Herd Protection- Efficacy vs effectiveness

The Importance of Cluster-Randomized Trials to assess Vaccine Herd Protection

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Outline

- Efficacy and effectiveness
- Herd effect, herd immunity, herd protection and other concepts
- Cluster randomized trials
  - Examples
  - Limitations

EFFICACY AND EFFECTIVENESS

Vaccine efficacy vs vaccine effectiveness

Vaccine efficacy – ability of the vaccine to reduce the incidence of disease when administered under *ideal conditions*

Vaccine effectiveness – actual *field* performance of the vaccine

$$VE = 1 - \frac{IR_v}{IR_u}$$

IR_v= Incidence rate in vaccinated group

IR_u= Incidence rate in unvaccinated group

* Greenland S, Frerichs RR. Int J Epid 1988;17(2):456-463

Efficacy vs effectiveness

	Vaccine efficacy	**Vaccine effectiveness**
Usually measured in	Clinical trials	Observational studies
Goal	Licensure of vaccine, measures protection conferred to a **healthy** individual	Conduct of study in real life settings, results that are meaningful to policymakers
Vaccine storage and administration	Strictly followed with constant monitoring	Storage and administration may not be optimum
Age administered and intervals between doses	Specific age groups enrolled and dosing intervals strictly followed	Recommended age for administration and intervals between doses
Persons vaccinated	STRICT: With specific exclusions in trials (screening out some disease conditions)	Not selective

Direct vaccine effect

- Protective effect conferred by the vaccine to the person who received the vaccine
- Often this is the one that is measured in efficacy trials which are usually individually randomized

HERD EFFECT, HERD IMMUNITY, HERD (INDIRECT) PROTECTION AND OTHER CONCEPTS

Herd immunity, herd effect and herd protection

John and Samuel. Eur J Epidemiology 16: 601-606, 2000

- Herd immunity
  - Proportion of subjects in a given population with immunity
- Herd effect
  - Reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population

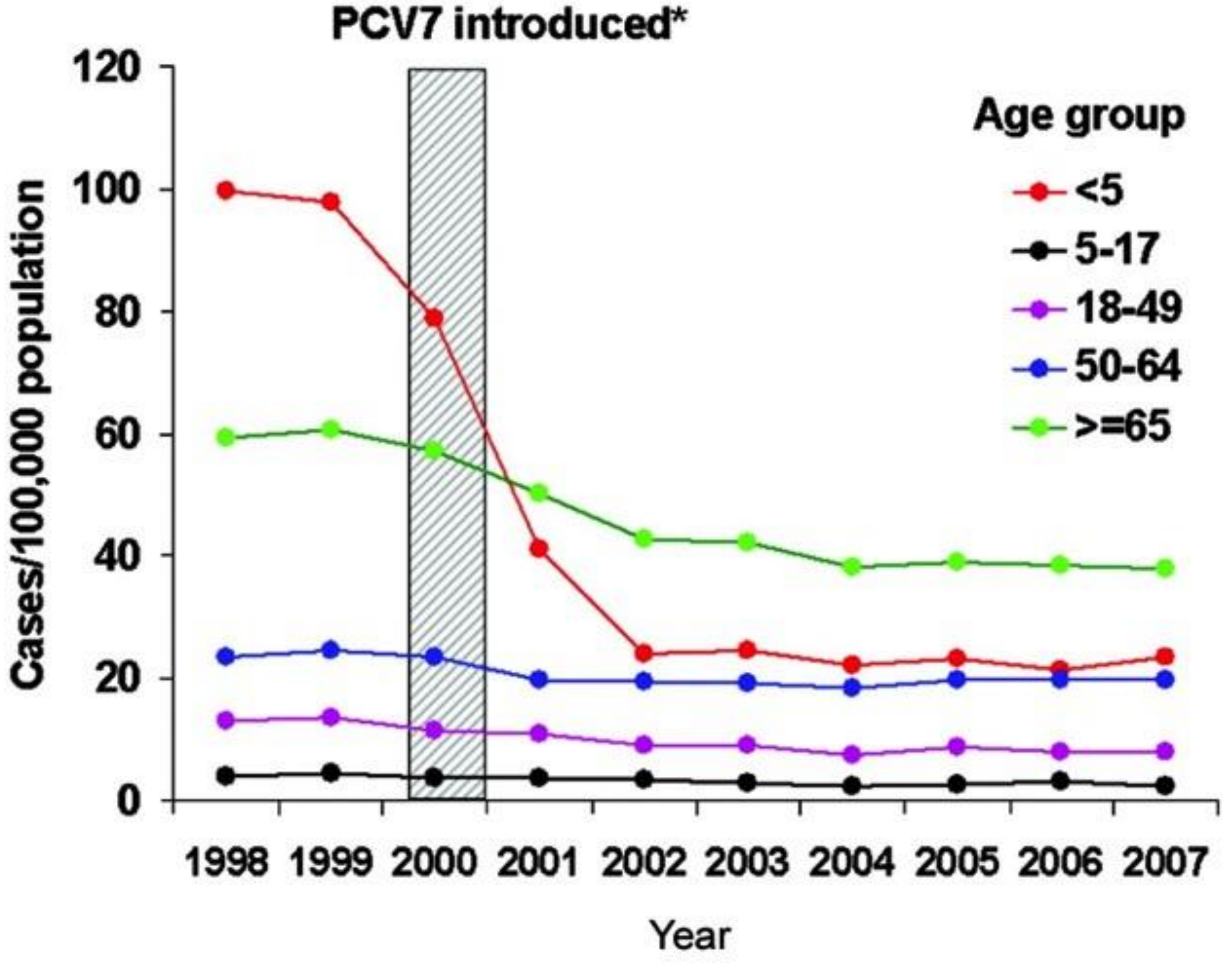
Clemens, et al. Lancet Infect Dis 2011;11: 482–87

- Herd immunity
  - Protection of non-vaccinated people exposed to live vaccine organisms transmitted by shedding of these organisms by vaccinees, leading to a protective immune response (only for live vaccines)
- Herd protection
  - Results from the reduction of the intensity of transmission of the targeted infection in the population due to the presence of vaccinated individuals in the population

Herd immunity, herd effect and herd protection

- Herd immunity
  - “Regardless of how they are defined, it implies that the risk of infection among susceptible individuals in a population is reduced by the presence and proximity of immune individuals”
    - (Fine, et al. Clinical Infectious Diseases 2011;52(7):911–916)
- Herd effect, herd protection, indirect effect used interchangeably
- Seen in
  - infections with person to person transmission (e.g. rubella, measles) or
  - infections for which humans are important reservoir (e.g. polio)

Changes in overall Invasive Pneumococcal Disease incidence rates by age group, 1998–2007, USA



Pilishvili, et al. J INFECT DIS.2009;201(1):32-41

Herd protection

- “If you don’t get it, you can’t pass it”
- Due to drop in infection among “transmitters”, subsequent decline seen in vulnerable populations who were not vaccinated

Herd effects are not intrinsic to the vaccine

- Vaccine herd effect depends on:
  1. Level of vaccine coverage
     - Ex. 50% Hib vaccine coverage in Finland resulted in drop of infection even among children ≥5 years
  2. Pattern of vaccine coverage
     - Vaccinating highly transmitting group will require overall lower vaccination coverage to protect the entire population
  3. Force of transmission

Identifying herd protection

- Usually performed post-licensure, however may also be detected in clinical trials e.g. cholera vaccine trial
- In developing countries, post-licensure assessment is difficult
  - Infrastructure may not be readily available in low-resource countries
  - Immunization records must be readily available
  - Disease surveillance must be consistently applied
  - Laboratory confirmation of target disease

Importance of herd protection in policy

- Improves cost-effectiveness profile of vaccines
  - E.g. cholera vaccines
- Increasingly countries are considering introduction of newer vaccines
  - Competing priorities

CLUSTER RANDOMIZED TRIALS

Cluster-randomized or Group-randomized trial

- Units of randomization are clusters or groups of people
- Eligible, consenting individuals within cluster receive agent assigned to the cluster (vaccine or control agent or no agent)
- Randomization usually performed prior to the enrolment of individuals within the clusters
- Units of observation are members of those groups nested within their group

Examples of clusters used in vaccine cluster-randomized trials

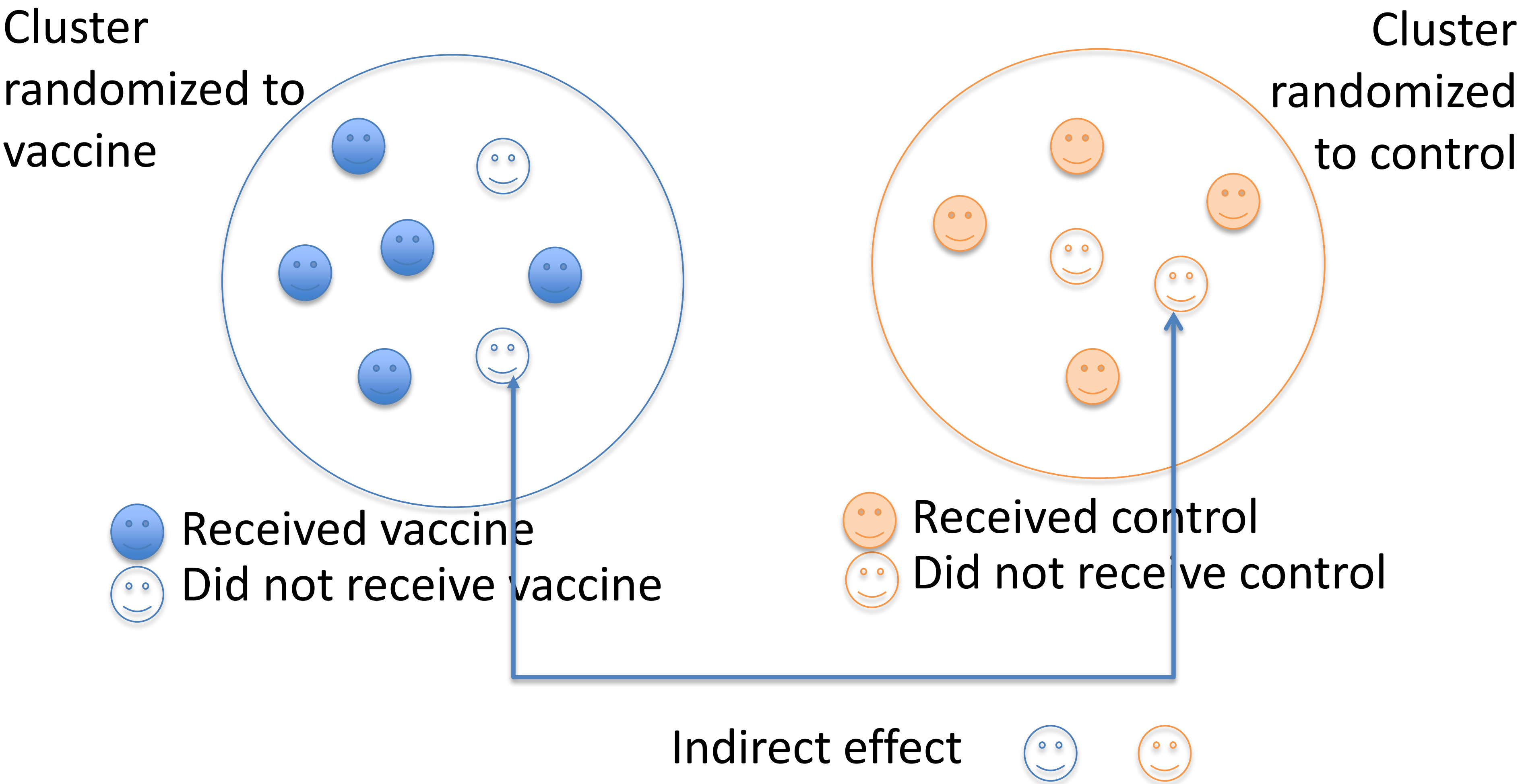
- Schools (Lehtinen M, et al. Vaccine 2015;33:1284-1290)
  - Live attenuated influenza vaccine vs Injected inactivated influenza vaccines in Ontario, Canada
  - Randomized 5 schools in each arm
- Communities
  - 33 communities randomized into 3 arms – girls and/or boys received Human papillomavirus (HPV) and/or Hepatitis B vaccine (Kwong JC, et al. Vaccine 2015;33:535-541)
- Dwellings or premises
  - 3,933 "premises" or dwellings randomized to receive oral cholera vaccine or placebo (Sur D, et al. Lancet 2009; 374: 1694–702)

Population-level effects of vaccination

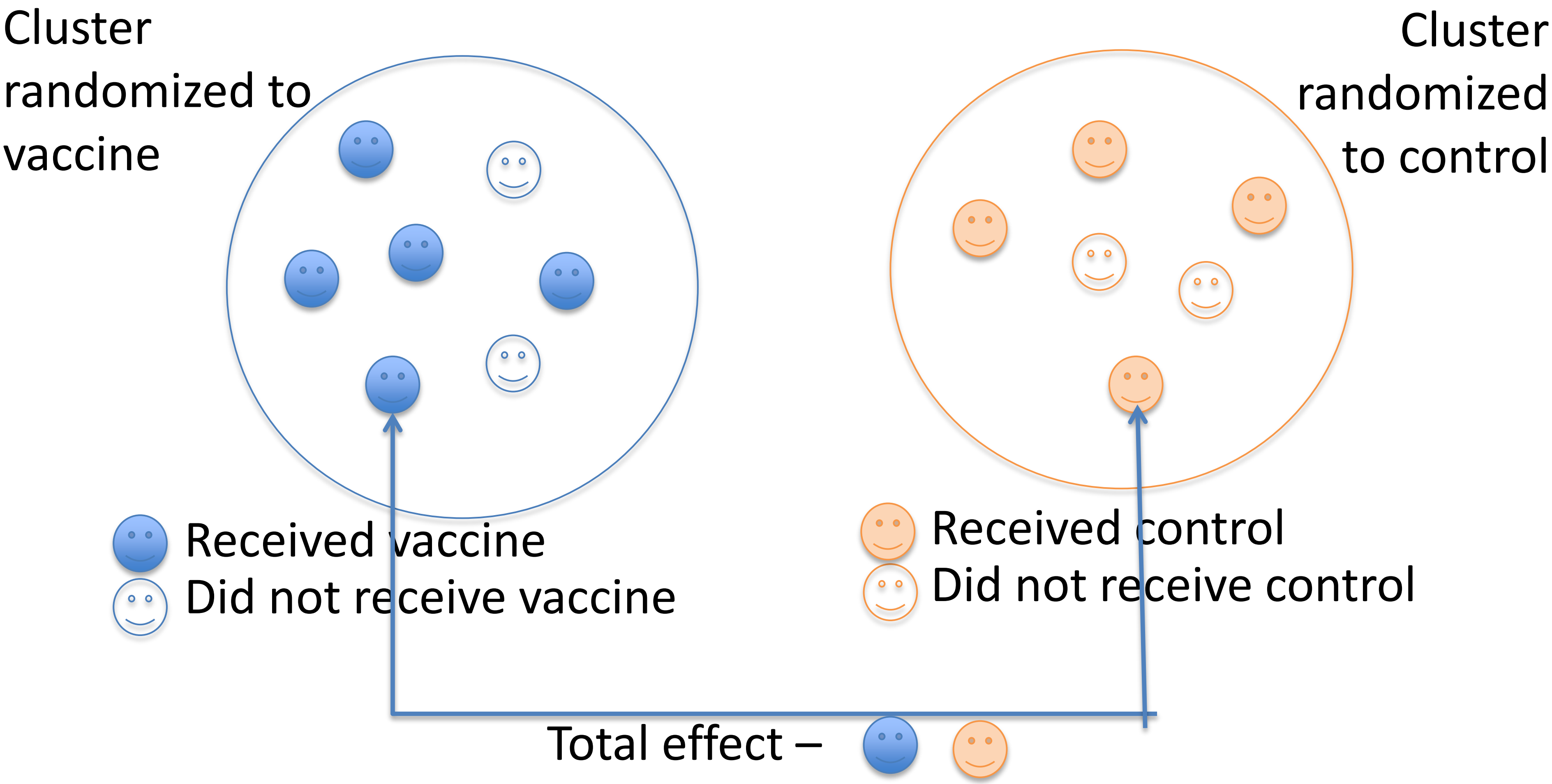
1. Indirect effect - effect in those individuals who were not vaccinated or at least who were not vaccinated as part of the strategy of interest
2. Total effect – combined effect of the vaccination strategy and the direct protective effects of vaccination in those individuals who received the vaccine
3. Overall effect – the effect in the population with vaccinees and non-vaccinees compared to if the population had not had the vaccination strategy

Halloran ME, et al. Epidemiol Method . 2012 August 1; 1(1): 83–105.

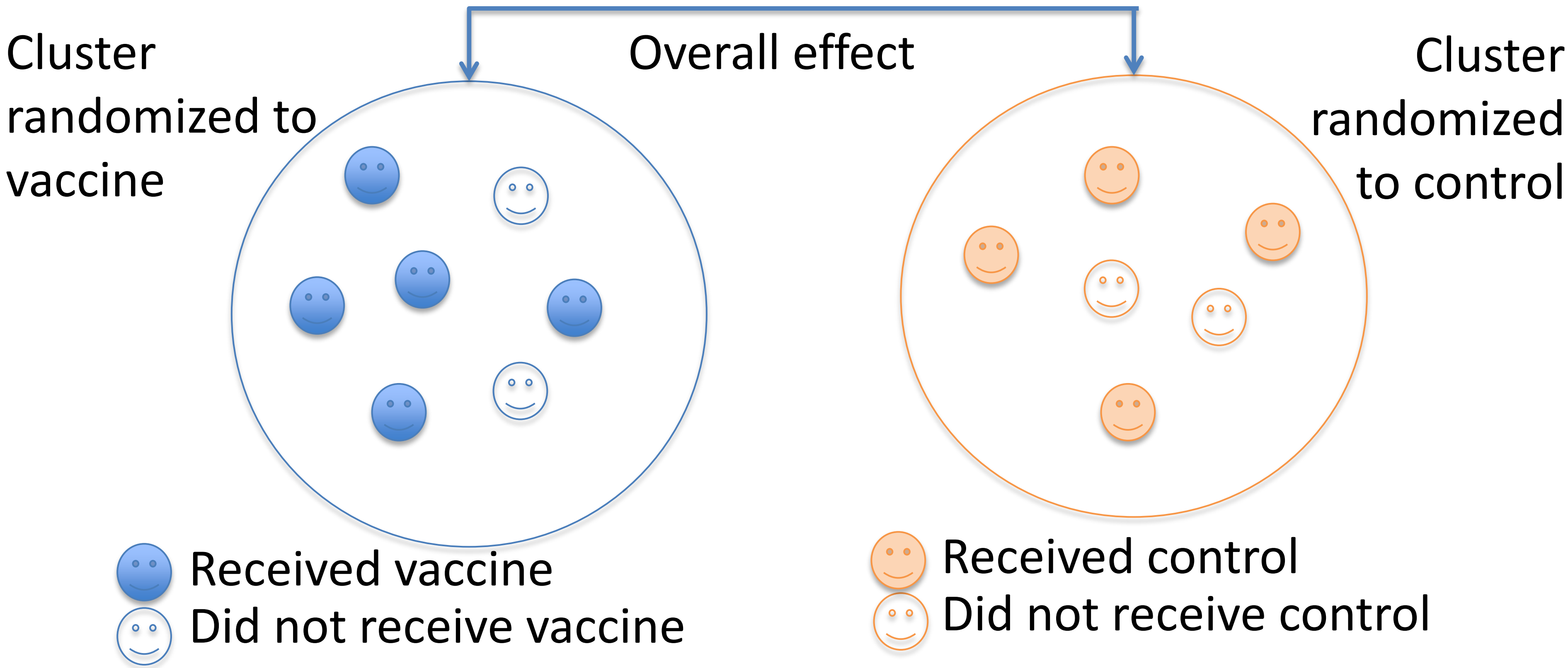
Indirect effect or herd effect



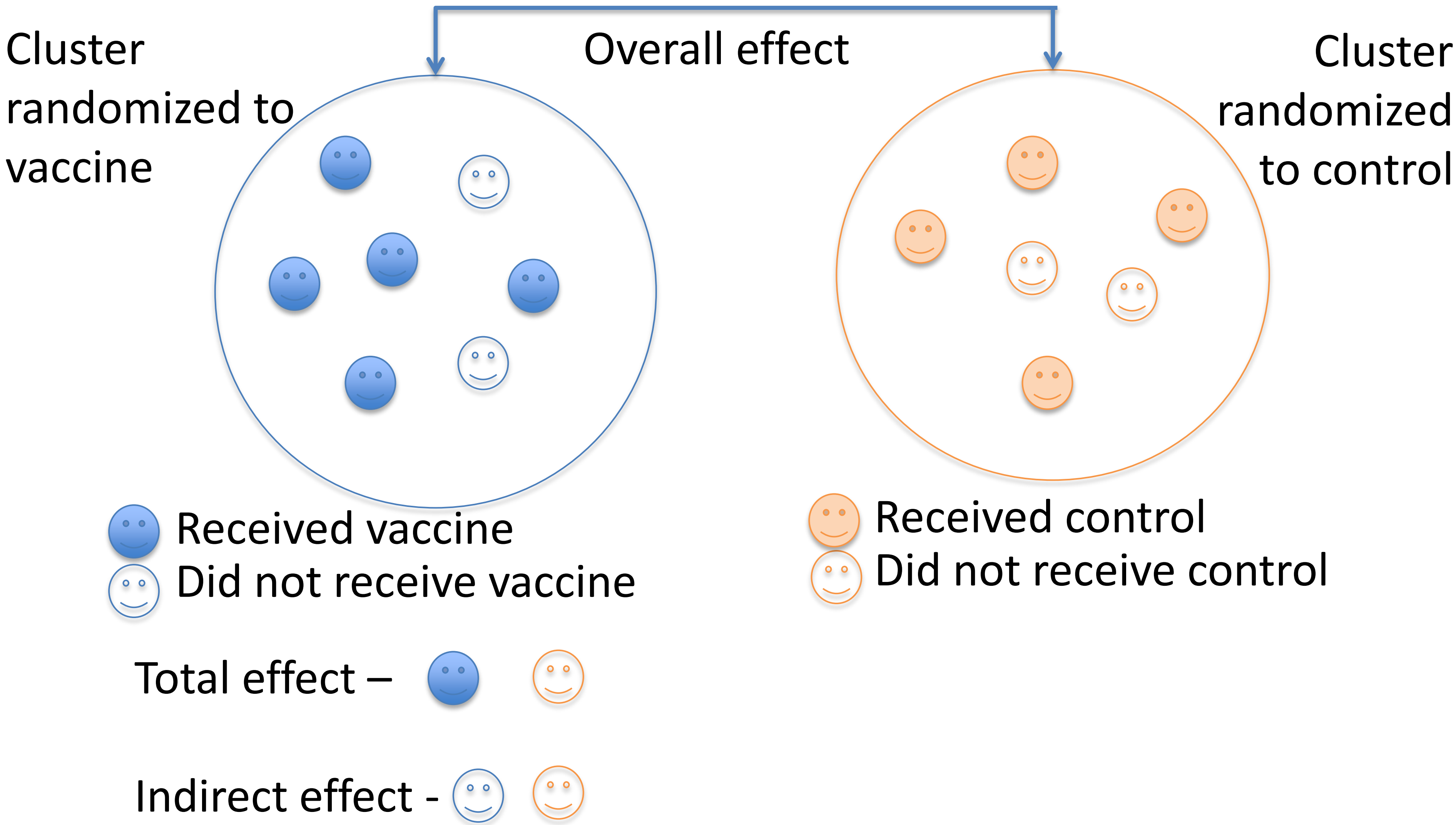
Total effect



Overall effect



Vaccine induced herd protection in a cluster randomized vaccine trial



Effectiveness of the Vi polysaccharide vaccine in Kolkata, India

- Objective: To assess the programmatic feasibility and effect of Vi vaccination in public health programs and whether the vaccine can confer herd immunity
- Cluster-randomized, controlled trial
- 80 geographic clusters – contiguous neighborhoods
- Clusters randomized to receive:
  - Vi polysaccharide vaccine
    - Average cluster size: 777 ±136
  - Hepatitis A
    - Average cluster size: 792±142

Total effectiveness of Vi vaccine

	Vi vaccine N=18,869	Hepatitis A vaccine N=18,804	Effectiveness of Vi vaccine % (95% CI)
Subjects with typhoid fever	34	96	
Person days of follow-up	13,309,337	13,214,761	
Incidence of typhoid fever	0.26	0.73	
Unadjusted analysis			65 (42-79)
Adjusted analysis			61 (41-75)

Sur D, et al. N Engl J Med 2009;361:335-44.

Indirect effectiveness of Vi vaccine

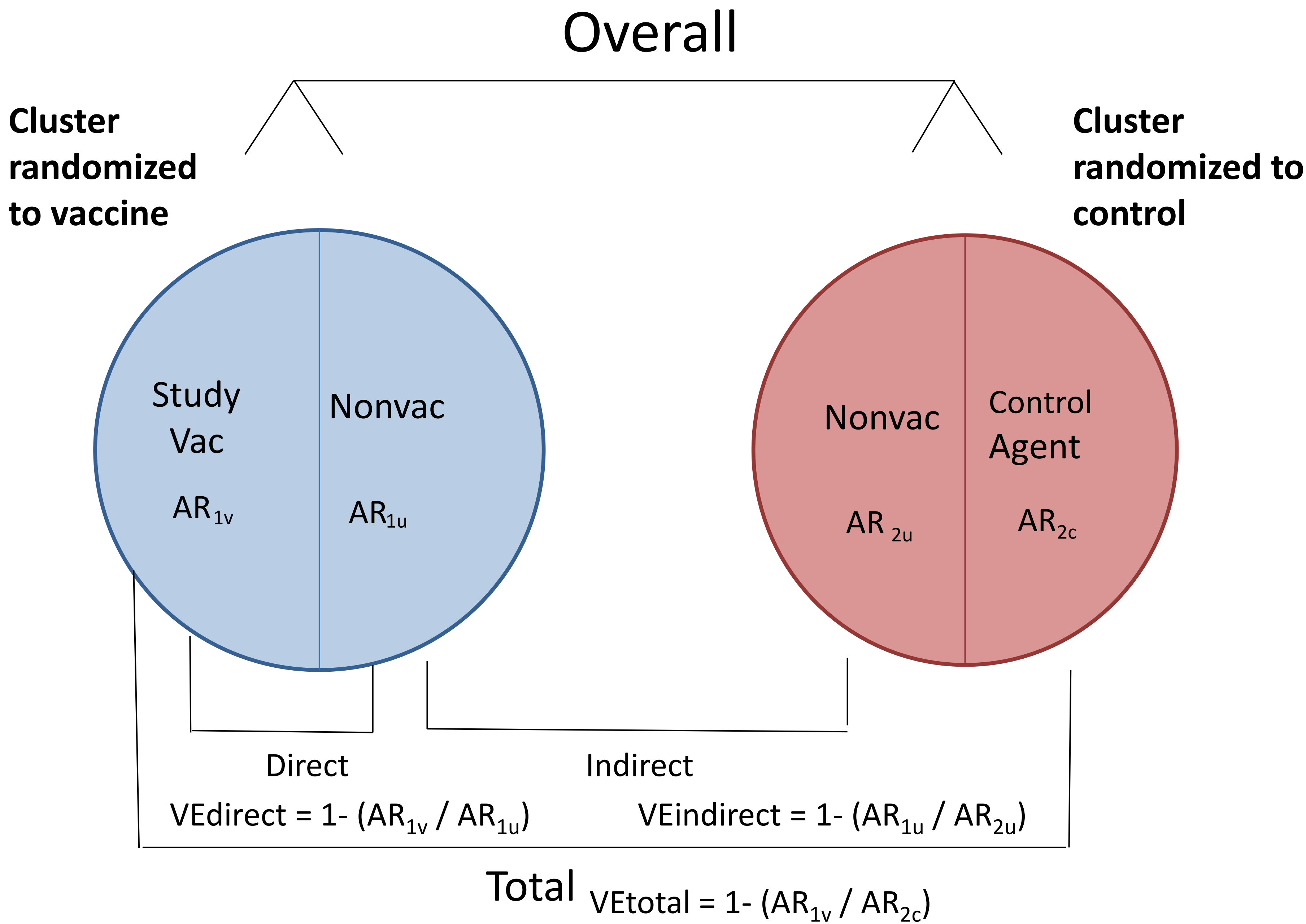
	Vi vaccine cluster N=12,206	Hepatitis A vaccine cluster N=12,807	Effectiveness of Vi vaccine % (95% CI)
Subjects with typhoid fever	16	31	
Incidence of typhoid fever (no. /100,000 person days)	0.19	0.35	
Unadjusted analysis			45 (1-70)
Adjusted analysis			44 (2-69)

Sur D, et al. N Engl J Med 2009;361:335-44.

Overall effectiveness of Vi vaccine

	Vi vaccine cluster N=31,075	Hepatitis A vaccine cluster N=31,681	Effectiveness of Vi vaccine % (95% CI)
Subjects with typhoid fever	50	127	
Incidence of typhoid fever (no. /100,000 person days)	0.19	0.58	
Unadjusted analysis			60 (39-74)
Adjusted analysis			57 (37-71)

Sur D, et al. N Engl J Med 2009;361:335-44.


Overall
Cluster randomized to vaccine
Cluster randomized to control
Study Vac
AR_{1v}
Nonvac
AR_{1u}
Nonvac
AR_{2u}
Control Agent
AR_{2c}
Direct
VEdirect = 1- (AR_{1v} / AR_{1u})
Indirect
VEindirect = 1- (AR_{1u} / AR_{2u})
Total
VEtotal = 1- (AR_{1v} / AR_{2c})

Study conclusions

- Vi vaccine conferred 61% total protection
  - Conferred indirect protection in the non-vaccinated individuals
- With 60% vaccine coverage, herd protection was detected contributing to overall protection of 57% in the whole population

Effect of vaccinating children against influenza in Hutterite communities in Canada

- **Objective**: To assess whether vaccinating children and adolescents with inactivated influenza vaccine could prevent influenza in other community members.
- Cluster-randomized trial with 49 “colonies”
  – Consist of families each residing in their own house, where children and adolescents between the ages of 3 years and 15 years attend school.

Effect of influenza vaccination

- Healthy children and aged 36 months to 15 years
  - Inactivated seasonal influenza vaccine recommended for the 2008-2009
  - Control vaccine: Hepatitis A
  - Children aged 3 to 15 years accounted for ~36% in the population
- Children aged 6 to 23 months eligible for routine influenza vaccination not included in the study
- Vaccination coverage among healthy children included in the study:
  - Influenza vaccine coverage: 83%
  - Hepatitis A vaccine coverage: 79%

Indirect effectiveness of influenza vaccine

	Influenza vaccine cluster N=1,271	Hepatitis A vaccine cluster N=1,055	Effectiveness of flu vaccine % (95% CI) p
Subjects with influenza (PCR+ve)	39	80	
Incidence of influenza (no. /100,000 person days)	2.13	5.27	
Unadjusted analysis			61 (8-83) 0.03
Adjusted analysis			61 (8-83) 0.03

Loeb M, et al. JAMA 2010;303(10):943-950

Overall effectiveness of influenza vaccine

	Influenza vaccine cluster N=1,773	Hepatitis A vaccine cluster N=1,500	Effectiveness of flu vaccine % (95% CI) p
Subjects with influenza (PCR+ve)	80	159	
Incidence of influenza (no. /100,000 person days)	3.16	7.54	
Unadjusted analysis			59 (5-82) 0.04
Adjusted analysis			59 (4-82)

Loeb M, et al. JAMA 2010;303(10):943-950

Study conclusions

- Significant herd effect was achieved with ~80% influenza vaccine coverage of individuals aged 3 to 15 years
  - Overall influenza vaccine coverage was 38% in influenza vaccine clusters compared to 8% in hepatitis A clusters
- Findings support selective influenza immunization of school aged children with inactivated influenza vaccine to interrupt influenza transmission

Efficacy of a Killed Oral Cholera Vaccine (OCV) in Kolkata, India

- Pre-licensure randomized controlled trial of inactivated bivalent OCV
- Clusters were neighborhood premises (a hut, group of huts or building as assigned by the Kolkata Municipal Corporation) randomized to receive either
  - Vaccine: 1,721 clusters and 31,932 participants
  - Placebo: 1,757 clusters and 34,968 participants

2-year efficacy of the killed OCV in Kolkata, India

	Vaccine	Placebo	Adjusted efficacy
Cholera Episodes	20	68	67%[a] (35%[b]) <0.0001
Population	31,932	34,968	
No. of days of follow-up	22,101,288	24,204,356	
Cholera incidence	0.09	0.28	

[a]The model was derived from 81 episodes in 65,238 individuals for whom there were complete data for all variables.
[b]99% CI (lower bound)

Study conclusions

- Indirect protection of OCV seen in this phase III study using the GIS approach but not in the cluster-randomized design
- Substantial transmission occurring between clusters

Limitations of cluster randomization

1. Requires minimal level of transmission among clusters in order to identify herd protection
2. Requires knowledge of the community beforehand to randomize
   - Even prior to obtaining informed consent
   - Population must be stable over time
3. Requires bigger sample size
4. Need to adjust during analysis

Summary

- Documentation of vaccine effectiveness is increasingly required as countries introduce vaccines into their immunization program
  - Competing priorities require rigorous review of evidence and in some countries evidences of local feasibility and effectiveness are required for nationwide uptake
- Herd effect improves cost-effectiveness profile of candidate vaccines
- Cluster-randomized design may be considered in assessing future vaccine efficacy and effectiveness