Supplementary materials

Contents

1.1 Acknowledgments

The authors acknowledge the valuable contributions made by the TyVAC Nepal Study Team: Aseem Poudel[a], Baibhav Mallik[a], Deepak Ghimire[a], Mamata Yadav[a], Roshan Subedi[a], Sachita Baniya[a], Sunil Thapa[a], Naheeda Haque[a], Aashata Dahal[a], Archana Maharjan[a], Pallavi Gurung[a], Kristina Joshi[a], James Meiring[b], Kopila Lama[c], Jasmine Maharjan[c], Sima Gurung[c], Nissa Humagain[c], Grishu Shrestha[c], Bhola Prasad Koirala[c], Pratikshaya Kisiju[c], Kabita Pathak[c], Surendra Adhikari[c], Anjali Joshi[c], Ashesh Chhetri[c], Alina Maharjan[c], Tan Trinh Van[d].

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1.2 Vaccines administered

The trial vaccine, Vi polysaccharide-tetanus toxoid conjugate vaccine (TCV, Typbar –TCV Bharat-Biotech, Hyderabad, India) was available as a 2.5ml 5-dose vial, with each 0.5 ml vaccine dose containing purified Vi-capsular polysaccharide of S. Typhi Ty2 conjugated to 25 mcg Tetanus Toxoid. Meningococcal capsular Group A conjugate vaccine (Men A; MenAfriVac, Serum Institute of India PVT Ltd) was used as the control vaccine. The Men A vaccine was produced in two formulations; a standard 10 mcg/0.5 ml dose for individuals $\geq$ 1 year of age and a 5 mcg/ 0.5ml dose for children 9 – 24 months of age. In the trial, children under 1 year of age were given the 5 mcg/ 0.5ml dose. The control vaccine was provided in a 10-dose vial of active vaccine, each vial containing a lyophilized powder of meningococcal group A polysaccharide conjugated to tetanus toxoid protein; and, 10 dose ampoules of diluent. Both vaccines were stored at 2 to 8 degrees C and cold chain maintained in vaccination clinics. The diluents were stored at room temperature. Opened vaccine vials were discarded 6 hours after opening. All vaccines were given intramuscularly.

1.3 Samples size assumptions

Sample size calculations were based on the 80% power and 5% alpha with the additional following assumptions:

1. An overall incidence of typhoid fever of 85 cases per year, per 100,000 persons in the entire population, with higher incidence rates in children under 16 years.
2. Age-specific distribution of typhoid cases in Kathmandu determined from published estimates and from unpublished site-specific surveillance data.

3. A direct effect of vaccination of 75% and an indirect effect of 25% based on mathematical modelling.
4. 25% loss to follow-up per year due to participants moving out of the area, based on current surveillance data from Patan.

With the above assumptions the required sample size was 17,395 children. To allow for variation in these assumptions, the total target sample size was increased 20,000 children to increase power (10,000 in each vaccination arm).

1.4 Deaths

A 38-month-old presented with fever, cough, fast and noisy breathing, and increasing lethargy. He was found to be in septic shock with bilateral crepitations on auscultation, and his blood culture revealed a heavy growth of *Staphylococcus aureus*. He was mechanically ventilated, required inotropic support and consequently developed multiple organ dysfunction.

2 Supplementary Figures and Tables

Figure S1 Trial flow diagram

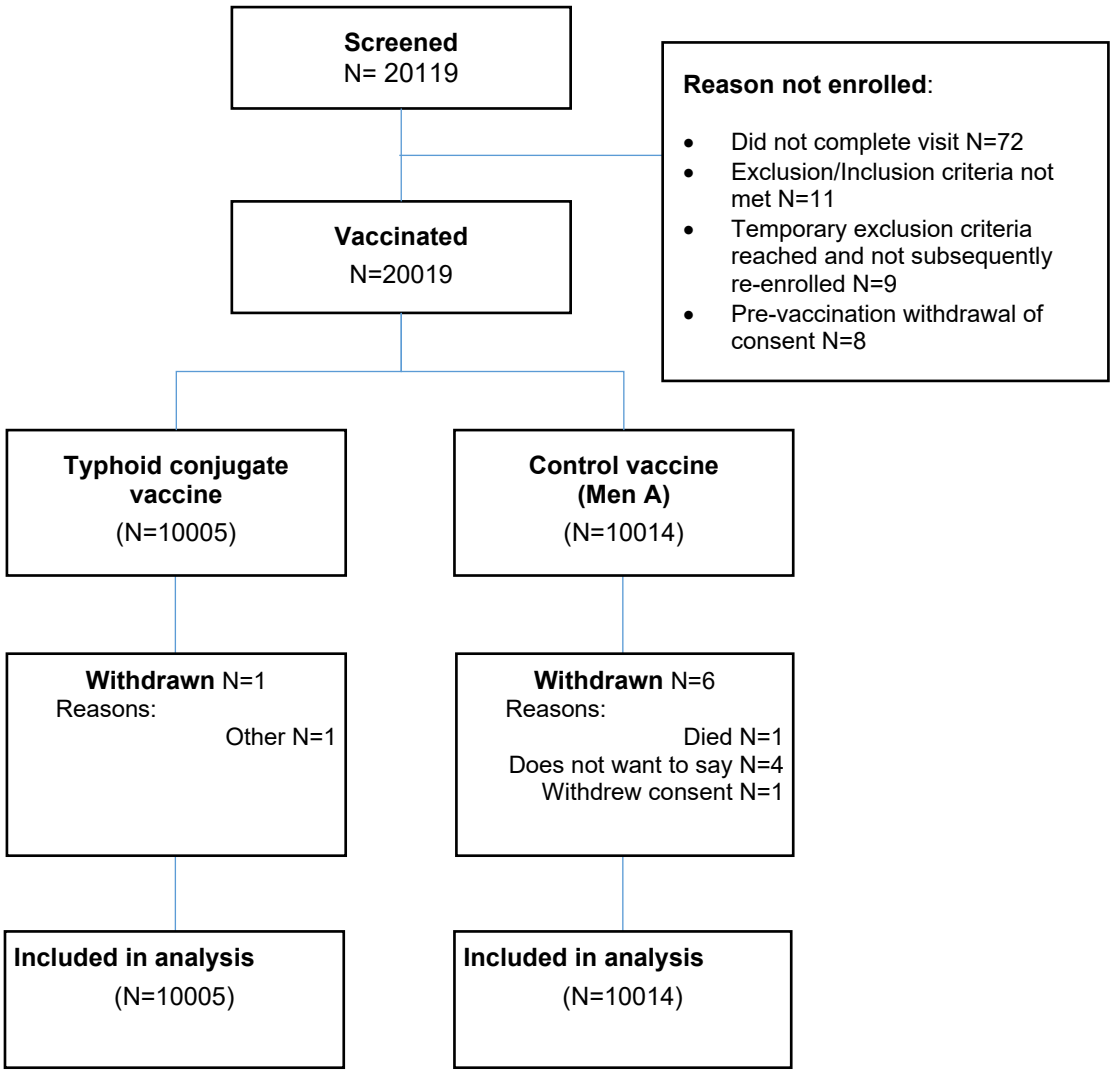

Table S1 Self-Reported solicited adverse reactions within 7 days of vaccination

	TCV		*Men A*		**All**	
	N	***%***	***N***	***%***	***N***	***%***
Pain						
None	8898	94.86	8732	93.26	17630	94.06
Mild	455	4.85	575	6.14	1030	5.50
Moderate	26	0.28	53	0.57	79	0.42
Severe	1	0.01	3	0.03	4	0.02
Swelling						
None	9322	99.38	9273	99.04	18595	99.21
Mild	53	0.57	81	0.87	134	0.72
Moderate	5	0.05	9	0.10	14	0.08
Redness						
None	9369	99.88	9345	99.81	18714	99.85
Mild	10	0.11	14	0.15	24	0.13
Moderate	1	0.01	4	0.04	5	0.03
Self-reported Fever*						
No	8907	94.96	8861	94.64	17768	94.80
Yes	473	5.04	502	5.36	975	5.20
Vomiting						
None	9272	98.85	9213	98.40	18485	98.62
Mild	84	0.90	121	1.29	205	1.09
Moderate	23	0.25	25	0.27	48	0.26
Severe	1	0.01	4	0.04	5	0.03
Diarrhoea						
None	9216	98.25	9195	98.21	18411	98.23
Mild	126	1.34	120	1.28	246	1.31
Moderate	37	0.39	44	0.47	81	0.43
Severe	1	0.01	4	0.04	5	0.03
Less active						
None	9326	99.42	9284	99.16	18610	99.29
Mild	43	0.46	69	0.74	112	0.60
Moderate	11	0.12	8	0.09	19	0.10
Severe	0		2	0.02	2	0.01
Cried persistently						
None	9362	99.81	9328	99.63	18690	99.72
Mild	15	0.16	27	0.29	42	0.22
Moderate	3	0.03	6	0.06	9	0.05
Severe	0		2	0.02	2	0.01
Eating less						

None	9207	98.16	9187	98.12	18394	98.14
Mild	144	1.54	144	1.54	288	1.54
Moderate	29	0.31	29	0.31	58	0.31
Severe	0		3	0.03	3	0.02
More irritable						
None	9348	99.66	9318	99.52	18666	99.59
Mild	26	0.28	40	0.43	66	0.35
Moderate	6	0.06	4	0.04	10	0.05
Severe	0		1	0.01	1	0.01
Generally Unwell						
Well	8780	93.60	8700	92.92	17480	93.26
Unwell	600	6.40	663	7.08	1263	6.74
All	9380	100.00	9363	100.00	18743	100.00

TCV = Typhoid conjugate vaccine. MenA = Group A meningococcal vaccine (control). * Self-reported fever or feeling feverish. No temperatures readings were taken.

Table S2 Serious adverse events (SAEs) occurring within 28 days of vaccination

Characteristics	TCV (N=10005)	Men A (N=10014)	Total (N=20019)
Number of participants with SAEs	7	10	17
Number of SAEs	7	11	18
Severity			
Mild	1	1	2
Moderate	5	7	12
Severe	1	3	4

SAEs were defined as outcomes requiring hospitalization, were life-threatening or resulted in disability, incapacity or death. SAEs were observed by the investigator, members of the study team or reported by parent or guardians by telephone contact.

Severity was defined as the intensity of the specific event as reported by parents or guardian.

One SAE was deemed related to vaccine but remains blinded until the end of the trial and is therefore not reported herein.

TCV = Typhoid conjugate vaccine. Men A = Group A meningococcal vaccine (control)

Table S3 MedDRA coded serious adverse events (SAEs) occurring within 28 days of vaccination

MedDRA System Organ Class and Preferred Terms		TCV	Men A	All
Gastrointestinal disorders	Gastrointestinal disorders	2	2	4
General disorders and administration site conditions	Pyrexia	1	3	4
Infections and infestations	Gastroenteritis	1	2	3
	Pneumonia/LRTI	3	3	6
	URTI /Viral infection	1	1	2
Metabolism and nutrition disorders	Dehydration	1	1	2
Nervous system disorders	Febrile convulsion	2	2	4

*Only events occurring more than once are shown in order to maintain blinding of participants experiencing rare events.

LRTI = Lower respiratory tract infection, URTI = upper respiratory tract infection, TCV = Typhoid conjugate vaccine. Men A = Group A meningococcal vaccine (control)

Table S4 Serious adverse events (SAEs) within 6 months of vaccination

Characteristics	TCV (N=10005)	Men A (N=10014)	Total (N=20019)
Number of participants with SAEs	58	63	121
Number of SAEs	61	71	132
Severity			
Mild	1	4	5
Moderate	59	63	122
Severe	1	4	5

SAEs were defined as outcomes requiring hospitalization, were life-threatening or resulted in disability, incapacity or death. SAEs were observed by the investigator, members of the study team or reported by parent or guardians by telephone contact.

Severity was defined as the intensity of the specific event as reported by parents or guardian.

One SAE was deemed related to vaccine but remains blinded until the end of the trial and is therefore not reported herein.

TCV = Typhoid conjugate vaccine. Men A = Group A meningococcal vaccine (control)

Table S5 MedDRA coded serious adverse events (SAEs) occurring within 6 months of vaccination

		TCV	Men A	All
Gastrointestinal disorders	Gastrointestinal disorders	9	9	18
General disorders and administration site conditions	Pyrexia	11	11	22
Infections and infestations	Appendicitis/appendicectomy	2	1	3
	Bacterial infection	1	1	2
	Gastroenteritis	7	7	14
	Pneumonia/LRTI	21	11	32
	Typhoid fever	1	2	3
	URTI	5	7	12
	Urinary tract infection	3	7	10
Metabolism and nutrition disorders	Dehydration	5	4	9
	Hyponatraemia	1	2	3
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders	1	2	3
Nervous system disorders	Febrile convulsion	5	8	13
	Seizure	1	2	3
Respiratory, thoracic and mediastinal disorders	Bronchospasm	3	5	8
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	2	1	3

*Only events occurring more than once are shown in order to maintain blinding of participants experiencing rare events.

LRTI = Lower respiratory tract infection, URTI = upper respiratory tract infection, TCV = Typhoid conjugate vaccine. Men A = Group A meningococcal vaccine (control)