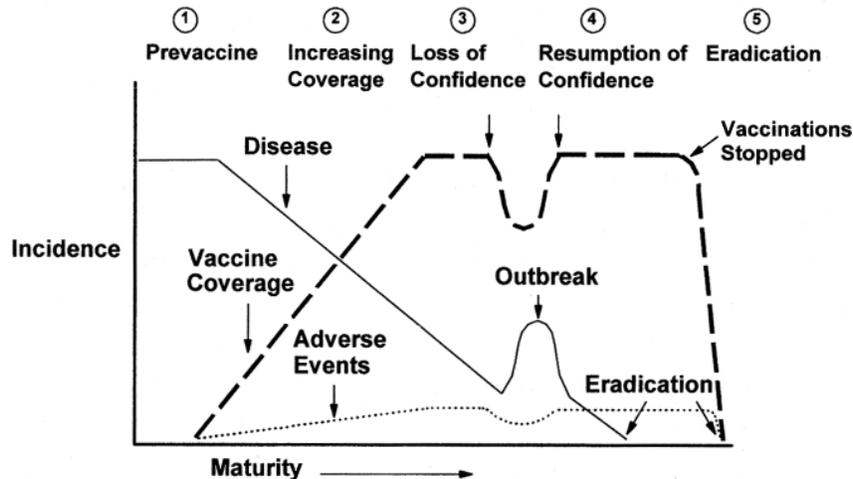


## MEASURING EFFECTIVENESS OF IMMUNIZATION PROGRAMS

### I. NATURAL HISTORY OF VACCINATION ACTIVITIES



**Figure 1.** Evolution of typical immunization program over time (see Chen and Orenstein, 1996, p. 102)

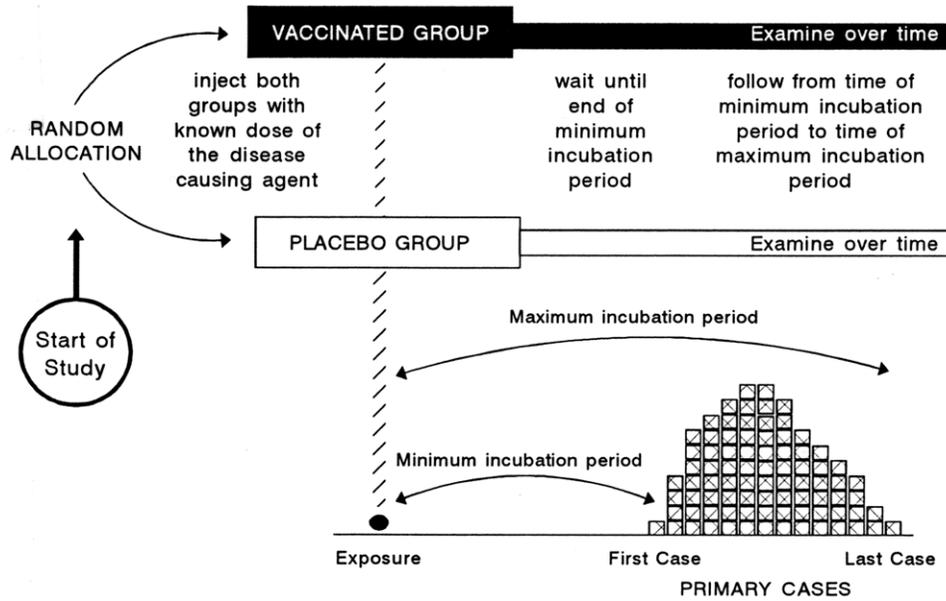
A. Relation between disease incidence, vaccine coverage, and adverse reactions

### II. EFFICACY VERSUS EFFECTIVENESS

A. Vaccine efficacy

1. The extent to which a vaccine prevents disease among vaccinated persons under **ideal** conditions
  - a. Influenced by...
    - (1) ability of vaccine to induce an immunologic response in the host
    - (2) persistence of immunity in the host
2. Determination is ideally based on a randomized vaccine trial
  - a. Random allocation to vaccine and "placebo" groups
  - b. Double blind
    - (1) Neither the investigator nor the vaccine recipient knows if he or she is receiving the vaccine or placebo
  - c. Both groups should have the same inherent risk of disease, independent of vaccination status
    - (1) Probability of contact with infective cases should be equal for vaccinated and unvaccinated groups

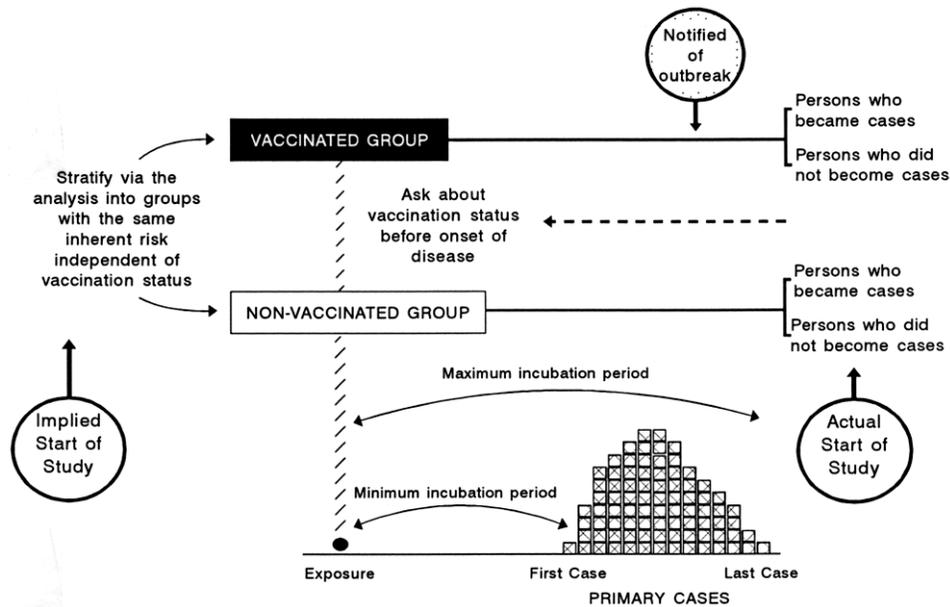
d. Example (UNETHICAL)



**Figure 2.** Randomized clinical trial of vaccine efficacy.

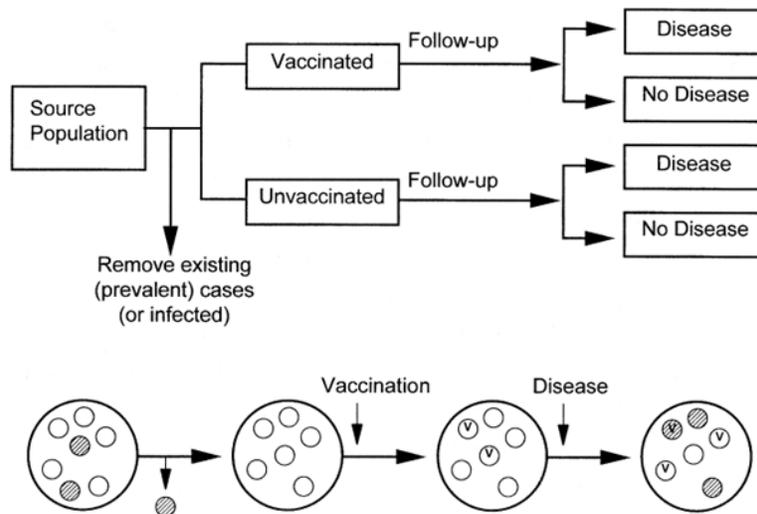
B. Vaccine effectiveness (VE)

1. The extent to which a vaccine prevents disease *among vaccinated persons* in community
2. Most studies of vaccine efficacy are really measuring *vaccine effectiveness*
3. Usually not based on randomized trials
  - a. Not ethical to inject persons with a known harmful agent
  - b. Not ethical to withhold vaccines of proven benefit from the placebo group
4. Assessment most often based on non-experimental (or observational) studies
  - a. Example One (historical cohort study)



**Figure 3.** Historical cohort study of vaccine effectiveness.

b. Example Two (prospective and historical cohort study)



**Figure 4.** Flow diagram of vaccine efficacy study (see Chen and Orenstein, 1996, p. 111)

C. Community effectiveness (CE)

1. The extent to which a vaccine prevents disease *among all persons* (i.e., both vaccinated and unvaccinated) at the community level
2. Influenced by...
  - a. coverage (prop. of community that has been vaccinated)
  - b. proper administration of vaccine (cold chain)
  - c. ability of the vaccine to induce an immunologic response in the host

- d. persistence of immunity in the host
  - e. ability of the investigator to accurately measure disease and immunization status
3. Often measured using a **pretest-posttest-control** type of evaluation design
- a. Change in disease incidence before and after a vaccination program in an intervention area as compared to a neighboring area with no vaccination program
  - b. Design

	Before	Program	After
Vaccination area	O <sub>1</sub>	X	O <sub>2</sub>
Control area	O <sub>3</sub>		O <sub>4</sub>

where O<sub>1-4</sub> are observations (or surveys) made in the community with the vaccination program (O<sub>1</sub> and O<sub>2</sub>) and in a non-vaccinated control area (O<sub>3</sub> and O<sub>4</sub>), both before (O<sub>1</sub> and O<sub>3</sub>) and after (O<sub>2</sub> and O<sub>4</sub>) the vaccination program (X) was offered

- c. Measurement

	Before		After	
Vaccination area	O <sub>1</sub>	minus	O <sub>2</sub>	= I <sub>p,1</sub> - I <sub>p,2</sub>
Control area	O <sub>3</sub>	minus	O <sub>4</sub>	= I <sub>p,3</sub> - I <sub>p,4</sub>

where I<sub>p,1-4</sub> is the incidence in the total population in each area before and after the vaccination program has taken place

- (1) If there is no change in disease incidence in the control area...

$$I_{p,3} - I_{p,4} = 0$$

Thus, the effectiveness of a vaccine program may be measured as...

$$I_{p,1} - I_{p,2}$$

or more appropriately, the decline in the incidence rate relative to the "before" incidence. Thus the effectiveness at the community level is often measured as...

$$CE = \frac{I_{p,1} - I_{p,2}}{I_{p,1}}$$

- d. Design assumes persons in both areas had the same probability of coming in contact with the disease agent
- (1) Since the disease is less likely to spread in the vaccinated area, the probability of contacting the agent is reduced
    - (a) As a result, CE is biased in an upward direction

$$CE = \frac{I_{p,1} - I_{p,2}}{I_{p,1}} \quad \leftarrow \text{numerator is larger because } I_{p,2} \text{ is too small}$$

$$\quad \quad \quad \leftarrow \text{denominator is unchanged}$$

- (b) The lower probability of disease contact among susceptibles in a group with many immunes is termed "herd immunity"

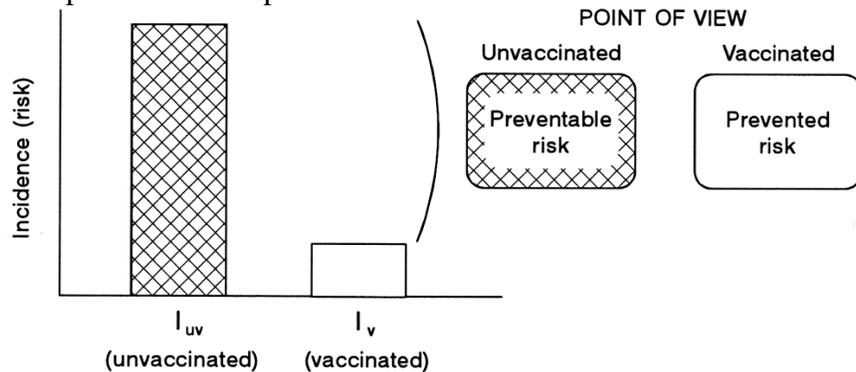
### III. QUANTITATIVE MEASURES OF VACCINE EFFECTIVENESS

#### A. Incidence rates among vaccinated and unvaccinated

1. Onset of new cases of the disease of interest during a specified period of time among individuals identified by vaccination status
  - a. May be referred to as "attack rates"
    - (1) Another form of incidence rate
    - (2) Term used when time period of interest is limited to the duration of an epidemic rather than some fixed period such as a year
2. Manner of identification of disease and vaccination status
  - a. Interview (self-reported)
    - (1) Most common approach
  - b. Examination of subjects
    - (1) Requires a knowledgeable field staff
  - c. Examination of clinical records
    - (1) Not always readily available
  - d. Laboratory tests
    - (1) May be too expensive for routine vaccine effectiveness assessment
  - e. Immunological studies
    - (1) Immuno-prevalence
      - (a) Observe prevalence of disease antibody levels in population
        - i) Serum (invasive)
        - ii) Saliva (non-invasive)

- (b) Provides historical view of past disease contact and proportion of the population that responded immunologically to the disease agent
- (2) Immuno-conversion
  - (a) Observe the change in antibody levels over time
    - i) Due to vaccination
    - ii) Due to the disease of interest
    - iii) Due to some other related disease
    - iv) Due to time (i.e., waning of immunity with time)
  - (b) Incident cases are identified as persons with a multiplicative rise in antibody titer over some specified period of time
    - i) Based on serum, since not yet an option with saliva
    - ii) Often use four-fold increase as the criteria
    - iii) Change based on paired (i.e., two) sera
- (3) Requires laboratory support
  - (a) May be too expensive for routine vaccine effectiveness assessment

3. Graphic relationship

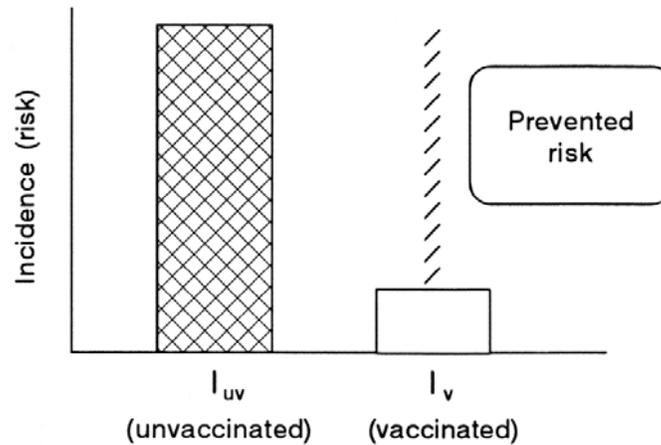


**Figure 5.** Prevented and preventable risk.

4. Formula for **Vaccine Effectiveness (VE)**

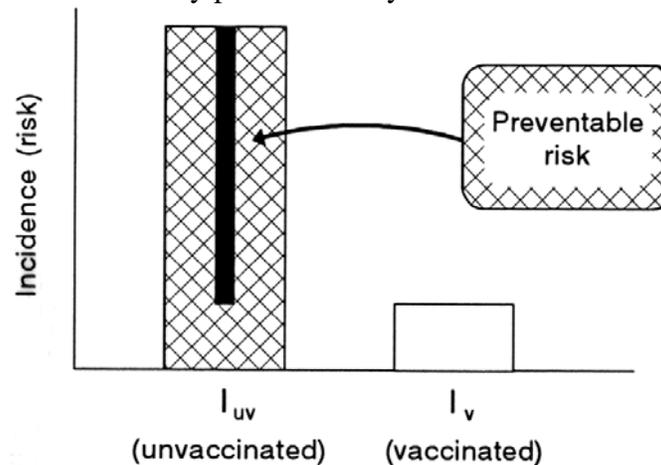
$$VE = \frac{I_{uv} - I_v}{I_{uv}}$$

- a. Measures the "Prevented Fraction among the Vaccinated" ( $PF_v$ )
  - (1) Proportion of the disease incidence among vaccinated persons which was prevented by vaccination



**Figure 6.** Graph of prevented risk in vaccinated.

- b. Measures the "Preventable Fraction among the Unvaccinated" ( $PF_{uv}$ )
- (1) Proportion of the disease incidence among unvaccinated persons which is theoretically preventable by vaccination



**Figure 7.** Graph of preventable risk in unvaccinated.

- c. If study findings are reported as a "risk ratio" (i.e.,  $I_v/I_{uv}$ )...
- (1) Formula for VE,  $PF_v$  or  $PF_{uv}$  is often reported as...

$$\frac{I_{uv} - I_v}{I_{uv}} = \frac{I_{uv}}{I_{uv}} - \frac{I_v}{I_{uv}} = 1 - \frac{I_v}{I_{uv}} = 1 - RR$$

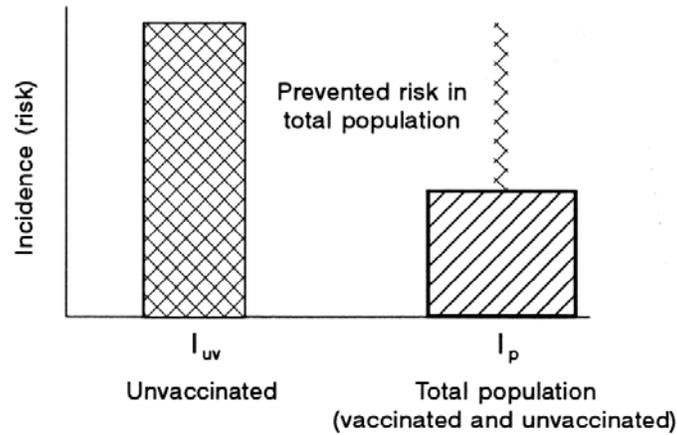
Note: RR must be less than 1.0 (vaccination is "preventive")

- (2) Remember, these formulas only apply if the probability of coming in *contact* with the disease is identical in the vaccinated and unvaccinated groups

## B. Measure based on the Total Population

1. **Community Effectiveness (CE) of a Vaccination Program**

- a. Incidence rates among vaccinated persons ( $I_v$ ) or unvaccinated ( $I_{uv}$ ) compared to the total population ( $I_p$ )
- b. Two measures of CE (fraction and cases)
  - (1) **Prevented fraction in population ( $PF_{p,v}$ )**
    - (a) Graphic relationship



**Figure 8.** Graph of prevented risk in total population.

- (b) Indicates what proportion of new disease cases in the total population have theoretically been prevented by vaccination
- (c) Formula

$$PF_{p,v} = \frac{I_{uv} - I_p}{I_{uv}} = 1 - \frac{I_p}{I_{uv}} = CE$$

- (d) Relationship to Vaccine Effectiveness

$$PF_{p,v} = CE = VE \times PPV$$

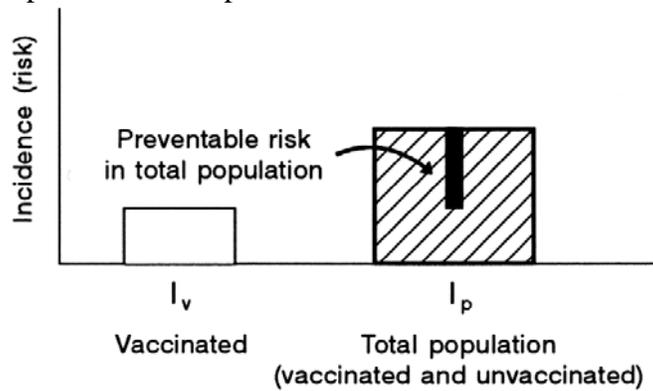
where **PPV** = proportion of the population vaccinated (coverage)

(2) **Prevented cases in the population**

Prevented cases	=	Total population	x	Incidence among the unvaccinated	x	Prevented fraction in the population
	=	N	x	$I_{uv}$	x	$1 - \frac{I_p}{I_{uv}}$
Expected cases if no one in the population had been vaccinated						CE

2. **Preventable fraction in population ( $PF_{p,uv}$ )**

a. Graphic relationship



**Figure 9.** Graph of preventable risk in total population.

- b. Indicates what proportion of new disease cases in the total population are theoretically preventable if everyone in the population was vaccinated  
 (1) Assumes everyone would have the same incidence of disease as those who were vaccinated
- c. Formula

$$PF_{p,uv} = \frac{I_p - I_v}{I_p} = 1 - \frac{I_v}{I_p}$$

d. Relationship to Vaccine Effectiveness (VE)

$$PF_{p,uv} = \frac{(1 - PPV) \times \frac{VE}{1 - VE}}{(1 - PPV) \times \frac{VE}{1 - VE} + 1}$$

where **PPV** = proportion of the population which is vaccinated (i.e., coverage)

C. Relationship between PCV, PPV, and VE

1. **Proportion of cases vaccinated (PCV)**

- a. Formula (see Chen and Orenstein, 1996, p. 110)

$$PCV = \frac{PPV - (PPV \times VE)}{1 - (PPV \times VE)}$$

where, PPV and VE are as defined previously

- b. While this formula describes the relationships shown in the graph on p. 110 of the Chen and Orenstein article (1996), it is not useful in its present form

(1) Knowing that some proportion of disease cases has not been vaccinated is of little relevance to policy- or decision-makers

- c. Note: the relationships in the above formula and those following in this section will hold true only if susceptible persons have had the same probability of disease *contact* as immune persons

2. **Vaccine effectiveness (VE)**

- a. Formula

$$VE = \frac{PCV - PPV}{PPV \times (PCV - 1)} \quad \text{or} \quad \frac{PPV - PCV}{PPV \times (1 - PCV)}$$

where PCV = proportion of the cases vaccinated and PPV is as defined above

- b. Very useful formula since it shows how two parameter estimates (i.e., PCV and PPV) can be combined to permit the indirect assessment of vaccine effectiveness as **actually** occurred in a field setting

(1) Not essential to measure  $I_v$ ,  $I_{uv}$ , or  $I_p$  in the population

(2) *Proportion of population vaccinated* (i.e., PPV) is derived in immunization surveys using the EPI "30 x 7" cluster sampling procedure  
(a) Procedure presented in EPI 418 *Rapid Epidemiological Surveys in Developing Countries*, Spring Quarter

(3) Proportion of the Cases Vaccinated (i.e., PCV) is derived from a detailed interview of a sample of disease cases

3. **Proportion of population vaccinated (PPV)**

- a. Formula

$$PPV = \frac{PCV}{VE \times (PCV - 1) + 1}$$

where PCV and VE are as previously defined

- b. This formula is presented so that all three parameters (i.e., PCV, PPV, and VE) can be estimated by knowing the values of any two
- c. Should be used to estimate proportion of the population which has been vaccinated with data from a disease monitoring program (see below)

D. Example of Calculations

1. Nomogram

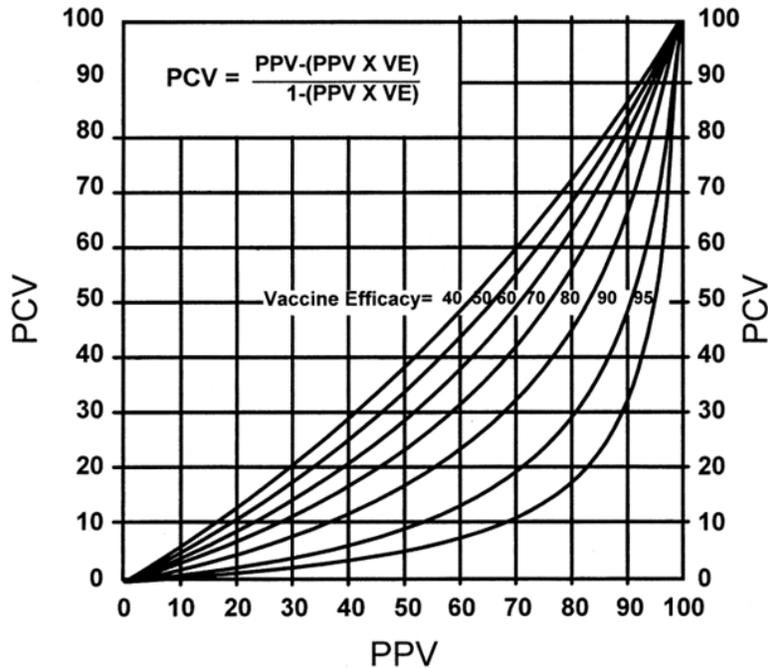


Figure 10. Relation between PPV and PCV (see Chen and Orenstein, 1996, p. 110)

	Measles	No measles	Total	
Vaccinated	1,000	64,000	65,000	$I_v = 0.0154$
Unvaccinated	11,500	23,500	35,000	$I_{uv} = 0.3286$
	12,500	87,500	100,000	$I_p = 0.1250$
			Risk Ratio =	$RR = I_v/I_{uv} = 0.0468$
			Vaccine Effectiveness =	$VE = 0.9532$
			Prevented Fraction in Population =	$PF_{p,v} = 0.6196$
			Preventable Fraction in Population =	$PF_{p,uv} = 0.8769$

E. Do calculations using MS Excel and VE program

1. Use both for calculations and sensitivity analysis
  - a. Available on the EPI 415 class website as *ve.xls*
2. Table

Field observations	Enter Observed Value	Calculated Value
Prop. of CASES who report having been vaccinated	0.080	PCV = 0.080
Prop. of POPULATION who report having been vaccinated	0.650	PPV = 0.650
VACCINE EFFECTIVENESS		VE = 0.953
Proportion of potential CASES in population that have been PREVENTED by vaccination		PF <sub>p,v</sub> = 0.620
Proportion of actual CASES in population that are PREVENTABLE by vaccination		PF <sub>p,uv</sub> = 0.877

Enter 2 of the 3 numbers in these spaces

- a. The operator must enter any two parameters (i.e., PCV, PPV, or VE) and the third parameter will be calculated by the program
- b. Most likely, PCV and PPV will be derived in a field survey and VE will be estimated using the above table

3. Formulas for table entries

- a. All entries are text or numbers except those in column D

Calculated Value	
PCV =	=IF(B6>0,B6,(B9-(B9*B11))/(1-(B9*B11)))
PPV =	=IF(B9>0,B9,B6/((B11*(B6-1))+1))
VE =	=IF(B11>0,B11,(B6-B9)/(B9*(B6-1)))
PF <sub>p,v</sub>	=D11*D9
PF <sub>p,uv</sub>	((1-D9)*(D11/(1-D11)))/((1-D9)*(D11/(1-D11))+1)

- b. Logic for PCV equation

If the entry in cell B6 is greater than 0 (the operator has entered a number), then accept the value in cell B6, otherwise compute for cell B6 the value using the formula  $(B9-(B9*B11))/(1-(B9*B11))$

c. Graph (text included only for this example)

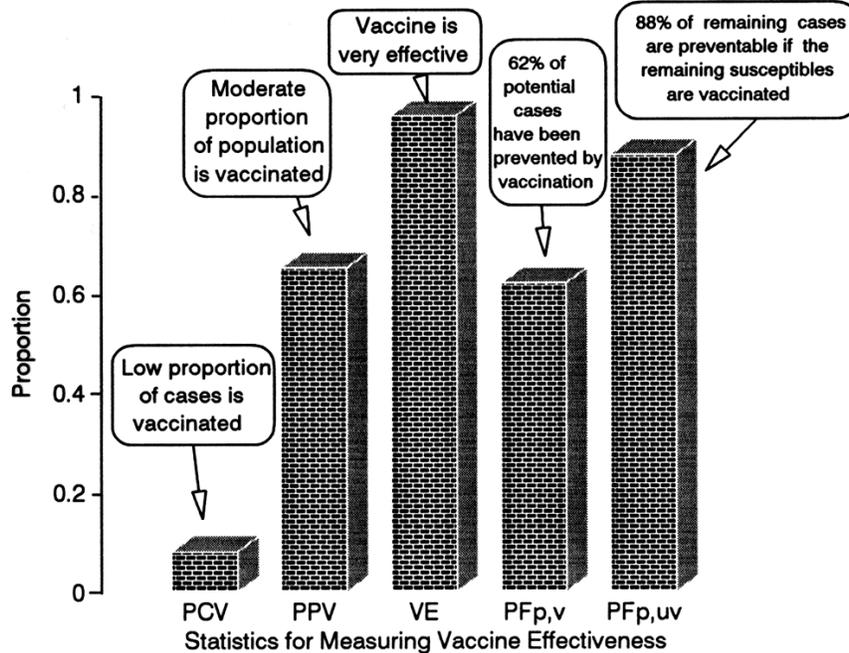


Figure 11. Graph for program *VE.xls* (annotated text not included)

#### IV. GENERAL PRINCIPLES FOR ASSESSMENT OF VACCINE EFFECTIVENESS

##### A. Case definition

1. Use uniform definition for all cases

##### B. Case ascertainment

1. Must be independent of vaccination status
  - a. Equal effort is made to detect cases among vaccinated and unvaccinated persons

##### C. Vaccination status ascertainment

1. Need to classify vaccination status **prior** to onset of disease or an outbreak

##### D. Comparability of exposure

1. Vaccinated persons should have the same probability of contact with cases or other sources of the disease as persons not vaccinated

#### V. SPECIFIC ASSESSMENT METHODS

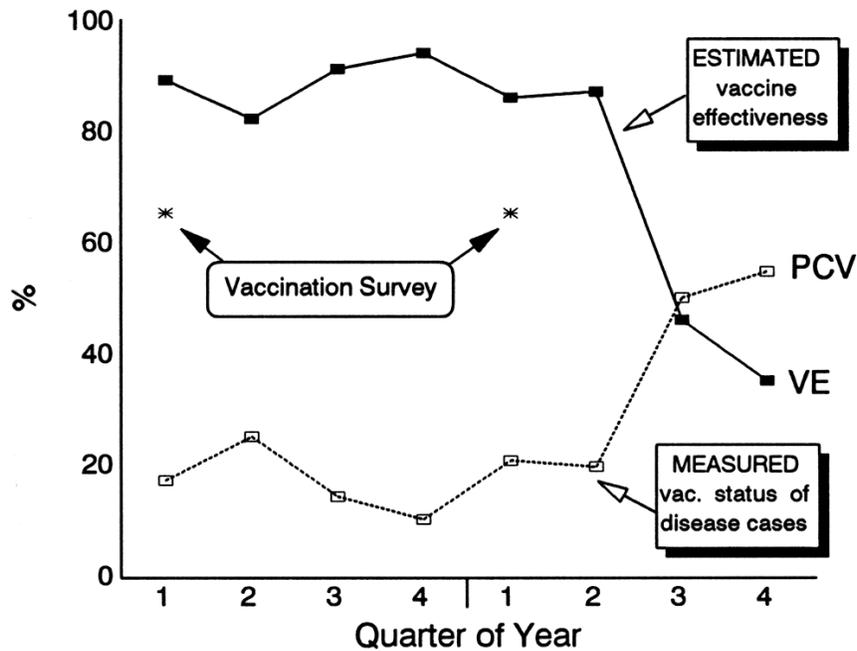
##### A. Establish a **surveillance system** for target diseases

1. This should always be done

2. Require health workers to report all cases of the target diseases
    - a. Teach primary health workers the signs and symptoms of the diseases of interest
      - (1) Need to make sure that sensitivity and specificity of the diagnostic process is relatively high
    - b. Require that the medical care staff in hospitals and clinics provide complete reporting
  3. Determine *Proportion of Cases Vaccinated* (PCV)
    - a. Interview cases (or other respondent) and determine vaccination history
      - (1) Assume respondent has either a good memory or a home record of vaccinations
    - b. Review clinic or hospital records of local cases seen in institutional settings
      - (1) Assume vaccination record is included in the patient's folder
  4. Determine *Proportion of Population Vaccinated* (PPV)
    - a. Based on existing information from a vaccination team or the health center staff
    - b. Conduct occasional **Rapid Surveys** (Spring Quarter, EPI 418, *Rapid Epidemiological Surveys in Developing Countries*)
  5. Derive *Vaccine Effectiveness* (VE)
    - a. Use formula described previously (*VE.xls* program)
- B. Create monitoring graph
1. This should always be done, but is much easier if a microcomputer and *Excel* are available
  2. Components
    - a. Measured variables
      - (1) Monthly or quarterly
        - (a) Proportion of disease cases that have been vaccinated (PCV)
      - (2) Once or twice a year
        - (a) Proportion of population that has been vaccinated (PPV)
    - b. Estimated variable
      - (1) Monthly or quarterly
        - (a) Vaccine effectiveness (VE)

3. Graph

a. By month or quarter for the administrative region of interest



**Figure 12.** Vaccination monitoring graph by quarter of year, XX state.

4. Interpretation

a. High vaccine effectiveness (VE)

(1) If measurement error

(a) Surveillance system underreports the vaccination status of disease cases

i) PCV is artificially low, resulting in VE being artificially high

(2) If lack of social mixing

(a) Disease cases are very uncommon in the vaccinated group due to lack of social interaction between vaccinated and unvaccinated persons

i) PCV is artificially low, resulting in VE being artificially high

(3) If accurate measurement

(a) Desired outcome

(b) Focus on improving vaccination coverage

i) Supervision

ii) Transportation

iii) Supplies and equipment

b. Low vaccine effectiveness (VE)

(1) If measurement error

(a) Cases report having been vaccinated when in truth they were not

i) PCV is artificially high, resulting in VE being artificially low

(b) Vaccination coverage is reported as being lower than it really is

- i) PPV is artificially low resulting in VE being artificially low
  - (2) If accurate measurement
    - (a) Undesirable outcome
    - (b) Focus on improving vaccine effectiveness before trying to improve vaccination coverage
      - i) Break in cold chain
      - ii) Poor administration of vaccine
      - iii) Fault in production quality of vaccine

C. Conduct a **field investigation**

1. This should occasionally be done, since it is costly and time consuming
2. Criteria to determine if an investigation can be successfully done
  - a. Disease was at a minimal level in the area prior to the present outbreak
    - (1) Few in the population of interest had developed natural, active immunity due to prior contact with the disease agent
  - b. Vaccination records are available to help determine who was and was not vaccinated
    - (1) Home immunization records
      - (a) Held by mother or head of household
    - (2) Clinic or hospital immunization records
      - (a) Use to evaluate accuracy of respondents memory
      - (b) May require considerable work if records are not easily accessible
  - c. Both vaccinated and unvaccinated persons are present in adequate number in the population and are mixing so that the disease could spread
    - (1) Otherwise cannot adequately assess the underlying disease rate in the two groups
  - d. Cases of the disease were relatively common in the population
    - (1) Both vaccinated and unvaccinated persons had similar opportunities for contact with infective cases
3. Define the eligible (i.e., "target") population
  - a. Persons who, according to their age, should theoretically have been vaccinated
  - b. Persons who, according to their age, should theoretically be susceptible to the disease if they had not been vaccinated and if they have not had the disease
    - (1) No maternal immunity
4. Types of field investigations
  - a. Acute outbreak
    - (1) An excess number of cases during a short period of time in one setting such as a community or school
    - (2) Study population = total eligible population
  - b. Large-scale epidemic or endemic disease
    - (1) An excess number of cases over time in larger populations

- (2) Study population = cluster sample of eligible population
  - (a) EPI "30 x 7" Cluster Sample (presented in EPI 418)
- (3) Determine both history of vaccination and post-vaccination disease status
  - (a) If cases are common in the sampled population, can derive VE from the results of the survey
  - (b) If cases are not common in the sampled population, extend the analysis to other cases in the total eligible population (derived via the surveillance system) and do a "case-base" analysis (see *APPENDIX*)
- c. Secondary Attack Rate Studies
  - (1) Criteria
    - (a) Disease is epidemic or endemic and is transmitted person-to-person
    - (b) Disease clusters in households or geographic clusters
    - (c) Index case can be identified in households or clusters
      - i) First case with the disease
    - (d) Households or clusters have more than one child in the eligible population
    - (e) Secondary cases can be identified in households or clusters
      - i) New cases arising one incubation period after the index case brought the disease into the household or geographic cluster
  - (2) Analysis
    - (a) For all eligible persons in household or clusters *other than the index case...*
      - i) Determine historical vaccination status
      - ii) Determine recent target disease status
    - (b) Derive  $I_v$  and  $I_{uv}$  in the usual manner for all vaccinated and unvaccinated eligible people in the combined households or combined clusters
      - i) Exclude the *index cases* from each household in the analysis
        - a) The *index case* brings the disease into the household

$$VE = 1 - \frac{I_v}{I_{uv}}$$

- d. Case-control Studies
  - (1) The approach of choice when resources for conducting investigations are scarce
    - (a) Since disease is relatively uncommon, community-based investigations of vaccinated and unvaccinated persons may require a large sample population to derive stable estimates of the underlying disease rates
    - (b) Fewer persons need to be interviewed or examined when using the case-control study design
  - (2) Cases
    - (a) Persons who recently became ill with the disease
      - i) signs and symptoms
      - ii) laboratory confirmation

- (b) Selected either during or at the end of the time period under consideration
- (3) Controls
  - (a) Free of the disease and selected at the same time as cases
    - i) Incidence-density type of case-control study
    - ii) Not often feasible since the epidemic has already occurred by the time the investigation is started
  - (b) Free of the disease and selected at the end of the time period under consideration
    - i) Cumulative incidence type of case-control study
    - ii) The usual method for selecting controls in studies of vaccine effectiveness
  - (c) A sample of the source population of the cases selected at the end of the time period under consideration
    - i) Case-base type of case-control study (see *APPENDIX*)
    - ii) The same persons may show up in both the case series and the control series
    - iii) Not often done but preferable since the odds ratio (OR) is an unbiased estimator of the risk ratio (RR)
      - a) Uncommon disease assumption is not required
    - iv) Formulas for calculating variance estimates and confidence intervals are presented in EPI 200A-C (for epidemiology majors)

## APPENDIX

The case-base study is a form of case-control study, with controls being a sample of the total sources population of the cases rather than a sample of non-cases. Thus both cases and non-cases may appear in the control series. The statistical analysis is complicated by the lack of independence of cases and controls. This issue is addresses in EPI 200A-C.

### EXAMPLE OF CASE-BASE ANALYSIS

#### COHORT STUDY

	Disease	No disease	Total (or "base")
Vaccinated	A	B	A+B
Unvaccinated	C	D	C+D

$$RR = \frac{I_v}{I_{uv}} = \frac{\frac{A}{A+B}}{\frac{C}{C+D}} = \frac{A}{C} \times \frac{C+D}{A+B}$$

---

the "base"

---

cross-product of case and base

#### CASE-CONTROL STUDY (Case-Base Type)

	Disease	Controls
Vaccinated	A	a+b
Unvaccinated	C	c+d

The odds ratio is an unbiased estimate of the risk ratio (no rare disease assumption is needed)

$$OR = \frac{\frac{A}{a+b}}{\frac{C}{c+d}} = \frac{A}{C} \times \frac{c+d}{a+b}$$

---

sample of the "base"

---

cross-product of case and base

Since  $OR=RR$ , we use the findings to derive VE with the formula,  $VE = 1 - RR$

### Combination of survey and surveillance system

DISEASE CASES DERIVED FROM....

	Sample survey	Surveillance system	Sample survey of population (the "base")
Vaccinated	a <sub>1</sub>	a <sub>2</sub>	a+b
Unvaccinated	c <sub>1</sub>	c <sub>2</sub>	c+d

$$OR = \frac{\frac{a_1 + a_2}{c_1 + c_2}}{\frac{a + b}{c + d}} = \frac{\frac{a_1 + a_2}{a + b}}{\frac{c_1 + c_2}{c + d}} = \frac{a_1 + a_2}{c_1 + c_2} \times \frac{c + d}{a + b} = RR$$

---

the "base"

---

cross-product of cases and base

Then use RR findings to derive VE using the formula,  $VE = 1 - RR$