



Beyond Protective Efficacy: Evaluating Different Population-Level Effects of Vaccination

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Framework

Dependent Happenings

Framework for Vaccine Effects

VE_S , VE_{SP}

Vaccine efficacy for progression

Estimating $VE_{S,p}$, VE_I , VE_T

Population-Level Effects

Overview

Cluster-randomized design

Cholera Vaccination



Dependent versus Independent Happenings

- Sir Ronald Ross (1916) *Proc R Soc Series A* 92:204-230.
- 2nd Nobel Prize in Medicine : elucidation of mosquitos as malaria transmitters
- Transmission models of malaria
- In dependent happenings, the number of individuals becoming affected depends on the number of individuals already affected.



Our Goal

- Due to the dependent happenings in infectious diseases, vaccination can produce several different kinds of effects
 - At the individual level
 - And at the population level.
- Demonstrating indirect effects of vaccination can have important consequences for global policies.
- Our goal in this talk is
 - to discuss direct, indirect, total, and overall effects of vaccination in populations
- Halloran, ME, Longini, IM, and Struchiner, CJ (2010) *Design and Analysis of Vaccine Studies*, Springer.



Vaccine efficacy and effectiveness

- Generally estimated as one minus some measure of relative risk, RR , in the vaccinated group compared to the unvaccinated group:

$$VE = 1 - RR .$$

- The groups being compared could be composed of individuals or of populations or communities.
- Other scales: risk ratio, difference, odds ratio



Table : Some Vaccine Effects of Interest

Symbol	Definition
VE_S	vaccine efficacy for susceptibility (infection)
VE_{SP}	vaccine efficacy for susceptibility to disease
VE_{COL}	vaccine efficacy for colonization
VE_P	vaccine efficacy for progression, pathogenicity
VE_I	vaccine efficacy for infectiousness
VE_T	total vaccine efficacy
$VE_{indirect}$	indirect effects of vaccination in those not vaccinated
VE_{total}	total effects of vaccination in those vaccinated
$VE_{overall}$	overall population-level effects



Table : Parameters used for measuring various effects of vaccination*

Level Parameter choice	Comparison groups and effect			
	Susceptibility	Infectiousness	Combined change in susceptibility and infectiousness	
Conditional on exposure:				
I Transmission probability	$VE_{S,p} \dagger = 1 - \frac{p \cdot 1}{p \cdot 0}$	$VE_{I,p} = 1 - \frac{p \cdot 1}{p \cdot 0}$	$VE_{T,p} = 1 - \frac{p \cdot 1}{p \cdot 0}$	
	Study design			
	I direct	IIA indirect	IIB total	III overall
Unconditional:				
II Incidence or hazard rate, IR, λ	$VE_{S,IR} = 1 - \frac{IR_{A1}}{IR_{A0}}$	$VE_{IIA,IR} = 1 - \frac{IR_{A0}}{IR_{B0}}$	$VE_{IIB,IR} = 1 - \frac{IR_{A1}}{IR_{B0}}$	$VE_{III,IR} = 1 - \frac{IR_{A \cdot}}{IR_{B \cdot}}$
	$VE_{S,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{A0}}$	$VE_{IIA,\lambda} = 1 - \frac{\lambda_{A0}}{\lambda_{B0}}$	$VE_{IIB,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{B0}}$	$VE_{III,\lambda} = 1 - \frac{\lambda_{A \cdot}}{\lambda_{B \cdot}}$
III Proport. hazards, PH	$VE_{S,PH} = 1 - e^{\beta 1}$	NA	NA	NA
IV Cumulative incidence	$VE_{S,CI} = 1 - \frac{CI_{A1}}{CI_{A0}}$	$VE_{IIA,CI} = 1 - \frac{CI_{A0}}{CI_{B0}}$	$VE_{IIB,CI} = 1 - \frac{CI_{A1}}{CI_{B0}}$	$VE_{III,CI} = 1 - \frac{CI_{A \cdot}}{CI_{B \cdot}}$

* From Halloran, Struchiner, Longini, Am. J. Epidemiol 1997; 146:789–803.

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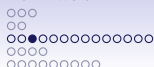
Cholera Vaccination



Vaccine efficacy for susceptibility, VE_S , VE_{SP}

The measure of risk can be

- a form of the transmission probability, such as the secondary attack rate (SAR) which conditions on exposure to infection, or
- the incidence rate, hazard rate, or cumulative incidence (attack rate), which do not condition on exposure to infection.



Hazard, incidence rate

- Primary vaccine efficacy studies often report $VE_{S,IR}$ based on relative events per person-time:

$$VE_{S,IR} = 1 - \frac{\text{vaccinated events/person-time}}{\text{unvaccinated events/person-time}}. \quad (1)$$

- VE_S can be based on the hazard rate ratio

$$VE_{S,\lambda}(t) = 1 - \frac{\lambda_1(t)}{\lambda_0(t)}. \quad (2)$$

- Cox proportional hazards model needs only ordering of the onset times to estimate $VE_{S,PH}$.



Conditions Necessary for Valid Inference

- From Greenwood and Yule (1915) The Statistics of Anti-typhoid and Anti-cholera Inoculations, and the Interpretation of such Statistics in general, Proc R Soc Med (1915) 8(part 2):113-94:
 1. The persons must be, *in all material respects*, alike.
 2. The effective exposure to the disease must be identical in the case of inoculated and uninoculated persons.
 3. The criteria of the fact of inoculation and of the fact of the disease having occurred must be independent.
- Relationship to randomization in current studies



TABLE 12

Persons in the study series exposed to pertussis according to "type" of exposure and proportions of those exposed who were attacked

	Classification according to history of exposure				No history of exposure
	Definite in own household	Definite in other household	Indefinite	Total	
Both groups					
No. of exposures . . .	243	161	166	570	3642
Attacks	172	39	14	225	175
Per cent	70.8	24.2	8.4	39.5	4.8
Vaccine group					
No. of exposures . . .	83	100	114	297	1518
Attacks	29	5	4	38	14
Per cent	34.9	5.0	3.5	12.8	0.9
Control group					
No. of exposures . . .	160	61	52	273	2124
Attacks	143	34	10	187	161
Per cent	89.4	55.7	19.2	68.5	7.6

PEARL KENDRICK AND GRACE ELDERING

Figure : Results of a pertussis vaccine trial in Michigan, USA, in the 1930s (from Kendrick and Eldering, Am J Hyg, Sect B, 38:133, 1939)



Kendrick and Eldering (1939): pertussis vaccine

Vaccinated = 29 attacks/83 exposures
Unvaccinated = 143 attacks/160 exposures

$$VE_{S,p} = 1 - \frac{.349}{.894} = 0.61.$$



TABLE 9

*Incidence of pertussis in test and control groups
based on period at risk*

Time at risk and subsequent attack	Groups in study		
	Both groups	In- jected	Con- trol
Number of children.....	4212	1815	2397
Person-years.....	4575	2268	2307
Number of attacks.....	400	52	348
Annual pertussis attack rate per 100.....	8.7	2.3	15.1

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Figure : Results of a pertussis vaccine trial in Michigan, USA, in the 1930s (from Kendrick and Eldering, Am J Hyg, Sect B, 38:133, 1939)



Estimating $VE_{S,IR}$

- Kendrick and Eldering (1939): pertussis vaccine based events per person time:

Vaccinated = 52 attacks/2268 person-years

Unvaccinated = 348 attacks/2307 person-years

$$\widehat{VE}_{S,IR} = 1 - \frac{\frac{52 \text{ cases}}{2268 \text{ person-years}}}{\frac{348 \text{ cases}}{2307 \text{ person-years}}} = 0.85$$

- Note difference to $\widehat{VE}_{S,p} = 0.61$ in the same study.



VE_S : Final value data

- Estimation of $VE_{S,CI}(T)$ based on the cumulative incidence requires only information about whether persons are infected by the end of the study at time T ,
- that is, final value data:

$$\begin{aligned}
 VE_{S,CI}(T) &= 1 - \frac{\text{vaccinated infection events/persons-at-risk}}{\text{unvaccinated infection events/persons-at-risk}} \\
 &= 1 - \frac{CI_1(T)}{CI_0(T)} .
 \end{aligned}$$



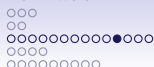
Belshe et al (2007): live versus killed influenza vaccine

- Double-blinded randomized trial of live-attenuated (LAIV) versus killed influenza vaccine in children 6 to 59 months
- Enrollment Oct 20 to Oct 29, 2004 in 249 sites in 16 countries (US, Europe, Middle East Asia)
- Outcome was culture-confirmed influenza ascertained on symptomatic flu-like illness
- Relative efficacy, not absolute efficacy

LAIV = 153 cases/3912 children

Killed vaccine = 338 cases/3936 children

$$\widehat{VE}_{SP,CI}(T) = 1 - \frac{153 \text{ cases}/3912 \text{ at-risk}}{338 \text{ cases}/3936 \text{ at-risk}} = 0.54 .$$



Hierarchy of VE_S measures

- Let p_{ij} be the transmission probability.
- Let c denote the contact rate in a population assuming random mixing.
- Let $P(t)$ denote the prevalence of infectives at time t .
- Then the hazard rate $\lambda(t)$ can be expressed

$$\lambda(t) = cp_{ij}P(t).$$

- We can consider the fundamental dependent happening underlying process that produces the infections we observe.



Hierarchy of Parameters

Transmission
Probability
(SAR)

$$p = \frac{\text{\# infections}}{\text{\# potentially infectious contacts}}$$

Hazard Rate
Incidence
(events per
person-time)

$$\lambda(t) = c \times p \times P(t)$$

contacts per time
transmission probability
prevalence

Cumulative
Incidence
(event by
time t ;
yes or no)

$$CI(t) = 1 - e^{-\int_0^t \lambda(u) du} = 1 - e^{-\int_0^t c p P(u) du}$$



What do we mean by efficacy?

- What does it mean to say a vaccine is 90% efficacious?
- Does it protect 90% of people completely?
- Does it reduce your risk of infection by 90% each time you are exposed?
- Smith, Rodriguez, and Fine (1984): Models I and II
- Halloran, Struchiner and Spielman (1989): Leaky and all-or-none
- Implications for the choice of efficacy measures and for long-term dynamics in populations.



Randomized versus Observational Studies

- Randomization: best, but often unfeasible.
- Observational studies
- Case-control studies
- Test-negative designs (relatively new)
 - Individuals show up at clinic with symptoms
 - Are tested
 - Cases are test-positive; Controls are test-negative
 - Examples: influenza; rotavirus



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Vaccine efficacy for progression: VE_P

- VE_P measures the effect of vaccination on some outcome that occurs only in people who get infected.
- Effect of vaccination on progression, pathogenicity, or severity of disease
- For binary outcomes:

$$VE_P = 1 - \frac{\frac{\text{no. severe vaccinated cases}}{\text{all vaccinated cases}}}{\frac{\text{no. severe unvaccinated cases}}{\text{all unvaccinated cases}}}.$$

- Or continuous post-infection outcome, say viral load.
- In randomized studies, post-infection selection bias can be an issue: infected individuals not a random sample.



Pertussis vaccine: Préziosi and Halloran (2003)

- Niakhar, Senegal, Jan 1 - Dec 31, 1993,
- children 6 mos - 8 yrs
- Vaccine efficacy for disease progression:

$$\begin{aligned}
 \widehat{VE}_P &= 1 - \frac{\frac{\text{no. severe vaccinated cases}}{\text{no. vaccinated cases}}}{\frac{\text{no. severe unvaccinated cases}}{\text{no. unvaccinated cases}}} \\
 &= 1 - \frac{\frac{176}{548}}{\frac{129}{206}} \\
 &= 0.49, \quad 95\% \text{ CI } [0.40, 0.56].
 \end{aligned}$$



Relation of VE_S , VE_{SP} , VE_P

- For any value of VE_{SP} , there are many possible combinations of VE_S and VE_P .
- $VE_S = 1 - \theta$
- $VE_P = 1 - \psi$
- $VE_{SP} = 1 - \theta\psi$
- $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$
- Vaccine studies that ascertain only symptomatic cases cannot differentiate VE_S from VE_P .

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$$VE_I, VE_T, VE_{S,p}$$

- Estimating vaccine efficacy from the transmission probability ratios requires information on who is infectious and when, and whom they contact and how.
- The concept of a contact is very broad and must be defined in each particular study.
- Often it is defined for individuals within a small transmission unit such as a household or sexual partnership.



Studies conditioning on exposure to infection: VE_S, VE_I, VE_T

- The general idea of a transmission unit is that individuals make contact sufficient for transmission within it.
- Households are the most common form of transmission unit used in studies: convenient.
- Partnerships, day care centers, or other small transmission units
- Two main approaches:
 - Households assuming independence of households
 - Households assumed within communities



Transmission Probability and SAR

- The SAR is a special case of the transmission probability.
- Possible to use SARs to estimate $VE_{S,p}$, VE_I and VE_T by also stratifying on vaccine status of the index case.



VE based on nonparametric secondary attack rates (SAR)

- The three main unstratified vaccine effects are

$$VE_{S.1/.0} = 1 - \frac{SAR_{.1}}{SAR_{.0}},$$

$$VE_{I1./0.} = 1 - \frac{SAR_{1.}}{SAR_{0.}},$$

$$VE_T = 1 - \frac{SAR_{11}}{SAR_{00}}.$$

- The stratified measures of VE_S and VE_I are

$$VE_{S01/00} = 1 - \frac{SAR_{01}}{SAR_{00}}, \quad VE_{S11/10} = 1 - \frac{SAR_{11}}{SAR_{10}},$$

$$VE_{I10/00} = 1 - \frac{SAR_{10}}{SAR_{00}}, \quad VE_{I11/01} = 1 - \frac{SAR_{11}}{SAR_{01}}.$$



Pertussis VE, Niakhar region, Senegal, 1993.

- Vaccine Efficacy (VE) \times 100% (95% confidence interval) based on SAR
- VE for susceptibility: 31 (7,52)
- VE for infectiousness: 63 (25,85)
- VE_T : 77 (52,92)
- Source: Préziosi and Halloran (2003)



Pertussis VE, Niakhar region, Senegal, 1993.

Vaccine Efficacy (VE) \times 100% (95% confidence interval)

Estimator	VE for susceptibility			Total VE VE _T
	VE _{S03/00}	VE _{S33/30}	VE _{S.3/.0}	
GEE (BC)	31 (7,52)	37 (9,60)	33 (9,53)	
Estimator	VE for infectiousness			Total VE VE _T
	VE _{I30/00}	VE _{I33/03}	VE _{I3./0.}	
GEE (BC)	63 (25,85)	67 (29,87)	67 (32,86)	77 (52,92)

* BC = bias-corrected bootstrap confidence interval

Source: Préziosi and Halloran (2003); Halloran, Préziosi and Chu (2003)



Households within a Community

- Analyses that assume the households or other transmission units are nested in a community.
- Community-acquired infection serves as a source of initial infection within households as well as possible further cases in the household.
- Infected household members can infect others in the household.



Two general types of parameters

- One for infection from the community,
→ CPI: the community probability of infection.
- the other for transmission from an infective to a susceptible within the household,
→ SAR: the secondary attack rate within the household.
- The first is an unconditional parameter, that is, it does not condition on exposure to infection, the second a conditional parameter.



POPULATION A

POPULATION B

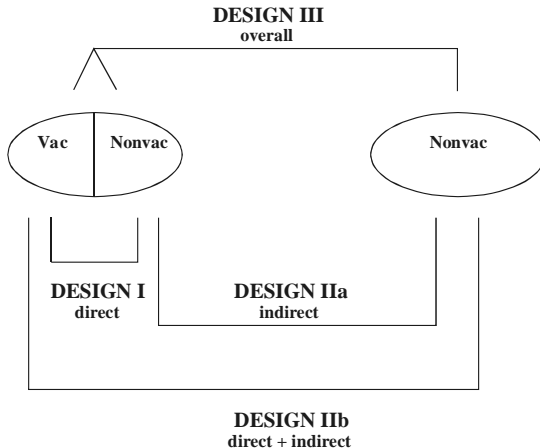


Figure : Study designs for dependent happenings; vaccination and vaccination programs (Halloran and Struchiner 1991, 1995).

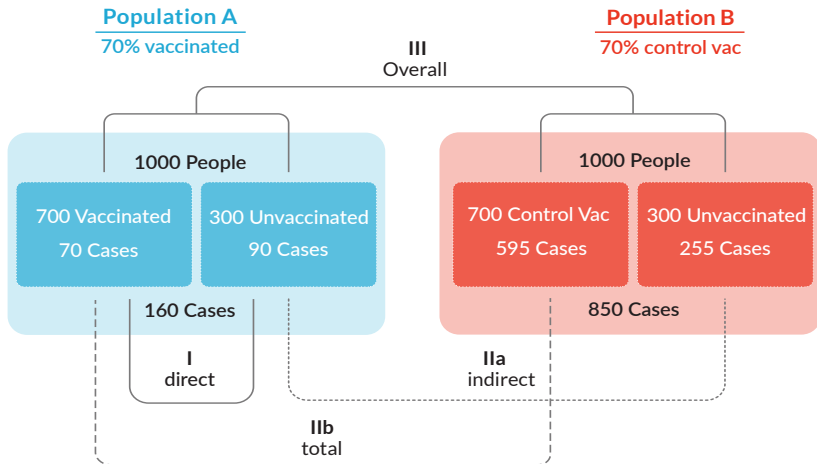


Figure : An example of estimating direct, indirect, total, and overall effects of vaccination.



Estimating Population-Level Effects

- $AR_B = 0.85$, under randomization also in the two subpopulations.
- $AR_A = 0.16$.
- $AR_{A1} = 0.10$ in the vaccinated, and $AR_{A0} = 0.30$ in the unvaccinated.
- The VE estimates of interest are

$$VE_{\text{direct}} = 1 - \frac{0.10}{0.30} = 0.66, \quad VE_{\text{indirect}} = 1 - \frac{0.30}{0.85} = 0.65,$$

$$VE_{\text{total}} = 1 - \frac{0.10}{0.85} = 0.88, \quad VE_{\text{overall}} = 1 - \frac{0.16}{0.85} = 0.81.$$



Two-Stage Randomization

- Drawing inference about treatment effects generally requires knowledge or modeling of the mechanism by which individuals select or are assigned treatment.
- Assuming a sequential two-stage randomization procedure:
 1. Stage one: randomize groups to different strategies
 2. Stage two: randomize individuals within groups conditional on the group assigned strategy.
- Hudgens and Halloran (2008) obtained unbiased estimators from the observed data under a certain randomization scheme.



Cluster-Randomized Designs

- Clusters, such as communities, villages, schools, are randomized in one-stage randomization
- Parallel design: clusters randomized and enrolled at beginning of study; no change in arms
- Stepped wedge design: clusters enrolled sequentially; no control vaccine
- Ebola ring vaccination trial: clusters are contacts and contacts of contacts: randomized to immediate or delayed vaccination; no control vaccine



Stepped wedge design

- Can be used when a parallel design is unfeasible either for practical or for ethical reasons.
- By the end of a trial using a stepped wedge design, all randomization units will have received the vaccination
- The time of the introduction of the vaccine intervention to each cluster is randomized
- Also referred to as phased implementation strategy.



Minicommunity Study Design

- Small transmission units such as households can be used to estimate indirect, total and/or overall effects
- Minicommunity design (Halloran 2012)



Not Usually Two Stage Randomization

- In most settings, randomization may occur only at the group level, at the individual level, or neither.
- Tchetgen Tchetgen and VanderWeele (2012) proposed estimators for direct, indirect, total and overall effects which do not require randomization of individuals or groups.
- The responses are weighted by group-level propensity scores (Rosenbaum 1983), that is probability that the group received that distribution of vaccination depending on some of the characteristics of the individuals and the group.



Example: Cholera Vaccination

- Perez-Heydrich, Hudgens, Halloran, Clemens, Ali, Emch (2014), *Biometrics*
- Used this approach to estimate the different effects of cholera vaccination
- In Matlab, Bangladesh between 1985-88, **all** children (2-15 yrs old) and women (>15 yrs old) randomly assigned with equal probability to either of two cholera vaccines and one placebo.
- Unvaccinated individuals included eligible non-participants and placebo recipients
- Vaccinated individuals included recipients of either vaccine.
- 121,982 individuals from 6,415 bars, i.e., clustered patrilineal households included in the analysis

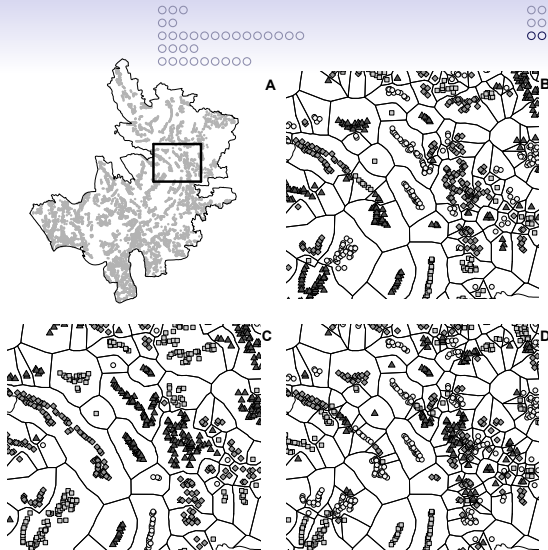


Figure : Definition of neighborhoods from geo-referenced data. The total number of groups set to (B) 700 for main analysis, and (C) 400 and (D) 1100 for sensitivity analysis.

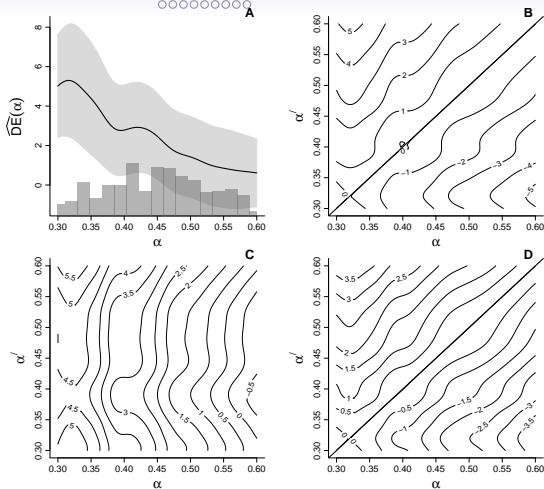


Figure : IPW estimates of (A) direct $\overline{DE}(\alpha)$, (B) indirect $\overline{IE}(\alpha, \alpha')$, (C) total $\overline{TE}(\alpha, \alpha')$, and (D) overall $\overline{OE}(\alpha, \alpha')$ effects based on the cholera vaccine trial data. In (A) the dark gray region represents approximate pointwise 95% confidence intervals.



Summary

- Many different types of vaccine effects .
- Study design needs to be chosen to estimate the effects of interest.
- Interpretation of vaccine efficacy and effectiveness estimates depends on the choice of study design and the choice of target parameter of interest.
- Challenge to develop these study designs to evaluate different effects of dengue, Zika, and chikungunya vaccines in conjunction with vector control.

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Thank You!