



Longevity of immune response after a single dose of Typhoid Conjugate Vaccine in children 6mths to 10 years in Hyderabad, Pakistan

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Disclosure

I have no actual or potential conflict of interest in relation to this presentation



Typhoid conjugate Vaccine

- Global typhoid incidence 11-21 million each year
 - ~222,000 deaths per year, > 90% from Asia
 - Typhoid incidence in Pakistan- 493.5 per 100,000/PY
- Outbreak of extensively drug resistant (XDR) typhoid in Pakistan -2016
- 2018- WHO recommended TCV introduction in high typhoid burden countries
- 2 TCV vaccines are prequalified by WHO
 - TypBar TCV
 - TyphiBEV





Questions asked

- How effective is TCV?
- Is the vaccine effective irrespective of AMR status?
- How long will the vaccine protect after a single dose?
- What's the duration of immunity and are there differences in immunogenicity across age groups?





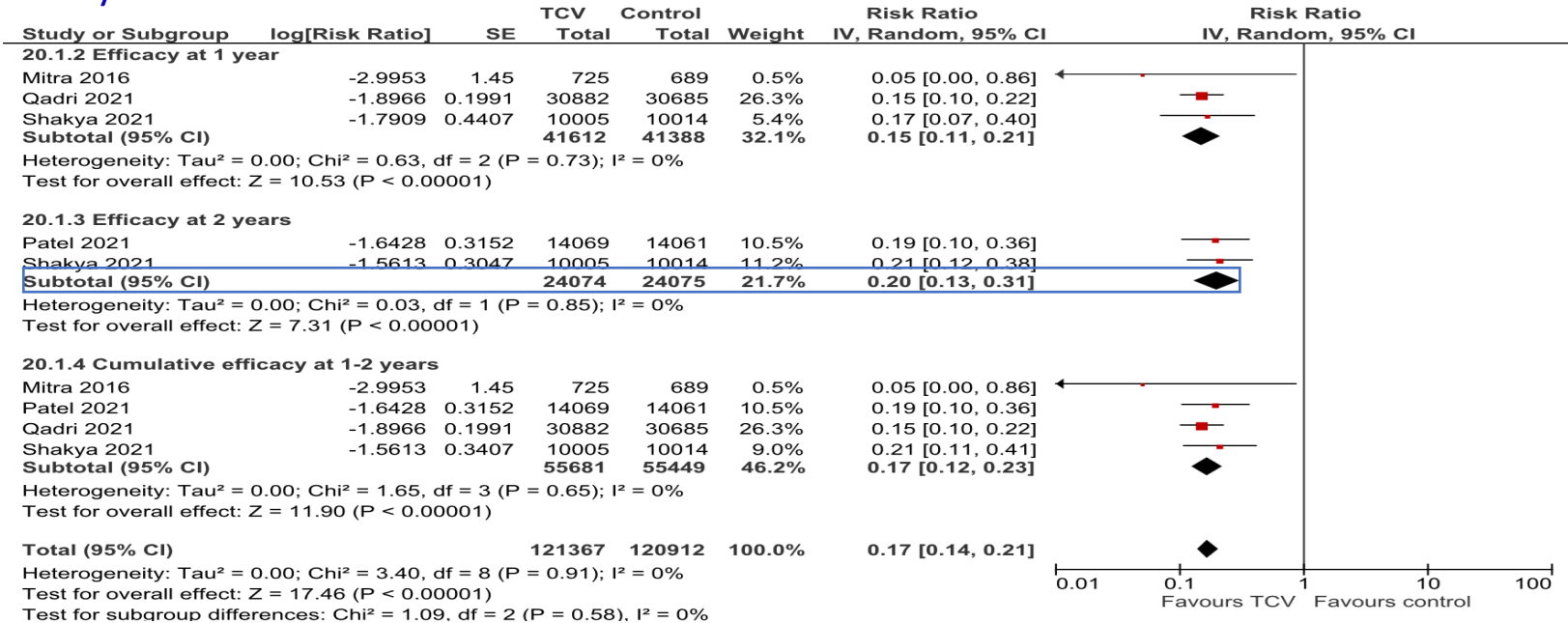
Typhoid conjugate vaccine –Efficacy

- Pakistan - first country to introduce TCV
- TCV in mass campaign provides 84% (Zimbabwe) and 95% (Pakistan) effectiveness against drug-resistant typhoid

(Lightowler MS, et al. 2022 & Yousafzai MT et al. 2021)

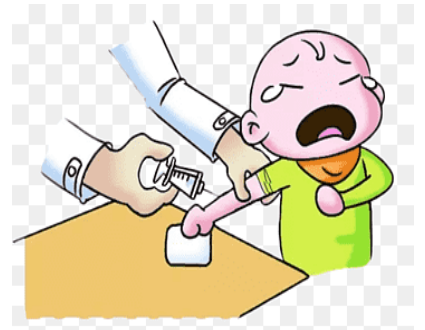
- A single dose of TCV provide 79% to 85% efficacy

Efficacy of typhoid vaccines against culture-confirmed *Salmonella* Typhi in typhoid endemic countries: A systematic review and meta-analysis



Questions asked

- ~~How effective is TCV?~~
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Effectiveness of typhoid conjugate vaccine against XDR typhoid in Hyderabad

	Vaccine effectiveness (95% CI)
Culture confirmed typhoid	
Age 6 to 59 months	94.5% (91.5% to 96.6%)
≥ 5 years	95.2% (92.9% to 97.0%)
XDR typhoid	
Age 6 to 59 months	94.4% (90.4% to 97.0%)
≥ 5 years	98.6% (96.4% to 99.6%)

VE in Zimbabwe – 75-84% (MDR and FQ resistance common)

Questions asked

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Data Gaps

- Limited data on long-term immune persistence following vaccination with TCV
- Differences in immune responses by age groups



Objective

To measure the immune response using anti-Vi IgG antibodies over time following immunization with Typbar-TCV in children 6 months to 10 years in Hyderabad, Pakistan





Methods

- **Study Design**

- Prospective cohort study

- **Duration**

- 5 years (March 2018)

- **Sample size**

- 958 healthy children

(Subset of children vaccinated in the outbreak response)

Inclusion criteria:

- Children 6 months to 10 years irrespective of gender and nutritional status
- Children whose parents consented for a single dose of TCV, and to provide blood sample at baseline and all subsequent visits
- Permanent residents of the outbreak area

Exclusion criteria:

- Acute illness or underlying chronic disease



Methods

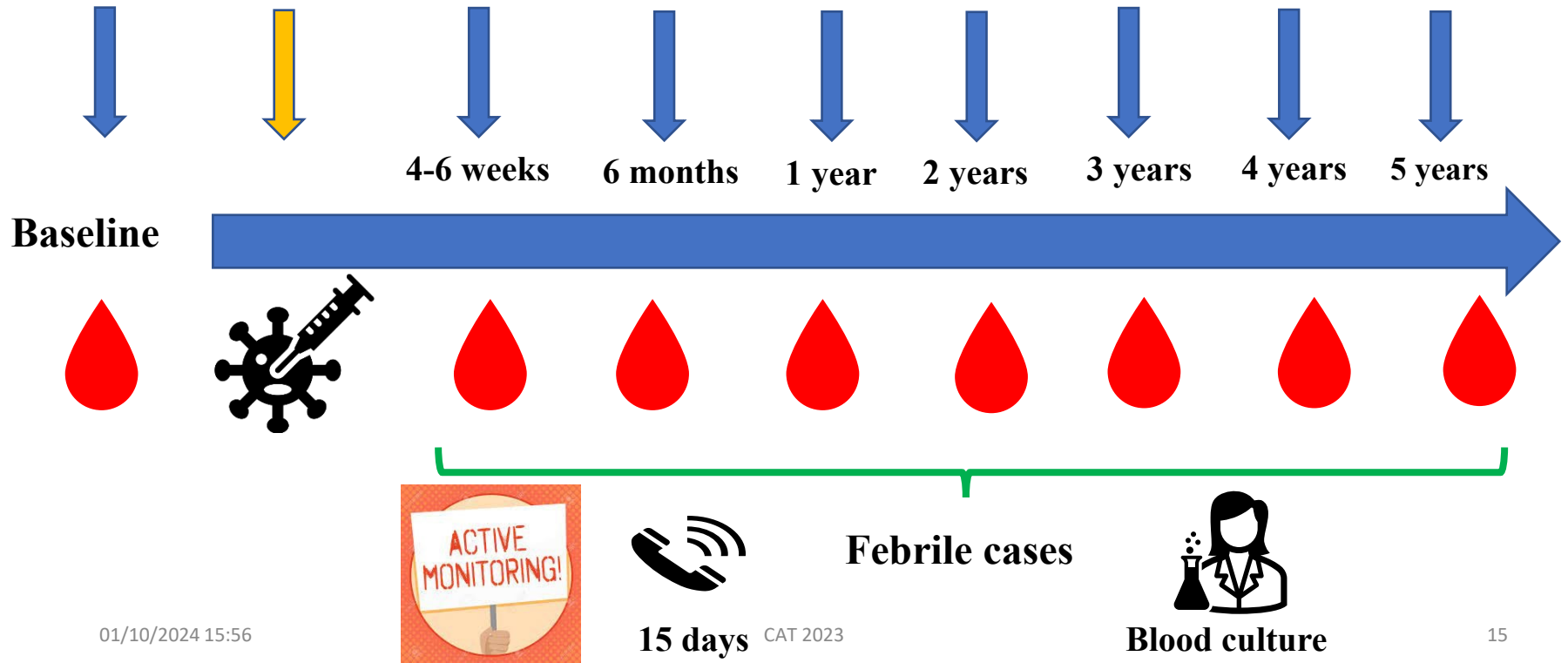
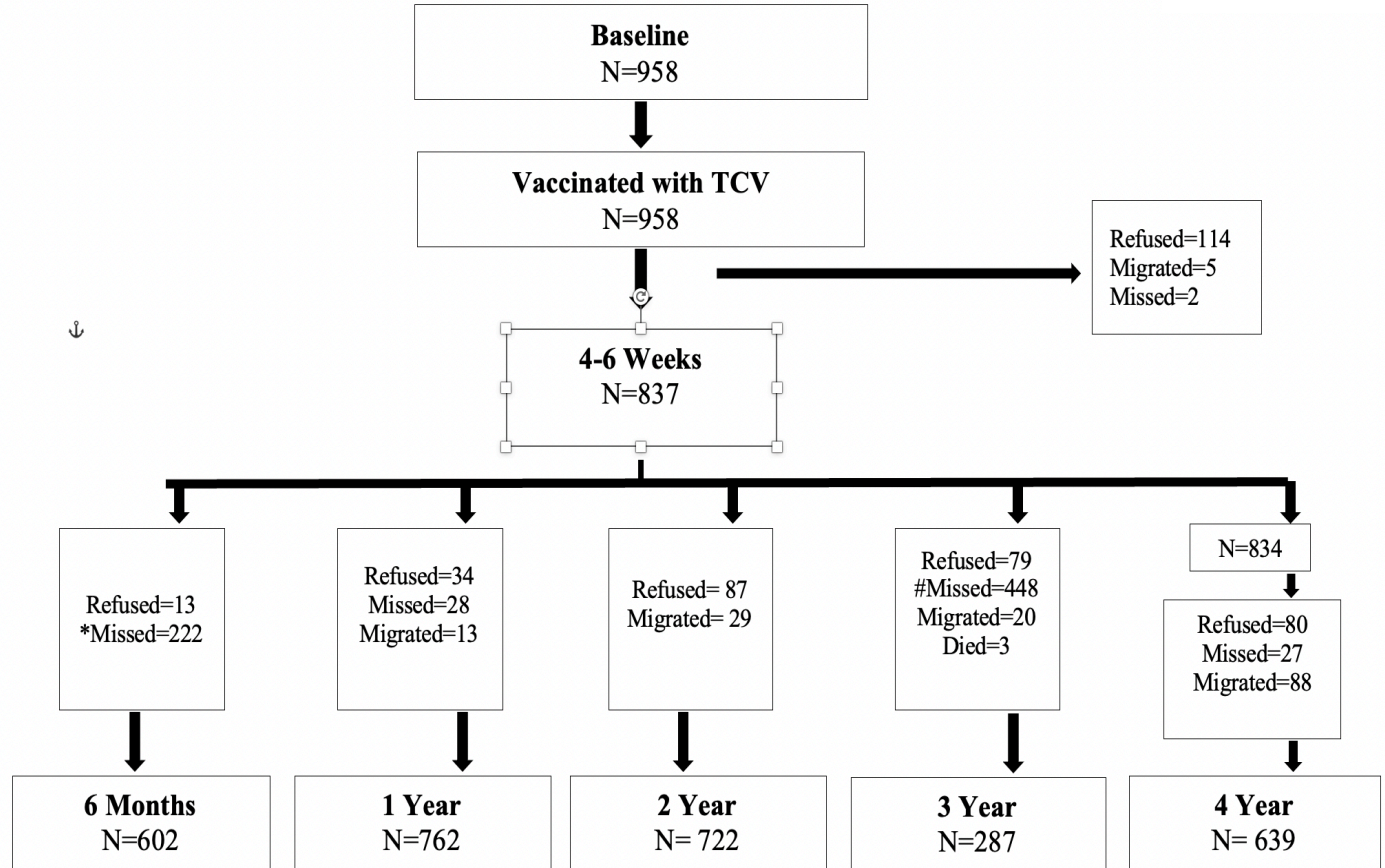
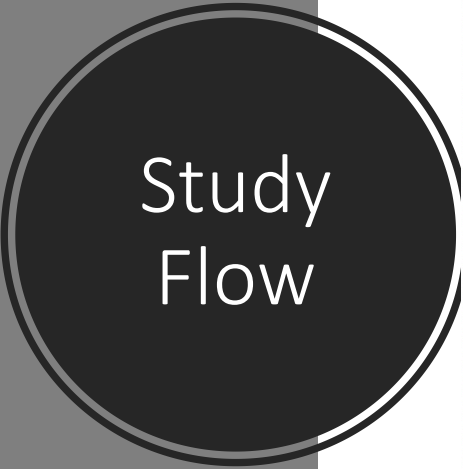




Figure 1: Study Flow



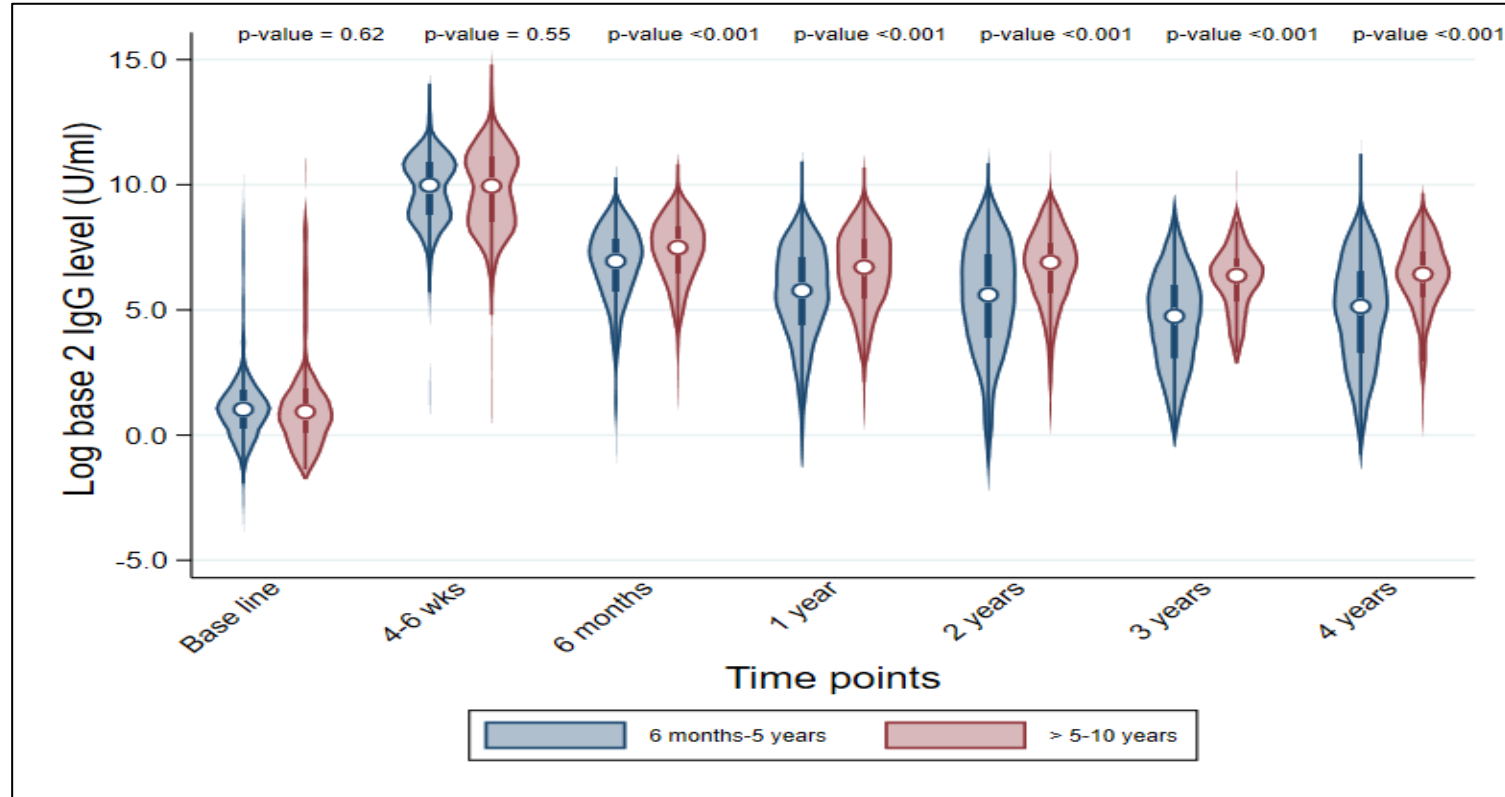
Demographics of participants at baseline

Variables		All Participants N=958 n (%)
Age (Years), Median (IQR)		3.5 (1.9-5.3)
Age category	6 mo-5 years	708 (73.9)
	> 5 – 10 years	250 (26.1)
Gender	Male	501 (52.3)
Fathers Education	No formal education or religious education only	248(24.9)
	Primary/Secondary	329 (34.3)
	Higher Secondary or above	381 (39.8)
Mothers Education	No formal education or religious education only	404 (42.2)
	Primary/Secondary	262 (27.3)
	Higher Secondary or above	292 (30.5)
Height (cm), Mean \pm SD		94.3 \pm 17.5
Weight (kg), Mean \pm SD		13.9 \pm 5.3
*MUAC (cm), Mean \pm SD		14.8 \pm 2.4
*Nutritional status (N=855)	Well nourished	693(81.1)

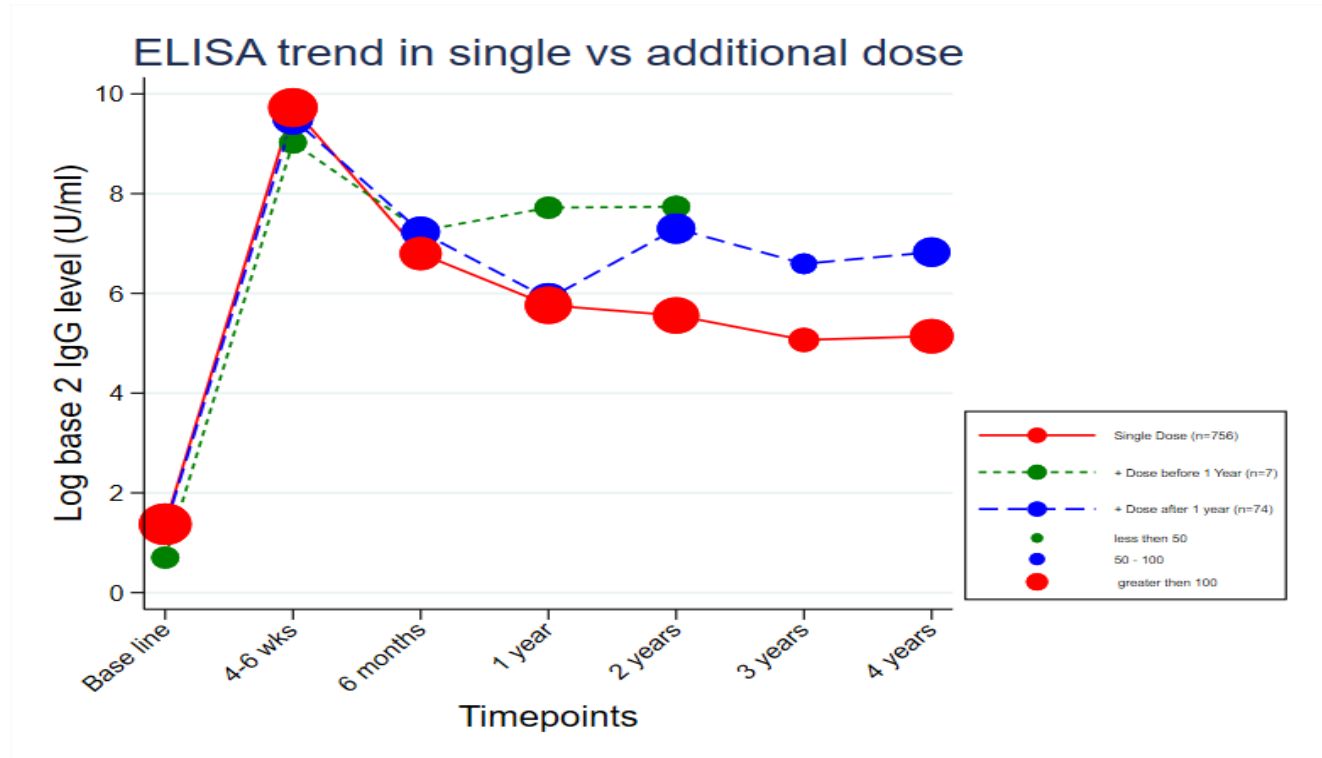
GMT and Seroconversion over time, stratified by age group

	Geometric Mean Antibody Titers (GMT)							Seroconversion			
	Overall		6M – 5 Years		>5 – 10 Years			Overall	6M – 5 Years	>5 – 10 Years	
Timepoints	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	#p-value	%	%	%	#p-value
Baseline	958	2.6 (2.4, 2.8)	708	2.5 (2.3, 2.8)	250	2.7 (2.2, 3.2)	0.62	--	--	--	--
4-6 wks	837	832.6 (768, 902.6)	609	845.1 (772.5, 924.6)	228	800.1 (671.7, 952.9)	0.55	95.8	97.0	92.5	0.004
6 months	602	115.2 (104.8,126.5)	396	99.4 (88.2, 112)	206	152.9 (132.4,176.6)	<0.001	89.9	89.9	89.8	0.97
1 year	755	54.7 (49.5,60.4)	548	45.8 (39.3, 50.3)	207	87.4 (80.8, 112.6)	<0.001	82.9	81.6	86.4	0.11
2 years	650	47 (41.7, 52.9)	478	38 (32.9, 43.8)	172	84.8 (70.6, 101.8)	<0.001	82.8	78.9	83.7	0.17
3 years	261	33.5 (28.4,39.5)	172	22.7 (18.5, 27.9)	89	71 (58.1, 86.8)	<0.001	77.8	75.0	83.1	0.13
4 years	579	35.2 (31.2,39.6)	411	26.4 (22.9, 30.4)	168	71.1 (59.5, 85)	<0.001	75.6	72.7	82.7	0.011

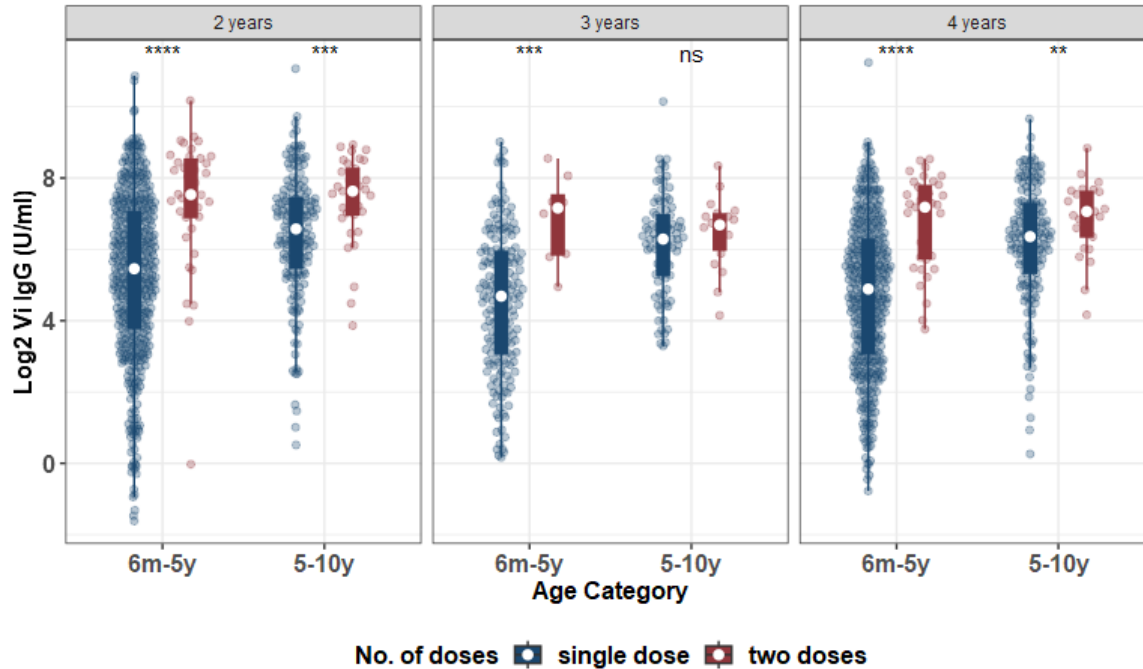
Age stratified median (IQR) level of anti-Vi-IgG



IgG levels of children who received a single versus two doses of Tybbar-TCV



IgG levels of children who received a single versus two doses of Tybbar-TCV by age group at 2-4y of follow-up.





Active Surveillance For Fever

- Blood cultures performed for suspected typhoid fever
 - 9 tested positive for *S. typhi* and 1 *S. Paratyphi A*
 - All cases had sero-converted at 4/6 weeks
- Median duration between vaccination and infection
 - 29.0 months (IQR: 18.4-41.6)

Characteristics of culture confirmed enteric fever cases (N=10)

Variables		n (%)
Seroconversion at 4/6 weeks	Yes	10 (100)
Serotype Isolated	Paratyphi	1 (10.0)
	Typhi	9 (90.0)
Drug susceptibility pattern of <i>S. Typhi</i> isolates (N=9)	Multi drug resistant (MDR)	2 (22.2)
	Extensively drug resistant (XDR)	4 (44.4)
	*Non MDR/XDR	3 (33.3)
Age category	6 mo-5 years	6 (60.0)
	> 5 – 10 years	4 (40.0)
*Nutritional status (N=855)	Well nourished	6 (75.0)
Antibody titers at the time of infection (U/ml)		24.3
GMT (95%CI)		(9.7 - 60.8)
Duration (months) between vaccination and infection Median (IQR)		29.0 (18.4-41.6)



Key Findings

- 95% seroconversion at 4-6 weeks following a single dose of TCV
- Faster antibody decay in children < 5years
- Better sustained immunogenicity following boosting with a second dose of TCV

Key Findings

- High degree of protection from clinical infection in the first 3 years following TCV
 - Median (IQR) duration between vaccination and infection 29.4 (18.4-41.6) months



Acknowledgement

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- Community Stakeholders
- Research lab staff (AKUH)
- Data Management team
- All study team members/co-investigators and participants





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THANK YOU!
dreamstime.

Details of culture confirmed cases

S. No	Age at baseline (Mo)	Age at illness (Mo)	Gender	WHZ/B MI Z-score	Date of TCV administration DD-MM-YYYY	Date of blood culture result DD-MM-YYYY	Time interval between vaccination and Infection (Mo)	Dose(s) of TCV	Antibody Titers Baseline U/ml	Antibody Titers 4/6 wks U/ml	Antibody Titers 6 months U/ml	Antibody Titers 1 year U/ml	Antibody Titers 2 years U/ml	Antibody Titers 3 years U/ml	Antibody Titers 4 years U/ml	Specie isolated
1.	29.4	37.8	M	2.72	22-11-2018	31-08-2019	8.4	2	1.31	1738.5	287.7 [#]	58.9	233.7	NA	130.5	S. Paratyphi A
2.	12.6	29.4	M	2.42	17-11-2018	01-03-2020	16.8	1	5.07	521.3	114.9	11.9 [#]	10.2	12.9	8.1	MDR-S. Typhi
3.	8.4	25.2	M	5.46	27-11-2018	10-06-2020	16.8	1	1.2	417.0	15.1	3.1	4.2 [#]	3.9	4.6	XDR-S. Typhi
*4.	79.8	109.2	M	-2.24	19-12-2018	20-05-2021	29.4	1	0.63	468.2	31.6	64.0	19.5 [#]	21.2	7.7	XDR-S. Typhi
*5	79.8	109.2	M	-5.59	19-12-2018	24-05-2021	29.4	1	0.6	81.4	12.3	8.2	14.7 [#]	13.3	10.9	XDR-S. Typhi
*6.	109.2	138.6	F	-4.53	19-12-2018	24-05-2021	29.4	1	0.74	388.7	146.2	145.8	136.6 [#]	96.8	80.2	XDR-S. Typhi
7.	16.8	58.8	F	5.87	04-07-2018	19-12-2021	42.0	1	5.5	1300.9	80.5	8.4	7.57 [#]	NA	26.2	Non-MDR/XDR-S. Typhi
8.	111.2	155.4	F	-2.12	11-07-2018	14-03-2022	46.2	1	1.3	2483.2	416.3	259.2	130.8 [#]	NA	159.4	Non-MDR/XDR-S. Typhi
9.	57.2	102.5	M	0.11	12-07-2018	21-04-2022	46.2	1	3.0	2982.2	177.4	112.4	68.7 [#]	NA	62.4	Non-MDR/XDR-S. Typhi
10	13.5	54.8	F	6.34	22-11-2018	01-05-2022	42.0	1 CAT 2023	148.2	1925.5	130.3	43.3	28.7	15.9 [#]	9.8	MDR-S. Typhi