Challenge studies - introduction

Andrew J Pollard
Thomas C Darton
2g NaHCO₃

3-10×10¹⁰ CFU Ty21a in milk
× 5-8 doses

Challenge with 10⁵ CFU

87% PROTECTIVE EFFICACY

Photo courtesy of Prof M Levine, University of Maryland; www.ovg.ox.ac.uk

Waddington CS, J Infect, 2012
Oxford Challenge Model

Mrs Quailes

S. typhi Quailes strain
B.N. ASS/VPU/2010/002
Oral Administration 1x10^5 cfu/ml
Volume: 1ml Vial Number: 678.
D.o.M. 12 AUG 10
Store: -65°C to -80°C
A.Pollard Tel: 01865 234226
FOR CLINICAL TRIAL USE ONLY

University of Oxford Centre for Clinical Vaccinology and Tropical Medicine

www.ox.ac.uk
Primary endpoint

- Fever >38°C +/- Positive blood culture

Field definition

Fever for 3 days + positive blood culture
DISEASE PHENOTYPES
Not typhoid

Temperature (°C)

C-reactive protein (mg/L)

Day

Blood Cx

Stool Cx

Widal O

Widal H

Not typhoid
Typhoid

Day 0 to 14

Temperature (°C)

C-reactive protein (mg/L)

Blood Cx

Stool Cx

QBC CFU/mL

Widal O

Widal H

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Oxford University Hospitals NHS Trust
Asymptomatic typhoid

Temperature (°C)

Temperature readings show a pattern of oscillation around 38°C, indicating a fever. The graph also indicates a rise in C-reactive protein (CRP) levels, which may suggest inflammation or infection.

Blood Cx
Stool Cx
QBC CFU/mL

Widal O: 2  4  32
Widal H: 4  4  16

The table and graph together provide a comprehensive view of the patient's condition over the course of 14 days.
Non-bacteraemic Typhoid

Day | Blood Cx | Stool Cx | QBC CFU/mL | Widal O | Widal H
--- | -------- | -------- | ---------- | ------- | -------
0   | -        | -        | 4          | 8       | 4       
1   | -        | -        | -          | 8       | 16      
2   | -        | -        | -          | 8       | 8       
3   | -        | -        | -          | -       | -       
4   | -        | -        | -          | -       | -       
5   | -        | -        | -          | -       | -       
6   | -        | -        | -          | -       | -       
7   | -        | -        | -          | -       | -       
8   | -        | -        | -          | -       | -       
9   | -        | -        | -          | -       | -       
10  | -        | -        | -          | -       | -       
11  | -        | -        | -          | -       | -       
12  | -        | -        | -          | -       | -       
13  | -        | -        | -          | -       | -       
14  | -        | -        | -          | -       | -       
15  | -        | +        | -          | -       | -       
16  | -        | -        | -          | -       | -       
17  | -        | -        | -          | -       | -       
18  | -        | -        | -          | -       | -       
19  | -        | -        | -          | -       | -       
20  | -        | -        | -          | -       | -       
21  | -        | -        | -          | -       | -       
22  | -        | -        | -          | -       | -       
23  | -        | -        | -          | -       | -       
24  | -        | -        | -          | -       | -       
25  | -        | -        | -          | -       | -       
26  | -        | -        | -          | -       | -       
27  | -        | -        | -          | -       | -       
28  | -        | -        | -          | -       | -       

Temperature (°C) vs. C-reactive protein (mg/L)
## Persistent shedders

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<tr>
<th>Day</th>
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### Oral Temperature (°C)

- Range: 36°C to 39°C
- Average: approximately 37°C

### C-reactive protein (mg/L)

- Range: 0 to 140 mg/L
- Average: approximately 40 mg/L

### Number days after challenge

- Blood and stool samples were collected daily from day 0 to day 15.
- Blood samples were negative throughout.
- Stool samples showed persistent shedding from day 8 to day 15.
Oxford Typhoid Programme

N=370

- **T1**: typhoid dose-escalation study, \( n=41 \)
- **T2**: double blind RCT (M01ZH09, Ty21a, placebo), \( n=99 \)
- **VAST**: double blind RCT (Vi-TT, Vi, MenACWY) & AZ vs Cip, \( n=111 \)

- **P1**: paratyphoid dose-escalation study, \( n=40 \)
- **PATCH**: Paratyphoid and Typhoid challenge and rechallenge, \( n=79 \)....in progress
- **Tyger**: toxin- strain.....in progress

1. Temperature +/-
2. Bacteraemia

D0

D4

D7

D10

D14

D28

D60

D90

+48hrs

+96hrs

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