Perspectives on the State of Combination Vaccines: Summary of the Rapporteur for the International Symposium on Combination Vaccines

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Recent advances in immunology, biotechnology, and other sciences now give the prospect of a wide variety of new vaccines that can bring further improvements in health but that pose some theoretical issues relating to safety and efficacy, as well as practical issues relating to logistics, number of injections, and other factors. Combination vaccines are essential if society is to take full advantage of new vaccines that can further reduce the burden of infectious diseases in this country and around the world. The major issues relating to combination vaccines are much the same today as those discussed at a 1993 meeting. However, considerable progress has been made in developing solutions to the problems, and prospects are good that many of these issues will be resolved in the next 2–3 years.

Our experience with vaccines represents one of the greatest human achievements. Through the appropriate use of vaccines, we have eradicated one disease from the face of the Earth (smallpox), we are on the verge of eradicating another (poliomyelitis), and we are currently preventing millions of deaths each year around the world from diseases such as measles, diphtheria, and pertussis. Recent advances in immunology, biotechnology, and other sciences now give the prospect of a wide variety of new vaccines that can bring further improvements in health but that pose some theoretical issues relating to safety and efficacy, as well as practical issues relating to logistics, numbers of injections, and other factors.

In this context, we need to realize that combination vaccines are not just desirable: they are essential if society is to take full advantage of new vaccines that can further reduce the burden of infectious diseases in this country and around the world. For example, in the United States, the currently recommended immunization schedule for infants and young children calls for 15–19 injections at 6 immunization visits by the sixth birthday. Of this number, 12–16 injections are due by 18 months, and this number will increase to 16–20 with use of recently licensed pneumococcal conjugate vaccine. In developing countries, where access to health services is much more limited, the current schedule calls for 8 injections (if hepatitis B vaccine is included, as recommended) at 5 immunization visits before the first birthday. The introduction of new vaccines clearly will require combinations.

According to the letter of invitation, the goal of this meeting was to “fully explore laboratory, clinical, and epidemiologic data integral to developing and licensing new safe and effective combination vaccines.” In preparing to summarize this meeting, I reviewed the proceedings of the 1993 Workshop on Combined Vaccines and Simultaneous Administration [1]. I found a considerable overlap between presenters and topics at that meeting and those at this meeting. There is good news,
bad news, and further good news. The good news is that there are not really any new issues. The bad news is that there are not really any new answers, although the 1997 US Food and Drug Administration (FDA) report "Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases" [2] was very helpful. The further good news is that the issues have been clarified and considerable effort has been undertaken to resolve them, with considerable progress. The presentations at this meeting should form the framework for reaching final resolution.

In summarizing the 1993 workshop, Barry Bloom quoted Leo Szilard, the nuclear physicist who developed the theoretical basis for the atomic bomb, as saying, "An optimist is someone who believes that the future is uncertain" ([3], p. 388). He mentioned 4 shared certainties and then outlined a number of opportunities for acquiring greater certainty for the future. Briefly, the certainties were as follows: (1) the importance of vaccines; (2) the "enormous power the FDA exercises in regulating vaccines, both nationally and internationally"; (3) the fact that there will shortly be a "great many more vaccine candidates developed...than there is currently the feasibility to evaluate by classical approaches"; and (4) "the complexity of issues regarding priorities and decisions that will have to be made" ([3], p. 388).

Bloom stated, and I agree, that "There are few fields in all of biomedical science in which the reciprocity between basic and applied science is as great as it is in immunology and vaccines" ([3], p. 389). He addressed the following important issues:

Calculations of the number of combinations that one can envision in the future, with variations in routes of infection, doses, and adjuvant, indicate with certainty that it will be impossible to carry out sufficient numbers of efficacy studies, as has been done with the few vaccines we have currently. The hope repeatedly expressed during the meeting, then, was to be able to define appropriate surrogates for protection or new, more efficient ways to assess effectiveness and safety.

...the only immunological surrogate that has been used for almost all vaccines to date has been mean titer of antibody. It is hardly surprising, therefore, that interference in antibody titers has been considered the principal measure of interference. Clearly reductions in geometric mean titers are meaningless unless one knows the minimum protective titer for protection against an infection. A fourfold drop in titer, if it is still a log above the minimum protective titer, is an acceptable interference; a similar drop in a circumstance in which protection is only marginal would be unacceptable. Do we have information on minimal protective titers? In most cases not. In addition to aggregate data on mean titers, we need to know the frequency of nonresponders....

Regrettably, it seems certain that large-scale human trials will remain necessary in the foreseeable future. But from them may come greater information on appropriate surrogates for protection that will allow new combinations and a new generation of vaccines to be tested more cost-effectively ([3], pp. 390–1).

Bloom also talked about the central role of education (both of the public and of health care providers), the importance of increasing attention to vaccine safety, and the need for an expanded role for the National Vaccine Advisory Committee [3]. Bloom’s comments seem nearly as applicable today as they were six and a half years ago, but there has been considerable progress.

Let me now summarize some of the main issues discussed at this meeting, as I perceive them, including areas of agreement and disagreement. There were 10 areas of agreement.

1. The use of vaccines, whether alone or in combination, actually decreases the number of antigens the immune system is exposed to compared with natural infection. There is no basis for worry about "immune system overload."

2. There is a need to develop more or better correlates of protection and, if possible, surrogates of protection. This would greatly simplify efficacy studies.

3. Priming is necessary, but may not be sufficient, for long-term protection in all primed vaccine recipients, particularly with diseases of short incubation or when exposure is to a high inoculum.

4. Testing of combinations of licensed components does not have to be as extensive as testing of unlicensed components.

5. The concept of noninferiority is not as well understood as it should be. The null hypothesis is that the combination is inferior by a clinically important amount. Studies are designed to reject the null hypothesis, not to demonstrate equivalence. How is the principle of noninferiority to be applied? If applied very strictly, it might lead to withdrawal of licensure for one of the whole-cell pertussis vaccines licensed in the United States, because European trials demonstrated that it was inferior to acellular vaccines with respect to relatively frequent adverse events.

6. We should shift focus from looking at geometric mean concentration of antibody and instead look at the proportion of vaccine recipients who respond (or achieve a stated level of antibody) when protective levels are known. When protective levels for a given disease are not known, there may be important information gained from looking at the proportion of vaccine recipients who do not respond. This information can be overlooked if the only analysis is to determine the geometric mean concentration. We should also make more use of clinical and epidemiologic data from experiences elsewhere.

7. There is a need to standardize definitions of adverse events to facilitate comparative studies.

8. There is a need to expand the current vaccine safety
There is a need to develop a bridge for collection of both efficacy and safety data (particularly safety) between phase 3 trials and postlicensure surveillance. There was no agreement on how much safety information needs to be obtained before licensure and how much can await postlicensure study. Standards have been evolving, particularly safety standards. We need to acknowledge this evolution without losing the benefits we have achieved. If current standards were applied, it is likely that some widely accepted simultaneous administrations or combination vaccines might not be approved. I am personally attracted by the schema envisioned by Paul Fine at the 1993 meeting, in which he categorized adverse events by frequency and severity [4]. Events that are both frequent and severe should be detected early in vaccine assessment and should be prevented. Those that are mild and rare are “trivial and unstu-
diable.” Those that are both common and mild should be de-
tected by prelicensure trials, and those that are serious and rare should be studied by postlicensure observational studies. I believe that formal postlicensure monitoring for safety should be a requirement for all newly licensed products. There was a call for simplified large-scale prelicensure safety studies. Such studies would not require the complex monitoring needed to evaluate efficacy and common adverse events but would focus on severe rare events. Although such studies might be somewhat easier with respect to monitoring, the difficult consent process involved in the use of unlicensed products would remain.

The experience in Alaska that was described by Jay Butler demonstrates the importance of considering potential differences in behavior of different formulations of antigens when considering the use of combined vaccines as opposed to separate use of their components. The issue in Alaska was not the use of combined vaccine but the fact that the *Haemophilus influenzae* type b (Hib) component in the combined vaccine that was used was not as protective after a single dose as was the single-component Hib vaccine (a different preparation) that was used previously. Thus, the advantage of a combination in reducing the number of injections might not outweigh the use of components if the single-component vaccine is substantially more effective.

Moving to areas where agreement or resolution was not clear, we heard repeatedly that the FDA reviews all information about vaccines that is submitted to it. We also heard from the sponsors of clinical trials that there is no clarity in defining exactly what is needed, particularly with respect to combination vaccines. Do immune responses to components in combination vaccines need to match those of the specific components that are given individually, or do they only have to match those of any of the currently licensed component vaccines of that type? That is to say, if several different products are considered to be equivalent, is it not adequate for the performance of a component in a combined vaccine to be equivalent to the performance of any of these products? Particularly in the case of vaccines that are available as several different licensed products, it would be useful for the FDA to specify the response that is considered adequate for any vaccine component to meet, whether given separately or in combination with others. Publication of the standard would certainly help vaccine developers and manufacturers.

Although it was said at the conference that all vaccine issues are local, it is important to recognize the need for policies and standards at the national level that can help in disease prevention or control, help prevent confusion among providers and the public, and help to deal with practical issues of vaccine production. However, national-level recommendations should take into account subgroups of the population who are at special risk and may warrant separate approaches.

As someone who works with immunization registries and believes they are essential for maintaining and improving on our current success, I find it interesting that in 1993, Bloom said that “among the highest priorities would clearly be the establishment of a national vaccine registry, perhaps most readily by developing an integrated system of state registries, linking the vaccination reminders and recalls to the data bases, allowing analysis of effectiveness and adverse events” ([3], p. 391). At this meeting, Bob Chen reiterated the important role that immunization registries can and should play in monitoring vaccine safety. At present, all states in the nation are working on population-based immunization registries, and in 34 states, the registries are at least partially operational. In 1999, the National Vaccine Advisory Committee called for the development of a “nationwide network of community/state population-based registries that are capable of sharing information while maintaining privacy and confidentiality” ([5], p. 3). Registries can help reduce what Chen Le and Bruce Weniger call “combination chaos” by maintaining accurate records of exactly what vaccines a child received at a particular visit.

Of necessity, this meeting focused on problems and unresolved issues. I hope the studies described at this meeting and subsequent actions will allow us to have another meeting on combined vaccines in 2–3 years that will be a celebratory event, focusing on solutions, with participants congratulating one another on the remarkable improvements in health that have resulted from widespread use of vaccines, and with participants excited about the prospects of even further improvements through the introduction of additional vaccines. There will be agreement on the need to consider all aspects of the potential risks and benefits of new and combined vaccines, including the risks associated with failure to make the vaccines available to those who would benefit the most. Manufacturers, regulators, investigators, public health officials, private health care providers, and the public will be meeting in workshops to agree on
standards for evaluating combination vaccines, particularly combinations of components that are currently licensed. The result will be a transparent process that has wide support and ensures that new vaccines are introduced in a way that is both reasoned and expeditious.

Vaccines are truly miracles of science that have the potential to save even more millions of lives. No investigator, manufacturer, regulator, private health care provider, or public health official wants to make or use an unsafe or ineffective product or one that has to be recalled for any reason. At the same time, it must be acknowledged that zero risk is not attainable—either with vaccines or with decisions about vaccines. It has repeatedly been said at this symposium that judgment is needed in addition to blind adherence to regulations and numbers. Let’s exercise good judgment and see how we can further benefit our population and the world population through improved provision of safe and effective vaccines. This can only be done through increased use of combination vaccines. If we take risks, let it be in the direction of bringing health improvements to the people of the world.

References