FIELD EVALUATION OF VACCINE EFFICACY

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1. Introduction

The ability of a vaccine to prevent disease effectively depends on the vaccine being potent and administered properly to an individual capable of responding. Useful techniques are available to test the potency of vaccines and the responses of the host. Potency testing is important in monitoring the production of vaccines to ensure that the product meets standards, and can be helpful in monitoring the handling of the vaccine (the "cold chain"). In the latter instance, vaccines from the field are retrieved and tested to ensure that they have not lost potency.

Serological studies can be used to determine vaccine efficacy. Sero-conversion is useful to measure the induction of an immune response in the host. In the absence of disease, seroprevalence can evaluate the persistence of antibody and presumably immunity.

Serological studies can be helpful prior to beginning an immunization programme to identify appropriate target groups for vaccination. Seroprevalence studies monitor the prevalence of antibodies due to disease in the population and indicate the pattern of occurrence of disease. Seroconversion studies are particularly useful in choosing the appropriate age for vaccination. By knowing the age distribution of measles cases and age specific seroconversion rates for example, estimates of the number of preventable cases using different vaccine policies can be derived.

These two techniques (vaccine potency testing and serological testing) can play useful roles in the establishment and execution of immunization programmes. However, since these procedures depend on laboratory support and may be expensive, it is not feasible to carry them out under all circumstances. Moreover, the use of seroconversion as an indicator of vaccine efficacy only measures efficacy under relatively controlled conditions, during a short period, since pre and post immunization sera must be collected and the vaccinator is aware that a test is being done. Under field conditions such as in an integrated immunization programme, many different immunization centers and vaccinators are involved.

The success of vaccination performed under field conditions is more realistically assessed by measuring protection against disease by epidemiologic means. This epidemiologic approach has the additional merit of not requiring laboratory support. Because of the ease of carrying out this technique it can be very useful, particularly when doubt is cast on the effectiveness of the vaccination programme because of the occurrence of disease in vaccinated individuals. This problem becomes increasingly prominent as vaccine coverage rises since the proportion of cases of illness occurring in vaccinated persons will increase even though vaccine efficacy remains constant. Lower than expected vaccine efficacy determinations should stimulate more intense investigations to determine causes and take corrective action if necessary.

The purpose of this paper is to describe the epidemiologic techniques available for measuring vaccine efficacy, beginning with the simplest and proceeding through increasingly complex techniques, and to recommend a practical approach to their use. Most of the text and the examples used will relate to measles vaccine since this is the primary setting in which the techniques have been used. However, many may be applicable to other vaccines as well. In the discussion section, a summary of the methods is given together with their major advantages and disadvantages. The paper provides sufficient tools in itself to perform a field evaluation of measles vaccine efficacy. For those interested in detailed aspects of the methodology, particularly regarding potential biases and methods to anticipate and correct them, an Appendix has been attached.

2. Calculation of vaccine efficacy - General principles

Vaccine efficacy is measured by calculating the incidence rates (attack rates) of disease among vaccinated and unvaccinated persons and determining the percent reduction in the incidence rate of disease among vaccinated persons relative to unvaccinated persons. The basic formula is written as:
Where

\[ VE = \frac{ARU - ARV}{ARU} \times 100 \]  

(1)

Where

\( VE \) = vaccine efficacy
\( ARU \) = attack rate in unvaccinated population
\( ARV \) = attack rate in vaccinated population.

For example, if the vaccine were totally effective, there would be no disease in the vaccinated population and the calculation would simplify to \( ARU - 0 \times 100 = 100 \) percent. By contrast, if the vaccine had no effect at all, \( ARU \) would equal \( ARV \) and the calculation would simplify to \( 0 \times 100 = 0 \) percent.

In practice, of course, vaccines are neither perfectly effective nor totally ineffective. Measles vaccine has typically been 80-95 percent effective when appropriately administered.\(^1,5-8\) To illustrate how the proportion of cases giving a history of vaccination increases with increasing levels of vaccine coverage, Table 1 depicts the proportion of all truly susceptible individuals\(^*\) who have received vaccine at three different levels of vaccine coverage: 20, 50, and 90 percent. Assuming 90 percent vaccine efficacy, the proportion of individuals with a history of prior immunization among all susceptibles will rise from 2.4 percent at 20 percent coverage to 47.4 percent at 90 percent coverage. This proportion will also be reflected in the proportion of cases who give a history of vaccination.

The ideal vaccine efficacy study is a clinical trial starting with persons susceptible to disease. In a double blind randomized placebo controlled fashion,\(^**\) half of the children receive vaccine and half receive placebo. To calculate vaccine efficacy both groups are followed prospectively to determine attack rates for disease in vaccinees and nonvaccinees. This type of study is generally not possible after a vaccine has been licensed because the vaccine is of proven benefit and use of a placebo is unethical. In most countries today, measles vaccine has been used in a proportion of the population. These vaccinees are a self-selected rather than a randomly selected group and their susceptibility prior to vaccination is generally unknown. Nonetheless, vaccine efficacy studies are still possible if biases are reduced to a minimum in order to recreate as closely as possible the "ideal" conditions of the prospective clinical trial.

Four major factors affect most epidemiologic studies of vaccine efficacy: (1) case definition, (2) case ascertainment (case detection), (3) vaccine status determination, and (4) comparability of exposure.

It is important that a uniform definition of cases be developed and applied to all individuals in the study. This definition should be as sensitive and specific as possible. Laboratory confirmation of at least some cases can help demonstrate the accuracy of the case definition. A clinical case definition for measles is shown in Table 2.\(^9\) Any illness meeting the three criteria is considered likely to represent measles.

Case ascertainment is the second requirement of vaccine efficacy evaluations. It is important to assure that there is equal detection of cases among vaccinated and unvaccinated populations. Total population based surveillance surveys in which investigators go door to door using a clinical case definition to find cases give the least biased estimate of vaccine efficacy.

\(^*\) both unvaccinated and vaccine failures.
\(^**\) neither investigators nor recipients know if they received vaccine or placebo. Persons receive vaccine or placebo by random allocation.
Third, vaccination status must be determined accurately. Whenever possible, vaccine history should be based on a record indicating the date of vaccination. If many vaccinees lack records, vaccine efficacy calculations may be biased. Definitions of vaccination status will depend on the actual type of investigation used. In general, persons can be considered vaccinated against measles if they received vaccine on or after the minimum recommended age for vaccination and at least 14 days prior to onset of disease or of an outbreak.

Persons who received vaccine prior to the recommended age should not be classified as unvaccinated but should be classified in a separate category. Persons vaccinated during outbreak control clinics should be classified based on their vaccination status prior to the outbreak.

Finally, efficacy should be measured under conditions where vaccinees and nonvaccinees have equal likelihood of exposure to measles disease. This is most likely to be the case when the incidence rate of disease is relatively high.

3. Specific Methods

3.1 Screening

A preliminary estimate can easily be made of whether efficacy is within expected limits. If attack rates in the vaccinated are known, an attack rate of greater than 10% immediately suggests the need for further evaluation since maximum efficacy will be less than 90 percent. (Under conditions of 90% efficacy, 10% of the vaccinated population is susceptible. Therefore less than 10% of persons would be expected to become ill). An attack rate of <10% in the vaccinated in the absence of other information does not mean vaccine is effective. A comparison with attack rates in the unvaccinated is necessary.

In most situations, attack rates in the vaccinated and unvaccinated will not be known. However, vaccine efficacy can be estimated from other available information. The vaccine efficacy equation can be manipulated to give the formula in Table 3 which consists of three variables, the proportion of cases occurring in vaccinated individuals (PCV), the proportion of the population that is vaccinated (PPV), and the vaccine efficacy (VE) (JM Kobayashi, JP Brennan—personal communication). By knowing any two of the three variables, the third can be calculated.

Figure 1 shows curves generated from the equation in Table 3. These curves indicate the theoretical proportion of cases that will have a vaccination history in a given setting for specified levels of vaccine efficacy. These curves do not predict the occurrence of an outbreak in any given set of circumstances, but they do show the expected proportional distribution of cases by vaccination status should an outbreak occur.

EXAMPLE

Consider a measles outbreak in a small town with 100 cases in 12 to 35 month-old children, 9 of whom were previously vaccinated. Prior coverage assessments showed that 50% of children in that age group had received measles vaccine. Figure 1 or the equation in Table 3 can be used to assess whether the 9% of cases that were vaccinated is compatible with high vaccine efficacy. Plotting 9% for PCV and 50% for PPV, indicates that the point is on the 90% vaccine efficacy curve. Thus, finding 9 percent of cases vaccinated in a locality with 50% vaccine coverage is compatible with high vaccine efficacy and extensive investigations would not be warranted. On the other hand, if the same proportion of cases occurred in individuals in a town with only a 10% vaccination coverage, plotting these points on the graph would show a vaccine efficacy well to the left of the 80% curve, indicating low vaccine efficacy and the need for a more thorough evaluation of the situation.
Percentage of Cases Vaccinated (PCV) per Percentage of Population Vaccinated (PPV), for 7 Values of Vaccine Efficacy (VE)

\[ PCV = \frac{PPV - (PPV \times VE)}{1 - (PPV \times VE)} \]
The major purpose of this screening technique is to indicate whether there is need for more careful evaluation. It should not be relied upon for precise estimates of vaccine efficacy. There is a small danger that vaccine efficacy may be over estimated if the vaccination levels in the community are over estimated* or if the proportion of cases with vaccination history is underestimated. However, in most circumstances with reasonably accurate estimates, overestimation of vaccine efficacy should be rare and this screening will provide a rough guide to whether further evaluation is necessary.

3.2 Outbreak investigations

a) Community-wide investigation - Total population assessment

Criteria for selection

The best occasion to measure vaccine efficacy is probably in defined outbreak settings such as villages, towns, cities or schools. More determinations of vaccine efficacy have been performed in these types of investigations than any other setting.\textsuperscript{5,7,8} Although any outbreak can be investigated, biases will be minimized if the criteria listed in Table 4 are kept in mind. First, efficacy is probably best measured in settings where measles has been intermittent rather than endemic. The population should consist of both vaccinees and nonvaccinees and should contain an adequate** number of persons in the age group to be studied. Generally the selected group should be old enough to be susceptible to measles and to have been vaccinated yet young enough not to have had substantial exposure to measles prior to the outbreak. In villages, the appropriate age group to be studied may be determined by questioning village elders about the time of the last outbreak and by determining the proportion of each age group that had a history of disease before the outbreak. Age groups in which substantial proportions of persons have had disease should not be included in the study.

The lower age limit is determined by the age at which vaccination is recommended.\textsuperscript{2} This is usually an age between the time that transplacentally derived immunity has waned and attack rates for disease become high. For measles, in most developing areas, the optimal age group should probably include persons nine months of age up to the third birthday. Overall attack rates in the selected age groups in excess of five percent ensure that exposure was somewhat comparable. Ideally, good vaccination records should be available.

Methods

1. Case definition - a sensitive and specific clinical case definition should be used. The definition given in Table 2 may be used to classify cases of measles.\textsuperscript{*}

2. Case ascertainment - a total population based surveillance survey should be conducted. In villages, workers should go door to door taking a census of all persons in the target age group and determining whether any have had illnesses clinically compatible with measles. Details of the clinical illness and vaccination status should be collected for persons in the target age group who have died during the outbreak period. These persons should be included as cases or noncases as appropriate.

* This is most likely under conditions of high vaccination coverage on the right part of the horizontal axis (PPV 80%) when small changes in the proportion of the population that is vaccinated are associated with large changes in the expected proportion of the cases that are vaccinated.

** To get an idea of the numbers needed, see Appendix, Section V.
(3) **Vaccination status determination** — as workers go door to door, they should obtain histories of vaccination for all persons in the target age group. Birth dates and dates of vaccination should be recorded, if available. If dates of vaccinations are not available, age at vaccination should be estimated. Equal efforts should be made to obtain vaccination status of cases and noncases. Persons should be considered immunized if they received vaccine at or after the minimum recommended age, and if vaccinated 14 or more days before the onset of the outbreak. Persons vaccinated before the recommended age should be classified separately. Persons vaccinated during the outbreak should be classified based on vaccination status prior to the outbreak.

(4) **Prior disease:** Disease which occurred prior to this outbreak will have minimal effect on vaccine efficacy calculation if the incidence rate of disease in the area under study and in the chosen age group was low. Hence, age groups that probably will have been heavily exposed to measles prior to the outbreak (e.g. persons > 3 years of age) should be excluded from the investigations. However, once the appropriate age group is selected, persons with prior disease should not be excluded from the denominators of the appropriate attack rate calculation. The numerator, for each attack rate should consist only of cases that occurred during the outbreak. (See Appendix for more detailed discussion of the effects of prior measles disease.)

**Analyses** (see Table 5)

(1) The attack rate in the unvaccinated (ARU) can be calculated by dividing

\[
\frac{b}{b + e}
\]

where \(b\) is the number of unvaccinated cases during the outbreak and \(e\) is the number of unvaccinated who did not develop measles during the outbreak.

(2) The attack rate in the vaccinated (ARV) can be calculated by dividing

\[
\frac{a}{a + d}
\]

where \(a\) is the number of vaccinated cases during the outbreak and \(d\) is the number of vaccinated who did not develop measles during the outbreak.

(3) Persons with unknown vaccination histories should be excluded from the calculation, whether or not they had illness. (Exclude \(c + f\))

(4) Vaccine efficacy can be calculated according to the formula in Table 5 which is derived from the formula on page 3.

Special analyses to evaluate efficacy by age at vaccination, duration of vaccine induced immunity and the effects of two doses can also be calculated using ARV for the specific group being studied. For example, to calculate vaccine efficacy for persons vaccinated at exactly twelve months of age, ARV would equal the number of cases vaccinated at twelve months of age divided by the total population vaccinated at twelve months of age. The overall ARU is usually used for each of the special analyses; ideally more refined estimates may be obtained by controlling for factors such as age. In the above example, ARU might be calculated only among children \(\geq 12\) months of age at the time of the outbreak.

Measurement of vaccine efficacy in outbreaks can be complicated if extensive vaccination programmes took place during the outbreak. This is because persons may change status during the middle of the outbreak from unvaccinated to vaccinated. Correction for control programmes is necessary if a substantial proportion of the cases occur after the programme and a substantial proportion of the population was vaccinated during the programme.\(^7,10,11\) When either of those proportions are small, no correction is necessary. Correction methods are discussed in the Appendix.
Hull et al investigated measles outbreaks in 3 villages in the Gambia. During the course of the study they assessed: (1) whether vaccine efficacy could be measured (2) the appropriate age groups to be included in the study and (3) the actual efficacy by age at vaccination.

To determine whether efficacy could be measured, they surveyed the proportion of the population that had vaccination records. From 80 to 97 percent of children 9 months through 3 years of age had records. The overall attack rate in children 9 months through 3 years was 17 percent, indicating high community exposure. In addition, discussions with village elders indicated that the last outbreak had occurred 3 years prior to the investigation, suggesting that measles transmission between the outbreaks was limited. The population 9 months through 3 years included substantial numbers of vaccinees and nonvaccinees – approximately 2/3 of the children had been vaccinated and 1/3 unvaccinated. Thus, the outbreak met the guidelines in Table 4 for undertaking an investigation of vaccine efficacy in this setting.

To determine the appropriate age group to be studied, the investigators determined clinical attack rates among unvaccinated children by age. The clinical attack rate was low from 0-8 months of age and rose dramatically beginning at 9 months (Table A). Therefore, the lower age limit chosen was 9 months, the time when measles vaccine was recommended and the effects of maternally derived transplacental antibody induced protection had waned. The upper age limit was chosen on the basis of interviews which indicated that by 4 years of age a history of measles was frequent, and further that the statements of village elders suggested that the last large outbreak of measles occurred 3 years before. The upper age limit chosen was 3 years (47 months).

To determine the actual vaccine efficacy, the investigators visited all household units in the village, obtaining name, age, sex, vaccination status before and measles history during the outbreak. The data collected are shown in Table B. The overall vaccine efficacy was 89 percent.
Table A

Specific measles attack rates among unvaccinated children in 3 villages in the Gambia

<table>
<thead>
<tr>
<th>Age</th>
<th>unvaccinated population</th>
<th># cases</th>
<th>Attack Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 mos</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-5 mos</td>
<td>33</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>6-8 mos</td>
<td>34</td>
<td>2</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Population chosen for study

<table>
<thead>
<tr>
<th>Age</th>
<th>Population chosen for study</th>
<th># cases</th>
<th>Attack Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-11 mos</td>
<td>21</td>
<td>7</td>
<td>33.3</td>
</tr>
<tr>
<td>1 yr</td>
<td>40</td>
<td>16</td>
<td>40.0</td>
</tr>
<tr>
<td>2 yr</td>
<td>22</td>
<td>10</td>
<td>45.5</td>
</tr>
<tr>
<td>3 yr</td>
<td>24</td>
<td>13</td>
<td>54.2</td>
</tr>
<tr>
<td>4 yr</td>
<td>15</td>
<td>4</td>
<td>26.7</td>
</tr>
<tr>
<td>5 yr</td>
<td>15</td>
<td>5</td>
<td>33.3</td>
</tr>
<tr>
<td>6-10 yr</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>238</td>
<td>59</td>
<td>24.8</td>
</tr>
</tbody>
</table>
**Table B**

Measles vaccine efficacy in the Gambia for children 9-47 months of age

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated at &gt;9 mos</th>
<th>Unvaccinated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># of cases</td>
<td>11</td>
<td>46</td>
<td>57</td>
</tr>
<tr>
<td># well</td>
<td>213</td>
<td>61</td>
<td>274</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
<td>107</td>
<td>331</td>
</tr>
<tr>
<td>Attack rates</td>
<td>5%</td>
<td>43%</td>
<td>17%</td>
</tr>
</tbody>
</table>

\[
VE\% = \frac{ARU - ARV}{ARU} \times 100
\]

\[
= \frac{46 - 11}{107 - 224} \times 100
\]

\[
= \frac{35}{117} \times 100
\]

\[
= 89\%
\]
b) Estimating vaccine efficacy in outbreaks in large populations - cluster samples

When outbreaks occur in large populations, determining vaccination status of all the individuals involved may be unmanageable. In those situations, a coverage survey of children in the at risk population can be used to estimate the pre-outbreak immunization levels. Thirty neighborhood clusters are chosen as described by Henderson, et al., and seven or more children in the age group selected for the study (e.g. 9-35 months) are chosen from each cluster.\textsuperscript{12} Vaccination status and history of an illness clinically compatible with measles are determined for each participant. Vaccination status is assessed preferably from vaccination records.

If attack rates are high so the number of cases in the sample is large, vaccine efficacy can be calculated directly from the coverage survey using Table 5. If the number of cases is low, they can be supplemented by other cases found through disease surveillance systems. This will increase the precision of the estimate (i.e. decrease the width of the confidence interval; see discussion of confidence intervals and numbers needed sections IV and V in the appendix).

The vaccine efficacy equation can be expressed in the form of relative risk, the ratio of ARV to ARU (Table 6). If supplemental cases are included, ARU and ARV should not be calculated. Instead the relative risk is estimated directly (Table 7). This is the equivalent of a case exposure study in chronic disease epidemiology.\textsuperscript{13}

**Methods**

1. **Case definition** - same as in outbreak investigations.
2. **Case ascertainment** - two forms can be used. If attack rates are high*, the number of cases in the sample may be sufficient to accurately estimate vaccine efficacy. If the attack rates are low, other surveillance data can be used to gain additional cases.
3. **Vaccination status determination** - preferably from written records of persons in the sample and all cases.
4. **Prior disease** - same as outbreak investigations.

**Analyses**

Attack rates and vaccine efficacy can be calculated as in an outbreak investigation using Table 5 when the coverage survey above is used. If supplemental cases are added, use Table 7.

3.3 Secondary Attack Rates in Families

The possibility that exposure of vaccinees and nonvaccinees to disease during outbreaks may be different can result in biased estimates of vaccine efficacy and is a potential problem with such investigations. An alternative approach to reduce this bias is to measure secondary attack rates for measles disease in family members of index cases. Prior studies have demonstrated that secondary attack rates in nonvaccinees are generally consistent from family to family, implying that within the household there is generally uniform exposure.\textsuperscript{14,15} Secondary attack rate determinations have not been used as

*See Appendix, Sections IV and V on numbers and confidence intervals for the effects of different attack rates on the confidence interval.
frequently as outbreak investigations in measuring measles vaccine efficacy.\textsuperscript{6,16} Nevertheless, the technique has been thoroughly evaluated and has proven useful not only for measles, but also for other vaccines such as pertussis.\textsuperscript{17-18} An additional advantage of the secondary attack rate method is that vaccinees and nonvaccinees from several families can be added to determine the overall attack rates in the vaccinated and unvaccinated populations provided the same definitions for cases and immunization status are used.

To minimize the effect of prior exposure to measles disease, the age group studied should be restricted generally to nine through 35 months.

**Methods**

(1) **Case definition** - same as above.

(2) **Case ascertainment** - As in outbreak investigations, a good population based surveillance survey should be carried out. Otherwise families with single cases may be less likely to be reported than families with multiple cases. For measles, all cases in a given family should be listed by date of rash onset. Families should be followed for at least 18 days after onset of rash in the first case in the family, the maximal interval for secondary cases determined from prior studies of measles. Persons should be classified as cases or non-cases by their status 18 days after onset of the first case in the family. For other diseases, the appropriate maximal incubation period can be substituted for the 18 day interval of measles.

(3) **Vaccination status determination** - same as in outbreaks. For measles, persons should be classified as vaccinated or unvaccinated by their status on the day of onset of rash of the first case in the family. For other diseases, the cutoff for determining vaccination status should be determined after considering the average incubation period for the disease in question and the average time required for the vaccination to become effective.

(4) **Prior disease** - same as above.

**Analyses**

(1) For measles, persons in the family with onset of rash within the first six days following onset of rash in the first (index) case are considered coprimary cases. The first case in a family and all coprimary cases should be excluded from the analysis. A similar approach should be taken with other diseases.

(2) **Length of followup** for all families should be at least 18 days after onset of rash in the first case.

(3) From all families, add up all secondary cases in the target age group (other than the index case and coprimaries) to get total cases, and all wells (non cases) to get total wells.

Fill in the data in Table 5 and calculate vaccine efficacy.

### 3.4 Secondary attack rate in clusters

A modified form of household investigation has been used in urban and semi-urban settings. This technique has been less well studied than outbreak investigations and secondary attack rates in families.\textsuperscript{19} It is less rigorous than the latter studies because comparability of exposure of vaccinees and nonvaccinees is less assured but is logistically easier than intra-household studies. In the course of an outbreak, or toward the end of the measles transmission season, the study is conducted in a group of neighborhood clusters in each of which at least one known case of measles occurred during the most recent transmission period or some other specified period. The study subjects (e.g. children 9-35 months) are those who live in close proximity to a known case such as no more than one house away from the open area in front of the doorway of a case.
Clusters are defined operationally by the investigators, who start at the household of an identified case,* then proceed to the neighboring households listing all children of target age. If another case which had occurred during the outbreak period is found in one of the visited households, the households adjacent to it are visited, and so forth, until no further cases are found. Thus all children studied, except possibly the initially identified case, have an equally close neighborhood relationship to a case. This approach requires a second visit to the neighborhood clusters at least 18 days later for confirmation of cases seen too early to determine whether they met the case definition and to detect any secondary cases among their contacts.

Methods

(1) **Case definition** - same as above

(2) **Case ascertainment** - all cases in the target age range found in the surveyed households during the predetermined time period, including the case which led to studying the cluster

(3) **Vaccination status determination** - same as in secondary attack rates in families

(4) **Prior disease** - same as above

Analyses - same as for outbreak investigations (3.2)

3.5 **Coverage Survey Methods in Endemic Areas**

Vaccine efficacy can be assessed in the absence of a definable outbreak in urban populations with highly endemic measles by using coverage survey methods. Conceptually this approach is similar to that used in outbreak investigations except that vaccination status is ascertained as of a given age (e.g. 12 months) rather than as of the beginning of the outbreak and disease history is ascertained up to the current age of the children in the survey rather than over a shorter outbreak period of time. No actual outbreak is required. However, because the interval from disease to the time of the survey may be long (up to 2 years), a parental history rather than specific clinical information is used to identify and define cases.

This coverage survey approach is appealing because the situation it seeks to deal with is one frequently encountered in urban measles control programmes, and because the sampling techniques used are well-recognized and easily applied. However, there has been only limited experience in the use of this approach. Modifications have been introduced over time to minimize biases, but more changes may be required as additional experience accumulates. At the present time, the key elements of this approach are as described below.

Thirty neighborhood clusters are randomly selected using the sampling methods described for vaccination coverage surveys (Table 8a). Fourteen or more 2 year old children are sampled from each neighborhood cluster, and two new questions on history of measles disease and age at time of disease if applicable are added to the usual coverage survey questions on current age and date of vaccination. Age at vaccination must be calculated from these data.

* The index case may be reported from any source including hospitals, clinics, schools or a population based surveillance survey.
The fourteen 2 year old children sampled from each cluster must include at least 7 never vaccinated children and at least 7 children vaccinated between 9-11 months of age (or within three months of the recommended age at vaccination if older than 9 months).*

This approach will yield an estimate of the efficacy of vaccine when administered between 9-11 months of age. To obtain an estimate of measles vaccine efficacy when administered without the interfering influence of maternal antibodies, 7 children vaccinated between 12-14 months should also be included in each cluster.

This technique requires an expansion of the usual age group employed in coverage surveys from 12-23 months to 24-35 months. If the usual coverage assessments are desired in the 12-23 month age group, the clusters should be expanded to include children in that age group as well.

With the information in hand on the age at disease of vaccinated and unvaccinated children, it is possible to calculate the measles attack rates experienced by both groups of children from 12 months of age** up to their current age at the time of the survey, and the resulting vaccine efficacy.

Methods

(1) Case Definition - This approach assumes that measles is sufficiently distinctive to be recognized as measles in areas of high endemicity by the mothers of the children surveyed. Since the recall period is two years or less, this is considered sufficiently recent for the mother to recall disease accurately. Any rash illness diagnosed as measles by the mother is accepted as a case of measles. In Abidjan, in the Ivory Coast where this method was developed, such histories were shown to be reliable.20

(2) Case Ascertainment - All cases of measles reported by maternal history are of interest. Determining the month of age at the time of disease in those with positive histories requires careful questioning. If exact month of age cannot be elicited, a determination of whether or not disease occurred before 12 months of age (or before 15 months if 12-14 month old vaccinees are also sampled) is the minimum information required. All cases which occurred among these two year old children when they were between 12 months and 2 years are included in this study.

(3) Vaccination Status Determination - Two year old children vaccinated between 9-11 months of age constitute the principal vaccinated group included in this survey. Children vaccinated prior to this age are excluded from the analysis. Children vaccinated after this age between 12-14 months or older should also be excluded from the analysis unless they are a specific target group included in the survey for vaccine efficacy purposes.

* If an estimate of vaccination coverage is desired for 2 year old children, the first seven such children encountered in each cluster should be used, regardless of their vaccination status or age at vaccination. Some of these children can be included in the group of fourteen children being sought for a vaccine efficacy if their vaccination status or age at vaccination qualify them for inclusion. In this manner, estimates of vaccine coverage and vaccine efficacy can be obtained simultaneously using the familiar coverage survey sampling methods.

** If vaccinees between 12-14 months are included, their disease experience would be calculated starting as of 15 rather than 12 months.
(4) Prior Disease - Some children vaccinated at 9-11 months will have a history of measles prior to 12 months of age either before or after their vaccination. Some unvaccinated children will also have a history of measles prior to 12 months. All vaccinated and unvaccinated children with such histories should be excluded from the numerators, but not from the denominators of the appropriate rates calculated. Such a procedure will insure that a minimally biased estimate is obtained. It assumes only that children with a history of measles disease are as likely to be vaccinated as children without a history.

Analyses

(1) Persons with uncertain vaccination or disease histories are excluded.

(2) Fill in the data for Table 8b using the criteria described in 1-4 above and calculate vaccine efficacy.

3.6 Case-Control Studies

Case-control studies can be most useful when personal immunization records are generally not available but some other source such as clinic records from 1 or more clinics can be obtained. Intensive efforts can be used to determine vaccination status of a limited number of cases and noncases (controls) instead of concentrating on the whole population at risk.

The traditional vaccine efficacy equation cannot be used in case control studies. Cases in a case-control study represent one sampling fraction of all cases and the controls represent a different sampling fraction of the non-ill population. In general, those sampling fractions are unknown so that the total population of vaccinated and total population of unvaccinated cannot be calculated, thus preventing calculations of attack rates. The vaccine efficacy equation can be expressed in the form of relative risk (RR) (Table 6). In case-control studies the RR can be approximated by the odds ratio and vaccine efficacy can be calculated. By knowing the vaccination histories of cases and of noncases (controls), the odds ratio and hence, vaccine efficacy can be estimated.

Case-control studies have not been thoroughly evaluated in the measurement of vaccine efficacy. Limited studies of measles and rubella outbreaks suggest that results do approximate vaccine efficacy accurately. With further use, refinements may be made. In addition, case-control sets can be added together from several outbreaks to increase the numbers and the power of the calculations.

Methods

(1) Case definition - same as in outbreak investigations

(2) Case ascertainment - same as in outbreak investigations, although all cases need not be detected

(3) Vaccination status determination - only necessary for selected cases and selected controls (noncases). Otherwise same as in outbreak investigation.

(4) Control selection - One control per case should be selected and matched to a case for age, sex and residence. The controls should be well at the time of the investigation. Preferably, controls should be selected at random from surrounding houses in a village. Potential controls should continue to be identified until one

* The odds ratio is the ratio of the odds a case is vaccinated divided by the odds a control is vaccinated. See Tables 9 and 14 for calculation of odds ratio.
is found which meets the matching criteria. Case age should be nine through 35 months. Controls should be between 9 months and 35 months of age, and within 2 months of the age of cases. Close matching on age is most important for cases \( \leq 18 \) months of age. Records of each case control pair should be kept.

(5) **Prior disease** - cases and controls with histories of prior disease should not be excluded from the calculation.²⁶ (see Appendix).

**Analyses**

(1) Case and control pairs in which either one has unknown vaccination status should be analyzed separately.

(2) Table 9 shows an analysis of the matched case control pairs. Instead of individuals, each cell contains pairs. For example, \( j \) represents the number of pairs in which both the case and control were vaccinated while \( l \) represents the number of pairs where the control was unvaccinated and the case was vaccinated. The sum of \( j + k + l + m \) is equal to \( 1/2 \) the participants. The odds ratio equals \( 1 \) divided by \( k \).

The odds ratio may not approximate the relative risk when attack rates are high. When the attack rates in the vaccinated are greater than 10 percent, the vaccine efficacy will be erroneously high. In most instances attack rates in the vaccinated will be \( \leq 10 \) percent so this error will not be important (for more detail see Appendix, Section II B).

4. **Discussion**

Clinical vaccine efficacy can be determined by a variety of means including screening, outbreak investigations, secondary attack rates in families or clusters, vaccine coverage assessments and case control studies. They all offer a means of monitoring vaccine programmes under conditions of day to day vaccine use.

The different techniques for measuring efficacy are summarized in Table 10. The screening technique is the most useful rapid means of determining whether there is a problem with vaccine. All that is needed is a reliable estimate of the proportion of cases occurring in vaccinated individuals and an estimate of the vaccine coverage in the population at risk. If estimated efficacy is within expected limits, more detailed studies are not warranted. However, if results suggest low efficacy, more rigorous methods are needed to more accurately assess efficacy.

Of the more accurate methods available, outbreak investigation offers the simplest means of measuring vaccine efficacy and is the preferred technique if the situation permits. The biases inherent to the method can be minimized, particularly if the disease incidence rate is high during the outbreak and accurate records exist. A low measles incidence rate prior to the outbreak is important, so the age group chosen should be narrow (e.g. 9-35 months) and rural areas where measles is less likely to be endemic are best used. In large populations, underlying immunization levels prior to the outbreak can be estimated using the same cluster sampling method used in coverage assessments.

Calculation of secondary attack rates in families is also an excellent and accurate means of measuring vaccine efficacy and is an acceptable alternative to the outbreak investigation. Secondary attack rates in clusters are also probably useful although further evaluation is needed.

Vaccine coverage methods in endemic areas are best suited to urban areas where the measles incidence rate is high after age 11 months and low before 12 months and maternal histories of disease are thought to be accurate. This technique has not been used widely and refinements may take place with greater experience.
Case-control studies are best suited to areas where reliable personal immunization records may be difficult to find but other information, such as clinic records may be available. In this way, intensive efforts can be applied to determining vaccination status on the cases and a few selected controls instead of on the entire population at risk.

Regardless of the method chosen, it should be remembered that no epidemiologic method is perfect because none can exactly duplicate the experimental conditions of a prospective randomized clinical trial. The most accurate results will be obtained when biases are anticipated and corrective measures taken when possible. The Appendix summarizes many of the issues involved.

The most important reason to perform clinical vaccine efficacy determinations is to assess whether the observed pattern of illness is consistent with proper use of a highly effective vaccine. The results can also be used to make changes in the programme if necessary. A lower than expected efficacy should lead to a careful evaluation of the vaccine management and vaccine administration technique. If those systems are unsatisfactory, corrective measures should be taken. If satisfactory, other explanations should be sought, such as a transient problem that might have existed in a single lot of vaccine on a single shipment.

The components of a vaccine efficacy evaluation, - case definition, case ascertainment, and vaccination status determination - apply to all vaccines. Case definitions will vary depending on the disease and some will require more laboratory support than others. Similarly, case ascertainment should generally be population based rather than clinic or hospital based. Diseases with high proportions of infections that are subclinical, such as polio, can be evaluated solely on clinical illness rather than total infections. Assuming that the proportion of infections that are subclinical is the same in the unvaccinated and in vaccine failures, vaccine efficacy will be accurate measuring clinical illness alone. As the overall infection rate increases, however, the odds ratio ceases to be a good measure of the relative risk. Consequently, case-control methodology is probably inappropriate when rates of total infection are high.

The general methodology can be applied to vaccines requiring multiple as well as single doses. The efficacy of each dose can be calculated using the attack rate in the unvaccinated, ARU (no prior doses) compared in successive calculations to the attack rates in recipients of 1 prior dose, 2 prior doses, 3 prior doses, etc.

Clinical vaccine efficacy studies provide useful information. They can assure health care providers that vaccine is highly effective and can help in evaluating policy decisions and determining trouble spots in vaccine programmes. By knowing how to measure clinical vaccine efficacy, coordinators of routine immunization programmes have a powerful tool to evaluate their programmes and ensure confidence in vaccination.
Appendix

I. Potential Problems in Calculating Vaccine Efficacy

Each component of the vaccine efficacy evaluation is potentially associated with problems that can lead to substantial biases in the estimate of vaccine efficacy. Awareness of these potential biases can lead to corrective measures to keep them to a minimum. In general, if a method cannot be totally corrected, the techniques recommended will tend to slightly underestimate vaccine efficacy. On occasion this may prompt unneeded intensive investigations of vaccine handling practices and other aspects of the immunization programme. However, it is better to occasionally investigate unnecessarily rather than to fail to investigate because of falsely high vaccine efficacy when an intensive examination may be important.

A. Case Definition

A case definition that is a poor predictor of the disease under study will lead to a biased estimate of vaccine efficacy because background illnesses common to both vaccinees and nonvaccinees will likely be classified as cases causing the attack rates in the vaccinated and unvaccinated to appear more similar (Table 11, 1a). Then, the calculated efficacy will probably be lower than the true efficacy.

A detailed scheme for classifying measles cases by stage of disease and 14 clinical signs and symptoms has been useful in Kenya. However, it requires extensive questionnaires and examinations which are not usually practical in most settings. The measles case definition in Table 2 is much easier to apply and is probably sufficiently specific, particularly in outbreaks for calculation of vaccine efficacy.

Suspected cases of measles should be classified as cases or noncases independent of their history of vaccination. Taking vaccination status into account when deciding whether a child with rash illness has measles will lead to a falsely high vaccine efficacy estimate because patients meeting clinical criteria who have a past history of vaccine are likely to be inappropriately classified as noncases (Table 11, 1b). In contrast, unvaccinated children with illnesses may be inappropriately classified as cases resulting in a falsely high ARU, and a falsely high vaccine efficacy estimate.

B. Case Ascertainment

Clinic or medical record based surveillance systems may give inaccurate estimates of the total number of cases occurring since not all cases will seek medical attention. Unvaccinated persons in general, including those with measles disease, may be less likely to receive medical care than vaccinated persons. This would result in finding a disproportionately low attack rate in the unvaccinated and a falsely low vaccine efficacy (Table 11, 2a). Population based surveillance surveys in which all cases are searched for independent of vaccination status will prevent selective reporting of vaccinated cases. As long as it is similar for both vaccinees and nonvaccinees, underreporting of cases will not affect vaccine efficacy estimates but may limit their precision.

C. Vaccination Status Determination

Persons with unknown vaccination status should be categorized separately and not included in the calculation of vaccine efficacy. If the unknowns were not categorized separately but were classified as unvaccinated, many may be vaccinees wrongly classified because they lacked records (Table 11, 3a). The vaccine efficacy would falsely decrease. Even if the unknowns were wrongly classified as vaccinated, the vaccine efficacy would decrease because the attack rate in the unknowns, some of whom are presumably unvaccinated, is probably between ARV and ARU (Table 11, 3b). Adding the unknowns to the vaccinated will probably increase ARV; adding the unknowns to the unvaccinated will decrease ARU.
VE studies are best not conducted where the proportion of unknowns is high (Table 11, 3c).* The calculated vaccine efficacy may be biased in either direction since the true ARV and ARU cannot be determined with accuracy.

D. Comparability of exposure

The fact that vaccinees and nonvaccinees will generally come from different subpopulations implies that exposure to measles is unlikely ever to be equal in the two groups (Table 11,4a). Vaccinees may have a lower risk of exposure. Under these conditions, attack rates in the vaccinated population will probably be falsely low resulting in a falsely high vaccine efficacy. The error will be less the higher the overall attack rate since high attack rates imply that most of the population, regardless of vaccination status have been adequately exposed.

E. Prior disease**

a. Outbreak investigations and secondary attack rates in families and clusters

Prior disease in vaccinated and unvaccinated populations can potentially confound the analyses and can be minimized if prior disease incidence is low. In most instances using outbreak and secondary attack rate techniques there is little effect of prior disease on the calculation provided the assumptions below are valid. If it is assumed that prior to the outbreak: (1) Vaccinees and nonvaccinees had similar likelihood of exposure to disease and (2) that persons who had disease prior to the outbreak had similar probabilities of obtaining vaccination as persons without disease prior to the outbreak, then occurrence of disease before the outbreak in the community will not influence the calculation of vaccine efficacy.

The lower the incidence rate of disease in a given area prior to an outbreak or other investigation the smaller the potential errors in vaccine efficacy. Corrections of the calculated vaccine efficacy because of prior disease are generally unnecessary because the error is usually small. Prior histories may not be accurate since they are not easily subject to clinical verification using the case definition.

b. Coverage survey methods in endemic areas

Disease prior to 12 months among children surveyed for vaccine efficacy purposes can have the same effects as disease prior to an outbreak among children investigated during an outbreak for similar purposes. Conceptionally the two situations are similar except that in a survey, the children are observed as of a given age rather than as of a fixed point in time. Excluding all cases which occur prior to the period of observation (i.e. 12 months) will not bias the estimate of vaccine efficacy providing the conditions described in a. above are met. When disease incidence prior to the period of observation is low as it would be in most areas among children under 1 year of age, then any potential biases will be minimal. If too few cases occur after age 1 because of high incidence at early ages, then the coverage survey methods should not be used.

II. PROBLEMS WITH CASE-CONTROL STUDIES

The problems with case definition, case ascertainment, vaccination status determination and prior disease, inherent to other methods of vaccine efficacy estimation, also apply to case-control studies.

* If vaccination records may be available but difficult to find, case-control studies may be appropriate.

** Applicable to all methods except case control.
A. Prior Disease

Prior disease poses special problems for case-control studies. Assuming such histories are accurate, few if any cases will have prior histories of measles disease. However, substantial numbers of controls may have such histories, particularly, if measles was highly endemic in the investigation area.

Including persons with prior disease as controls will tend to decrease vaccine efficacy if persons with disease were less likely to obtain vaccination than persons without disease. In general, this error will be small particularly if prior disease incidence was low. Therefore prior disease in both cases and controls should be ignored.24

B. High attack rates

A major problem of case-control studies of vaccine efficacy is that when disease is common in the vaccinated (e.g. ARV > 10%), the odds ratio fails to be a good estimate of relative risk resulting in an inaccurate measure of vaccine efficacy. The nature of the error is such that vaccine efficacy by case-control study will always be higher than the vaccine efficacy by the more traditional cohort study, used in outbreak investigations.

The error in vaccine efficacy measured by case-control studies may be expressed as a proportion of the true vaccine efficacy measured in cohort studies. The proportional error is defined as the difference in vaccine efficacies divided by the vaccine efficacy by cohort study (Table 12). Algebraically, the proportional error is a function of the attack rate among the vaccinated (ARV) and is unrelated to the overall attack rate of measles or the attack rate among the unvaccinated (Table 13)23. For example, when ARV = 10 percent, the proportional error in the calculated VE will be 11 percent. If the true vaccine efficacy was 80 percent, the calculated vaccine efficacy would be 89 percent. The higher the ARV, the greater the error.

In practice, ARV is usually unknown in a case-control study; however, if it is suspected to be low (≤10%), the estimate will be close enough to the true efficacy. If ARV is suspected to be high, case-control methodology should either not be used or should be corrected by auxiliary information.

The data for the case-control study were collected by matching controls to cases. However, to correct the odds ratio, the data must first be analyzed in an unmatched fashion to assure that the controls are representative of the general population of the study area. Table 14 shows how to calculate the odds ratio when cases and controls are analyzed separately instead of in pairs. In this analysis, \( a + b + c + d \) equals the total number of study participants. If the odds ratio calculated from Table 9 is similar to the odds ratio in Table 14, correction can proceed. If not, the calculated vaccine efficacy cannot be corrected and should be presented with the knowledge that it is higher than the true efficacy.

If the overall attack rate in the community is known, the odds ratio can be corrected using an adaptation of Bayes theorem.13 ARU and ARV can be calculated using the formulas in Table 15. Once ARU and ARV are determined, VE can be calculated using the formula on page 3.

To collect the auxiliary information, workers can go door to door in an affected village, determining the entire population at risk and the total number of cases, which are needed for use of the formulas. Vaccination status need only be determined for the cases and the selected controls.

III. CORRECTING FOR VACCINATION PROGRAMMES THAT OCCUR DURING OUTBREAKS

When outbreak control vaccination programmes reach a substantial proportion of the population so that initially unvaccinated persons become vaccinees or a substantial proportion of cases to be studied occurs after the beginning of the programme, vaccine efficacy can be corrected to take the effects of the control programme into account. In most circumstances, the error is so small that it is not important. There are 3 possible approaches described below for correction, if it is desired: only consider cases up to the beginning of the vaccination programme, calculate person weeks of exposure, or construct life tables.7,10,11
A. Limiting the investigation

In this method, all cases with onset up to the first day of the control programme are included and classified according to prior vaccination status. Cases occurring after the vaccination programme are considered noncases. Noncases are classified according to vaccination status prior to the control programme. Vaccine efficacy is calculated using the formula on page 3.

B. Other methods

More details on the person weeks and life tables methods can be obtained from the cited references or from the Division of Immunization, Centers for Disease Control, Atlanta, Georgia 30333, U.S.A.

IV. CONFIDENCE INTERVALS FOR VACCINE EFFICACY

Confidence intervals for vaccine efficacy determinations are shown in Table 16. The formulas in Table 16A apply to outbreak investigations and secondary attack rates in households or clusters. Approximate confidence intervals can also be obtained for efficacy using cluster samples.

Formulas for approximate confidence intervals using supplementary cases and cluster samples in outbreaks can be obtained from Hogue et al. under case exposure studies. The same reference can be used for confidence intervals for case control studies supplemented by Bayes Theorem.

V. NUMBER OF PERSONS NEEDED

Frequently vaccine efficacy determinations are made because of specific concerns with the high proportions of cases that are vaccine failures in a specific locality at a specific time. Under those circumstances, efficacy must be estimated based on the population at hand and calculation of sample sizes needed is unnecessary. The investigator must make do with the population available.

However in certain instances, efficacy evaluations can be planned so that a desired level of precision is obtainable and appropriate sample sizes can be estimated. The formula in Table 16A for the lower 95% confidence limit can be used to estimate approximate sample sizes. Table 17 illustrates sample sizes required under different sets of attack rates and where the anticipated vaccine efficacy is 90% (i.e. RR= 0.1). The lower the attack rates in the unvaccinated and vaccinated, the larger the sample size needed to obtain an equivalent level of precision. For example if ARU = 50% and ARV = 5%, a sample of 200 in each group will give a lower confidence limit of 81%, 9 percentage points from the true efficacy of 90%. If the attack rates are only half as high, a sample size of 400 in each group is required for the same level of precision. The lower the true vaccine efficacy the more the lower bound will differ from the efficacy given a fixed sample size.

In general, a lower bound within 15 percentage points of the observed efficacy should be a reasonable goal. To estimate sample size needed, Table 17 can be used. Approximate attack rates in unvaccinated and vaccinated must be estimated in advance. Knowing these attack rates and assuming true efficacy is 90%, the minimum sample size n in each group can be determined. The formula in Table 16A for the lower limit can be used on a trial and error basis if attack rates in the vaccinated and unvaccinated are assumed to be substantially less than 12.5% and 1.25% respectively. Simply use the projected attack rates and different sample sizes (different n's) to determine how far from 90% the lower bound of the estimate may be.
Reference


9. Expanded Programme on Immunization, WHO EPI/GEN/83/4 Provisional Guidelines for the diagnosis and classification of the EPI Target diseases for primary health care, surveillance and special studies.


Table 1

Proportion of susceptibles with a history of vaccination at differing levels of coverage in a population of 1000 assuming vaccine efficacy of 90%

<table>
<thead>
<tr>
<th>Vaccine coverage (percent)</th>
<th>20%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>No. vaccinated</td>
<td>200</td>
<td>500</td>
<td>900</td>
</tr>
<tr>
<td>No. protected (90%)*</td>
<td>180</td>
<td>450</td>
<td>810</td>
</tr>
<tr>
<td>No. vaccinated but still susceptible (10%)**</td>
<td>20</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>No. unvaccinated</td>
<td>800</td>
<td>500</td>
<td>100</td>
</tr>
<tr>
<td>Total susceptibles</td>
<td>820</td>
<td>550</td>
<td>190</td>
</tr>
</tbody>
</table>

Proportion of susceptibles with a history of vaccination

- 20/820 = 2.4%
- 50/550 = 9.1%
- 90/190 = 47.4%

* estimate assuming 90% efficacy
**vaccine failures
Table 2

Clinical case definition for measles

1) Generalized rash of 3 or more days duration
2) Fever ($\geq 101$ degrees Fahrenheit (38.3C), if measured)
3) Any one of the following:
   a) Cough
   b) Coryza
   c) Conjunctivitis

Cases must meet all 3 criteria to be classified as measles
Table 3

Relationship of Proportion of cases occurring in vaccinated individuals, vaccine coverage, and vaccine efficacy

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

PCV = proportion of cases occurring in vaccinated individuals

PPV = proportion of the population vaccinated

VE = vaccine efficacy
Table 4

Guidelines for selecting an outbreak setting to measure vaccine efficacy

1. Absence of substantial prior disease activity in the studied age group.
2. Population containing both vaccinees and nonvaccinees.
3. Adequate population in the age group to be studied.
4. High overall attack rate - for measles, generally in excess of 5% in chosen age group.
5. Good vaccination records available to differentiate nonvaccinees from vaccinees.
### Table 5

Data to be collected in outbreak investigation of vaccine efficacy

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Vaccine Status</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccinated</td>
<td>Unvaccinated</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Ill</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td></td>
</tr>
</tbody>
</table>

\[
VE = \frac{ARU_{-ARV}}{ARU} \times 100
\]

\[
VE = \frac{b - a}{b + e \cdot a + d} \times \frac{b}{b + e} \times 100
\]
Table 6

Vaccine efficacy in terms of relative risk

\[ \text{VE} = \frac{\text{ARU} - \text{ARV}}{\text{ARU}} \times 100 \]

\[ = 1 - \frac{\text{ARV}}{\text{ARU}} \times 100 \]

\[ = (1 - \text{RR}) \times 100 \]

**VE** = vaccine efficacy  
**ARU** = attack rate in the unvaccinated  
**ARV** = attack rate in the vaccinated  
**RR** = relative risk
Table 7
Calculation of vaccine efficacy using a coverage survey and supplemental information on cases

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Vaccine Status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill from coverage survey</td>
<td>a</td>
<td>b</td>
<td>c</td>
</tr>
<tr>
<td>Total in coverage survey</td>
<td>d</td>
<td>e</td>
<td>f</td>
</tr>
<tr>
<td>Other ill from population surveillance</td>
<td>g</td>
<td>h</td>
<td>i</td>
</tr>
<tr>
<td>Total ill</td>
<td>a + g</td>
<td>b + h</td>
<td>c + i</td>
</tr>
</tbody>
</table>

\[
VE = (1 - RR) \times 100 \\
(1 - RR) \times 100 = \frac{1 - (\frac{a + g}{b + h})}{d} \times 100
\]
Table 8
Coverage surveys in endemic areas

a. Sampling
1. 30 clusters of children 24-35 months
2. 7 children in each cluster, never vaccinated
3. 7 children in each cluster, vaccinated between 9 and 11 months of age

b. Calculation of attack rates

\[
\text{ARU} = \frac{\text{# cases after age 11 months++ in never vaccinated}}{\text{Total number of never vaccinated}}
\]

\[
\text{ARV} = \frac{\text{# cases after age 11 months in vaccinated}}{\text{Total number of vaccinated}}
\]

\[
\text{VE(\%)} = \frac{(\text{ARU} - \text{ARV}) \times 100}{\text{ARU}}
\]

+ or any other appropriate age group desired
++ if age of vaccine group changes, this should be adjusted (see text)
Table 9

Matched pair analysis of vaccine efficacy in a case control study

**Controls**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>j</td>
<td>l</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>k</td>
<td>m</td>
</tr>
</tbody>
</table>

RR \sim odds ratio

\[ \text{Odds Ratio} = \frac{l}{k} \]

\[ \text{VE} \% = (1 - \frac{l}{k}) \times 100 = (1 - \frac{j}{k}) \times 100 \]
Table 10
Summary of Techniques for measuring vaccine efficacy and major advantages and disadvantages

<table>
<thead>
<tr>
<th>Technique</th>
<th>Comments</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Screening</td>
<td>1. If estimate &gt;80%, no further investigations are needed</td>
<td>1. Rapid</td>
<td>1. Estimates may be inaccurate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Requires few resources</td>
<td>if proportions of vaccinated and of vaccinated cases are inaccurate</td>
</tr>
<tr>
<td></td>
<td>2. If estimate &lt;80%, more accurate techniques needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Outbreak</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Total census</td>
<td>1. The preferred technique, situation permitting</td>
<td>1. Most frequently evaluated</td>
<td>1. Requires substantially more resources than screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>technique</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Indicated during outbreaks in small populations where immunization and disease status of all individuals can be assessed</td>
<td>2. Allows collection of clinical information on cases for more accurate diagnosis</td>
<td>2. Exposure of vaccinees and nonvaccinees to disease may not be absolutely equivalent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Biases can be kept to a minimum using a population based surveillance survey in an area with high attack rates and low incidence of disease before the outbreak</td>
<td>3. With high attack rates, exposure of vaccinees and nonvaccinees to disease becomes more comparable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. One of the easiest of the more accurate methods to do</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 10 - continued

<table>
<thead>
<tr>
<th>Technique</th>
<th>Comments</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Cluster samples</td>
<td>1. Most indicated during large outbreaks in large populations when determination of vaccination and disease status on all individuals is not feasible. Otherwise same as 2a</td>
<td>1. Same as 2a</td>
<td>1. Same as 2a</td>
</tr>
<tr>
<td>3. Secondary attack rates in families</td>
<td>2. Because samples are taken rather than a census, there may be some loss in precision of the estimate</td>
<td>2. Potentially can add the results of many different family investigations in different areas together allowing more accurate estimates</td>
<td>2. Only a small number of children will be in the right age group in a given family meaning many families must be visited</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Technique</th>
<th>Comments</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Vaccine efficacy using coverage survey methods in endemic areas</td>
<td>2. Most indicated when resources for family investigations are limited. Because the numbers of persons exposed in a cluster are greater than in a family, fewer visits are needed</td>
<td>2. Assuming exposure within clusters is comparable from cluster to cluster, can add the results of multiple clusters together</td>
<td>2. Needs further evaluation of uniformity of exposure within clusters</td>
</tr>
<tr>
<td>6. Case-control studies</td>
<td>1. The vaccination histories of cases and matched non-cases are compared. Vaccine efficacy is calculated by using the odds ratio to approximate relative risk</td>
<td>1. Allows maximal resources to be placed in finding vaccination status on cases and a few matched controls instead of the entire population</td>
<td>1. Will give a falsely high vaccine efficacy if attack rates in the vaccinated are high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Requires similar resources as in a coverage survey</td>
<td>2. If coverage assessments in 12-23 month olds are desired will require increasing the number of children per cluster</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Requires only minor changes of a technique with which most EPI personnel are familiar</td>
<td>1. Relies on parental diagnosis and recall of disease rather than clinical information</td>
</tr>
<tr>
<td></td>
<td>1. Modification of routine coverage assessment using older age groups, 24-35 months and adding questions on disease history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 11

Effects of different methodologic problems on estimation of vaccine efficacy

<table>
<thead>
<tr>
<th>Element</th>
<th>Problem</th>
<th>Likely effects on ARU⁺</th>
<th>ARV⁺</th>
<th>VE⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. case definition</td>
<td>a. non-specific definition; background illnesses are classified as measles</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>b. cases are classified with knowledge of vaccination status</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>2. case ascertainment</td>
<td>a. clinic based reporting system</td>
<td>↓</td>
<td>little change</td>
<td>↓</td>
</tr>
<tr>
<td>3. vaccination status</td>
<td>a. poor record system; unknowns classified as unvaccinated</td>
<td>↓</td>
<td>no change</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>b. poor record system; unknowns++ classified as vaccinated</td>
<td>↑</td>
<td>↑ or ↓</td>
<td>↓ or ↓</td>
</tr>
<tr>
<td></td>
<td>c. Many unknowns+ excluded</td>
<td>↑ cr ↓</td>
<td>↑ or ↓</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>4. comparability</td>
<td>a. unvaccinated more likely to be exposed to measles than vaccinated</td>
<td>↑</td>
<td>no change</td>
<td>↑</td>
</tr>
<tr>
<td>of exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁺ ARU = attack rate in the unvaccinated
ARV = attack rate in the vaccinated
VE = vaccine efficacy

++ assumes attack rate in unknowns is intermediate between unvaccinated and vaccinated because some will probably be vaccinated and some unvaccinated.
Table 12

Proportional error in measurement of vaccine efficacy by case control methods versus cohort methods+

Proportional error (%) = \( \frac{VE_{CC} - VE_{C}}{VE_C} \times 100 \)

\( VE_{CC} = \) vaccine efficacy, case control
\( VE_{C} = \) vaccine efficacy, cohort

+ Assumes vaccine efficacy by cohort method is the true vaccine efficacy
Table 13

Relationship of the proportional error to the attack rate in the vaccinated population (ARV)

Proportional error (PE) (%) = \frac{ARV}{1-ARV} \times 100

For example

If ARV = 5%, then PE = 5.3%
  = 10%   = 11.1%
  = 20%   = 25.0%
<table>
<thead>
<tr>
<th></th>
<th>cases</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>vaccinated</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>unvaccinated</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

RR \(\geq\) odds ratio

odds ratio = \(\frac{ad}{bc}\)

VE(%) = \((1 - RR) \times 100\)

= \(1 - \frac{ad}{bc} \times 100\)
Table 15

Calculation of the attack rates in the unvaccinated (ARU) and the attack rate in the vaccinated (ARV) using a modification of Bayes Theorem

\[
\text{ARU} = \frac{\text{# unvacc. cases} \times \text{# cases}}{\text{total pop.}} \times \frac{\text{# cases}}{\text{total pop.}} \\
\]

\[
\frac{\text{# unvacc. cases} \times \text{# cases}}{\text{total pop.}} + \frac{\text{# unvacc. controls} \times \text{total well}}{\text{total pop.}} \\
\]

\[
\text{ARV} = \frac{\text{# vaccinated cases} \times \text{# cases}}{\text{total pop.}} \times \frac{\text{# cases}}{\text{total pop.}} \\
\]

\[
\frac{\text{vaccinated cases} \times \text{# cases}}{\text{total pop.}} + \frac{\text{vaccinated controls} \times \text{total well}}{\text{total pop.}} \\
\]
I. Calculation of 95% Confidence limits in Cohort Studies

Table 16

95% confidence intervals for vaccine efficacy estimates

A. All studies except case control and outbreak investigations using cluster samples and supplementary cases.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Non cases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>vaccinated</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>unvaccinated</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>total</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

\[ RR = \frac{a}{a+b} \]

\[ VE(\%) = (1 - RR) \times 100 \]

Where RR = relative risk

To get 95% confidence intervals, the following formulas are used:

(1) for lower limit of VE

\[ \text{upper limit of relative risk} = RR_u = (RR) \exp \left( + 1.96 \sqrt{\frac{1 - (\frac{a}{a+b})}{a}} + \frac{1 - (\frac{c}{c+d})}{c} \right) \]

\[ \text{lower limit of VE} = (1 - RR_u) \times 100 \]

(2) for upper limit of VE

\[ \text{lower limit of relative risk} = RR_L = (RR)\exp \left( - 1.96 \sqrt{\frac{1 - (\frac{a}{a+b})}{a}} + \frac{1 - (\frac{c}{c+d})}{c} \right) \]

\[ \text{upper limit of VE} = (1 - RR_L) \times 100 \]
Example of calculation of 95% Confidence limits for Vaccine Efficacy using a cohort method.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Non-cases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>100</td>
<td>900</td>
<td>1000</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>500</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>600</td>
<td>1400</td>
<td>2000</td>
</tr>
</tbody>
</table>

\[ VE(\%) = 1 - \left( \frac{100}{1000} \right) \times 100 \]

\[ = 80\% \]

\[ RR = \left( \frac{100}{1000} \right) = 0.2 \]

For lower limit of vaccine efficacy:

upper limit of RR = RR_u = 0.2 \exp \left( 1.96 \sqrt{1 - \left( \frac{100}{1000} \right)} + 1 - \left( \frac{500}{1000} \right) \right)

\[ RR_u = 0.2 \exp 1.96 \sqrt{0.01} \]

\[ = 0.2 \exp (1.96) (0.1) \]

\[ = 0.2 (1.2165) \]

\[ = 0.2433 \]

lower limit of VE = (1 - RR_u) \times 100

\[ = 75.7\% \]

The upper limit of vaccine efficacy can be calculated in an analogous manner.
II. Calculation of 95% Confidence limits in matched case control studies

Because of the confusion in the letters and numbers used in Table 16B of EPI/GEN/84/10, the formula for confidence limits has been rewritten using different letters. A typographical error in the calculation of "b" has been corrected. The formula is:

B. Case-control studies, matched pair analysis

<table>
<thead>
<tr>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>vaccinated</td>
</tr>
<tr>
<td>vaccinated</td>
</tr>
<tr>
<td>unvaccinated</td>
</tr>
</tbody>
</table>

Cases

\[
\begin{align*}
\text{vaccinated} & : j & p \\
\text{unvaccinated} & : k & q \\
\end{align*}
\]

Relative Risk = \( RR \approx \) odds ratio = \( \frac{p}{k} \)

upper limit of RR = \( RR_U = \frac{P_u}{1 - P_u} \)

and lower limit of VE = \((1 - RR_U) \times 100 \)

where \( P_u = \frac{b + b^2 - 4ac}{2a} \)

\[
\begin{align*}
a &= (p+k) \times (p+k+3.84) \\
b &= (p+k) \times (2(p+1)+3.84) \\
c &= (p+1)^2 \\
\end{align*}
\]

The lower limit of RR = \( RR_L = \frac{P_l}{1 - P_l} \)

and the lower limit of VE = \((1 - RR_L) \times 100 \)

where \( P_l = \frac{d - d^2 - 4ae}{2a} \)

\[
\begin{align*}
a &= (p+k) \times (p+k+3.84) \\
d &= (p+k) \times (2(p-1)+3.84) \\
e &= (p-1)^2 \\
\end{align*}
\]
Example of Calculation of 95% Confidence limits for vaccine efficacy using matched pair case-control methodology

Assume that there are 100 cases and 100 controls for a total of 200 persons but a total of 100 pairs that distribute themselves as follows:

<table>
<thead>
<tr>
<th>Cases</th>
<th>Vaccinated</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

Then the relative risk (RR) = p/k = 10/40 = 0.25
Vaccine efficacy = (1 - RR) x 100 = (1 - 0.25) x 100 = 75%

To calculate the lower limit of vaccine efficacy, we must calculate Pu and to calculate Pu we must first calculate a, b and c.

\[
a = (p + k) \times (p + k + 3.84)
= (10 + 40) \times (10 + 40 + 3.84)
= 2692
\]

\[
b = (p + k) \times (2(p + 1) + 3.84)
= (10 + 40) \times (2(10 + 1) + 3.84)
= 1292
\]

\[
c = (p + 1)^2
= (10 + 1)^2
= 121
\]
Therefore $P_u = \frac{b + \sqrt{b^2 - 4ac}}{2a}$

$$= \frac{1292 + \sqrt{(1292)^2 - (4)(2692)(121)}}{(2)(2692)}$$

$$= \frac{1292 + 605.25697}{5384}$$

$$= .352387$$

Upper limit of $RR = RR_u = \frac{Pu}{1-Pu}$

$$= \frac{0.352387}{1 - 0.352387}$$

$$= 0.544132$$

$VE_u = (1 - RR_u) \times 100$

$$= (1 - 0.544132) \times 100$$

$$= 45.6\%$$

The upper limit of vaccine efficacy can be calculated as follows:

$$P_L = \frac{d - \sqrt{d^2 - 4ae}}{2a}$$

$$d = 50 \times (2(9) + 3.84) = 1092$$

$$e = (p - 1)^2 = (10 - 1)^2 = 81$$

$$P_L = \frac{1092 - (1092)^2 - 4(2692)(81)}{5384}$$

$$= .097713$$

$$RR_L = \frac{.097713}{1 - .097713} = .108295$$

Therefore,

Upper limit of $VE = VE_u = (1 - RR_L) \times 100$

$$= (1 - 0.108295) \times 100$$

$$= 89.2\%$$
Table 17
Sample size estimations for different levels of precision and attack rates during an outbreak investigation*

<table>
<thead>
<tr>
<th>Minimum Sample Size in each group</th>
<th>ARU</th>
<th>ARV</th>
<th>Lower bound of the 95% CI for vaccine efficacy**</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50%</td>
<td>5%</td>
<td>76%</td>
</tr>
<tr>
<td>200</td>
<td>50%</td>
<td>5%</td>
<td>81%</td>
</tr>
<tr>
<td>100</td>
<td>25%</td>
<td>2.5%</td>
<td>64%</td>
</tr>
<tr>
<td>200</td>
<td>25%</td>
<td>2.5%</td>
<td>75%</td>
</tr>
<tr>
<td>300</td>
<td>25%</td>
<td>2.5%</td>
<td>79%</td>
</tr>
<tr>
<td>400</td>
<td>25%</td>
<td>2.5%</td>
<td>81%</td>
</tr>
<tr>
<td>200</td>
<td>12.5%</td>
<td>1.25%</td>
<td>64%</td>
</tr>
<tr>
<td>400</td>
<td>12.5%</td>
<td>1.25%</td>
<td>75%</td>
</tr>
<tr>
<td>800</td>
<td>12.5%</td>
<td>1.25%</td>
<td>81%</td>
</tr>
</tbody>
</table>

* True vaccine efficacy = 90% (i.e. RR = 0.1)
** Assumes upper bound maximum is 100%. Therefore since this is within 10% of the true estimate, only lower bound is important.