3

Initial Clinical Evaluation of New Vaccine Candidates

Carol O. Tacket and Karen L. Kotloff
Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, U.S.A.

INTRODUCTION

Among the tools available to control infectious diseases, vaccines rank high in effectiveness and economic feasibility. Vaccines once consisted of either live whole virus analogues or killed virus or bacterial preparations. Now, new viral, bacterial, and parasitic vaccines are frequently defined by gene sequences or amino acid epitopes. Likewise, vaccine testing has progressed to become a discipline of its own, which includes scientific, epidemiologic, ethical, economic, and feasibility aspects. This chapter deals with some of these issues related to phase I and II vaccine testing.

SELECTION OF VACCINE CANDIDATES

Creative and innovative vaccine candidates emerge from research laboratories in academic institutions, government agencies, and private pharmaceutical and biotechnology companies all over the world. The decision to begin human testing of a candidate vaccine depends on a number of criteria.

First, the vaccine candidate must address a public health need and be a logical means of control for the disease of interest. For example, in the United States, outbreaks of *Cryptosporidium parvum* may best be prevented by improved water treatment rather than by vaccination. Similarly, infections with Shiga toxin producing *Escherichia coli* can best be prevented by improved meat inspection and consumer education about cooking practices, rather than by mass vaccination of children.

Second, the vaccine candidate must have been designed with a sound scientific rationale. There are two mirror-image principles commonly used to develop vaccines. On the one hand, the vaccine may consist of a known or suspected protective antigen, for example, purified hepatitis B surface antigen or *Haemophilus influenzae* type b polysaccharide. Alternatively, the vaccine may be a live strain of a pathogen, attenuated by genetic deletion of known virulence factors, for example, live oral cholera vaccine CVD 103-HgR.

Third, there must be an expectation of safety. The risk-benefit ratio for vaccines against most infectious diseases must be very low since such vaccines are designed for use in healthy individuals who may be at low risk of disease. In contrast, in the development of therapeutic agents, a larger risk may be acceptable since there is the opportunity for therapeutic benefit. Safety of the vaccine candidate, therefore, must be formally demonstrated in an appropriate animal model using a dose and route of administration that is proposed for clinical studies.

Fourth, there must be animal studies demonstrating the immunogenicity of the product when given in the appropriate dose and by the appropriate route and, if possible, a demonstration of efficacy against challenge with the wild-type pathogen in animals. Animal models to demonstrate immunogenicity and efficacy against challenge have been developed for a number of vaccines, for example, cotton rats for respiratory syncytial virus and mice for *Salmonella*.

Fifth, it is desirable that the vaccine be prepared in a practical formulation at the onset of phase I studies. This is not an absolute requirement since it is often necessary to first establish the safety and immunogenicity of a prototype vaccine in a preliminary formulation. However, changes in responses to vaccine can be observed when scale-up manufacturing is done or practical formulations are produced (1,2).

Finally, issues related to commercial development must be considered. In a free market, public health need and scientific rationale supporting the likelihood of success of a candidate vaccine will increase the chances that a new vaccine will attract the financial resources needed for its development to licensure and use as a public health tool.

GENERAL DESCRIPTION: PHASES OF CLINICAL TRIALS

The clinical investigation of a new candidate vaccine progresses in three phases on the road to licensure. Although these phases are usually conducted sequentially, they may overlap. A phase I trial is the first human use of the vaccine candidate in healthy volunteers. Participants in phase I studies are typically closely monitored. These studies are designed to determine the frequently occurring, short-term side effects and the dose response to a candidate vaccine. In a phase I vaccine study, the immune response to the vaccine is measured; the analogous information in a similar study of a new drug would be its pharmacological characteristics in a small number of subjects. The information generated in phase I about the vaccine's safety profile and immunogenicity should be sufficient to design expanded studies of safety and immunogenicity in phase II.

Phase II studies are controlled, closely monitored studies of safety and immune response in an expanded number of subjects, perhaps several hundred. Some individuals who participate in phase II studies may represent the target population for which the test vaccine is intended. For example, infants or elderly subjects may be enrolled if the vaccine candidate is intended for ultimate use in these populations. Multiple phase II studies are often conducted to develop a database to direct the design of phase III studies.