The Lancet · Saturday 30 April 1988

PLACEBO-CONTROLLED TRIAL OF TWO ACELLULAR PERTUSSIS VACCINES IN SWEDEN—PROTECIVE EFFICACY AND ADVERSE EVENTS

AD HOC GROUP FOR THE STUDY OF PERTUSSIS VACCINES*

Summary 3801 children aged 5–11 months were entered into a blind placebo-controlled trial of pertussis vaccine. 954 were randomised to receive placebo (vaccine solvent), 1419 to receive a two-component vaccine containing formaldehyde detoxified lymphocytosis promoting factor (LPF) and filamentous haemagglutinin, and 1428 to receive an LPF-toxoid vaccine. After 7–13 weeks 3724 infants received a second dose. Immediate side-effects were mild. Small local reactions occurred more often in the vaccinated infants than in those who received placebo, especially after the second dose of the two-component vaccine. During 15 months of follow-up from 30 days after the second dose, culture-confirmed whooping cough (cough and a positive culture of *Bordetella pertussis*) occurred in 40 placebo, 27 LPF-toxoid vaccine, and 18 two-component vaccine recipients. The point estimate of protective efficacy was 54% (95% confidence intervals 26–72%) for the LPF-toxoid vaccine and 69% (47–82) for the two-component vaccine; protection against culture-confirmed whooping cough of over 30 days duration was 80% (59–91%) and 79% (57–90%), respectively.

Introduction

WHOLE-CELL pertussis vaccines protect against disease but different preparations vary in composition and efficacy.[1,2] Such vaccines may be associated with acute neurological illnesses.[3] Acellular pertussis vaccines, developed in Japan,[4,5] cause fewer side-effects than whole-cell pertussis vaccines[4] and there is some evidence of protection from disease in household studies.[5] Opinion is still divided on which antigens to include to protect against both infection and disease.[2,6] If whooping cough is primarily a toxin-mediated disease,[7] vaccines based on inactivated lymphocytosis promoting factor (LPF) may suffice.

In Sweden general vaccination with whole-cell pertussis vaccine was discontinued in 1979 because of the low protective efficacy of the vaccine available there and public concern about rare severe adverse events.[2] Whooping cough is now endemic in the country.[8] These circumstances offered a unique opportunity to assess clinical efficacy and safety of acellular pertussis vaccines by randomised controlled trials.[9] Two Japanese acellular vaccines have been investigated. One contains formaldehyde-inactivated LPF and filamentous haemagglutinin (FHA);[4] the second was specially prepared for the trial and contains the LPF toxoid alone. The vaccines were examined in several laboratories,[10] and preliminary clinical evaluaton of safety and immunogenicity was done in Sweden.[11,12] We report the main findings of a randomised double-blind placebo-controlled trial of the efficacy and safety of the two vaccines.

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Subjects and Methods

Sample Size Considerations

The trial was designed to have a high probability (80%) of disproving the null hypothesis that vaccine efficacy was 70% or less with a type-I error of 5% (one-sided) on the assumption that actual efficacy was 90%. Since equal allocation of study subjects to all groups was not judged to be optimum,[13] we decided that 25% of the estimated sample at randomisation (estimated n = 3720) should receive placebo injections and 37·5% should receive each vaccine.

Study Population

At 13 study sites 8221 infants were identified who were born between March 4 and Sept 29, 1985, and who were living in the catchment areas of defined child-health centres. From a review of child-health centre records or interviews with study nurses, 1123 infants were excluded because they did not meet the medical or other eligibility criteria for entry into the trial, as follows: chronic illness with signs of cardiac or renal failure or failure to thrive (n = 47), suspected progressive neurological disease (n = 37), previous pertussis (n = 70), previous pertussis vaccination (n = 48), long-term treatment with erythromycin or co-trimoxazole (n = 6), probable difficulty of follow-up for social reasons (n = 145), language difficulty (n = 385), or planned move from study areas (n = 385). 1 child died before the date of the first trial dose. The parents of 3296 infants did not wish to participate. Thus 3801 5–11-month-old infants were randomised at the first trial dose. This age group was selected because post-exposure erythromycin prophylaxis is the recommended medical practice in Sweden for infants under 6 months and this treatment could have lowered the expected incidence of whooping cough in the trial population; moreover, maternal antibodies present in infants under 6 months might have modified the response to vaccination.[14]

The trial was approved by the ethics committees at the Karolinska Institute, and at Umeå, Uppsala, and Linköping Universities. Human subjects clearances were obtained from the World Health Organisation and the National Institute of Allergy and Infectious Diseases, USA.

Vaccines and Placebo

The acellular pertussis vaccines were developed by the National Institute of Health, Japan (JNIH) and produced by the Kanonji Institute, Osaka University, Japan. JNIH-6 contains 7·5 μg protein nitrogen per ml each of LPF antigen and FHA antigen.[4] JNIH-7 contains 12·0 μg protein nitrogen per ml of LPF antigen. The two vaccines and the placebo preparation contain formaldehyde ≤0·01% weight:volume, thiomersal ≤0·01% weight:volume, and aluminium phosphate in phosphate-buffered saline in a final concentration of 0·15 mg Al per ml. Characteristics of the vaccines are described elsewhere.[10,15]

Blinding and randomisation.—Vaccine and placebo preparations were in identical vials. Each set of 8 vials was randomly allocated in the proportion 2:3:3 (placebo:JNIH-6:JNIH-7) by computer program. The vaccine code for each child was not disclosed to families, nurses, laboratory personnel, and investigators until after the main analysis in October, 1987. Blinding was checked by questioning of the nurses 14 days after the second dose.

Administration of vaccines.—The first of two trial doses was administered between February and April, 1986; the second dose was scheduled for 8–12 weeks later. Study nurses gave deep subcutaneous injections of 0·5 ml on the side of the thigh. Either dose was deferred if the child was febrile (≥38·0°C), was on short-term medication, had received any vaccine within 1 week, or had received immunoglobulin within 3 months. Contraindications for the second dose were: cyanosis within 24 hours of the first dose, fever (≥40·0°C), shock-like reaction, or persistent cry for 3 hours within 48 hours; any serious event within 1 month; and convulsions at any time after the first dose.

Analysis of Adverse Events

The parents measured the child's rectal temperature at 3 and 6 hours after each dose. If the temperature was over 37·9°C they were asked to measure it twice daily until it was below 38·0°C. They were also asked to record all symptoms for 14 days. The study nurses did structured interviews, examined the child, and measured the rectal temperature 24 hours after each dose; they also performed structured interviews 14 days after each dose. The injection site was inspected at the time of the second dose and when post-vaccination blood samples were taken 60–120 days after the second dose.

The planned analysis of adverse events followed a stepwise strategy. Calculations of χ^2, confidence intervals for differences between proportions, and McNemar's test for comparison of paired proportions were done as appropriate.

Serological Assays

Sera were obtained before the first trial dose and 60–120 days after the second dose by fingerprick or venepuncture. Neutralising antibodies against pertussis toxin were measured by the Chinese hamster ovary cell assay.[16] Enzyme-linked immunosorbent assays (ELISA) for LPF and FHA immunoglobulin G (IgG) antibodies were done with a modified parallel line assay.[14]

Follow-up and Case Ascertainment

The parents were instructed to call a study nurse if the child had a cough for more than 7 days; if they suspected whooping cough in the household; if any specific symptom, such as whoops, coughing spasms, or cough with vomiting occurred in any household member, or if a doctor diagnosed whooping cough in the household. The study nurses telephoned all households every month for 17–19 months after the first dose.

When pertussis was suspected in a study child, clinical information was collected on a standardised form. Nasopharyngeal swabs were immediately inoculated on isolation-medium plates[17] and were also transferred to enriched transport medium for isolation and identification of *Bordetella pertussis*. The strains were verified at the National Biological Laboratory, Sweden. Serological tests were done on acute blood samples, if they were obtained within

TABLE I—CASE DEFINITIONS OF WHOOPING COUGH IN STUDY CHILDREN

Category	Definition
1 Culture-confirmed	Cough and verified culture of *B pertussis*
2 Serologically confirmed	Cough and significant serological response,* excluding category 1 cases
3 Epidemiologically linked	Cough of > 7 days with coughing spasms or whoops or vomiting in direct contact with culture verified case of pertussis, excluding category 1–2 cases
4 Clinical, only	Cough of > 21 days with whoops, excluding category 1–3 cases

*Four-fold rise in neutralising antibodies and two-fold rise in IgG antibodies against LPF and FHA by ELISA.

TABLE II—CHARACTERISTICS OF STUDY CHILDREN AND THEIR FAMILIES

Background factor	JNIH-6 (n = 1419)	Placebo (n = 954)	JNIH-7 (n = 1428)
Age at first dose (days)*	260 (186–333)	260 (186–336)	258 (184–332)
Girls (%)	49·3	48·4	48·5
No of persons in household*	4 (3–5)	4 (3–5)	4 (3–5)
% of persons sharing room with 1 or more others	1·8	2·3	1·6
% of study children having 1 or more unprotected siblings†	42·7	42·0	41·6
Child care at home only (% of follow-up period)	52·7	52·4	52·2

*Median (5–95 percentile) shown.
†Sibling with no previous pertussis and/or previous pertussis vaccination at randomisation.

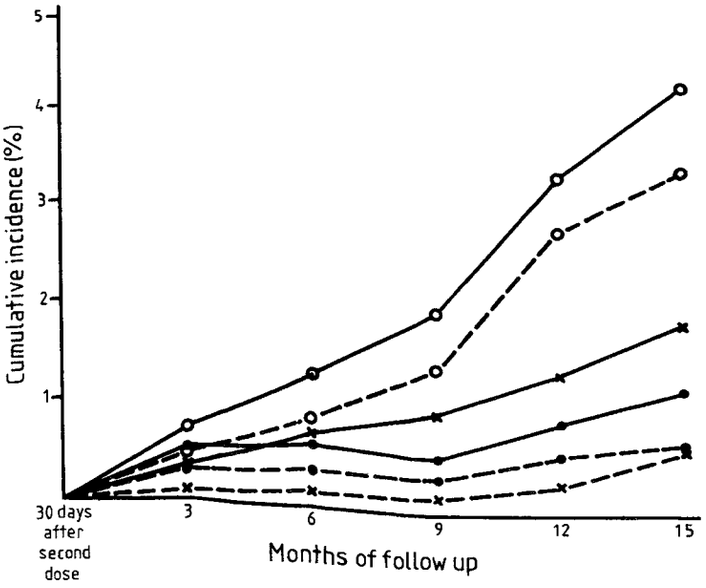

Fig 1—Cumulative incidence (%) of culture-confirmed whooping cough from 30 days after the second trial dose.

○ = placebo; ● = JNIH-6; × = JNIH-7; ——— = all cases; ---- = cases with cough for > 30 days (32 in placebo, 10 in JNIH-6, and 9 in JNIH-7 group).

14 days of onset of cough, and on convalescent samples obtained not earlier than six weeks after onset. A significant serological response was defined as a four-fold rise in neutralising antibody titres and a two-fold rise in IgG antibodies against LPF and FHA by ELISA. Suspected pertussis in other household members was also investigated.

Estimates of Vaccine Efficacy

Vaccine efficacy was defined as the percentage reduction in the attack rate of whooping cough in a vaccine group compared with the placebo group. Table I shows the case definitions used in the analysis of vaccine efficacy. Severe whooping cough was defined as either a cough for more than 30 days or more than 8 coughing spasms per day.[18] All estimates of efficacy based on clinical case definitions or on subgroups are regarded as exploratory.

The analysis was done according to a preplanned stepwise strategy. Vaccine efficacy and confidence intervals (CI) were estimated by survival analysis; the actuarial method with intervals of 30 days was used.[19] Curves of the proportion of study infants remaining free of culture-confirmed pertussis in households exposed to culture-confirmed pertussis were calculated by the Kaplan-Meier method.[20]

Results

The three groups did not differ in several prognostic characteristics (table II). At the first dose 1419 children received JNIH-6 (two-component) vaccine, 1428 received JNIH-7 (LPF-toxoid) vaccine, and 954 received placebo. A total of 77 children received only one dose: 22 because of pertussis; 11 (6 in the placebo, 2 in the JNIH-6, and 3 in the JNIH-7 group) because of contraindicating symptoms after the first dose; 26 because of intercurrent infections or other medical investigations; and 18 because of parental withdrawal or communication difficulties. Thus 1389 children received JNIH-6 vaccine, 1406 received JNIH-7 vaccine, and 929 received placebo at the second dose. There was no imbalance in withdrawals between the groups. Until August, 1987, 72 study children had moved out of study areas and 42 did not complete follow-up. 5 had died during the 17–19 months follow-up. The causes of death were, respectively, *Haemophilus influenzae* type-b meningitis, heroin intoxication with concomitant pneumonia, suspected pneumococcal septicaemia, *Neisseria meningitidis* group-B septicaemia, and nephroblastoma and brain tumour. The first three deaths occurred in the JNIH-6 vaccine group and the other two occurred in the JNIH-7 group. Data were collected in special studies during the trial and analysis of the possible relation between vaccination and the causes of death did not support an aetiological role for the vaccines. However, larger studies are needed to clarify this issue (Storsaeter J, Renemar B, Romanus V, Lagergård T, Norberg R, Tiru M, Olin P, unpublished).

Efficacy

Fig 1 shows the cumulative incidence of culture-confirmed pertussis (category 1 in table I) during 15 months of follow-up from 30 days after the second dose. The curves of the cumulative attack rates in the two vaccine groups did not differ (log rank test, $p = 0{\cdot}19$). Both vaccines gave significant protection against laboratory-confirmed pertussis (table IIIA). In addition to the primary case definitions (categories 1 and 2), which were judged to be most specific for pertussis, additional cases were identified on the basis of clinical symptoms either with (category 3) or without (category 4) known contact with a culture-confirmed case (see table I). Inclusion of these cases reduced the overall vaccine efficacy estimates for both vaccines (table IIIB). For JNIH-6 the protective efficacy against culture-

TABLE III—NO OF CASES, CUMULATIVE INCIDENCE, AND VACCINE EFFICACY CALCULATED FROM 30 DAYS AFTER SECOND DOSE BY CASE DEFINITIONS

Case definition	JNIH-6 (n = 1385)			Placebo (n = 923)		JNIH-7 (n = 1403)		
	No of cases	Cumulative incidence (%)	Vaccine efficacy (%)*	No of cases	Cumulative incidence (%)	No of cases	Cumulative incidence (%)	Vaccine efficacy (%)*
A.								
Category 1†	18	1·4	69 (47–82)	40	4·5	27	2·0	54 (26–72)
Category 2	24	1·8	62 (37–77)	43	4·8	33	2·5	48 (19–67)
B.								
Category 1–3	31	2·4	58 (35–73)	50	5·6	45	3·3	41 (12–60)
Category 1–4	53	4·0	45 (22–62)	65	7·3	67	4·9	32 (6–51)

*95% confidence intervals (CI) are shown in parentheses.
†Cumulative incidence rates from the date of the first dose were placebo = 5·4%. JNIH-6 = 1·9%, and JNIH-7 = 2·5%. Vaccine efficacy was 65% (95% CI 44–78) for JNIH-6 and 53% (28–69) for JNIH-7.

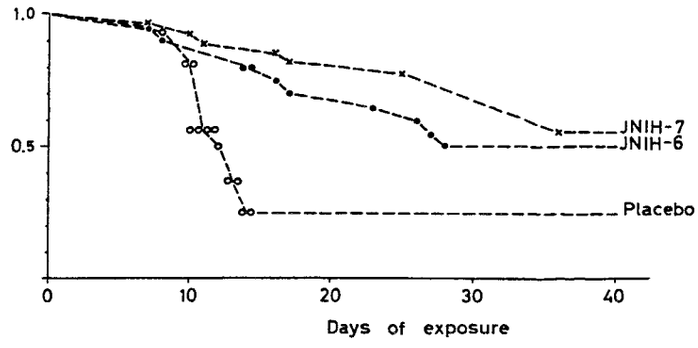

Fig 2—Proportion of study children remaining free of culture-confirmed whooping cough during exposure to culture-confirmed whooping cough within the household.

JNIH-6, 20 exposed, 10 cases (●); JNIH-7, 26 exposed, 7 cases (×); placebo, 16 exposed, 12 cases (○). Day 0 = onset of cough in primary cases.

confirmed pertussis with more than 30 days of cough was 79% (95% CI 57–90%) and against culture-confirmed pertussis with more than 8 coughing spasms per day it was 85% (65–93%). For JNIH-7 the corresponding figures were 80% (59–91%) and 71% (45–85%). For category 1–3 cases with a cough for more than 30 days vaccine efficacy was 78% (58–89%) for JNIH-6 and 78% (57–88%) for JNIH-7. Culture-confirmed pertussis developed in 29 of the 62 study children who were exposed later than 30 days after the second dose to culture-confirmed whooping cough within the household; 17 of the 29 children were in the vaccine groups. Bacteriological confirmation of the cases was obtained while the study child had a cough, with the exception of 1 JNIH-7 and 2 JNIH-6 recipients. The onset of cough and culture positivity was often later in vaccine failures than in placebo controls (fig 2).

Serological Response (Table IV)

The serological antitoxin response 60–120 days after the second dose, as measured by neutralisation assay and ELISA LPF-IgG, was significantly higher in the JNIH-7 group than in the JNIH-6 group. The JNIH-6 group had a significantly higher ELISA FHA-IgG antibody response than had the JNIH-7 and placebo groups. The post-vaccination antibody concentrations did not differ between the study children who subsequently had whooping cough and those who did not. Additional serological data in suspected cases and in relation to household exposure will be reported elsewhere.

Adverse Reactions

The rates of systemic reactions within 24 hours of each dose did not differ between the groups with two exceptions—after the first trial dose fever was more frequent in both vaccine groups than in the placebo group, and persistent crying was somewhat more common in the JNIH-7 group than in either of the other groups (table V). There were no collapses or hypotonic hyporesponsive episodes, as defined by Cody et al,[21] within 2 weeks of any trial dose. 1 JNIH-6 recipient had a febrile convulsion on the 12th day after the second trial dose. During 14 days of follow-up after each dose a rectal temperature of 40°C or more was reported in about 2% and rhinitis was noted in 40–44% of children in all groups. Furthermore, 21 children had symptoms listed as contraindications for further trial doses. There was no overrepresentation of any treatment group.

Early local reaction at the site of injections were rare and mild after the first trial dose. Higher rates were noted after the second dose (table VI). Both redness (10–45 mm) and swelling (10–50 mm) at the injection site occurred significantly more often after the second dose in JNIH-6 recipients than in JNIH-7 or placebo recipients.

Discussion

Our overall estimates of vaccine efficacy, based on culture-confirmed whooping cough and on all laboratory-confirmed cases, were lower than expected.[5,11] However, the case definition we used included any duration of cough and any number of coughing spasms per day. We found that protection was better against more severe disease and that the course of the illness seemed to be modified in vaccine failures, who also had a later onset of cough during exposure than had placebo recipients.

The reduction in vaccine efficacy when category 3 and 4 cases were included (see table III) may reflect the difficulty of distinguishing the symptoms of whooping cough from coughs caused by other agents in 1–2-year-old children or higher sensitivity of pertussis culture in the placebo than in the vaccine groups. To control for the latter bias, further analysis is in progress to identify additional cases by modified serological criteria. However, when category 1–3 cases with a cough for more than 30 days were analysed separately, the vaccine efficacy estimates (78% for both JNIH-6 and JNIH-7) were much the same as the estimates obtained for culture-confirmed cases of the same severity. Efficacy of over 80% has been reported for whole-cell[22,23] and acellular pertussis vaccines.[5] Such high estimates should be viewed with respect to case ascertainment and case definition. In the present trial, blinding, randomisation, and active case ascertainment, irrespective of clinical severity, have averted many biases that could have led to spuriously high estimates of overall efficacy.[2]

TABLE IV—ANTIBODY LEVELS IN SERA OBTAINED 60–120 DAYS AFTER SECOND DOSE IN 10% RANDOM SAMPLE OF NON-CASES (CATEGORY 1–4 CASES EXCLUDED), AND IN STUDY CHILDREN WHO SUBSEQUENTLY BECAME CATEGORY 1 CASES DURING FOLLOW-UP

—	JNIH-6		Placebo		JNIH-7	
	Non-cases	Cases	Non-cases	Cases	Non-cases	Cases
No of children	122	17	84	36	143	25
Antitoxin NT titre (geometric mean and range)	81 (1–512)	118 (32–1024)	1 (1–128)*	1 (1–2)	164 (16–2048)†	211 (64–512)
ELISA LPF-IgG units (geometric mean and range)	77 (5–1080)	81 (20–313)	5 (5–80)*	5 (5–15)*	185 (30–4500)†	276 (47–1023)
ELISA FHA-IgG units (geometric mean and range)	25 (2–400)	20 (7–138)	2 (2–2)	2 (2–2)	2 (2–93)*	2 (2–2)

*All tested sera except one were below or at the lower limit of sensitivity for the assay. High values were recorded for different children in each assay.
†Highest values were recorded for 2 individuals with high antibody levels in pre-vaccination sera, suggesting pre-existing immunity had been boostered.
NT = neutralisation assay.

TABLE V—SYSTEMIC ADVERSE EVENTS WITHIN 24 HOURS OF FIRST AND SECOND TRIAL DOSES

—	Dose	% adverse event*		
		JNIH-6	Placebo	JNIH-7
Seizure or hypotonic hyporesponsiveness	1	0	0	0
	2	0	0	0
Hypotonia	1	0 5	0·6	0·5
	2	0·1	0·1	0·2
Twitching/spasm	1	0·3	0 4	0·5
	2	0·1	0	0·5
Anorexia	1	7·1	6·2	6·0
	2	6 1	7·5	5·8
Vomiting	1	5·6	5·0	4·1
	2	4·7	4·1	3·2
Persistent crying	1	1·1	0·8	2·1†
	2	1·4	1·1	1·4
Persistent crying 1 h or more	1	0·3	0·3	0·7
	2	0·4	0·4	0·4
Fever ⩾38°C at 3 or 6 h after dose	1	6·1	4·0	6·7‡
	2	4·9	5·2	6·0
Drowsiness, no fever	1	7·0	6·0	6·8
	2	6·6	6·7	6·7
Palor	1	1·3	1·3	0·8
	2	0·5	0·6	0·4

*Percentages based on number of children with each symptom among responders to a 24 h questionnaire. Questionnaires were completed for 3799 of 3801 first doses and 3720 of 3724 second doses.
†95% CI for differences of proportions between groups expressed as percentages: JNIH-7 *vs* placebo 0·3–2·2 (p = 0·02), JNIH-7 *vs* JNIH-6 0–1·9 (p = 0 04).
‡Percentage of fever is based on children for whom both a 3 and a 6 h recording were obtained (3426 [90%] first and 3122 [84%] second doses). There was no imbalance in the reporting rate between groups. 95% CI for differences of proportions between groups expressed as percentages: JNIH-6 *vs* placebo 0·3–4 0 (p = 0·03), JNIH-7 *vs* placebo 0·8–4·6 (p = 0·007).

In general, three doses are used for primary pertussis immunisation.[2,5] Because satisfactory serological responses to LPF and FHA antigens have been reported,[4,11,12] we used only two doses in this trial. Antibodies to LPF and FHA protect against pertussis in animals;[24,25] however, we found no correlation between post-vaccination serum concentrations of these antibodies and subsequent protection against whooping cough. The biological mechanisms for protection by pertussis vaccines remain unknown. The role of cellular immunity[26] and secretory antibodies[6] in parenteral administration of pertussis vaccines need further study.

The two-component vaccine (JNIH-6) gave a significantly lower antitoxin antibody response than the toxoid vaccine (JNIH-7) but still offered at least the same protection during the 17–19 months of follow-up. Long-term protection will be assessed by continued surveillance of laboratory-confirmed whooping cough in the study cohort. The need for and timing of booster doses will also be studied.

The acellular pertussis vaccines caused fewer reactions than have been reported for aluminium-adsorbed diphtheria-tetanus toxoid whole-cell pertussis preparations (DTP).[21,27] The types and rates of reactions in our study correspond to those for aluminium containing diphtheria-tetanus toxoid vaccines reported by Cody et al,[21] who used follow-up methods similar to ours. However, Pollock et al[28] recorded fewer fevers after adsorbed DTP immunisation in the United Kingdom than in the United States and suggested that variations between batches and between manufacturers might explain the differences in reported rates of adverse reactions. Fewer local reactions occurred in our study than in previous open studies of older children receiving acellular DTP vaccines.[4,5] The aluminium-containing placebo caused less local reaction than did the vaccine preparations, and the LPF-toxoid vaccine caused less than did the two-component vaccine. These findings are in accord with those of the preliminary trials in Sweden.[11,12] Most local reactions occurred early, and a small fraction only had an onset in the second week after the first dose. These results are not easily reconciled with other reports[5] that acellular pertussis vaccines, when given together with DT preparations, cause late occurring local reactions in up to 30% of recipients, with a mean time of appearance about 7 days after the first dose. Apart from a possible role of the diphtheria vaccine component, we cannot explain this inconsistency.

TABLE VI—LOCAL REACTIONS AFTER FIRST AND SECOND TRIAL DOSE

—	Dose	% reactions*			95% CI for differences between groups†		
		JNIH-6	Placebo	JNIH-7	JNIH-6 *vs* placebo	JNIH-7 *vs* placebo	JNIH-6 *vs* JNIH-7
24 h questionnaire							
Local redness, swelling and/or tenderness	1	10·2	7·8	10·4	—	—	—
	2	17·8	9·1	12·7	6·0–11·5	1 1–6·1	2·5–7 8
24 h examination							
Redness ⩾10 mm	1	0·2	0·1	0·4	—	—	—
	2	8·6	0·7	3·4	6 3–9 5	1·6–3 9	3·3–6·9
Swelling ⩾10 mm	1	0 4	0·1	0·6	—	—	—
	2	5 3	0 9	2·6	3·0–5·7	0 6–2 8	1 2–4·2
Tenderness	1	1·5	1·2	1·8	—	—	—
	2	5·1	2 7	2·9	0 7–3·9	—	0·7–3·6
14 day questionnaire							
Nodule on day 14	1	9 2	1 7	5·1	5·7–9 3	1·9–4·8	2·2–6·1
	2	11 1	2 6	4 9	6·4–10·5	0·6–3·8	4·1–8 3
Local reactions, one or more, within 14 days	1	15·4	9 9	11 7	2 9–8 2	—	1 2–6 2
	2	28·9	14·5	19·0	11 1–17·7	1·4–7 5	6·8–13 1
Examination at dose 2/post-vaccination blood sampling							
Remaining nodule	1	1 9	0·4	0·9	0·6–2·3	—	0·2–1 9
	2	0 3	0 0	0 1	—	—	—

*Percentages based on responders to questionnaire. 3724 (98%) children were examined 24 h after first and 3535 (95%) after second doses. A 14 day questionnaire was completed after 3781 (99 5%) first and 3711 (99·7%) second doses. Information on remaining nodule was obtained for 3656 children (96%) at dose 2 and for 3662 children (98%) at post-vaccination blood sampling. There was no imbalance between groups.
†95% CI for differences of proportions between groups are shown when $p < 0·05$ by an overall χ^2.

Clinical and immunological studies were done because of a cluster of three deaths associated with severe bacterial infections in the JNIH-6 group 2–10 weeks after the second trial dose (unpublished results). The results did not support a causal relation with vaccination. However, our study was too small to determine the safety of these vaccines with respect to rare events temporally related to vaccination.

The results from this trial suggest that both types of acellular vaccine may be used on a larger scale in 6-month-old infants, provided that rare events are carefully monitored. The mild illness found among vaccine failures may be acceptable to parents and others. From a public health point of view it is more important to protect against severe illness. Only experience will show if mass vaccination with the tested types of acellular pertussis vaccine will induce sufficient population immunity to reduce the attack rate of whooping cough to a low level.

This work depended on the dedication of participating families and study personnel in Umeå, Sundsvall, Uppsala, Västerås, Örebro, and Linköping-Motala, and in Taby-Östermalm, Jarfälla-Upplands Väsby, Kungsholmen-Bromma-Spånga-Ekerö, Huddinge-Botkyrka, Nacka-Tyresö/Haninge, and Södermalm-Enskede-Skarpnäck within Stockholm. The trial was funded by the Swedish National Bacteriological Laboratory, the Centers for Disease Control (contract no 200-85-0822), and the National Institute of Allergy and Infectious Diseases (contract no N01-A1-62527). Part funding for contract no N01-A1-62527 was provided through a Participating Agency Service Agreement between the US Agency for International Development and the Office of International Health, Public Health Services. The Swedish Medical Research Council funded the independent steering committee. The vaccine and placebo preparations were donated by the Kanonji Institute, The Research Foundation for Microbial Diseases (Biken) of Osaka University through The National Institute of Health, Tokyo, Japan.

Report prepared by L. O. Kallings, P. Olin, J. Storsaeter.

The study protocol and a comprehensive technical report from the trial will be available in the autumn of 1988 and can be ordered from the National Bacteriological Laboratory, S-105 21 Stockholm, Sweden.

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EPITHELIOID HAEMANGIOMA-LIKE VASCULAR PROLIFERATION IN AIDS: MANIFESTATION OF CAT SCRATCH DISEASE BACILLUS INFECTION?

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Summary Papular and nodular skin lesions that clinically resembled Kaposi sarcoma, but histologically showed a distinct epithelioid haemangioma-like appearance, were noted in seven patients with the acquired immunodeficiency syndrome. Clusters of bacteria that had the structure of gram-negative rods were identified within each of the vascular proliferations by electron microscopy. The bacteria did not stain with the Brown-Brenn, acid-fast, or other histochemical stains for infectious organisms, but did stain with Warthin-Starry—ie, the staining profile was that described for the cat scratch disease (CSD) bacillus. Immunoperoxidase staining, using antisera raised in rabbits against cultured CSD bacillus, showed a positive reaction with the bacterium in all five cases tested. The two surviving patients have both given histories of having been scratched by a cat. In several patients, the vascular lesions regressed after therapy with antibiotics appropriate for CSD bacillus infection.

Introduction

MANY infectious, neoplastic, and inflammatory conditions have been described in the skin of patients with the acquired immunodeficiency syndrome (AIDS). Kaposi sarcoma has been regarded as a hallmark of the AIDS epidemic since it was first recognised in young homosexual

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