Increasing evidence that the currently available acellular pertussis vaccines are not providing optimal control of pertussis in the United States and many other countries has stimulated interest in improvements of the current vaccines and in the development of new vaccines. A better understanding of the limitations of the current vaccines and the basis for the pertussis resurgence is needed to design improved vaccines. This article outlines several alternate approaches and summarizes the challenges related to the development of new or modified vaccines.

Keywords. Acellular Pertussis Vaccines; Resurgence

Although the recent marked increase in reported pertussis cases in the United States and other countries [1] has stimulated interest in the development of new or improved pertussis vaccines, development and eventual approval of new vaccines offer many challenges [2]. Whole-cell pertussis (wP) vaccines generally resulted in acceptable control of the disease [3]; however, concerns over adverse reactions prompted an international effort to develop safer vaccines, culminating in the introduction of acellular pertussis (aP) vaccines during the 1990s. In the United States, aP vaccines have been used exclusively since about 2000. A similar shift from wP to aP vaccines has been seen in Europe and is currently being considered at a global level.

Currently, 2 aP vaccines, a 3-pertussis-antigen vaccine and a 5-pertussis-antigen vaccine are used in the United States [3], and the same vaccines or similar vaccines containing 1–5 pertussis antigens are also used in most other industrialized countries [3]. These aP vaccines are combined with diphtheria toxoid (D/d) and tetanus toxoid (T) to produce either full-strength diphtheria, tetanus, and aP (DTaP) vaccines or reduced-antigen-content (Tdap) vaccines, which are used for primary (DTaP) or booster (Tdap) immunization.

The efficacy of the pertussis vaccine components for currently approved aP vaccines was demonstrated in a series of randomized, controlled efficacy studies [3, 4]. Although these aP vaccines were shown to be highly effective for the period of follow-up, ongoing monitoring has suggested that the current vaccines and vaccination programs are not controlling pertussis as well as desired [1, 2]. There is, however, an incomplete understanding of the reasons why this is true. Increasing evidence suggests that the adaptive immunity following immunization is relatively short-lived [5–7] and may not provide long-term protection against infection and transmission. Suggested reasons include a suboptimal balance of cell-mediated immune responses (eg, T-helper [Th] 1/Th2/Th17) [8], the omission of potentially important protective antigens, an insufficient quantity or incorrect balance of antigens, or a poor match between the specific antigens in the vaccines and those produced by the currently circulating strains [9].

Recent epidemiological evidence that wP vaccines provide more durable protection than aP vaccines [10, 11] has prompted questions regarding the feasibility of reintroducing wP (or modified wP) vaccines for ≥1 of the doses in the primary series. At this time, there is no wP vaccine licensed in the United States, and, to our knowledge, relicensing and reintroduction are not being considered at this time.

CHALLENGES FOR THE DEVELOPMENT OF NEW PERTUSSIS VACCINES

Vaccine development requires a substantial investment of financial and personnel resources and an expectation

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of a sustainable market. To justify these expenditures, clarity is needed regarding the optimal vaccine and target population. Although the primary goal is a reduction in the number of deaths and severe morbidity in infants too young to be protected by immunization with current vaccines, reduced disease and transmission in all age groups is also important and is likely an essential step for full protection of infants. However, a vaccine specifically designed to reduce deaths and severe morbidity in infants may not necessarily be the same as one designed to protect the general population; for example, a vaccine containing only pertussis antigens has been considered for neonatal or maternal immunization.

Although the current DTap and Tdap vaccines may not be optimal, they are safe and efficacious and have a significant impact on disease burden [12]. Thus, with any change, there should be a high degree of assurance that the new vaccine is safe and would control the disease better than (or at least as well as) current aP vaccines. Furthermore, because the current DTap vaccines serve as a foundation for many widely used pediatric combination vaccines, any change in the pertussis component of the DTap vaccines intended for infants would have to take into consideration the physicochemical compatibility of all antigens in the combination vaccine, as well as the safety and immunogenicity of the coadministered antigens. Fewer difficulties are anticipated when modifying the Tdap vaccines used for booster doses in older age groups, primarily because there are, at this time, a limited number of Tdap-based combination vaccines.

Development of new vaccines continues to be hindered by limitations in the nonclinical tools (eg, immunological assays and animal models) that can be used to gather the scientific evidence that a novel vaccine merits progression to clinical evaluation. Although mouse respiratory challenge models remain valuable for investigations of mechanisms of immunity and for proof-of-concept studies, limitations of mouse models have prompted interest in more relevant models [13].

The recent development of a baboon model that more accurately reflects human infection and disease has the potential to accelerate evaluations of new candidates [14].

Although human safety and immunogenicity trials for candidate vaccines are feasible, efficacy studies for pertussis vaccines seem impractical, because there are few sites, if any, with sufficient disease burden and necessary infrastructure. Furthermore, a placebo control group would not be ethically acceptable, and trials would require an exceedingly large number of subjects and several years of follow-up to demonstrate superiority with respect to magnitude and/or duration of protection. Innovative approaches therefore may be required to obtain the evidence to support effectiveness of new vaccines. For example, human challenge studies have been considered. One particularly important approach is the identification and validation of correlates of protection. Correlates come in 2 varieties, mechanistic and nonmechanistic, according to recent consensus terminology [15]. Whereas a mechanistic correlate (ie, an immune function responsible for protection) is preferable, a nonmechanistic correlate (ie, an immune function that statistically correlates with protection but may not be responsible for it) may be helpful. In the case of pertussis, more than a single immune response may be important. If confirmed and accepted by the scientific and public health communities, the demonstration that a new vaccine gives a higher response for an immune marker (antibody or T-cell response) that correlates with protection might offer an approach for approval of new vaccines. Studies aimed at identifying immune responses that distinguish protected from unprotected vaccinees remain vital.

OPTIONS FOR NEW PERTUSSIS VACCINES

Consideration has been given to the development of new vaccines that could improve control by increasing population coverage, allowing more frequent boosters or eliminate the need for periodic boosters, inducing a more protective or more durable immune response, offering a better match to circulating strains, and/or allowing the immunization of neonates [2, 16, 17]. Various options to reach these goals are considered below.

1. Vaccines containing only aP components: Availability of a vaccine that contains only aP components by removing other antigens (ie, T and D [or d] toxoid components) from DTap and/or Tdap vaccines [17] would allow more frequent pertussis booster doses without providing unnecessary doses of D (or d) and T toxoids, because frequent, repeated administrations of these toxoids are not recommended. Potential uses for an aP-only vaccine include a booster dose for 8–10-year-olds, a neonatal dose, and/or periodic boosters for adolescents and adults. Manufacturing would require relatively modest changes in formulation, and the existing data for those aP vaccine components in the currently licensed vaccines could be used to support and accelerate the development and evaluation of the aP-only vaccines. Nevertheless the collection of nonclinical and clinical data supporting the stability, safety, and immunogenicity of the final formulated product, along with regulatory review of these data, would still require some time (approximately 3 years).

2. Modification of antigens in current vaccines: Possible modifications of the current vaccines while maintaining the same antigenic composition include changing the content of ≥1 of the antigens (eg, increasing the PT content), changing ≥1 of the individual antigens (eg, PRN and PT) to match antigens of currently circulating stains of Bordetella pertussis, or changing in the method for detoxifying PT (eg, from a chemical to a genetic approach). A change in antigen content with no other changes in the manufacturing of the aP antigens may require only limited nonclinical and clinical assessments to verify safety and immunogenicity. A change in the antigen itself
from a new strain or using a different detoxification method for PT) represents a more significant developmental effort. In addition to the manufacturing issues, a developer must demonstrate that the modified vaccine is safe and must provide evidence from proof-of-concept animal models and/or clinical studies that the immune response to the modified antigen is likely to provide an acceptable level of clinical benefit.

3. Addition of antigens to current vaccines: Consideration has been given to adding ≥1 of the new antigens (eg, adenylate cyclase toxin, the autotransporter BrkA, and the iron-repressible protein IRP1–3) to broaden the antigenic coverage and potentially improve the magnitude and/or duration of protection [16]. However, considerable developmental work would be required to show that the new vaccine is adequately stable, safe and immunogenic in nonclinical and clinical assessments. Perhaps the greatest challenge would be gathering data to show that the new antigens would provide added benefit without interfering with the responses to the other vaccine antigens.

4. Modification of adjuvant in current vaccines: Recent advances in adjuvant technology have renewed interest in replacing the currently used aluminum adjuvants with a new adjuvant or in including a new adjuvant in addition to the aluminum adjuvant [18]. In theory, such changes could alter the nature of the immune response (eg, the balance of Th1, Th2, and Th17 responses) and improve the magnitude and/or duration of protection [18]. However, these formulation changes would necessitate substantial developmental work to demonstrate the physical and immunological compatibility of the adjuvant with all antigens in the vaccine (ie, D, T, and others) and to provide evidence that the modified vaccine is safe and likely to provide better control than the current vaccines. Given the difficulties in showing superior efficacy in a comparative trial, initial evidence may be indirect and most likely would emphasize data from relevant animal models and human immunogenicity assessments.

5. Change in delivery system: All the vaccines discussed above involve parenteral administration of a combination of B. pertussis antigens with at least 1 adjuvant component and induce essentially systemic immune responses, whereas B. pertussis infection is a strictly respiratory mucosal infection. The inherent limitations in the nature of the immune responses generated by the current aP vaccines have encouraged substantial interest in other delivery systems [16]. Possible approaches include (1) a live attenuated B. pertussis strain for intranasal administration, (2) other live bacterial or viral vectors genetically engineered to produce B. pertussis antigens, and (3) alternate delivery vehicles (eg, particulates, vesicles, or fusion proteins) designed to stimulate a different type of primary immune response, including mucosal immunity. A change in delivery system offers the potential to induce a more durable protective response by changing the nature of the primary immune response; nevertheless, such vaccines will require substantial efforts to refine the product and to gather evidence for safety and efficacy, as well as lack of interference with other vaccines administered concurrently.

Although there is interest in developing new vaccines, relatively few vaccines are under advanced development. One specific vaccine that has progressed to a phase 1 trial in young healthy adults is the live attenuated vaccine using B. pertussis strain BPZE1. This experimental vaccine is intended for intranasal administration (eg, shortly after birth), with the goal of inducing a long-lasting immune response similar to that induced by natural infection. Reports have been published of proof-of-concept studies for safety and efficacy using the mouse models [19, 20]; however, evaluation in other models (eg, nonhuman primates) and/or human challenge studies may be needed. As with all live attenuated vaccines, a variety of issues have been or must be addressed, including genetic stability, safety to the recipient, and transmissibility to contacts.

CONCLUSIONS

Improvements in pertussis control require a better understanding of the problem and the basis for the pertussis resurgence. Conflicting opinions and data remain regarding whether significant improvement would be provided by modification of antigens, addition of new antigens and/or changes in the adjuvant or delivery system. The options that offer the greatest potential to influence the duration of protection also offer the greatest scientific and regulatory hurdles and will require more time for development. More research is needed to improve the tools to gather the evidence that a new vaccine will provide superior control, including more relevant animal models, improved immunoassays, and a better definition of correlates of protection. The timelines for development are highly dependent on these improvements in these evaluation tools.

Note

Potential conflicts of interest. S. A. P. has served as a consultant for vaccine manufacturers, including GlaxoSmithKline and Sanofi Pasteur. C. L. has a patent pending (WO 2007/104451). B. D. M. reports no potential conflicts.

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