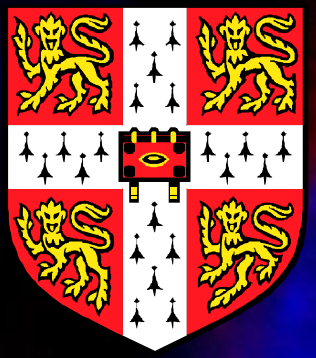
Antimicrobial treatment and pathogen behavior during invasive *Salmonella* infections



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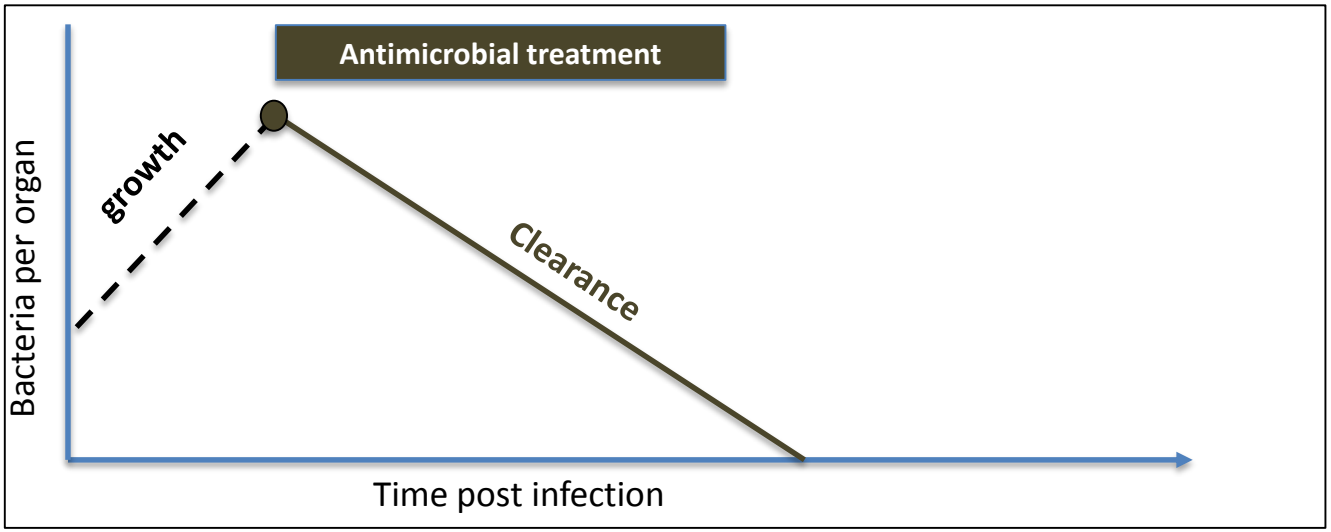
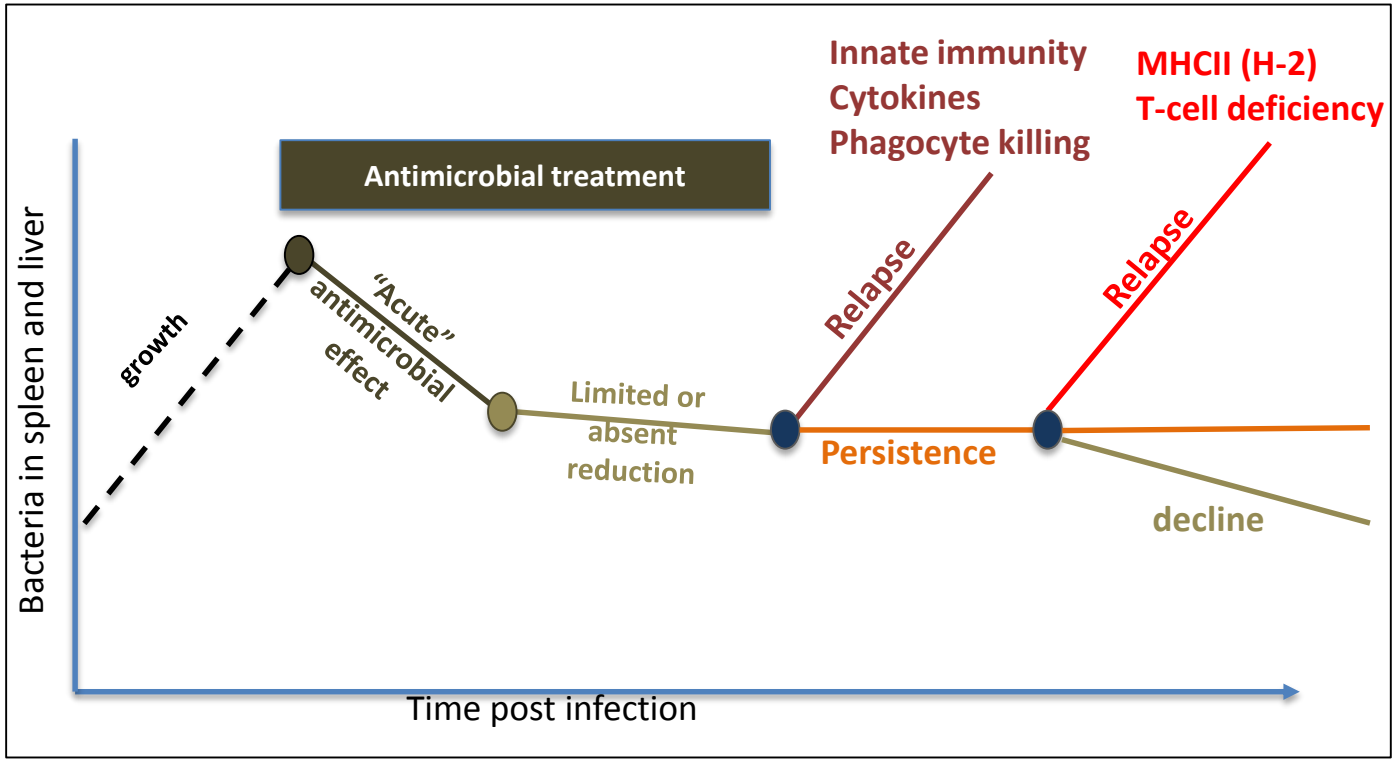
The ideal situation

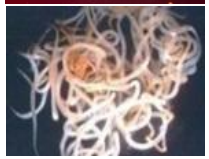


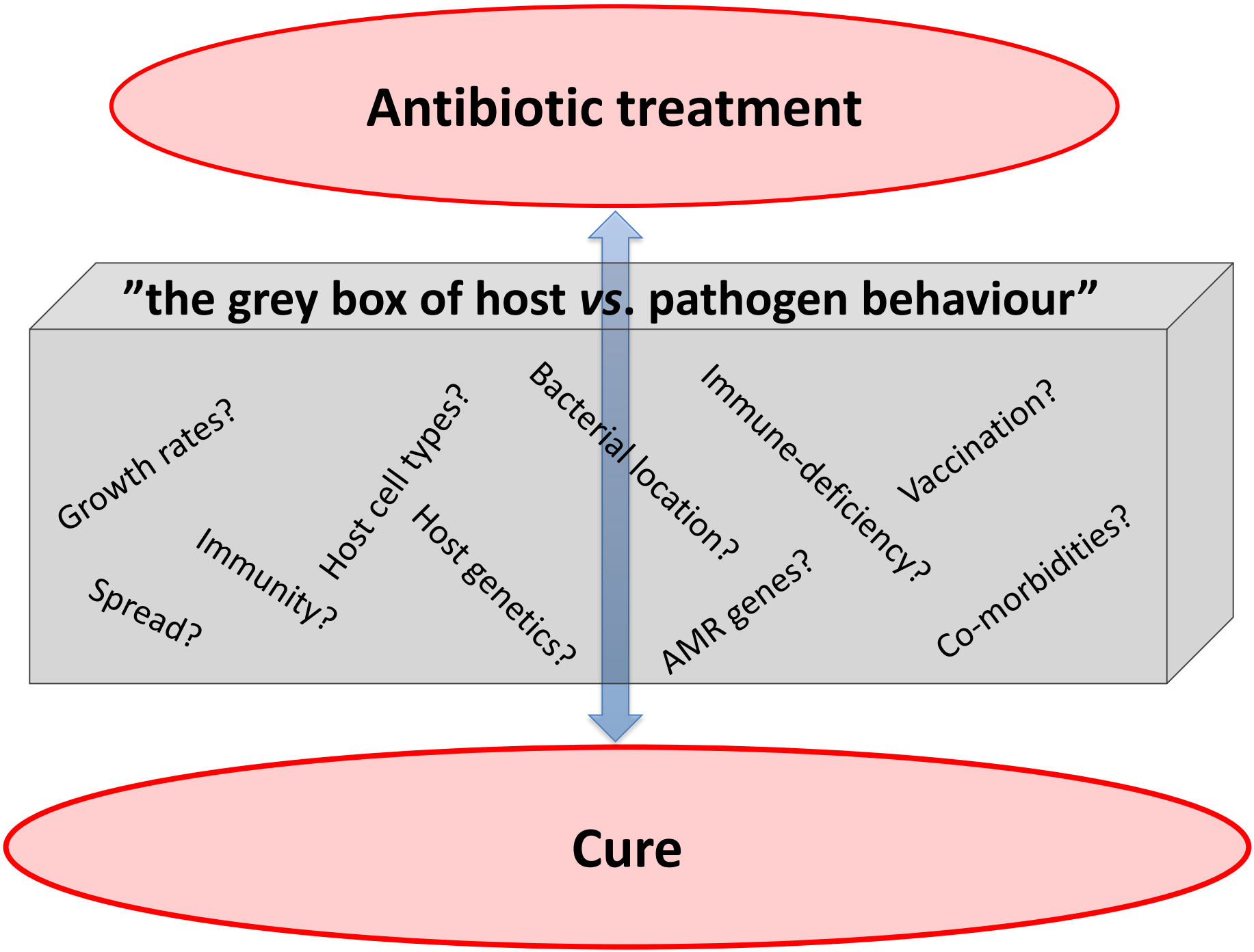
The real world

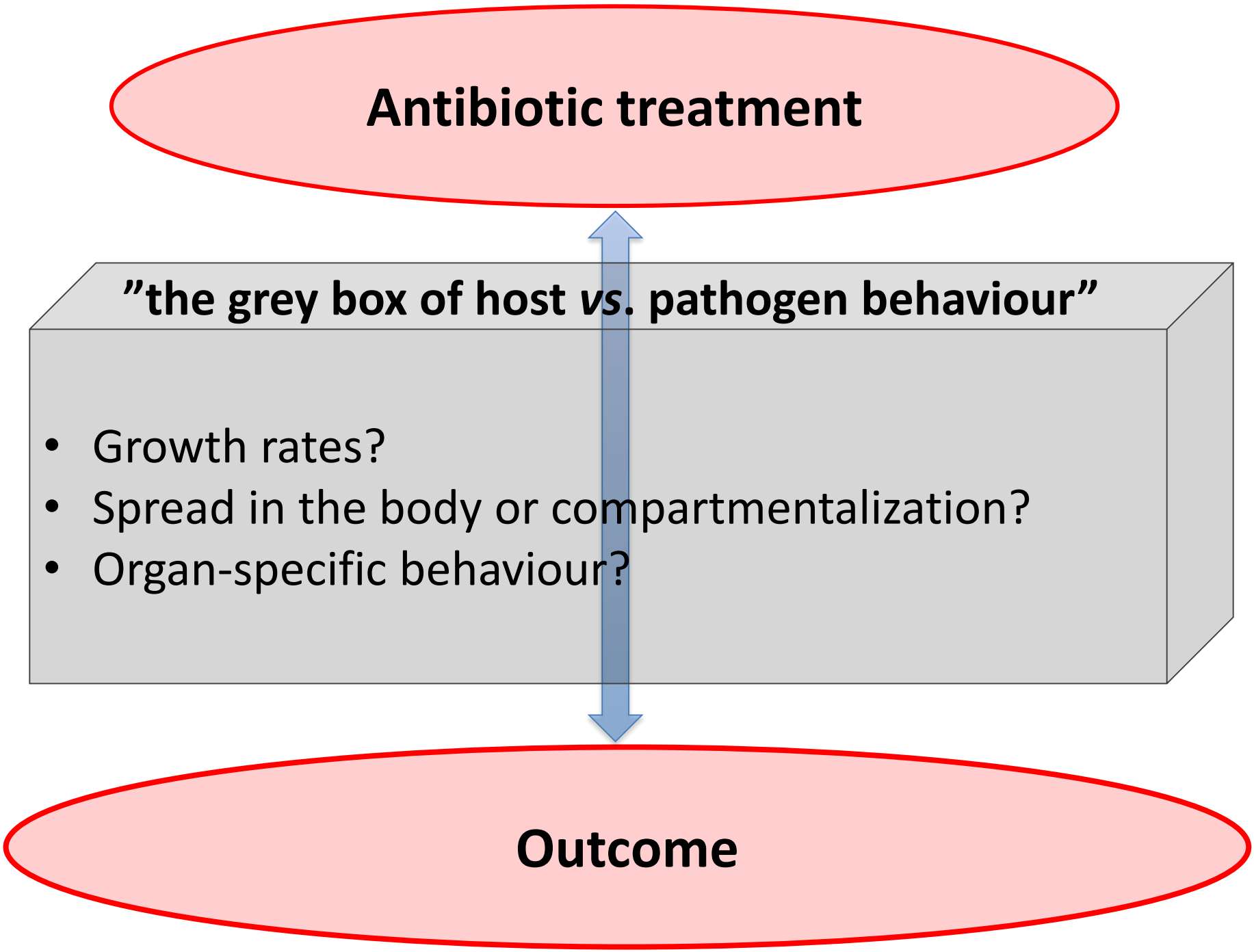
Complex scenarios and challenges to treatment and clearance

Difficulties in treatment are not just due to AMR genes!

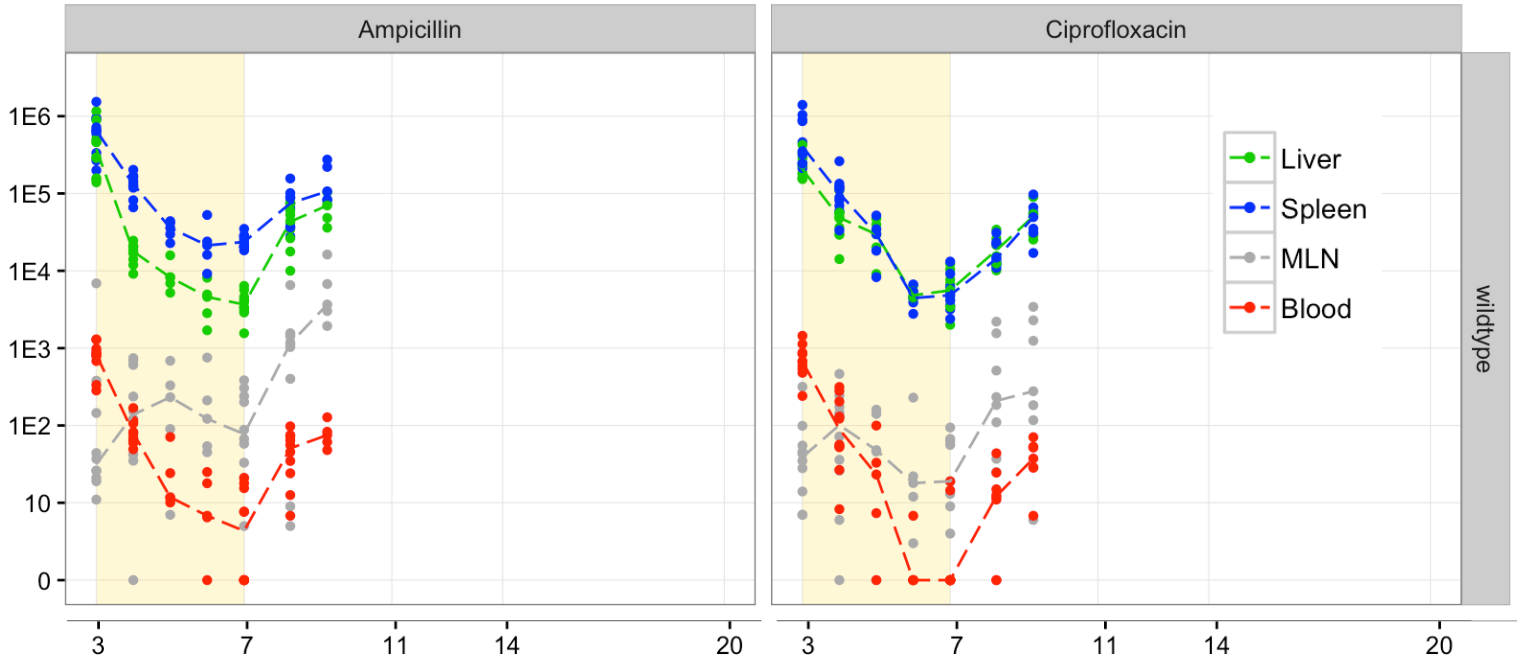





Antibiotic treatment
"the grey box of host *vs*. pathogen behaviour"
Growth rates?
Spread?
Immunity?
Host cell types?
Host genetics?
Bacterial location?
AMR genes?
Immune-deficiency?
Vaccination?
Co-morbidities?
Cure


Antibiotic treatment
”the grey box of host *vs*. pathogen behaviour”
• Growth rates?
• Spread in the body or compartmentalization?
• Organ-specific behaviour?
Outcome

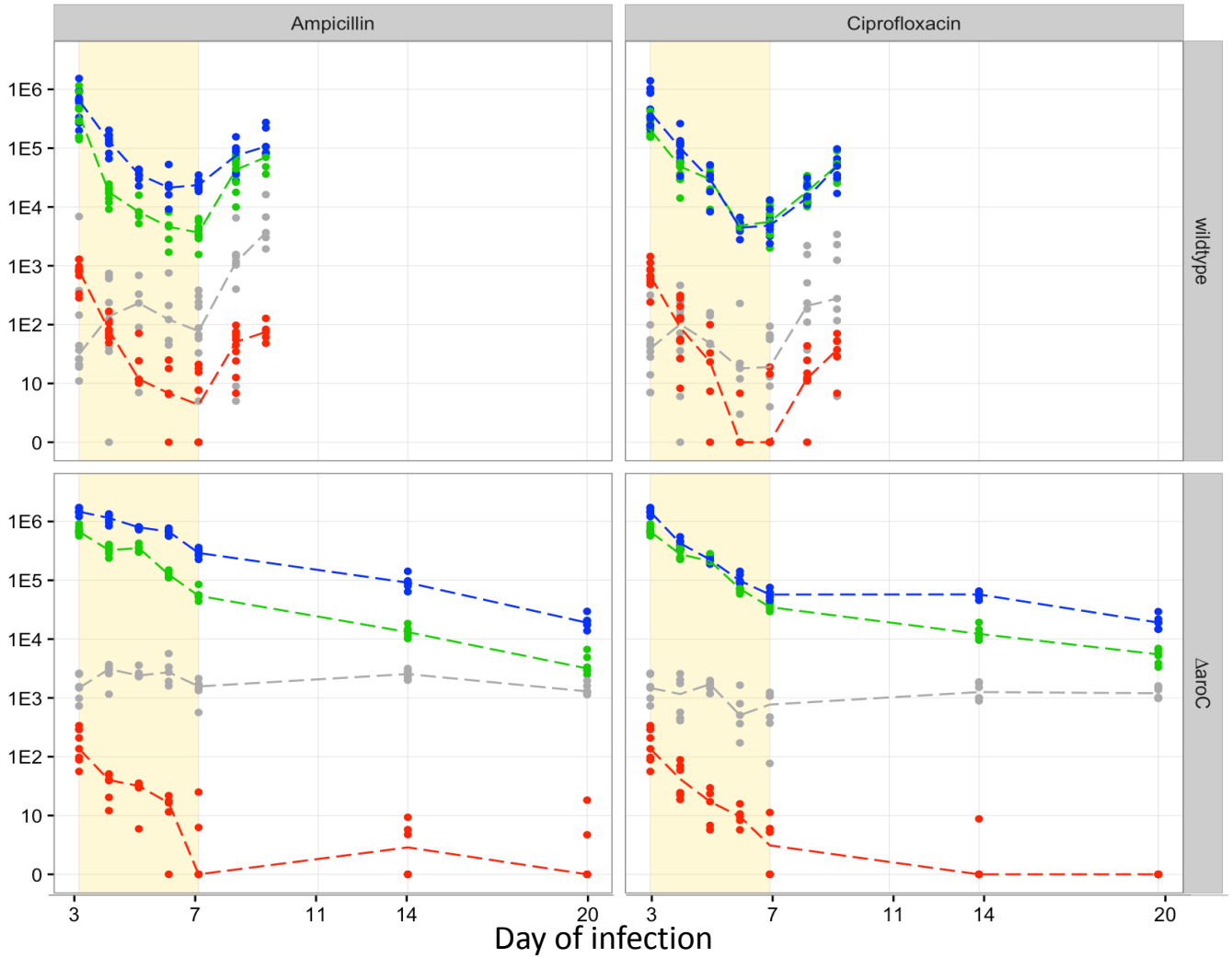
Effect of antibiotic treatment in spleen, liver and MLN



- Biphasic effect in spleen and liver
- Bacteria persist despite treatment

- **No reduction in MLNs**
- Relapse in ALL of the tissues **including MLNs**

Growth rates and antibiotic treatment



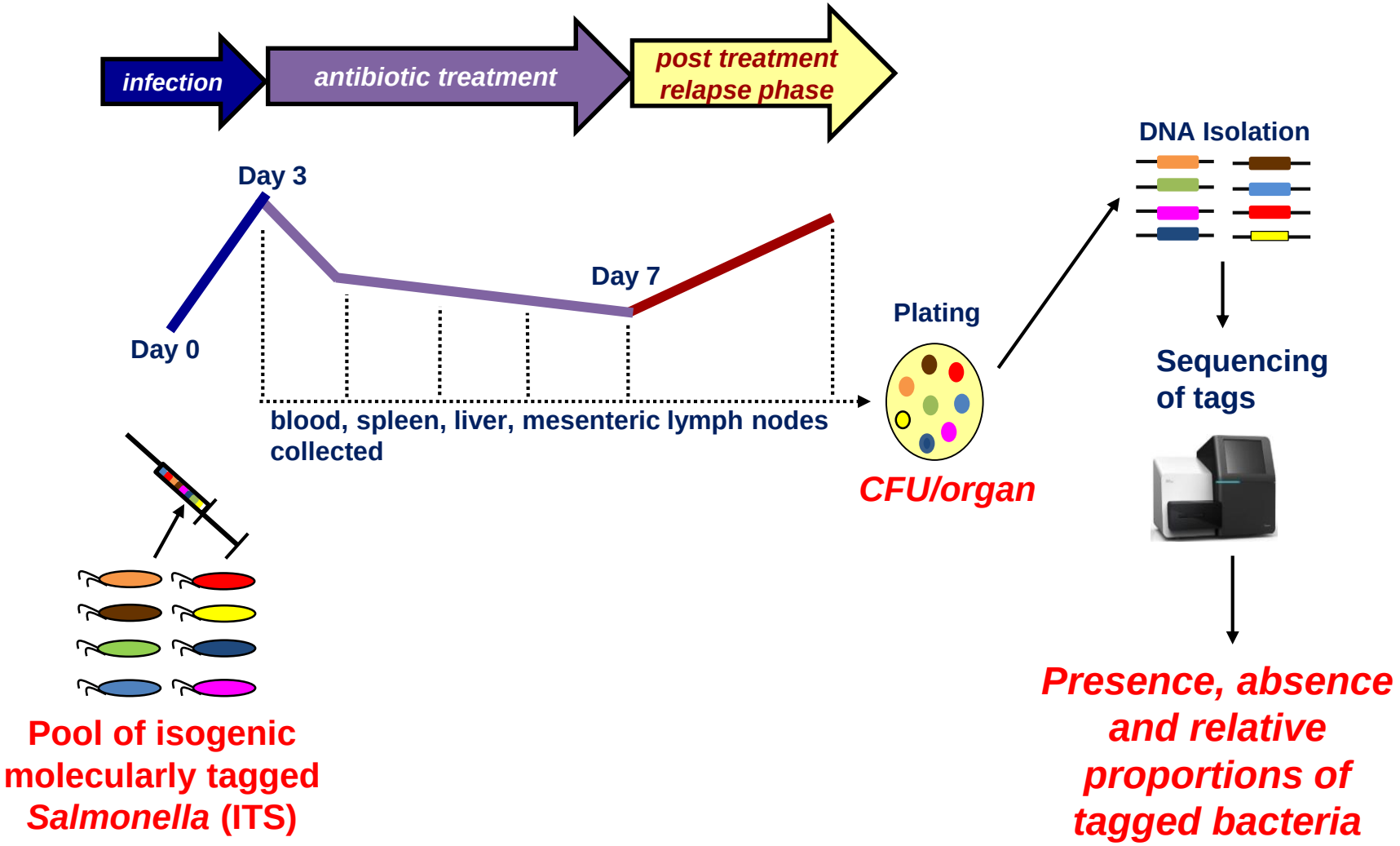
WT strain

aroC mutant

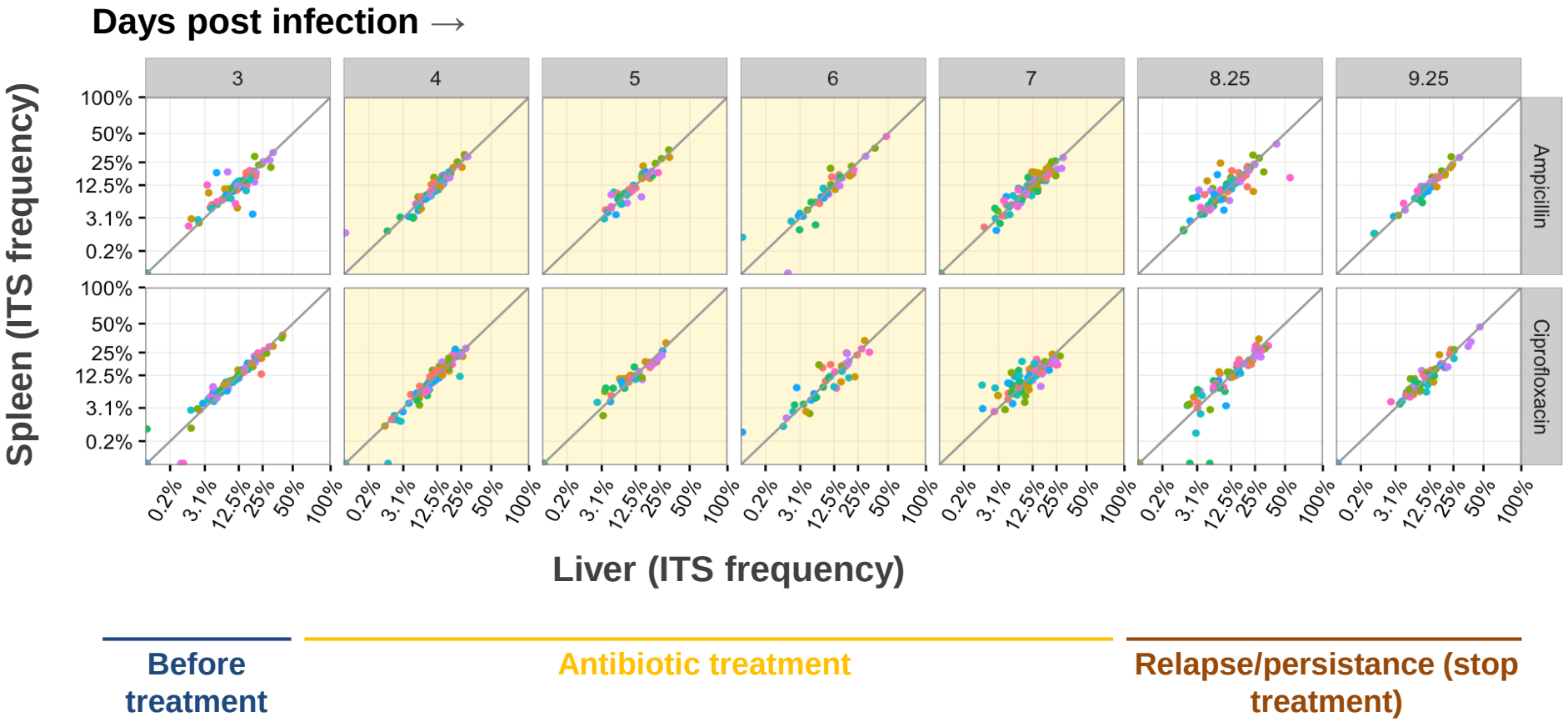
- Correlation between net growth rates and efficacy.
- **No reduction in bacterial numbers in the MLNs with either bacterial strain and antibiotic**

- Lack of effect of the antibiotics in MLNs
- Relapse upon cessation of antibiotic treatment

Compartmentalized site?
Endogenous relapse or colonisation from other organs?

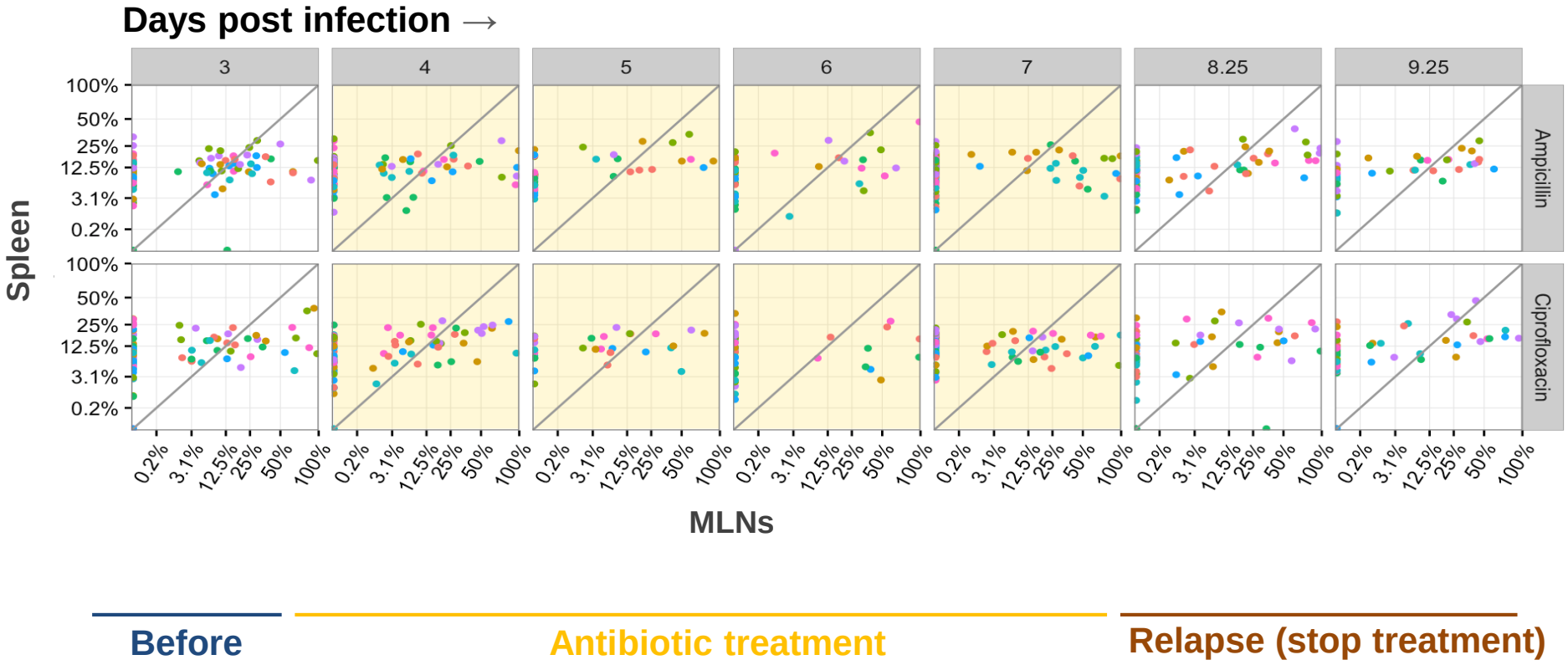

infection
antibiotic treatment
post treatment
relapse phase
Day 3
Day 0
Day 7
blood, spleen, liver, mesenteric lymph nodes
collected
Plating
CFU/organ
DNA Isolation
Sequencing
of tags
Pool of isogenic
molecularly tagged
Salmonella (ITS)
Presence, absence
and relative
proportions of
tagged bacteria

Each ITS is present at similar frequencies in the spleen and liver



Most ITS are present at different frequencies in the MLN *vs.* spleen and liver (not shown)

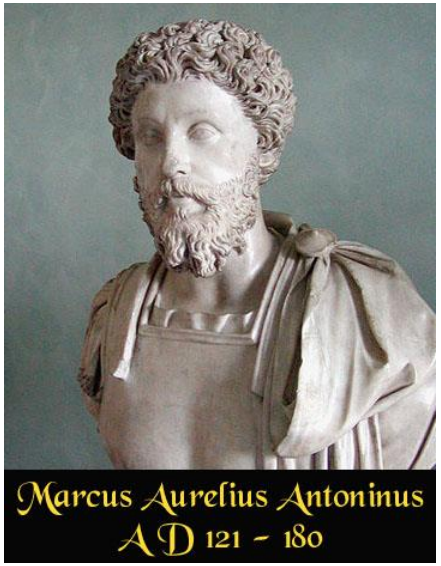
MLNs are compartmentalized throughout the infection and relapse



Conclusions

- Antibiotic sensitive bacteria persist in all tissues despite treatment
- Bacterial net growth rates correlate with efficacy of treatment
- MLNs are a compartmentalized, privileged site where antibiotic treatment has poor efficacy and *Salmonella* can resume growth after cessation of therapy

Because a thing **seems difficult**, **do not** think it impossible



Pathogen behaviour

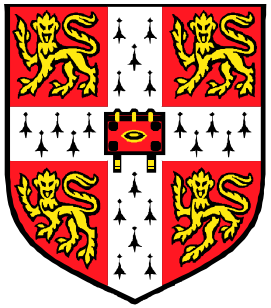
- Location
- Growth
- Spread

Host

- Organs
- Cells
- Immune system
- Genetics
- Co-morbidities

Successful treatment

- Choice of antibiotic
- Non-compound strategies
- Formulations
- Delivery systems



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