Measuring vaccine effects on infectious diseases

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Overview/Summary

Learning objectives

At the end of this presentation, attendees will be able to:

- Describe the difference between vaccine efficacy and vaccine effectiveness studies
- Describe the impact of vaccines on microbial transmission
- Describe the difference between unconditional and conditional vaccine effect measures
- Describe the study designs for dependent happenings

Immunization

- Natural infection
- Passive immunization (immune globulin)
- Active immunization (vaccination)

Vaccine types

- Live, attenuated vaccine (MMR, oral polio)
- Inactivated “killed” vaccines (hepatitis A)
- Toxiods (Tetanus)
- Subunit vaccines (Pertussis)
- Conjugate vaccines (H. influenzae B; S. pneumoniae)
- Recombinant vaccines (hepatitis B)

Vaccine development

- Preclinical studies
- Phase I: Dose finding and safety
- Phase II: Safety and immunogenicity trials
- Phase III: Vaccine efficacy trials
- Post-licensure studies
  - Surveillance (disease, adverse effects)
  - Vaccine effectiveness studies

Type of vaccine effect studies

- Efficacy (Does it work?)
- Effectiveness (Does it really work?)
- Efficiency (Which is more cost-effectiveness?)

Essential design feature of vaccine effect studies

Vaccine Study Design*	Vaccine-preventable Outcome†	
	Lab-confirmed	Non-lab confirmed
Experimental	Efficacy	Effectiveness
Observational	Effectiveness	Effectiveness

* vaccine exposure is randomly assigned or not

† e.g., influenza-like illnes, hospitalization, or death

Potential vaccine impacts are several

Effective reproductive number

$$R = R_0 x = cpdx$$

Infection rate among susceptibles

$$IR(t) = cpP(t)$$

Control points	Control strategies
Contact rate (c)	1. Reduce contact rate
Prob. source infectious (P)	2. Reduce P(source infectious)
Transmission prob. (p)	3. Reduce infectiousness
	4. Reduce susceptibility
	5. Interrupt transmission
Duration infectiousness (d)	(see #3)
Fraction susceptible (x)	6. Increase herd immunity

Vaccine effect measure

$$
\begin{aligned}
VE &= \frac{R_0 - R_1}{R_0} \\
&= 1 - \frac{R_1}{R_0} \\
&= 1 - RR
\end{aligned}
$$

where R is a "risk" measure, and RR is a "relative risk" measure comparing vaccinated to unvaccinated

Unconditional VE on susceptibility (VE_S)

General formula

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

Incidence rate

$$VE_{S,IR} = 1 - \frac{IR_{A1}}{IR_{A0}}$$

Cumulative incidence

$$VE_{S,CI} = 1 - \frac{CI_{A1}}{CI_{A0}}$$

Incidence (infection) rate among susceptibles

Standard definition

$$IR(\Delta t) = \frac{\text{Number of new infections during}\Delta t}{\text{Person-time at risk during}\Delta t}$$

Definition by components

$$IR(t) = c_j p_{ij} P_j(t),$$

where c_j is the average contact rate of susceptible hosts (with vaccination status j) with a potentially infectious source, $P_j(t)$ is the probability that the potential source is infectious, and p_{ij} is the probability of transmission to the susceptible host given contact with the infectious source (with vaccination status i).

Transmission probability depends on . . .

- Infectious case
- Susceptible host
- Contact definition
- Microbial agent

Unconditional VE on susceptibility (VE_S)

Incidence rate

$$\begin{aligned} VE_{S,IR} &= 1 - \frac{IR_{A1}}{IR_{A0}} \\ &= 1 - \frac{c_1 p_{\bullet 1} P_1(t)}{c_0 p_{\bullet 0} P_0(t)} \\ &\approx 1 - \frac{p_{\bullet 1}}{p_{\bullet 0}} \end{aligned}$$

Conditional VE on susceptibility ($VE_{S,p}$)

Transmission probability ratio

$$VE_{S,p} = 1 - \frac{p_{\bullet 1}}{p_{\bullet 0}} = 1 - \frac{SAR_{\bullet 1}}{SAR_{\bullet 0}}$$

where SAR is the secondary attack risk.

Methods

- Secondary attack (case-contact) risk (measles, pertussis)
- Binomial model (HIV)

Conditional VE on susceptibility ($VE_{S,p}$)

Transmission probability ratio

$$\begin{aligned} VE_{S,p} &= 1 - \frac{p_{01}}{p_{00}} \\ &= 1 - \frac{SAR_{01}}{SAR_{00}} \end{aligned}$$

when the vaccination status of the infectious case is known.

Conditional VE on infectiousness ($VE_{I,p}$)

Transmission probability ratio

$$VE_{I,p} = 1 - \frac{p_{10}}{p_{00}} = 1 - \frac{SAR_{10}}{SAR_{00}}$$

when the vaccination status of the infectious case is known.

Conditional VE on susceptibility & infectiousness ($VE_{T,p}$)

Transmission probability ratio

$$VE_{I,p} = 1 - \frac{p_{11}}{p_{00}}$$
$$= 1 - \frac{SAR_{11}}{SAR_{00}}$$

when the vaccination status of the infectious case is known.

Study designs in epidemiology

- Experimental
- Observational
    - Cohort
    - Case-Control
    - Case-Cohort

Study designs for depending happenings

Dependence happening . . .

are those in which incidence depends on prevalence. Consequently, interventions have direct and indirect effects.

Direct effects

Protective effects in the person receiving the treatment

Indirect effects . . .

result from the change in transmission of an infectious agent in a population because of an intervention program

Direct effects of a vaccination program

Definition

Difference between the outcome in a vaccinated individual compared to an unvaccinated individual in same population receiving the vaccination program

Indirect effects of a vaccination program

Definition

Difference between the outcome in an unvaccinated individual in a population receiving the vaccination program compared to an unvaccinated individual in a different comparable population not receiving the vaccination program

Total effects of a vaccination program

Definition

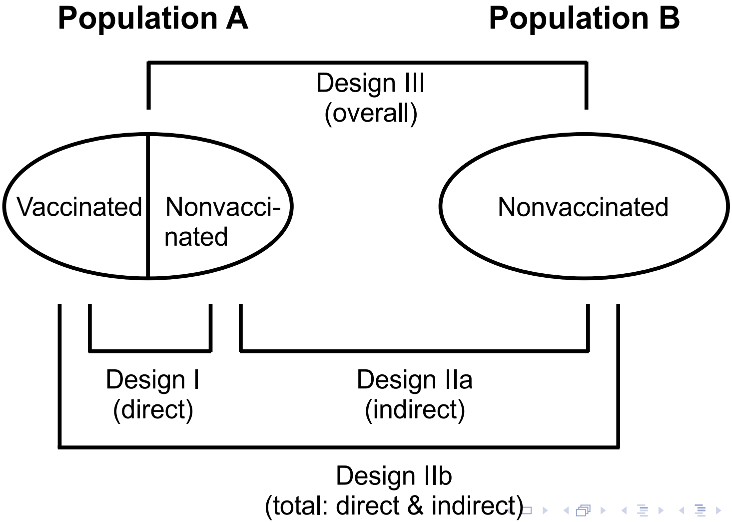
Difference between the outcome in a vaccinated individual in a population receiving the vaccination program compared to an unvaccinated individual in a different comparable population not receiving the vaccination program

Overall effects of a vaccination program

Definition

Difference between the outcome in an average individual in a population receiving the vaccination program compared to an average individual in a different comparable population not receiving the vaccination program

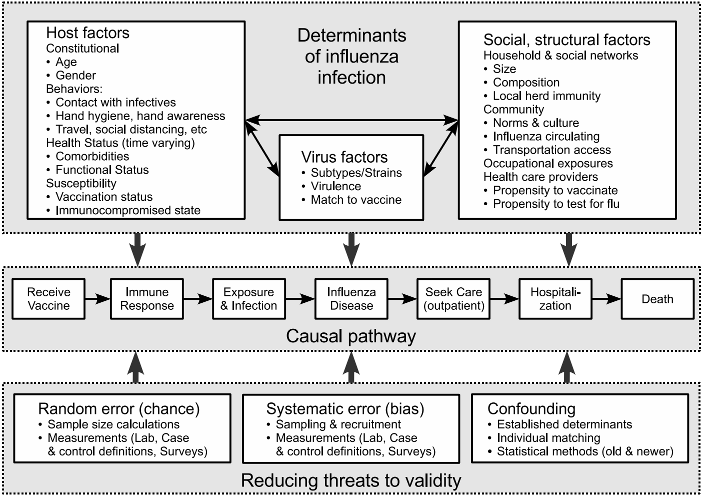
Study designs for effects on dependent happenings



Parameters for measuring vaccination effects

	Comparison groups & effect			
Level	Susceptibility	Infectiousness	Combined	
I	$1 - \frac{p_{01}}{p_{00}}$	$1 - \frac{p_{10}}{p_{00}}$	$1 - \frac{p_{11}}{p_{00}}$	
	Study design			
	I Direct	IIA Indirect	IIB Total	III Overall
II	$1 - \frac{IR_{A1}}{IR_{A0}}$	$1 - \frac{IR_{A0}}{IR_{B0}}$	$1 - \frac{IR_{A1}}{IR_{B0}}$	$1 - \frac{IR_{A1\&A0}}{IR_{B0}}$
IV	$1 - \frac{CI_{A1}}{CI_{A0}}$	$1 - \frac{CI_{A0}}{CI_{B0}}$	$1 - \frac{CI_{A1}}{CI_{B0}}$	$1 - \frac{CI_{A1\&A0}}{CI_{B0}}$

Studying determinants of influenza transmission



Source: Aragon T.J. et al. California ALIVE Study grant, 2007

Simonsen's 'bias detection framework' for influenza VE studies

- Seasonality
- Vaccine match
- Severity
- Age
- Endpoint specificity

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Simonsen's 'bias detection framework' for influenza VE studies

Table: Identifying residual bias in influenza VE studies of elderly people

	Setting of greater expected RR reduction	Setting of lower expected RR reduction
Seasonality	Influenza period	Pre-influenza periods
Vaccine match	Well-matched season	Mismatched seasons
Severity	Severe seasons	Mild seasons
Age	Younger people	Older people
Specificity	High-spec. endpoints	Low-spec. endpoints

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