



# Challenge studies - introduction

Andrew J Pollard

Thomas C Darton



# University of Maryland

1952 - 1974



T.E. Woodward



Mrs Quailles

Photo courtesy of Prof M Levine, University of Maryland;  
[www.ovg.ox.ac.uk](http://www.ovg.ox.ac.uk)

2g NaHCO<sub>3</sub>



3-10x10<sup>10</sup> CFU Ty21a in milk  
 x 5-8 doses



Challenge with 10<sup>5</sup> CFU



**87% PROTECTIVE EFFICACY**

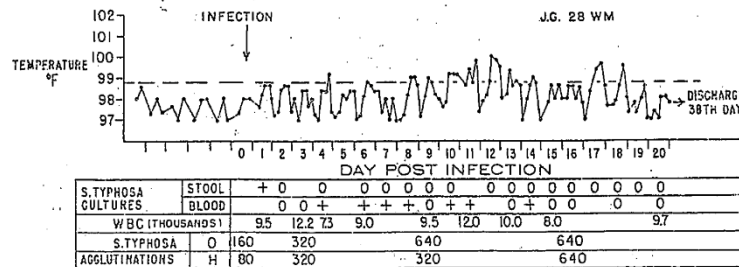


FIG. 1. Clinical summary of volunteer no. 9, J. G., after the ingestion of 10<sup>8</sup> viable *Salmonella typhosa* Quailles strain. Rectal temperatures are recorded.



Waddington CS, J Infect, 2012



# Oxford Challenge Model



Mrs Quail



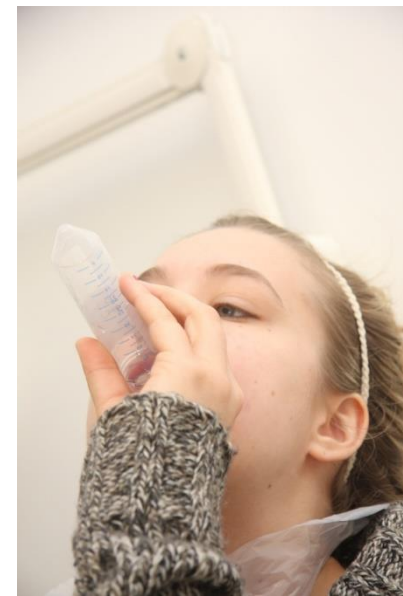
**S.typhi Quail's strain**  
B.N. ASS/VPU/2010/002  
Oral Administration  $1 \times 10^5$  cfu/ml  
Volume: 1ml Vial Number: 678.  
D.o.M. 12 AUG 10  
Store:  $-65^{\circ}\text{C}$  to  $-80^{\circ}\text{C}$   
A.Pollard Tel: 01865 234226  
**FOR CLINICAL TRIAL USE ONLY**





# Primary endpoint

- Fever  $>38^{\circ}\text{C}$  +/- Positive blood culture



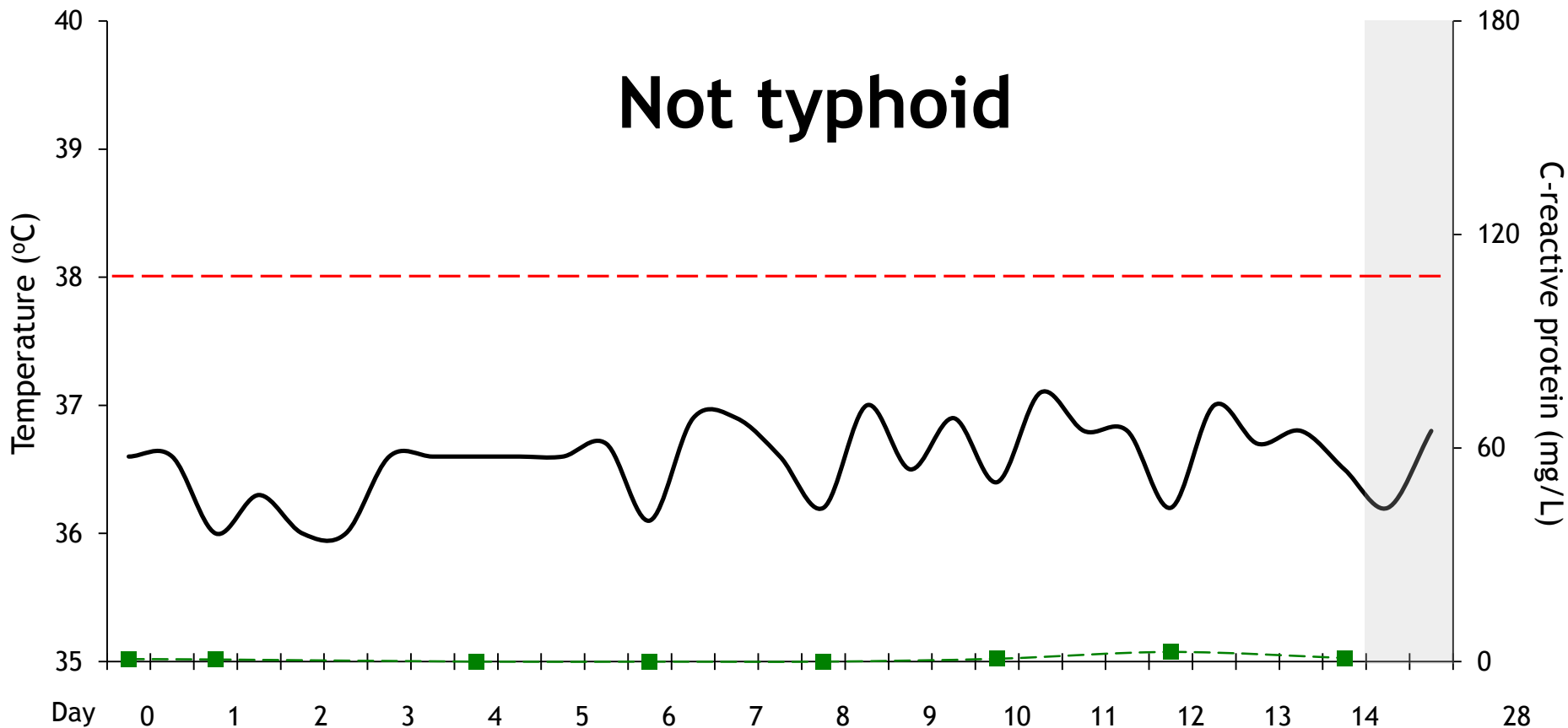
## Field definition

Fever for 3 days + positive blood culture



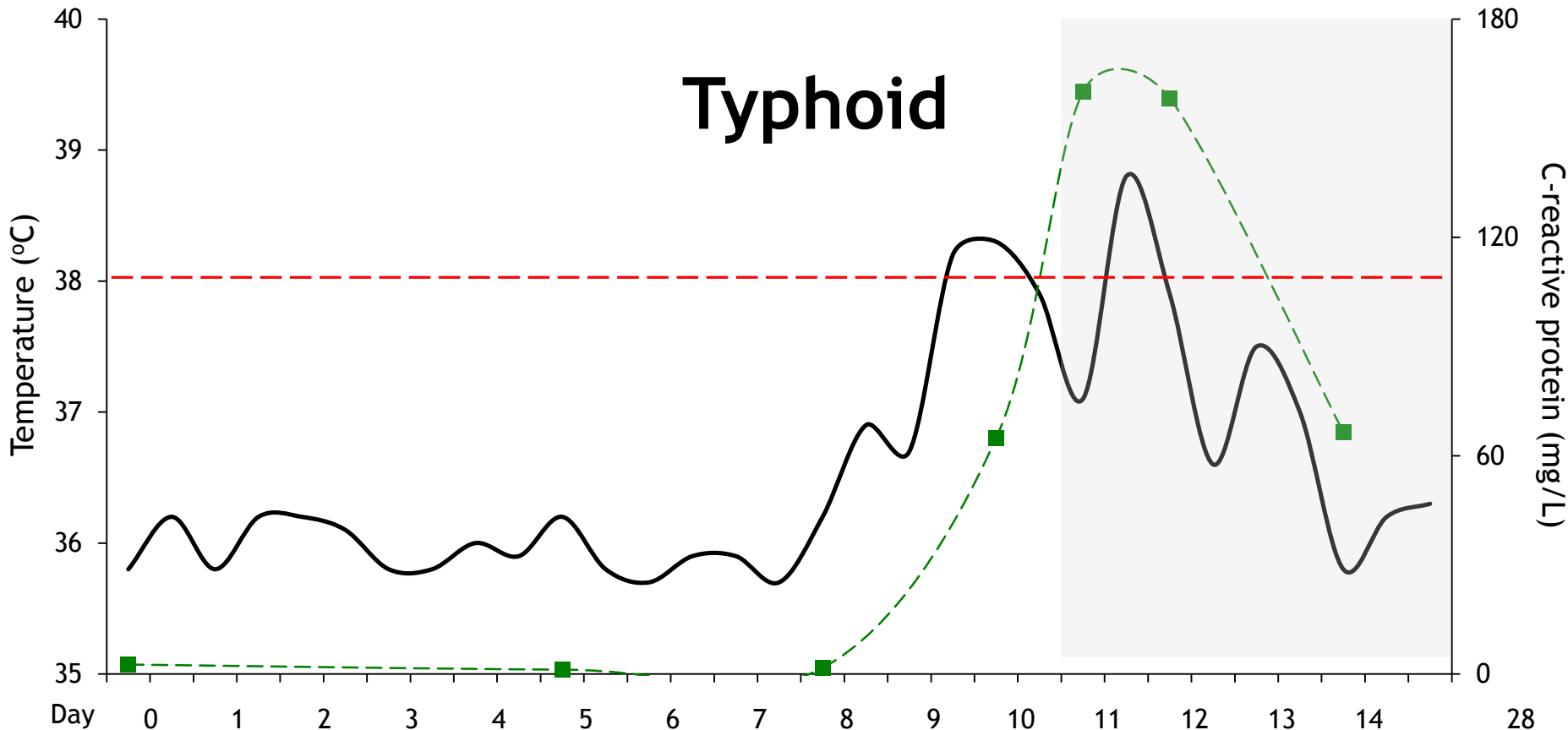
# DISEASE PHENOTYPES

# Not typhoid



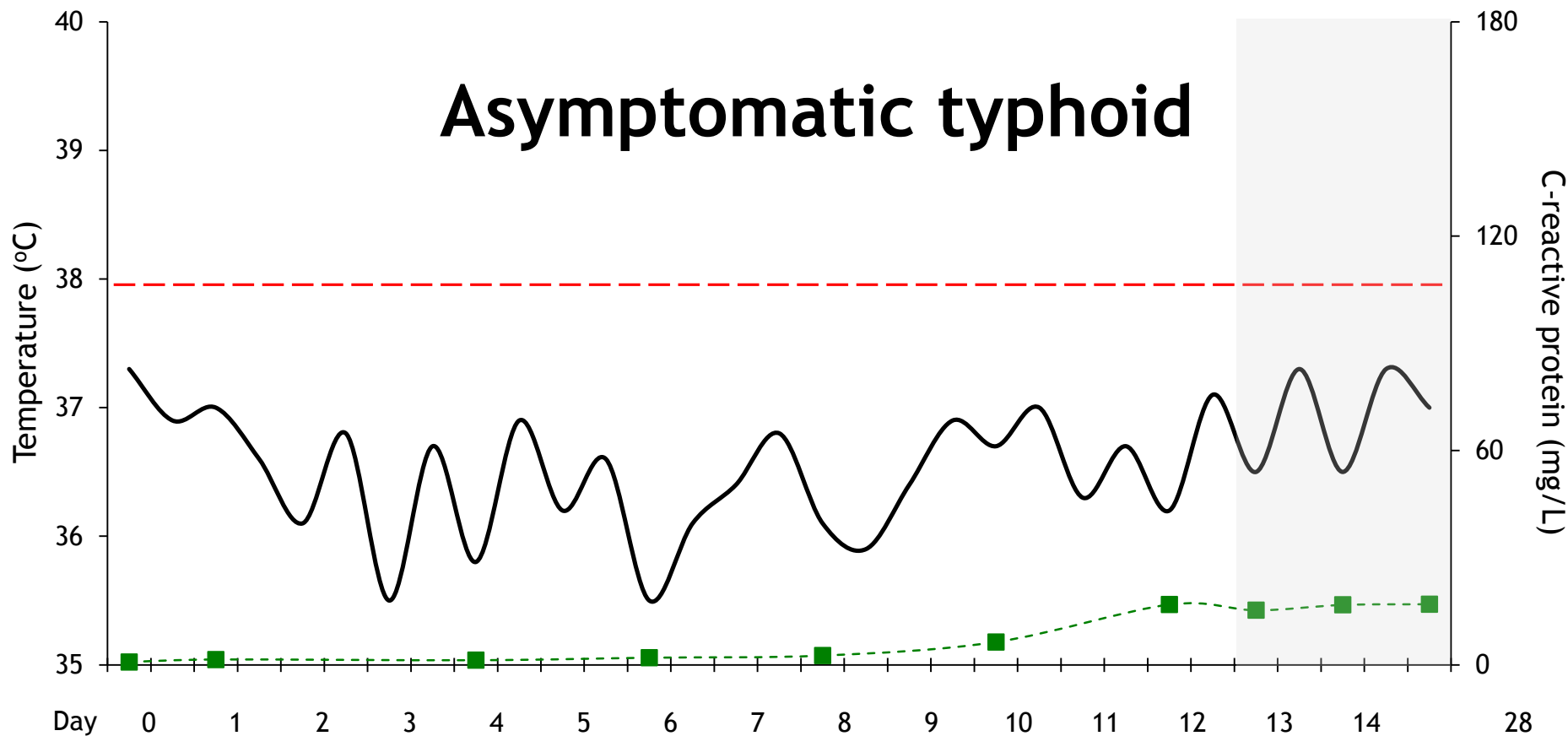
Blood Cx	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stool Cx	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Widal O	2														4	8
Widal H	NA														NA	NA

# Typhoid



Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Blood Cx	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-
Stool Cx	-	+	-	-	-	-	-	-	+	+	+	+	-	-	-	-
QBC CFU/mL												6.2				
Widal O	2											4				16
Widal H	NA											4				16

# Asymptomatic typhoid



Blood Cx	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-
Stool Cx	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

QBC CFU/mL

0

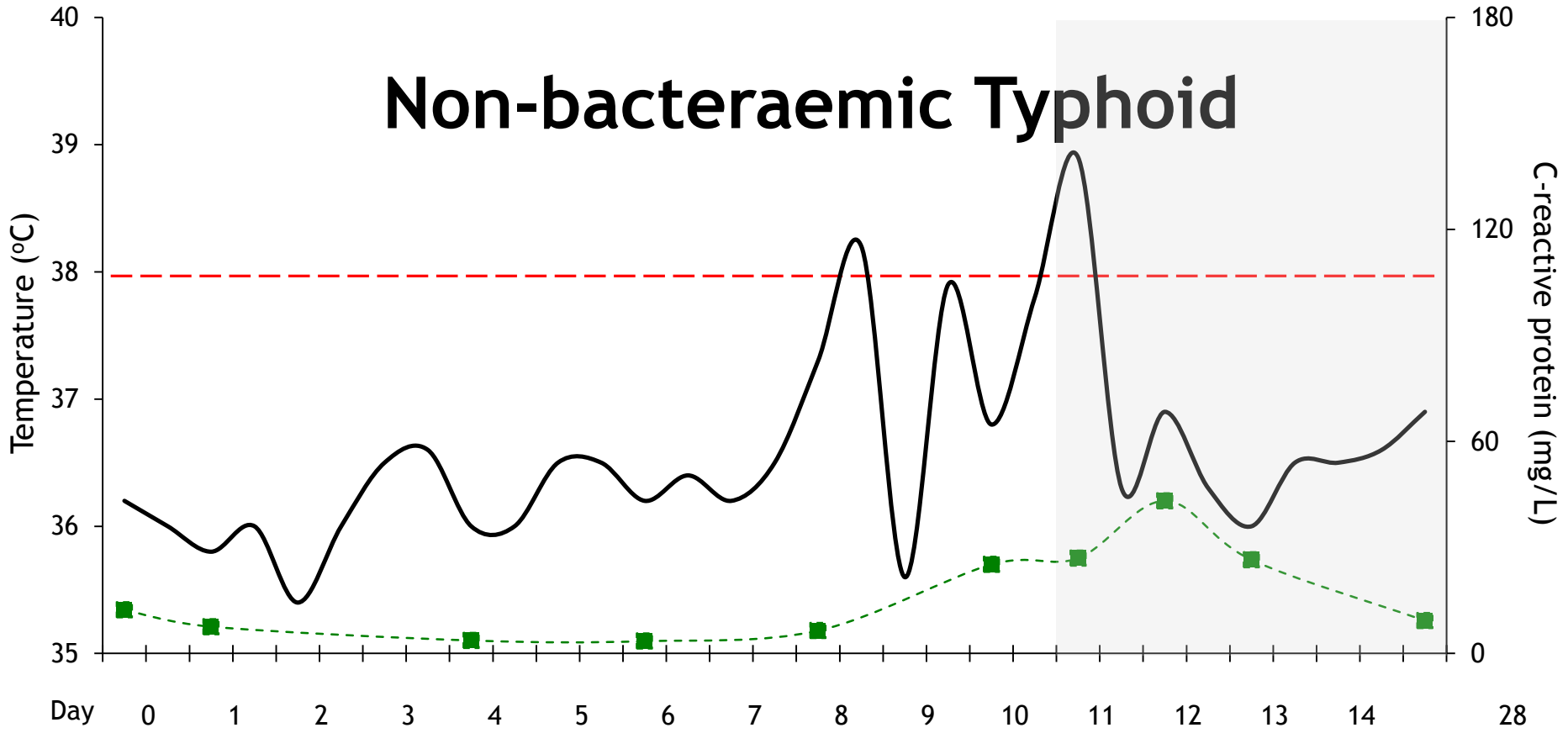
Widal O	2
Widal H	4

4
4

32
16



# Non-bacteraemic Typhoid



Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Blood Cx	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stool Cx	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-

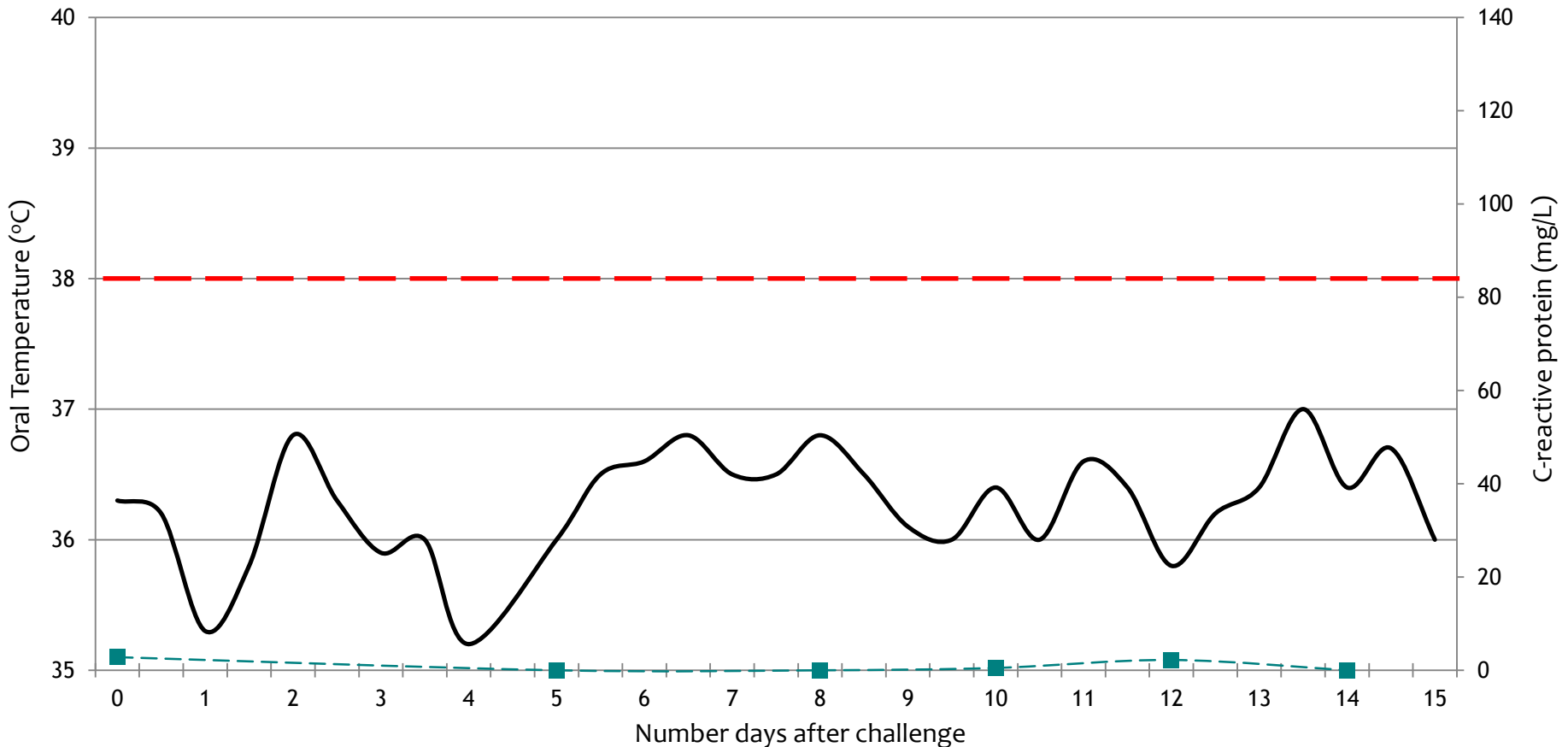
QBC	0	8	16
CFU/mL	0	8	8
Widal O	4	8	8
Widal H	4	16	8



# Persistent shedders



Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Blood						-		-		-		-		-		-
Stool	-	+				-		-		+		+		+		+





# 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

