Herd Protective Effects of Vaccines

- Are demonstrated by a protective impact of a vaccine in a population that exceeds an impact expected on the basis of:

  1. The proportion of the population vaccinated

  2. The protective efficacy of the vaccine

Herd Protective Effects of Vaccines

- Can result from:

  1. Transmission of a live vaccine from vaccinee to neighboring non-vaccinee

     * OPV

Herd Protective Effects of Vaccines

- Can result from:

  2. Passive transfer of vaccine-induced immunity from one person to another

     * Maternal immunization (tetanus toxoid, influenza vaccine)

Herd Protective Effects of Vaccines

- Can result from:

  3. Reduction of transmission of the target pathogen in a population in which a proportion become immune due to vaccination ("herd protection").

     -- Can occur with either live or inactivated vaccines

     -- Applies only to pathogens transmitted from person to person.

Herd Protection Effects of Vaccines

- Can result in:

  1. Protection of non-vaccinees

  2. Enhanced protection of vaccinees (if due to reduction of pathogen transmission)

- Can dramatically improve the benefits that can be obtained from vaccination, including improved cost-effectiveness

Transmissability of Pathogens from Person to Person

- The transmissability of an infectious agent can be quantified by "basic reproduction number (R_0)"

  -- Average number of transmissions expected from a single primary case introduced into a fully susceptible population

  -- Depends on:
    * Biological properties of the infectious agent and host
    * Rate and pattern of contacts
    * Characteristics of the site

Limitation of R_0

- R_0 is an idealized concept

  -- One major deviation of reality from the ideal is population immunity

  -- If some contacts of infectious individuals are immune, the contacts will fail to lead to transmission

  -- Effective reproduction number (R_n) is actual number of transmissions under realistic conditions

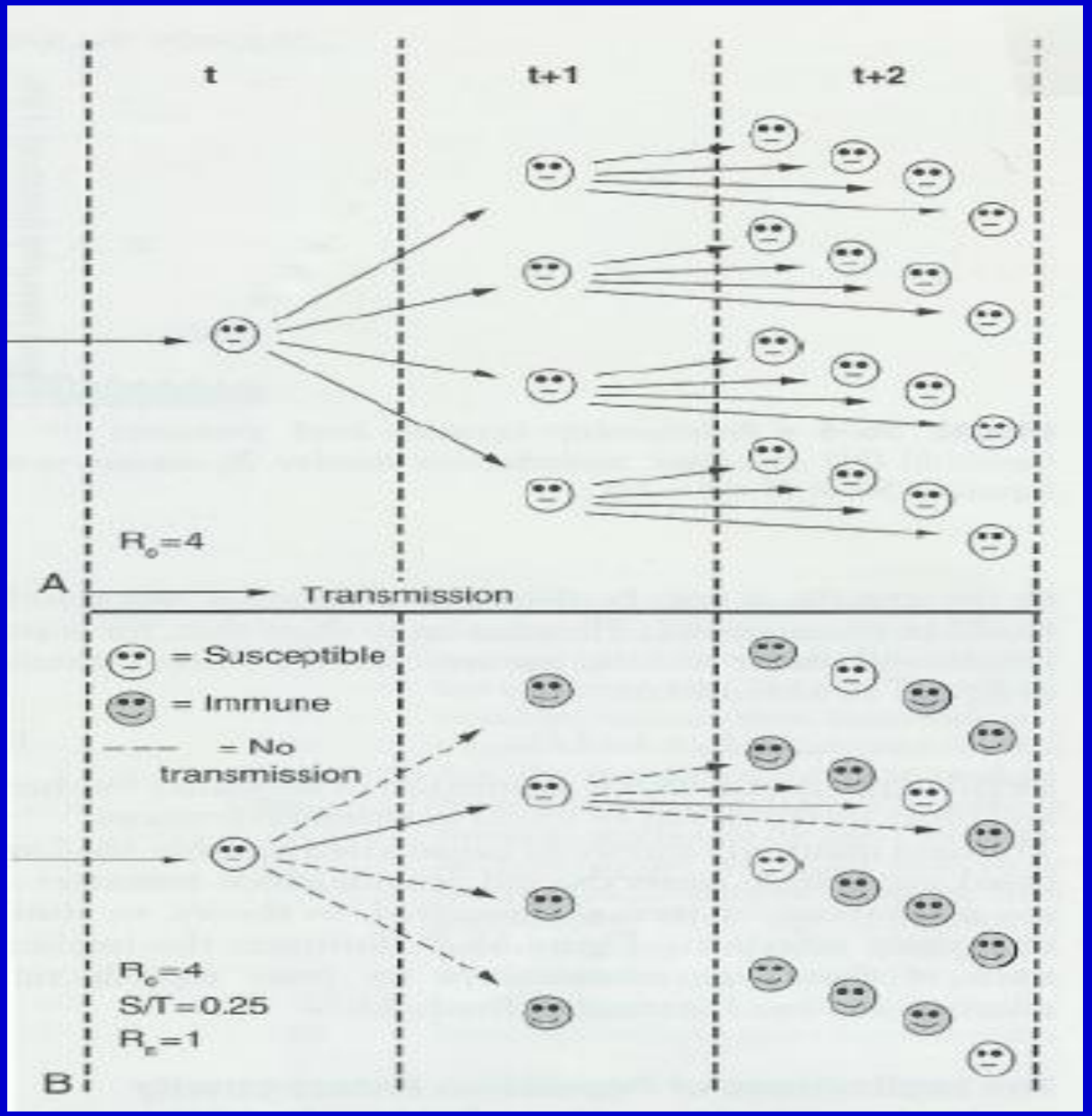
Implications of R_n vs. R_0

- $R_n = R_0$ X S (proportion susceptible)

  -- If S = 1/ R_0 , R_n = 1, and the incidence of the disease should be stable

  -- If S < 1/ R_0 , R_n < 1, and the incidence of the disease should die out over time

  -- H (*Herd immunity threshold*)= 1 - 1/ R_0


t
t+1
t+2
R_o=4
A
Transmission
= Susceptible
= Immune
= No transmission
R_o=4
S/T=0.25
R_e=1
B

Approximate Basic Reproduction Numbers (in Developed Countries) and Implied Crude Herd Immunity Thresholds (*H*, Calculated as *1-1*/R_0) for Common Vaccine-Preventable Diseases

Infection	Basic Reproduction Number (R_0)	Herd Immunity Threshold (%)
Diphtheria	6-7	85
Influenza	?	?
Measles	12-18	55-94
Mumps	4-7	75-86
Pertussis	12-17	92-94
Polio	2-15	50-93
Rubella	6-7	83-85
Smallpox	5-7	80-85
Tetanus	Not applicable	Not applicable
Tuberculosis	?	?
Varicella	8-10?	?

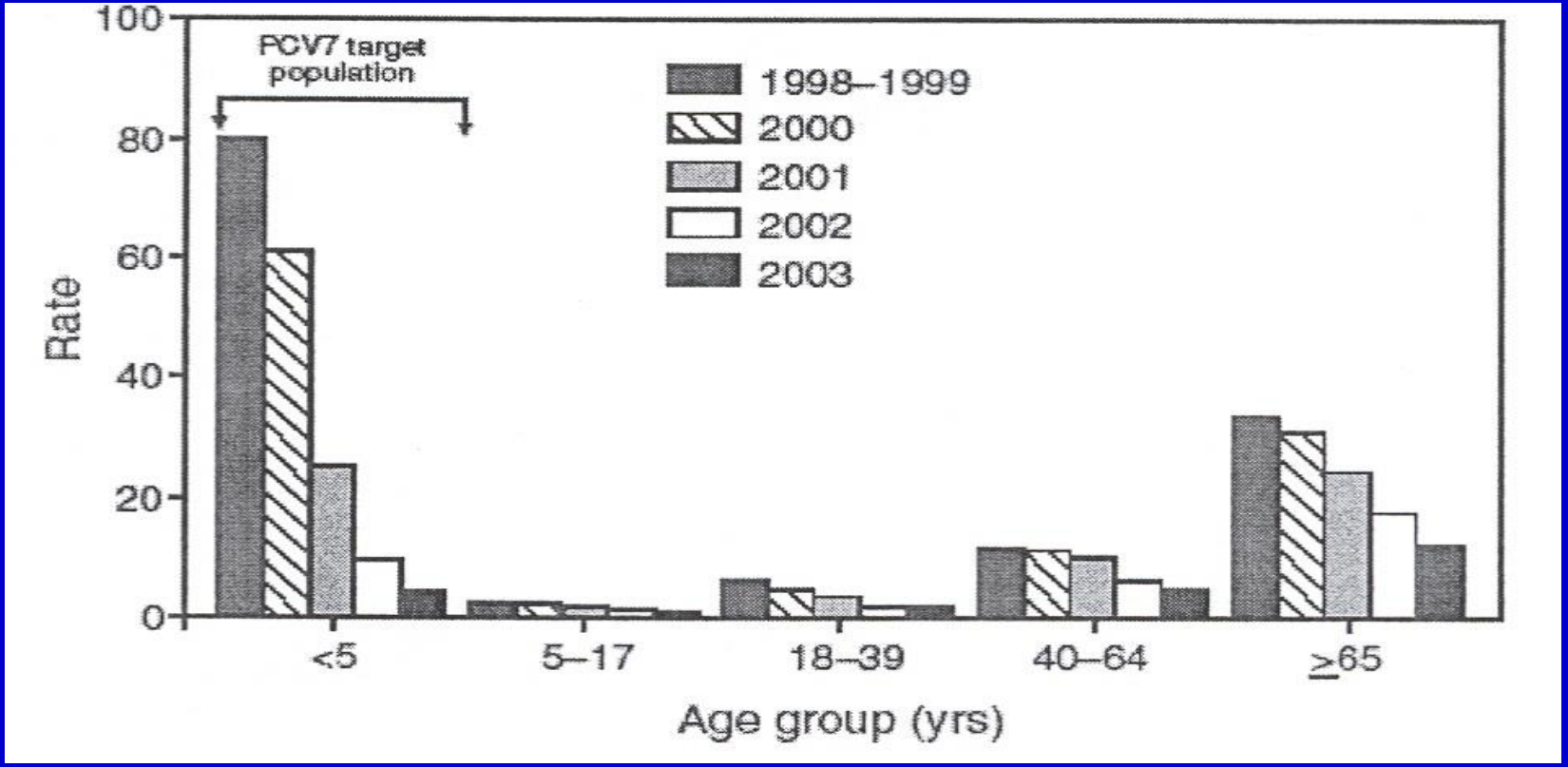
Limitations of the Argument

- This argument is a simplification:
  - -- Heterogeneous mixing patterns
  - -- All infectious individuals are not equally infectious
  - -- All susceptibles are not equally susceptible
  - -- All immunes are not completely or equally protected
- But it usefully illustrates the concept

Important Point About Herd Protection

- Herd protection short of extinction of the infection can occur when the level of population immunity is below the herd immunity threshold

Rate* of Vaccine-Type (VT) Invasive Pneumococcal Disease (IPD) before and after Introduction of Pneumococcal Conjugate Vaccine (PCV7), by Age Group and Year – Active Bacterial Core Surveillance, United States, 1998-2003 (CDC, 2004)



* Per 100,000 population.

† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998-1999 baseline is statistically significant ($p<0.05$).

Limitations of Post-licensure Observational Assessments of Vaccine Herd Protective Effects

- Can only be done if vaccine is already in use
- Require high quality data on vaccination and disease outcomes (rare in LDCs)
- Susceptibility to bias

Are There Options for Evaluating Vaccine Herd Protection Even Before a Vaccine is Licensed?

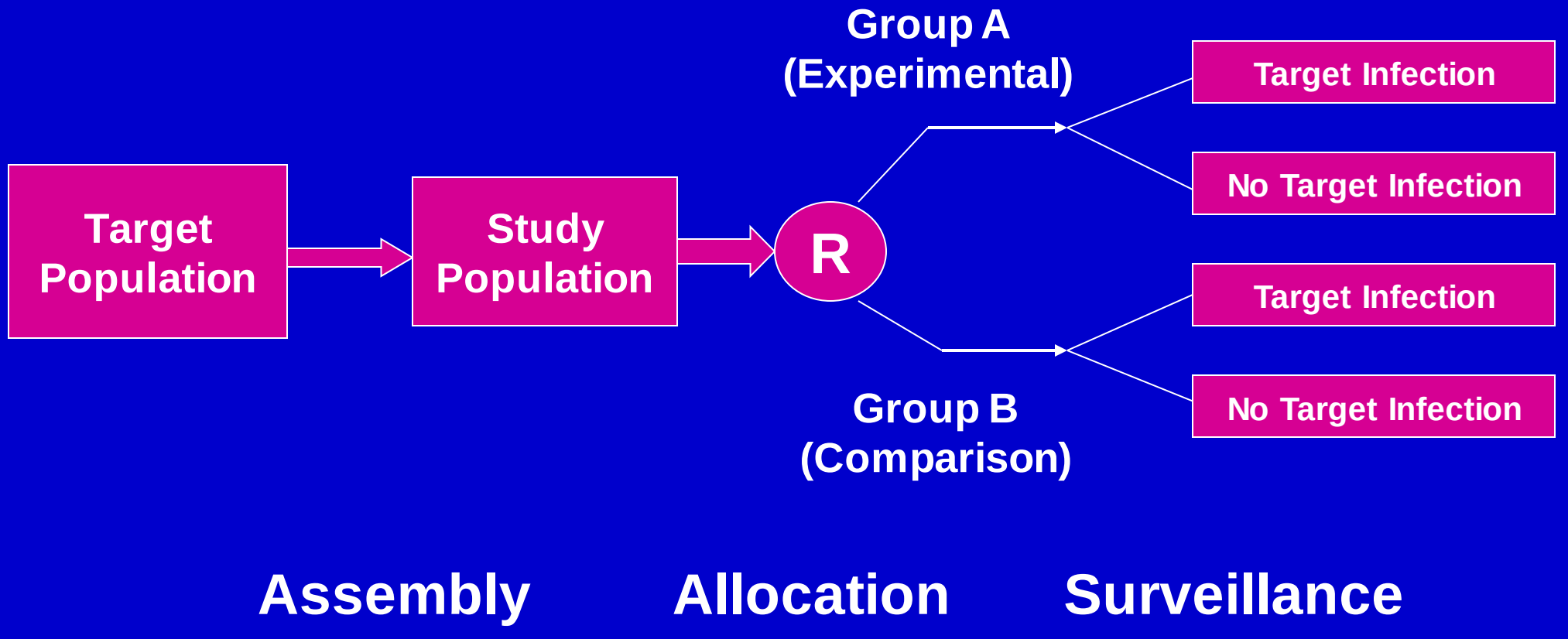


Figure 1 A schematic of the sequence of events in a two-group, randomized controlled trial. In this sequence, the study population is assembled from a target population and is then Randomized to constitute the experimental vaccine and comparison groups, which are then Followed longitudinally and concurrently for ascertainment of the occurrence of target infections.

Conventional Analysis of Vaccine Protection in Phase III Trials

Protective Efficacy (PE) =

$$\frac{(\text{Incidence}_{\text{controls}} - \text{Incidence}_{\text{vaccinees}})}{\text{Incidence}_{\text{controls}}} \times 100\%$$

Vaccine Protective Efficacy (PE) Calculated from an Individually Randomized Trial

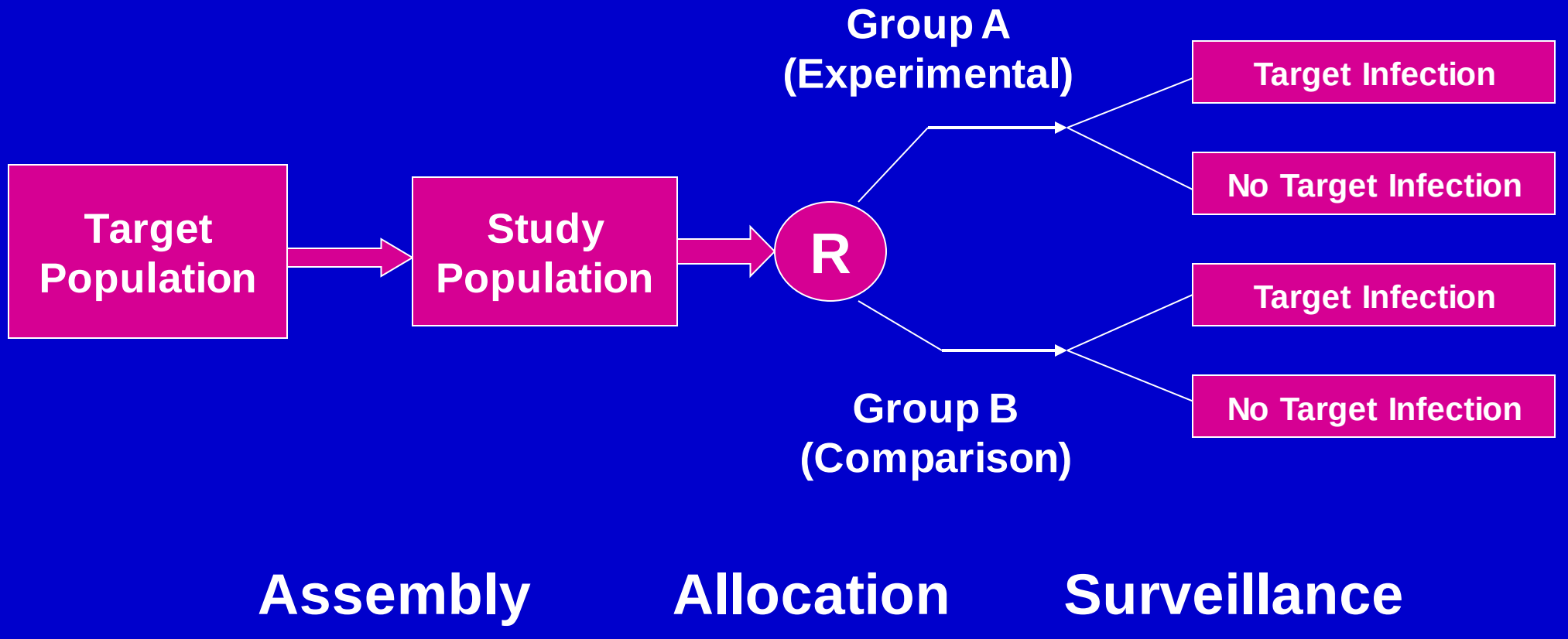
- PE is intended to measure the *direct* protective benefit of vaccination to an individual in isolation from other persons in the same population
- Due to individual randomization, PE is thought not to reflect the two protective benefits that may occur due to herd effects:
    1. Protection of unvaccinated neighbors ("indirect protection")
    2. Enhanced protection of vaccinees ("total protection")
- Yet it can be argued that it would be desirable to have a "read-out" on whether a vaccine can elicit herd protection even before the vaccine is licensed

Options for Assessing Herd Protection in Randomized Trials

- Cluster-randomized trials

Elements of Cluster-Randomized Trials

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



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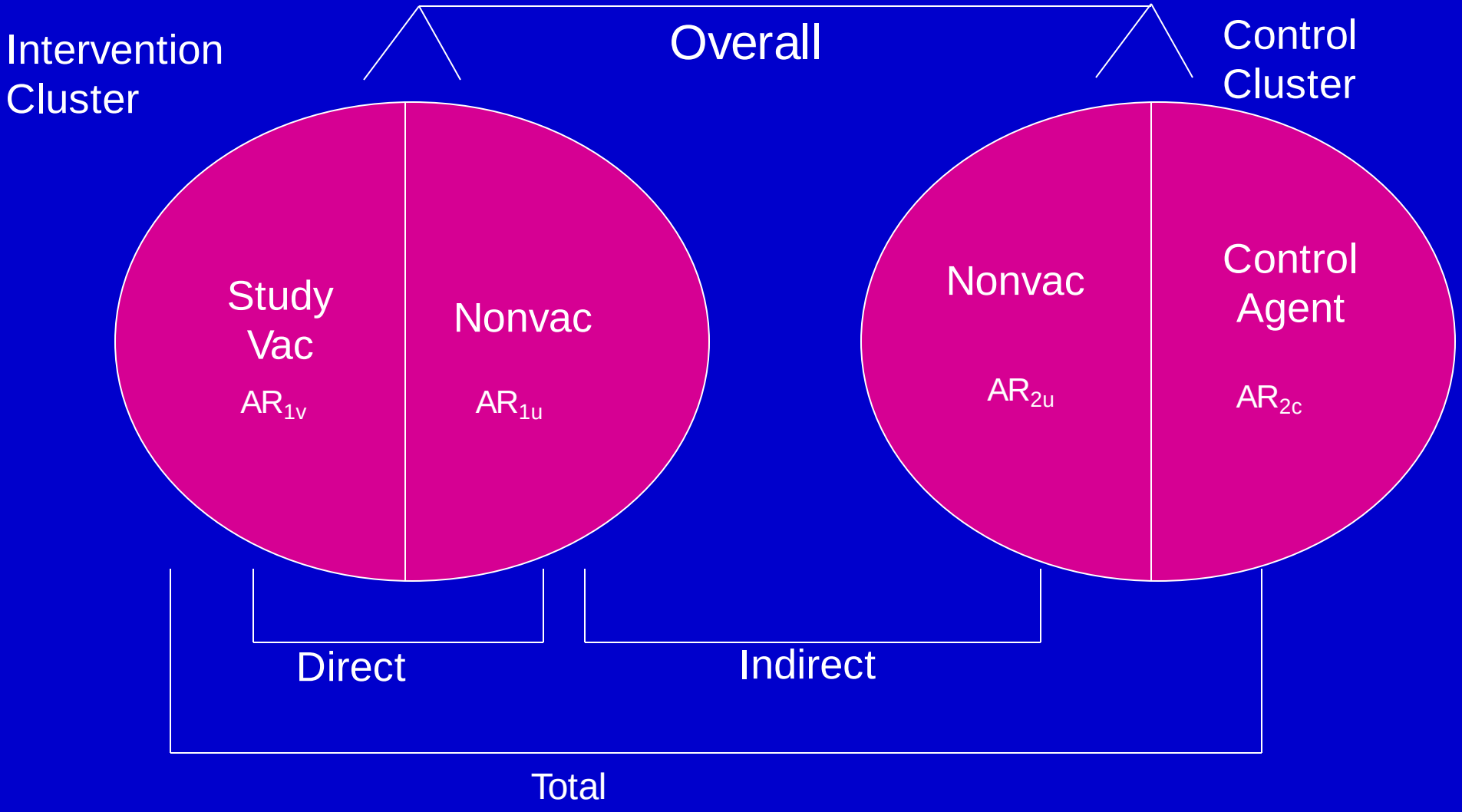
Evaluation of Vaccine Protection in CRTs



Considerations for Measuring Herd Protection in Cluster-Randomized Trials

- If 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

Vi Vaccine against Typhoid Fever

- Based on Vi polysaccharide capsule of *S. typhi*
- Internationally licensed, based on efficacy trials done in Nepal and South Africa. Protective efficacy = 60-70%.
- Several features make Vi attractive for developing country programs:
  - Single dose vaccine
  - Effective in settings with high incidence of typhoid
  - Not patent-protected, easily transferred, and cheap to produce
- Licensed for travellers, but used sparsely in public sector for control of typhoid in developing countries

Kolkata *Bustees*

Phase IV Cluster-Randomized Trial of Vi Polysaccharide (PS) against Typhoid Fever

- Eligibility : Age ≥ 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

Analysis of *Total Protection* against Typhoid Fever by Vi Polysaccharide

	Vi vaccinees (N=18,869)	Hep A vaccinees (N=18,804)
Typhoid Episodes	34	96
Rate (per 1,000 person-years)	0.9	2.7
Total Protection	65% (P<.0001; 95%CI:42%,79%)	-

Analysis of *Indirect Protection* against Typhoid Fever by Vi Polysaccharide

	Non-vaccinees Vi clusters (N=12,206)	Non-vaccinees Hep A clusters (N=12,877)
Typhoid Episodes	16	31
Rate (per 1,000 person-years)	0.7	1.3
Indirect Protection	45% (P<.05; 95%CI:1%,70%)	-

Analysis of *Overall Protection* against Typhoid Fever by Vi Polysaccharide

	All residents Vi clusters (N=31,075)	All residents Hep A clusters (N=31,681)
Typhoid Episodes	50	127
Rate (per 1,000 person-years)	0.8	2.1
Overall Protection	60% (P<.0001; 95%CI:39%,74%)	

Options for Assessing Herd Protection in Randomized Trials

- Individually randomized trials

Use of Individually Randomized Trials to Analyze Herd Effects

- In any individually randomized trial 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 older than 15
- Exclusions: Pregnancy; too ill to leave bed on 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 (per 1,000)	1.9	2.5	5.2
PE	63% (P<.0001; 95%CI; 46%,74%)	53% (P<.0001; (95%CI:33%,66%)	

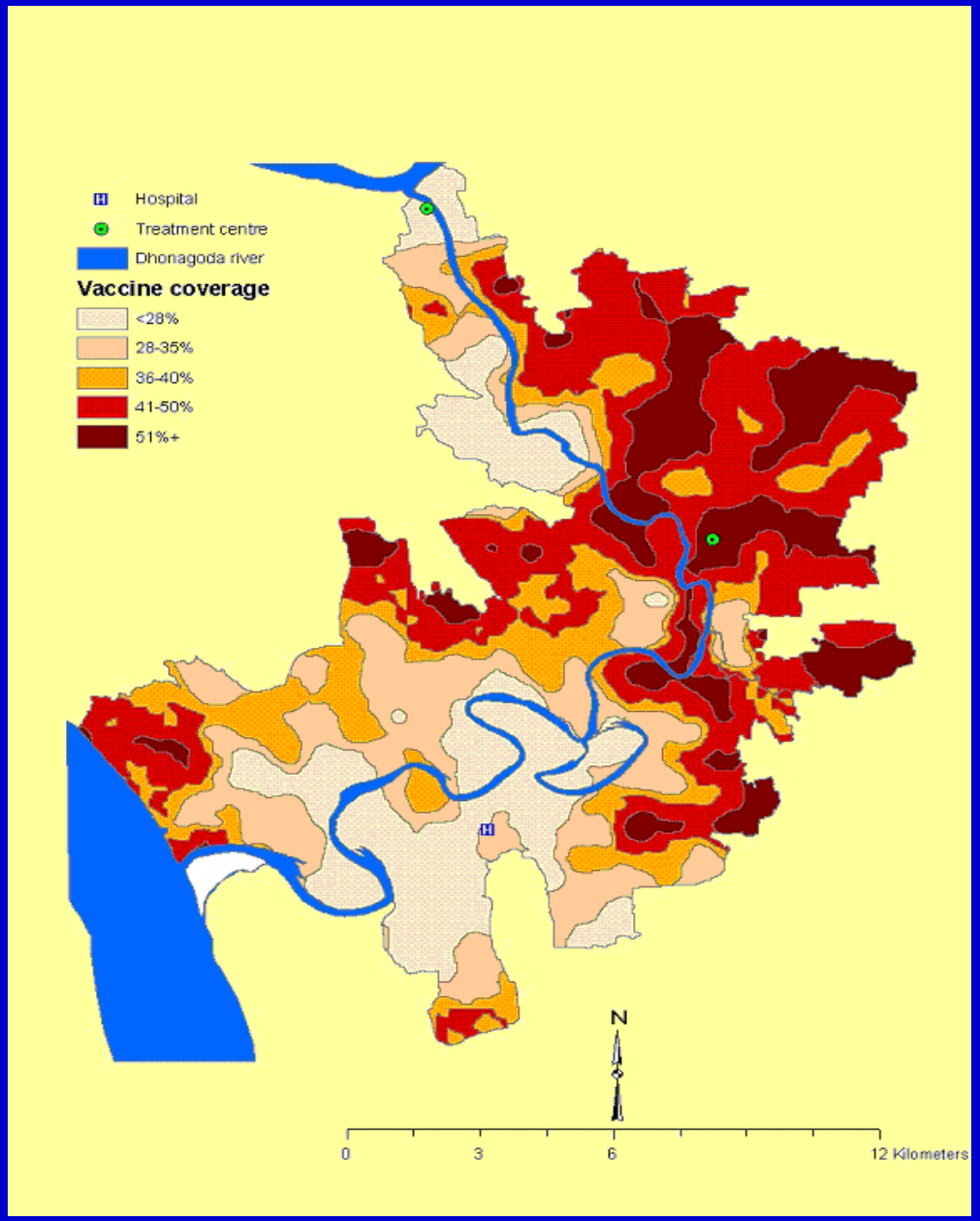
Research Questions

- 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

- 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.

Levels of Vaccine Coverage, Matlab, 1985

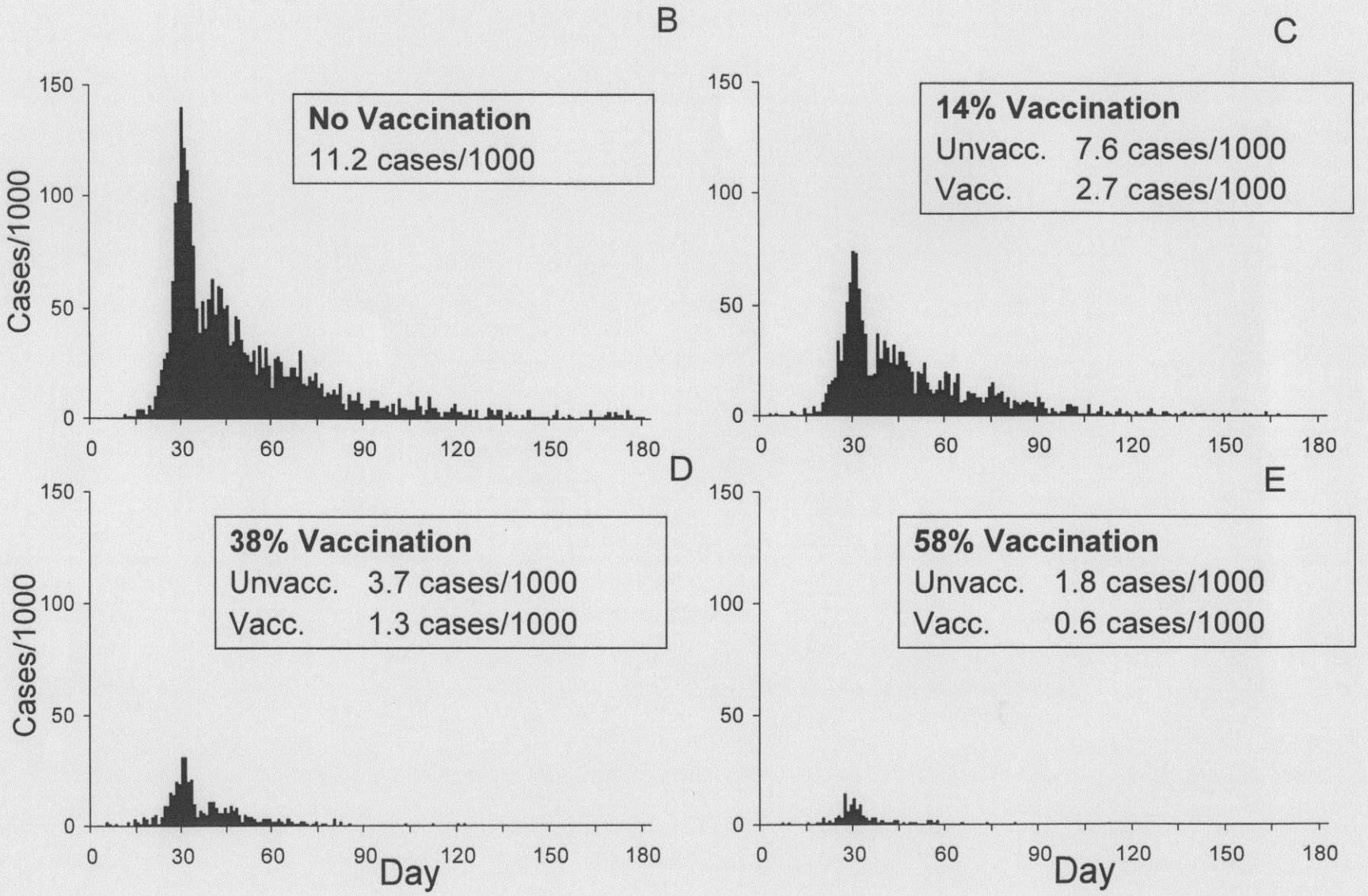


Cholera Risk by the Level of Cholera Vaccine Coverage, Matlab, Bangladesh 1985-1986

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
Total	**121,149**	**100**	**49,336**	**96**	**1.94**	**24,667**	**108**	**4.37**

* P=.05 for trend

** P<.0001 for trend


B
No Vaccination
11.2 cases/1000
C
14% Vaccination
Unvacc. 7.6 cases/1000
Vacc. 2.7 cases/1000
D
38% Vaccination
Unvacc. 3.7 cases/1000
Vacc. 1.3 cases/1000
E
58% Vaccination
Unvacc. 1.8 cases/1000
Vacc. 0.6 cases/1000
Cases/1000
Day
0
30
60
90
120
150
180
50
100

Summary

- Rational decisions about introducing new vaccines often require knowledge about both direct and herd vaccine protective effects
- However, evidence about the herd protective effects of vaccines typically comes from post-licensure studies after vaccine introduction: Catch 22
- Cluster-randomized, controlled clinical trials have been shown to be a valid approach for evaluating vaccine herd protection if several assumptions are met

Summary

- Although traditionally espoused as a way of evaluating direct vaccine protection *per* se, individually randomized, controlled clinical trials, when supplemented by geographic information systems data, can be powerful approaches for also analyzing vaccine herd protection