SCIENTIFIC STUDIES OF VACCINES

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Scientific studies are conducted throughout the many stages of vaccine research, development, licensure and general use. Results of studies on the prevalence and burden on society of a particular disease help manufacturers and advisory committees decide whether developing a particular vaccine would be useful to the public. Market and social research conducted prior to the development of a vaccine helps manufacturers determine a vaccine's potential profitability. Laboratory studies help researchers and manufacturers to develop quality, safe vaccines that provide protection against infectious disease. Scientific research helps federal agencies evaluate whether a vaccine is safe and effective enough to be licensed for use by the general public. Surveillance studies conducted following a vaccine's licensure and its widespread use provide ongoing assessment for manufacturers, government agencies, state and local health departments, independent agencies and the public of the vaccine's safety and effectiveness. Such studies also provide evidence to the public of the safety, value and importance of vaccines for themselves, their families and their communities.

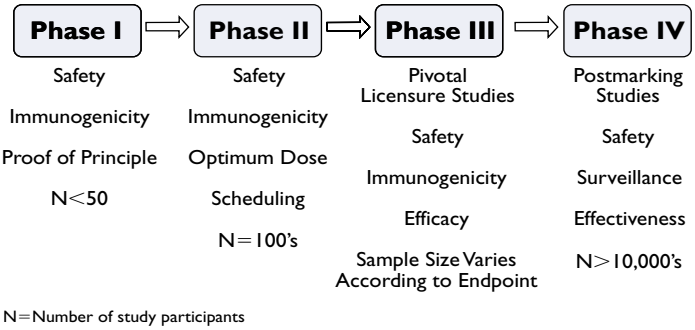
Evaluation of Need

The first step in vaccine development is to determine whether a vaccine to protect against a particular disease is needed. Such identification requires an understanding of the disease that the potential vaccine would protect against, its burden on both the general population and on particular risk groups, disease treatments currently available and the costs associated with treating the disease. Surveys and reviews of medical records are often used to find this information. These studies provide justification to the potential vaccine sponsor (an individual physician, university, hospital, government agency or commercial firm/manufacturer) that the development of a particular vaccine would be necessary or desirable by either the general public or a specific risk group. From a commercial perspective, such studies can indicate whether the vaccine would be profitable or in the best interest of the sponsor to produce.

Vaccine Development

Once the development of a vaccine has been deemed necessary by the vaccine sponsor, laboratory tests must be conducted in order to identify the antigen(s) that can be used in the vaccine to elicit an immune response against a particular disease. Animal studies are often critical at this stage of vaccine development and may also be used to provide evidence that the antigen used in the vaccine is safe and is able to trigger a strong immune response. If these studies produce a viable vaccine that provides a certain level of protection in animal models, clinical studies can be initiated.

The Stages of Vaccine Clinical Trials



N=Number of study participants

The above diagram summarizes the types of studies conducted in humans that occur during the development of a safe and effective vaccine. Phase I clinical vaccine studies are conducted to evaluate safety and immunogenicity. The first studies are conducted in a small number of healthy study participants who are at low risk for infection to determine whether the vaccine can be used safely in humans. Additional Phase I studies may be conducted to provide vaccine safety data for other populations,

GLOSSARY TERMS

Adverse events
Antigen
Association
Bias
Blinded
Case-control studies
Cases
Case series
Causal association
Clinical trial
Cohort studies
Confounder
Controls
Cross-sectional studies
Disease
Dose-response relationship
Ecologic studies
Efficacy
Immunogenicity
Incidence
Mumps
Odds ratio
Prevalence
Prospective cohort studies
Relative risk
Retrospective cohort studies
Risk
Rubella
Temporal relationship
Threshold
Vaccine
Vaccine sponsor

WEB RESOURCES

Centers for Disease Control and Prevention
http://www.cdc.gov/nip/vaccine/develop-approval.htm

e.g. minority groups, populations at high-risk for disease, immunosuppressed persons, etc. If the vaccine is found to be safe and immunogenic in these study participants, Phase II clinical trials are initiated. The objective of Phase II vaccine trials is to determine the optimum vaccine dose and schedule to obtain maximum protection from the disease. These studies are performed in the proposed target group, e.g., adults, children or others at risk of exposure to the pathogen. The results of Phase I and II studies determine whether the vaccine sponsor will proceed to a large Phase III trial to determine the vaccine's efficacy.

If the decision is made to proceed to a Phase III efficacy trial, the size and duration of the trial will be determined by many factors. Trial size must take into account disease prevalence in the population being studied and the study must continue long enough to be able to at least partially assess how long the vaccine will protect a person from developing the disease. A single, definitive Phase III trial may provide sufficient efficacy data for licensing a vaccine, but other trials may be necessary.

Types of Studies Utilized

In the effort to evaluate the value and safety of vaccines at all stages of vaccine research, development, licensure and general use, researchers can utilize several types of study methods. Different studies are utilized depending on the type of information desired or the research question being raised. An understanding of the strengths and weaknesses of each study method assists in the assessment of a study's conclusions. Study biases constitute a major flaw in study methods and should be avoided. A bias is any systematic error in the design, methods or conclusions of a study that results in a mistaken estimation of the vaccine's effect on the risk of a particular disease.[1] These errors make study interpretations difficult as strong preconceptions by researchers may unintentionally affect data analysis and interpretation.[2]

A. Ecologic studies: These studies look at group characteristics and often are the first approach used by researchers in determining whether or not an association exists.[2]

Strengths: Ecologic studies allow researchers to use types of data that are easy to obtain such as registries, birth certificates, average values for disease rates, vaccine uptake, etc. These studies can suggest avenues of research that may cast more light on whether an exposure led to adverse events or whether an adverse event led to a symptom.[2]

Weaknesses: Because these studies use group data, they are unable to account for variability among individuals within a group. Thus, characteristics could be attributed to members of a group that do not in fact possess these characteristics as individuals. Therefore, ecologic studies alone cannot demonstrate that a causal association exists.[2]

B. Studies of individual characteristics: e.g., case-control, cohort and cross-sectional studies.

(1) Case-control studies: In one form of a case-control study, researchers identify a group of persons with the adverse event (cases) and a group of persons without the adverse event (controls) and then determine the proportion of each group that was exposed to the vaccine. In another form of these studies, researchers compare the prevalence of adverse events in vaccinated and unvaccinated cases.[2]

Strengths: Case-control studies are relatively inexpensive and require fewer study participants than cohort studies. This strength is especially important if the adverse event under study is rare, making the identification and recruitment of study participants difficult.

Weaknesses: Because case-control studies require data about whether a person was vaccinated or not, participants may have forgotten this information. Selection of a control group is extremely difficult and can also introduce numerous biases.[2]

(2) Case series: Researchers identify cases exposed to the vaccine that has been identified as a proposed risk factor for a certain adverse event. These cases are followed through time and evaluated for the development and severity of any adverse event that may occur. Case series studies do not compare adverse event development and severity of the adverse event in unvaccinated groups versus vaccinated groups.[2]

Strengths: This study method allows researchers to do extensive studies on a small group of people known to have the adverse event under study and may identify temporal patterns of the appearance of the adverse event after immunization. Case series are useful when the vaccine being studied is administered to nearly all persons in a population and, therefore, few unvaccinated persons are available for study.[3]

Weaknesses: Without knowing whether the adverse event would also develop in the unvaccinated population, researchers cannot conclude definitively that the vaccine caused the adverse event. Controls similar to cases in all factors other than having been vaccinated with a particular vaccine are necessary in order to demonstrate that the vaccine and not some other factor is responsible for causing the adverse event.[3]

(3) Cohort studies: Researchers select a group of individuals exposed to the vaccine and a group of individuals who were not exposed to the vaccine and follow both groups to compare the number of new cases of adverse event (or rate of death from the adverse event) in the two groups over time. This information is usually obtained from past medical records and death certificates.[2]

Strengths: These studies are an excellent means of identifying causal relationships as the study design eliminates many of the biases that can be introduced in the selection of cases and controls. Cohort studies should be used when good evidence exists that vaccine use is associated with an adverse event.[2]

Weaknesses: Cohort studies can be very lengthy and expensive. Researchers who determine whether the adverse event developed may be biased due to knowledge of participant exposure or other presenting characteristics if they are not "blinded" or kept unaware of this information. The quality and extent of information obtained in the study may differ between

vaccinated and unvaccinated persons or persons classified either as having or not having the adverse event or by the loss of participants to follow-up over time.

(a) Prospective cohort studies: Researchers identify the groups of individuals to be used in the study at the beginning of the study and follow the individuals through time until the adverse event does or does not develop. Exposure to the vaccine is determined as it occurs during the study and the groups are followed for several years to measure the adverse event incidence. These studies assess the vaccination status of study participants and determine, with strong validity, if the adverse event develops after exposure to the vaccine being evaluated.[2] The vaccine can only be implicated as causing the adverse event if administration of vaccine occurs prior to the development of the adverse event.

Strengths: Prospective cohort studies introduce fewer biases by researchers as the study progresses.

Weaknesses: These studies can be extremely lengthy and expensive.

(b) Retrospective cohort studies: Researchers use past historical data to define a study period and obtain study results more quickly. Exposure to the vaccine is determined using past records and/or data taken at the beginning of the study on whether the study individuals have developed the adverse event.[2]

Strengths: Retrospective cohort studies require less time, resources and funding than prospective studies.

Weaknesses: Due to their reliance on past records that may not be complete, accurate or fully applicable (and therefore may require interpretation); retrospective studies are often less useful than prospective studies and are more prone to investigator bias.[2]

(4) Cross-sectional studies: Researchers determine both vaccine exposure and adverse event outcome simultaneously. Disease prevalence rather than incidence is used. Therefore, cross-sectional studies do not include persons who died after the disease developed but before the study was initiated.[2]

Strengths: Cross-sectional studies require less time and often are less expensive than cohort or case-control studies.

Weaknesses: These studies cannot determine whether vaccine use in study participants preceded the development of the adverse event. Instead cross-sectional studies can only suggest a possible risk factor for an adverse event.[2]

Post-Licensure Evaluation

The pre-licensure Phase I, II and III studies described above provide close, detailed follow-up of study participants that allows for easy causality assessment. However, these studies cannot adequately detect rare or delayed adverse events nor adequately evaluate how various sub-populations of people might respond to certain vaccines. Historically, populations in pre-licensure studies have been fairly homogeneous, often including primarily young, healthy Caucasian males. More recent prelicensure studies include a more heterogeneous group of people more closely reflecting the diversity of the US population. But post-licensure studies of large populations over longer periods of time are necessary to provide ongoing assessment of vaccine safety and effectiveness.[4]

If the safety of a vaccine is questioned by national surveillance mechanisms (see page 21), by research studies or by public concern, a two-step evaluation process of the vaccine in question takes place. First, studies are conducted to determine whether there is an association between the vaccine and either an adverse event or risk of a particular disease. If an association is demonstrated, the second step is to conduct studies to ascertain whether the observed association is likely to be a causal one.

Analysis of a highly publicized 1981 study on coffee consumption and pancreatic cancer demonstrates the distinction between association and causation. Investigators noted that persons who drank more coffee had higher rates of pancreatic cancer, especially women. This finding initially led researchers to believe that drinking coffee caused pancreatic cancer.[5] Critiques of this study noted that most people who smoke also drink coffee and hence, the increased risk of pancreatic cancer was more likely to be caused by smoking rather than coffee drinking.[2] Several years later, another group of investigators attempted to replicate the original study findings while accounting for the smoking status of study participants. However, the association was no longer apparent in this second study.[6] This example highlights the importance of carefully assessing safety studies to determine whether an identified association is or is not causal.

Causal Assessment

During the debate over the possible link between smoking and lung cancer, the US Surgeon General appointed an expert committee to review the evidence. This committee developed a set of guidelines that have since been revised and utilized to assess whether or not an association is causal.[7] The following is the list of these guidelines as they might be applied to evaluating associations between vaccines and their possible adverse events:

1. **Temporal relationship:** If a vaccine is believed to be the cause of a particular adverse event, exposure to the vaccine must occur before the adverse event develops.

2. **Strength of the association:** This criterion is measured by the relative risk or odds ratio. Relative risk is measured by dividing the incidence of the particular event in vaccinated individuals by the event incidence in unvaccinated individuals. If the relative risk is equal to one, the risk of the event occurring is the same in both the vaccinated and unvaccinated groups, indicating no increased risk of the event in either group or for any association of the event with the vaccine. If the relative risk is greater than one, the risk of the event occurring is higher in the vaccinated group as compared to the unvaccinated group, thus providing evidence of a positive association between vaccination and the

event that may be causal. The stronger the association, i.e., the greater the relative risk value, between the vaccine and the adverse event, the more likely it is that the relation is causal. A relative risk ratio less than one indicates that the risk of the event occurring is higher in the unvaccinated group as compared to the vaccinated group, thereby suggesting a negative association that may indicate that the vaccine actually protects the individual from the event. In some studies, relative risks cannot be calculated because data on actual event incidence does not exist or the risk of the event is low. Odds ratios are often used in such cases to estimate the relative risk. Odds ratios use prevalence estimates to calculate the ratio between vaccinated and unvaccinated individuals of the chance that an event will occur rather than a ratio of actual event incidence.

3. **Dose-response relationship:** As the amount or number of doses of vaccine increases, the risk of the adverse event should also increase. The absence of a dose-response relationship does not necessarily rule out a causal relationship. In some cases, no adverse events will develop until a certain level of vaccine exposure (a threshold) is reached; above this level, the adverse event may develop.

4. **Replication of findings:** If the relationship is causal, the relationship between a vaccine and an adverse event should be seen consistently in different studies and in different populations.

5. **Biologic plausibility:** This criterion refers to coherence with current biologic knowledge. Although epidemiologic observations have sometimes preceded biologic knowledge, a biological explanation of the mechanisms by which the vaccine causes the adverse event lends enormous weight to the conclusion that the association is causal.

6. **Consideration of alternative explanations:** Are there other agents or factors that have been suggested or identified as risk factors for the adverse event? Reports suggesting a causal association should thoroughly account for any factors other than the one in question that may alter study results/analyses (confounders) in their analyses.

7. **Cessation of exposure:** The risk of the adverse event occurring should decline if exposure to the vaccine in question is reduced or eliminated. In the case of vaccines, the disease process may be irreversible following an initial exposure to the vaccine.

8. **Specificity of the association:** If an adverse event only occurs after being vaccinated with a particular vaccine, a specific association exists. When specificity of an association is found, it provides additional support for a causal relationship. However, absence of specificity in no way negates a causal relationship.

9. **Consistency with other knowledge:** Strong evidence that a vaccine does cause an adverse event includes findings that show the association to be consistent across different geographic populations, ages, sex and ethnicities. However, causal associations can also exist that are very specific to a particular group of people.[2,7]

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