Clinical trial results:
Vaccines Against Salmonella Typhi: a phase IIb, single centre, observer-blind, randomised controlled trial to assess the immunogenicity and protective efficacy of Vi conjugated (Vi-TCV) and unconjugated (Vi-PS) polysaccharide vaccines in preventing typhoid infection compared to a control vaccine (meningococcal ACWY), using a human challenge model of typhoid infection

Summary

EudraCT number	2014-002978-36
Trial protocol	GB
Global end of trial date	27 June 2022

Results information

Result version number	v1 (current)
This version publication date	12 July 2023
First version publication date	12 July 2023

Trial information

Trial identification

Sponsor protocol code	OVG2014/08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02324751
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS: 162909

Notes:

Sponsors

Sponsor organisation name	University of Oxford, Research Governance, Ethics & Assurance Team (RGEA)
Sponsor organisation address	Boundary Brook House, Oxford, United Kingdom, OX3 7GB
Public contact	Andrew Pollard, University of Oxford, +44 1865611400, andrew.pollard@paediatrics.ox.ac.uk
Scientific contact	Andrew Pollard, University of Oxford, +44 1865611400, andrew.pollard@paediatrics.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: To determine the relative protective effect of Vi-TCV or Vi-PS compared to control vaccine in a healthy adult typhoid challenge model
Secondary objectives:
i. Compare clinical and laboratory features following S. Typhi challenge in participants vaccinated with Vi-TCV, Vi-PS or control vaccine
ii. Compare the host immune response following vaccination with Vi-TCV, Vi-PS or control vaccine
iii. Compare the host immune response following S. Typhi challenge in Vi-TCV, Vi-PS and control groups
iv. Persistence of immunological markers following vaccination and S. Typhi challenge
v. Genomic response to vaccination with Vi-TCV, Vi-PS and control and subsequent S. Typhi challenge
vi. Novel diagnostic methods for detecting S. Typhi infection
vii. Compare clinical and microbiological data following treatment of typhoid fever with antibiotics
viii. Immunological correlates of protection for S. Typhi infection
ix. Safety and tolerability of Vi-TCV

Protection of trial subjects:

The trial staff ensured that the participants' anonymity was maintained.
The general risks to the participants were linked to venepuncture, use of the vaccines and challenge with live-causing bacteria. In view of the low infectivity of S.Typhi without gastric suppression and the general level of hygiene and sanitation in the UK, secondary transmission of S.Typhi to household or other close contacts was highly unlikely.
Participants were instructed to complete a Diary Card, recording oral temperatures and describing any symptoms or usage of any medications daily. The diary card was completed from point of first vaccination for 7 days. After 7 days following vaccination, participants were asked to document additional details regarding any visits seeking medical advice (including GP and Emergency Department visits). The e-diary was reviewed by the study team and when participants attended post-vaccination visits.
Participant were issued with a Medic Alert-type card containing information including the antibiotic sensitivity of the S. Typhi strain, study doctor contact details and instruction for the research team to be contacted immediately in the event of illness/accident.
Participants did not have to remain on site between assessments but a rest area was provided which participants could use if they wished.
Participants had access to a study physician 24-hours a day, from the time of vaccination until they were deemed to be clear of S. Typhi infection. Following challenge, participants were encouraged to contact one of the study investigators on the 24-hour emergency telephone number if they developed symptoms of typhoid between regular clinical reviews, or when their temperature exceeded 38C. The investigators considered extra clinical reviews if the participants' symptoms were moderate or severe, or at their request. Severity of symptoms was assessed and if participants were unwell as a result of S. Typhi infection, they were visited in their homes.

Background therapy:

Four weeks after completion of the immunisation course, participants were challenged with Salmonella Typhi (Quailes strain) at an infective dose (1-5x10^4 CFU) previously demonstrated to give the desired clinical/laboratory attack rate.
The S. Typhi (Quailes strain) for inoculation of participants is stored as a frozen suspension in soya tryptone medium containing 10% sucrose.

Evidence for comparator:

Current Licensed Vaccines:
The virulence factor (Vi) capsular polysaccharide (Vi-PS) vaccine does not generate immunological memory. Additionally, subsequent vaccinations do not booster its effect on immunity. In common with other polysaccharide vaccines, the Vi-PS vaccine is non-immunogenic in children under 2 years of age and is only moderately efficacious. Its duration of efficacy is also very limited, with protection lasting only 2 to 3 years.
As a live attenuated oral vaccine, Ty21a stimulates local mucosal immunity, within the gut, as well as systemic antibody and cell-mediated immune responses. Currently, it is the only licensed oral vaccine for the prevention of typhoid fever. Limitations include the multiple dosages required for full immunogenicity and efficacy to occur (a three dose, alternate day regimen or a four dose schedule). Furthermore, Ty21a is not licensed for use in children below 6 years of age.
Similar to the Vi-PS vaccine, the Ty21a vaccine is only moderately efficacious.

Currently licensed typhoid vaccines are either not immunogenic in early childhood (parenteral Vi capsular polysaccharide vaccine) or are unsuitable for administration in children younger than 5 years (the oral live attenuated typhoid vaccine Ty21a is unsuitable for use in children younger than 5 years because of its formulation in capsules, which are difficult for young children to swallow). By contrast, typhoid conjugate vaccines, which combine the Vi-polysaccharide capsule with a protein carrier, have improved immunological properties and can be used from early infancy.
Vi-TCV is a Vi polysaccharide-conjugate vaccine. Similar to other tetanus toxoid conjugate vaccines used to prevent encapsulated bacterial infections, Vi-TCV induces a T-cell dependent immune response resulting in improved immunogenicity in infants and the potential to produce a durable immune response by inducing immunological memory.

Actual start date of recruitment	18 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 112
Worldwide total number of subjects	112
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	112
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy adults aged between 18 and 60 years were recruited via several methods including poster, media and website advertising, direct mail-out, email campaign, Oxford Vaccine Centre database and exhibitions.

Pre-assignment

Screening details:

For Group A 1486 participants were assessed for eligibility between Aug 18, 2015 and Nov 4, 2016. Of the 207 volunteers who were screened, 73 failed to meet the eligibility criteria and 22 declined further study participation. 112 were enrolled, randomised and vaccinated.

Period 1

Period 1 title	Group A (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Participants were randomised 1:1:1 to receive Vi-TCV, Vi-PS or meningococcal ACWY vaccines.
The randomisation schedule was generated by an independent statistician using a fixed block size of six and stratified according to baseline anti-Vi IgG titre to ensure participants with pre-existing detectable antibodies were equally distributed between vaccine groups. The allocation sequence was implemented using a randomisation system to ensure allocation concealment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vi-TCV (IMP)

Arm description:

Single dose intramuscular vaccine; 28 days pre-challenge

Arm type	Experimental
Investigational medicinal product name	Vi polysaccharide-tetanus toxoid conjugate vaccine (Vi-TCV)
Investigational medicinal product code	
Other name	Typbar-TCV®, Bharat Biotech
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each 0.5mL vaccine dose contains 25µg of purified Vi capsular polysaccharide (S. Typhi Ty2 strain) conjugated to non-toxic tetanus toxoid.
The vaccine is supplied in a prefilled syringe containing sodium chloride solution and water for injection.

Arm title	Vi-PS

Arm description:

Single dose intramuscular vaccine; 28 days pre-challenge

Arm type	Active comparator
Investigational medicinal product name	Plain Vi capsular polysaccharide vaccine (Vi-PS)
Investigational medicinal product code	
Other name	TYPHIM Vi®, Sanofi Pasteur
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each 0.5 mL vaccine dose contains 25 µg of purified Vi capsular polysaccharide (S. Typhi Ty2 strain).

The vaccine is supplied in a prefilled syringe containing phosphate buffer and sodium chloride solution and 0.25% phenol preservative.

Arm title	Control group
Arm description:	
Single dose intramuscular vaccine; 28 days pre-challenge	
Arm type	Placebo
Investigational medicinal product name	Quadrivalent Meningococcal ACWY oligosaccharide Diphtheria CRM197 conjugate vaccine
Investigational medicinal product code	
Other name	MENVEO®, Novartis Vaccines and Diagnostics
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

A single vaccine dose after reconstitution is 0.5 mL.
Each vaccine dose contains N. meningitidis oligosaccharides (10µg MenA oligosaccharide, 5µg of each of MenC, Men Y and MenW-135 oligosaccharides) conjugated to 32.7 µg to 64.1µg Diphtheria CRM197 protein with residual formaldehyde dose less than 0.30µg.
The vaccine is supplied as a lyophilised MenA conjugate vaccine component to be reconstituted with the accompanying Men CYW-135 liquid conjugate vaccine component.

Number of subjects in period 1	Vi-TCV (IMP)	Vi-PS	Control group
Started	41	37	34
Completed	37	35	31
Not completed	4	2	3
Consent withdrawn by subject	3	2	1
Physician decision	1	-	1
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Vi-TCV (IMP)
Reporting group description:	
Single dose intramuscular vaccine; 28 days pre-challenge	
Reporting group title	Vi-PS
Reporting group description:	
Single dose intramuscular vaccine; 28 days pre-challenge	
Reporting group title	Control group
Reporting group description:	
Single dose intramuscular vaccine; 28 days pre-challenge	

Reporting group values	Vi-TCV (IMP)	Vi-PS	Control group
Number of subjects	41	37	34
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18-60 years)	41	37	34
Age continuous Units: years			
arithmetic mean	31.2	33.8	31.3
standard deviation	± 11.9	± 11.9	± 12
Gender categorical Units: Subjects			
Female	19	13	10
Male	22	24	24

Reporting group values	Total		
Number of subjects	112		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Adults (18-60 years)	112		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	42		
Male	70		

End points

End points reporting groups	
Reporting group title	Vi-TCV (IMP)
Reporting group description:	
Single dose intramuscular vaccine; 28 days pre-challenge	
Reporting group title	Vi-PS
Reporting group description:	
Single dose intramuscular vaccine; 28 days pre-challenge	
Reporting group title	Control group
Reporting group description:	
Single dose intramuscular vaccine; 28 days pre-challenge	

Primary: Typhoid Diagnosis	
End point title	Typhoid Diagnosis
End point description:	
To determine the relative protective effect of Vi-TCV compared to control vaccine, and the relative protective effect of Vi-PS compared to control vaccine, in a healthy adult typhoid challenge model	
End point type	Primary
End point timeframe:	
During the 14-day challenge period	

End point values	Vi-TCV (IMP)	Vi-PS	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	35	31	
Units: number of participants				
Total diagnosed	13	13	24	

Statistical analyses

Statistical analysis title	Vaccine Efficacy Vi TCV (IMP) vs Control group
Comparison groups	Vi-TCV (IMP) v Control group
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Chi-squared
Parameter estimate	Vaccine Efficacy
Point estimate	54.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	26.8
upper limit	71.8

Statistical analysis title	Vaccine Efficacy Vi PS vs Control group
Comparison groups	Vi-PS v Control group
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Chi-squared
Parameter estimate	Vaccine Efficacy
Point estimate	52
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.2
upper limit	70

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse Event were reported during the whole trial.
Solicited symptoms were reported for 7 days following vaccination and for 21 days following challenge.

Adverse event reporting additional description:

The frequency of solicited adverse events during the 21 days after challenge, according to vaccine group allocation are reported in the following publication:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32149-9/fulltext#supplementaryMaterial

Assessment type	Systematic

Dictionary used

Dictionary name	Protocol
Dictionary version	10.0

Reporting groups

Reporting group title	Vi TCV (IMP)

Reporting group description:

Single dose intramuscular vaccine; 28 days pre-challenge

Reporting group title	Vi PS

Reporting group description:

Single dose intramuscular vaccine; 28 days pre-challenge

Reporting group title	Control group

Reporting group description:

Single dose intramuscular vaccine; 28 days pre-challenge

Serious adverse events	Vi TCV (IMP)	Vi PS	Control group
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	3 / 37 (8.11%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Reactive arthritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 37 (2.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inflammatory bowel disease			
subjects affected / exposed	1 / 41 (2.44%)	0 / 37 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Tonsillectomy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 37 (2.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 41 (0.00%)	1 / 37 (2.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Vi TCV (IMP)	Vi PS	Control group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	37 / 37 (100.00%)	34 / 34 (100.00%)
General disorders and administration site conditions			
Headache			
subjects affected / exposed	14 / 41 (34.15%)	12 / 37 (32.43%)	9 / 34 (26.47%)
occurrences (all)	14	12	9
Malaise			
subjects affected / exposed	9 / 41 (21.95%)	4 / 37 (10.81%)	7 / 34 (20.59%)
occurrences (all)	9	4	7
Injection site pain			
subjects affected / exposed	25 / 41 (60.98%)	33 / 37 (89.19%)	13 / 34 (38.24%)
occurrences (all)	25	33	13
Injection site erythema			
subjects affected / exposed	1 / 41 (2.44%)	1 / 37 (2.70%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Injection site swelling			
subjects affected / exposed	1 / 41 (2.44%)	0 / 37 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	3 / 41 (7.32%)	3 / 37 (8.11%)	2 / 34 (5.88%)
occurrences (all)	3	3	2
Musculoskeletal and connective tissue			

disorders			
Myalgia			
subjects affected / exposed	13 / 41 (31.71%)	8 / 37 (21.62%)	8 / 34 (23.53%)
occurrences (all)	13	8	8
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)	4 / 37 (10.81%)	5 / 34 (14.71%)
occurrences (all)	3	4	5
Infections and infestations			
Fever	Additional description: Fever between 37.5C and 38C		
subjects affected / exposed	1 / 41 (2.44%)	2 / 37 (5.41%)	2 / 34 (5.88%)
occurrences (all)	1	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2015	Changes to the Study Protocol: 1. Use of contraception changed for consistency across the protocol (as requested by MHRA) 2. Clarification of safety reporting 3. Amendment to sample collection 4. Amendment to Secondary Objective 5. Amendment to Section 10 – Laboratory Changes to the Study Information Booklet and the Study Card: Changes in sample collection.
17 June 2015	Changes to the Study Protocol: 1. Administrative amendment to sample collection 2. Administrative amendment to Section 10.8 Other laboratory investigations 3. Substantial amendment to Section 8.5 Randomisation, blinding and code-breaking 4. Substantial amendment to Section 6.2 (Sample collection) The volume of blood collected at screening has been increased from 11ml to 14ml. The additional 3ml will be used to screen for baseline anti-Vi capsular polysaccharide antibody. Changes to the Study Information Booklet: Changes in total blood volume and the time of unblinding. Changes to the Diary Card Backup: Administrative amendment to the diary card backup

09 October 2015	Changes to the Study Protocol 1. Substantial Amendment for Sample Collection Chart (Table 2 of Section 6.2) 2. Substantial Amendment for Recruitment methods (Section 8.1) GP Eligibility Letter Simplification of the letter to the GP and eligibility form Screening Invitation Text (administrative amendment) Addition of the following sentence: "Your Abdominal Ultrasound appointment is on [date at time] in the Radiology Department at the Churchill Hospital. Please do not have anything to eat for 6 hours prior to this appointment. You may drink clear fluids." Additional change in the wording of the text to remind participants to bring bank account details for reimbursement purposes. Participant Invitation Letter (administrative amendment) Change from "Recruiting 2015" to "Recruiting Now" Addition of the following: "We are inviting healthy adults aged 18 to 60 years to take part in this study. We use various ways to contact anyone who may be interested in this study, including via the Electoral Roll or the National Health Applications and Infrastructure Services (NHAIS). As a result of this, you may have previously received this invitation. We apologise for any inconvenience caused." "If you are aged 18 to 60 yrs old, in good health and have never previously received a typhoid vaccine, you may be eligible to take part in the study" D-28 Visit reminder (administrative amendment) Addition of the following sentence: "Please remember to bring your signed 24-hour contact letter to this visit." Removal of the following sentence: "We require you to bring a stool sample to the vaccination appointment. The stool specimen collection procedure is attached to this email" Study Information Booklet, page 13 (administrative amendment) The total blood volume taken over the 13-month study duration has been changed from 1,398ml to 1,399ml.

26 January 2016	Changes to the Study Protocol The sections of the protocol that have been changed include: • Synopsis – Addition of tertiary objective • Section 4.5 (Aim of project) - Explanation of rationale behind creating an anti-Vi IgG serum standard • Objectives and Endpoints – Addition of tertiary objective • Section 6.3 (Study Design) – Explanation of Group B participants study timeline and sample collection • Section 7 (Participants) – Highlighting differences in inclusion/exclusion criteria for Group B participants compared to Group A participants • Section 8.1-8.8 (Trial procedures) - Explanation of trial procedures for Group B participants • 10.2 (Laboratory) – Serum processing and manufacture of serum standard • Section 11 (Safety reporting) – Minor wording changes • Section 16.6 (Participant Reimbursement) – Inclusion of participant reimbursement for Group B participants New documentation for submission relating to Group B participants: 1. Group B Informed Consent Form 2. Group B Study Information Booklet 3. Group B GP enrolment letter 4. Group B GP study completion letter 5. Group B Diary Card Backup New documentation for submission relating to both Group A and Group B participants: Vaccine Alert Card This vaccine alert card will be given to participants at the vaccination visit for use in case of medical emergency to notify medical staff that the participant is taking part in a study and has received a vaccine (potentially an investigational vaccine). Group A participants will also receive a Medic Alert Card (previously reviewed and approved by REC) to be used from the time of challenge until completion of antibiotics.

11 July 2016	Study Protocol 1. Substantial Amendment to Number of Participants (Section 2, Section 6.1, Section 12.2) 2. Substantial Amendment for Sample Collection (Table 1 and 2 of Section 6.2, Section 7.11) 3. Amendment to S. Typhi clearance stool culture requirements (Section 8.15 and Section 7.8) 4. Amendment to Section 8.5 Group A Randomisation, Blinding and Code Breaking 5. Substantial Amendment to Section 6.2 Group A visit structure Study Information Booklet Page 4 – change to the number of participants enrolled in the study from 99 participants to "a minimum of 105 participants". Page 5 – addition of the word "approximately" to explain that challenge will occur around one month after vaccination, in keeping with the window period changes described in the protocol. Page 13 – the total blood volume collected (maximum) has been changed from 1,399ml to 1,324ml. Page 16 – clarification of payment processing; now stating that payments may take up to 6 weeks to be processed after being requested. Pages 15 and 17 – clarification of clearance stool requirements for all participants as three negative clearance stool samples collected 48 hours apart one week after completion of antibiotics. Consent Quiz Change to question 12. "After completing a course of antibiotics, to ensure you are clear of infection we will: A. Require three stool samples, 48 hours apart"
08 September 2016	Changes to the Study Protocol 1. Substantial Amendment To Randomisation Process (Section 8) 2. Substantial Amendment to Statistical Analysis (Section 12)
24 November 2017	Changes to the Study Protocol 1. Synopsis – Addition of tertiary objective (ii) 2. Section 4.5 (Aim of project) - Explanation of rationale behind boosting Vi-TCV participants with Vi-PS vaccine to investigate the B cell receptor repertoire 3. Objectives and Endpoints – Addition of tertiary objective (ii) 4. Section 6.4 (Study Design) – Explanation of Group C participants study timeline and sample collection 5. Section 7 (Participants) – Highlighting differences in inclusion/exclusion criteria for Group C participants compared with Group A and B participants. Page 2 of 2 6. Section 7.13 – Updates regarding total blood volume collected. • Section 8.1-8.8 (Trial procedures) - Explanation of trial procedures for Group C participants including recruitment. 7. Section 10.3 (Laboratory) – Serum and PBMC processing and generation of Vi-specific monoclonal antibodies 8. Section 11 (Safety reporting) – Participants in Group C will not complete an eDiary. AEs and SAEs will be collected for participants continuing into Group C up until and including their Day 28 post-vaccination. 9. Section 16.6 (Participant Reimbursement) – Inclusion of participant reimbursement for Group C participants In addition to the protocol, new documents have been created for Group C participants due to the difference in study involvement from Groups A or B.

24 May 2018	Changes to the Study Protocol 1. Synopsis – Group C sample size changed to 10-15 2. Section 6.1 (Summary of the study design) – sample size changed to 10-15, deletion of the exclusion criteria (re: taken part in two challenge studies) 3. Section 7.7 (Group C – Exclusion criteria) – deletion of the exclusion criteria (re: taken part in two challenge studies) 4. Section 16.6 (Participant reimbursement) – Group C participants will be reimbursed at the end of their study participation. Wording changed to reflect information in SIB In addition, the Participant Invitation Letter, Participant Email Invitation Text, and SIB-ICF have been changed to reflect these adjustments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Full report of the primary, the secondary end point and the safety reporting are included in the publications.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28965718

http://www.ncbi.nlm.nih.gov/pubmed/34203328

http://www.ncbi.nlm.nih.gov/pubmed/33424833

http://www.ncbi.nlm.nih.gov/pubmed/31781100

http://www.ncbi.nlm.nih.gov/pubmed/33180929

http://www.ncbi.nlm.nih.gov/pubmed/35254093

http://www.ncbi.nlm.nih.gov/pubmed/30252031

http://www.ncbi.nlm.nih.gov/pubmed/31877141

http://www.ncbi.nlm.nih.gov/pubmed/30201529

http://www.ncbi.nlm.nih.gov/pubmed/34714686