From Pertussis to Tuberculosis: What Can Be Learned?

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Following the introduction of whole-cell pertussis vaccines into the general population, the number of cases of *Bordetella pertussis* disease declined dramatically. As disease incidence declined, the public's concern for pertussis as a national health problem gradually waned. However, a shift in paradigm occurred, and various groups and the media began to voice their concerns regarding adverse events associated with whole-cell vaccines. These events provided an impetus for the expedited development of safer and as efficacious subunit acellular vaccines. Effective public health leadership, public advocacy, scientific ingenuity, and collaborative interactions between government, academia, and industry culminated in the licensure of acellular pertussis vaccines. In this article, emphasis is placed on conceptualizing how a national public health agenda was implemented that allowed better insight into various public health concerns related to the development and use of acellular pertussis vaccines, concerns that were eventually translated into concrete actions. Knowledge of the environment in which this occurred may play a major role in relating the pertussis experience to tuberculosis vaccine development.

Relevancy of the Pertussis Experience to Tuberculosis Vaccine Development

Much of the experience derived from pertussis vaccine research and field trials may provide useful information toward the development and licensure of tuberculosis vaccines. Both diseases have significant national and international importance that has drawn the attention of various groups, including politicians, scientists, and the lay public. The success of the pertussis program required a pooling of resources and the development of working partnerships among governments, industry, and academia.

In attempting to use the pertussis model as a paradigm for the development of effective vaccines to prevent tuberculosis, one immediately sees several outstanding differences between the epidemiological pattern and pathogenesis of the 2 diseases. For example, pertussis is an acute disease with specific end points. This is not the case for tuberculosis, for which it may take 30 years before end points manifest themselves and become recognized. The need for a surrogate end point thus becomes even greater in the case of tuberculosis. Furthermore, reactivation, which is a major concern associated with tuberculosis disease, is not a part of the pertussis syndrome.

Other significant differences between the 2 diseases involve the fact that several protective antigens have been identified for pertussis that are now part of the acellular vaccines. This is not the case with tuberculosis; we currently do not know what the protective antigens are, although candidates do exist. Studies in animals suggest that some of these candidates may be protective, but phase III studies will be necessary to confirm this observation in humans. Nevertheless, many of the logistical, ethical, political, and scientific obstacles that were encountered during the development and testing of acellular pertussis vaccines bear a strong resemblance to the uncertainties and concerns outlined in the Blueprint for Tuberculosis Vaccine Development. This report represents the summation and recommendations of a workshop held at the National Institutes of Health to provide a national strategy for the development of effective tuberculosis vaccines.

Examining the pertussis experience thus may provide an opportunity to increase the tuberculosis knowledge base, especially in the areas of transmission, pathogenesis, and host immunity. Overall, the pertussis experience will provide insight as to how a major public health problem was addressed and the steps taken to provide a satisfactory outcome.

Characteristics of Pertussis

*Bordetella pertussis* disease (whooping cough) is a severe/fatal respiratory infectious disease spread by airborne transmission that occurs primarily in infants and children. Although not considered to be a serious disease in adults, it is quite insidious in infants because of the small size of the airway, which is much more easily compromised than that of an older child or adult. In fact, most serious disease occurs in children <6 months old [1], partly owing to the incomplete protection afforded them following vaccination.

Studies suggest that although adults are at risk for milder disease, they serve as the primary reservoir for the pertussis
organism [2, 3]. Infection and reinfection are common despite immunization. There is also no indication of a carrier state, as demonstrated by the lack of asymptomatic carriage. Ancillary data derived from studies with whole-cell pertussis vaccines suggest that these vaccines may provide only a certain level of protection for up to 10 years, at which time there is a rapid waning of immunity [4]. Furthermore, disease does not appear to always confer either long-term or lifetime protection. In the future, it may become necessary to provide booster vaccinations at specified intervals to adolescents and adults to help eliminate or control the transmission of the disease to children.

The pathogenesis of the disease suggests that it may be in part toxin-mediated, although the clinical success of a monovalent pertussis toxoid vaccine in protecting against pertussis does not preclude the possibility that antibodies to pertussis toxin may be successful in blocking the attachment of the organism to the host or that cell-mediated immunity may play a predominant role. Regardless, it is most likely that pertussis toxin plays a significant role in the disease process and does this in concert with other important virulence factors that are responsible for the various pathological features associated with this organism. There are currently no satisfactory animal models available that mimic the disease.

Serological correlates of protection have not been conclusively demonstrated for any of the acellular pertussis vaccines that can accurately predict whether individuals are adequately immunized against pertussis. Recent data, however, have suggested the importance of several acellular vaccine components (i.e., pertactin and fimbriae), on the basis of household-contact studies [6, 7]. These components, in addition to pertussis toxin and filamentous hemagglutinin, have served as protective antigens in various animal studies.

Even though effective vaccines and antibiotics are available, on a global scale, 1400 children needlessly die from pertussis disease every 24 h. Compared with that for tuberculosis this number is small, but it does emphasize the fact that having available vaccines does not guarantee the control or elimination of an infectious disease agent and that other factors do come into play.

### Whole-Cell Pertussis Vaccines

In previous decades, pertussis was a leading cause of illness among infants in the United States. In 1934, pertussis reached its peak, with 265,269 cases reported, and caused about 12,000 deaths annually [8]. When a whole-cell vaccine against pertussis was first licensed for use in the United States in 1947, parents and physicians welcomed it gladly [9]. Following large, controlled, randomized field trials in the late 1940s and early 1950s with the whole-cell vaccine, efficacy was estimated to be 80%–90% [10]. Universal immunization in childhood subsequently resulted in dramatic reductions in the occurrence of typical childhood disease in the United States (figure 1) [11].

Unfortunately, worries about the disease itself were replaced by worries about the side effects associated with the whole-cell vaccine, which were relatively more frequent than those ob-

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**Figure 1.** No. of reported cases of pertussis among children in the United States during the past 49 years
served with other vaccines. The side effects associated with the vaccine ranged from vomiting, fussiness, high rates of local reactions, and low-grade fever in >50% of the vaccinees to less frequently occurring events such as persistent crying, seizures, high fevers, shock, and encephalopathy [12]. Although there is no conclusive evidence that the vaccine is associated with any severe adverse events, public advocacy groups, scientists, and the news media became increasingly concerned [13–17].

In response to public concerns regarding the whole-cell vaccine, several countries, including Great Britain, Japan, and Sweden, ceased immunizing their infant populations with the vaccine in the 1970s [13, 18, 19]. This resulted in a dramatic resurgence of pertussis in these countries, during which time epidemics and deaths ensued. In Japan, once acellular pertussis vaccines were introduced, the epidemic quickly subsided. In the United States, a crisis developed in the early 1980s due to insufficient supplies of vaccine, as manufacturers left the marketplace because of the burdens of vaccine-related liability and lawsuits [20].

All this resulted in a political mandate to accelerate the development of and clinical testing for equally effective but safer pertussis vaccines. It also resulted in passage of the National Childhood Vaccine Injury Compensation Act in 1986, designed to protect manufacturers from excessive lawsuits and the tort system as well as to pay for the care and medical expenses of those seriously injured by a preselected list of vaccines [14, 20, 21]. Thus, pertussis became a United States Public Health Service priority, and along with it came millions of dollars earmarked by Congress for initiating studies to develop and test new pertussis vaccines that were as effective as the conventional vaccine but with fewer or minimal harmful side effects.

The number of pertussis cases has decreased dramatically in the past 50 years, with 6564 cases and 6 deaths reported in 1997 [22]. Most children in the United States now receive a series of 5 pertussis vaccinations as part of a diphtheria-tetanus–acellular pertussis (DTaP) formulation. Although the incidence of disease has been reduced significantly, on a global scale >50 million cases and 300,000 deaths still occur per year [23].

Potential reasons for persistent disease include circulation of the microorganism in adult and nonimmunized populations, ineffective vaccines, poor coverage (especially in large metropolitan areas), and incomplete immunization schedules among children. It appears that adequate protection against severe disease is achieved only after a 3-dose priming series at 2, 4, and 6 months of age, followed by 2 booster doses at 15–20 months and 4–6 years of age. Unfortunately, even though the vaccine works in principle, there are other problems that may limit its effectiveness in developing countries, such as lack of availability, inadequate priming, or missed booster doses later on in life.

**Early Efforts to Develop and Test Acellular Pertussis Vaccines**

Scientists worldwide decided that more basic scientific research at the laboratory level was needed to thoroughly analyze the components of the *B. pertussis* bacterium that causes pertussis. They needed to know as much as possible about how humans—in particular, infants—were susceptible to the bacterium and how it was transmitted. With this basic information, scientists could devise new weapons with which to develop ideal vaccines and strategies for controlling the disease.

While basic scientific research was progressing on many different fronts, efforts were initiated by the National Institute of Allergy and Infectious Diseases (NIAID) and the World Health Organization (WHO) that allowed for collaboration among government, academia, and private industry. These collaborations helped accelerate the development of acellular pertussis vaccines consisting of specific, well-characterized, purified components (i.e., pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae) [24, 25], as well as standardized case definitions necessary for the determination of efficacy. Most of the recently licensed and unlicensed acellular pertussis vaccine formulations contain pertussis toxoid in different concentrations, in addition to one or more other antigens for the multicomponent vaccines. Furthermore, the pertussis toxoid component for most of the vaccines is inactivated differently. Most of the acellular vaccines also contain different amounts and/or types of diphtheria and tetanus toxoids, aluminum salts, and preservative.

The first efficacy trial supported by NIAID was initiated when 2 Japanese acellular vaccines (i.e., Biken-6 and Biken-7) became available following their successful introduction among 2-year-old Japanese children in 1981 [26]. The efficacy data from Japan looked very impressive; unfortunately, the data were not based on a prospective, randomized, controlled trial [27]. For this reason, the US Food and Drug Administration (FDA) would not accept the data for licensing the acellular vaccines in the United States. NIAID felt it was important to conduct appropriate phase III trials to provide the necessary efficacy data applicable to the United States. To accomplish this, a large-scale efficacy trial in Swedish infants was initiated in 1986 because of a high incidence of disease (i.e., ~6% per year) in that pediatric population and the fact that Swedish health officials were anxious to reintroduce a new pertussis vaccine into the routine childhood vaccination schedule [28].

Overall, the results demonstrated reasonable efficacy for both vaccines (i.e., 69% for the Biken-6 vaccine and 54% for the Biken-7 vaccine), along with a greater safety profile for these products when compared historically with the whole-cell vaccine. It should be noted that only 2 doses of the acellular vaccines were administered to 2800 infants, at approximately 6 and 8 months of age. Unfortunately, in the minds of many, the efficacy data were equivocal since a standardized case definition was not available at that time, nor was there a whole-cell vac-
cine control arm in the trial with which the acellular vaccines could be directly compared. Ultimately, the case definition used during the trial to define disease (i.e., culture confirmation with any cough) was more characteristic of mild rather than typical pertussis disease, the latter involving at least 3 weeks of paroxysmal cough [29, 30].

**Building a Better Mousetrap**

Many other unanswered questions and concerns remained following this trial and could be addressed only through additional efficacy studies. Some of the outstanding issues included (1) examining the use of additional doses of vaccine (3 vs. 2); (2) inclusion of a whole-cell vaccine control arm; (3) use of a US immunization schedule starting at 2–3 months of age; (4) evaluation of diphtheria-tetanus-pertussis (DTP) vaccines rather than vaccines containing just the “P” component; (5) evaluation of additional purified pertussis antigens in new candidate vaccines; (6) a need for more safety data from a larger subject pool; and (7) a search for immunologic correlates for protection [31].

To help in the establishment of new clinical trials, NIAID placed two “sources sought” advertisements. One requested the availability of acellular pertussis vaccines formulated as DTaP, and the other requested the availability of potential phase III study sites. NIAID also invited vaccine manufacturers to participate in a phase II trial to help select candidate vaccines for inclusion in the NIAID-funded phase III trials. Following much discussion and several workshops, the phase II trial began at 6 of NIAID’s contracted Vaccine and Treatment Evaluation Units, which are designed to evaluate and test new candidate vaccines in phase I–, II–, or III–type studies [32].

The design of the phase II trial included 13 acellular pertussis vaccines containing different antigenic components (i.e., monovalent to pentavalent) and involving different approaches for inactivating the pertussis toxin. However, all were subunit vaccines containing the D and T components. The trial was randomized, double-blind, and controlled with the US whole-cell vaccine. In fact, 2 licensed whole-cell vaccines, received by 6 of NIAID’s contracted Vaccine and Treatment Evaluation Units, which were responsible for vaccine and serum distribution [32].

The Pertussis Task Force was assigned the responsibility of selecting acellular pertussis vaccines for possible inclusion in various phase III trials. Selections were based on a set of pre-selected criteria (i.e., safety issues; anti-pertussis toxin responses that were \( \geq 16 \) times the minimum detectable levels; a series of laboratory characteristics that measured for purity, residual enzymatic activity, and potency; acceptability by the host country; and the presence of more than one component in the vaccine). Two locations, Sweden and Italy, were eventually selected as optimal sites in which to evaluate the absolute and relative efficacy of 4 different acellular pertussis vaccines in infants, with use of an immunization schedule of 2, 4, and 6 months.

Both trials were prospective, randomized, double-blind, placebo (DT)–controlled, and US whole-cell vaccine (DTP)–controlled and included a WHO case definition for typical pertussis [30] and vigorous case surveillance. The results of these studies showed that all 4 acellular vaccines were regarded as safer than whole-cell vaccines, and 3 of the 4 acellular vaccines were highly efficacious, with point estimates of \(~85\% [34, 35].

**Challenges and Hurdles**

There were many challenges and hurdles that were necessary to overcome to achieve success in both the Swedish and Italian phase III pertussis trials. Initially, getting industry involved was difficult because of a reluctance to participate in head-to-head studies and because industry officials sensed a loss of control and an absence of direct oversight in the conduct of the efficacy trials. Data-management issues were a major concern of industry members, especially with regard to having immediate access to the data for purposes of filing product-license applications with the FDA. To help facilitate data management and provide adequate oversight, NIAID assigned an epidemiologist from the Centers for Disease Control and Prevention to serve on location in the Italian trial. NIAID also shared clinical monitoring responsibilities with the various manufacturers.

Prior to initiating the phase III trials, NIAID established a Collaborative Research and Development Agreement with 2 of the vaccine manufacturers associated with the Italian trial to help defray the overall trial costs. Without the support and cooperation of industry, it is unlikely that the Italian efficacy trial would ever have gotten underway. Together, the total cost for both the Italian and Swedish trials was \(~$26\) million over a 3-year period. Both trial sites continue to monitor their re-
Table 1. Issues to address when establishing efficacy trials with vaccines for tuberculosis.

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<th>Issues</th>
<th>Details</th>
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<td>Identify immunologic correlates for protection.</td>
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<td>Standardize, optimize, and validate all laboratory assays to reduce variability.</td>
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<td>Establish sensitive and specific diagnostic tests for rapid detection of true cases and noncases of disease.</td>
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<td>Monitor epidemiological trends and other epidemiological studies of disease transmission at potential sites for phase III trials.</td>
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<td>Establish a standardized case definition.</td>
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<td>Identify sites with relatively high disease incidence rates to enhance the probability of demonstrating statistical significance.</td>
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<td>Develop a strong, well-coordinated on-site effort, good centralized data management, good laboratory infrastructure, and a clinical design that takes into account local needs.</td>
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<td>Eliminate the possibility of exclusive markets for vaccine manufacturers.</td>
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<td>Introduce basic research questions into the protocol.</td>
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<td>Determine what the trial is designed to do: have an impact on primary disease, block infectivity, block reactivation, or all of these.</td>
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spective populations for long-term safety and efficacy and for determining the effects of a booster dose of DTaP vaccine in previously immunized children.

Other issues also needed to be addressed before either of the efficacy trials could begin. For example, there were blinding issues that required the use of identical vials, stoppers, and caps for each of the vaccines and placebos to minimize any differences in vaccine appearance. Coordination of this task involved considerable cooperation on the part of both manufacturers and a tremendous amount of compromise.

During the course of the trial, several ethical issues arose that required skilled negotiations and lengthy discussions. One of the concerns involved the incorporation of a whole-cell pertussis vaccine arm into the trial. At first, this was found to be unacceptable because of reluctance on the part of most pediatricians to use this vaccine. Following a series of media campaigns and other promotional efforts, the vaccine was eventually introduced into the trial.

A second issue involved the use of a DT placebo in the Italian trial, which was considered by many to be unethical and unacceptable. Because only ~40% of the population was receiving pertussis vaccine before the start of the trial, the introduction of acellular pertussis vaccines to an overwhelming majority (i.e., 90%) of the study population and DT to only a small minority (i.e., 10%) justified the use of DT as a placebo. In essence, proportionately more individuals were receiving pertussis vaccine in the trial than in the general population.

A third issue also arose in Sweden and involved the use of a consent form, which was not commonly employed or considered “standard procedure” for recruitment in a clinical trial. Swedish health officials felt that such a document put the burden of consent on the shoulders of the parents rather than on the physician, where it properly belonged, since it is the physician who is primarily responsible for informing parents about the design of the trial. This eventually was resolved through a compromise whereby parents agreed to sign a document stating that they had been adequately informed about the various aspects of the trial and were familiar with its conditions, benefits, and safety concerns, outlined in the study informational brochure.

The last of the major hurdles involved regulatory issues. For the FDA, it was very important that the trial be designed to address all the important questions, maintain vigorous standards in the conduct of laboratory and clinical procedures, and provide answers to the many outstanding issues necessary to make future licensure decisions.

The Final Chapter

Many factors contributed to the success of the pertussis vaccine development program. First, there was the perception that a new, alternative vaccine was needed because of safety concerns associated with the whole-cell product. There was also a clear consensus on priorities, and NIAID played a very active role here. Having a political mandate and resource allocation from Congress certainly helped push the program forward. The integrated efforts of various organizations in the “vaccine continuum,” including manufacturers, were instrumental in promoting the success of the project. The ability to ascertain protective efficacy over a relatively short period of time helped control costs and maintain a strong level of interest.

The availability of several candidate vaccines allowed for the testing of more than one vaccine per trial, which again advanced the field. The fact that the clinical trials were well designed further contributed to a successful outcome. Some of the important trial design factors included (1) a standardized case definition, (2) standardized laboratory procedures, (3) a strong data-analysis plan, (4) active rather than passive surveillance, (5) centralized data management, (6) uniform protocols for the Italian and Swedish efficacy trials, (7) rigorous masking, and (8) good quality assurance and quality control measures.

The entire process of testing and evaluating acellular pertussis vaccines in the clinic was long and arduous. The effort lasted >13 years from the time the trials were first planned until licensure of the products for infants. The overwhelming desire of several manufacturers to develop new and safer pertussis vaccines was very instrumental in the eventual licensure of these products. The magnitude of this effort can be appreciated only when one realizes that a total of 8 international trials, testing 9 different acellular vaccines produced by 5 vaccine manufacturers and involving ~172,000 infants, were simultaneously in progress between 1991 and 1995 [31]. On the basis of a consensus of opinion and review by several regulatory agencies in different countries, the acellular vaccines were considered safer overall than whole-cell vaccines and (with one exception) as efficacious [34–37].

Four acellular pertussis vaccines have been licensed in the US for administration to infants and children. Because of various legal issues regarding intellectual property rights associated
with the pertactin component, several of the successful, highly efficacious acellular pertussis vaccines have not yet been licensed in the US. However, this situation is expected to change in the near future.

Designing an Acceptable Tuberculosis Vaccine

There are a number of critical steps in designing an acceptable vaccine. First, it is important to define the components that are necessary for providing protection. Under these circumstances, a natural infection should induce an immune response to the same components that make up the vaccine. Also important is to understand the mechanism of action for each of these components, both in vitro and in vivo, and to recognize that the mechanism of immunity may involve multiple immune responses that are not directed against a single protective antigen.

On the basis of the pathogenesis of a respiratory disease such as tuberculosis, it would appear reasonable to examine the role of mucosal immunity, as well as cell-mediated and innate immunity. In addition to developing an effective tuberculosis vaccine, it also may become necessary to develop or use existing adjuvants other than alum to help sustain and/or enhance host immunity while limiting the number of doses used in parenteral immunizations. Finally, questions on the optimal use of a vaccine with regard to schedule, combinations, and route of immunization must be addressed. Other questions may involve variables such as persistence of protection (e.g., whether a single dose of vaccine provides sustained immunity or whether multiple doses will be required at fixed intervals) and whether the vaccine can be used therapeutically as well as prophylactically.

Issues to Address When Conducting Phase I/II Trials for Tuberculosis Vaccines

When clinical trials are conducted to test new candidate tuberculosis vaccines in developing countries, a neonatal vaccine should be given according to the WHO’s Expanded Programme of Immunization (EPI) schedule or a schedule practical for an EPI plan. Under these circumstances, the possible interference with other childhood vaccines must be substantiated. It would be ideal for epidemiological studies to be conducted on selected populations to help define the potential for eradication and possible reservoirs of disease. There is also a need to examine the question of whether to use placebo-controlled and/or BCG vaccine-controlled trials and what the placebo and other potential controls need to be, but one must keep in mind that it would be unethical to withdraw the use of BCG vaccine in most countries.

For purposes of defining serological correlates of immunity, one might want to consider conducting household-contact studies. Unfortunately, studies of this type tend to provide estimates of efficacy that are lower than those in prospective studies. This circumstance is due to the more intense observation used in household-contact studies, which tends to reveal more mild and inadvertent cases of disease. There is also a more prolonged exposure to the studied organism among households. Case-control studies in a local or countrywide setting may yield data comparable to those from prospective studies done under a variety of epidemiological conditions. Through the use of phase I studies, clinicians can establish the optimal composition, number of doses, interval between doses (i.e., in situations where more than one dose is needed), and age for initiating immunization.

Prior to initiation of phase III trials, it will be important to determine potential field sites in which the use of BCG vaccine is either incomplete or not routine and where the incidence of AIDS will not compromise the study. In settings where AIDS is prevalent, ethical concerns must also be considered.

Summary and Conclusions

Tables 1 and 2 examine other issues that may contribute significantly to the successful development of a tuberculosis vaccine and the conduct of clinical trials that evaluate these products. Because scientists tend to build on previous research in an attempt to eliminate problems and enhance outcomes, learning from the pertussis experience may offer tremendous insight and advantages toward establishing state-of-the-art clinical trials to evaluate candidate tuberculosis vaccines.

References