

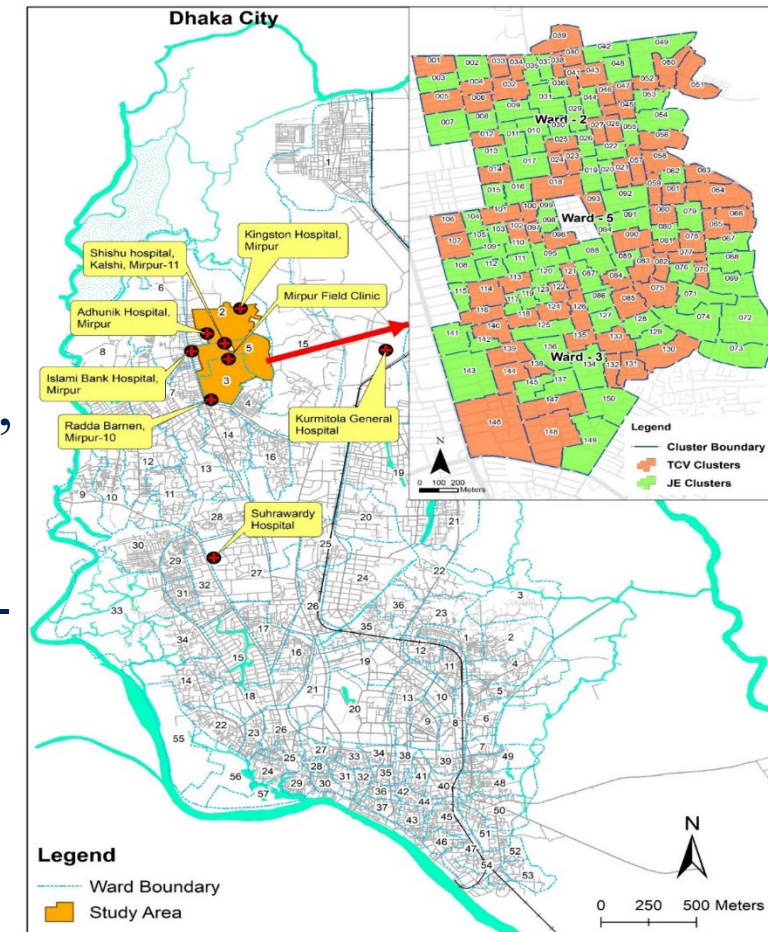
Assessing the Medium-Term Impact of a Vi-Polysaccharide Conjugate Vaccine in Preventing Typhoid Infection among Bangladesh Children

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TyVAC Bangladesh

- Cluster randomised controlled trial of Vi-TT efficacy in children aged 9 months to <16 years
- 150 clusters at a 1:1 ratio to either Vi-TT or SA 14-14-2 Japanese encephalitis (JE) vaccine
- Baseline census carried out between Feb 14, and March 25, 2018 (updated semiannually)
- 67,395 children were vaccinated during baseline and catch-up vaccinations
- Surveillance for typhoid fever conducted at 8 treatment centers started in Feb 2018
- Patients with ≥ 2 days of fever or axillary temperature of $\geq 38^{\circ}\text{C}$ were enrolled and blood was collected for culture



Study site:
Mirpur (wards 2, 3, and 5) Dhaka

Protective effectiveness of Vi-TT (18 months interim analysis in TyVAC Bangladesh)

| Analyses | JE | TCV | Vaccine protection | P-value |
|------------------------------------|--------------|-------------|--------------------|---------|
| Total Vaccine Protection | N=30685 | N=30882 | | |
| Typhoid fever (no.) | 192 | 29 | | |
| Person-Years of follow up | 30253 | 30349 | | |
| Incidence rate (per 1000 PYs) | 6.4(5.5,7.3) | 1.0(.6,1.7) | | |
| | | | 85 (77, 90) | <0.001 |
| Overall Vaccine Protection | N=155448 | N=155841 | | |
| Typhoid fever (no.) | 331 | 144 | | |
| Person-Years of follow up | 155458 | 154449 | | |
| Incidence rate (per 1000 PYs) | 2.1(1.9,2.4) | .9(.8,1.1) | | |
| | | | 57 (45, 67) | <0.001 |
| Indirect Vaccine Protection | N=134835 | N=135110 | | |
| Typhoid fever (no.) | 139 | 115 | | |
| Person-Years of follow up | 125205 | 124100 | | |
| Incidence rate (per 1000 PYs) | 1.1(.9,1.3) | .9(.8,1.1) | | |
| | | | 19 (-12, 41) | 0.2 |

Typhoid Conjugate Vaccine →
The study involved over 67,000
children 9 months to <16 years of age



85% protective effectiveness conferred by the Vi-TT vaccine

Recommendation made by NITAG, Bangladesh resulting in Gavi support

Based on available evidence on disease burden and its public health impact, vaccine and immunization characteristic, cost-effectiveness, resource use, immunization policy, and programmatic readiness, the Technical Working Group under new and underused vaccine have made the following recommendations to the NITAG committee for consideration:

Introduction of Typhoid conjugate vaccine (TCV) into routine immunization in Bangladesh

- o Single dose
- o The TCV vaccine should be given at 9 months
- o Can be co-administered with MR vaccine

Along with the introduction of TCV into routine immunization (9 months) and conducting catch-up campaigns targeting children 9 months to 15 years of age

Continue to strengthen surveillance for typhoid fever to generate disease burden information for the effectiveness of vaccination along with AEFI surveillance

The NITAG and then the 62nd ICC approved the TCV vaccine application along with the Japanese Encephalitis vaccine and the request was sent to the Gavi Secretariat on 13th September 2022 which has been approved.

Bangladesh will start TCV vaccination from around Oct 2024

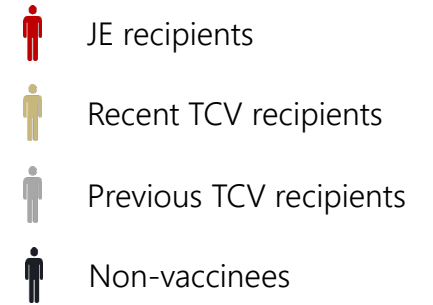
TyVOID Bangladesh

- There is little evidence about the medium to long-term protection of typhoid conjugate vaccine
- TyVOID is an observational study built on TyVAC Bangladesh
- TyVOID baseline (TyVAC final visit):
 - At the end of TyVAC, Bangladesh in 2021, all participants were unblinded and informed of vaccination status
 - All JE-recipients were offered Vi-TT (recent-Vi-TT cohort), while Vi-TT-recipients (previous-Vi-TT cohort) were not offered JE
- TyVOID:
 - A further two years of surveillance for enteric fever (until August 2023)
 - Aims to address questions regarding the change in the medium-term efficacy of the Vi-TT vaccine
 - Good news- We are moving to the TyVOID 2.0 in Bangladesh

Objectives

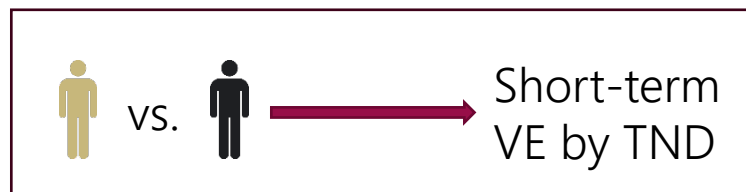
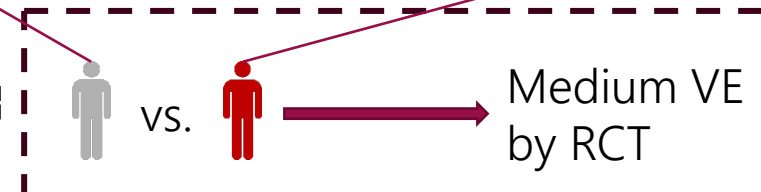
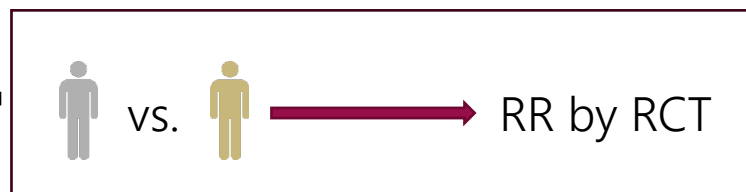
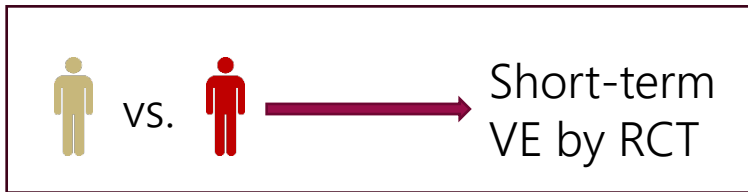
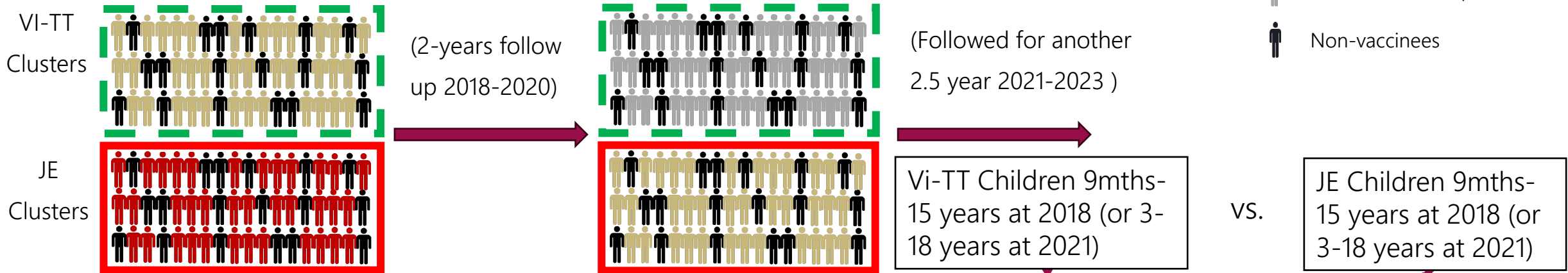
- Primary outcome: the change of ViTT vaccine protection in the medium-term compared with the initial 2-year after vaccination:
 - Typhoid incidence in vaccinees of previous-ViTT clusters (original ViTT clusters) vs. recent-ViTT clusters (original control clusters)
- Exploratory outcomes:
 - ViTT protection against typhoid among non-vaccinees in previous-ViTT clusters and recent-ViTT clusters
 - ViTT protection against typhoid among all residents in previous-ViTT clusters and recent-ViTT clusters
 - Rate of blood culture-confirmed symptomatic infection caused by S. Paratyphi among ViTT-vaccinees in previous-ViTT clusters and recent-ViTT clusters (bias indicator)
 - Short-term and medium-term ViTT protection against typhoid using a test-negative design

Methods

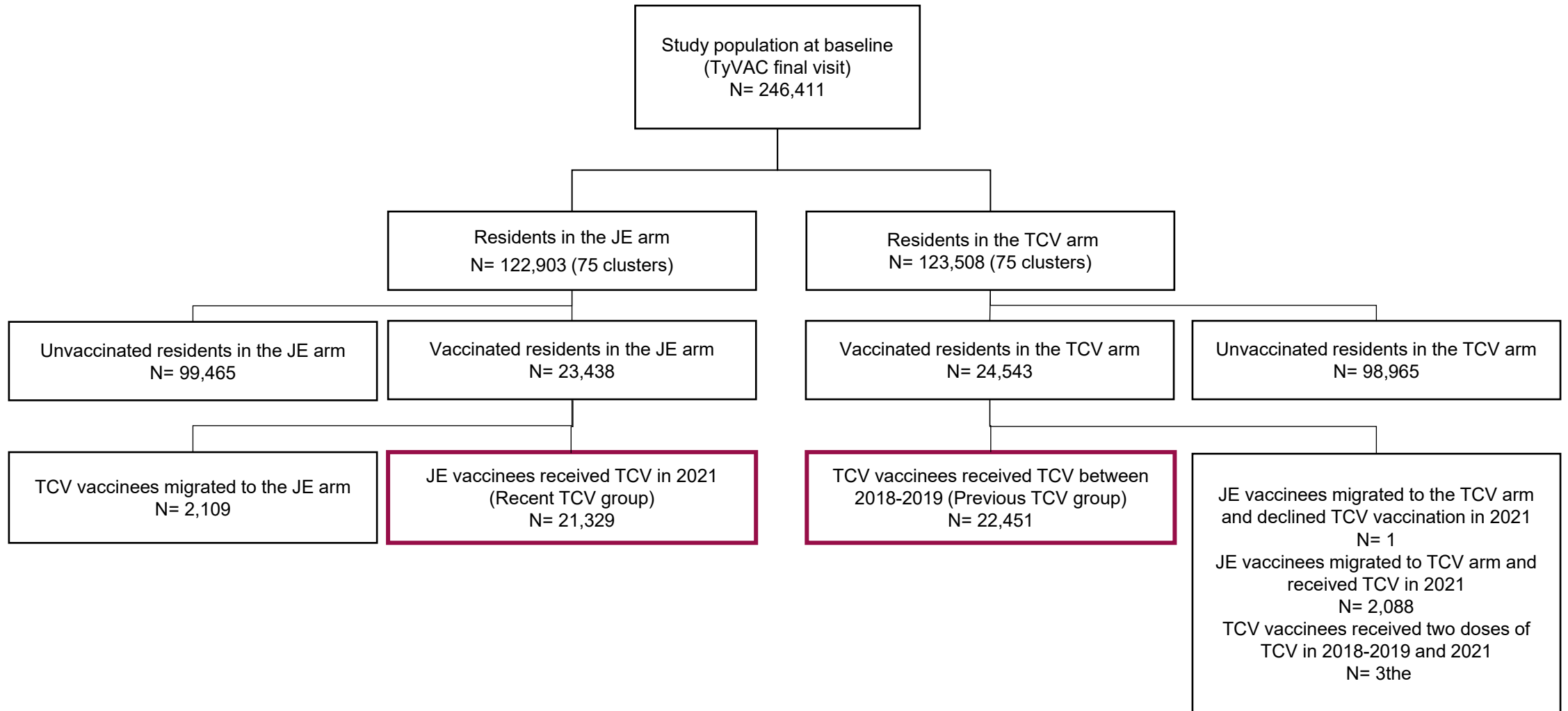


Aged 9 months – 15 years at 2018 (TyVAC Baseline)

Aged 3– 18 years at 2021 (TyVAC Final visit, TyVOID baseline)



Consort Diagram



Incidence of typhoid fever

| | | | Adjusted IRR* |
|---|---------------------------------------|--------------------------------------|------------------|
| | Previous vaccinees | Recent vaccinees | |
| | N=22,451 | N=21,329 | |
| Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up | 45/46,404 | 14/44,848 | |
| Incidence rate (per 100,000 PYs) (95% CI) | 97 (71,130) | 31 (17,52) | 3.10 (1.39,6.95) |
| | Non-vaccinees [†] in TCV arm | Non-vaccinees [†] in JE arm | |
| | N=25,445 | N=25,035 | |
| Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up | 58/39,218 | 65/38,950 | |
| Incidence rate (per 100,000 PYs) (95% CI) | 148 (112,191) | 167 (129,213) | 0.94 (0.55,1.62) |
| | Non-vaccinees [‡] in TCV arm | Non-vaccinees [‡] in JE arm | |
| | N=106,642 | N=107,137 | |
| Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up | 28/192,183 | 23/193,320 | |
| Incidence rate (per 100,000 PYs) (95% CI) | 15 (10,21) | 12 (8,18) | 1.28 (0.65,2.53) |

* Adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age and gender) and random effect (cluster)

[†] Non-vaccinees who were age-eligible (9 months - <16 years) for vaccination during TyVAC vaccination campaigns

[‡] Non-vaccinees aged ≥ 16 years during TyVAC vaccination campaigns

Incidence of typhoid fever

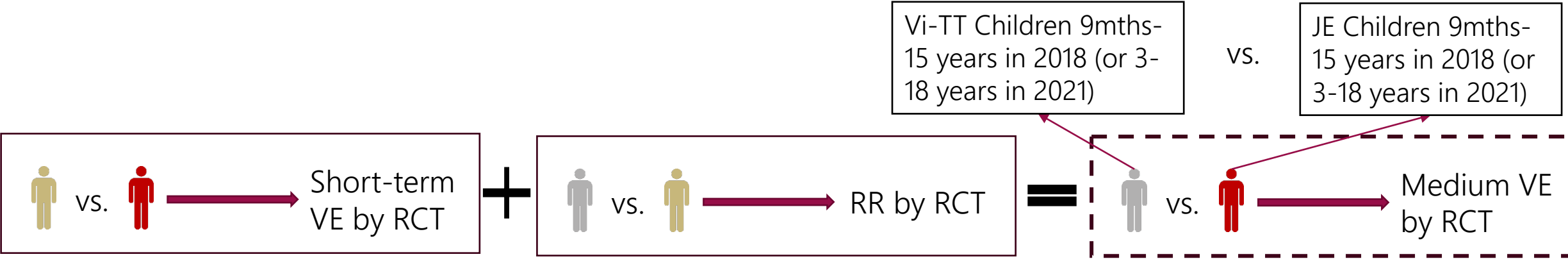
| | Residents in TCV arm | Residents in JE arm | Adjusted IRR* |
|---|----------------------|---------------------|------------------|
| | N=169,452 | N=168,312 | |
| Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up | 174/299,926 | 141/298,905 | |
| Incidence rate (per 100,000 PYs) (95% CI) | 58 (50,67) | 47 (40,56) | 1.28 (0.88,1.87) |

Incidence of paratyphoid fever (Bias indicator)

| | Previous vaccinees | Recent vaccinees | Adjusted IRR* |
|---|--------------------|------------------|------------------|
| | N=22,451 | N=21,329 | |
| Blood-culture confirmed paratyphoid fever (no.)/ Person-Years of follow-up | 27/46,404 | 26/44,848 | |
| Incidence rate (per 100,000 PYs) (95% CI) | 58 (38,85) | 58 (38,85) | 0.94 (0.42,2.13) |

* Adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age and gender) and random effect (cluster)

Medium-term vaccine effectiveness (VE) of Vi-TT vaccine



| | | | | |
|-----|--|---|---|--------------------|
| 1 - | $\left(\frac{Vi - TT (previous)}{Vi - TT (recent)} \right)$ | X | $\frac{Vi - TT (recent)}{non - vaccinee}$ | = VE (medium-term) |
| 1 - | (3.10 | X | 0.16) | = 50% |

#Assuming the vaccine effectiveness (VE) is consistent in 2018-2020 and 2021-2023

*Adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility) and covariates (age and gender)

Qadri F, Khanam F, Liu X, et al. Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial[J]. The Lancet, 2021, 398(10301): 675-684.

Relative risk of Typhoid by TND

| | | | Adjusted OR* | VE (%)* |
|--|-------------------|----------------------------|------------------|------------|
| | Negative control† | Test positives for typhoid | | |
| Non-vaccinees | 726 (33%) | 125 (65%) | | |
| TCV-recipients (vaccinated in 2018/2019) | 682 (31%) | 48 (25%) | 0.43 (0.30,0.61) | 57 (39,70) |
| TCV-recipients (vaccinated in 2021) | 769 (35%) | 19 (10%) | 0.16 (0.10,0.26) | 84 (74,90) |
| | | | | |
| | Negative control‡ | Test positives for typhoid | | |
| Non-vaccinees | 32 (35%) | 125 (65%) | | |
| TCV-recipients (vaccinated in 2018/2019) | 30 (33%) | 48 (25%) | 0.42 (0.22,0.80) | 58 (20,78) |
| TCV-recipients (vaccinated in 2021) | 29 (32%) | 19 (10%) | 0.18 (0.08,0.37) | 82 (63,92) |

Population: all persons who had passive surveillance visits for care of fever after TyVOID baseline and were age-eligible (9 months - <16 years) for vaccination during TyVAC vaccination campaigns (closed cohort).

* Adjusted for gender, age at fever visit, fever clinics, timing of fever visit (by quarters, i.e. 2021Q1, 2021Q2, ..., 2023Q3), distance of the cluster of living to the nearest health facility, and geographic ward

† Defined as specimens with no growth in blood culture

‡ Defined as specimens that were positive for *S.paratyphi*

Relative risk of paratyphoid by TND

| | | | Adjusted OR* | VE (%) |
|--|-------------------------------|--------------------------------|------------------|------------------|
| | Negative control [†] | Test positives for paratyphoid | | |
| Non-vaccinees | 726 (33%) | 32 (35%) | | |
| TCV-recipients (vaccinated in 2018/2019) | 682 (31%) | 30 (33%) | 1.04 (0.62,1.75) | 4 (-0.38,0.75) |
| TCV-recipients (vaccinated in 2021) | 769 (35%) | 29 (32%) | 0.97 (0.57,1.63) | -3 (-0.43, 0.63) |

Population: all persons who had passive surveillance visits for care of fever after TyVOID baseline and were age-eligible (9 months - <16 years) for vaccination during TyVAC vaccination campaigns (closed cohort).

* Adjusted for gender, age at fever visit, fever clinics, timing of fever visit (by quarters, i.e. 2021Q1, 2021Q2, ..., 2023Q3), distance of the cluster of living to the nearest health facility, and geographic ward

† Defined as specimens with no growth in blood culture

Relative risk of Typhoid by TND (children 9 months – <2 years between 2018-2019)

| | | | Adjusted OR* | VE (%)* |
|--|-------------------|----------------------------|------------------|-------------|
| | Negative control† | Test positives for typhoid | | |
| Non-vaccinees | 382 (38%) | 48 (63%) | | |
| TCV-recipients (vaccinated in 2018/2019) | 293 (29%) | 23 (30%) | 0.69 (0.40,1.19) | 31 (-19,60) |
| TCV-recipients (vaccinated in 2021) | 326 (33%) | 5 (6%) | 0.16 (0.06,0.40) | 84 (60,94) |

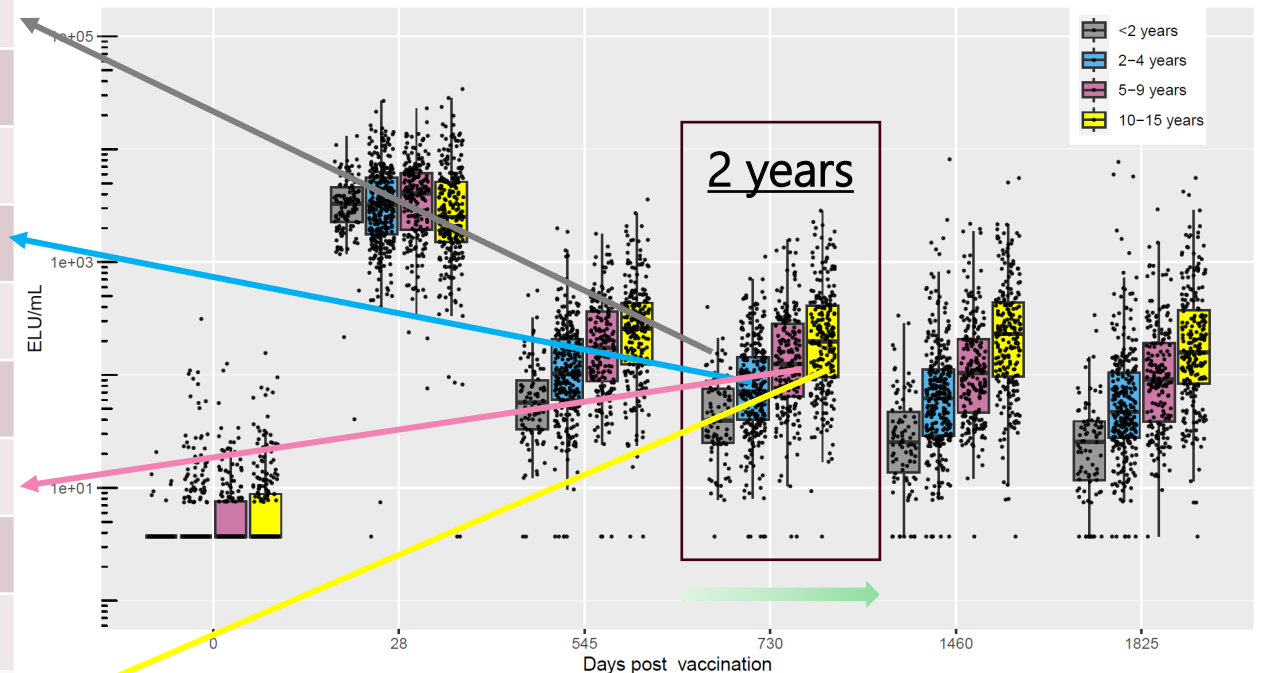
Population: all persons who had passive surveillance visits for care of fever after TyVOID baseline, were age-eligible (9 months - <16 years) for vaccination during TyVAC vaccination campaigns (closed cohort), and aged < 7 years at fever visit.

* Adjusted for gender, age at fever visit, fever clinics, timing of fever visit (by quarters, i.e. 2021Q1, 2021Q2, ..., 2023Q3), distance of the cluster of living to the nearest health facility, and geographic ward

† Defined as specimens with no growth in blood culture

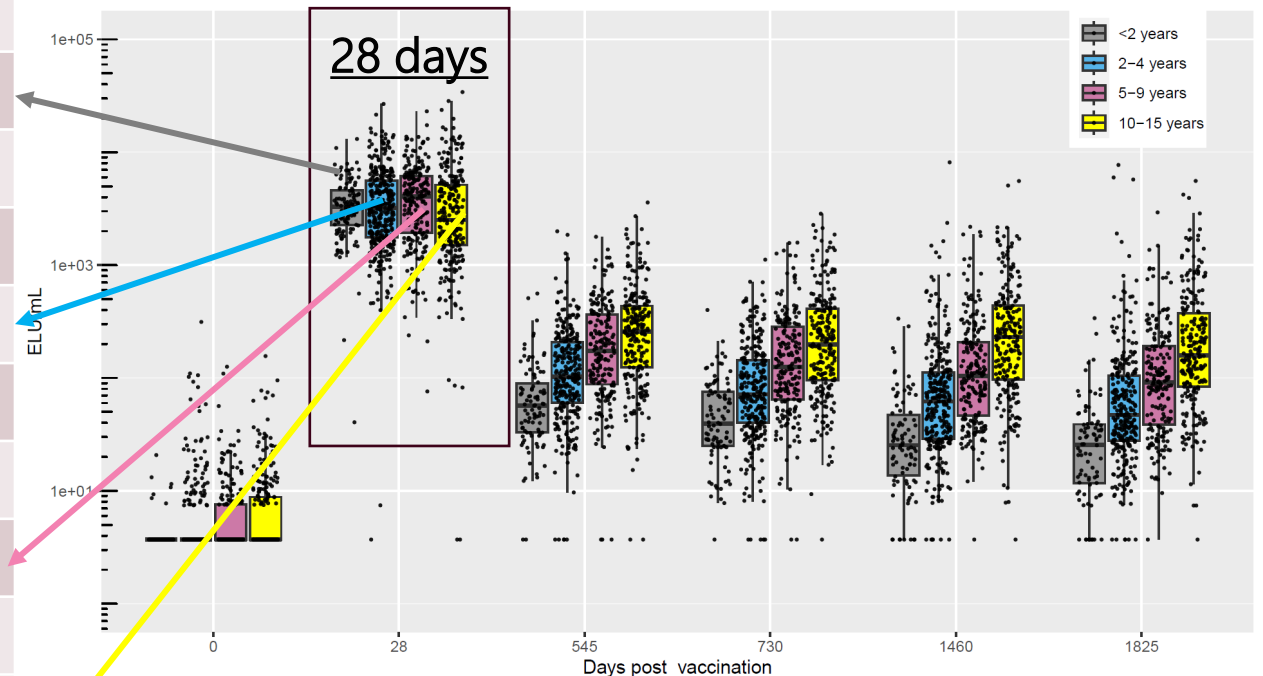
Relative risk of Typhoid by TND in different age groups (Age between 2018-2019)

| | VE (%)* |
|--|-------------|
| 9 months - <2 year | |
| TCV-recipients (vaccinated in 2018/2019) | 31 (-19,60) |
| TCV-recipients (vaccinated in 2021) | |
| 2-4 years | |
| TCV-recipients (vaccinated in 2018/2019) | 60 (12,82) |
| TCV-recipients (vaccinated in 2021) | |
| 5-9 years | |
| TCV-recipients (vaccinated in 2018/2019) | 74 (40,88) |
| TCV-recipients (vaccinated in 2021) | |
| 10-15 years | |
| TCV-recipients (vaccinated in 2018/2019) | 84 (49,95) |
| TCV-recipients (vaccinated in 2021) | |

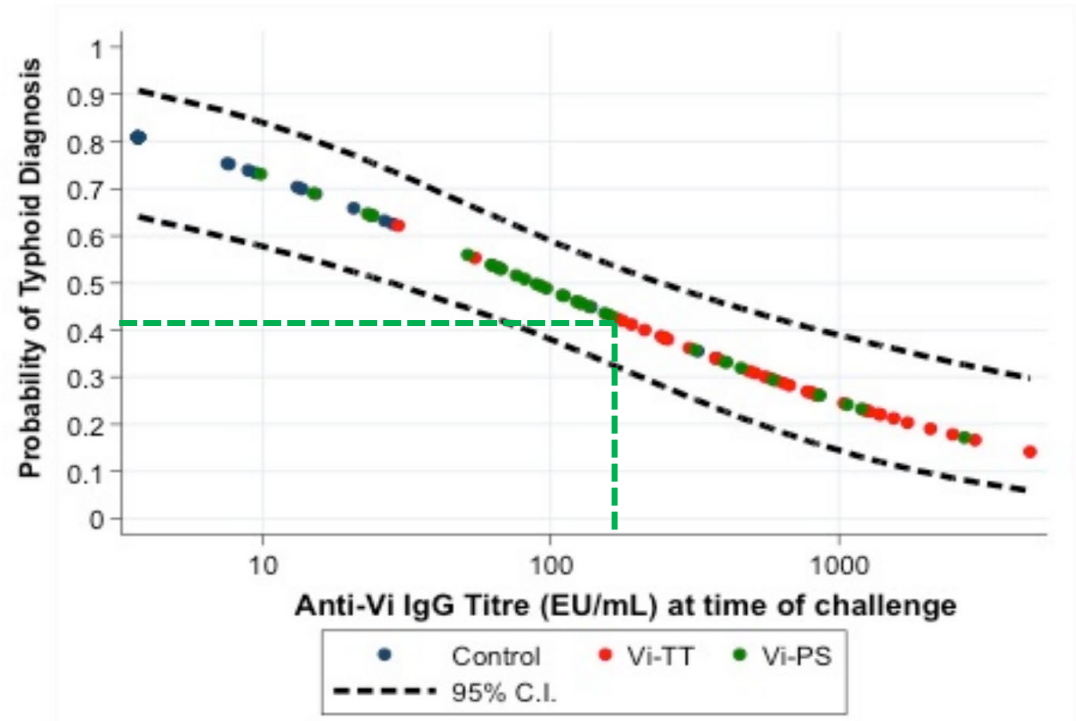
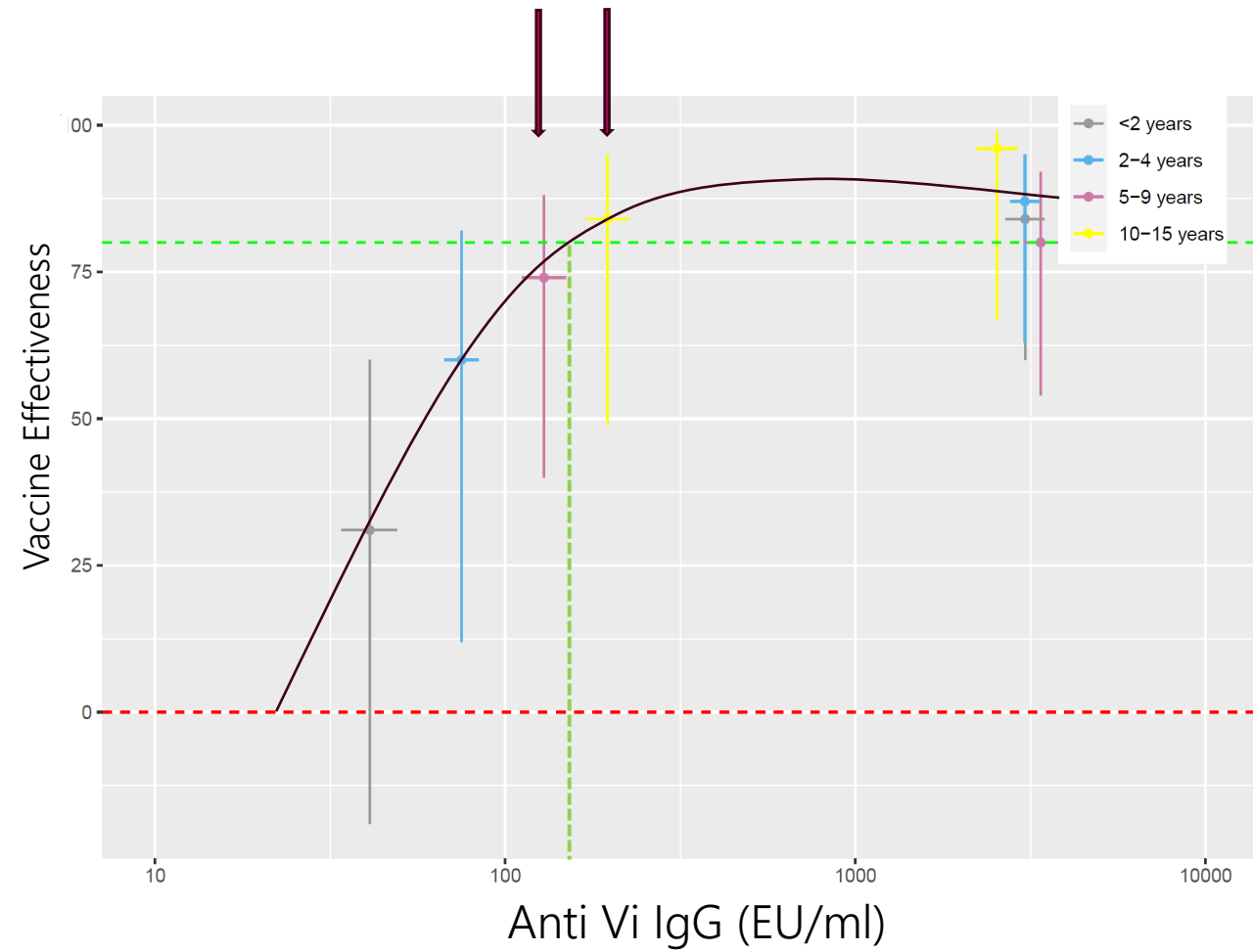


Relative risk of Typhoid by TND in different age groups (Age between 2018-2019)

| | VE (%)* |
|--|-------------|
| 9 months - <2 year | |
| TCV-recipients (vaccinated in 2018/2019) | 31 (-19,60) |
| TCV-recipients (vaccinated in 2021) | 84 (60,94) |
| 2-4 years | |
| TCV-recipients (vaccinated in 2018/2019) | 60 (12,82) |
| TCV-recipients (vaccinated in 2021) | 87 (63,95) |
| 5-9 years | |
| TCV-recipients (vaccinated in 2018/2019) | 74 (40,88) |
| TCV-recipients (vaccinated in 2021) | 80 (54, 92) |
| 10-15 years | |
| TCV-recipients (vaccinated in 2018/2019) | 84 (49,95) |
| TCV-recipients (vaccinated in 2021) | 96 (67, 99) |



Correlates of Protection



Interpretation

- **Consistent with previous RCTs, high early protection was seen following a single dose of TCV (VE in year 1-2: 84%, 95%CI: 74-90);**
- **Protection waning was noted in year 4-5, but still substantial (VE in year 4-5: 57%, 95%CI: 39-70);**
- **Further follow-up will be needed to determine the duration of protection and consider the use of boosters, especially in those vaccinated in the first few years of life.**



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TyVAC works closely with global partners



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Learn more at:

<http://takeontyphoid.org>



TyVAC Typhoid Vaccine
Acceleration Consortium
CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

Subgroup direct protection

| | | | Adjusted IRR* | |
|--|---|------------------|---------------|-------------------|
| Age < 5 years at TyVOID baseline (in 2021) | Previous vaccinees | Recent vaccinees | | |
| | N=3,667 | N=3,442 | | |
| | Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up | 20/7,572 | 3/7,139 | |
| | Incidence rate (per 100,000 PYs) (95% CI) | 264 (161,408) | 42 (9,123) | 6.51 (1.62,26.10) |
| Age ≥ 5 years at TyVOID baseline (in 2021) | Previous vaccinees | Recent vaccinees | | |
| | N=18,784 | N=17,887 | | |
| | Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up | 25/38,823 | 11/37,709 | |
| | Incidence rate (per 100,000 PYs) (95% CI) | 64 (42,95) | 29 (15,52) | 2.19 (0.89,5.44) |

* Adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age and gender) and random effect (cluster)