



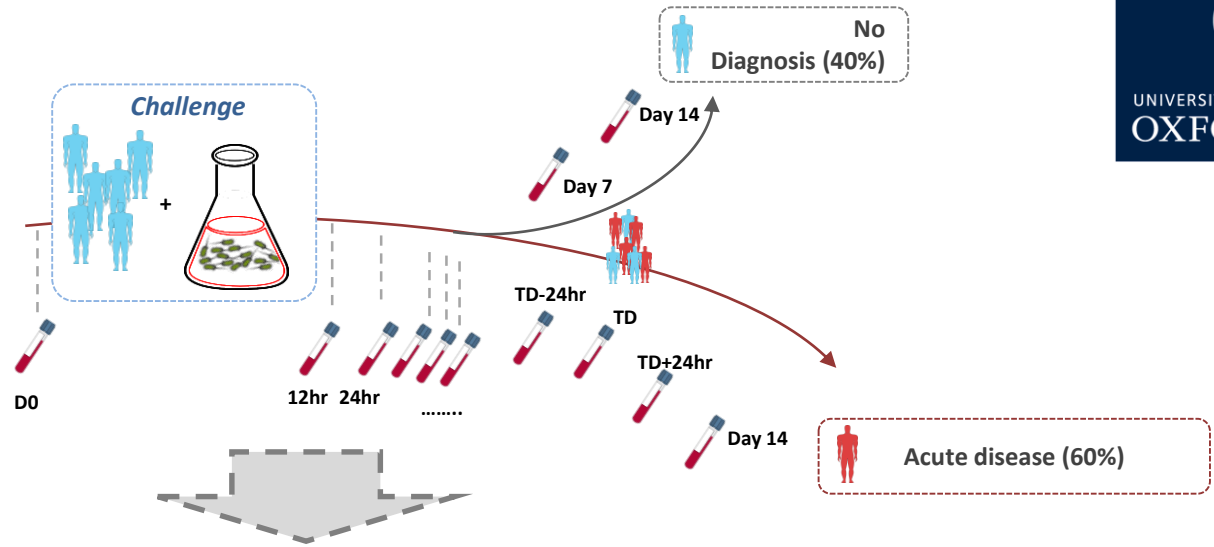
The human challenge model for *Salmonella* Paratyphi A: The clinical response and importance for future vaccine development

Dr Hazel Dobinson
Oxford Vaccine Group
Coalition Against Typhoid, Bali 2015

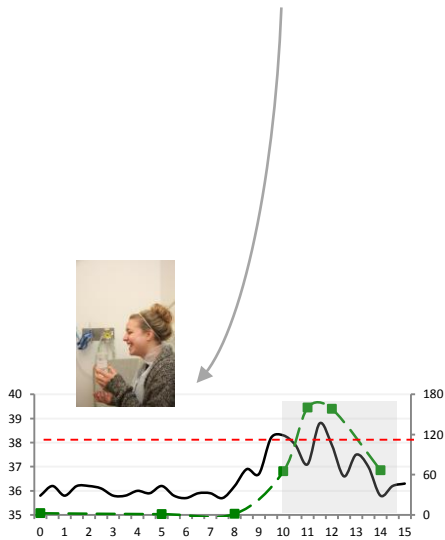
Salmonella Paratyphi A Challenge model

- Human-restricted pathogen
- CL3 pathogen in UK
- Inclusion and exclusion criteria
- Non-specific symptoms with fever
 - diagnostics
- Monitoring
- Antibiotic treatment and clearance

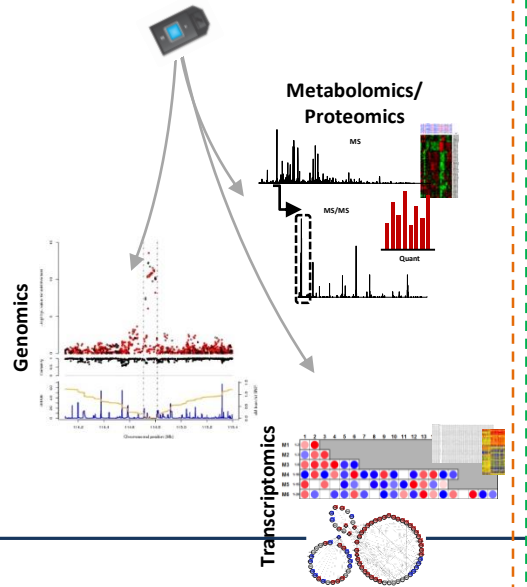
Paratyphoid Challenge Model



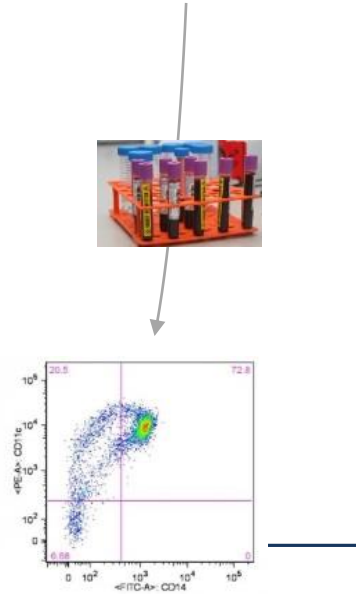
Clinical features



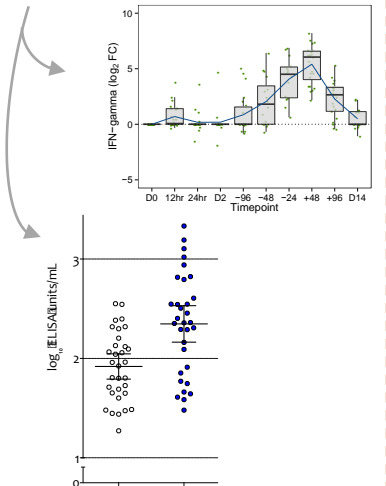
Omics



CMI



Serology & Cytokines



Criteria for diagnosis

Paratyphoid fever is diagnosed if ANY of the following apply

A positive blood culture for *Salmonella* Paratyphi from 72 hours post-challenge

A positive blood culture for *Salmonella* Paratyphi within 72 hours post-challenge, with one or more signs/symptoms of paratyphoid infection (such as recorded temperature $\geq 38^{\circ}\text{C}$)

Persistent positive blood cultures (two or more blood cultures taken at least 4 hours apart) for *Salmonella* Paratyphi within 72 hours post-challenge.

Oral temperature $\geq 38^{\circ}\text{C}$ persisting for 12 hours

Clinical outcomes

Primary outcome: 'attack rate' of 60-75%

'High dose' 10^3 CFU:

– 12/20

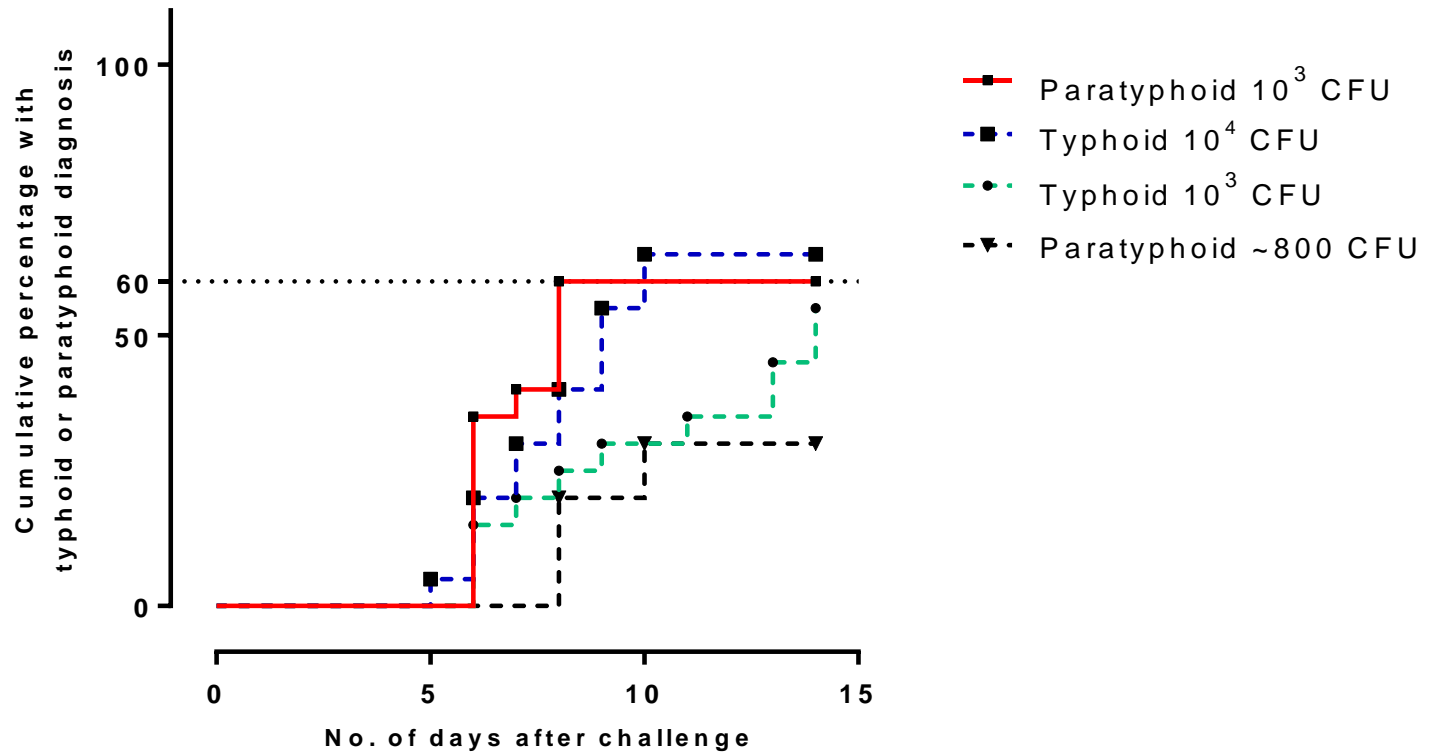
- Clinical criteria (fever) 3/12
- Bacteraemia 9/12 (additional 4 cases with fever $\geq 38^\circ$)

'Low dose' ~ 800 CFU:

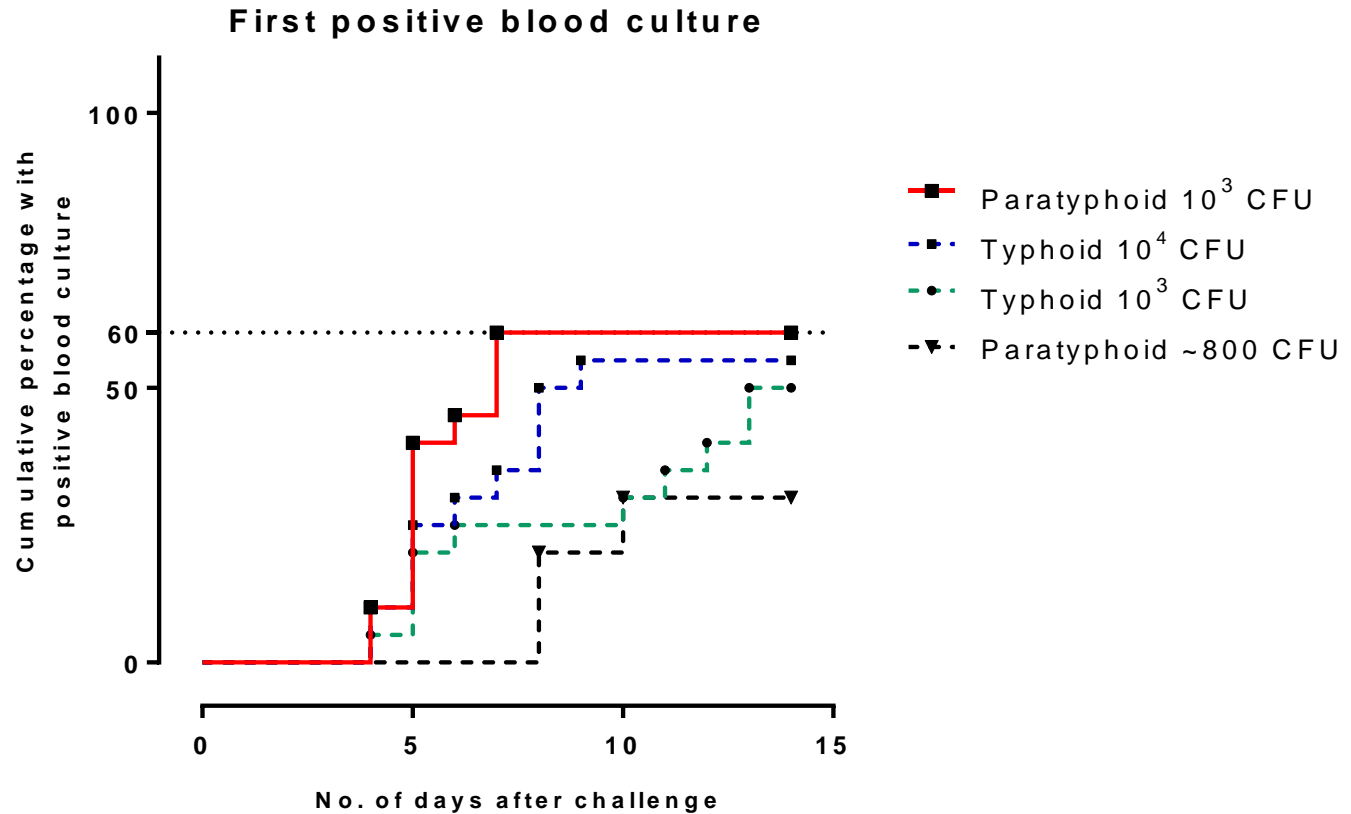
– 8/20

- All diagnoses based on BC (2 cases with fever $\geq 38^\circ$)

All typhoid and paratyphoid diagnoses

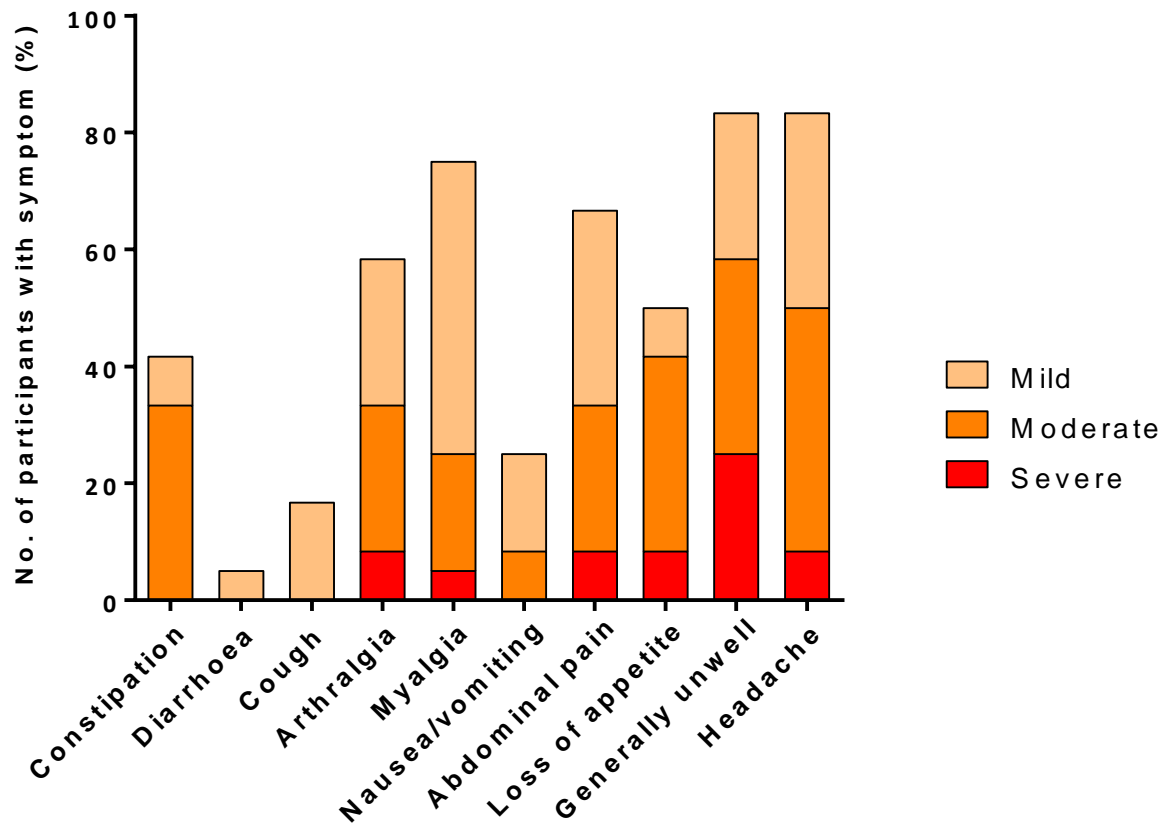


Kaplan-Meier plots demonstrating time to diagnosis following challenge at two dose levels with *S. Paratyphi* (10^3 CFU and ~ 800 CFU) and *S. Typhi* (10^3 and 10^4 CFU).



Kaplan-Meier plot demonstrating time to first positive blood culture following challenge at two dose levels with *S. Paratyphi* (10^3 CFU and ~ 800 CFU) and *S. Typhi* (10^3 and 10^4 CFU).

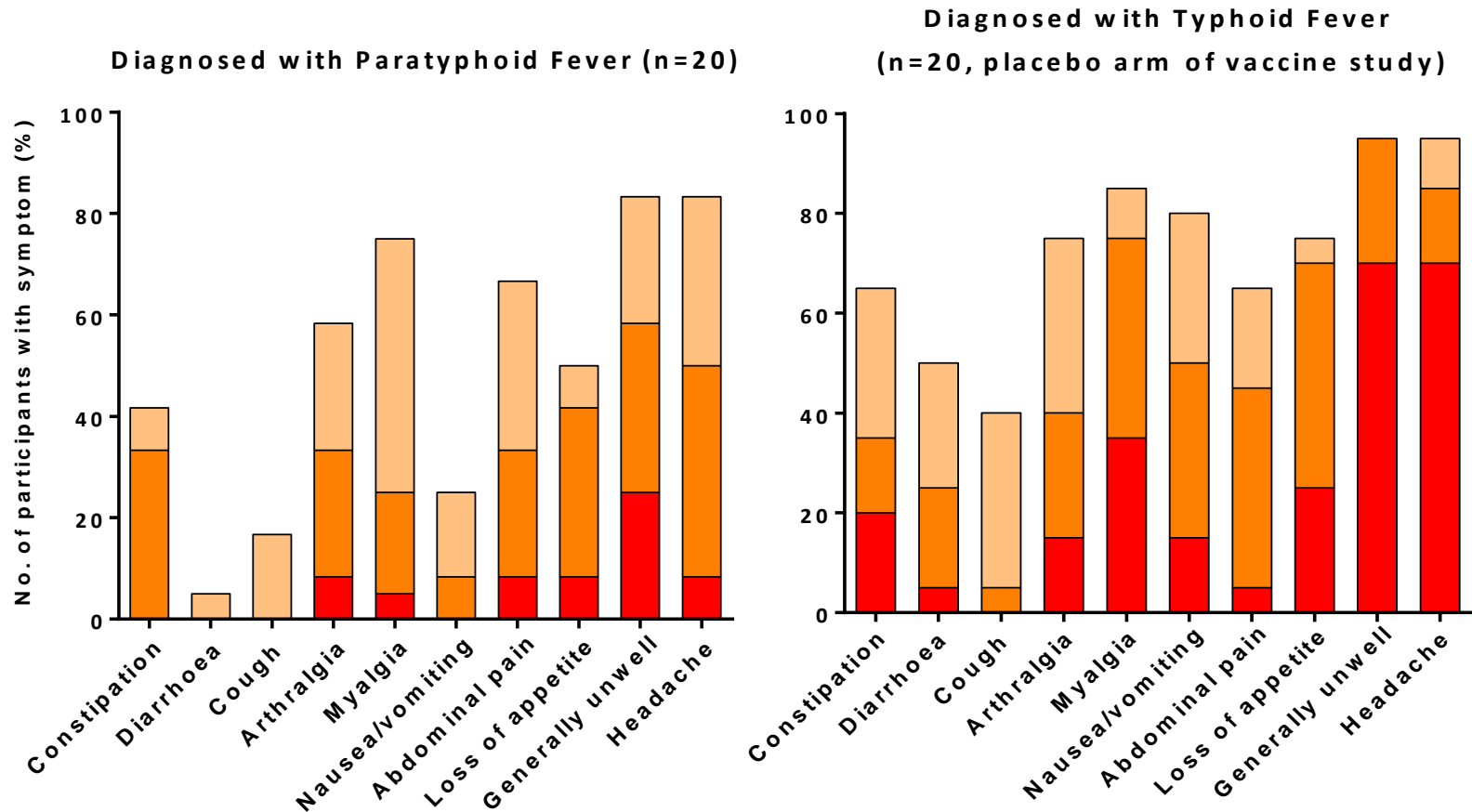
Diagnosed with Paratyphoid Fever (n=20)



A mild headache, muscle and/or joint pain often preceded diagnosis by 3-4 days, resolved and then returned with increased intensity.

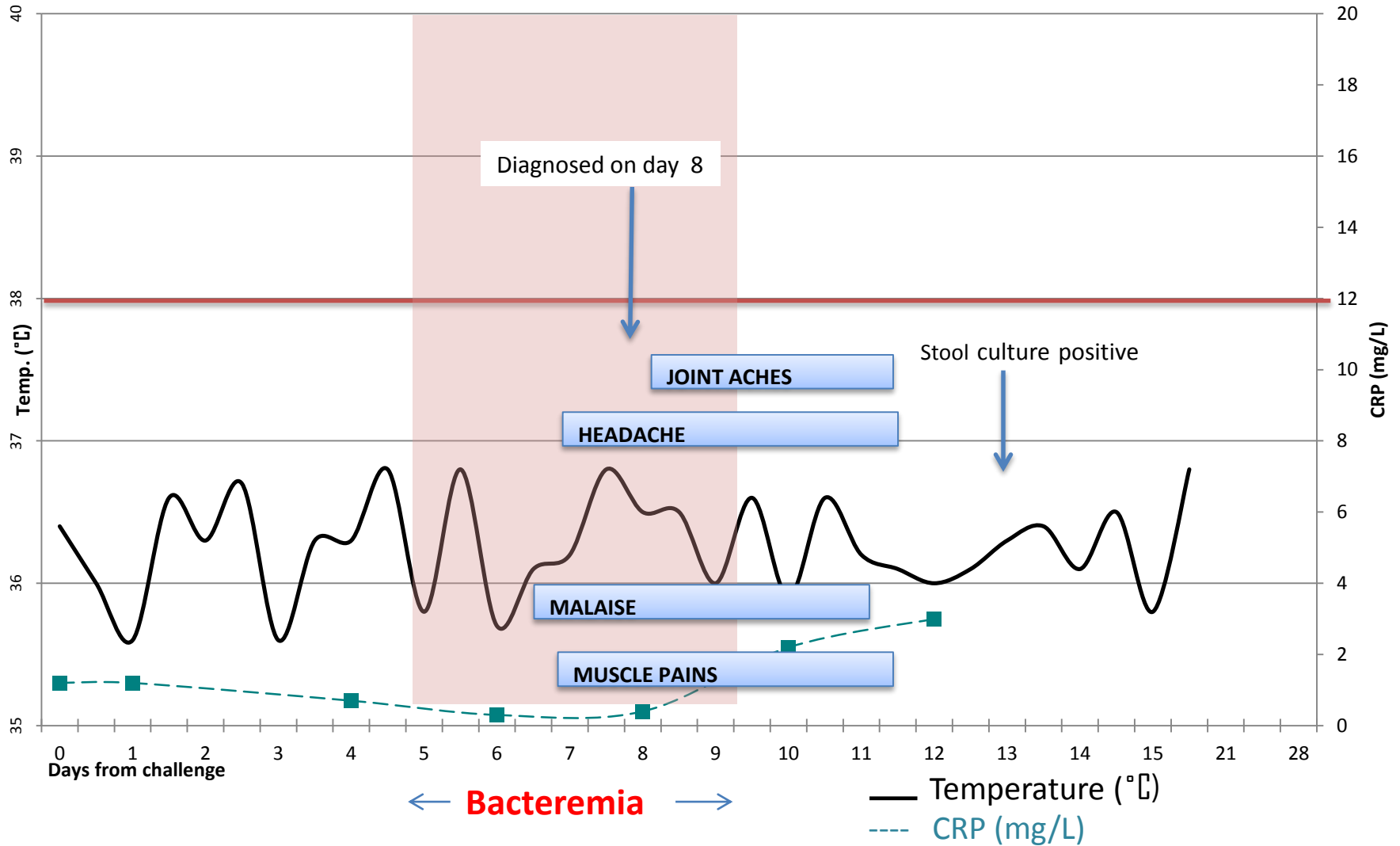
All participants who were diagnosed with paratyphoid fever (positive blood culture or fever $\geq 38^{\circ}\text{C}$ for 12 hours). Percentage of participants who recorded symptoms related to paratyphoid infection at any time during the intense challenge period.

Paratyphoid vs. typhoid experience

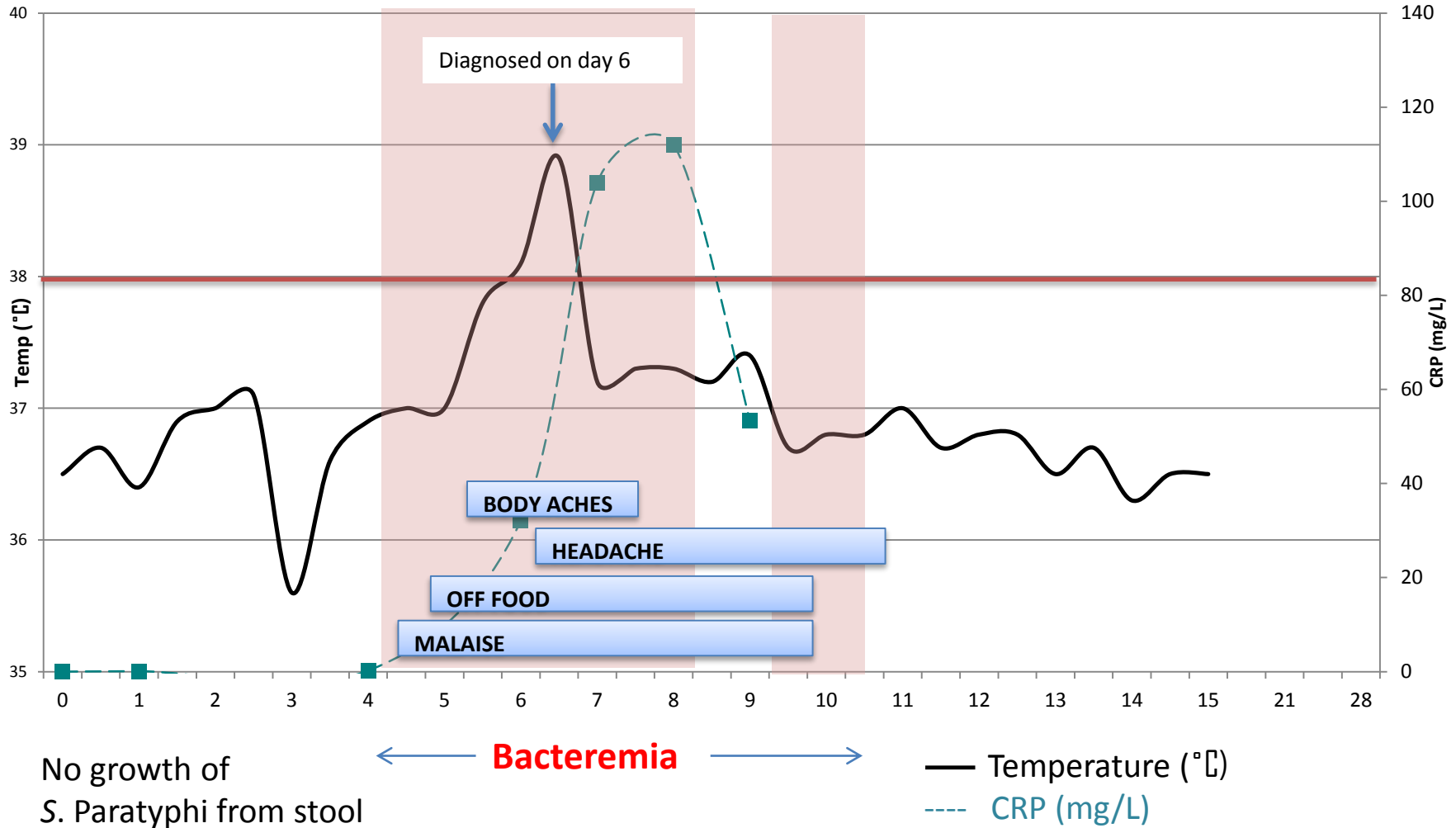


Paratyphoid participants had fewer and less severe symptoms than those in typhoid studies.

Microbiological diagnosis



Symptomatic diagnosis



Duration of bacteraemia

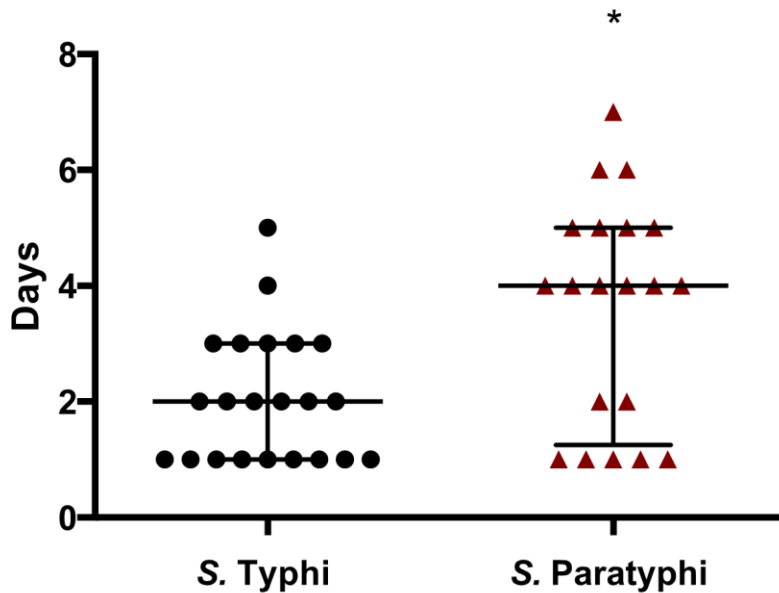


Figure 1 - Duration of *S. Typhi* and *S. Paratyphi* bacteraemia in participants with enteric fever diagnosis (Days - Median, IQR; * p= 0.0078).

See M. Gibani et al. poster

CFU/ml at time of diagnosis

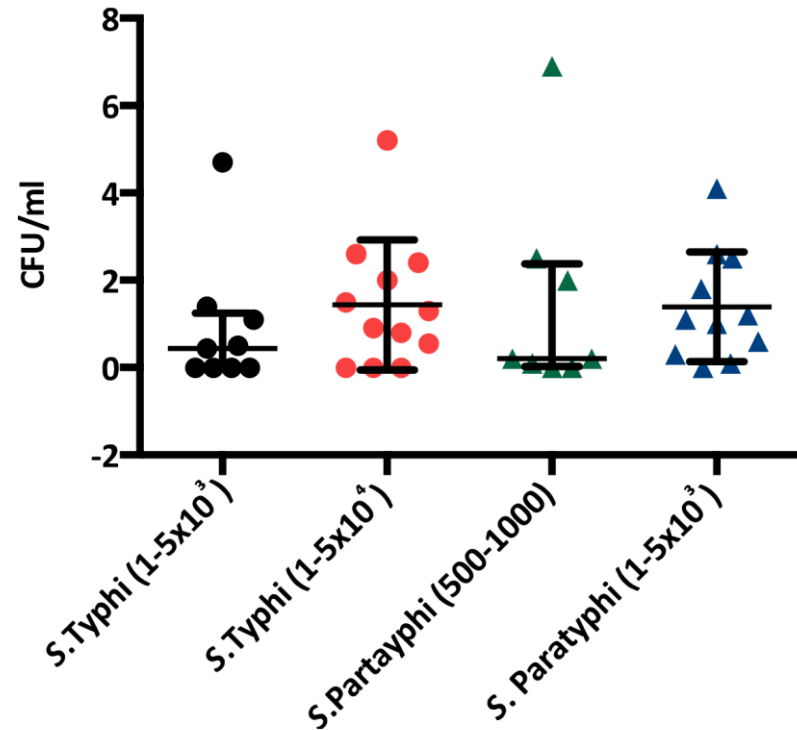
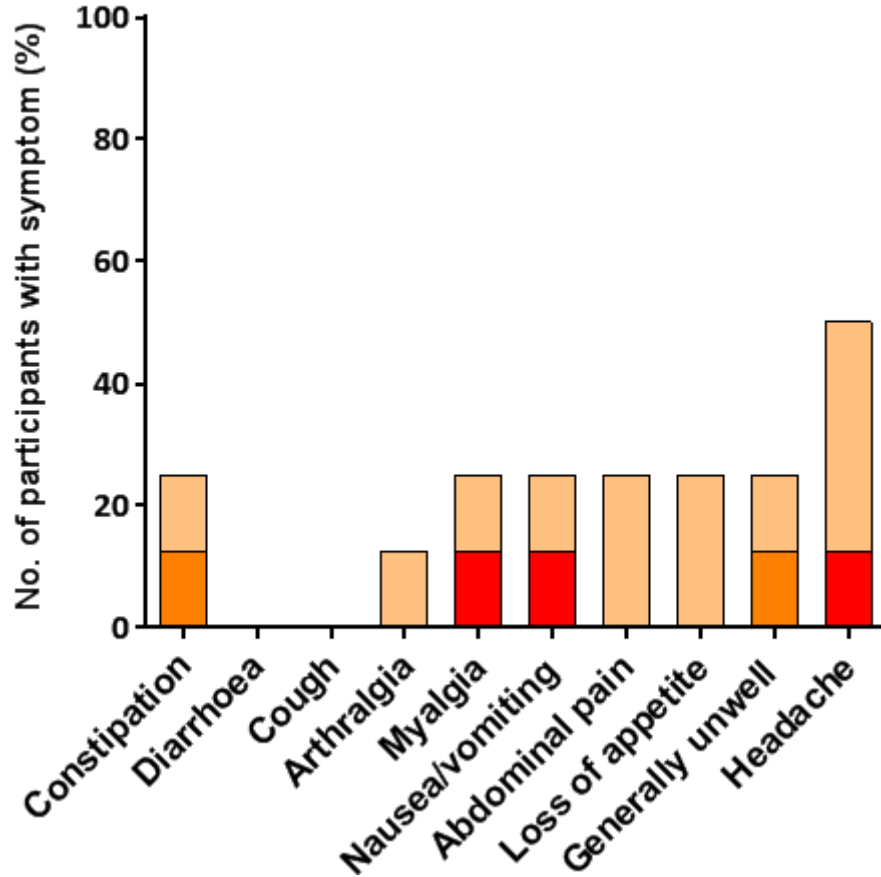


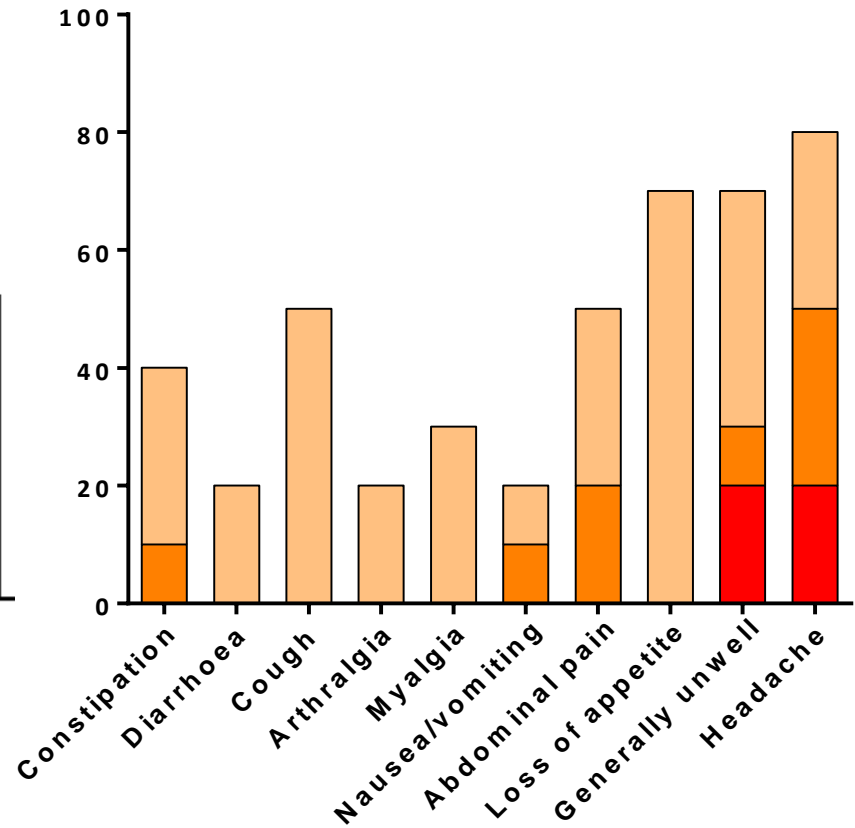
Figure 2 - Quantitative blood culture at time of diagnosis (CFU/ml - median, IQR). There was no significant difference in bacteraemic burden at time of diagnosis following challenge at all doses tested (p=0.493).

Paratyphoid vs. typhoid in non-diagnosed participants

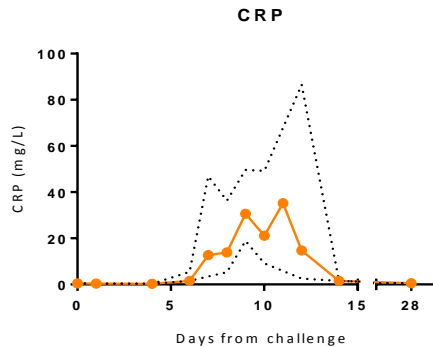
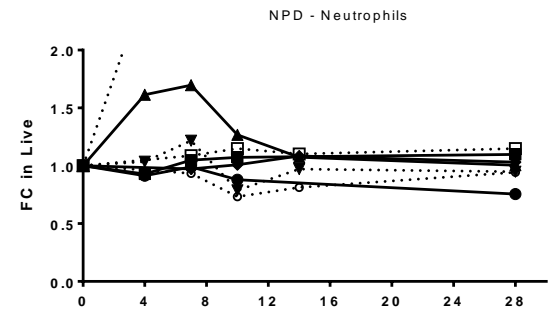
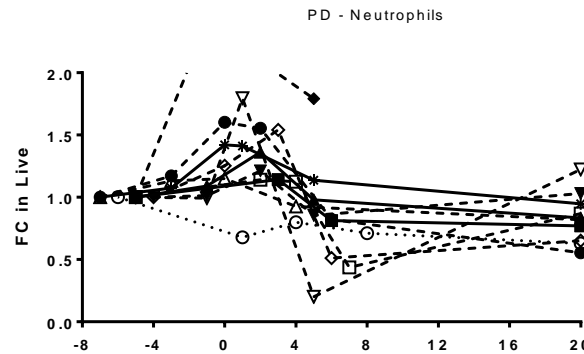
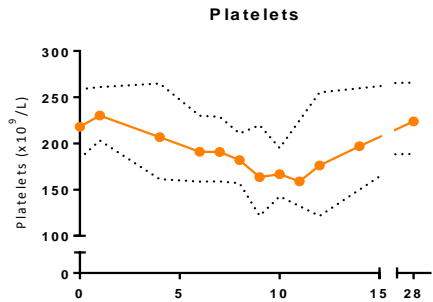
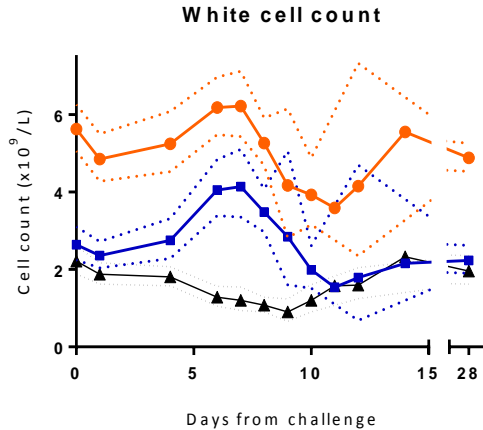
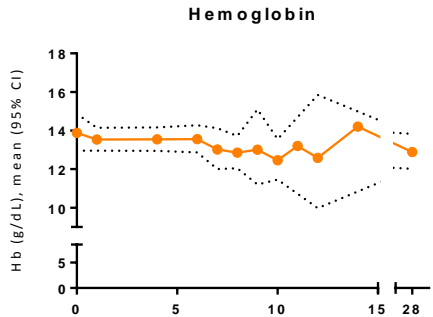
Not Diagnosed with Paratyphoid Fever



Not diagnosed with Typhoid Fever
(n=10, placebo arm of vaccine study)



Paratyphoid Blood parameters



See G. Napolitani et al. poster

Paratyphi and stool

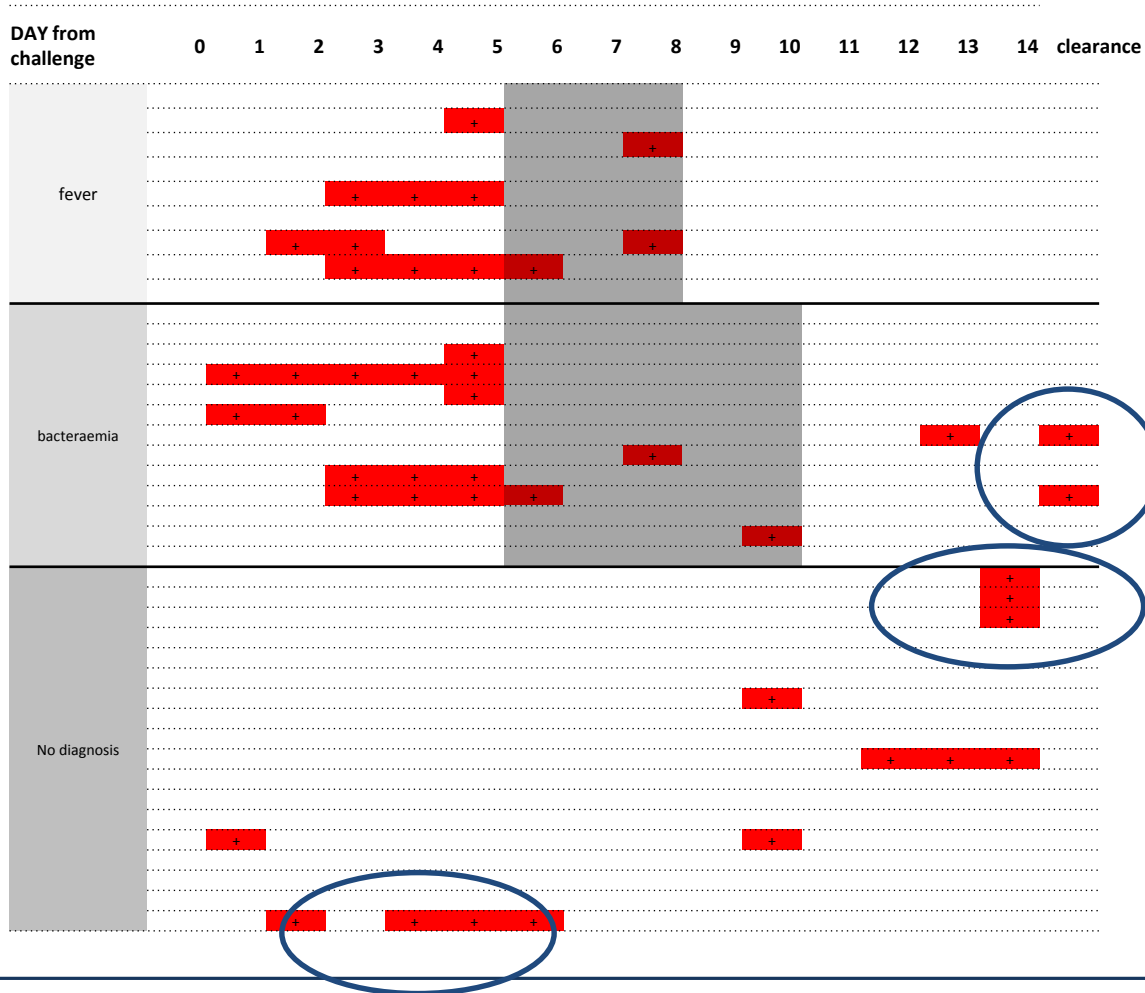
- Stool clearance
- Carriage question



Typical appearance of the organisms is as follows:

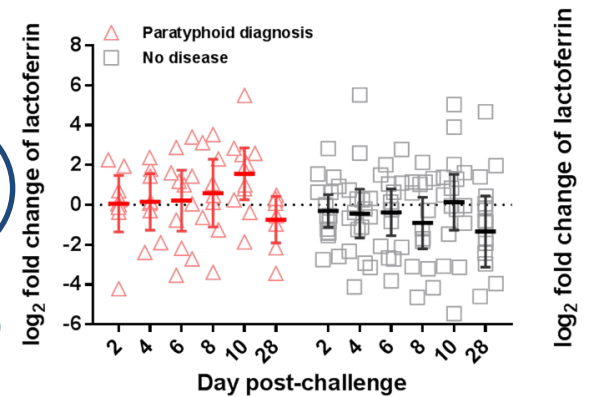
Organisms	BBL CHROMagar Salmonella	XLD Agar
<i>E. coli</i> , <i>Citrobacter</i>	Inhibited or blue-green colonies with or without mauve halos	Large, flat, yellow. Some strains may be inhibited.
<i>Enterobacter</i> / <i>Klebsiella</i>	Partially inhibited; blue-green to blue colonies with or without mauve halos	Mucoid, yellow
<i>Proteus</i>	Inhibition partial to complete	Red to yellow. Most strains have black centers.
<i>Salmonella</i> , H ₂ S-positive	Growth; mauve (=rose-violet) to violet colonies*	Black or red with black centers
<i>Salmonella</i> , H ₂ S-negative		Red
<i>Shigella</i>	Partially to completely inhibited; colorless or (rarely) blue-green colonies	Red
<i>Pseudomonas aeruginosa</i>	Inhibition partial to complete	Red
<i>Aeromonas hydrophila</i> , <i>Stenotrophomonas maltophilia</i>	Inhibition partial to complete; may rarely produce rose to mauve colonies; oxidase positive (<i>S. maltophilia</i> may be weakly positive or negative)*	Yellow or pink
Gram-positive bacteria	Inhibition partial to complete	Inhibition partial to complete

Stool shedding after challenge



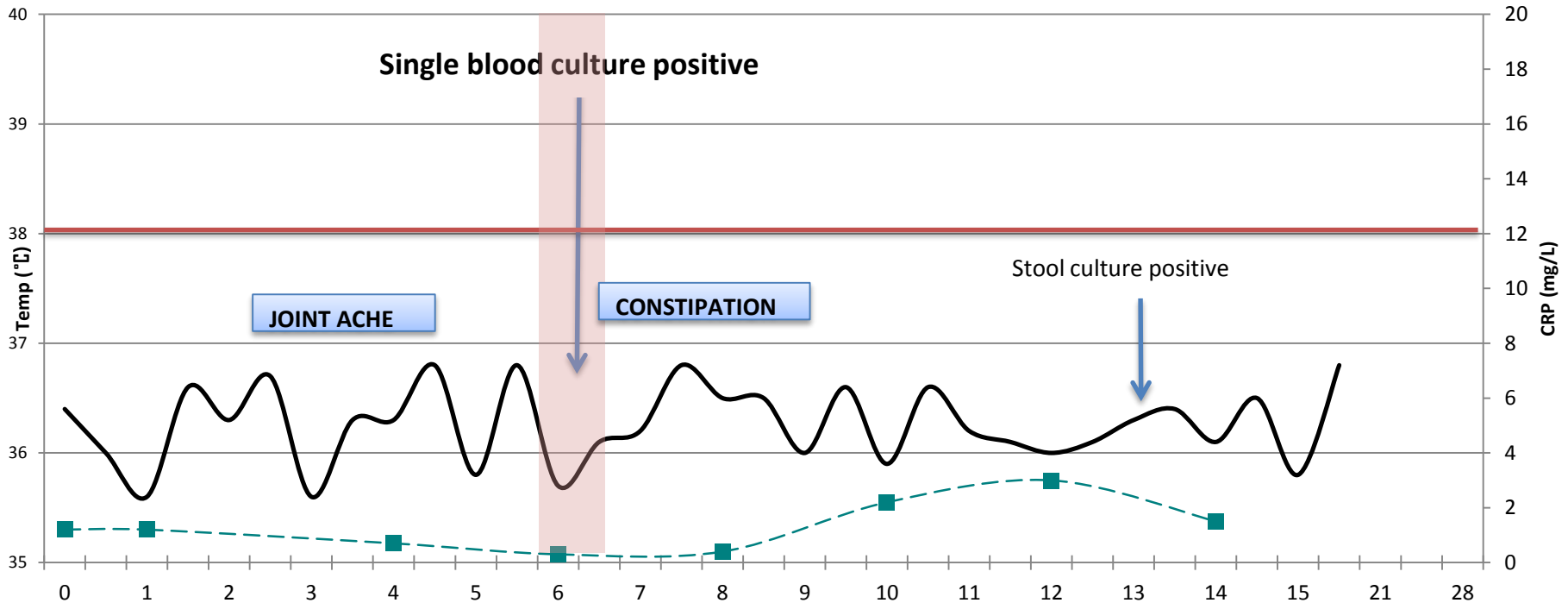
biomarker of neutrophil degranulation from mucosal surfaces

Lactoferrin after challenge



See H. Thomaidis-Brears et al. poster

Spontaneous clearance without antibiotics



No fever, minimal symptoms and unremarkable blood results.

— Temperature (°C)
- - - CRP (mg/L)

New control measures urgently needed

Future enteric fever prevention strategies in Asia must focus on *S. Typhi* and *S. Paratyphi*

Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Salmonella enterica* (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives[☆]

Bharat M. Pokharel^a, Janak Koirala^{b,*}, Rajan K. Dahal^a, Shyam K. Mishra^a, Prem K. Khadga^a, N.R. Tuladhar^a

- Emergence of drug-resistant strains
- Clinically indistinguishable disease
- Diagnostics: Need for improved diagnostics

A bivalent vaccine is needed to address enteric fever

Further enteric studies at OVG

Paratyphoid And Typhoid Challenge and re-challenge (PATCH):

- The mechanisms and determinants of mucosal and systemic protection against typhoid and paratyphoid fever, following controlled human challenge and natural disease.

Paratyphoid model developed for vaccine evaluation and now looking for candidates to test!

The Paratyphoid team

Clinical Research Fellows

Hazel Dobinson

Iain Milligan

Malick Gibani

Research Nurses

Danielle Campbell (lead)

Anna Peters

Rachel Wendler

Paulo Alves Abreu

Priscilla McRitason

Juliette Meek

Brian Angus

Andrew Pollard

Simon Kerridge

OUH Microbiology Department

Thames Valley Health Protection Unit

Project Management

Emma Harper (lead)

Emma Plested

Elizabeth Nuthall

Laboratory

Claire Jones (lead)

Liqing Zhou

Christoph Blohmke

Sonu Shrestha (lead RA)

Ricky Lagah

Helena Thomaidis-Brears

Leanne Marsay

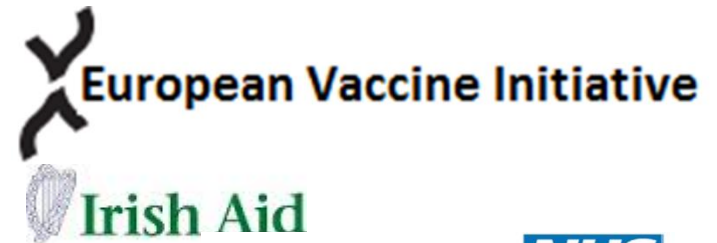
Harri Hughes

Statistical Support

Merryn Vossey

IT Support

Jama Farooq



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