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Pertussis in a rural area of Kenya: epidemiology and a preliminary report on a vaccine trial *

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In the course of 2 years' surveillance of whooping cough by fortnightly home visits among a population of 24 000 in a rural area of Kenya, 918 cases were observed with a peak of 218 in December 1974–January 1975. The attack rate was highest (15.8 %) during the first year of life ; for the age group 0–6 years it was 12.8 %. Ninety percent of cases occurred in children 6 years of age and younger. The median age was 3.5 years, the age range 1 month to 13 years. Girls were significantly more affected than boys. The overall case fatality rate was 1.3 % but among infants it was 2.5 times higher. In order to contribute to the improvement of immunization coverage in countries where health resources are limited, a schedule of child immunization requiring a minimum number of contacts with the children was introduced in the study area with the aim of evaluating its effectiveness in protecting children from clinical pertussis. In this trial, the effect of two and three diphtheria–pertussis–tetanus vaccine (DPT) doses was compared. Pertussis agglutinating antibody determinations showed an equally satisfactory response after two and three DPT vaccine doses.

There is growing concern to improve the efficacy of infant immunization in countries where a full permanent network of basic health services has not been realized. Through its Expanded Programme on Immunization, the World Health Organization has embarked on a worldwide effort to control those childhood diseases that are preventable by immunization. Diphtheria, pertussis, and tetanus may be prevented by the administration of a combined vaccine (DPT) on three occasions during the first year of life.

An immunization schedule that required a minimum of contact with the children would greatly help to improve rates of coverage in countries where health resources are limited. If only two injections of DPT vaccine provided sufficient protection, a schedule could be devised whereby all necessary antigens could be provided at only two immunization sessions.

Before schedules involving a reduced number of injections are introduced on a large scale, their effectiveness in protecting the susceptible childhood population against the disease for which the vaccines are administered should be established. The disease surveillance system of the Machakos Project of the Medical Research Centre, Nairobi offers an opportunity to study the epidemiology of diseases before and after the introduction of mass immunization.

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Also, by randomized controlled vaccine trials the clinical effectiveness of a reduced number of immunizations can be compared with the effect of established schedules.

The present preliminary report describes the epidemiology of pertussis before the introduction of DPT immunizations on a mass scale, the design of a controlled vaccine trial, and the pertussis antibody response to two and three doses of DPT vaccine. Diphtheria and tetanus have not been encountered during 3 years of disease surveillance among preschool children in the study area.

MATERIALS AND METHODS

The Machakos Project covers an area of 87 km² in the nortwestern part of the Machakos district of Kenya, with a total population of 24 000 living in approximately 4000 households scattered over the countryside. Each household is visited once every 2 weeks by one of 12 local field workers who collects demographic information on all members of the household and records the presence of measles (*1*) and whooping cough (*3*) in any of the children and of other acute respiratory infections and diarrhoea in children 0–4 years of age. The average field worker has spent a maximum of 4 years at secondary school and receives continuous on-the-job training.

Children suspected of having measles or pertussis are seen by one of the project's physicians for verification of the diagnosis and, with the mother's permission, a perinasal swab is taken for culture and a capillary blood sample for antibody determination and, in the case of pertussis, a white blood cell count and differential smear. Children reported by the mother to have whooping cough are given one of the following diagnostic scores:

0. No clinical or laboratory evidence; the case history makes a positive diagnosis unlikely but it cannot be ruled out.
1. No clinical or laboratory evidence; the case history makes a positive diagnosis possible.
2. Clinical signs and/or laboratory results make a positive diagnosis likely but not certain.
3. Clinical signs and/or laboratory results make a positive diagnosis definite.

For estimating the total number of cases, probabilities of pertussis of 0.15, 0.40, 0.75, and 1 were assigned to the scores 0, 1, 2, and 3, respectively.

Details of the project design and the diagnostic criteria used for pertussis are given by Muller et al. (*2*) and Voorhoeve et al. (*3*).

The diphtheria–pertussis–tetanus (DPT) vaccine trial was started in December 1975. Subsequent immunization rounds, each including children that had reached the age of 3 months since the previous round, were carried out every 3 months until June 1977. In September and December 1977 the last cohort of infants, entered in the trial in June 1977, completed their immunizations. Children with uneven project numbers (the control group) received BCG, the first dose of DPT, and oral poliomyelitis vaccine during their first round; smallpox vaccine, the second dose of DPT, and poliomyelitis vaccine during their second round; and the third dose of DPT and poliomyelitis vaccine, as well as measles vaccine, during the third round. Children with even numbers (the study group) differed from the control group only in respect of the second round, when the second DPT dose was replaced by Salk poliomyelitis vaccine.[a] By the end of 1977, approximately 400 children had received three DPT injections 3 months apart and a similar number had received two DPT injections 6 months apart.

In July 1976, 1 month after the second or third DPT injection was given to the first cohort, blood for pertussis agglutinating antibody determination was obtained by finger prick from 49 children in the study group and 54 children in the control group.

The DPT vaccine used in the trial was prepared by the Rijks Instituut voor de Volksgezondheid, Bilthoven, Netherlands; the pertussis component contained 16 Opacity Units of *Bordetella pertussis* cells and 7 International Units per dose.

Antibodies against *B. pertussis* were determined by the agglutination test, using a microtechnique. Various *B. pertussis* antigens were tested for specificity and sensitivity. As a result, antigen prepared from *B. pertussis* strain No. 3838 by the Rijks Instituut voor de Volksgezondheid was selected. The antigen was obtained freeze-dried in flasks. Before use, the required amount of freeze-dried antigen was reconstituted in distilled water and diluted with phosphate buffered saline to a density of 40×10^9 organisms/ml. All agglutination tests were performed with the same batch of antigen. Two-fold dilutions of each serum sample were made and equal volumes (0.05 ml) of antigen and diluted serum (initial dilution 1: 3) were

[a] Because Metselaar et al. (*4*) found a poor antibody response to oral poliomyelitis vaccine in the study area, Salk vaccine was considered to be a suitable " placebo ".

thoroughly mixed. The end-point titre was determined after 3 hours of incubation at 37°C, followed by incubation overnight at 4°C.

Negative human sera and anti-*B. pertussis* rabbit serum, prepared with the stable Kenyan 1, 2, 3 strain isolated in the Machakos district, were used as negative and positive controls, respectively.

RESULTS

Table 1 shows the estimated numbers of children, born during 1970–1975 in the study area, who were immunized once, twice, or three times with DPT. The information was obtained from the immunization cards issued by health services running child welfare clinics both inside and outside the study area. The first immunization round of the vaccine trial in December 1975 was not included. Some mothers lost the immunization cards of their children and the percentages therefore underestimate to a certain extent the true coverage.

Table 1. Estimated percentage coverage for DPT immunizations in the Machakos Project area, October 1976

No. of immunizations	Year of birth					
	1970	1971	1972	1973	1974	1975
One	1.1	3.3	8.2	8.7	13.9	16.4
Two	1.1	1.1	4.2	7.2	10.5	14.7
Three	2.3	2.8	11.2	16.2	21.5	21.4

The pertussis epidemic

During the period April 1974–March 1976, a total of 918 pertussis cases were encountered. The distribution over the four diagnostic scores for males and females is shown in Table 2. Significantly more girls than boys were affected ($P<0.01$). In the first and last 2-month periods fewer than 10 cases were diagnosed, while a peak of 218 cases occurred in December 1974–January 1975 (Fig. 1). Between April and October 1976 not a single case was diagnosed. The largest number of cases occurred in children under 1 year of age. There was a marked

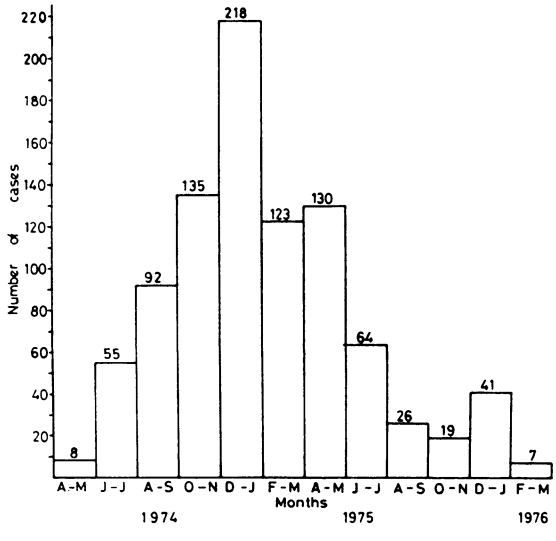

Fig. 1. Distribution of whooping cough cases over the period April 1974–March 1976.

Table 2. Distribution of cases reported for whooping cough according to diagnostic score for males and females

	Diagnostic score				
	0 (no whooping cough)	1 (possible whooping cough)	2 (probable whooping cough)	3 (definite whooping cough)	Total
Males	244	88	95	287	714
Females	293	123	76	338	830
Total	537	211	171	625	1544
Probability of whooping cough	0.15	0.40	0.75	1	
Estimated number of cases	81	84	128	625	918

decrease in the number of cases in those more than 6 years old (Fig 2); almost 90% of the cases occurred in children 6 years of age or younger. The median age was 3.5 years, the age range 1 month to 13 years. The attack rate in the total population was 3.8% and was highest for the age group 0–12 months (15.8%); for the age group 0–6 years it was 12.8% (Table 3). A serological baseline survey of 897 children 0–4 years of age revealed the presence of agglutinating antibodies in 34%, 49%, 32%, 26%, and 26% of those aged 0–1, 1–2, 2–3, 3–4, and 4–5 years, respectively. The overall case fatality rate was 1.3%; it was highest during the first year of life (Table 4). Mortality from pertussis was 48 per 100 000 population and it contributed to 7% of all deaths in those aged 0–14 years.

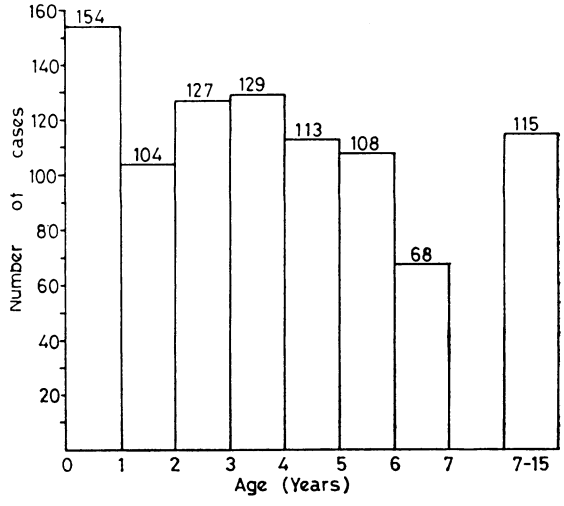

Fig. 2. Age distribution of whooping cough cases, April 1974–March 1976.

Antibody response to two and three pertussis immunizations

The mean pertussis agglutinating antibody titre 1 month after the administration of the last of two and three DPT injections was 1 : 70 and 1 : 96, respectively. No appreciable difference was apparent between the distribution of titres after two and three doses (Fig. 3). In contrast, among children of similar age not in the trial, some of whom may have received DPT, antibodies were absent in nearly 60%; when antibodies were present, only low titres were recorded. No adverse reactions to the vaccine were encountered.

Clinical pertussis among children in the trial

Sixteen months after the intake of the first cohort of children, a total of 470 children had completed the three scheduled rounds of immunizations. One

Table 3. Pertussis cases and incidence rates according to age, April 1974–March 1976

Age (years)	Estimated number of cases [a]	Percentage	Total number of children	Incidence per 1000		
				Minimum [b]	Point estimate	Maximum [b]
< 1	154	16.8	977	148	158	169
1	104	11.3	1 068	89	97	105
2	127	13.8	914	131	139	148
3	129	14.1	847	143	152	161
4	113	12.3	826	128	137	146
5	108	11.8	938	107	115	123
6	68	7.4	719	88	95	102
7–14	115	12.5	4 954	21	23	25
Total	918	100.0	11 243	80	82	84
Total population (all ages)			24 400	37	38	39

[a] Rounded to the nearest whole number.
[b] 95 % confidence limits.

Table 4. Pertussis deaths, percentage case fatalities, death rate, and proportion of total deaths according to age, April 1974–March 1976

Age (years)	Estimated number of deaths [a]	Case fatality (%)			Death rate per 100 000			Pertussis deaths as percentage of all deaths [a]		
		Minimum [b]	Point estimate	Maximum [b]	Minimum [b]	Point estimate	Maximum [b]	Minimum [b]	Point estimate	Maximum [b]
<1	5	2.3	3.2	4.1	409	511	716	5.1	6.4	9.0
1	2	0.6	1.4	3.8	0	140	281	0.0	4.2	8.3
2	2	0.1	1.6	3.8	219	219	219	11.8	11.8	11.8
3	1	0.3	0.8	1.1	118	118	118	11.1	11.1	11.1
4	2	0.5	1.8	3.9	242	242	242	18.2	18.2	18.2
⩾5	0	0.0	0.05	0.3	0	2	15	0.0	0.7	7.1
0–14	12	1.0	1.3	1.5	89	104	124	6.1	7.1	8.5
Total population (all ages)					41	48	57			

[a] Rounded to the nearest whole number.
[b] 95 % confidence limits.

child developed pertussis a few weeks after the first DPT dose, one 2 months after, and another 3 months after the first injection. Clinical pertussis was observed in one child 2 months after the second DPT dose, i.e., 5 months after the first dose.

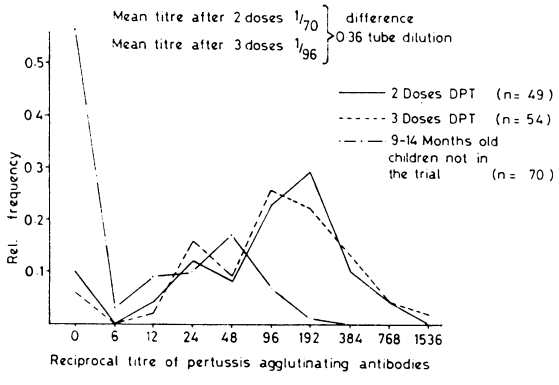

Fig. 3. Frequency distribution of pertussis agglutinating antibody titres after 2 and 3 doses of DPT vaccine.

DISCUSSION

In spite of the availability of laboratory results for many children reported by mothers to suffer from whooping cough, a positive diagnosis was difficult to obtain under field conditions because often the clinical manifestations were not apparent during the brief episode when the child was under observation. In addition, the absence of agglutinating antibodies in the serum and of lymphocytosis in the peripheral blood did not exclude a positive diagnosis of pertussis. Two thirds of 52 patients from whom *B. pertussis* was isolated and in whom antibody levels were determined were serologically negative (*3*). Although almost 70% of the patients were under 5 years of age, a serological baseline survey showed that only 26% of children in their fourth year of life had pertussis agglutinins in the serum. In fact, the prevalence of agglutinating antibodies was found to decrease with age after a peak of 49% seropositive children in the age group 1–2 years. It seems likely that in the majority of cases, the presence of antibody reflected recent immunization rather than clinical disease. This would mean that periodic serological surveys cannot provide information as to whether pertussis cases were missed during surveillance. A more detailed analysis of this aspect is given elsewhere (*3*). In spite of these diagnostic problems, we are confident that we have been able to document an epidemic of the disease with reasonable accuracy.

Our finding that more girls than boys were affected was consistent with results of other studies (*5*). The suggestion of Morley et al. (*6*) that in most developing countries the median age for whooping cough infection is only half that in industrial countries prior to the widespread use of immunization is not confirmed by our study. We have no reason to believe that this is due to under-reporting of the disease among infants: although the whoop is often absent in infants, the paroxysmal cough

cannot easily be missed. Case fatality during the first year of life was 2.5 times higher than the overall case fatality rate; it is well known that whooping cough tends to be more serious during infancy than later in life.

In the United Kingdom, the significance of immunization against pertussis for the control of the disease has given rise to considerable controversy (*7–9*). In the Netherlands, on the other hand, where approximately 90% of children receive three DPT doses between 3 and 6 months of age and a booster dose at the end of the first year of life, whooping cough has practically disappeared (*10*).

In developing countries, where pertussis incidence and mortality is high, the value of pertussis immunization appears to be beyond doubt. The public health significance of the disease in a rural area of Kenya has been clearly demonstrated by this study. Although in the Machakos study area the case fatality rate was much lower than for measles (*1*), the attack rate for pertussis was twice as high and the contribution of pertussis to total mortality considerable.

The agglutinating antibody response to two and three doses of pertussis vaccine was quite encouraging. It should be realised, however, that the vaccine used was of high potency, which could have led to an increase in the number of adverse reactions. During the immunization sessions, the mothers were told that mild febrile reactions and irritability are a fairly common consequence of pertussis immunization, but that anything more serious should be reported to the local field worker, who would arrange for one of the project physicians to visit the child. No reports of this nature were ever made. If adverse reactions had occurred after the first DPT dose, one would have expected some mothers to resist the second or third injection; this did not happen either. We are therefore satisfied that serious side effects were rare, if they occurred at all.

Retitration of the sera after absorption of cross-reacting antibodies was not possible owing to the small amount of serum available. This may have led to a number of aspecific reactions (N.W. Preston, personal communication, 1975), but is unlikely to have altered the relative position of the titre distribution curves. It is not known to what extent the presence of agglutinating antibodies indicates protection against clinical disease. Conversely, clinical immunity may exist in spite of low levels of agglutinins or even in their absence (*11*). Although the antibody response to two immunizations was quite similar to the response to three, it does not necessarily follow that antibody levels will be sustained for the same period of time: children who have received three injections may retain their immunity longer than those who have received only two (F. T. Perkins, personal communication, 1976). It will be of interest to compare antibody levels 2 or more years after immunization. From the point of view of experimental design, the inclusion of an unvaccinated control group would have been desirable but it would not have been ethical deliberately to exclude children from the protection one may expect from immunization.

The objection may be raised that no antibody determinations were carried out before the start of the trial. These were deliberately omitted because we had reason to believe that most mothers would strongly object to our repeatedly taking blood from their children and we think it is reasonable to assume that the baseline titres in these infants were similar in both groups. Ruben et al. (*12*) reported a pertussis seroconversion rate of almost 80% after two DPT immunizations 2 months apart in a study in northern Nigeria. In this study, the post-vaccination titre distribution did not show the marked peak for the higher titres found by us in both the control and study groups. However, such a comparison may not be valid since neither the vaccines nor the agglutination tests used in the two studies were identical.

The Machakos project involved an attempt to determine to what extent two doses of DPT protect against clinical pertussis. So far, the few cases of pertussis among the trial subjects observed do not allow any conclusions to be drawn. The present disease surveillance system in the study area must be continued in order to monitor the epidemiology of pertussis in general and in particular the incidence of the disease among the children included in the trial. This is not an easy task. One cannot even predict how many years of follow-up will be needed; herd immunity is increasing owing both to the administration of vaccine for the trial and to the gradual increase in immunization coverage in general.

Another problem was the rather small proportion of children that could be entered in the trial in relation to the total number eligible; by April 1977, only 470 children had completed three immunization rounds out of a total of 1341 eligible children. The two major reasons for exclusion were repeated absence—population movements in the study area are considerable—and interference by permanent health units. In spite of extensive dissemination of

information on the purpose and the advantage of mass immunization near the children's homes, mothers often preferred to go to the hospital or health centre, especially if they had done so in the past for older siblings. Moreover, the staff of these health institutions naturally had difficulty in differentiating between children who should be immunized by them and those who should be left for the vaccination team responsible for the children in the trial. In spite of these difficulties, however, about 800 children had participated by the end of 1977. The fact that they were included in the first place suggests that they belong to the more settled section of the population and most of them should be available during the follow-up period.

In conclusion, both the Nigerian study mentioned above and the present one suggest that two DPT immunizations may be adequate for protection against clinical pertussis. If this can be proved beyond doubt it should have far reaching consequences for health administrators and planners responsible for immunization programmes. During an epidemic with an attack rate between 10% and 15% for children below 5 years of age, a significant number of cases should be observed if two DPT doses are substantially less effective than three.

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RÉSUMÉ

LA COQUELUCHE DANS UNE ZONE RURALE DU KENYA. ÉPIDÉMIOLOGIE ET RAPPORT PRÉLIMINAIRE SUR UN ESSAI DE VACCINATION

Un plan de vaccination infantile qui n'exige qu'un contact minimal avec les enfants a des chances de contribuer à l'amélioration de la couverture dans des pays aux moyens sanitaires limités.

Depuis avril 1974, une surveillance de la coqueluche a été réalisée au moyen de visites à domicile effectuées tous les quinze jours dans une zone de 87 km² comptant une population de 24 000 habitants dans le district de Machakos au Kenya. Ce système de surveillance offre une occasion d'étudier l'épidémiologie de certaines maladies contre lesquelles il existe un vaccin, et ceci avant et après l'introduction de plans simplifiés de vaccination de masse. Le présent article apporte des données sur l'épidémiologie de la coqueluche au cours des deux premières années de surveillance ainsi que le schéma d'un essai de vaccination lancé à la fin de cette période. Cet essai vise à comparer les effets de l'injection de deux ou trois doses de vaccin DTC (diphtérie-tétanos-coqueluche) au cours de la première enfance, jugés d'après la réponse sérologique et la protection conférée contre les signes cliniques de la maladie. Seule la coqueluche a été étudiée; ni la diphtérie, ni le tétanos n'ont été observés. Le vaccin à éprouver était d'une activité supérieure à la moyenne, la composante coquelucheuse offrant une concentration de cellules de *B. pertussis* qui correspondait à 16 unités d'opacité et à 7 unités internationales par dose.

Au total, 918 cas de coqueluche ont été vus entre avril 1974 et mars 1976. L'incidence maximale s'est produite en décembre 1974–janvier 1975 (218 cas). Le plus grand nombre de cas s'est manifesté au-dessous de l'âge d'un an; dans ce groupe, la mortalité a été deux fois et demie supérieure à la létalité générale de 1,3%. Près de 90% des cas ont été observés chez des enfants d'âge inférieur ou égal à 6 ans; la médiane était de 4 ans et demi, la fourchette d'âge allant de 1 mois à 13 ans. Les filles étaient notablement plus touchées que les garçons. La maladie a contribué pour 7% à tous les décès survenus entre 0 et 15 ans.

Un mois après l'administration de la dernière des deux ou trois injections de DTC, le titre moyen d'anticorps agglutinants anticoquelucheux était respectivement de

1:70 et 1:96. La distribution des titres était presque identique, que l'on ait injecté deux ou trois doses. Très peu de cas de coqueluche ont jusqu'ici été notés chez les sujets ayant participé à l'essai. L'évaluation de l'efficacité clinique de deux doses de DTC demandera, pense-t-on, au moins deux années de surveillance supplémentaire de la maladie, mais les résultats sérologiques indiquent que deux injections de ce vaccin pourraient être suffisantes.

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