Safety of a Typhoid Conjugate Vaccine Booster Dose in Malawian Children

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TyVAC Typhoid Vaccine Acceleration Consortium

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Photo: PATH/Nurudeen Sanni

Main efficacy study design Malawi

Site	Design	Control vaccine	Study duration	Number vaccinated	*AEFI cohort	Age
Malawi	Individually randomized	Group A meningococcal vaccine (Men-A, MenAfriVac)	Feb 2018 – Sep 2022	28,130	602	9 months – 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

Efficacy against blood-culture confirmed S Typhi by age at vaccination, ITT analysis – 48-52 months

Comparatively lower efficacy in younger children – not statistically significant.

Age (years)	<2		2-<5		5 and over	
	TCV	Men-A	TCV	Men-A	TCV	Men-A
N	1555	1600	3503	3579	9011	8882
S Typhi cases	4	14	5	25	15	71
Incidence per 100,000 person-years (95% CI)	61 (23, 162)	207 (122, 349)	33 (14, 80)	163 (110, 242)	39 (23, 64)	186 (148, 235)
Vaccine efficacy (95% CI)	70.6% (6.4%, 93.0%)		79.6% (45.8%, 93.9%)		79.3% (63.5%, 89.0%)	

Patel PDP et al. Efficacy of Typhoid Conjugate Vaccine: Final Analysis of a Four-Year, Randomised Controlled Trial in Malawian Children. SSRN 2023.

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

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Summary

Background Typhoid fever is a substantial public health problem in Africa, yet there are few clinical trials of typhoid conjugate vaccine (TCV). We assessed immunogenicity and safety of Typbar TCV in Malawi.

Methods This substudy was nested within a phase 3, double-blind, parallel design, randomised controlled trial of TCV in children from Ndirande Health Centre in Ndirande township, Blantyre, Malawi. To be eligible, participants had to be aged between 9 months and 12 years with no known immunosuppression or chronic health conditions, including HIV or severe malnutrition; eligible participants were enrolled into three strata of approximately 200 children (9–11 months, 1–5 years, and 6–12 years), randomly assigned (1:1) to receive TCV or control (meningococcal serogroup A conjugate vaccine [MCV-A]) intramuscularly. Serum was collected before vaccination and at 28 days and 730–1035 days after vaccination to measure anti-Vi antibodies by ELISA. Because of COVID-19, day 730 visits were extended up to 1035 days. This nested substudy evaluated reactogenicity, safety, and immunogenicity by age stratum. Safety outcomes, analysed in the intention-to-treat population, included solicited adverse events within 7 days of vaccination (assessed on 3 separate days) and unsolicited adverse events within 28 days of vaccination. This trial is registered with ClinicalTrials.gov, NCT03299426.

Findings Between Feb 22 and Sept 6, 2018, 664 participants were screened, and 631 participants were enrolled and randomly assigned (320 to the TCV group and 311 to the MCV-A group). 305 participants in the TCV group and 297 participants in the MCV-A group were vaccinated. Among TCV recipients, anti-Vi IgG geometric mean titres increased more than 500 times from 4·2 ELISA units (EU)/mL (95% CI 4·0–4·4) at baseline to 2383·7 EU/mL (2087·2–2722·3) at day 28, then decreased to 48·0 EU/mL (39·9–57·8) at day 730–1035, remaining more than 11 times higher than baseline. Among MCV-A recipients, anti-Vi IgG titres remained unchanged: 4·3 EU/mL (4·0–4·5) at baseline, 4·4 EU/mL (4·0–4·7) on day 28, and 4·6 EU/mL (4·2–5·0) on day 730–1035. TCV and MCV-A recipients had similar solicited local (eight [3%] of 304, 95% CI 1·3–5·1 and three [1%] of 293, 0·4–3·0) and systemic (27 [9%] of 304, 6·2–12·6 and 27 [9%] of 293, 6·4–13·1) reactogenicity. Related unsolicited adverse events occurred similarly in TCV and MCV-A recipients in eight (3%) of 304 (1·3–5·1) and eight (3%) of 293 (1·4–5·3).

Interpretation This study provides evidence of TCV safety, tolerability, and immunogenicity up to 730–1035 days in Malawian children aged 9 months to 12 years.

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Lancet Glob Health 2022; 10: 1326–35

See **Comment** page e1224

*Deceased

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24 to 34 months of safety and immunogenicity follow-up published in Lancet Global Health 2022

Safe, tolerable, and immunogenic up to 730–1035 days post-vaccination

Anti-Vi immunoglobulin G antibody immunogenicity by age at vaccination, PP analysis – 24-34 months

Trend toward faster waning of antibody over time in younger children – not statistically significant

	TCV		Men-A	
Age at vaccination	Seroconversion % (95% CI) Day 0 to day 28	Seroconversion % (95% CI) Day 0 to day 1035	Seroconversion % (95% CI) Day 0 to day 28	Seroconversion % (95% CI) Day 0 to day 1035
All	98.6 (96.4-99.5)	79.9 (74.1-84.7)	0.4 (0.1-2.1))	4.4 (2.4-8.2)
9-11 months	99.0 (94.4 - 99.8)	68.3 (55.8 -78.7)	0.0 (0.0 - 4.4)	1.9 (0.3 - 9.9)
1-5 years	97.8 (92.3 - 99.4)	78.4 (67.7 - 86.2)	1.1 (0.2 - 5.7)	4.1 (1.4-11.3)
6-12 years	99.0 (94.3 - 99.8)	89.4 (81.1. - 94.3)	0.0 (0.0 - 4.1)	6.6 (2.8 - 14.5)

Nampota-Nkomba et al. Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months through 12 years in Malawi: results from a randomised, double-blind, controlled trial. Lancet Glob Health 2022.

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 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 cohort provides a unique opportunity to evaluate the performance of a booster dose of TCV at about 5 years following original dose (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.

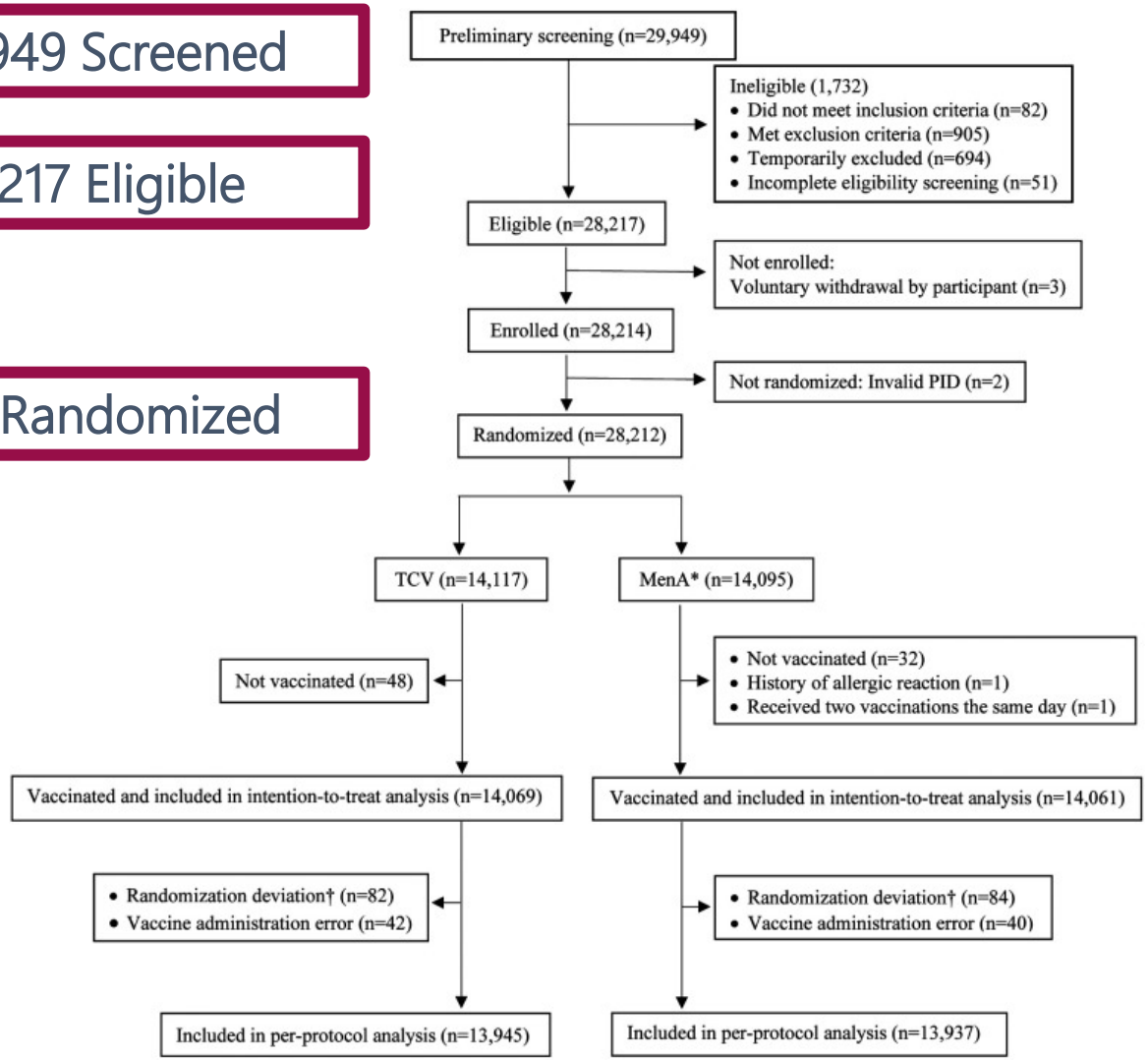
- Objective: in children who received the Men-A or TCV at 9-11 months of age,
  - Determine **immunogenicity** to a dose of TCV given at 5 years of age.
    - Serum anti-Vi IgG antibodies pre-vaccination , at 28 days (Day 28) and 120-180 days (Day 160) post vaccination.
  - Determine **safety profile** of a second TCV given at 5 years of age.
    - Local and systemic solicited AEs within 7 days after vaccination.
    - Local and systemic unsolicited AEs within 28 days after vaccination.
    - SAEs within 180 days after vaccination.
  - Determine **tetanus antibody response** to a dose of Vi-TCV at 5 years of age.

Malawi trial consort diagram

29,949 Screened

28,217 Eligible

28,212 Randomized



14,069 ITT (TCV)

14,061 ITT (Men-A)

13,945 PP (TCV)

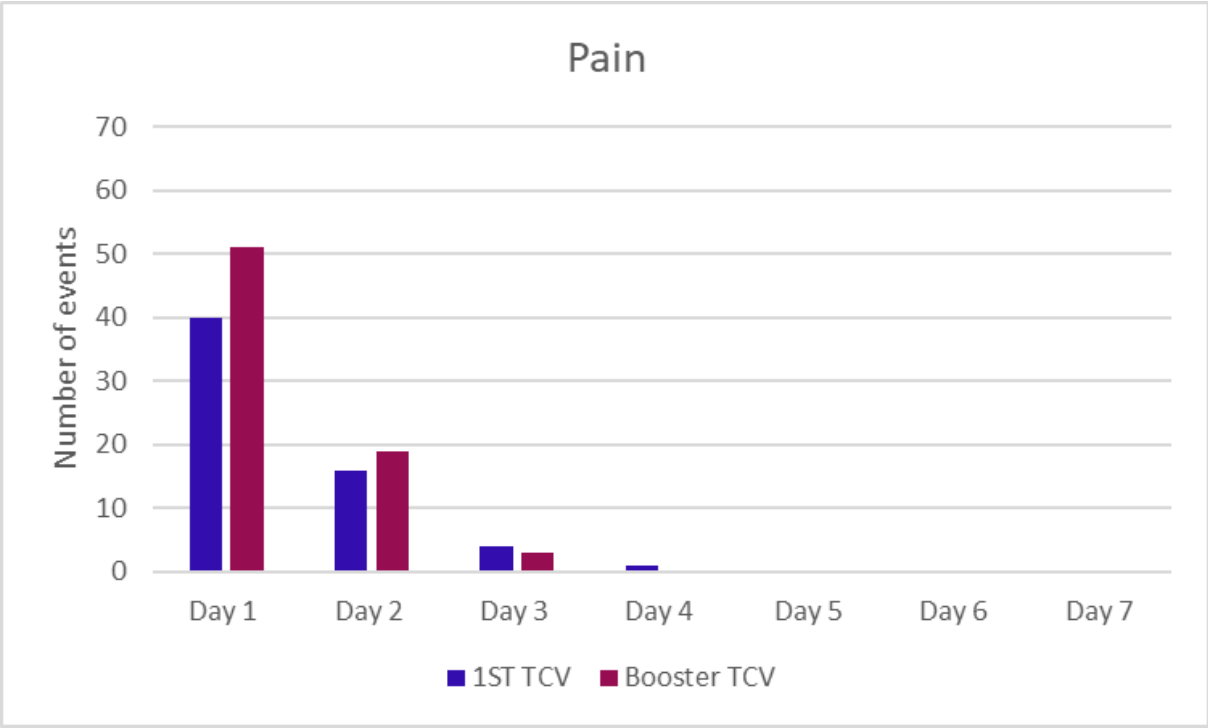
13,937 PP (Men-A)

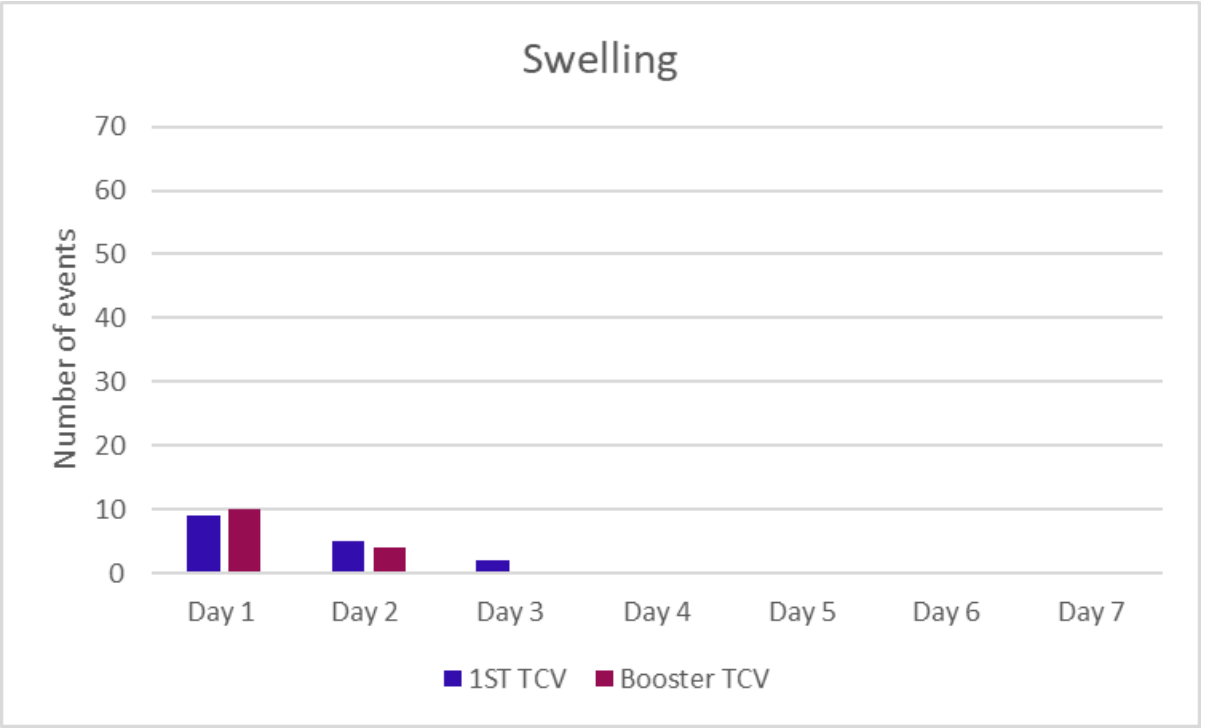
72 aged 9-11 months at first vaccination enrolled in booster (Booster TCV)

64 aged 9-11 months at first vaccination enrolled in booster (1ST TCV)

Local adverse events at day 7 post-vaccination

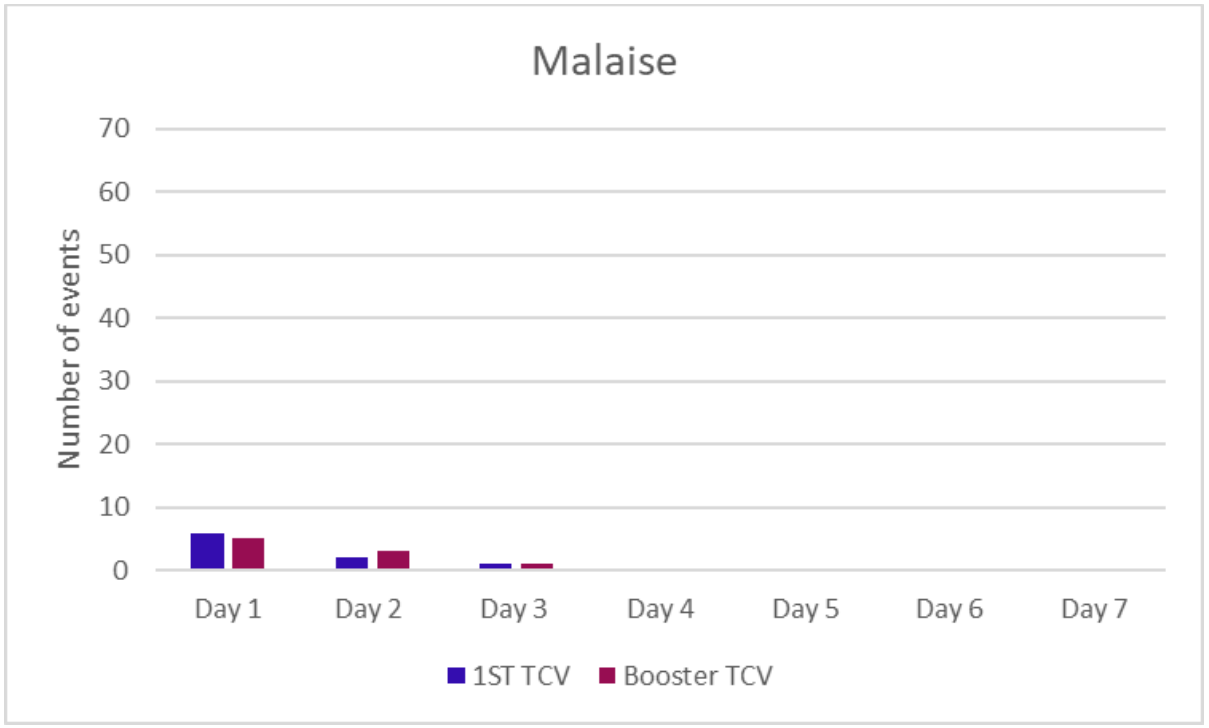
- Similar rate in both arms - p-value 1.0
- Mostly mild and moderate
- All reactions resolved by day 5 post-vaccination

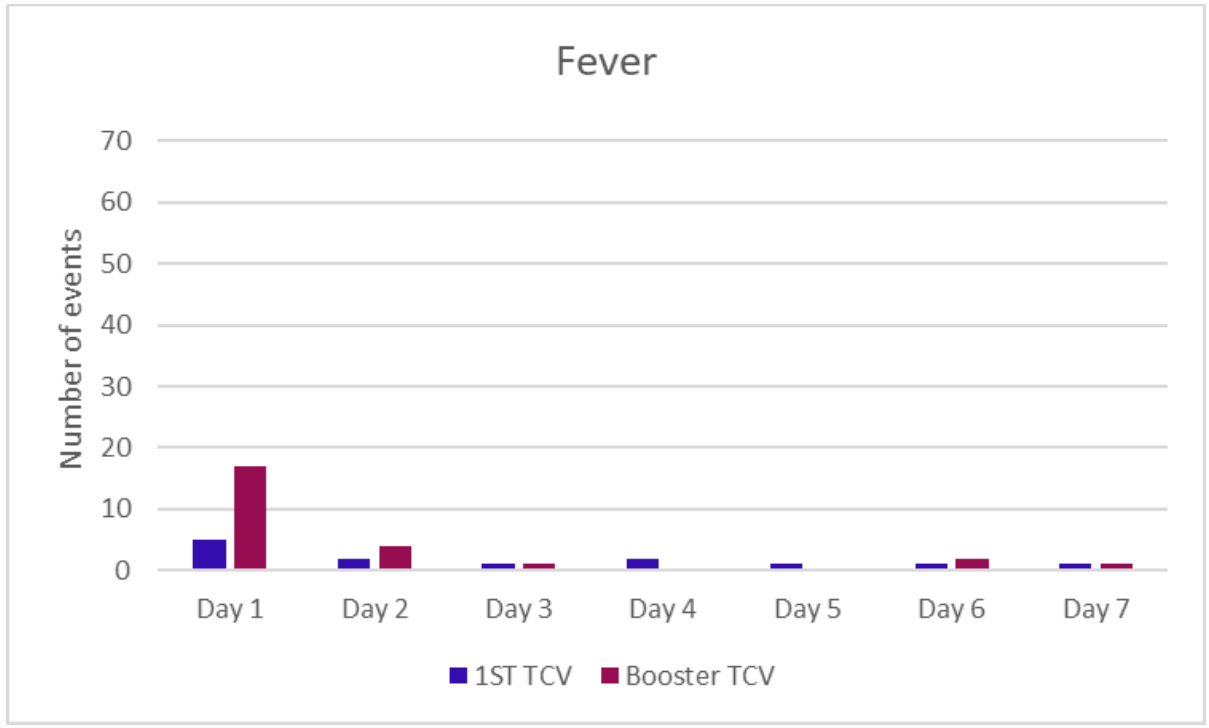




Systemic adverse events at day 7 post-vaccination

- Similar rate in both arms - p-value 0.27
- Mostly mild and moderate
- Fever persisted to day 7 for one participant in each arm





Conclusions

- First study to document TCV booster dose safety in African children.
- TCV caused few AEs after first or booster dose.
  - Mostly mild and moderate.
- Tolerability of first and booster doses of TCV at age 5 years was similar.
- Data support TCV introduction into routine immunization schedules in similar settings.

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Learn more at:

http://takeontyphoid.org

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