Pertussis Vaccine Trials in the 1990s

Linda C. Lambert

Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

The significant burden of disease due to pertussis, which predominantly affects newborns during their first few months of life, was substantially decreased following the introduction of inactivated whole-bacterial-cell vaccines in the middle of the 20th century. Although these vaccines were effective in reducing the incidence of pertussis in the countries that implemented their widespread use, increasing concerns about pertussis vaccine–associated adverse events led the development of acellular pertussis vaccines containing 1 or more purified *Bordetella pertussis* proteins. During the 1990s, collaborative international clinical trials were conducted to evaluate the safety, immunogenicity, and/or efficacy of different acellular vaccines.

Keywords. Bordetella; pertussis; vaccine; whole-cell; acellular; DTwP; DTaP; efficacy.

PERTUSSIS VACCINE DEVELOPMENT: BACKGROUND

Pertussis remains a highly infectious respiratory infection that causes a significant burden of disease. Between the 1920s and early 1940s, an average of 175 000 cases of pertussis were reported each year in the United States, with the majority occurring in children younger than 5 years [1–3]. Highly effective, inactivated whole-bacterial-cell–derived pertussis vaccines that also contained diphtheria and tetanus toxoids (DTwP) were developed and approved in the early part of last century and, by the late 1940s, were being used in infants in many countries. In the United States, use of DTwP vaccine decreased the incidence of pertussis to <5000 cases per year by 1970 [3]. While their introduction led to a significant decrease in the number of reported cases of pertussis, DTwP vaccines were frequently reported to be associated with injection site reactions (eg, pain, swelling, redness), irritability, and with more-severe reactions, including rare neurologic side effects, such as febrile seizures [4]. Although DTwP vaccines are highly effective, the resulting decrease in pertussis cases led to increasing concerns about the frequency of the associated reactions, and several countries that suspended their DTwP vaccination programs, reported a resurgence of pertussis cases within a few years [5]. As a result, there was a call for the accelerated development of new pertussis vaccines that were as effective as the whole-cell vaccines but less reactogenic. Importantly, research in the 1970s to characterize *Bordetella pertussis* proteins led to the development of candidate acellular pertussis, diphtheria, and tetanus toxoid (DTaP) vaccines containing 1 or more purified antigenic components [6]. By the early 1980s, DTaP vaccines had been developed and licensed in Japan, with promising results [7]. This led to the initiation of clinical research efforts and field trials in the 1990s to pursue the licensure of DTaP vaccines in the United States and in Europe.

During the 1990s, there was an intense international effort to compare the safety, immunogenicity, and efficacy of DTaP and DTwP vaccines in infants [8]. The following describes key studies conducted to generate data supportive of licensure of DTaP vaccines as part of the pediatric primary series and booster doses.

COMPARING THE SAFETY AND IMMUNOGENICITY OF DTAP VACCINES: THE COMPARISON TRIAL

In the early 1990s, the National Institute of Allergy and Infectious Diseases (NIAID) sponsored a multicenter

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Correspondence: Linda C. Lambert, PhD, Respiratory Diseases Branch, Division of Microbiology and Infectious Diseases, NIAID/NIH/DHHS, Rm 3401, 6610 Rockledge Dr, Bethesda, MD 20817 (LL153P@nih.gov).

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phase 1/2 clinical trial in infants to directly compare the safety and immunogenicity of 13 different candidate DTaP vaccines with the safety and immunogenicity of 2 DTwP vaccines to help determine which DTaP vaccines should progress to phase 3 evaluation. The DTaP vaccines evaluated met prespecified criteria and varied in the number and amounts of their antigenic components, how they were manufactured, and their stage of development [9]. This prospective, randomized, double-blind, multicenter clinical trial, which enrolled 2342 infants who were vaccinated at 2, 4, and 6 months of age, showed, in general, a lower frequency of reactions with all of the DTaP vaccines, compared to reactions with the DTwP vaccines [10]. Across the different DTaP vaccines, there were some differences in reaction rates; however, no one vaccine was consistently the most or least reactogenic, and all had fewer and less severe adverse events, compared with the DTwP vaccines. Similar results were also reported when a booster dose was administered to children between 15 and 20 months of age [11]. The DTaP vaccines were immunogenic, eliciting antibody responses to all antigens included in each vaccine; however, no one acellular vaccine was the most or least immunogenic for all included antigens. The geometric mean titers (GMTs) of antibodies generated by the different vaccines differed significantly across the vaccine groups. While the antibody responses to pertussis toxin (PT) generated by the acellular vaccines exceeded those generated by the whole-cell vaccines, there was no correlation between GMTs to PT and the amount of PT in the vaccine [12]. Vaccine selection for subsequent efficacy evaluation by NIAID was based on multiple variables, including safety profile, immunogenicity, and antigen purity, and availability, which were reviewed by a scientific advisory group. Industry and other federal agencies pursued the evaluation of some of the same candidates, as well as others [9].

DTAP EFFICACY TRIALS

A series of prospective, randomized, double-blind efficacy trials were subsequently conducted 1990s, with the majority performed in countries that had suspended DTwP vaccination programs. Before the initiation of these trials, a study in the United States showed that DTwP efficacy estimates depended on the case definition used and that the use of a more severe case definition for pertussis (eg, paroxysmal cough with laboratory confirmation of *B. pertussis* infection) resulted in higher vaccine efficacy than less specific case definitions (eg, mild cough) [13]. While the majority of the efficacy trials used the World Health Organization (WHO) primary case definition (≥21 days of paroxysmal cough confirmed by culture or serology or documented epidemiological contact with a household member or other individual with a culture-confirmed case [14]), differences in individual study designs, study populations, vaccines evaluated, and study schedule limited direct comparisons across these studies [8]. A brief summary of the results of several key efficacy studies follows (Table 1).

A prospective efficacy trial was conducted in Italy in which 14 832 infants received 3 doses of one of two 3-component DTaP vaccines (SmithKline or Chiron Biocine), a DTwP vaccine (Connaught Laboratories), or a diphtheria and tetanus antigens (DT) only vaccine (Biocine) at 2, 4, and 6 months of age [15]. In this study, a pertussis case was defined as ≥21 days of paroxysmal cough with *B. pertussis* infection confirmed either by culture or serology. The results showed that the efficacy of the 2 DTaP vaccines was nearly identical (SmithKline, 83.9% [95% confidence interval {CI}, 75.8–89.4]; Chiron Biocine, 84.2% [95% CI, 76.2–89.7], and both were more efficacious against pertussis than the DTwP vaccine (Connaught, 36.1% [95% CI, 14.2–52.1]). The authors noted the substantially lower-than-expected efficacy results for the DTwP in this study, compared to that in other studies, and suggested that it may have been due to differences in study-specific methods and the influence of booster doses in other studies. The follow-up period for infants in this study was extended to further assess the duration of protection. The overall high level of efficacy of the DTaP vaccines persisted as children were followed for an additional 9 months (through 33 months of age) [16]. Through 3–6 years of age, the 2 DTaP vaccines continued to provide a similar degree of protection, indicating that a fourth dose of a DTaP vaccine could be postponed until preschool age in children who received a 3-component DTaP vaccine as their primary immunization in infancy [17].

A prospective efficacy trial was also conducted in Sweden among 9829 infants who were given 3 doses of either a 2-component or a 5-component DTaP vaccine, a DTwP vaccine, or a DT vaccine [18]. The primary case definition for pertussis in this study was defined as at least 21 days of paroxysmal cough and confirmed infection with *B. pertussis* by either culture or serology or as documented contact with an infected household member who had culture-confirmed pertussis. The investigators for this study reported that the efficacy for the 5-component vaccine (Connaught Laboratories, 85.2% [95% CI, 80.6–88.8]) was higher than that of the 2-component vaccine (SmithKline Beecham, 58.9% [95% CI, 50.9–65.9]). The DTwP vaccine efficacy was lower than anticipated (Connaught Laboratories/USA, 48.3% [95% CI, 37.0–57.6]). When participating children were followed over an additional 24-month period, the 5-component DTaP vaccine maintained a greater sustained level of protection, compared with the 2-component DTaP vaccine and the DTwP vaccines [18].

Building on these findings, an efficacy study was conducted in a large proportion of the birth cohort in Sweden between 1993 and 1994 [19]. In this randomized, double-blind trial, 82 892 infants were prospectively enrolled and randomized to receive 3 doses of a 2-, 3-, or 5-component DTaP vaccine or a DTwP vaccine. The results from this study showed that against

Table 1. Summary of Efficacy Results From Selected Pertussis Vaccine Trials Conducted in the 1990s

Study Site (Reference[s]), Manufacturer (Location)	Study Characteristics			Vaccine Characteristics		
	Design	Vaccination Schedule, Age, mo.	Primary Case Definition	Antigen(s)	Postvaccine Follow-up[a,e]	Efficacy, % (95% CI)
Italy [15, 16]	Prospective, randomized, double blind, placebo controlled	2, 4, 6	≥21 d of paroxysmal cough, with culture- or serologically confirmed *B. pertussis* infection	. . .	. . .	. . .
Chiron Biocine (Italy)	. . .	. . .	. . .	PT, FHA, PRN	17 mo	84 (76–90)
	. . .	. . .	. . .	. . .	26 mo[b]	89 (79–94)
SmithKline Beecham (Belgium)	. . .	. . .	. . .	PT, FHA, PRN	17 mo	84 (76–89)
	. . .	. . .	. . .	. . .	26 mo[b]	78 (62–87)
Connaught Laboratories (United States)	. . .	. . .	. . .	Pertussis whole cell	17 mo	36 (14–52)
Sweden [18]	Prospective, randomized, double blind, placebo controlled	2, 4, 6	≥21 d of paroxysmal cough, with culture- or serologically confirmed pertussis or documented contact with an infected household member who has culture-confirmed pertussis	. . .	. . .	. . .
Smithkine Beecham (Belgium)	. . .	. . .	. . .	PT, FHA	21–23.5 mo	59 (51–66)
Connaught Laboratories (Canada)	. . .	. . .	. . .	PT, FHA, FIM2, FIM3, PRN	21–23.5 mo	85 (81–89)
Connaught Laboratories (United States)	. . .	. . .	. . .	Pertussis whole cell	21–23.5 mo	48 (37–58)
Senegal [21]	Prospective, randomized, double blind, nested contact	2, 4, 6	≥21 d of paroxysmal cough, with culture- or serologically confirmed pertussis or direct epidemiological linkage to a culture-confirmed pertussis case	. . .	. . .	. . .
Pasteur Mérieux Sérums and Vaccines (France)	. . .	. . .	. . .	PT, FHA	1.7–1.8 y	85 (66–93)
Pasteur Mérieux Sérums and Vaccines (France)	. . .	. . .	. . .	Pertussis whole cell	1.7–1.8 y	96 (86–99)
Germany [22]	Prospective, blinded, household-contact study	3, 4, 5	≥21 d of paroxysmal cough, with culture- or serologically confirmed pertussis[c]	. . .	. . .	. . .
SmithKline Beecham (Belgium)	. . .	. . .	. . .	PT, FHA, PRN	2 y	89 (77–95)
SmithKline Beecham (Belgium)	. . .	. . .	. . .	Pertussis whole cell	2 y	98 (83–100)

Table 1 continued.

Study Site (Reference[s]), Manufacturer (Location)	Study Characteristics			Vaccine Characteristics		
	Design	Vaccination Schedule, Age, mo.	Primary Case Definition	Antigen(s)	Postvaccine Follow-up[a,e]	Efficacy, % (95% CI)
Sweden [19]	Prospective, randomized, double blind	3, 5, 12; 2, 4, 6[d]	≥21 d of paroxysmal cough, with culture-confirmed pertussis	. . .	. . .	. . .
					RR of Pertussis With Cough (95% CI)	
SmithKline Beecham (Belgium)	. . .	. . .	. . .	PT, FHA	Not done[f]	
Chiron Vaccines (Italy)	. . .	. . .	. . .	PT, FHA, PRN	1.4 (.7–2.7)	
Pasteur-Merieux-Connaught, (Canada)	. . .	. . .	. . .	PT, FHA, PRN, FIM2, FIM3	0.85 (.4–1.8)	
Evans Medical (United Kingdom)	. . .	. . .	. . .	Pertussis whole cell	1.0	

The table is adapted from contents in the article by Halperin [8].

Abbreviations: CI, confidence interval; FHA, filamentous hemagglutinin; FIM2, type 2 fimbriae; FIM3, type 3 fimbriae; PRN, pertactin; PT, pertussis toxoid; RR, relative risk.

[a] Data are duration of follow-up after the last dose, which composed the period examined in the efficacy analysis.

[b] After the 17-month follow-up period was completed (stage I), eligible children were followed for an additional 9 months (stage II).

[c] Children presenting with ≥21 days of spasmodic cough with either culture or serological confirmation of *B. pertussis* infection were considered index cases. Vaccine efficacy was measured in nonvaccinated household contacts.

[d] An independent analysis was not done in infants enrolled in the 2-, 4-, 6-month vaccination schedule.

[e] Post vaccine follow up period [19] was 3 years.

[f] Assignment of infants randomized to the 2-component acellular vaccine was made known during the trial because of poor efficacy.

culture-confirmed pertussis infection with or without ≥21 consecutive days of paroxysmal cough, the 5-component or 3-component DTaP vaccine and the whole-cell vaccine, when given in a 3-, 5-, and 12-month schedule, had similar efficacy against pertussis, as assessed by relative risk (Pasteur-Merieux-Connaught 5-component, 0.85 [95% CI, .41–1.79]; Chiron 3-component, 1.38 [95% CI, 0.78–2.69]; Evans whole-cell vaccine, 1.0). The treatment assignment of infants randomized to the 2-component DTaP group was made known during the trial because of poor efficacy. Against more mild disease (culture-confirmed *B. pertussis* with or without any cough), results in this study showed a 2–3-fold higher relative risk of pertussis for the 3-component vaccine, compared with the 5-component vaccine. The investigators concluded that the addition of *B. pertussis* fimbriae 2 and 3 proteins in the 5-component vaccine may provide increased effectiveness [19]. Ongoing follow up of these children continued, and while the incidence of pertussis remained low for nearly 5 years, an increase in cases among individuals aged 7–8 years in this cohort suggested a waning of the vaccine-induced protection and the need for a booster dose between 5 and 7 years of age [20].

A prospective, randomized, double-blind efficacy trial comparing a 2-component DTaP vaccine to a DTwP vaccine was conducted in Senegal. Three doses of the vaccine were administered to 4181 infants at 2, 4, and 6 months of age. Against the primary protocol definition of cough of at least 21 days duration that was confirmed by culture, serology, or direct epidemiological linkage (epilink) to a culture-confirmed case, the efficacy of the acellular vaccine was 31% (95% CI, 7%–49%), compared with 55% (95% CI, 38%–68%) for the whole-cell vaccine. The efficacies based on the more severe WHO case definition, in which exposure via epilink required a positive polymerase chain reaction result, were 85% (95% CI, 66%–93%) and 96% (95% CI, 86%–99%) for the DTaP and DTwP vaccines, respectively [21].

Results from a prospective household contact study in Germany showed that the DTaP vaccine was highly effective in preventing pertussis under conditions of household exposure [22]. In this study, 22 505 infants received their 3-dose primary vaccination series with a 3-component DTaP vaccine at 3, 4, and 5 months of age. Potential index cases among vaccinated infants were identified by passive monitoring, and if a child presented with ≥21 days of spasmodic cough and had either culture or serological confirmation of *B. pertussis* infection, the remaining members of the household were eligible for enrollment. Vaccine efficacy was measured by assessing the attack rates of pertussis in blinded, prospectively followed household contacts, using the WHO definition of spasmodic cough of at least 21 days. From 412 evaluable household contacts, the DTaP vaccine had an efficacy of 88.7% (95% CI, 76.6%–94.6%), based on the number of cases in the nonvaccinated household contacts, leading the investigators to conclude that acellular vaccines given as a primary series were highly protective in preventing pertussis until the time recommended for booster vaccination.

PERSISTING QUESTIONS

The pertussis vaccine clinical trials conducted during the 1990s were widely regarded as highly successful. The need to conduct the trials was clear. Industry, academia, and US and international governmental partners quickly came together, which resulted in the trials largely starting and concluding in the first half of the decade. In addition to rapidly generating efficacy data that supported the licensure of acellular vaccines in many countries, the unprecedented level of collaboration across these groups laid a foundation for ongoing vaccine development efforts and collaborations in many different areas—a legacy that persists today. As the trials in the 1990s were concluding, however, the following unanswered questions about the DTaP vaccines remained: Is there an optimum number of *B. pertussis* components in the acellular vaccine, and if so, what is it? Are there optimum amounts of each antigen? Is there an optimum schedule for DTaP administration? What is the duration of protection that they provide? The immunological correlates of protection from pertussis were also unknown during the trials in the 1990s and remain so today. The increase in pertussis cases being reported in many countries around the world today underscores the importance of these questions, and it is hoped that the ongoing research efforts that lead to their answers will become the legacy of this decade.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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