Evidence on vaccine benefit from Human Infection Models: insights and considerations

Robert Read

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United Kingdom

circa 1796

23 Subjects

Inoculated with Cowpox pus

Subsequently injected with *variolous* material

£10,000 grant from Royal Society

Widespread vaccination with cowpox begun 1840

Controlled Human Infection Models

Bacterial

Campylobacter
Cholera
E. Coli – (ETEC, EPEC, DAEC, EAggEG)
Francisella tularensis
Gonorrhoea
H. Pylori
Salmonella Typhi and Paratyphi
Shigella

BCG
Bordetella pertussis
Streptococcus pneumoniae
Streptococcus pyogenes
Neisseria lactamica

Viral

Dengue
Influenza
RSV
Norovirus
Rhinovirus
Coronavirus
Rotavirus

Parasitic

Malaria
Giardia
Cryptosporidium
Leishmania

Rickettsial

Rocky Mountain Spotted FEver

Helminthic

Hookworm

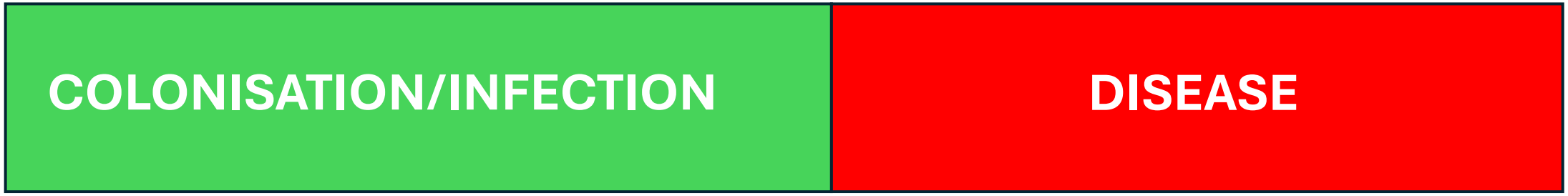
Ethics and Informed Consent

- Risk of harm
  - Immunity, virulence/attenuation, antimicrobial activity, monitoring
- Quality and Value of Research
  - Benefit:risk
  - Professionalism and competence
- Justice
  - Self determination
  - Equality

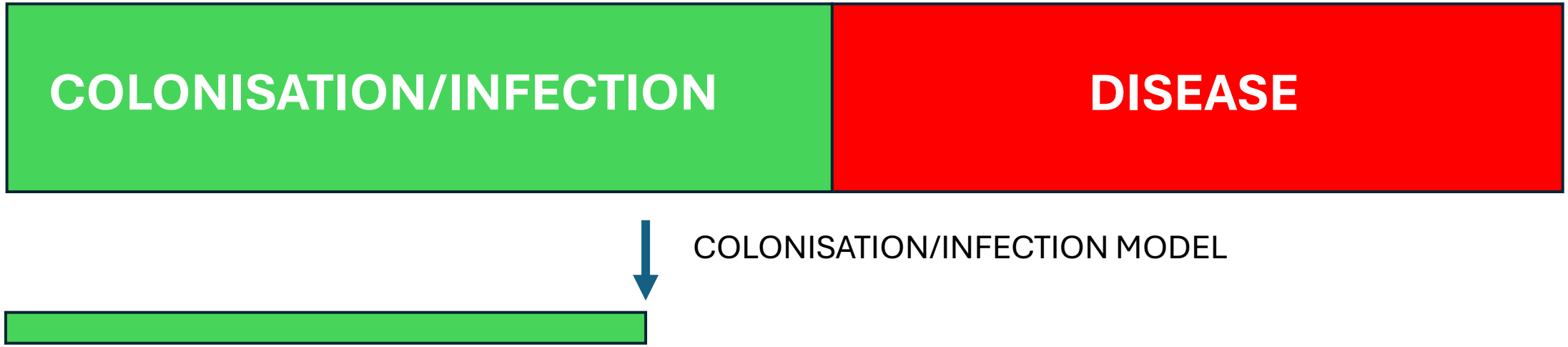
Ethical Considerations: Controlled Human Infection

- **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**

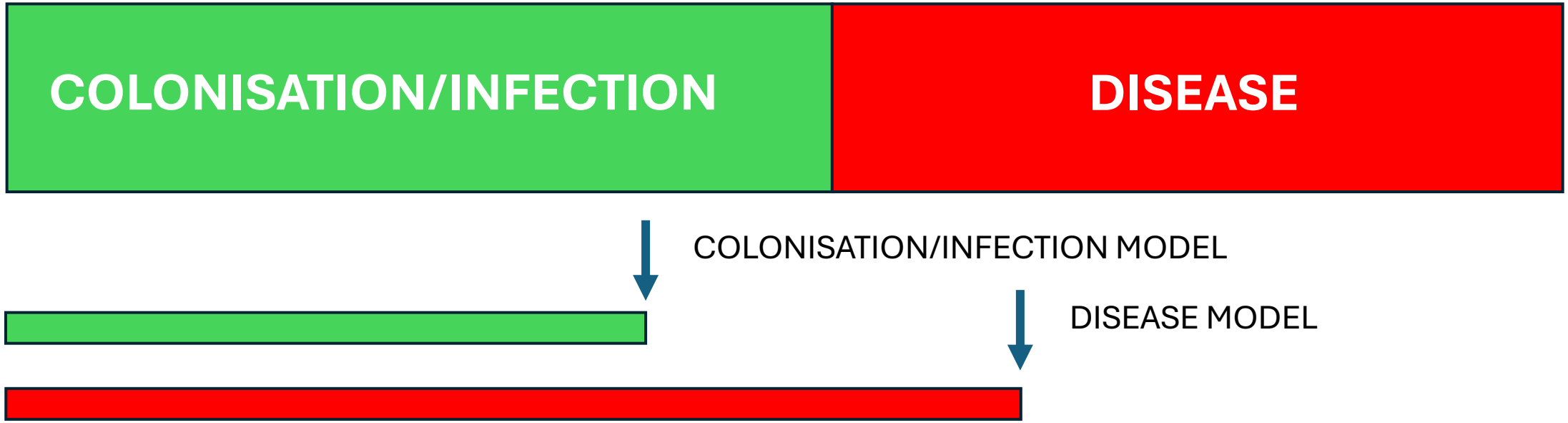
Controlled Human Infection models



Controlled Human Infection models



Controlled Human Infection models



Single-dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection With *Vibrio cholerae* O1 El Tor

Clinical and Bacteriologic Responses to Challenge

					Vaccine Efficacy (95% CI) or *P* Value	
Clinical or Bacteriological Endpoint	**All Vaccinees**	**Vaccine Day 10**	**Vaccine 3 mo**	**All Placebos**	**Day 10**	**3 mo**
Total challenged	68	35	33	66		
No. with severe cholera (%)	3 (4.4)	1 (2.9)	2 (6.1)	28 (42.4)	93.3% (56.2%–100%)	85.7% (46.2%–100%)
No. with moderate or severe cholera (%)[a]	6 (8.8)	2 (5.7)	4 (12.1)	39 (59.1)	90.3% (61.7%–100%)	79.5% (49.1%–100%)
No. with mild cholera[b] or worse (%)	20 (29.4)	5 (14.3)	15 (45.5)	61 (92.4)	84.5% (67.0%–100%)	50.8% (33.6%–66.8%)
Median diarrheal stool volume, mL (IQR)	0 (0–311)	0 (0–0)	178 (0–988)	4377 (1563–8087)	<.0001	<.0001
Median number of diarrheal stools (IQR)	0 (0–3.8)	0 (0–0)	2.0 (0–5.5)	22.5 (9.8–39.3)	<.0001	<.0001
Median peak *Vibrio cholerae* O1 count, CFU/mL (IQR)	4.2×10^1 ($0–3.5 \times 10^5$)	0 ($0–2.7 \times 10^3$)	9.7×10^4 ($0–1.7 \times 10^7$)	3.2×10^7 (6.1×10^6–1.2×10^8)	<.0001	<.0001
No. with fever (%)[c]	3 (4.4)	1 (2.9)	2 (6.1)	18 (27.3)	.0025	.0159
No. with nausea/vomiting (%)	16 (23.5)	9 (25.7)	7 (21.2)	38 (57.6)	.0032	.0006
No. with abdominal cramping (%)	18 (26.5)	8 (22.9)	10 (30.3)	45 (68.2)	<.0001	.0005
No. with malaise (%)	16 (23.5)	8 (22.9)	8 (24.2)	41 (62.1)	.0003	.0006

Chen WH, *CID* 2016

Abbreviations: CFU, colony-forming units; CI, confidence interval; IQR, interquartile range.

[a] Moderate and severe cholera (study primary endpoint) is defined as ≥3 L and ≥5 L of cumulative diarrheal stool, respectively.

[b] Mild diarrhea is defined as the passage of ≥2 unformed stools (grade 3–5) over a 48-hour period that equals or exceeds 200 mL or a single unformed stool of ≥300 mL and <3 L total diarrhea.

[c] Fever is defined as ≥38.0°C (100.4°F).

Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella* Typhi: a randomised controlled, phase 2b trial

Lin et al 2017
Lancet

Celina Jin, Malick M Gibani, Maria Moore, Helene B Juel, Elizabeth Jones, James Meiring, Victoria Harris, Jonathan Gardner, Anna Nebykova, Simon A Kerridge, Jennifer Hill, Helena Thomaides-Brears, Christoph J Blohmke, Ly-Mee Yu, Brian Angus, Andrew J Pollard

Lancet 2017; 390: 2472–80
Published Online September 28, 2017
http://dx.doi.org/10.1016/

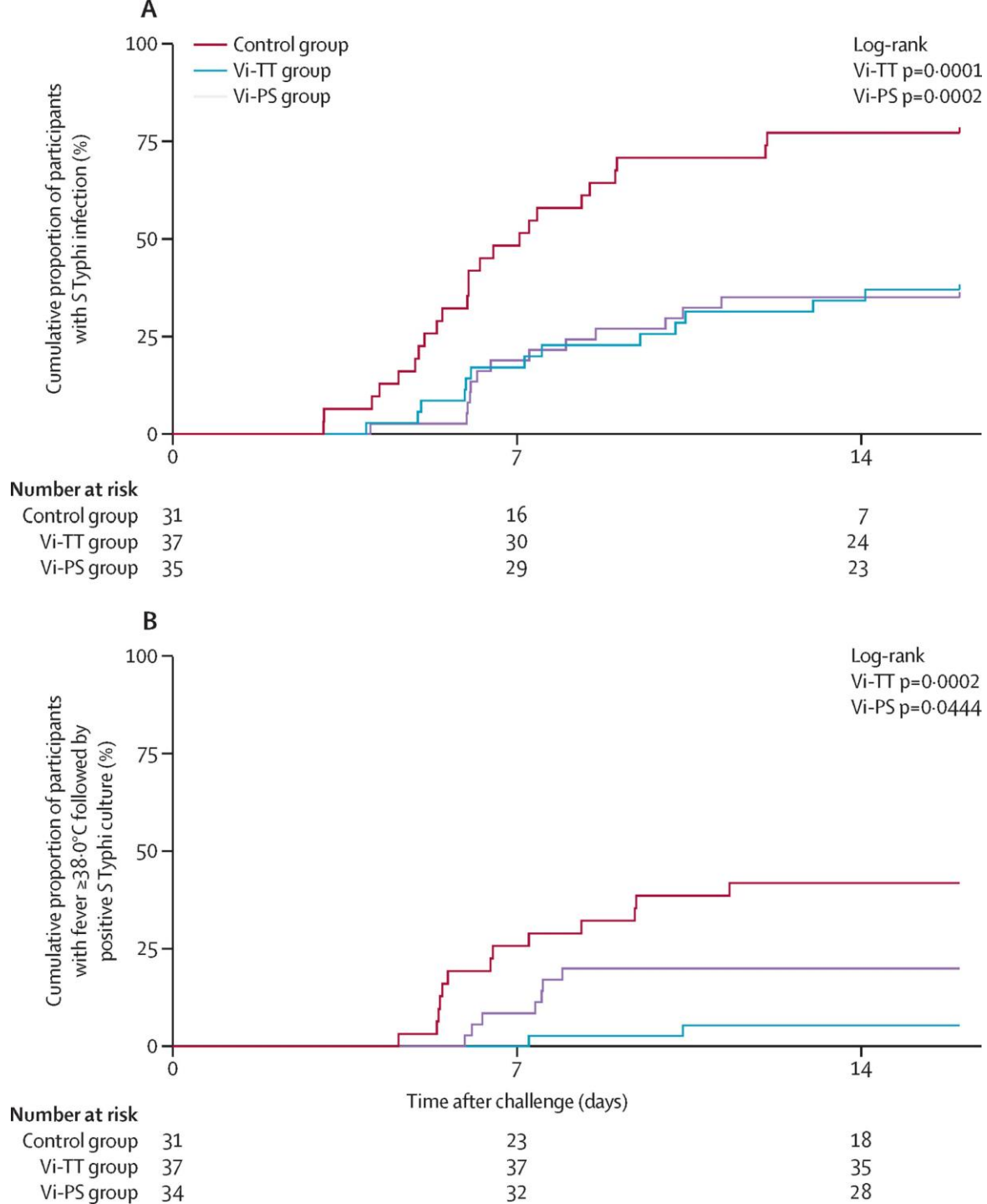
Summary

Background *Salmonella enterica* serovar Typhi (*S* Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines (Vi-conjugate vaccines) are immunogenic and can be used from infancy but there are no efficacy data for the leading candidate vaccine being considered for widespread use. To address this knowledge gap, we assessed the efficacy of a

	Control group (n=34)	Vi-TT group (n=41)	Vi-PS group (n=37)
Primary outcome			
Completed challenged	31	37	35
Total diagnosed (composite definition, clinical or microbiological typhoid diagnosis)	24/31 (77%)	13/37 (35%)	13/35 (37%)
Relative risk (95% CI)	..	0·45 (0·28–0·73)	0·48 (0·30–0·77)
Vaccine efficacy (%, 95% CI)	..	54·6% (26·8–71·8)	52·0% (23·2–70·0)
p value	..	0·0005	0·0010
Secondary outcomes			
Time to diagnosis (days)	6·0 (5·1–7·8)	6·5 (6·1–8·6)	7·2 (5·9–10·2)
Microbiological diagnosis	16/31 (52%)	12/37 (32%)	9/35 (26%)
Time to microbiological diagnosis (days)	6·0 (4·6–8·0)	6·3 (6·0–8·3)	6·1 (5·1–10·2)
Clinical diagnosis	8/31 (26%)	1/37 (3%)	4/35 (11%)
Time to clinical diagnosis (days)	6·8 (5·4–7·8)	10·4	8·5 (6·5–10·0)
Clinical outcomes			
Fever ≥37·5˚C (any duration)	20/31 (65%)	13/37 (35%)	18/35 (51%)
Fever ≥38·0˚C (any duration)	17/31 (55%)	6/37 (16%)	11/35 (31%)
Fever ≥38·5˚C (any duration)	14/31 (45%)	4/37 (11%)	9/35 (25%)
Time to first fever ≥38·0˚C (any duration; days)	7·2 (5·4–8·5)	10·4 (10·2–15·5)	7·5 (6·2–8·7)
Microbiological outcomes			
S Typhi bacteraemia	24/24 (100%)	13/13 (100%)	11/13 (85%)
Time to first positive blood culture (days)	6·1 (5·0–7·6)	6·5 (6·1–8·6)	6·1 (5·0–10·2)
Participants with positive S Typhi stool culture	22/31 (71%)	22/37 (59%)	21/35 (60%)
Diagnosed participants with positive S Typhi stool culture	19/24 (79%)	12/13 (92%)	10/13 (77%)
Median quantitative blood culture (CFU/mL; range)	0·4 (0·05–22·7)	0·075 (0·05–1·2)	0·1 (0·05–5·6)

Data are n, n/N (%), or median (IQR) unless otherwise stated. Vi-TT=Vi-tetanus toxoid conjugate vaccine. Vi-PS=Vi-polysaccharide vaccine. S Typhi=*Salmonella* Typhi. CFU=colony forming units.

***Table 2*: Primary and secondary outcomes**

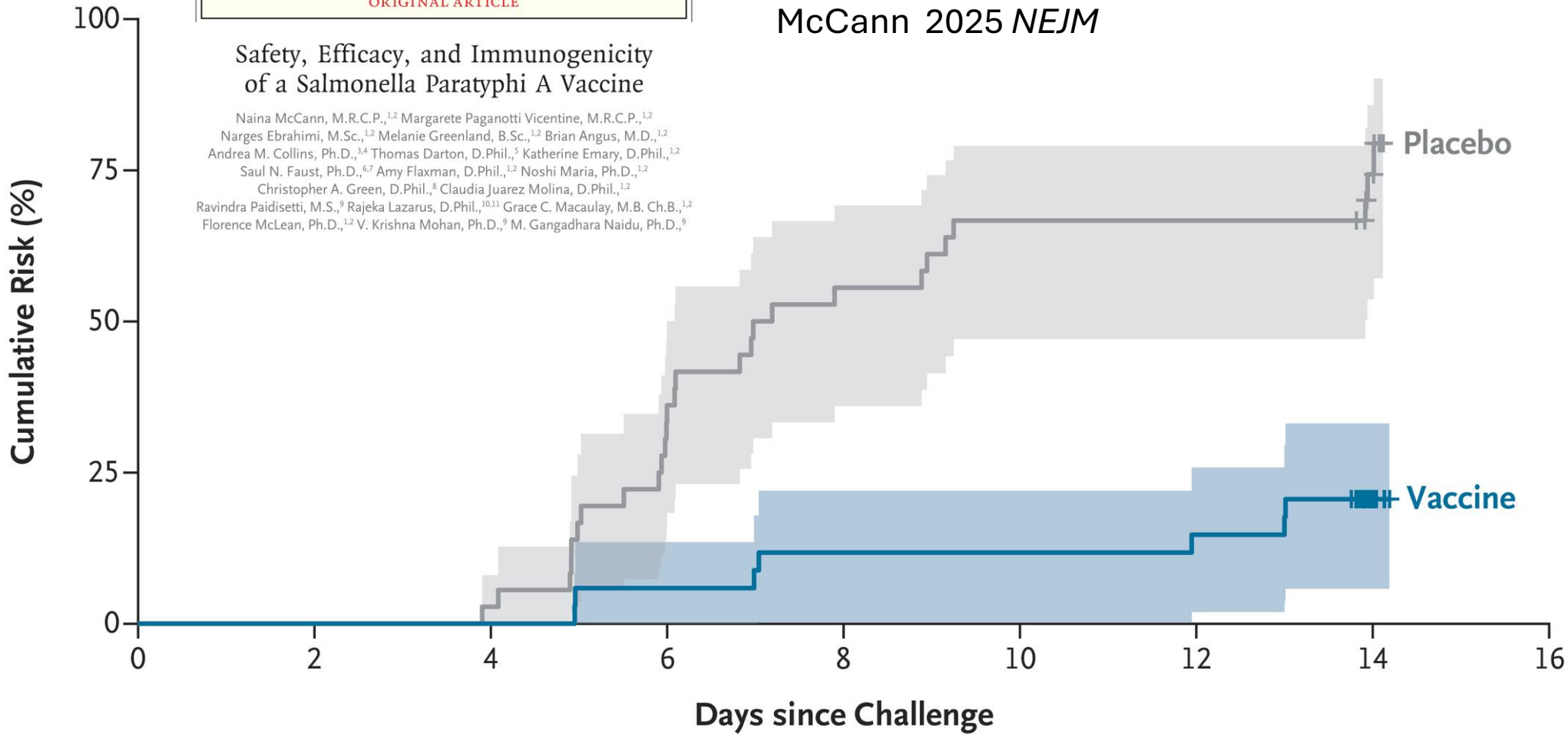


ORIGINAL ARTICLE

Safety, Efficacy, and Immunogenicity of a Salmonella Paratyphi A Vaccine

Naina McCann, M.R.C.P.,[1,2] Margarete Paganotti Vicentine, M.R.C.P.,[1,2] Narges Ebrahimi, M.Sc.,[1,2] Melanie Greenland, B.Sc.,[1,2] Brian Angus, M.D.,[1,2] Andrea M. Collins, Ph.D.,[3,4] Thomas Darton, D.Phil.,[5] Katherine Emary, D.Phil.,[1,2] Saul N. Faust, Ph.D.,[6,7] Amy Flaxman, D.Phil.,[1,2] Noshi Maria, Ph.D.,[1,2] Christopher A. Green, D.Phil.,[8] Claudia Juarez Molina, D.Phil.,[1,2] Ravindra Paidisetti, M.S.,[9] Rajeka Lazarus, D.Phil.,[10,11] Grace C. Macaulay, M.B. Ch.B.,[1,2] Florence McLean, Ph.D.,[1,2] V. Krishna Mohan, Ph.D.,[9] M. Gangadhara Naidu, Ph.D.,[9]

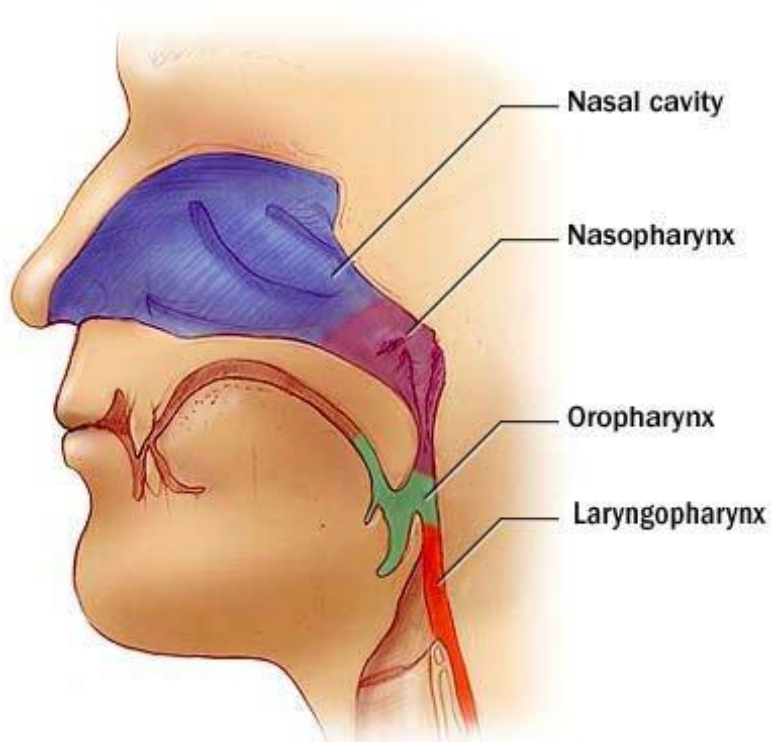
McCann 2025 *NEJM*



No. at Risk

Placebo	36	36	35	23	16	12	12	6	0
Vaccine	34	34	34	32	30	30	29	8	0

The nasopharynx…the root of all…..



- Pneumonia
- Otitis Media
- Sinusitis
- Pharyngitis
- Chronic Bronchial Sepsis
- Meningitis
- Staphylococcal sepsis

Haemophilus influenzae
Streptococcus pneumoniae
Bordetella pertussis
Moraxella catarrhalis

Neisseria meningitidis
Streptococcus pyogenes
Staphylococcus aureus
Streptococcus agalactiae

Mycobacterium spp.
Fusobacterium spp.
Klebsiella spp
Corynebacterium spp.

Experimental inoculation of *S.pneumoniae* 6B following 13 valent PCV Collins et al *AJRCCM* 2015

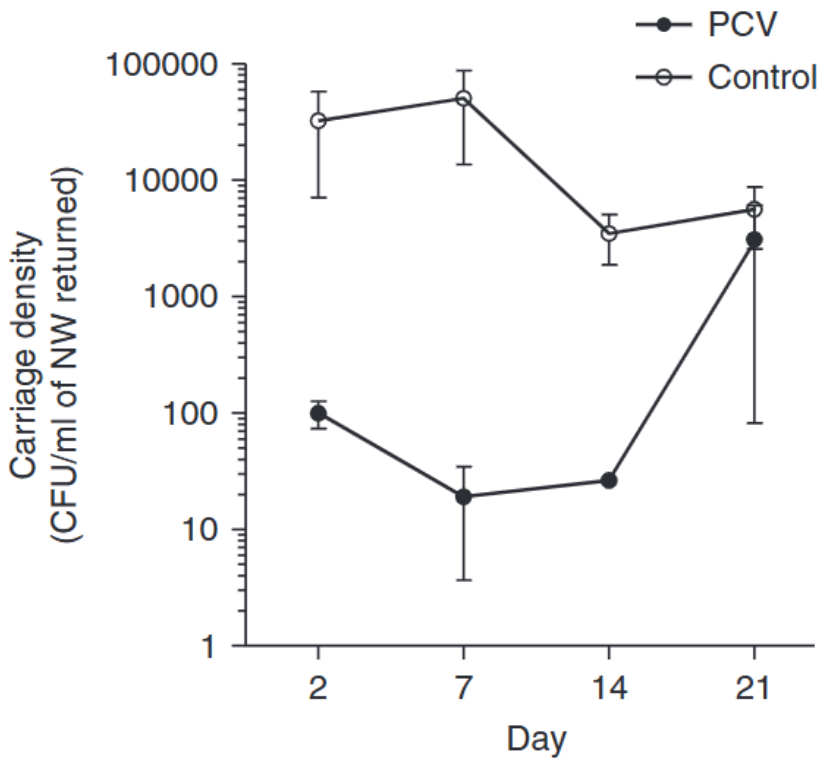


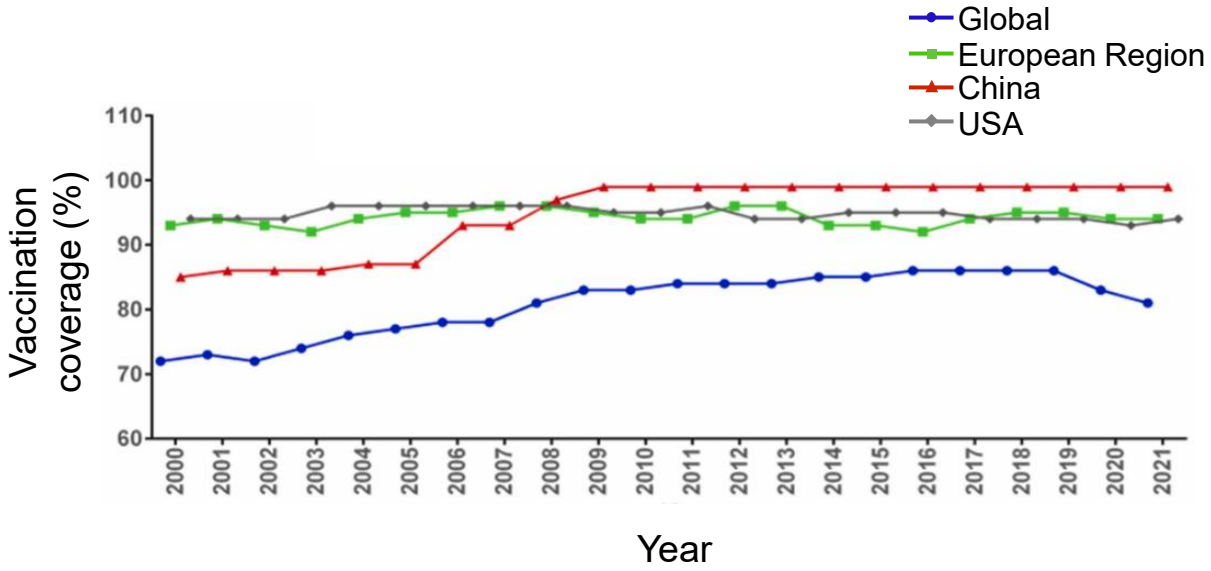
Table 3. 6B Colonization Density According to Vaccination Group at Each Time Point

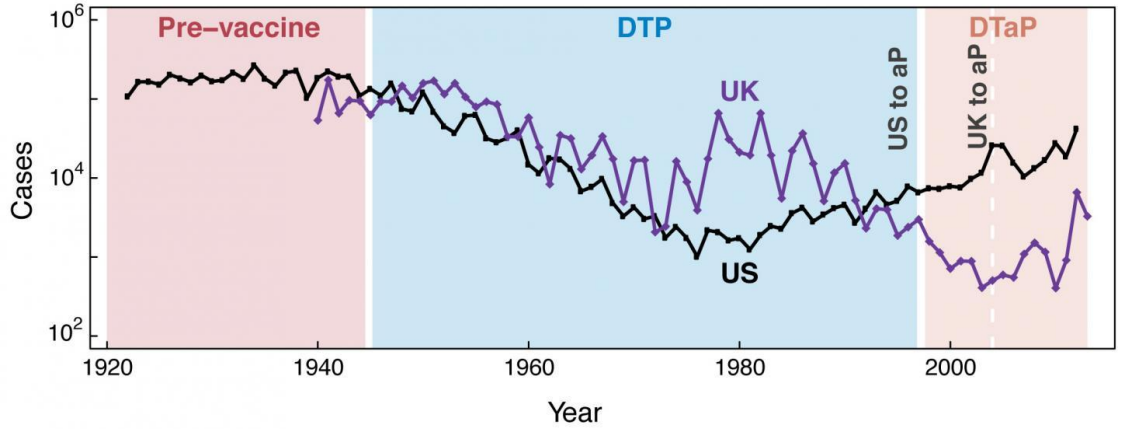
Day	Density (*CFU/ml*) Geometric Mean ± SD		Ratio (95% CI)	*P* Value
	PCV (No. Colonized at Each Time Point)	Control (No. Colonized at Each Time Point)		
Day 2	99 ± 53 (4)	33,694 ± 120,812 (21)	0.17 (0.04–0.65)	0.0099
Day 7	19 ± 31 (4)	50,517 ± 169,172 (21)	0.02 (0.00–0.14)	<0.0001
Day 14	26* (1)	3,476 ± 6,962 (19)	1.94 (0.09–43.90)†	0.6767†
Day 21	3,085 ± 4,247 (2)	5,623 ± 11,855 (15)		

Definition of abbreviations: CI = confidence interval; PCV = pneumococcal conjugate vaccine.
Density is only reported in participants who are colonized with 6B.
*Only one observation, and SD is unavailable.
†Days 14 and 21 were combined to generate a stable estimate.

Pertussis

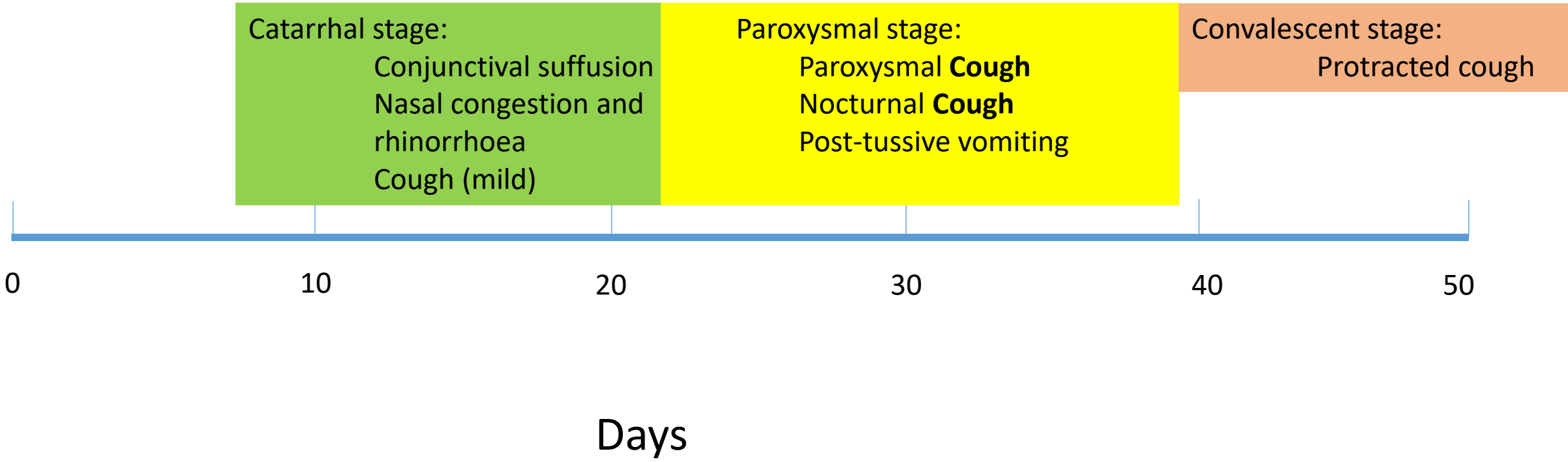
- Resurgence of Pertussis disease despite high vaccine coverage.
- ~ 24.1 million cases and ~ 160,700 deaths annually.
- Occurring despite high vaccine coverage.



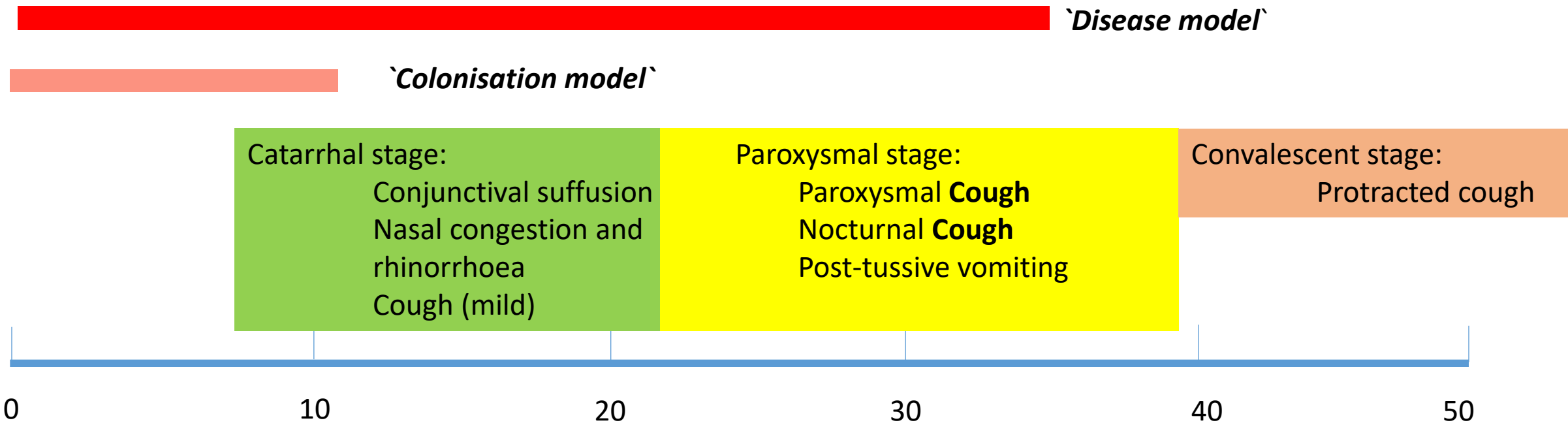


Althouse and Scarpino, *BMC Med*, 2015.
Yeung et al, *Lancet Infect Dis*, 2017.
Liu et al, J Infect, 2024.

Clinical Pertussis

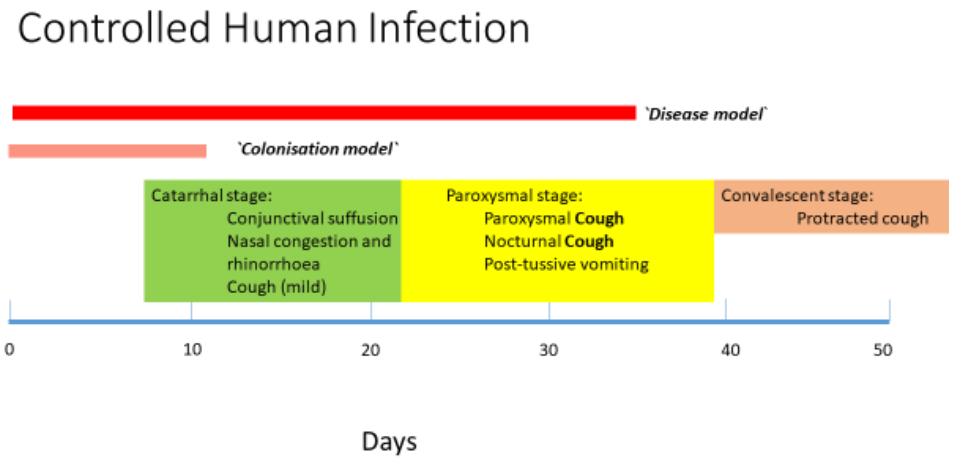


Controlled Human Infection



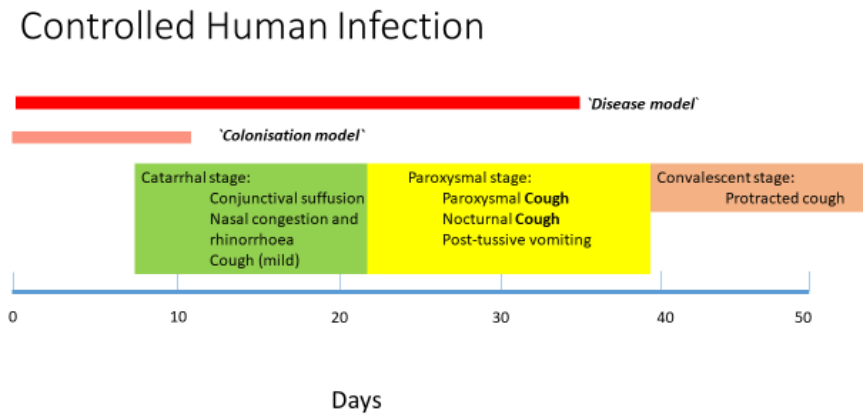
Disease model

ADVANTAGES	DISADVANTAGES
Clear Clinical and Regulatory Relevance	
Paroxysmal cough is easily detected and measured	
Correlate micro/immunology with clinical endpoints	
Study the full/mature disease process	
Interventions measured against clinical endpoints	



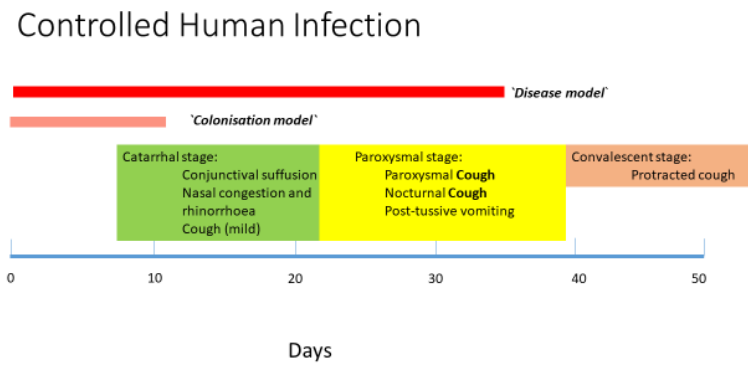
Disease model

ADVANTAGES	DISADVANTAGES
Clear Clinical and Regulatory Relevance	Unable to quantify risk
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



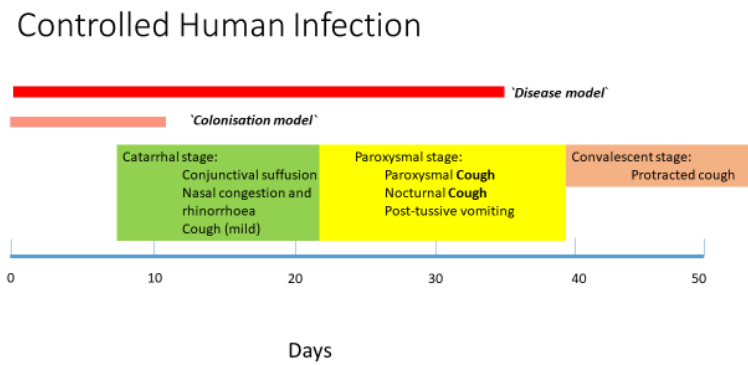
Colonisation model

ADVANTAGES	DISADVANTAGES
Safe	
Detection of bacteria is an objective endpoint	
Probably less infection control issues	
May be the commonest manifestation of wild infection	
Colonisation is pre-requisite to disease so Vaccine/Challenge studies would inform herd protection estimates	



Colonisation model

ADVANTAGES	DISADVANTAGES
Safe	*Bordetella pertussis* is difficult to detect in asymptomatic people
Detection of bacteria is an objective endpoint	The site of colonisation is unknown
Probably less infection control issues	Duration of carriage is unknown
May be the commonest manifestation of wild infection	Detection of *B.pertussis* in an asymptomatic person may not imply active biological interaction
Colonisation is pre-requisite to disease so Vaccine/Challenge studies would inform herd protection estimates	Different carriage states – density??



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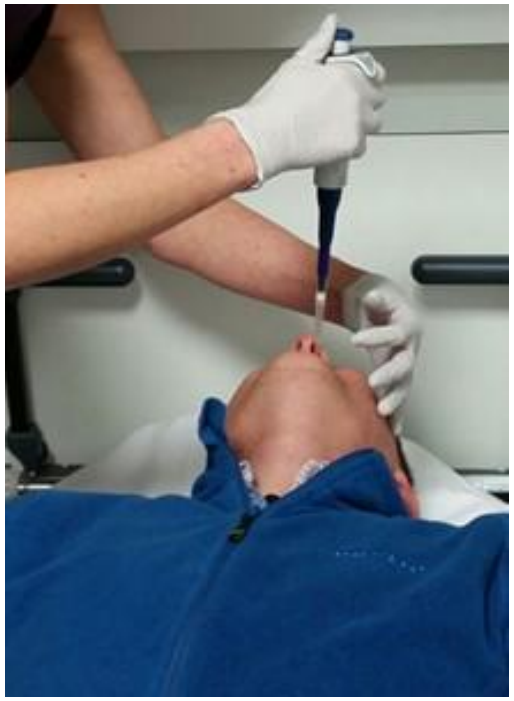
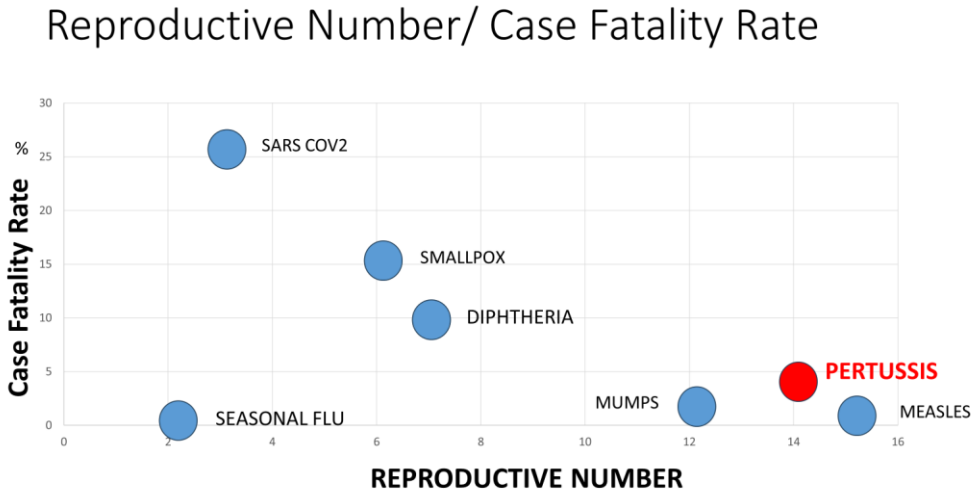
Bp Controlled Human Infection Model

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

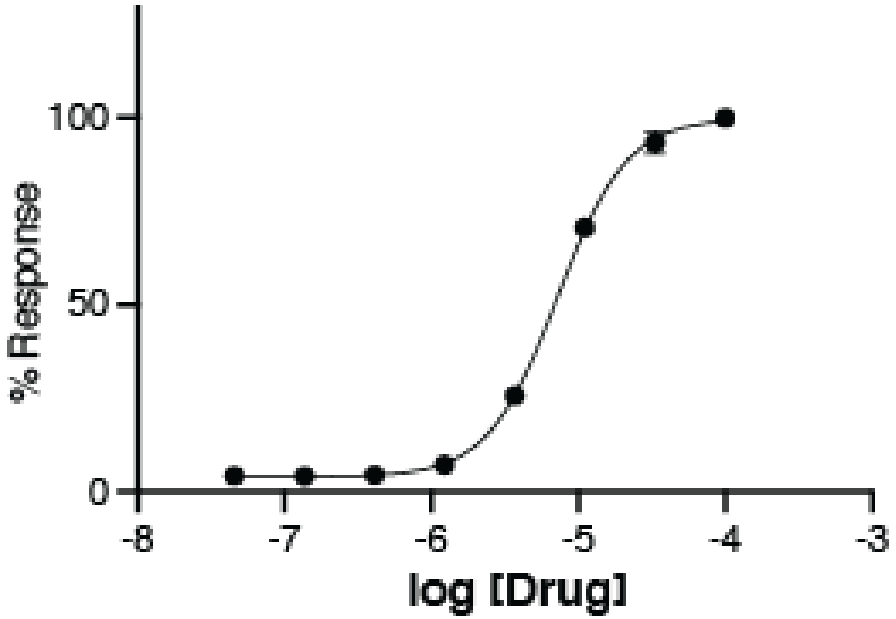
- Potential utilities:
  - Biomarkers associated with protection
  - Platform for vaccine testing



Dose and Administration



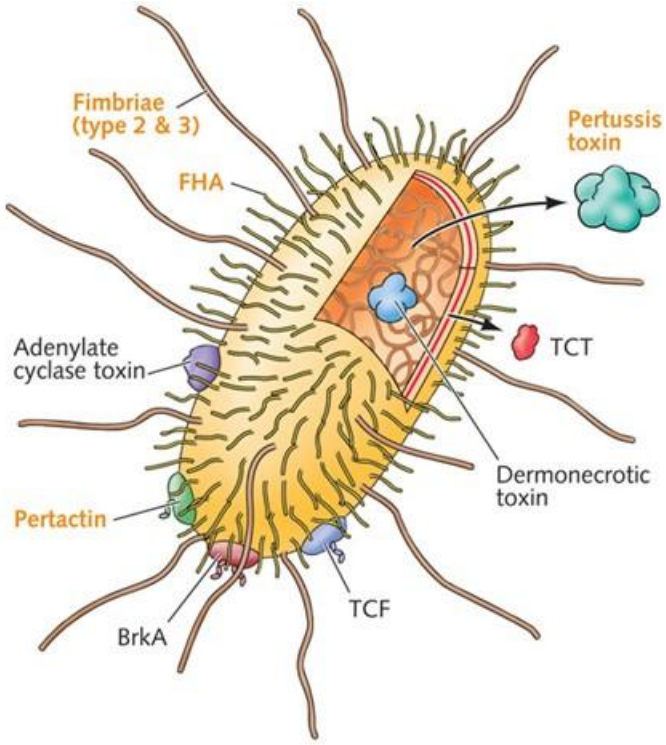
- *B.pertussis* is highly infectious
- Human-adapted infection
- Natural infection requires <10cfu
- Aerosol transmission



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

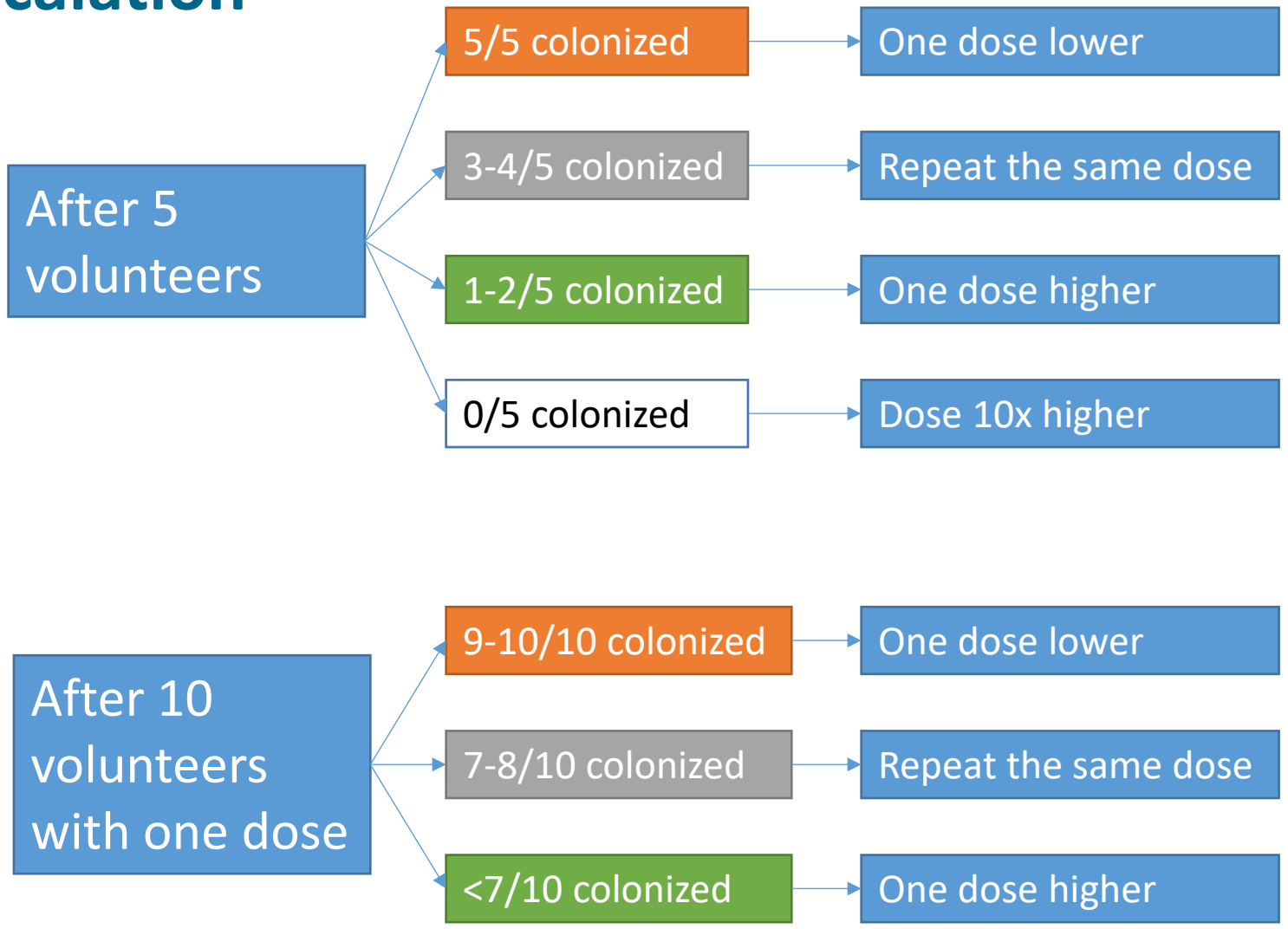


PERISCOPE Phase A

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

To determine the dose of the standard inoculum: Dose escalation

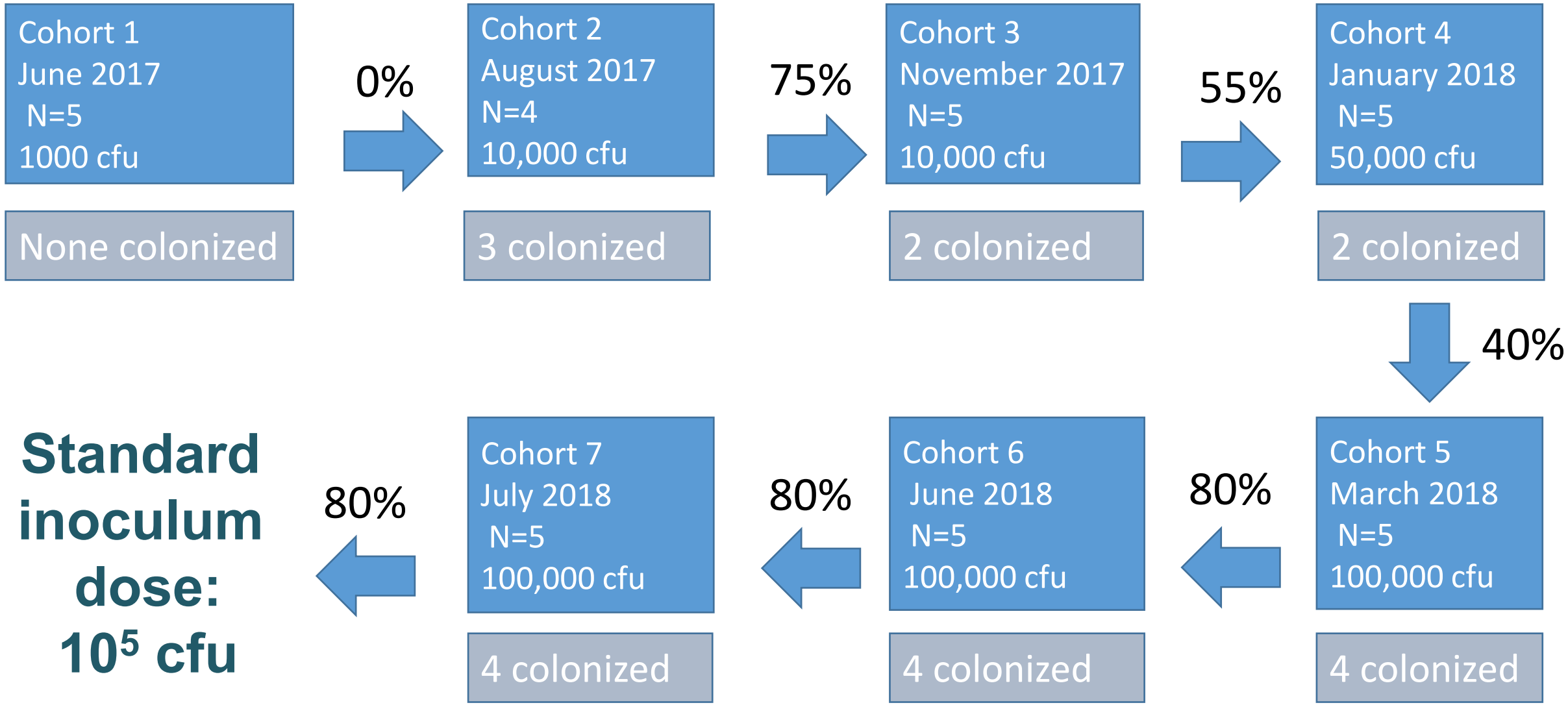
Inoculum doses to be used in cfu
5×10^2
10^3
5×10^3
10^4
5×10^4
10^5
5×10^5



University of Southampton | University Hospital Southampton NHS
NHS Foundation Trust

peri scope

Time line dose escalation

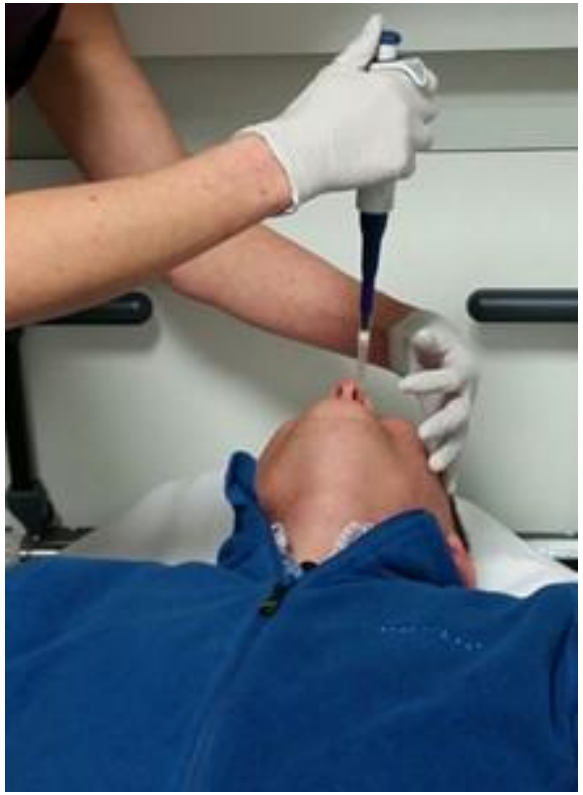


Phase A – main findings

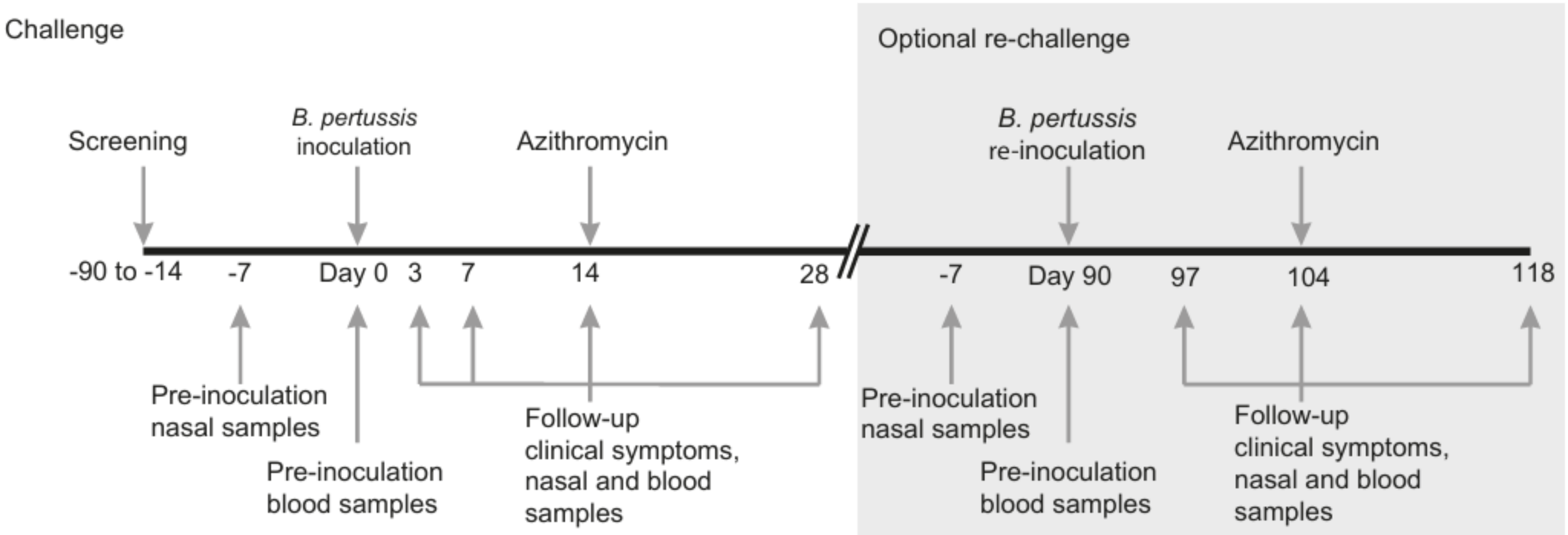
- Standard inoculum dose 10^5 CFU
- Colonisation fraction 0.8 (12 of 15 participants colonised)
- Safe
- Azithromycin effective in clearing colonisation
- No shedding detected
- Seroconversion in some colonised participants

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%)

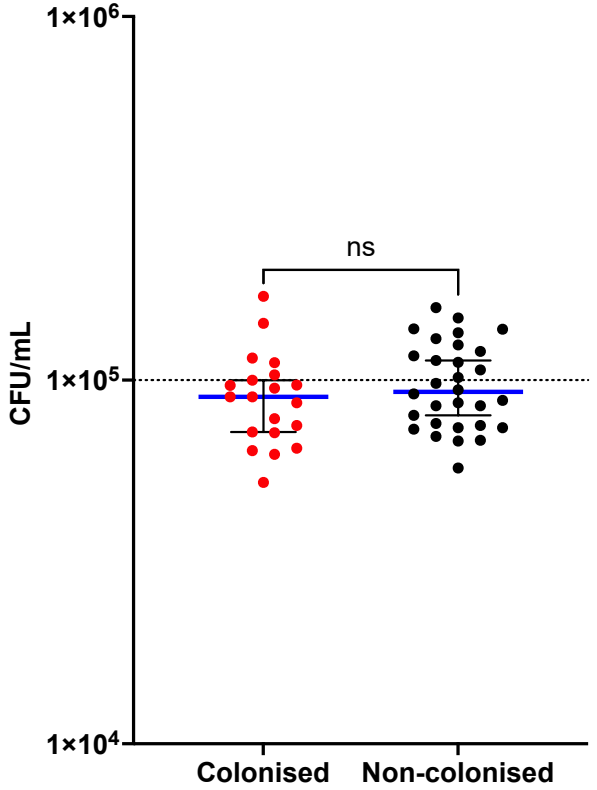


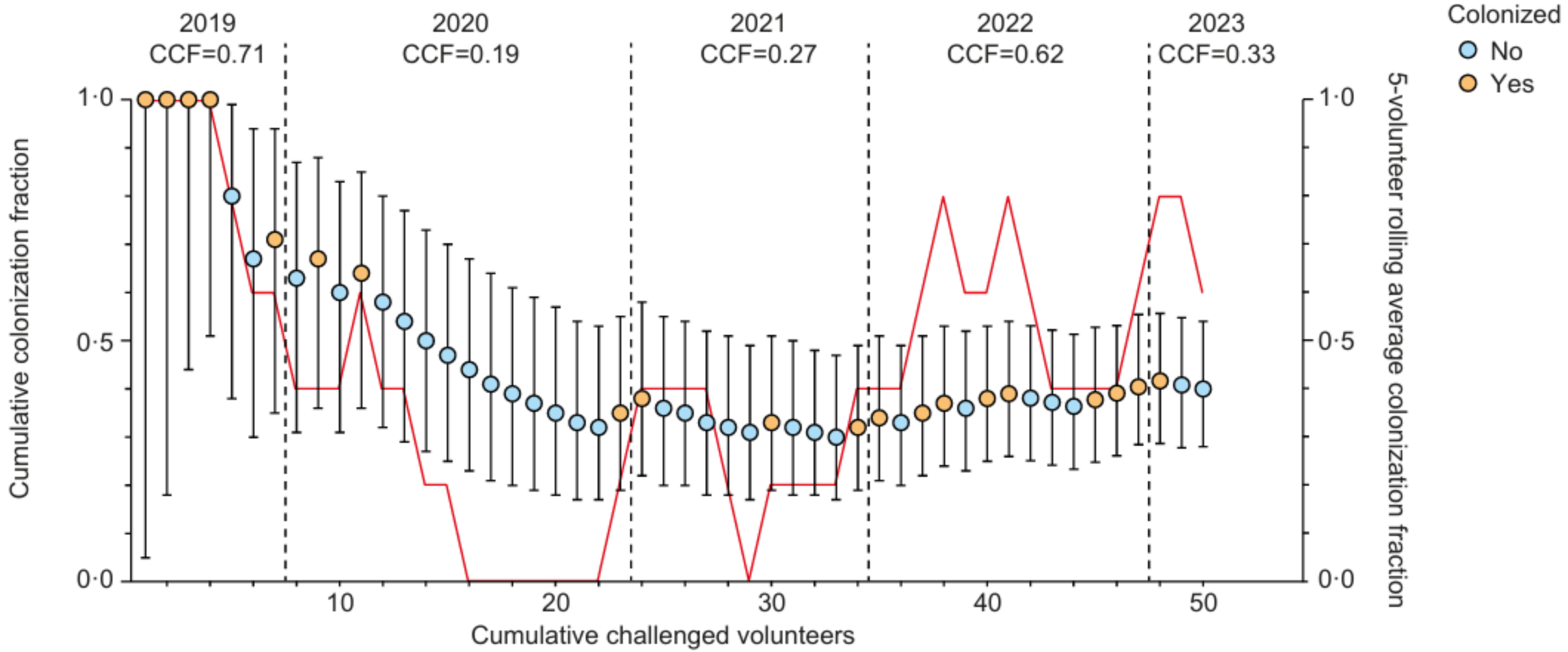
de Graaf H. et al 2026 *Lancet Microbe*

Primary challenge: Colonisation

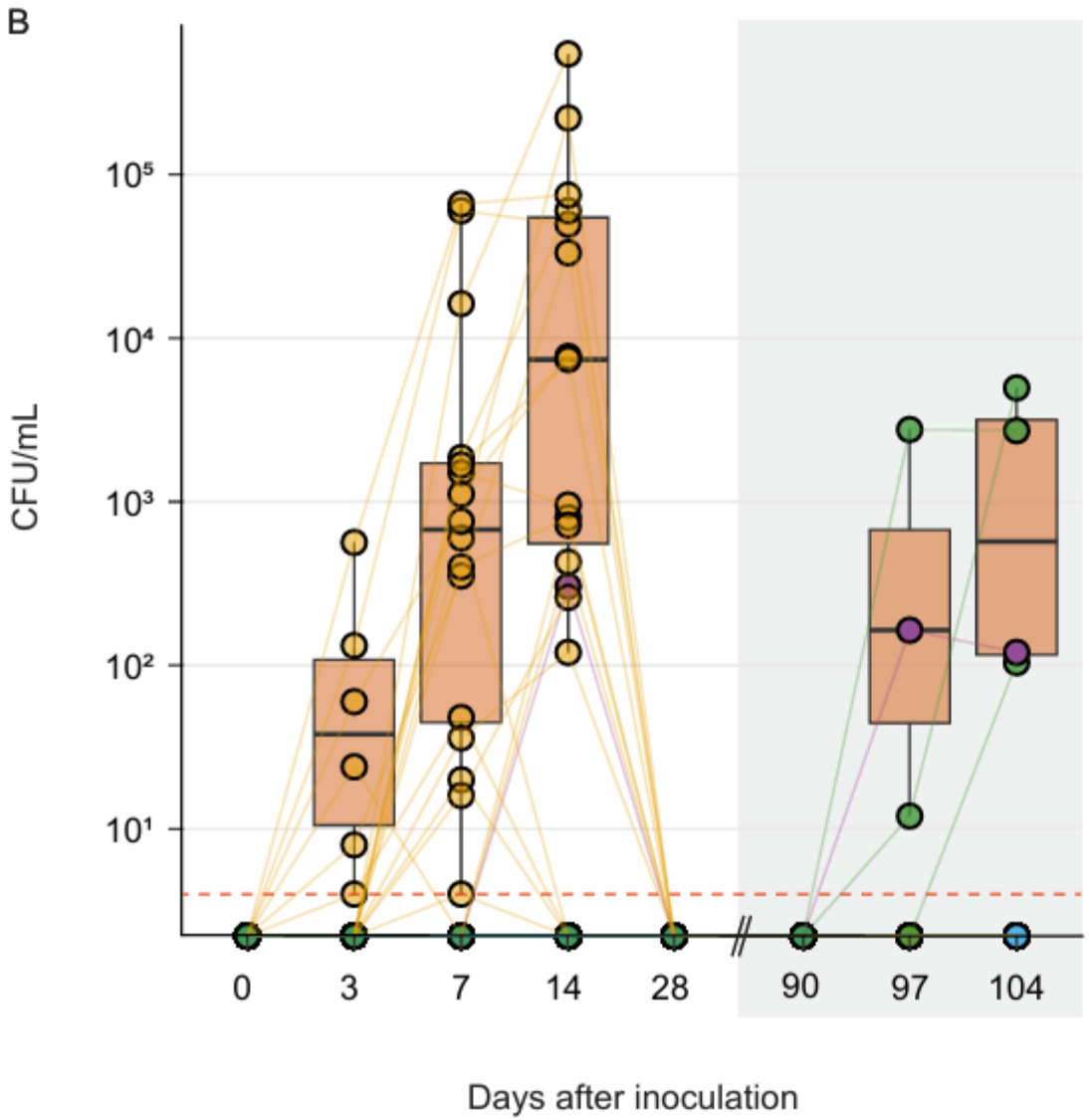
- **20 of 50** Challenge volunteers colonised
- Colonisation fraction = 0.4
- No difference in inoculum

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

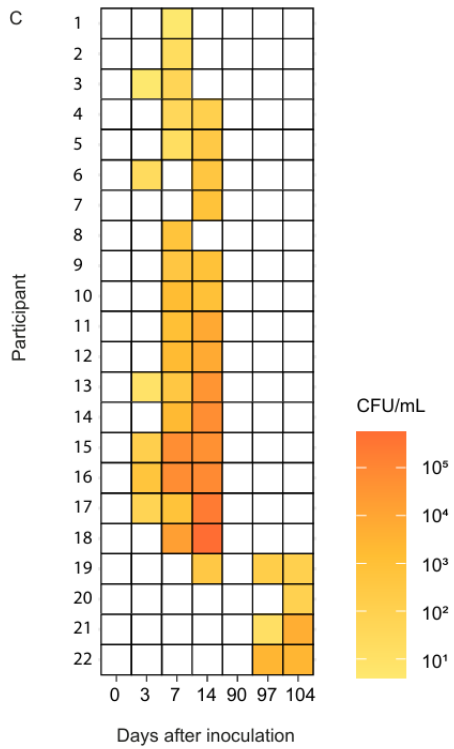




de Graaf H. et al 2026 *Lancet Microbe*



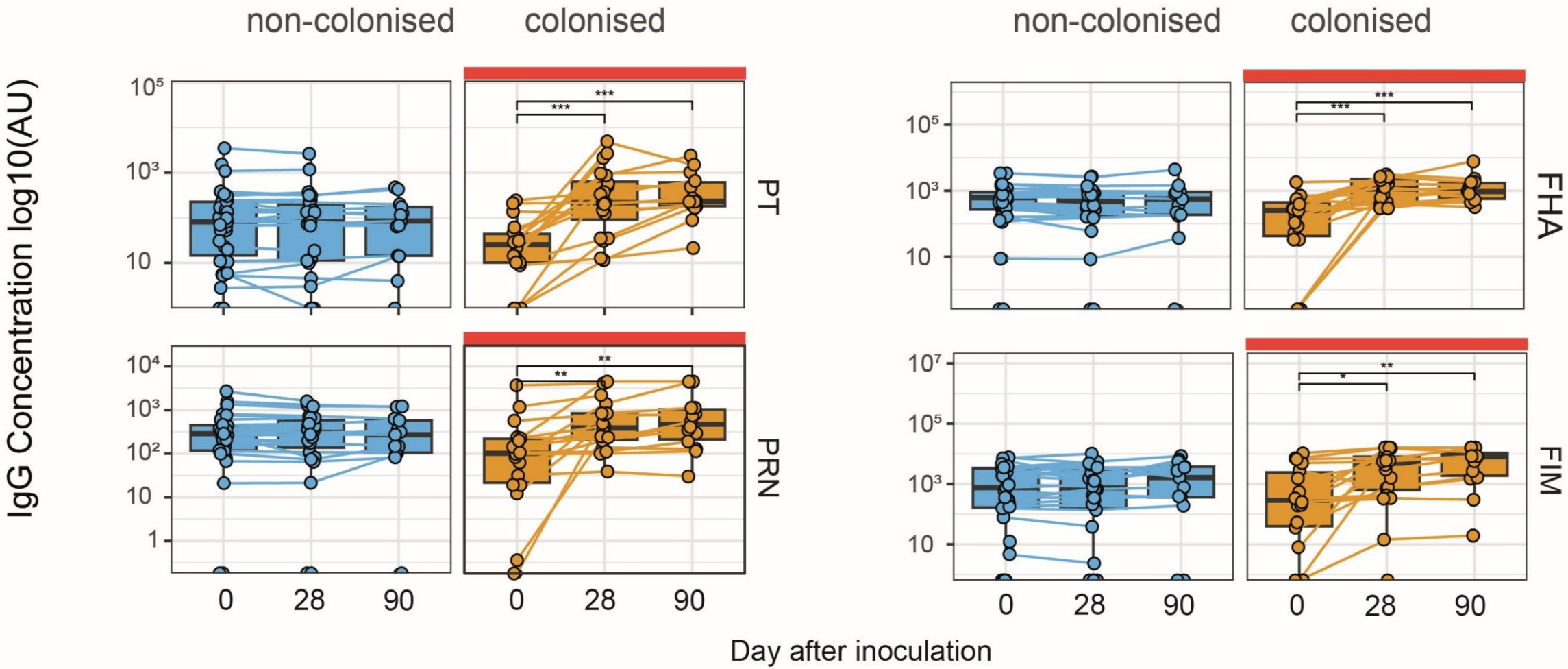
First challenge	Re-challenge
Colonized	Colonized
Colonized	Non-colonized
Non-colonized	Colonized
Non-colonized	Non-colonized



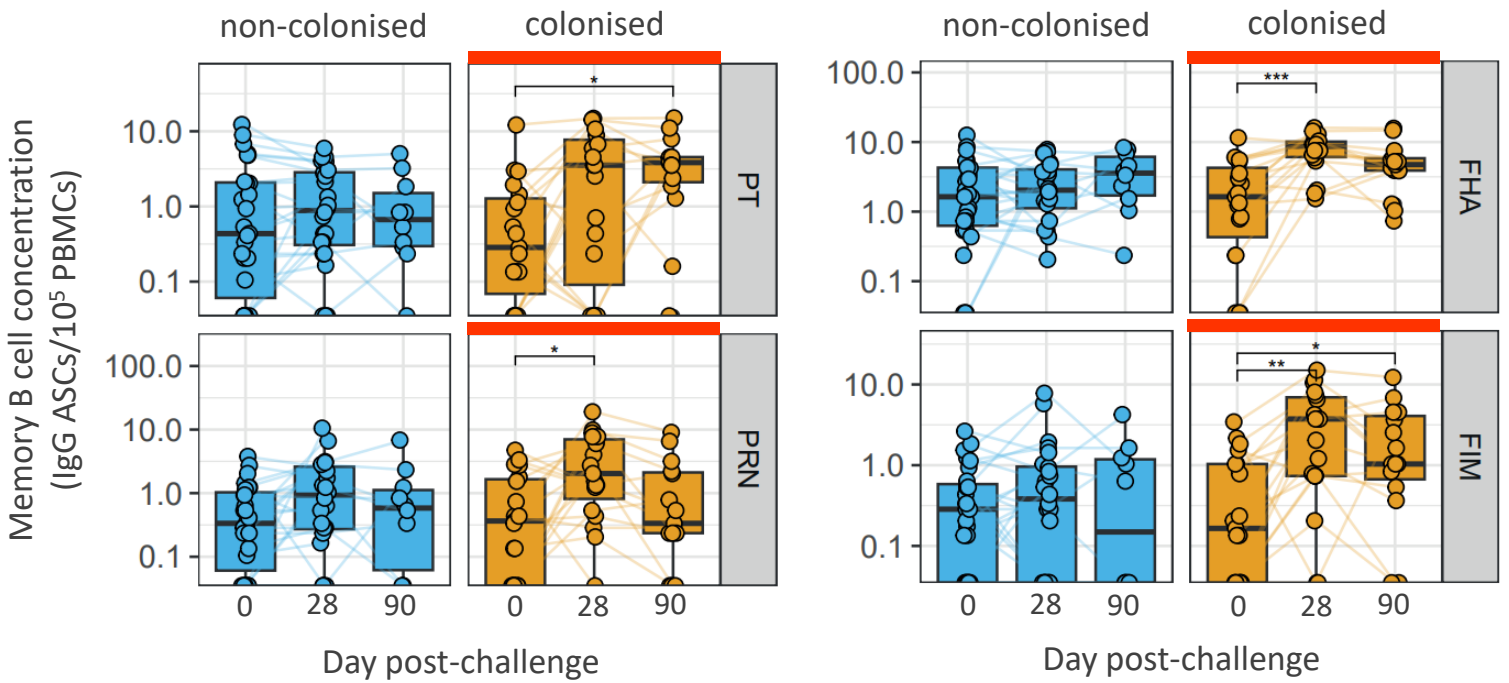
de Graaf H. et al 2026 *Lancet Microbe*

Does experimental infection induce an immune response?

Colonisation is an immunising event - IgG

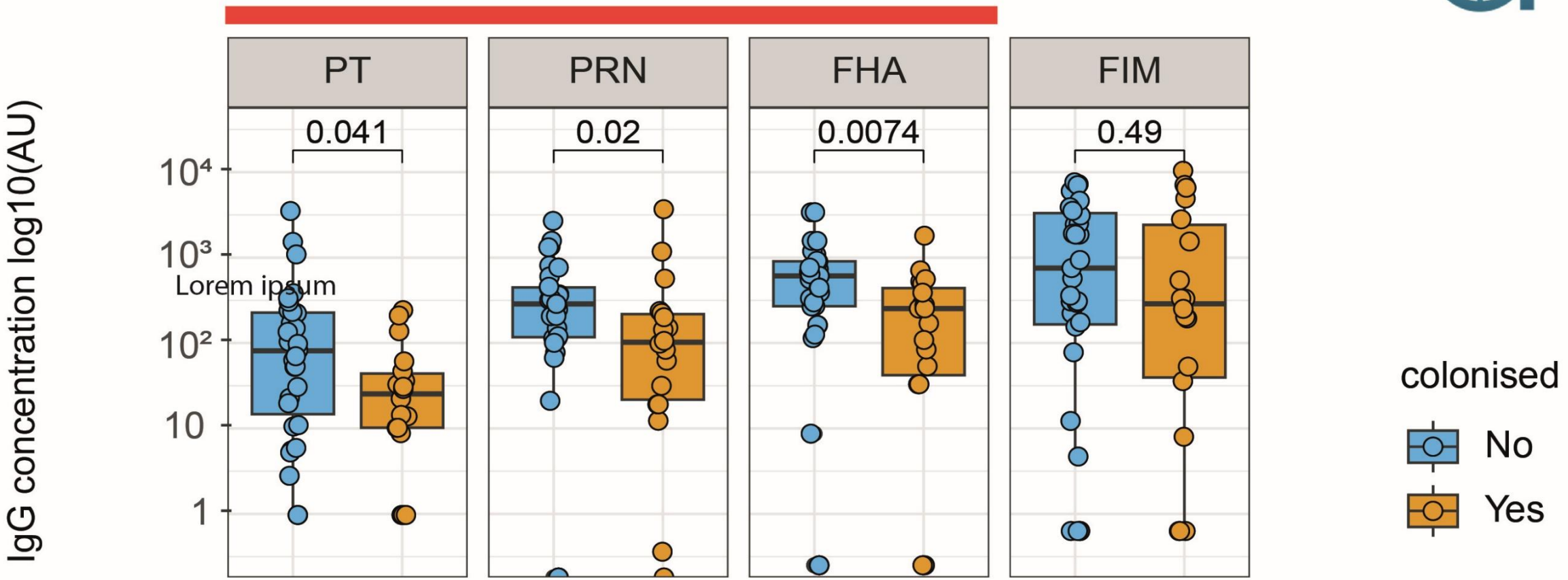


Colonisation induces Bp-specific memory B cell responses



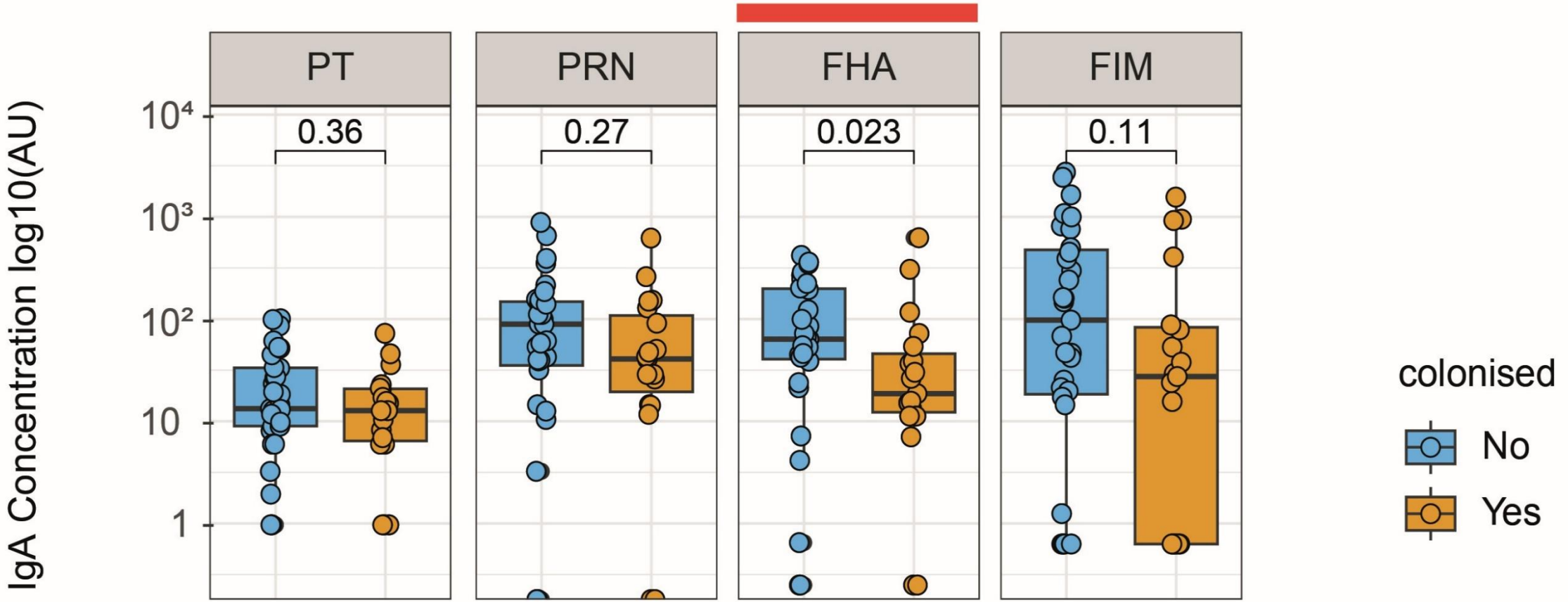
Non-colonised versus colonised – serum IgG

Baseline



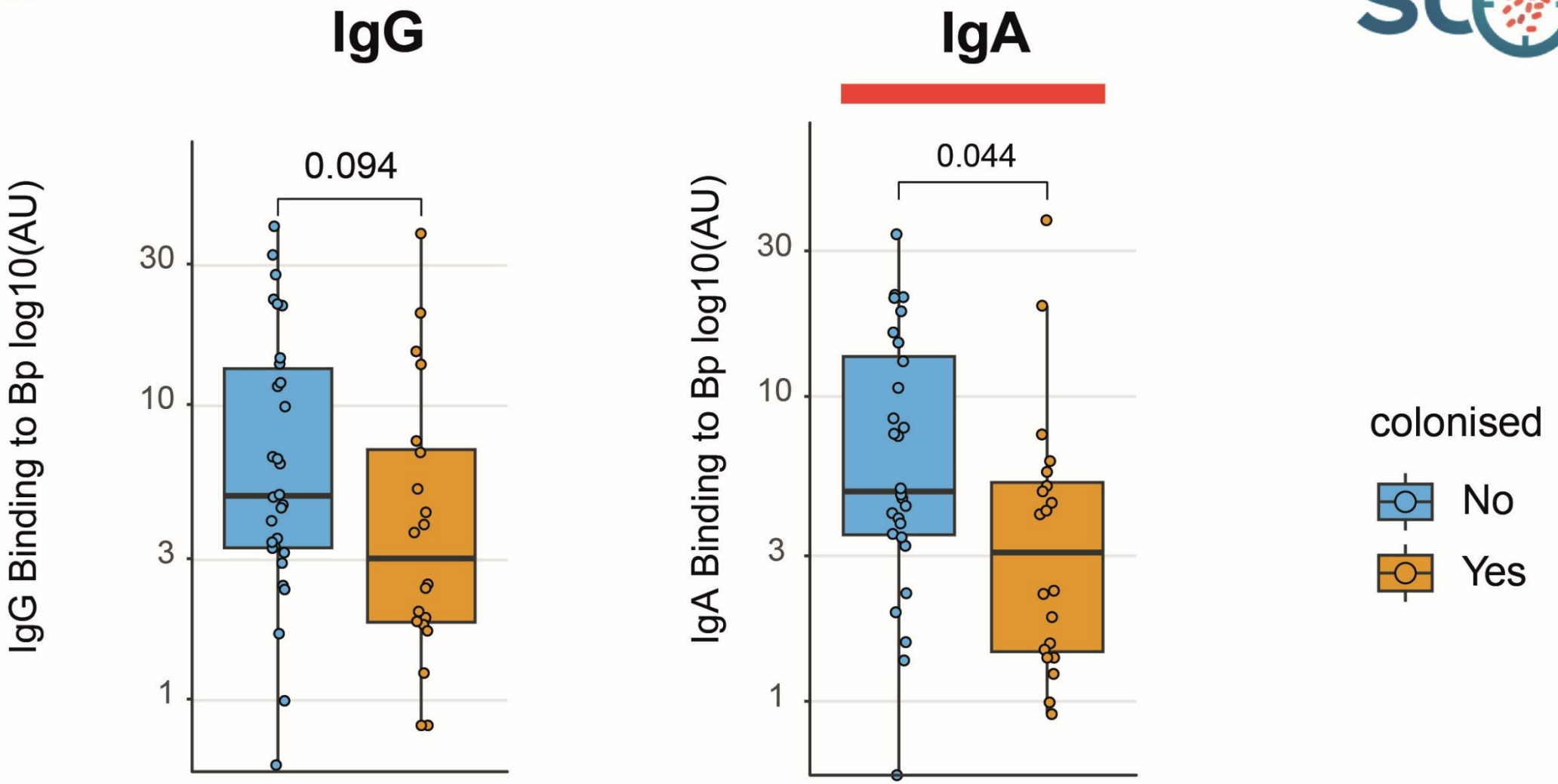
Non-colonised versus colonised – serum IgA

Baseline

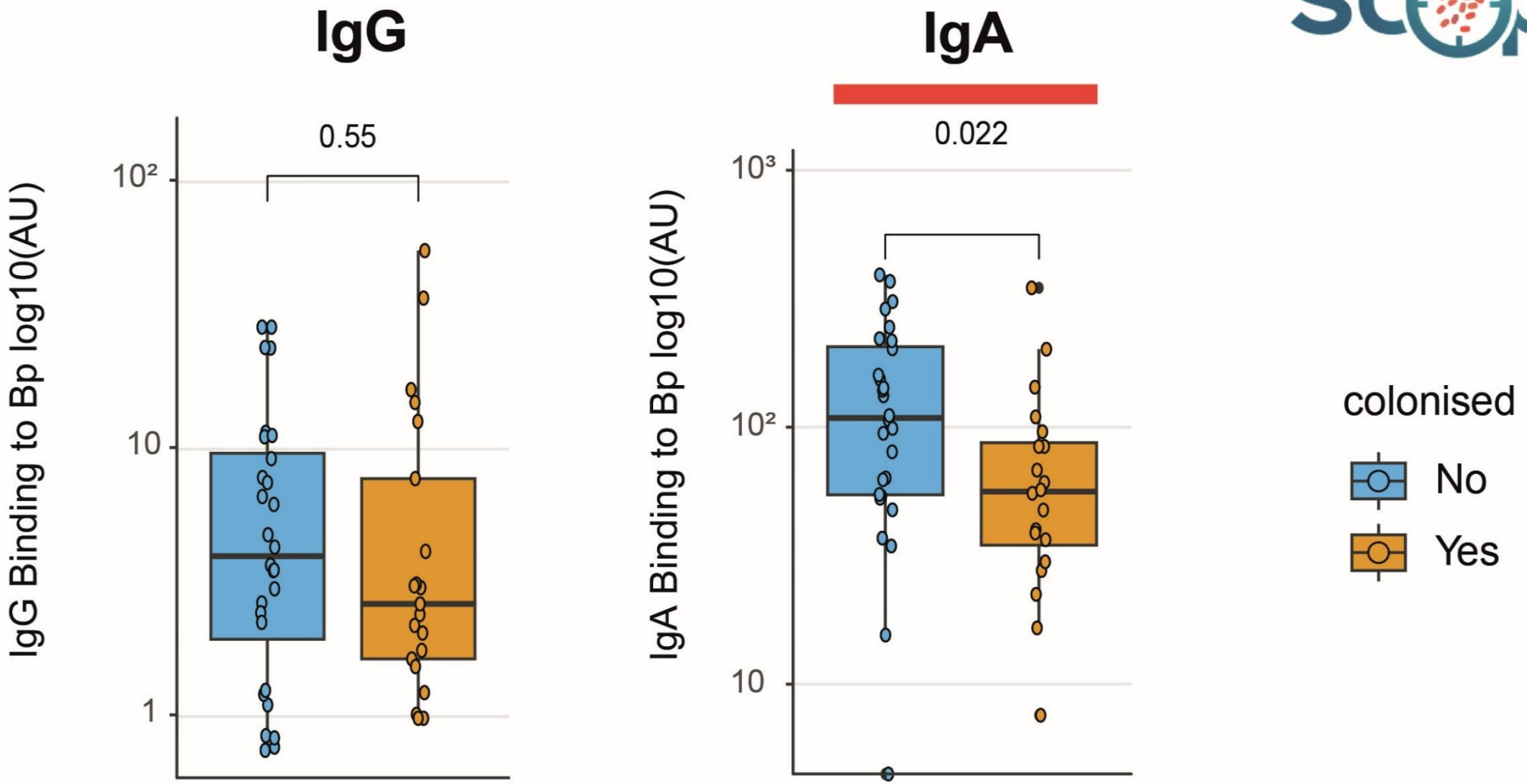


Non-colonised versus colonised – serum Bp binding

Baseline

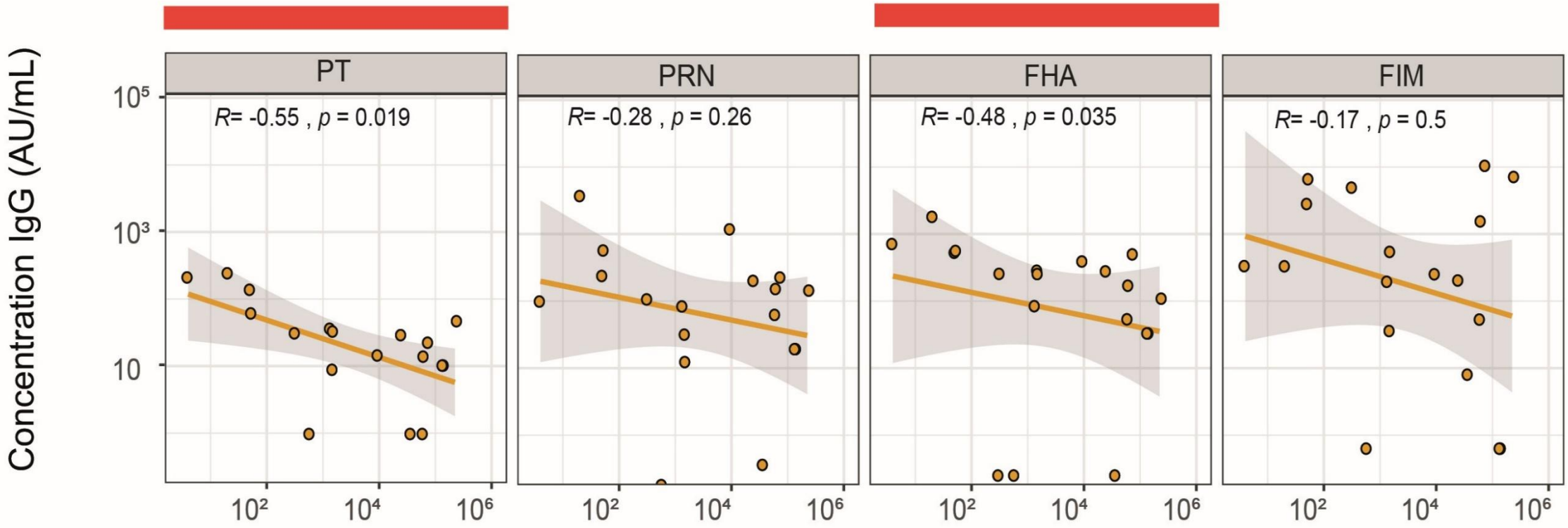


Non-colonised versus colonised – mucosal fluid Bp binding

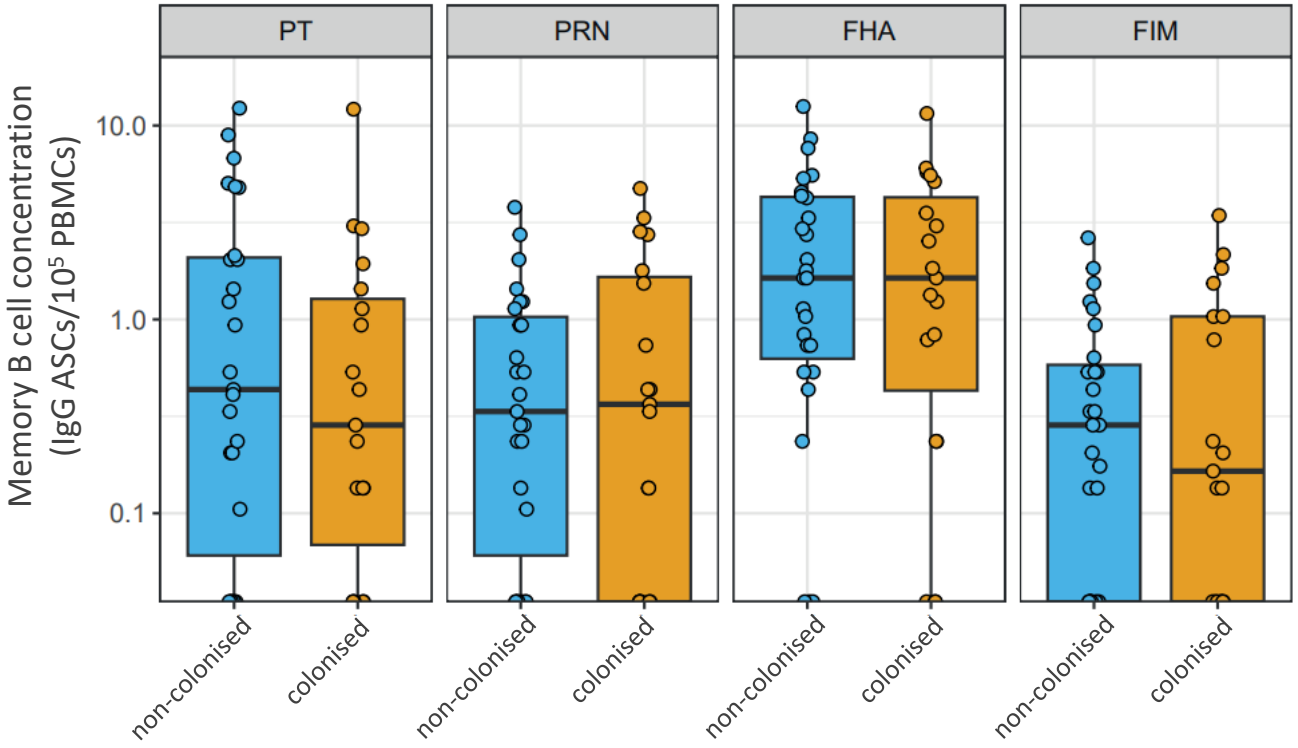


Control of colonisation density - Serum IgG

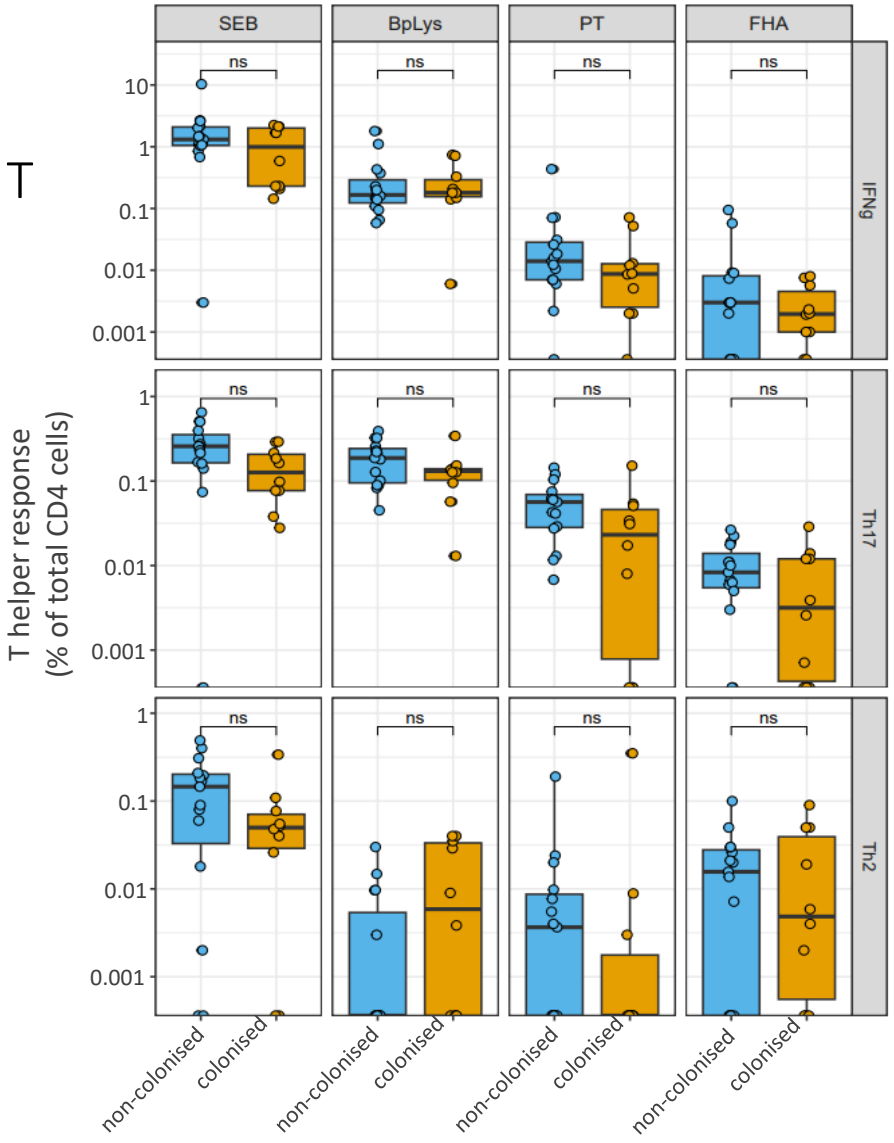
Baseline



Baseline memory B cell concentrations

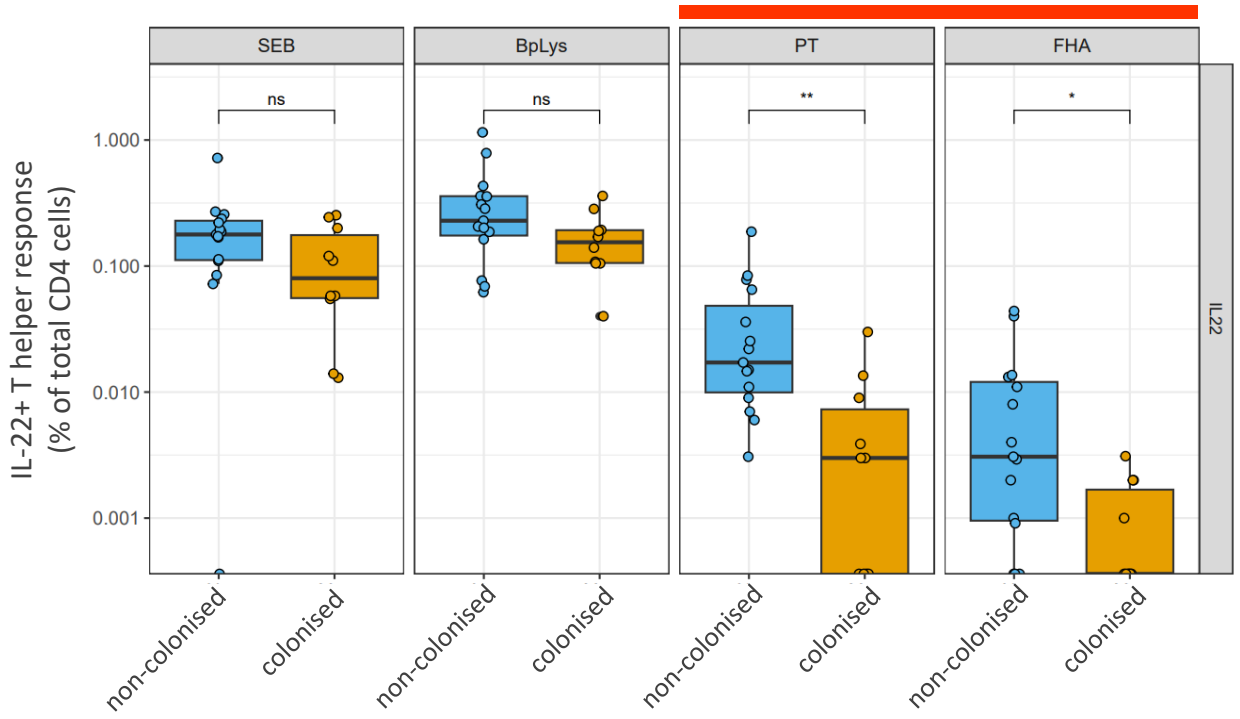


Baseline comparison between T helper cell responses in non-colonised and colonised volunteers



Data is mock subtracted

Baseline IL-22+ T helper cell responses



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

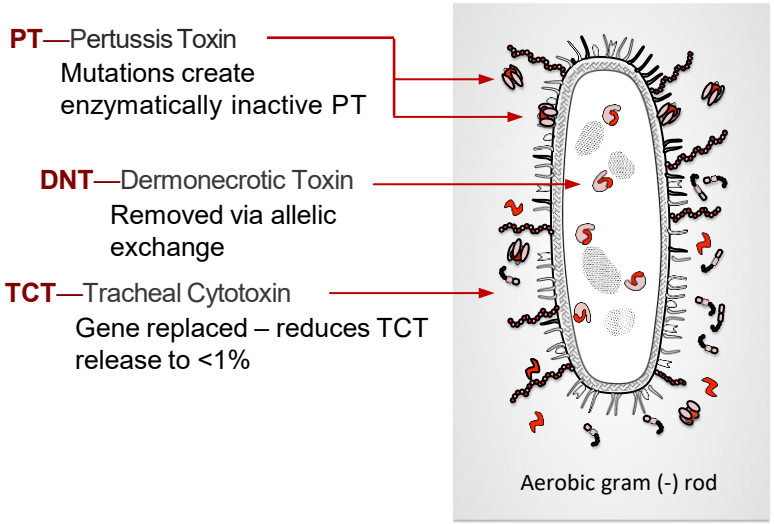
Overall Summary – PERISCOPE Human Challenge Programme

- **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**

BPZE1 Vaccine

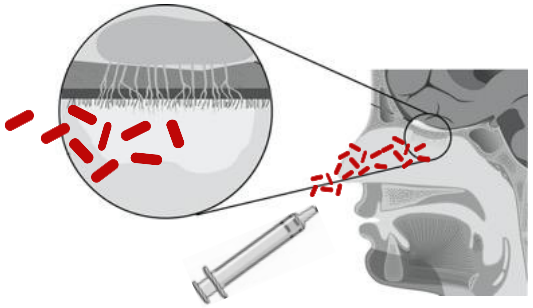
Live attenuated vaccine

- *B. pertussis* Tohama I strain
- Genetically modified with 3 toxins inactivated or removed



Mucosal delivery

- Lyophilised formulation
- Nasally administered by mucosal atomization device



Characteristics

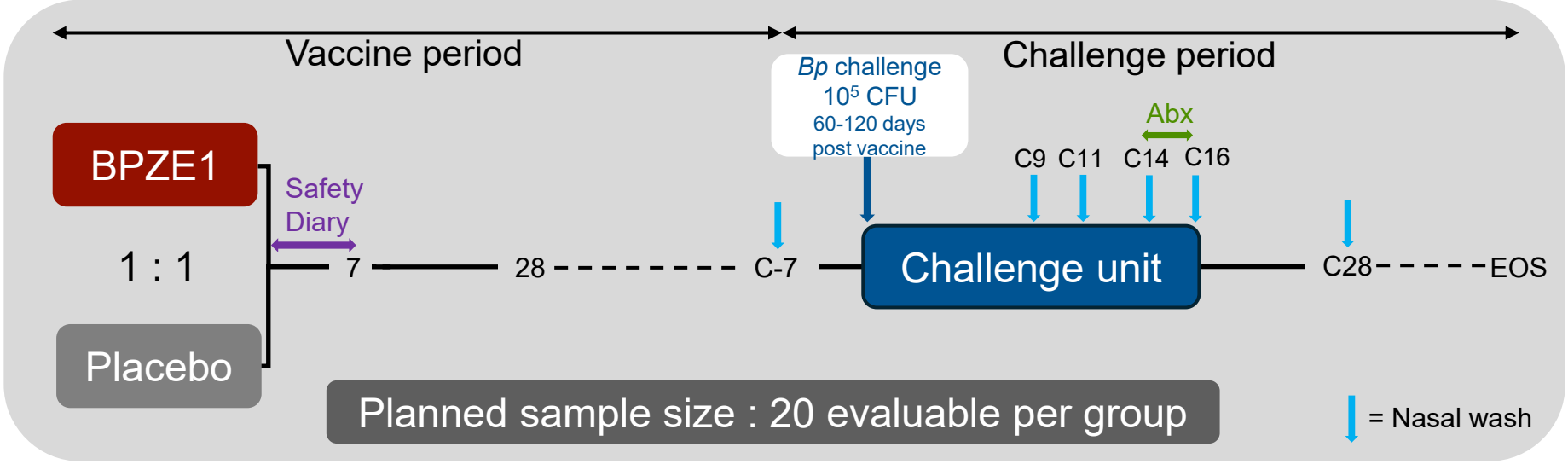
- Acceptable safety profile
- Transient colonisation
- Protection against rechallenge with BPZE1
- Immunogenic
  - Mucosal s-IgA
  - Serum IgG and IgA
- Functional
  - Serum bactericidal activity against PRN+ and PRN- *B. pertussis*
  - Pertussis toxin neutralisation assay

Jahnmatz et al 2020, Creech et al 2022, Keech et al 2023

Gbesemete D. et al 2025 *Lancet Microbe*

BPZE1 Vaccine-challenge study

- BPZE1 impact on asymptomatic colonisation
- Anti-PT IgG < 20 IU/mL; Anti-PRN IgG < 30 IU/mL
- Primary endpoint: no colonisation in nasal wash cultures on Days 9, 11 and 14 post virulent *Bp* challenge




Articles

Efficacy, immunogenicity, and safety of the live attenuated nasal pertussis vaccine, BPZE1, in the UK: a randomised, placebo-controlled, phase 2b trial using a controlled human infection model with virulent *Bordetella pertussis*

Diane Gbesemete, Maheshi N Ramasamy, Muktar Ibrahim, Allison R Hill, Lucy Raud, Daniela M Ferreira, Jonathan Guy, Adam P Dale, Jay R Laver, Tyween Coutinho, Saul N Faust, Thomas A N Reed, Gavin Babbage, Lisa Wetsfeld, Wei Lang, Camille Locht, Vivek Samal, Peter Goldstein, Ken Soloway, Keith Rubin, Stephanie Novielle, Robert C Read

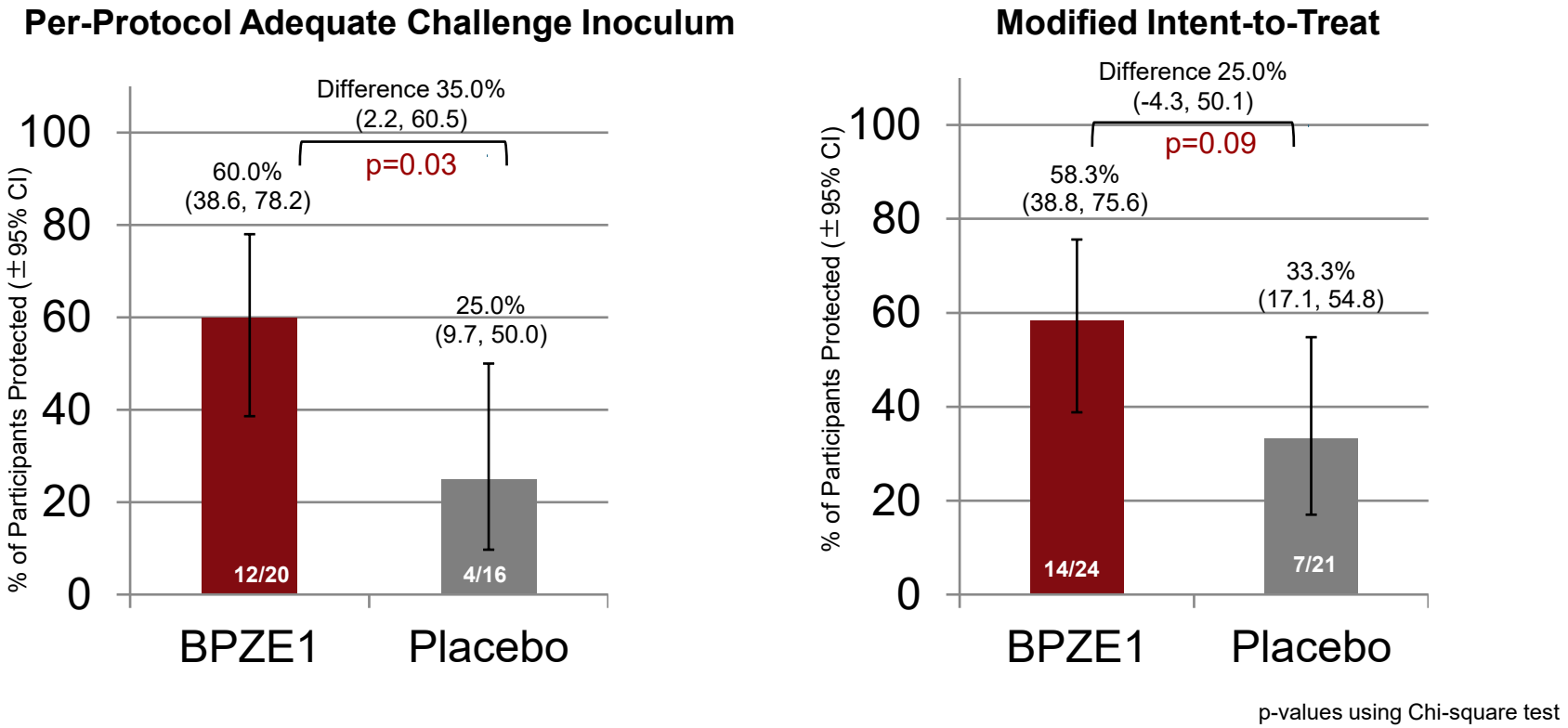
Summary

Background Pertussis is a severe respiratory disease caused by *Bordetella pertussis*. Although vaccines prevent disease for a limited duration, they do not prevent infection and transmission. We aimed to assess the safety and efficacy of BPZE1 at preventing or substantially reducing colonisation by virulent *B pertussis* using a robust controlled human infection model.

Methods This randomised, placebo-controlled, phase 2b trial was conducted at University Hospital Southampton and

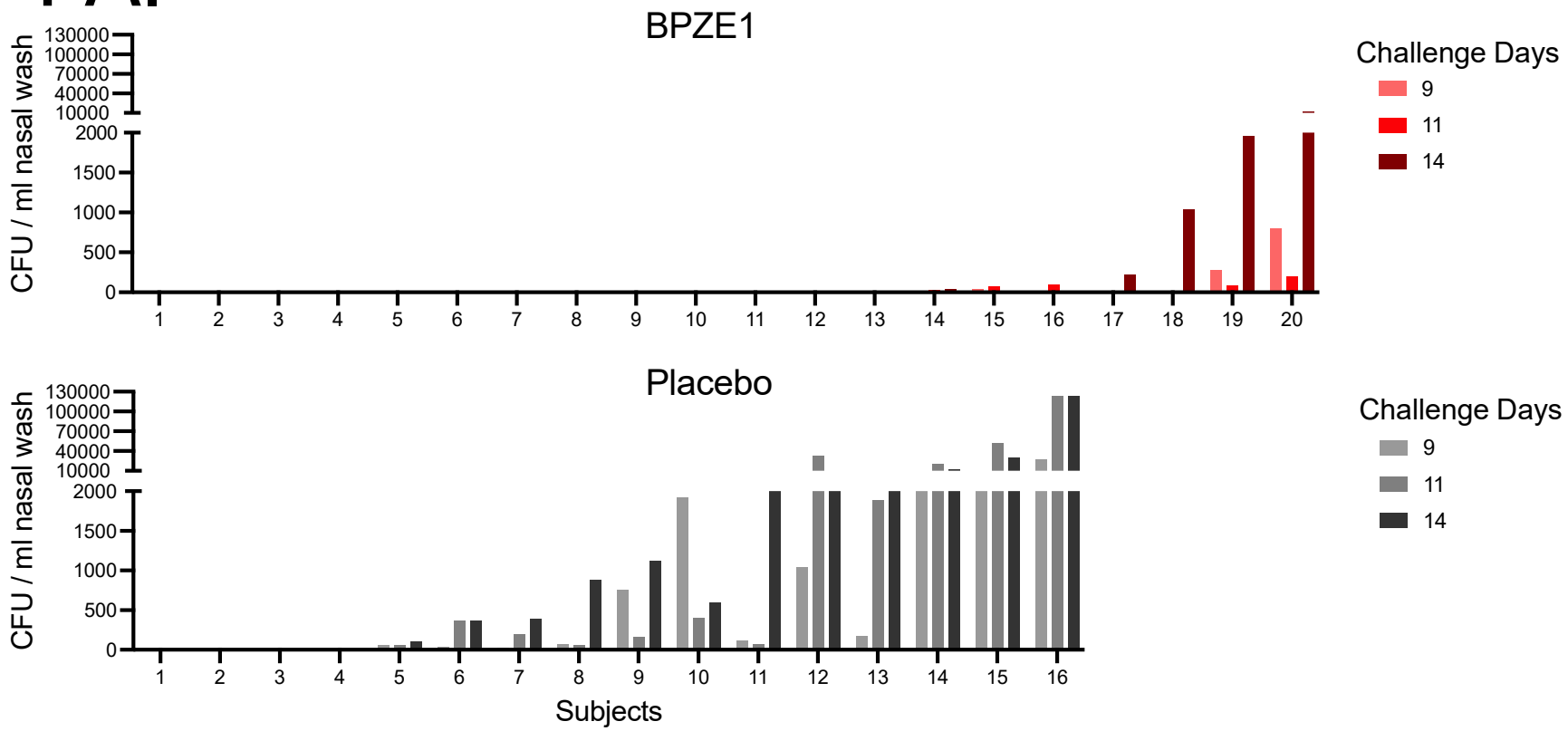
Lancet Microbe 2025
Published Online
https://doi.org/10.1016/j.lanmic.2025.101211
NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University

Colonisation



p-values using Chi-square test

By-subject Colonisation Density - PPAI



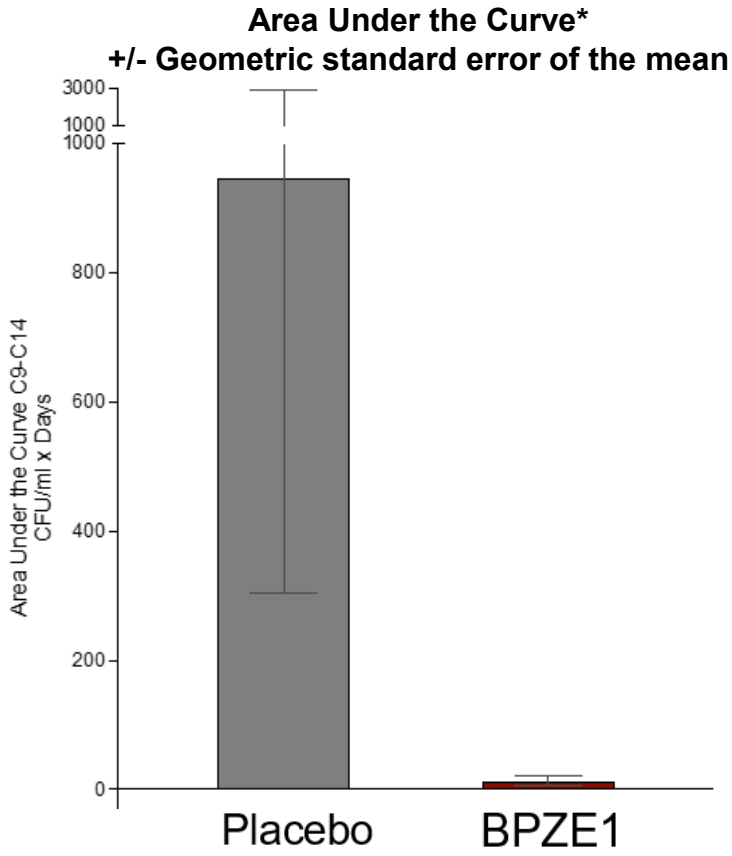
B. pertussis burden

Per-protocol Adequate Inoculum

- BPZE1-vaccinated participants had a 98.7% reduction vs placebo

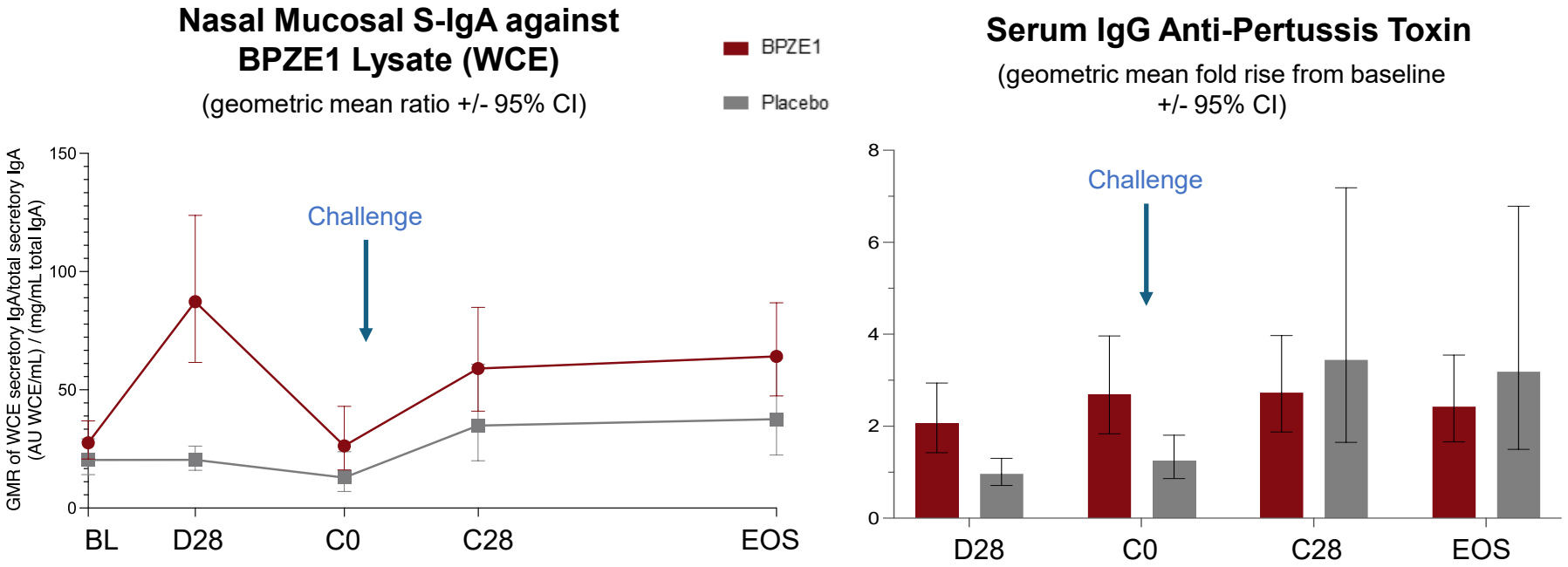
Modified Intent-to-Treat

- BPZE1-vaccinated participants had a 97.1% reduction vs placebo



*Geometric means of individual AUCs from C9 through C14 using the trapezoidal rule

Immunogenicity



- Similar trends in S-IgA antibodies against PRN, FHA, FIM, PT

BL = baseline; D28 = Day 28 post vaccine; C0 = pre-challenge; C28 = Day 28 post challenge; EOS = End of study; GMR = geometric mean ratio; IgG = immunoglobulin G; mL= millilitre; WCE=whole cell extract

Immune correlates (Hill A, Dale A. et al manuscript submitted)

- Vaccination with BPZE1 induced circulating $CD4^+$ T cells of Th17 and Th22 effector phenotype.
- These responses correlated positively with BPZE1-induced SIgA responses
- In BPZE1 recipients who developed breakthrough infection following virulent *B. pertussis* challenge, higher vaccine-induced SIgA titres were significantly associated with reduced colonisation density (but serum IgA and IgG titres were not)

- A Th17/Th22-SIgA immune axis as a key feature of BPZE1 vaccination and highlight SIgA as a candidate correlate of reduced *B. pertussis* colonisation in humans.

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

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