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EXPANDED PROGRAMME ON IMMUNIZATION Field evaluation of vaccine efficacy

The ability of a vaccine to prevent disease effectively depends on its potency and proper administration to an individual capable of responding. The success of immunization performed under field conditions may be assessed by measuring protection against clinical disease by epidemiological means. This epidemiological approach has the merit of not requiring laboratory support. It can be very useful, particularly when doubt is cast on the effectiveness of the immunization programme because of the occurrence of disease in immunized individuals. This problem becomes increasingly prominent as immunization coverage rises, since the proportion of cases of illness occurring in immunized persons will increase even with high vaccine efficacy.¹ This article describes 2 epidemiological techniques available for measuring vaccine efficacy: screening and outbreak investigations. 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, they may be applicable to other vaccines as well. A more comprehensive document (EPI/GEN/94/10 Rev. 1) giving details of these techniques as well as others, is available through the Expanded Programme on Immunization, World Health Organization, Geneva.

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

$$VE = \frac{ARU - ARV}{ARU} \times 100$$

(VE = vaccine efficacy; ARU = attack rate in the unimmunized population; and ARV = attack rate in the immunized population.)²

Four major factors affect most epidemiological studies of vaccine efficacy:

Case definition. A uniform definition of cases should be developed and applied to all individuals in the study. This definition should be as sensitive and specific as possible. A recommended clinical case definition for measles is: (1) generalized rash of ≥ 3 days duration, (2) fever ($\geq 101^\circ\text{F}/38.3^\circ\text{C}$ if measured) and (3) one of the following: cough, coryza or conjunctivitis.

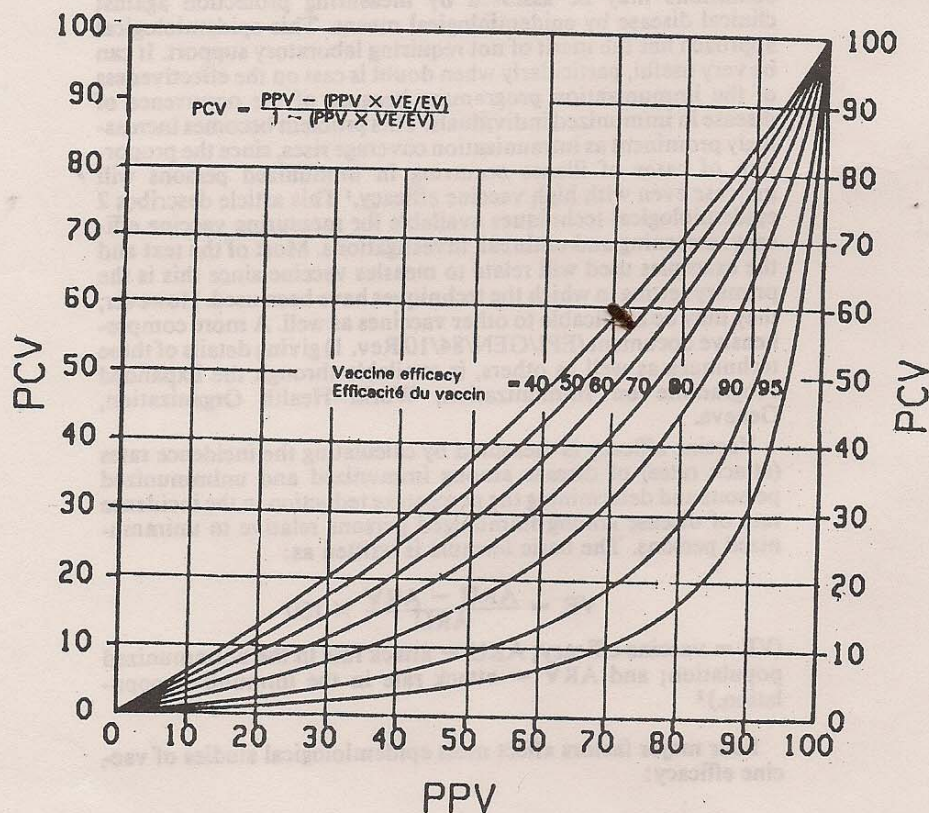
Case ascertainment (case detection). It is important to ensure that there is equal detection of cases among immunized and unimmunized populations. Surveillance surveys based on total population in which investigators go door to door using a clinical case definition to find cases give the least biased estimate of vaccine efficacy.

Immunization status determination. Immunization status must be determined accurately. Whenever possible, vaccine history should be based on a record indicating the date of immunization. Persons of unknown immunization status or with an incomplete series of immunizations should be eliminated from both the numerator and denominator of calculations.

Comparability of exposure. Efficacy should be measured under conditions where vaccinees and non-vaccinees have equal likelihood of exposure to measles. This is most likely to be the case when the incidence rate of disease is relatively high.

Fig. 1

Percentage of cases immunized (PCV) per percentage of population immunized (PPV), for 7 values of vaccine efficacy (VE)



Screening

In most situations, attack rates in the immunized and unimmunized will not be known with precision. However, vaccine efficacy can be estimated from other available information. The vaccine efficacy equation can be manipulated to give the formula in *Fig. 1* which consists of 3 variables: the proportion of cases occurring in immunized individuals (PCV), the proportion of the population that is immunized (PPV), and the vaccine efficacy (VE). When any 2 of the 3 variables are known, the third can be calculated.

Fig. 1 also shows curves generated from the equation. These curves indicate the theoretical proportion of cases that will have an immunization history in a given setting for specified levels of vaccine efficacy. They show the expected proportional distribution of cases by immunization status should an outbreak occur, and indicate whether further investigation is warranted. For example, consider a measles outbreak in a small town with 100 cases in children aged 12 to 35 months, 9 of whom were previously immunized. Prior coverage assessments showed that 50% of children in that age group had received measles vaccine. Plotting 9% for PCV and 50% for PPV on *Fig. 1* indicates that the point is on the 90% vaccine efficacy curve, i.e. a high vaccine efficacy. Extensive investigations would not be warranted. On the other hand, consider if the same proportion of cases occurred in immunized individuals in a setting where vaccine coverage was only 10%. Plotting these points on the graph would show a vaccine efficacy substantially to the left of the 40% curve, indicating low vaccine efficacy and the need for a more thorough evaluation of the situation.

The major purpose of this screening technique is to indicate whether more careful evaluation is required. It should not be relied upon for precise estimates of vaccine efficacy. In most circumstances with reasonably accurate estimates, overestimation of vaccine efficacy should be rare and this screening will provide a rough guide to determine whether further evaluation is necessary.

Outbreak investigations

The best situation in which to measure vaccine efficacy is probably in defined outbreak settings such as villages, towns, cities or schools. Most determinations of vaccine efficacy have been performed in these types of investigations. Although any outbreak can be investigated, biases will be minimized if the criteria in *Table 1* are kept in mind. For measles, in most developing areas, the optimal age group should probably include infants and children 9 months of age up to the third birthday. Equal efforts should be made to obtain immunization status of cases and non-cases. Persons should be considered immunized if they received vaccine at or after the minimum recommended age (usually 9 months) and if immunized 14 or more days before the onset of the outbreak. Persons immunized before the recommended age should be classified separately. Persons immunized during the outbreak should be classified according to immunization status prior to the outbreak.

Table 1 Guidelines for selecting an outbreak setting to measure vaccine efficacy

1. Absence of substantial prior disease activity in the age group to be studied.
2. Population containing both vaccinees and non-vaccinees.
3. Adequate population in the age group to be studied.
4. High overall attack rate
5. Good immunization records available to differentiate non-vaccinees from vaccinees.

Diseases which occurred prior to the outbreak will have minimal effect on the vaccine efficacy calculation if the incidence rate of disease in the area under study and in the chosen age group was low. 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. Data should be collected and VE calculated as described in Table 2.

Table 2. Data to be collected in an outbreak investigation of vaccine efficacy

Clinical status	Immunized	Unimmunized	Vaccine status unknown
Ill	a	b	c
Well	d	e	f

$$VE = \frac{ARU - ARV}{ARU} \times 100$$

1. $ARU = \frac{b}{b + e}$ where b is the number of cases during the outbreak in unimmunized children and e is the number of unimmunized children who did not develop measles during the outbreak.

2. $ARV = \frac{a}{a + d}$ where a is the number of cases during the outbreak occurring in immunized children and d is the number of immunized children who did not develop measles during the outbreak.

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

Comment

Clinical vaccine efficacy can be determined by a variety of means including screening, outbreak investigations and a number of other techniques such as secondary attack rates in families or clusters, vaccine coverage assessments and case control studies.

EXPANDED PROGRAMME ON IMMUNIZATION (ต่อจากหน้า 16)

Field evaluation of vaccine efficacy

All techniques offer a means of monitoring vaccine programmes under conditions of day-to-day vaccine use.

The screening technique is the most 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 immunized 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 assess efficacy more accurately. 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 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 vaccine management and vaccine administration technique. If those systems are unsatisfactory, corrective measures should be taken. If satisfactory, other explanations should be sought.

Clinical vaccine efficacy studies 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 vaccine efficacy in the field, managers of routine immunization programmes have a powerful tool to evaluate their programmes and ensure confidence in immunization.

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บรรณาธิการ vaccine efficacy เป็นวิธีการวัดประสิทธิผลหรือความสามารถของวัคซีนในการป้องกันโรค วัคซีนหนึ่ง ๆ จะป้องกันโรคได้อย่างมีประสิทธิภาพขึ้นกับ potency ของวัคซีน, วิธีการให้วัคซีนอย่างถูกต้อง, และการตอบสนองด้วยการสร้างภูมิคุ้มกันของร่างกาย การประเมิน vaccine efficacy เป็นกิจกรรมที่จำเป็นสำหรับผู้บริหารงานสร้างเสริมภูมิคุ้มกันในห้องที่ต่าง ๆ ในการตรวจสอบว่าวัคซีนที่ใช้ในโครงการมีประสิทธิผลในการป้องกันโรคตามวัตถุประสงค์หรือไม่ บทความข้างต้นกล่าวถึงวิธีการวัด vaccine efficacy โดยใช้วิธีการทางระบาดวิทยา 2 วิธี คือ screening และ outbreak investigations แม้จะมีข้อดีคือไม่ต้องอาศัยการเจาะเลือดตรวจทางห้องปฏิบัติการ ทำได้รวดเร็วในห้องที่ แต่ก็ยังมีข้อควรระวังในเรื่องของ case definition, case ascertainment, immunization determination, comparability of exposure ที่จะทำให้ผลคลาดเคลื่อนจากความเป็นจริงได้

ถ้าพบว่า vaccine efficacy มีค่าต่ำกว่าค่าที่คาดคะเนไว้ ควรจะได้มีการตรวจสอบถึง potency ของวัคซีน วิธีการให้วัคซีน หรือกลุ่มผู้ได้รับวัคซีน ถ้าพบว่ากระบวนการเหล่านี้มีข้อใดบกพร่องจะต้องรีบลงมือแก้ไข โดยทันที