

**S5** Introduction to Surrogate Markers

D. S. Krause, MD,\* SmithKline Beecham (SB) Biologicals, Collegeville, PA

Randomized, blinded clinical trials with proper controls and definitive endpoints are the "gold standard" by which new pharmaceutical products are judged. Surrogate endpoints are an important issue for pharmaceutical and academic researchers as well as regulatory authorities in all therapeutic areas. Proper use of such markers allows for accelerated product development, smaller clinical trials and has been highlighted by the rapid clinical development of drugs to combat human immunodeficiency virus (HIV) disease. The misuse of surrogate markers can result in serious clinical errors, however, as has been demonstrated with some antiarrhythmic drugs.

For vaccines, once efficacy is established, serological correlates of protection become a critical issue, since further efficacy trials are usually not feasible or ethical. In order to bridge to new schedules, populations, formulation/manufacturing improvements and vaccine combinations therefore, reliance is placed on the immune response as the marker of protection. Unlike hepatitis B vaccine, the immune response to many vaccines is not associated with an absolute antibody level that is known to confer protection. Additionally, antibody concentrations alone do not convey information about cell-mediated immunity or other aspects of bio-individuality.

The regulatory and historical use of immune correlates of protection will be discussed.

**S6** Surrogate Markers: Lessons from the Past

G. R. Siber,\* R. Kohberger, F. Xie, Wyeth-Lederle Vaccines and Pediatrics, Pearl River, NY

The importance of serologic correlates is that they allow us to predict the efficacy of improved vaccines or new vaccine combinations based on their immunogenicity without performing cumbersome and expensive efficacy trials.

Three methods have been used to estimate serologic correlates. The first, termed an "individual based" correlate, is based on the assumption that individuals who have achieved a protective post-immunization antibody concentration are reliably protected from disease and those who fail to achieve this level are susceptible. It is assumed that individuals who have "break-through" infections after immunizations, therefore, did not achieve the protective level. Examples from studies of *H. influenzae b*, diphtheria, and pertussis show that this method is not appropriate because "break-through" infections do occur in individuals despite high antibody responses.

The second method, termed a "population-based" correlate, simply compares the antibody concentrations in a population that was protected by immunization with those in unprotected controls. An antibody level that is achieved by the majority of the protected individuals (i.e.,  $\geq 90\%$ ) and not achieved by the majority of unprotected individuals is estimated to be the protective level. This method was used to estimate the protective level of anti-PRP antibody for *H. influenzae b* infection after polysaccharide vaccine (1mg/ml).

The third and most precise method is the direct measurement of "antibody concentration specific protection." In this method, the risk of developing disease is calculated for individuals who have achieved various antibody concentrations, preferably measured shortly after immunization. Examples of concentration-specific risk curves will be given using data from trials of varicella zoster vaccine and acellular pertussis vaccines. Concentration-specific risk curves allow the precise estimation of protective efficacy of new vaccines based on the distribution of post-immunization antibody concentrations that they induce.

**S7** Correlates of Immunity: A Regulatory Perspective

Karen Midthun,\* Karen L. Goldenthal, Center for Biologics Evaluation and Review, FDA

Serologic correlate(s) of immunity may be identified from data from one or more vaccine efficacy trials for the same clinical indication, as well as inferred from other data (e.g., protection afforded by related hyperimmune globulin or observed in serological surveys of immunized populations). Evaluation of the validity of using a serological endpoint instead of a clinical endpoint for a particular immunogen often includes assessments of both quantitative antibody titers and functional assays, in addition to the physicochemical characteristics of the product. Serological endpoints may provide the efficacy data to support new product approval in the event that a well-established correlate of immunity has been identified.

Serological endpoints are also used in the evaluation of new combination vaccines that contain components for which clinical efficacy has been previously demonstrated. Comparative trials with serological endpoints can typically be conducted with sample sizes in the Phase 2 range, e.g., up to several hundred subjects per group. The demonstration that the immune responses to the combination vaccine are not inferior to those induced by the control vaccines may be adequate to support efficacy, even when there is no clear serologic correlate of protection. However, when no correlate of immunity is known for a particular antigen, or the correlate is not well defined quantitatively, it will be more difficult to evaluate the clinical relevance of a decreased immune response to this antigenic component. The statistical hypothesis for the "acceptable differences" in such cases will be especially critical.

**S8** Overview of Maternal Immunization

Pamela M. McInnes,\* NIAID, NIH

While significant progress has been made in the development of more immunogenic bacterial and viral vaccines, prophylaxis in the vulnerable neonate and young infant remains problematic. Attempts at inducing early protection by immunizing newborns have been generally disappointing. Maternal immunization resulting in passive transfer of antibodies to the neonate provides a potentially powerful alternative strategy for protection during the neonatal and early infant periods. Perhaps the best known example has been the worldwide impact of maternal immunization during pregnancy against tetanus. Neonatal tetanus remains a major cause of infant mortality in much of the developing world, and active maternal immunization with tetanus toxoid vaccine has been shown to be the most cost-effective intervention to prevent tetanus neonatorum. Other pathogens causing significant disease incidence, mortality and morbidity in neonates and young infants include group B streptococci (GBS), pneumococci, *B. pertussis*, and respiratory viruses such as influenza and respiratory syncytial virus (RSV). Maternal immunization of the pregnant woman in the third trimester of pregnancy can increase her specific antibody titers and has the potential to provide her infant(s) with high levels of protective antibody that could confer protection for the first six months of life against relevant infections. This approach could eliminate that window of susceptibility of infants both in the US and the developing world to Hib, pneumococcal, GBS, pertussis and respiratory viral infections prior to the age when protective, active antibody responses from active immunization can be generated.