replacement with serotypes not included in the initial seven-valent conjugate vaccine formulation, such as serotypes 19A and 6A (13,14). Also, Pnc vaccines need to meet the demands of highly diverse high-risk groups (including infants in developing countries where serotypes 1 and 5 are particularly important) and also special groups of older children and adults who are at risk. The need for additional serotype coverage has prompted the development of 10- and 13-valent formulations, despite the successful use of the licensed 7-valent formulation (Prevnar^{TM}, Wyeth-Lederle vaccines).

VACCINE EVALUATION

The complexity of efficacy trials can also increase as formulations with more antigens are evaluated. The gold standard method for vaccine evaluation is through a phase III efficacy trial with a control or placebo formulation as part of the evaluation. Using correlates of protection can facilitate vaccine licensure of vaccines against diseases where the burden of disease is difficult to estimate or when a licensed product is already available and efficacy trials with placebo controls are not ethically possible. Efficacy trials are not required in some cases because there is enough preexisting data on efficacy and appropriate correlates of protection that can be used in vitro to measure immunogenicity (3,15). For example, in 1993, the current Hib vaccine (PRP-T) (ActHib^{TM}, Sanofi Pasteur, Pennsylvania, U.S.) was licensed in the United States based on immunogenicity, persistence of the immune response, induction of memory response, isotype and immunoglobulin G (IgG) subclass distribution, and functional Ab activity (3). Another example is the meningococcal group C vaccine (MenC-(CRM)$_{197}$) introduced in the United Kingdom in a phased approach in infants to 24-year-old adults (1999–2001), which was licensed on the basis of immunogenicity rather than clinical efficacy trials (16).

SURROGATES AND CORRELATES OF PROTECTION

Correlates of protection are measurable biomarkers that correlate with the protective effect of a vaccine in a target population, while surrogates are indicators of protection that can substitute for the true correlate (15). Surrogates can be either laboratory or non-laboratory measurements. For example, x-rays can be used to predict efficacy of a Pnc or Hib vaccine against pneumonia. The finding of fewer X rays showing pneumonia in vaccinated children than that in unvaccinated children would be an indicator that a Hib or Pnc vaccine is working in the target population (17). The problem is the difficulty in interpretation of X rays. Despite the efforts of the World Health Organization (WHO) to standardize the reading and interpretation of X rays to diagnose pneumonia, this surrogate of protection cannot achieve the same levels of specificity, standardization, and reproducibility of laboratory-based immunological assays.

Correlates of protection are not always perfect estimates and breakthrough cases can occur (15). Some correlates are based on older studies measuring one single parameter or are derived from studies in populations living in other countries. The surrogate of protection for Hib vaccines has not changed since the licensure of the first Ps vaccine and is used to facilitate the licensure of new Hib vaccine formulations (18). Based on immunogenicity studies using radioimmunoassay to detect antibodies to PRP in Finnish children vaccinated with a single dose of Hib PRP and a population of unimmunized adults and neonates, a minimum circulating concentration of 0.15 μg/ml of anti-PRP Ab was found to protect against invasive disease in both the vaccinated population and non-vaccinated population. However, at least 1 μg/ml of antiPRP antibody must be present in 80% of the vaccinated population between 12 and 17 months of age for protection against disease (18). This higher level discriminates between the vaccinated and non-vaccinated population later in life (older infants). This study allowed for the establishment of the minimum concentration that must be achieved in the target population to consider the population protected at that point in time (short term surrogate of protection). Since antibodies have a half life and concentrations decline unless there is a new encounter with the antigen, a long term-surrogate was established ($\geq$1 μg/ml). If the majority of the population achieves higher concentrations, protection for a longer period of time is expected. Thus, these thresholds are used for Hib vaccine licensure. The concentration of circulating antibodies required to protect against nasopharyngeal colonization is thought to be higher ($\geq$5 μg/ml) (19). Since this higher concentration protects against colonization it also leads to increased herd immunity. For Pnc the minimal concentration of type-specific Abs that must be achieved is in the range of 0.2 to 0.35 μg/mL to protect infants against invasive Pnc disease with a given serotype (20,21). Higher concentrations may be needed for protection against other forms of disease like acute otitis media and/or nasopharyngeal colonization (22–24). Exceptions to the correlate can also be found when we look at individuals. For example, a child may have antibodies (Abs) above a minimum level of protection and yet succumb to disease (25).

MEASUREMENT OF CORRELATES OF PROTECTION

Techniques to measure correlates of protection are often complex and difficult to standardize. In addition, the identification of appropriate correlates is best achieved if immunogenicity studies are performed during vaccine efficacy trials (21). In some cases, identification of the correlates has not been possible. For example, despite many efforts, correlates of protection for pertussis vaccines have been difficult to establish (8,26). It has been difficult to identify among the various markers measured for pertussis which one is the true correlate of protection. In addition, standardization in assay techniques is lacking there. A common marker of vaccine induced protection used is the measurement of Abs above a minimum threshold level that has been associated with vaccine induced protection. The concentrations given above for Hib and Pnc are examples of this type of correlate. However, Abs measured in binding assays such as ELISA do not always correlate with protection and some high-risk groups (e.g., Pnc Ab in the elderly) with concentrations above these minimum levels prior to vaccination but with low functional Ab after vaccination (27). The thresholds were established for infants receiving a complete vaccination regimen and for different populations at risk, the minimum concentrations using this correlate, still need to be identified. Assays that measure a function of the Abs rather than a total Ab concentration are more likely to be better correlates of protection because they measure a biological