Acellular Pertussis Vaccines: The Rationale for an Efficacy Trial in Germany

Heinz-J. Schmitt, Anne Schuind, Markus Knuf, Fred Zepp, Karin Beutel, Carl H. Wirsing von König, Albrecht Neiss, Hans L. Bock, Hugues Bogaerts, and Ralf Clemens

After concern about the safety of diphtheria–tetanus toxoid–whole cell pertussis vaccines (DTPw), the recommendation to vaccinate children with DTPw was withdrawn in 1974 in the former West Germany. This led pertussis cases to increase to an estimated 100,000 annually. Despite renewal of the vaccination recommendation in 1991, vaccine use remained low. The German health care structure assures regular contact between most children and pediatricians. This enabled the conduct of a large efficacy trial with a diphtheria–tetanus toxoid–acellular pertussis (DTPa) vaccine. Because a placebo-controlled trial was not ethically possible, a prospective household contact study with a blinded clinical follow-up was done. Possible study participants were screened by their pediatrician, who also initiated diagnostic procedures. Clinical follow-up was done by another locally based but independent and blinded physician. Vaccine efficacy was calculated to be 89% (95% confidence interval, 76.6%–94.6%). None of the identified confounding factors biased results in favor of the DTPa vaccine.

Diphtheria–tetanus toxoid–acellular pertussis (DTPa) vaccines are well tolerated and highly immunogenic [1–4]. However, as there is no surrogate serologic marker to predict pertussis vaccine efficacy [5], a mandatory requirement for vaccine registration, efficacy in young infants was not adequately demonstrated until recently. Here we describe the rationale behind the decision to conduct a DTPa vaccine efficacy trial in the former West Germany, summarize study design and logistics, and present results.

Pertussis in the Former West Germany, 1991

In the former West Germany, a general recommendation for diphtheria–tetanus toxoid–whole cell pertussis (DTPw) vaccination was withdrawn in 1974 because of concern about serious neurologic side effects. Although reporting of pertussis cases was also discontinued at that time, it is estimated that in 1991 there were 100,000 pertussis cases in children. Studies from one area led to a conservative estimate of a 5.2% incidence of typical pertussis in children ages 0–6 years [6]. This high incidence, with many pertussis-related deaths each year, led health care authorities to reinstate the recommendation for DTPw vaccination in all children at ages 3, 4, and 5 months, starting in July 1991. However, after a 16-year lapse in pertussis vaccinations, it was difficult to convince pediatricians and parents of the safety and the benefits of DTPw, and vaccine use remained low. Because of the urgent need for well-tolerated pertussis vaccines, efficacy trials were done with a new DTPa vaccine.

DTPa Efficacy: Available Data

There have been several unsuccessful attempts to assess pertussis vaccine efficacy by laboratory tests [5]. Antibody titers against pertussis toxin (PT) and filamentous hemagglutinin (FHA) were thought to be protective [7, 8]. However, in a vaccine efficacy trial with a monocomponent (PT) and a bicomponent (PT and FHA) DTPa vaccine, no correlation between anti-PT and anti-FHA antibodies and protection could be demonstrated [5, 9]. For this reason, vaccine efficacy of DTPa vaccine had to be assessed by clinical trials.

Six different DTPa vaccines with different compositions have been in routine use in Japan since 1981. The efficacy of DTPa vaccines in Japan was evident from epidemiologic data that showed a decrease in pertussis incidence after the vaccines were introduced [2]. Efficacy trials in Japan with DTPa vaccines, where vaccine efficacy was estimated from household contact studies, varied from 78% to 92% [2, 10, 11]. Differences in results could be attributed to differences in methodology aspects. However, until recently in Japan, the primary DTPa immunization was given at age 2 years.

In a double-blind, placebo-controlled Swedish clinical study of monocomponent (12 μg of PT) and bicomponent (7.5 μg of PT and 7.5 μg of FHA) DTPa vaccines done during 1986–1987, infants aged 5–11 months received two doses 2 months apart. Vaccine efficacy was assessed with three different study designs: active blinded surveillance over 15 months, unblinded follow-up over 3 years, and a household contact study. Results
varied widely according to study design and case definitions (53%-80%) [5, 9, 12]. In addition, the small numbers of patients in the household contact study produced a wide confidence interval (CI) for vaccine efficacy. Also, only two doses were given, there was no DTPw group, and children were vaccinated late in infancy. Thus, a study was needed to allow the licensure of DTPa when given according to the recommended schedule, usually starting at age 2 months or no later than age 5 months in most countries.

**Study Design Selection**

There are four basic methods by which vaccine efficacy can be assessed [13]. One is the use of prospective controlled trials in which, after random allocation of vaccine and placebo, active case detection of disease is done blindly in both the vaccinated and the unvaccinated population. Such a study design has been considered the reference standard. However, because pertussis vaccination had been recommended by health care authorities in Germany since 1991, this type of study could not be done as it would have been unethical to offer a placebo.

The second method is the use of cohort studies with unblinded passive or active follow-up for disease in populations in which subjects are allocated to vaccine or control groups nonrandomly. The disadvantages of such studies include the lack of randomization, possible introduction of bias (including bias due to nonblinded evaluation of “cases” with and without pertussis), and the long observation period required.

Case-control studies with comparison of the vaccination status of ascertained cases with that of a control group matched for age and other variables is another option. Although such studies are comparatively easy and inexpensive to perform and produce results in a short time period, there are many opportunities for bias. Results must be interpreted with caution [13].

The fourth technique is use of household contact studies in which the attack rate is calculated for vaccinated and unvaccinated subjects exposed to a household member with pertussis. The advantage of this design is that in the household setting, the risk of developing pertussis after exposure to someone with the disease is high. Thus, the number of cases needed for calculation of vaccine efficacy is low, although the total number of households under surveillance is high due to an unknown incidence of pertussis in each household at the initiation of surveillance [14]. The time required to complete such a trial is comparatively short. As the analysis focuses on relatively few households with pertussis cases, the costs of such a study are lower than for studies that require the follow-up of a large cohort. Because the unvaccinated “control” group is generated from the general population (children whose parents refused pertussis vaccination), there is no need for a placebo, which circumvents ethical issues. Nevertheless, various confounding factors may affect the results, since there is no random allocation of DTPa, DTPw, or DT vaccines, and this must be considered in the study report, analysis plan, and in the analysis of the final data. If such a trial is done retrospectively and unblinded with regard to the vaccination status of household members, then biases introduced by the observer are a major concern. However, if such a trial is done prospectively, using both an observer and a laboratory blinded to the vaccination status of the subjects, bias related to the observer can be avoided.

In the past, vaccine efficacy rates derived from household contact studies were usually lower than those obtained by other methods [13]. This is thought to result from the intense exposure to large quantities of bacteria caused by the closer contacts that occur within households than would normally occur outside the family.

Apart from the study design used, estimates of vaccine efficacy also vary according to the case definition of disease and case ascertainment. The calculated efficacy of the vaccine increases as the definition of clinical severity of the cases increases. Using a clinical case definition alone without microbiologic confirmation of *Bordetella pertussis* infection, sensitivity increases, but specificity decreases. For case definition, the requirement of positive culture or a significant rise in antibodies against pertussis antigens increases specificity. The WHO definition of pertussis (≥ 21 days of spasmodic cough with confirmation by culture, serologic results, or household exposure to culture-confirmed pertussis) has been proposed as a standardized case definition [15, 16].

Recommended pertussis vaccination schedules in different countries can also influence vaccine efficacy. For all of these reasons, results from different studies may vary widely [13, 17].

**Study Design and Logistics**

The availability of an excellently structured health care system in which all charges are reimbursed and most children are regularly seen by private pediatricians, together with the high incidence of pertussis in the former West Germany and low DTPw vaccination coverage, enabled us to conduct a DTPa efficacy trial. Since administration of a placebo was ethically not possible, we used a prospective household contact study design with blinded follow-up of study participants.

A large multicenter safety trial involving 22,505 infants was done with a DTPa vaccine from September 1991 until December 1994 in the former West Germany [18]. Children enrolled in the study received a primary vaccination course of three consecutive doses of a tricomponent DTPa vaccine (Smith-Kline Beecham Biologicals, Rixensart, Belgium) at ages 3, 4, and 5 months. The vaccine contained PT (25 µg), FHA (25 µg), and pertactin (8 µg) combined with diphtheria and tetanus toxoids. Detailed data from this study are published elsewhere [18, 19]. The large population enrolled to receive this primary course of vaccination provided a unique opportunity to conduct a household contact study in areas participating in the safety trial.
In each of the six study areas, there was a main regional center and 10–27 collaborating investigational sites with pediatricians who participated in this household contact study. About half of the pediatricians had been involved in the safety trial; the others had been using licensed DT or, to a lesser extent, DTPw. After external advertising and increasing the general awareness among the pediatricians in the six areas, suspected pertussis cases were identified in the resident population in each study area by the following symptoms: coughing ≥7 days and coughing with spasms, vomiting, or whoops. The study area had >200,000 households with children in the age-range foreseen in the protocol.

Clinical pertussis was confirmed using cultures for *B. pertussis* from nasopharyngeal swabs obtained by physicians. Although cultures were prepared in laboratories at each study center, the main laboratory (located in Krefeld) that performed all serologic analyses also received isolates from the other study laboratories for verification of culture results. All laboratory analyses were done in a blinded manner with regard to the vaccination status of the household members.

The follow-up of a household contact was initiated directly after identification of a suspected index case. Secondary household contacts (vaccinated against pertussis or not) between ages 6 months and 4 years were followed prospectively. To avoid the possibility that a physician's knowledge of the patient's vaccination status might influence the disease diagnosis, an independent physician or medical field supervisor (MFS), usually a pediatrician, was selected in each study area. The MFS was informed of families with possible pertussis cases who had agreed to participate in the study so that clinical follow-up was done in a blinded fashion with regard to vaccination status of the household members and the laboratory outcome.

Surveillance was done by weekly telephone calls or household visits, and the symptoms of the index cases and of other household contacts were recorded. The MFS instructed the family to visit the family pediatrician, who initiated diagnostic procedures in suspected secondary pertussis cases. A portable computer was used for direct data entry at each regional site. Data were regularly transferred (at least monthly) into the main data management system, thereby allowing almost constant monitoring of the progress of the study. Verification of data entry was done by electronic double-entry comparison. Statistical analysis was done continuously by an independent institution (GMI, Munich), which received the vaccination status of study participants in a sealed envelope directly from the family pediatrician. Only this institute had access to all data for assessing vaccine efficacy (i.e., laboratory, clinical, and vaccination status). Since families were entered into the database at the time a first (index) case was suspected and since follow-up of contacts started at that time, it was impossible to drop households based on outcome of contacts (development of pertussis).

Assuming a vaccine efficacy of 80% and an expected pertussis attack rate in nonvaccinated subjects of 75%, it was calculated that evaluation of 100 secondary contacts was required for both the DTP and the control groups so that the width of the 95% CI was limited to 20% with a lower limit of ≥68%. Taking into account the local expected annual incidence of the disease and the known composition of households in this part of Germany, the vaccinated population had to be ≥20,000 subjects for a sufficiently high probability of household exposure. Possible covariables, such as age of the index cases and of secondary contacts, administration of antibiotics, and the socioeconomic status of the family were recognized and considered in the analysis.

Results of the household contact study showed that the protective efficacy of the tricomponent DTPa vaccine against culture or serologically confirmed pertussis with ≥21 days of spasmodic cough (WHO definition) was 88.7% (95% CI, 76.6%–94.6%) [19]. Two other efficacy trials with DTPa vaccines in infants in Italy [20] and Sweden [17] were recently reported. The Italian study, a double-blind comparison of two acellular vaccines including the vaccine tested in our study, used a licensed DTPw vaccine as a control. In the Swedish study, bicomponent and five-component acellular vaccines were compared with a licensed whole cell vaccine. In the latter study, children were randomized to receive DT or DTPa or DTPw, which was ethically permissible, since DTP vaccines were not recommended in Sweden at the time of the trial. In both studies, the whole cell vaccines had surprisingly poor efficacy, 36.1% in Italy and 48.3% in Sweden. In contrast, and with the exception of the bicomponent vaccine (58.9%), the acellular vaccines had good protective efficacies of 83.9%–85.2%.

In the Italian trial, the vaccine efficacy of the three-component DTPa that we used in Germany was 83.9% (75.8%–89.4%). This confirms that none of the confounding factors in our study biased results and validates the approach we used. As a result of our study, DTPa was licensed in Germany in early 1994 for use in infants. Since late 1995, the incidence of hospitalization for pertussis-related complications has decreased ~10-fold, fulfilling our ultimate goal.

**References**


