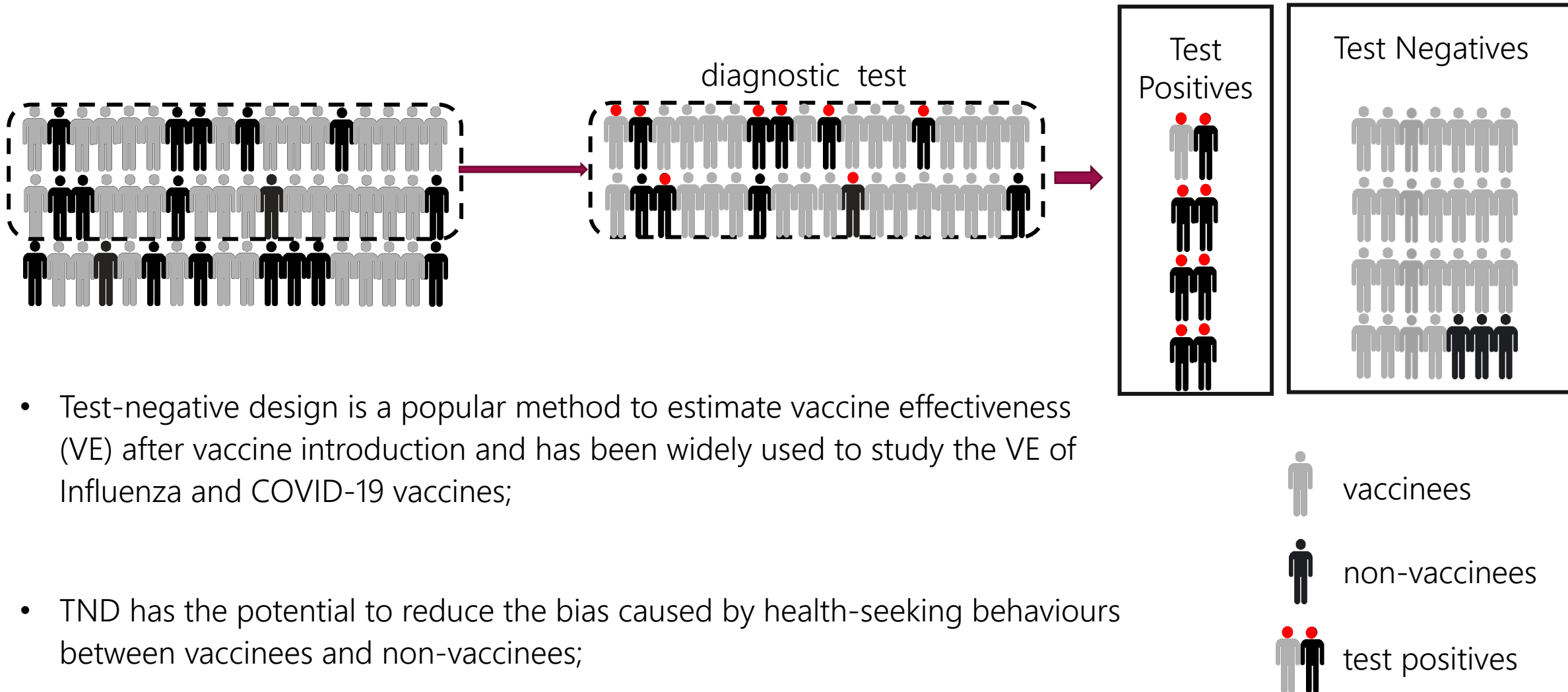


Test-Negative Design in Estimating Vaccine Protection: Results from TyVAC Bangladesh, a Cluster-Randomised Trial

Dr Xinxue Liu
Oxford Vaccine Group
University of Oxford



Test Negative Design



TND simulation study using IRCT and CRCT

- The TND design concept has been proved in the TyVAC Malawi, where MenA vaccinees were considered as a surrogate for non-vaccinees in the community;
- The impact of health-seeking bias on the TND requires further investigation before conducting TND to monitor VE of TCV

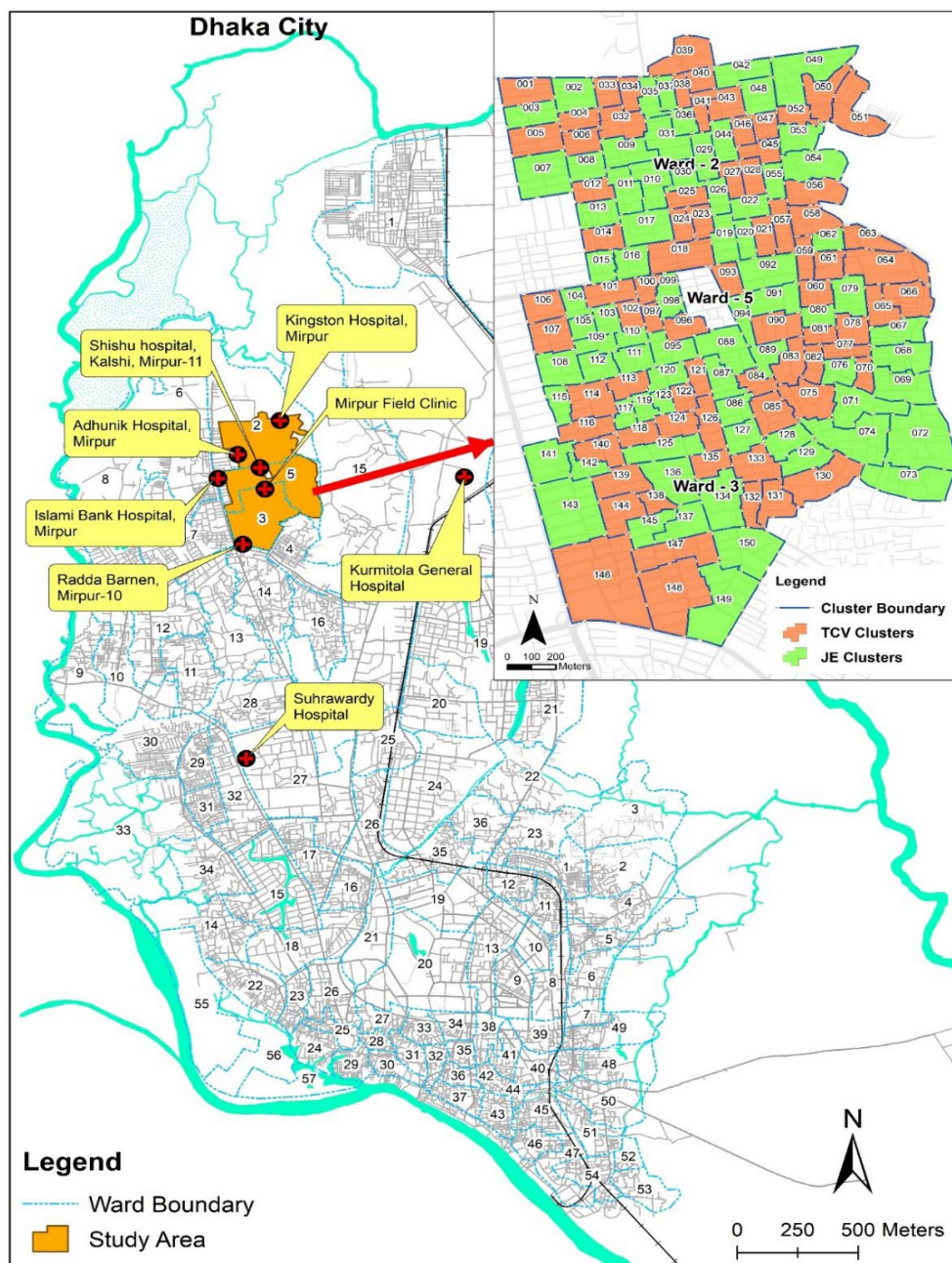
	Individual RCT	Cluster RCT
Vaccinee distribution	Vaccinees in both arms live in the same area	Vaccinees in two arms live in separate clusters
Study follow-up	Vaccinees only	Both vaccinees and non-vaccinees
Vaccination campaign	One campaign at the start of the study	Regular catch-up vaccination campaigns
Surveillance coverage	Vaccinees only	All residents

TyVAC Bangladesh

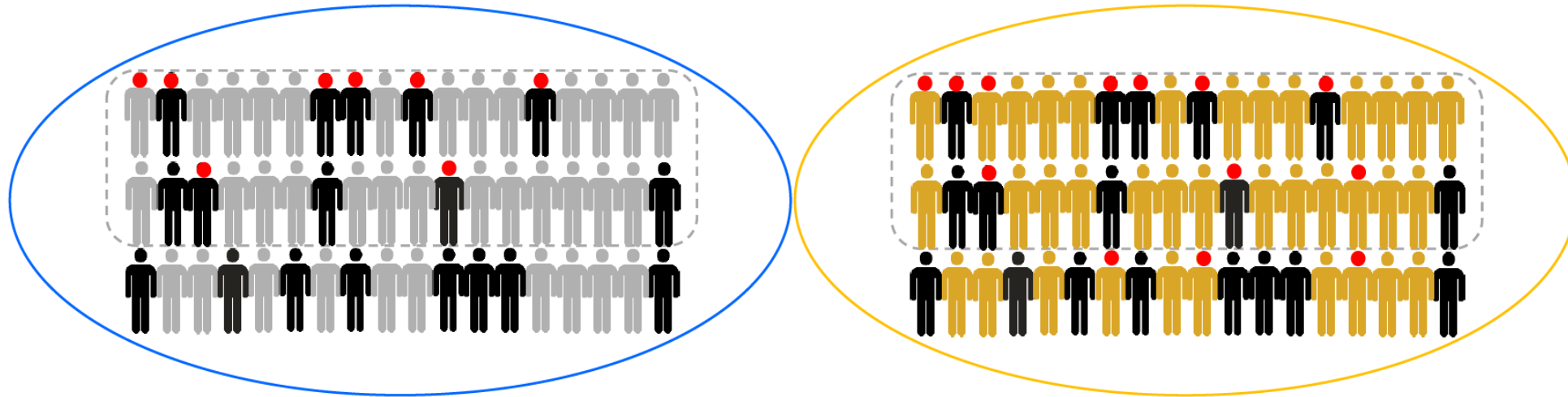
Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial

Firdausi Qadri, Farhana Khanam*, Xinxue Liu*, Katherine Theiss-Nyland, Prasanta Kumar Biswas, Amirul Islam Bhuiyan, Faisal Ahmed, Rachel Colin-Jones, Nicola Smith, Susan Tonks, Merryn Voysey, Yama F Mujadidi, Olga Mazur, Nazmul Hasan Rajib, Md Ismail Hossen, Shams Uddin Ahmed, Arifuzzaman Khan, Nazia Rahman, Golap Babu, Melanie Greenland, Sarah Kelly, Mahzabeen Ireen, Kamrul Islam, Peter O'Reilly, Karin Sofia Scherrer, Virginia E Pitzer, Kathleen M Neuzil, K Zaman, Andrew J Pollard†, John D Clemens†*

- Participant- and observer-masked cluster randomized trial
- Population divided into 150 contiguous clusters with approximately equal-sized populations
- Eligible children aged 9 mths to <16 yrs were offered JE or TCV
- Surveillance for typhoid fever conducted at 8 treatment centres serving the study population
- All patients with at least 2 days of fever or axillary temperature of $\geq 38^{\circ}\text{C}$ were approached to give a blood culture, after giving informed consent



Methods – Vaccine protections



Analysis methods

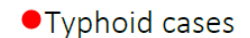
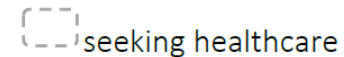
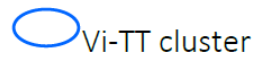
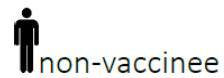
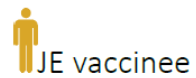
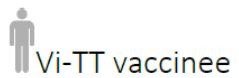
CRCT

Analysis population

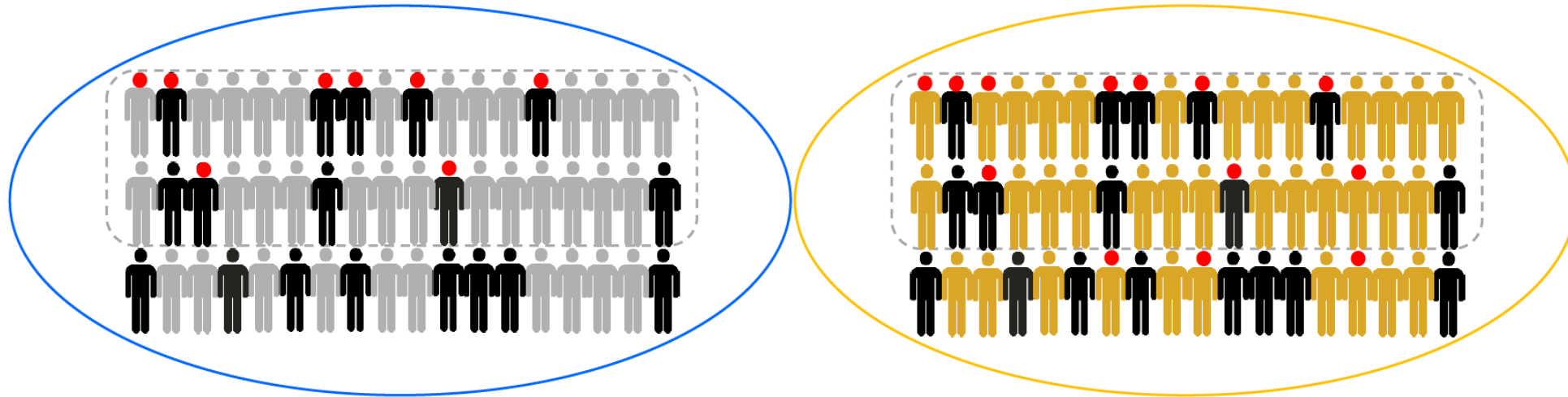


Comparisons

Vi-TT vaccinees vs. JE vaccinees in 150 clusters



Methods – Vaccine protections

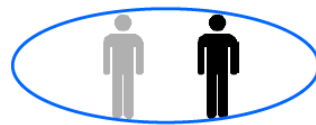


Analysis methods

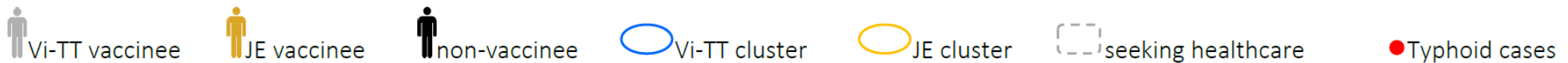
Analysis population

Comparisons

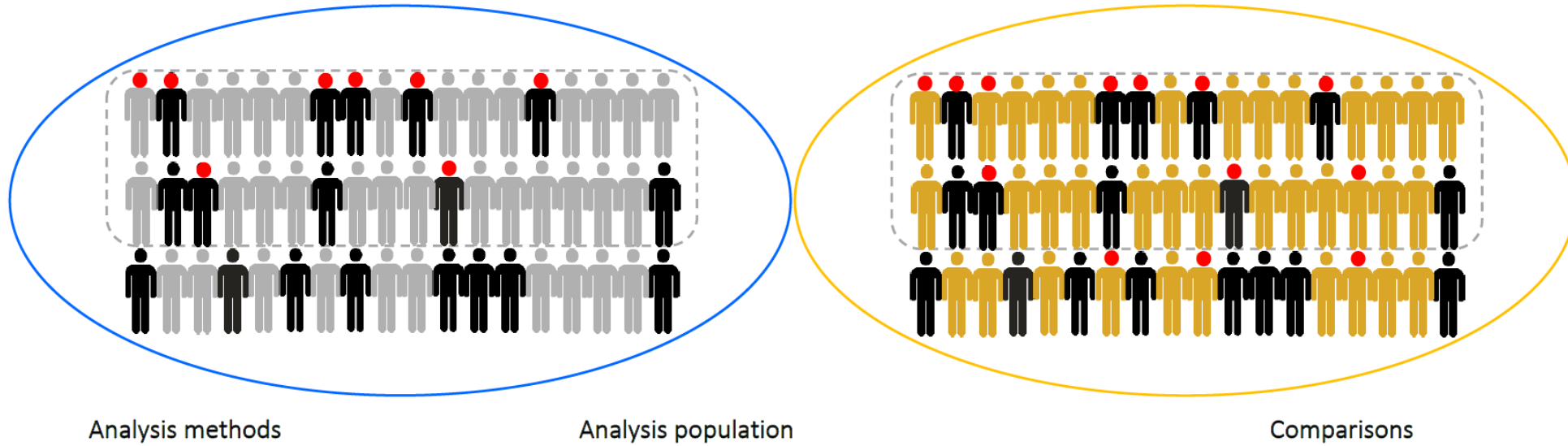
Cohort design



Vi-TT vaccinees vs. non-vaccinees in 75 clusters randomised to Vi-TT



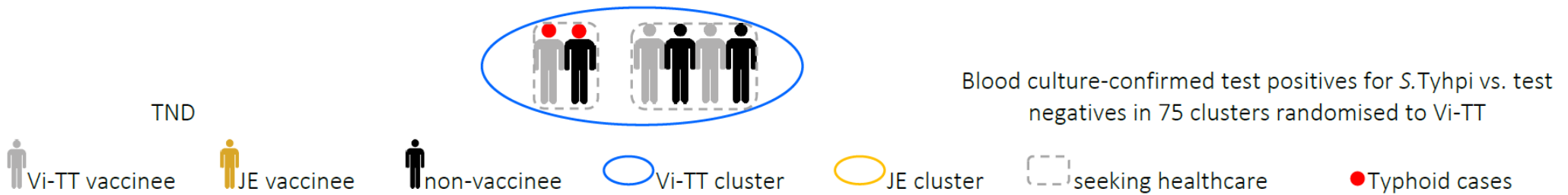
Methods – Vaccine protections



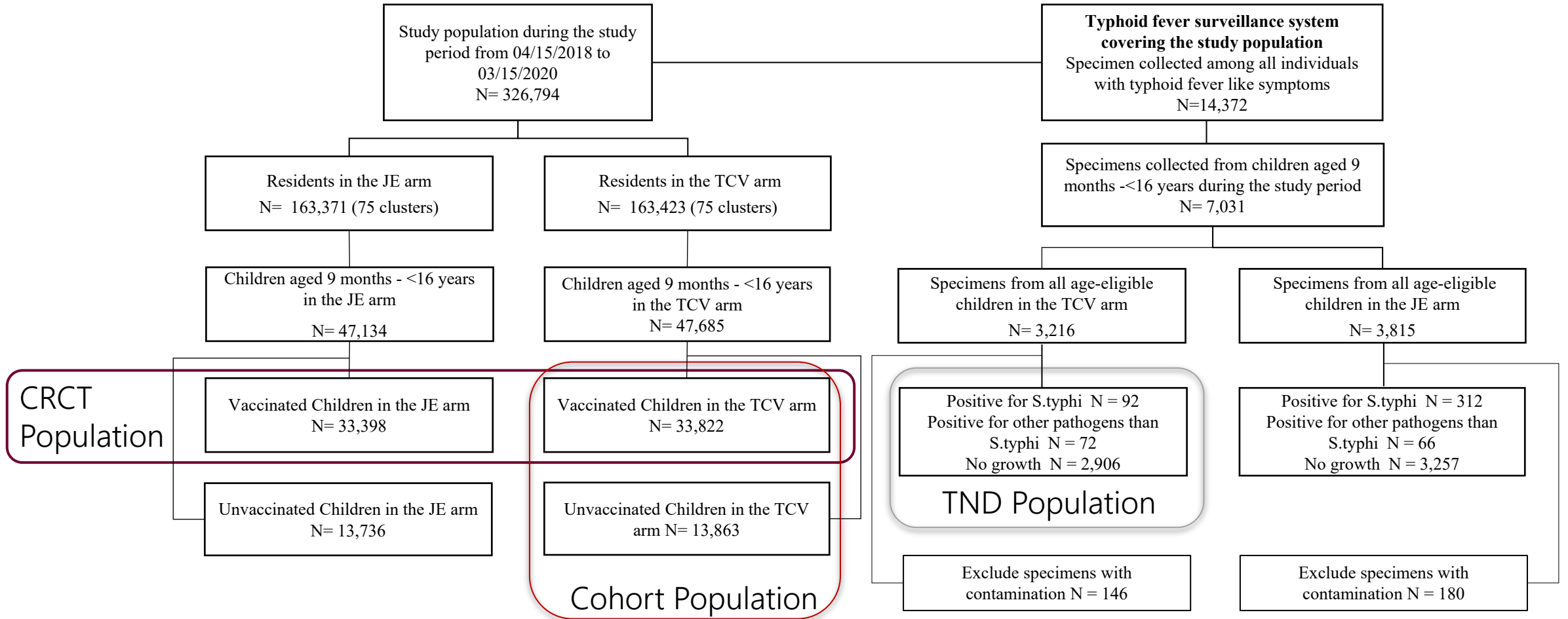
Analysis methods

Analysis population

Comparisons

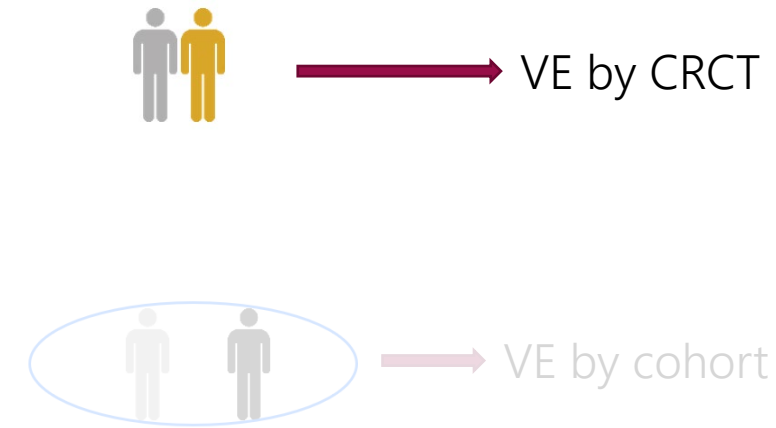


Consort Diagram-Vaccine Protections

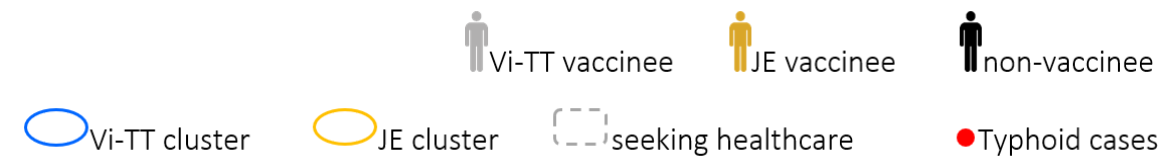
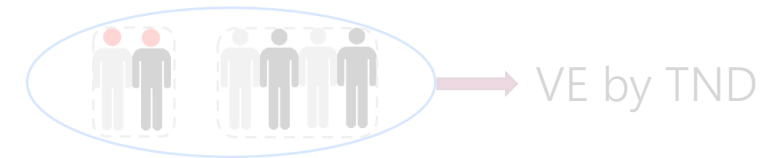


Vaccine protection by CRCT

CRCT (150 clusters)	JE-recipients	TCV-recipients	Adjusted IRR	VE (%)
	N=33398	N=33822		
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	262/43480	45/43697	0.17 (0.12,0.26)	83(74,88)
Incidence rate (per 100,000 PYs) (95% CI)	603(532,680)	103(75,138)		



Adjusted for the cluster as a random effect, and randomisation stratification variables at the cluster level (geographical ward, distance to study clinics, number of eligible children at baseline), demographic factors (age and sex) and household hygiene factors as fixed effects

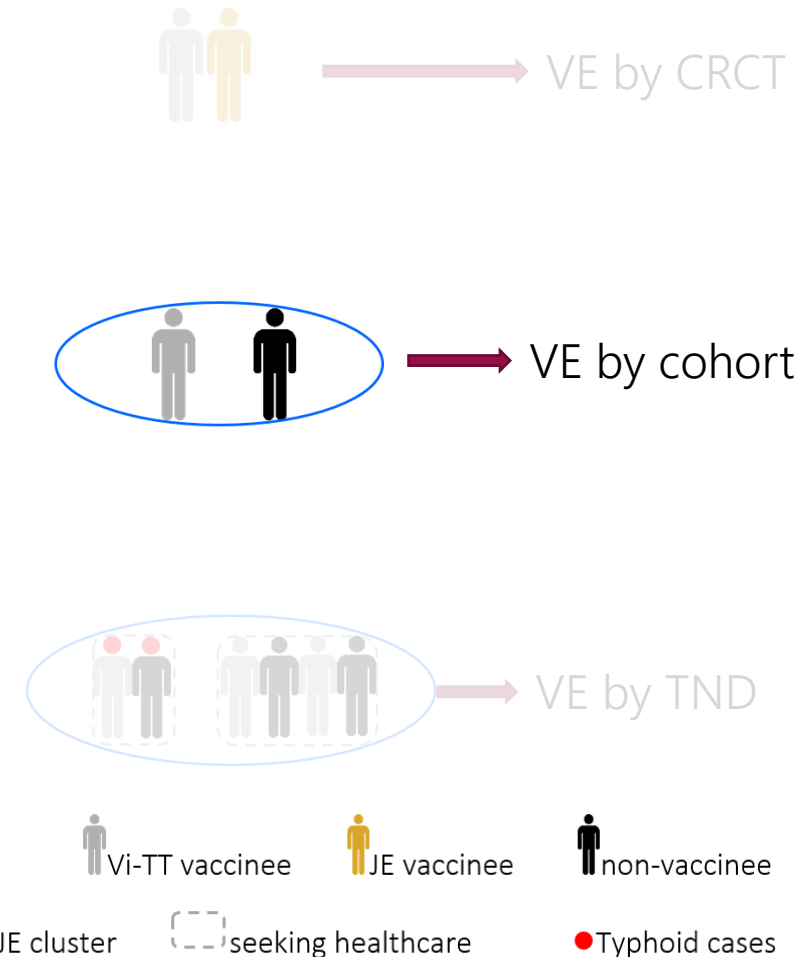


Vaccine protection by Cohort

CRCT (150 clusters)	<u>JE-recipients</u>	<u>TCV-recipients</u>	<u>Adjusted IRR</u>	<u>Adjusted VE</u>
	N=33398	N=33822		
Incidence rate (per 100,000 PYs) (95% CI)	603(532,680)	103(75,138)	0.17 (0.12,0.26)	83(74,88)

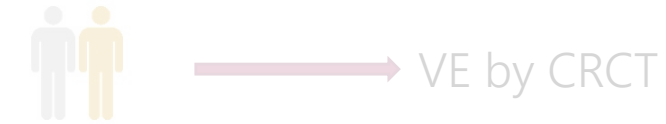
<u>Cohort (75 TCV clusters)</u>	<u>Non-vaccinees</u>	<u>TCV-recipients</u>	<u>Adjusted IRR</u>	<u>Adjusted VE</u>
	N=13863	N=33822		
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	47/16283	45/43697	0.34 (0.21,0.55)	66 (45,79)
Incidence rate (per 100,000 PYs) (95% CI)	288(212,384)	103(75,138)		

Adjusted for the cluster as a random effect, and randomisation stratification variables at the cluster level (geographical ward, distance to study clinics, number of eligible children at baseline), demographic factors (age and sex) and household hygiene factors as fixed effects

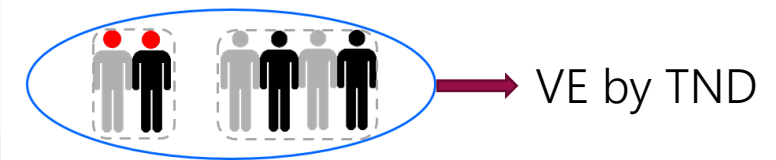


Vaccine protection by TND

CRCT (150 clusters)	JE-recipients	TCV-recipients	Adjusted IRR	Adjusted VE
	N=33398	N=33822		
Incidence rate (per 100,000 PYs) (95% CI)	603(532,680)	103(75,138)	0.17 (0.12,0.26)	83(74,88)



Test negative design (75 TCV clusters)#	Test negatives#	Test positives	Adjusted OR	Adjusted VE
Non-vaccinees	9 (13%)	47 (51%)	0.11 (0.05,0.27)	89 (73,95)
TCV-recipients	63 (88%)	45 (49%)		
	Test negatives*	Test positives		
Non-vaccinees	416 (14%)	47 (51%)	0.16 (0.10,0.24)	84 (76,90)
TCV-recipients	2490 (86%)	45 (49%)		



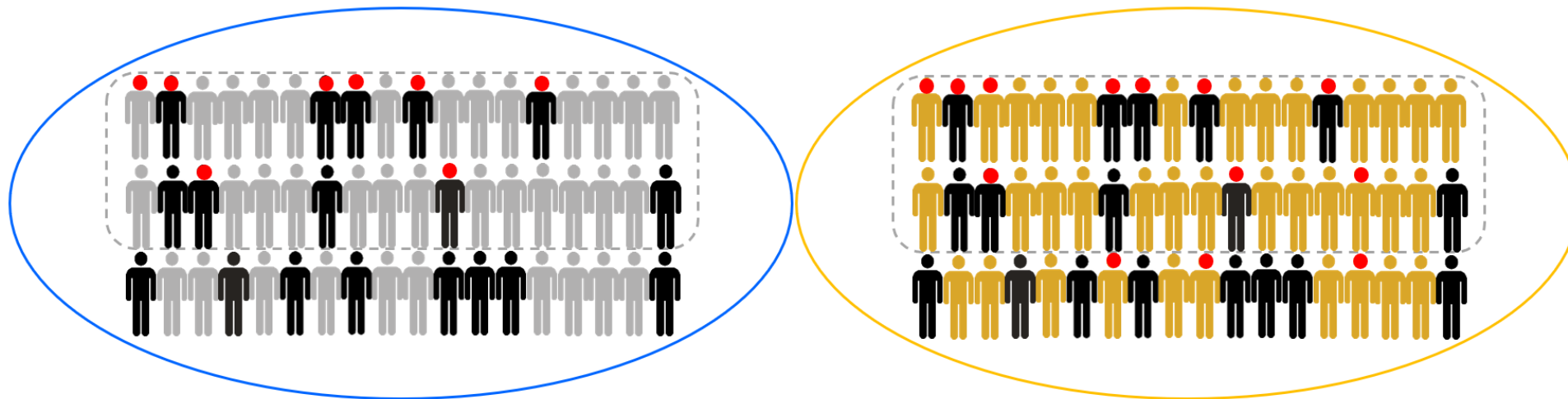
Defined as specimens that were positive for pathogens other than *S.Typhi*;

* Defined as specimens with no growth;

Adjusted for the same sets of covariates.



Methods-Negative Control Exposure (Bias indicator)

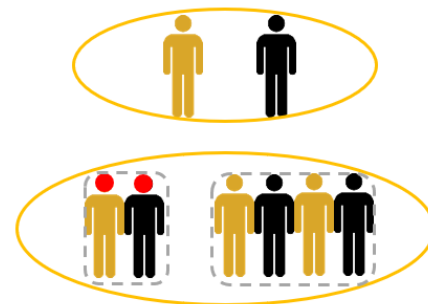


Analysis methods

Analysis population

Comparisons

Cohort design



JE vaccinees vs. non-vaccinees in 75 clusters randomised to JE

Blood culture-confirmed test positives for *S.Typhi* vs. test negatives in 75 clusters randomised to JE



TCV vaccinee



JE vaccinee



non-vaccinee



TCV cluster



JE cluster



seeking healthcare



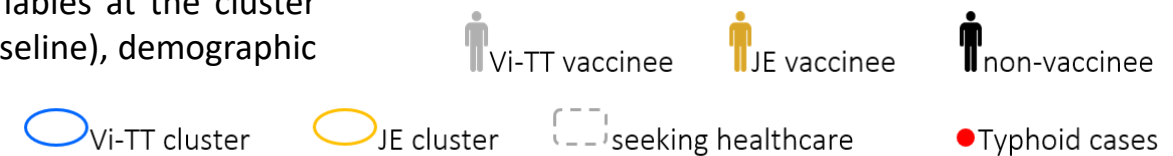
Typhoid cases

Negative Control Exposure Analysis (Association between typhoid fever and JE)

Cohort (75 JE clusters)	Non-vaccinees	JE-recipients	Adjusted IRR
	N=13736	N=33398	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	45/16470	262/43480	2.09 (1.45,3.00)
Incidence rate (per 100,000 PYs) (95% CI)	273(199,366)	603(532,680)	



Adjusted for the cluster as a random effect, and randomisation stratification variables at the cluster level (geographical ward, distance to study clinics, number of eligible children at baseline), demographic factors (age and sex) and household hygiene factors as fixed effects



Negative Control Exposure Analysis (Association between typhoid and JE)

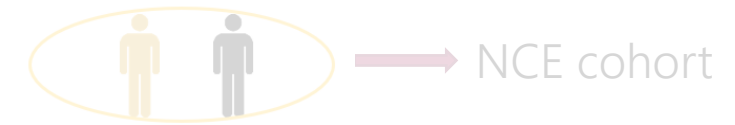
Cohort (75 JE clusters)	Non-vaccinees	JE-recipients	Adjusted IRR
	N=13736	N=33398	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	45/16470	262/43480	2.09 (1.45,3.00)
Incidence rate (per 100,000 PYs) (95% CI)	273(199,366)	603(532,680)	




Test negative design (75 JE clusters)	Test negatives [#]	Test positives	Adjusted OR
Non-vaccinees	10 (15%)	46 (15%)	0.99 (0.46,2.12)
JE-recipients	56 (85%)	266 (85%)	
	Test negatives [*]	Test positives	
Non-vaccinees	411 (13%)	46 (15%)	0.82 (0.59, 1.14)
JE-recipients	2846 (87%)	266 (85%)	

[#] Defined as specimens that were positive for pathogens other than *S.Typhi*;

^{*} Defined as specimens with no growth;

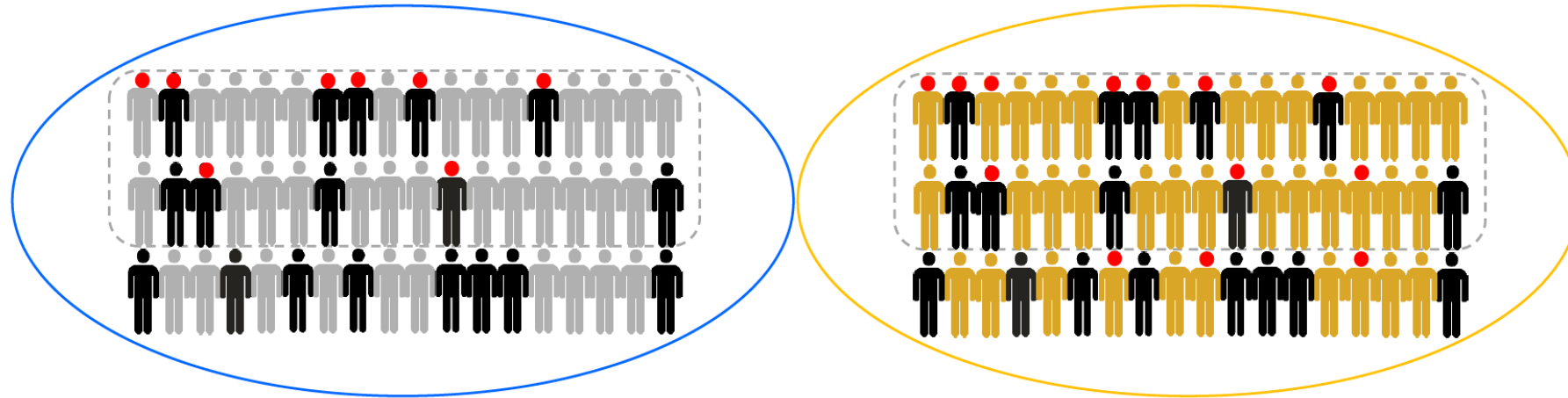
Adjusted for the same sets of covariates.



 Vi-TT vaccinee
  JE vaccinee
  non-vaccinee

 Vi-TT cluster
  JE cluster
  seeking healthcare
  Typhoid cases

Methods – Negative Control Outcome (Bias indicator)



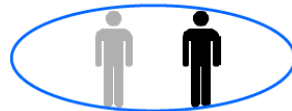
Analysis methods

Analysis population

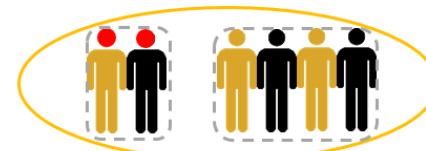
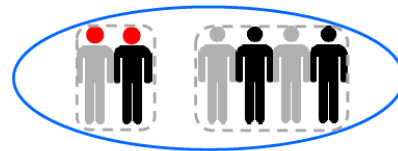
CRCT



Cohort design



TND




Vi-TT vaccinee




JE vaccinee




non-vaccinee

 Vi-TT cluster

 JE cluster

 seeking healthcare

 Typhoid cases

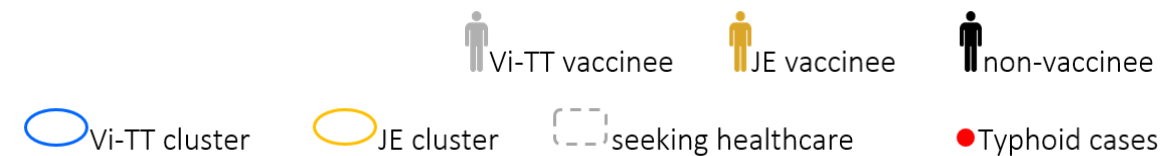
Blood culture-confirmed test positives other than *S.Typhi*

Negative Control Outcome Analysis (Association between non-typhoid fever and TCV/JE)

CRCT (150 clusters)	JE-recipients	TCV-recipients	Adjusted IRR
	N=33398	N=33822	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	56/43480	63/43697	1.14 (0.73,1.78)
Incidence rate (per 100,000 PYs) (95% CI)	129(97,167)	144(111,184)	



Adjusted for the cluster as a random effect, and randomisation stratification variables at the cluster level (geographical ward, distance to study clinics, number of eligible children at baseline), demographic factors (age and sex) and household hygiene factors as fixed effects

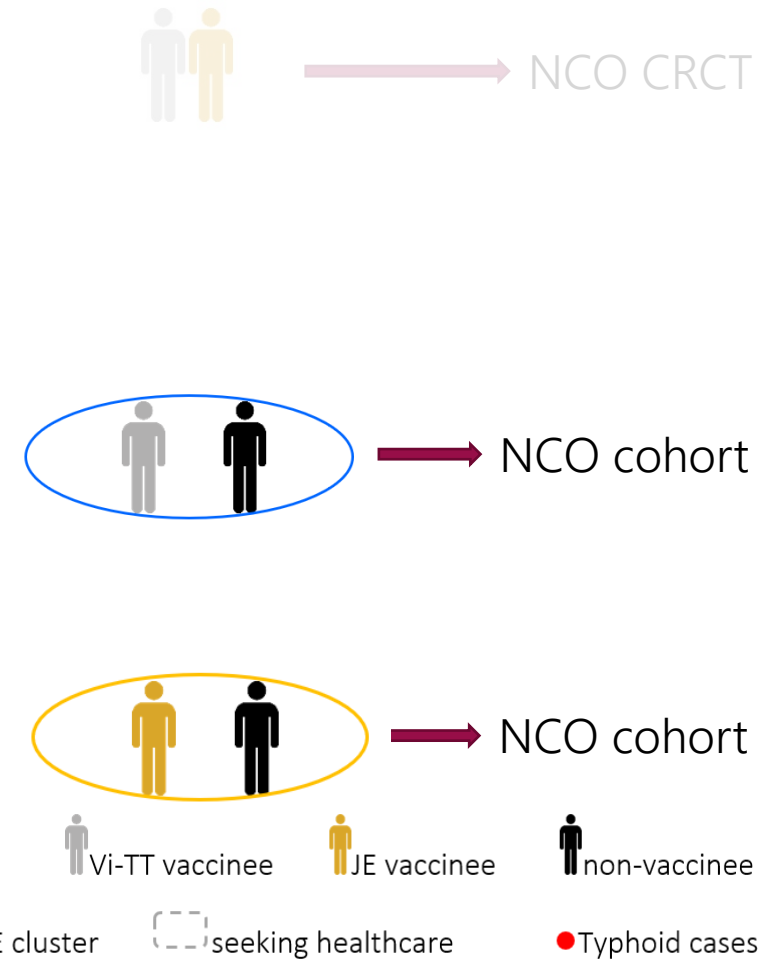


Negative Control Outcome Analysis (Association between non-typhoid and TCV/JE)

CRCT (150 clusters)	JE-recipients	TCV-recipients	Adjusted IRR
	N=33398	N=33822	
Incidence rate (per 100,000 PYs) (95% CI)	129(97,167)	144(111,184)	1.14 (0.73,1.78)

Cohort analysis (in TCV clusters)	Non-vaccinees	TCV-recipients	Adjusted IRR
	N=13863	N=33822	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	9/16293	63/43697	2.38 (1.07,5.30)
Incidence rate (per 100,000 PYs) (95% CI)	55(25,105)	144(111,184)	

Cohort analysis (in JE clusters)	Non-vaccinees	JE-recipients	Adjusted IRR
	N=13736	N=33398	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	10/16470	56/43480	1.93 (0.89,4.17)
Incidence rate (per 100,000 PYs) (95% CI)	61(29,112)	129(97,167)	

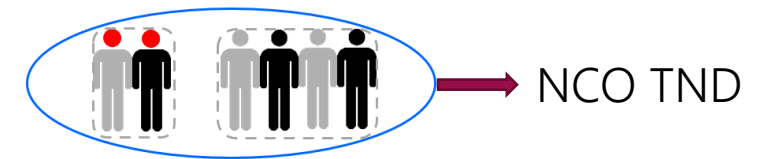


Negative Control Outcome Analysis (Association between non-typhoid and TCV/JE)

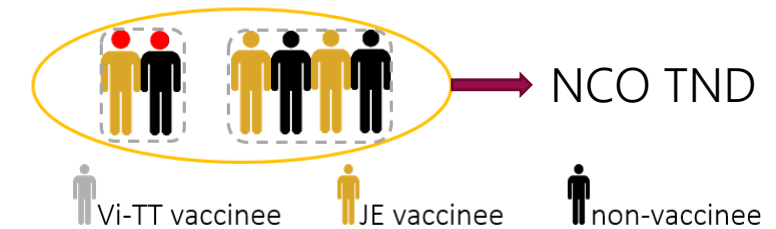
CRCT (150 clusters)	JE-recipients	TCV-recipients	Adjusted IRR
	N=33398	N=33822	
Incidence rate (per 100,000 PYs) (95% CI)	129(97,167)	144(111,184)	1.14 (0.73,1.78)



Test negative design (75 TCV clusters)	Test negatives	Test positives	Adjusted OR
Non-vaccinees	416 (14%)	9 (13%)	1.17 (0.57,2.37)
TCV-recipients	2490 (86%)	63 (88%)	



Test negative design (75 JE clusters)	Test negatives	Test positives	Adjusted OR
Non-vaccinees	411 (13%)	10 (15%)	0.78 (0.39,1.54)
JE-recipients	2846 (87%)	56 (85%)	

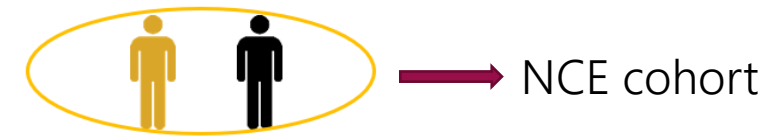


Before adjustment for health-seeking behaviours

<u>Cohort (75 TCV clusters)</u>	<u>Non-vaccinees</u>	<u>TCV-recipients</u>	<u>Adjusted IRR</u>	<u>Adjusted VE</u>
	N=13863	N=33822		
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	47/16283	45/43697	<u>0.34</u> <u>(0.21,0.55)</u>	<u>66 (45,79)</u>
Incidence rate (per 100,000 PYs) (95% CI)	288(212,384)	103(75,138)		



<u>Cohort (75 JE clusters)</u>	<u>Non-vaccinees</u>	<u>JE-recipients</u>	<u>Adjusted IRR</u>
	N=13736	N=33398	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	45/16470	262/43480	<u>2.09</u> <u>(1.45,3.00)</u>
Incidence rate (per 100,000 PYs) (95% CI)	273(199,366)	603(532,680)	



Average fever visits:

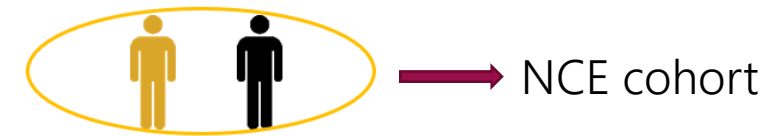
- 0.11 among vaccinees;
- 0.03 among non-vaccinees

After adjustment for health-seeking behaviours

<u>Cohort (75 TCV clusters)</u>	<u>Non-vaccinees</u>	<u>TCV-recipients</u>	<u>Adjusted IRR</u>	<u>Adjusted VE</u>
	N=13863	N=33822		
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	47/16283	45/43697	<u>0.16 (0.08,0.31)</u>	<u>84 (69,92)</u>
Incidence rate (per 100,000 PYs) (95% CI)	288(212,384)	103(75,138)		



<u>Cohort (75 JE clusters)</u>	<u>Non-vaccinees</u>	<u>JE-recipients</u>	<u>Adjusted IRR</u>
	N=13736	N=33398	
Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up	45/16470	262/43480	<u>1.00 (0.61,1.65)</u>
Incidence rate (per 100,000 PYs) (95% CI)	273(199,366)	603(532,680)	



Interpretations

- Our findings underscore the validity of TND as an efficient method to monitor effectiveness
- We recommend the adoption of TND alongside bias identification techniques such as NCE and NCO to support the TND results
- In using a cohort design, it is crucial to account for healthcare-seeking behaviours for valid effectiveness estimates.



The Typhoid Vaccine Acceleration Consortium (TyVAC) is led by the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH. TyVAC is funded by the Bill & Melinda Gates Foundation.

TyVAC works closely with global partners



Acknowledgements



icddr,b

Firdausi Qadri, Farhana Khanam, Prasanta Kumar Biswas

International Vaccine Institute

John D Clemens

University of Oxford

Andrew J Pollard, Elaine Shuo Feng, Yiyuan Zhang, Sarah Kelly, Yama F Mujadidi



Learn more at:

<http://takeontyphoid.org>



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