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PERtussIS COrrelates of Protection Europe

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A human challenge model of *Bordetella pertussis* infection

Robert C Read University of Southampton

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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

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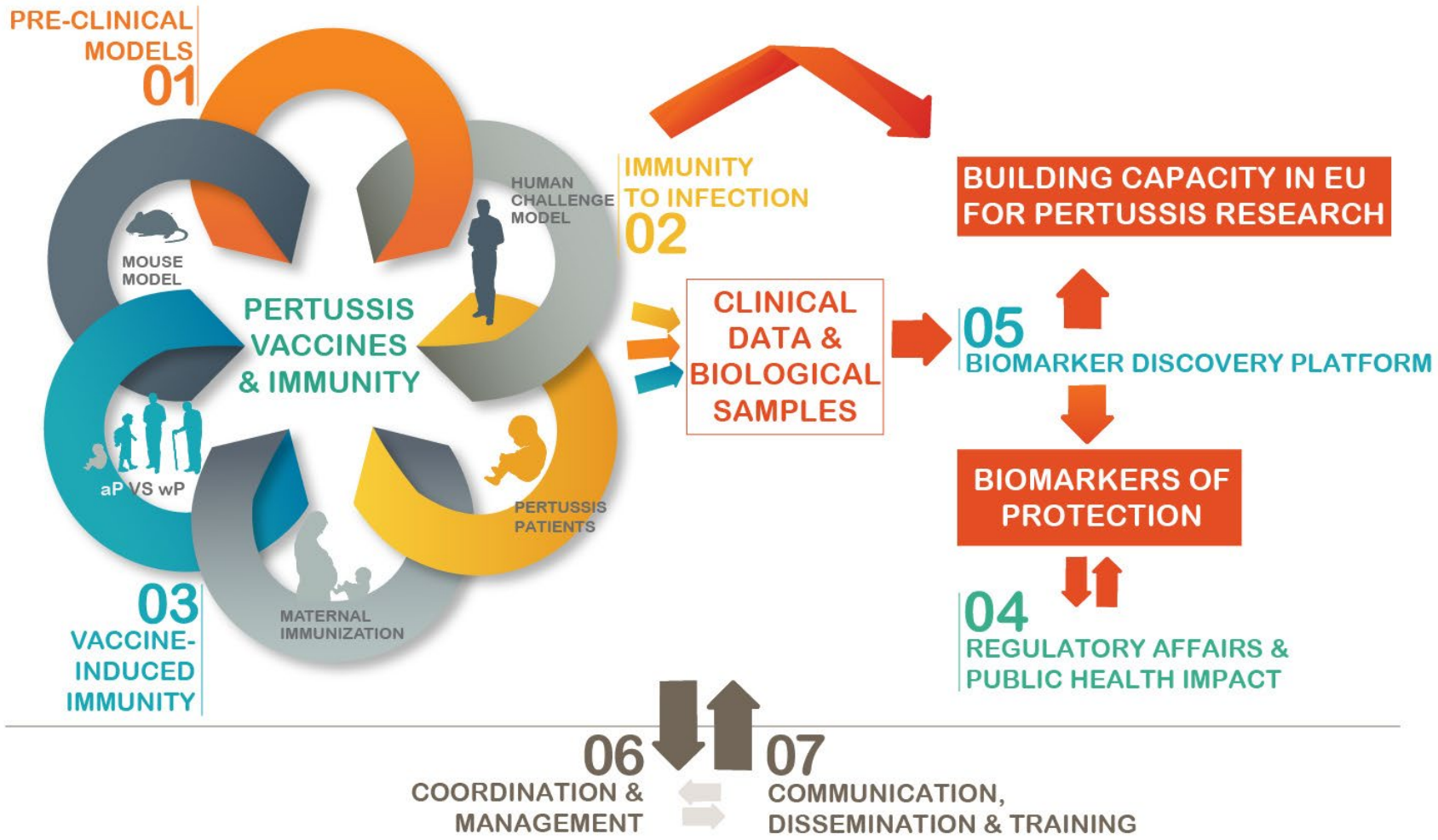

peri scope

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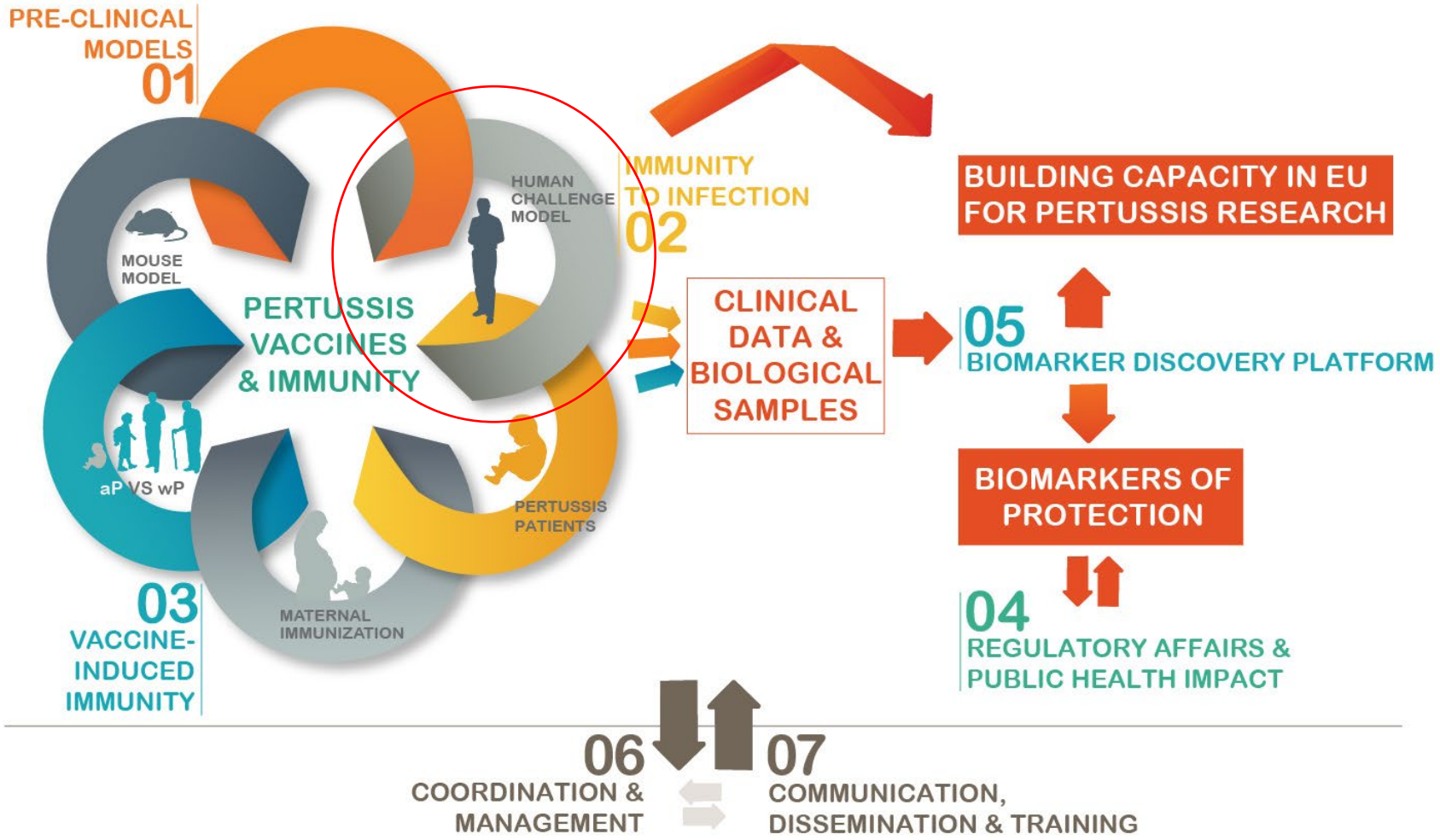

peri scope

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**

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Bp Controlled Human Infection Model

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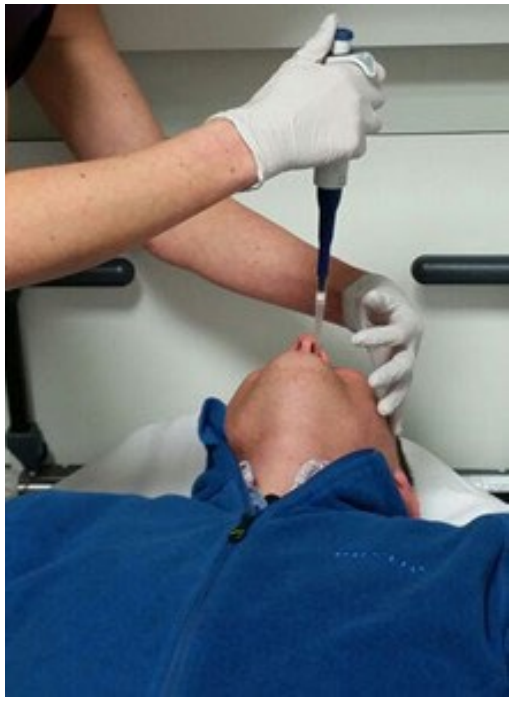
- *Primum non nocere*
- Asymptomatic nasopharyngeal colonisation
- *Bordetella pertussis* strain B1917
- Clearance with azithromycin

- Potential utilities:
  - Biomarkers associated with protection
  - Platform for vaccine testing



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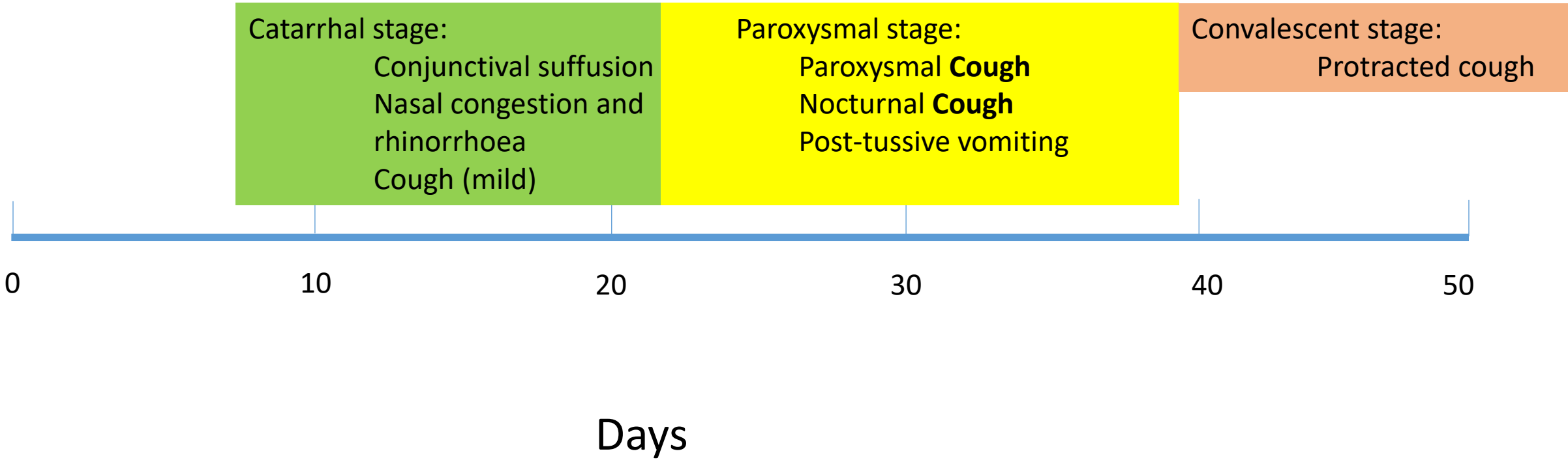
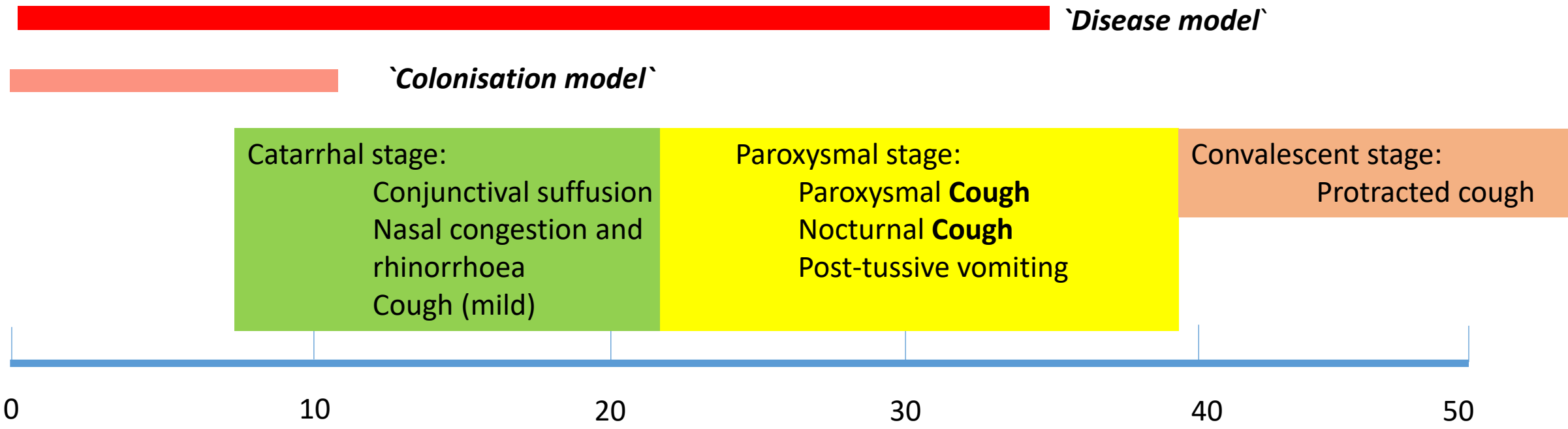
Clinical Pertussis



Controlled Human Infection



CDC: Pertussis clinical case definition

Clinical Criteria

In the absence of a more likely diagnosis, a cough illness lasting ≥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)

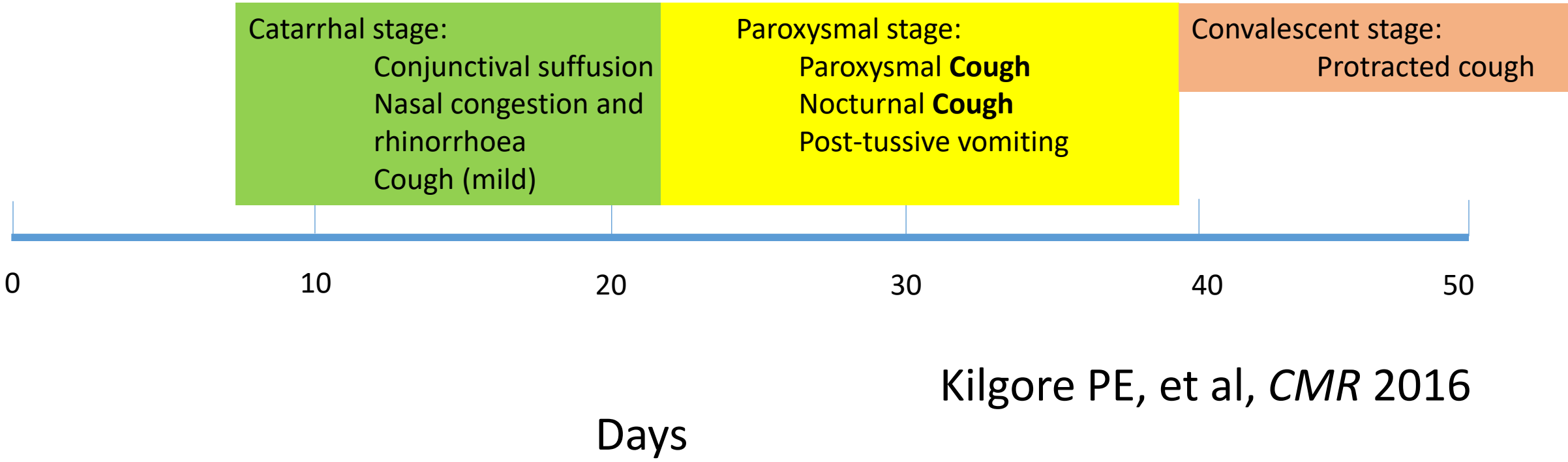
Laboratory Criteria

Confirmatory laboratory evidence:

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

Clinical Pertussis

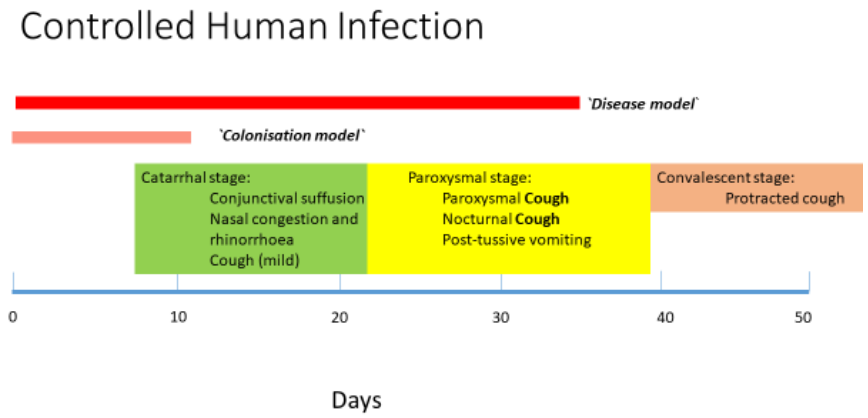
Complications in Adults/Adolescents	percent
Apnoea	27-86
Insomnia	77
Weight loss	3-33
Urinary incontinence	3-28
Death	0.01



Kilgore PE, et al, *CMR* 2016

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

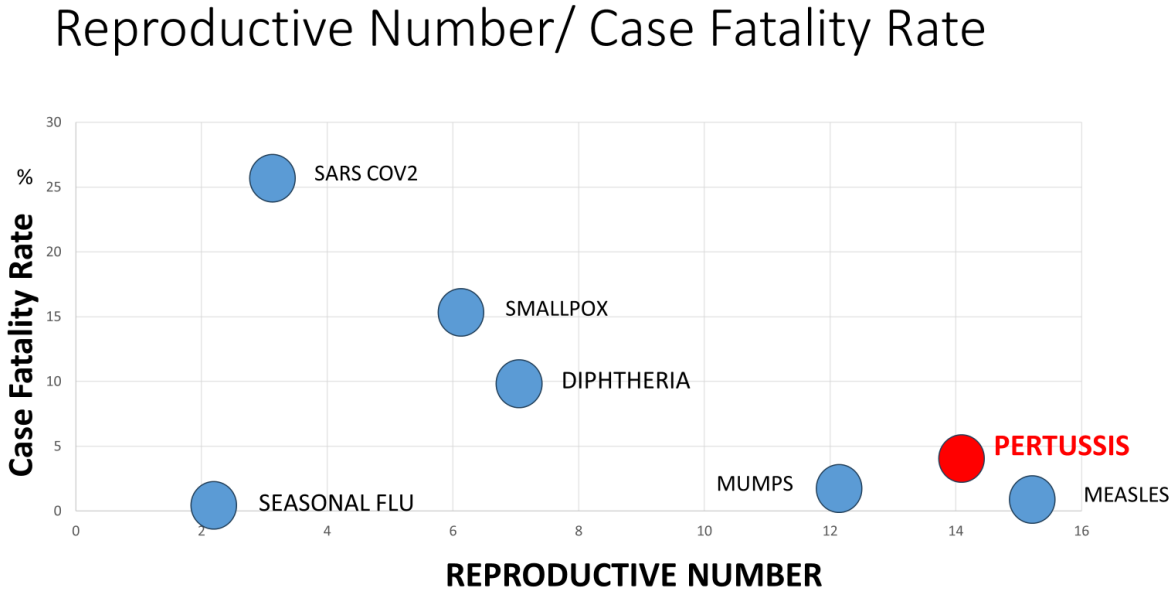


Colonisation model

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	*Bordetella pertussis* is difficult to detect in asymptomatic people Duration of carriage is unknown Relevance of carriage density
Probably less infection control issues	Detection of *B.pertussis* 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

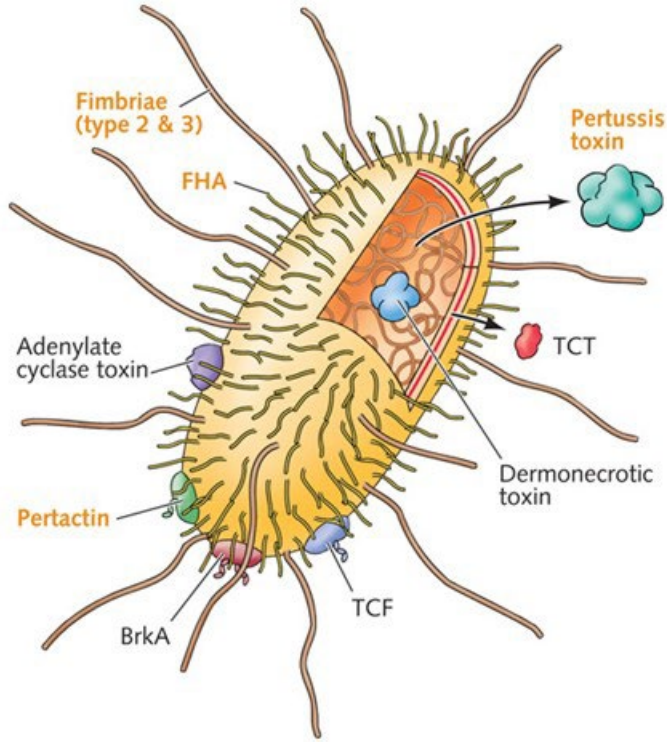
Dose and Administration

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



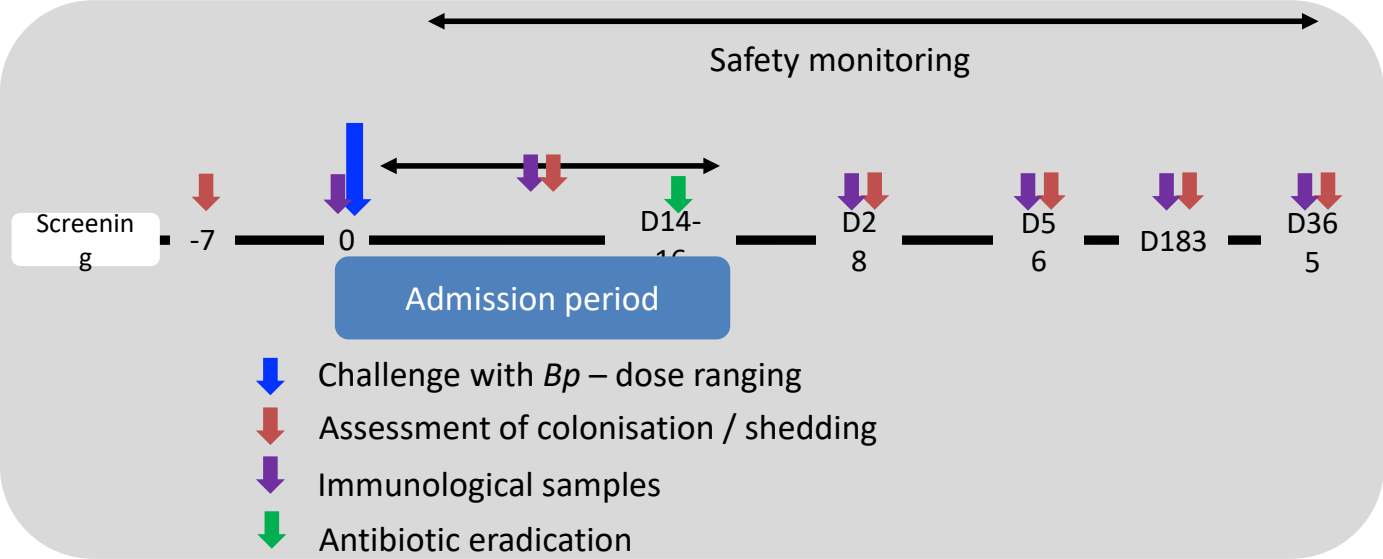
Selected organism

- 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



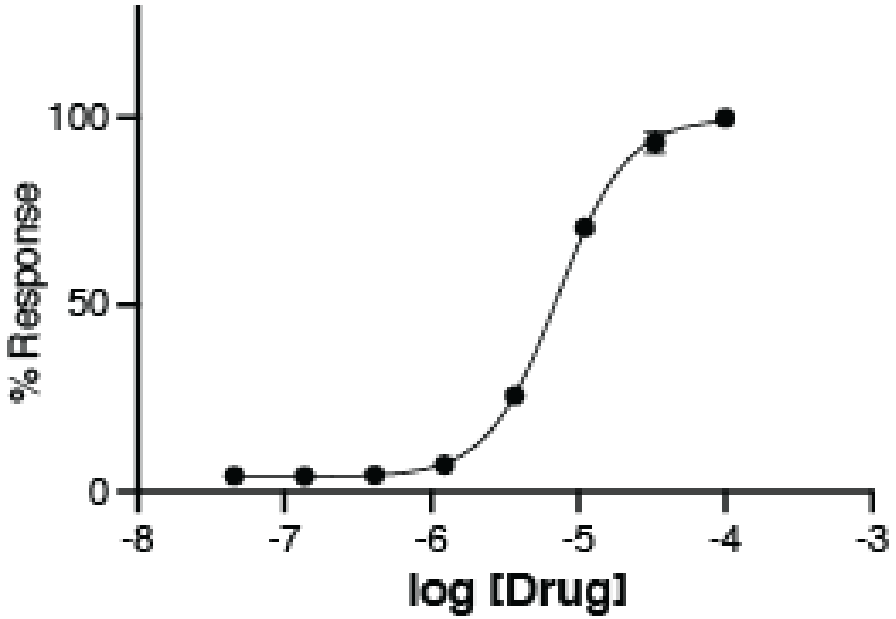
PERISCOPE Phase A

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



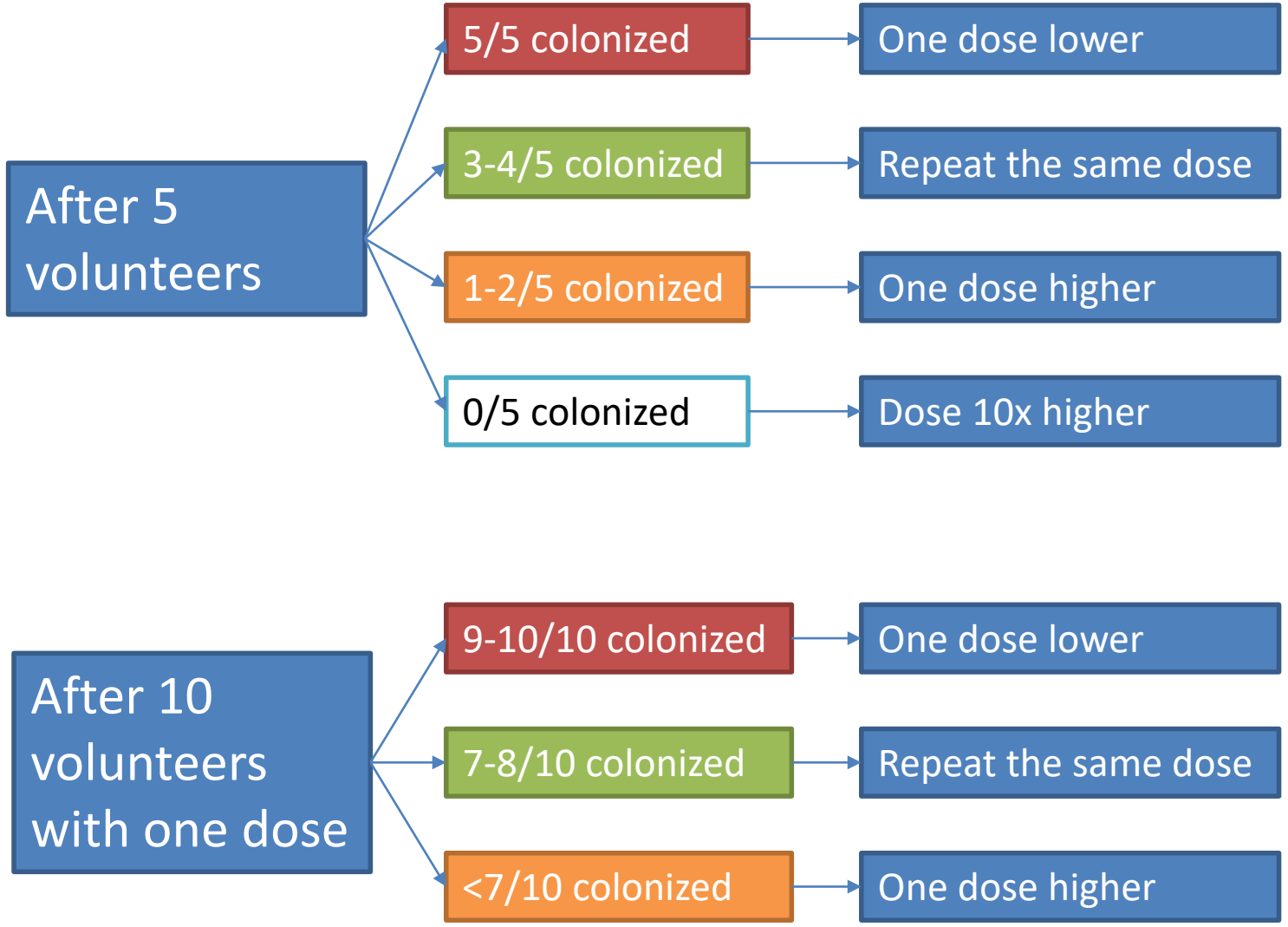
PERISCOPE: colonisation model

- Target colonisation fraction ≤80%



Dose ranging study

Inoculum doses to be used in cfu
5×10^2
10^3
5×10^3
10^4
5×10^4
10^5
5×10^5



Phase A – main findings

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- 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

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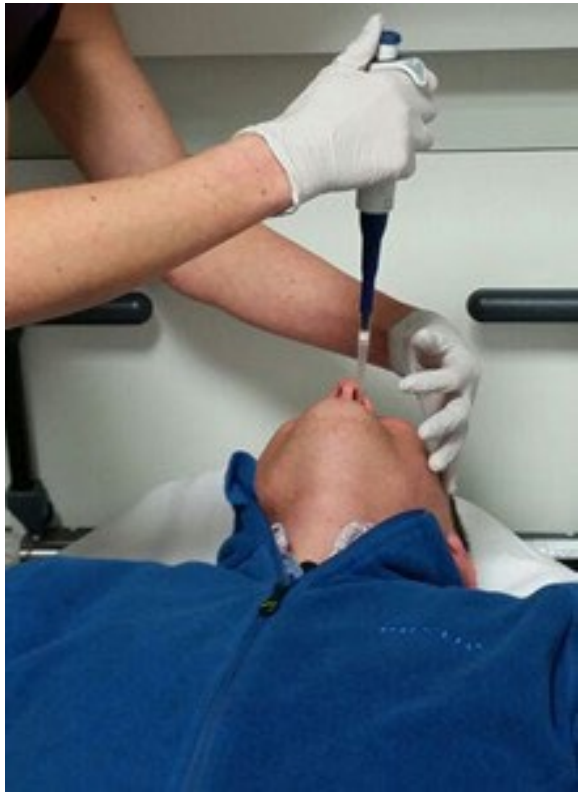
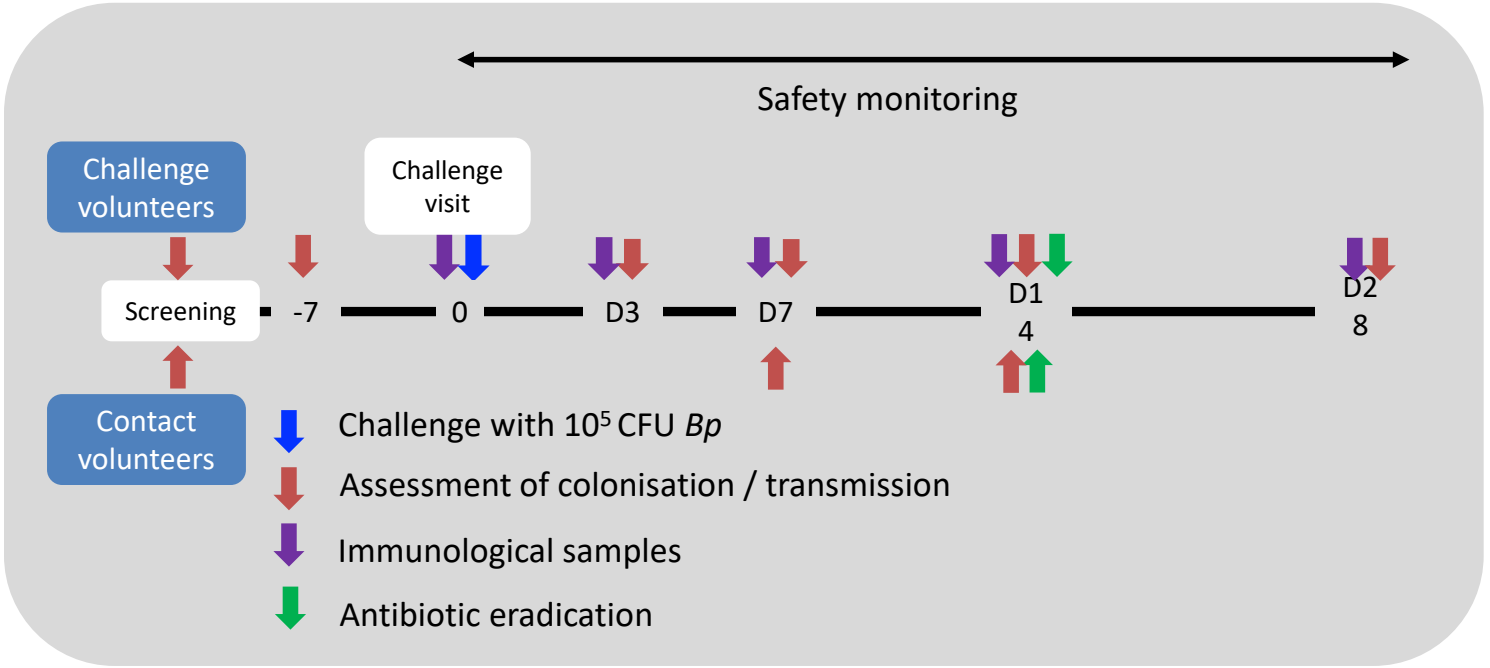


- Nasal wash most sensitive sampling technique
- Nasal wash culture and PCR equivalent
- Pernasal swab- culture 36% sensitive versus PCR 77%
- PCR of throat swabs detected 36% of all PCR positive samples (for pernasal swab this was 54%, and nasal wash 94%)

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

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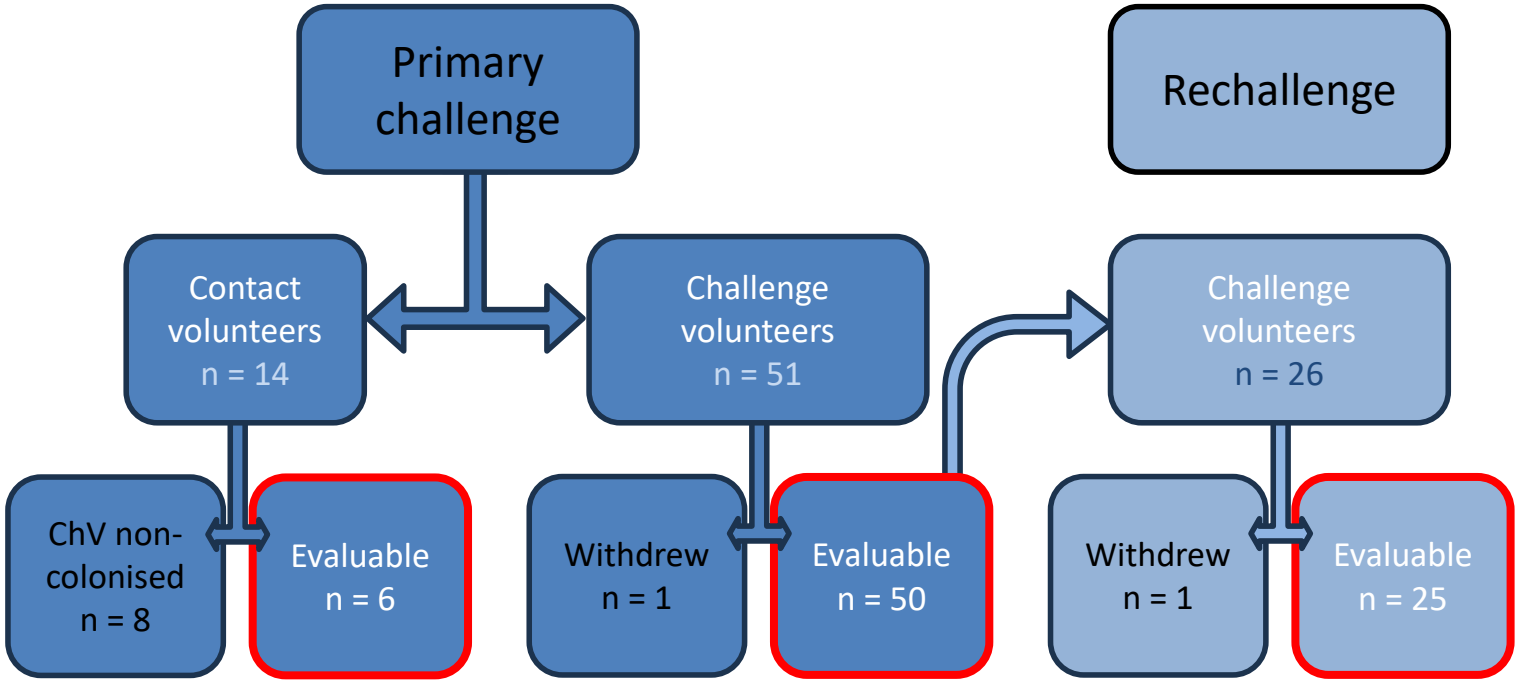

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Primary challenge: Colonisation

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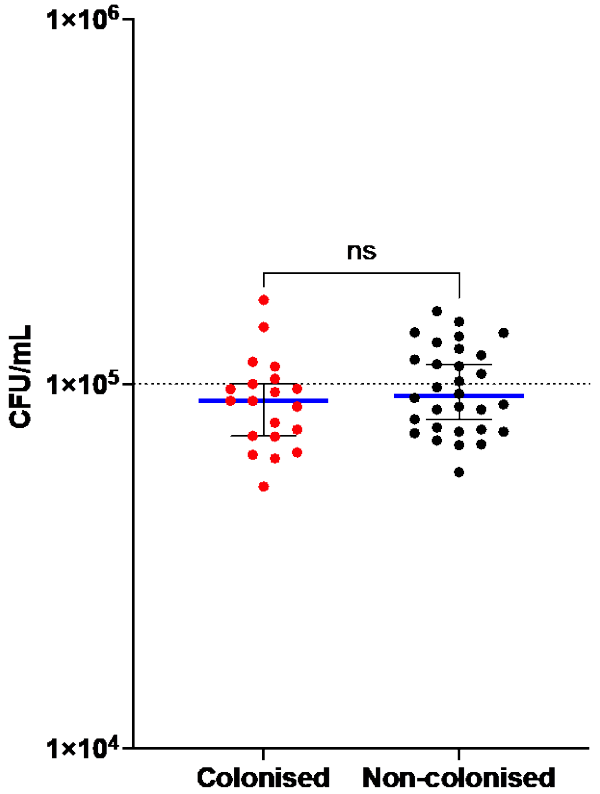
- **20 of 50** Challenge volunteers colonised
- Colonisation fraction = 0.4
- No difference in inoculum

- 14 contact volunteers enrolled
  - 6 corresponding Challenge volunteer colonised
  - No transmission detected



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Primary challenge: Colonisation

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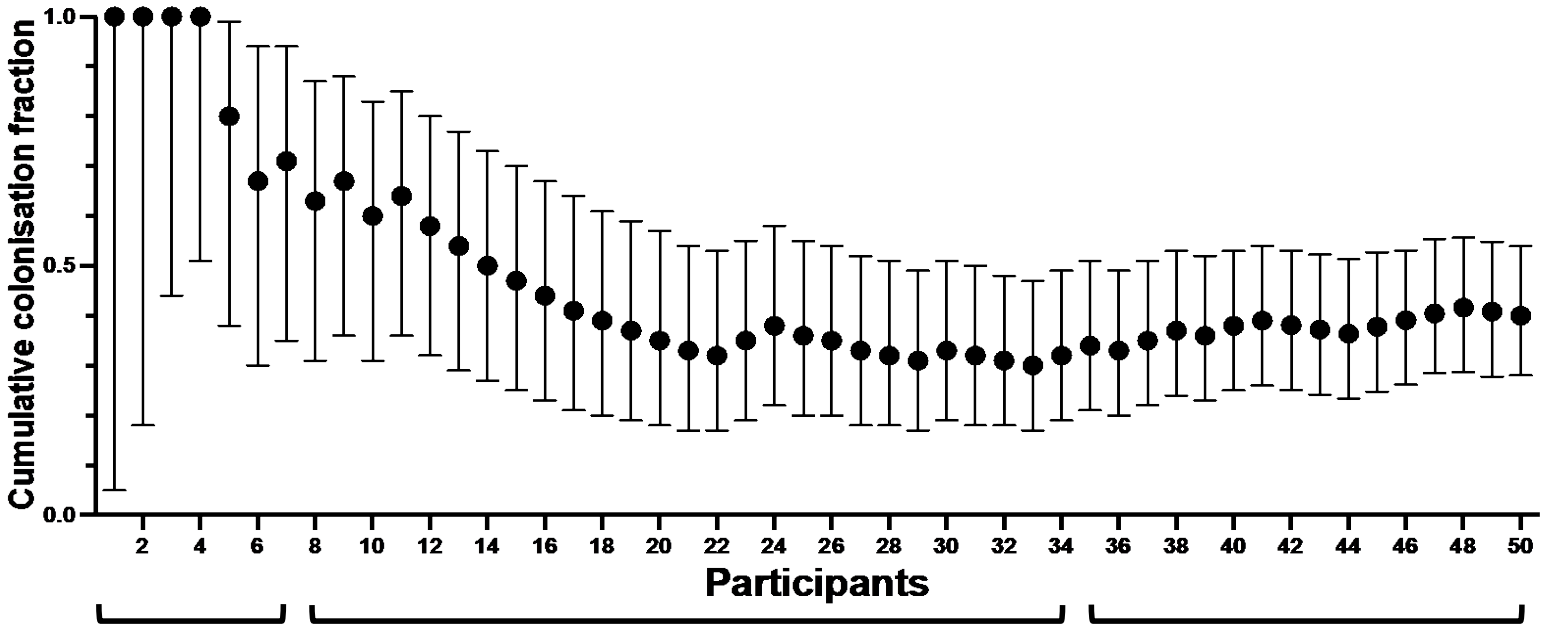

Pre 2020
CF = 0.71

2020-2021
CF = 0.22

2022-2023
CF = 0.56

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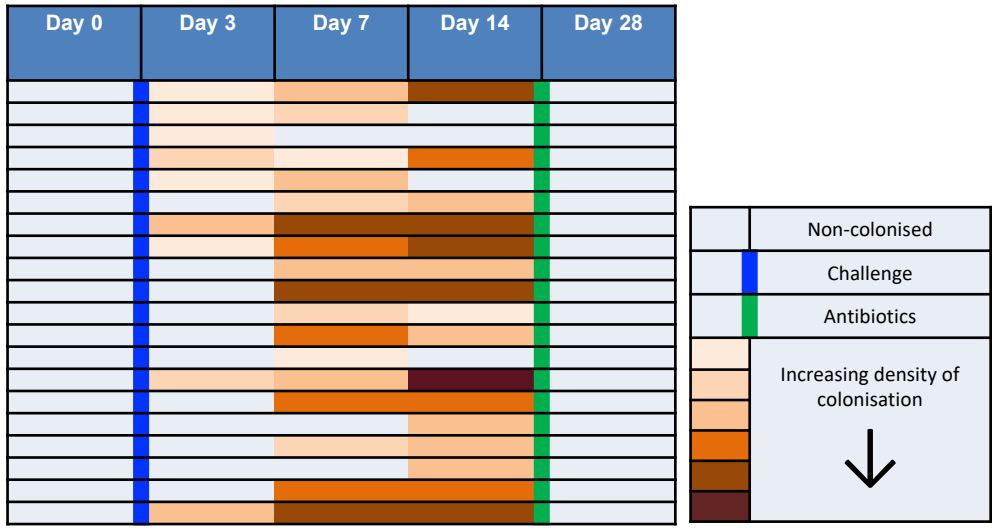
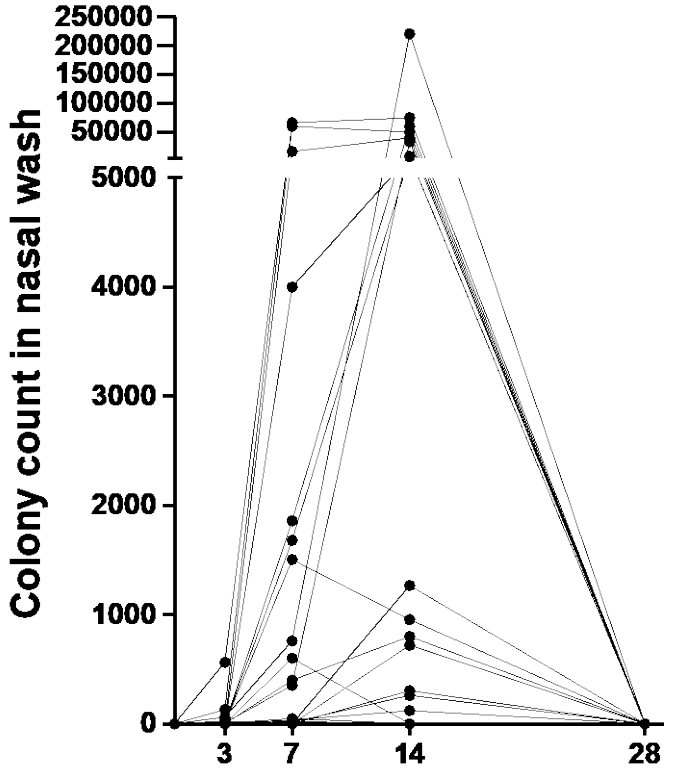
Primary challenge: Colonisation dynamics

- Most colonisation detectable by Day 7
- Peak density at Day 14
- Some spontaneous clearance (4 of 20)
- 100% clearance with azithromycin





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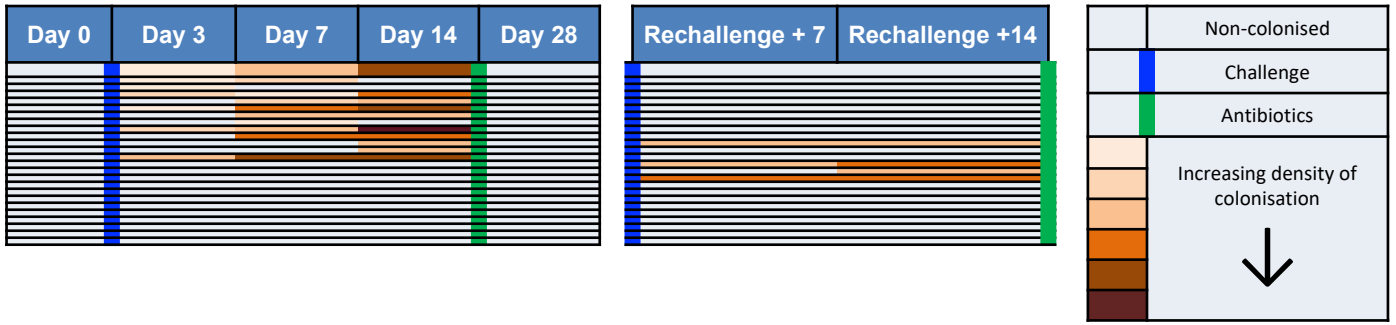
Rechallenge: Colonisation

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



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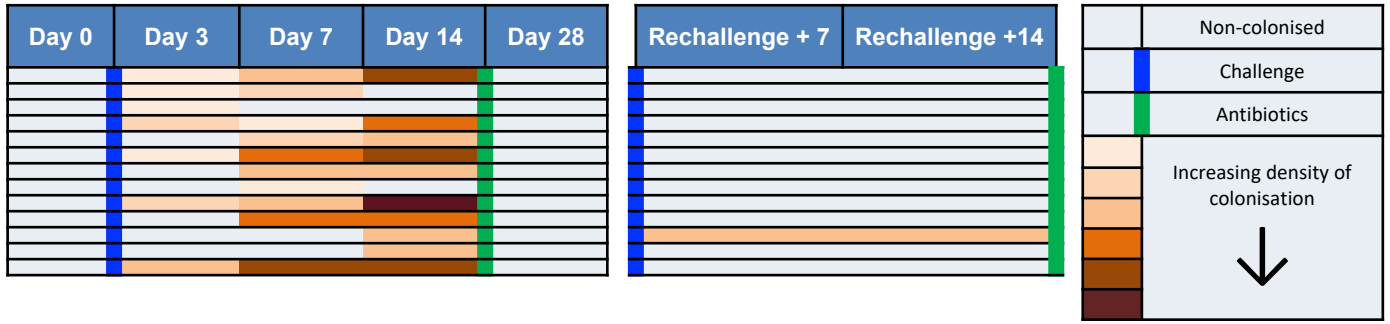
Rechallenge: Colonisation

- 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

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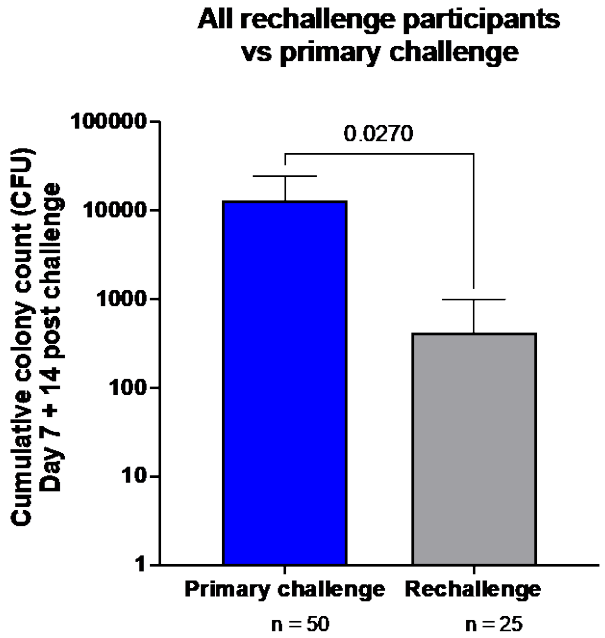
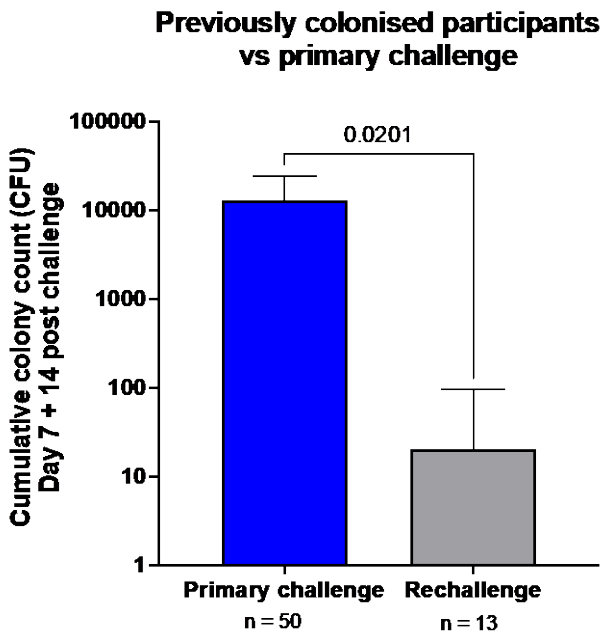
- Colonisation density at rechallenge is lower than at primary challenge (Mann Whitney test)





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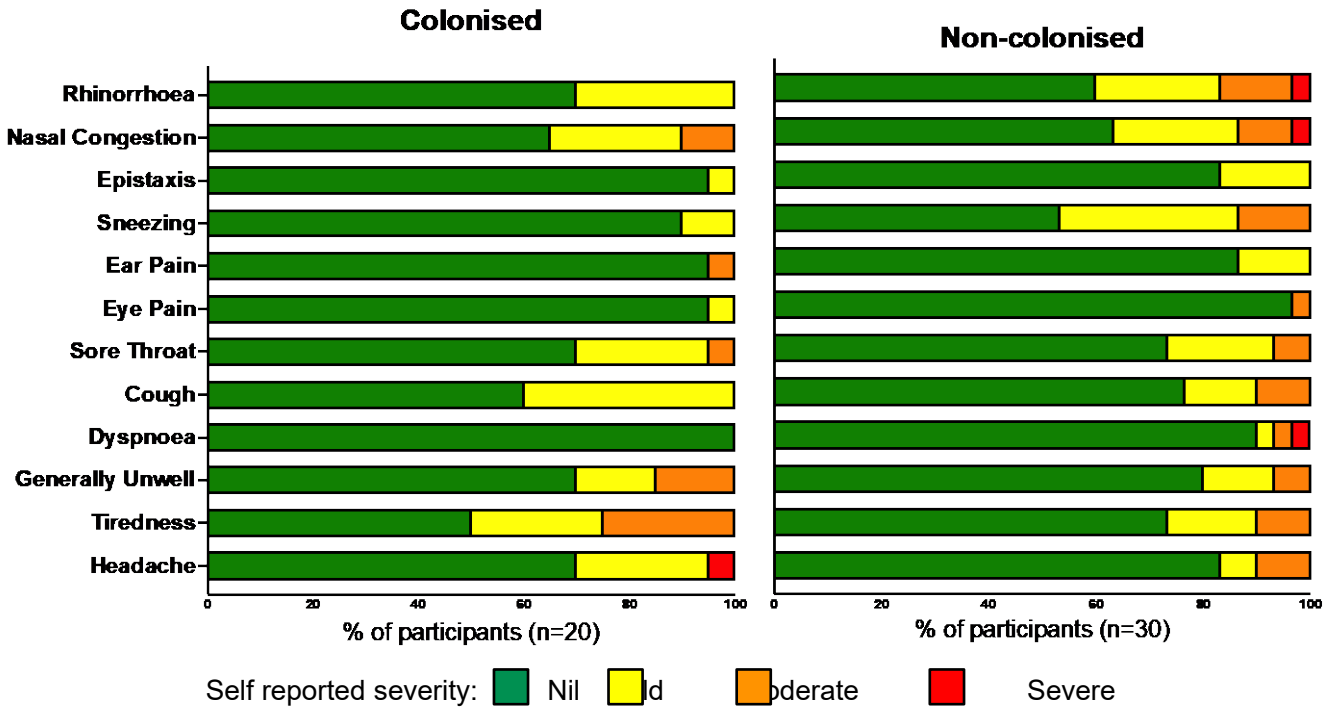
Safety: Solicited adverse events
Day 0-14 post primary challenge



Symptoms in colonised participants

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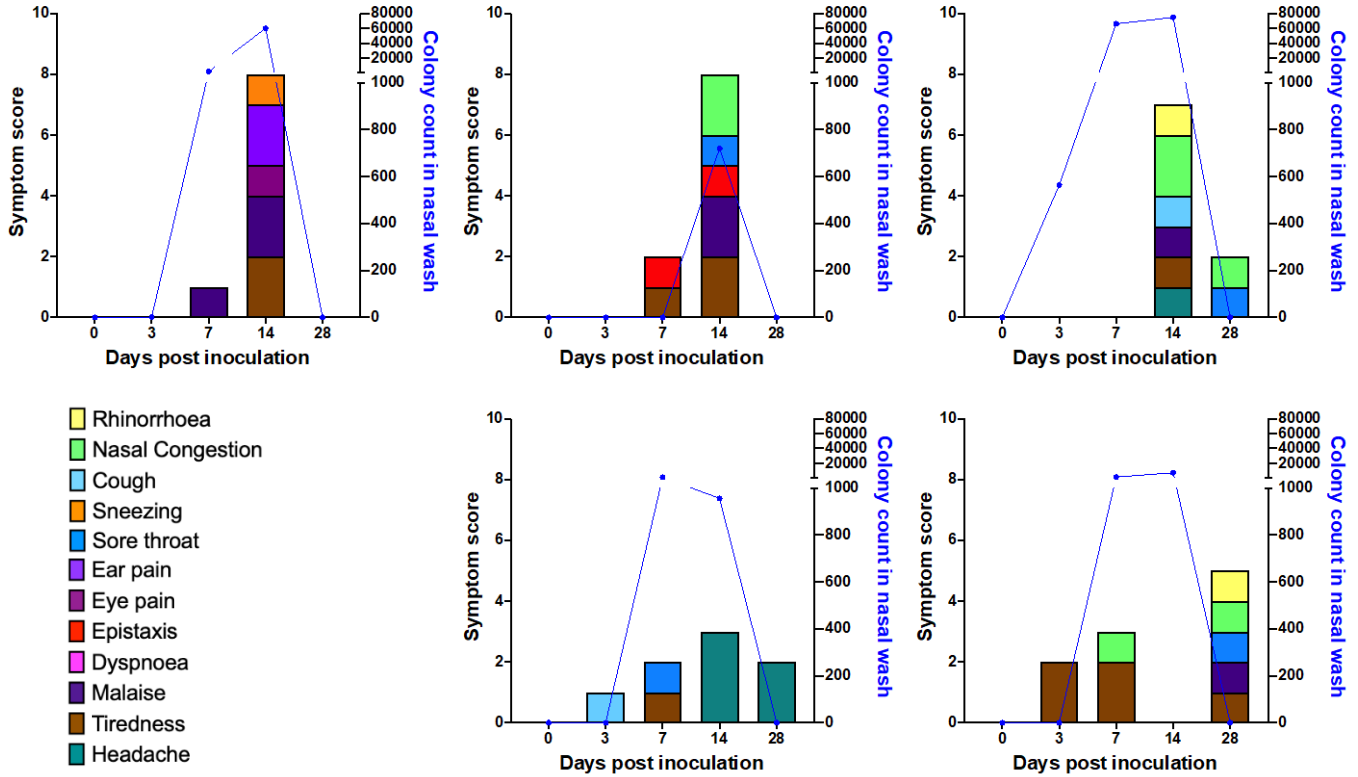

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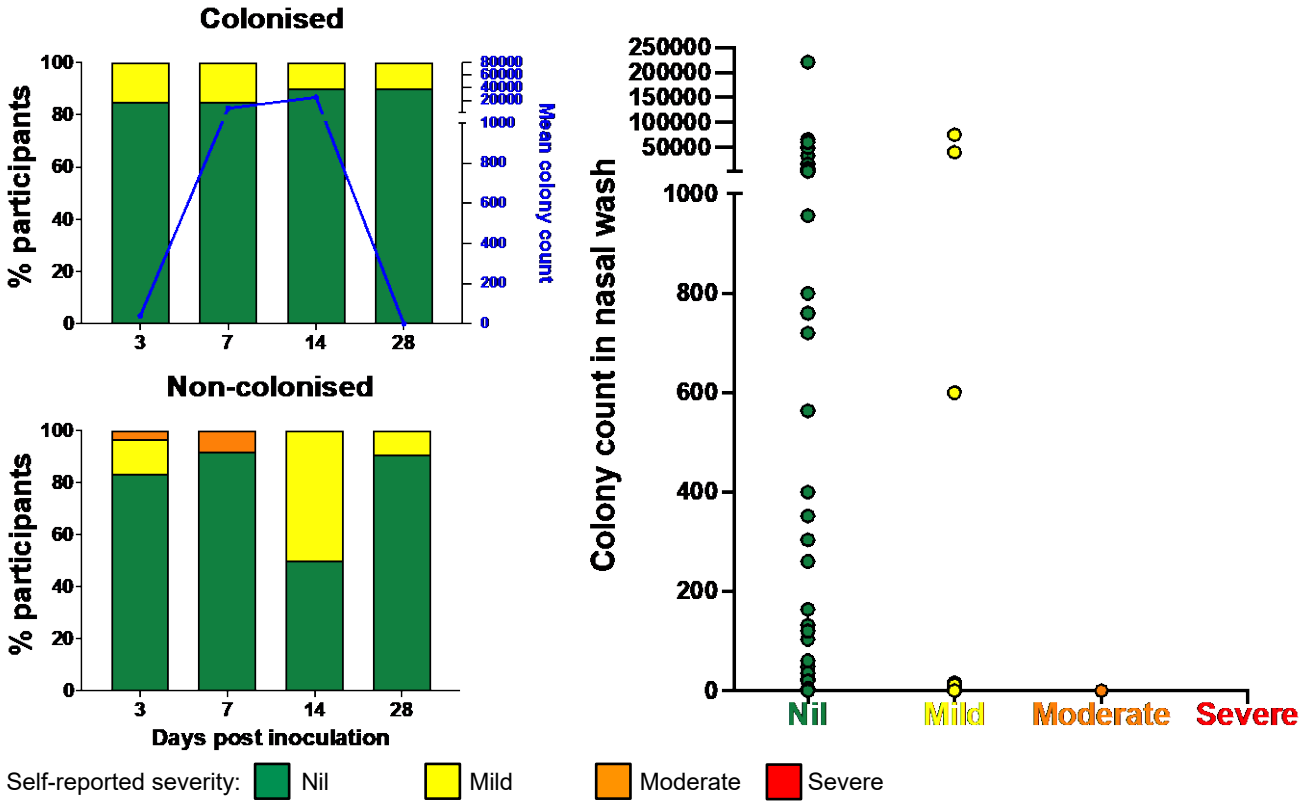
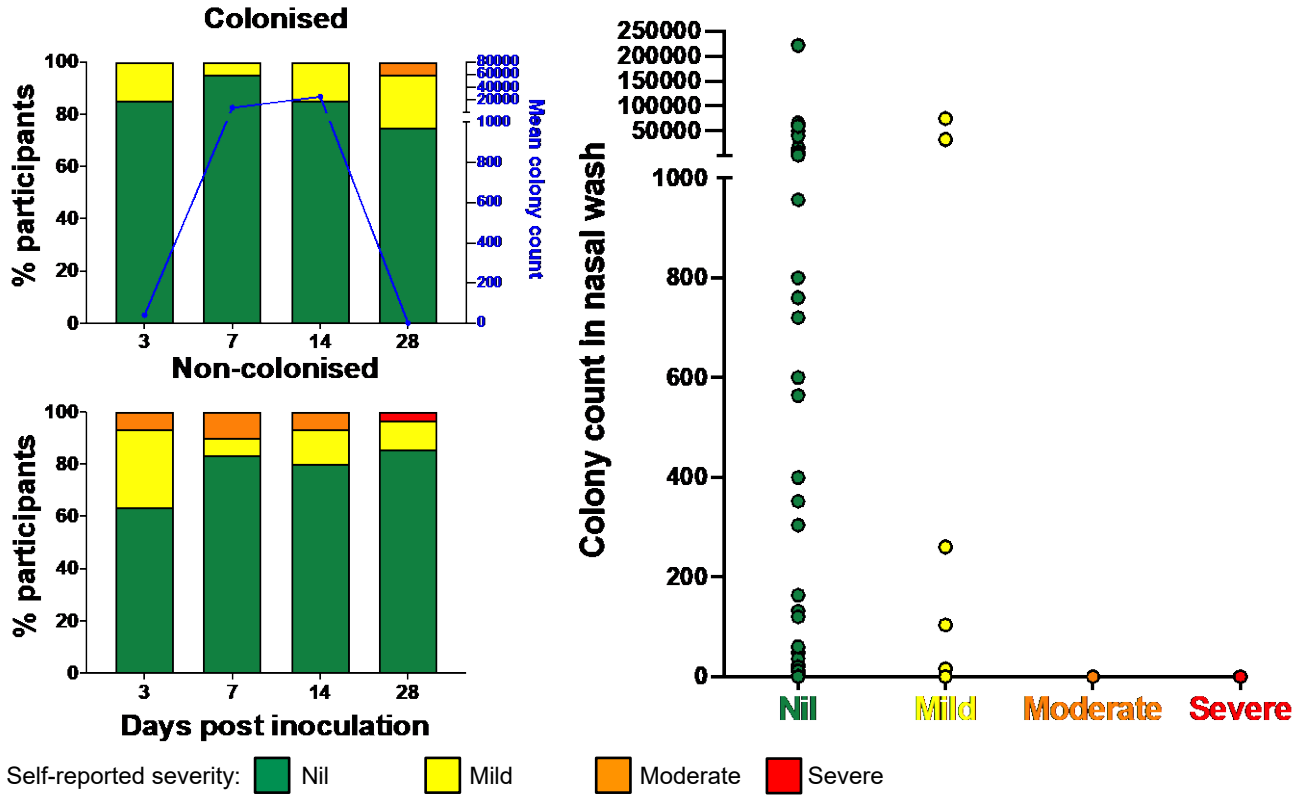
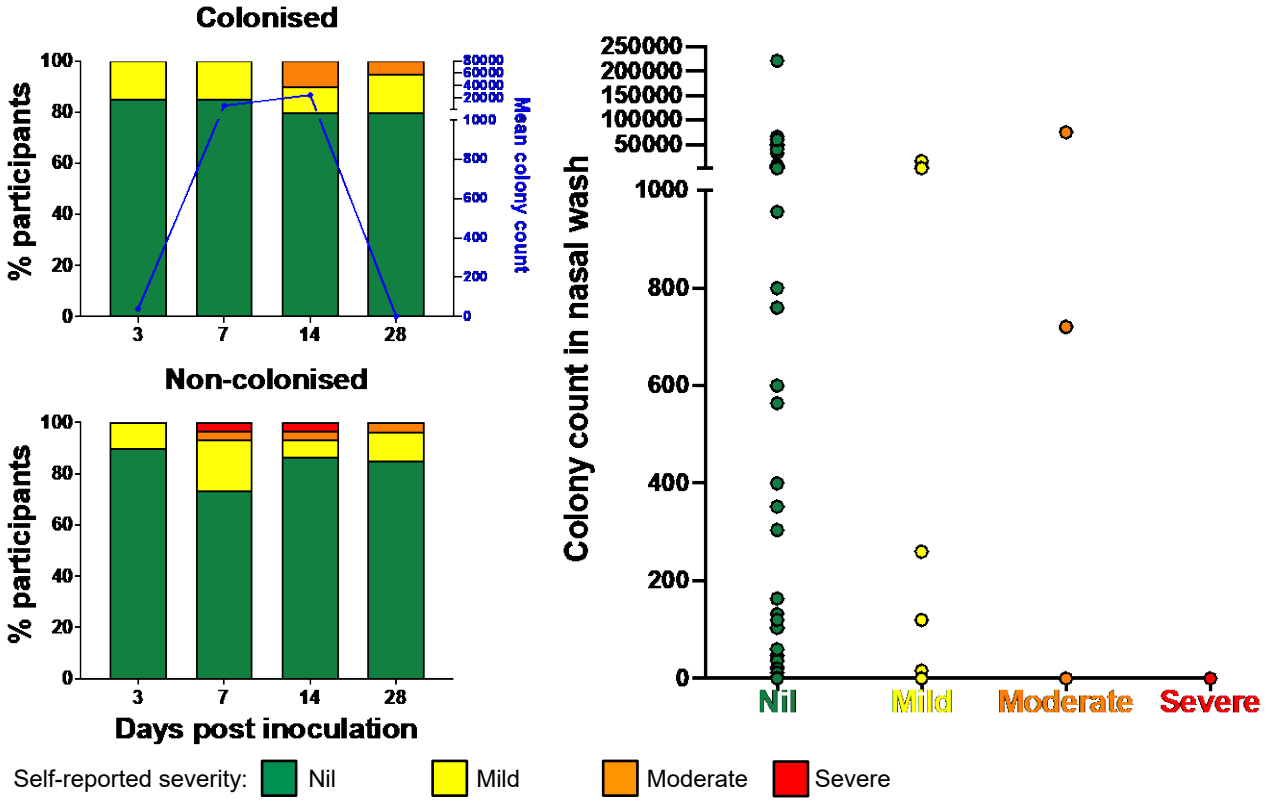
Cough


Colonised
% participants
Mean colony count
3
7
14
28
Non-colonised
% participants
Days post inoculation
Colony count in nasal wash
Nil
Mild
Moderate
Severe
Self-reported severity:
Nil
Mild
Moderate
Severe

Rhinorrhoea



Nasal congestion



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Phase C – Extended colonisation

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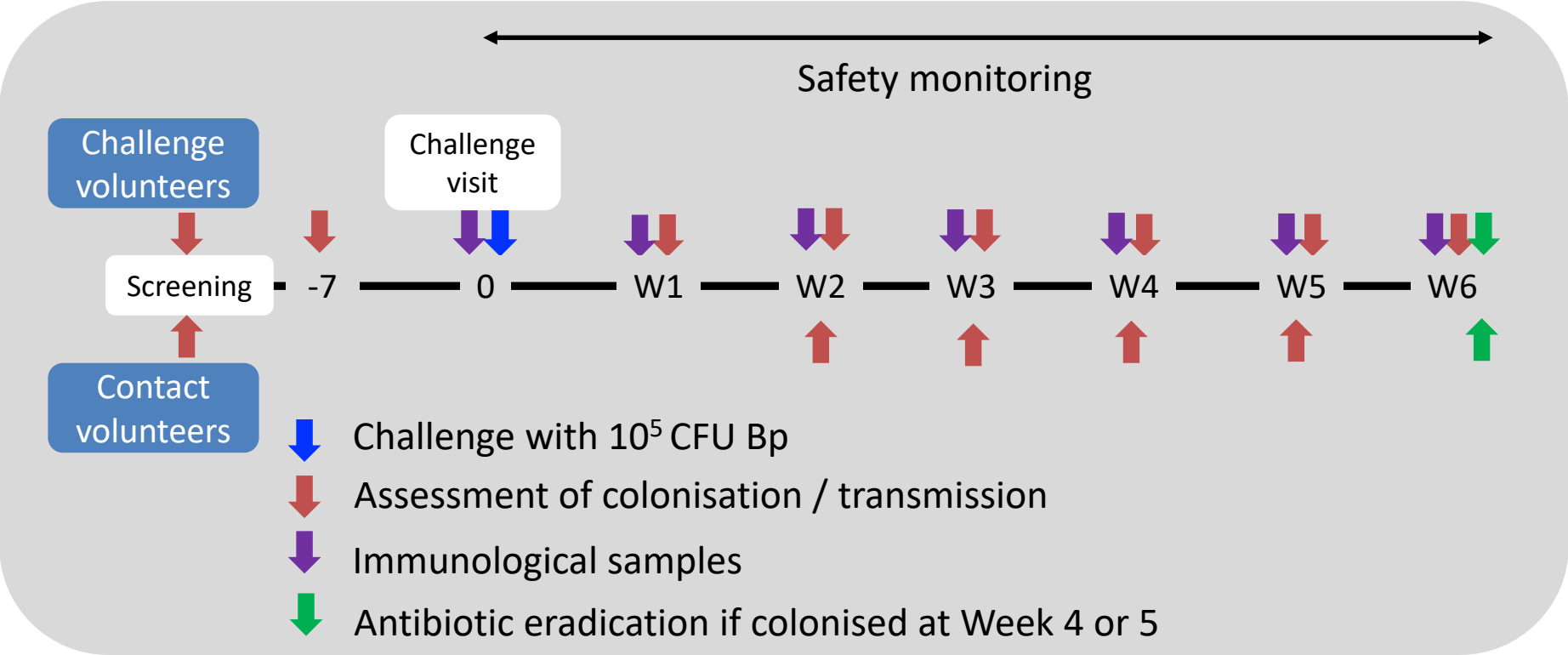

- Planned sample size = 10 colonised challenge volunteers

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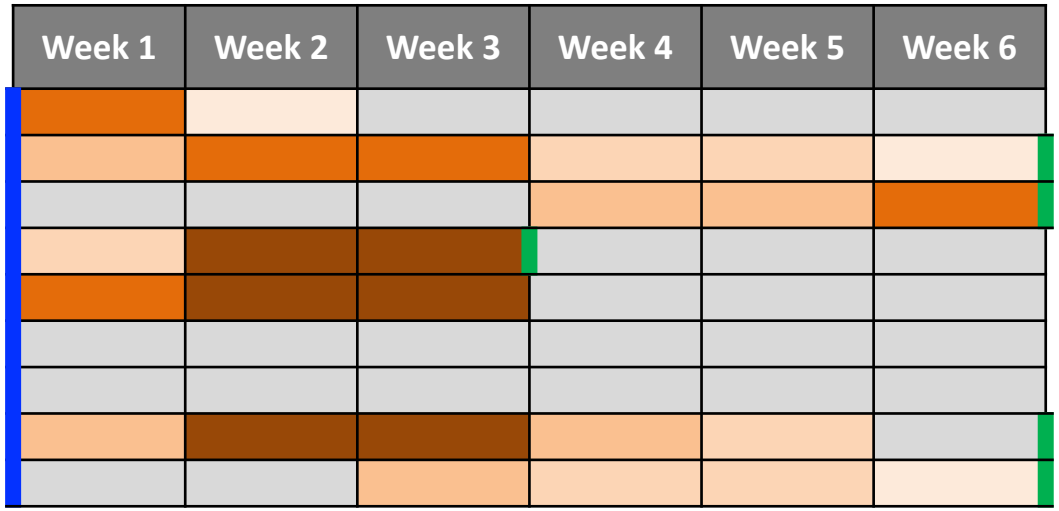
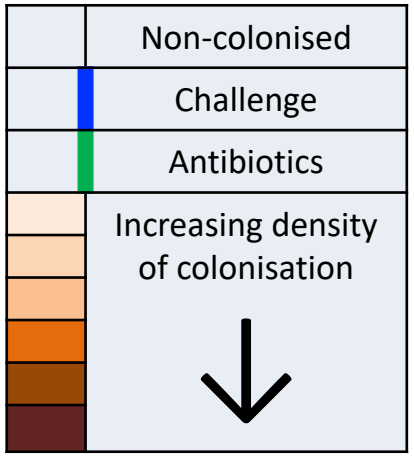
Colonisation

- 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

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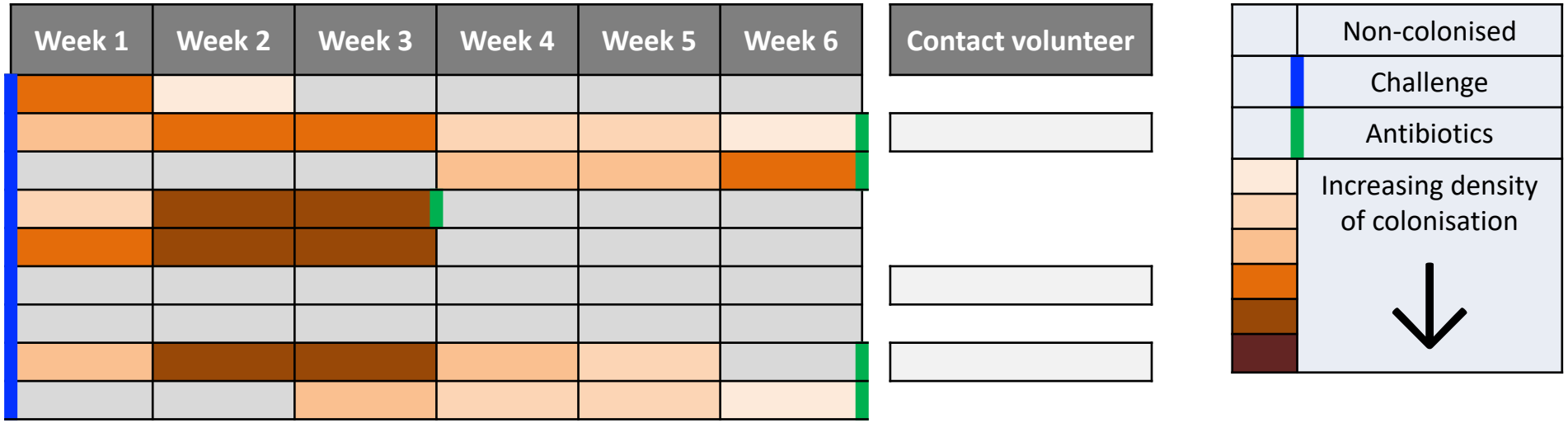
- 3 Contact volunteers enrolled
  - 2 corresponding challenge volunteer colonised
  - No transmission detected



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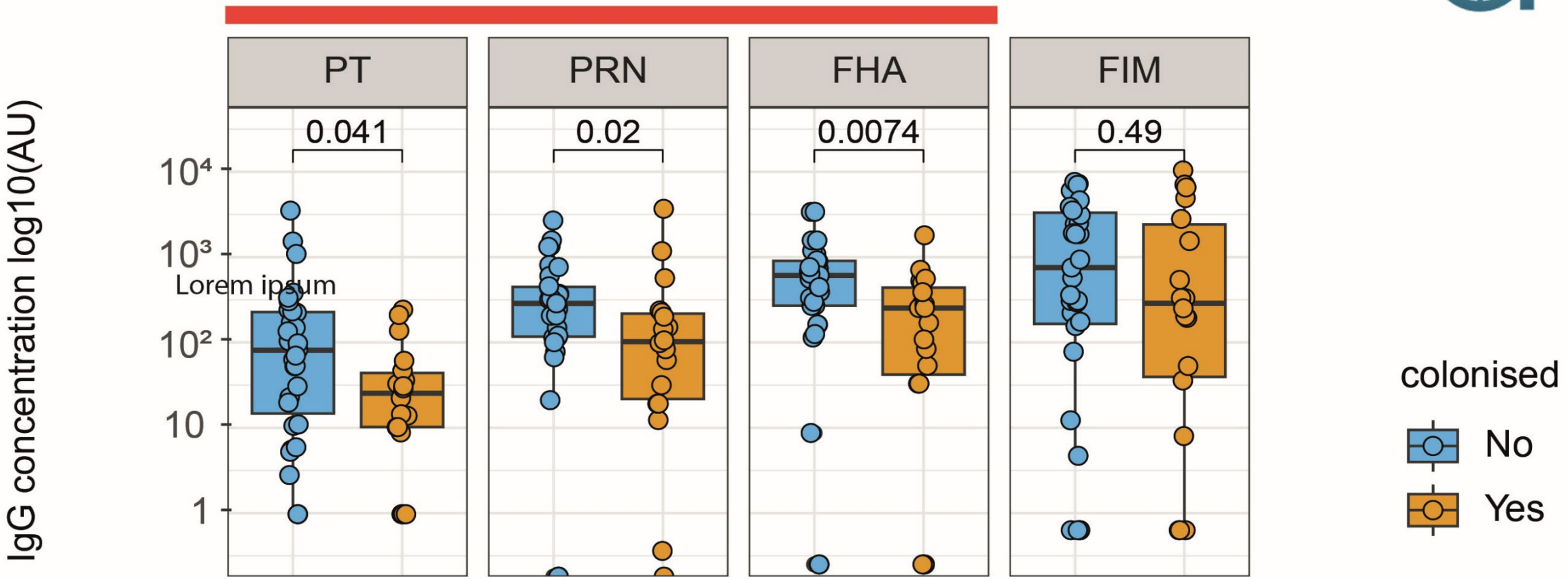
Do colonised and non-colonised volunteers differ immunologically?

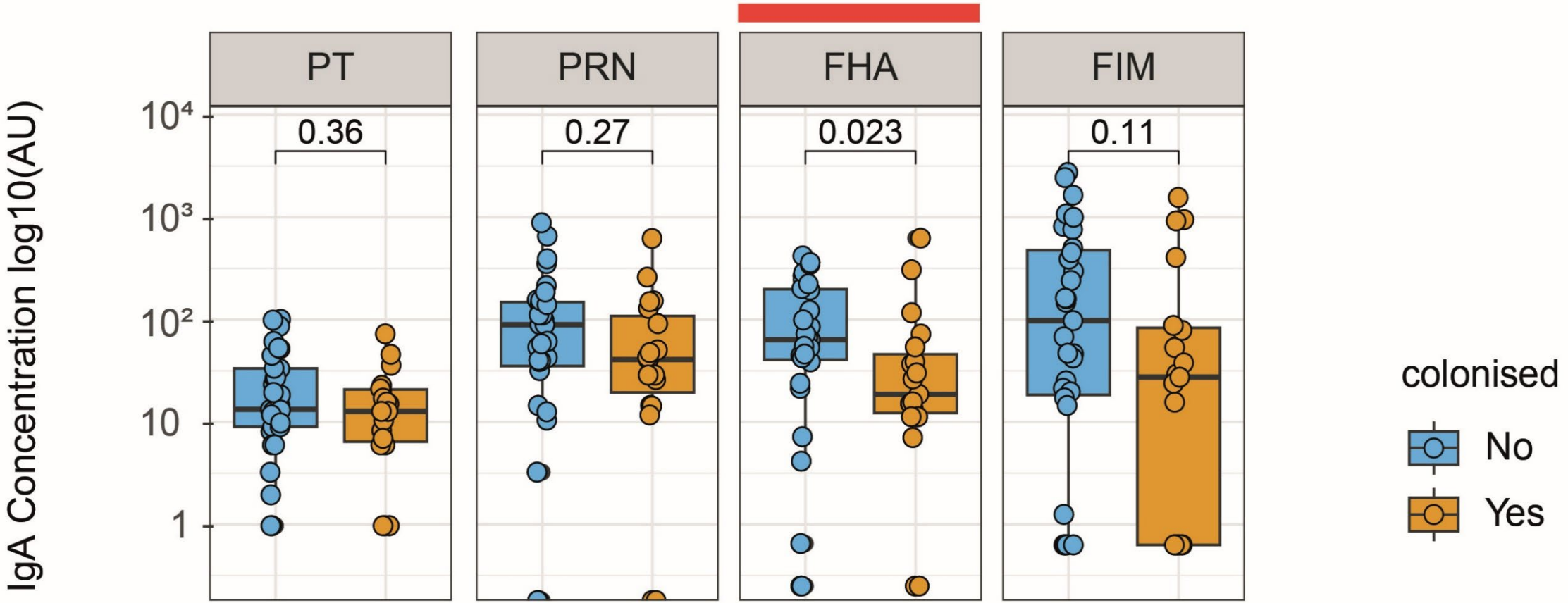
Non-colonised versus colonised – serum IgG

Baseline



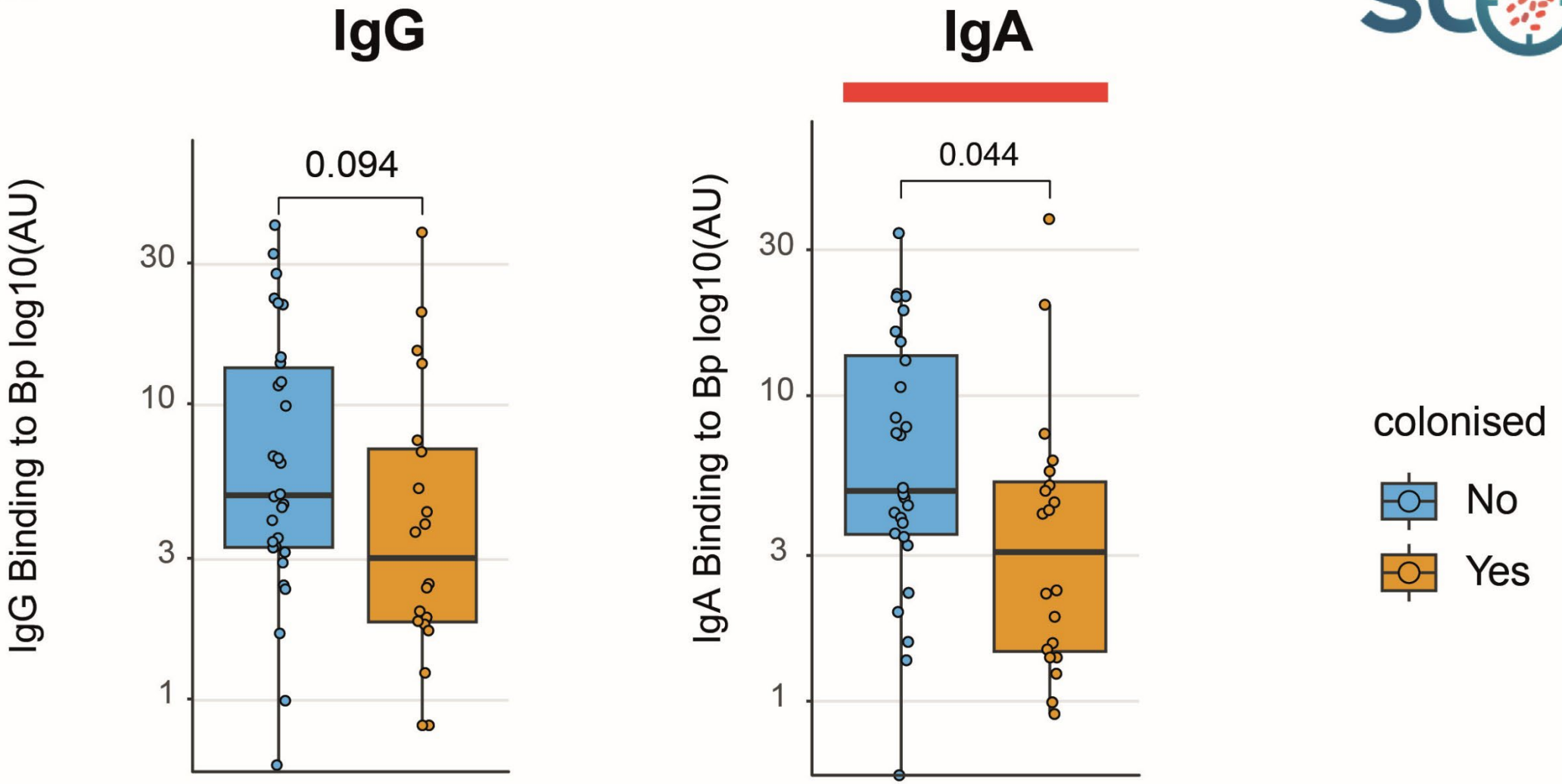
Non-colonised versus colonised – serum IgA

Baseline

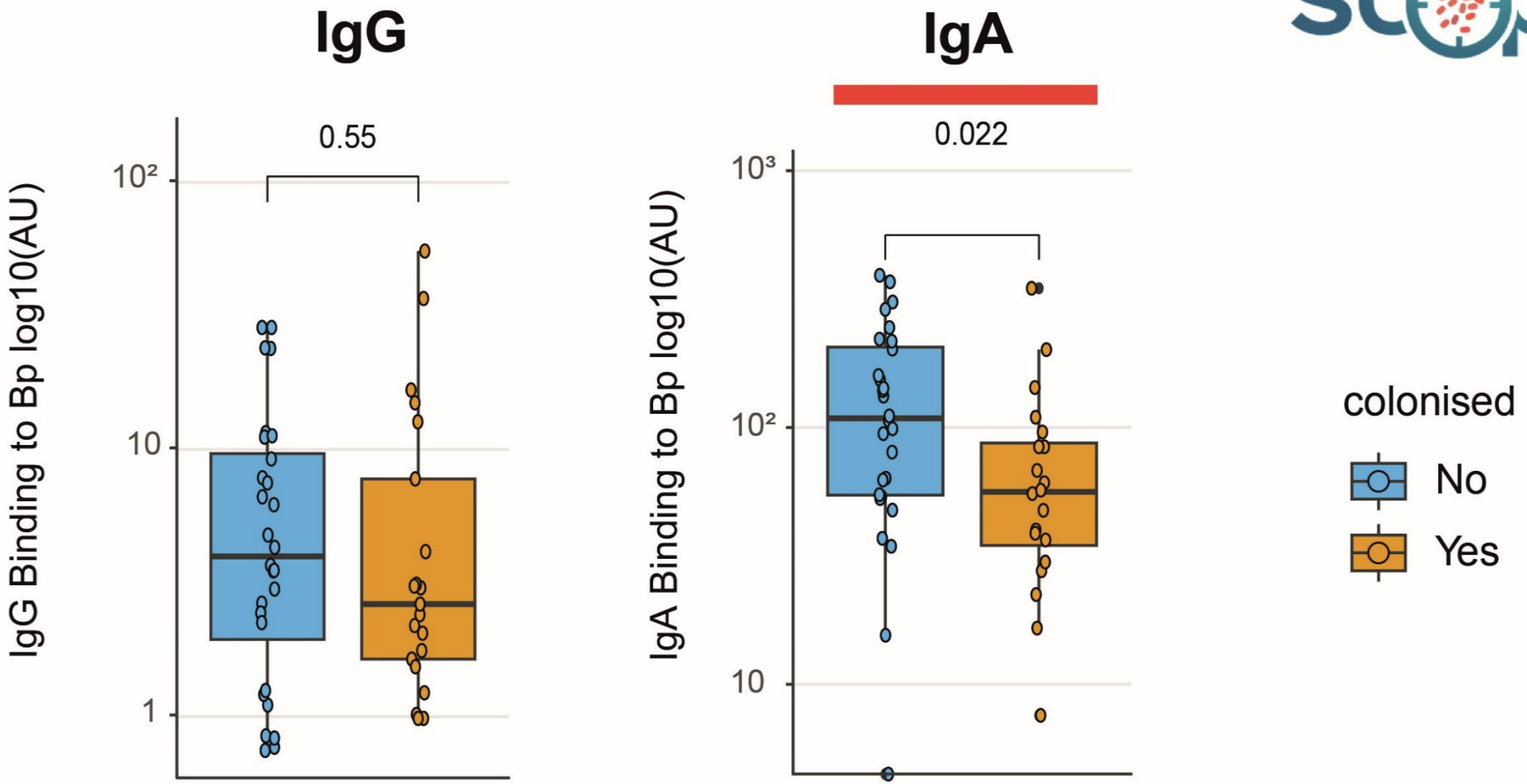


Non-colonised versus colonised – serum Bp binding

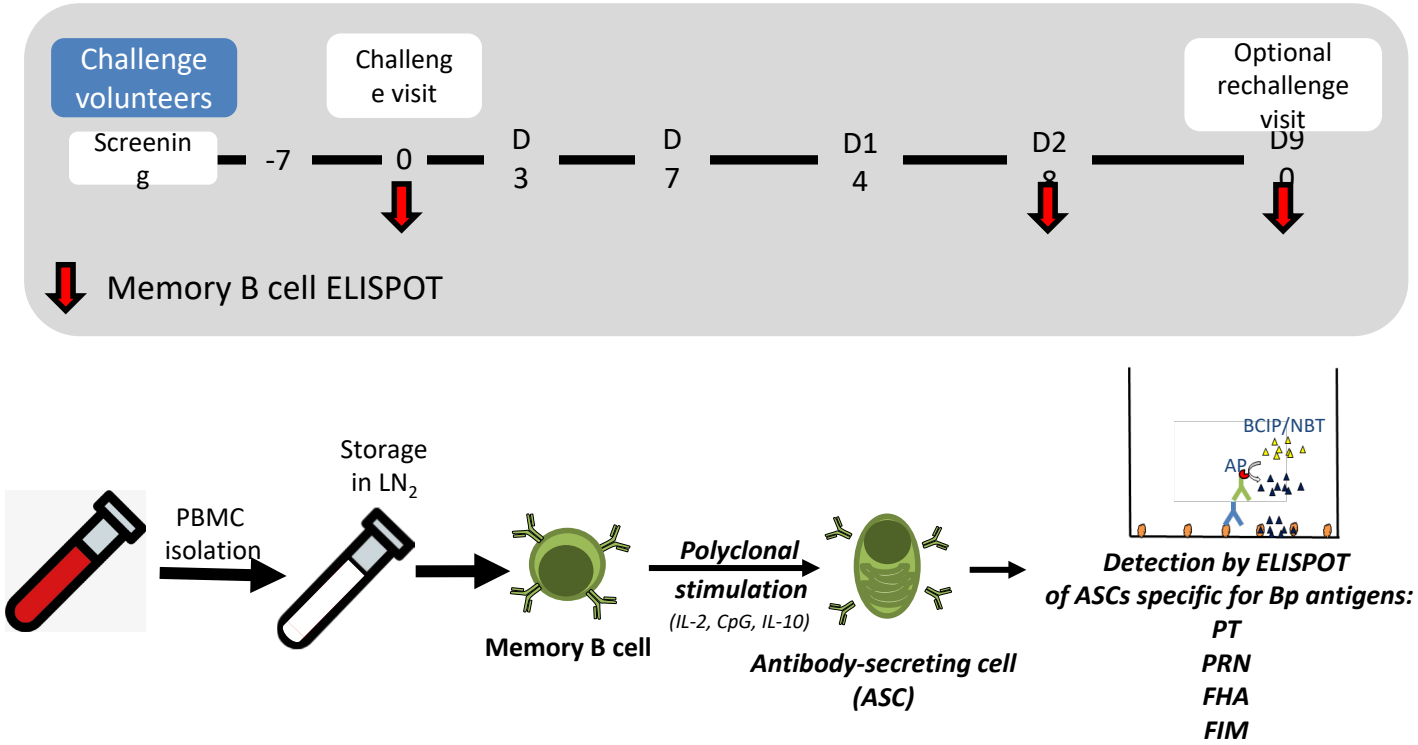
Baseline



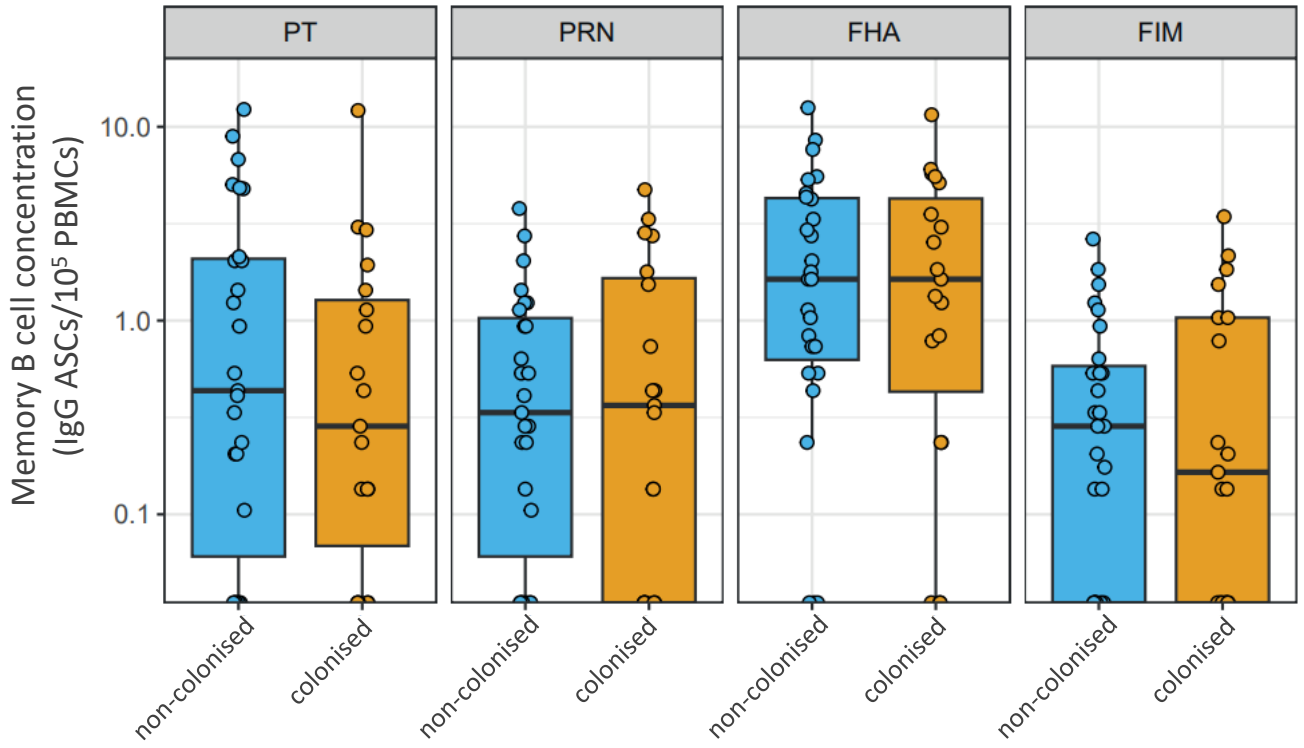
Non-colonised versus colonised – mucosal fluid Bp binding



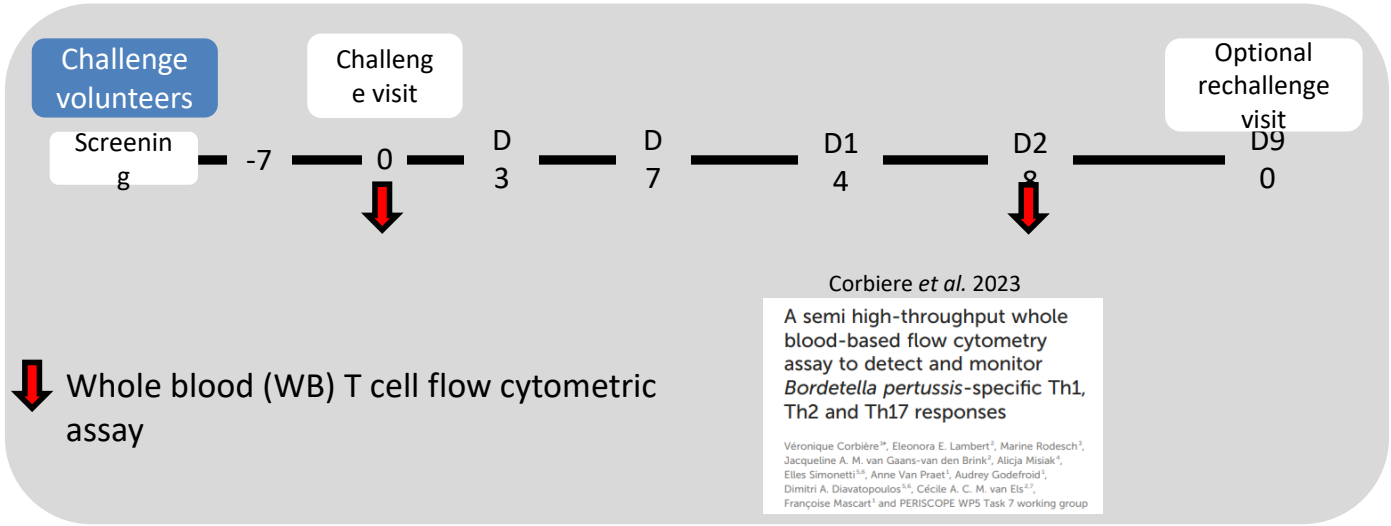
Investigating memory B cell responses



Baseline memory B cell concentrations



Investigating T helper cell responses



Stimulation of diluted whole blood with positive control antigen (SEB) or *B. pertussis* antigens

- Bp Lysate
- PT
- FHA

Cytokine secretion blockade
+ Brefeldin A
+ Goligistop (monesin)

19 h

37°C 24h

RBC lysis and fixation

Stored in LN_2

Staining and flow cytometric analysis of CD4+ populations at baseline and post-challenge:

- **Th1 (IFNg)**
- **Th2 (IL-4, IL-5, IL-13)**
- **Th17 (IL-17A, IL-17F)**
- **IL-22**

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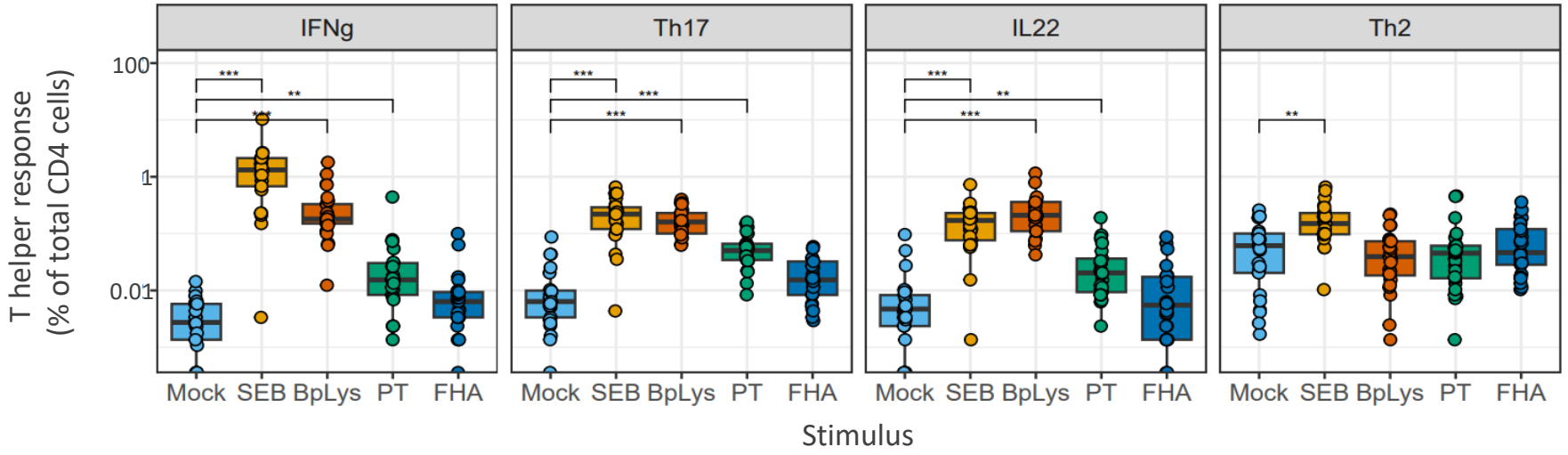
Baseline T helper cell responses to Bp antigens



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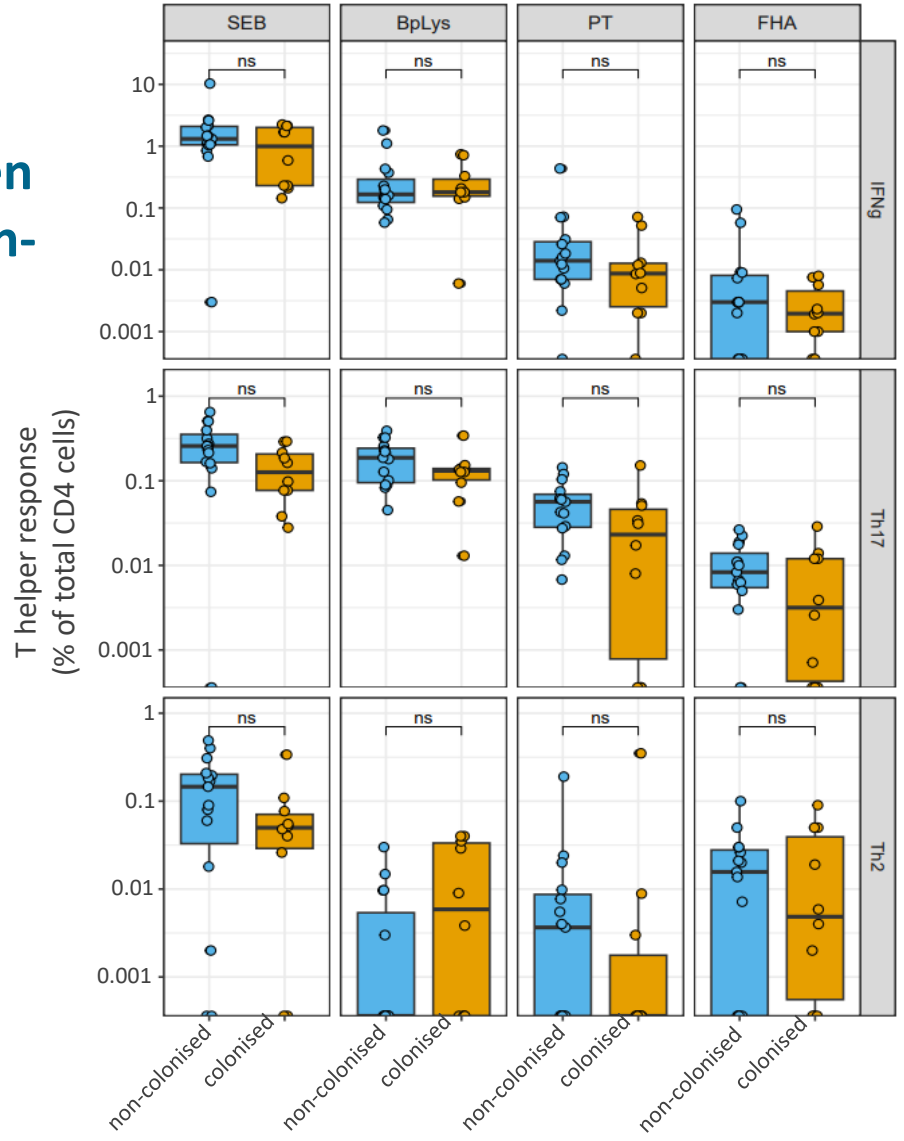
Baseline comparison between T helper cell responses in non-colonised and colonised volunteers



Data is mock subtracted

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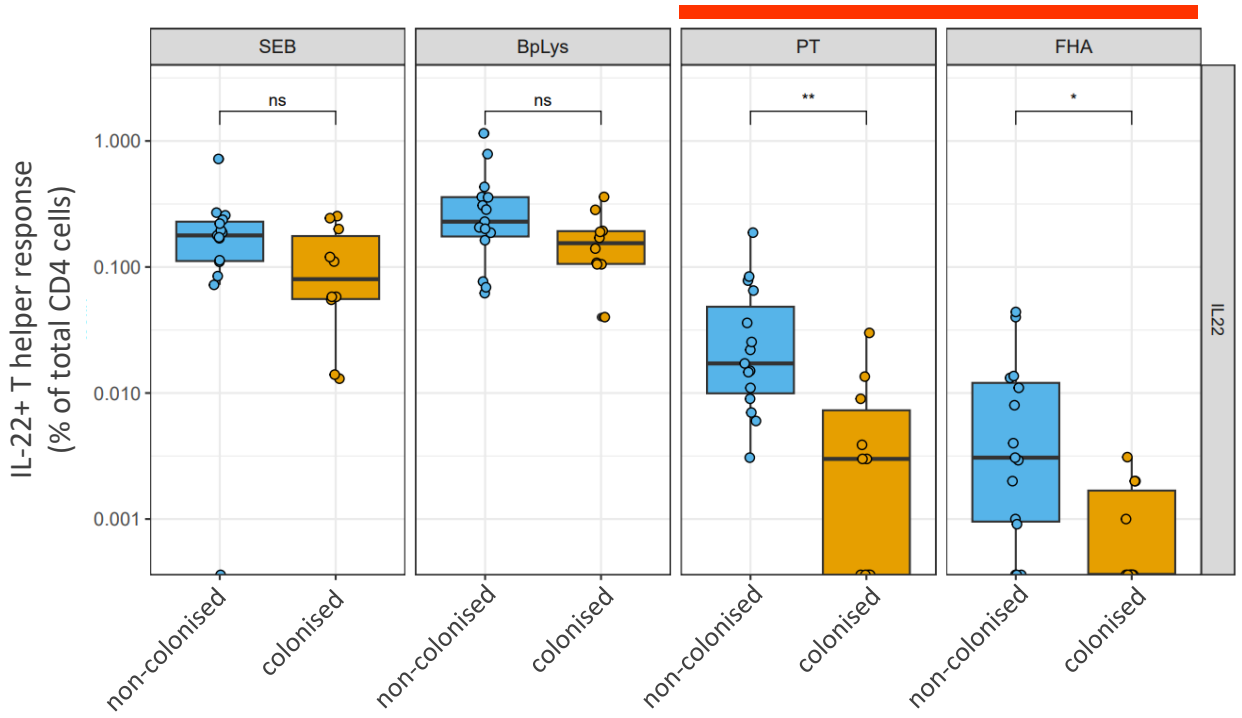
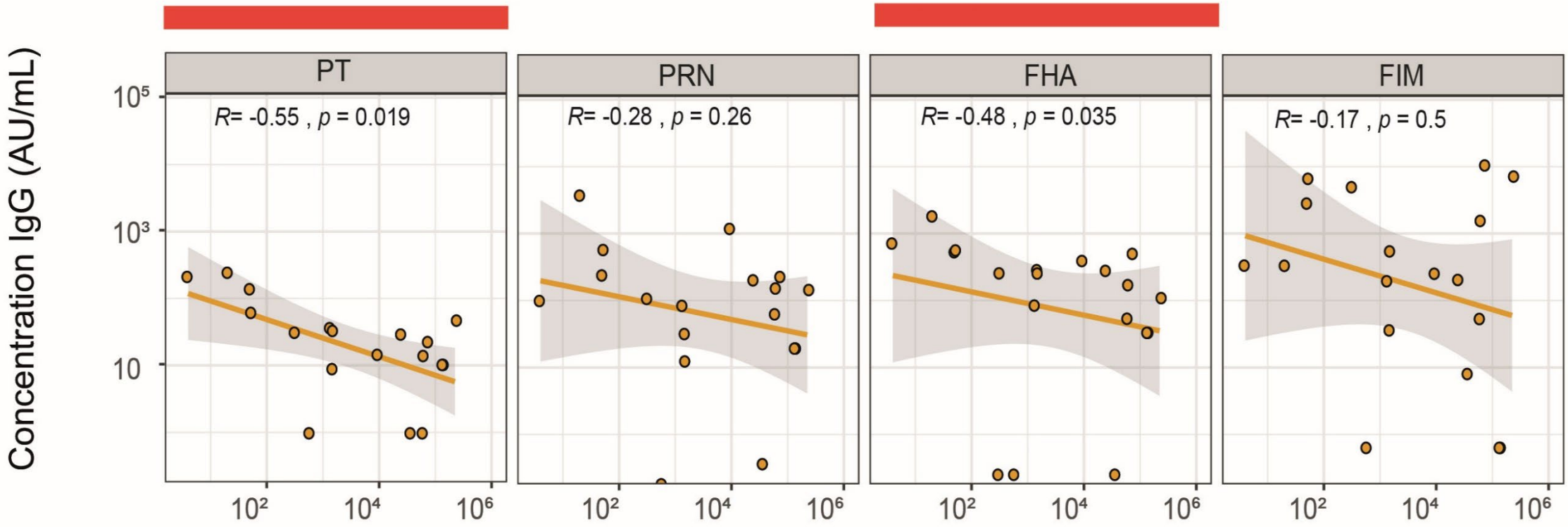
Baseline IL-22+ T helper cell responses



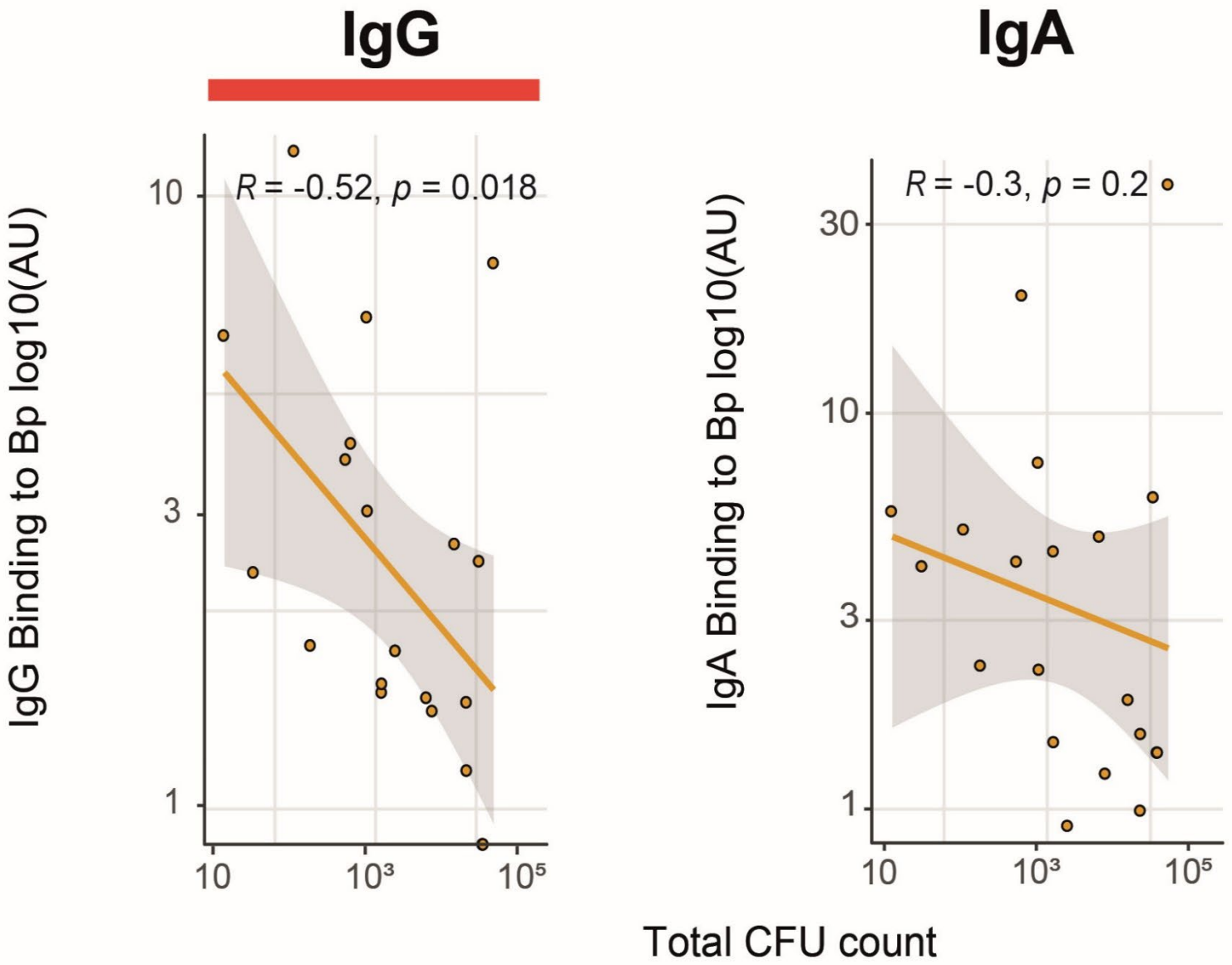
Control of colonisation density - Serum IgG

Baseline



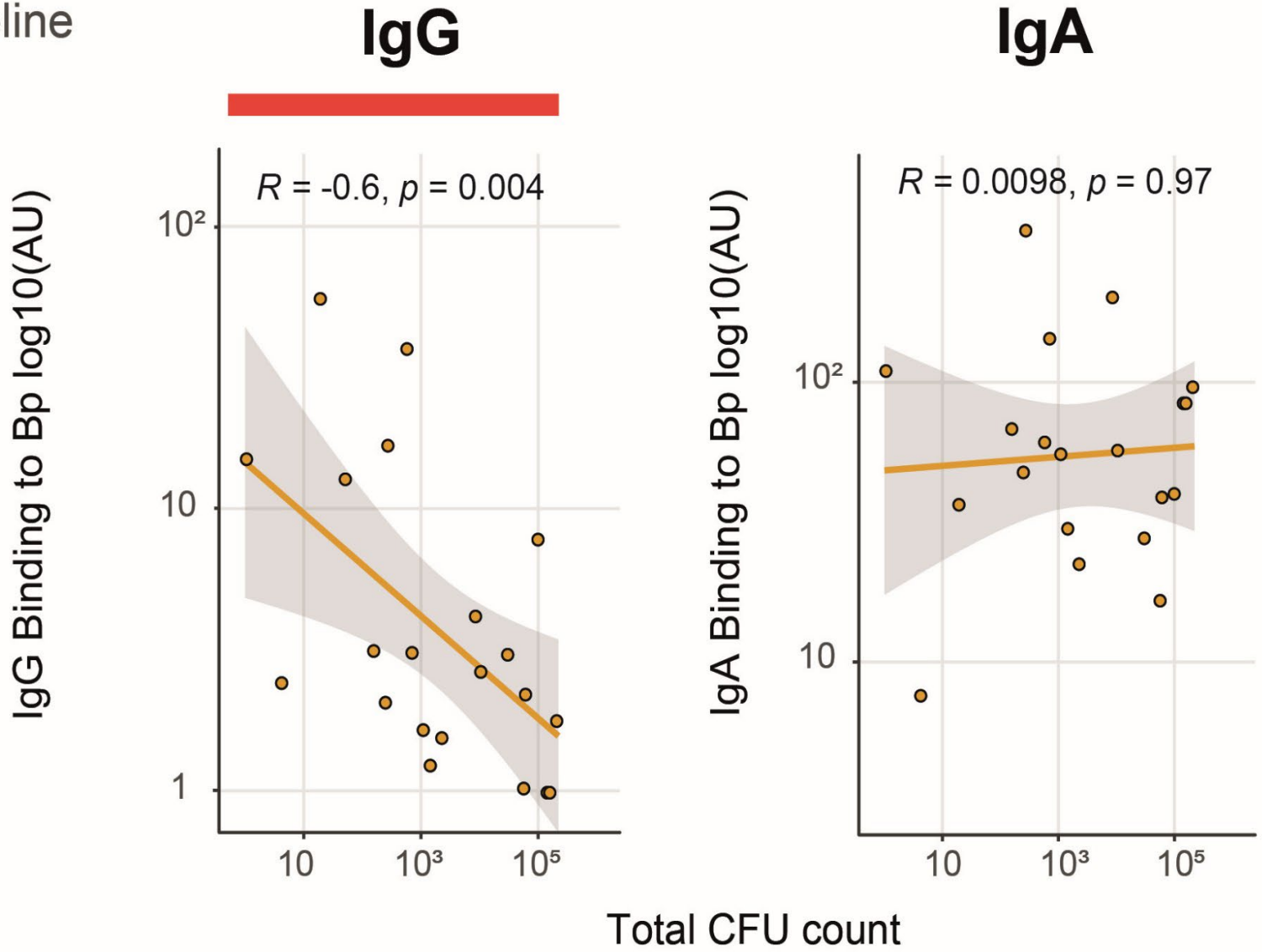
Control of colonisation density - Serum Bp binding

Baseline



Control of colonisation - MLF Bp binding

Baseline



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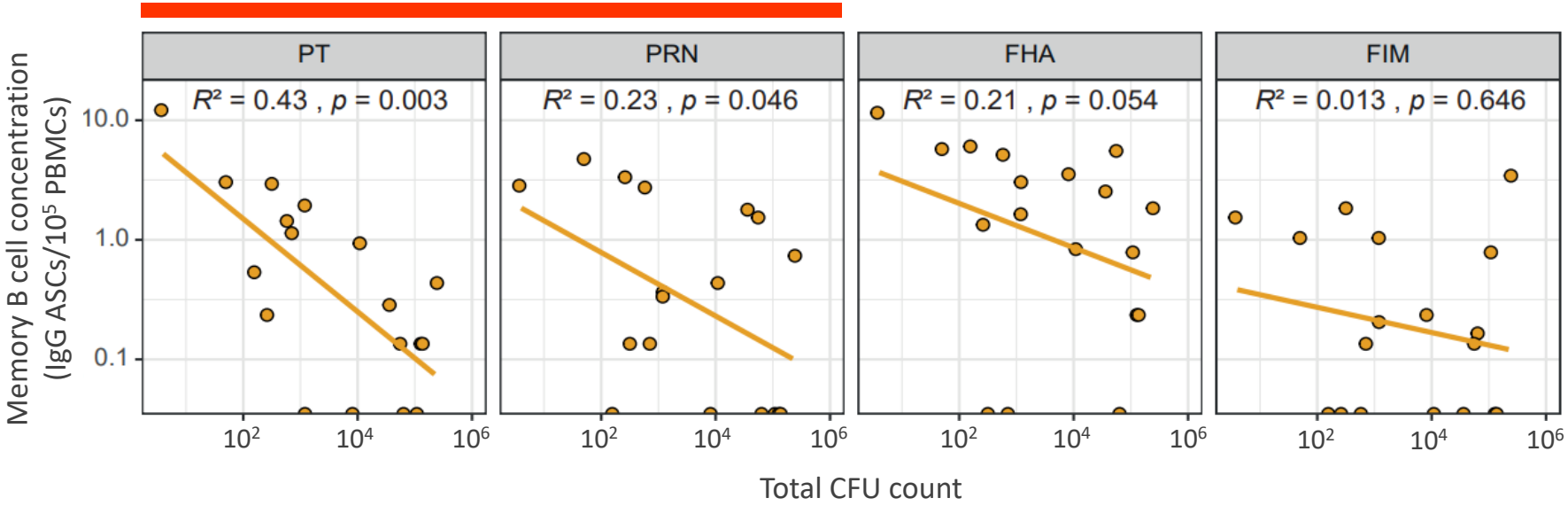
Baseline memory B cell concentrations inversely correlate with colonisation density



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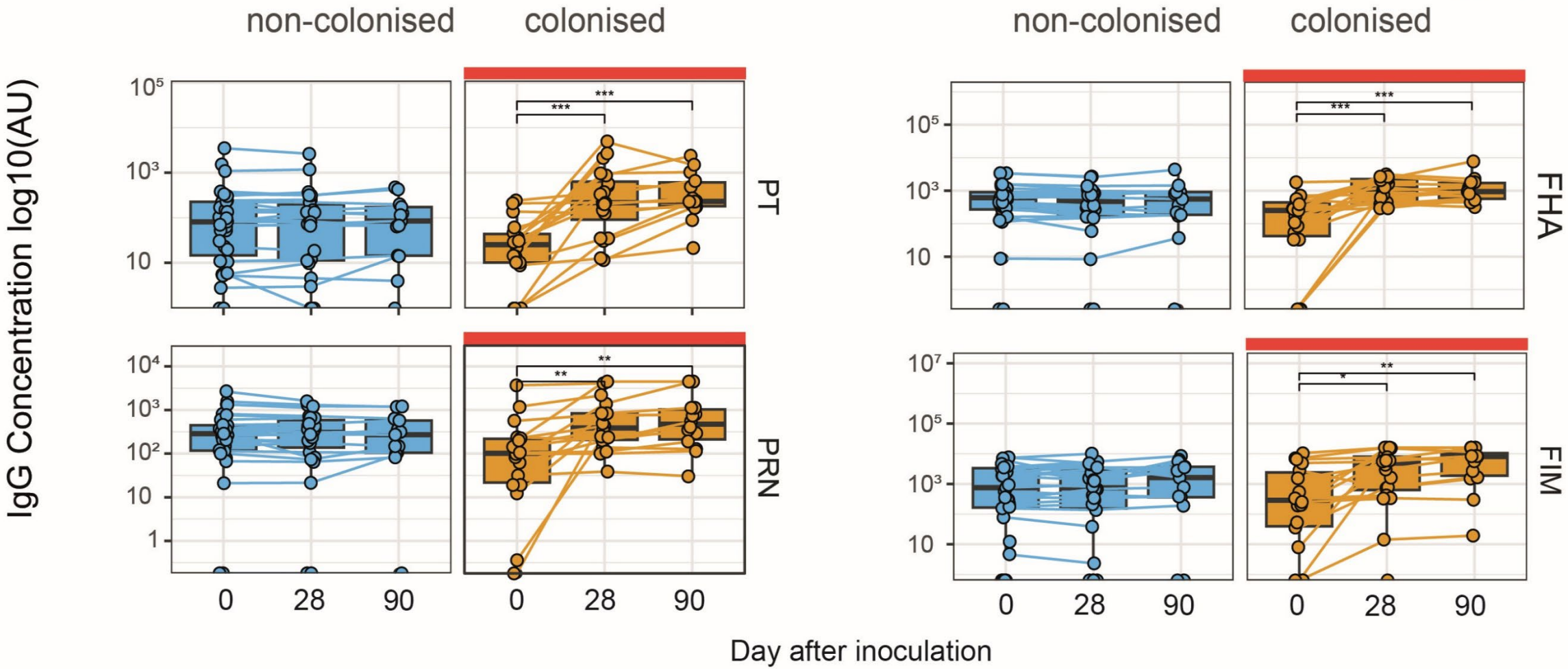
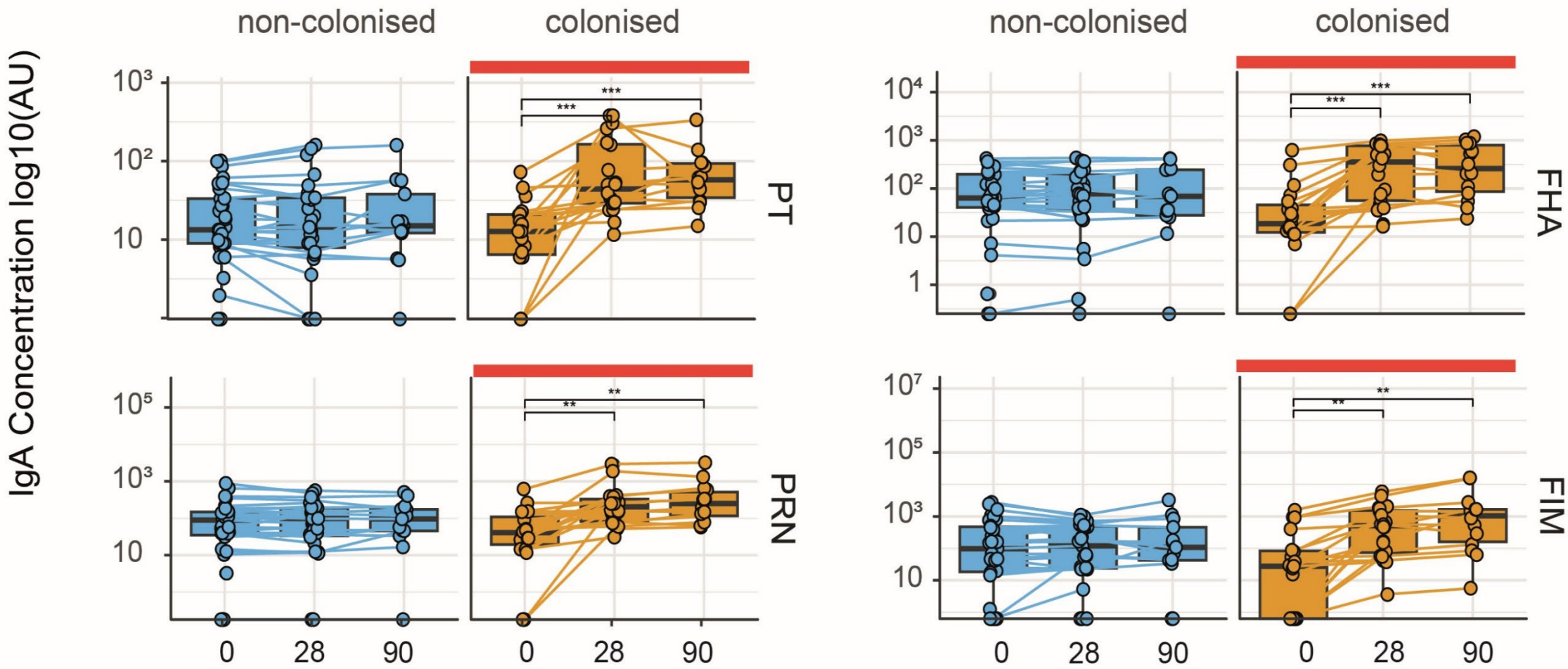
Does experimental infection induce an immune response?

Colonisation is an immunising event - IgG



Colonisation is an immunising event - IgA



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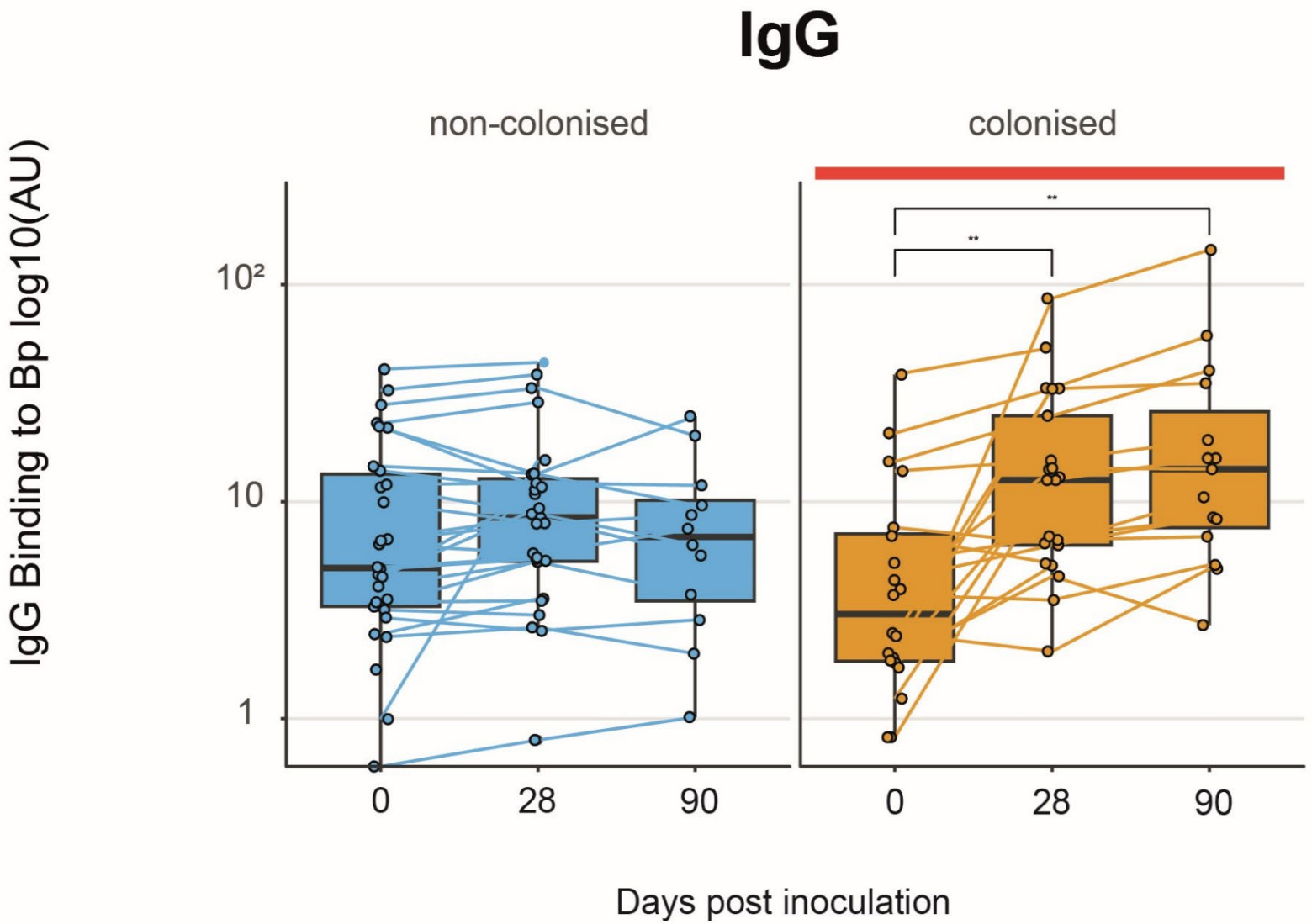
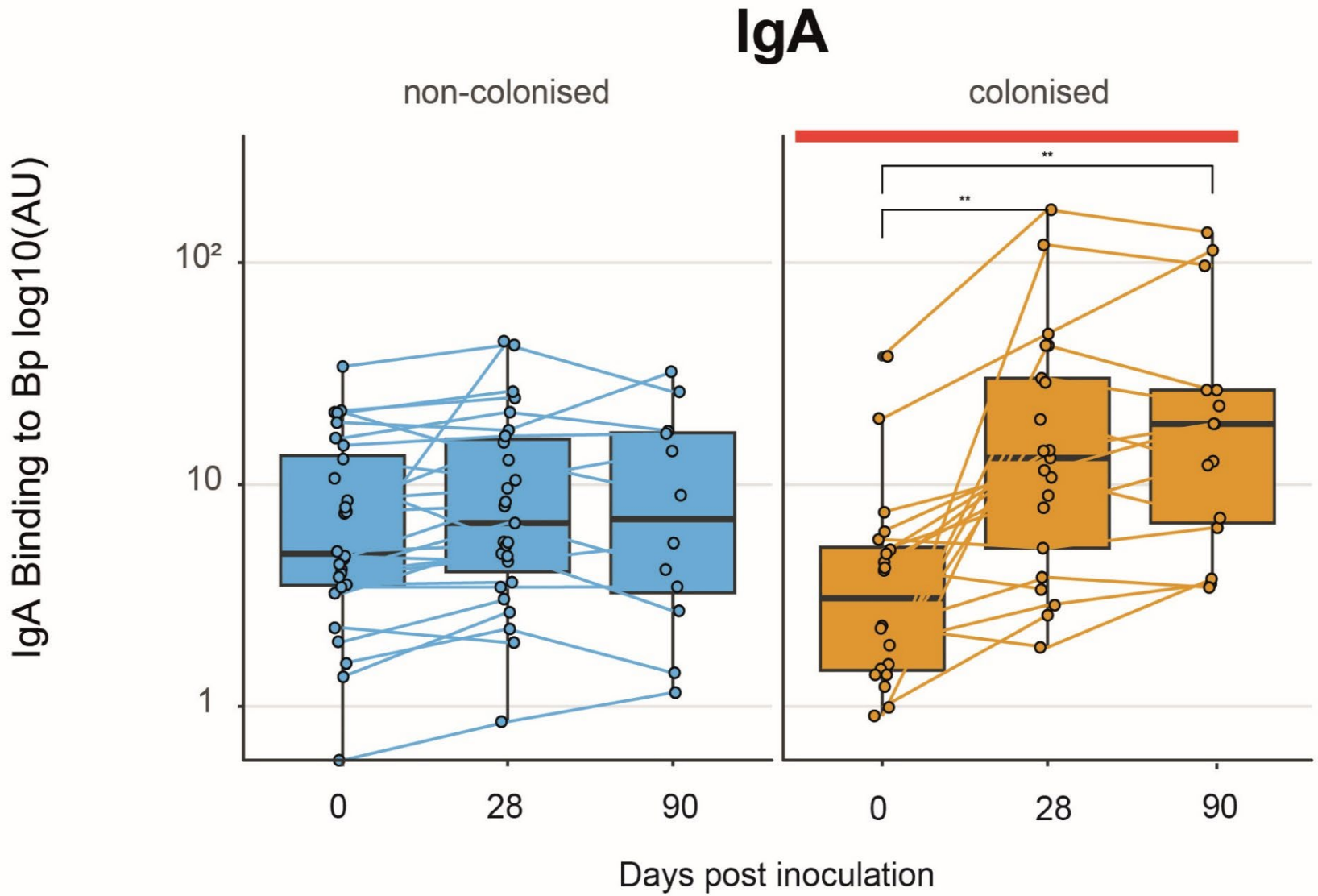
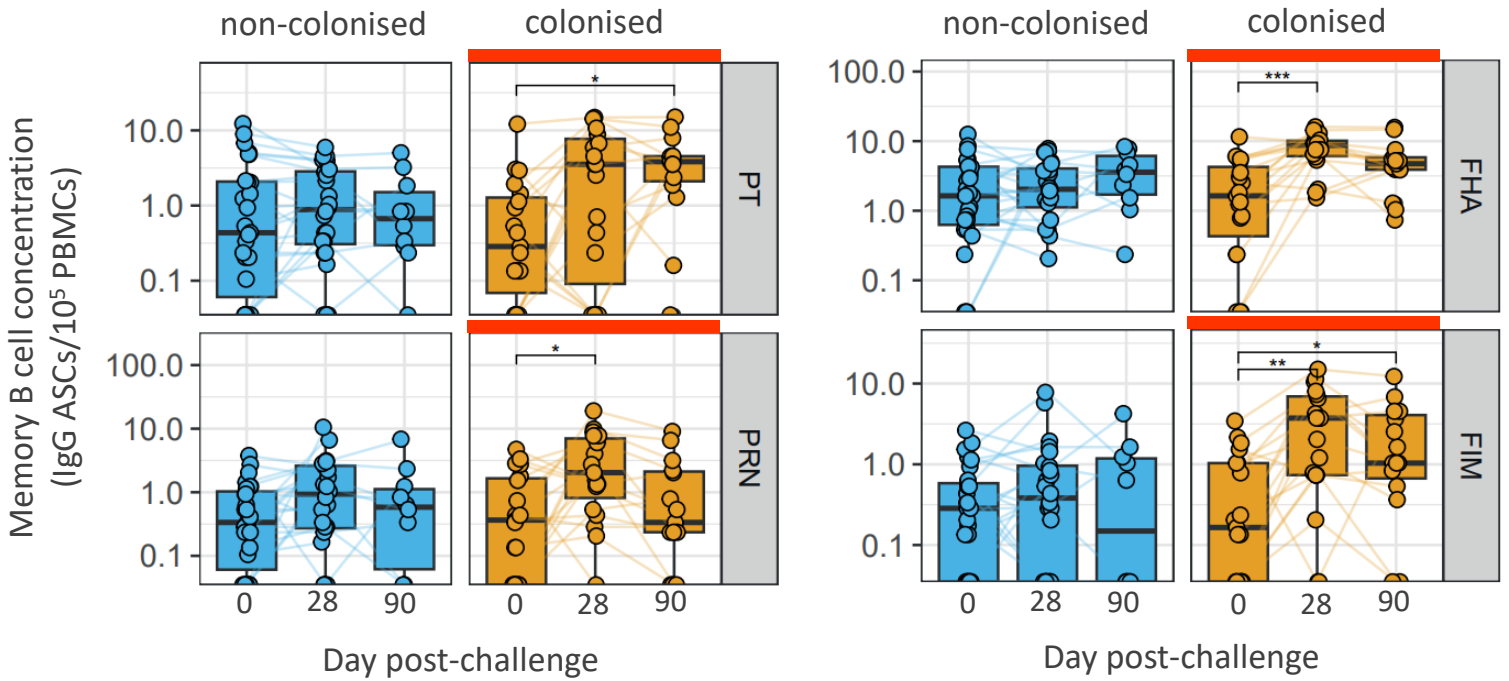
Colonisation is an immunising event - Bp binding



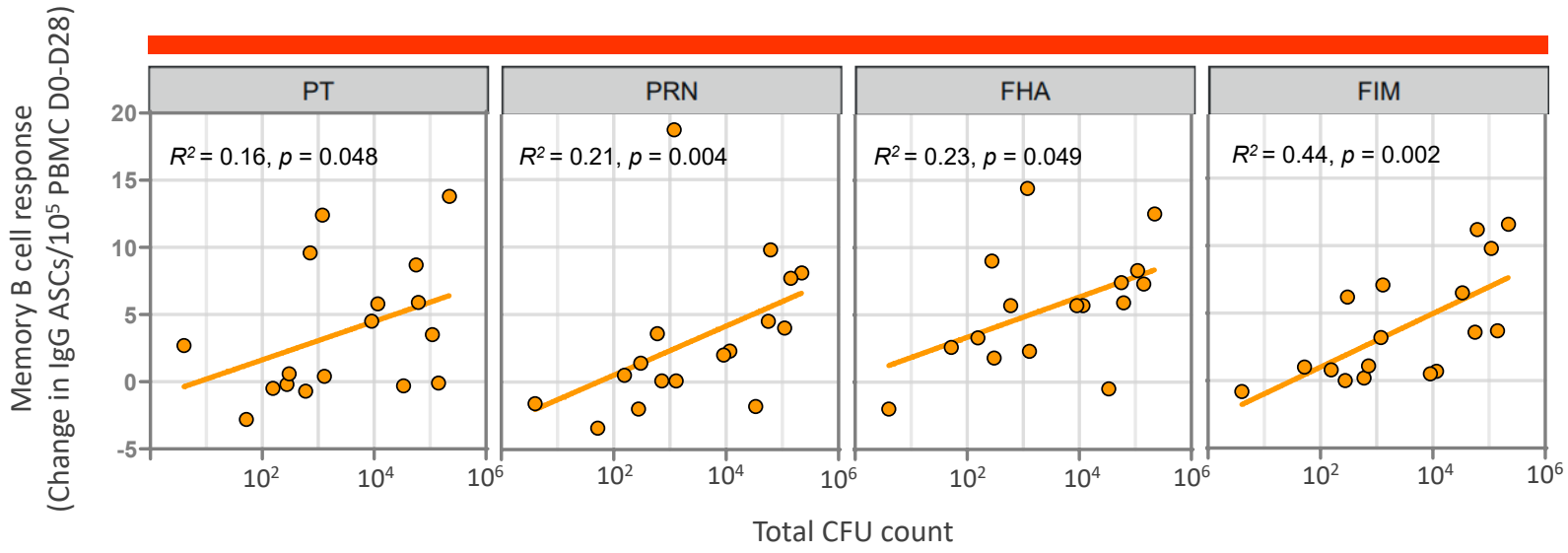
Colonisation is an immunising event - Bp binding



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≤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?

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