The development of a vaccine candidate can be accelerated if there is a human challenge model for the disease against which the vaccine is directed. This allows a preliminary assessment of vaccine efficacy (so-called phase IIb) by comparing disease attack rates in vaccinees and unvaccinated control volunteers. These challenge studies can be ethically justified if they are conducted by qualified investigators with rigorous adherence to a scientifically valid protocol and clear safeguards for the volunteers (3,4). It should be recognized that such challenge studies represent experimental models and may not exactly reproduce the disease as it occurs in an endemic area. For example, the inoculum used for challenge for diarrheal illnesses such as cholera and enterotoxigenic *E. coli* are probably higher than commonly occur in nature. This is to ensure that the attack rate among challenged volunteers is high enough to achieve statistical differences when comparing small numbers of vaccinated and unvaccinated individuals. However, the experimental challenge model is designed so that the challenge is not so rigorous as to overcome immunity; often the model has been tested by establishing that immunity induced by primary challenge-induced infection is not overwhelmed by a second challenge with the same pathogen (5). This level of immunity, that is, immunity after primary infection, is often the gold standard for immunity induced by vaccination. At the Center for Vaccine Development, University of Maryland, challenge models have been applied to testing vaccines against cholera, diarrheagenic *E. coli*, *Shigella*, Rocky Mountain spotted fever, malaria, influenza, and typhoid fever.

If acceptable safety and immunogenicity are observed during phase II, phase III studies are planned to evaluate efficacy. Occasionally, phase III studies are designed to measure immunogenicity only. For example, if the protective immune response is known, then demonstration that most subjects attain that response after vaccination may be sufficient for licensure. Generally, a phase III study is a double-blind, controlled study of the new vaccine in a more heterogeneous population, under conditions more closely resembling those under which the vaccine may eventually be used. The study may include as a control group a true placebo, a licensed vaccine against another disease, or another licensed or experimental vaccine against the same disease. In a phase III study, the rate of occurrence of side effects that occur infrequently may be measured more accurately. Defined endpoints must be chosen, and a hypothesis stated. A sample size should be chosen on the basis of assumptions of the expected incidence of disease, and the reduction in disease incidence that is anticipated in vaccinees. Recently, phase III trials of rotavirus vaccines were specifically designed with large sample sizes to exclude the rare occurrence of an adverse event, intussusception. A pivotal study is a phase III study, which provides the most convincing data supporting the licensure of the vaccine. The pivotal protocol must be rigorously designed and analyzed with impeccable statistical considerations.

After phase III studies demonstrating the safety and efficacy of the vaccine candidate, the sponsor of the vaccine who will market the product in the United States submits a Biologic Licensing Application (BLA) to the Food and Drug Administration (FDA). Approval requires that the safety and efficacy be demonstrated in well-designed, controlled studies. Once the application is approved, the vaccine may be sold commercially for the specific indication. After the BLA is approved, FDA requires that the holder of the BLA conduct postmarketing surveillance and submit periodic reports including incidence of adverse reactions and follow-up of ongoing phase III studies. These data are generally descriptive in nature. After marketing approval, additional formal studies may also be designed to continue to measure efficacy and side effects. These studies, termed phase IV studies, may detect previously unknown, rare adverse reactions among recipients of the marketed vaccine. Many countries have formal systems in place to detect these events and determine using various epidemiologic methods whether there appears to be a relationship to vaccine administration. In the United States, for example, the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Data Link (VSD) systems are used for this purpose.

FACILITIES

In general, facilities for vaccine testing include clinical office space for interviews for screening, obtaining consent, and conducting follow-up procedures; facilities for specimen collection and storage; and emergency equipment for treating anaphylactic reactions. The majority of studies can be conducted in an outpatient facility. In phase I and II studies of vaccines, unlike drug studies, participants usually take only one to three doses of the experimental agent. Many early studies of new vaccines require that signs and symptoms be recorded for a relatively short period after vaccination and that a limited number of blood tests be obtained to measure immune response over a period of weeks to months.

The intensity of surveillance depends on the type of vaccine and the anticipated nature and incidence of side effects. Phase I studies of live vaccines in adults are usually conducted in an inpatient facility to collect preliminary safety data, and to determine the excretion of vaccine and potential for person-to-person transmission. For example, the degree of attenuation of some live enteric vaccines is unknown; these must be given under close inpatient supervision (6,7). Live vaccine studies may require frequent collection of stool samples or respiratory secretions for culture. In addition, for studies requiring very intense surveillance or frequent collection of specimens, inpatient studies may be required to ensure that every event (e.g., fever) is detected and recorded and to ensure compliance with collection of every specimen. For example, live oral *Salmonella enterica* serovar *Typhi* vaccine strain CVD 906 was found to be insufficiently attenuated, and to cause symptoms of typhoid fever in some inpatient volunteers (8). Concerns about the release of genetically engineered organisms into the environment before their preliminary safety and potential for person-to-person transmission have been established requires that some studies be conducted on a closed isolation ward with strict contact isolation measures.

In the United States, the National Institute of Allergy and Infectious Diseases supports several vaccine evaluation and treatment centers at academic institutions. Some of these centers have access to inpatient units where volunteers can be housed for intensive surveillance and specimen collection.

In studies of experimental vaccines in children and infants, surveillance for adverse effects and collection of specimens is carried out in an outpatient setting. Telephone interviews with parents or guardians, collection of questionnaires filled out by parents, and review of medical records are means utilized to collect safety information. Children return to the clinic or physician's practice for blood drawing or collection of respiratory secretions. Collection of stools can be accomplished either by instructing the caretaker to bring in soiled diapers or by sending a