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# A human challenge model of *Bordetella pertussis* infection

Robert C Read University of Southampton



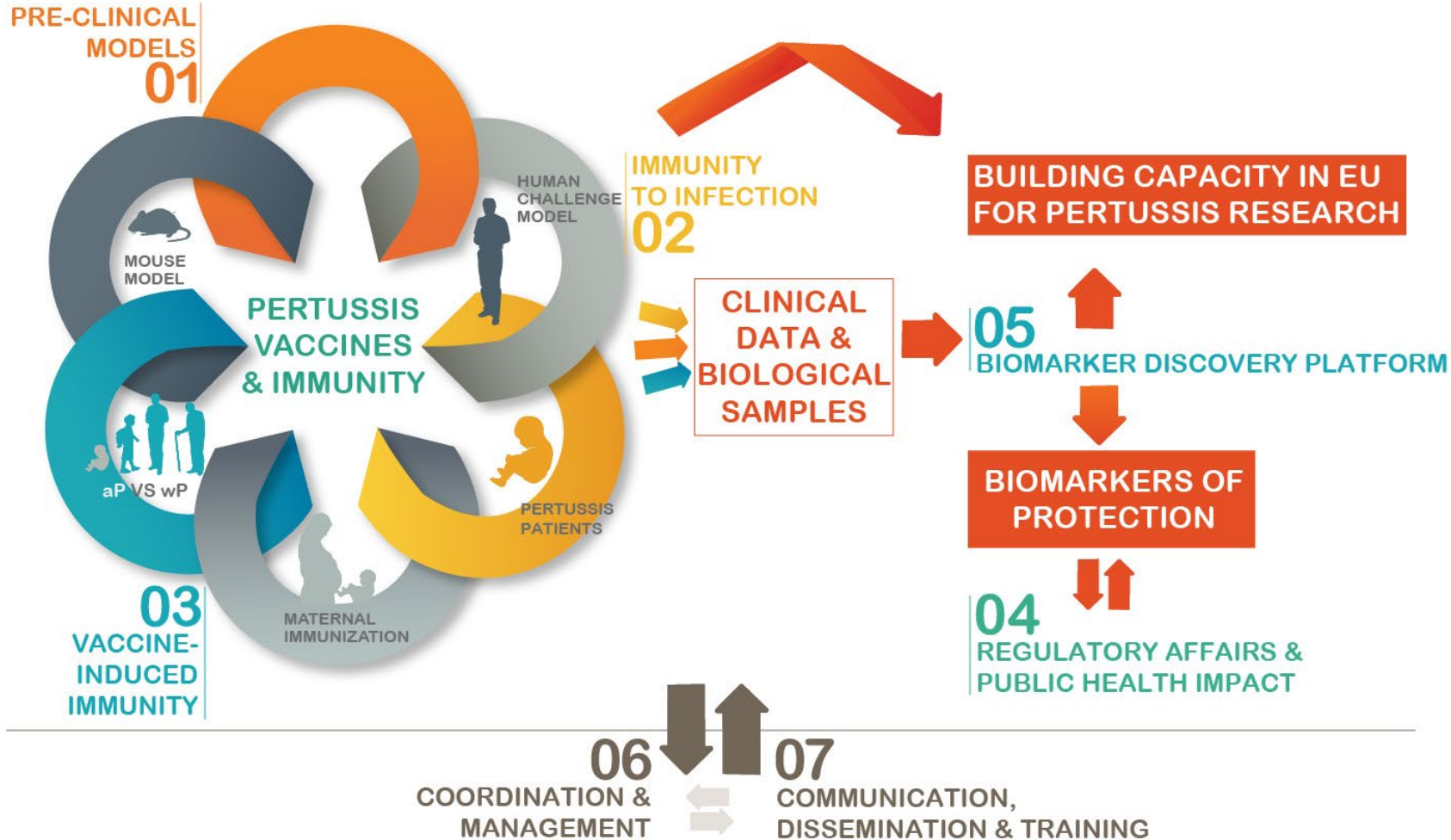
# Disclosures

- ILIAD Biotechnologies; Chief Investigator BPZE1 vaccine-challenge
- EU IMI grant support
- Editor in Chief, *Journal of Infection*
- UK Joint Committee for Vaccination and Immunisation

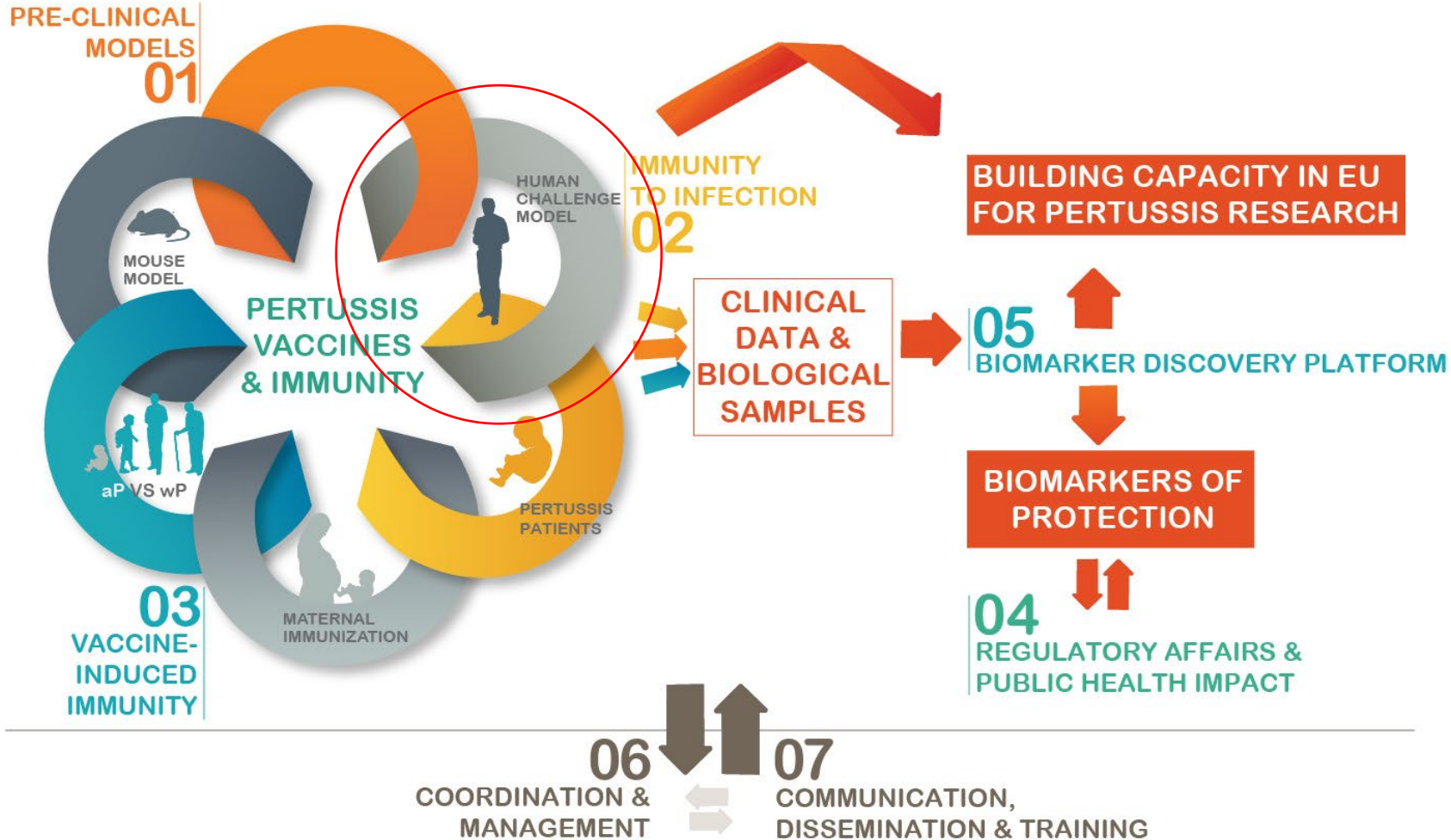
# PERISCOPE consortium



BILL & MELINDA  
GATES foundation



# PERISCOPE consortium



# Ethical Considerations: Controlled Human Infection

- **The objective can be justified**
- **The minimum adequate sample is used**
- **The challenge inoculum is the minimum required to provide a clear outcome measure**
- **Induced symptoms can be treated, and treatment is not withheld**

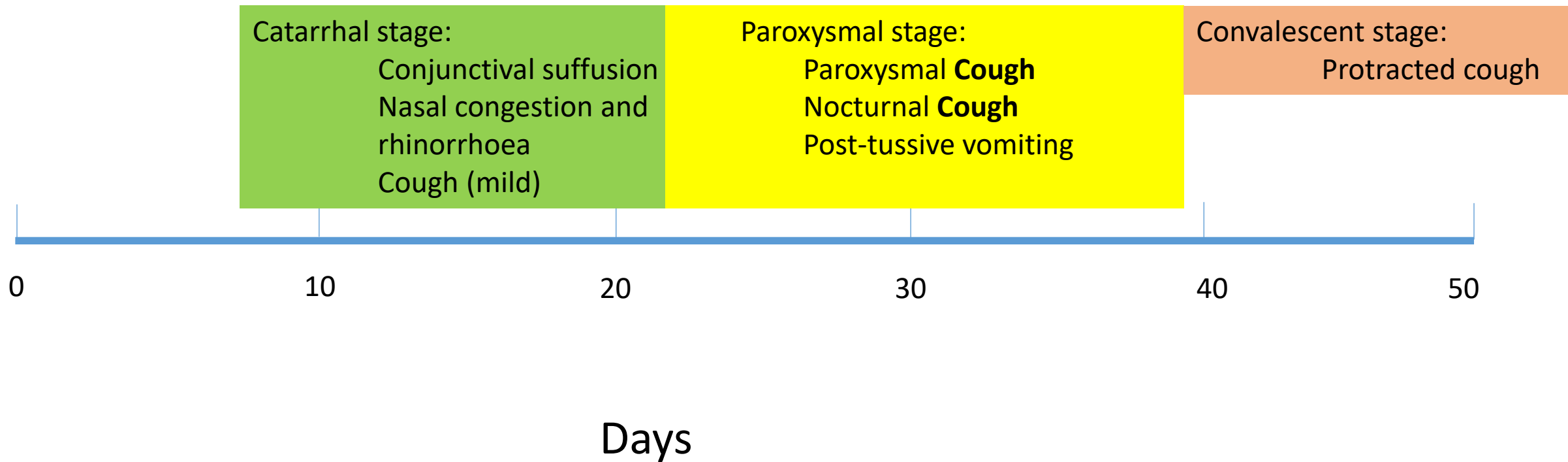
# University of Southampton

## *Bp* Controlled Human Infection Model

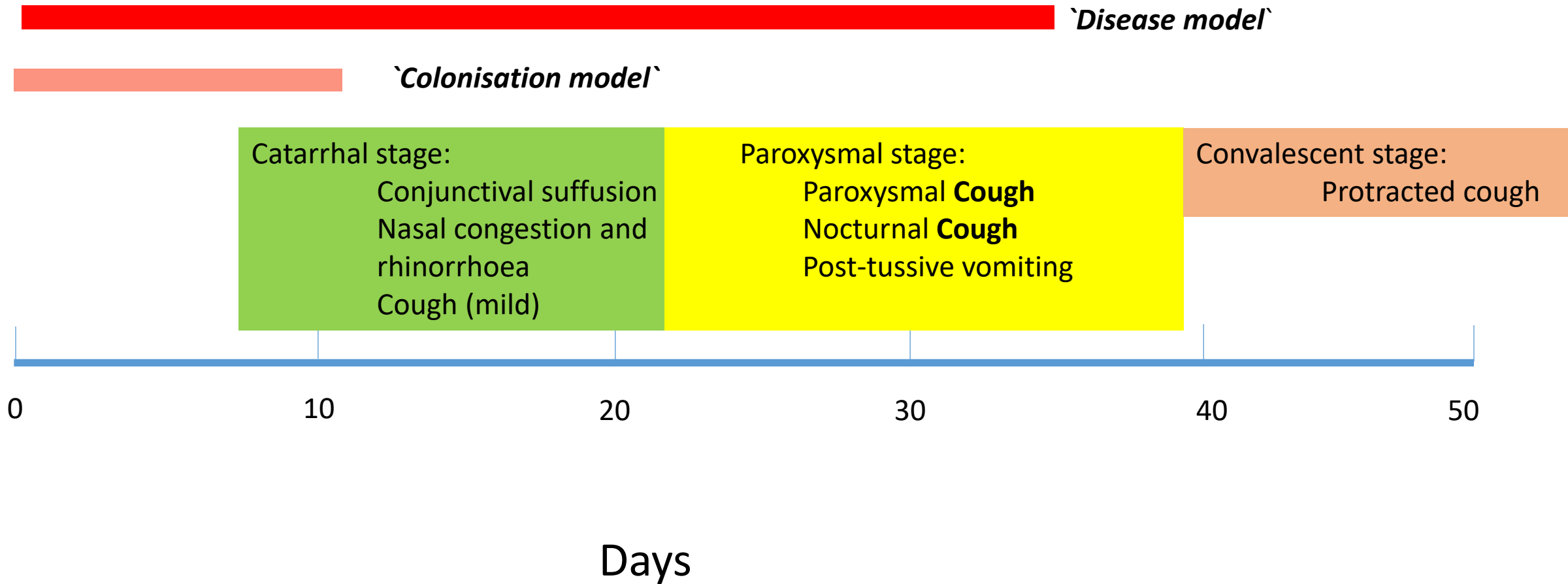
- *Primum non nocere*
- Asymptomatic nasopharyngeal colonisation
- *Bordetella pertussis* strain B1917
- Clearance with azithromycin
  
- Potential utilities:
  - Biomarkers associated with protection
  - Platform for vaccine testing



# Clinical Pertussis



# Controlled Human Infection



# CDC: Pertussis clinical case definition

## **Clinical Criteria**

In the absence of a more likely diagnosis, a cough illness lasting  $\geq 2$  weeks, with at least one of the following signs or symptoms:

- Paroxysms of coughing; **OR**
- Inspiratory whoop; **OR**
- Post-tussive vomiting; **OR**
- Apnea (with or without cyanosis)

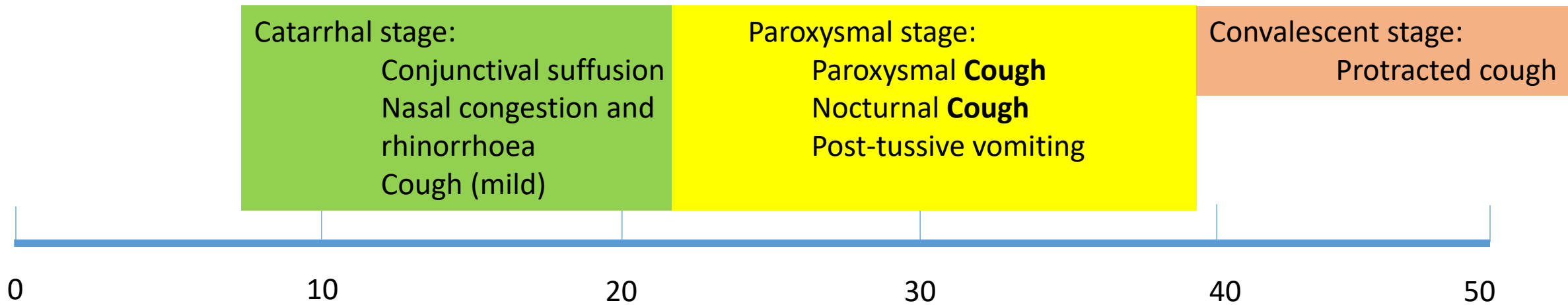
## **Laboratory Criteria**

*Confirmatory laboratory evidence:*

- Isolation of *B. pertussis* from a clinical specimen
- Positive Polymerase Chain Reaction (PCR) for *B. pertussis*

# Clinical Pertussis

Complications in Adults/Adolescents	percent
Apnoea	27-86
Insomnia	77
Weight loss	3-33
Urinary incontinence	3-28
<b>Death</b>	<b>0.01</b>



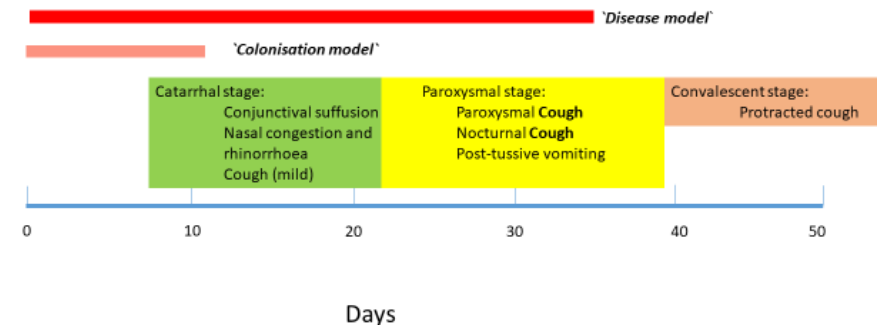
Kilgore PE, et al, *CMR* 2016

Days

# Disease model

ADVANTAGES	DISADVANTAGES
Clear Clinical and Regulatory Relevance	Unable to quantify risk including long term sequelae
Paroxysmal cough is easily detected and measured	Unable to reverse disease after paroxysmal cough onset
Correlate micro/immunology with clinical endpoints	Secondary cases
Study the full/mature disease process	Risk to nursing staff
Interventions measured against clinical endpoints	Reputational risk

## Controlled Human Infection



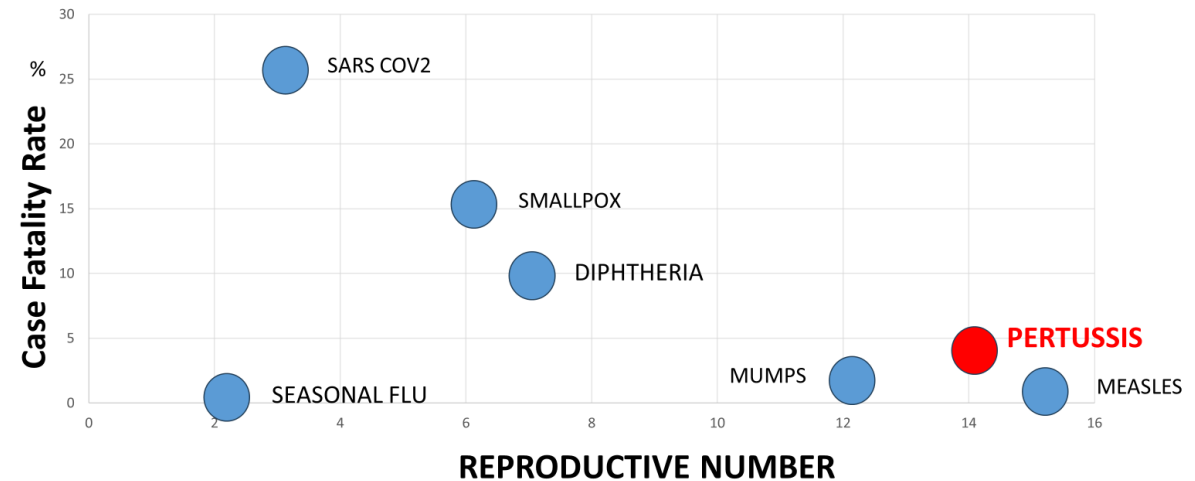
# Colonisation model

ADVANTAGES	DISADVANTAGES
Safe, any symptoms likely to be treatable	Symptoms likely to be mild and subjective
Detection of bacteria and concentration in nasal samples as an objective endpoint	<i>Bordetella pertussis</i> is difficult to detect in asymptomatic people Duration of carriage is unknown Relevance of carriage density
Probably less infection control issues	Detection of <i>B.pertussis</i> in an asymptomatic volunteer may not reflect active biological interaction
The commonest manifestation of wild infection	Uncertain how well the colonisation reflects clinical epidemiology
Colonisation is pre-requisite to disease so Vaccine/Challenge studies might inform herd protection estimates	Difficult regulatory pathway without proof that vaccine protection in a colonisation model translates to clinical efficacy

# Dose and Administration

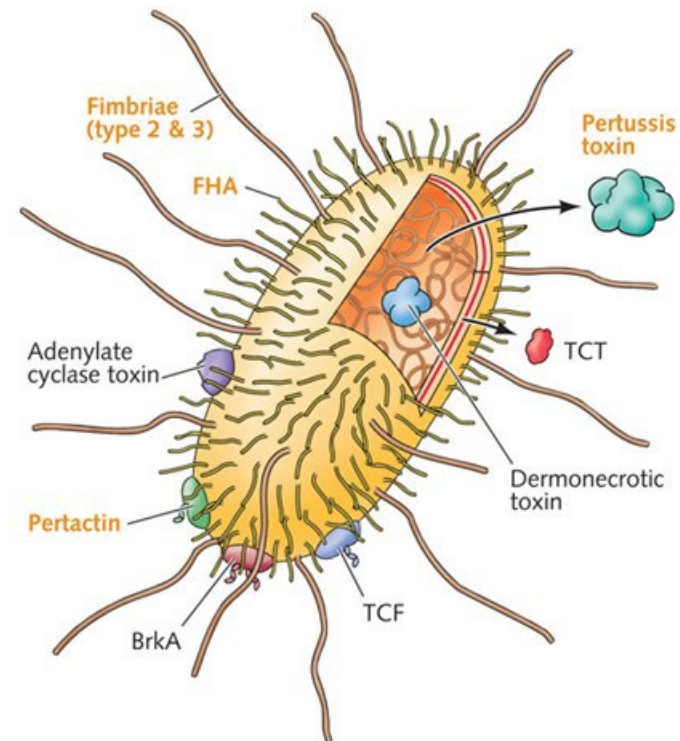
- *B.pertussis* is considered highly infectious
- Dose required for natural infection is unknown
- Airborne droplet transmission

Reproductive Number/ Case Fatality Rate



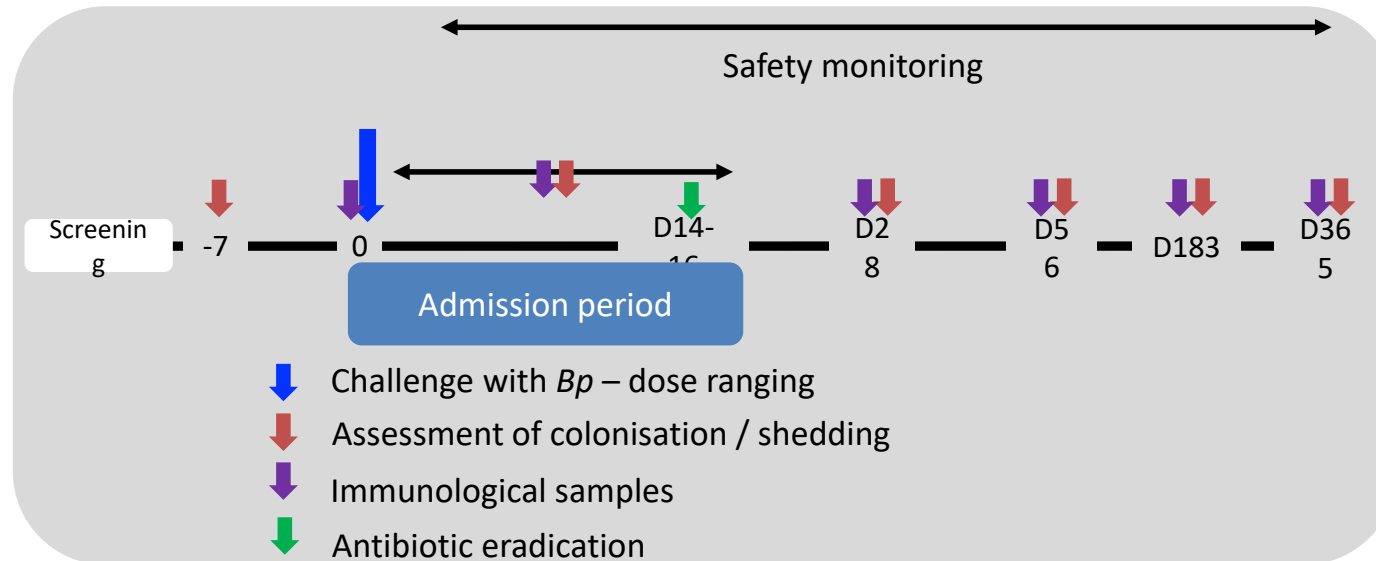
# Selected organism

- GMP manufactured by Q Biologicals, Belgium
- B1917, characterised by *ptxP3-ptxA1-prn2-fim3-2, fim2-1* MLVA27, PFGE BpSR11
- Expresses
  - Pertactin
  - Pertussis Toxin
  - Filamentous haemagglutinin
- Representative of current isolates in Europe



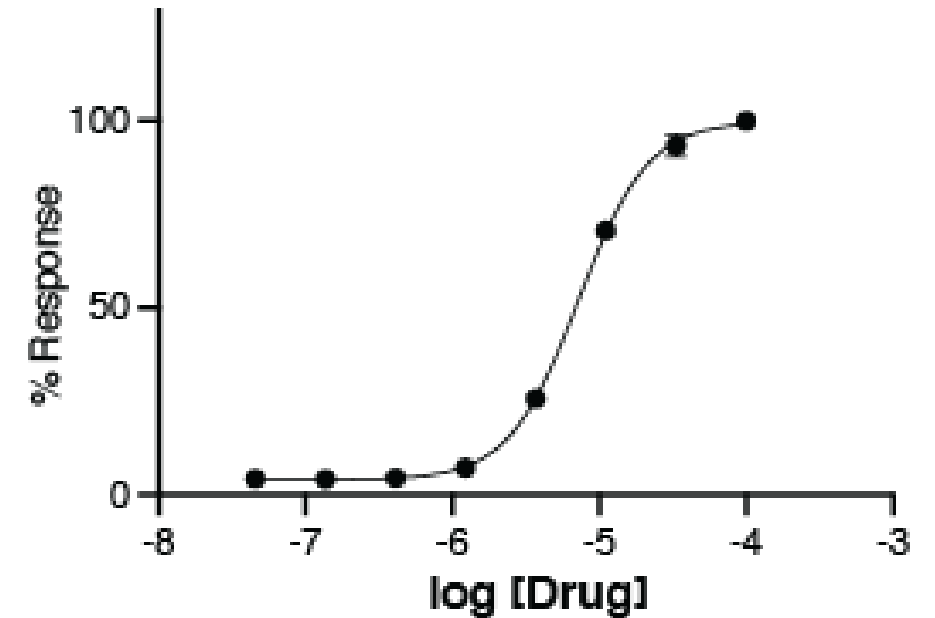
# PERISCOPE Phase A

- Dose ranging study : selected for anti-PT IgG < 20 IU/mL
- Inpatient model : 16-day admission period
- Completed in 2019, n=34

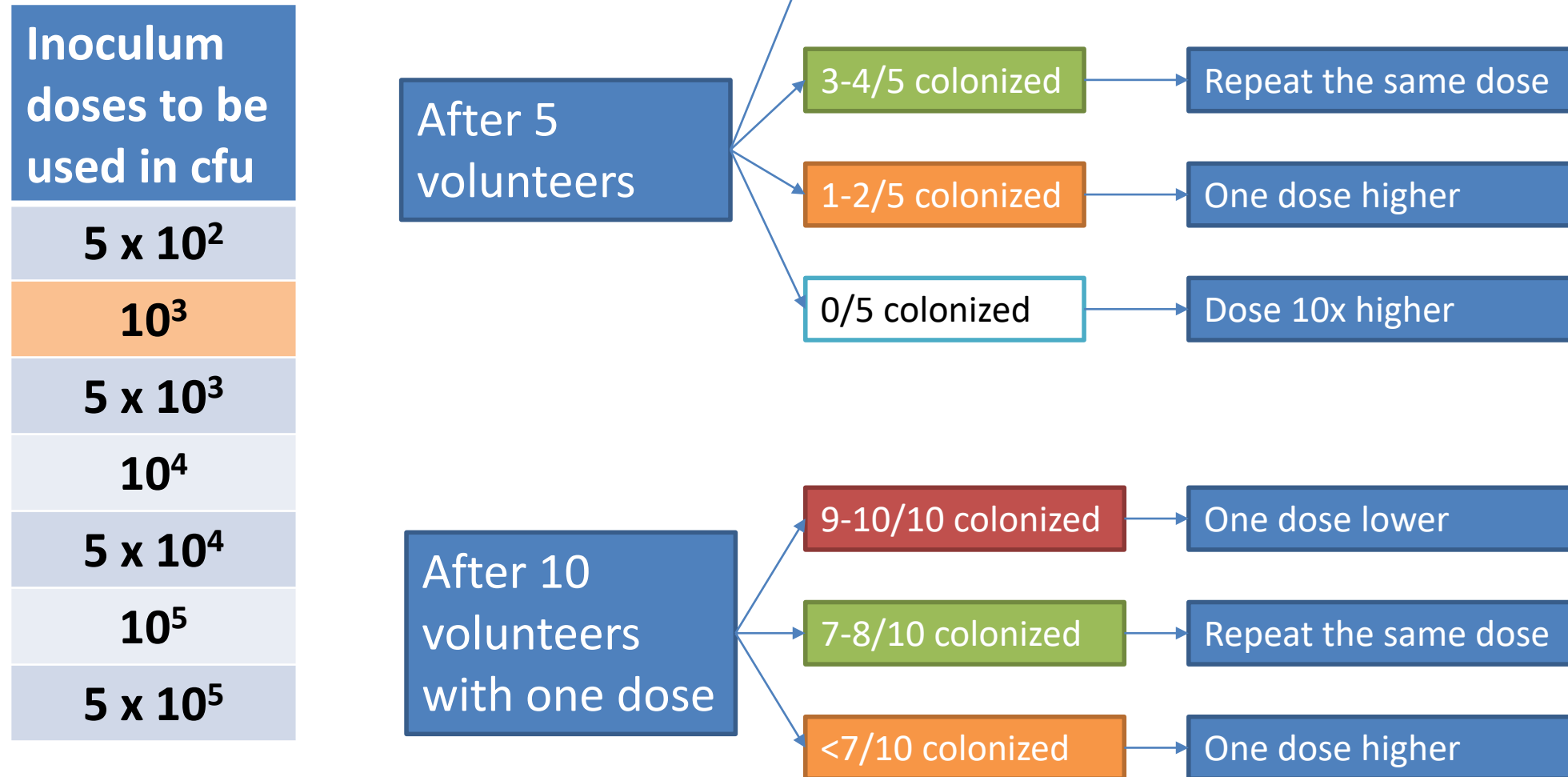


# PERISCOPE: colonisation model

- Target colonisation fraction  $\leq 80\%$



# Dose ranging study

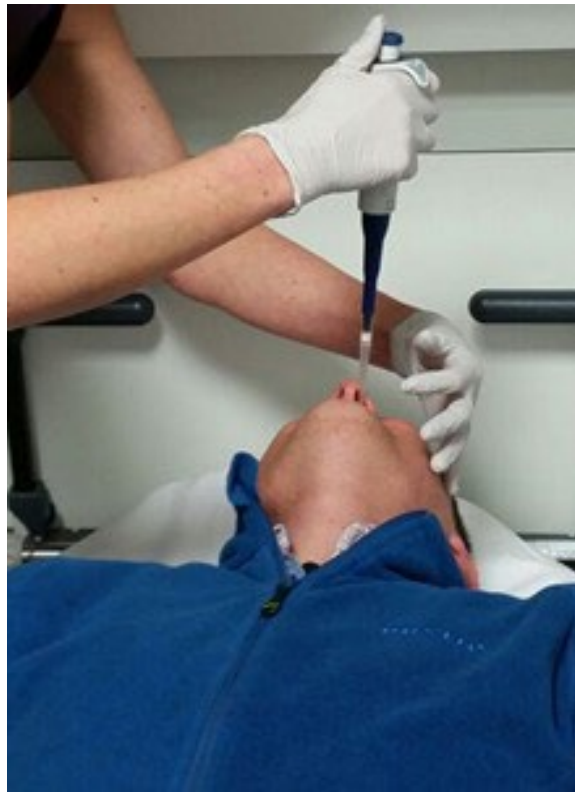


## Phase A – main findings

- Standard inoculum dose  $10^5$  CFU
- Colonisation fraction 0.8 (12 of 15 participants colonised)
- Safe
- Azithromycin effective in clearing colonisation
- No shedding detected
- Seroconversion in some colonised participants

De Graaf H. et al *Clinical Infectious Disease* 2000

# Diagnostics – Phase A

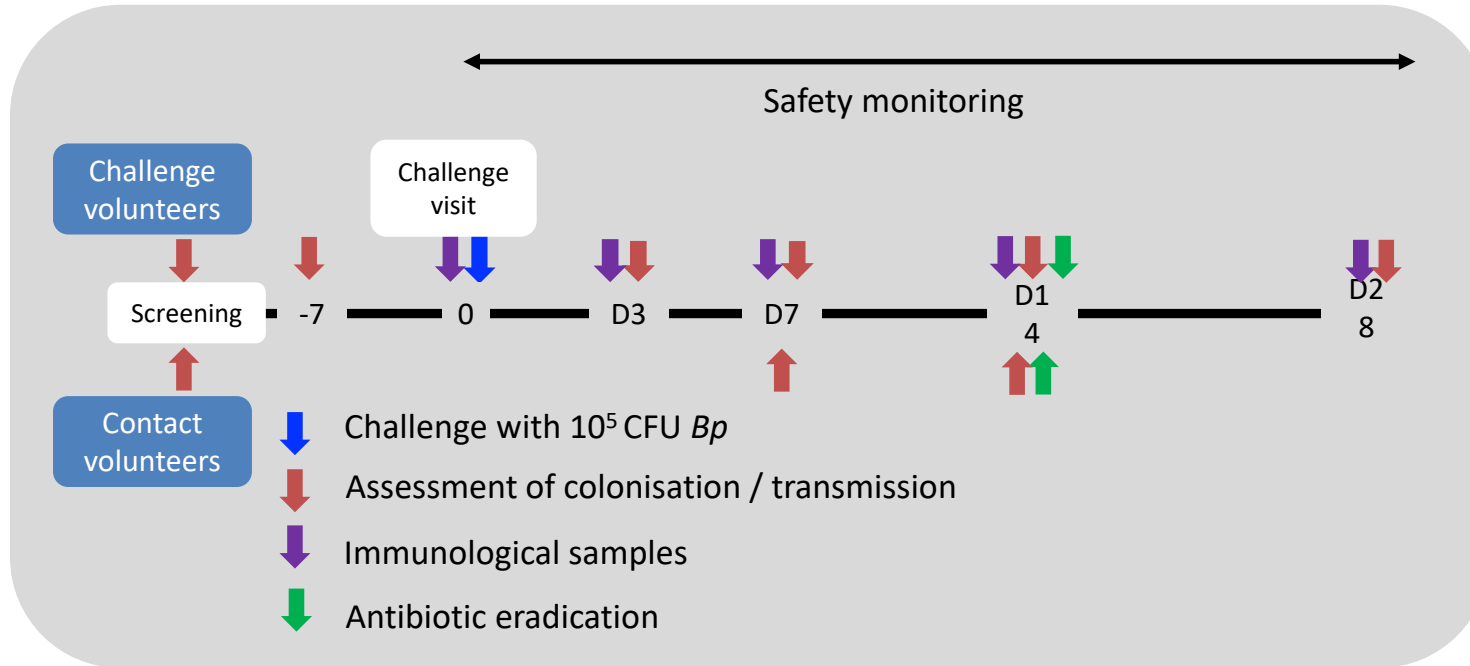


- Nasal wash most sensitive sampling technique
- Nasal wash culture and PCR equivalent
- Pernasal swab- culture 36% sensitive versus PCR 77%
- PCR of throat swabs detected 36% of all PCR positive samples (for pernasal swab this was 54%, and nasal wash 94%)

# Periscope Human Challenge Program Phase B

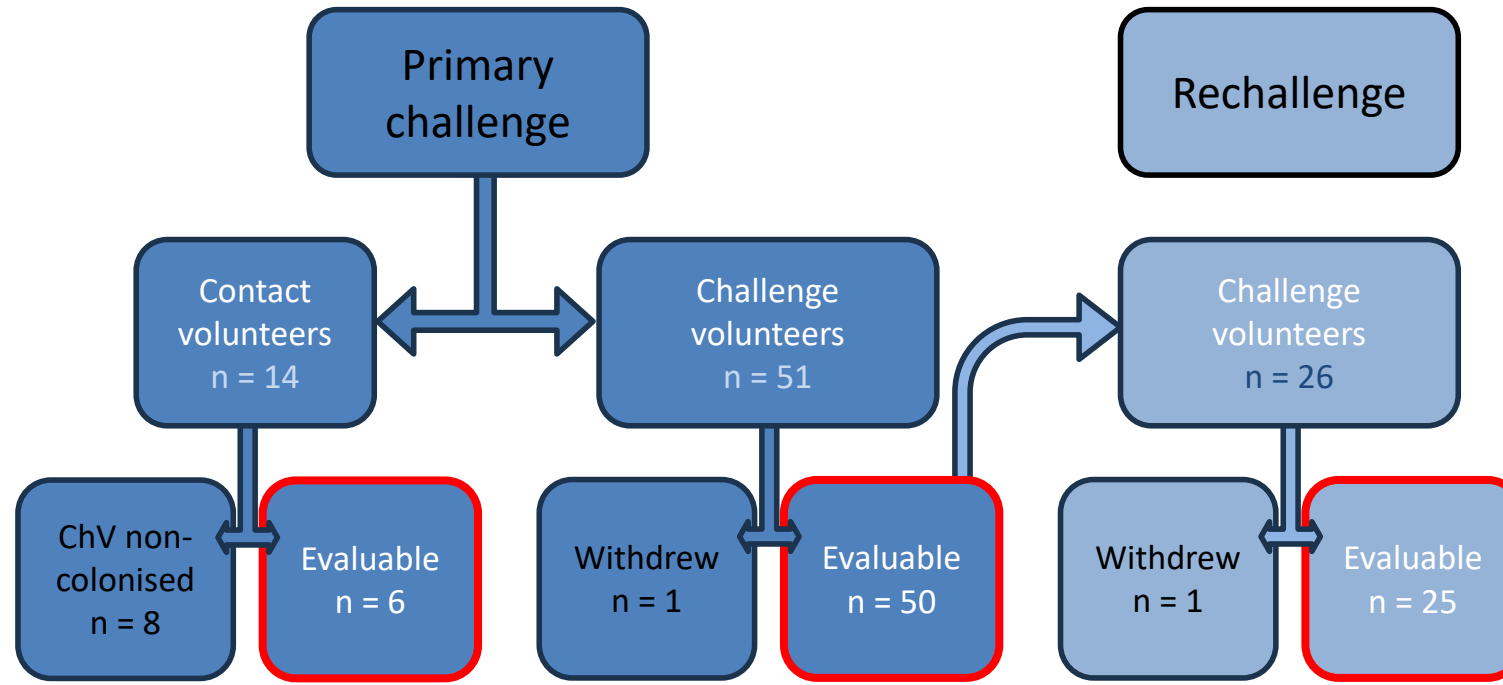
- Is there a pragmatic colonisation fraction in unselected volunteers?
- Does experimental colonisation elicit an immune response similar to natural infection?
- Is that immune response associated with protection on repeated challenge?
- Are non-colonised (`protected`) volunteers immunologically distinct?
- Do colonised people transmit to close contacts?
- Can the experimental model be conducted in an outpatient setting?

# PERISCOPE Phase B



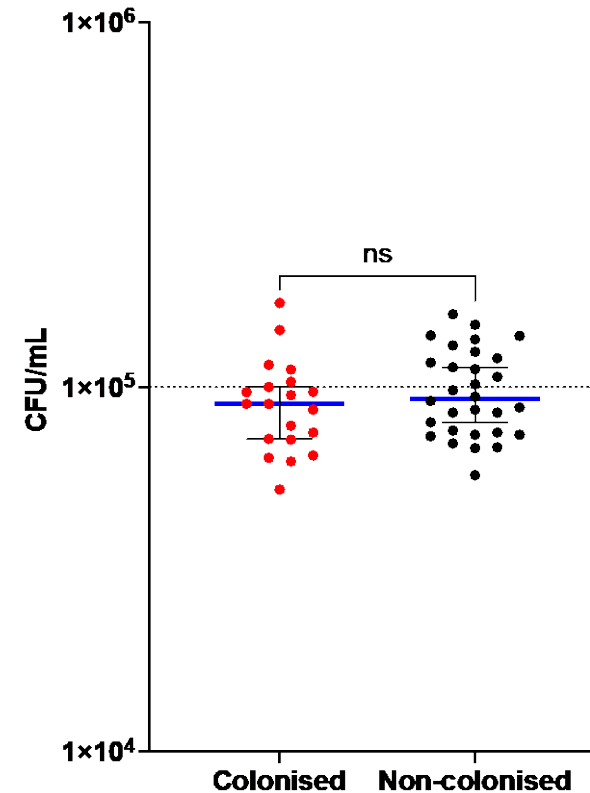
- Optional rechallenge after 3 – 4.5 months

# Phase B recruitment

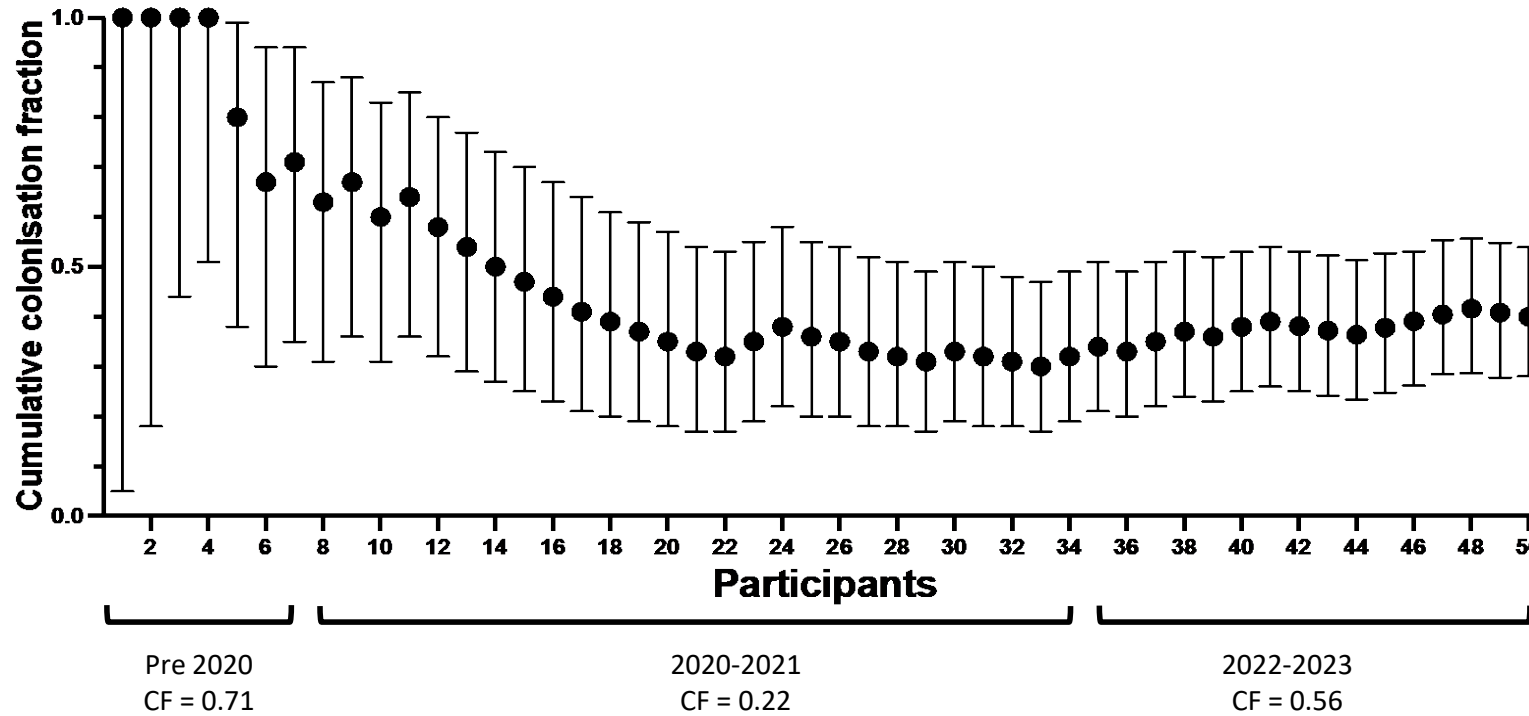


## Primary challenge: Colonisation

- **20 of 50** Challenge volunteers colonised
- Colonisation fraction = 0.4
- No difference in inoculum
- 14 contact volunteers enrolled
  - 6 corresponding Challenge volunteer colonised
  - No transmission detected



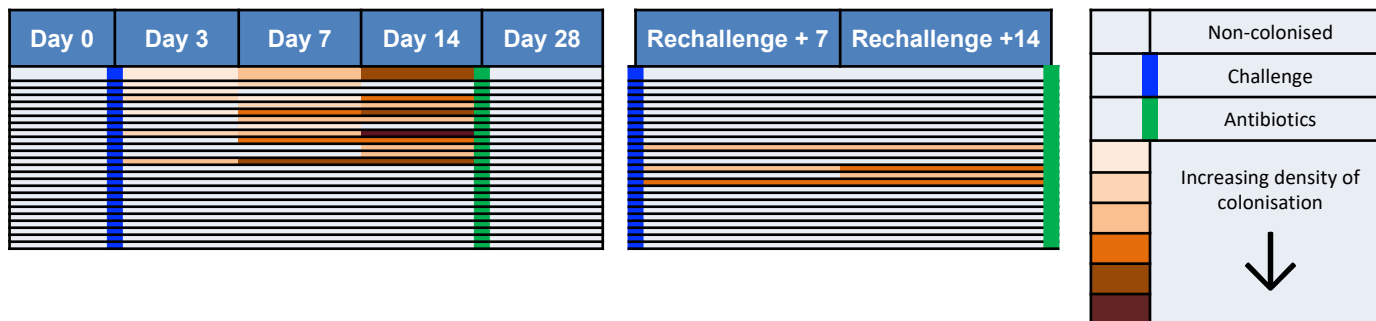
# Primary challenge: Colonisation





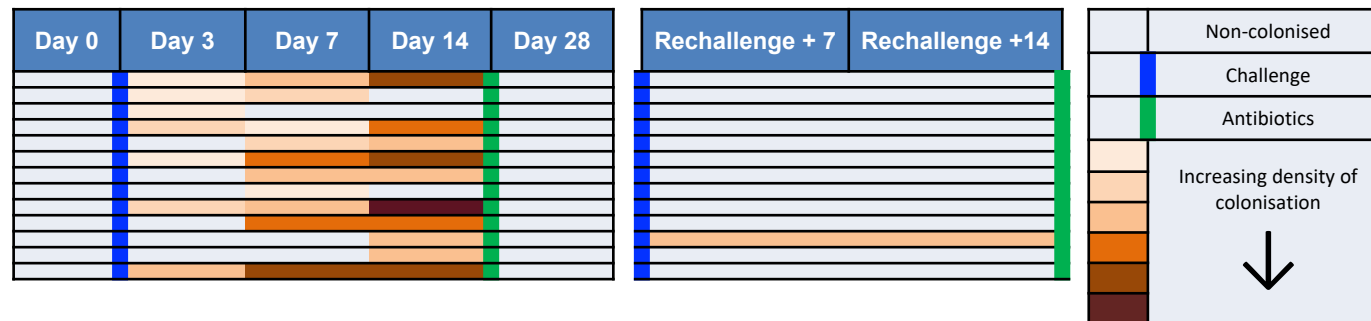
## Rechallenge: Colonisation

- 25 rechallenged
  - 4 colonised, colonisation fraction 0.16
  - Primary challenge is protective against colonisation at rechallenge
  - $p = 0.04$  (Fisher's exact test)



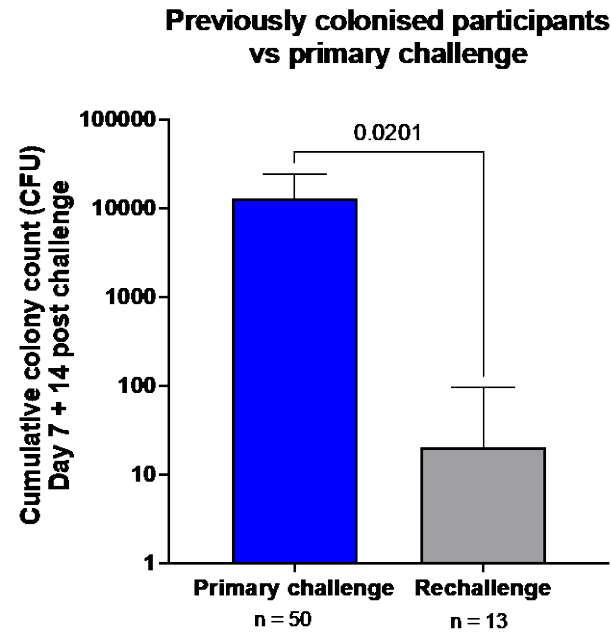
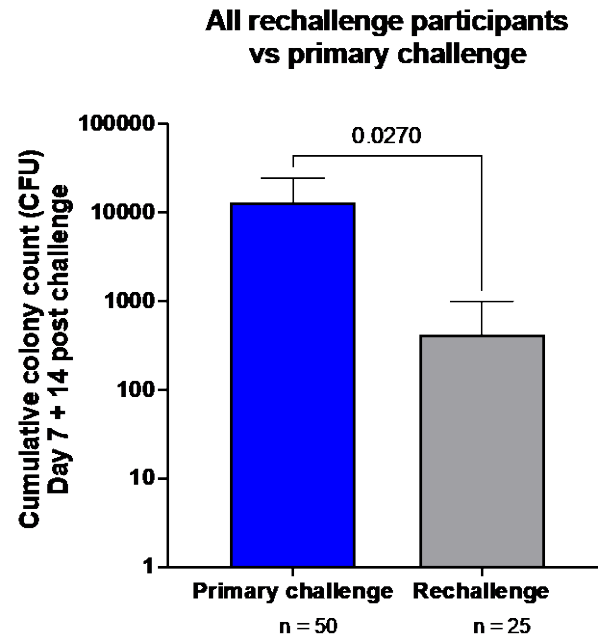
## Rechallenge: Colonisation

- 13 colonised at primary challenge
  - 1 recolonised
  - Colonisation fraction 0.08
  - Previous colonisation is protective against colonisation at rechallenge
  - $p = 0.045$  (Fisher's exact test)

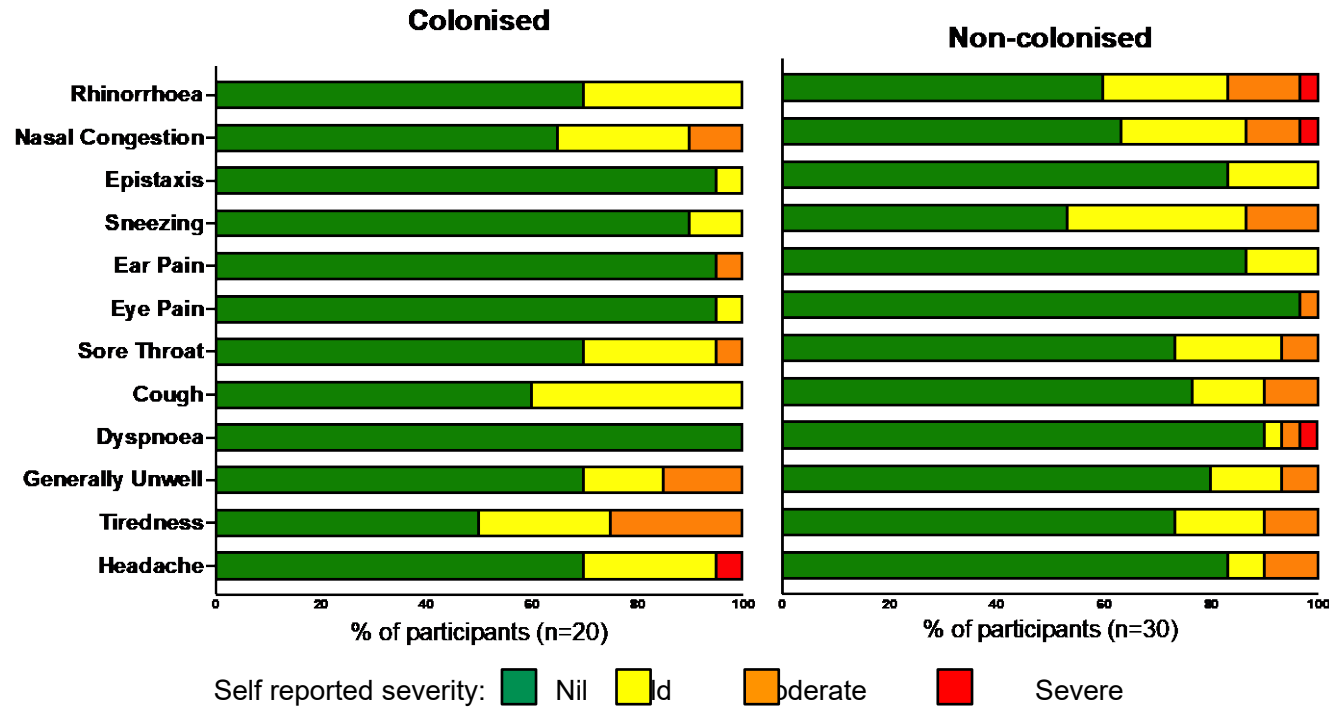


# Rechallenge: Colonisation density

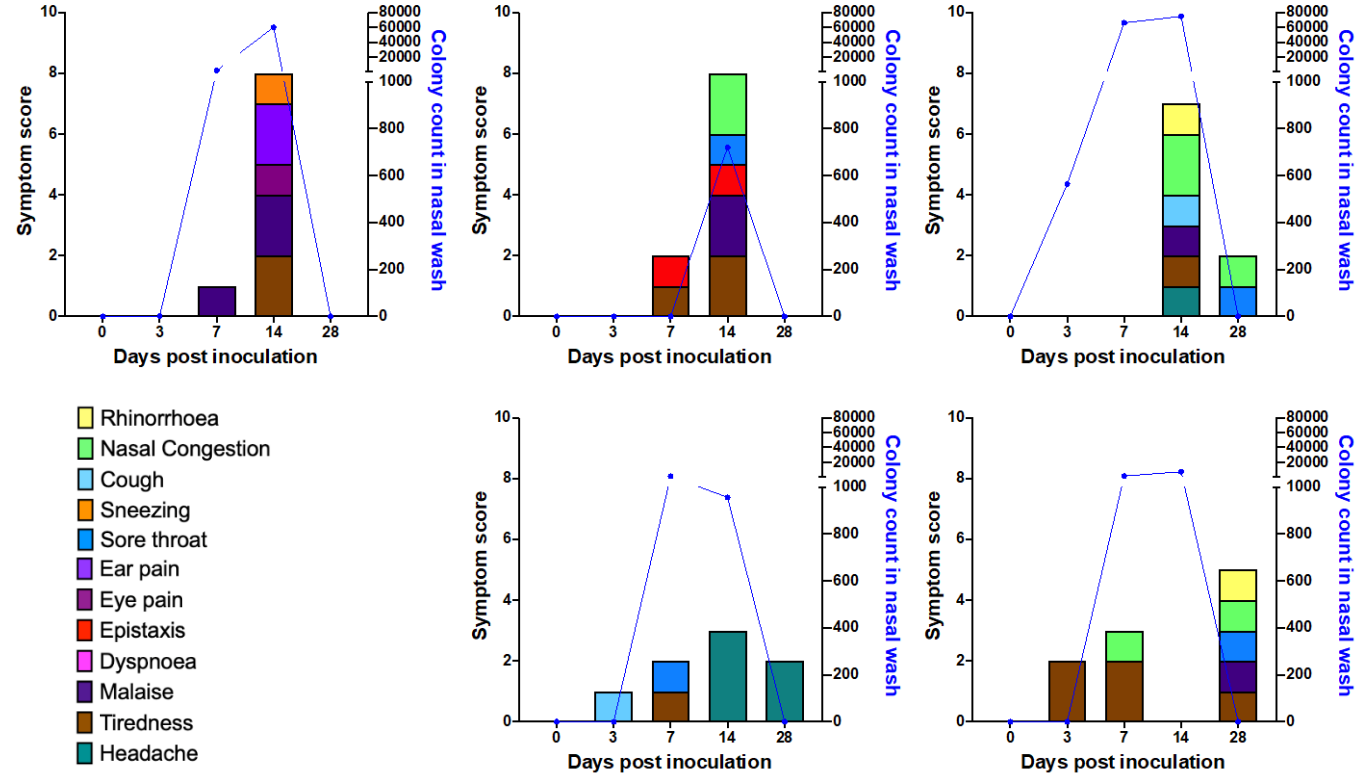
- Colonisation density at rechallenge is lower than at primary challenge (Mann Whitney test)



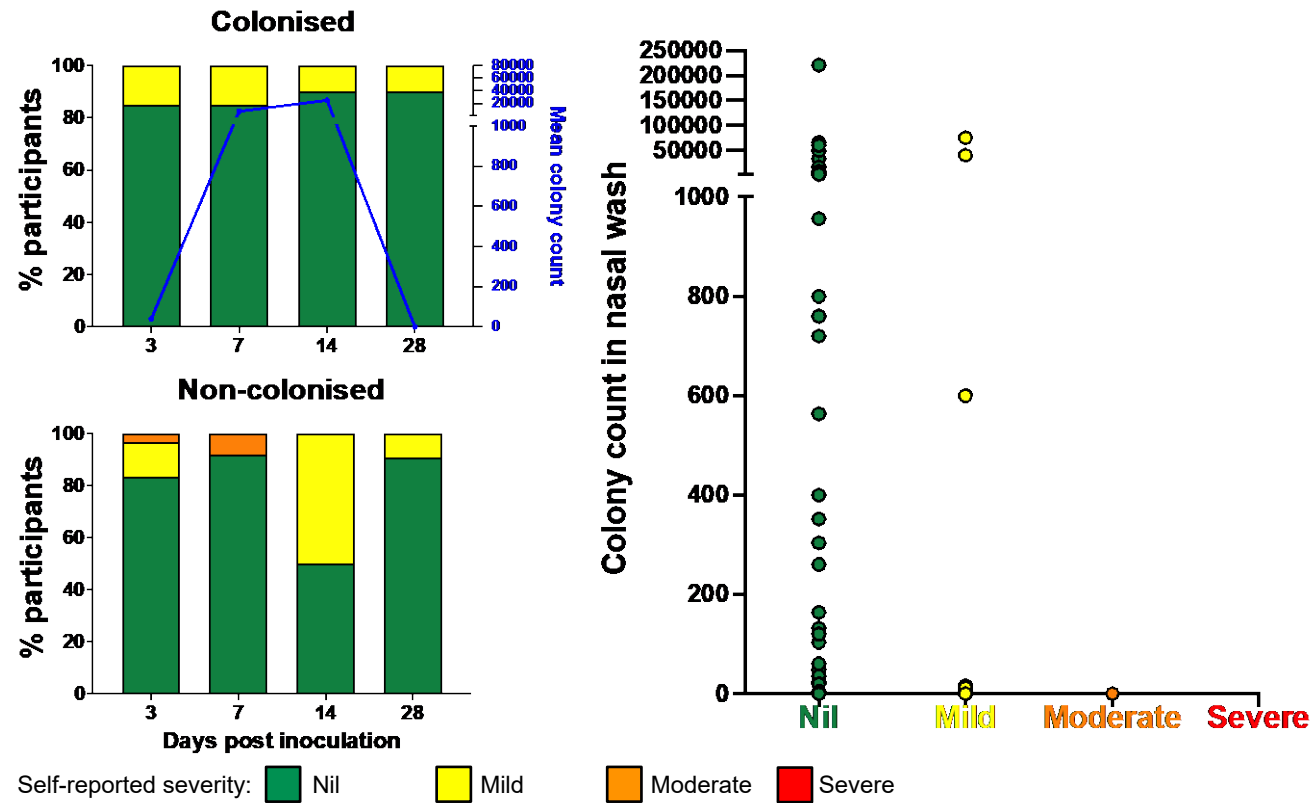
# Safety: Solicited adverse events Day 0-14 post primary challenge



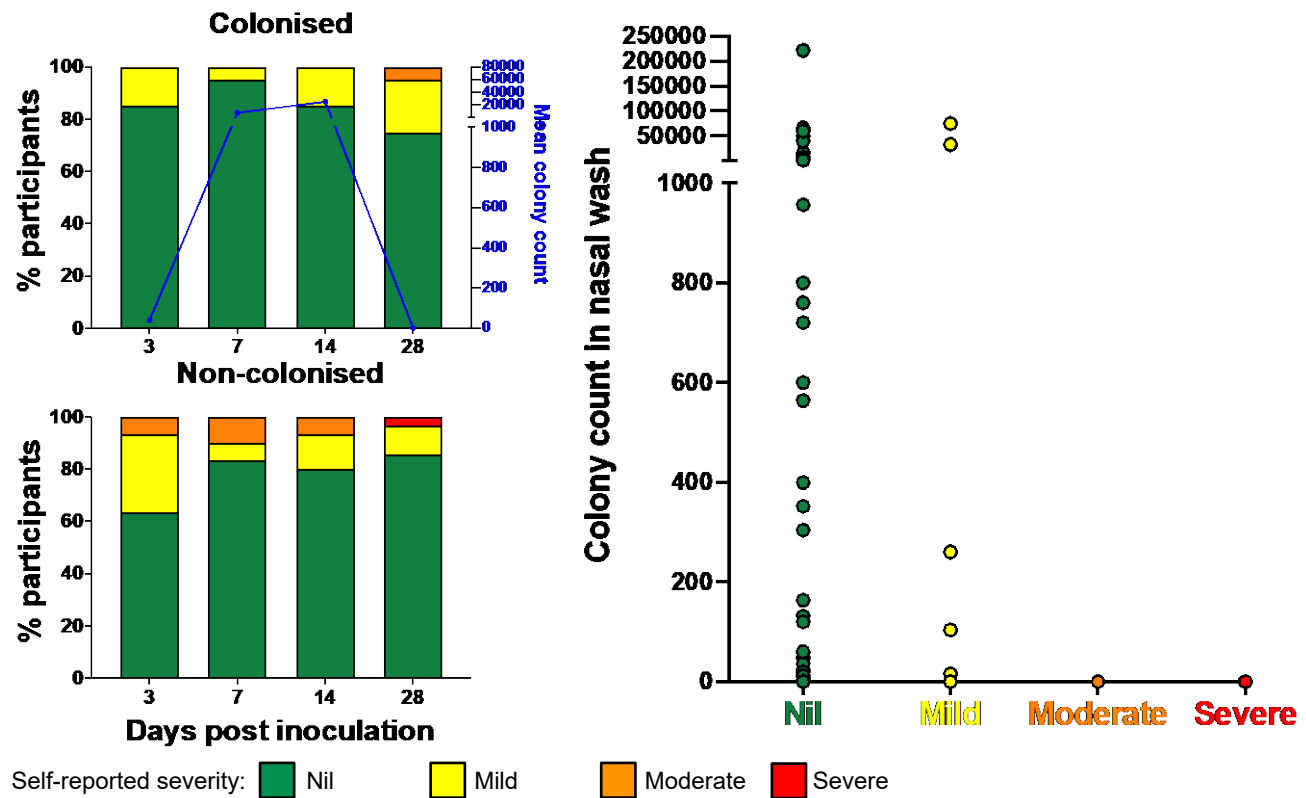
# Symptoms in colonised participants



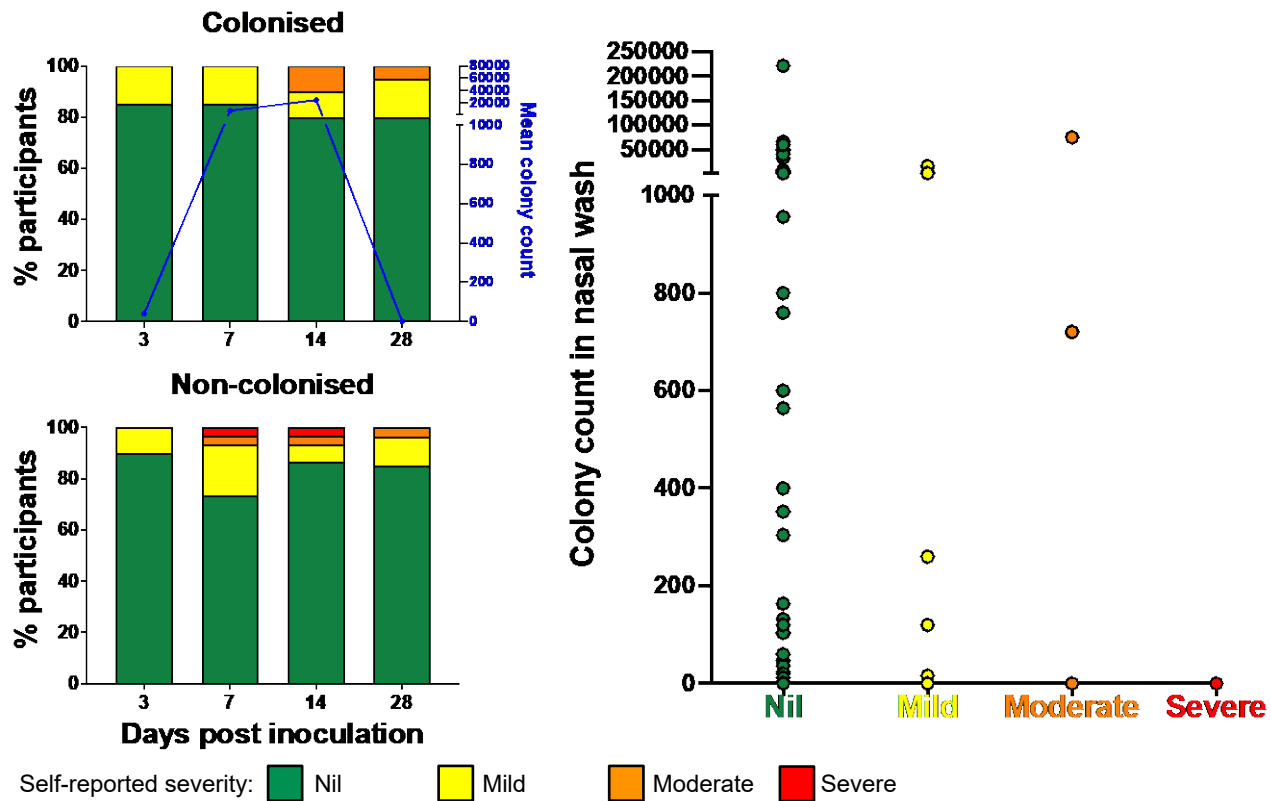
# Cough



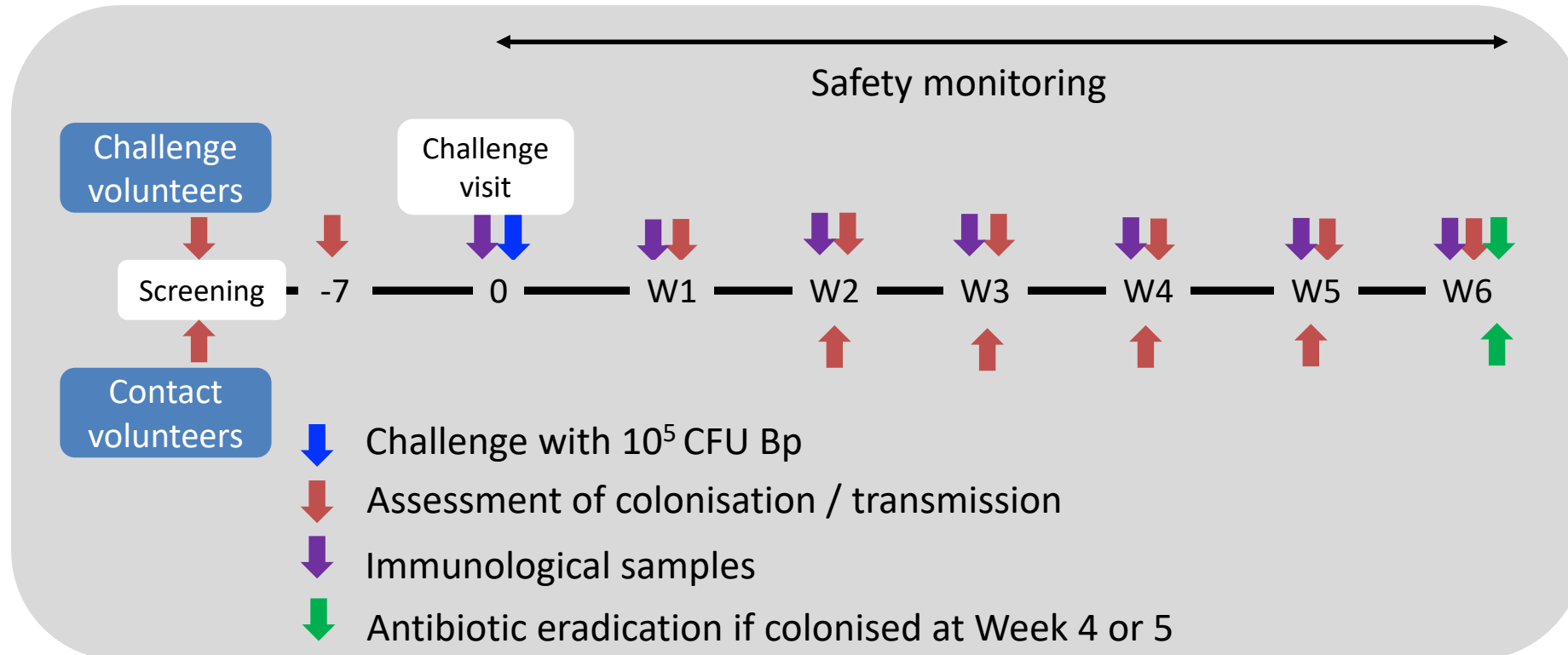
# Rhinorrhoea



## Nasal congestion



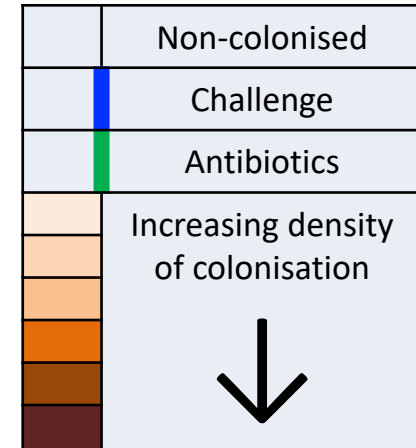
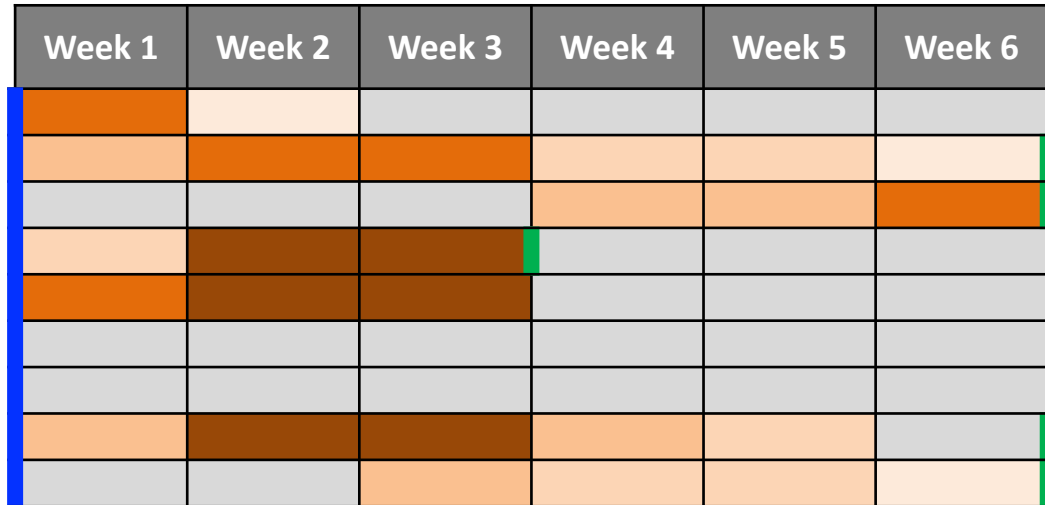
# Phase C – Extended colonisation



- Planned sample size = 10 colonised challenge volunteers

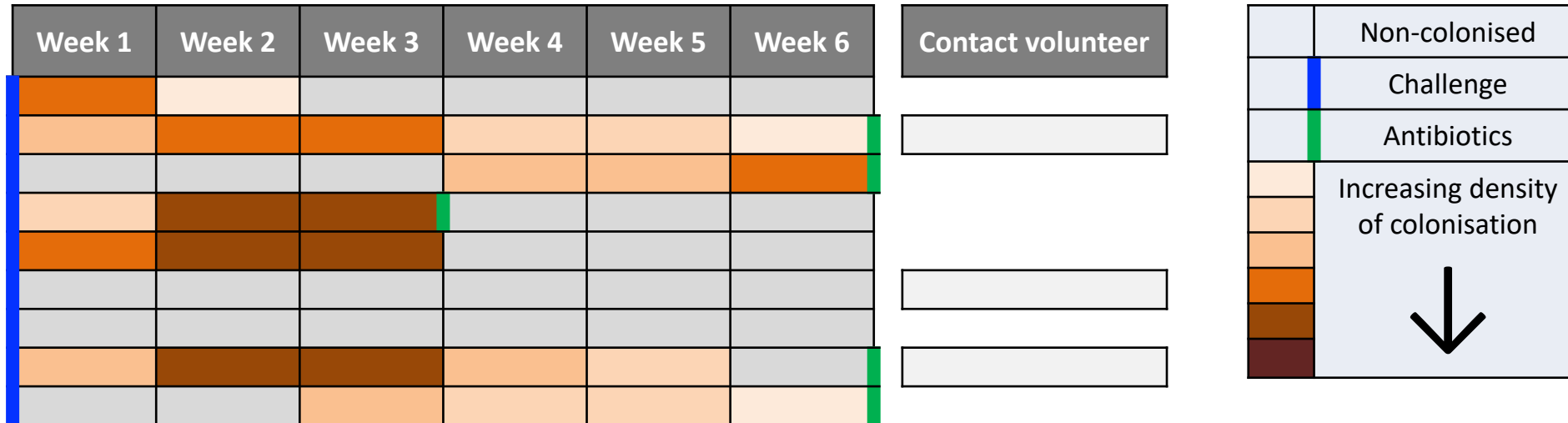
# Colonisation

- 9 Challenge volunteers completed study, 1 ongoing
  - Colonisation fraction 0.56 by Day 14 (5 of 9), 0.78 by Day 28 (7 of 9)
  - Spontaneous clearance seen in three participants
  - No safety concerns related to *Bp* colonisation



# Transmission

- 3 Contact volunteers enrolled
  - 2 corresponding challenge volunteer colonised
  - No transmission detected

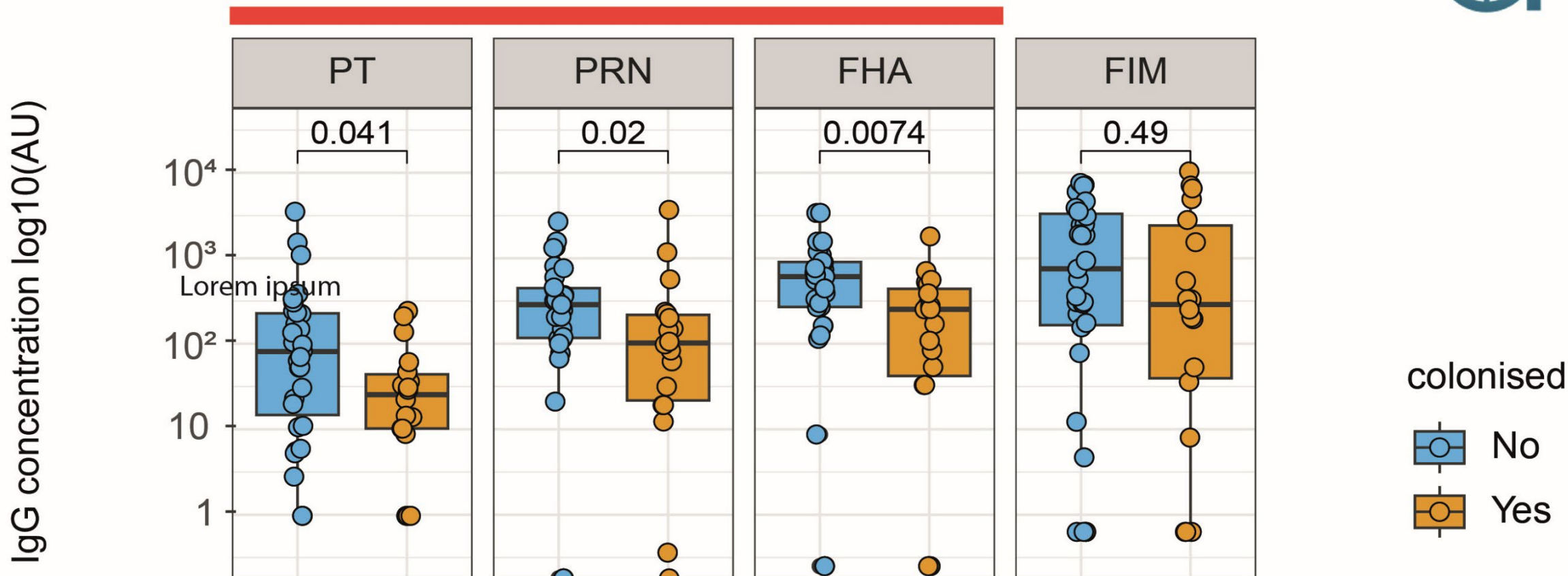


Do colonised and non-colonised volunteers differ immunologically?

# Non-colonised versus colonised – serum IgG



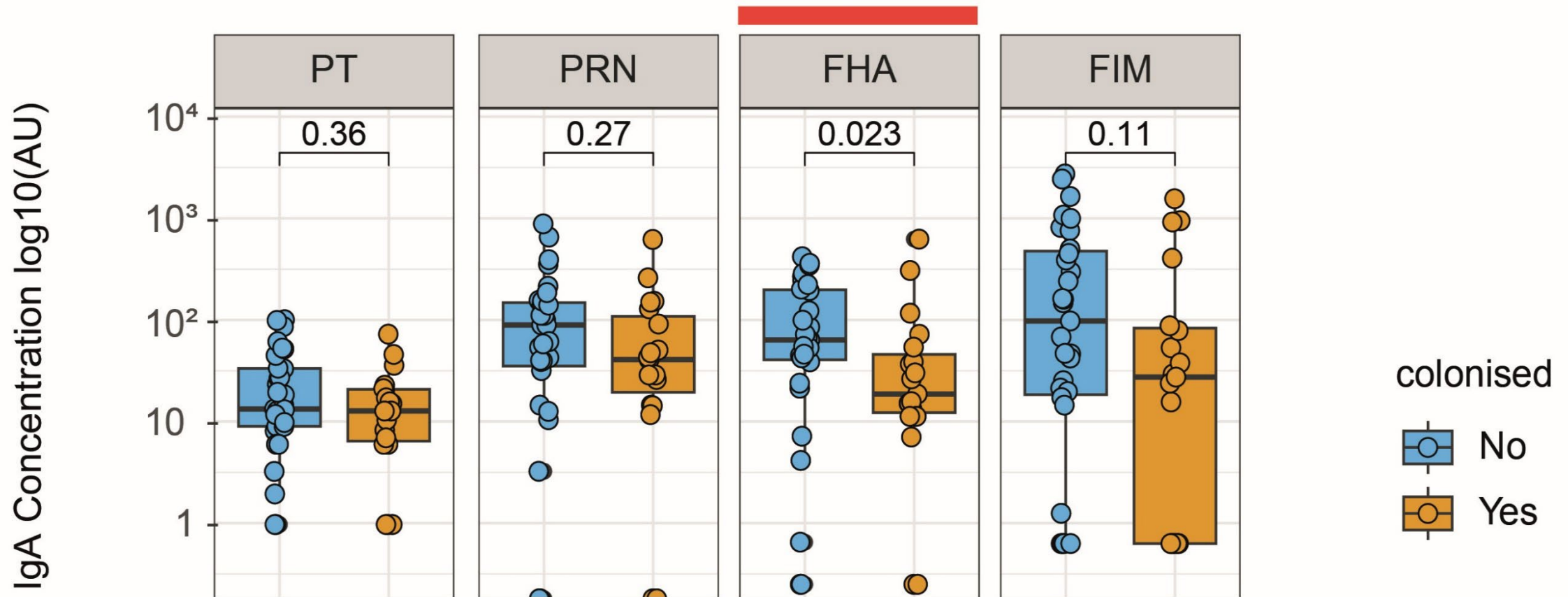
Baseline



# Non-colonised versus colonised – serum IgA



Baseline

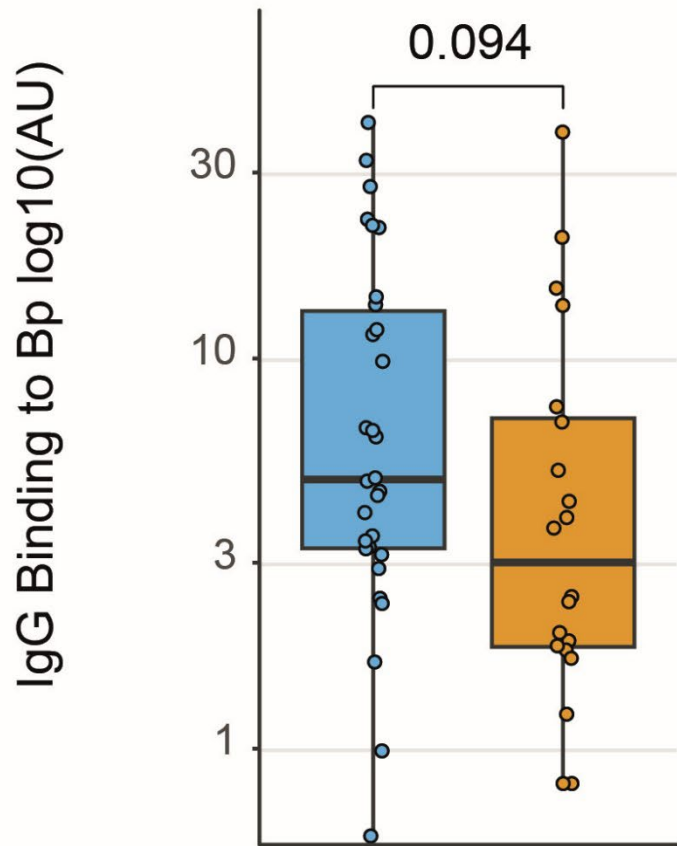


# Non-colonised versus colonised – serum Bp binding

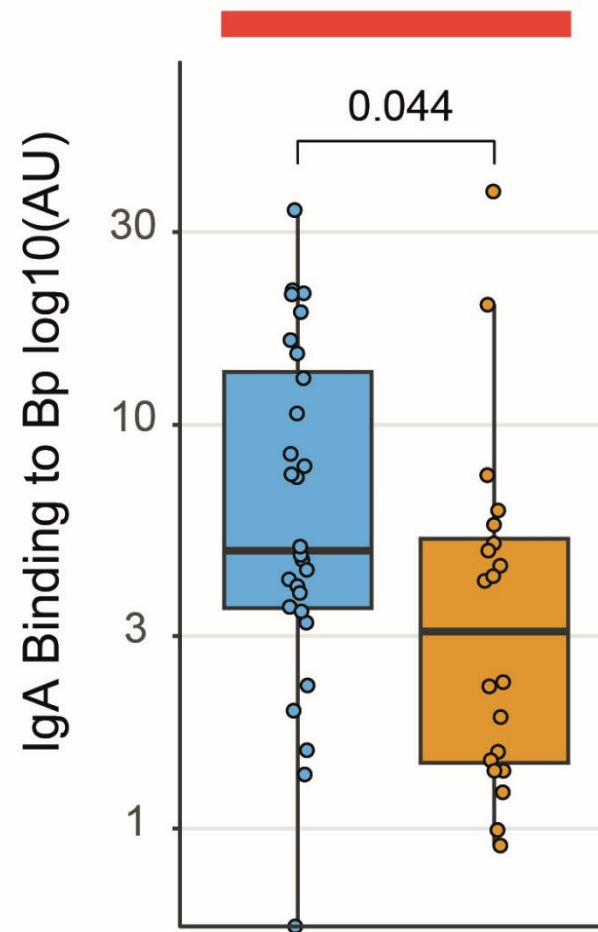


Baseline

## IgG



## IgA

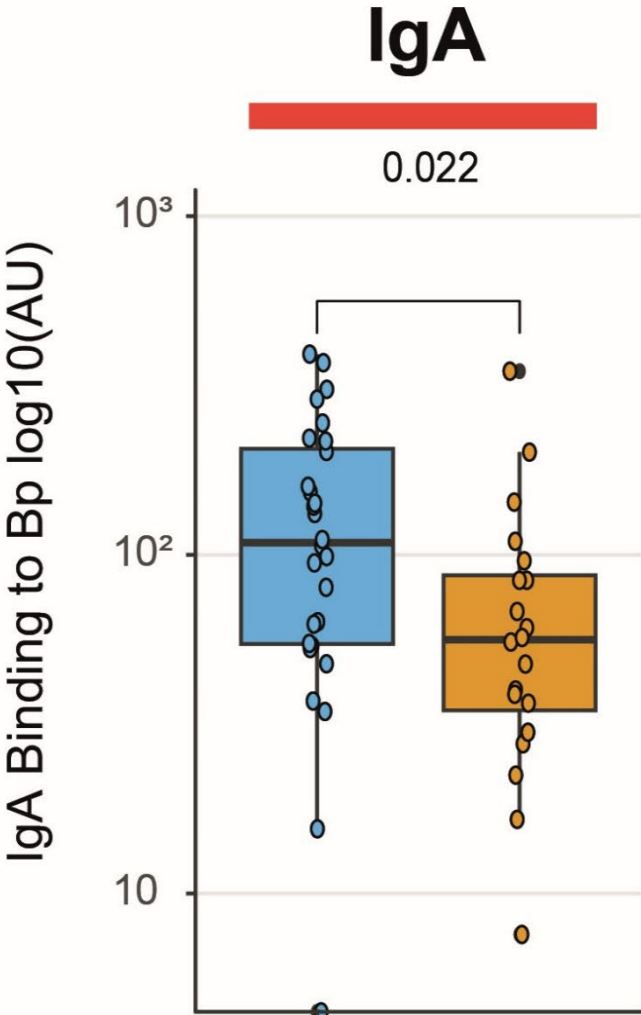
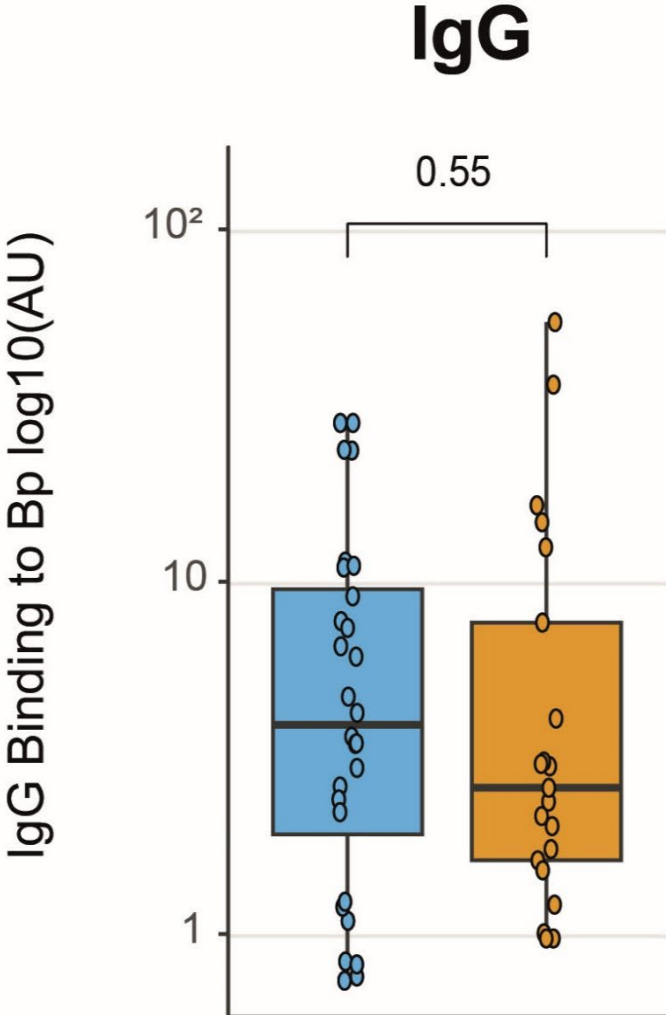


colonised

 No

 Yes

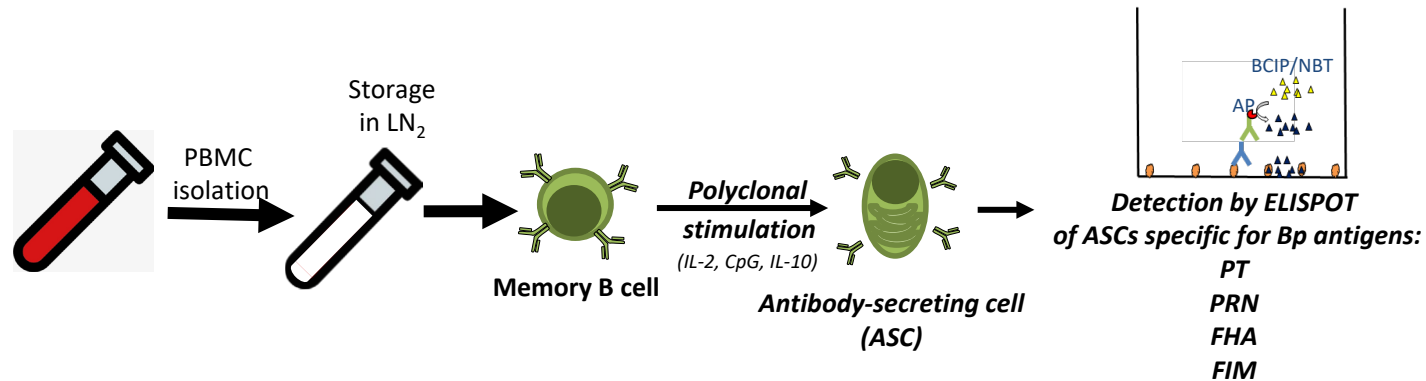
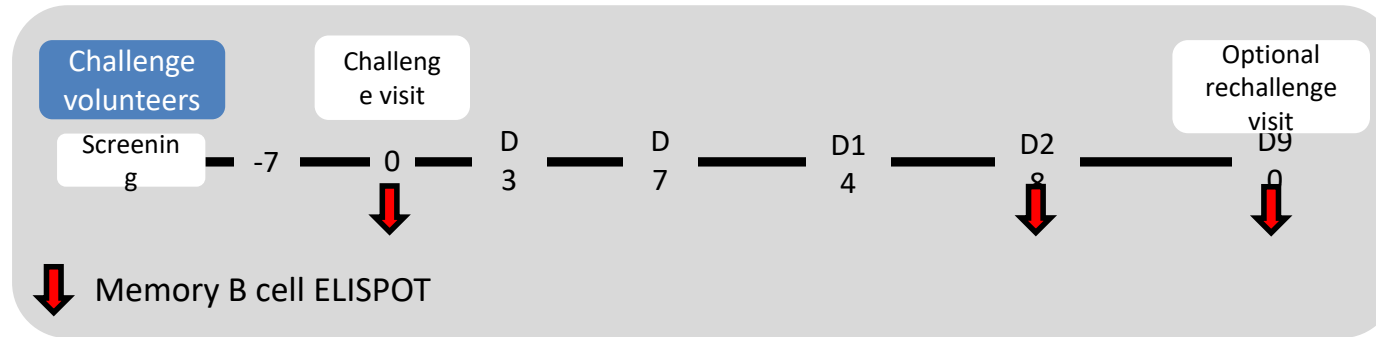
# Non-colonised versus colonised — mucosal fluid Bp binding



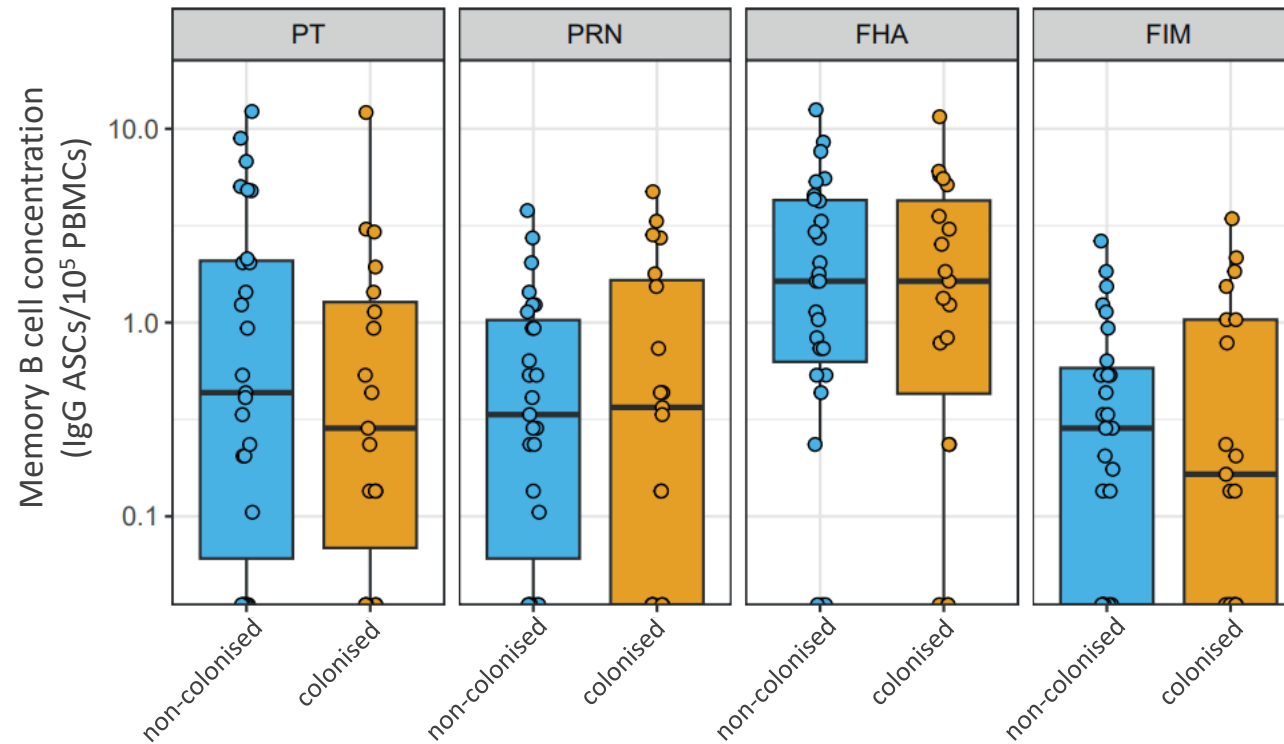
colonised

- No
- Yes

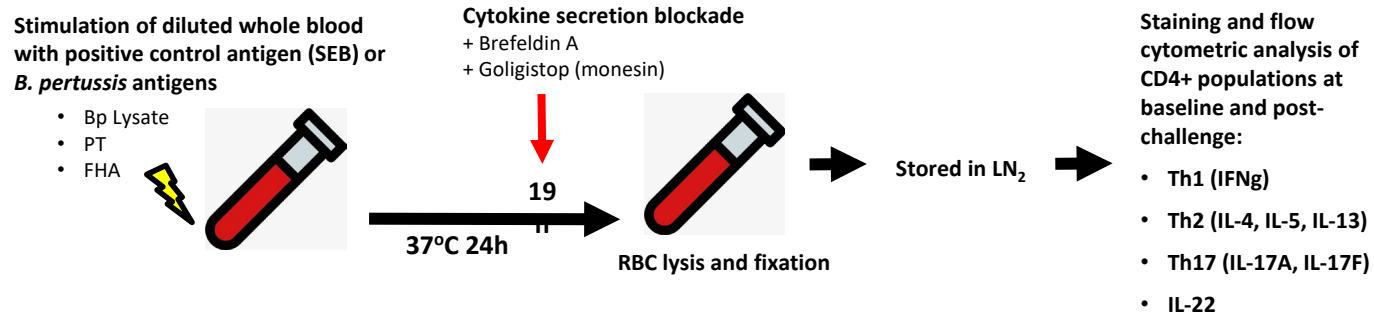
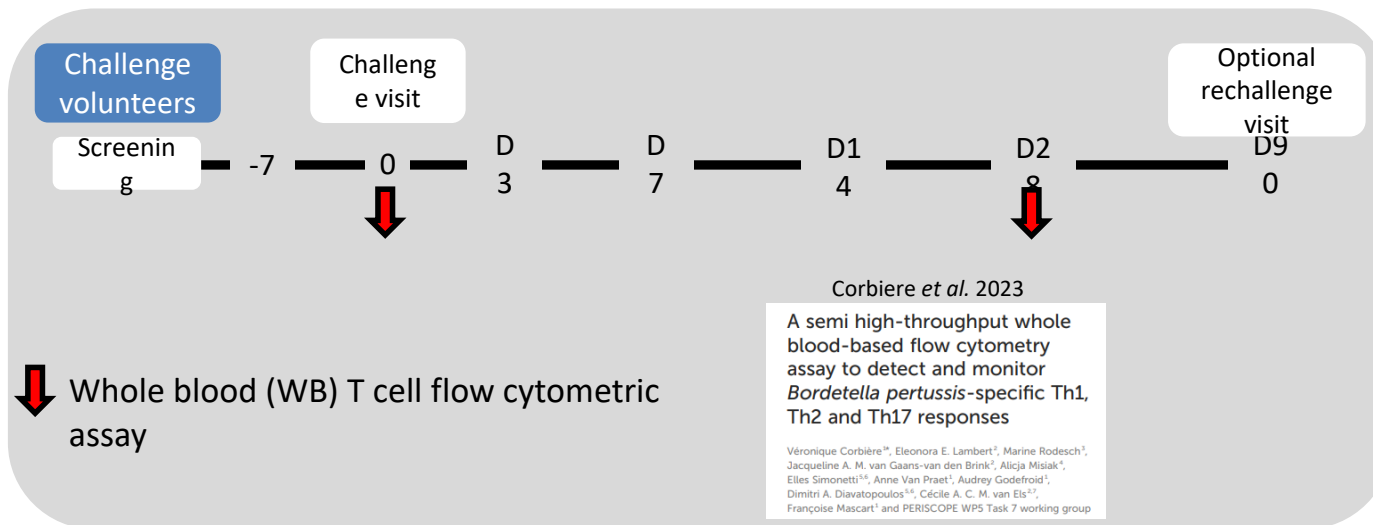
## Investigating memory B cell responses



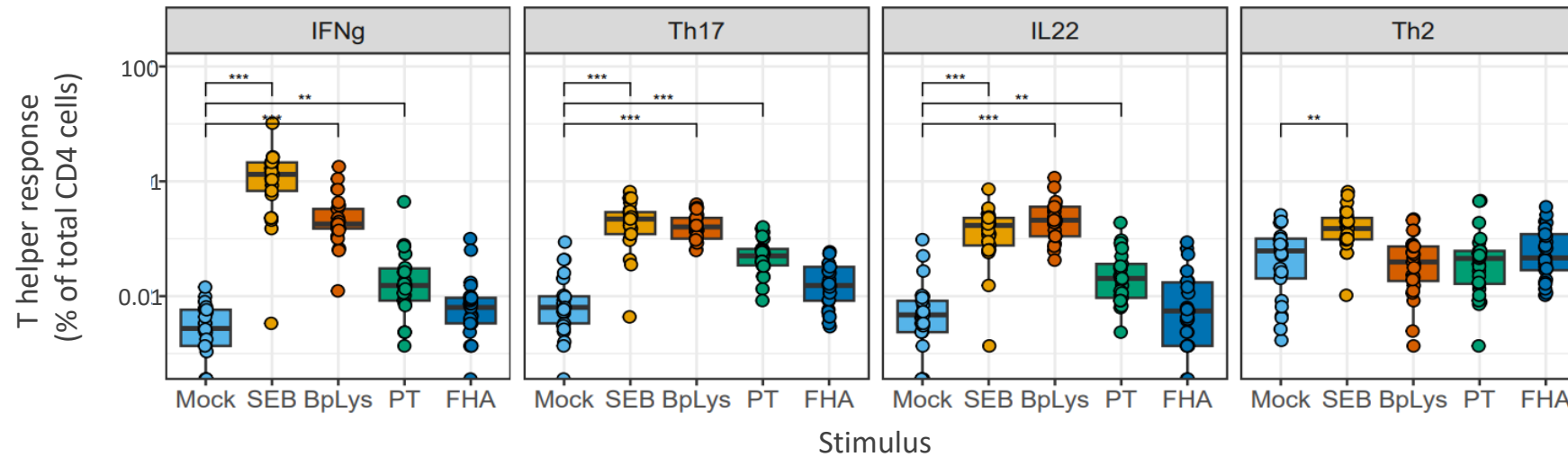
## Baseline memory B cell concentrations



# Investigating T helper cell responses

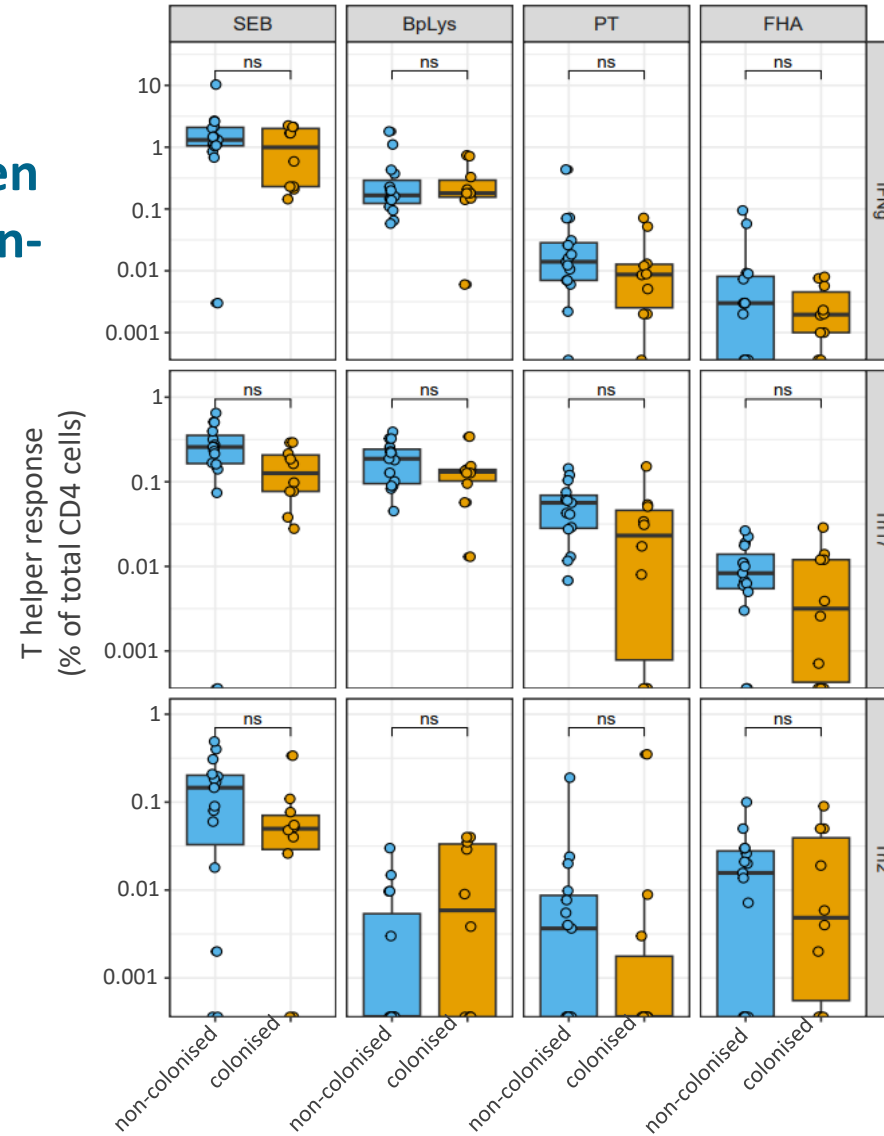


## Baseline T helper cell responses to Bp antigens

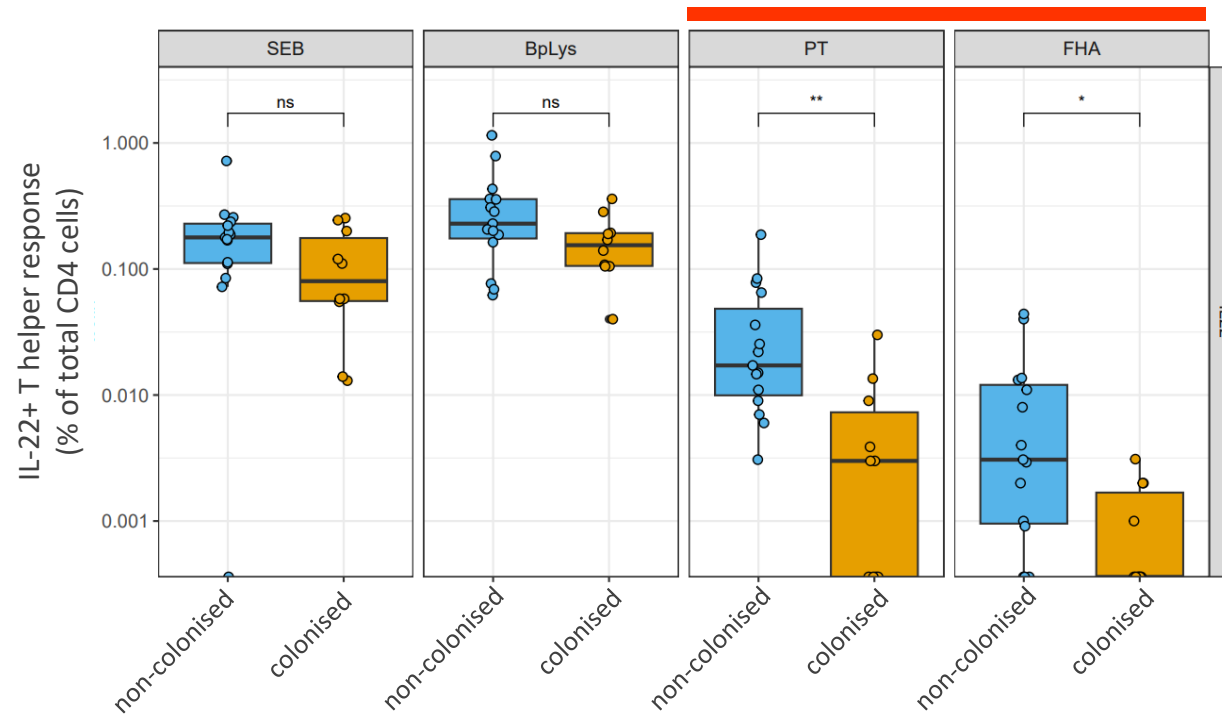


# Baseline comparison between T helper cell responses in non-colonised and colonised volunteers

Data is mock subtracted

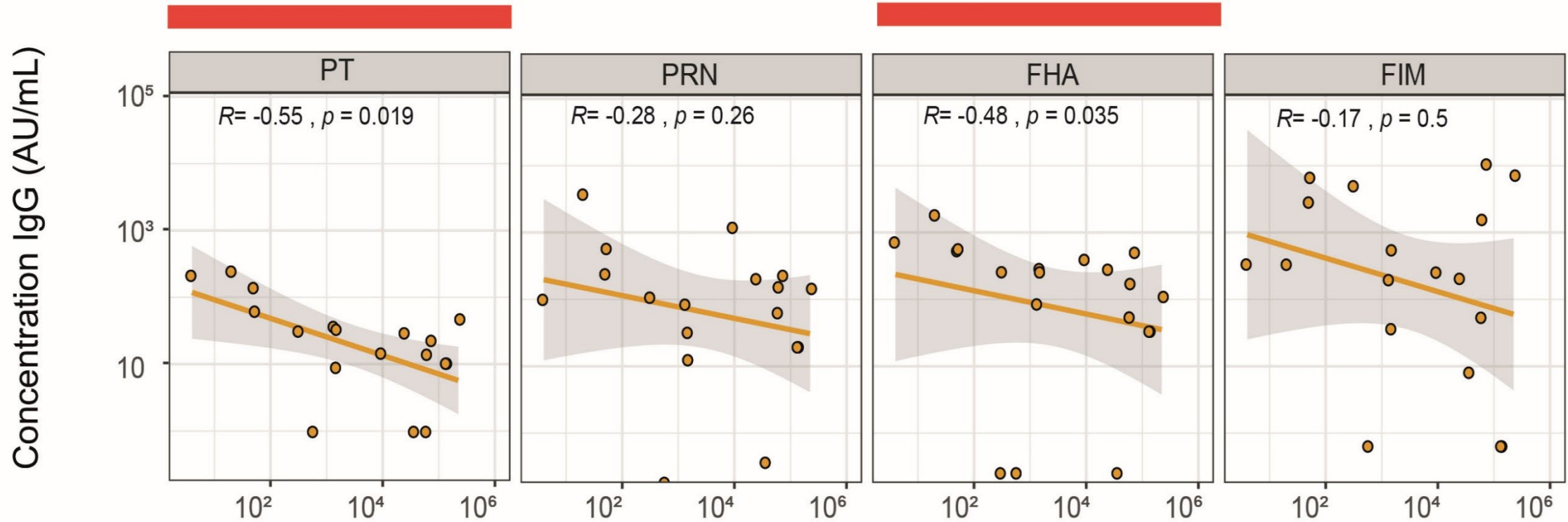


# Baseline IL-22+ T helper cell responses



# Control of colonisation density - Serum IgG

Baseline

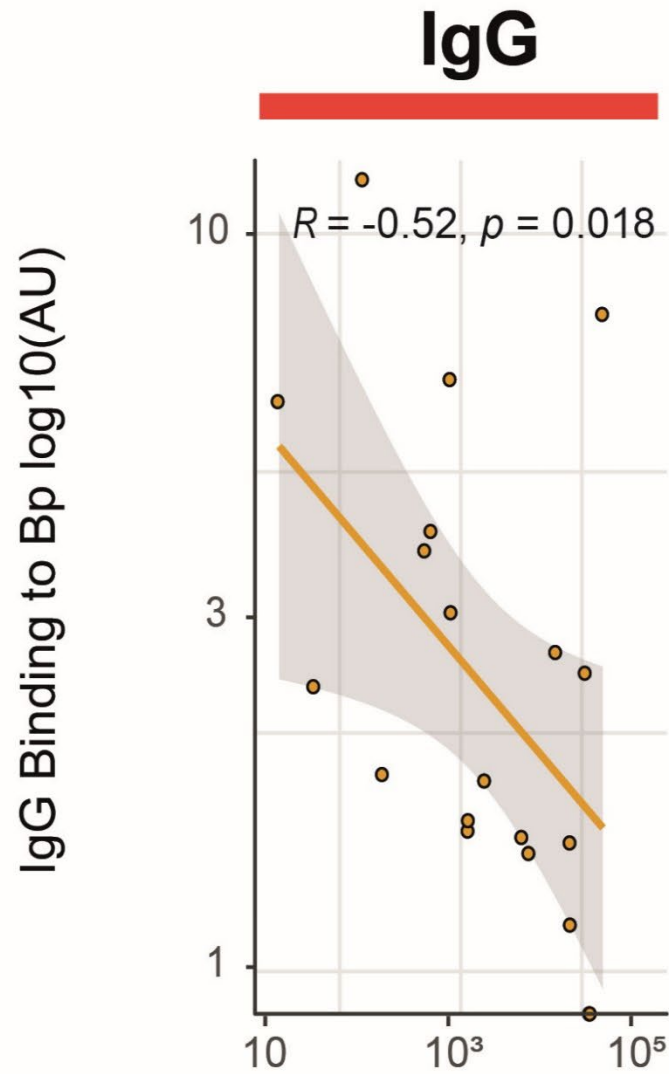


Total CFU in period 0 - 14 days after challenge



# Control of colonisation density - Serum Bp binding

Baseline

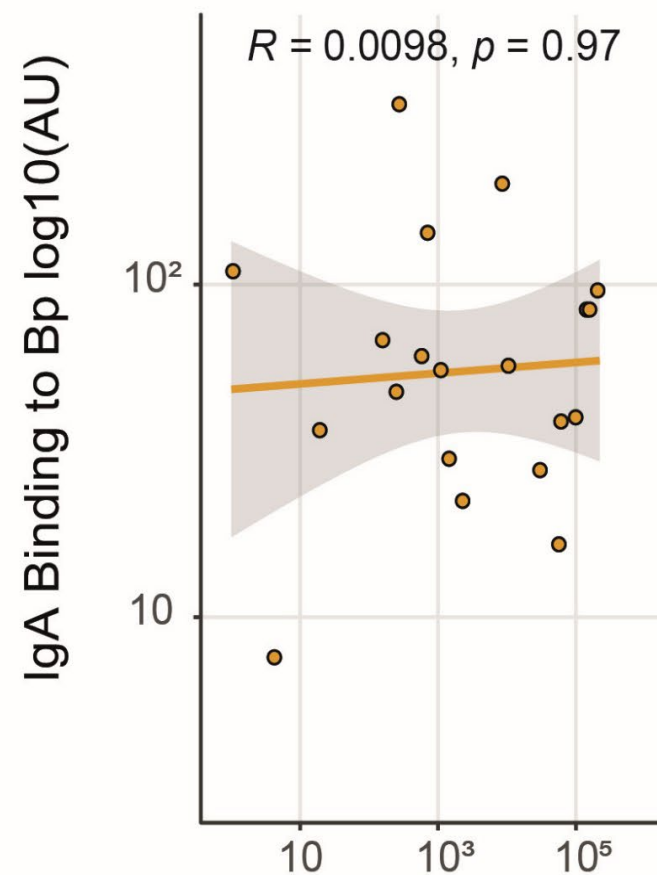
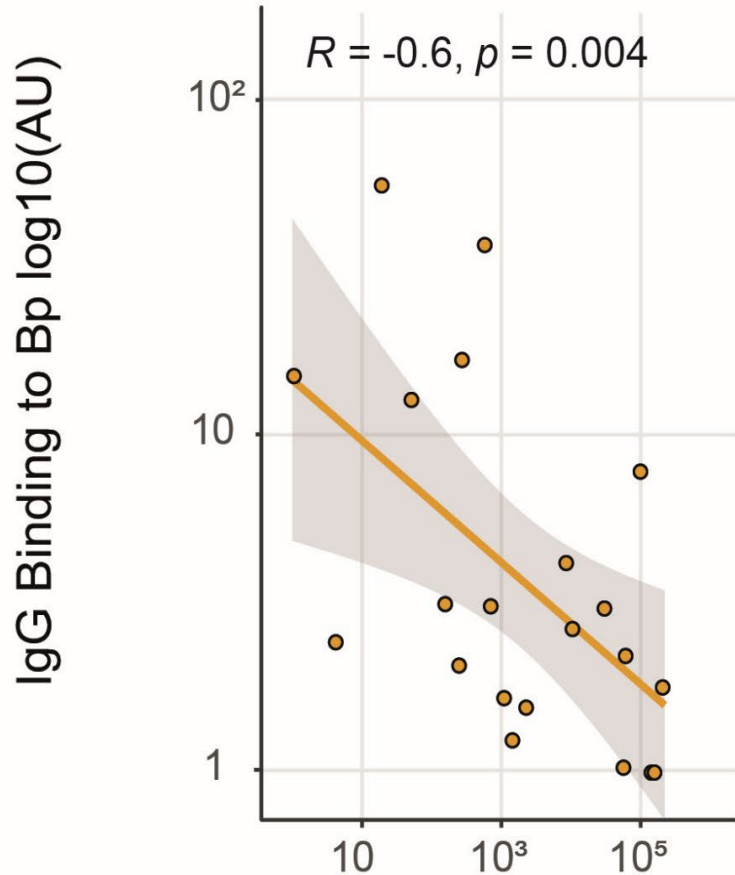


# Control of colonisation - MLF Bp binding

Baseline

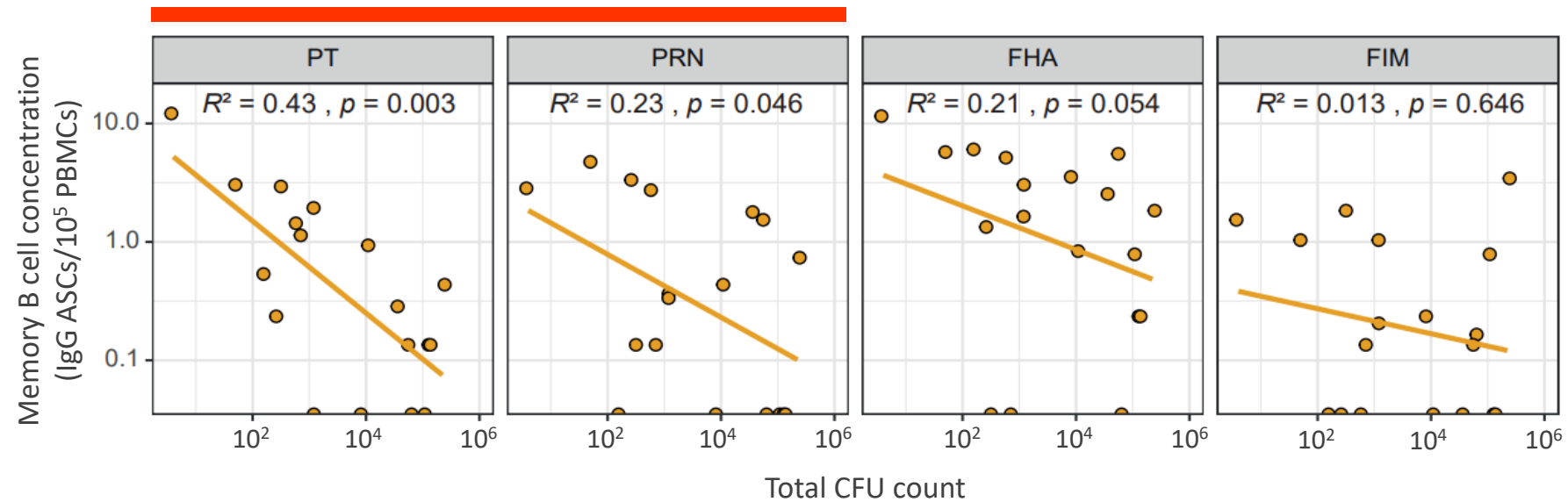
**IgG**

**IgA**



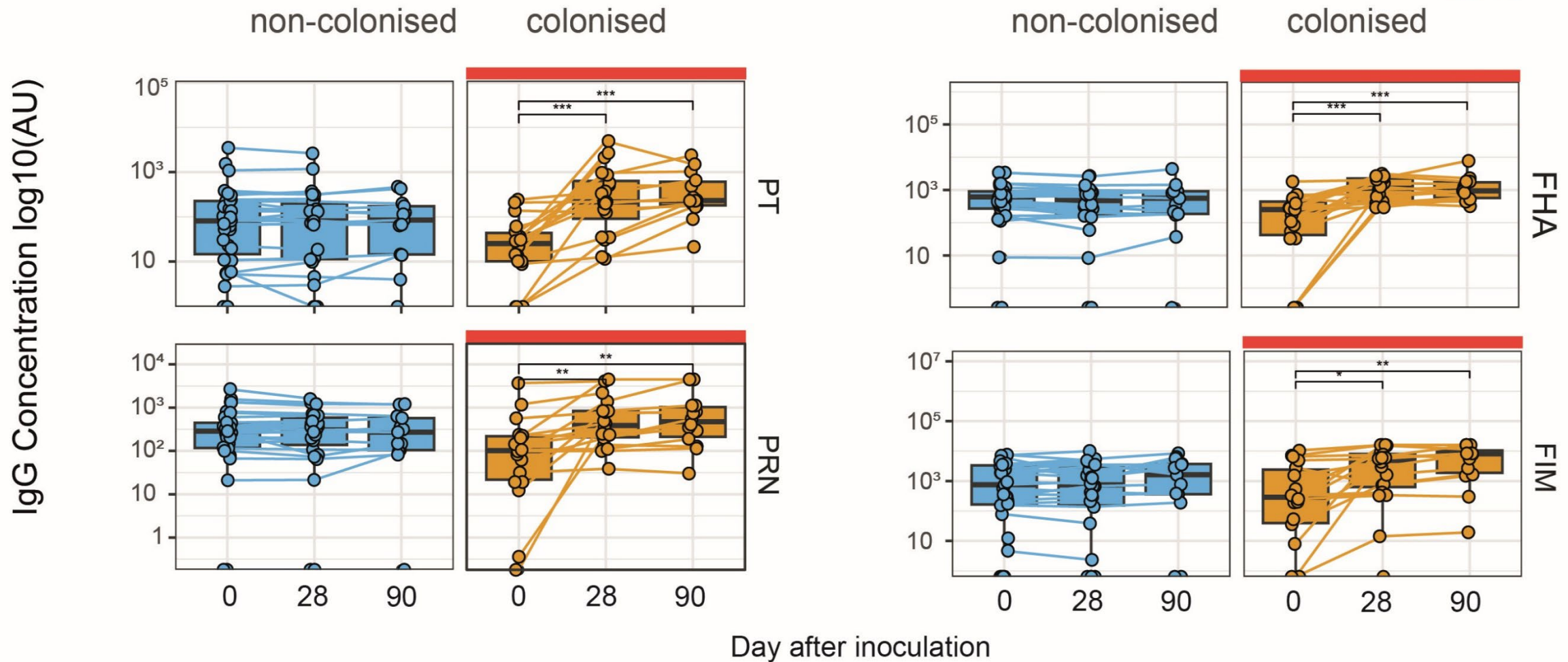
Total CFU count

## Baseline memory B cell concentrations inversely correlate with colonisation density

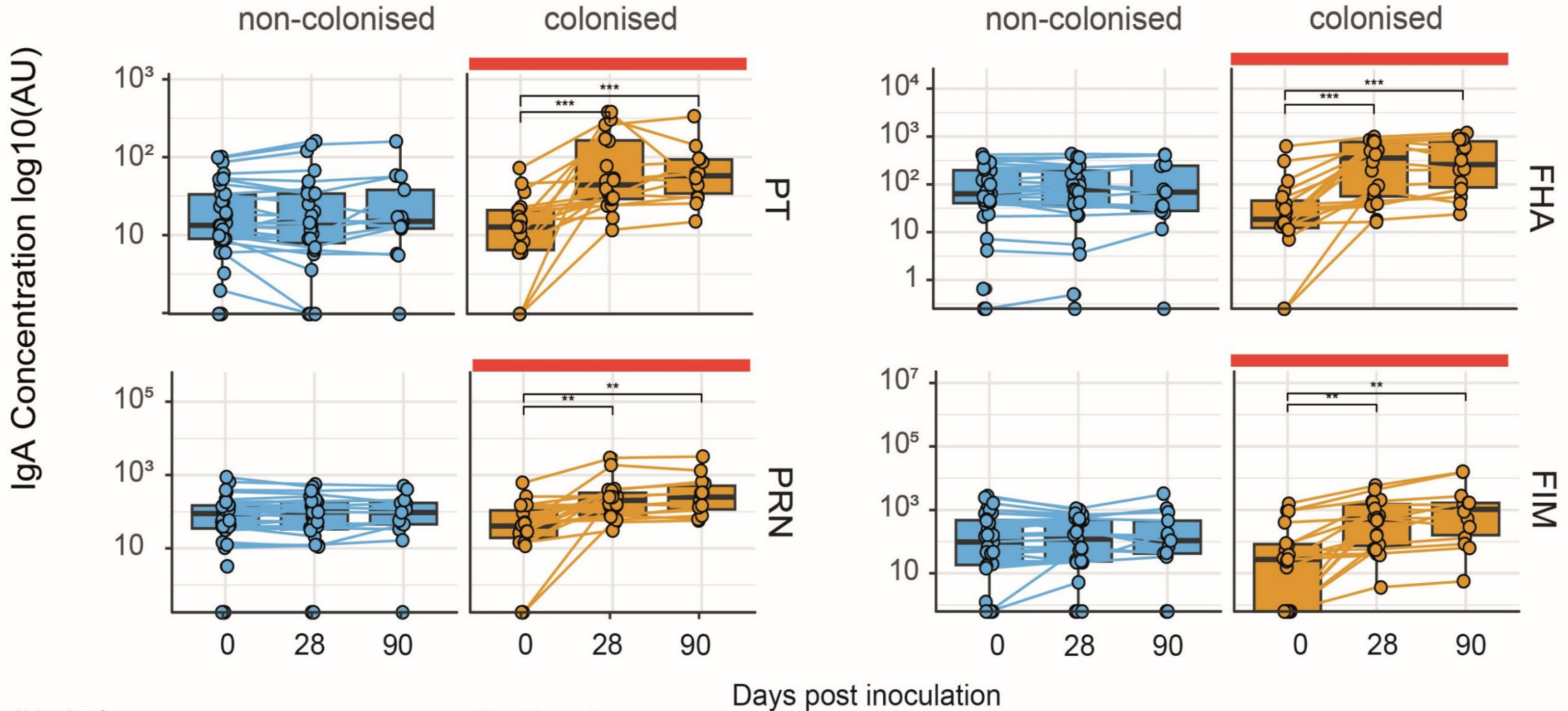


Does experimental infection induce an immune response?

# Colonisation is an immunising event - IgG



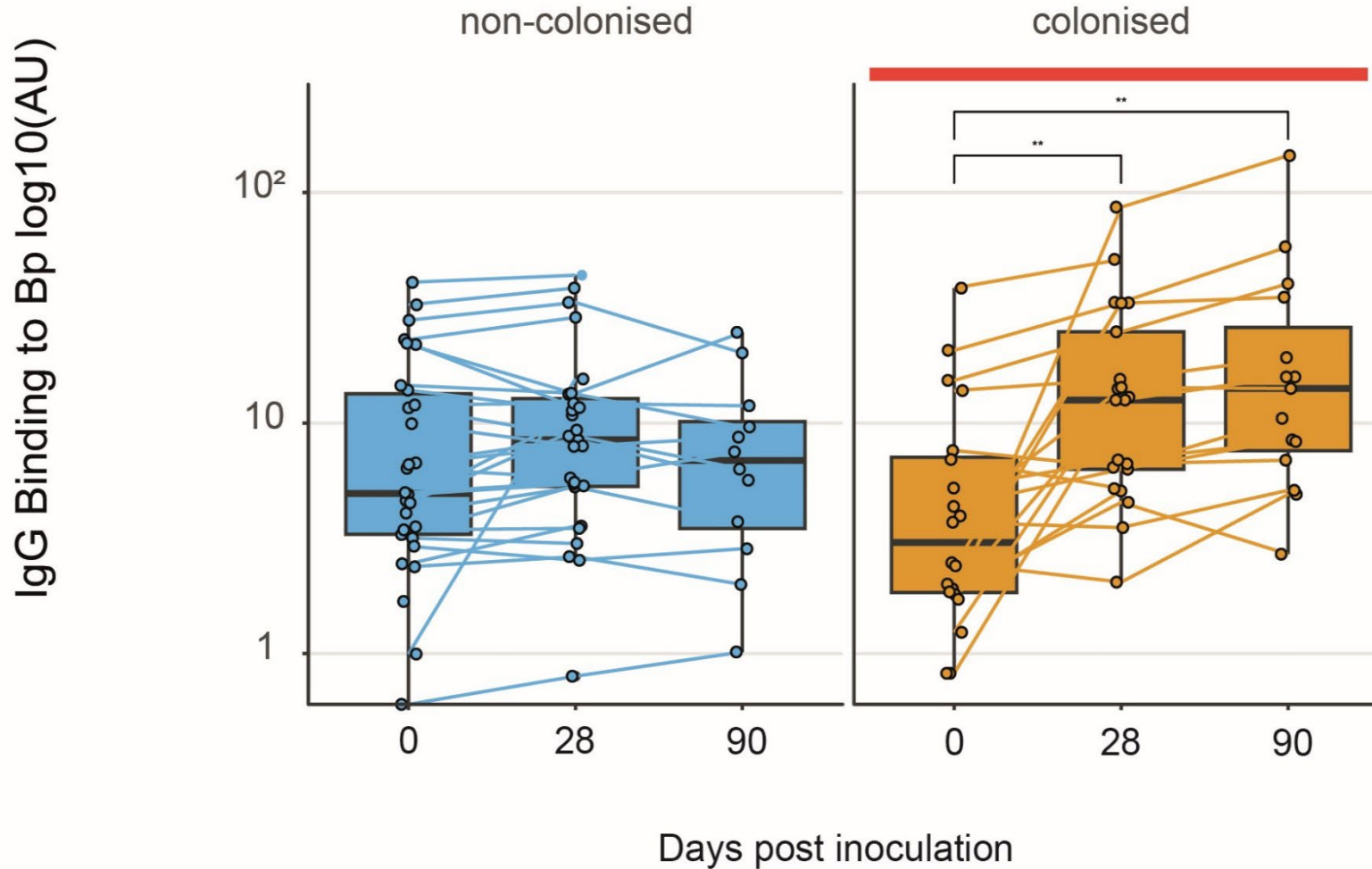
# Colonisation is an immunising event - IgA



# Colonisation is an immunising event - Bp binding



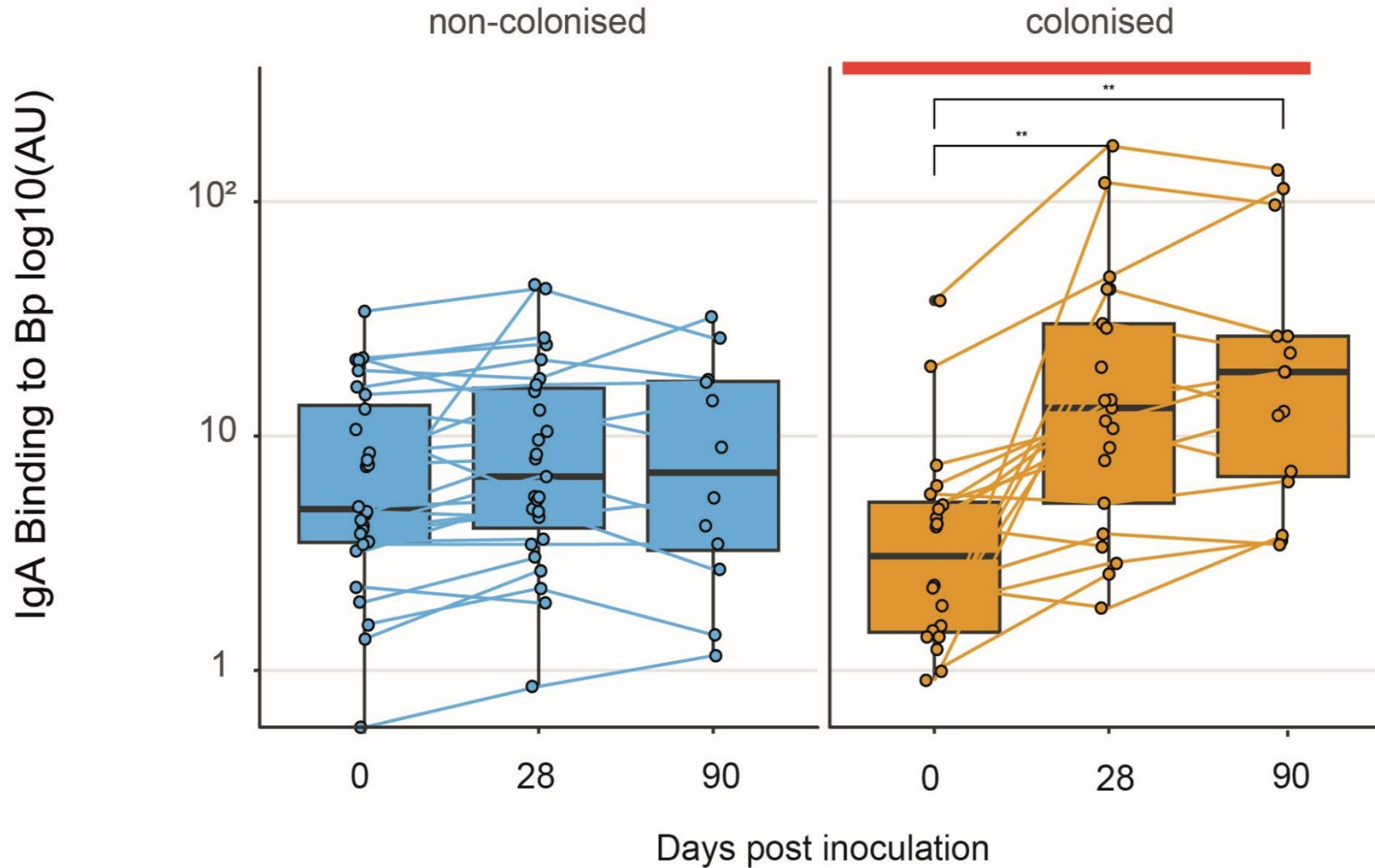
## IgG



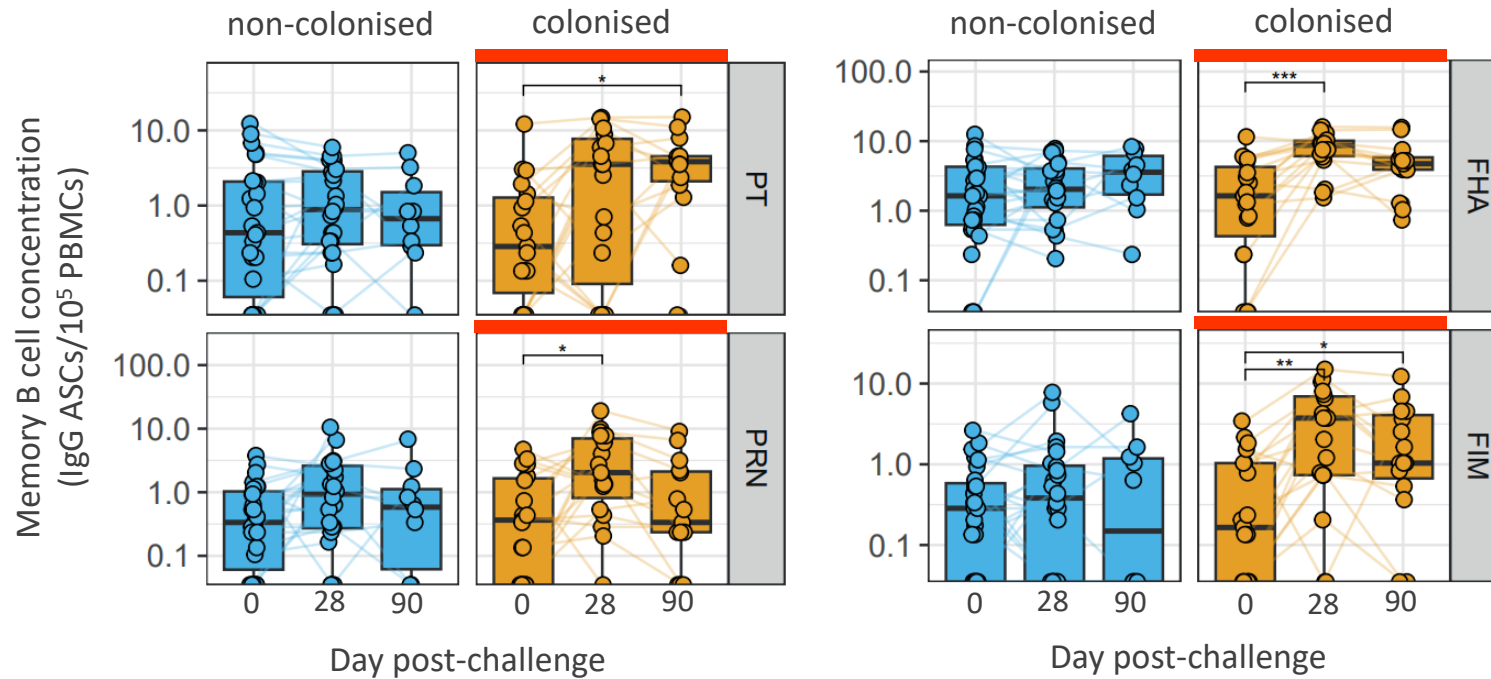
# Colonisation is an immunising event - Bp binding



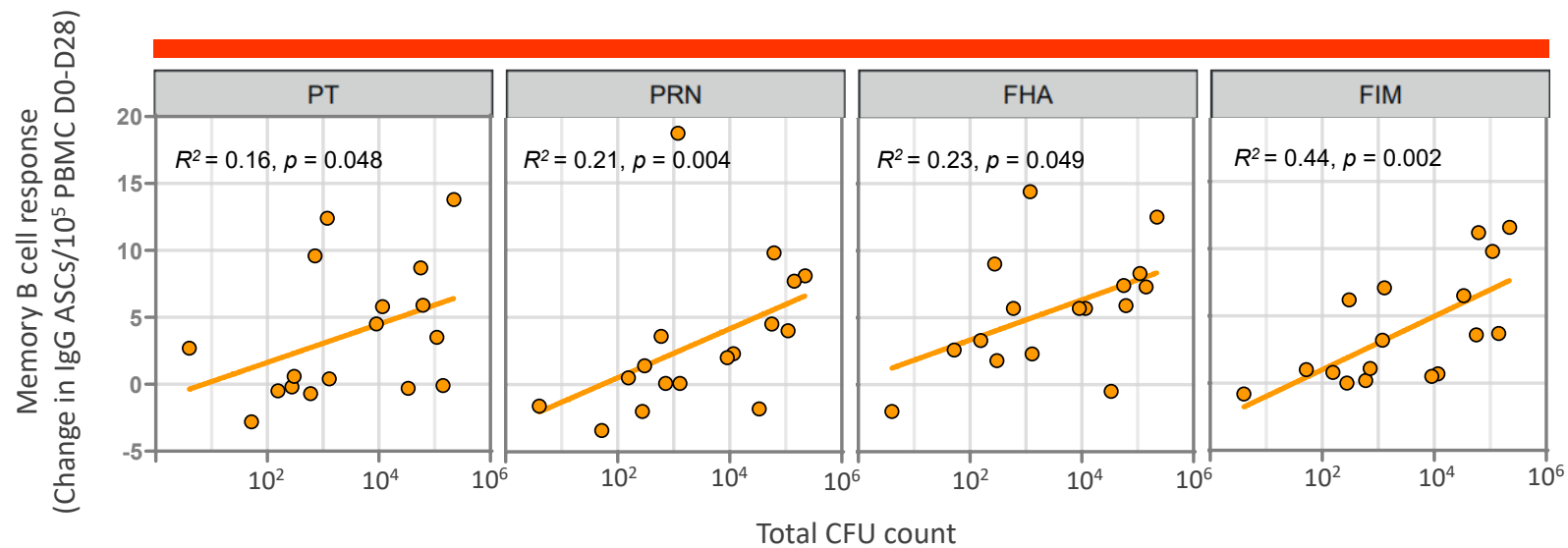
## IgA



# Colonisation induces Bp-specific memory B cell responses



# Memory B cell responses to colonisation correlate with bacterial density



# Overall Summary – PERISCOPE Human Challenge Program

- A dose of  $10^5$  cfu BP1917 induces:
  - In selected participants ( $PT \leq 20$ )
    - Colonisation Fraction 0.8
  - In unselected participants
    - Colonisation Fraction 0.4-0.56

# Overall Summary – PERISCOPE Human Challenge Program

- Minor symptoms occur and are tolerated, even in non-colonised
- Nasal washing is the most sensitive microbiological sampling technique
- Colonisation is detected in most by day 7 and density peaks at Day 14
- Colonisation clears spontaneously but this may take weeks
- Azithromycin clears infection by 48 hours in most cases
- There is no environmental shedding, and transmission has not been observed
- The model can be safely conducted in an outpatient environment
- Colonisation induces a `protected` phenotype

# Overall Summary – PERISCOPE Human Challenge Programme

- **Protection against colonisation is associated with:**
  - Serum IgG anti-PT, anti-PRN, anti-FHA
  - Serum IgA anti-FHA, and IgA binding to Bp
  - Nasal mucosal lining fluid IgA binding to Bp
  - IL22-expressing T helper cell responses to PT and FHA
- **Control of colonisation density is associated with:**
  - Serum IgG anti-PT and anti-FHA
  - Nasal mucosal lining fluid IgG binding to Bp
  - Bp-specific Memory B cell responses
- **Colonisation induces a `protective` immunophenotype**

# Periscope Human Challenge Program Phase B

- Is there a pragmatic colonisation fraction in unselected volunteers?
- Does experimental colonisation elicit an immune response similar to natural infection?
- Is that immune response associated with protection on repeated challenge?
- Are non-colonised (`protected`) volunteers immunologically distinct?
- Do colonised people transmit to close contacts?
- Can the experimental model be conducted in an outpatient setting?

# Thanks to the volunteers, the teams in Southampton and Radboud, and our partners within PERISCOPE

Southampton University, UK: **Nursing staff, Clinical Research Facility lab, CHIG Technician team, Muktar Ibrahim, Alison R. Hill, Diane Gbesetmete, Robert C. Read**

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RIVM, The Netherlands: **Annemarie Buisman, Cecile Van Els, Guy A.M. Berbers**

UK Health Security Agency, UK: **Andrew Gorringe**

IAVI, USA: **Kent E. Kester**

ULB, Belgium: **Véronique Corbière, Françoise Mascart**

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