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Assessment of Vaccine Herd Protection: Lessons learned from vaccine trials Part II

This is the second article of a series of 3 articles on the "Assessment of Vaccine Herd Protection: Lessons learned from vaccine trials".

Assessment of Vaccine Herd Protection using examples from Cholera & Typhoid Vaccine Studies

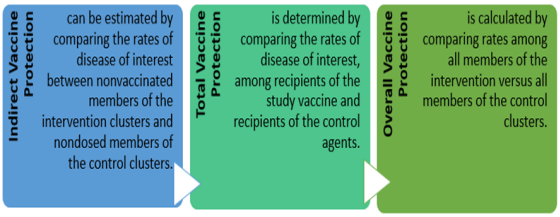
Vaccine Herd Protection can be assessed either via:

- **Cluster randomized trials**
- **Individually randomized trials &**
- **Nonrandomized (observational) studies**

While randomized trials are useful to avoid bias, non-randomized studies may be the only designs acceptable from an ethical, logistical and financial point of view and are also valuable to show the real-world impact of vaccination.

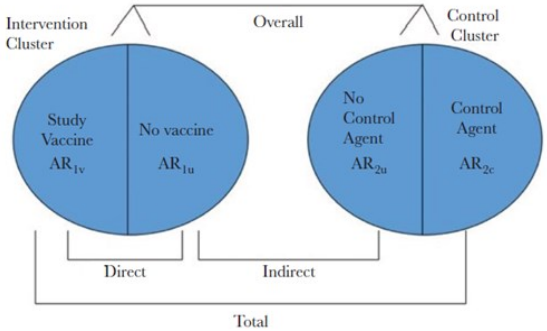
Cluster-Randomized Controlled Trials

Groups of individuals are randomized to receive the study vaccine (intervention clusters) or the control agent (control clusters), usually in a blinded manner, in **Cluster-Randomized Control Trials (CRCT).** Potential units of randomization are diverse and include workplaces, clinics, hospitals, schools, households etc. Further, some members of the clusters may choose to not receive the study vaccine or control agent. Indirect and total protection is assessed by comparing sub-samples within the clusters.



**Participation bias* is avoided by comparing those who receive the study vaccine with those who receive the control agent (all study participants) to assess total protection; while those who chose not to receive the study vaccine are compared with those who chose not to receive the control agent (all nonparticipants) to assess indirect protection. Thus, estimates are based on concurrent comparisons of groups that are similar by virtue of cluster randomization, hence strengthening the credibility of inferences made from CRCTs. (*figure 1*)

A **CRCT** was conducted in Kolkata, India, where slum-dwellers who were 2 years of age or older were randomly assigned to receive a single dose of either typhoid Vi polysaccharide vaccine (intervention) or inactivated hepatitis A vaccine (control agent), according to geographic clusters, with 40 clusters in each of the 2 study arms.[8]



- AR = Attack rate
- v = Vaccinated
- u = Unvaccinated or did not receive control agent
- c = Received control agent
- 1 = Intervention clusters
- 2 = Control clusters

Where:

- Indirect vaccine protection = [(1-AR1u/AR2u) × 100%].
- Total vaccine protection = [(1-AR1v/AR2c) × 100%].
- Overall protection = 1–(AR1)/(AR2) × 100%.
- Direct protection = [(1–AR1v/AR1u) × 100%].

Figure 1. Evaluation of vaccine protection in cluster-randomization trials [17].

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Primary endpoint of this trial was to assess the total Vi vaccine protection against typhoid fever when the vaccine was given under realistic public health conditions. Rates of typhoid episodes during the ensuing 2 years of surveillance was compared across different groups to calculate the Indirect Vaccine Protection (IVP), Total Vaccine Protection (TVP) & Overall Vaccine Protection (OVP). (*table 1*)

Results revealed (during 2 years of follow up), that TVP was 61% (95%CI: 41%-75%), IVP was 44% (95%CI: 2%-69%), and OVP was 57% (95%CI: 37%-71%). Further, the Vi (typhoid vaccine) coverage was around 60%, making the population impact of OVP *equivalent* to that for a vaccine with 100% direct protection but not conferring herd protection.

In contrast, a similar clinical trial in Karachi, Pakistan with similar study design and follow up period was conducted, with the difference being that children between the ages of 2-16 years were only vaccinated. Results revealed TVP of 57% (95%CI: 6%-81%) among children 5-16 years of age but none among children between ages of 2-5 years of age. This study also did not detect a statistically significant IVP and OVP either. This difference in results between the studies carried out in Kolkata and Karachi have been ascribed to the non-inclusion of adults as vaccine recipients in the Karachi site, potentially allowing continued transmission of typhoid fever in the intervention clusters.

These differences in outcome in 2 rather similar **CRCTs** shows the importance of study design. A) The disease of interest shouldn't ideally be transmitted to a great extent by groups not targeted for the vaccination within the chosen clusters, as this could have an effect on estimation of vaccine-induced herd effects. B) The intercluster migration of participants should be minimal, as this could change the vaccine recipient to nonvaccinee composition of the clusters and alter estimates of herd protection. C) Sample size needs to be considered carefully and adequate number of clusters need to be allocated to prevent imbalance in baseline factors between vaccinated and control clusters.

Several variations to **CRCTs** to assess **vaccine herd protection** have come up recently such as the double randomization design or fried-egg design.[9]

Adapted from the following Sources

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Table 1. Typhoid Vi Vaccine Effectiveness Estimates From a Cluster-Randomized Trial in Kolkata, India [26, 27]

Vaccine Protection	Number of Persons	Number of Typhoid Fever Episodes	Rate per 1000 Person-Years	% VE (95% CI)
Total				
Typhoid vaccine recipients	18 869	34	0.9	61 (41–75)
Hepatitis A vaccine recipients	18 804	96	2.7	*P* < .0001
Indirect				
Nonvaccinees in the intervention clusters	12 206	16	0.7	44 (2–69)
Nonvaccinees in the control clusters	12 877	31	1.3	*P* < .0429
Overall				
All residents in the intervention clusters	31 075	50	0.8	57 (37–71)
All residents in the control clusters	31 681	127	2.1	*P* < .0001

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

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 to be continued ...

Table 1: Selected notifiable diseases reported by Medical Officers of Health 16th– 22nd Sep 2023 (38th Week)

RDHS	Dengue Fever		Dysentery		Encephalit		Enteric Fever		Food Poi-		Leptospirosis		Typhus		Viral		Human		Chickenpox		Meningitis		Leishmania-		WRCD	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	T*	C**
Colombo	73	11593	0	14	0	11	0	2	0	12	7	266	0	0	0	5	0	0	6	259	1	37	0	6	**40**	**100**
Gampaha	58	11680	0	19	2	16	0	7	0	5	18	477	2	10	1	16	0	0	3	233	11	102	3	40	**9**	**100**
Kalutara	58	4115	2	22	1	3	0	1	5	16	26	711	0	2	0	10	0	1	16	422	2	87	0	2	**63**	**200**
Kandy	132	6124	0	33	1	2	0	10	0	17	4	241	2	51	0	3	0	2	12	230	1	23	0	25	**89**	**100**
Matale	19	1343	0	4	0	3	0	1	0	27	0	126	0	14	0	6	0	0	2	54	0	7	8	259	**28**	**100**
NuwaraEliya	3	235	3	136	0	4	0	3	0	49	2	121	2	63	0	5	0	0	10	151	1	23	0	3	**62**	**100**
Galle	49	2339	1	40	0	13	0	5	1	28	8	764	6	70	0	2	0	1	16	281	0	24	0	3	**38**	**100**
Hambantota	7	1265	1	10	0	3	0	1	0	9	4	253	1	68	0	9	0	0	3	126	0	17	15	511	**32**	**100**
Matara	35	1616	1	23	0	8	0	1	0	18	7	449	1	31	0	5	0	2	8	256	1	18	7	156	**59**	**100**
Jaffna	25	2008	2	85	0	2	0	12	0	30	0	12	2	503	0	5	0	2	2	156	1	15	0	2	**67**	**93**
Kilinochchi	3	89	0	9	0	0	0	1	0	16	0	8	0	7	0	0	0	0	2	19	0	2	0	0	**36**	**100**
Mannar	1	82	0	6	0	0	0	1	0	0	1	36	0	5	0	1	0	0	0	2	0	8	0	1	**51**	**100**
Vavuniya	3	152	0	10	0	1	0	0	0	17	0	30	0	8	0	2	0	0	2	23	0	12	0	10	**17**	**100**
Mullaitivu	0	117	0	13	0	1	0	4	0	12	0	36	0	6	0	1	0	0	2	14	0	2	0	7	**27**	**100**
Batticaloa	9	2149	2	165	0	8	0	5	0	18	4	82	0	1	0	8	1	2	4	84	2	33	0	1	**66**	**100**
Ampara	5	218	2	9	0	1	0	1	0	53	0	114	0	2	0	1	0	0	1	70	4	47	1	8	**11**	**100**
Trincomalee	2	1996	0	22	0	1	0	1	2	67	0	64	0	15	0	3	0	0	2	62	1	29	0	5	**31**	**100**
Kurunegala	22	2611	0	38	0	15	0	1	1	7	6	327	0	16	1	11	0	2	10	450	2	171	20	444	**29**	**100**
Puttalam	13	2890	0	30	0	3	0	1	0	2	6	77	0	8	0	1	0	0	1	93	3	61	0	19	**28**	**100**
Anuradhapur	10	678	0	13	0	1	0	1	0	8	0	242	0	30	0	4	0	2	3	207	0	43	20	499	**30**	**100**
Polonnaruwa	4	527	1	15	0	6	0	1	0	11	3	154	0	6	1	13	0	0	2	75	0	17	16	357	**37**	**100**
Badulla	20	960	3	36	0	5	0	0	0	44	8	290	0	51	1	81	0	0	3	141	1	40	3	38	**67**	**100**
Monaragala	10	618	0	21	0	6	0	0	0	5	4	458	0	35	1	24	0	1	0	61	3	71	5	151	**30**	**100**
Ratnapura	23	1923	2	41	0	15	0	2	0	19	25	1003	0	27	0	16	0	2	4	178	4	133	20	160	**36**	**100**
Kegalle	36	2685	0	22	0	2	0	2	0	15	8	575	4	41	1	6	0	0	17	384	5	75	2	36	**33**	**100**
Kalmune	4	1678	0	65	0	10	0	0	0	0	1	49	0	1	0	0	0	0	3	112	0	34	0	0	**51**	**100**
SRILANKA	**624**	**61691**	**20**	**901**	**4**	**140**	**0**	**64**	**9**	**505**	**142**	**6965**	**20**	**1071**	**6**	**238**	**1**	**17**	**134**	**4143**	**43**	**1131**	**120**	**2743**	**42**	**99**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 22nd Sep, 2023 Total number of reporting units 358 Number of reporting units data provided for the current week: 358 **C****-Completeness

A = Cases reported during the current week. B = Cumulative cases for the year.

Table 2: Vaccine-Preventable Diseases & AFP

16th– 22nd Sep 2023 (38th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2023	Number of cases during same week in 2022	Total number of cases to date in 2023	Total number of cases to date in 2022	Difference between the number of cases to date in 2023 & 2022
	W	C	S	N	E	NW	NC	U	Sab					
AFP*	00	00	00	00	00	00	00	00	00	00	00	72	53	35.8 %
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	00	02	01	00	00	00	01	00	02	06	01	180	68	164.7 %
Measles	52	03	07	01	00	01	02	01	05	72	00	493	17	2800 %
Rubella	00	00	00	00	00	00	00	00	00	00	00	05	00	0 %
CRS**	00	00	00	00	00	00	00	00	00	00	00	02	00	0 %
Tetanus	00	00	00	00	00	00	00	00	00	00	00	06	05	100 %
Neonatal Tetanus	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Japanese Enceph-alitis	00	00	00	00	00	00	00	00	00	00	00	02	01	100 %
Whooping Cough	00	00	00	00	00	00	00	00	00	00	00	07	01	600 %
Tuberculosis	96	27	08	07	10	39	17	05	14	223	162	6797	5006	35.7%

Key to Table 1 & 2

Provinces: **W**: Western, **C**: Central, **S**: Southern, **N**: North, **E**: East, **NC**: North Central, **NW**: North Western, **U**: Uva, **Sab**: Sabaragamuwa.

RDHS Divisions: **CB**: Colombo, **GM**: Gampaha, **KL**: Kalutara, **KD**: Kandy, **ML**: Matale, **NE**: Nuwara Eliya, **GL**: Galle, **HB**: Hambantota, **MT**: Matara, **JF**: Jaffna, **KN**: Killinochchi, **MN**: Mannar, **VA**: Vavuniya, **MU**: Mullaitivu, **BT**: Batticaloa, **AM**: Ampara, **TR**: Trincomalee, **KM**: Kalmunai, **KR**: Kurunegala, **PU**: Puttalam, **AP**: Anuradhapura, **PO**: Polonnaruwa, **BD**: Badulla, **MO**: Moneragala, **RP**: Ratnapura, **KG**: Kegalle.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Neonatal Tetanus, Whooping Cough, Chickenpox, Meningitis, Mumps., Rubella, CRS,

Special Surveillance: AFP* (Acute Flaccid Paralysis), Japanese Encephalitis

CRS =**Congenital Rubella Syndrome

NA = Not Available

Number of Malaria Cases Up to End of September 2023,

02

All are Imported!!!

Comments and contributions for publication in the WER Sri Lanka are welcome. However, the editor reserves the right to accept or reject items for publication. All correspondence should be mailed to The Editor, WER Sri Lanka, Epidemiological Unit, P.O. Box 1567, Colombo or sent by E-mail to **chepid@sltnet.lk. Prior approval should be obtained from the Epidemiology Unit before publishing data in this publication**

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