

Analytic Methods for Infectious Disease
Lecture 3

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January 13, 2009

Herd Immunity

Definition

Manifestations

Examples

VE Overview

General

VE_S

VE_S: Exposure data available

VE_S: Time-of-event

VE_S: Final value data

Conditional VE

Estimating VE_S, VE_I, VE_T

Population Effects

Study Designs for Dependent Happenings

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Herd Immunity

- the collective immunological status of a population of hosts, as opposed to an individual organism, with respect to a given infectious agent.
- can be low or high
- can be from previous natural infection or immunization



Herd Immunity

- a higher herd immunity will reduce R
- herd immunity is a biological condition that can be measured in various ways
- herd immunity due to vaccination can produce population-level effects



Figure: Anti-HAV and Anti-HEV: 97% vs 16% prevalence

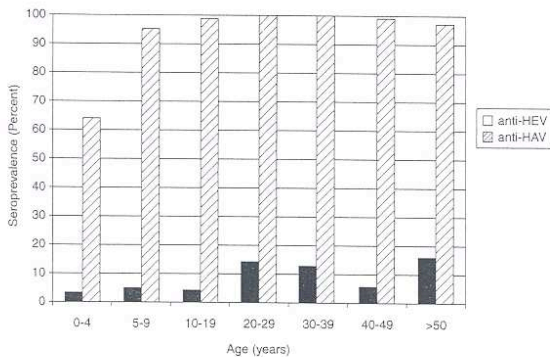


Figure 4-5. Age-specific prevalences of anti-HEV and anti-HAV immunoglobulin G in Vietnam.
Source: Hau et al. 1999



Threshold Herd Immunity

- What level of herd immunity is necessary for elimination of transmission?
- Related to R_0 and R
- Elimination versus eradication
- Smallpox versus measles



Results of increased herd immunity

- Reduced incidence of infection
- Increased age of first infection
- Population- level effects



Danger of increased age of first infection

- Rubella: danger of congenital rubella syndrome
 - Vaccinate young teenage girls only
 - Vaccinate boys and girls in first year of life
- Mumps in the US
 - Mid-levels of vaccination produced age-shift with high incidence of post-pubertal mumps



Recent examples: Conjugate vaccines

- *Hemophilus influenzae* (Hib) vaccination
- Pneumococcal vaccines
- Meningococcal vaccines

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.



Table: Some Vaccine Effects of Interest

Symbol	Definition
VE_S	vaccine efficacy for susceptibility
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



Dependent Happenings and Vaccine Effects

- Due to the dependent happenings in infectious diseases (Ross 1916), vaccination can produce several different kinds of effects
- At the individual level
- And at the population level.



Vaccine Efficacy and Effectiveness

- Vaccine efficacy for susceptibility, VE_S :
 - direct protective effects
 - sometimes outcome is infection, VE_S
 - sometimes outcome disease, VE_{SP}
 - carriage, VE_{col}
- Vaccine efficacy for progression, VE_P
 - after being infected, the effect on probability of developing symptoms (pathogenicity)
 - or after developing symptoms, probability of severe disease
 - other post-infection outcomes, such as viral load



Vaccine Efficacy and Effectiveness

- Vaccine efficacy for infectiousness, VE_I
 - the effect in reducing transmission from a vaccinated compared to an unvaccinated infected person.
- Vaccine efficacy if both are vaccinated, VE_T
 - the effect in reducing transmission if both infected and susceptible are vaccinated compared to if neither are vaccinated.



Population-level Vaccine Effectiveness

- Indirect effects, VE_{IIa}
 - effects of widespread vaccination on someone who is not vaccinated
- Total Effects, VE_{IIb}
 - possibly synergistic effect of being vaccinated and widespread vaccination on someone who is vaccinated
- Overall effects, VE_{III}
 - overall population effect, say, reduction in incidence, (change of average of of first infection, R_0) of widespread vaccination.

Vaccine efficacy and effectiveness

- Prevented risk in the exposed (vaccinated)

$$VE = 1 - RR .$$

- Extension in two directions of family of parameters of attributable or prevented risk in the exposed (Greenland and Robins 1988, 1989)



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	$VE_{S,p} \dagger = 1 - \frac{P_{\cdot 1}}{P_{\cdot 0}}$	$VE_{I,p} = 1 - \frac{P_{1\cdot}}{P_{0\cdot}}$	$VE_{T,p} = 1 - \frac{P_{11}}{P_{00}}$	
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* From Halloran, Struchiner, Longini, Am. J. Epidemiol 1997; 146:789–803.

Vaccine efficacy for susceptibility, VE_S (VE_{SP})

- Under the assumption of equal exposure to the infectious agent in the vaccinated and unvaccinated groups (Greenwood and Yule 1915),

$$VE_S = 1 - \frac{R(\text{vaccinated people})}{R(\text{unvaccinated people})},$$

where R denotes one of the measures of risk.

- VE_{SP}

Vaccine efficacy for susceptibility, VE_S

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.

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

Conditions Necessary for Valid Inference

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.

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Hierarchy of VE_S Parameters

TABLE 1
Levels and amount of information for each history

<i>Level</i>	<i>Type of information for each history</i>	
I	(a)	All contacts between individuals and outcomes of those contacts (whether an infection is transmitted)
	(b)	Only those contacts between infective and susceptible individuals and infection outcome of those contacts
IIA	(c)	Only contacts leading to infections (who infects whom)
IIB	(d)	Infectious periods, i.e. the times at which individuals become and cease to be infectious
III	(e)	The times at which individuals become infected
IV	(f)	Whether or not an infection occurs to each individual in some time period $(0, T]$

- Rhodes, Halloran, Longini (1996)



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)

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

From
Catch-22 by Joseph Heller

All the officer patients in the ward were forced to censor letters written by all the enlisted-men patients, who were kept in residence in wards of their own. It was a monotonous job, and Yossarian was disappointed to learn that the lives of enlisted men were only slightly more interesting than the lives of officers. After the first day he had no curiosity at all. To break the monotony he invented games. Death to all modifiers, he declared one day, and out of every letter that passed through his hands went every ad-verb and every adjective. The next day he made war on articles. He reached a much higher plane of creativity the following day when he blacked out everything in the letters but a, an and the. That erected more dynamic intralinear tensions, he felt, and in just about every case left a message far more universal. Soon he was proscribing parts of salutations and signatures and leaving the text untouched. One time he blacked out all but the salutation "Dear Mary" from a letter, and at the bottom he wrote, "I yearn for you tragically. A. T. Tappman, Chaplain, U.S. Army." A. T. Tappman was the group chaplain's name.



Data structure I: contact and exposure data

	Infected	Total Exposures
Vaccinated	a_1	J_1
Unvaccinated	a_0	J_0

- p = transmission probability
- SAR = secondary attack rate

$$VE_{S,p} = 1 - \frac{a_1/J_1}{a_0/J_0} = 1 - \frac{p \cdot 1}{p \cdot 0}$$

$$VE_{S,p} = 1 - \frac{p \cdot 1}{p \cdot 0}$$

Kendrick and Eldering (1939): pertussis vaccine

Vaccinated = 29 attacks/83 exposures

Unvaccinated = 143 attacks/160 exposures

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



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Hazard, incidence rate

- dependent happening: function of contact rate, prevalence
- c_0, c_1 = contact rate, unvaccinated and vaccinated
- $I^0(t), I^1(t)$ = prevalence in contacts
- p_0, p_1 = transmission probability

$$\lambda_0(t) = c_0 p_0 I^0(t)$$

$$\lambda_1(t) = c_1 p_1 I^1(t)$$

Data structures II, III

	Person-time	
	Infected	At Risk
Vaccinated	a_1	Y_1
Unvaccinated	a_0	Y_0

- IR = incidence rate
- λ = hazard rate, force of infection

$$VE_{S,\lambda} = 1 - \frac{c_1 p_{.1} I^1(t)}{c_0 p_{.0} I^0(t)} = 1 - \frac{\lambda_1}{\lambda_0}$$

- Cox proportional hazards model: needs only ordering of the onset times

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

PEARL KENDRICK AND GRACE ELDERING

Kendrick and Eldering (1939): pertussis vaccine

Vaccinated = 52 attacks/2,268 Person-years
 Unvaccinated = 348 attacks/2,307 Person-years

$$VE_{S,\lambda} = 1 - \frac{a_1/Y_1}{a_0/Y_0} = 0.85.$$

Data structure IV

	Infected	Total Persons At Risk
Vaccinated	a_1	N_1
Unvaccinated	a_0	N_0

- CI = cumulative incidence (closed cohort)
- AR = attack rate

$$VE_{S,CI} = 1 - \frac{a_1/N_1}{a_0/N_0} = 1 - \frac{CI_1}{CI_0} = 1 - \frac{AR_1}{AR_0}$$

- If loss to follow-up, need to use 1 minus survival function assuming time to event data.

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

- Double-blinded randomized trial of live-attenuated (LAIV) versus killed influenza vaccine versus killed 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/3,912 children

Killed vaccine = 338 cases/3,936 children

$$\text{relative VE}_{SP,CI} = 1 - \frac{a_1/N_1}{a_0/N_0} = 0.55 \text{ (95\% CI 0.45, 0.63).}$$

Models of Action of Vaccination

- Smith, Rodriguez, and Fine (1984): Models I and II
- Model I: multiplicative on the hazard rate
- Model II: vaccination renders a proportion of the vaccinated completely protected
- Choice of case-control sampling

Models of Action of Vaccination

- Halloran, Struchiner and Spielman (1989)
- Leaky vaccines (malaria)
- All-or-none vaccines
- Distributions of protection
- Choice between cumulative incidence, hazard rate and frailty mixing models
- Critical implications in population dynamics (imperfect vaccines)



Vaccine efficacy for progression: VE_P

- after becoming infected, what is the vaccine effect?
- progression, pathogenicity, or severity of disease
- or other post-infection outcome, say viral load
- in randomized studies, post-infection selection bias can be an issue.

Relation of VE_S , VE_{SP} , VE_P

- $VE_S = 1 - \theta$
- $VE_P = 1 - \psi$
- $VE_{SP} = 1 - \theta\psi$
- $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$

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

- Households, partnerships, or other small transmission units
- Households assuming independence of households
- Households within communities using final value data
- Households within communities using time-to-event data

Exposure in small transmission units

- The secondary attack rate (SAR), the proportion of susceptibles exposed to an infectious person who become infected, has been used to estimate protective effects of vaccination since the 1930's (Kendrick and Eldering 1939).
- Possible to use SARs to estimate 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

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

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

Study Designs for Dependent Happenings

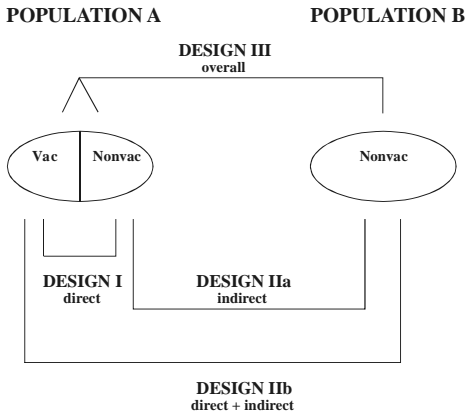


Figure: Halloran and Struchiner (1991)

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Group-randomized studies

- Several populations needed for inference
- Should be comparable for characteristics related to transmission, covariates → matching
- Effects of intervention possibly ill-defined: defined within
 - context of a particular intervention program
 - depends on level of coverage, distribution of vaccine, mixing patterns
 - Halloran and Struchiner (1995); Hudgens and Halloran (2008)
- subpopulations can also be compared

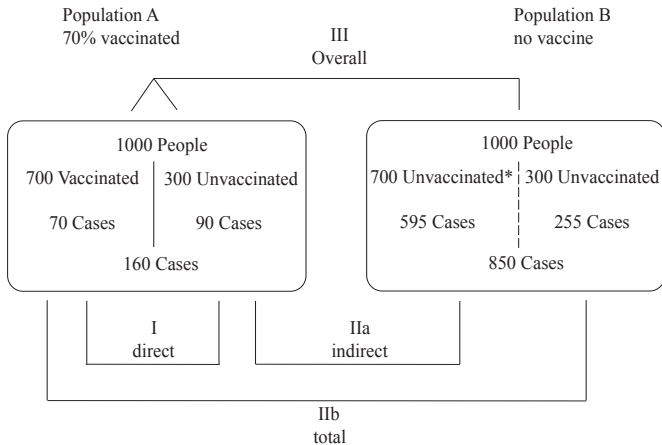


Figure: Comparison of two populations.



Simple Example, cont'd

- Direct effect: $CI(A, unvac) - CI(A, vac)$
 $= 90/300 - 70/700 = 0.30 - 0.10 = 0.20$
- Indirect effect: $CI(B, unvac) - CI(A, unvac)$
 $= 850/1000 - 90/300$ or
 $= 225/300 - 90/300 = 0.85 - 0.30 = 0.55$
- Total effect: $CI(B, unvac) - CI(A, vac)$
 $= 850/1000 - 70/700 = 0.85 - 0.10 = 0.75$
- Overall effect: $CI(B) - CI(A)$
 $= 850/1000 - 160/1000 = 0.85 - 0.16 = 0.69$
- Direct + Indirect = Total
- Overall essentially weighted average of pop B.

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Thank You!