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

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

Individually Randomized Controlled Trials

Individually Randomized Controlled Trials (IRCT) were primarily utilized for measuring direct vaccine protection of vaccine recipients. The **Vaccine Protective Efficacy (PE)** calculated in **IRCTs**, measures the direct protective benefit of vaccination to an individual *in isolation from other persons in the same population*. To reiterate, the IRCT aims to estimate vaccine protection *independent of vaccine herd effects.* However, if suitable geographic clusters can be identified with sufficient variation in vaccine coverage between these clusters, vaccine herd effects can be estimated by evaluation of the *correlation* of disease incidence with levels of vaccine coverage in these clusters. These clusters are usually defined by Geographic Information Systems (GIS), and level of vaccine coverage in surrounding clusters.

A reanalysis of a placebo controlled, **IRCT** of the inactivated cholera vaccine in Matlab, Bangladesh[10] was carried out in 2005. Advantage was taken of the differing levels of vaccine coverage of geographically defined groups of individuals that could have occurred due to the randomization process or different participation rates. The geographic unit of analysis was noted as the '*bari'* – which is a patrilineal linked cluster of households (grouped by descent through the male line or relationship with the father), due to the assumption that most cholera transmission tends to occur within rather than between '*baris*'. Incidence rates of cholera among placebo recipients was inversely related to levels of vaccine coverage in & around the 'baris' (7 cases per 1000 in lowest quintile of coverage vs 1.5 cases per 1000 in the highest quintile; P<0.0001), thus displaying the IVP that the oral cholera vaccine induced among nonvaccinees. Using information from the same trial, a dynamic population-based model of cholera transmission was developed and showed that if roughly half of the population were vaccinated, the number of cholera cases would considerably reduce among unvaccinated people by 89% and among the entire population by 93%.[11]

	Target population (%)	Vaccine group			Placebo group		
		n	Cases	Risk per 1000*	n	Cases	Risk per 1000†
<28%	24 954 (20·6%)	5627	15	2·66	2852	20	7·01
28–35%	25 059 (20·7%)	8883	22	2·47	4429	26	5·87
36–40%	24 583 (20·3%)	10772	17	1·57	5503	26	4·72
41–50%	24 159 (19·9%)	11 513	26	2·25	5801	27	4·65
>50%	22 394 (18·5%)	12 541	16	1·27	6082	9	1·47
Total	121 149 (100%)	49 336	96	1·94	24 667	108	4·37

Adapted from reference 44. *p=0·05 for trend and †p<0·0001 for trend in adjusted analyses.

Table 2: Cholera risk by the level of cholera vaccine coverage of baris, Matlab, Bangladesh 1985–86

Contents **Page**

Non-Randomized (Observational) Studies

In such studies, as there is no comparator group receiving a control agent or placebo, comparisons are made between the vaccinated and unvaccinated individuals in the community itself. The geographic area where the vaccine is administered is divided into clusters with a mixture of vaccinated and unvaccinated persons. IVP is estimated through comparisons of the disease incidence in nonvaccinated individuals in each geographic cluster, by level of vaccine coverage.
Following a mass oral cholera vaccination campaign in Zanzibar[12], the incidence of acute watery diarrhea that was laboratory confirmed as cholera over course of 14 months was assessed in both vaccine recipients and nonvaccinees. The subsequent lower risk of cholera in nonvaccinated individuals residing in areas with low vaccine coverage was considered as IVP. There was a statistically significant difference ($P<0.0001$) in the lowest quintile of coverage (2.29 cases per 1000) versus the highest quintile (0.87 cases per 1000). Further, the absence of vaccine protection against non-cholera diarrhea inferred that the vaccine effectiveness found against cholera could not be explained by bias.

Conclusion

Vaccine herd protection could be critical to the ability of the vaccine to control a disease under realistic public health conditions. Studies on **vaccine herd protection** are now often required to inform in policy decisions about vaccine introduction including in assessments of the cost effectiveness of vaccines. Herd protection by vaccines has conventionally been assessed through observations of disease trends after the vaccine is included in the national immunization programme. Potential suitability of newer study designs such as **CRCTs** and **IRCTs** for measurement of **vaccine herd protection** offers the opportunity to assess this type of protection even before the vaccine is licensed and with a greater protection against bias.[2]

CRCTs are a relatively straightforward method to assess **vaccine herd protection** with unbiased measurements of IVP, TVP & OVP. Similarly, methodological advances such as usage of mapping techniques has allowed **vaccine herd protection** to be assessed in **IRCTs** and nonrandomized trials as well. These approaches also allow the estimation of dose-response relations between vaccine coverage levels and magnitude of these effects.[2]

However, it needs to be noted that several limitations exist for the above approaches. Herd protective effects for a particular vaccine could vary between populations dependent on levels and patterns of vaccine coverage, differences in host immune responses to the vaccine & differences in transmission patterns of the target disease.[2] Thus, demonstration of **vaccine herd protection** prior to vaccine licensing would only indicate the potential for the vaccine to induce herd protection and does not guarantee that the vaccine will confer herd protection when it is used in the community. The same holds true conversely as well. Absence of herd protective effects in pre-licensing trials does not exclude the possibility of a vaccine to confer herd protection.

Moreover, pre-licensure assessments of **vaccine herd protection** should not be seen as a suitable replacement for post-licensure assessment as only the latter studies can provide a widely comprehensive picture of a vaccine's herd protective effects. Nevertheless, the ability of randomized trials to yield important information about vaccine herd protective effects and possibility of having these assessments during vaccine development and implementation gives support to greater use of these approaches as complimentary to conventional pre-licensure individually randomized trials.

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Adapted from the following Sources

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Table 1: Selected notifiable diseases reported by Medical Officers of Health 23rd- 29th Sep 2023 (39th 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	62	11655	0	14	1	12	0	2	0	12	3	269	0	0	0	5	0	0	9	268	1	38	0	6	**40**	**100**
Gampaha	46	11726	0	19	0	16	0	7	0	5	9	486	0	10	0	16	0	0	5	238	4	106	3	43	**9**	**100**
Kalutara	34	4149	0	22	0	3	0	1	0	16	12	723	0	2	0	10	0	1	6	428	0	87	0	2	**63**	**200**
Kandy	120	6244	0	33	0	2	0	10	0	17	6	247	2	53	0	3	0	2	12	242	1	24	1	26	**89**	**100**
Matale	26	1369	0	4	0	3	0	1	2	29	1	127	0	14	0	6	0	0	0	54	0	7	6	265	**28**	**100**
NuwaraEliya	3	238	0	136	0	4	0	3	0	49	5	126	1	64	0	5	0	0	6	157	0	23	0	3	**62**	**100**
Galle	45	2384	3	43	0	13	0	5	1	29	16	780	1	71	0	2	0	1	10	291	1	25	0	3	**38**	**100**
Hambantota	5	1270	1	11	0	3	0	1	0	9	2	255	0	68	0	9	0	0	3	129	1	18	16	527	**33**	**100**
Matara	21	1637	1	24	0	8	0	1	1	19	4	453	1	32	0	5	0	2	8	264	2	20	4	160	**59**	**100**
Jaffna	26	2034	0	85	0	2	0	12	1	31	0	12	3	506	0	5	0	2	1	157	0	15	0	2	**68**	**93**
Kilinochchi	0	89	0	9	0	0	0	1	0	16	0	8	0	7	0	0	0	0	0	19	0	2	0	0	**37**	**100**
Mannar	1	83	0	6	0	0	0	1	0	0	0	36	0	5	0	1	0	0	0	2	0	8	0	1	**52**	**100**
Vavuniya	4	156	0	10	0	1	0	0	1	18	0	30	0	8	0	2	0	0	0	23	0	12	0	10	**17**	**100**
Mullaitivu	1	118	0	13	0	1	0	4	0	12	0	36	0	6	0	1	0	0	3	17	0	2	0	7	**28**	**100**
Batticaloa	10	2159	2	167	0	8	0	5	0	18	0	82	0	1	0	8	0	2	4	88	1	34	0	1	**66**	**100**
Ampara	5	223	0	9	0	1	0	1	0	53	1	115	0	2	0	1	0	0	3	73	1	48	0	8	**12**	**100**
Trincomalee	3	1999	0	22	0	1	0	1	0	67	0	64	0	15	0	3	0	0	1	63	0	29	0	5	**31**	**100**
Kurunegala	16	2627	0	38	0	15	0	1	0	7	14	341	1	17	0	11	0	2	8	458	6	177	19	463	**29**	**100**
Puttalam	4	2894	1	31	0	3	0	1	0	2	1	78	0	8	0	1	0	0	2	95	3	64	0	19	**29**	**100**
Anuradhapur	4	682	0	13	0	1	0	1	0	8	4	246	0	30	0	4	0	2	8	215	0	43	12	511	**30**	**100**
Polonnaruwa	1	528	0	15	0	6	0	1	0	11	2	156	1	7	0	13	0	0	0	75	0	17	3	360	**37**	**100**
Badulla	9	969	0	36	0	5	0	0	0	44	7	297	0	51	2	83	0	0	3	144	3	43	0	38	**67**	**100**
Monaragala	6	624	0	21	0	6	0	0	3	8	4	462	0	35	0	24	0	1	2	63	0	71	3	154	**30**	**100**
Ratnapura	14	1937	1	42	1	16	1	3	13	32	9	1012	0	27	1	17	0	2	5	183	0	133	2	162	**36**	**100**
Kegalle	14	2699	0	22	0	2	0	2	0	15	9	584	1	42	0	6	0	0	4	388	1	76	2	38	**34**	**100**
Kalmune	9	1687	0	65	0	10	0	0	0	0	1	50	0	1	0	0	0	0	4	116	1	35	0	0	**51**	**100**
SRILANKA	**489**	**62180**	**9**	**910**	**2**	**142**	**1**	**65**	**22**	**527**	**110**	**7075**	**11**	**1082**	**3**	**241**	**0**	**17**	**107**	**4250**	**26**	**1157**	**71**	**2814**	**42**	**99**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 29th Sep, 2023 Total number of reporting units 358 Number of reporting units data provided for the current week: 358 **C****-Completeness

Table 2: Vaccine-Preventable Diseases & AFP

23rd– 29th Sep 2023 (39th 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	03	72	60	35.8 %
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	00	02	00	01	00	00	00	00	01	04	01	184	69	166.6 %
Measles	22	03	04	04	00	01	03	00	00	37	00	530	17	3017.6 %
Rubella	00	01	00	00	00	00	00	00	00	01	00	06	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	101	10	18	04	04	00	03	07	04	151	94	6948	5100	36.2%

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

Take prophylaxis medications for leptospirosis during the paddy cultivation and harvesting seasons.

It is provided free by the MOH office / Public Health Inspectors.

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ON STATE SERVICE

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