Antimicrobial treatment and pathogen behavior during invasive *Salmonella* infections

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The ideal situation

- Bacteria per organ vs. Time post infection
- Growth and Clearance trajectories
- Antimicrobial treatment
The real world
Complex scenarios and challenges to treatment and clearance
Difficulties in treatment are not just due to AMR genes!

- Bacteria in spleen and liver
- Time post infection
- Antimicrobial treatment
  - "Acute" antimicrobial effect
  - Limited or absent reduction
  - Persistence
- Innate immunity
  - Cytokines
  - Phagocyte killing
- MHCII (H-2)
  - T-cell deficiency
- Relapse
- Decline
Antibiotic treatment

"the grey box of host vs. pathogen behaviour"

Growth rates? Immunity? Spread?
Host cell types? Host genetics?
Bacterial location? Immune-deficiency?
AMR genes? 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

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

WT strain

aroC mutant
• Lack of effect of the antibiotics in MLNs
• Relapse upon cessation of antibiotic treatment

Compartmentalized site?
Endogenous relapse or colonisation from other organs?
Pool of isogenic molecularly tagged *Salmonella* (ITS)

**DNA Isolation**

**Sequencing of tags**

Presence, absence and relative proportions of tagged bacteria

**Post treatment relapse phase**

**Plating**

**Day 0**

**Day 3**

**Day 7**

**blood, spleen, liver, mesenteric lymph nodes collected**

**CFU/organ**

**Infection**

**Antibiotic treatment**
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.

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**Before**  |  **Antibiotic treatment**  |  **Relapse (stop treatment)**

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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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