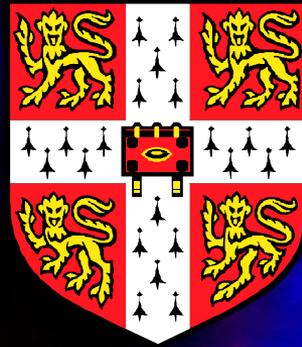


# Immunity to invasive *Salmonella* infections: lessons from animal models and man

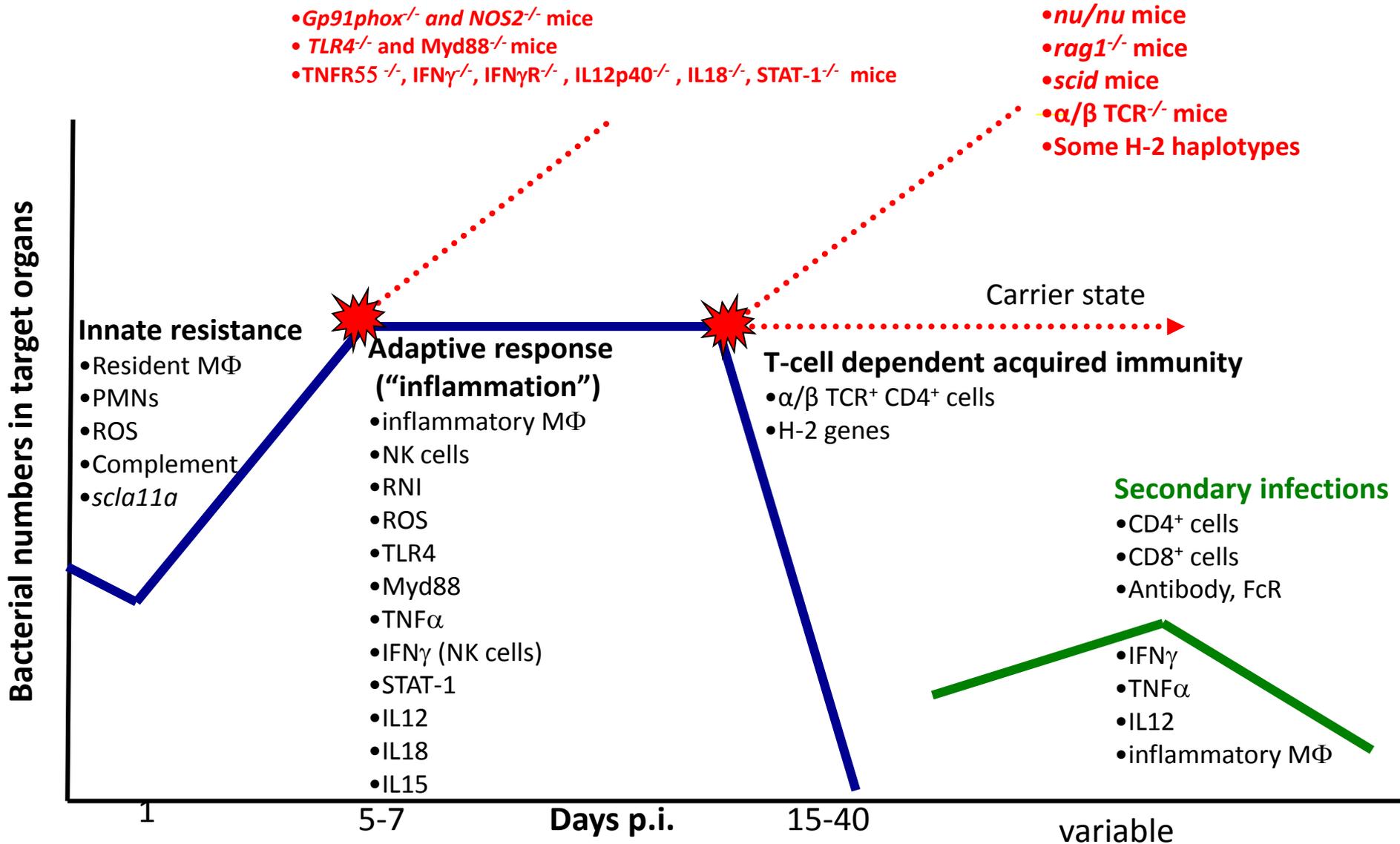


**Pietro Mastroeni**

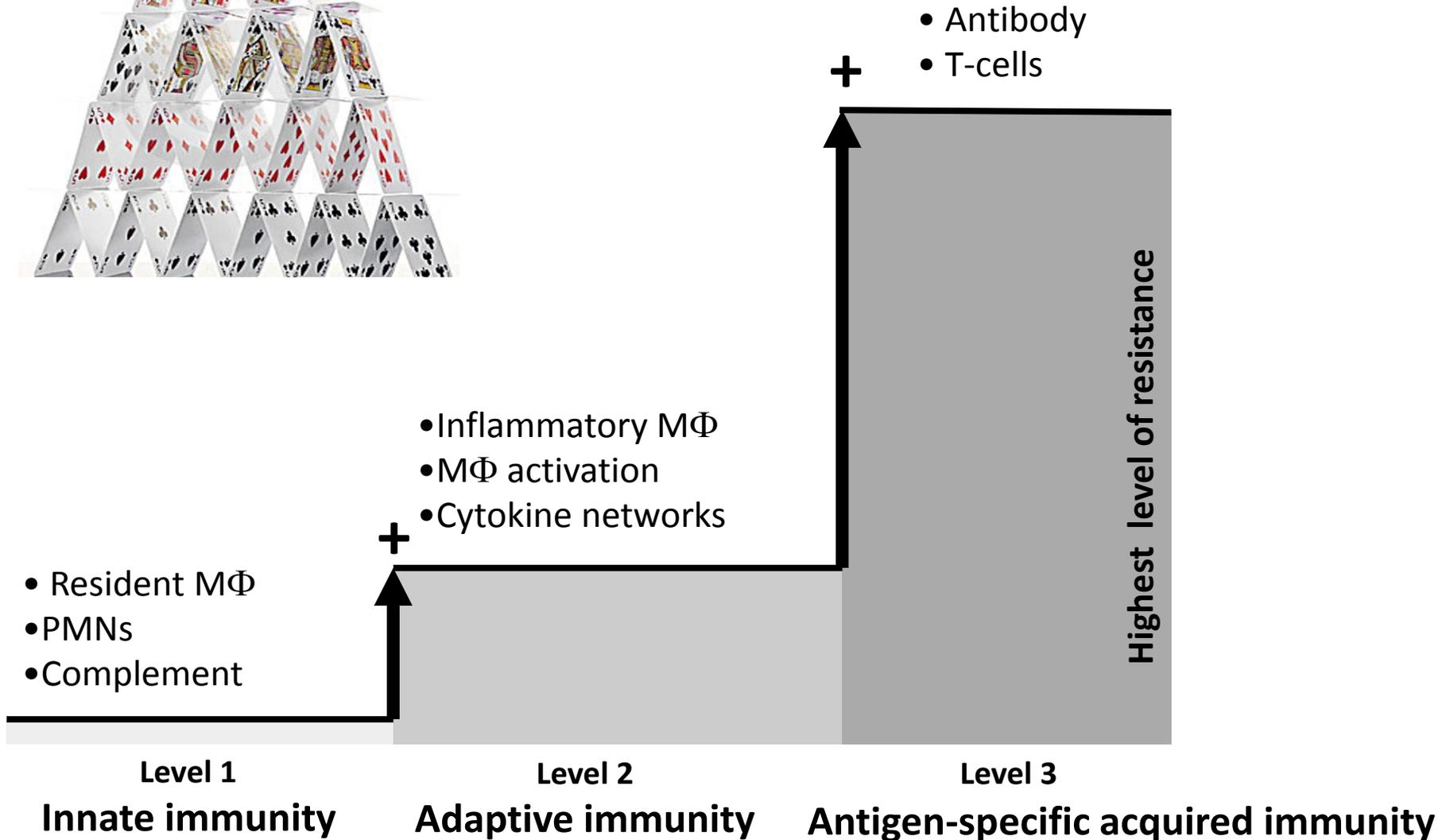
University of Cambridge

# Lessons from mice

## Systemic infections progress in distinct phases



Like a “castle of cards”

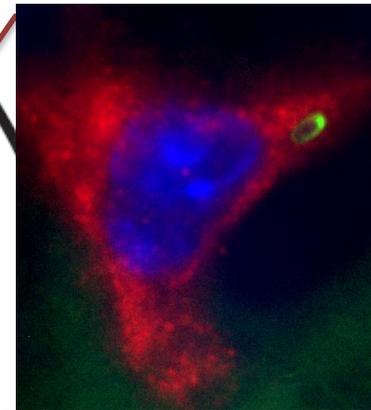
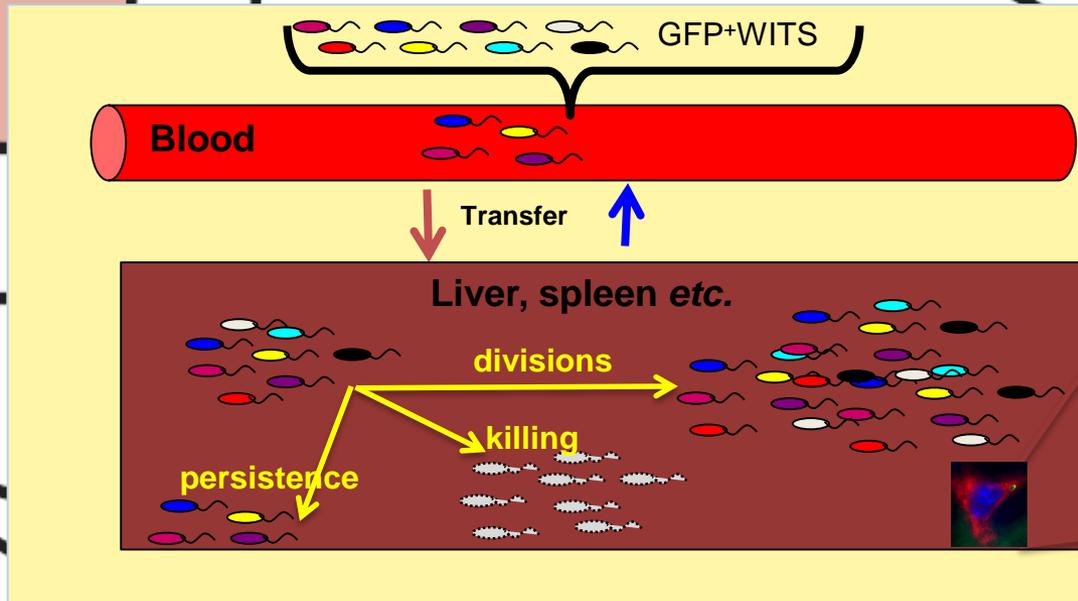


# Dynamics of the *in vivo* infection process, immunity and vaccination

Molecularly tagged, fluorescent *Salmonella* subpopulations

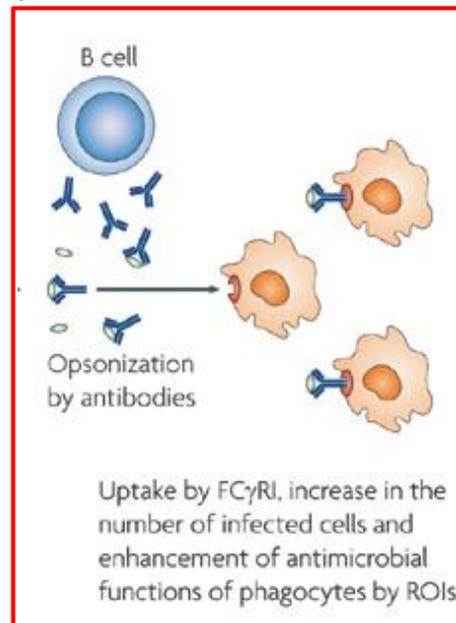
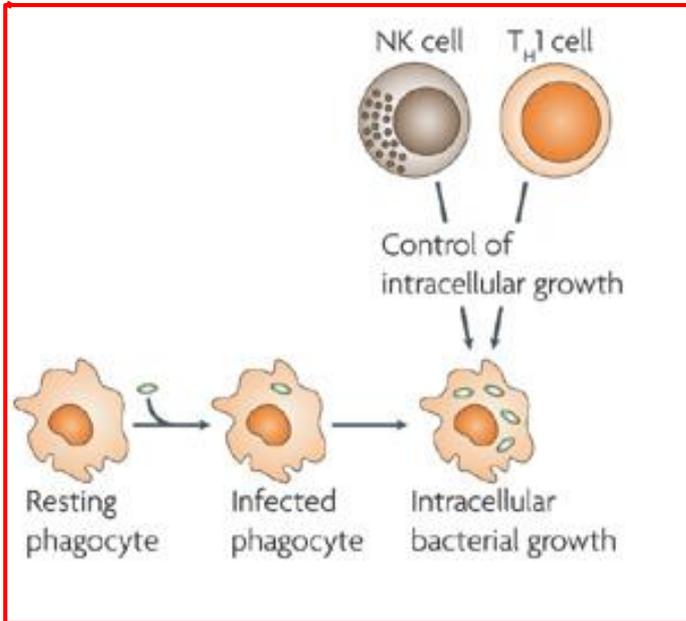
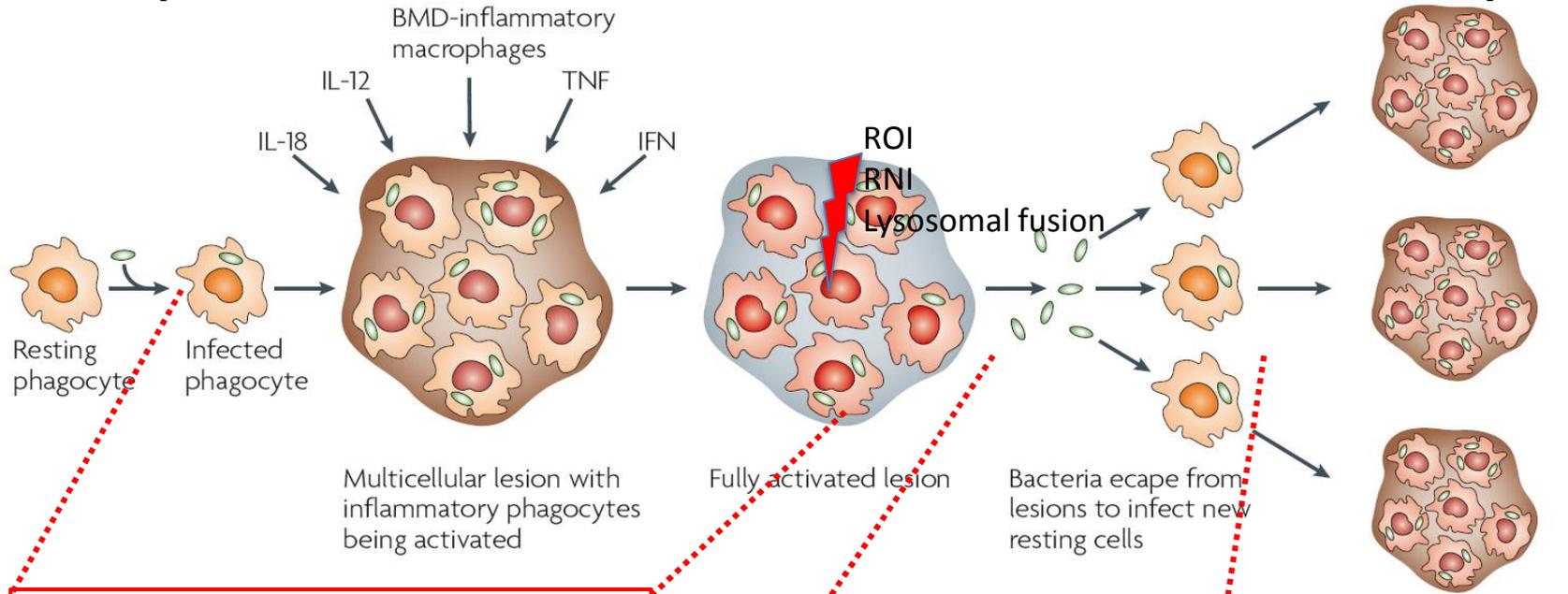
## Tag analysis (PCR or sequencing)

- presence
- absence
- relative proportions
- population heterogeneity



- location
- intracellular numbers

# Dispersive infections with intracellular and extracellular phases



# Lessons from humans: genetic immunodeficiencies/associations

Mastroeni *et al*, Rev. Med. Microbiol. 2003; Gilchrist *et al*, Nature Rev. Immunol, 2015 in press

- **iNTS**
- **Typhoid**

## Humoral/antibody

- **Complement deficiencies**

## T-cell mediated immunity

- Variants in cytokine-inducible Src-homology-2-containing (*CISH*)
- ***HLA-DRB1\*04:05*; *HLA-DRB1* (rs7765379)**

## Phagocyte antimicrobial functions

- **CGD**- X-linked and autosomal recessive deficiencies
- $\beta$ -thalassaemia/HbE disease

## Signalling

- **TLR4** rs4986790
- ***IKBK*** (encoding NEMO) mutations
- ***NFKBIA*** (encoding I $\kappa$ B $\alpha$  ) mutations
- **MyD88**-defects
- **TIRAP** missense variant (rs8177374)

## Cytokine networks

- **IL12/IL23p40** deficiency
- **IL12R $\beta$ 1** deficiency
- Anti-IFN $\gamma$  autoantibodies
- **IFNR1** deficiency
- **STAT1** deficiency
- **TNF $\alpha$**  (protective MHC class III haplotype (*DDX39B*, *LTA*, *TNF*))

# Lessons from humans: epidemiological risk factors/comorbidities in endemic areas

## Antibody

- absence of anti-*Salmonella* antibodies in young children
- dysregulated antibody responses in HIV patients

## Phagocyte functions

## T-cell mediated immunity

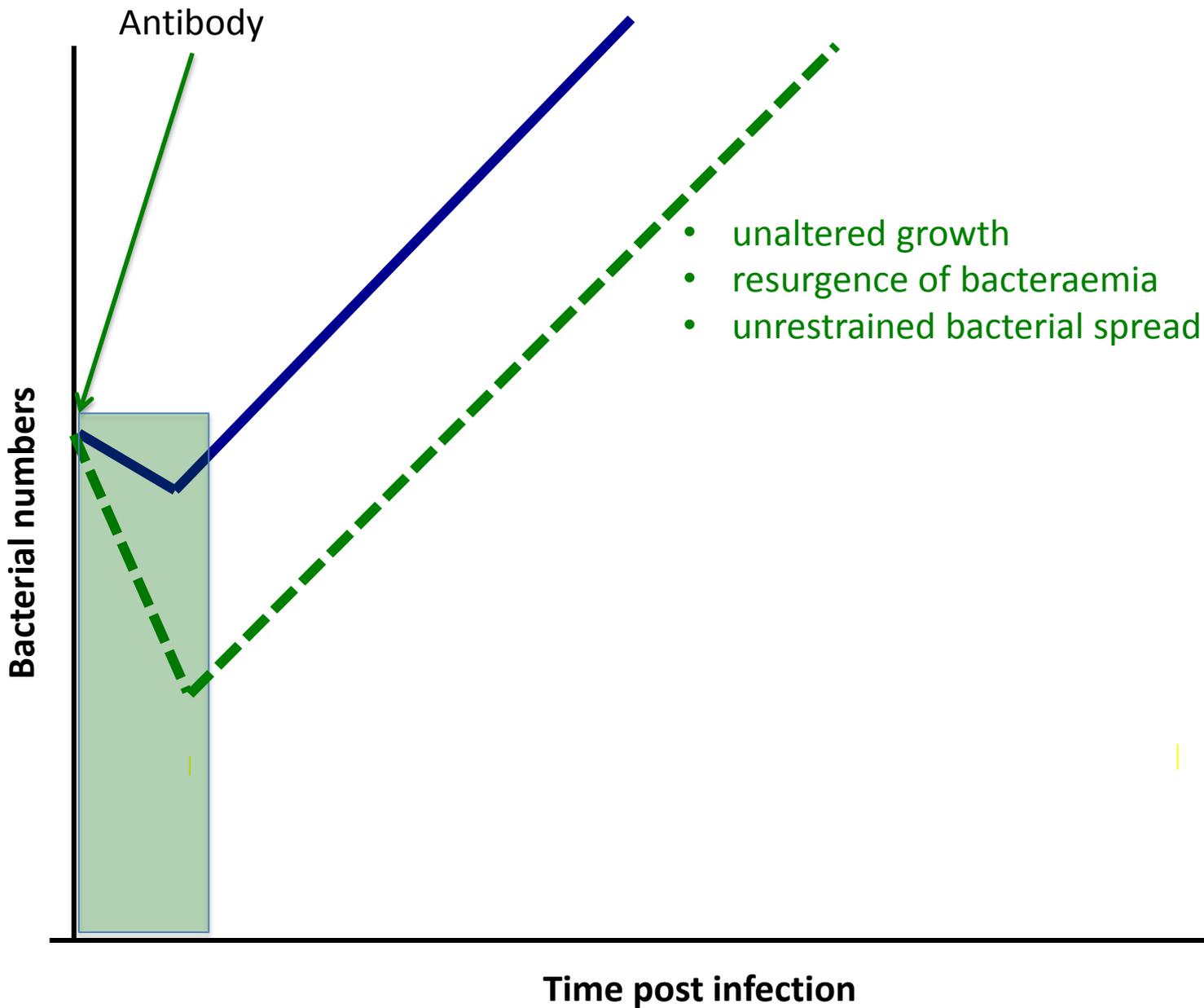
- malaria
- HIV
- malnutrition
- anaemia

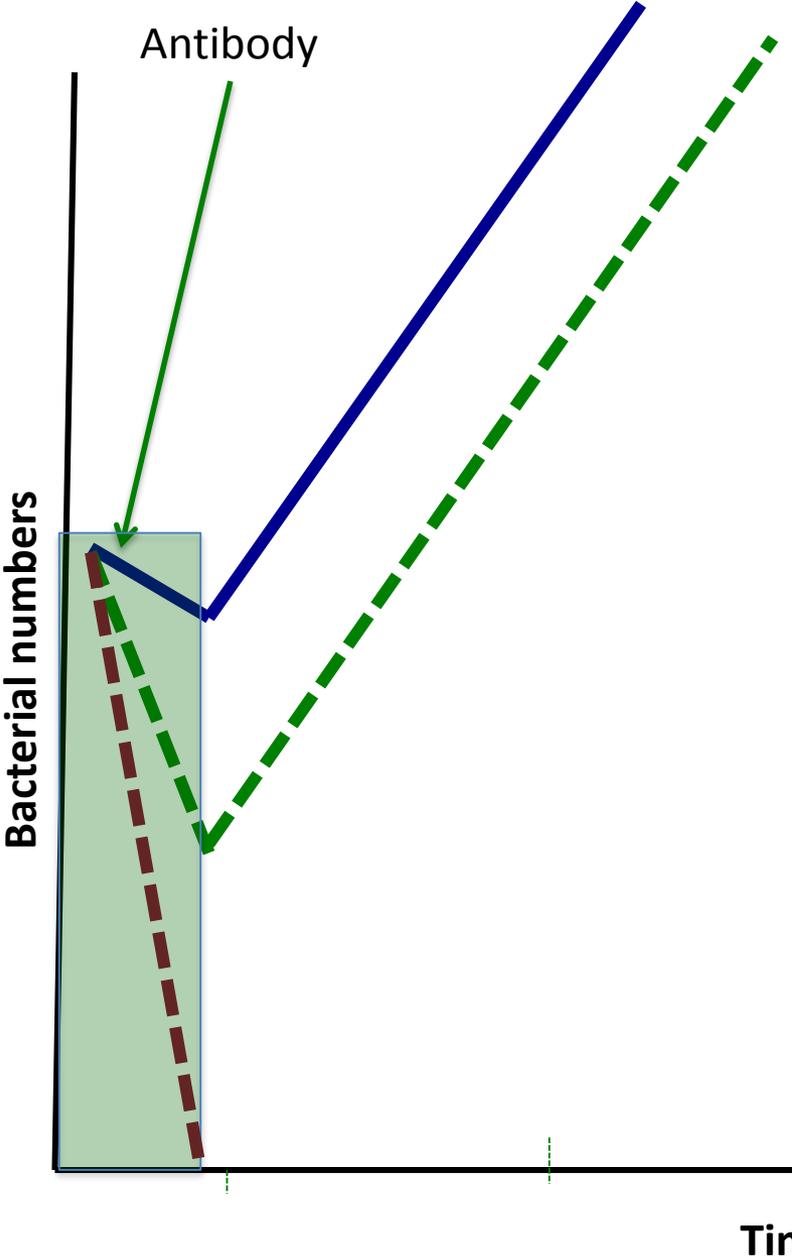
# Vaccines

Are we making the most of the lessons that we have learnt from mice and man?

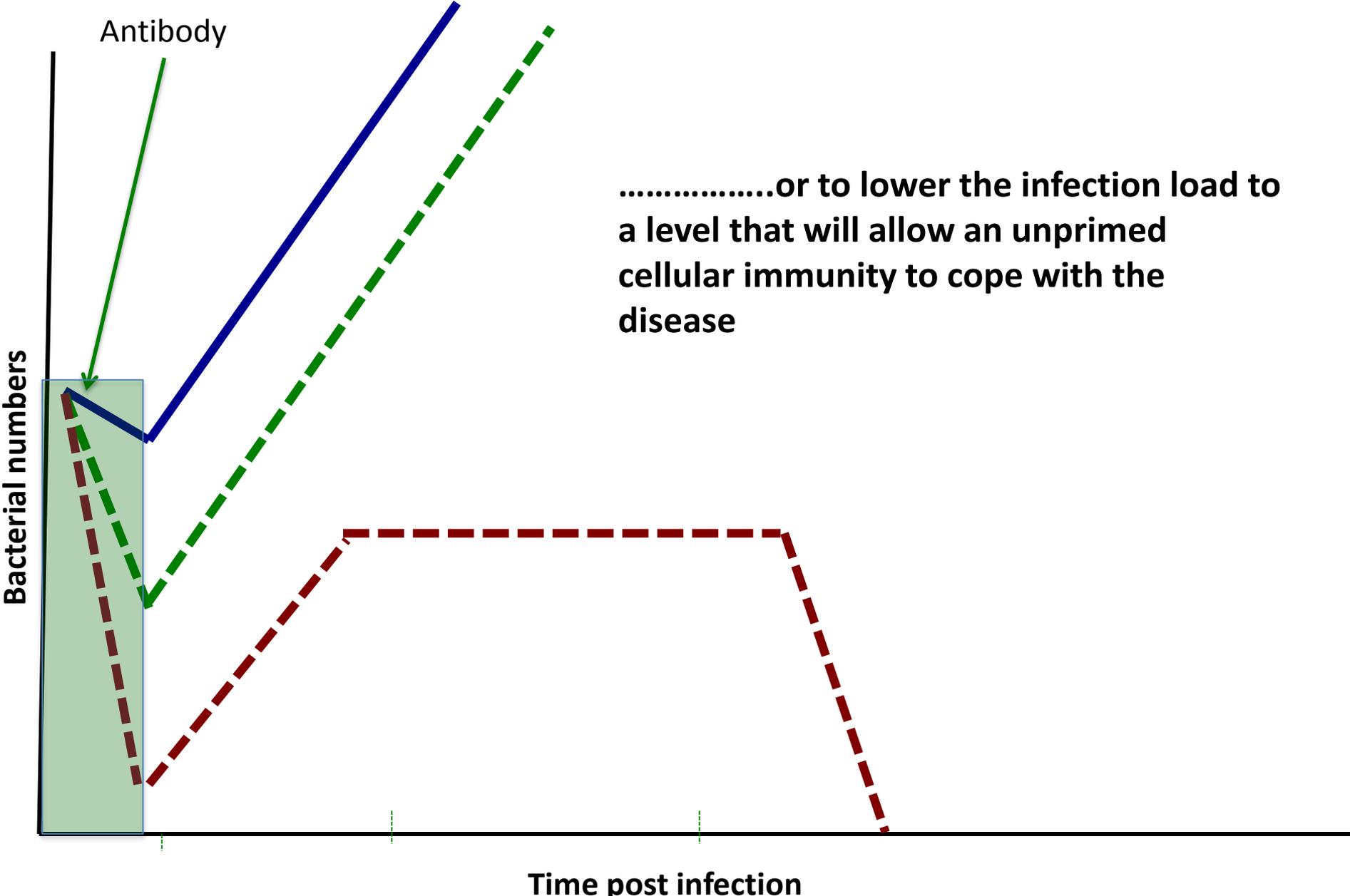
# Lessons from mice

## How can we affect the infection with external intervention?





If we are going to use vaccines whose efficacy is based on antibody responses, we must strive to increase the efficacy of these responses to eliminate the infection in the early stages.....



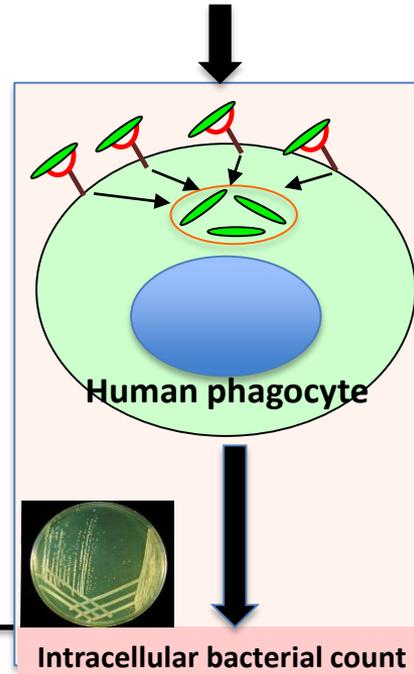
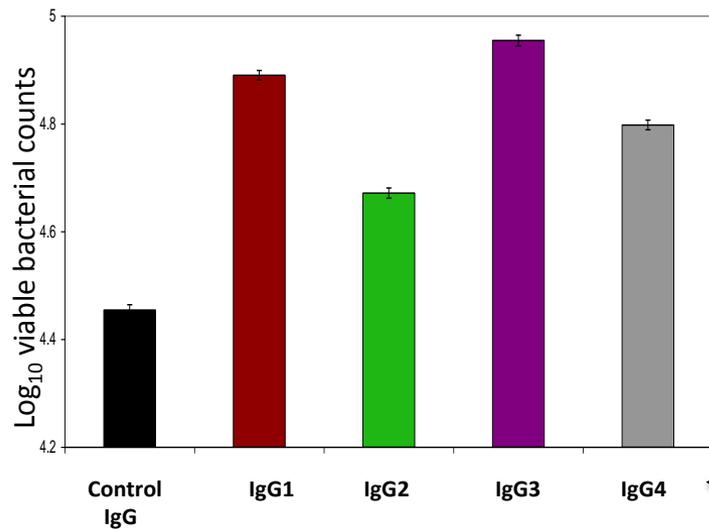
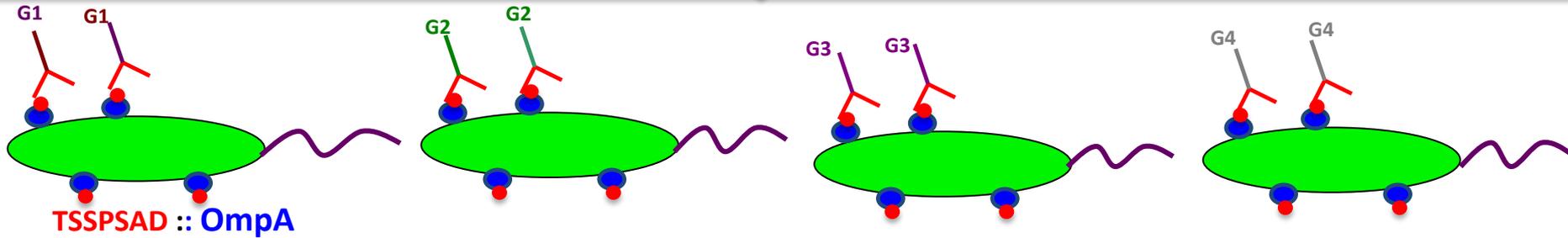
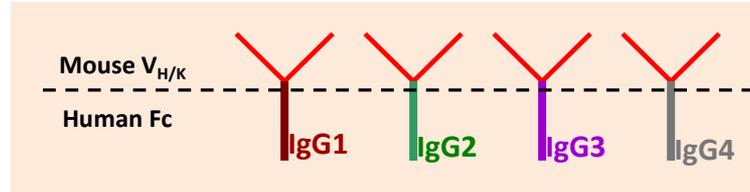
Antibody

Bacterial numbers

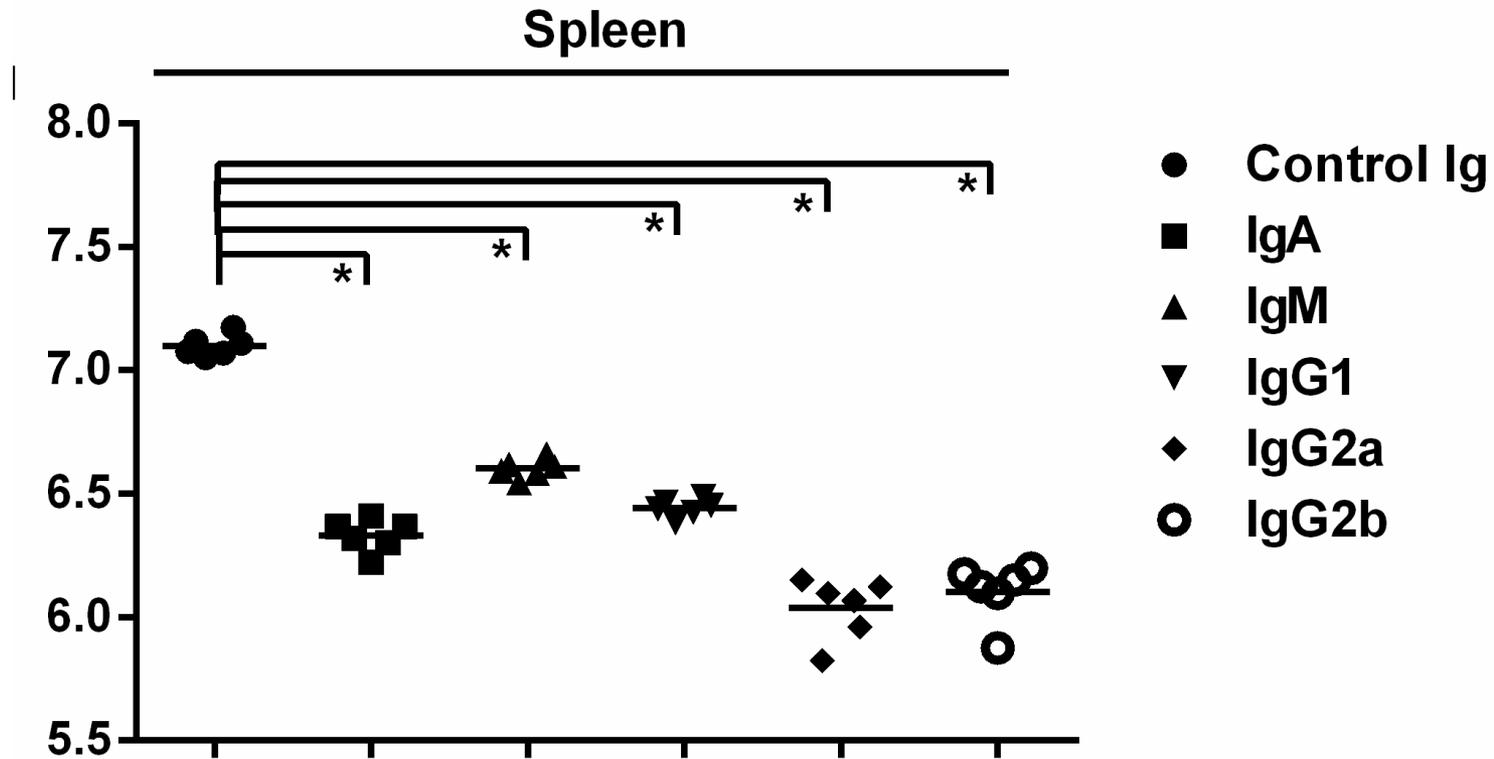
Time post infection

.....or to lower the infection load to a level that will allow an unprimed cellular immunity to cope with the disease

# Optimise the antibody response: isotypes and effector functions

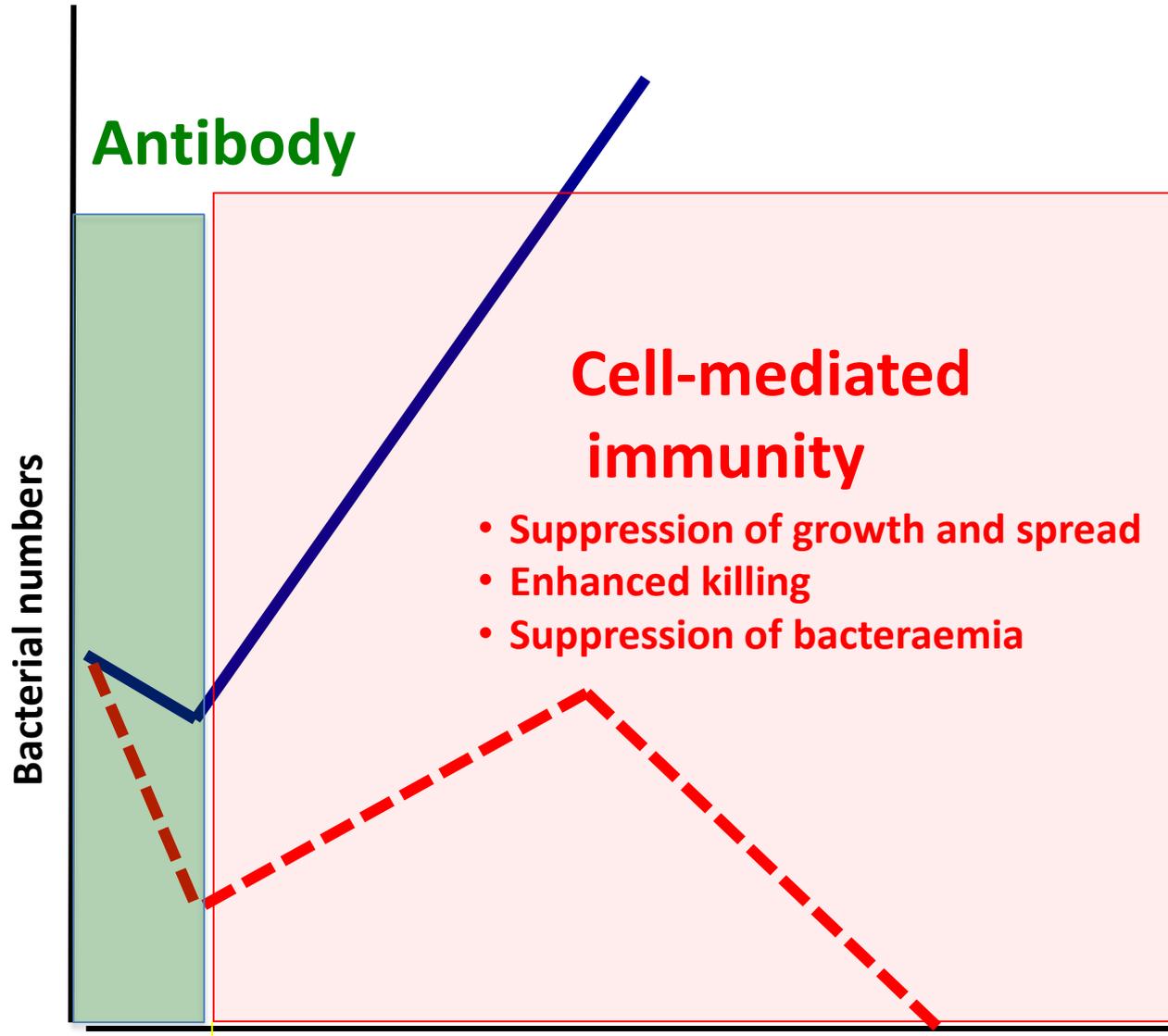


# “Quality” and effector functions of mouse antibodies *in vivo*





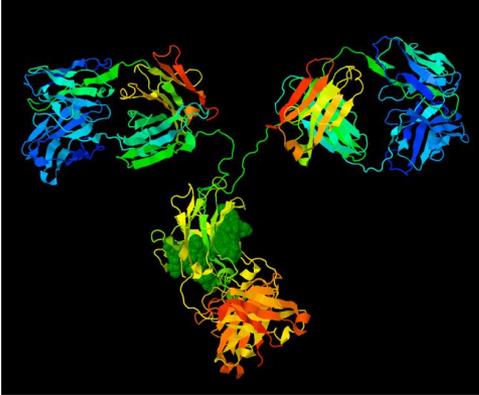
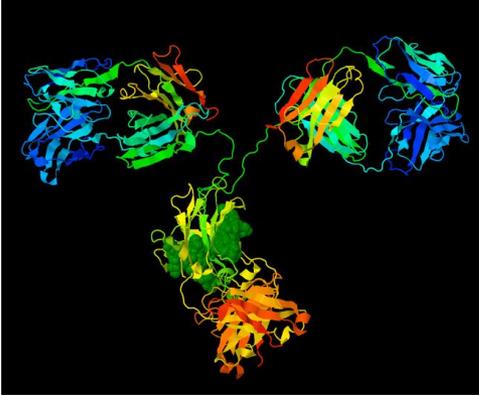
# Should we also push forward research on live attenuated vaccines as an additional/alternative option?



To decide on a **rational** path for vaccination in **endemic areas** we need to better understand the immunological **determinants of resistance/susceptibility** to typhoid and iNTS disease **in the context of predisposing factors.**

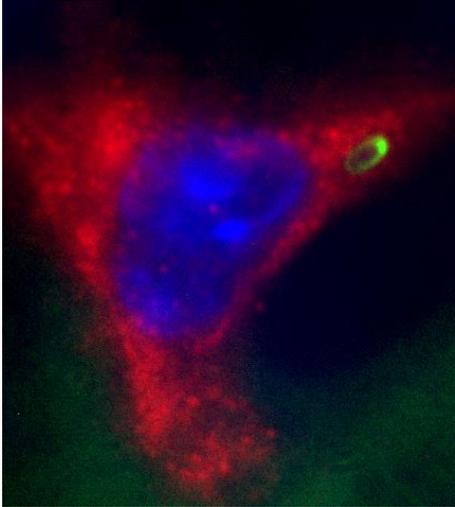
# Epidemiological risk factors

(e.g. age, co-morbidities, genetic)

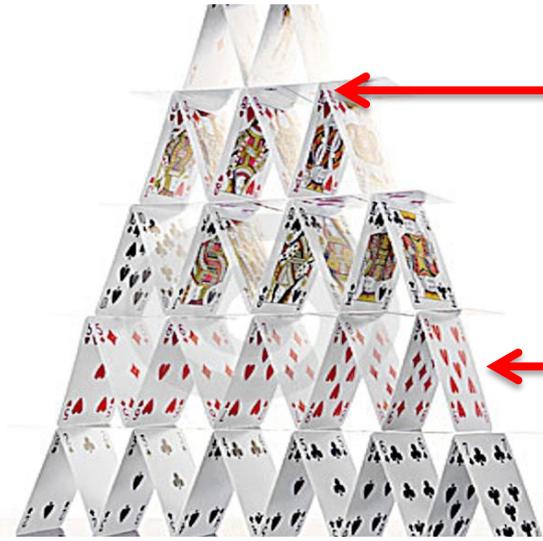


Immunological  
signatures

Functional defects  
of immune effectors



Susceptibility to disease



- Resident M $\Phi$
- PMNs
- Complement

**Level 1**

**Innate immunity**

- Inflammatory M $\Phi$
- M $\Phi$  activation
- Cytokine networks

+

**Level 2**

**Adaptive immunity**

- Antibody
- T-cells

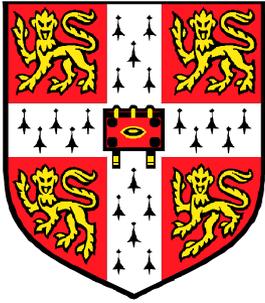
+

Highest level of resistance

**Level 3**

**Antigen specific acquired immunity**

*A lot has been done, but much remains to be done*



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1209 ~ 2009

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Chris Coward  
Richard Dybowski  
Mark Sheppard  
Gemma Foster  
Olivier Restif  
Yun Shan Goh  
Mike Clark  
Duncan Maskell  
Pietro Mastroeni



Gordon Dougan  
Simon Clare  
Chris Hale  
George Vassilou  
Cal MacLennan



Allan Saul  
Simona Rondini  
Francesca Micoli



David Gray  
Tom Barr



Sjef Verbeek



Ferric Fang



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