

The association between vaccine coverage and herd protection: exploratory analyses of a cluster-randomised trial of Vi conjugate vaccine

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Background

- Two typhoid vaccines studied by CRCT:
 - Vi polysaccharide vaccine, made from the purified Vi capsular polysaccharide from the Ty2 Salmonella Typhi strain
 - Vi-tetanus toxoid conjugate vaccine (TCV), using tetanus toxoid as the carrier protein with Vi polysaccharide

Vaccine	Vi polysaccharide vaccine	Vi-tetanus toxoid conjugate vaccine (TCV)
Vaccine efficacy	61% in Kolkata ¹	85% in Bangladesh ²
Indirect protection	Significant indirect protection (45%)	No evidence
Vaccine population	Residents aged >24 mths	Children aged 9 mths - < 16 yrs
Vaccine coverage	61%	20%

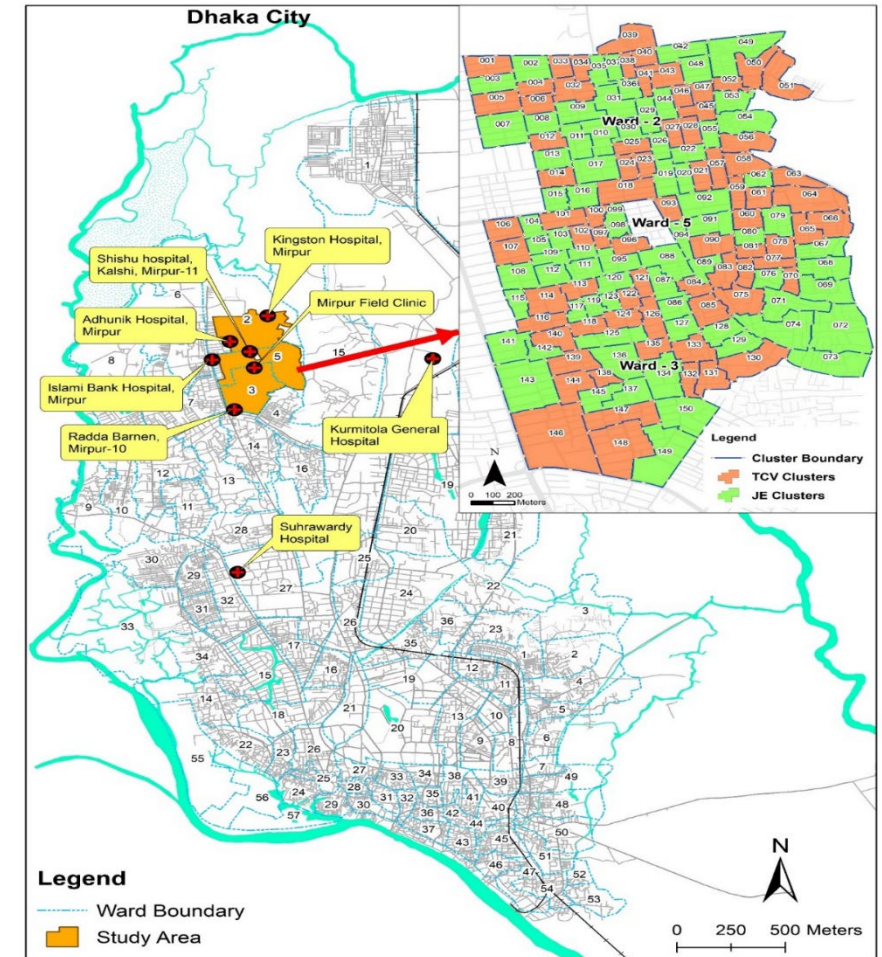
- Question: Does the vaccine coverage have an impact on the herd protection?

¹ Sur D, Ochiai R L, Bhattacharya S K, et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India[J]. New England Journal of Medicine, 2009, 361(4): 335-344

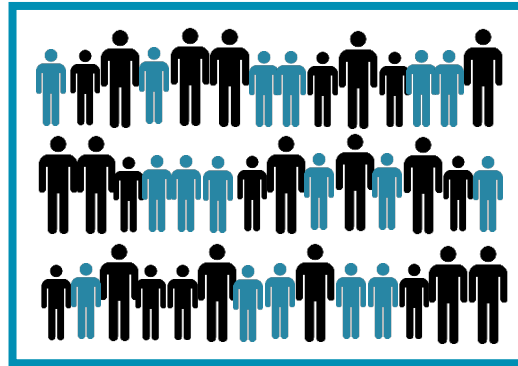
² Qadri F, Khanam F, Liu X, et al. Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial[J]. The Lancet, 2021, 398(10301): 675-684.

Description of TyVAC Bangladesh

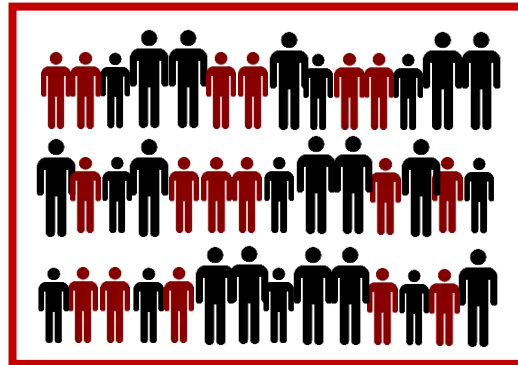
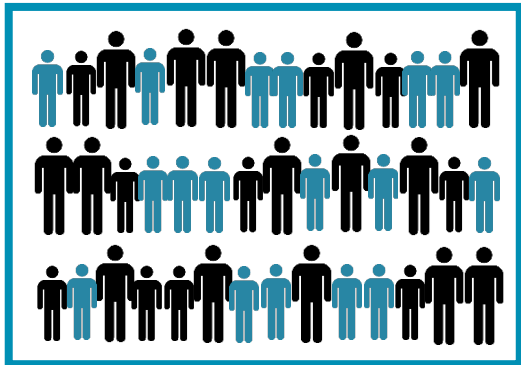
- Cluster randomised controlled trial of TCV efficacy in children (9 mths to <16 yrs)
- Apr 15, 2018 - March 15, 2020
- 150 contiguous clusters, 1:1 to either TCV or SA 14-14-2 Japanese encephalitis (JE) vaccine
- 67,395 children vaccinated (33,727 TCV and 33,315 JE)
- Baseline census between Feb 14, and March 25, 2018 (updated semiannually)
- Surveillance for typhoid fever started in Feb 2018 (all population)
- Patients with ≥ 2 days fever or axillary temperature of $\geq 38^{\circ}\text{C}$ taken blood culture



Cluster Randomised Controlled Trial



 vs.  → protection for vaccinated persons




 vs.  → protection for unvaccinated persons

TCV clusters

JE clusters

 Received TCV

 Received JE

 Non-vaccinees (child, adult)

Methods

- Cluster-level
 - Question: whether the herd protection increases with the increase in cluster-level vaccine coverage
 - 75 TCV (JE) clusters, 4 groups, based on the quantile of vaccine coverage rate (17% - 26%)

Methods: Cluster-level

TCV clusters

JE clusters

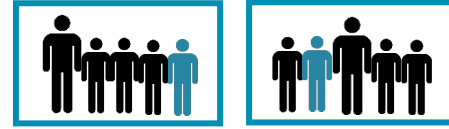
 Received TCV

 Received JE

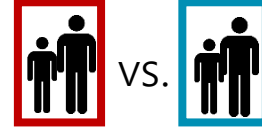
 Non-vaccinees (child, adult)



TCV clusters in group 1 (Q1)
17%-19%



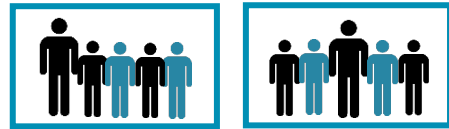
JE clusters in group 1 (Q1)
17%-19%



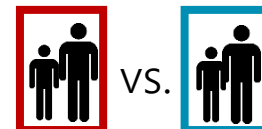
IRR in Q1



TCV clusters in group 2 (Q2)
19%-20%



JE clusters in group 2 (Q2)
19%-20%



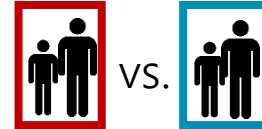
IRR in Q2



TCV clusters in group 3 (Q3)
20%-22%



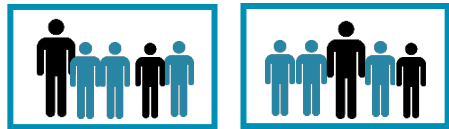
JE clusters in group 3 (Q3)
20%-21%



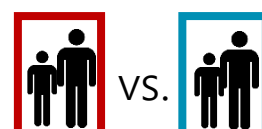
IRR in Q3



TCV clusters in group 4 (Q4)
22%-26%



JE clusters in group 4 (Q4)
21%-25%



IRR in Q4

Results: Cluster-Level

	N/PYs		Incidence, per 100,000 PYs		Adjusted VE [%]	P value for interaction*
	JE	TCV	JE	TCV		
Q1	71/9,664	12/9,702	735	124	88 [69,95]	0.97
Q2	68/10,309	13/10,207	660	127	79 [58,89]	
Q3	68/10,217	10/9,938	666	101	81 [56,92]	
Q4	47/11,550	9/12,062	407	75	80 [55,90]	
Q1	23/5,423	19/5,483	424	347	22 [-57,62]	0.40
Q2	23/5,079	20/5,048	453	396	10 [-84,56]	
Q3	20/4,618	29/4,416	433	657	-71 [-302,28]	
Q4	13/4,985	12/4,921	261	244	17 [-156,73]	
Q1	47/44,338	49/43,780	106	112	2 [-64, 42]	0.72
Q2	47/42,592	39/42,589	110	92	16 [-55, 54]	
Q3	44/39,308	41/38,464	112	107	-9 [-99,40]	
Q4	43/40,433	25/40,129	106	62	46 [-16,75]	

N/PYs: Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up

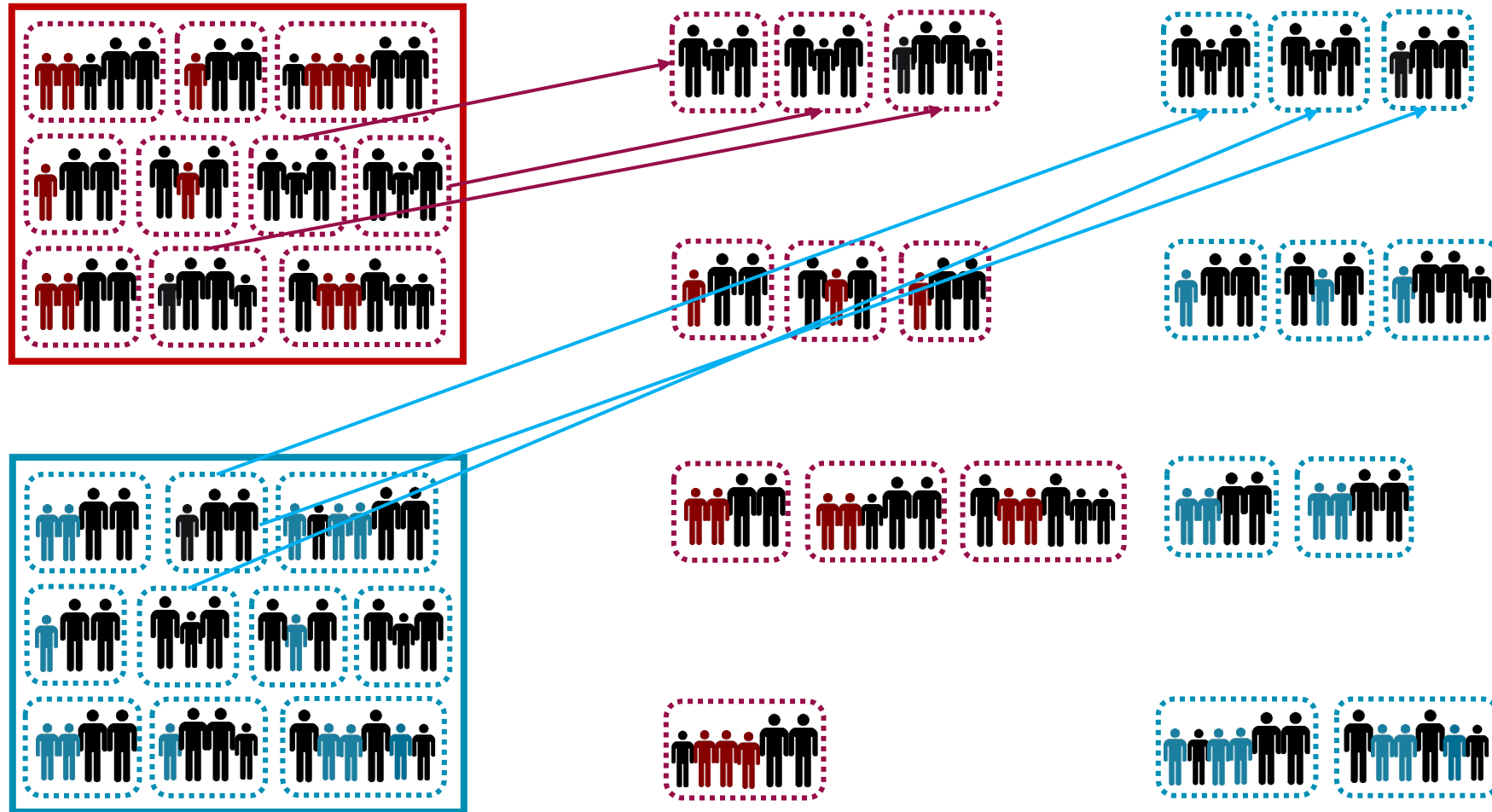
Adjusted IRR: Adjusted Incidence Rate Ratio, using Poisson regression adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation), and random effect (cluster)

* Interaction between quantile group and arm

Methods

- Cluster-level
 - Question: whether the herd protection increases with the increase in cluster-level vaccine coverage
 - 75 TCV (JE) clusters, 4 groups, based on the quantile of vaccine coverage rate (54% - 72%)
- Family-level:
 - Question: whether the herd protection on adults of a family increases with the increase in the number of vaccinated children in the family
 - Families in TCV (JE) arm, 4 groups, based on the number of TCV (JE) recipients

Methods: Family-level



Results: Family-level

TCV clusters

JE clusters



Received TCV

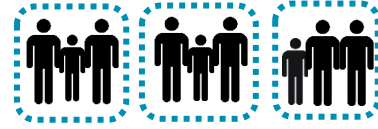


Received JE



Non-vaccinees (child, adult)

Family



vs.



IRR in adults of families with no vaccinated children (with age-eligible children)

Number of vaccinated children	N/PYs (n)		Incidence, per 100,000 PYs		Adjusted VE [%]	P value for interaction*
	JE	TCV	JE	TCV		
0	11/26,408 (n=23,206)	10/25,409 (n=22,740)	42	39	4 [-223, 71]	

N/PYs(n): Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up (number of adults >18 yrs)

Adjusted IRR: Adjusted Incidence Rate Ratio, using Poisson regression 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, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation), random effect (cluster), and number of eligible children for vaccination

* Interaction between family group and arm

Outcome: Family-level

TCV clusters

JE clusters



Received TCV



Received JE



Non-vaccinees (child, adult)

Family



vs.



IRR in adults of families with one vaccinated child

Number of vaccinated children	N/PYs (n)		Incidence, per 100,000 PYs		Adjusted VE [%]	P value for interaction*
	JE	TCV	JE	TCV		
0	11/26,408 (n=23,206)	10/25,409 (n=22,740)	42	39	4 [-223, 71]	
1	27/35,069 (n=30,015)	13/35,685 (n=30,387)	77	36	51 [-7,78]	

N/PYs(n): Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up (number of adults >18 yrs)

Adjusted IRR: Adjusted Incidence Rate Ratio, using Poisson regression 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, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation), random effect (cluster), and number of eligible children for vaccination

* Interaction between family group and arm

Outcome: Family-level

TCV clusters

JE clusters



Received TCV

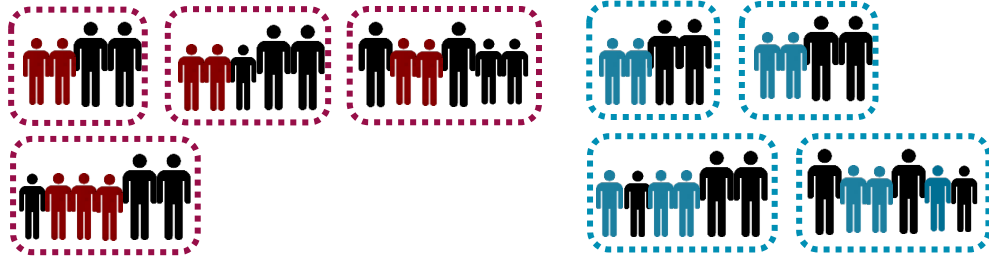


Received JE



Non-vaccinees (child, adult)

Family



vs.



IRR in adults of families with 2 or 3 vaccinated children

Number of vaccinated children	N/PYs (n)		Incidence, per 100,000 PYs		Adjusted VE [%]	P value for interaction*
	JE	TCV	JE	TCV		
0	11/26,408 (n=23,206)	10/25,409 (n=22,740)	42	39	4 [-223, 71]	0.97
1	27/35,069 (n=30,015)	13/35,685 (n=30,387)	77	36	51 [-7,78]	
2 & 3	10/29,206 (n=24,154)	10/29,105 (n=24,574)	34	34	-15 [-284,66]	

N/PYs(n): Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up (number of adults >18 yrs)

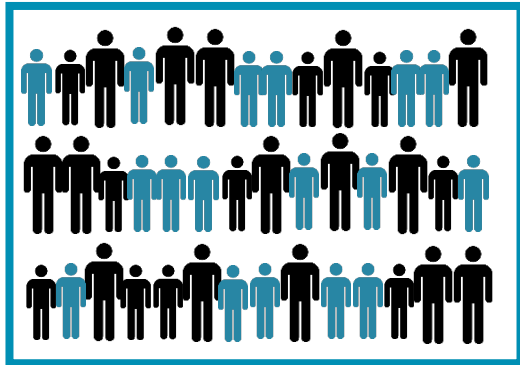
Adjusted IRR: Adjusted Incidence Rate Ratio, using Poisson regression adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation), random effect (cluster), and number of eligible children for vaccination

* Interaction between family group and arm

Methods

- Cluster-level
 - Question: whether the herd protection increases with the increase in cluster-level vaccine coverage
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- Family-level:
 - Question: whether the herd protection on adults of a family increases with the increase in the number of vaccinated children in the family
 - Families in TCV (JE) arm, 4 groups, based on the number of TCV (JE) recipients
- School-level:
 - Question: whether the herd protection on non-TCV vaccinated children (JE + non-vaccinees) increases with the increase in the school-level TCV coverage
 - School information collected by additional questionnaire
 - 35 schools with a size of >100 students, 2 groups, based on TCV coverage rate* (8% - 55%)

Methods: School-level



School TCV coverage
above median TCV
coverage rate (37%-55%)

School TCV coverage
below median TCV
coverage rate (8%-37%)



vs.



Incidence of typhoid
compared between non-
TCV recipients in high
TCV coverage schools
and that in low TCV
coverage schools

TCV
clusters

JE
clusters

Received TCV

Received JE

Non-vaccinees (child, adult)

Results: School-Level

	N/PYs (n)	Incidence, per 100,000 PYs	Adjusted VE [%]
Non-TCV recipients			
Below median	10/4,785 (n=3,101)	209	Ref
Above median	11/3,269 (n=2,178)	337	-7 [-4268,97]
TCV recipients			
Below median	1/2,018 (n=1,217)	50	
Above median	1/2,468 (n=1,445)	41	

N/Pys(n): Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up (number of non-TCV recipients)

Adjuster IRR: Adjusted Incidence Rate Ratio, using Poisson regression 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, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation), and random effect (cluster)

Summary

- Our study did not find an association between vaccine coverage and herd protection
- Vaccinating children may not result in a detectable level of herd protection in Bangladesh



THE AGA KHAN UNIVERSITY



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Major Contributors



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icddr,b

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Learn more at:

<http://takeontyphoid.org>



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