Durability of Anti-Vi IgG and IgA Responses in 15-month-old Children Vaccinated with a Typhoid Conjugate Vaccine in Burkina Faso

Alphonse OUEDRAOGO MD, PhD
Groupe de Recherche Action en Santé (GRAS)
Ouagadougou, Burkina Faso, West Africa

TyVAC Typhoid Vaccine Acceleration Consortium

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Introduction

- Typhoid is a public health threat that disproportionately impacts children in sub-Saharan Africa.
- Typhoid conjugate vaccine (TCV) has demonstrated efficacy against *S.* Typhi.
- TCV-induced IgA and IgG responses correlate to protection in a controlled human infection model (Jin et al., 2021).

Study Overview and Aims

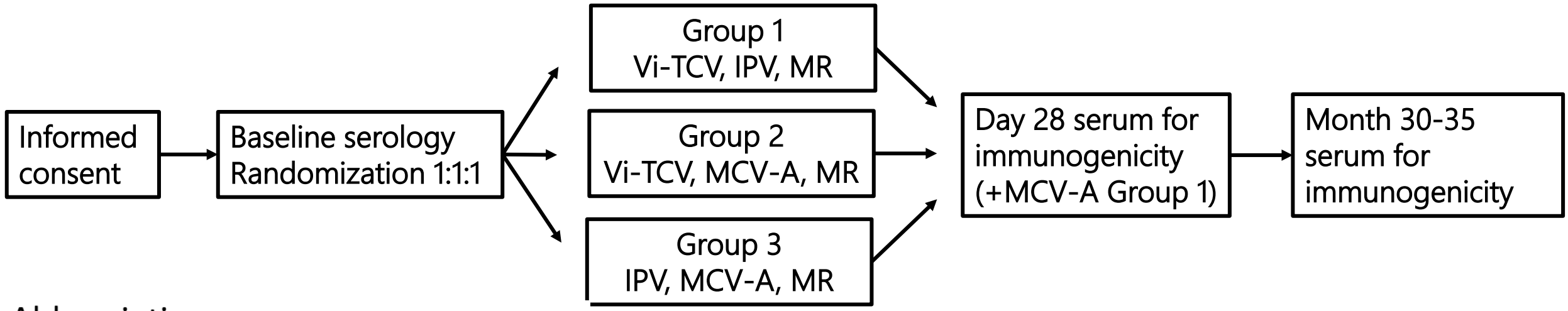
- Aim
  - Assess long-term immunogenicity of Vi-TT, co-administered with EPI vaccines, among healthy children from the 15 - 23 months of age cohort in Burkina Faso
- Objective
  - Compare anti-Vi IgA and IgG responses at 28 days and 30-35 months after Vi-TT versus control vaccination
- Study Vaccines
  - Typbar TCV® (Vi-TT, Bharat Biotech, Hyderabad, India)
  - Inactivated Poliovirus Vaccine (IPV)

Site-Specific Information

- Groupe de Recherche Action en Santé (GRAS), Burkina Faso
- Schiphra Hospital in Ouagadougou, Burkina Faso
- Center for Vaccine Development and Global Health, University of Maryland School of Medicine

Trial Design

Infants 15-23 months of age who present for second MR and MCV-A EPI visit



Abbreviations

MR: Measles-rubella vaccine
YFV: Yellow fever vaccine
EPI: Expanded Program on Immunization
Vi-TCV: Vi-typhoid conjugate vaccine
IPV: Inactivated polio vaccine
MCV-A: Meningococcal A conjugate vaccine

Methods

- Symptoms solicited at days 3 & 7
  - Local: pain/tenderness, swelling and redness at injection site
  - Systemic: fever or feverishness, and irritability
- TCV immunogenicity
  - Enzyme-linked immunosorbent assay (ELISA) at days 0, 28 and 30-35 months
  - VaccZyme *Salmonella* Typhi anti-Vi IgG & IgA ELISA
- Seroconversion at day 28 and 30-35 months
  - Seroconversion: ≥4-fold rise in anti-Vi IgG antibody titer from baseline day 0
  - Participants re-contacted & re-enrolled for immunogenicity at 30-35 months

UMB/Elizabeth Rotrosen

Results

Study Time Period: 03 December 2018 - 24 September 2021

Baseline Demographics

	Group 1: TCV +IPV (delayed MCV-A)	Group 2: TCV +MCV-A	Group 3: MCV-A +IPV
Vaccinated	49	50	51
Attended final visit (%)	38 (78%)	33 (66%)	44 (86%)
Female Sex (%)	16 (42%)	15 (45%)	26 (59%)
Age at enrollment ± SD (months)	16.4 ±1.7	16.1 ±1.7	15.7 ±1.2
Age final visit ± SD (months)	47.4 ±1.6	47.3 ±1.8	46.6 ±0.9

Anti-Vi IgG Seroconversion at 28 days and 30-35 months after vaccination

	Day 0 to 28		Day 0 to 30-35 months	
	n/N	Percent (95%CI)	n/N	Percent (95%CI)
Group 1: TCV +IPV (delayed MCV-A)	44/47*	93.6% (82.5-98.7)	34/38	89.5% (74.2-97.1)
Group 2: TCV +MCV-A	48/50	96.0% (86.3-99.5)	29/33	87.9% (71.8-96.6)
Group 3: MCV-A +IPV	2/51	3.9% (0.5-13.5)	3/44	6.8% (1.4-18.7)

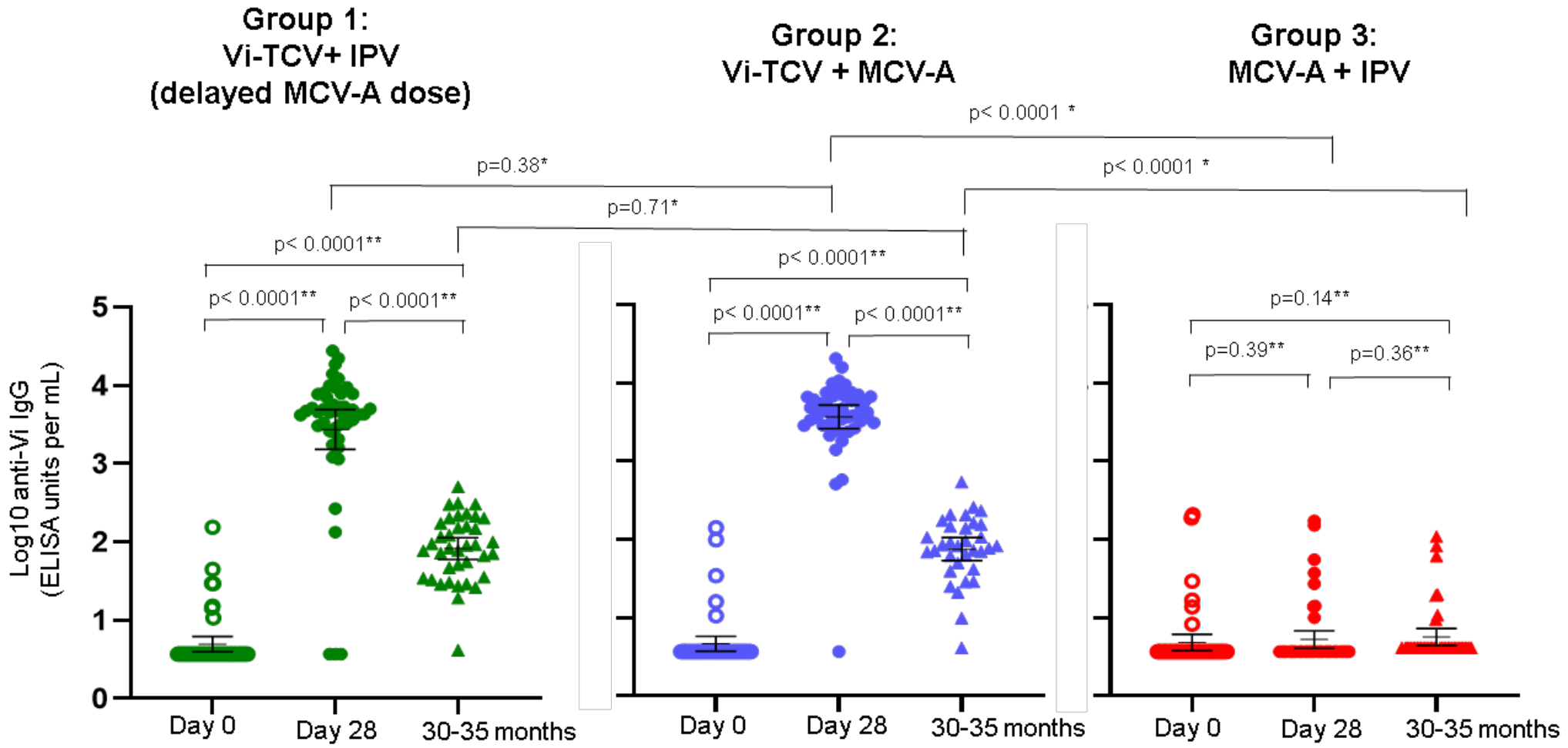
Data are % (95% CI). n=number of participants. N= total number. CI=confidence interval.
*One participant excluded in analysis for late Day 28 visit.

Anti-Vi IgG Antibody Titers
Baseline (day 0), and 28 days & 30-35 months after vaccination

	Day 0		Day 28		30-35 months	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT(95% CI)
Group 1: TCV +IPV (delayed MCV-A)	49	5.0 (3.9-6.2)	47*	2754.1 (1537.3-4934.1)	38	82.6 (60.0-113.6)
Group 2: TCV +MCV-A	50	4.7 (3.7-5.8)	50	3707.3 (2632.0-5222.0)	33	75.6 (53.7-106.6)
Group 3: MCV-A +IPV	51	4.8 (3.8-6.2)	51	5.3 (4.1-6.9)	44	5.7 (4.4-7.3)

Data are mean (95% CI). n=number of participants. GMT=geometric mean titer. CI=confidence interval.
*One participant excluded in analysis for late Day 28 visit.

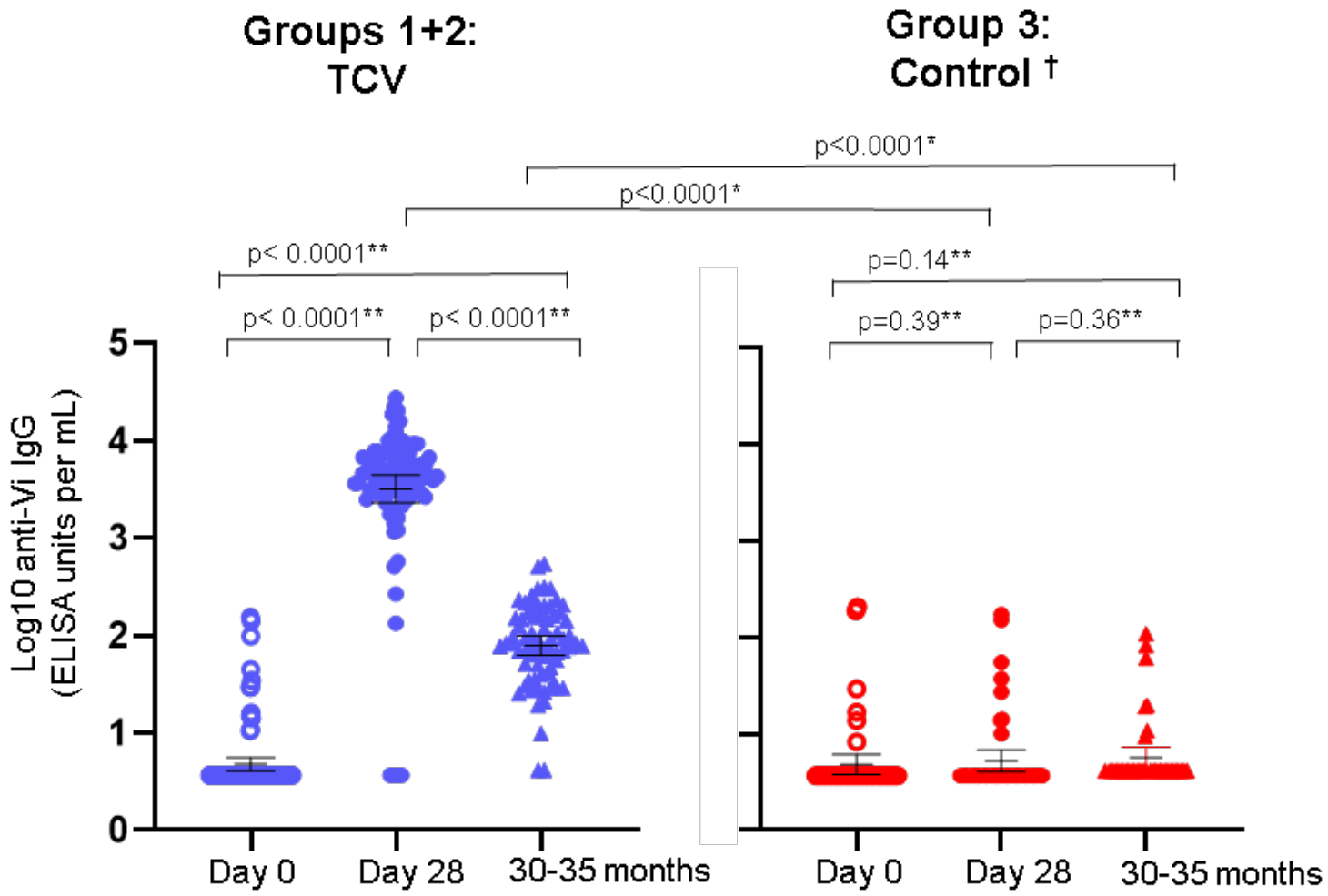
Anti-Vi IgG Antibody Titers
Baseline (day 0), and 28 days & 30-35 months after vaccination



* Using two sample t-test with unequal variances on log_{10} transformed data

** Using paired t-test on log_{10} transformed data

Anti-Vi IgG Antibody Titers
Baseline (day 0), and 28 days & 30-35 months after vaccination



* Using two sample t-test with unequal variances on $\log_{10}$ transformed data

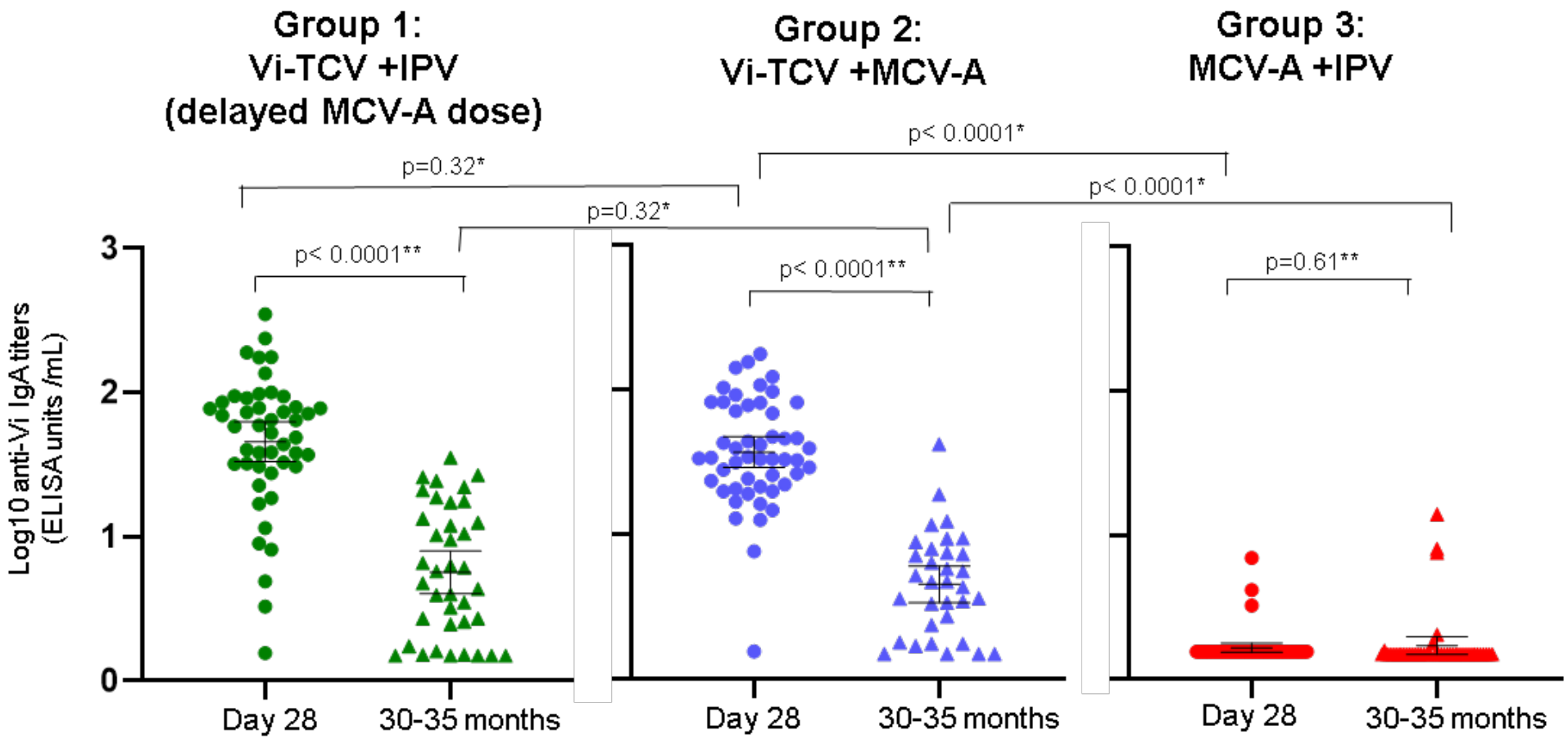
** Using paired t-test on $\log_{10}$ transformed data † MCV-A and IPV

Anti-Vi IgA Antibody Titers
28 days & 30-35 months after vaccination

	Day 28		30-35 months	
	n	GMT (95% CI)	n	GMT(95% CI)
Group 1: TCV +IPV (delayed MCV-A)	47*	45.5 (33.1- 62.4)	38	5.7 (4.0-8.0)
Group 2: TCV +MCV-A	50	37.3 (29.3- 47.6)	33	4.5 (3.4-6.1)
Group 3: MCV-A +IPV	51	1.7 (1.5-1.8)	44	1.7 (1.5-2.0)

Data are mean (95% CI). n=number of participants. CI=confidence interval. GMT=geometric mean titre.
*One participant excluded in analysis for late Day 28 visit.

Anti-Vi IgA Antibody Titers
28 days & 30-35 months after vaccination



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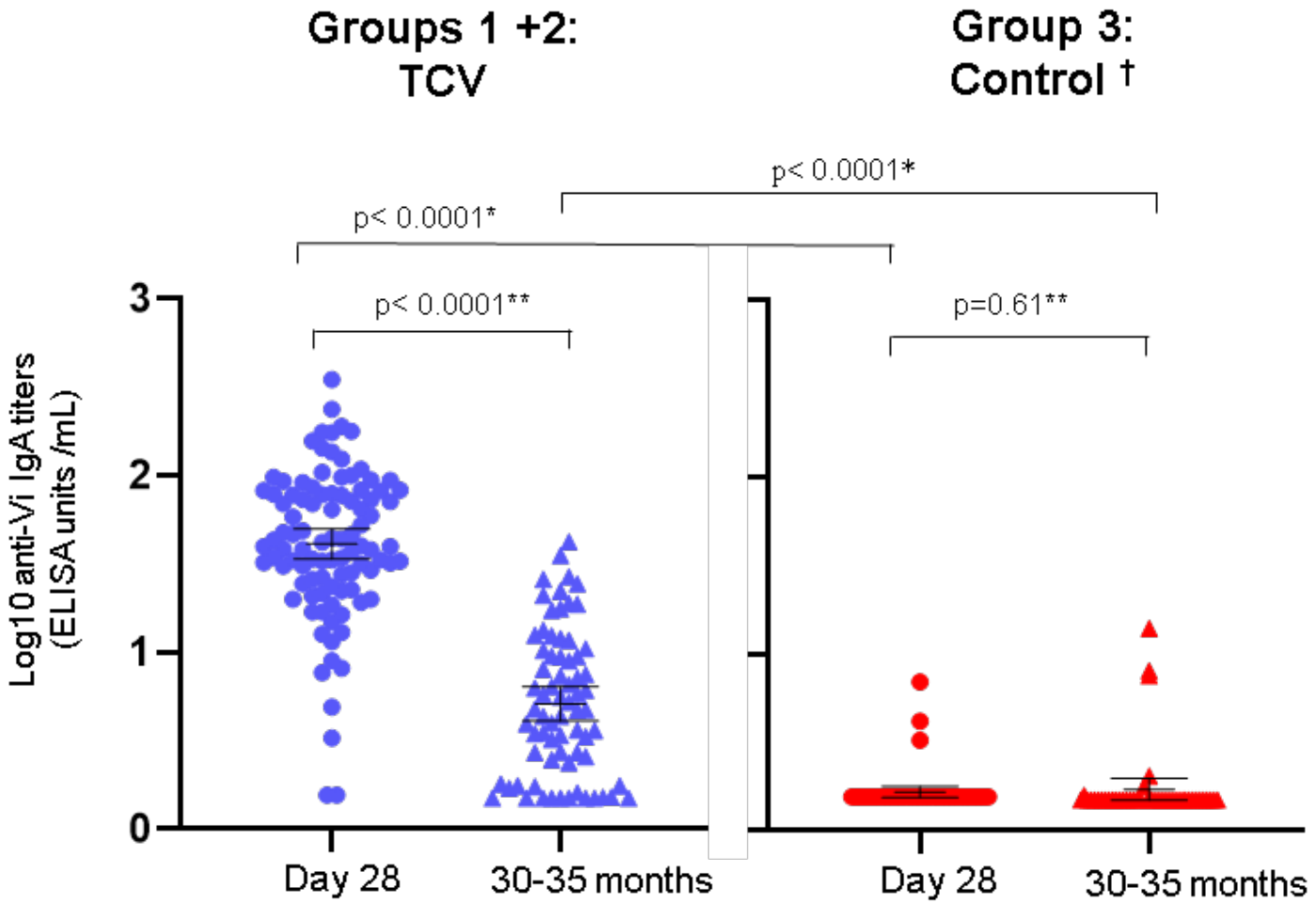
Anti-Vi IgA Antibody Titers
28 days & 30-35 months after vaccination



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** Using paired t-test on $\log_{10}$ transformed data † MCV-A and IPV.

Comparison: Nepal & Burkina Faso Anti-Vi IgG Antibody Titers Baseline (day 0), and 28 days & 30-35/18 months after vaccination

Burkina Faso	Day 0		Day 28		30-35 months		% Seroconversion			
15 months	n	GMT	n	GMT	n	GMT	n/N	Day 0 to 28	n/N	Day 0 to 30-35 months
Groups 1+2: TCV	99	4.8 (4.1-5.6)	97*	3210.1 (2311.7-4457.6)	71	79.3 (63.1-99.6)	92/97	94.9 (88.4-98.3)	63/71	88.7 (79.0-95.1)
Group 3: Control†	51	4.8 (3.8-6.2)	51	5.3 (4.1-6.9)	44	5.7 (4.4-7.3)	2/51	3.9 (0.5-13.5)	3/44	6·8 (1.4-18.7)

Data are mean (95% CI) or % (95% CI). n=number of participants. N=total number. CI=confidence interval. GMT=geometric mean titre.
*One participant excluded in analysis for late Day 28 visit. † MCV-A and IPV.

Nepal*	Day 0		Day 28		18 months		% Seroconversion			
< 5 years	n	GMC	n	GMC	n	GMC	n/N	Day 0 to 28	n/N	Day 0 to 18 months
TCV	99	4.5 (3.9-5.1)	67	1488.3 (1160.8-1908.2)	76	81.0 (67.3-97.6)	54/55	98	55/58	94
MCV-A	66	4.6 (3·9-5·6)	49	4.5 (3.8-5.2)	57	4.5 (3.8-5.4)	0/46	0	1/47	2

Data are mean (95% CI) or % (95% CI). n=number of participants. N=total number. GMC=geometric mean concentration. CI=confidence interval.
*Shakya M, Colin-Jones R, Theiss-Nyland K, et al. Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal. *N Engl J Med* 2019.

Comparison: Nepal & Burkina Faso Anti-Vi IgA Antibody Titers before (day 0), 28 days and 18/30-35 months after vaccination

Burkina Faso	Day 28		30-35 months	
15-month cohort	n	GMT	n	GMT
Groups 1 +2: TCV	97*	41.1 (33.8-49.9)	71	5.1 (4.1-6.4)
Group 3: Control†	51	1.7 (1.5-1.8)	44	1.7 (1.5-2.0)

Data are mean (95% CI). n=number of participants. CI=confidence interval. GMT=geometric mean titre.
*One participant excluded in analysis for late Day 28 visit. † MCV-A and IPV.

Nepal*	Day 0		Day 28		18 months	
< 5 years	n	GMC	n	GMC	n	GMC
TCV	55	1.6 (1.5-1.9)	55	46.8 (34.5-63.3)	76	6.0 (4.8-7.5)
MCV-A	46	1.6 (1.5-1.7)	46	1.7 (1.5-1.8)	57	1.7 (1.5-1.8)

Data are mean (95% CI) or % (95% CI). n=number of participants. N=total number. GMC=geometric mean concentration. CI=confidence interval.
*Shakya M, Colin-Jones R, Theiss-Nyland K, et al. Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal. *N Engl J Med* 2019.

Conclusions

- TCV is highly immunogenic in young children
- Demonstrated durability of the immune response for ~3 years
- TCV efficacy + durability = longer-term protection
- 4-year efficacy data together with this evidence of durable immunogenicity in Burkina Faso when co-administered with routine immunizations makes a strong case for TCV introduction in endemic countries
- Burkina Faso has submitted an application to Gavi for TCV and intends to implement it during the 9-month vaccination visit in January 2025.

Authors

GRAS
Amidou Diarra
Issa Nébié
Nouhoun Barry
Jean Moise Kabore
Alfred B. Tiono
Sodiomon B. Sirima

CVD
Shrimati Datta
Yuanyuan Liang
Ifayet Mayo
Jennifer J. Oshinsky
J. Kathleen Tracy
Tsion Girmay
Marcela F. Pasetti
Leslie P. Jamka
Kathleen M. Neuzil
Matthew B. Laurens

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BRIEF REPORT

Durable Anti-Vi IgG and IgA Antibody Responses in 15-Month-Old Children Vaccinated With Typhoid Conjugate Vaccine in Burkina Faso

Alphonse Ouedraogo,[1] Amidou Diarra,[1] Issa Nébié,[1] Nouhoun Barry,[1] Jean Moise Kabore,[1] Alfred B. Tiono,[1] Shrimati Datta,[2] Yuanyuan Liang,[2,3] Ifayet Mayo,[2] Jennifer J. Oshinsky,[2] J. Kathleen Tracy,[2] Tsion Girmay,[2] Marcela F. Pasetti,[2] Leslie P. Jamka,[2] Kathleen M. Neuzil,[2] Sodiomon B. Sirima,[1,†] and Matthew B. Laurens[2,†]

[1]Groupe de Recherche Action en Santé, Ouagadougou, Burkina Faso, [2]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland, USA, [3]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, USA

[4]. In Burkina Faso, TCV was safe and immunogenic when coadministered with measles-rubella (MR) and yellow fever vaccines at 9–11 months [5], and with MR and meningococcal serogroup A conjugate vaccine (MCV-A) at 15–23 months in a double-blind, randomized, controlled Phase 2 clinical trial [6].

We evaluated anti-Vi IgA antibodies 28 days after vaccination, and anti-Vi IgG and IgA antibodies 30–35 months post-vaccination in participants from a clinical trial where TCV was coadministered with routine MR vaccine, with and without MCV-A, at the 15-month vaccination visit [6]. The study was approved by ethics committees in Burkina Faso and Maryland, USA. Parents/guardians of study participants provided informed consent (Clinicaltrials.gov NCT03614533).

METHODS

Detailed methods of this randomized, double-blinded, controlled, Phase 2 trial were published previously [6]. Briefly,

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http://takeontyphoid.org

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Extra Slides

TCV Immunogenicity in Malawian Children

	Group 1 TCV		Group 2 MCV-A	
	n or n/N	Mean or percentage (95% CI)	n or n/N	Mean or percentage (95% CI)
Age stratum: 1–5 years				
GMT				
Day 28	91	2085·9 (1635·6–2660·2)	99	4·6 (3·9–5·4)
Day 730*	74	36·9 (27·1–50·3)	77	4·8 (4·1–5·5)
GMFR				
Day 0 to 28	90	490·6 (378·6–635·6)	95	1·1 (0·9–1·2)
Day 0 to 730*	74	8·9 (6·5–12·1)	74	1·0 (0·9–1·2)
Seroconversion four times or higher increase from:				
Day 0 to 28	88/90	97·8 (92·3–99·4)	1/95	1·1 (0·2–5·7)
Day 0 to 730*	58/74	78·4 (67·7–86·2)	3/74	4·1 (1·4–11·3)

Data are mean (95% CI) or percentage (95% CI). TCV=typhoid conjugate vaccine. MCV-A=meningococcal serogroup A conjugate vaccine. n=number of participants. N=total number. GMT=geometric mean titre. GMFR=geometric mean-fold rise. *Day 730 visits were extended by a year because of COVID-19 restrictions (730–1035 days).

***Table 2:* Anti-Vi immunoglobulin G antibody immunogenicity 28 days and 730–1035 days after vaccination by ELISA, in the intention-to-treat population**

Nampota-Nkomba N, 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 Glob Health. 2022 Sep;10(9):e1326-e1335.