

# Measuring Vaccine Herd Protection in Individually Randomized Trials

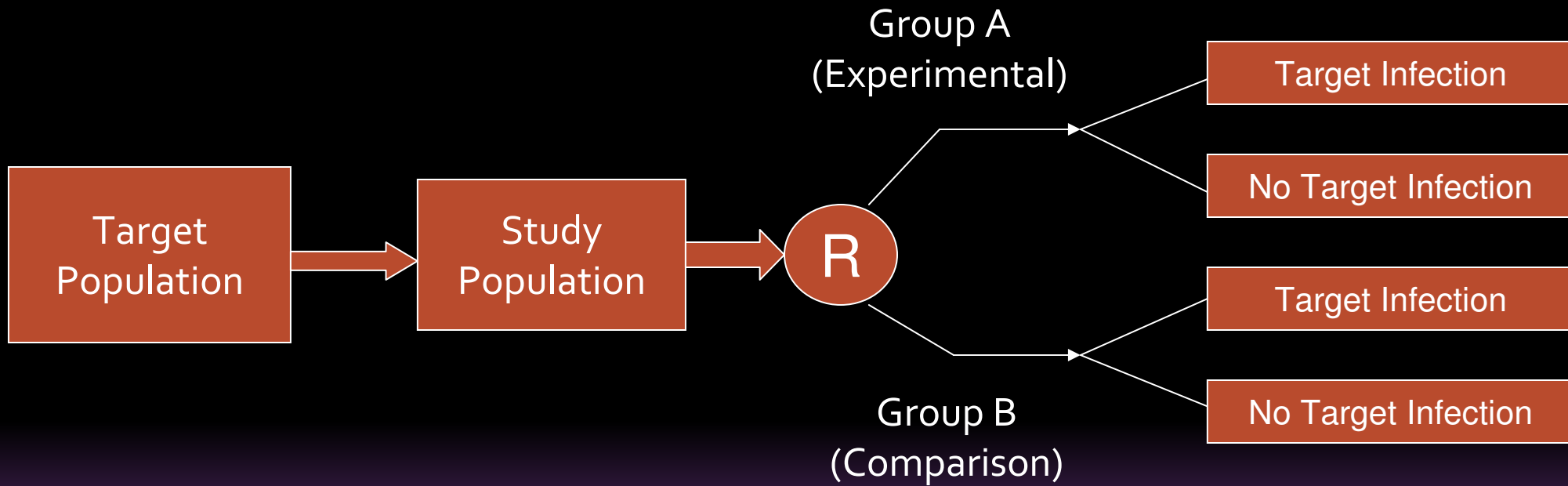


Mohammad Ali, Ph.D.  
International Vaccine Institute

# Options for Assessing Herd Protection in Randomized Controlled Trials (RCTs)

- Cluster-randomized trials (CRTs)
- Individually-randomized trials (IRTs)

# Schema of a RCT



Assembly

Allocation

Surveillance

# Conventional Analysis of Vaccine Protection in Phase III Trials

$$\text{Protective Efficacy (PE)} = [1 - (\text{IR}_v \div \text{IR}_c)] \times 100\%$$

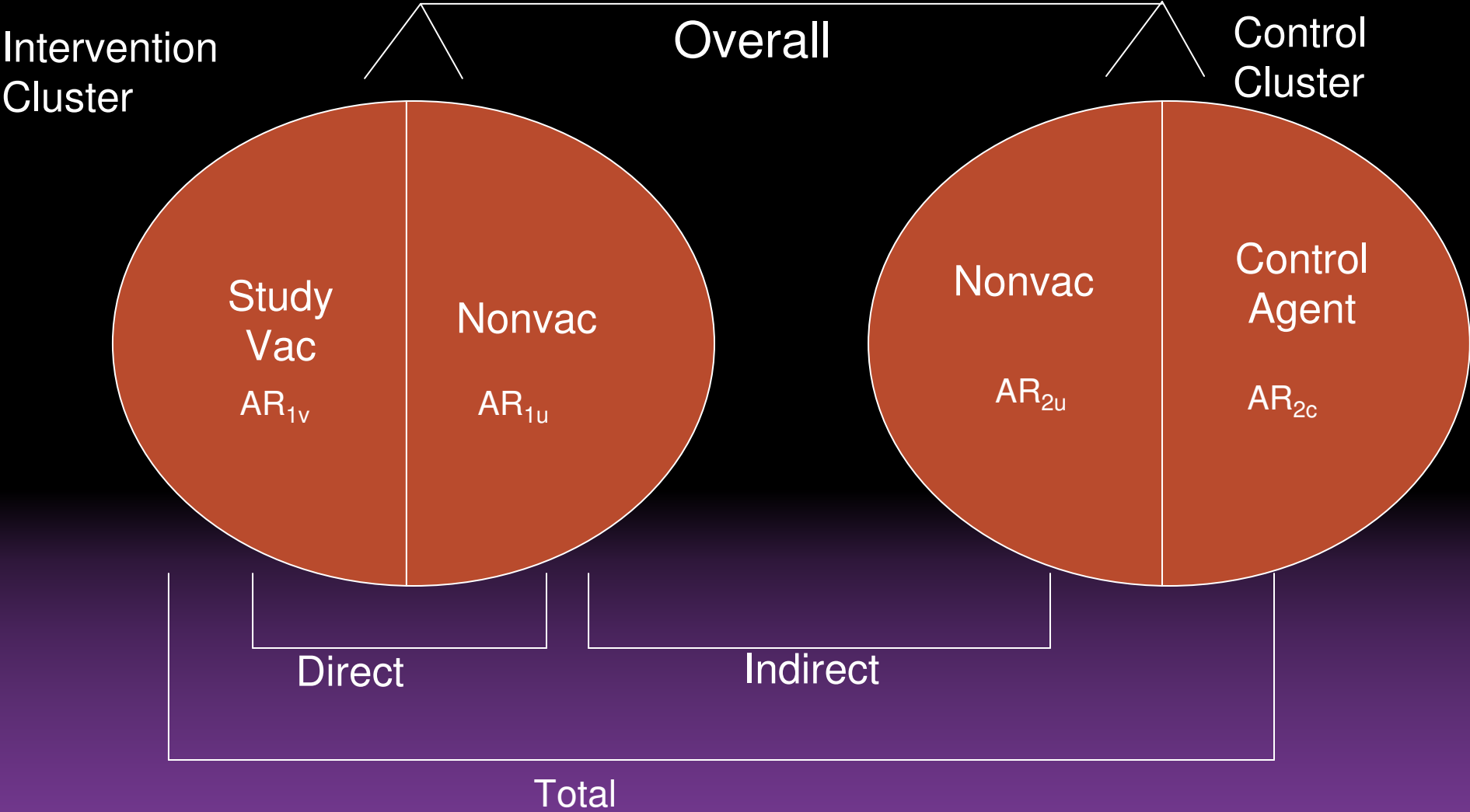
$\text{IR}_v$  = Incidence rate in vaccinated group

$\text{IR}_c$  = Incidence rate in control group

# Elements of CRTs

- Unit of randomization: cluster of people
- Randomization of clusters is typically done before enrollment of individuals in the clusters
- Eligible, consenting individuals within cluster receive agent (vaccine or control agent) assigned to the cluster
- Longitudinal follow-up for target outcomes

# Evaluation of Vaccine Protection in CRTs



# Considerations for Measuring Herd Protection in CRTs

- If the target infection is transmitted from person to person, clusters must correspond to unit of transmission (negligible between-cluster transmission)
- The population in each cluster must be stable over time
- Sample size calculations must take account of non-independence of outcome events within clusters

## Phase IV CRT of Vi Polysaccharide (PS) against Typhoid Fever in Kolkata

- Eligibility: Age  $\geq$  2years
- Vaccine under study: Vi PS
- Control vaccine: Hepatitis A
- Units of randomization: 80 clusters (40 per arm)
- Participants: 37,073 (total population : 62,756)
- Target outcome: Blood culture-proven typhoid fever detected during 2 years of follow-up
- Primary goal: Measurement of total Vi vaccine protection against typhoid when Vi is given programmatically

# The Geographic Clusters for the Vi Trial in Kolkata



# Total, Indirect, and Overall Protections against Typhoid Fever by Vi Polysaccharide

	Total		Indirect		Overall	
	Vi vac. N=18,869	Hep A vac. N=18,804	Non-vac. Vi clusters N=12,206	Non-vac. Hep A clusters N=12,877	All residents Vi clusters N=31,075	All residents Hep A clusters N=31,681
Typhoid Episodes	34	96	16	31	50	127
Rate/1000 person-years	0.9	2.7	0.7	1.3	0.8	2.1
Protection	65% (P<.0001; 95%CI:42%,79%)		45% (P<.05; 95%CI:1%,70%)		60% (P<.0001; 95%CI:39%,74%)	

# Elements of Individually Randomized Trials (IRT)

- Unit of randomization = individual
- Randomization is typically done before enrollment of individuals
- Eligible, consenting individuals receive agent (vaccine or control agent)
- Longitudinal follow-up for target outcomes

# Vaccine Protective Efficacy (PE) Calculated from an IRT

- PE is intended to measure the *direct* protective benefit of vaccination to an individual in isolation from other persons in the same population
- Due to individual randomization, PE is thought not to reflect herd protective benefits

# Use of IRTs to Analyze Herd Effects

- In any IRT there will be geographic differences in vaccine coverage of the target population due to chance variations in randomized assignments and to different rates of eligibility and participation
- If suitable geographic clusters can be identified and if there is sufficient variation in vaccine coverage between these clusters, vaccine herd effects can be assessed by evaluating the *correlation* of disease incidence with levels of vaccine coverage in these clusters

# 1985 Efficacy Trial of Orally-Administered, Killed Whole Cell-based Cholera Vaccines

- Compared agents: BS-WC vaccine; WC vaccine; *E.coli* K12 placebo
- Site: Matlab, Bangladesh (ICDDR,B)
- Eligibility: Children aged 2-<15 yrs; Women 15 years and older
- Exclusions: Pregnancy; too ill to leave bed on the day of vaccination
- Regimens: 3 doses, at 6-week intervals
- Allocation: Individually randomized
- Surveillance: Treatment-center based
- Enrollment: 89,596; 62,285 received complete 3 dose regimens

# 1985 Field Trial of Killed Oral Cholera Vaccines: Analysis of Data for First Year of Surveillance

Feature	Group		
	BS-WC	WC	K12
Cholera episodes	41	52	110
Cholera risk/1,000	1.9	2.5	5.2
PE	63% (p<.0001; 95% CI: 46%, 74%)	53% (p<.0001; 95% CI: 33%, 66%)	

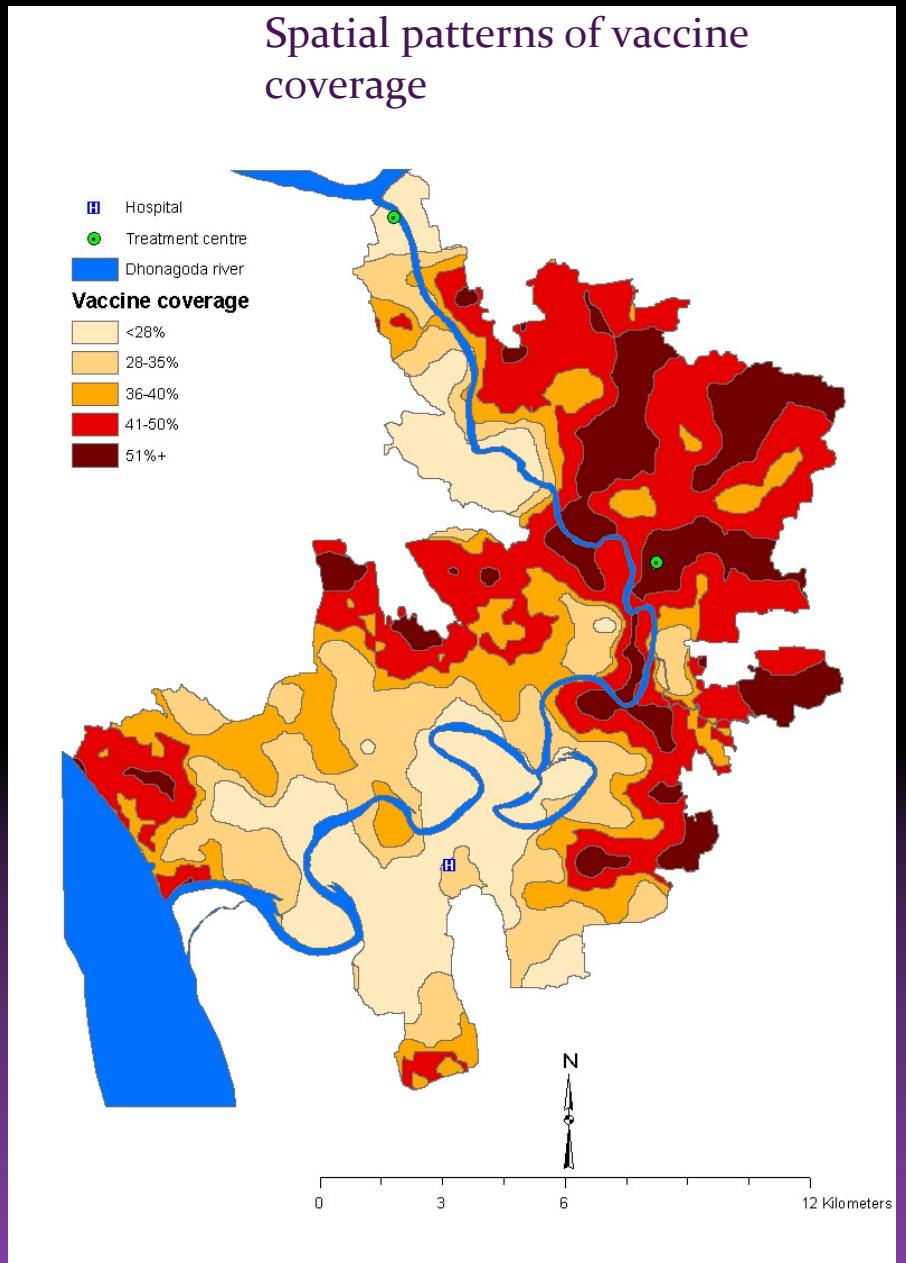
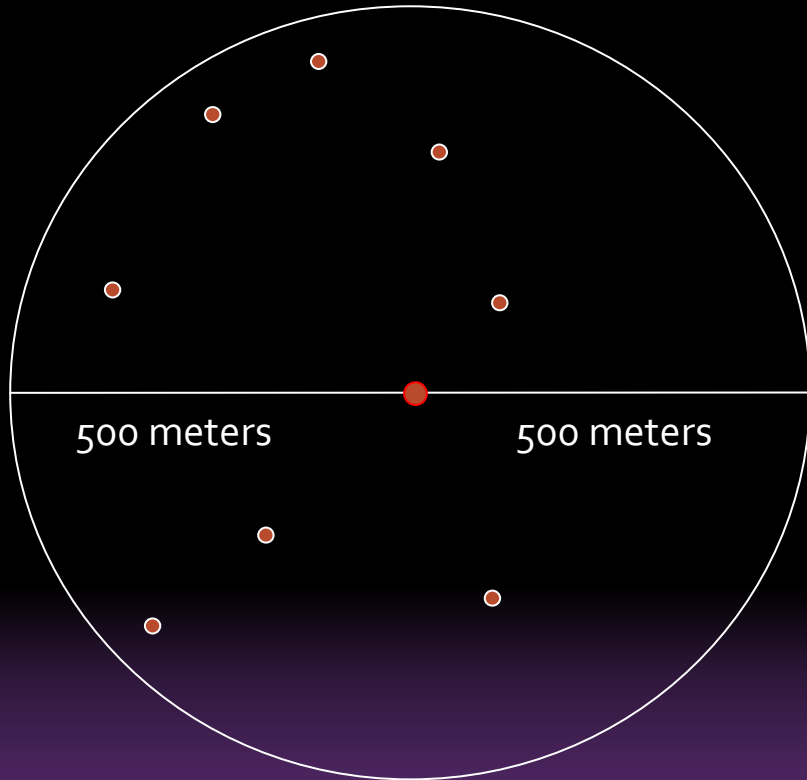
# Research Questions

- Was the risk of cholera among non-vaccinated neighbors of vaccinees inversely related to the level of vaccine coverage? This would indicate *indirect* protection of non-vaccinees
- Was the risk of cholera among vaccinees inversely related to the level of vaccine coverage? This would indicate *direct plus indirect* (“*total*”) protection of vaccinees

# Strategy for Defining Geographic Units and Vaccine Coverage

- Geographic unit of analysis: *bari*, which is a patrilineally linked cluster of households (N=6,423). Most transmission of cholera thought to occur within rather than between *baris*
- “Vaccine coverage of the *bari*” defined as proportion of eligible subjects who were vaccinated in the *bari* and in a 500m radius from the *bari* (ascertained by GIS mapping)

# Levels of Vaccine Coverage, Matlab, 1985



# Cholera Risk by the Level of Cholera Vaccine Coverage, Matlab, Bangladesh 1985-1986

Level of vaccine coverage	Target population		Vaccinated group			Placebo group		
	N	%	N	Cases	Risk/ 1000 persons*	N	Cases	Risk/1000 persons**
<28%	24,954	20.6	5,627	15	2.66	2,852	20	7.01
28-35%	25,059	20.7	8,883	22	2.47	4,429	26	5.87
36-40%	24,583	20.3	10,772	17	1.57	5,503	26	4.72
41-50%	24,159	19.9	11,513	26	2.25	5,801	27	4.65
51%+	22,394	18.5	12,541	16	1.27	6,082	9	1.47
<b>Total</b>	<b>121,149</b>	<b>100</b>	<b>49,336</b>	<b>96</b>	<b>1.94</b>	<b>24,667</b>	<b>108</b>	<b>4.37</b>

\* P=.05 for trend

\*\* P<.0001 for trend

# Cholera Risk in Children Aged <2years at Baseline by the Level of Vaccine Coverage, Matlab, Bangladesh, 1985-86

Level of vaccine coverage	Number of children	Number of cholera cases	Risk/1000 Children*
<28%	2,378	45	18.92
28-35%	2,371	27	11.38
36-40%	2,297	36	15.67
41-50%	2,207	29	13.14
>50%	2,205	19	8.61

\* P<.001

# Summary

- Moderate levels of direct vaccine protection have impeded introduction of licensed newer generation vaccines into developing countries
- Convincing evidence about the herd protective effects of these vaccines has been difficult to obtain due to the fact that their use in developing countries has been so limited
- CRTs have been proposed as a way to evaluate herd protection even introduction into practice

# Summary

- A Phase IV CRT in Kolkata has demonstrated that Vi polysaccharide vaccine confers herd protection against typhoid fever, a fact that should be considered in future policy decisions about this vaccine
- Although it had traditionally been thought that IRTs were suited only for measurement of direct protection, recent methodological advances in the analyses of these trials provide the opportunity to analyze herd protection
- Re-analysis of an IRT of killed oral cholera vaccines demonstrated major herd protective effects

*Thank you*