Lecture 9: Study designs for evaluating vaccine efficacy

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Goal of vaccine studies

Evaluate vaccine efficacy and effectiveness

Evaluate vaccine safety

Support regulatory decision-making

- Licensure
- Target population
- Co-administration with other vaccines

Vaccine efficacy

Attack rates/cumulative incidence: $VE = 1 - \frac{AR_1}{AR_0}$ (risk ratio)

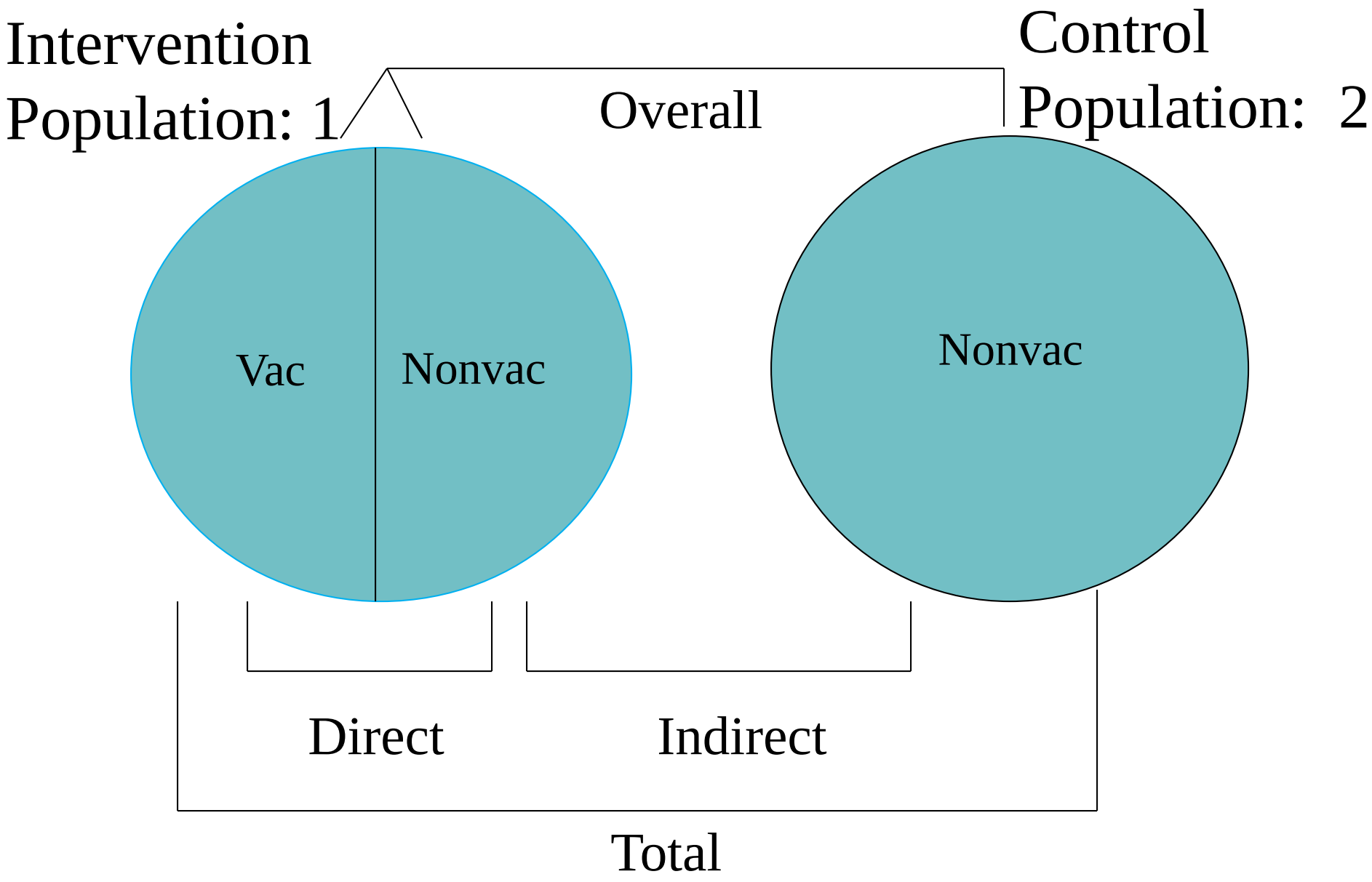
Incidence rates: $VE = 1 - \frac{IR_1}{IR_0}$ (rate ratio)

Hazard rates: $VE = 1 - \lambda_1/\lambda_0$ (hazard ratio)

Types of vaccine effects

Vaccine effect	Description
Direct	Reduction in disease (or infection) experienced by an individual as the direct result of vaccination
Indirect	Reduction in disease (or infection) experienced by an individual attributable to being in contact with others who have been vaccinated
Total	Reduction in disease (or infection) experienced by an individual attributable to both being vaccinated AND being in contact with others who have been vaccinated (combines direct and indirect effects)
Overall	Reduction in disease (or infection) experienced by a population attributable to some members of the population being vaccinated

Vaccine Effectiveness



Types of vaccine effects

Vaccine effect	Public health value
Direct	• Intended to replicate effect of challenge studies • Effect of primary interest for vaccines that prevent infection or reduce severity of disease
Indirect	• Measures herd effects • Effect of primary interest for transmission-blocking vaccines
Total	• Measures individual-level impact of vaccination program
Overall	• Measures population-level impact of vaccination program

Study endpoints

Study endpoints should be selected to support the broader intended use of the vaccine

Typically a single primary endpoint and up to 3 or 4 secondary endpoints are defined in a study protocol

The ideal primary endpoint should directly measure the disease-related outcome of public health interest

The most common primary endpoint is clinical disease with laboratory confirmation as public health interest is in lessening disease

There are examples of vaccines that have been shown to prevent disease but not infection, including rubella, mumps, measles, and polio

Alternative endpoints or biomarkers may be considered under certain circumstances

Study endpoints - description

Endpoint	Description
Clinical disease with laboratory confirmation	• Laboratory assays used to confirm infection (e.g. PCR) or confirm seroconversion (e.g. ELISA) • Most reliable, especially if symptoms are non-specific • May have reduced sensitivity if pathogen is only detectable for a limited period of time
Clinical disease without laboratory confirmation	• Pathogen should have a highly distinct clinical syndrome • May be necessary in settings with limited laboratory infrastructure • Studies should consider using laboratory confirmation on a validation subset

Study endpoints - description

Endpoint	Description
Infection	• Limited value because infection alone is rarely the outcome of public health interest • Useful for diseases with long latent periods • May serve as a replacement endpoint (e.g. Zika congenital syndrome) • Can increase event rate for diseases with high asymptomatic rate • May be difficult to measure unless there is a test of seroconversion that can distinguish between natural- and vaccine-induced immunity
Disease severity or complication of interest	• Endpoint may be rare and make powering the study difficult • Rates of severe disease may be confounded by changes in patient care over time

Study endpoint - examples

Disease	Endpoint	Reference
Dengue	Virologically confirmed symptomatic disease, regardless of the severity of illness or infecting serotype	Villar et al. 2015 NEJM
HIV	Laboratory-confirmed infection	Rerks-Ngarm et al. 2009 NEJM
HPV	Incident HPV16/18-associated cervical intraepithelial neoplasia, adenocarcinoma in situ, or cervical cancer	Schiller et al. 2012 Vaccine

Study analysis period

We only observe illness (symptom) onset times

- Time of infection is typically unknown
- The difference between these two events is known as the **incubation period**

Events occurring immediately after vaccination may be attributable to infections that occurred before vaccination

Vaccines are also not immediately protective

- A period of **immune ramp-up** is required to reach peak efficacy

Including these early events in the primary analysis can bias efficacy towards the null

- Further discussion in Dean et al. 2018 Annals of Applied Statistics

Intention-to-treat or per protocol

Intention-to-treat (ITT)

- Includes all participants regardless of protocol violations (e.g. failure to receive all doses of the vaccine)
- Includes cases immediately from time of randomization/vaccination

Per protocol

- Includes only participants receiving all doses per protocol
- Includes only cases with symptom onset occurring after the last dose, plus an additional delay period reflecting the incubation and immune ramp-up periods

Modified intention-to-treat

- Originally intended to refer to ITT analysis in which individuals determined to already be infected at baseline are excluded

Randomized trials

Clinical trial phases

Vaccine effect	Description
Phase 1	• Typically 30-100 healthy human volunteers • Study different doses and/or vaccine schedules • Primarily focus on safety/tolerability • Preliminary assessment of immunogenicity
Phase 2	• Larger and more targeted population • Safety and immunogenicity data • Limited data on efficacy
Phase 3	• Typically thousands of participants • Establish field efficacy • Establish safety
Phase 4	• Post-licensure surveillance • Detect rare adverse events

Comparator arm

Placebo

Active control – licensed vaccine for some other geographically relevant indication that does not affect the probability of the study endpoint

Delayed vaccination

Another vaccine candidate (non-inferiority)

- Other vaccine candidate should have established efficacy
- Non-inferiority trial estimates **relative vaccine efficacy**

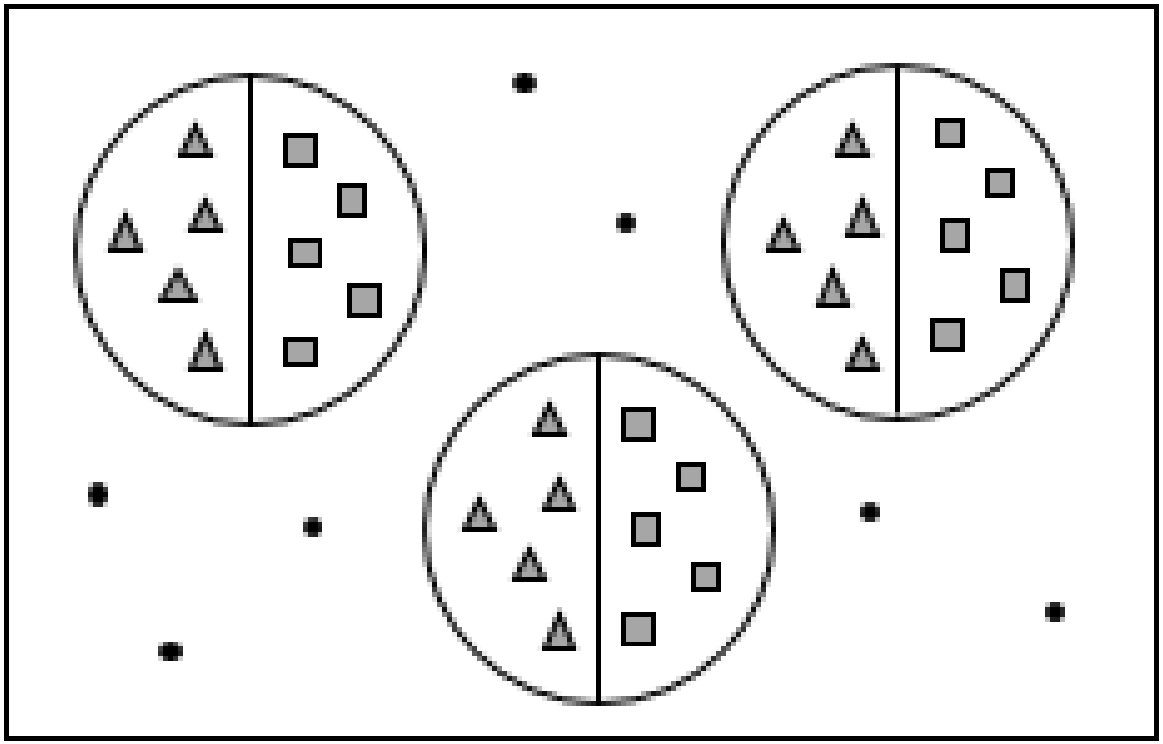
Individually randomized trials - overview

Individuals within the same population(s) are randomized to receive either vaccine or control

Because large sample sizes are typically required due to low disease incidence, most are multi-center trials

Individually randomized trials achieve the best overall balance of measured and unmeasured confounders

Individual RCT (iRCT) within Sites



△ vaccinated participant

□ comparator participant

• non-participant

Individually randomized trials - analysis

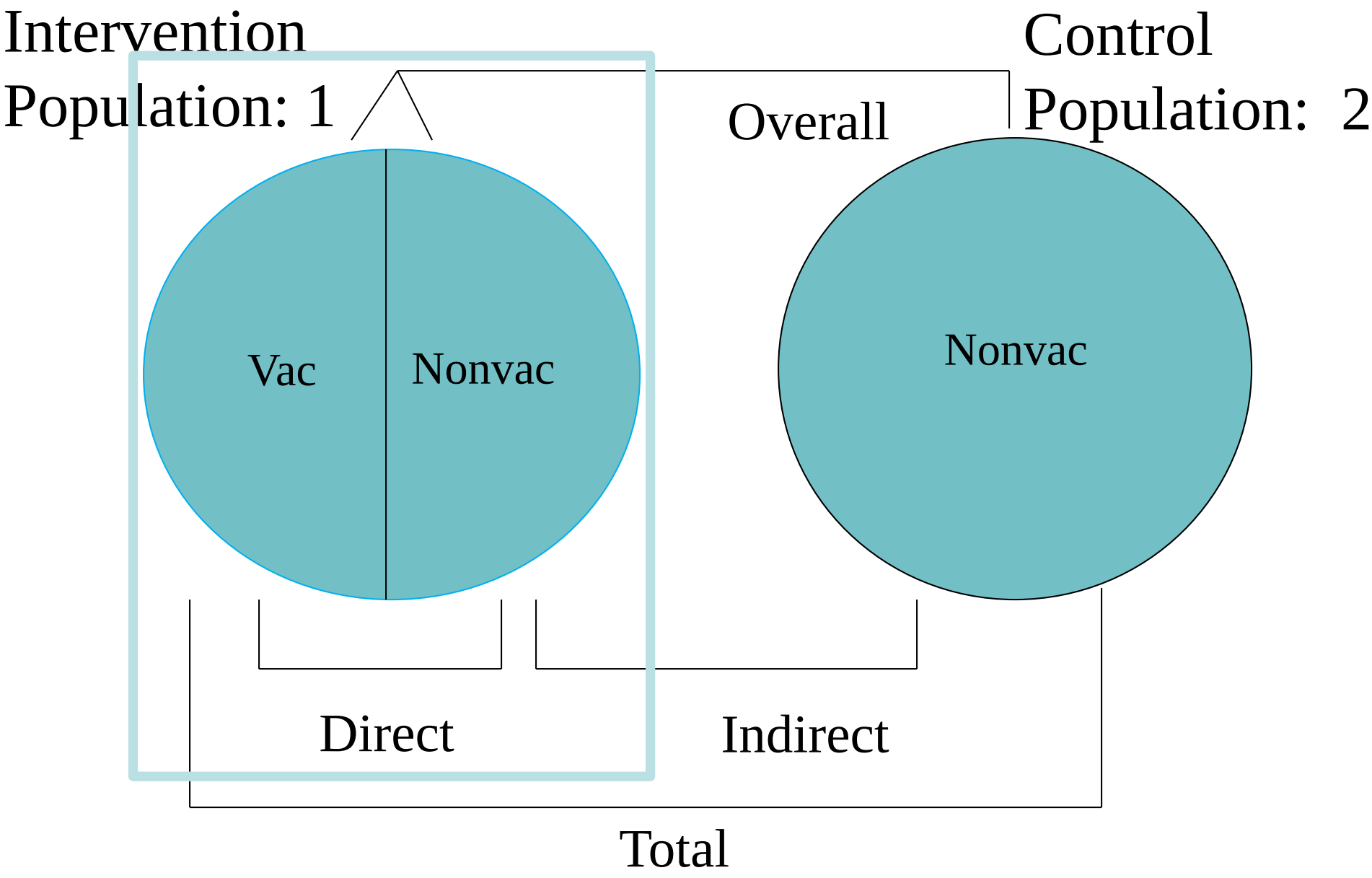
The analysis is handled with a standard comparison of two independent groups using proportions, rates, or time to event methods

For multi-site trials, individuals within sites may have similar outcomes, so the analysis should account for within-site correlation

- Adjusting for site improves precision because there may be significant variability in disease incidence across sites
- Options include regression with site as a fixed effect or shared random effect, a stratified analysis, or a conditional regression model treating site as a nuisance variable

The primary analysis estimates the direct effect of vaccination

Dr Effectiveness



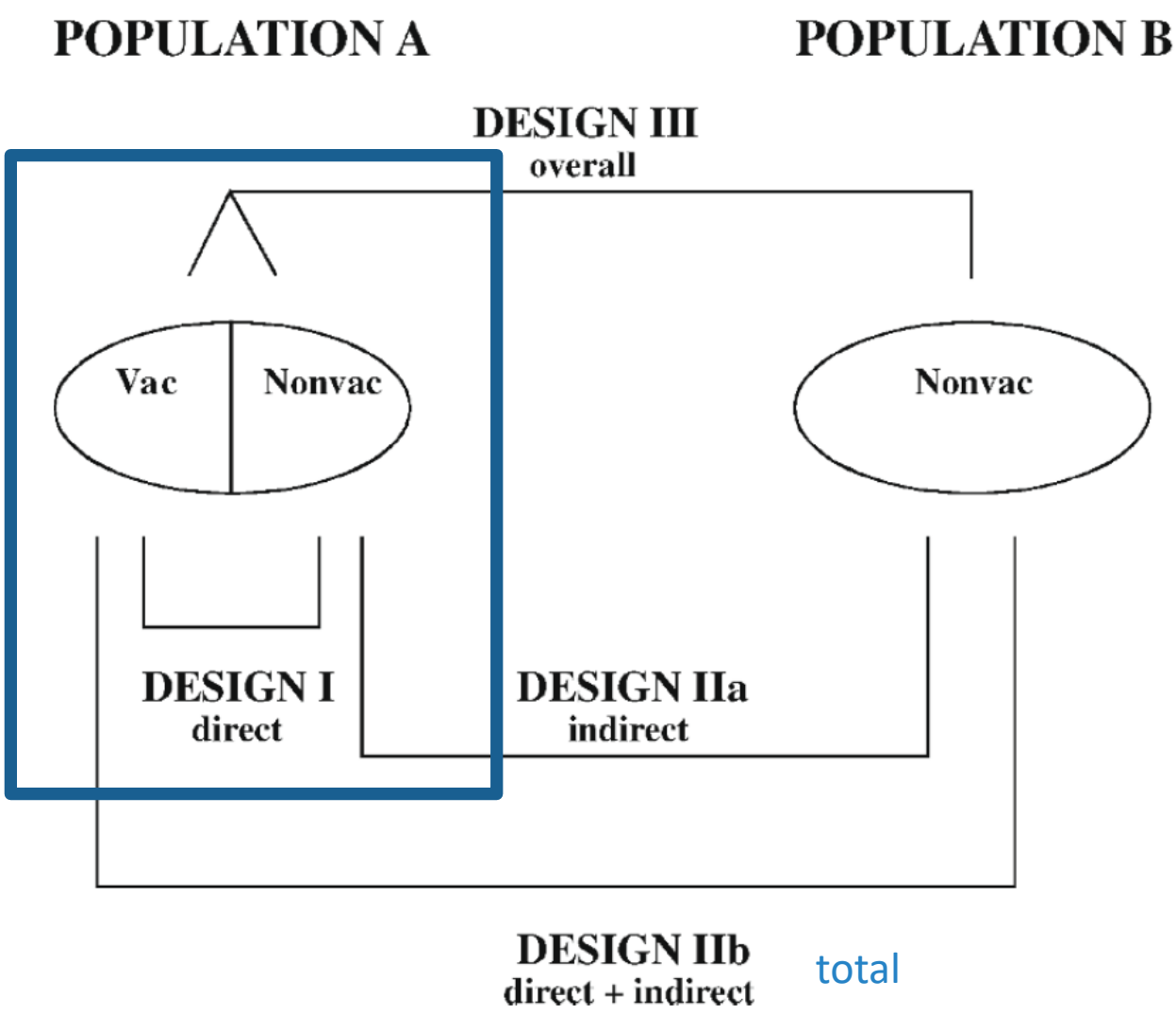


Fig. 2.3 Study designs for dependent happenings. Types of effects of vaccination programs and different study designs based on comparison populations for their evaluation (Halloran and Struchiner 1991, Epidemiology, 2:331–338. Reprinted with permission).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 8, 2015 VOL. 372 NO. 2

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

Dengue vaccine trials

Two large individually-randomized multi-center Phase 3 trials were conducted to evaluate the efficacy of a recombinant, live-attenuated, tetravalent candidate dengue vaccine (CYD-TDV)

One trial was conducted at twelve centers in five Asian Pacific countries (Capeding et al. 2014), and the other trial was conducted at twenty-two centers in five Latin American countries (Villar et al. 2015).

Healthy children were individually randomized in a 2:1 ratio to receive three doses of vaccine or placebo at 0, 6, and 12 months

Participants were followed using active surveillance for 25 months following the first dose

The primary endpoint was symptomatic, virologically-confirmed dengue occurring between months 13 and 25 measured per protocol

Dengue vaccine trial

Estimated that 20,875 children needed to identify 57 cases of virologically confirmed dengue

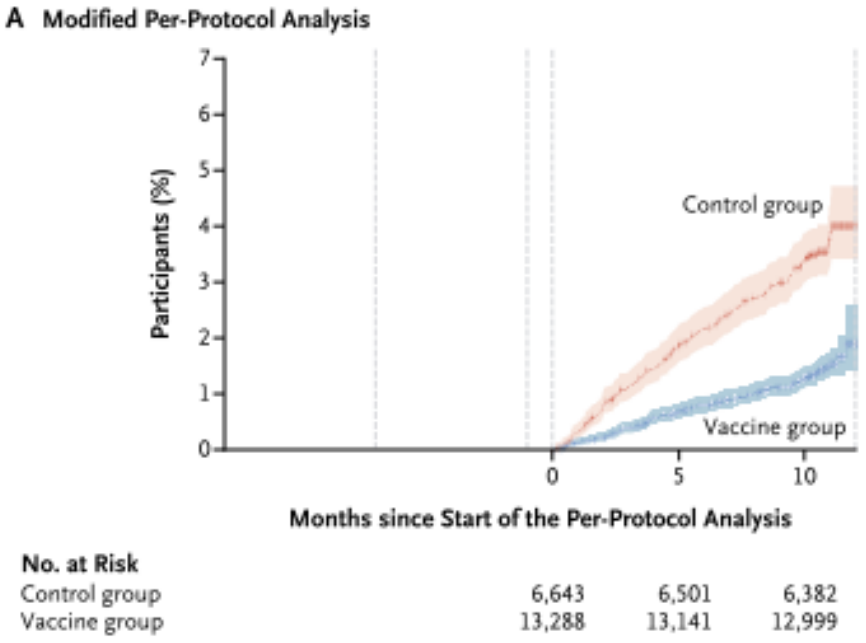
- To achieve power of 90% or more to show vaccine efficacy of more than 25% (lower boundary of confidence interval more than 25%)
- Assume a true vaccine efficacy of 70% after three injections
- One-sided alpha level of 2.5%
- Dropout rate of 20%
- Disease incidence of 0.64%

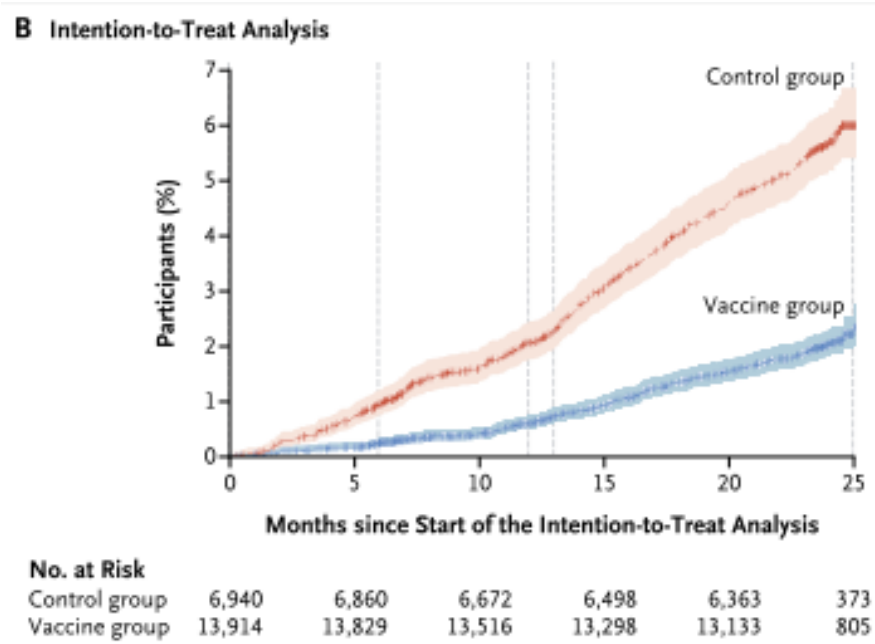
Conducted modified per protocol analysis, starting 28 days after the third injection in all participants who received three doses, regardless of protocol deviations

Calculated vaccine efficacy as 1 – incidence rate ratio

Table 2. Vaccine Efficacy against Any Serotype of Dengue.

Analysis	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Per-protocol analysis	176/176	11,793	1.5 (1.3–1.7)	221/221	5,809	3.8 (3.3–4.3)	60.8 (52.0–68.0)
Intention-to-treat analysis	277/280§	26,883	1.0 (0.9–1.2)	385/388§	13,204	2.9 (2.6–3.2)	64.7 (58.7–69.8)





Parallel cluster randomized trials - overview

Clusters of individuals are randomized as a unit to vaccine or control

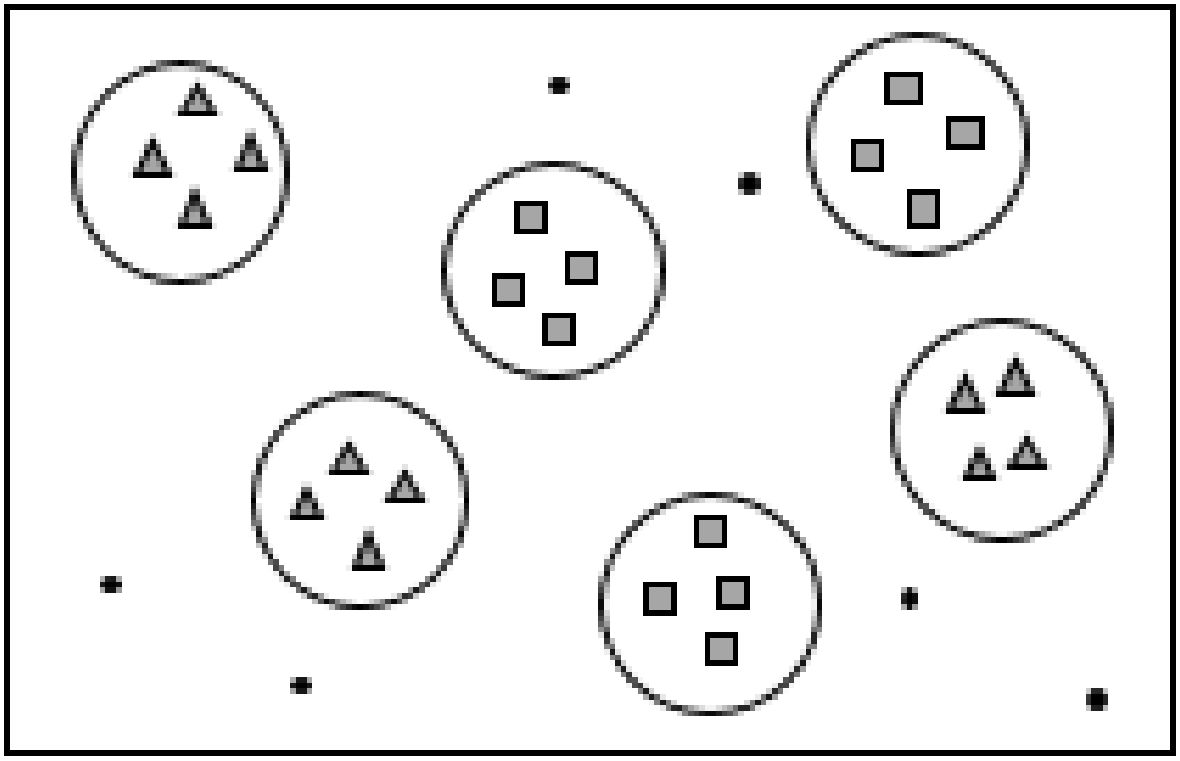
Parallel means that clusters are randomized to one arm and this allocation does not change during the study

Clusters should be well-defined, stable, self-contained, and non-overlapping

Movement or transmission between clusters is referred to as **contamination**

Choices for clusters include communities, villages, households, worksites, schools, medical centers/hospitals

Parallel Cluster RCT (cRCT)



△ vaccinated participant

□ comparator participant

• non-participant

Parallel cluster randomized trials - design

Outcomes within individuals are expected to be correlated

This is referred to as **intracluster** or **intraclass correlation**, and it is measured by **intracluster correlation coefficient (ICC)**

$$ICC = \frac{\text{Variance between clusters}}{\text{Variance within clusters} + \text{Variance between clusters}}$$

When the ICC is high, it is especially important to sample more, smaller clusters rather than sampling few, larger clusters

The **design effect** quantifies how much larger a cluster randomized trial must be as compared to a comparable individually randomized trial

Let m be the number of participants per cluster

$$DEFF = 1 + (m - 1)ICC$$

It is necessary to estimate ICC from previous studies

Parallel cluster randomized trials - design

Cluster randomized trials are more subject to baseline imbalance because there are fewer randomized units

Trialists may consider stratified randomization or matching using cluster-level covariates to reduce the chance of severe imbalance

Common covariates include cluster size and geographic area

The number of stratification/matching factors should be limited as they add model complexity and reduce model degrees of freedom

For matched designs, there is a further risk of unmatched clusters

Parallel cluster randomized trials - analysis

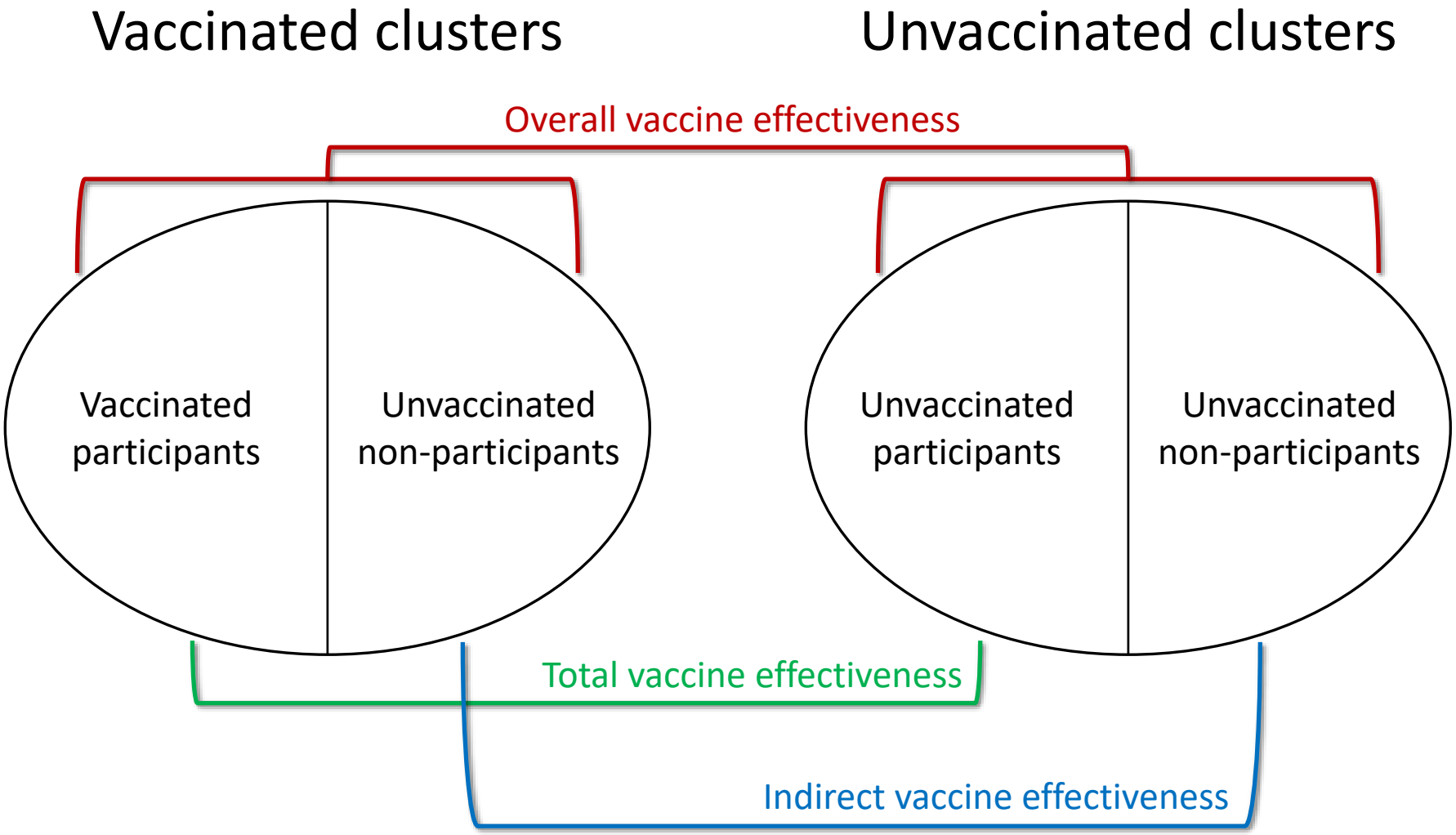
Trial analysis can be conducted at the cluster level, treating each cluster as the unit of analysis

More commonly, analysis is conducted at the individual level adjusting for correlation between individuals within the same cluster

- Mixed effects model with a cluster-level random effect
- Generalized estimating equations (GEE) with a robust variance estimator
- Adjusting for cluster decreases precision but is necessary to maintain type 1 error

The primary analysis returns an estimate of total vaccine effectiveness

Indirect and overall vaccine effectiveness are also observable if data on other cluster members is collected


Vaccinated clusters
Unvaccinated clusters
Overall vaccine effectiveness
Vaccinated participants
Unvaccinated non-participants
Unvaccinated participants
Unvaccinated non-participants
Total vaccine effectiveness
Indirect vaccine effectiveness

The NEW ENGLAND JOURNAL of MEDICINE

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A Cluster-Randomized Effectiveness Trial of Vi Typhoid Vaccine in India

Dipika Sur, M.D., R. Leon Ochiai, M.H.S., Sujit K. Bhattacharya, M.D., Nirmal K. Ganguly, Ph.D., Mohammad Ali, Ph.D., Byomkesh Manna, Ph.D., Shanta Dutta, M.D., Ph.D., Allan Donner, Ph.D., Suman Kanungo, M.B., B.S., D.I.H., Jin Kyung Park, Ph.D., Mahesh K. Puri, M.Sc., Deok Ryun Kim, M.Sc., Dharitri Dutta, M.B., B.S., D.C.H., Barnali Bhaduri, M.Sc., Camilo J. Acosta, M.D., Ph.D., and John D. Clemens, M.D.

Typhoid vaccine trial

The efficacy of a single dose of the Vi polysaccharide typhoid vaccine was evaluated in a Phase 4 parallel cluster randomized trial in slum-dwelling residents of Kolkata, India

The study area encompassing most of two wards in Eastern Kolkata was partitioned into 80 contiguous geographic clusters

Clusters were divided into eight strata according to ward, the number of residents who were 18 years of age or younger (<200 vs. ≥200), and the number of residents who were older than 18 years (<500 vs. ≥500)

Stratified randomization was used to allocate clusters to receive the Vi typhoid vaccine or hepatitis A vaccine

Cluster members 2 years of age or older were targeted for vaccination

Typhoid vaccine trial

Vaccine coverage in clusters was about 60%

The endpoint of interest was laboratory-confirmed typhoid fever

The primary outcome was total vaccine effectiveness

The secondary outcomes were indirect and overall vaccine protection

Cox proportional hazards models were fit to individual data, and standard errors were adjusted using a robust variance estimator

A set of analyses adjusting for the stratifying variables and other key-individual-level covariates were also conducted

Table 2. Occurrence of Typhoid Fever at 2 Years and Protective Effectiveness of Vi Vaccine.

Variable	Vi Vaccine (N=18,869)	Hepatitis A Vaccine (N=18,804)	Protective Effectiveness of Vi Vaccine (95% CI)*	
			Simple Analysis	Adjusted Analysis†
			percent	
Subjects with typhoid fever — no.	34	96		
Person-days of follow-up — no.	13,309,337	13,214,761		
Incidence of typhoid fever — no. of cases/100,000 person-days	0.26	0.73	65 (42–79)	61 (41–75)

* P<0.001 for the comparison between the Vi vaccine group and the hepatitis A vaccine group.

† Protective effectiveness was adjusted for the variables used to stratify the clusters for randomization, as well as age, religion, living in a household with a monthly per capita expenditure above the median, and living in a household with a specific place for waste disposal. The model for the adjusted analysis was derived from 128 cases of typhoid fever among 37,164 subjects for whom complete data were available on all variables.

Table 4. Cases of Typhoid Fever in Analyses of Indirect and Overall Protection at 2 Years and Protective Effectiveness of Vi Vaccine.

Type of Protection	Vi Vaccine	Hepatitis A Vaccine	Protective Effectiveness of Vi Vaccine (95% CI)	
			Simple Analysis	Adjusted Analysis*
			percent	
Indirect protection				
Subjects with typhoid fever — no./total no.	16/12,206	31/12,877		
Incidence of typhoid fever — no. of cases/100,000 person-days	0.19	0.35	45 (1–70)†	44 (2–69)†‡
Overall protection				
Subjects with typhoid fever — no./total no.	50/31,075	127/31,681		
Incidence of typhoid fever — no. of cases/100,000 person-days	0.23	0.58	60 (39–74)§	57 (37–71)§¶

* Protective effectiveness was adjusted for the variables used to stratify the clusters for randomization, as well as age and living in a household with a longer distance to the nearest treatment center (in the analysis of indirect protection) and age, religion, living in a household with a monthly per capita expenditure above the median, and living in a household with a longer distance to the nearest treatment center than the median (in the analysis of overall protection).

† $P=0.04$.

‡ This model was derived from 47 cases of typhoid in 25,083 subjects for whom data on all variables were complete.

§ $P<0.001$.

¶ This model was derived from 177 cases of typhoid among 61,996 subjects for whom data on all variables were complete.

Stepped wedge cluster randomized trials - overview

All clusters commence the trial in the control arm

The intervention is then introduced gradually at regular intervals until it is in place in all clusters

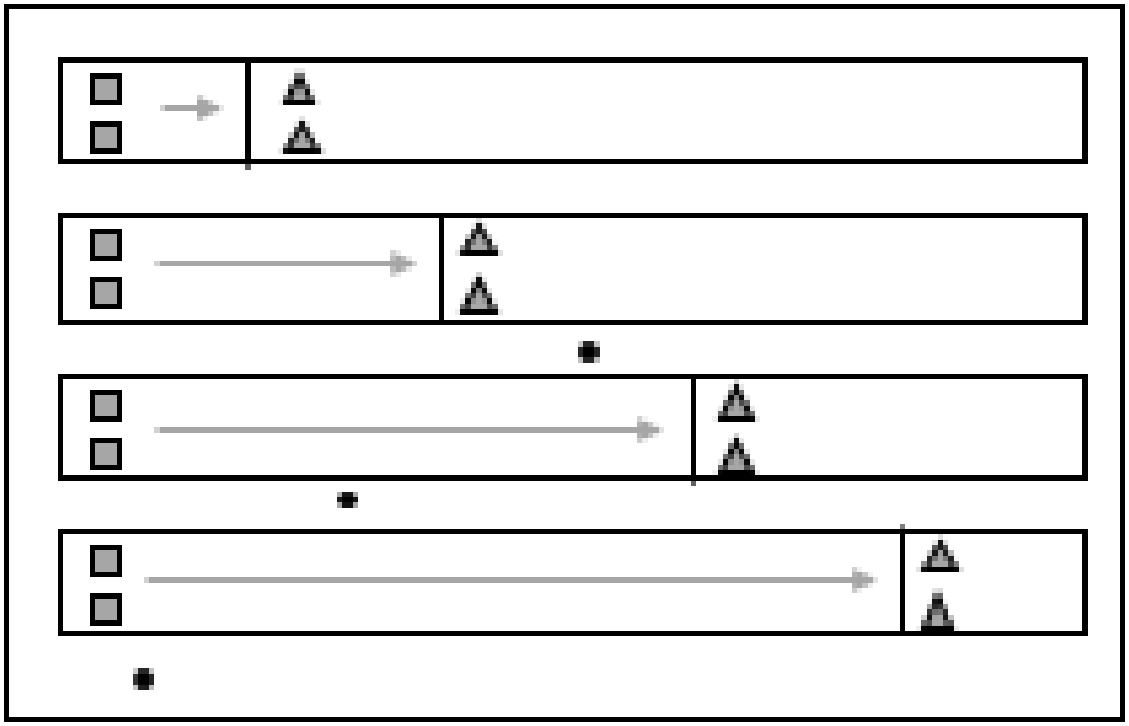
The order of roll-out is randomized to support principled inference

Stepped wedge designs are sometimes also referred to as one-way crossover trials or phased implementation designs

This design is adopted in settings where there is already considerable evidence that the vaccine will have a beneficial effect

If the vaccine cannot be delivered simultaneously in a large area, either for logistical reasons or insufficient supply, random selection is a fair way to determine the order of roll-out

Stepped Wedge Cluster RCT



△ vaccinated participant

□ comparator participant

• non-participant

Stepped wedge cluster randomized trials - design

It is necessary to specify:

- The size of the clusters
- The number of clusters receiving the intervention per step
- The number of steps
- The length of time between successive crossover points (step length)
- The rollout period (baseline data collection before first crossover)

Like parallel cluster randomized trials, the sample size must be inflated by the trial design effect

Simulation studies may be worthwhile for estimating power because of the complexity of designing stepped wedge trials

Stepped wedge cluster randomized trials - analysis

A standard two-arm comparison is not possible because clusters change allocation over time

A simple before vs. after approach cannot be adopted because of secular time trends

The analysis either takes a horizontal or vertical approach

In the horizontal approach, time trends are explicitly modeled

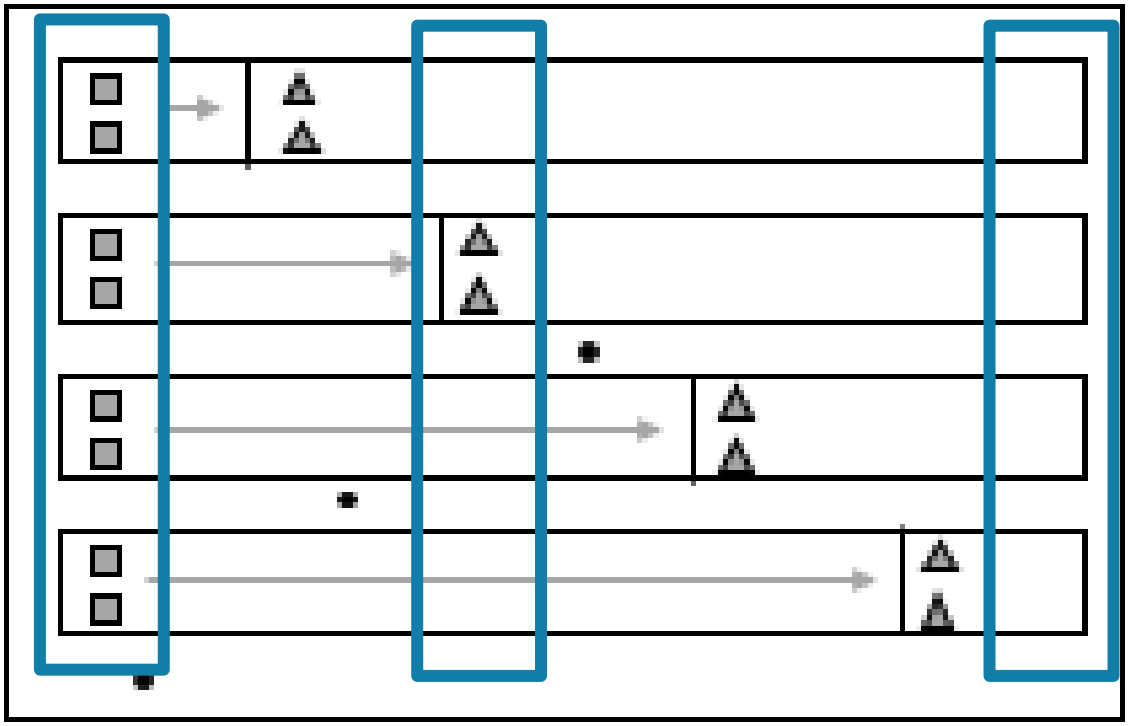
- Susceptible to model misspecification

In the vertical approach, time is conditioned out as a nuisance

- Comparisons are only made within time steps
- This approach does not use all available data (e.g. periods when everyone is unvaccinated and when everyone is vaccinated)

Same estimands as parallel cluster randomized trials

Stepped Wedge Cluster RCT



△ vaccinated participant

□ comparator participant

• non-participant

[CANCER RESEARCH 47, 5782–5787, November 1, 1987]

The Gambia Hepatitis Intervention Study[1]

The Gambia Hepatitis Study Group[2]

ABSTRACT

The Gambia Hepatitis Intervention Study is a large-scale vaccination project in The Gambia, initiated in July 1986, in which the introduction of national hepatitis B (HBV) vaccination of young infants progressively over a 4-year period is proposed. During this time it is anticipated that about 60,000 infants will receive a course of HBV vaccine and a similar number will not receive the vaccine. All children in the study will receive the normal childhood vaccinations. Identification data for each child will be collected and stored with information on their vaccination records. A national surveillance system will be set up to detect new cases of hepatocellular cancer and other chronic liver diseases over a period of 30 to 40 years. An attempt will be made to trace each case, of relevant age, to determine if they are included in the HBV vaccination study. In this way, the efficacy of HBV vaccine in the prevention of HCC and chronic liver diseases will be evaluated. Details of the study design are discussed.

Hepatitis B vaccine study

The Gambia Hepatitis Intervention Study evaluated the long-term effects of infant hepatitis B vaccination on preventing chronic liver disease and liver cancer

Seventeen vaccination teams were each assigned a portion of 104 vaccine delivery points that were visited at least once every two weeks to conduct routine immunizations

Every 10-12 weeks, a new vaccination team was instructed to introduce hepatitis B vaccine, with teams selected in randomized order

After a four-year period, all delivery points included hepatitis B in routine vaccination

Hepatitis B vaccine study

The statistical analysis used a vertical approach, dividing time into three month time periods and comparing outcomes for vaccinated and unvaccinated children

As the primary endpoints were long-term endpoints (chronic liver disease and liver cancer), over 20 years of follow-up have been conducted so far, and the trial is ongoing

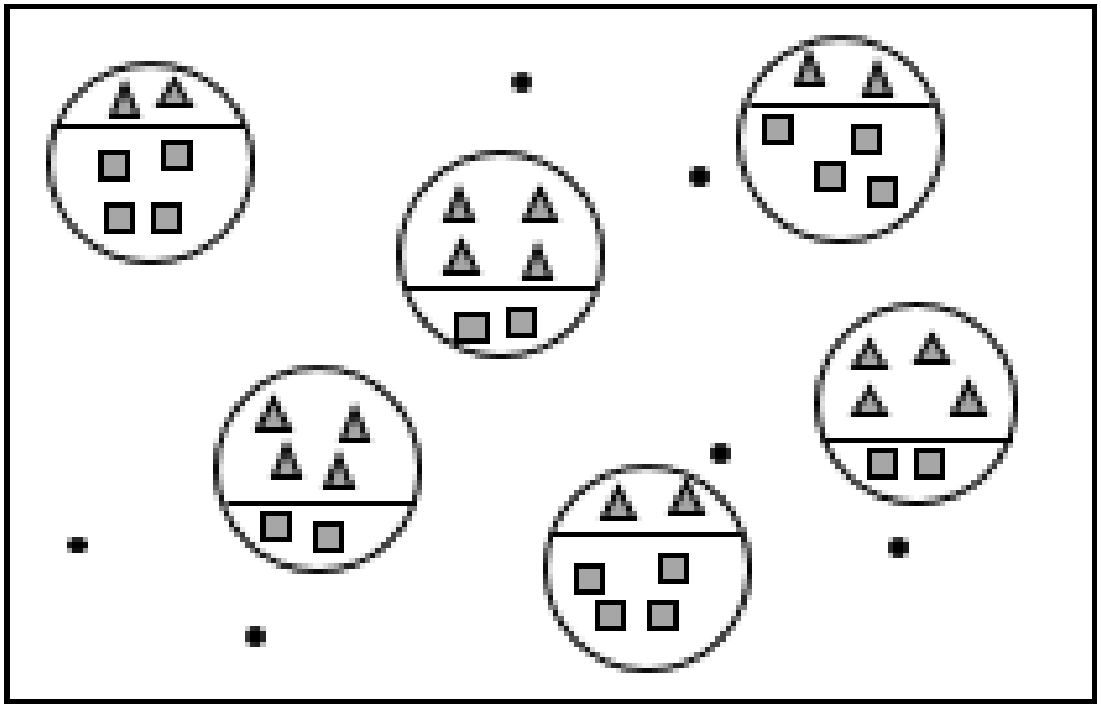
Two-stage randomization designs - overview

Clusters are first randomized to some fixed level of vaccine coverage (e.g. low = 20% or high = 80%)

Individuals are then randomized within each cluster based on the coverage level determined in the first stage

This design is also referred to as two-step randomization, split-plot randomization, pseudo-randomization, or randomized saturation

Two-Stage Randomization



△ vaccinated participant

□ comparator participant

• non-participant

Two-stage randomization designs - analysis

It is one of the only designs to support estimation of both direct and indirect vaccine effects

For detecting major effects, two-stage designs are less powerful than individually randomized and parallel cluster randomized trials

- Standard designs offer a sharper contrast between trial arms

This design is complex, and it has not been used for vaccine trials in practice

Trials with multiple vaccine candidates - overview

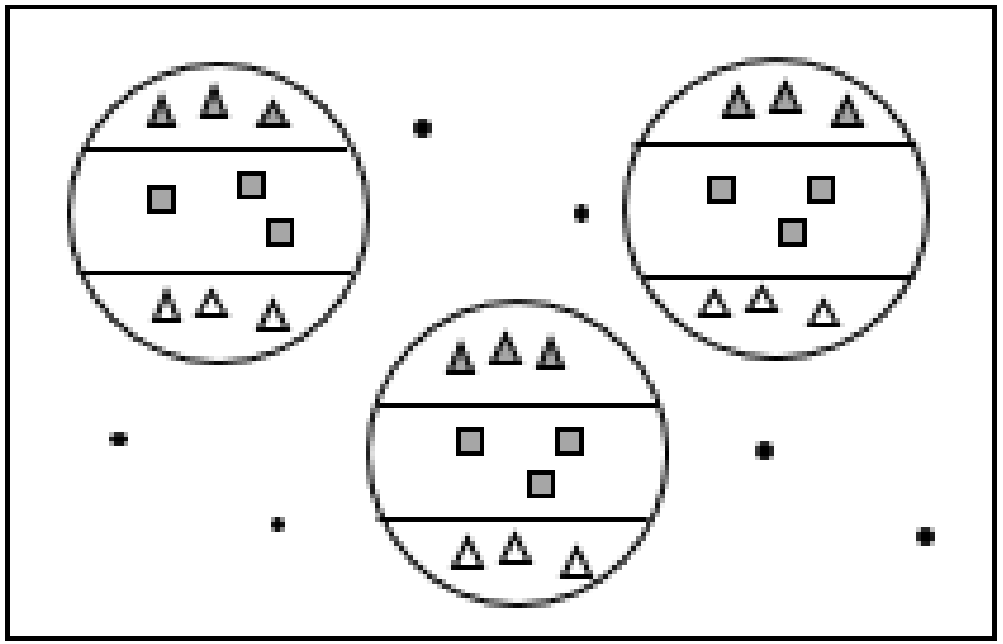
Trials may be designed to include multiple experimental vaccines and a pooled control arm

The same trial infrastructure is used and so may require fewer resources than multiple, independent two-arm trials

This design facilitates direct comparison between the candidates

This approach works best when the vaccines have similar target populations

Multi-Arm Trials (iRCT within Sites)



△ vaccinated participant

□ comparator participant

• non-participant

△ vaccinated participant (other candidate)

Trials with multiple vaccine candidates - extensions

Trials could include adaptive strategies to drop poorly performing candidates

- More common in Phase 2 trials

Phase 2 and Phase 3 trials may be formally combined into Phase 2/3 trials

- These are also known as seamless Phase 2/3, “discovery into confirmatory”, or “combined-phase” trials
- Phase 2: safety and immunogenicity data in a limited and focused study population; may include a preliminary assessment of efficacy
- Phase 3: large trial to collect data on safety and vaccine efficacy
- Analysis of the Phase 2 trial provides a clear “GO” or “NO GO” decision for how to proceed to the next phase, following a decision-making strategy defined in the protocol

Trials with multiple vaccine candidates - extensions

Phase 2/3 trials can be **inferentially** or **operationally seamless**

- Inferentially seamless: data from the Phase 2 portion contribute to the Phase 3 analysis
- Operationally seamless: data from each portion are analyzed separately

A natural application of this approach is to evaluate multiple vaccine candidates in Phase 2, with only the most promising being advanced to Phase 3

Gilbert et al. (JID 2011) described a Phase 2b design strategy for simultaneously evaluating multiple prime-boost HIV vaccine regimens against a shared placebo group

- The design uses sequential monitoring to drop vaccines with evidence of poor safety or efficacy
- The trial design has not yet been implemented in the field

Effectiveness trials - overview

Vaccine efficacy can be distinguished from vaccine effectiveness

- Vaccine efficacy = the intrinsic vaccine effect measured in an idealized setting
- Vaccine effectiveness = vaccine effect measured in a real world setting

Vaccine effectiveness trials are population-specific trials that focus on estimating the public health impact of the vaccine under non-idealized settings

- E.g. difficulty maintaining a cold chain

Results are not generalizable but could support country-specific licensure and provide useful information to local policy makers

PLOS | MEDICINE

RESEARCH ARTICLE

Effectiveness of a live oral human rotavirus vaccine after programmatic introduction in Bangladesh: A cluster-randomized trial

K. Zaman[1], David A. Sack[2], Kathleen M. Neuzil[3], Mohammad Yunus[1], Lawrence H. Moulton[2], Jonathan D. Sugimoto[4], Jessica A. Fleming[3], Ilias Hossain[1], Shams El Arifeen[1], Tasnim Azim[1], Mustafizur Rahman[1], Kristen D. C. Lewis[3], Andrea J. Feller[2], Firdausi Qadri[1], M. Elizabeth Halloran[4,5], Alejandro Cravioto[1], John C. Victor[3]*

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Rotavirus vaccine trial

142 villages in Matlab, Bangladesh were cluster-randomized (1:1) to two doses of human rotavirus vaccine at 6 and 10 weeks of age or control

Surveillance was conducted to identify children less than 2 years of age presenting with acute laboratory-confirmed rotavirus diarrhea during the trial period

Overall effectiveness of the vaccine program was measured by comparing the incidence rate of disease among all children age-eligible for vaccination in villages where vaccine was introduced compared to villages were vaccine was not introduced

Total effectiveness among vaccinees and indirect effectiveness were also evaluated

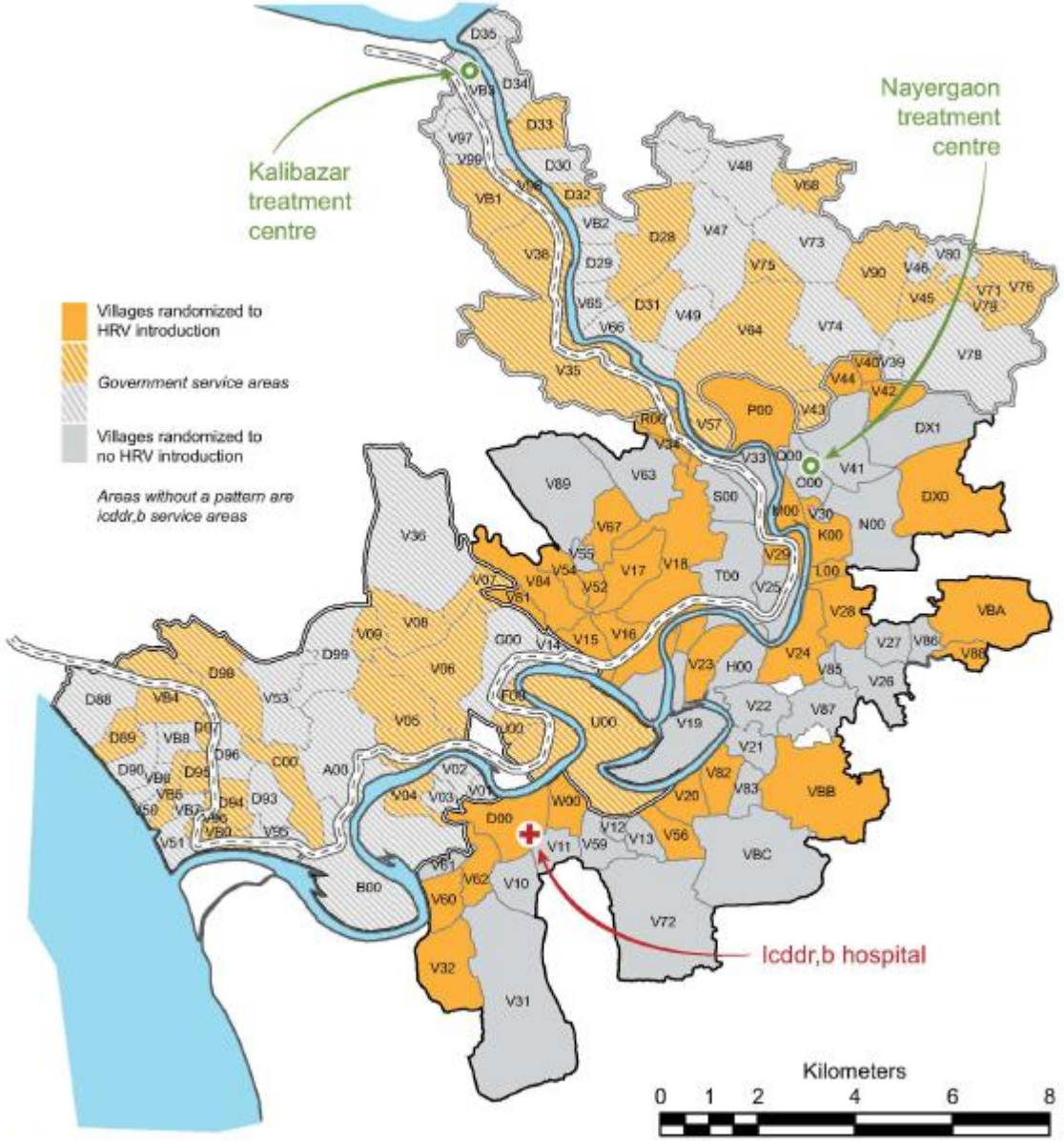

Fig 1. Distribution of villages randomized to human rotavirus vaccine introduction or no human rotavirus vaccine introduction during the trial, Matlab Health and Demographic Surveillance System. HRV, human rotavirus vaccine; icddr,b, International Centre for Diarrhoeal Disease Research, Bangladesh.

Rotavirus vaccine trial

Sample size

- For the primary objective, assumed an overall effectiveness of 50%
- For a comparable individually randomized trial, 77 outcomes among all age-eligible infants would have been required to ensure that the study had a minimum power of 80% to rule out a lower bound of the two-sided 95% CI of zero
- Estimated intracluster correlation coefficient of 0.02
- With an average of 65 children younger than 2 years in each cluster, the design effect was 3.48
- Total number of outcomes required is 268
- Assuming a 3.5% cumulative incidence in control villages during the study period, a total sample size of 10,210 infants (5,105) in each group was estimated

Coverage was 73.7% in villages randomized to vaccine

Table 2. Overall effectiveness of the human rotavirus vaccination program in preventing presentations of acute rotavirus diarrhea of any severity and severe acute rotavirus diarrhea among age-eligible children less than 2 y of age, regardless of actual receipt of human rotavirus vaccine.

ARD analysis	HRV villages			Non-HRV villages			Adjusted VE_O[b], percent (95% CI)	Adjusted rate difference[c], percent (95% CI)
	Cases (*n*)	Person-years	Incidence rate[a]	Cases (*n*)	Person-years	Incidence rate[a]		
Including resident infants who turned 6 wk of age on or after study initiation								
Any severity[d]	164	5,857	2.80	206	5,026	4.10	29.0 (11.3, 43.1)	1.28 (0.31, 2.25)
Severe ARD[e]	128	5,880	2.18	149	5,058	2.95	22.9 (−0.2, 40.7)	0.83 (−0.04, 1.71)
Including above infants plus those up to 20 wk of age at study initiation								
Any severity	195	6,960	2.80	235	6,031	3.90	24.9 (7.7, 38.9)	1.12 (0.24, 2.01)
Severe ARD[e]	151	6,992	2.16	172	6,068	2.83	20.4 (−1.8, 37.7)	0.74 (−0.07, 1.54)

[a]Per 100 person-years.

[b]Estimated using a Poisson regression model with a Pearson chi-squared scale parameter to account for clustering.

[c]Estimated per 100 person-years using the approach described in Section 12.3.2 of [21].

[d]Primary analysis.

[e]Person-time censored at first severe ARD episode, regardless of severity of previous ARD.

ARD, acute rotavirus diarrhea; HRV, human rotavirus vaccine; VE_O, overall vaccine effectiveness.

For the estimation of total vaccine effectiveness, an intention-to-treat like approach was used that disregarded actual receipt of vaccine

An analysis was also conducted “According to Protocol” (ATP)

Table 3. Total effectiveness of human rotavirus vaccine in preventing presentations of acute rotavirus diarrhea of any severity and severe acute rotavirus diarrhea among vaccinees, by age of onset and rotavirus strain detected.

ARD analysis	HRV villages			Non-HRV villages			Adjusted VE_T[c], percent (95% CI)	Adjusted rate difference[d], percent (95% CI)
	Cases (*n*)	Person-years[a]	Incidence rate[b]	Cases (*n*)	Person-years[a]	Incidence rate[b]		
VE_T (mITT)								
Any severity, all ages	108	4,735	2.28	194	4,998	3.88	38.7 (20.6, 52.7)	1.39 (0.47, 2.32)
VE_T (ATP)								
Any severity, all ages	102	4,117	2.48	172	3,893	4.42	41.4 (23.2, 55.2)	1.73 (0.64, 2.81)

Case-control studies - overview

Case-control studies are conducted by enrolling disease cases and comparable disease-free controls and comparing vaccination status

Cohort study

	Disease	No disease	Total
Vax	a	b	n_V
Unvax	c	d	$n_{\overline{V}}$

Case-control study

	Disease	No disease
Vax	a	b
Unvax	c	d
Total	n_D	$n_{\overline{D}}$

$$OR = \frac{ad}{bc}$$

Case-control studies - design

Studies can be prospectively integrated into a surveillance program, enrolling cases and controls over time

Studies can be entirely retrospective, using diagnostic or electronic health records

Cases should be detected using a highly specific test or case definition

- Inclusion of false positives biases vaccine effectiveness towards the null, especially if the false positive rate varies over time or place

Case-control studies - design

Validity of inference depends heavily on the quality of the controls

Controls should

- Have the same risk of exposure to the target pathogen as the cases
- Be similarly susceptible to the disease before vaccination
- Be recruited independently of vaccination status
- Have the same access to medical care and vaccination

Healthy community controls are often selected from the same source populations

A good rule of thumb for selecting a control is that if a control developed the disease of interest, he or she would become a case in the study

Case-control studies - design

Cases and control may be matched for key confounders linked to both vaccination and disease

- E.g. age, gender, socioeconomic status, geography
- For rare outcomes, multiple controls may be matched to a single case

The case-control design does not work well if only a small proportion of the source population is vaccinated because vaccination rates will be low among both cases and control

- By the same logic, challenging if vaccine coverage is very high

Case-control designs are especially useful when the outcome is rare because the population analyzed is enriched with cases

- Much more cost-effective than a large, prospective cohort

Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis

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Summary

Background Between April and June, 2012, a reactive cholera vaccination campaign was done in Haiti with an oral inactivated bivalent whole-cell vaccine. We aimed to assess the effectiveness of the vaccine in a case-control study and to assess the likelihood of bias in that study in a bias-indicator study.

Methods Residents of Bocozel or Grand Saline who were eligible for the vaccination campaign (ie, age ≥12 months, not pregnant, and living in the region at the time of the vaccine campaign) were included. In the primary case-control study, cases had acute watery diarrhoea, sought treatment at one of three participating cholera treatment units, and had a stool sample positive for cholera by culture. For each case, four control individuals who did not seek treatment for acute watery diarrhoea were matched by location of residence, enrolment time (within 2 weeks of the case), and age (1–4 years, 5–15 years, and >15 years). Cases in the bias-indicator study were individuals with acute watery diarrhoea with a negative stool sample for cholera. Controls were selected in the same manner as in the primary case-control study. Trained staff used standard laboratory procedures to do rapid tests and stool cultures from study cases. Participants were interviewed to collect data on sociodemographic characteristics, risk factors for cholera, and self-reported vaccination. Data were analysed by conditional logistic regression, adjusting for matching factors.

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Cholera vaccine study

Between April and June 2012, a reactive cholera vaccination campaign was implemented in Haiti with an inactivated bivalent whole-cell vaccine

Investigators conducted a case-control study to evaluate vaccine effectiveness

Study included residents of Bocozel or Grand Saline who were eligible for the vaccination campaign (e.g. age ≥12 months, not pregnant)

Cases had acute watery diarrhea, sought treatment at one of three participating cholera treatment units, and were culture-positive for cholera

Community health workers were trained to refer acute cases to treatment units, and these cases were asked to participate in the study

Cholera vaccine study

For each case, four controls who did not seek treatment for watery diarrhea were selected

- Matched for location of residence, enrolment time (within 2 weeks of case), and age (1-4 years, 5-15 years, and >15 years)

Individuals who reported receipt of at least one dose of the vaccine were asked to produce their vaccine card as verification

- Vaccine registries were used to verify vaccination status for individuals who reported vaccination but could not produce a vaccine card

Analyzed data by conditional logistic regression, adjusting for matching factors

To assess potential bias, they conducted a parallel analysis of vaccine effectiveness on non-cholera diarrhea

	Cases	Controls	Crude RR* (95% CI)	Adjusted RR (95% CI)	Vaccine effectiveness (95% CI)	p value
Cholera vaccine effectiveness case-control study						
Vaccinated, self-report	33/47 (70%)	167/188 (89%)	0·27 (0·12–0·61)	0·37 (0·15–0·92)†	63% (8 to 85)	0·031
Number of self-reported doses						
None	14/47 (30%)	21/188 (11%)	Reference	Reference	..	..
One	3/47 (6%)	19/188 (10%)	0·20 (0·05–0·87)	0·33 (0·07–1·62)†	67% (–62 to 93)	0·17
Two	30/47 (64%)	148/188 (79%)	0·28 (0·13–0·63)	0·38 (0·15–0·94)†	62% (6 to 85)	0·036
Proof of vaccination (card or registry record)	27/47 (57%)	147/188 (78%)	0·35 (0·17–0·72)	0·42 (0·20–0·87)‡	58% (13 to 80)	0·020
Bias-indicator case-control study						
Vaccinated, self-report	39/42 (93%)	158/168 (94%)	0·83 (0·22–3·09)	0·82 (0·22–3·08)‡	18% (–208 to 78)	0·77
Number of self-reported doses						
None	3/42 (7%)	10/168 (6%)	Reference	Reference		
One	7/42 (17%)	11/168 (7%)	2·50 (0·47–13·25)	2·53 (0·48–13·37)‡	–153% (–1237 to 52)	0·28
Two	32/42 (76%)	147/168 (88%)	0·73 (0·19–2·78)	0·72 (0·19–2·74)‡	28% (–174 to 81)	0·63
Proof of vaccination (card or registry record)	36/42 (86%)	137/168 (82%)	1·39 (0·52–3·70)	1·21 (0·43–3·38)§	–21% (–238 to 57)	0·72

Data are number (%), unless otherwise specified. Some percentages do not total 100 because of rounding. RR=relative risk. *Adjusted for matching factors. †Adjusted for matching factors, female sex, age (continuous), electricity in the home, main toilet type, and whether the participant completed the interview (*vs* a proxy). ‡Adjusted for matching factors, female sex, and age (continuous). §Adjusted for matching factors, female sex, age (continuous), and earthen floor in the household.

***Table 3*: Effectiveness of the oral cholera vaccine in rural Haiti**

Test-negative studies

It is difficult to control for confounding due to differential access to care and health-seeking behavior in case-control studies

In test-negative studies, controls are selected form the pool of people who are tested for the pathogen of interest but test negative

By restricting the study population to individuals meeting the clinical case definition who receive testing, controls are expected to have similar health-seeking behavior

Direct vaccine effectiveness is estimated as one minus the odds ratio of vaccination for positive-testing cases versus negative-testing controls

Test-negative studies

A central assumption is that vaccination does not confer cross-protection to other diseases with similar symptoms

A highly specific test is required to reduce bias in estimated vaccine efficacy

Test-negative designs can be easily embedded into existing surveillance programs

MAJOR ARTICLE

Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates

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Flu vaccine study

The US annually evaluated effectiveness of vaccines for preventing medically attended acute respiratory illness caused by influenza

Patients with acute respiratory illness of ≤7 days duration were enrolled at participating ambulatory care facilities in five communities

- Washington, Wisconsin, Michigan, Pennsylvania, Texas

Influenza infection was confirmed by RT-PCR

Receipt of influenza vaccine was defined based on medical records or immunization registries

Vaccine effectiveness was calculated from a logistic regression model for vaccination, with and without adjustment for key covariates

- Network center, age, sex, race/ethnicity, high-risk health status, self-rated health status, number of days between illness onset and specimen collection, calendar time

Table 3. Percentage Vaccinated by Influenza Case/Control Status, Plus Unadjusted and Adjusted Vaccine Effectiveness Estimates by Age Group and Vaccine Type

	Influenza-Positive Cases		Influenza-Negative Controls		Unadjusted		Adjusted[a]	
Age Group	No. Vaccinated[b]/Total	% Vaccinated	No. Vaccinated[b]/Total	% Vaccinated	VE %	(95% CI)	VE %	(95% CI)
Any seasonal vaccine								
All ages	213/681	31.3	1983/4090	48.5	52	(43 to 59)	47	(36 to 56)
6 mo – 8 y[c]	65/190	34.2	724/1300	55.7	59	(43 to 70)	45	(20 to 62)
9–17 y	26/111	23.4	204/555	36.8	47	(16 to 67)	58	(27 to 76)
18–49 y	58/231	25.1	492/1318	37.3	44	(23 to 59)	44	(21 to 60)
50–64 y	32/96	33.3	309/586	52.7	55	(29 to 72)	54	(23 to 72)
≥65 y	32/53	60.4	254/331	76.7	54	(15 to 75)	43	(–18 to 72)
Inactivated vaccine								
2–8 y[c]	38/158	24.1	302/787	38.4	49	(25 to 66)	40	(6 to 62)
9–17 y	20/105	19.0	139/483	28.8	42	(2 to 66)	61	(28 to 79)
Live-attenuated vaccine								
2–8 y[c]	9/121	7.4	87/537	16.2	58	(15 to 80)	61	(16 to 82)
9–17 y	5/88	5.7	39/368	10.6	49	(–33 to 81)	60	(–15 to 86)

Vaccine effectiveness was estimated by comparing the vaccination coverage in influenza positive cases and influenza negative controls and calculated as 100 × (1 – odds ratio) in logistic regression models.

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

[a] Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

[b] Subjects were considered vaccinated if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the current season ≥14 days before illness onset.

[c] Partially or fully immunized.

Thank you