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Effects of Early *Versus* Late Treatments by Marbofloxacin in a Mouse-Model of *Pasteurella multocida* Pulmonary Infection

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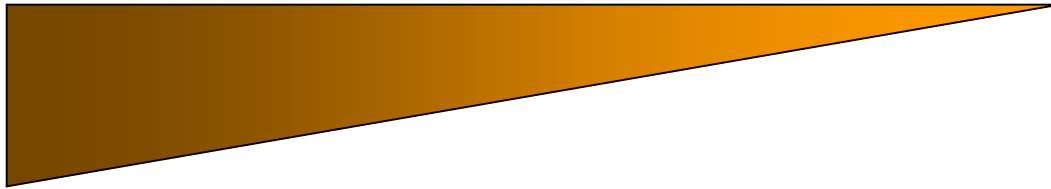
Antibiotics in food animals

Prophylaxis and Metaphylaxis are the major contributors to antibiotics consumption
Collective and massive administrations on all animals in a group
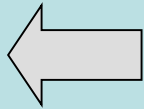Oral route
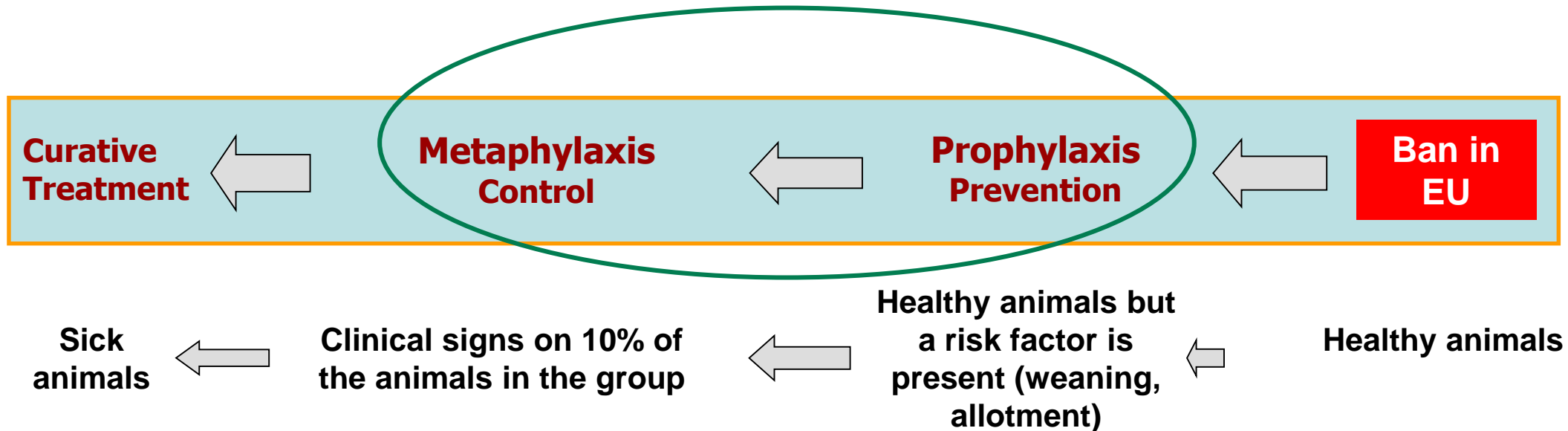
Curative Treatment ← **Metaphylaxis Control** ← **Prophylaxis Prevention** ← **Ban in EU**

Sick animals ← Clinical signs on 10% of the animals in the group ← Healthy animals but a risk factor is present (weaning, allotment) ← Healthy animals

Antibiotics in food animals
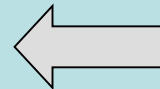
Disease ▰ **Health**
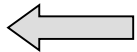
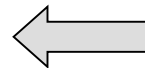**Curative Treatment** ← **Metaphylaxis Control** ← **Prophylaxis Prevention**

Sick animals ← **Clinical signs on 10% of the animals in the group** ← **Healthy animals but a risk factor is present (weaning, allotment)**
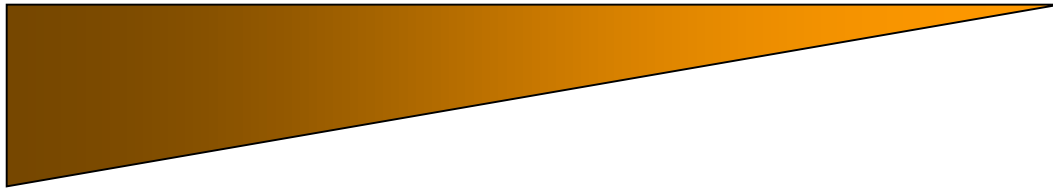
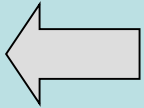# Antibiotics in food animals

Disease   **Health**
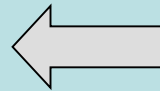
Curative Treatment	←	Metaphylaxis Control	←	Prophylaxis Prevention

High

Bacterial load (infectious site)

←   **Low**   ←   No

Our hypothesis

Sick animals

Curative treatments

No Clinical signs

Later → Earlier

HIGH bacterial load

Bacterial load (infectious site)

LOW bacterial load

The size of the bacterial load at the infectious site influences antimicrobial efficacy and resistance selection

Objectives

To *in vivo* assess the impact of **early versus late treatments** with a fluoroquinolone on :

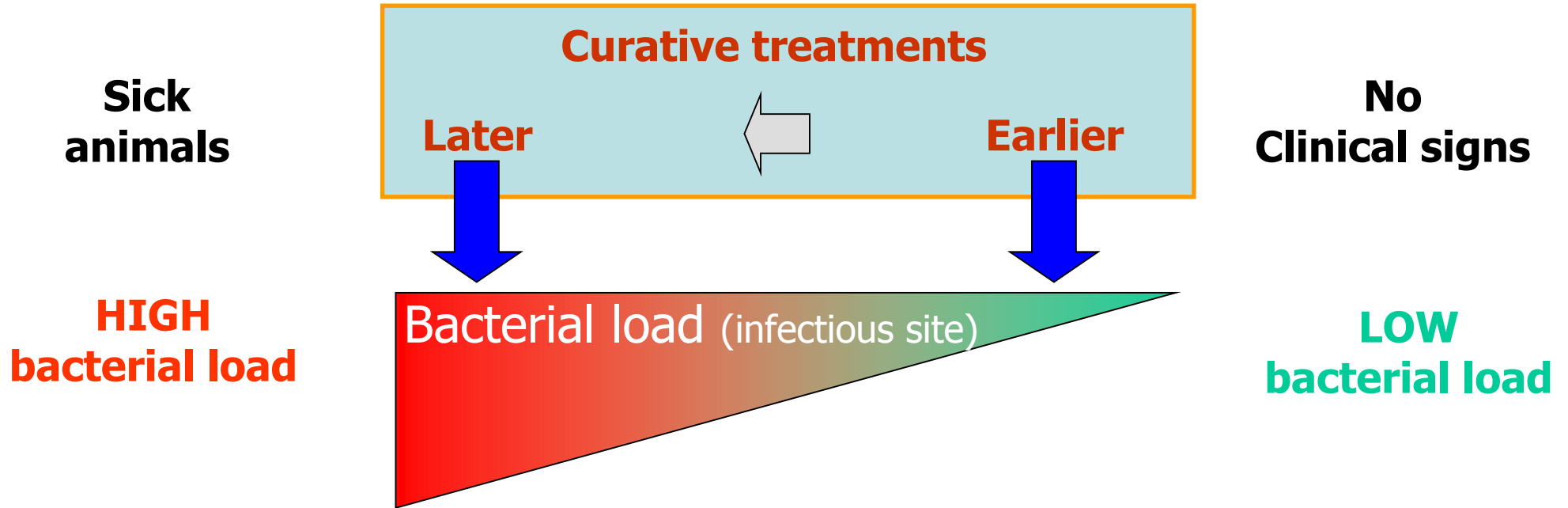1. **Clinical cure**

2. **Microbiological cure**

3. **Selection of resistant pathogens**

The methodology (1)

Progression of the infection

anorexia
lethargy
dehydration

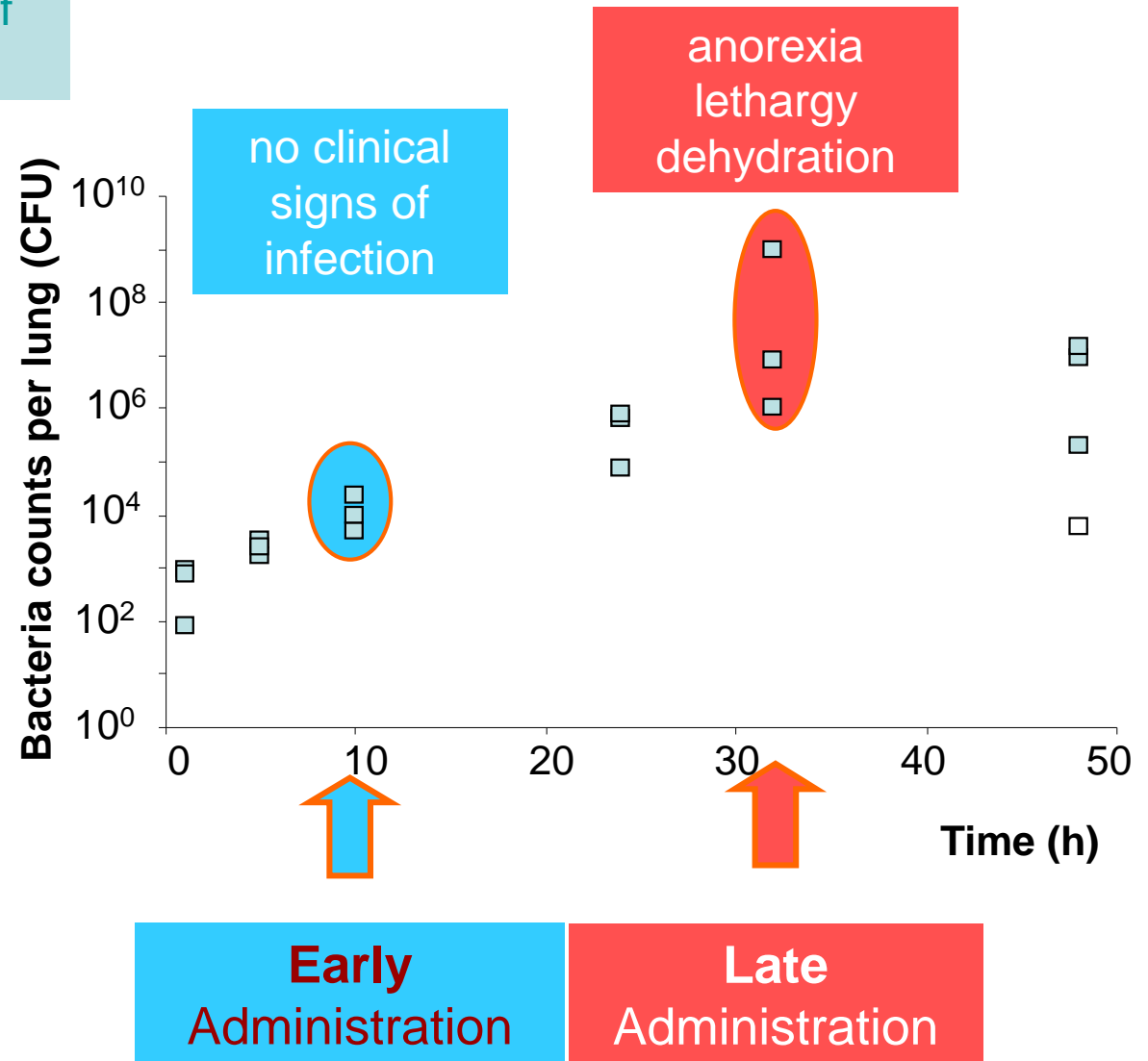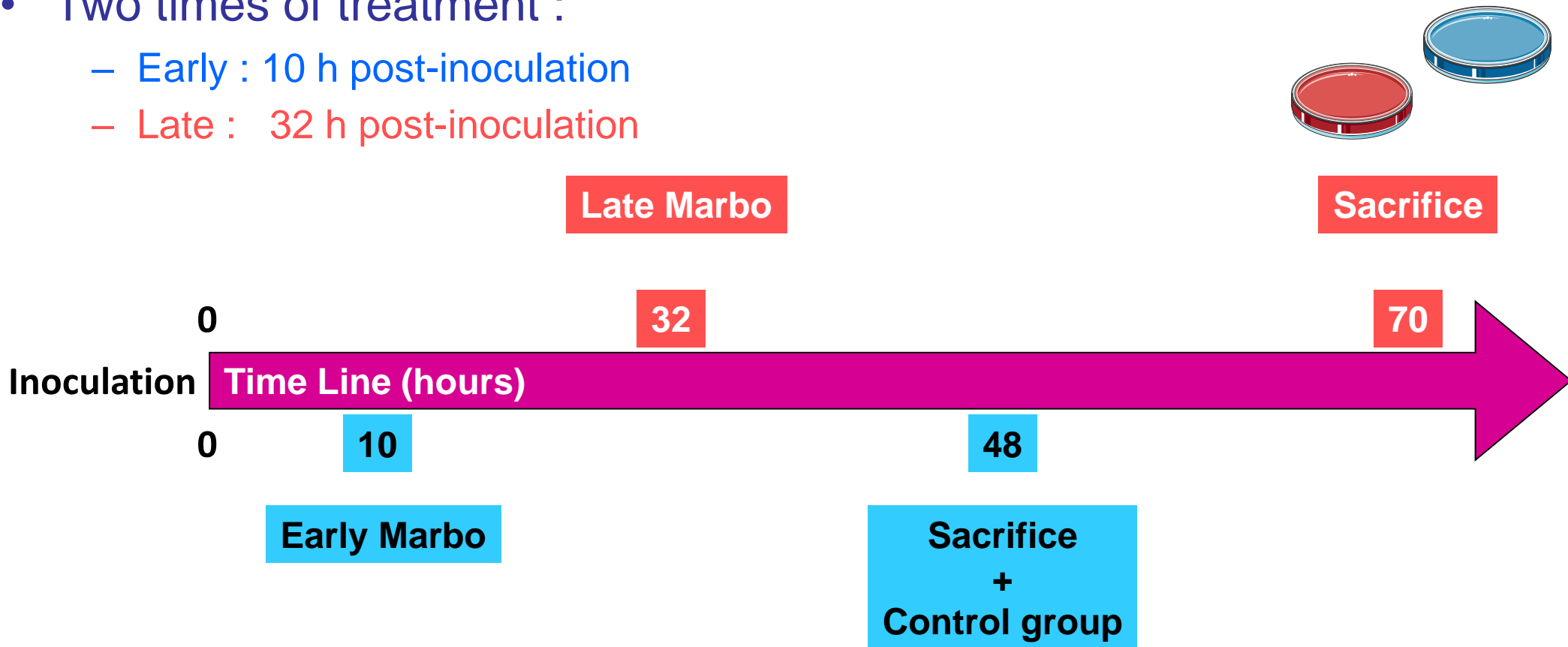no clinical signs of infection

Intratracheal inoculation of 1 000 CFU/lung of *Pasteurella multocida*

Third generation FQ Marbofloxacin
MIC = 0.016 µg/mL
MPC = 0.256 µg/mL

Bacteria counts per lung (CFU)

10^{10}

10^8

10^6

10^4

10^2

10^0

0   10   20   30   40   50

Time (h)

Early Administration

Late Administration

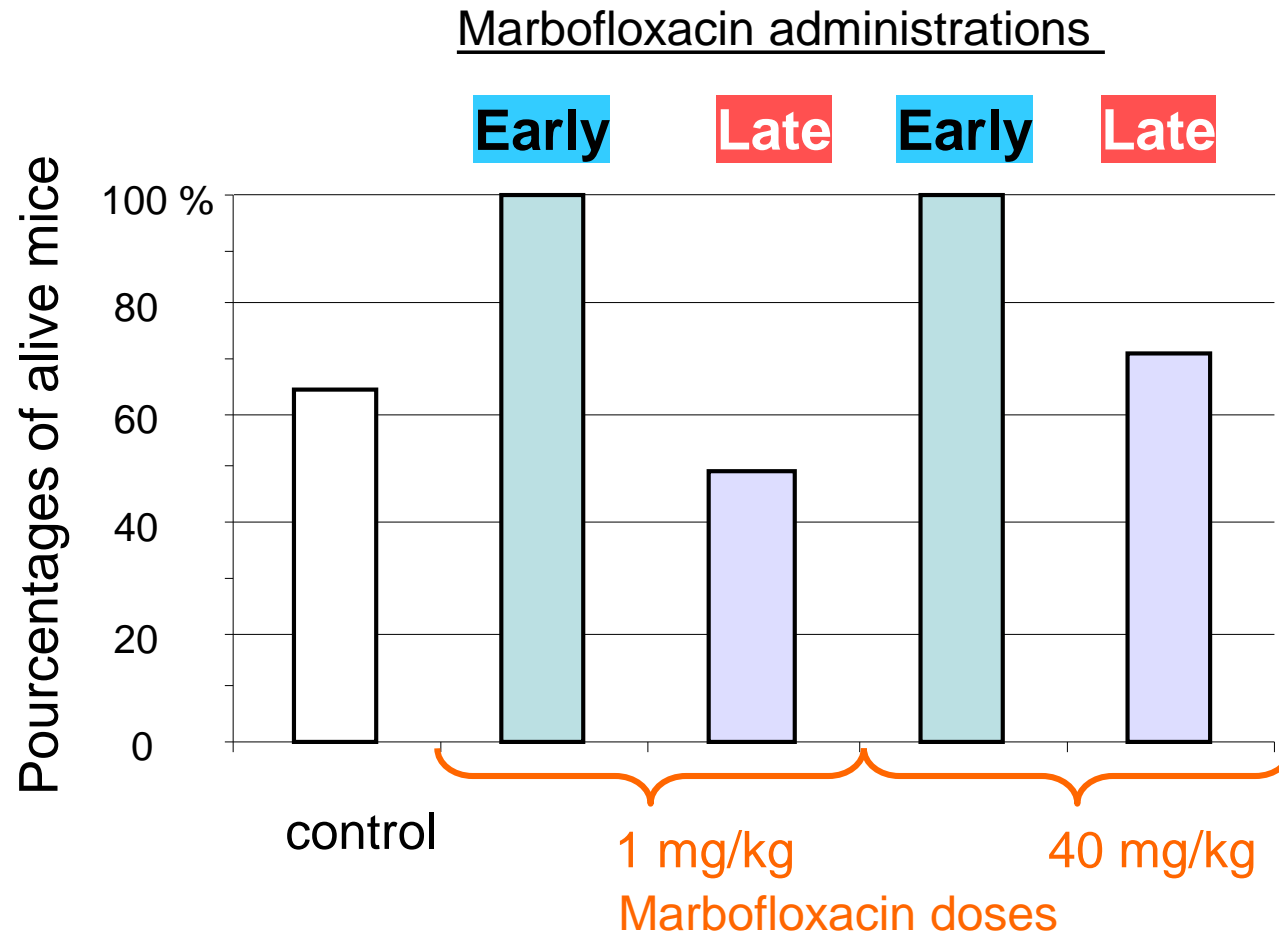# The methodology (2)

- Two times of treatment :
  - Early : 10 h post-inoculation
  - Late :   32 h post-inoculation

Late Marbo

Sacrifice

0   **32**   **70**

Inoculation Time Line (hours)

**0**   **10**   **48**

Early Marbo

Sacrifice + Control group

- Two marbofloxacin doses :
  - Low :   1 mg/kg
  - High : 40 mg/kg

The results – 1. Clinical outcome (survival)

Marbofloxacin administrations

Early **Late** **Early** **Late**

Observations : 38 hours after marbofloxacin administration
or 48 hours after infection for the control group and the « early group »

The results – 1. Clinical outcome (survival)

Marbofloxacin administrations

Early   Late   Early   Late

Pourcentages of alive mice

100 %
80
60
40
20
0

control

1 mg/kg   40 mg/kg

Marbofloxacin doses

Observations : 38 hours after marbofloxacin administration
or 48 hours after infection for the control group and the « early group »
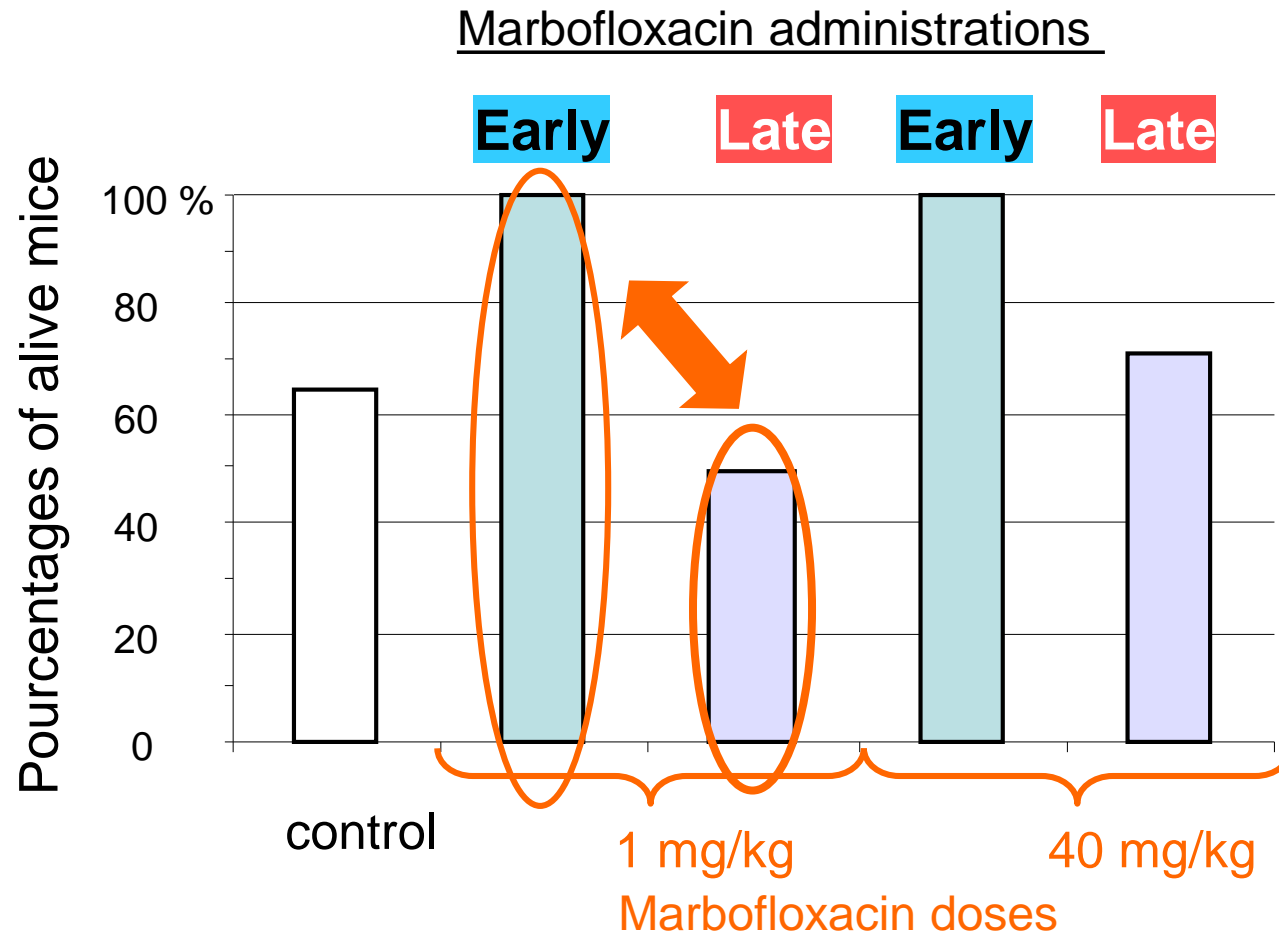
The results – 1. Clinical outcome (survival)
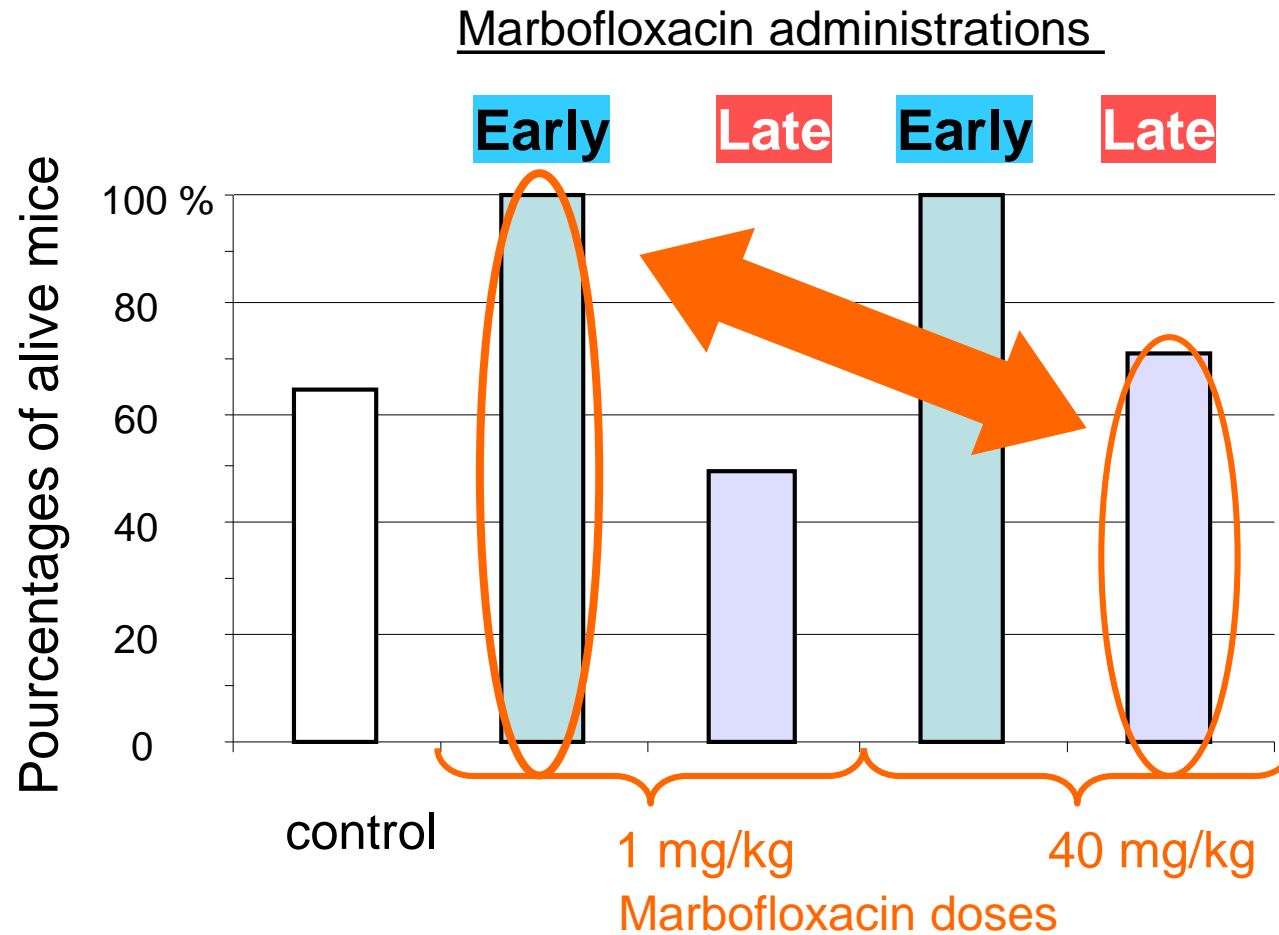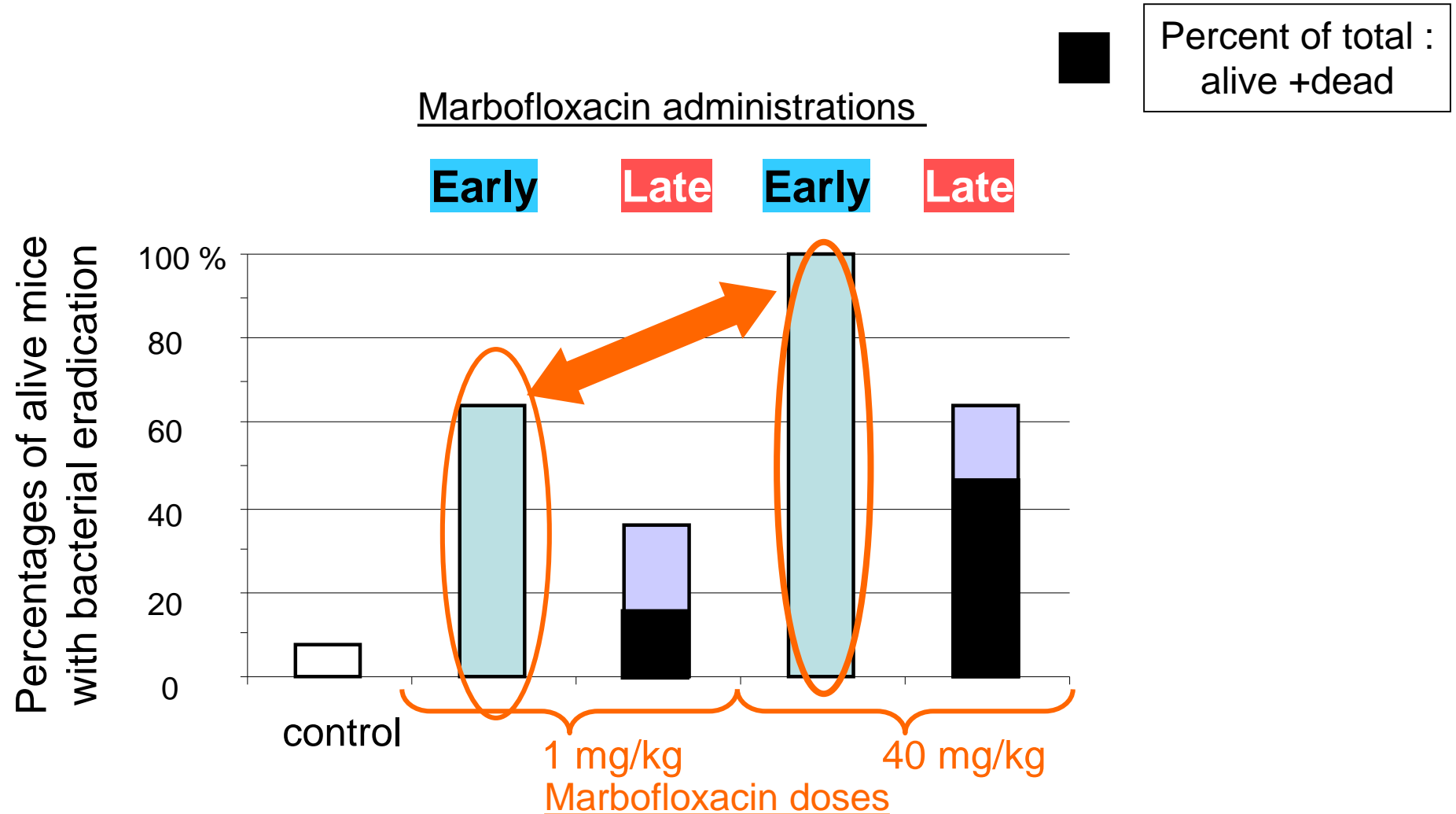

Marbofloxacin administrations

Observations : 38 hours after marbofloxacin administration
or 48 hours after infection for the control group and the « early group »

The results – 2. Microbiologial outcome (eradication)

Observations : 38 hours after marbofloxacin administration
or 48 hours after infection for the control group and the « early group »

The results – 2. Microbiologial outcome (eradication)

Marbofloxacin administrations

Early   Late   Early   Late

Percentages of alive mice with bacterial eradication

100 %
80
60
40
20
0

control
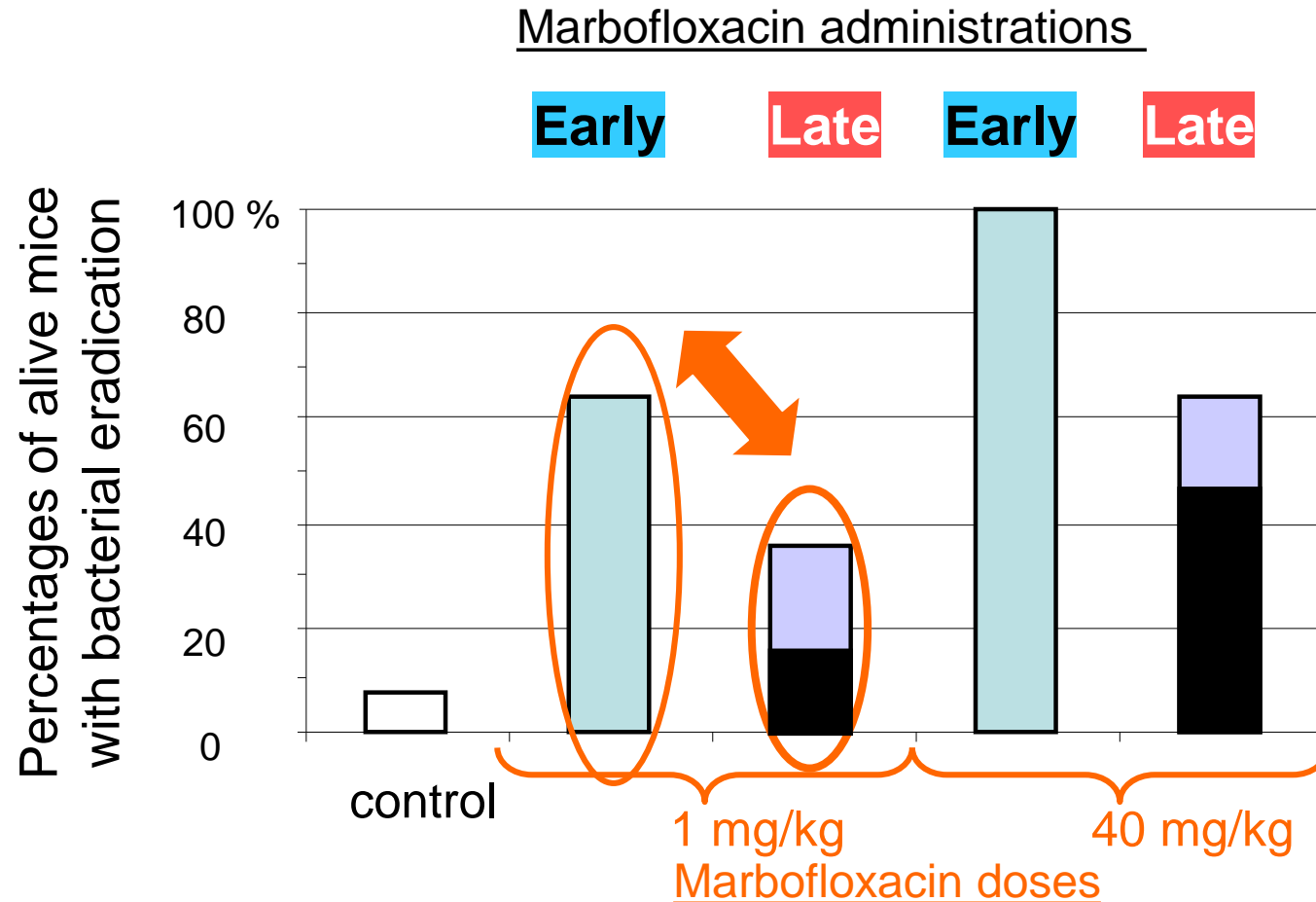
1 mg/kg   40 mg/kg
Marbofloxacin doses

Observations : 38 hours after marbofloxacin administration
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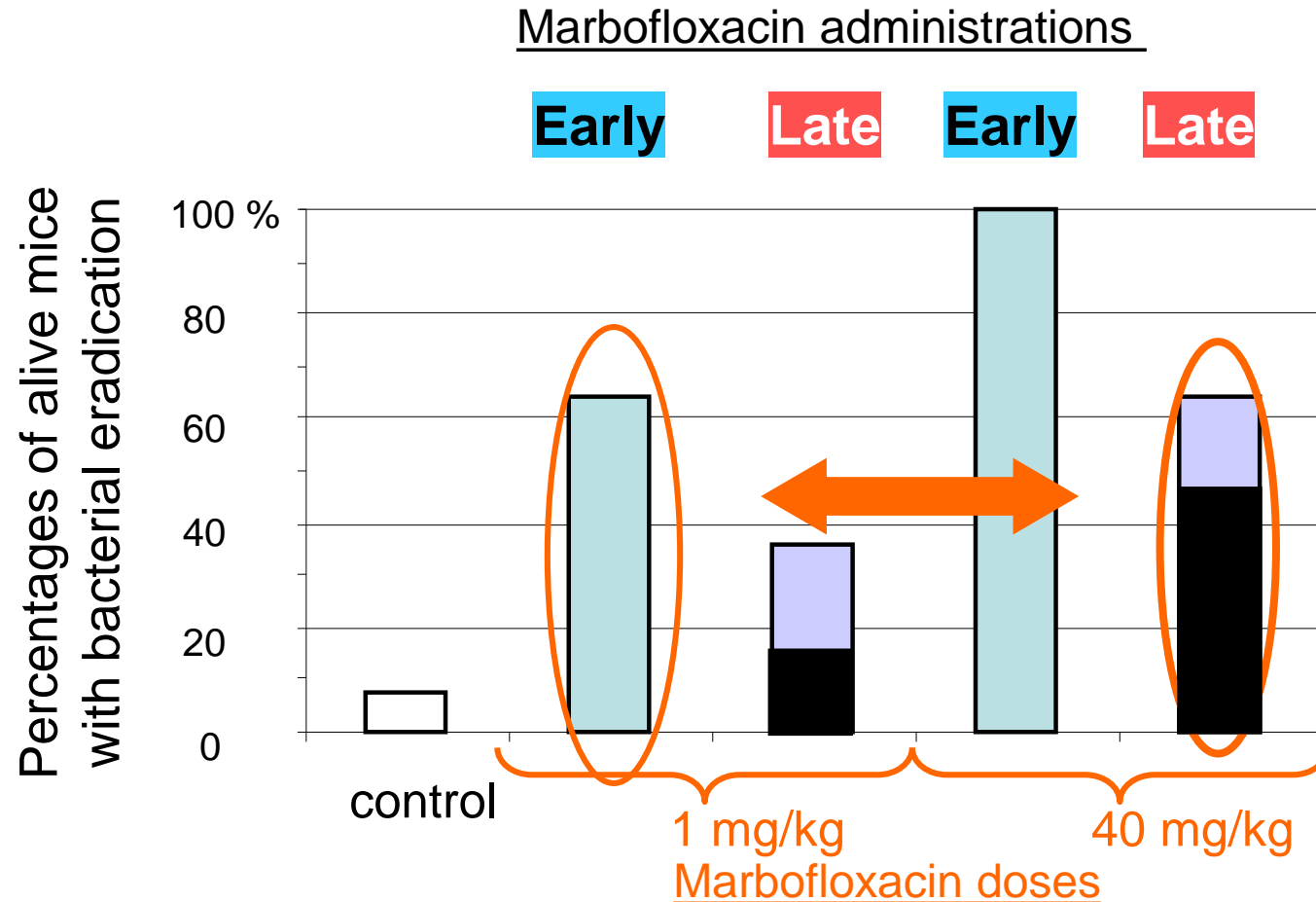
The results – 2. Microbiologial outcome (eradication)

Marbofloxacin administrations

Observations : 38 hours after marbofloxacin administration
or 48 hours after infection for the control group and the « early group »

The results − 3. Selection of resistant bacteria

" RESISTANT BACTERIA" :
Bacteria growing in the
presence of marbofloxacin
0.128 µg/mL = half MPC

Marbofloxacin administrations

Early   **Late**   **Early**   **Late**

Percentages of alive mice with resistant bacteria

50 %
40
30
20
10
0

control

1 mg/kg   40 mg/kg

Marbofloxacin doses

✳ No resistant bacteria

Observations : 38 hours after marbofloxacin administration
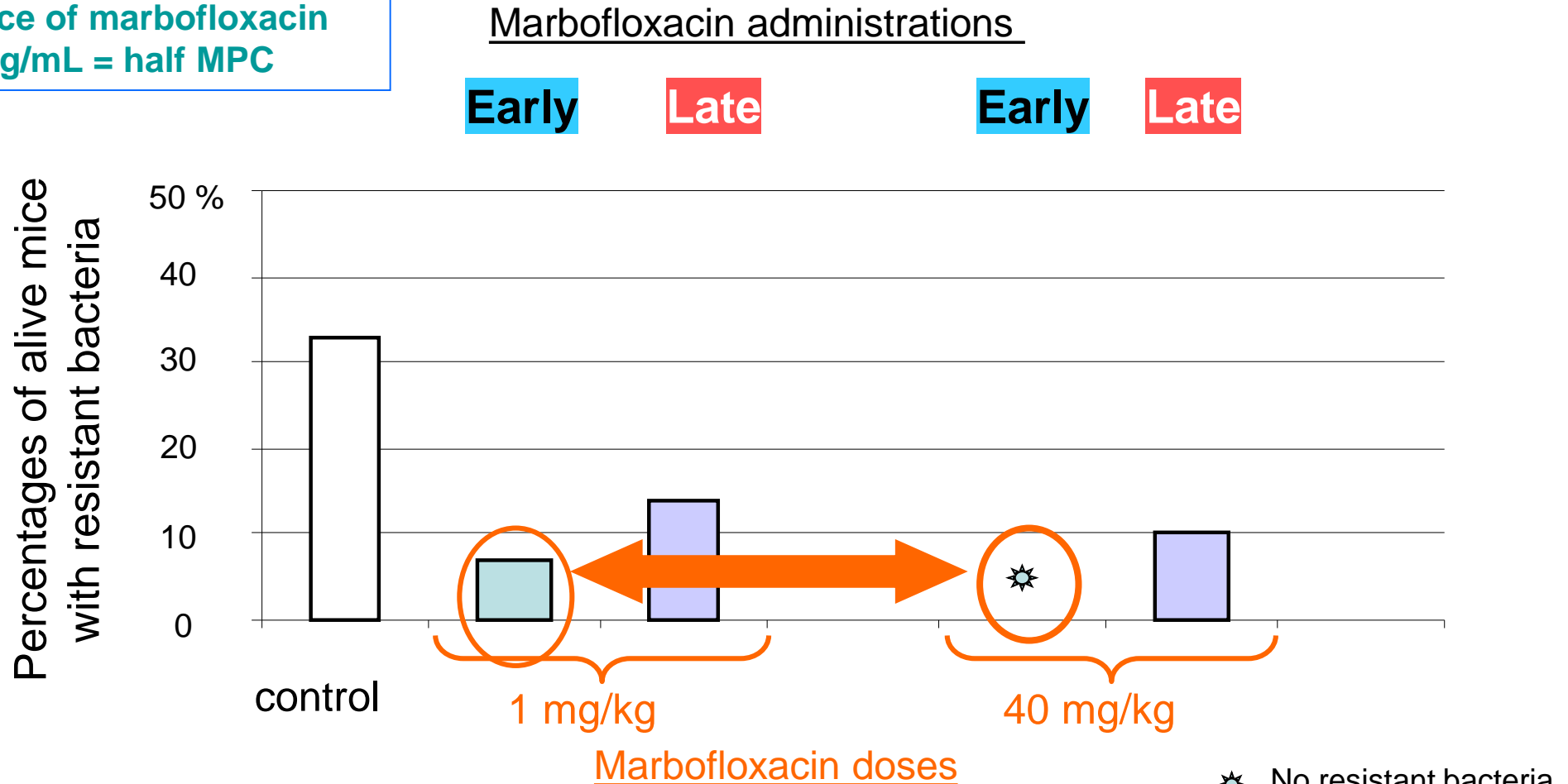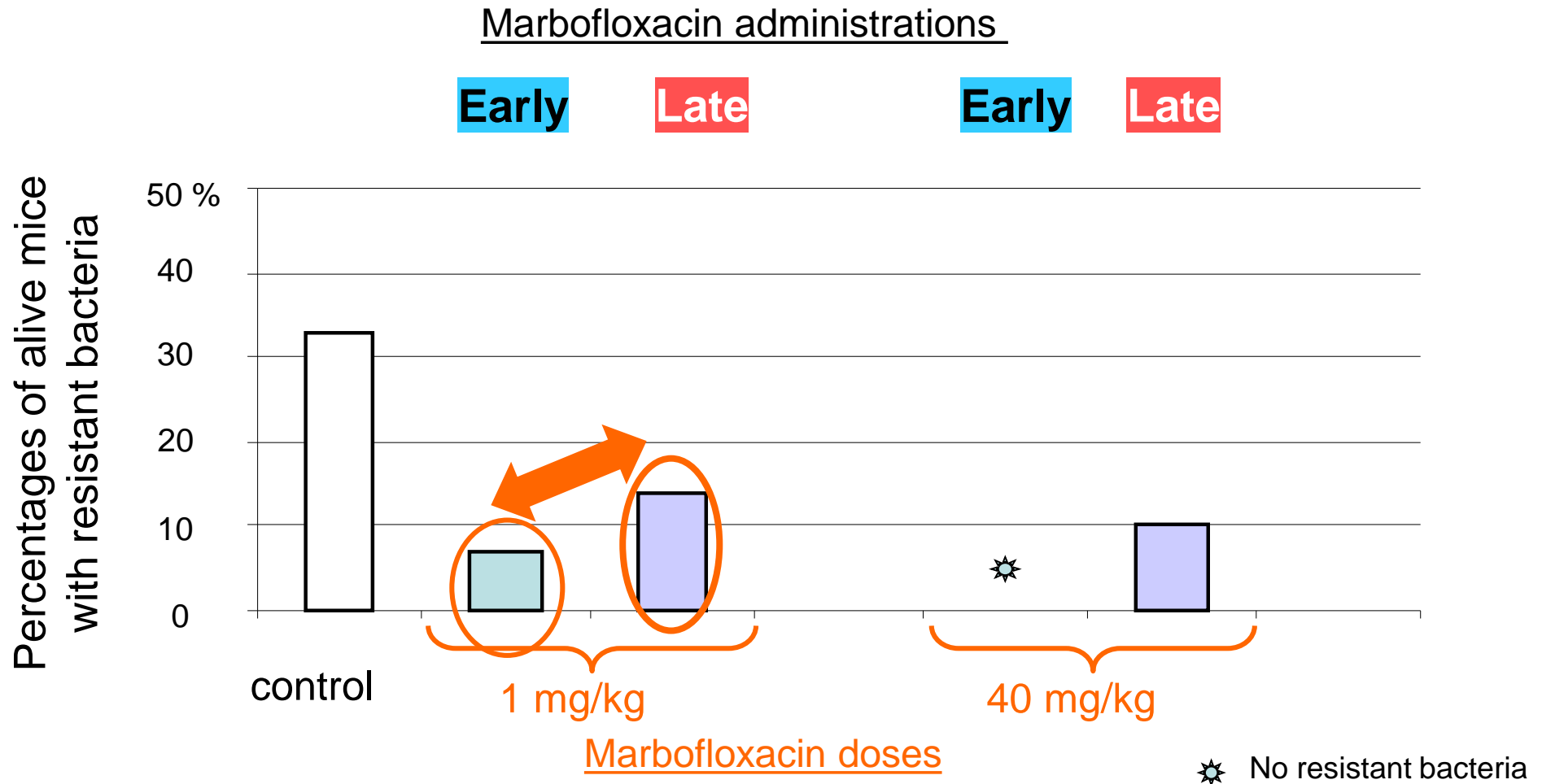or 48 hours after infection for the control group and the « early group »

The results – 3. Selection of resistant bacteria

Marbofloxacin administrations

Early **Late** **Early** **Late**

Percentages of alive mice with resistant bacteria

50 %

40

30

20

10

0

control

1 mg/kg

40 mg/kg

Marbofloxacin doses

✹ No resistant bacteria

Observations : 38 hours after marbofloxacin administration
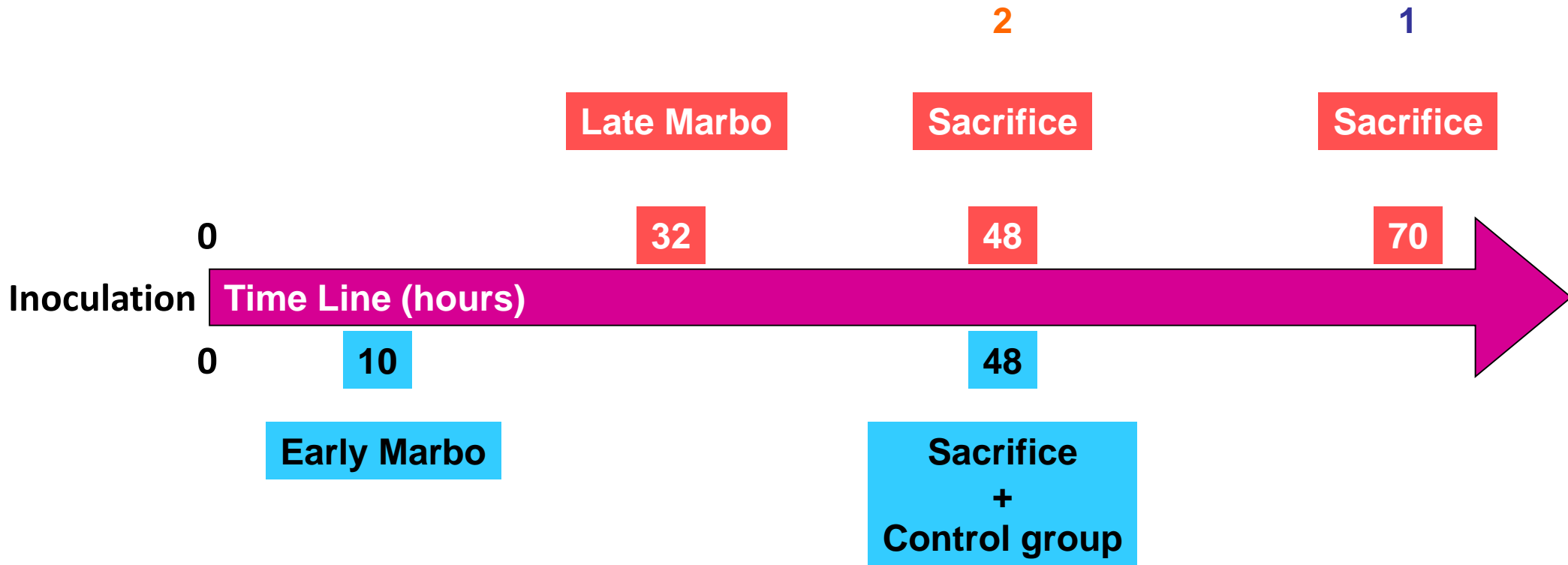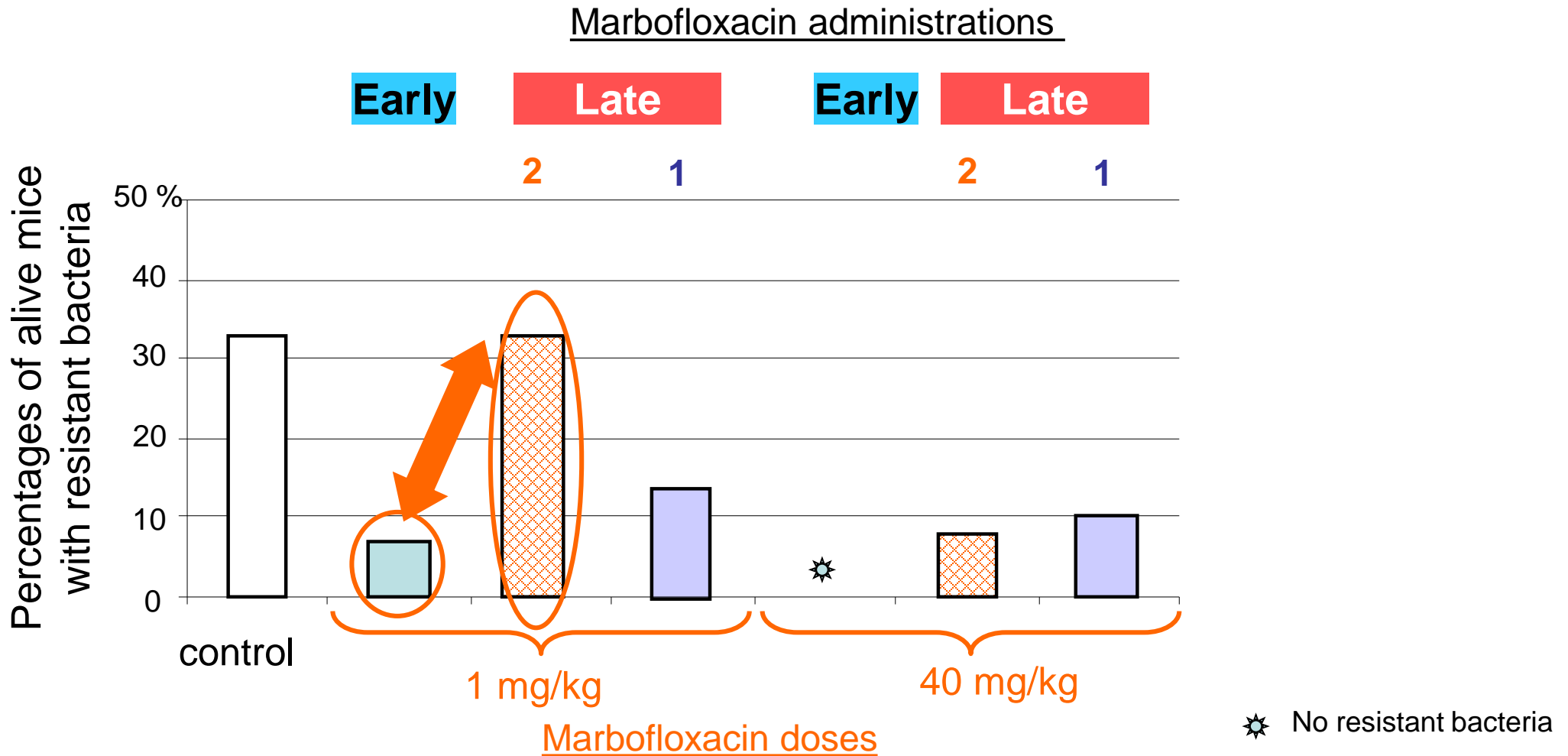or 48 hours after infection for the control group and the « early group »
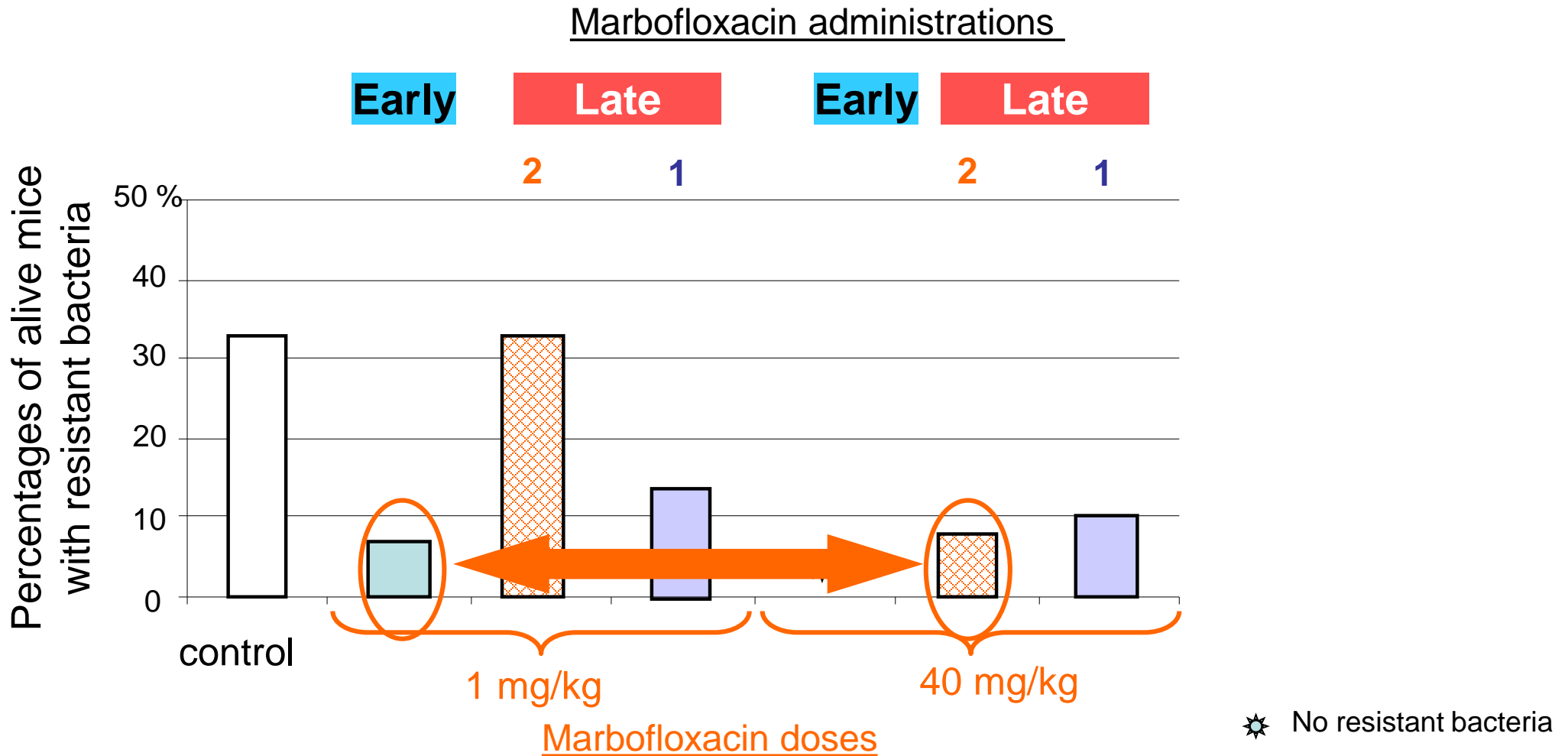
The methodology (3)

The results – 3. Selection of resistant bacteria

The results – 3. Selection of resistant bacteria

To summarize

- For the same dose of marbofloxacin, early treatments (10 hours after the infection) were associated to :

  – more frequent clinical cure
  – more frequent bacteriological cure
  – less frequent selection of resistant bacteria

  Than late treatments (32 hours after the infection)

To summarize

- The early lower dose of 1 mg/kg marbofloxacin was associated to :

  – more frequent clinical cure
  – similar bacteriological cure
  – similar selection of resistant bacteria

  Than the late higher dose of 40 mg/kg

Perspectives and conclusion

- Favourable features of early treatments at the individual level
    - Ferran et al. AAC 2009, Vet Microbiol 2011 / Kesteman et al., AAC 2009, AAC 2010
    - Further experiments in target species for optimization of **dose levels** and **treatment duration**

- Favourable features in terms of public health ?
    - Reduction of the selective pressure on the commensal gut flora ?
    - *Klebsiella pneumoniae* lung infection in rats : the early dose of marbofloxacin in the same animal simultaneously eradicated *KP* in the lung and selected resistant *KP* that had previously colonized the gut (Kesteman et al., AAC 2010)

- Moving early treatment from the lab to the field ?
    - Developing **methodologies for early detection** of infected animals ?
    - Treatment strategies : treatment of only detected animals or treatment of the group ?
    - Depends on the epidemiology of the infection in the group