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A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal

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A randomized, double-blind trial comparing a diphtheria–tetanus–acellular pertussis vaccine (DTaP) (pertussis toxoid and filamentous hemagglutinin) with a whole-cell vaccine (DTwP) was conducted. A case–contact study was nested in the trial to estimate absolute efficacy. From 1990 through 1994, 4181 children were randomized to receive one of the vaccines at 2, 4, and 6 months. Severe adverse events were monitored weekly during two visits after vaccination. Fewer serious adverse events were observed after DTaP. Surveillance for cough illnesses persisting more than 7 days, in children under 15 years of age, was made by weekly home visits. Examining physicians, blind to vaccination status, took samples for culture and serologic testing. Pertussis was defined as 21 or more days of cough confirmed by culture, serology, or contact with a culture-confirmed person. Beginning 28 days after the third vaccine dose, the overall ratio of pertussis incidence in the DTaP group relative to the DTwP group ($RR_{ac/wc}$) was 1.54 (95% CI, 1.23–1.93). In children younger than 18 months of age, $RR_{ac/wc}$ was 1.16 (95% CI, 0.77–1.73) and 1.76 (95% CI, 1.33–2.33) in children older than 18 months, which suggests a shorter duration of protection with the acellular vaccine ($P = 0.090$). Absolute efficacy estimates derived from the case–contact study confirmed the lower protection afforded by the acellular vaccine compared with the whole-cell vaccine: 31% (95% CI, 7–49) versus 55% against the protocol case definition, and 85% (95% CI, 66–93) versus 96% for the more severe WHO case definition. Although vaccination with DTaP provided a lower degree of protection than the highly effective DTwP, this difference was less prominent before 18 months of age, the customary age for a fourth dose. The safer DTaP vaccine may prove a valuable substitute for whole-cell vaccines when used in a schedule that includes a booster dose. © 1997 Elsevier Science Ltd.

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The development of highly purified acellular pertussis vaccines was triggered by concern over known and purported adverse events associated with conventional whole-cell vaccines, as well as by some controversy regarding their efficacy[1].

A randomized, controlled trial demonstrated the protective efficacy of both a monocomponent formalin-inactivated, pertussis toxoid (PT) vaccine and a two-component PT and filamentous hemagglutinin (FHA) acellular pertussis vaccine when the two doses were given at 5-11 months of age[2]. Post-trial surveillance showed the significantly higher efficacy of the two-component vaccine[3].

In the absence of a whole-cell control group, it was not possible to evaluate the benefit of these acellular vaccines over the whole-cell pertussis vaccines currently given to infants in most countries. New trials that included whole-cell vaccine controls were necessary to establish new vaccination policies.

The relative merits of acellular and whole-cell vaccines are also debated in developing countries. For

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this reason, we conducted a randomized clinical trial that compared the efficacy of diphtheria–tetanus–pertussis whole-cell pertussis vaccine (DTwP) commonly used in Europe and West Africa, with a two-component acellular pertussis vaccine (DTaP). This acellular vaccine had previously been found to be safe and immunogenic in this[4] and other settings[5].

This trial took place in the Niakhar area of rural Senegal, which has been under continuous demographic and epidemiological surveillance since 1983.

The introduction of the World Health Organization's (WHO) expanded program on immunization in 1986 was followed by a decrease in the incidence and severity of pertussis cases, thus precluding the randomization of a non-immunized placebo group.

The primary objective of this study was to assess the relative efficacy of DTaP with respect to DTwP. The nested case–contact study allowed estimation of the absolute protective efficacy of both vaccines in order to interpret the relative efficacy data.

METHODS

Study design

The relative efficacy of the vaccines was assessed in a double-blind, controlled trial. Before the first dose, enrolled infants were randomly assigned to one of the two vaccine groups based on consecutive numbers randomized by computer at the National Institute of Health (Bethesda, MD, USA) and balanced in blocks of ten. Pertussis surveillance by weekly home visits included all children in the study area aged 0-15 years, irrespective of, and blind to, their vaccination status. Thus, surveillance was not restricted to study children. The comprehensive nature of this surveillance allowed a prospective, nested case–contact study to estimate absolute efficacy of each vaccines to be conducted simultaneously.

The study protocol was reviewed and approved by the Ministry of Health of Senegal and by the investigational review board Centers for Disease Control and Prevention (Atlanta, GA, USA), which approved it annually. Initial study approval by village chiefs was followed by community information meetings and individual informed consent[6]. Verbal informed consent was given by a mother before each dose, based on standardized information.

Population

In the Niakhar area of Senegal, the residential unit is the compound where an extended family lives in one or more households. Of the 30 villages in the study area, each compound was visited weekly by a field worker who collected demographic and epidemiological data that were recorded in a centralized database.

Infants were eligible for the trial if born between 1 February 1990 and 30 April 1994 to mothers who resided in the study area and attended the vaccination sessions. Non-inclusion criteria were: (a) serious congenital or chronic illness such as failure to thrive or cardiac failure; (b) a history of seizures or other neurological disorders; (c) previous physician-diagnosed clinical pertussis; (d) previous pertussis vaccination; or (e) parental refusal to participate. Non-included children received DTwP and IPV (criteria a, d, or e) or DT and IPV (criteria b or c).

Acute febrile infection (temperature $\geq$38.5°C) or other significant illness delayed inclusion.

Study vaccines

The heat-inactivated, whole-cell pertussis vaccine had a potency ranging from 5.8 to 11.4 international units (IU), according to WHO and European Pharmacopoeia requirements. It also contained at least 30 IU of diphtheria toxoid and 60 IU of tetanus toxoid adsorbed on aluminum hydroxide (aluminum content 0.54–0.65 mg per 0.5 ml dose).

Each dose of the acellular vaccine contained 25 μg of glutaraldehyde-detoxified PT, 25 μg of native FHA, at least 30 IU of diphtheria toxoid, and 40 IU of tetanus toxoid, all adsorbed on aluminum hydroxide (aluminum content 0.29–0.61 mg per 0.5 ml dose). The two vaccines, identical in appearance, were produced by Pasteur Mérieux Sérums and Vaccins (P.M.s.v., Lyon, France) in three lots (D1379, H0834, K0920) for DTwP and in four lots (S2112, S2301, S2684, S2938) for DTaP.

Administration of vaccines

Based on the central database, children due to be vaccinated were visited by a field worker the week before a monthly vaccination session and offered transportation. Vaccines were given simultaneously with IPV at approximately 2, 4, and 6 months of age. (In addition, BCG was given to all 2-month-old children.) DTP vaccines were injected i.m. into the anterolateral aspect of the right thigh. Later, children also received yellow fever and measles vaccines at 9 months of age.

The contraindications to receiving further DTP vaccine doses were persistent crying (for an estimated 3 h or more), a high-pitched cry, fever (rectal temperature > 40.5°C), or severe alteration in consciousness, collapse, or an anaphylactic reaction within 48 h of DTP vaccination.

Surveillance of adverse events

During the first two routine weekly visits following each vaccine dose, possible adverse events were screened by the field worker using a standardized questionnaire. For any positive answer, a physician interviewed the parents at home, examined the child, organised further investigations, and treated if needed. Children with a serious adverse event were re-evaluated after 1 month and then further examined 6 months to 1 year later.

Case ascertainment

Surveillance for cough illnesses. Active surveillance of pertussis cases of all children under 15 years of age living in the Niakhar area was initiated in 1988, i.e. before the first infants eligible for the study were born. Field workers visited all compounds weekly in search of children coughing for longer than 7 days. Every coughing child younger than 15 years of age was examined weekly, until the end of all cough illnesses in the compound, by a physician blind to vaccination status. Culture specimens were collected at the first visit and 1 week later. Blood specimens for serology

were collected at the first visit and approximately 6 weeks later. Erythromycin prophylaxis was administered at the first visit to all infants from the compound aged <6 months.

Laboratory methods

Bacteriology.. Nasopharyngeal aspirates were collected from both nostrils by a catheter connected to a manual vacuum pump. The catheter tips were directly plated for culture, and were rinsed in 1% casamino acid. Primary plates and aspirates were transported within 10 h at ambient temperature to the laboratory in Dakar, where aspirates were plated. Specimens were cultured on Regan Lowe agar plates containing 10% defibrinated horse blood[7]. Colonies were identified by morphology, Gram staining, oxidase and urease reactions, and direct immunofluorescence with specific *Bordetella pertussis* and *Bordetella parapertussis* antiserum (DIFCO Laboratories, Detroit, MI, USA).

Serology. Blood samples were collected by finger prick into microtainer tubes, centrifuged at the field station and the serum kept at −80°C. IgG titers to PT or FHA (supplied by P.M.s.v., Lyon, France) were measured by enzyme-linked immunosorbent assay (ELISA)[8]. Serial dilutions of paired serum samples, starting at a 1:60 dilution, were added to a microtiter plate, with the internal reference being human serum that had been calibrated against the FDA human serum lot 3. The ELISA units were calculated by the reference line method using standardized software (UNITCALC, Biosys-inova, Sweden). The minimum levels of detection were 2.0 ELISA units ml^{-1} for anti-PT IgG and 2.5 ELISA units ml^{-1} for anti-FHA IgG.

Polymerase chain reaction (PCR). PCR amplification of the pertussis toxin promoter region was used to detect *B. pertussis* DNA in nasopharyngeal aspirates[9,10].

Case definition

The primary protocol case definition considered children with at least 21 days of cough confirmed by at least one of the following: (a) isolation of *B. pertussis*; (b) diagnostic serology defined by a twofold increase in IgG antibodies to PT or FHA between the acute and the convalescent serum samples; or (c) epidemiological linkage (epilink), defined as the child who had contact in the compound with a culture confirmed child, and who started coughing within 28 days before or after onset of illness in the culture confirmed child.

A definition adopted at a WHO meeting after the beginning of the trial was used as a secondary case definition[11]. This definition considered 21 days of paroxysmal cough with the same confirmation criteria. Another secondary case definition required confirmation of the epilink by a positive PCR to *B. pertussis* from nasopharyngeal mucus in the child in question.

Statistical analysis

The calculated sample size assumed that the efficacy of the whole-cell vaccine was 75%, and allowed detection of a relative ratio of 1.5 in the incidences of pertussis between the acellular and whole-cell vaccine recipients at a 5% significance level. The analysis considered all cases occurring ≥28 days after the third dose. For each child, surveillance ended either at the onset of pertussis or upon refusal of investigation, additional pertussis immunization, emigration, or death. All surveillance ended 31 December 1994.

Relative efficacy of the acellular vaccine, compared with the whole-cell vaccine, is given as a ratio of the pertussis incidence rates between the acellular and whole-cell vaccine groups ($RR_{ac/wc}$). Because of the epidemic nature of pertussis in this area, $RR_{ac/wc}$ and 95% confidence interval (*CI*) were estimated in a proportional hazards model with calendar time as the time scale, and they were stratified by village[12]. This model allows village-specific incidence rates to vary over calendar time, while preserving a rate ratio that is common to all villages. A multivariate proportional hazards model was used to investigate confounding factors. A secondary intention-to-treat analysis was performed and included all children receiving at least one dose of the study vaccines, regardless of later pertussis immunizations.

Epidemiological surveillance registered cases of pertussis among both study and non-study children residing in the Niakhar area. Thus, the authors were able to determine the index cases within each compound. An index case was defined as the first case with cough in the compound which was laboratory confirmed (same confirmation criteria as secondary cases). Secondary cases were those who had onset of cough starting more than 7 days after the index case. Co-primary cases, whose onset of cough occurred <8 days after beginning of cough of the index case, were excluded from the analysis.

To be considered in the case–contact analysis, unvaccinated children had to be similar to study children, i.e. permanent residents of the area and passing the non-inclusion criteria defined in the Population section. The absolute vaccine efficacy was estimated relative to unvaccinated for both the acellular and whole-cell vaccines as $VE = (1 - AR_v/AR_u) \times 100\%$, where AR_v and AR_u are the secondary attack rates of pertussis for vaccinated and unvaccinated children, respectively. The 95% *CI* values were derived from a normal approximation of the logarithm of the risk ratio, AR_v/AR_u[13].

A cohort analysis, similar to the analysis of relative efficacy, was performed to support the case–contact study results.

Calculations were performed with SAS 6.10[14] and Epi-Info 6.0[15].

RESULTS

Group comparability

Between May 1990 and July 1994, 4181 infants were included and received a first dose of vaccine: 2089 in the DTwP group and 2092 in the DTaP group. More withdrawals were observed in the DTwP group ($n = 317$) than in the DTaP group ($n = 245$) ($P = 0.001$). Comparability between study groups for several background factors was evaluated at 28 days

after the third dose among 3619 children, and no significant differences were found (*Table 1*).

Adverse events

Vaccinations continued after the closure date chosen for analysis (December 1994). From May 1990 to June 1995, 4821 children receiving a total of 13724 doses of the study vaccines, were under surveillance for serious adverse events. This surveillance was completed after each dose in 97% of children. As shown in *Table 2*, no episode of hypotonia hyporesponsiveness, collapse or generalized cyanosis, suggesting an anaphylactic reaction, was observed. All four seizures observed within 48 h following a vaccine dose were febrile seizures. One child (vaccinated with DTaP) had recovered completely at the time of the medical visit. The other three were hospitalized: two (vaccinated with DTwP) suffered from simple febrile convulsions and one (vaccinated with DTaP) experienced symptoms in the context of bacterial meningitis, the onset of which was within a few hours after vaccination. The child initially recovered promptly after i.v. antibiotherapy but subsequently had neurologic sequelae (including seizures and learning disabilities).

Persistent crying was more frequent in the DTwP group ($P = 0.02$).

A similar number of deaths within 2 months of vaccination happened in the DTwP ($n = 38$) and DTaP ($n = 34$) groups, while the overall infant mortality rate in the study area is 85 per thousand.

Surveillance

During the period of surveillance, 2567 compounds were visited by a physician because of coughing episodes reported to the field worker that lasted more than 7 days. In 837 of these compounds, the physician confirmed at least one episode of more than 7 days of daily cough, and could not ascertain other definite diagnosis, such as acute lobar pneumonia, asthma, or tuberculosis. For children in these compounds, the physician initiated laboratory investigations and follow-up. In the course of further observation, a total of 3292 children less than 15 years of age and living in these 837 compounds were sampled, yielding positive *B. pertussis* cultures in 764 persons.

The total duration of follow-up was 3165 (DTwP group) and 3193 (DTaP group) person-year at risk. Mean duration of follow-up was 1.79 years in the whole-cell group (median 1.65 years), ranging from 0.01 to 4.25 years, not significantly different than 1.73 years in the acellular group (median 1.58 years), ranging from 0.01 to 4.25 years.

Among randomized groups of children followed at least 28 days after the third study dose, 587 were sampled for bacteriology and serology (with a median 10 days of cough).

Relative vaccine efficacy

The protocol case definition was met by 123 and 197 children in the DTwP and DTaP groups, respectively (*Table 3*). DTaP recipients showed a significantly greater rate of pertussis than DTwP recipients, i.e. $RR_{ac/wc} = 1.54$ (95% *CI*, 1.23–1.93). The intention-to-treat analysis displayed a slightly smaller point estimate of the rate ratio, as would be expected.

Case confirmation criteria are reported in *Table 4*. The pertussis rate ratio was greater if confirmation was based on bacteriology or serology rather than epilink. When considering epilink alone, the rate ratio point estimate was even lower ($RR_{ac/wc} = 1.28$), probably due to lower specificity, which could be corrected by the addition of a PCR validation ($RR_{ac/wc} = 2.31$).

Requiring paroxysmal cough and PCR validation in the case definition markedly limited the observed pertussis incidence in both groups, but more so in the DTwP group (*Table 3*), thus increasing $RR_{ac/wc}$ to 2.80.

Table 1 Comparability of vaccine groups at inclusion for analysis

Background factor		Whole-cell vaccine ($n = 1772$)	Acellular vaccine ($n = 1847$)
Age at inclusion for follow-up[a] (days)		208 [189–257]	209 [189–261]
% female		49.4	50.2
Weight at first dose[a]		5.4 [4.2–6.9]	5.5 [4.2–6.9]
Rank of birth no. (%)	1	228 (12.9)	234 (12.7)
	2–4	616 (34.8)	690 (37.3)
	5–9	813 (45.9)	776 (42.0)
	10–16	112 (6.3)	143 (7.7)
Age of mother[a] (years)		28.6 [18–41.3]	28.4 [18–40.8]
No. of persons in compound[a]		20 [7–60]	20 [7–60]
No. of persons (<15 years of age) in household[a]		7 [2–15]	7 [2–16]

[a]Median [5–95 percentile] shown

Table 2 Severe adverse events occurring within 48 h of a dose

	Whole-cell vaccine (6595 doses)		Acellular vaccine (6881 doses)	
Event[a]	*n*	%	*n*	%
Seizure	2	0.03	2	0.03
Persistent crying ≥3 h	8	0.12	0	0
HHE[b]/collapse or generalized cyanosis	0	0.0	0	0.0

[a]Physician's assessment or mother's report; [b]hypotonia hyporesponsiveness episode

Table 3 Relative vaccine efficacy of DTaP compared with DTwP for different case definitions

	No. of cases		
	Whole-cell vaccine	Acellular vaccine	Incidence rate ratio with 95% *CI*
≥21 days of cough (protocol definition)			
Protocol confirmation criteria[a]	123	197	1.54 [1.23–1.94][b]
Intention-to-treat	162	233	1.43 [1.16–1.74]
With PCR[c]	65	128	1.87 [1.38–2.52]
≥21 days of paroxysmal cough (WHO definition)			
Protocol confirmation criteria[a]	16	41	2.42 [1.35–4.34]
Intention-to-treat	23	49	2.06 [1.25–3.39]
With PCR[c]	10	31	2.80 [1.36–5.74]

[a]Cases confirmed by culture, serology, epidemiological contact with a culture confirmed case; [b]95% confidence interval; [c]direct proof of exposure for epilink cases provided by positive PCR

A multivariate proportional hazards analysis, using continuous and discrete background factors listed in *Table 1*, was performed. Only the size of the compound had a significant effect on the risk of pertussis: vaccinated children from compounds with more than 30 members had a greater rate of pertussis than vaccinees from smaller compounds, $RR = 2.12$ (95% *CI*, 1.66–2.71). However, including those background factors in the model did not change the value of $RR_{ac/wc}$, which was still 1.57 (95% *CI*, 1.25–1.96).

Duration of protection

Duration of protection could be examined by including current age, which is almost equivalent with time since last vaccination, as a time-dependent covariate. For children younger than 18 months, the age-specific rate ratio was 1.16 (95% *CI*, 0.77–1.73) and for children older than 18 months $RR_{ac/wc}$ was 1.76 (95% *CI*, 1.33–2.33) ($P = 0.09$). When PCR validation of the epilink was applied, $RR_{ac/wc}$ was 1.13 (95% *CI*, 0.66–1.95) for the younger group and was 2.30 (95% *CI*, 1.59–3.32) for the older ($P = 0.035$).

Absolute vaccine efficacy

Three hundred and eighty-seven vaccinated children from the trial cohort (190 DTwP, 197 DTaP), and 17 unvaccinated children fulfilling the criteria for inclusion in the case–contact study were exposed to pertussis. Considering PCR as a validation criterion, the numbers were 13 from the unvaccinated group, 159 from the DTwP and 168 from the DTaP group. Sex, birth rank, age at exposure, and characteristics of the index case (e.g. vaccination status, age, and cough duration) were compared between vaccinated and unvaccinated children. Unvaccinated children were more frequently exposed to unvaccinated index cases ($P = 0.043$, Fisher's exact test); however, this association was not significant by multivariate logistic regression, thus supporting the assumption of similar risk of infection between groups.

As shown in *Table 5*, vaccine efficacy against illnesses with 21 or more days of cough was estimated to be 55% (95% *CI*, 38–68%) for the DTwP vaccine and 31% (95% *CI*, 7–49%) for the DTaP vaccine. When considering illness involving 21 or more days of paroxysmal cough that had a PCR-validated epilink, the efficacy values were 96% (95% *CI*, 86–99%) for the DTwP vaccine and 85% (95% *CI*, 66–93%) for the DTaP vaccine.

In a cohort analysis on 229 unvaccinated children, using the proportional hazards model as was used for the determination of relative efficacy, and with similar inclusion and exclusion for the unvaccinated children of each age cohort, absolute efficacy by the protocol case definition was 66% (95% *CI*, 46–78) for DTwP and 48% (95% *CI*, 18–66) for DTaP. The corresponding figures for the WHO definition were 91% (95% *CI*, 81–96%) for DTwP and 79% (95% *CI*, 58–89%) for DTaP.

DISCUSSION

For the adverse events under surveillance in this study, both whole-cell and acellular vaccines were found to be safe. Still, the acellular vaccine was associated with a lower frequency of persistent crying. A prior study in the same population showed markedly lower frequen-

Table 4 Confirmation of pertussis episodes of ≥21 days of cough. Number of cases and rate ratios when only using one diagnostic criterion

	DTwP		DTaP		
Criterion	*n*[a]	%[b]	*n*[a]	%[b]	Rate ratio ($RR_{ac/wc}$) with 95% *CI*
Per protocol	123	100	197	100	1.54 [1.23–1.93]
Bacteriology	30	24	59	30	1.82 [1.17–2.84]
Serology	37	30	69	35	1.83 [1.23–2.74]
Epilink[c]					
All	106	86	159	81	1.46 [1.14–1.87]
Bac neg., Ser neg.[d]	66	54	87	44	1.28 [0.92–1.77]
Bac neg., Ser neg.[e] PCR positive	8	7	20	10	2.31 [1.01–5.28]

[a]Number of cases confirmed by this criterion; [b]percent of the total number of confirmed cases; [c]contact within 28 days of onset of cough with a culture confirmed case of the same compound; [d]excluding cases not directly confirmed by culture or serology; [e]epilink cases validated by positive PCR for *B. pertussis* on nasopharyngeal specimens from the ill child

Table 5 Absolute efficacy of three doses of DTaP and DTwP according to different case definitions by case contact analysis

	Unvaccinated c/E[a]	DTwP			DTaP		
		c/E[a]	VE[b] (%)	95% *CI*	c/E[a]	VE[b] (%)	95% *CI*
≥21 days of cough (protocol definition)							
Protocol confirmation criteria[c]	13/17	65/190	55	38–68	104/197	31%	7–49
With PCR[d]	8/13	25/159	74	55–85	49/168	53%	23–71
≥21 days of paroxysmal cough (WHO definition)							
Protocol confirmation criteria[c]	8/17	7/190	92	81–97	24/197	74%	51–86
With PCR[d]	6/13	3/159	96	86–99	12/168	85%	66–93

[a]Number of secondary cases/number of exposed children; [b]absolute efficacy; [c]cases confirmed by culture, serology or epidemiological contact with a culture confirmed case; [d]direct proof of exposure for epilink cases provided by positive PCR

cies for the acellular vaccine for more common adverse events, such as fever, fussiness, and local reactions, compared with the whole-cell vaccine[4]. These results are consistent with other studies of the same acellular vaccine[16,17].

Even though less reactogenic, the acellular vaccine afforded significantly less protection than the whole-cell vaccine. The primary estimate of the relative risk was confirmed by secondary analyses.

A large proportion of cases was confirmed by the epilink alone, without direct laboratory confirmation, and thus had lower specificity. When strengthening the epilink by PCR validation, thus adding direct proof that this exposed child was carrying *B. pertussis*, the case definition became more specific. $RR_{ac/wc}$ increased with more severe disease and more specific case definition limiting misclassification bias[13], as already observed[18].

The difference in protection between the two vaccines also was associated with a shorter duration of protection with the DTaP.

Interpretation of the relative efficacy data is aided by the estimate of absolute vaccine efficacy as an internal yardstick. Indeed, the same relative risk can have a different practical significance depending on whether it is applied to vaccines of moderate efficacy or to high efficacy vaccines. Absolute efficacy was estimated by the case–contact method[19]. This analysis was performed within the same population and at the same time, with case detection blind to vaccination status. Characteristics of the unvaccinated group were not found to be different from those of vaccinated children, although the small sample size limited the power of the comparison. Nonetheless, absolute efficacy estimates derived from the cohort analysis were consistent with those of the case–contact study. As already observed[1], the estimation from the case–contact method was lower. The overall efficacy estimate of the DTwP vaccine was closer to estimates obtained for the same vaccine from other countries where it is routinely used[20,21].

The practical significance of the inferior protection afforded by this DTaP in the control of pertussis is debatable. DTaP will be given most often in a schedule that includes a fourth, and even a fifth dose, which should increase its efficacy. Also, the effectiveness of a vaccination program with acellular vaccines can be enhanced by their better safety.

In developing countries, however, children may be deprived of further vaccination after one year of age. Data from a trial in Sweden[22], where DTaP vaccine was given at 3, 5 and 12 months of age may indicate that the third dose augments protection if administered at the end of the first year of life. This is consistent with the recommended age for vaccination against measles and could warrant specific studies on optimal vaccination schedules.

Efficacy trials of other acellular vaccines have been reported recently[22–27]. The content of the vaccines varied from one (PT) to five components (PT, FHA, pertactin and fimbriae). The interpretation of the results across the studies is difficult. One cannot simply compare specific efficacy figures. In addition to the statistical variability, any comparison of absolute efficacy is complicated by marked differences in study design and execution, duration of follow-up, vaccination schedule and disease exposure.

In this population, factors such as the family size, nutritional habits, and high infectious background (e.g. malaria parasitemia) are other specificities.

As an example, in our study, paroxysmal cough was diagnosed by a physician; the diagnosis of cough was likely to have been more specific than in other studies where information was collected from the parents by non-physicians. Also, the duration of observation in the present study was longer than in any other trial.

However, comparing the present findings with those of previously reported studies emphasizes that other studies have usually found that whole-cell vaccines were superior to acellular vaccines[26] except for one whole-cell vaccine in two trials[23,24]. This reinforces two general conclusions. First, these findings confirm the heterogeneity of whole-cell vaccines suggested by immunogenicity studies[28]. In practice, the low efficacy of a particular whole-cell vaccine should not deter national or international health authorities from promoting the use of effective and inexpensive whole-cell vaccines. Furthermore, the extensive use of whole-cell vaccines, including the one found to be less effective, in a five dose regimen, has satisfactorily controlled pertussis in the USA.

Second, the optimal antigen content of acellular vaccines cannot be derived from the available results, and acellular vaccine choice should consider further aspects such as cost, combinations with other vaccines, and duration of protection. In our study, the shorter duration of protection provided by the acellular vaccine was revealed through a prolonged period of follow-up. This finding may well apply to other acellular vaccines, and should encourage long term follow-up and post-licensure surveillance for all acellular pertussis vaccines.

A decision to change to this acellular vaccine should take into account the type of whole-cell vaccine

routinely used, the possibility for a booster dose, combinations with other vaccines and cost.

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