

# Estimating vaccine efficacy

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# Background and 'vaccine effects'

Vaccine efficacy: a measure of how effective a vaccine is (0=useless, 1=perfect)

Traditional estimator of vaccine efficacy:

$$\begin{aligned}\widehat{VE} &= 1 - \text{rel attack-rate} = 1 - \frac{\text{prop vacc inf}}{\text{prop unvacc inf}} \\ &= 1 - \frac{C_v/nv}{C_u/n(1-v)}, \quad \text{where}\end{aligned}$$

$C_v$  = # vaccinated who become infected

$C_u$  = # unvaccinated who become infected

$n$  = population under observation

$v$  = proportion vaccinated

**Today's topic:**

Is  $\widehat{VE}$  a sensible estimator, and if so, what does it estimate?

Suggestion for better efficacy measures and how to estimate them

Efficacy in what sense?

- a) Reducing **susceptibility** (risk of getting infected)
- b) reducing **symptoms**
- c) reducing **infectivity** if infected

From an individual's point of view a) and b) are of main interest

From population perspective (prevention of major outbreaks) a) and c) are of main interest, and b only indirectly

From now on we focus on a) and c):

reduction in **susceptibility** and **infectivity**

## 2. Stochastic epidemic models

### General stochastic epidemic

#### Assumptions:

S-I-R (susceptible-infectious-removed) epidemic

Community mixes uniformly

Homogeneous individuals (equally susceptible & infectious)

$n$  (population size) large

#### Model:

- Individuals “meet” others at constant rate  $\lambda$  (all individuals equally likely)
- An individual who gets infected remains infectious for an  $Exp(\gamma)$  period and then recovers and becomes immune
- If an infective “meets” a susceptible the latter gets infected with probability  $p$

**Start:** 1 infective and the rest susceptible

$R_0$  = expected number of infections caused by one individual during early stages of outbreak

$$R_0 = \lambda \cdot p \cdot \frac{1}{\gamma}$$

**Known model result:**

If  $R_0 > 1$  a major outbreak may occur and its expected size is known and depends only on  $R_0$

## Model extension allowing for households

Most things as before, only now individual reside in households

An infected individual infects

- a household member at rate  $\lambda_H$
- an individual outside household at rate  $\lambda_G/n$

**Loosely speaking:**

To avoid infection, an individual must escape infection from outside (prob  $q_G$ ) and from all its infected household members (prob  $q_H$  from each member)

### 3. Modelling vaccine response:

If an *unvaccinated* infective meets a *vaccinated* susceptible the latter gets infected with probability  $A \cdot p$

If an *vaccinated* infective meets a *unvaccinated* susceptible the latter gets infected with probability  $B \cdot p$

If an *vaccinated* infective meets a *vaccinated* susceptible the latter gets infected with probability  $A \cdot B \cdot p$ ,

$A$  is the (random) relative susceptibility

$B$  is the (random) relative infectivity

$(A, B)$  are independent for different individuals but  $A$  and  $B$  may be dependent

#### Definitions of vaccine efficacies

$VE_S = 1 - E(A)$  (efficacy in terms of susceptibility)

$VE_I = 1 - E(AB)/E(A)$  (efficacy in terms of infectivity)

So what does

$$\widehat{VE} = 1 - \frac{C_v/nv}{C_u/n(1-v)} = 1 - \text{relative attack rate,}$$

estimate?

Clearly,  $\widehat{VE}$  estimates  $1 - \frac{P(\text{a vaccinee gets infected})}{P(\text{a non-vaccinee gets infected})}$

In our model (and in reality!) the higher social activity ( $\lambda$ ) the more people will get infected.

As a consequence,  $\widehat{VE}$ , depends on the social activity!

So how does  $\widehat{VE}$  relate to  $A$  and  $B$ ?

Short answer: It depends on the situation

## 4. Some examples of $VE$ estimates

a) A completely homogeneous community

Proportion  $v$  vaccinated and proportion  $(1 - v)$  unvaccinated

The initial stages of the epidemic can be approximated by a two-type branching process

From this it can be shown that, if few are infected:

$\widehat{VE}$  estimates  $VE_S$

## b) Varying susceptibility

Suppose that there are two types of individual with different initial susceptibility:  $s_1$  and  $s_2$  say, and few get infected

Then  $VE$  can lie anywhere between  $1 - \frac{s_1}{s_2}VE_S$  and  $1 - \frac{s_2}{s_1}VE_S$  depending on the fractions vaccinated of the two types

Suppose for example that  $s_1/s_2 = 5$ ,  $A \equiv 0.5$ ,  $B \equiv 1$  and  $v_1 = 1$  and  $v_2 = 0$  (only the more susceptible type is vaccinated)

Then  $VE = -1.5!!$

The vaccine clearly has positive effect ( $VE_S = 0.5$ ), but  $\widehat{VE}$  estimates  $VE$  which is negative because vaccinated were initially more susceptible

c) A community of households

Suppose that

- all individuals are identical
- all "households" are of size 2
- one individual in each household is vaccinated

Then  $VE \leq VE_S$  and quite often considerably less

If for example

- prob of disease transmission within household =0.9
- $A \equiv 0.9$  (little reduction in susceptibility)
- $B \equiv 0.1$  (high reduction in infectivity)

then  $VE = -0.479!!$

Eventhough vaccine is effective, in particular in reducing infectivity,  $VE$  is negative indicating an inverse effect.

Explanation: Unvaccinated are more protected because their household mates have hardly any infectivity

## 4. Improved inference procedures

Instead of estimating  $VE$  which depends on both vaccine effects and other model parameters, differently depending on community structure, we recommend estimating the model parameters

$$VE_S = 1 - E(A), \text{ and}$$

$$VE_I = 1 - E(AB)/E(A)$$

**Advantage:** Well-defined. Do not change for different community structures (only their estimators)

**Disadvantage:** Estimators are more involved and are **not** consistent (unless further assumptions are made about distribution of  $(A, B)$ )

Household model (and data) allows consistent estimation of:  $q_G, q_H, E(q_H^A), E(q_G^A), E(q_G^A q_H^A), E(q_H^A q_G^B), \dots$

Bounds on  $VE_S$  and  $VE_I$  can be obtained using these quantities:

It can be shown that

$$\frac{E(q_G^A) - q_G}{1 - q_G} \leq VE_S \leq \frac{\log(q_G) - \log(E(q_G^A))}{\log(q_G)}$$

and a similar but longer bound for  $VE_I$

Examples:

In general the bounds for  $VE_S$  are much narrower than the bounds for  $VE_I$

# Take home message:

Traditional estimate

$$\widehat{VE} = 1 - \text{rel attack-rate} = 1 - \frac{\text{prop vacc inf}}{\text{prop unvacc inf}}$$

is not a good measure of vaccine efficacy!!

In particular not in structured communities and when vaccine also reduces infectivity

Better (but harder) to estimate model parameters  $VE_S$  and  $VE_I$

It is harder to estimate  $VE_I$ .

In general, infectivity is much harder to estimate since it is not observed who infects whom

# References

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