New findings on immunogenicity of TCV: booster dose in school-aged children and 1 versus 2 dose regimens in HIV-exposed infants

Osward Nyirenda
Blantyre Malaria Project
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TyVAC Typhoid Vaccine Acceleration Consortium
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Main efficacy study design Malawi

Site	Design	Control vaccine	Study duration	Number vaccinated	*Safety and immunogenicity cohort	Age
Malawi	Individually randomized	Group A meningococcal conjugate vaccine (Men-A, MenAfriVac)	Feb 2018 to Sep 2022	28,130	602	9 months to 12 years

*Sub-study of 602 age-stratified children.

Protocol as published in: Meiring et al., *Clin Infect Dis* 2019.

*AEFI: adverse events following immunization

Outcomes

- Primary
  - Vaccine efficacy: Blood-culture confirmed *S.* Typhi among TCV compared to Men-A recipients
  - 18-month analysis (minimum surveillance 18 months; data lock April 3, 2020)*

  48-month analysis (minimum surveillance 48 months; data lock Sept 30, 2022) ***
- Secondary
  - Safety profile adverse events (AEs, n=602) and SAEs (whole cohort n=28,130)**
  - Immunogenicity by serum anti-Vi IgG antibodies at 28 days (n=602)**
  - HIV exposed uninfected child population safety and immunogenicity (n=100)
  - Booster dose safety and immunogenicity (n=136)

*Patel PD, Patel P, Liang Y, et al. Safety and efficacy of a typhoid conjugate vaccine in Malawian children. *New England Journal of Medicine*. 2021

**Nampota-Nkomba N, Laurens MB, et al. Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomised controlled trial. Lancet Global Health. 2022

***Patel P, Liang Y, et al. Efficacy of Typhoid Conjugate Vaccine: Final Analysis of a Four-Year, Randomised Controlled Trial in Malawian Children. Accepted, The Lancet.

Rationale for booster study

WHO research priority: Need for a booster dose?

- Single dose TCV is efficacious for >4 years in all age groups.
- However, the youngest age group aged 9-11 months has a trend toward:
  - Lower point estimate of efficacy at 4 years (NOT statistically significant)
  - Quicker waning of immunogenicity over time (NOT statistically significant)
- But…
  - Will continue to be exposed to *S.* Typhi throughout childhood, and into adulthood
  - Target for routine immunization is 9 months in Malawi
- Therefore…
  - Malawi 9-11-month cohort provides a unique opportunity to evaluate a booster dose of TCV at about 5 years of age (school-age booster).

Booster study methodology

- Study design: Open label
- Study population: Children in Malawi efficacy trial vaccinated with study vaccines between 9-11 months of age
- Main objective: in children who received the Men-A or TCV (Vi-TT) at 9-11 months old.
  - Determine immunogenicity to a dose of TCV given at age 5
    - Serum anti-Vi IgG antibodies
      - Day 0 pre-vaccination
      - Day 28 days post-vaccination
      - Day 120-180 (Day 160) post-vaccination
  - Men-A recipients – 1st dose of TCV (Vi-TT)
  - TCV recipients – Booster dose with TCV (Vi-TT)

Baseline characteristics at Age 5 years

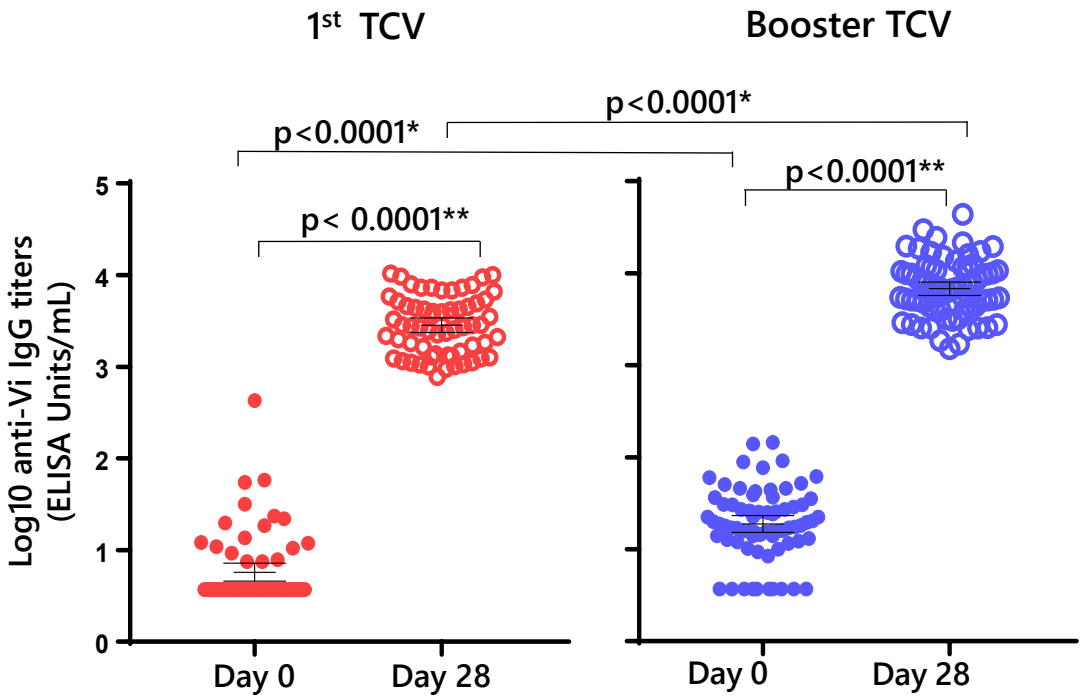
Characteristic	1st TCV (Vi-TT)	Booster TCV (Vi-TT)
Number enrolled & vaccinated	64	72
Female Sex N (%)	30 (46.9%)	32 (44.4%)
Median Age in years (IQR)	5.5 (0.3)	5.5 (0.3)
Detectable* anti-Vi IgG titers	17 [26.6%, (95% CI: 16.3-39.1)]	61 [85.9%, (95% CI: 75.6-93.0)]
Detectable** anti-Vi IgA titers	2 [3.1%, (95% CI: 0.4-10.8)]	29 [40.9%, (95% CI: 29.3-53.2)]
Mean GMT IgG (95% CI)	5.7 (4.6-7.2)	18.8 (15.2-23.2)
Mean GMT IgA (95% CI)	1.7 (1.5-1.9)	2.8 (2.3-3.4)

* ≥7.4 EU/mL ** ≥3.125 EU/mL

Anti-Vi IgG GMT before and 28 days after TCV vaccination given 4+ years after receipt of first TCV or Men-A

	Day 0		Day 28	
	n	GMT EU/ml (95% CI)	n	GMT EU/ml (95% CI)
1st TCV	64	5.7 (4.6-7.2)	62	2837.2 (2360.9-3409.6)
Booster TCV	71	18.8 (15.2-23.2)	71	6794.2 (5738.2-8044.6)

EU: ELISA Units

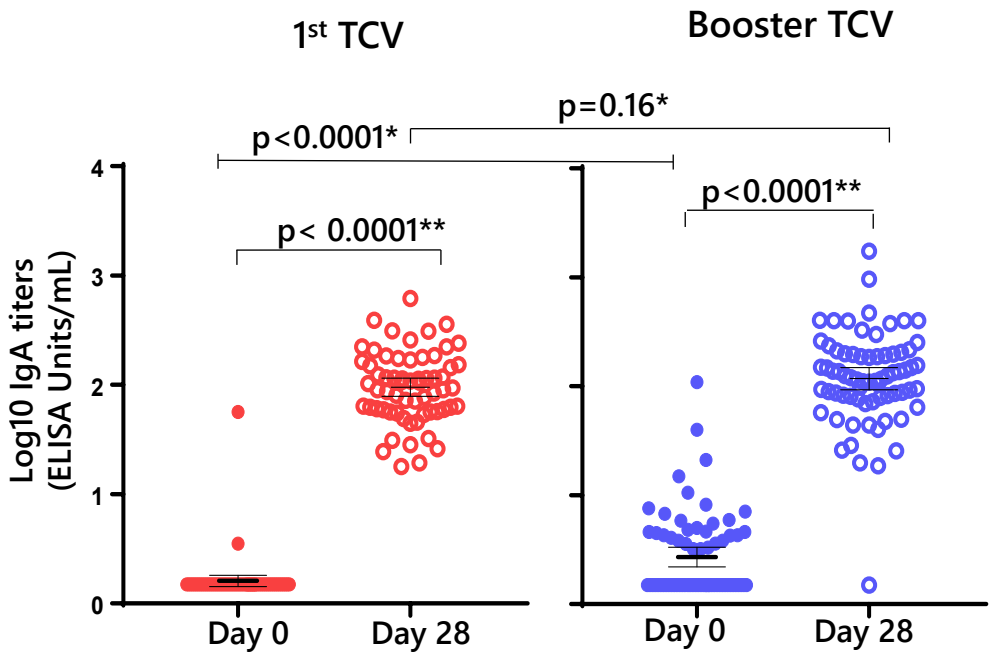


* Using two sample t-test with unequal variances on log10 transformed data
** Using paired t-test on log10 transformed data

Anti-Vi IgA GMT before and 28 days after TCV vaccination given 4+ years after receipt of first TCV or Men-A

	Day 0		Day 28	
	n	GMT EU/ml (95% CI)	n	GMT EU/ml (95% CI)
1st TCV	64	1.7 (1.5-1.9)	62	95.0 (78.5-115.0)
Booster TCV	71	2.8 (2.3-3.4)	71	117.7 (93.0-148.9)

EU: ELISA Units



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Seroconversion and Geometric Mean Fold Rise (GMFR)

Day 0 to Day 28				
	n/N	% Seroconversion* (95% CI)	n	GMFR (95% CI)
Anti Vi IgG				
1st TCV	61/62	98.4 (91.3-100.0)	62	501.5 (373.5-673.4)
Booster TCV	70/70	100.0 (94.9-100.0)	70	370.1 (289.4-473.4)
Anti Vi IgA				
1st TCV	61/62	98.4 (91.3-100.0)	62	56.7 (44.1-73.0)
Booster TCV	67/70	95.7 (88.0-99.1)	70	42.7 (31.6-57.7)

* ≥ 4-fold increase

Conclusions and next Steps

- TCV immunogenic in Malawian children after a first and booster dose at 5 years of age
- Anti-Vi IgG titers after single dose TCV comparable to immunogenicity data from initial Malawi trial
- Booster dose of TCV administered at age 5 after a first dose at 9-11 months of age produced a more robust immune response than a single dose at 5 years of age
- Antibody responses 3-6 months after first or booster dose are being analyzed

Rationale for one and two dose study in HIV exposed uninfected children

- Single dose TCV is:
  - Efficacious for >4 years after administration
  - Immunogenic in HIV unexposed uninfected children (HUU)
  - Safe in HUU children
- However,
  - TCV is being rolled out in countries where HIV and typhoid are co-endemic
  - High population of HIV exposed uninfected infants and children (HEU)
  - TCV response may differ by HIV exposure status
- Therefore, the following research questions arose:

  - Is TCV immunogenicity in HEU children comparable to HUU children?
  - Is more than one dose of TCV needed in HEU children?

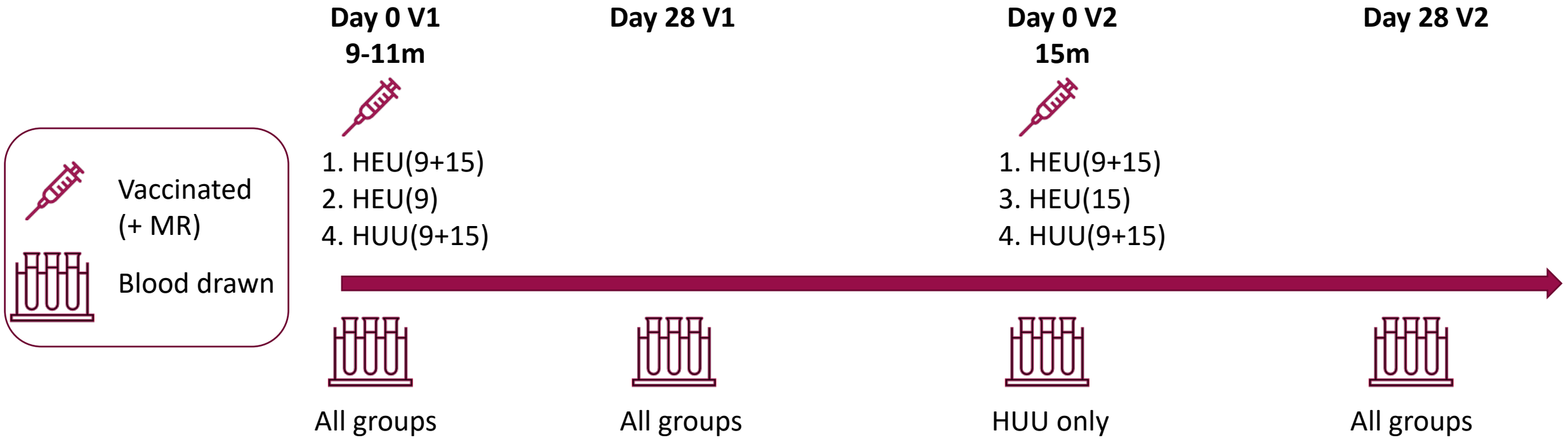
Open-label immunogenicity study of one and two doses of TCV in HEU and HUU Malawian children – HIV Substudy

- Study Objectives:
  - Determine typhoid-specific antibody responses to one and two doses of Vi-TCV - anti-Vi IgG titers (VaccZyme kit)

- Study population: Malawian infants aged 9-11 months
  - HEU: documented maternal history of HIV
  - HUU: documented maternal HIV test <3m from enrollment day
  - All: non-detectable infant HIV viral load at enrollment

- Vaccination groups (measles rubella co-administered)
  1. HEU-9,15: TCV at 9-11 months and 15 months
  2. HEU-9: TCV at 9-11 months only
  3. HEU-15: TCV at 15 months only
  4. HUU-9,15: TCV at 9-11 months and 15 months

HIV Substudy Methodology



Blood draws

- All: Anti-Vi IgG, HIV viral load
- HUU: Maternal HIV test at enrollment

Distribution of Analyzed Children by Cohort Type (Before vs During COVID-19 Pandemic)

	Day 0V1			Day 28V1			Day 28V2		
	Before Pandemic N(%)	**During Pandemic N(%)**	**Total**	**Before Pandemic N(%)**	**During Pandemic N(%)**	**Total**	**Before Pandemic N(%)**	**During Pandemic N(%)**	**Total**
HEU (9+15)	22 (45.8)	26 (54.2)	48	16 (38.1)	26 (61.9)	42	0 (0.0)	24 (100.0)	24
HEU(9)	20 (42.6)	27 (57.5)	47	14 (34.2)	27 (65.9)	41	0 (0.0)	27 (100.0)	27
HEU(15)	21 (48.8)	22 (51.2)	43	15 (40.5)	22 (59.5)	37	0 (0.0)	22 (100.0)	22
HUU(9+15)	0 (0.0)	25 (100.0)	25	0 (0.0)	24 (100.0)	24	0 (0.0)	23 (100.0)	23

- Original cohort recruited before COVID-19 pandemic enrolled between December 2019 – late March 2020
- Study paused due to pandemic related disruptions, then restarted 2021
- Cohort recruited during pandemic in restarted study enrolled between March 2021 – late August 2021

Anti-Vi IgG Geometric Mean Titers (GMT) Before and 28 days after vaccination – V1 and V2

	Day 0 V1 – 9-11m		Day 28 V1		Day 0 V2 – 15m		Day 28 V2	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
1. HEU-9,15	48	5.0 (3.7, 6.7)	42	3136.6 (2037.2, 4829.4)	NA	NA	24	3498.6 (2758.1, 4438.0)
2. HEU-9	47	4.3 (3.8, 4.9)	41	3086.6 (1986.2, 4796.6)	NA	NA	27	292.1 (217.5, 392.2)
3. HEU-15	43	4.9 (4.0, 6.1)	37	4.6 (3.3, 6.4)	NA	NA	22	4117.6 (2362.8, 7175.8)
4. HUU-9,15	25	4.1 (3.5, 4.9)	24	3493.7 (2729.4, 4471.9)	24	333.7 (236.1, 471.6)	23	2572.0 (1844.6, 3586.2)

Data are mean (95% CI). n=number of participants. GMT=geometric mean titer. CI=confidence interval. HEU=HIV exposed, uninfected. HU=HIV unexposed. NA=not applicable.

*Only HU-Group D had blood sample collected at Day 180.

Anti-Vi IgG Seroconversion and Geometric Mean Fold Rise 28 days after vaccination – V1 and V2

	From Day 0 V1 to Day 28 V1				From Day 0 V1 to Day 28 V2			
	n/N	% Seroconversion (≥ 4-fold increase)	n	GMFR	n/N	% Seroconversion (≥ 4-fold increase)	n	GMFR
1. HEU-9,15	40/42	95.2 (83.8, 99.4)	42	602.6 (350.3, 1036.4)	24/24	100 (85.8, 100.0)	24	855.5 (649.0, 1127.8)
2. HEU-9	40/41	97.6 (87.1, 99.9)	41	728.4 (466.2, 1137.9)	27/27	100 (87.2, 100.0)	27	70.2 (49.1, 100.3)
3. HEU-15	1/37	2.70 (0.1, 14.2)	37	0.9248 (0.6, 1.4)	22/22	100 (85.6, 100.0)	22	837.7 (417.4, 1681.0)
4. HUU-9,15	24/24	100.0 (85.8, 100.0)	24	842.7 (634.1, 1119.9)	23/23	100.0 (85.2, 100.0)	23	617.3 (400.6, 951.2)

Seroconversion: 4x rise in titers from day 0. GMFR = geometric mean fold rise in titers from day 0 (mean and 95% CI) n=number of participants. N= total number.

Conclusions

- TCV was safe and immunogenic in Malawian children
- Anti-Vi titres were comparable in HEU and HUU children after one and two dose TCV administration
- Seroconversion was sustained for at least six months in HEU children after single dose TCV at 9-11 months
  - Current routine TCV schedule in Malawi
- Trends in titers comparable to results of Nepal two-dose immunogenicity trial

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Learn more at:

http://takeontyphoid.org

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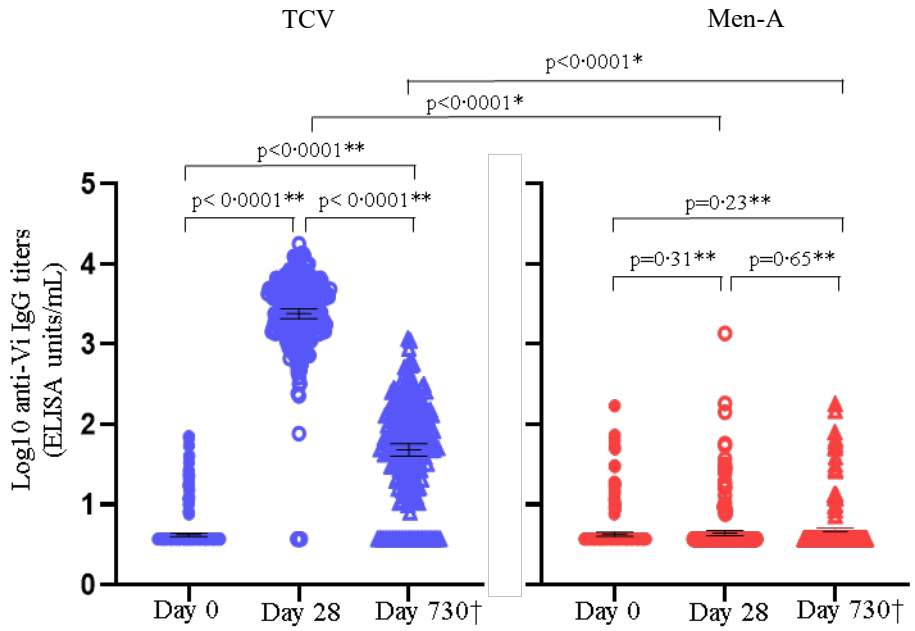
Extra Slides

Previous data: Anti-Vi IgG Geometric Mean Titers (GMT) Baseline, 28, and 730+ days after vaccination (N=597)

	Day 0		Day 28		Day 730†	
	n	GMT EU/ml (95% CI)	n	GMT EU/ml (95% CI)	n	GMT EU/ml (95% CI)
9-11 months						
TCV	105	3·9 (3·7–4·1)	98	2594·8 (2115·8–3182·2)	60	24·2 (18·3–31·9)
Men-A	93	4·0 (3·7–4·4)	83	4·0 (3·7–4·3)	53	3·9 (3·6–4·3)
1-5 years						
TCV	99	4·2 (3·8–4·7)	91	2085·9 (1635·6–2660·2)	74	36·9 (27·1–50·3)
Men-A	101	4·4 (3·9–4·9)	99	4·6 (3·9–5·4)	77	4·8 (4·1–5·5)
6-12 years						
TCV	100	4·5 (4·0–5·0)	98	2478·7 (1953·0–3145·9)	87	96·3 (73·2–126·7)
Men-A	99	4·4 (3·9–4·9)	93	4·4 (4·0–4·9)	78	4·9 (4·1–5·9)

† 730-1035 days post-vaccination; EU: ELISA Units

85 children included in Booster study



* Using two sample t-test with unequal variances on log10 transformed data
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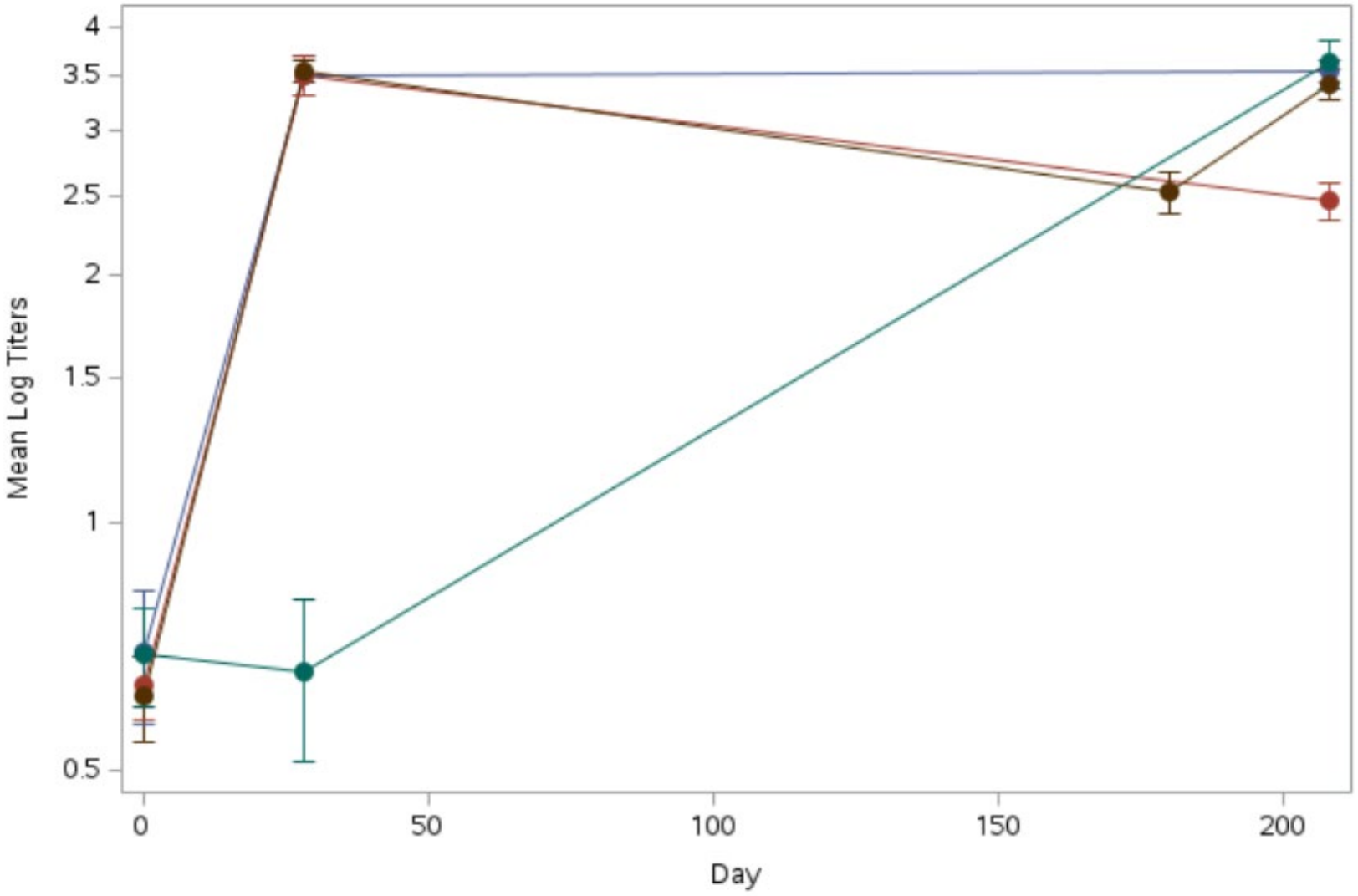
Baseline characteristics

	HIV Exposed Uninfected			HIV Unexposed	
Characteristic	**HEU-9,15**	**HEU-9**	**HEU-15**	**HUU-9,15**	**P-value**
Number enrolled	53	54	54	29	
Number vaccinated	48	50	43	25	
Median Age (IQR)	9.4 (0.7)	9.2 (0.8)	9.4 (0.7)	9.6 (0.7)	0.2
Sex N[%, (95% CI)]					
Male	25 [52.1 (37.2, 66.7)]	18 [38.3 (24.5, 53.6)]	26 [60.5 (44.4, 75.0)]	16 [64.0 (42.5, 82.0)]	0.7
Female	23 [47.9 (33.3, 62.8)]	29 [61.7 (46.4, 75.5)]	17 [39.5 (25.0, 55.6)]	9 [36.0 (18.0, 57.5)]	
Mean length (STD)	69.4 (3.3)	68.8 (2.6)	69.7 (2.9)	71.4 (2.8)	0.007
Mean weight (STD)	8.1 (1.2)	8.1 (1.0)	8.3 (1.1)	9.1 (1.4)	0.003
Mean MUAC (STD)	14.7 (1.3)	14.1 (1.1)	14.7 (1.2)	15.3 (1.4)	0,047
Had detectable titer N[%, (95% CI)]	7 [14.6 (6.1, 27.8)]	6 [12.8 (4.8, 25.7)]	8 [18.6 (8.4, 33.4)]	2 [8.0, (0.98, 26.0)]	<0.001
Data collected at day 0 of enrollment in the study. Percent with detectable titers defined as individuals that had ≥7.4 U/mL IgG, detected using S. Typhi Vi VaccZyme IgG EIA kit.					

Mean Log Titers



Group	Line Color
HEU(9+15)	
HEU(9)	
HEU(15)	
HUU	

DAY 0: no difference between groups.

Day 28V1: no difference between vaccinated groups

- HEU-9,15, HEU-9, HUU-9,15

Day 28V2: no difference between vaccinated groups

- HEU-9,15, HEU-15, HUU-9,15