

Safety and Efficacy of Acellular Pertussis Vaccines: The Mainz Study and Other Recent Studies^{††}

J A I Weigl,^{*MD, MTropPaed, DTMH}, H L Bock,^{**MD}, R Clemens,^{***MD}, F Zepp,^{****MD}, P Habermehl,^{†MD}, K Beutel,^{‡MD}, S Müschenborn,^{‡MD}, G Sümenicht,^{‡MD}, A Schuind,^{§MD}, C H W von König,^{¶MD}, A Neiss,^{+MD}, S Laukamp,⁺⁺, S Kiederle,^{++Dip (Stat)}, H J Schmitt,^{+++MD}

Abstract

Following concerns about the safety and reactogenicity profile of diphtheria, tetanus and whole cell pertussis vaccines (DTwP), new and less reactogenic alternatives were developed over the last two decades. The new diphtheria, tetanus and acellular pertussis vaccines (DTaP) no longer consist of the whole bacterial cell but of either extracts or of a few highly purified components. While it soon became clear that DTaP vaccines are significantly less reactogenic than DTwP vaccines, their efficacy was disputed and remained unproven. First studies and epidemiological data from Japan suggested vaccine efficacy rates (VE) of about 80%; however, the first blinded clinical trial from Sweden documented a much lower VE. Worldwide, seven large DTaP efficacy trials have recently been completed. Our own efforts included a large safety trial with 22 505 vaccinees and, nested in this setting, a prospective household contact study. Typical WHO-defined pertussis developed in 7 of 112 DTaP vaccinated children following household exposure as compared to 96 cases in 173 children not vaccinated against pertussis. Thus, vaccine efficacy was calculated to be 88.7% (95% CI 76.6 to 94.6). The median duration of spasmodic cough in the few children vaccinated with DTaP who did start coughing was 17 days as compared to 35 days in unvaccinated children. No waning of protection was observed. None of the confounding variables analyzed influenced study results in favour of DTaP. Following administration of more than 67 000 DTaP doses, 153 serious adverse events were reported. Eight events were considered possibly related and five were considered related to the study vaccine. According to additional study results from the other trials it can be concluded that DTaP vaccines, like DTwP vaccines, are safe and effective. The choice between DTwP and DTaP should be based on acceptance of the reactogenicity profile, coverage rates achieved, costs and other factors in each individual country.

Ann Acad Med Singapore 1997; 26:320-5

Key words: Adverse events, Household, Vaccine efficacy, Whooping cough

Introduction

Whole cell pertussis vaccines, combined with diphtheria- and tetanus-toxoids (DTwP) have been available and in widespread use worldwide since the 1950s. This had resulted in a dramatic decline of pertussis-related morbidity and mortality. Nevertheless, DTwP was well known to frequently cause local side effects and fever as

compared to the diphtheria and tetanus (DT) vaccine. Following case reports on a temporal association between the administration of whole cell pertussis vaccine and the occurrence of severe neurological sequelae, health authorities in Japan, Sweden, Italy and Germany withdrew DTwP from their vaccination schedules for infants.¹⁻⁴ A sharp increase in the incidence of pertussis

* Research Associate

‡ Paediatric Resident

+++ Professor of Paediatrics and Microbiology

Hospital-department of General Paediatrics, Christian-Albrecht University, Kiel, Germany

** Medical Director Asia-Pacific

*** Vice President

SmithKline Beecham Biologicals, Rixensart, Belgium

**** Associate Professor of Paediatrics

† Paediatric Resident

§ Research Fellow

Paediatric Hospital, Johannes-Gutenberg University, Mainz, Germany

¶ Associate Professor and Director

Department of Hygiene, Microbiology and Laboratory Medicine, Municipal Hospital, Krefeld, Germany

+ Associate Professor of Biostatistics and Director

Department of Medical Statistics and Epidemiology, Technical University, Munich, Germany

++ Employee

Society of Applied Mathematics and Information, Munich, Germany

Address for Reprints: Professor Heinz-J Schmitt, Klinik für Allgemeine Pädiatrie der Christian-Albrechts-Universität zu Kiel, Schwanenweg 20, 24105 Kiel, Germany.

†† Based on a presentation made by Dr H J Schmitt at the 30th Singapore-Malaysia Congress of Medicine, 3 August 1996.

was an almost immediate result. Despite reintroduction of DTwP in Japan in 1979 for children two years of age and older, and in Germany in 1991 for primary immunization in the first six months of life, public acceptance was reluctant and thus immunization coverage remained low. This situation prompted the interest in effective alternatives.

Acellular pertussis vaccines (DTaP when combined with D- and T-toxoids) no longer consist of the whole inactivated organism but of either extracts from *Bordetella pertussis* cultures (T-type vaccines) or of highly purified antigens of the organism (B-type vaccines). Candidate antigens to be included in DTaP vaccines included pertussis toxoid (PT, formerly LPF), filamentous haemagglutinin (FHA), pertactin (PRN, or 69 kD outer membrane protein) and agglutinogens (Aggl, mainly 2 and 3) (Table I).

Acellular pertussis vaccines were introduced in Japan as early as 1981 for routine use in children two years of age or older.⁵ While it was known from earlier trials in Sweden and Italy^{6,7} that the new vaccines were significantly less reactogenic than the older whole cell vaccines, the efficacy of DTaP had yet to be proven. Since there is no serological marker for protection from pertussis after immunization or, likewise, after the natural disease, documentation of DTaP vaccine efficacy (VE) could only be demonstrated in prospective clinical trials.

Early Japanese experience with DTaP included only children two years of age or older. The unblinded follow up and other potential sources of bias raised additional concerns about the validity of these data. Efficacy data from Japan are summarized in Table II. In addition with the epidemiological observation that the incidence of pertussis in Japan declined with the continuous use of DTaP, there was little doubt that the acellular vaccines were efficacious, although exact efficacy rates were still debated. No data on the use of acellular pertussis vaccines were available for the use in children younger than two years of age. A first trial with one and two-component acellular pertussis vaccines in Sweden showed that VE

was between 54% and 69% (Table II). This was disappointingly low, since at that time most experts believed that whole cell vaccines offered a much higher protection rate.

To finally solve the question on the efficacy of DTaP candidate vaccines from different manufacturers, seven large clinical trials were launched in the 1990s (Table III). The composition of the vaccines used varied and covered most options from PT only to a vaccine with five *B. pertussis* components (Table I). The pertussis case definition proposed by a WHO working group or similar definitions were used and it was hoped that this would allow a comparison of VE estimates from the different studies. Since licensing agencies requested that DTaP vaccines should have a point estimate of efficacy of at least 80% with the lower margin of the 95% confidence interval (CI) of not less than 68% and with a limit of width of less than 20%, large sample sizes were required for epidemiological and statistical reasons. While a double-blind trial design was possible in studies conducted under the auspices of the American National Institutes of Health in Sweden and in Italy, this approach was considered as unethical in the four trials conducted in Germany and in Senegal. Thus, different innovative study designs were chosen to circumvent the ethical dilemma of using a placebo, in a situation where effective vaccines are available. Also sample size, epidemiological frame, population and vaccination schedule varied largely. Here we describe the different studies with emphasis on our own trial.

Household Contact Study and Cohort Study, Mainz, Germany

Low public acceptance of DTwP and considerable endemicity of pertussis in former West Germany allowed the conduct of a large multicenter trial of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus vaccine [DTaP-3, SmithKline Beecham Biologicals, Rixensart, Belgium (Table I)]. Starting from September 1991, this vaccine was administered to 22 505 healthy infants aged 3, 4, and 5 months

TABLE I: DTaP VACCINES USED IN RECENT EFFICACY TRIALS; AMOUNTS OF ANTIGEN IN µg UNLESS OTHERWISE SPECIFIED¹⁰

Number of components	Manufacturer	PT	FHA	PRN	AGGL	D	T
1	Amvax	40	0	0	0	25 Lf	7Lf
2	PasteurMérieux-MSD-Connaught	23,4	23,4	0	0	6,7 Lf	5 Lf
2	Pasteur Mérieux	25	25	0	0	30 IU	40 IU
2	SmithKline Beecham	25	25	0	0	25 Lf	10 Lf
3	SmithKline Beecham	25	25	8	0	25 Lf	10 Lf
3	Chiron Biocine	5‡	2,5	2,5	0	15Lf	10 Lf
4	Lederle†	3,2	34,4	1,6	0,8§	9Lf	5 Lf
5	Connaught	10	10	3	5¶	25 Lf	10 Lf

Number of components: †extraction vaccine, ‡genetically detoxified, §contains AGGL 2, ¶contains AGGL 2,3

DTaP: diphtheria, tetanus and acellular pertussis vaccines; PT: pertussis toxin/toxoid; FHA: filamentous haemagglutinin; PRN: pertactin=69 kD protein;

AGGL: agglutinin; D: diphtheria toxoid; T: tetanus toxoid; Lf: limits of flocculation

TABLE II: SUMMARY OF EFFICACY STUDIES IN THE 1980s (VACCINATION EFFICACY CHOSEN AS CLOSE AS POSSIBLE TO THE WHO DEFINITION UNLESS SPECIFIED OTHERWISE)

First Author	Year	Design	Vaccine composition	VE(%)†	95% CI
Aoyama ⁸	1985	household contact of hospitalized children	Japanese DTaP vaccines DTwP	79 79	
Kimura ⁹	1988	household contact	Japanese DTaP vaccines DTwP	94 80	
Aoyama ¹⁰	1988	household contact	various T-type B-type DTwP	88‡ 77‡ 78‡	68; 95 0; 96
Mortimer ¹¹	1990	household contact	Takeda DTaP extract vaccine	98 81§	84; 99 64; 90
Swedish ad hoc group ¹²	1988	double-blind randomized, placebo controlled	JNIH-6 (PT & FHA) JNIH-7: (PT)	69¶ 54¶	47; 82 26; 72
Storsaeter ¹³	1992	unblinded follow-up of ad-hoc group study	JNIH-6 JNIH-7	77¥ 65¥	65; 85 50; 75

i-different definitions of pertussis used: ‡difference not significant

§VE for milder disease including cases with atypical pertussis (i.e. less severe disease)

¶VE for both vaccines 80% for prevention against severe, culture confirmed pertussis with >30 days of cough

WE 79% for JNIH-7 and 92% for JNIH-6 for prevention against severe, culture confirmed pertussis with >30 days of cough

DTaP: diphtheria, tetanus and acellular pertussis vaccine; DTwP: diphtheria, tetanus and whole cell pertussis vaccine; PT: pertussis toxin/toxoid;

FHA: filamentous haemagglutinin; VE: vaccination efficacy; CI: confidence interval; JNIH: Japanese National Institute of Health

to document immunogenicity, reactogenicity and safety.¹⁴ Study subjects were recruited from six pediatric outpatient clinics and 88 private offices in six separate areas of former West Germany with a proven high incidence of pertussis (4.0% to 6.4%).¹⁵ Besides documentation of safety in the whole cohort, detailed reactogenicity analysis was obtained from the first 2 500 participants, and complete immunogenicity data from the first 600 participants. The immune-response to PT was analyzed in 5800 subjects. 'An additional objective was lot-to-lot analysis of consecutive vaccine lots in the detailed reactogenicity and immunogenicity study to demonstrate consistency.

Incorporated in this large prospective cohort study, a prospective household contact study with blinded follow up was performed from October 1992 through September 1994 (Schmitt et al¹⁶). The objective of this second nested study was to rapidly document vaccine efficacy.

The basic principle of a household contact study is that a first patient with proven pertussis (irrespective of age) is identified and the occurrence of pertussis in persons living in the same household is monitored. Finally the vaccination status of household contacts is solicited and the incidence of pertussis after household exposure in children vaccinated with DTaP, DTwP or no vaccine (controls) is calculated. Since the risk for pertussis in susceptible contacts is much higher (>50%) than the risk in the general population (which is 3% to 6% per year), only a small sample size is needed (100 evaluable household contacts in each group). Thus, investigators can concentrate their efforts on relatively

few subjects. (This type of study could be conducted even faster in countries where the average family size is bigger than in Germany). All these advantages make a household contact study easier to control, much cheaper and the results available sooner (Table IV). The prospective household contact study design had been recommended as a reliable trial tool for pertussis vaccines before.^{17,18} Some important details, however, need attention:

Classification of Contacts

Household contacts were classified as

- secondary case: onset of cough between ≥ 7 days but ≤ 28 days after onset of cough in the index case;
- co-index case: onset of cough < 7 days after onset of cough in the index case;
- tertiary case: onset of cough > 28 days after onset of cough in the index case

Tertiary and co-index cases were excluded from analysis of vaccine efficacy since presumably they had not contracted their infection from the index case.

Enrollment of Households

All pediatricians in the study areas were asked to monitor for households with a potential first (index) case of typical, i.e. WHO-defined pertussis (spasmodic cough ≥ 21 days plus cultural or serological proof of *B. pertussis* infection). Pertussis was suspected in patients with cough of any type for at least 7 days, or with coughing for any period of time but complicated by spasms, and/or vomiting, and/or whoops. Culture, immunoglobulin (Ig) G and IgA-ELISA were performed to prove infection.

TABLE III: SUMMARY OF EFFICACY STUDIES IN THE 1990s (VACCINATION EFFICACY CHOSEN AS CLOSE AS POSSIBLE TO THE WHO DEFINITION UNLESS SPECIFIED OTHERWISE)

Place	Design	Sample Size	Vaccination schedule (months)	Manufacturer	Vaccine composition	VE (%)	95% CI
Mainz	prospective, observerblinded household contact study	360 (22 505 cohort)	3, 4, 5	SmithKline Beecham Behringwerke	DTaP-3 DTwP	88 97	76; 94 82; 99
Göteborg	double-blind, randomized	3450	3, 5, 12	Amvax	DTaP-1	71"	63; 78
Stockholm	double-blind, randomized	9829	2, 4, 6	SmithKline Beecham Connaught Connaught	DTaP-2 DTaP-5 DTwP	58 85 48	46; 64 79; 88 36; 57
Rome	double-blind, randomized	15 601	2, 4, 6	SmithKline Beecham Chiron Biocine Connaught	DTaP-3 DTaPrecPT-3 DTwP	84 84 36	76; 89 76; 90 14; 52
Munich	case control study* *	16 780	2, 4, 6	Pasteur Mérieux MSD Connaught	DTaP-2 DTwP	95 96	63; 99 71; 100
Senegal	double-blind, randomized; combined with household contact study	4181	2, 4, 6	Pasteur Mérieux Pasteur Mérieux	DTaP-2 DTwP	86 96	71; 73 87; 99
Erlangen	double-blind, randomized with open DT-arm	8532	2, 4, 6	Lederle Lederle	DTaP (extraction), DTwP	80 89	75; 84 85; 91

* 55% (95% CI 12% to 78%) in the first year of life before dose 3

** all cases were culture positive, serology not done

VE: vaccination efficacy; CI: confidence interval; DTaP: diphtheria, tetanus and acellular pertussis vaccine; DTwP: diphtheria, tetanus and whole cell pertussis vaccine; DTaPrecPT-3: DtaP-vaccine with 3 pertussis components, where recombinant PT is used

TABLE IV: COMPARISON OF THE PROSPECTIVE HOUSEHOLD CONTACT STUDY AND OTHER STUDIES/TRIALS

Variable	Household Contact Study	Other Studies/Trials
sample size	small	large
time required	dependent on family size (short)	long
validity	yes	yes
frequent side effects detectable	yes	yes
rare side effects detectable	no	dependent on sample size
price	lower	higher

Households were eligible for enrollment in the study, if there was at least one additional household member (= contact) aged 6 to 47 months and if informed consent for participation had been provided by parents or legal guardians. For analysis of VE, a full three-dose primary vaccination course completed at least 28 days before exposure to pertussis was required but the booster dose had still to be pending. Exclusion criteria were serious chronic disease, immunocompromising condition or history of pertussis or pertussis exposure. After enrollment of a household, the pediatrician documented the vaccination status of all household members and forwarded copies of the vaccination cards directly to the data analyst.

Follow up

After enrollment of households with a potential index

case, a medical field supervisor, unaware of the vaccination status of household members ("blinded"), monitored all family members for the occurrence of cough by weekly structured interviews. Data on household composition, socioeconomic status, antibiotic use, diagnostic procedures and hospitalization were also collected. The final interview was not earlier than 56 days after onset of cough in the index case.

Microbiological methods to document *B. pertussis* infection were either culture (Regan-Lowe-medium, incubation at 37°C for 7 days) or serology (IgG and IgA antibody titres to PT and to FHA by ELISA).

Statistical Analysis

Vaccine efficacy (VE) was defined as

$$VE = (1 - P_v / P_n) \times 100$$

TABLE V: CHARACTERISTICS OF HOUSEHOLD CONTACTS (SECONDARY CASES)

	n	Mean Age (range in months)*	% females	% middle/high socioeconomic status	Use of erythromycin (%) in index cases	Mean age of index case of subset (months)
unvaccinated	173	27.6 (6-47)	47.4	46.5	63.1	59.9
DTaP vaccinated	112	13.0 (6-25)	50.9	53.5	51.8	55.0
DTwP vaccinated	75	18.6 (6-43)	53.3	49.3	72.0	52.6

* Differences reflecting the fact that children with the booster dose (administered at 15 to 24 months of age) were excluded.

DTaP: diphtheria, tetanus and acellular pertussis vaccine; DTwP: diphtheria, tetanus and whole cell pertussis vaccine

with P_v and P_n being the probabilities of developing pertussis within the observation period (attack rate) in vaccinated (P_v) and unvaccinated (P_n) subjects, respectively. With a presumed VE of 80% and a P_n of 75%, the sample size for a two-sided 95% confidence interval (CI) of 20% width was calculated to be 100 subjects in each of the vaccinated and unvaccinated group of children. Possible confounding factors were analyzed by Chi-square test and the Fisher's exact test (if cell count too low) for discrete variables; for continuous variables the t-test or Mann Whitney U-test (if no normal distribution could be assumed) were used.

Results

Index cases: 453 typical pertussis index cases were detected. They had a median age of 55.0 months, a mean age of 56.9 months and an age range of 2 weeks to 60 years; 52.3% were females, 50.6% from middle or higher social classes, and 97.8% had never been vaccinated against pertussis.

Contacts: 360 secondary cases were eligible for calculation of VE against typical pertussis (173 unvaccinated, 112 DTaP recipients, and 75 DTwP recipients). For further characteristics see Table V.

Vaccine efficacy: The time lapse from 28 days after the third vaccine dose in the contacts until the time of exposure to pertussis ranged from 57 to 627 days for DTaP vaccinees. Seven of 112 DTaP vaccinated contacts compared to 96 of 173 unvaccinated contacts developed typical pertussis. Thus, protective efficacy of DTaP was 88.7% (95% CI, 76.6% to 94.6%) for typical pertussis. Protection from milder disease (spasmodic cough ≥ 7 days and laboratory confirmation was 81.3% ; 95% CI, 68.4% to 88.9%). There was no correlation between time lapse after vaccination and development of disease, indicating the absence of waning protection. The incidence of spasmodic cough in contacts vaccinated with DTaP was 28% compared to 77% in unvaccinated contacts ($P \leq 0.001$). The median duration of spasmodic cough in vaccinated contacts (17 days) was significantly shorter than in unvaccinated contacts (35 days; $P = 0.0001$). Of the 75 contacts vaccinated with DTwP only one developed typical pertussis (VE = 97.6%, 95% CI, 83.1% to 99.7%). None of the confounding variables

analyzed (age/erythromycin treatment/vaccination status of index cases, family composition, socioeconomic status, age/number of household contacts/erythromycin treatment of household contacts) influenced study results in favour of DTaP. However, erythromycin was used much more often in index cases of non-vaccinated children ($P = 0.006$) and this reduced the attack rate of typical pertussis in unvaccinated contacts from 64.1% to 50.5% ($P = 0.08$). If anything at all, the use of erythromycin may have led to an underestimation of DTaP vaccine efficacy. No centre effect was observed when VE was calculated with and without those centres, which contributed the most or the least number of contacts to the pooled sample.

For the study design it is remarkable that 74.5% of all households involved had only one contact child for analysis of VE (small family size in Germany).

Results of the Mainz Prospective Cohort Study¹⁴

Safety: Following administration of 67 000 doses of DTaP to 22 505 subjects, 153 serious adverse events (0.23%) were reported. Eight were considered possibly related and 5 were considered related to the vaccination. The latter included one hypotonic-hyporesponsive episode. Incidence rates of Sudden Infant Death Syndrome (7 cases; 0.01%) or acute neurological events (20 cases; 0.03%) were lower than expected for the general population in the study area and all cases were not considered to be related to vaccination. Redness and local swelling of 20 mm or more occurred after 44 (0.6%) and 40 (0.6%) of 7270 doses, respectively, in the 2500 vaccinees analyzed in detail. High fever ($>39.5^\circ\text{C}$) occurred in 6 children (0.08%) within 48 hours of vaccination. In the immunogenicity analysis of 580 infants, 98% responded to PF, 96% to FHA and 98% to PRN.

From the data presented above, the SmithKline Beecham Biologicals' DTaP-3 vaccine was proven to be safe, well tolerated and immunogenic. Given a VE of 88.7%, it was highly efficacious with no indication of a waning protection rate.

Results of Other Studies

The results of the Mainz household contact study were later confirmed in a double-blind randomized

NIH-trial in Italy, where VE of the same 3-component vaccine was shown to be 84% (95% CI: 76% - 89%). The efficacies of other DTaP vaccines are summarised in Table III. Despite the differences between the studies, some conclusions can be drawn. PT seems to be the most important component of acellular pertussis vaccines contributing approximately 55% protection (Göteborg trial). FHA and PRN added a further 10% to 20% VE (SmithKline Beecham 2-component versus 3-component vaccine). Agglutinogens do not seem to add any additional protection in a vaccine where PT, FHA and PRN are combined (Connaught 5-component vaccine versus SmithKline Beecham and Chiron Biocine 3-component vaccines). Data with 2-component vaccines are more difficult to interpret. There was a high efficacy of the Biken vaccine used in the Munich study which was in contrast with the low efficacy of the 2-component vaccine used in the Stockholm study. This phenomenon was explained by different ways of antigen preparation for the two vaccines and/or differences in the trial design.¹⁹

A surprising collateral finding was that the Connaught DTwP-vaccine had a low VE (36% in Italy and 48% in Sweden). Thus a striking argument for the use of acellular pertussis vaccines is that their contents can be better controlled and this should guarantee better reproducibility and reliability in efficacy (Table VI).

Looking at these data, derived from different populations in Sweden, Germany, Italy and Senegal, with different vaccination schedules, different study designs from case-control to double-blind randomized trials, different types of case finding, follow up and documentation of *B. pertussis* infection, it is apparent that DTaP vaccines offer high protection rates against pertussis. Consequently, since early 1994, licenses have been granted in many countries. This has already resulted in a 10-fold decrease in severe pertussis-related complications in Germany. Concluding their household contact study in 1988, Aoyama et al¹⁰ envisioned that DTaP vaccines soon would replace DTwP vaccines.

At least for health care systems with larger budgets

and with low DTwP-compliance that vision has arrived already. In countries where DTwP is still used and where a high vaccination coverage rate is achieved, a careful choice could be made on pharmaco-economical evaluation. The good news for these countries is the high vaccine efficacy of at least some DTwP vaccines based on the studies presented here. Undoubtedly the better tolerated acellular pertussis vaccines will be the cornerstone for future, extended combinations like DTPa-HBV-HiB-IPV.

REFERENCES

- Cherry J D. The epidemiology of pertussis and pertussis immunization in the United Kingdom and the United States: a comparative study. *Curr Probl Pediatr* 1984; 14:1-78.
- Romanus V, Jonsell R, Bergquist S-O. Pertussis in Sweden after the cessation of general immunization in 1979. *Pediatr Infect Dis J* 1987; 6:364-71.
- Noble G R, Bernier R H, Esber E C, Hardegree M C, Hinman A R, Klein D, et al. Acellular and whole-cell pertussis vaccines in Japan. Report of a visit by US scientists. *JAMA* 1987; 257:1351-6.
- Finger H, von König C H W, Tacken A, Wassilak S G F. The epidemiological situation of pertussis in the Federal Republic of Germany. *Dev Biol Stand* 1991; 73:343-55.
- Sato Y, Kimura M, Fukumi H. Development of a pertussis component vaccine in Japan. *Lancet* 1984; 1:122-6.
- Edwards K M. Acellular pertussis vaccines-a solution to the pertussis problem? *J Infect Dis* 1993; 168:15-20.
- Edwards K M, Karzon D T. The search for an improved pertussis vaccine. *Pediatr Ann* 1990; 19:695-701.
- Aoyama T, Murase Y, Kato T, Iwata T. Efficacy of an acellular pertussis vaccine in Japan. *J Pediatr* 1985; 107:180-3.
- Kimura M, Kuno-Sakai H. Pertussis vaccines in Japan. *Acta Paediatr Jpn* 1988; 30:143-53.
- Aoyama T, Murase Y, Gonda T, Iwata T. Type-specific efficacy of acellular pertussis vaccine. *Am J Dis Child* 1988; 142:40-2.
- Mortimer E A, Kimura M, Cherry J D, Kuno-Sakai H, Stout M G, Dekker C L, et al. Protective efficacy of the Takeda acellular pertussis vaccine combined with diphtheria and tetanus toxoids following household exposure of Japanese children. *Am J Dis Child* 1990; 144:899-904.
- Ad hoc group for the study of pertussis vaccines. Placebo-controlled trial of two acellular pertussis vaccines in Sweden-protective efficacy and adverse events. *Lancet* 1988; 1:955-60.
- Storsaeter J, Olin P. Relative efficacy of two acellular pertussis vaccines during three years of passive surveillance. *Vaccine* 1992; 10:142-4.
- Schmitt H J, Schuind A, Knuf M, Beutel K, Schulte-Wissermann H, Gahr M, et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22,505 infants. *J Pediatr* 1996; 129:695-701.
- Schmitz M, Wassilak S G F, Schulte-Wissermann H, von König C H W. Schätzung zur Pertussisinzidenz am linken Niederrhein. *Monatsschr Kinderheilkd* 1994; 142:41-4.
- Schmitt H J, von König C H W, Neiss A, Bogaerts H, Bock H L, Schulte-Wissermann H, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA* 1996; 275:37-41.
- Orenstein W A, Bernier R H, Dondero T J, Hinman A R, Marks J S, Bart K J, et al. Field evaluation of vaccine efficacy. *Bull WHO* 1985; 63:1055-68.
- Muller A S, Leeuwenberg J, Pratt D S. Pertussis : Epidemiology and control. *Bull WHO* 1986; 64:321-31.
- Schmitt H J, von König C H W. Pertussis vaccines 1996. *Baillieres Clin Paediatr* 1997; 5:1-18.

TABLE VI: COMPARISON OF DTWP- AND DTAP-3-VACCINES

Variable	DTwP	DTaP-3
Vaccine efficacy	38% to 95%	79% to 89 %
Immunogenicity	lower than DTaP	higher than DTwP
Reactogenicity	high	low
Safety	yes	yes
Purity	low	high
Controllability	no	yes
Acceptance	low (in some countries)	presumed high

DTaP: diphtheria, tetanus and acellular pertussis vaccine;

DTwP: diphtheria, tetanus and whole cell pertussis vaccine