Challenges in the Development, Licensure, and Use of Combination Vaccines

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Before substantial public health benefits associated with use of combination vaccines can be realized, a variety of challenges must be addressed. In February 2000, the National Vaccine Program Office convened the International Symposium on Combination Vaccines to explore solutions for barriers to development, licensure, and use of safe and effective combination vaccines. The symposium focused on the following questions: (1) What immunologic standards should be used to evaluate new combination vaccines? (2) How should correlates of protection be developed, and how should the data they provide be interpreted? (3) What sample size is adequate for prelicensure safety trials of combination vaccines? (4) Should standards for evaluation of combination vaccines containing licensed components be different from standards for evaluation of combinations containing unlicensed components? (5) How can the “great expectations” of postlicensure surveillance be realized? Available data relevant to these issues were presented, providing a foundation for furthering the science of combination vaccines.

Vaccination is one of the greatest public health achievements of the 20th century [1]. Vaccines to protect against 26 diseases have been developed or licensed (10 of those are currently recommended for universal use in the United States), and many more are in the development pipeline [2]. As the number of vaccine-preventable diseases increases, so does the number of injections a child must receive to be fully protected. Judging by the year 2000 recommended childhood immunization schedule [3] and the number of vaccines licensed in the United States as of February 2000 [4], it is possible that a child could receive as many as 5 separate injections during a single office visit. The current number of injections indicated during a single office visit does not appear to negatively affect the decision to vaccinate, as shown by coverage levels [5]; however, it is anticipated that there is a threshold number of injections above which acceptance of the vaccine program would begin to decline.

The use of combination vaccines is one mechanism by which the number of injections can be reduced without reducing the number of diseases against which a child is protected. A combination vaccine is defined as a vaccine that consists of 2 or more separate immunogens physically combined into a single product [6]. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention suggests that, in addition to reducing the number of injections (and therefore the amount of trauma and pain experienced by the recipient), use of combination vaccines might improve the timeliness of vaccination coverage, reduce costs associated with stockpiling and administering separate vaccines, reduce costs associated with extra health care visits that result from delayed vaccinations, and facilitate the integration of new vaccines into the childhood immunization schedule [7].

Although substantial potential advantages are associated with the use of combination vaccines, significant challenges exist regarding development, licensure, and
The use of these products. The National Vaccine Program Office convened the International Symposium on Combination Vaccines in February 2000 on the campus of the National Institutes of Health (Bethesda, Maryland). The symposium provided a forum for representatives from regulatory agencies, the pharmaceutical and health care industries, academia, and public health institutions, as well as interested consumers, to discuss the epidemiologic, laboratory, and clinical data integral to development, licensure, and use of new, safe, and effective combination vaccines. The goal of the symposium was to promote the science of combination vaccines, define a research agenda, and stimulate the development of state-of-the-art, useful, and safe combination vaccines.

Achieving optimal safety and effectiveness of all vaccines is recognized as a foremost priority, particularly because vaccines are administered to large numbers of healthy children. Presentations from researchers at the US Food and Drug Administration (FDA) sought to clarify regulatory perspectives regarding the assessment of safety and immunogenicity of combination vaccines, and presenters from academia, industry, and government discussed how to best evaluate combination vaccines for efficacy and safety and how to interpret study results. During discussions of immunogenicity, presenters considered mechanisms of diminished immune responses and stressed the importance of establishing acceptable correlates of protection. Experience with vaccines for diseases such as pertussis and Haemophilus influenzae type b (Hib) or pneumococcus infections was used to illustrate some of the difficulties encountered in interpreting the clinical significance of the somewhat lower immune responses observed with use of certain combination vaccines. In addition, both pre- and postlicensure safety assessment issues were discussed. The issue of use of adequate and yet realistic sample size for prelicensure safety evaluations of combination vaccines composed of previously licensed components and combinations composed of novel antigens was extensively discussed.

Manufacturing and use challenges were also discussed. These include development of combination vaccines that address both public health and commercial interests and fulfill regulatory requirements. As the number of licensed combination and noncombination vaccines increases, stocking and using a formulary becomes increasingly complex, and issues of cost and potential morbidity associated with extra-antigen immunization, complex record-keeping, and reimbursement need to be addressed.

Although the symposium speakers addressed a wide range of issues, deliberation and debate focused on 5 key questions.

**DISCUSSION**

**What immunologic standard should be used to evaluate new combination vaccines?** The FDA’s Code of Federal Regulations [8] states that “a biological product may combine two or more safe and effective components...when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components.” The effectiveness of combination vaccines is evaluated by use of “noninferiority” immunogenicity trials, because it is often not feasible or necessary to conduct clinical end-point efficacy trials for each new combination product. The premise behind a noninferiority trial is that a new vaccine is acceptable if there is a decrease of some predetermined amount (e.g., 10%) in the proportion of vaccinated people who seroconvert to protective (or what are presumed to be protective) levels of antibody when investigational and licensed vaccines are compared. An undesirable outcome from this type of evaluation could occur if each new vaccine has lower immunogenicity (yet is within the margin of acceptability). In this scenario, licensed vaccines could be considerably inferior to the original vaccine. A potential method for avoiding such “creeping inferiority” would be to define specific immunogenicity standards for each antigen, against which all investigational vaccines, whether combination or monovalent, would be evaluated.

The FDA’s Code of Federal Regulations is typically implemented by institution of a requirement that a combination vaccine be compared with its separate but simultaneously administered component vaccines (antigens), rather than with licensed vaccines that are similar to its components, because immune responses to similar vaccine products can differ both qualitatively and quantitatively. For example, the immunogenicity of the Hib component of a new diphtheria-tetanus-pertussis-Hib vaccine would be compared with the immunogenicity of the same Hib conjugate when it was administered separately, instead of with that of any licensed Hib conjugate vaccine. Some symposium participants expressed concern that, as a result of this procedure, combination vaccines are held to higher immunologic standards than noncombination vaccines. Again, definition of a set of industry standards might ensure that a combination product would not be penalized by comparison with a particularly immunogenic individual component and would be helpful in avoiding creeping inferiority.

Development of an industry standard for every vaccine antigen would be a similar process to that already in place for diphtheria and tetanus antigens. The antibody concentration induced by a vaccine (combination or noncombination) would be compared with a concentration that, judging by the best available data, can be assumed to induce protection. This procedure would eliminate inequality between evaluation criteria for combination and noncombination vaccines and would minimize creeping inferiority, because each new vaccine would be compared with the same standard.

However, this approach may be less useful when multiple antigens are used to prevent a disease and the precise protective response (i.e., antigens that stimulate protective responses) is
uncertain. For example, because acellular pertussis vaccines may include up to 5 antigens, there is no clear way to derive a standard that could be used to evaluate and compare new products.

**How should correlates of protection be developed, and how should the data they provide be interpreted?** Accepted correlates of protection, defined as specific immune responses to vaccines that are directly correlated with disease prevention, would allow the licensure of new vaccines based on immunogenicity studies rather than clinical end-point efficacy trials. This is essential for the licensure of new, potentially improved vaccines, because it is ethically unacceptable to conduct placebo-controlled trials of a vaccine for a disease for which there is already a routinely recommended and effective vaccine.

The standard measure of immunogenicity is systemic immune response to vaccine antigen. Humoral antibody level has been the primary measure used to correlate with protection. Other factors that likely contribute to protection and should be evaluated as potential correlates of immunity include presence of mucosal antibodies, cell-mediated immunity, antibody subclass, antibody avidity, immunologic memory (priming), and measures of functional antibody responses.

Defining surrogate immune markers for efficacy has often proved difficult. For example, the effect of antibody quality and the importance of priming and boosting inspired considerable discussion at the symposium. It was suggested that, particularly in the case of encapsulated bacteria, no single threshold concentration of antibody is necessarily protective, because antibody quality likely also plays a role in disease prevention [9]. For example, antibody avidity tends to increase over time, possibly resulting in continued protection, even in the face of decreasing antibody concentration [10, 11]. Further, immunologic memory may be induced and then activated when the immune system is exposed to natural infection [12].

Several related questions remain unanswered. Can changes in antibody levels be used to predict changes in clinical efficacy? Does the impact of a decreased immune response vary by target population? If a decrease in clinical efficacy were documented, what, if any, level of decrease would be acceptable in exchange for the advantages offered by combination vaccines? Incomplete data on immune responses also create difficulties in making vaccine use recommendations and filling vaccine formularies. For instance, data often are insufficient to assess the implications of the use of multiple vaccine products aimed at prevention of the same disease to immunize a single child during the course of a vaccination series. When feasible, companies should be encouraged to conduct “mix and match” immunologic studies that compare new vaccine products with existing products. In addition to these questions, research focusing on correlates of protection should address the importance of immunologic memory, the role of antibody isotype and avidity, disease pathogenesis, and mechanisms of protection.

**What sample size is adequate and realistic for prelicensure safety trials of combination vaccines?** A small change in adverse event rates associated with any childhood vaccine might not be detected until a large number of children had been immunized. The symposium discussion focused on what constitutes an adequate and yet realistic sample size for safety trials of combination vaccines consisting of previously licensed components and for those consisting of novel antigens. Appropriate prelicensure safety trial design (including sample size) depends on a variety of factors, including the age of the target population (which affects expected background rates of various conditions), the adverse event profiles of the vaccine components, and the public health impact of the disease or diseases that the vaccines are aimed at preventing.

Sample size calculations are routinely based on the magnitude of the relative risk to be identified and the expected background rate of the event in question. In the case of safety trials, there is no primary end point on which to base calculations, because any adverse event is of interest, including unexpected events with obviously unknown background rates. Although appropriate sample size will vary according to the product and the target population, one suggested approach was that phase III efficacy and safety trials be designed to detect a 2–3-fold increase in serious adverse events that are expected to occur at a rate of $≥$1%. More rarely occurring risks and detection of smaller changes in risks would only be detectable through postlicensure surveillance and investigations.

Concern was raised that requiring large prelicensure trials would create an obstacle for vaccine development, interfering with introduction of effective vaccines that offer substantial public health benefit. One option for adequately evaluating safety while maintaining realistic sample size requirements would be to pool data from multiple studies. This approach would require interpretation of results on the basis of varying vaccination schedules, use of different control arms, variable safety monitoring, differing protocols, and unique case report forms. These potential variations could be minimized with careful and consistent implementation of a single study protocol.

A second suggestion was to develop a tiered approach to design of prelicensure studies. Following this approach, studies involving smaller numbers of subjects would be conducted and reviewed for evidence of adverse events. If none were noted, those studies might be considered sufficient. If any suggestion of an increase in adverse event rates was seen, larger studies, with sample sizes based on estimates of adverse event rates extrapolated from the original study, would be conducted. This approach, which is informally followed now, does not address concerns about adverse events that might not be observed in the smaller studies.
A third suggestion was to develop a bridge from phase III trials to postlicensure studies. Three specific proposals were outlined: (1) conduct further studies after licensure, but before establishing recommendations for vaccine use; (2) continue to collect safety data after breaking the code of phase III efficacy trials; and (3) monitor vaccination of control subjects who cross over to receipt of vaccine at the conclusion of phase III trials. Concerns were raised that delaying recommendations for vaccine use when administration of vaccines was indicated would, in many cases, prevent administration of vaccines to children who might benefit from them the most—those dependent on federal assistance or those covered by health insurance programs, including managed care organizations, that do not offer a vaccine until it is universally recommended. Extending phase III trials by continuing to collect data beyond breaking of the code and by monitoring for adverse events when controls are vaccinated could provide additional valuable information. A clear statement from relevant organizations on the appropriateness of this methodology would be helpful in addressing the ethical concerns of institutional review boards and the public regarding continuation of a placebo-controlled trial after convincing efficacy results are available.

When the risks and benefits of vaccines are assessed, it is inevitably necessary, regardless of the sample size studied, to make subjective judgments on the basis of risk of disease, known risk of adverse events, and alternatives for disease prevention. The benefit of assessing safety more precisely so that more-informed decisions can be made must be balanced against the risk of delaying or inhibiting the introduction of new, effective vaccines.

Should the standard for evaluating the safety and efficacy of combination vaccines containing previously licensed components be different from the standard used to evaluate combinations of unlicensed components? Safety evaluation standards for combination vaccines containing novel components are, and should be, more stringent than standards for combination vaccines composed of licensed components. Prospective randomized, controlled studies are needed to examine both types of vaccine; however, some considerations may vary, depending on the nature of the components (licensed vs. unlicensed). Given that safety experience with vaccines containing novel components is limited, there is greater potential for unanticipated adverse events. In the case of licensed components, which have been thoroughly tested, data from “real world” postlicensure experience involving large numbers of people often are available, and the components often are already being administered simultaneously (although not in the same injection). The likelihood is small (but not nonexistent) that new safety issues would emerge as a result of combining the components in a single injection.

Several symposium participants from government, academia, and industry agreed that sample sizes of prelicensure safety studies of combinations consisting of licensed components could, in most cases, be smaller than sample sizes for studies of combinations composed of novel components, because a significant safety database would already exist for each component. The current practice for combinations of unlicensed components is to derive the safety database from efficacy trials for which sample size was determined on the basis of clinical efficacy, not safety, endpoints. In addition, for combination vaccines composed of components with previously proven efficacy, immunogenicity trials used to support licensure may enroll an insufficient number of subjects to assess safety with precision. In the latter case, an additional “safety only” study may be needed to generate an adequate safety database.

The FDA also requires that each component of a combination vaccine be evaluated for immunogenicity, efficacy, or both and stipulates that, ideally, these evaluations should be conducted by means of randomized, controlled clinical trials that compare the combination vaccine with its separate but simultaneously administered components. The appropriate endpoint (i.e., clinical efficacy or immune response) will vary according to whether the combination consists of previously licensed components or novel components. A clinical efficacy trial is likely to be required for licensure when a combination vaccine composed of a novel, previously unlicensed component is being evaluated. However, immunogenicity studies that evaluate vaccine-elicited immune responses may be sufficient and indicated if the components being evaluated have been previously licensed and if there are accepted immune correlates of protection. In such cases, clinical end-point efficacy trials generally would not be ethical or feasible.

How can the “great expectations” for postlicensure surveillance be fulfilled? Difficulties associated with conducting large prelicensure safety assessments result in “great expectations” that postlicensure surveillance systems will detect rare vaccine-associated adverse events in a timely manner. Postlicensure surveillance is often viewed as a safety net that can detect or rule out rare but serious adverse events that are impossible to detect during prelicensure evaluation. Current postlicensure surveillance methods can detect moderate changes in background rate of events fairly reliably but are limited by changes in background rate over time that result from factors other than vaccination, and they may, therefore, be less likely to capture conditions with delayed onset and diagnosis.

Postlicensure safety assessment tools include passive surveillance (the Vaccine Adverse Event Reporting System [13]), large, linked databases [14], and ad hoc controlled epidemiologic studies. In the future, it may be possible to conduct enhanced passive surveillance by the use of vaccine registries [15]. Registries could provide and link data on children who receive each combination vaccine and those who experience adverse
events that may be temporally linked to administration of vaccines. These linked data would make it possible to generate more accurate estimates of risk, although identification of concurrent and comparable controls could still be problematic.

A variety of steps are being taken to accomplish the task of better quantifying who receives which vaccines and what, if any, vaccine-associated adverse events occur. Funding was recently made available to establish regional clinical vaccine safety assessment centers to intensively study patients with known vaccine-associated adverse events, determine if there were particular genetic or other risk factors, and collect other relevant data. The Vaccine Identification Standards Initiative, a cooperative effort involving state and federal public health agencies, vaccine manufacturers, relevant professional medical associations, health care delivery institutions, and nongovernmental organizations, is developing a standard peel-off bar code that contains information about each vaccine, including manufacturer and lot number. This information could be scanned into a computerized database and would provide more-accurate means of determining the number of children who receive each combination of vaccines. Methods to improve the linkage between records of who receives which vaccines and reported adverse events include enlarging the Vaccine Safety Datalink System and using computerized immunization registries to track both vaccine coverage and any vaccine-associated adverse events.

Another needed tool is a precise and systematic method for review and analysis of data collected in the complex postlicensure adverse event surveillance system, particularly as they relate to combination vaccines. Data are available on multiple exposures (different combinations of vaccines produced by different manufacturers) and multiple outcomes (any temporally associated adverse event). The current system requires review of paper reports to identify trends that warrant further investigation. Work is under way to determine whether various types of automated exploratory methods could be used to identify patterns that might serve as an early warning of potential vaccine-associated problems.

CONCLUSION

The development, evaluation, and licensure of combination vaccines is an extraordinarily complex process with enormous public health implications. Although the symposium explored many of these complexities and provided available data and rationales that could contribute to solutions, policy changes must await further consideration, planning, and, in some cases, additional research.

Many of the unresolved issues discussed during the symposium apply to new monovalent vaccines as well as to combination vaccines. Topics requiring additional research include identification of quantitative correlates of protection for all vaccine-preventable diseases, determination of what constitutes a clinically meaningful difference in levels of immune responses, and development of a better understanding of the effect of qualitative aspects of antibodies (e.g., avidity and memory) on immunity. Vaccinology would benefit from the development and use of standards against which vaccine antigens could be compared.

Guidelines are needed for the development of efficient safety study designs that will, with reasonable precision, predict the likelihood of specific vaccine-associated adverse events. Standardization of definitions of adverse events would also allow current safety tools to function more efficiently and would allow data from a variety of sources to be compared.

Although advances in the field of combination vaccines have occurred only slowly since the Combined Vaccines and Simultaneous Administration workshop [16], we are closer to having solutions to many difficult problems. Although it is often not perceived to be as glamorous as development of new vaccine technology (e.g., DNA vaccines, mucosal and other needless delivery approaches, and immunization registries), combination vaccine development has the potential to greatly impact the effectiveness of vaccination programs in achieving the goal of preventing infectious diseases and their complications. Scientific gains inexorably beget new questions. Addressing the complex issues inherent in this process requires interaction of all components of the delicate fabric of the vaccine community: industry, academia, consumers, and government [17].

References