

Intracellular models of infection to evaluate antibiotic activity

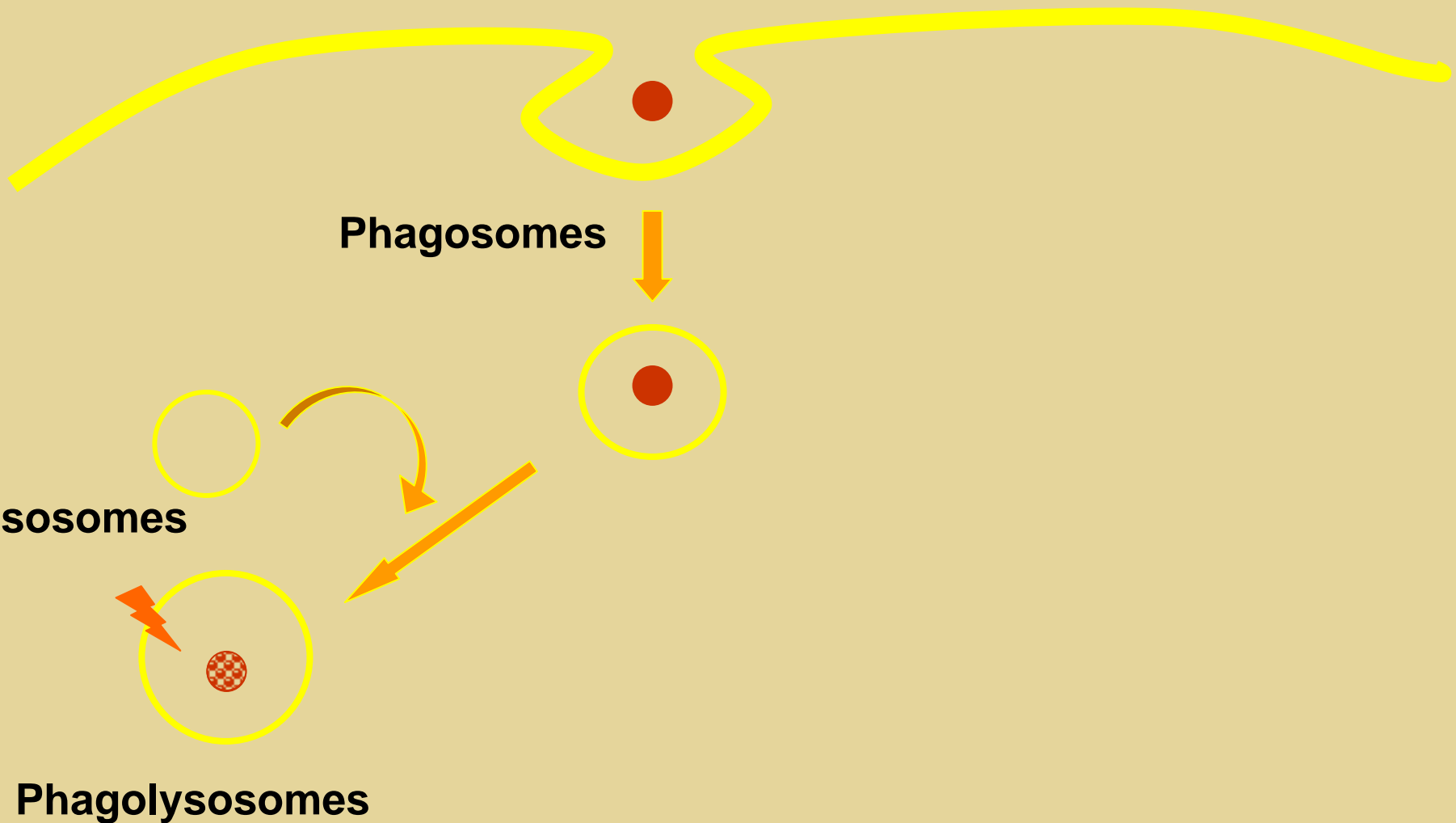
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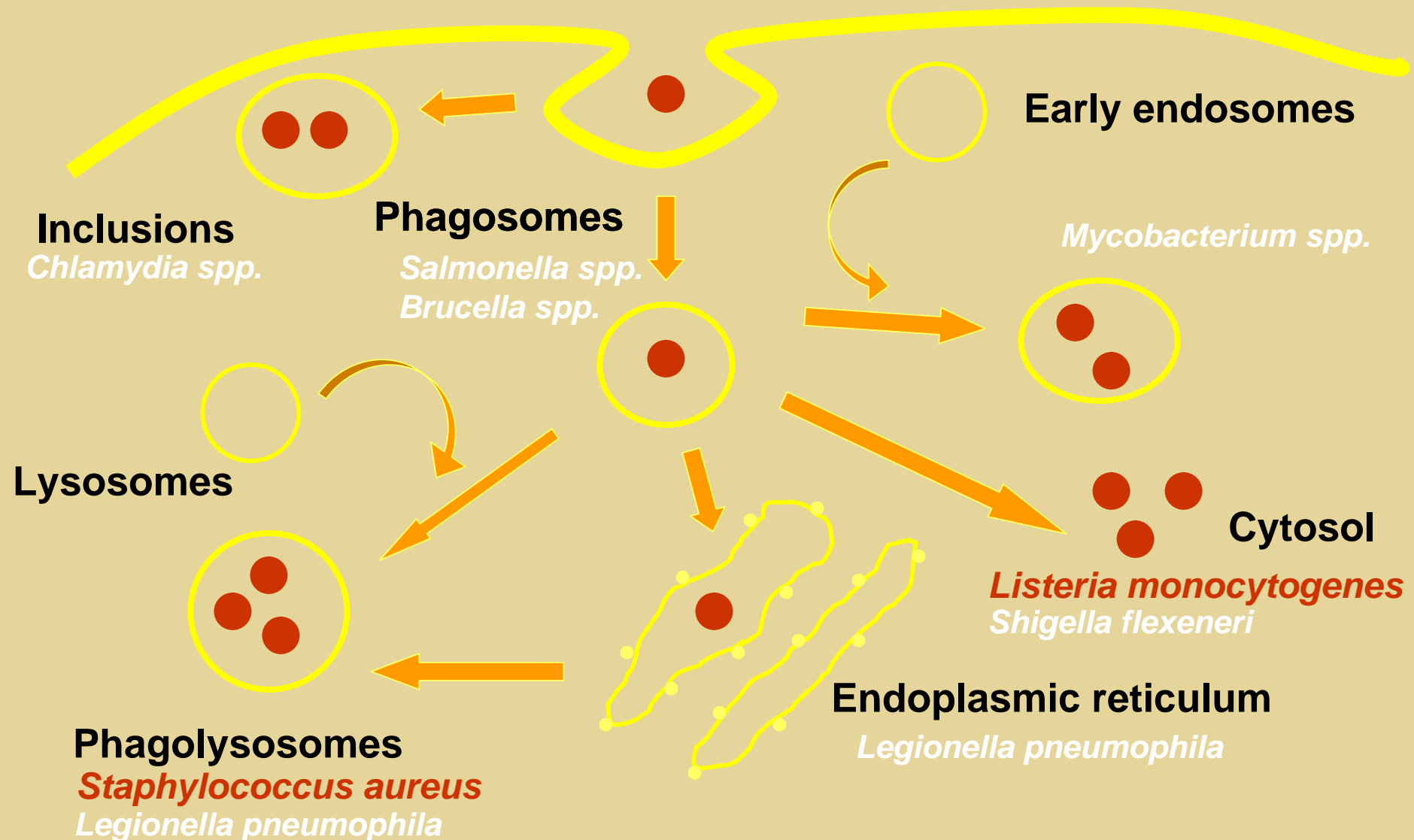
Intracellular killing of bacteria by host cell defense mechanisms

Carryn *et al*, Infect Dis Clin North Am. (2003) 17:615-34



Some bacteria can escape host cell defense mechanisms

Carryn *et al*, Infect Dis Clin North Am. (2003) 17:615-34



Setting – up models of intracellular infections

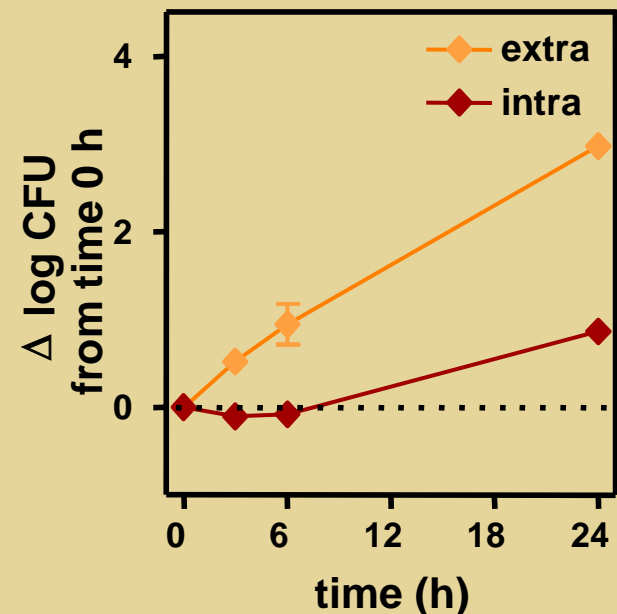
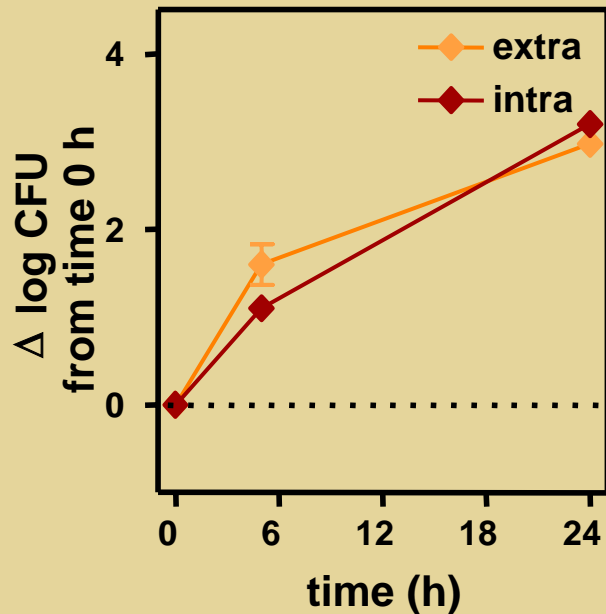
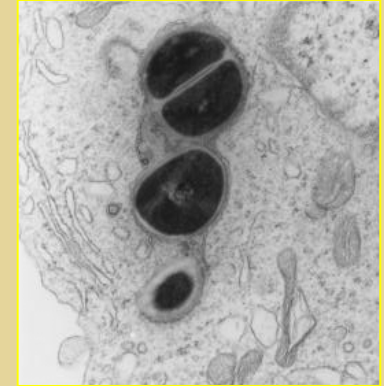
	<i>L. monocytogenes</i>	<i>S. aureus</i>
infection of THP-1 macrophages and phagocytosis	decomplemented serum; 5 bact./cell	serum-opsonized; 4 bact./cell
elimination of extracellular bacteria	washing	washing 1 h with GEN 50 mg/L
incubation for 24 h <ul style="list-style-type: none">• control: + GEN (1 X MIC)• antibiotic	1.0 mg/L Cmax	0.5 mg/L Cmax

Setting – up models of intracellular infections



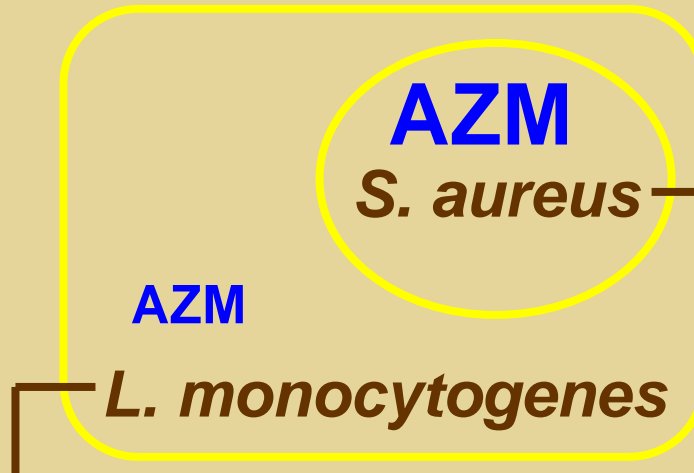
S. aureus

L. monocytogenes



Testing antibiotics : azithromycin

cellular
accumulation:
38 X

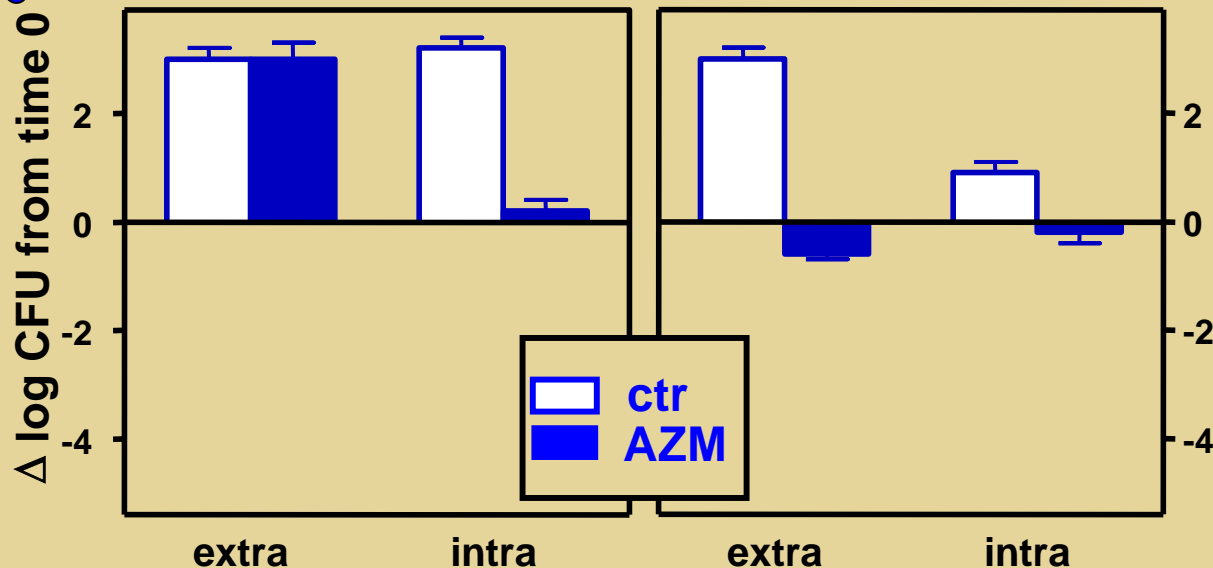


C_{max}: 0.4 mg/L

MIC *L.m.*: 0.5 mg/L

MIC *S.a.*: 0.5 mg/L

poorly active extra- and intra-cellularly !



Testing antibiotics : gentamicin

cellular
accumulation:
4.4 X

GEN
S. aureus

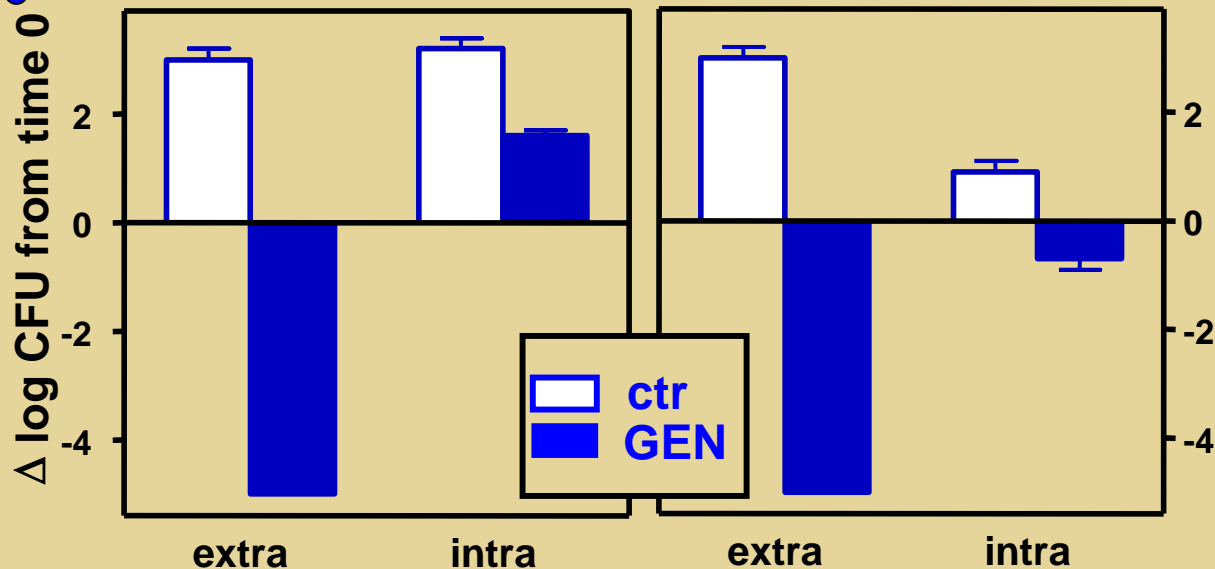
C_{max}: 18 mg/L

MIC *L.m.*: 1.0 mg/L

MIC *S.a.*: 0.5 mg/L

L. monocytogenes

highly active extra; static intra-cellularly !



Testing antibiotics : moxifloxacin

cellular
accumulation:
7.6 X

MXF

MXF
S. aureus

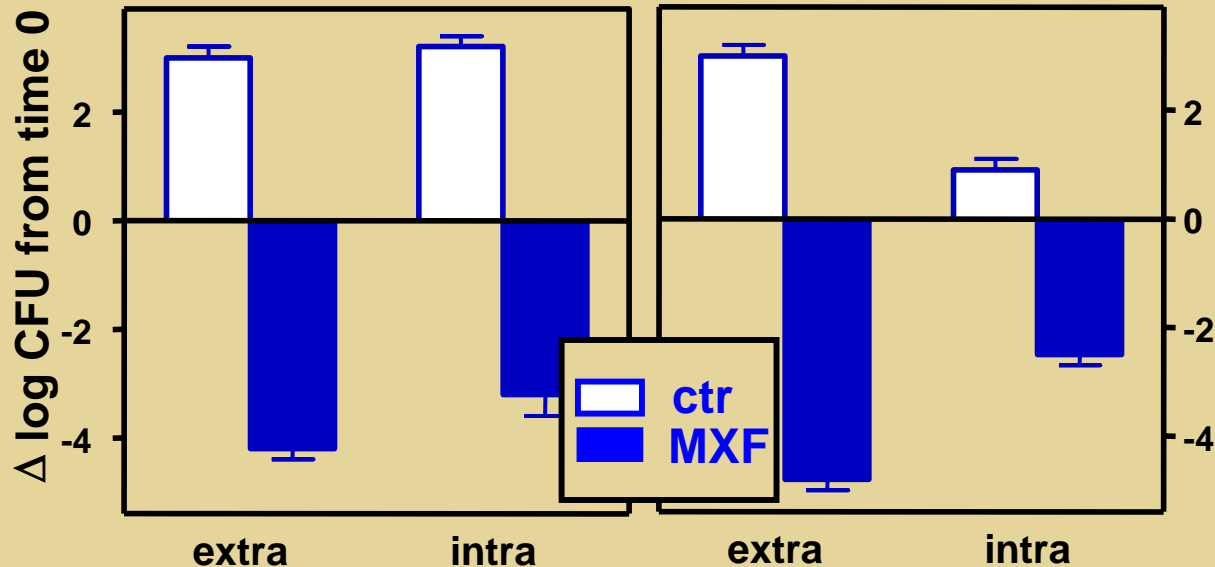
C_{max}: 4 mg/L

MIC *L.m.*: 0.5 mg/L

MIC *S.a.*: 0.06 mg/L

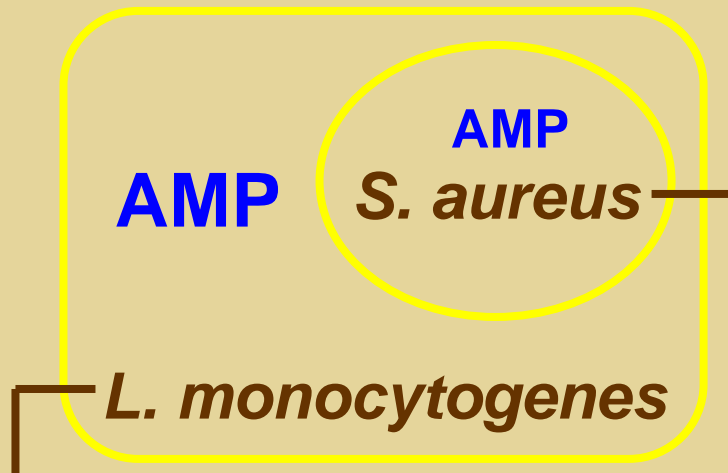
L. monocytogenes

somewhat more active extra- than intra-cellularly !



Testing antibiotics : ampicillin

cellular
accumulation:
1 X

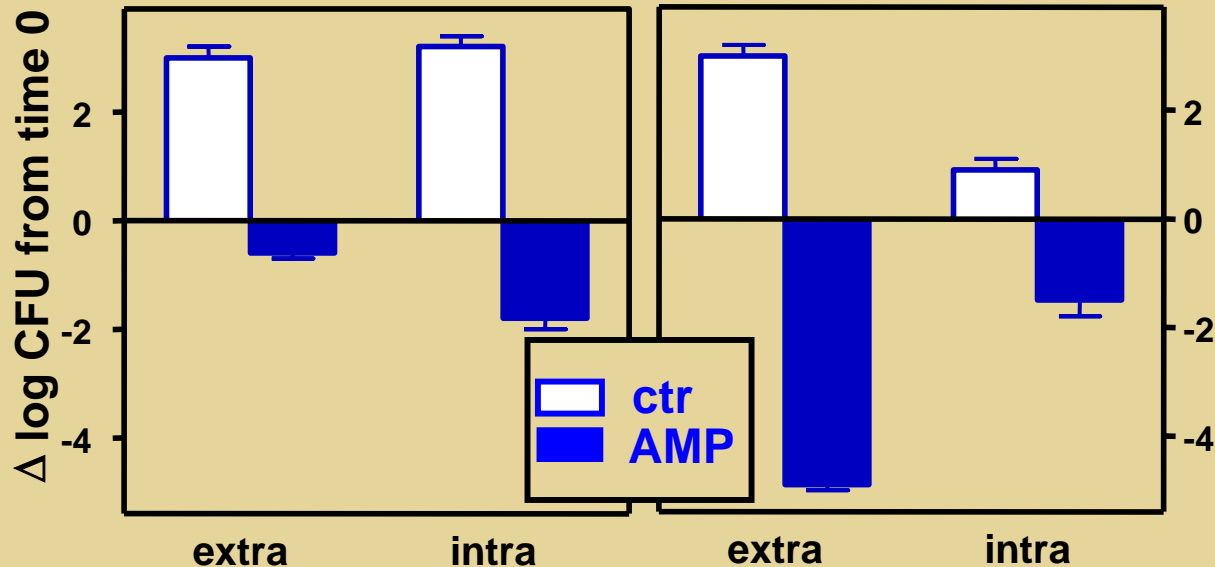


C_{max}: 50 mg/L

MIC *L.m.*: 1 mg/L

MIC *S.a.*: 0.06 mg/L

more active intra- than extra-cellularly against *L.m.* !



Intracellular activity of antibiotics: what have we learned ?

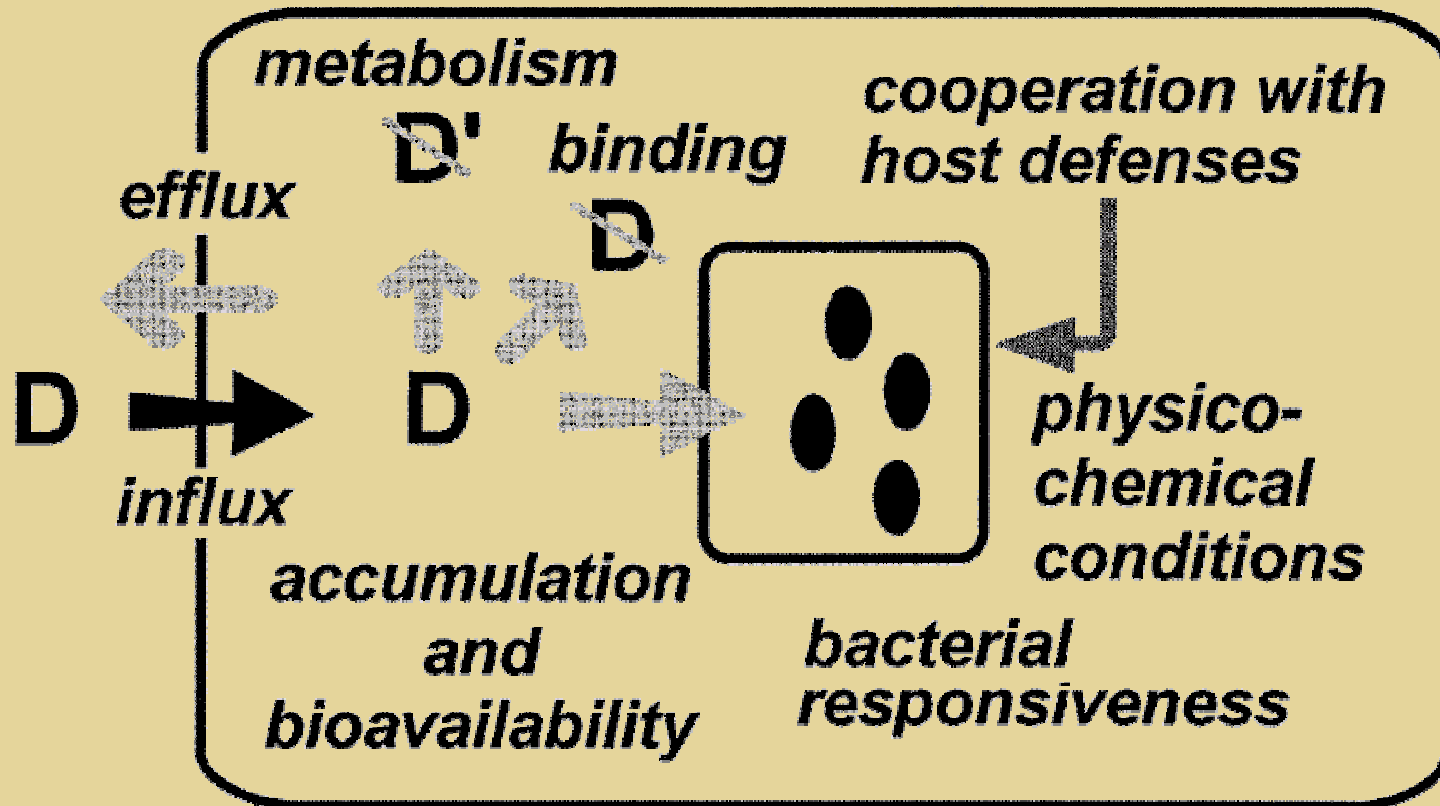
- intracellular activity variable according to the localization
 - of the bacteria
 - of the antibiotic
- intracellular activity most often lower than extracellular activity
(exception : ampicillin and *L. monocytogenes*)
- intracellular activity not predictable on the basis of
 - MIC
 - accumulation



appropriate models are needed !

Why these discrepancies ?

Intracellular PK/PD parameters should be taken into account



Take home message ...

1. identify your target
2. choose the right weapon



you may avoid serious problems ...