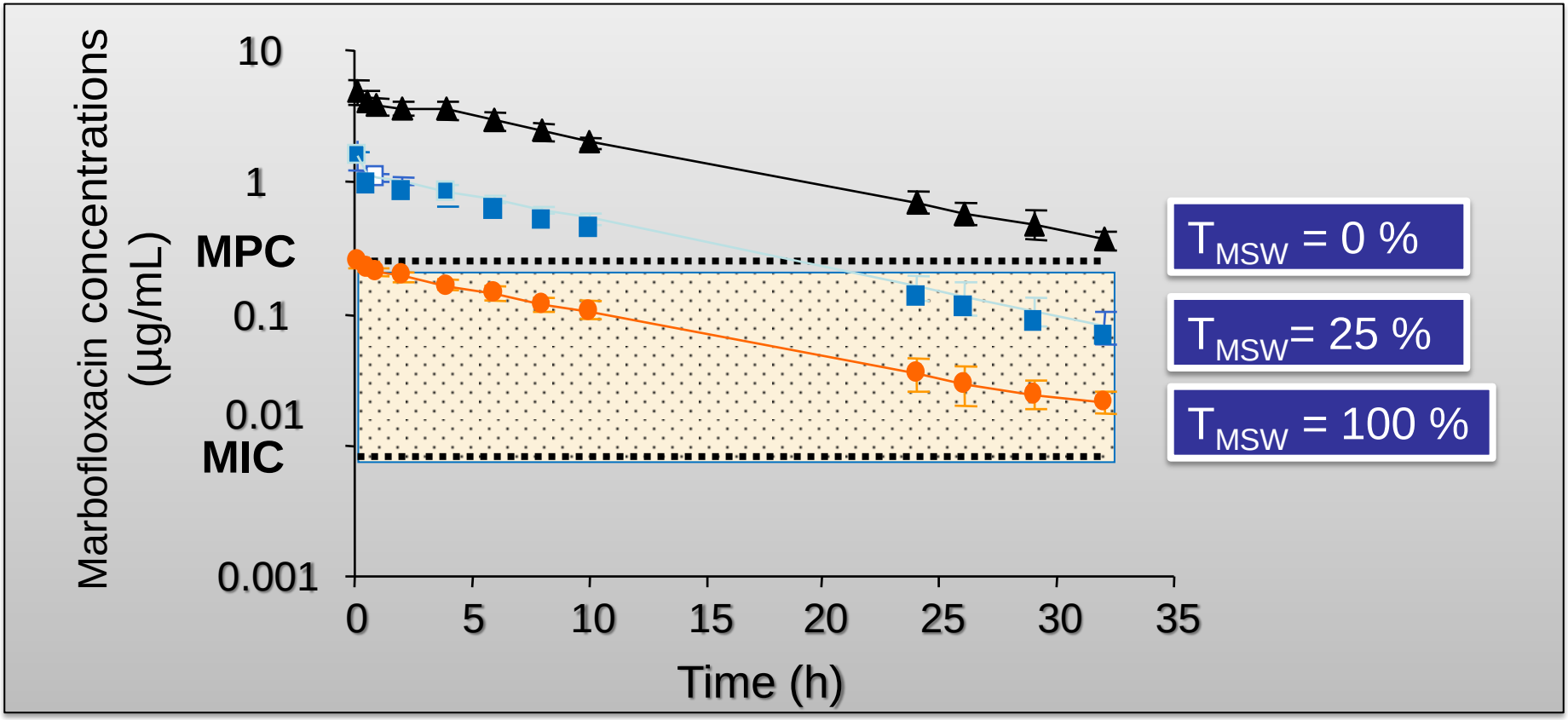
Received 2 February 2007/Returned for modification 13 June 2007/Accepted 13 August 2007

In vitro dynamic system



In vitro dynamic system

- Marbofloxacin concentrations profiles in an *in vitro* dynamic system



Marbofloxacin and the selection window

Interaction *in vitro* between T_{MSW} and inoculum size

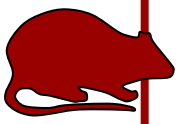
- Selection of resistant bacteria when :
  - When marbofloxacin concentrations are within the mutant selection window
  - With a higher frequency in higher bacterial inoculum

The inoculum effect: in vivo investigations

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2009, p. 4740–4748 Vol. 53, No. 11
0066-4804/09/$12.00 doi:10.1128/AAC.00608-09

Influence of Inoculum Size and Marbofloxacin Plasma Exposure on the Amplification of Resistant Subpopulations of *Klebsiella pneumoniae* in a Rat Lung Infection Model[▽]

Anne-Sylvie Kesteman,[1,2] Aude A. Ferran,[1] Agnès Perrin-Guyomard,[2] Michel Laurentie,[2] Pascal Sanders,[2] Pierre-Louis Toutain,[1] and Alain Bousquet-Mélou[1]*



- Hypothesis:
  - the bacterial load at the infection site impact the PK/PD parameters (AUC/MIC) of fluoroquinolones (marbofloxacine).

- Methods
  - rat lung infection model, *Klebsiella pneumoniae*.
  - we measured the influence of different marbofloxacin dosage regimens on selection of resistant bacteria
  - low (10^5 CFU) vs. a high (10^9 CFU) inoculum size
- **Results: prevention of resistance**
  - **(AUC)/MIC ratio of 189 h for the low inoculum**
  - **AUC/MIC ratios up to 756 h for the high inoculum.**

Rodent model of metaphylaxis

G Model
VETMIC-5020; No. of Pages 6

ARTICLE IN PRESS

Veterinary Microbiology xxx (2010) xxx–xxx

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Veterinary Microbiology

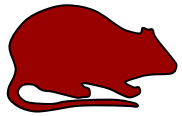
journal homepage: www.elsevier.com/locate/vetmic

Impact of early versus later fluoroquinolone treatment on the clinical; microbiological and resistance outcomes in a mouse-lung model of *Pasteurella multocida* infection

Aude A. Ferran, Pierre-Louis Toutain, Alain Bousquet-Mélou *

UMR181 Physiopathologie et Toxicologie Expérimentales, INRA, ENVT, Ecole Nationale Vétérinaire de Toulouse, 23 chemin des Capelles, BP 87 614, 31076 Toulouse Cedex 3, France

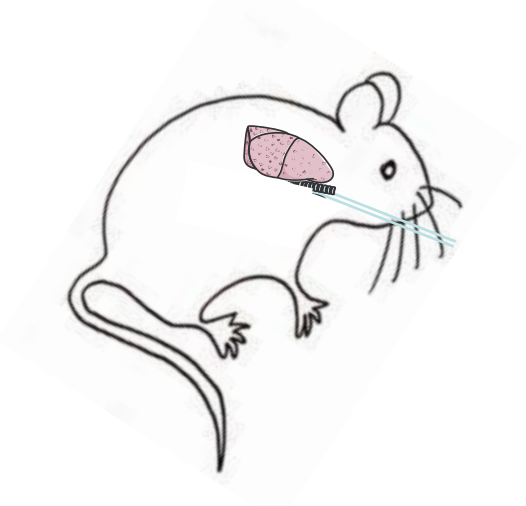
Objectives:



- To assess the impact of early (metaphylaxis, control) versus later fluoroquinolone treatment on:
  - The **clinical cure** (survival of mice)
  - The **microbiological cure** (bacterial eradication)
  - the **resistance outcomes** (selection of resistant (target) bacteria)

Materials and methods

Model of pulmonary infection

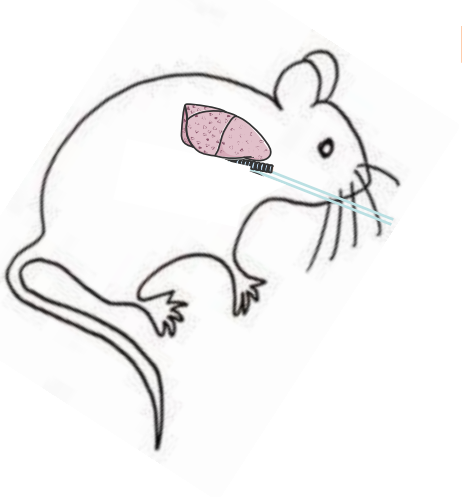


Inoculation of
Pasteurella multocida
1500 CFU/lung

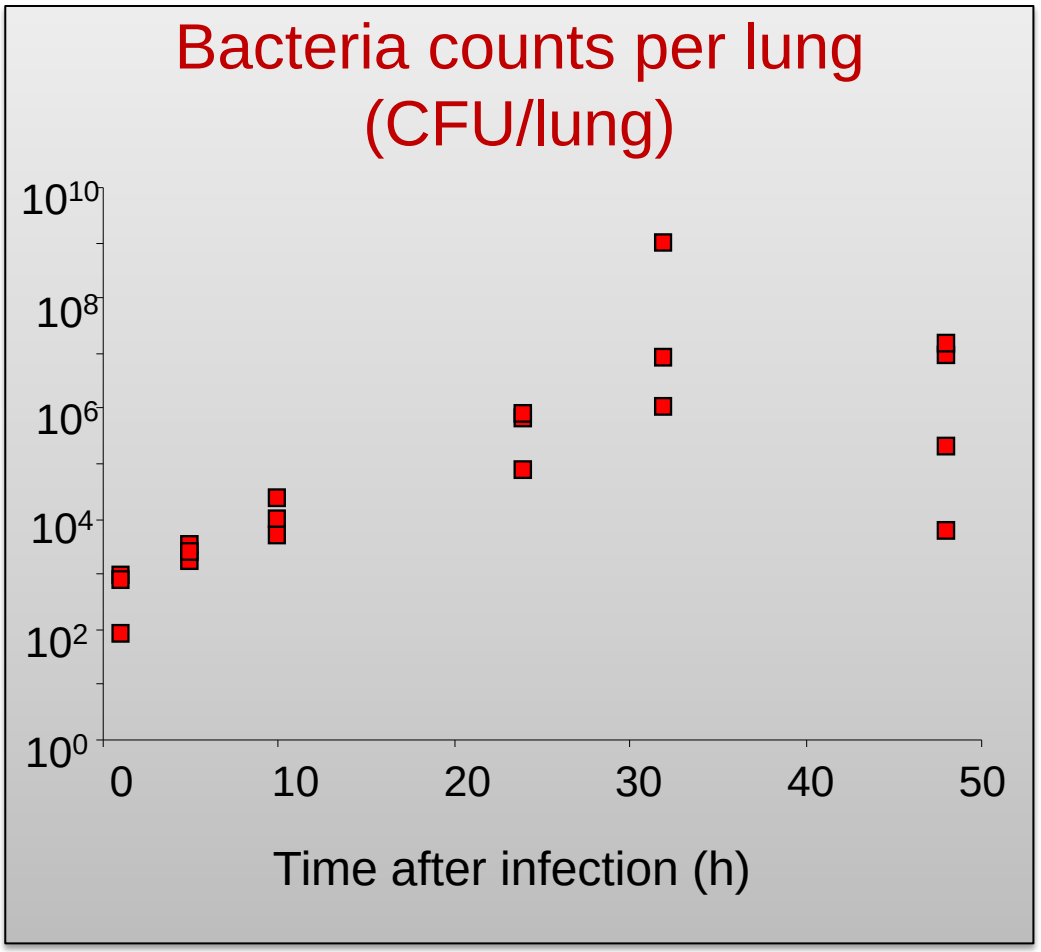
A strain of *Pasteurella multocida* isolated from the trachea of a pig with clinical symptoms of a bacterial lung infection

Model of pulmonary infection

Inoculation of
Pasteurella multocida
1500 CFU/lung



Progression of infection

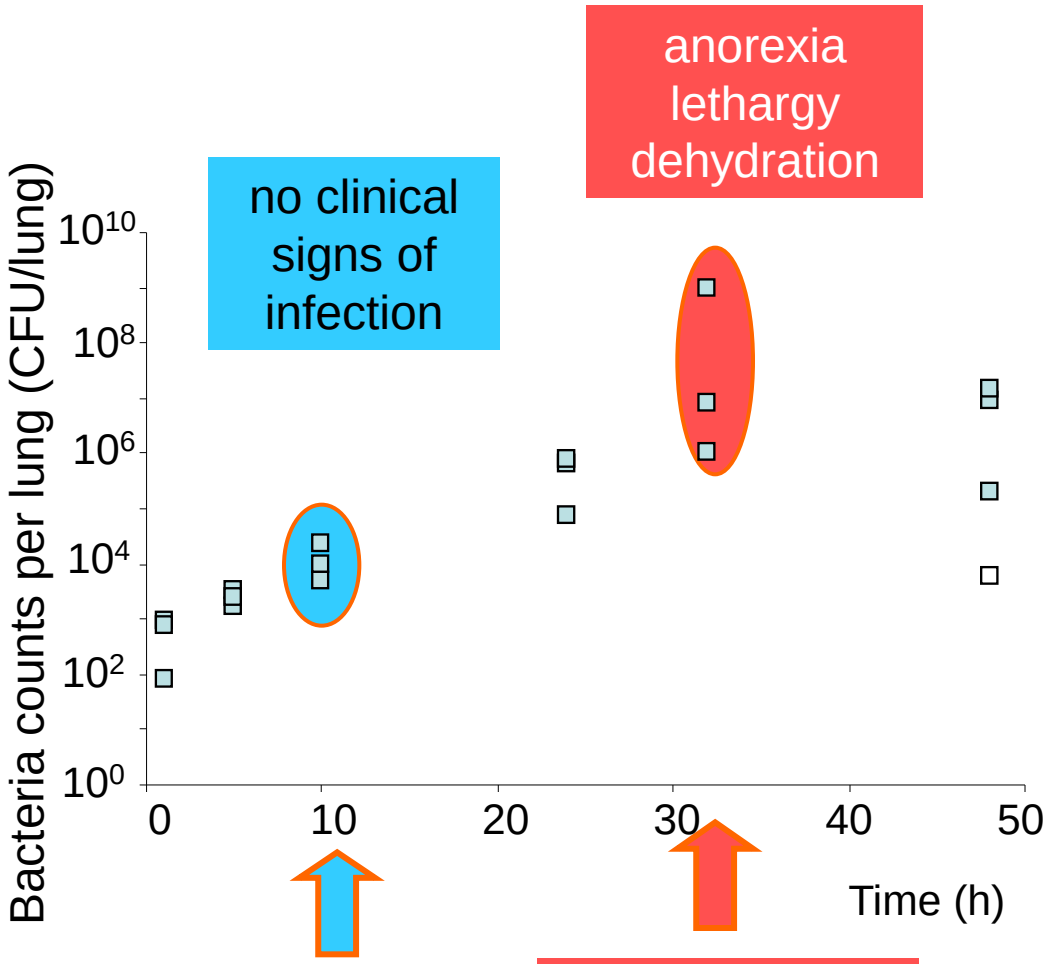


18 control mice were used to assess the natural growth of *Pasteurella multocida* in the lungs.

Time of marbofloxacin administration

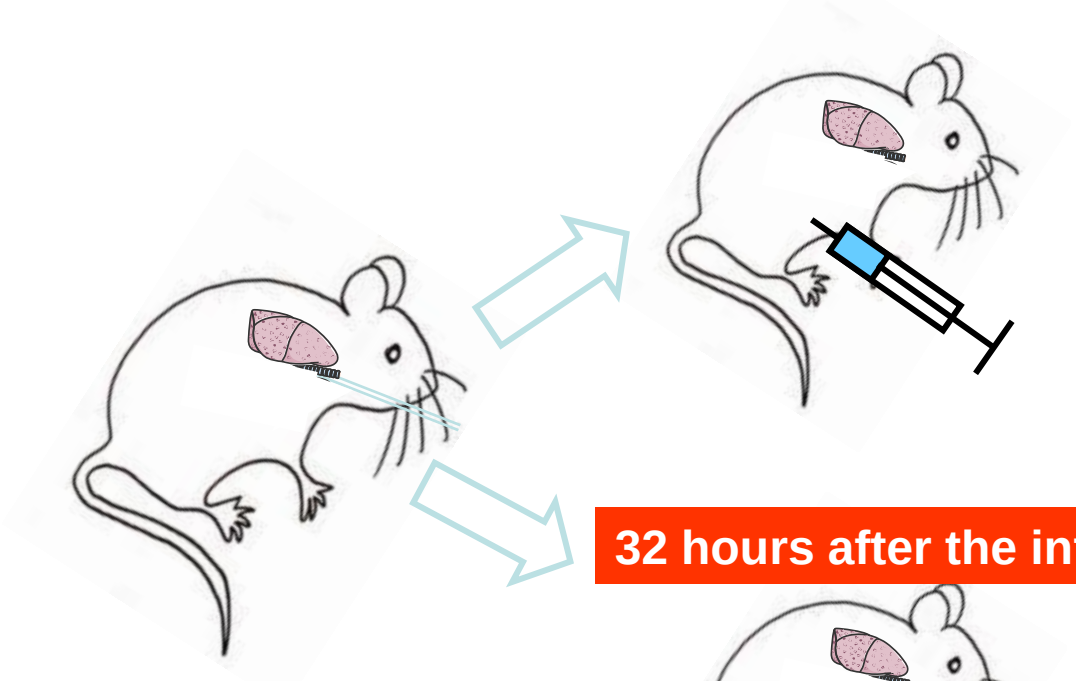
Progression of infection

Inoculation of
Pasteurella multocida
1500 CFU/lung

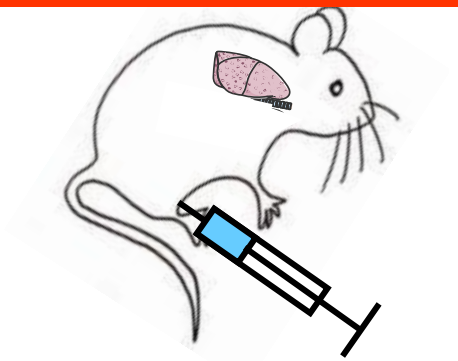


Marbofloxacin: Doses administered

10 hours after the infection (n=14)



32 hours after the infection (n=14)



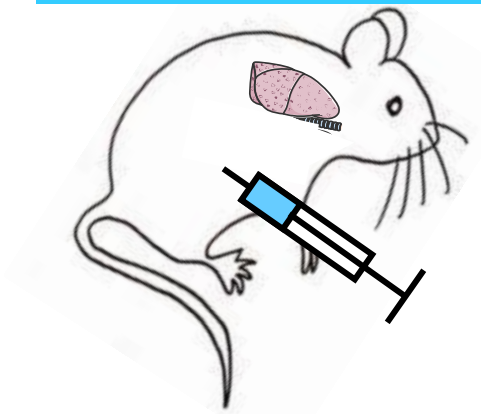
Inoculation of
Pasteurella multocida
1500 CFU/lung

- A single administration of marbofloxacin
- Two doses tested for each group
  1 mg/kg and 40 mg/kg

Pharmacokinetic study

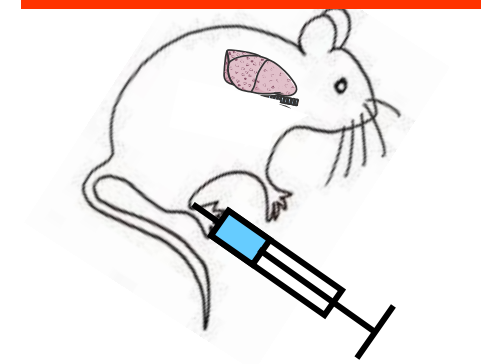
Inoculation of
Pasteurella multocida
1500 CFU/lung

10 hours after the infection



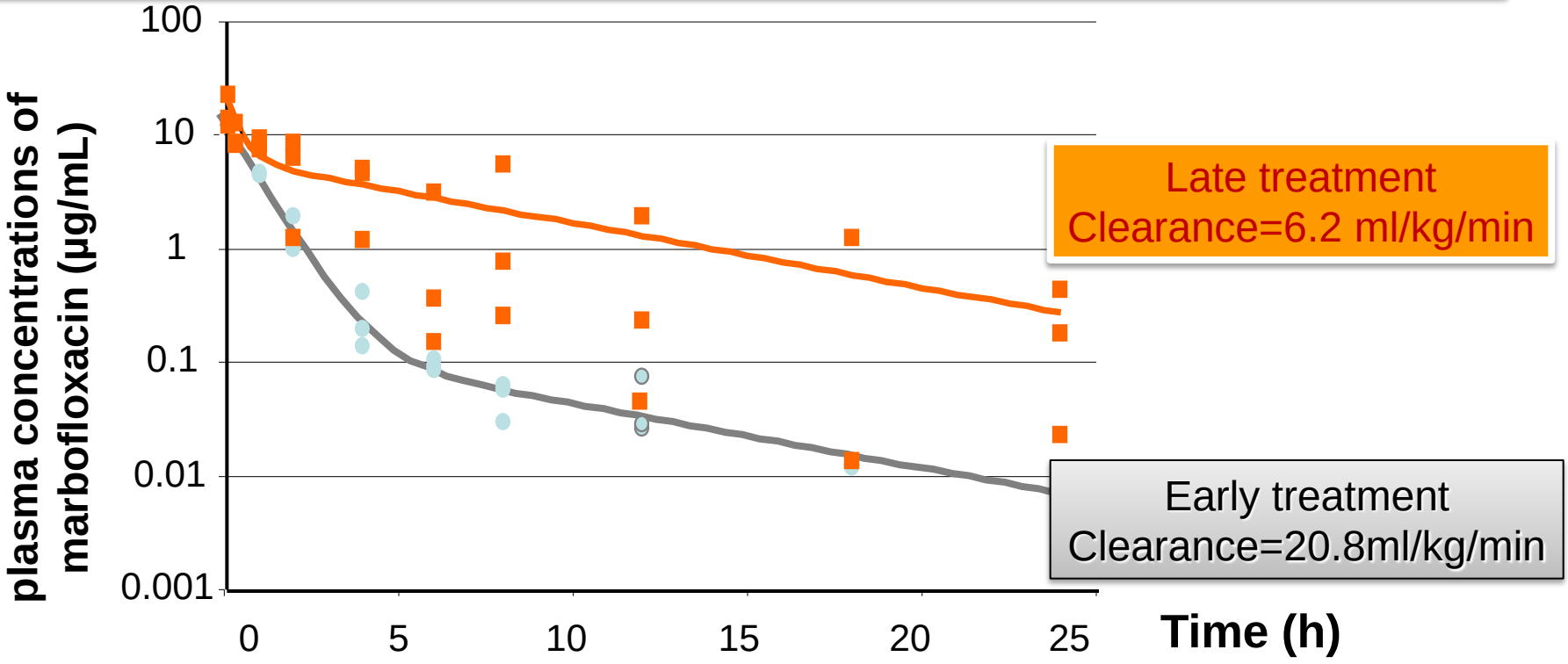
One administration of marbofloxacin
(20 mg/kg)

32 hours after the infection



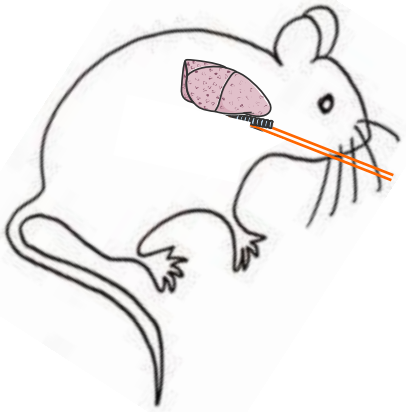
Results

Marbofloxacin IP administration at 20mg/kg



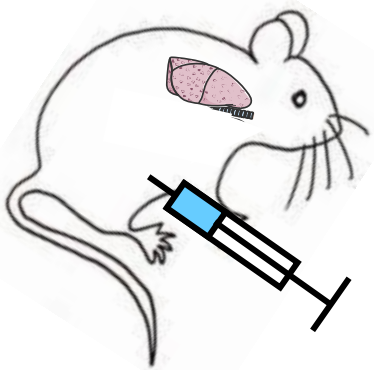
Exposure was 3-times higher for the late group than for the early treated group

Endpoints measured

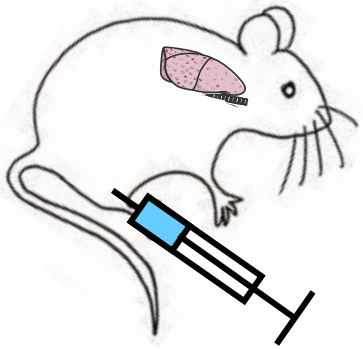


Inoculation of
Pasteurella multocida
1500 CFU/lung

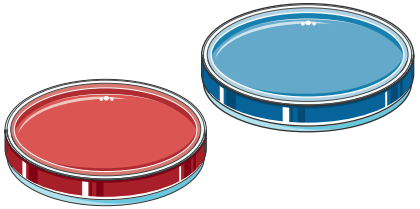
10 hours



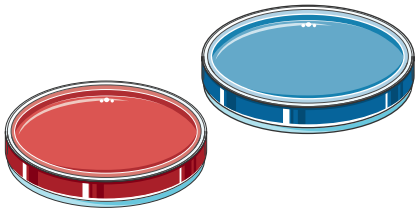
32 hours



48 hours after inoculation

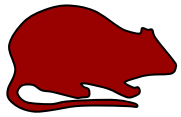


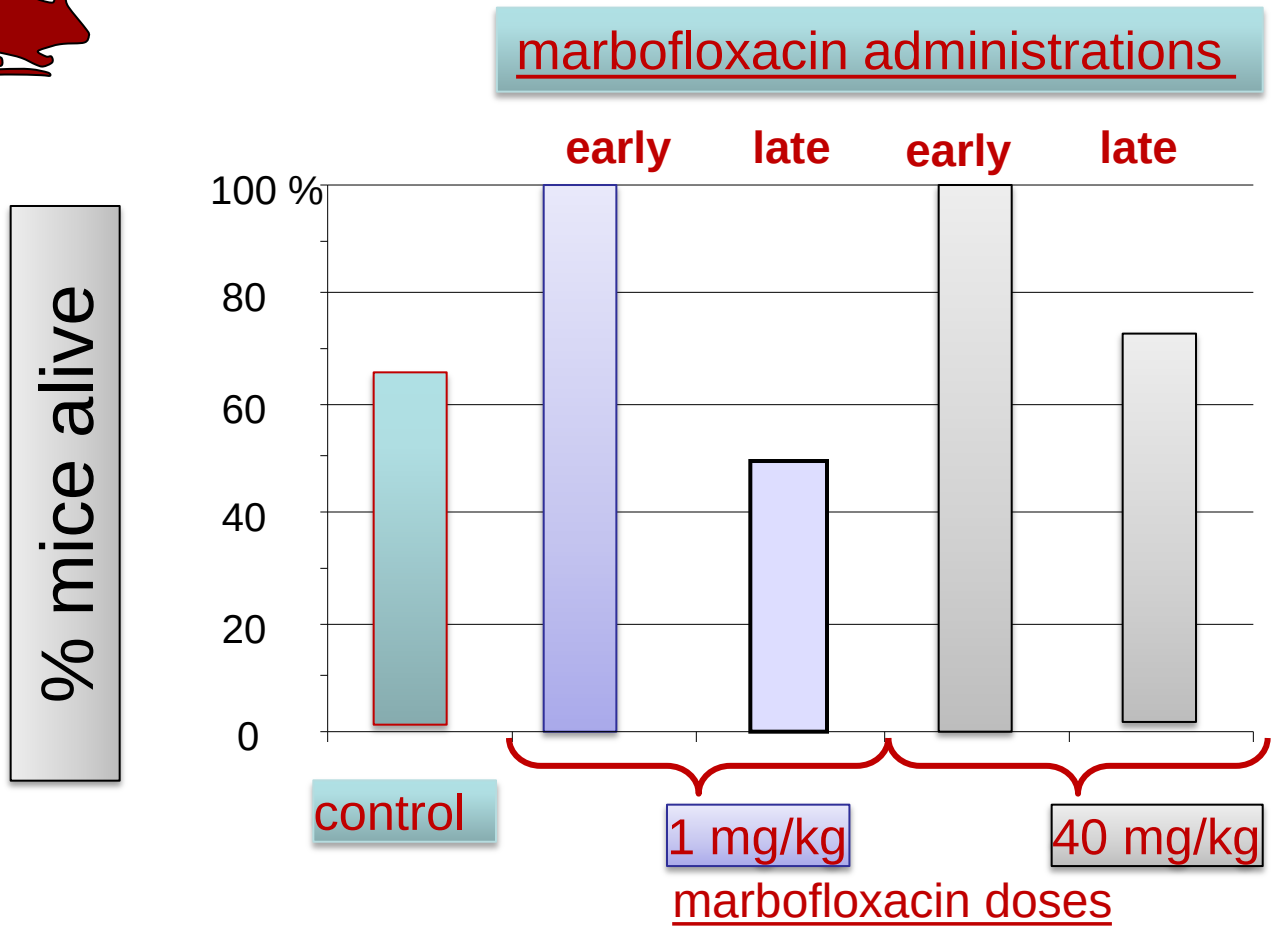
Counting of bacteria
38 hours after marbofloxacin administration



70 hours after inoculation

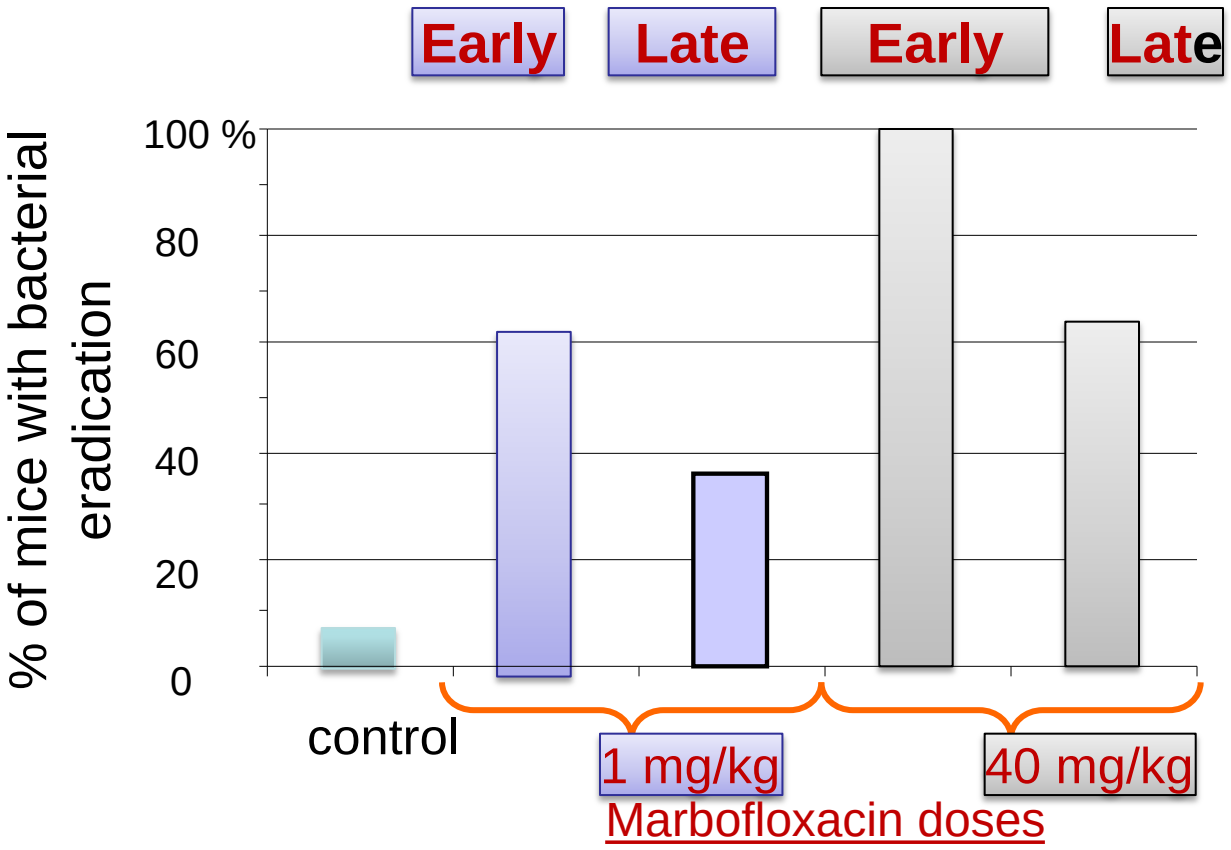
1-Clinical outcome (survival)





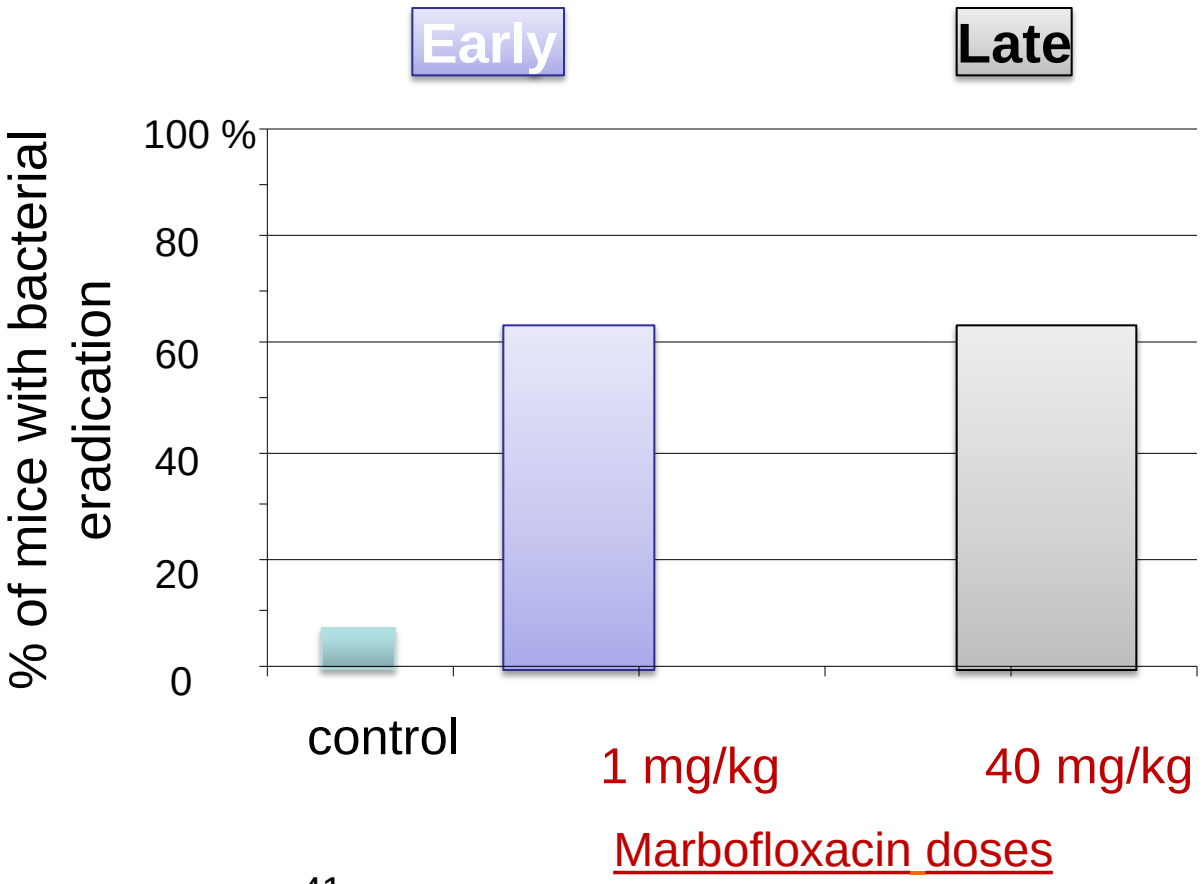
2-Bacterial eradication

only the early high dose

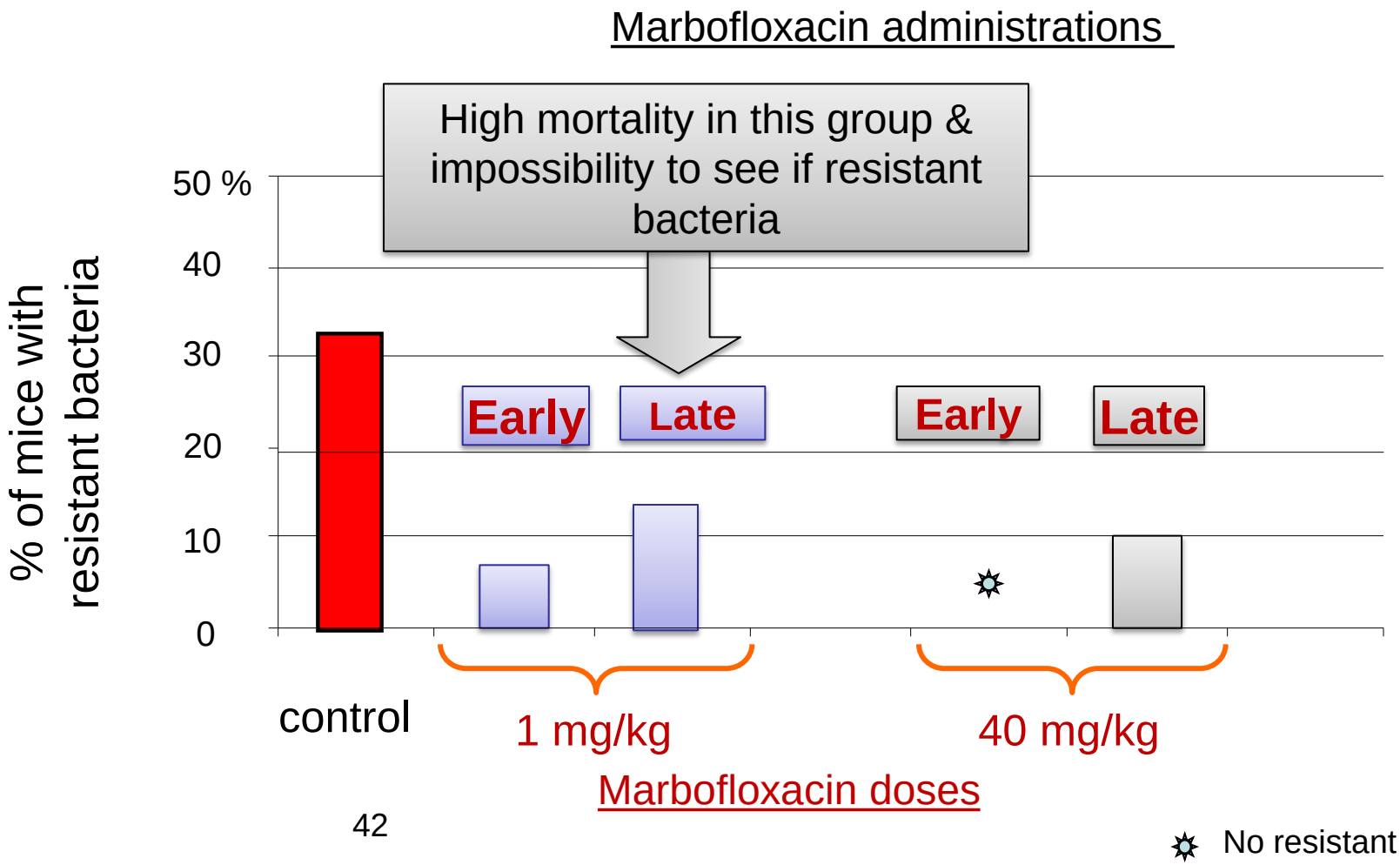


2-Bacterial eradication

Early low dose= late high dose



3-Selection of resistant (target) bacteria



Conclusions

1. In the present study, the early administration of 1 mg/kg marbofloxacin gave a higher survival rate and a similar percentage of bacterial eradication as the late administration of 40 mg/kg marbofloxacin.
2. If considering emergence of resistance, the likely optimal regimen should be an early treatment (slightly) higher than 1 mg/kg

Antimicrobial Agents and Chemotherapy

Low or High Doses of Cefquinome Targeting Low or High Bacterial Inocula Cure Klebsiella pneumoniae Lung Infections but Differentially Impact the Levels of Antibiotic Resistance in Fecal Flora

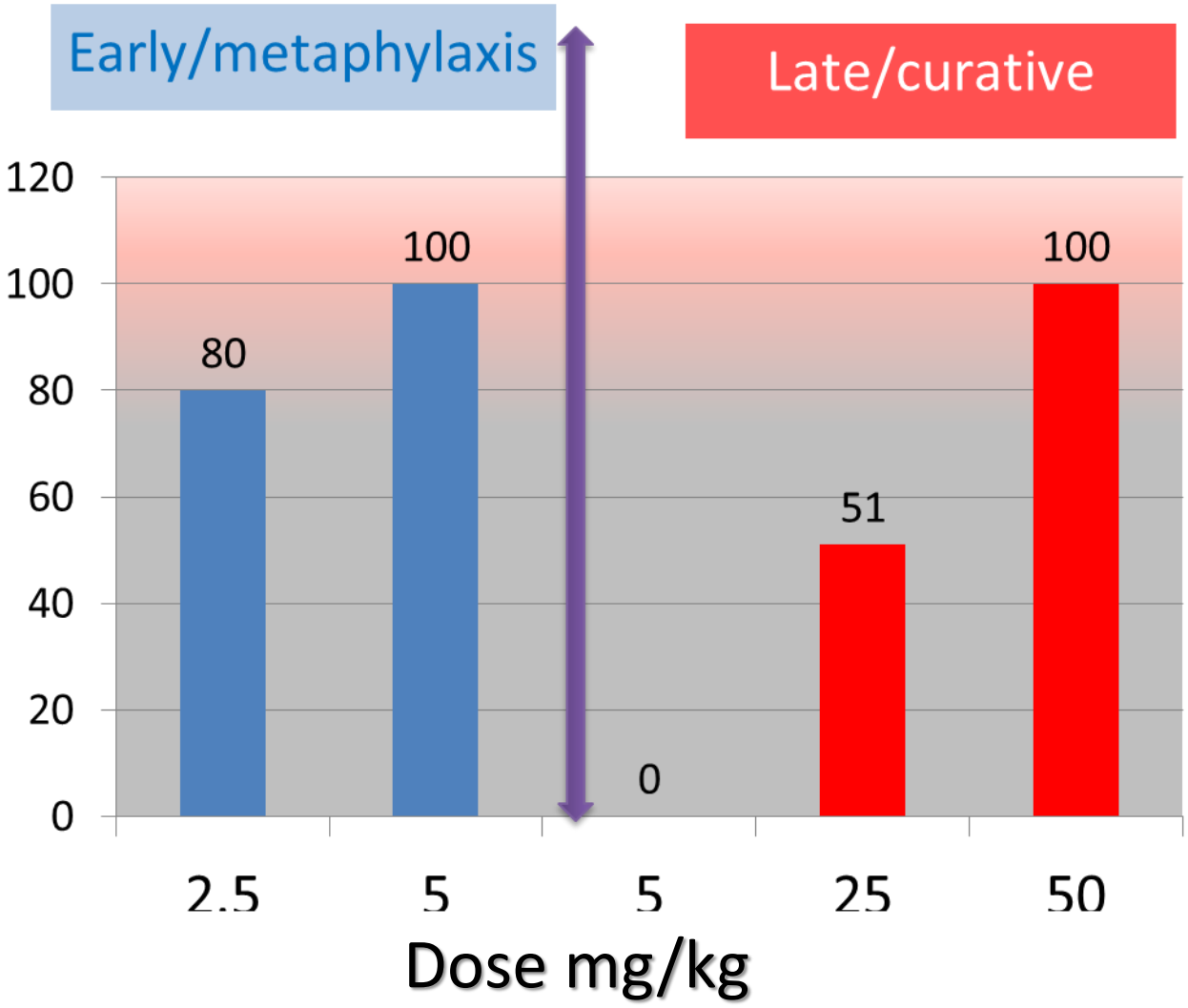
Maleck V. Vasseur, Michel Laurentie, Jean-Guy Rolland, Agnès Perrin-Guyomard, Jérôme Henri, Aude A. Ferran, Pierre-Louis Toutain and Alain Bousquet-Mélou

Antimicrob. Agents Chemother. 2014, 58(3):1744. DOI: 10.1128/AAC.02135-13.
Published Ahead of Print 6 January 2014.

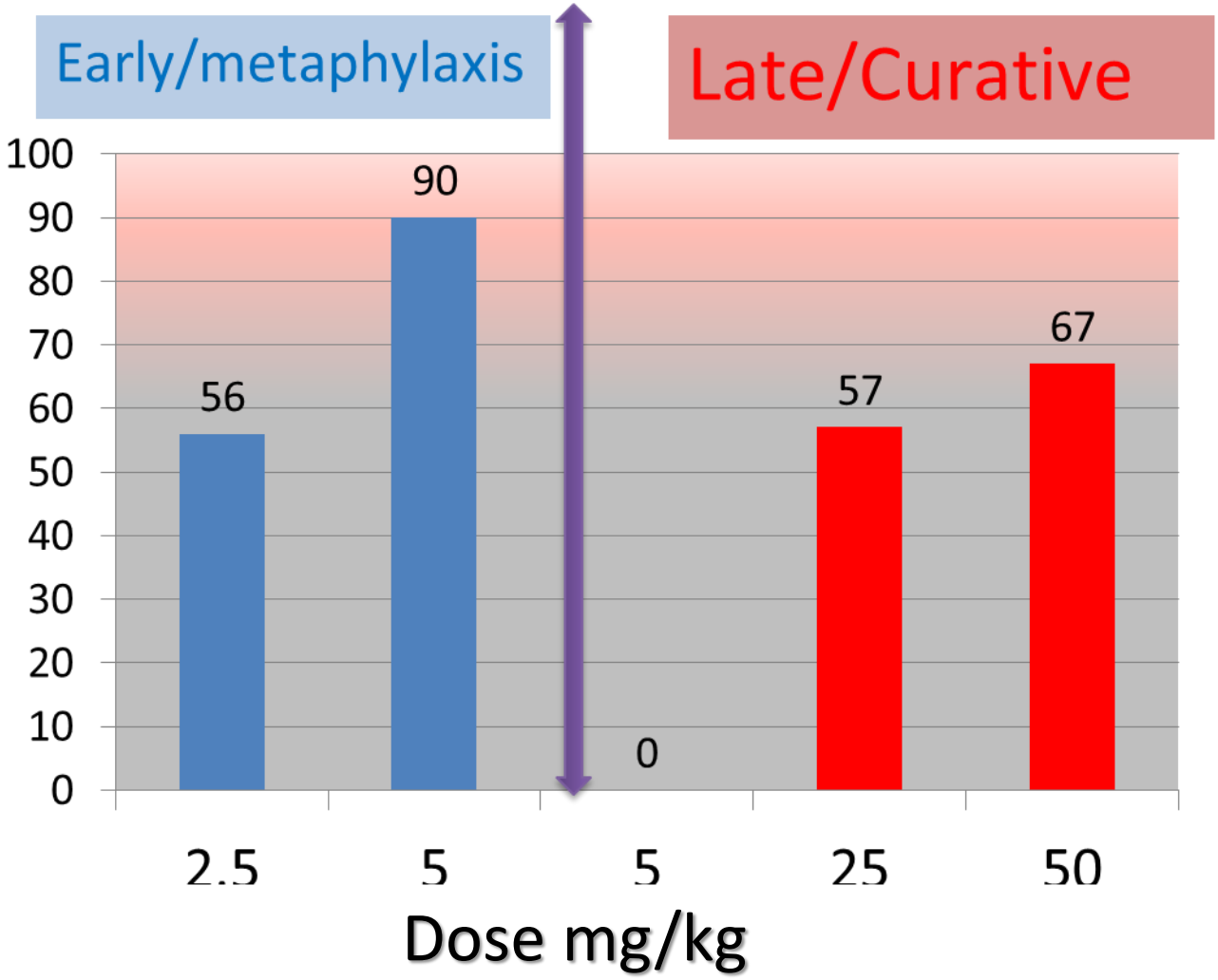
Metaphylaxis vs. curative

- Pulmonary infectious model by inhalation (*P multocida)*
- Amoxicillin & et cefquinome
- Treatment during the prepatent (incubation) period (24h) vs. when symptoms are present

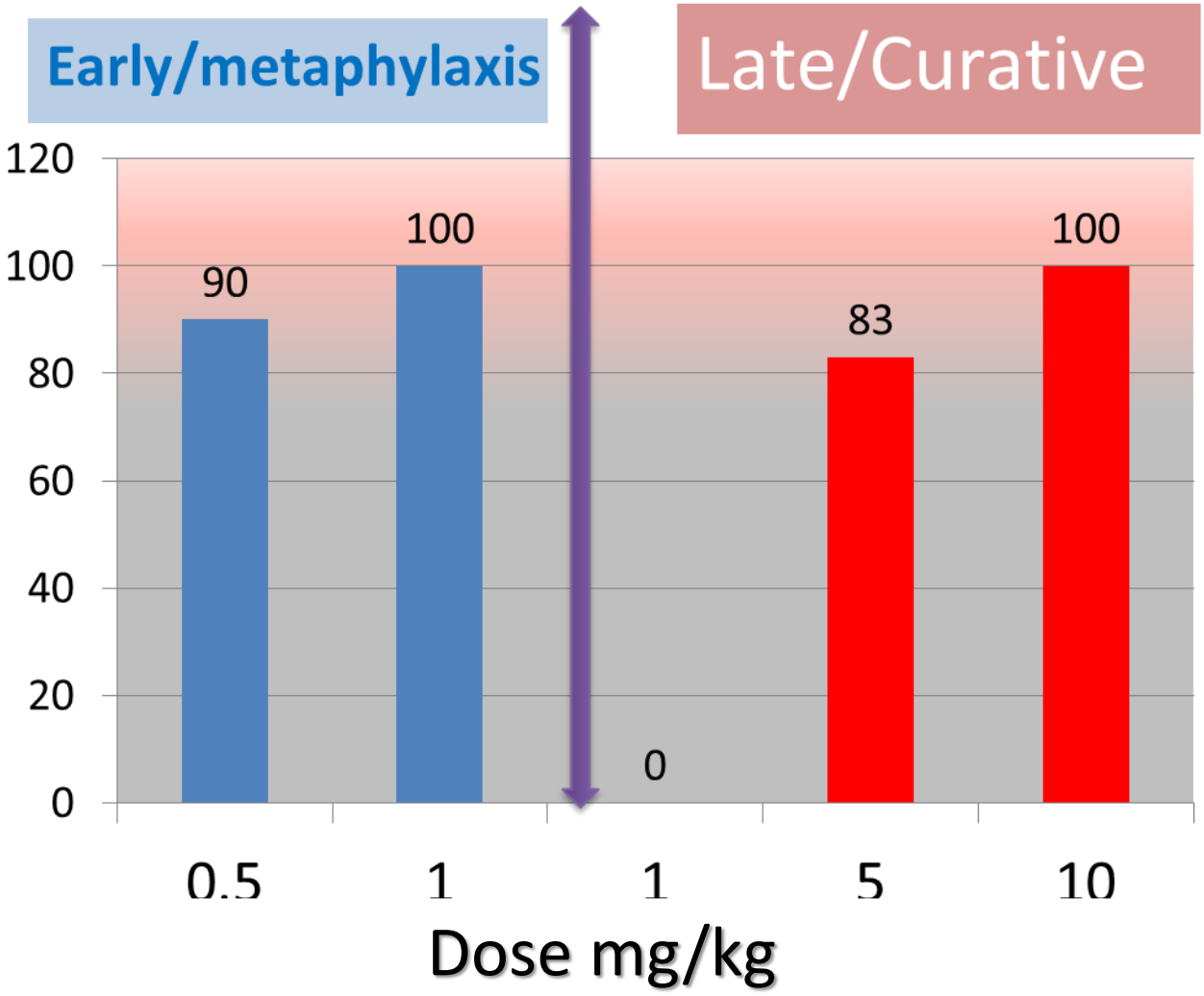
Effect of amoxicillin (clinical cure) metaphylaxis vs. curative



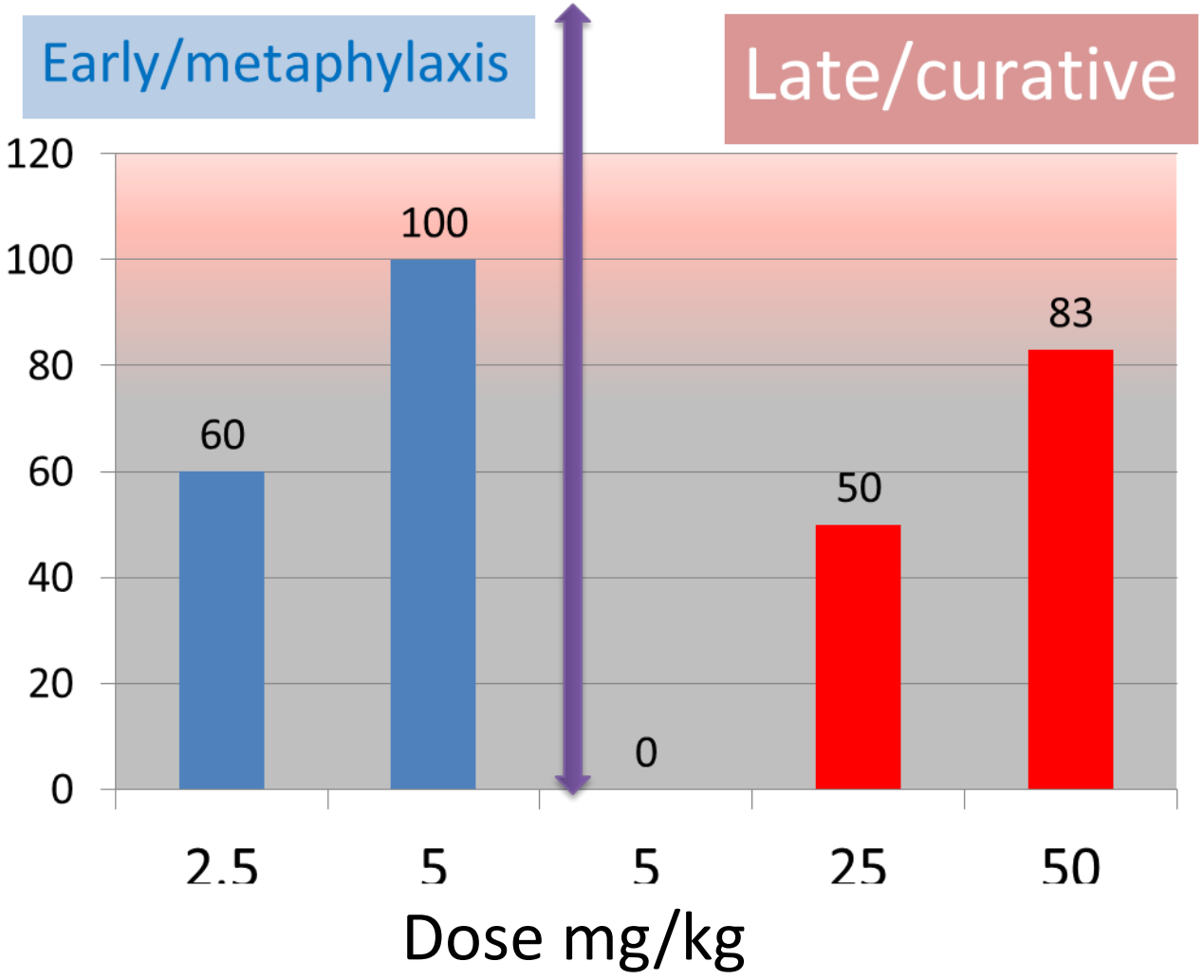
Effect of amoxicillin (bacteriological cure) metaphylaxis vs. curative



Effect of cefquinome (clinical cure) metaphylaxis vs. curative



Effect of cefquinome (bacteriological cure) metaphylaxis vs. curative



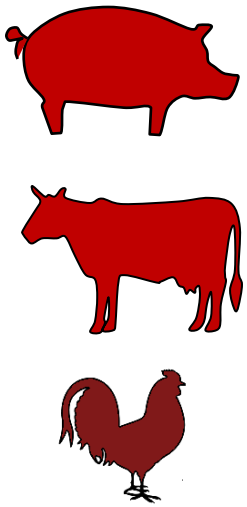
Impact on gut microbiota

Why gut microbiota

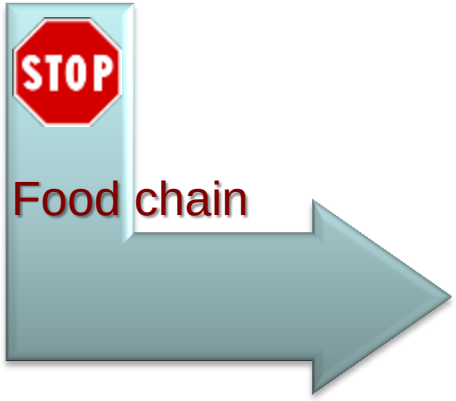
- Any antibiotic treatment can impact the gut microbiota (commensal flora)
- Gut microbiota is the main location for the genesis of resistant bacteria and it constitute the main pool of genes of resistance
- It is a public health objective to mitigate the impact of any antibiotic on the gut microbiota
- An optimal dose regarding the target pathogen can be detrimental to the gut microbiota

Greening our AB

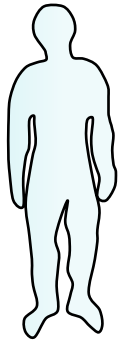
One world, one health



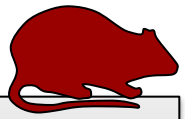
Environment



Commensal flora



Example of conflict of interest



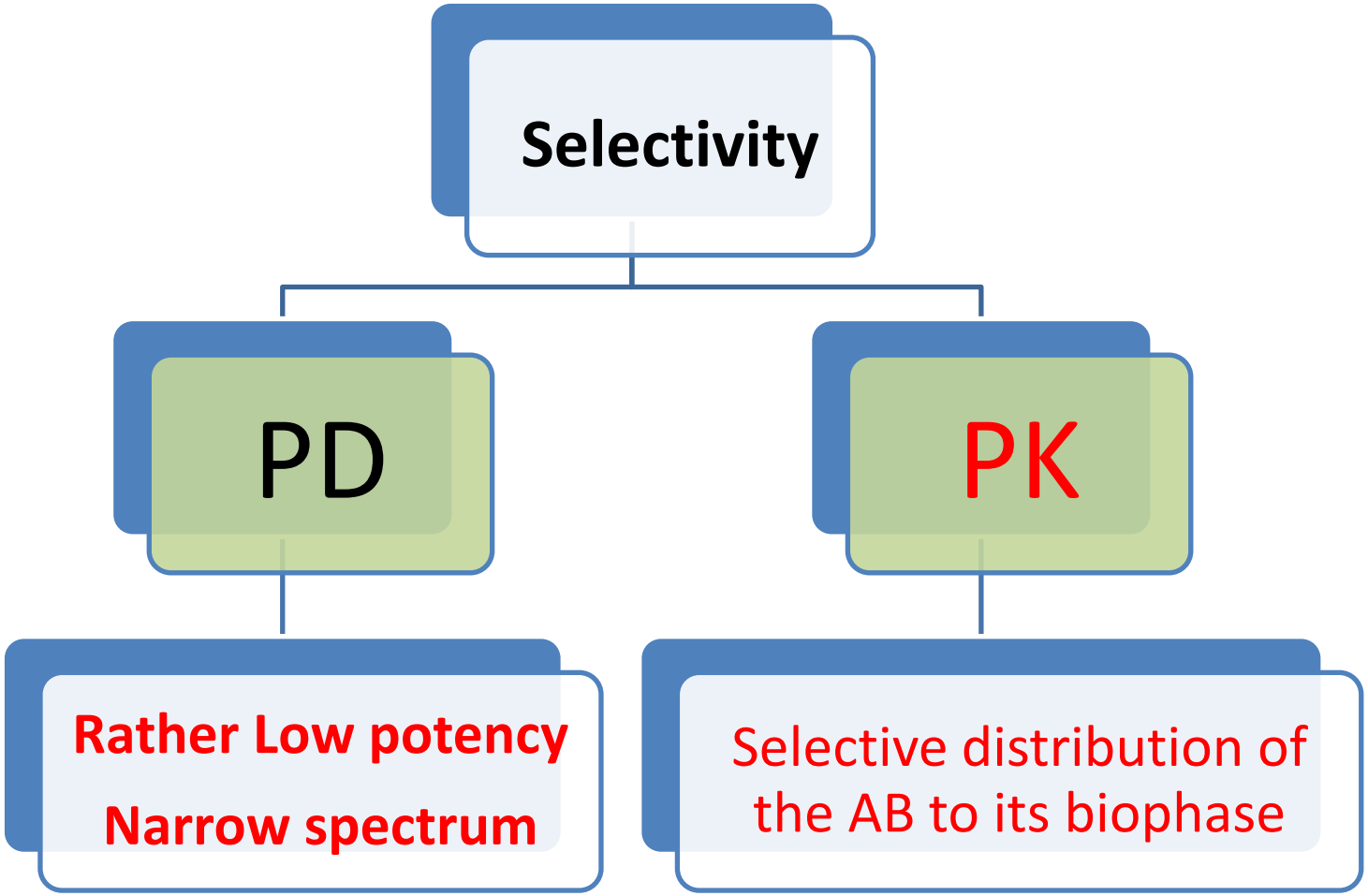
- the optimal dose in terms of pathogen eradication was detrimental to the gut microbiota

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2010, p. 2960–2964 Vol. 54, No. 7
0066-4804/10/$12.00 doi:10.1128/AAC.01612-09

Emergence of Resistant *Klebsiella pneumoniae* in the Intestinal Tract during Successful Treatment of *Klebsiella pneumoniae* Lung Infection in Rats[▽]

Anne-Sylvie Kesteman,[1,2] Agnès Perrin-Guyomard,[2] Michel Laurentie,[2] Pascal Sanders,[2] Pierre-Louis Toutain,[1] and Alain Bousquet-Mélou[1]*

Selectivity of antimicrobial drugs in veterinary medicine



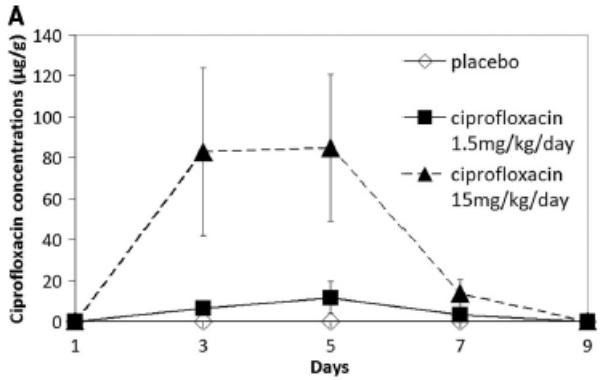
Impact of antibiotics on the gut microbiota is dose-dependent

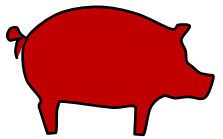
Correlation between Fecal Concentrations of Ciprofloxacin and Fecal Counts of Resistant *Enterobacteriaceae* in Piglets Treated with Ciprofloxacin: toward New Means To Control the Spread of Resistance?

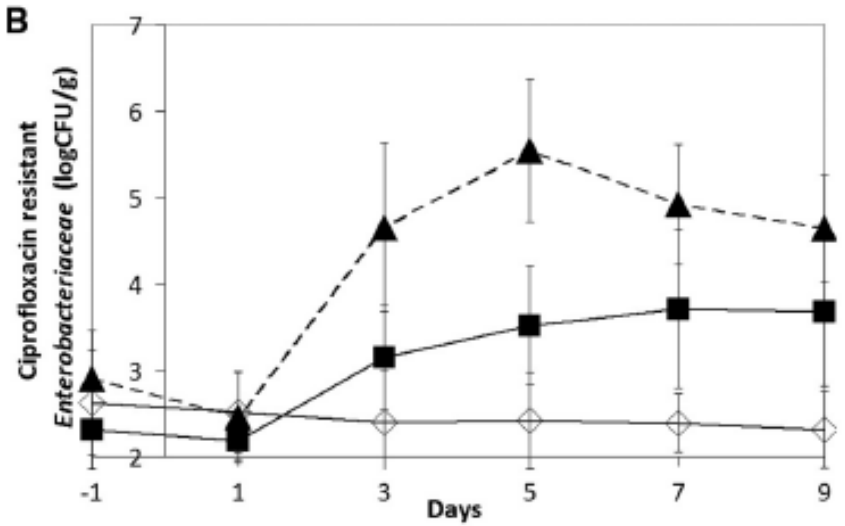
Thu Thuy Nguyen,[a,b] Elisabeth Chachaty,[c] Clarisse Huy,[d] Carole Cambier,[e] Jean de Gunzburg,[d] France Mentré,[a,b,g] and Antoine Andremont[a,f,g]

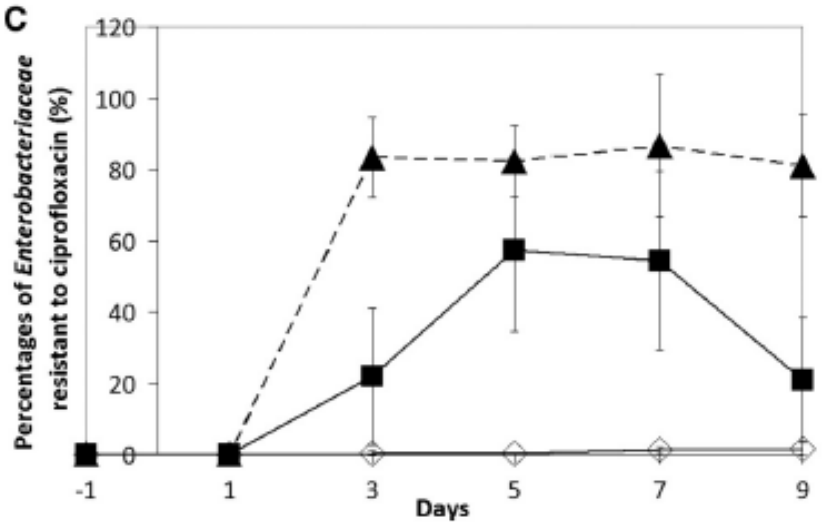
Impact of antibiotics on the gut microbiota is dose-dependent

Ciprofloxacin:
1.5 or 15mg/kg/days









In vitro assessment of the selectivity of antibiotics on the target pathogen vs. commensal flora: eradication of a low vs. high inoculum size of *P multocida*

Antimicrobial Agents and Chemotherapy

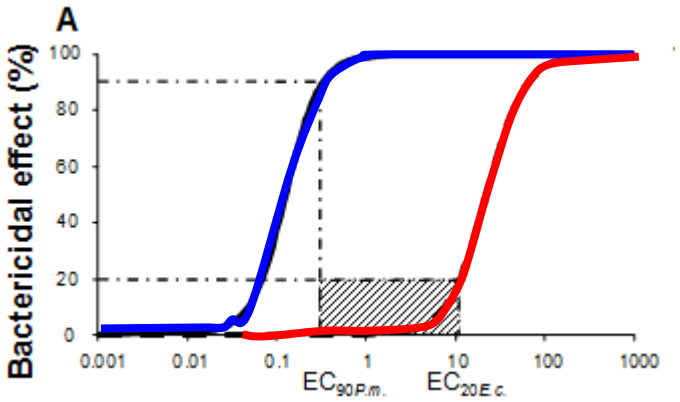
Low or High Doses of Cefquinome Targeting Low or High Bacterial Inocula Cure Klebsiella pneumoniae Lung Infections but Differentially Impact the Levels of Antibiotic Resistance in Fecal Flora

Maleck V. Vasseur, Michel Laurentie, Jean-Guy Rolland, Agnès Perrin-Guyomard, Jérôme Henri, Aude A. Ferran, Pierre-Louis Toutain and Alain Bousquet-Mélou

Antimicrob. Agents Chemother. 2014, 58(3):1744. DOI: 10.1128/AAC.02135-13.
Published Ahead of Print 6 January 2014.

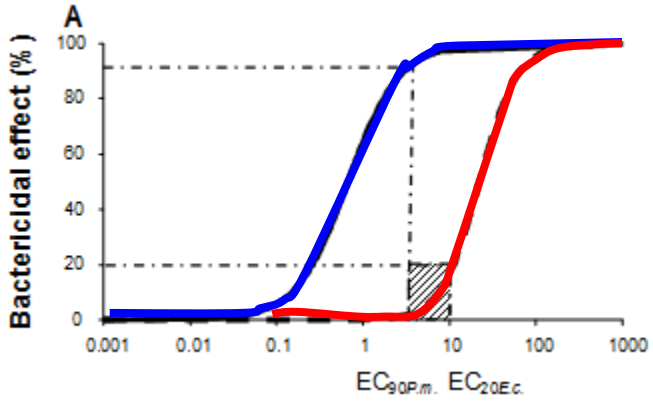
Amoxicillin has a good selectivity regarding E coli when eradicating a low but not a high inoculum size of lung *P. multocida*

Low: 10^5 CFU/mL



SI=51

High:10^7 CFU/mL

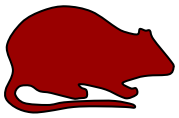


SI=5.54

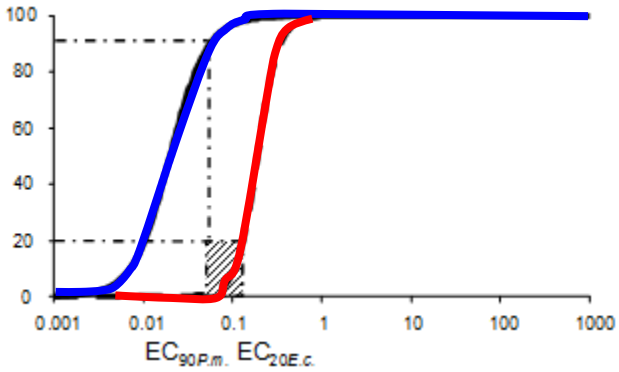
P. Multocida (10^5 or 10^7 CFU/ml)

E coli (10^7 CFU/mL)

Cefquininome has no selectivity regarding E coli when eradicating either a low a or a high inoculum size of lung *P. multocida*

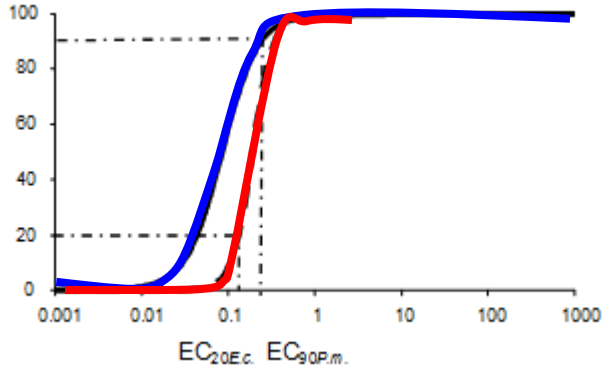


Low:10^5 CFU/mL



SI=2.9

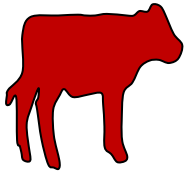
High:10^7 CFU/mL



SI=0.66

P. Multocida (10^5 or 10^7 CFU/ml)

E coli (10^7 CFU/mL)



Impact of early versus later fluoroquinolone treatment on the clinical and microbiological outcomes in calves challenged with *Mannheimia haemolytica*

Experimental challenge with *M. haemolytica*

- Calves
  - N= 32;
- Bacteria strain
  - *M. haemolytica* (MIC 0.03 µg/mL)
- Challenge
  - Intratracheal injection,
  - 10^7 CFU tot/calf
- Inclusion criteria
  - Rectal T°C recording every 3h after inoculation
  - increase temperature >1°C of basal individual temperature mean (before challenge)

Experimentation

Control

X 4

No treatment

E2 (Early, 2mg/kg) group

X 6

marbofloxacin
2mg/kg,
2-4h post-inclusion

L2 (Late, 2mg/kg) group

X 6

L10 (Late, 10mg/kg) group

X 6

marbofloxacin
2mg/kg (L2) or 10mg/kg (L10)
36-38h post-inclusion

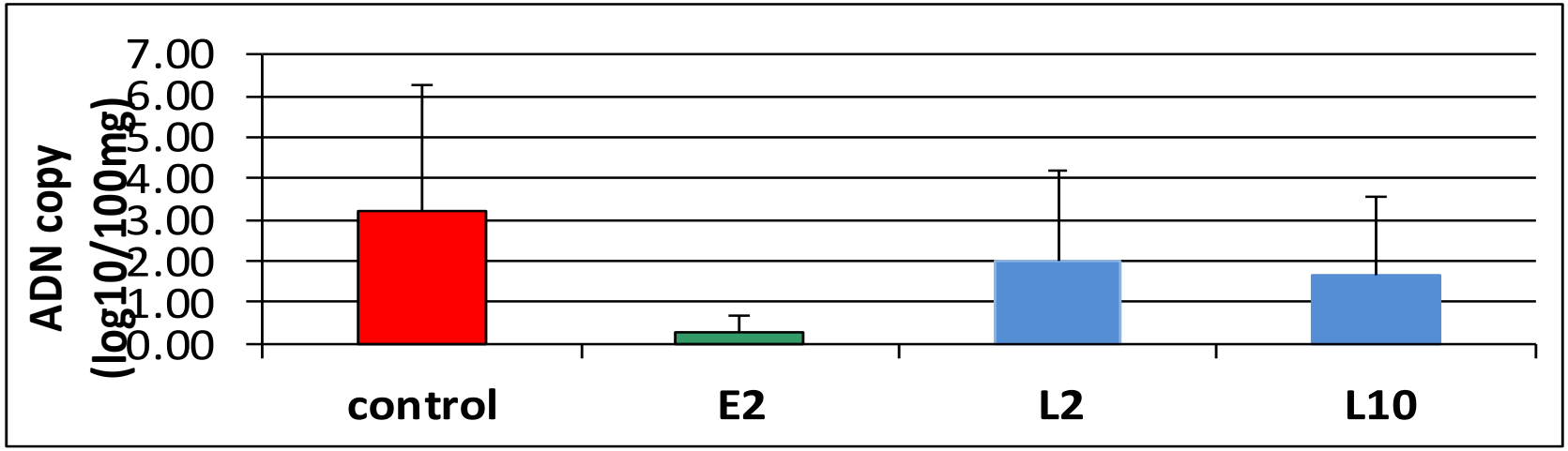
Evolution of the bacterial load in the lower respiratory tract

PCR in lung tissues samples

(110h after an experimental lung infection *P haemolytica*)

Early +12h

Late +24-36h

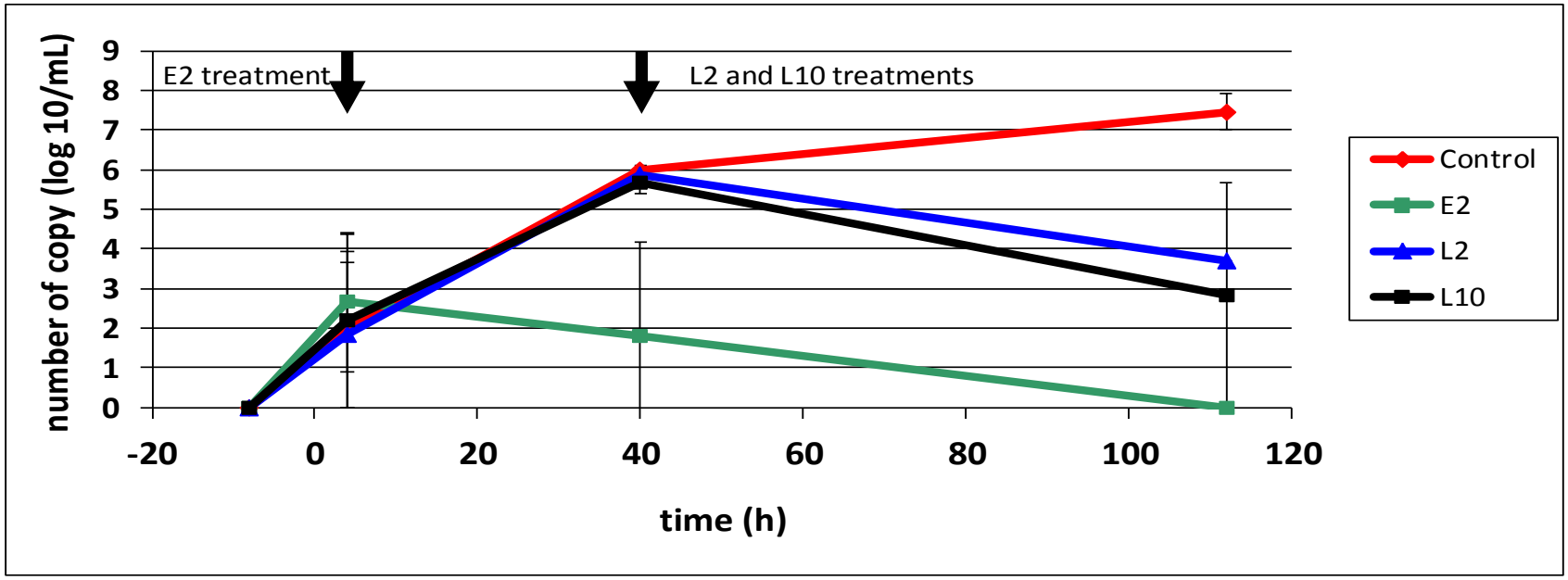


2mg/kg

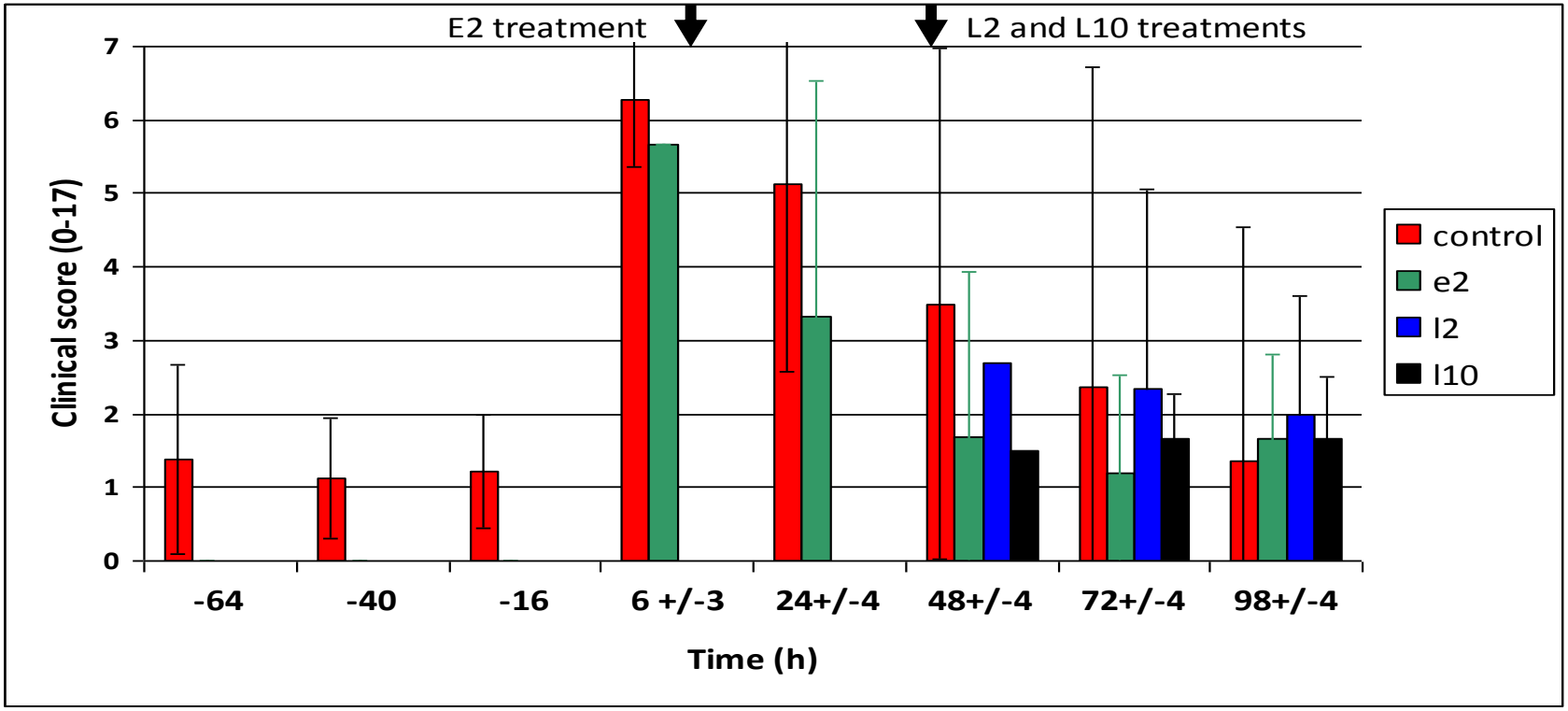
2mg/kg

10mg/kg

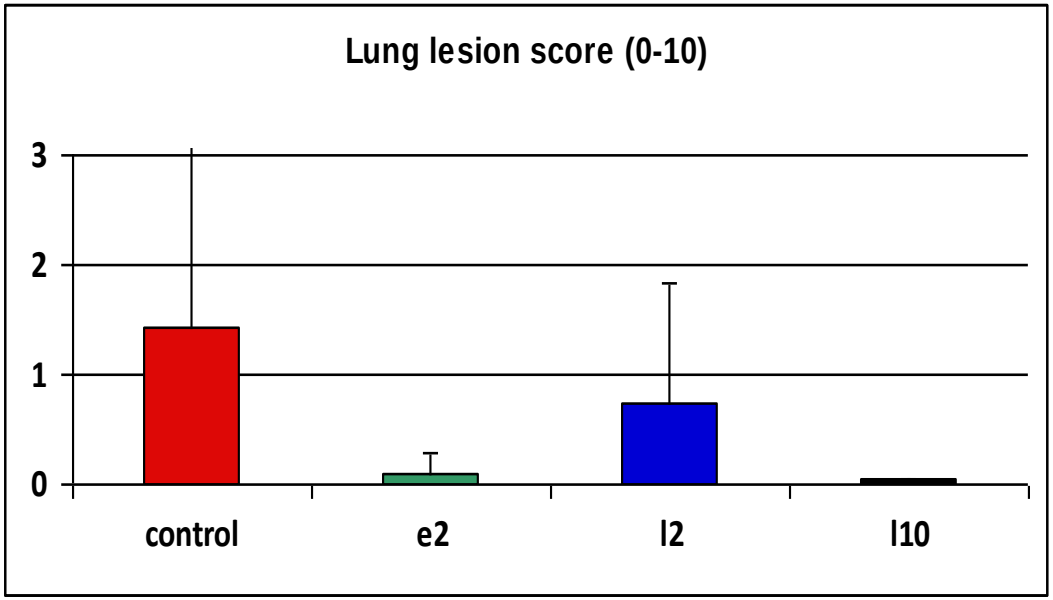
Detection of *M. haemolytica* in BAL



Clinical score



Pulmonary lesions



- Typical lesions of *M. haemolytica*
- Moderate extension and severity
- Increased frequencies in control and L2 groups

Discussion

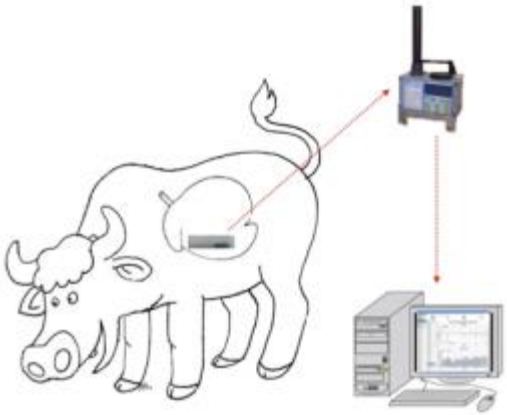
- E2 *vs* L2
  - Early treatment ⇨ fast eradication of bacterial load
  - No pulmonary lesions

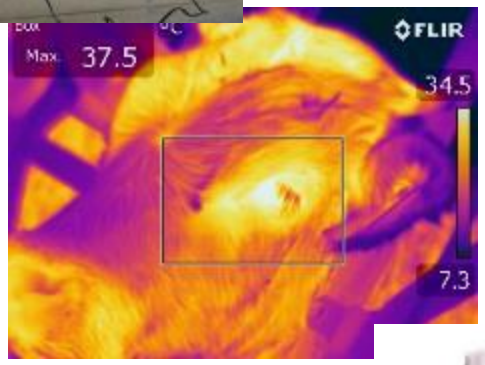
- E2 *vs* L10
  - Equivalence on bacteriological and clinical issues ⇒ how perform a fast assessment of the bacterial charge to adjust antibiotic regimen ??
- Sustainability
  - Repeatability among pathogens and molecules?
  - Evaluating the treatment « window »
  - Impact of the lower dose on commensal flora

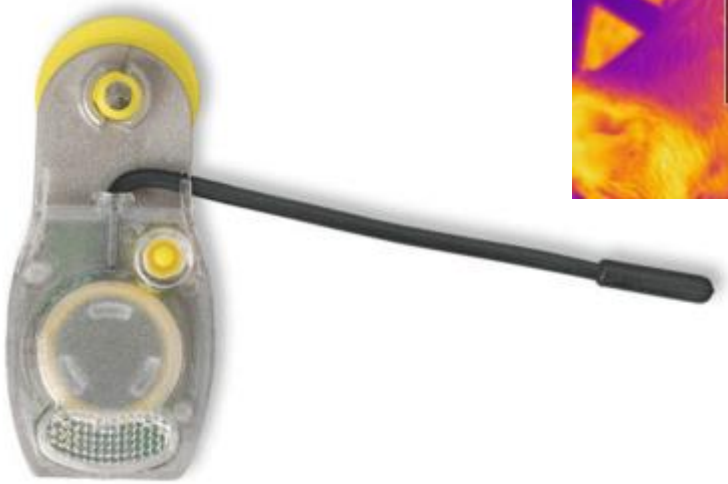
Difficulties for a very early treatment with a lower dose

- Early diagnostic
- Regulatory considerations
- Marketing consideration

Fever Alert:
fever tags, intraruminal transponders, eye temperature, locomotor activity…., .







Regulatory considerations

- Difficulty to manage two dosage regimen
- EMA is against the priciple
- Difficulty to establish a dosage regimen using a dose titration

Conclusions (1) efficacy

- For 3 antibiotics (marbofloxacin, cefquinome and amoxicillin), it was shown that the efficacious dose (clinical and bacteriological endpoints) was lower when treatment is initiated early

Conclusion (2)
Resistance selection

- In the case of resistance selection at the infectious site, for a given dose, early treatments were always associated with less selection for resistant bacteria than the late treatments.

Conclusions (3)
gut flora

- Using a lower doses thanks to an early treatment can improve the selectivity of antibiotics regarding the gut flora

Conclusion (4)
other expected effects of a low dose

- Reduction of the overall antibiotic consumption
- Limitation of the environmental contamination

Overall conclusion on metaphylaxis

- It is not acceptable to condemn metaphylaxis (control) by the argument that it is a collective treatment i.e. ineluctably as an overuse of antibiotics especially if we are in position to optimise (decrease) dosage regimen and condition of use of this kind of administration