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Epidemiological assessment of vaccine efficacy

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Abstract

The success of an epidemiological program against infectious diseases depends on an effective prophylactic vaccine. Although efficacy and effectiveness are used interchangeably, effectiveness depends upon efficacy. Few methods are in use to assess the efficacy of the vaccine, a randomized double blind controlled trial is the least ambiguous method for evaluation. Observational designs for vaccine efficacy include cohort and case control and are useful when comparing vaccines with very large effectiveness. Modeling helps in designing vaccine. Serologic responses to antigens in combination vaccine differ from those obtained with separate administration of the components. Creation of a vaccine advisory and control authority is imminent.

Keywords : Vaccine efficacy, epidemiology

Introduction

One of the most widespread prophylactic measures used against infectious diseases is vaccination and the purpose is to reduce morbidity and mortality (Halloran *et al.*1998). The tremendous success of disease prevention through vaccination is the use of highly effective products and the implementation of epidemiologically sound policies (Regina and Walter 1999). The success of any vaccination program in a community is dependant on the efficacy of vaccine used and its coverage in the target population (Noah 1980). High vaccination coverage and vaccine efficacy are required to prevent major epidemics (Leissel and Peter 2003). An effective vaccine must

1. induce right sort of immunity
2. be stable on storage
3. have sufficient immunogenecity (Peter 2001)

Efficacy of a vaccine refers to the reduction in disease measured in a carefully monitored, randomized controlled clinical trial conducted in a homogeneous population according to a defined protocol. Effectiveness refers to the reduction in disease measured under conditions of use of the vaccine in ordinary clinical practice (Simon and Vonkorff 1995). Effectiveness would be somewhat less than efficacy (Harry 1999).Vaccine efficacy and vaccine effectiveness are often used interchangeably (Siranda and Peter 2002).

Evaluation of field vaccine efficacy is a critical but under utilized component of program monitoring in emergencies and is particularly important in rural areas where the integrity of cold chain is difficult to guarantee. It can be used to rapidly assess the quality of vaccine and gauge the need for more formal evaluation (Leissel and Peter 2003). Surveillance and quantitative methods can be combined to improve the design and evaluation and to understand the limitations of vaccines, vaccination strategies and delivery system (Halloran *et al*.1998). In designing a study to evaluate the effects of vaccination, the question of interest guides the choice of unit of observation, comparison groups, parameter of effect and level of information required (Halloran *et al*.1997).

Randomized control trial

Vaccination can produce several different kinds of effects, at both the individual and the population levels. The groups being compared could be composed of individual animals or the populations of animals (Halloran *et al*.1999).

The least ambiguous method with which to estimate the protective effect of a vaccine and to assess possible adverse effects associated with its use is a double blind randomized controlled trial (RCT). It remains the gold standard for the initial evaluation of the safety and efficacy of a vaccine. Once an RCT of a vaccine has been conducted and the vaccine has been shown to be efficacious, further such trials may be considered unethical, especially after the vaccine has been introduced in to the field use. However, it is often of interest to know not only whether a vaccine is effective in the context of the trial but also what its efficacy is under routine conditions, which are often less, favorable than those in a trial. Through this approach issues of confounding and bias have minimal influence on the estimation of vaccine efficacy (Regina and Walter 1999,Rodrigues and Smith 1999).

The steps involved in the RCT of vaccine efficacy are:

A. Pre- licensing evaluation of vaccine

Phase I - Safety in adults (natural host)
Phase II - Immunogenecity and reactogenecity in the target Population
Phase III - Protective efficacy

B. Post- licensing evaluation

- Safety and efficacy of vaccine
- Measurement of vaccine coverage
- Disease surveillance
- Serological surveillance (Norman and Elizabeth 1990).

Protective efficacy should be estimated according to prior established strict case definitions and based on uniform case ascertainment. Differences in case ascertainment may be decisive, many atypical cases would not have been detected (Patrick 1989). Case definition, case ascertainment with laboratory confirmation is essential (Norman and Elizabeth 1990). The sensitivity and specificity of case definition can be crucial in determining the magnitude of the efficacy or effectiveness of an estimate (Halloran *et al*.1999).

A vaccine is not licensed for general use without undergoing evaluation in atleast one RCT (phase III trial).The efficacy measured in phase III trial may be greater than that applicable when the vaccine is in field use, since it is designed to evaluate the efficacy of the vaccine under carefully controlled conditions, and may exclude animals which would not be excluded from a routine vaccination program (those with concurrent illness).In addition the conditions for the storage of the vaccine, the interval between doses, and the population selected for vaccination can be controlled more carefully in a trial than in a routine vaccine program (Rodrigues and Smith 1999).

Observational studies

Observational studies, direct (cohort) and indirect (case- control), have played a crucial role in determining whether persisting disease is the result of vaccine failure or failure to vaccinate, the critical question in evaluation of the vaccine program (Regina and Walter 1999). Observational designs are useful when comparing vaccines with very large differences in effectiveness (Harry 1999).

The logic for the cohort studies are similar to RCT and mainly undertaken during an outbreak investigation. The allocation is non random and there is potential for bias and confounding which could be controlled (Rodrigues and Smith 1999,Siranda and Peter 2002).

The case control approach has been widely used to assess disease risks associated with " non-interventional exposures " but with rare early exceptions, only relatively recently have case – control studies been applied in the context of vaccine evaluation (Erdman *et al*.1993). Mainly used with respect to two issues: vaccine efficacy and adverse effects. Case – control studies can be used after the implementation of routine vaccination to estimate the protection given by the vaccine under normal conditions. It is used to determine whether the outbreak of a vaccine – preventable disease was due to poor vaccine efficacy and to identify cause for this. There may be reasons to study the protection conferred by a vaccine in population or against disease types that were not included in phase III investigations (Rodrigues and Smith 1999).

The strengths of case –control studies include, its more rapid since it is retrospective and cheaper compared to RCT. The logistics are at handy. End points could be studied. Sample size requirement is less and avoids ethical issues. The possibility of selection bias due to selection of groups of controls who are not representative of the population where the cases came is the weakness of this study design (Rodrigues and Smith 1999).

Case population studies are similar to case-control instead of data on a control group data on the whole population are used for contrast with vaccine coverage in the cases. It's a crude method to assess vaccine efficacy than case-control but it is rapid and cheaper. Reliable information on vaccination history is essential for estimating vaccine efficacy in case-control studies. Non-differential misclassification may push the vaccine efficacy towards zero. When the validity of the vaccine history is different in cases and controls (differential misclassification) the efficacy may be biased towards or away form zero (Rodrigues and Smith 1999). As new vaccines are introduced to the schedule, booster doses are added and the timings of doses changed, the role of observational methods in the evaluation of vaccine efficacy will become more important (Siranda and Peter 2002).

Statistics

Vaccine efficacy could be studied in sub-groups, specific forms of disease and the level of severity (Rodrigues and Smith 1999). The efficacy and 95 % confidence intervals are estimated by survival analysis (Patrick 1989). Sample size calculations should be based on the analysis method that is going to be used for, the precision desired, the expected incidence of the disease in the unvaccinated group (Norman and Elizabeth 1990, Halloran *et al*.1999).

Interrupted time-series with controlling for temporal trends are used to estimate the effects of policy changes on health and outcomes (Harry

1999).The analysis in case control studies employ odds ratios, conditional or unconditional logistic regression, if other variables need to be controlled for (Halloran and Struchiner 1995). However, statistical correlations might not have anything to do with actual correlation, since, the dynamics of the immune response could be highly non-linear (Anderson 1994).

Vaccine efficacy and effectiveness (VE) are generally estimated as one minus some measure of Relative Risk (RR) in the vaccinated group compared with the unvaccinated group (Ross 1916).

$$VE = 1 - RR$$

Furthermore, it is the percentage reduction in the disease rate among vaccinated subjects that is attributed to vaccination (Rodrigues and Smith 1999).

$$VE = 100 (IU - IV) / I U = 100 (1 - RR V / U)$$

IU - Disease incidence in the unvaccinated group

IV - Disease incidence in the vaccinated group

In disease surveillance programme, the information most readily available may be the proportion of cases who have been vaccinated (Pc) and the proportion of target population who have been vaccinated (Pp) (Rodrigues and Smith 1999).

VE without adjustment for confounding variables

$$= \{1 - [Pc (1 - Pp)] / [Pp (1 - Pc)]\} \times 100$$

The vaccine coverage is calculated from records or by vaccine usage which is crude since no account of wastage and incomplete courses is dealt with (Norman and Elizabeth 1990).

$$Pc = Pp - (Pp \times VE) / 1 - (Pp \times VE)$$

An overestimate in Pp will result in an overestimate of VE and this error is particularly noticeable when vaccine coverage is greater than 80 percent (Siranda and Peter 2002).

Comparison of attack rates in vaccinated and unvaccinated individuals during outbreaks provides an acceptable alternative for post licensing study of VE. Efficacy estimates are obtained from cohorts or diseases with least incidence from case control (Orenstein *et al*.1985).

$$VE = 1 - (ad / bc)$$

a/b - ratio of odds that a case is vaccinated

c/d - ratio of odds that a control is vaccinated

Adverse effects are usually studied in phase III trials. The rate of induced adverse reaction can be estimated in a nested case control study in a case control study and in a case series, if the proportion of the population that is vaccinated and the frequency of the suspected adverse reaction in the population are known or can be estimated (Farrington *et al* 1996, Black *et al* 1997).

This attributable risk (adverse reaction) = $r (R - 1) / (Rp - p+1)$

p – proportion of the population vaccinated

r – rate of the putative adverse event in the total population

R – relative risk of the adverse event in vaccinated animals compared with the unvaccinated animals.

Susceptibility, Infection and Progression

For many infectious agents with short incubation periods, disease is used as the outcome of interest in vaccine trials rather than infection. Becoming infected results with some probability from contact with an infectious source, while developing disease depends on with in host interaction subsequent to successful infection. In many vaccine studies, the distinction between infection and disease as outcome is not made. Studies with either of these outcomes are sometimes used to measure vaccine efficacy for susceptibility (VEs), though the distinction between infection and disease should always be kept in mind. Another measure of effect to evaluate the degree of protection once a person has become infected, is vaccine efficacy for progression (VEp) with infectious agents like tuberculosis this sort of effect is particularly important. VEs evaluate susceptibles and the exposure to infection would need to be taken in to account. VEp are conditional on the participants already being infected, so the progression within infected individuals is important.

A vaccinated person who becomes infected may also be less infectious to other susceptibles or be infectious for a shorter period of time. The vaccine efficacy for infectiousness (VEi) is of interest because a vaccine that reduces infectiousness could have important health consequences. To evaluate the direct protective effects of vaccination VEs and VEp, usually the individual animal is the unit of observation. To evaluate VEi generally small transmission units such as a flock or herd are needed. This small transmission unit could also be used to evaluate VEs.

Under the assumption of equal exposure to the infectious agent in the vaccinated and unvaccinated groups, the estimate of VEs are obtained from the relative risk of infection or disease in the vaccinated individuals compared to the unvaccinated individuals.

$$VEs = 1 - RR (vaccinated) / RR (unvaccinated)$$

$$VEs = 1 - q$$

q = transmission probability among vaccinated

The estimates of VEi and VEp are similar to VEs.

Differences in transmission intensity, exposure to infection and pre existing partial immunity and heterogeneities across communities result in different VEs estimates (Halloran *et al*.1999). Cases can be excluded from the study or can be considered unvaccinated if the interval between the last dose of vaccine and the onset of symptoms is shorter than the

incubation period (*Malfait et al* 1994, *Pinner et al* 1992). Reduced infectiousness could also play a role in the transmission dynamics in populations that are nearly 100% vaccinated (*Erdman et al.*1993).

Modeling

Widespread vaccination increases herd immunity (the collective immunologic status of a population of hosts). Vaccination however has its limitations. Often there are tensions and trade-offs between the protection of individuals and the protection of populations. There are two types of mathematical modeling.

1. Within host-dynamics of the immune system and its interaction with infectious agents and vaccines. It is more recent and draws extensively from theoretical ecology and evolutionary biology to tackle specific problems.
2. Transmission of infectious agents in a population of hosts and vaccination might affect this: It is extensively used to study effects of many different types of vaccines and vaccination strategies in population.

Dynamic population models can help in understanding how a vaccine might better be designed, structural models may help predict which epitopes might be useful to include. Current goal is to develop multivalent or combination vaccination strategies. Models of interactions of various antigen with the immune system could give insight which antigen might be good with in the same vaccine and which should not be combined. There could be complex antagonism or synergy between different types if used simultaneously. Competitive exclusion models are used for studying species interaction. Similarly modeling for adjuant interaction with the immune system (Hunter and Lol 1994).

Models showed that a vaccine giving total protection for an average of 10 years was only as good as vaccine giving 30 % protection indefinitely in reducing overall morbidity (McLean and Blower 1993). Modeling can be very useful in looking at the role of cross reactive or general immunity in understanding the co-existence of strains or evolutionary pressure exerted by the immune system (*Gupta et al* 1994). When most of the population is vaccinated most cases will be vaccine failures, so a high proportion of vaccine failures is not necessarily indicative of a declining vaccine effectiveness or efficacy (*Siranda and Peter* 2002).

Multiple strains and combination vaccines

With some infectious diseases we are dealing with a basket of strains, so that cross reactivity may be important. Memory cells are more cross reactive than other immune cells, so that stimulation of low specificity may play an important role in maintaining memory (*Halloran et al* 1998). Wide spread vaccination could allow the expansion of non vaccine sero types that had been less important before vaccination or put extraordinary pressure on the existing strains.

There are a number of physical, chemical and immunologic mechanisms by which serologic responses to antigens in combination vaccines may differ from those obtained with separate administration of the components (Insel 1995). Preservatives used in one component may alter the potency of other components. Buffers used with different components may be incompatible (Harry 1999). Antibody titres to some live virus may be lower when administered in a combination vaccine than when administered separately (*White et al* 1997). Reduced antibody responses have also been shown when multiple protein conjucated vaccines sharing common epitopes have been administered simultaneously (*Dagan et al* 1998). Seroconversion rates (percentage of vaccinees achieving a previously established "protective level" of antibody) need to be considered in the immunologic evaluation of combination of vaccines (Harry 1999). Trade-off between a low efficacy vaccine that is useful against several strains, and a very good vaccine that is only good against one strain has to be made (*Nowak et al* 1995).

Eradication of diseases like Foot and mouth disease (FMD) is not possible by vaccination alone since the currently manufactured vaccines against FMD are not 100% efficacious. Existence of antigenically distinct types, sub types within types and emergence of antigenically variant strains of FMD virus (picorna virus with positive sense RNA) due to mutation. The rate of mutation is estimated to be $0.9x10^2$ to $7.4x10^2$ substitutions per nucleotide per year (s/n/y)prevents to have a fixed vaccine strain under each type, to present as a live attenuated efficacious vaccine (Gebauer *et al* 1988).

Conclusion

Vaccine efficacy studies are the fundamental aspect of any disease control or elimination or eradication program. Recent advances in molecular biology, immunology, microbiology and genetics have paved way for more efficacious vaccines compared to conventional killed and modified live vaccines. We have eradicated rinderpest through national project for rinderpest eradication. It was achievable by mass vaccination of the susceptibles with RBOK (Rinderpest bovine old kabete) strain of tissue culture rinderpest vaccine (Plowright and Ferris 1959) which is 100% efficacious (Plowright,1962) and confers solid life-long immunity in animals free from maternally derived antibodies while vaccination (Plowright,1984). However, we are unable to conquer the age old

diseases, (FMD) emerging and reemerging diseases. Most of the emerging diseases are zoonotic and this poses a greater challenge for the researchers to design effective vaccines to protect the food and companion animals. Above all the biodefence in the event of bioterror and the protection of public health with efficacious vaccines is the need of the hour.

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