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Report of the 1966–67 Cholera Vaccine Field Trial in Rural East Pakistan*

1. Study Design and Results of the First Year of Observation

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A controlled cholera vaccine field trial was carried out in rural East Pakistan during the 1966–67 cholera season. A commercial cholera vaccine of average potency was tested in 40 000 children aged 3 months to 14 years in 1- and 2-dose schedules. In the cholera season extending for 8 months following immunization, a single dose produced an over-all protection of 46 % ; 2 doses at an interval of 1 month provided 64 % protection. The single dose was virtually ineffective in children under 5 years, but provided significant protection in older children. The enhanced effect of the 2-dose schedule was primarily due to the boosting of protection in children under the age of 5 years. The duration of significant protection, even with the 2-dose schedule, did not appear to extend beyond the first 3 months of the 8-month cholera season.

The 2 cholera vaccine field trials conducted by the Pakistan–SEATO Cholera Research Laboratory (PSCRL) in rural East Pakistan in 1963–64 and 1964–65 demonstrated that the use of a whole-cell cholera vaccine of unusually high antigenic potency (Oseasohn et al., 1965; Benenson et al., 1968) resulted in protection of 60%–80% effectiveness during the short cholera seasons that ensued. The duration of protection provided fell markedly in the second year, particularly among children who, in this cholera endemic area, have the highest case rate.

Serological studies in the field trial population, however, demonstrated a correlation of case rate with vibriocidal antibody titres suggesting that this serological test might be a useful tool for guiding future vaccine evaluations. It seems reasonable that by more intensive immunization, with either multiple injections or larger doses, the antibody level of children might be raised to that of adults, providing them with a correspondingly greater degree of protection (Mosley et al., 1968). This hypothesis was the basis for the third vaccine trial conducted during the cholera season of 1966–67.

In the present study, begun in October 1966, it was decided to limit the population under observation to children aged from 3 months to 14 years. A commercial cholera vaccine of average antigenic potency was employed and 1-dose and 2-dose schedules were followed in order to measure the level and duration of protection.

In the under 5 years age-group, 2 doses appeared to be highly effective for a short period of about

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3 months, after which further protection was not observed. In children 5–14 years of age, 1 dose gave as much protection as 2. The duration of effectiveness was somewhat longer, but showed a decline after 3 months.

Three random serological surveys were conducted at the beginning, during the middle, and at the end of the cholera season. These surveys permitted: (1) the evaluation of antibody response in the population at large; (2) the study of the relation of vibriocidal antibody to the incidence of cholera; and (3) the estimation of the inapparent infection rate in the study populations.

This first paper in the series reports on the design and results of the field trial. The 2 subsequent papers present an analysis of the serological data and a clinical evaluation of the cases occurring in the various vaccine groups (Mosley et al., 1969; McCormack et al., 1969).

METHODS

Vaccines

The cholera vaccine was prepared by a commercial manufacturer in the USA. The organisms included in the vaccine were classical *Vibrio cholerae* of the Ogawa (NIH 41) and Inaba (NIH 35A3) serotypes. The organisms were grown on nutrient agar, suspended in an isotonic sodium chloride solution, and killed and preserved with 0.5% phenol. The vaccine was standardized by opacity measurement to contain 4000 million organisms of each serotype per millilitre.

Potency assays

Protective activity against Inaba strain NIH 35A3 and Ogawa strain NIH 41 was determined relative to the homologous serotype reference vaccine by the mouse-protection test (Feeley & Pittman, 1962; Pittman & Feeley, 1963). This assay is prescribed as the official US potency test for cholera vaccine.[1]

The control preparation was "Tetanus and Diphtheria Toxoids (for adult use)". The vaccines were supplied in identical 50-ml vials for use with jet injectors. The cholera vaccine was designated vaccine X and the control vaccine, vaccine O, with colour-coded labels.

Assignment and administration of vaccines

The trial covered 132 villages in the Matlab area of Comilla District, East Pakistan. This included 58 villages which had participated in the previous trials, as well as an additional 74 villages. A house-to-house census was performed during March 1966. Every village was given a separate code number and each individual within the village was assigned a serial number which was used for identification purposes. Each family was issued with a census card giving the village number and the serial numbers of the family members.

Upon completion of the census, census books were prepared from the family census sheets, in geographical sequence. Two copies were used for identification of the individuals in the field. The vaccine assignment was made in advance in the third copy. This was done by first stratifying the population into the following age-groups: 0–4 years, 5–9 years and 10–14 years. Individuals within these 3 age-strata were then assigned to each of the following vaccine groups in strict alternation: (1) Group OO—2 injections of vaccine O; (2) Group XO—1 injection of vaccine X followed by 1 injection of vaccine O; (3) Group XX—2 injections of vaccine X. There were 2 assignments to group XX for each assignment to group OO and group XO in order that group XX should be twice as large as the others.

The vaccine was administered by 4 teams, each equipped with 2 foot-operated hypodermic jet injectors[2]—one for vaccine X and the other for vaccine O. The dosage of vaccine given was 0.5 ml per injection to all participants in the trial. The teams went from house to house, located the children, identified them by census number, administered the designated vaccine and stamped the date of vaccination in the census book. The first round of vaccination extended from 20 September to 18 October 1966. The second round of vaccination extended from 20 October to 17 November 1966. The progress of the teams through the villages was planned so that there were not less than 25 nor more than 35 days between the 2 injections.

Surveillance for cases

Field surveillance for acute diarrhoea was maintained by daily house-to-house visits by a female field assistant who was usually a resident of the village

[1] *Recommendations relating to the manufacture of cholera vaccine*, 1964, Division of Biologics Standards, National Institutes of Health, Public Health Service, US Department of Health, Education, and Welfare, Bethesda, Md., USA.

[2] Ped-O-Jet; Scientific Equipment Manufacturing Corporation, 99 Dell Glen Avenue, Lodi, New Jersey 07644, USA.

under observation and she was supervised by male field assistants who visited each house at least twice a week. A rectal swab culture was obtained from all individuals with acute severe diarrhoea—defined as a diarrhoeal illness with acute onset resulting in the person being unable to perform his usual activities.

All deaths were registered by the field workers. To identify suspect cholera deaths, rectal swab cultures were taken in all deaths associated with diarrhoea. If the body had been removed, cultures were taken from soiled clothes or bedding of the deceased, and family contacts were also tested. If any of these cultures were positive for *V. cholerae*, the death was considered to have been due to cholera.

Patients with severe diarrhoea were treated in a centrally located field hospital. The methods of treatment are described in detail in the third report in this series (McCormack et al., 1969). Five speed-boat ambulances were stationed at various points along the major river and canals to provide rapid transportation to the hospital.

Bacteriological methods

All hospitalized cases had daily rectal swab cultures made until 3 consecutive cultures negative for *V. cholerae* were obtained. The swabs were first plated directly on tellurite–taurocholate–gelatin agar (TTGA) (Monsur, 1963) and plain gelatin agar and then placed in liquid alkaline–taurocholate–peptone medium and plated on the same media after overnight incubation. Cultures from field diarrhoeas were obtained with a tellurite-impregnated rectal swab which was placed in liquid alkaline–taurocholate–peptone medium and plated after overnight incubation on TTGA and gelatin agar. *Vibrio cholerae* was identified by agglutination of suspicious colonies in specific absorbed antisera. A case of diarrhoea was classified as cholera only if a positive culture for *Vibrio cholerae* was obtained.

Serological studies

Random sample serological surveys were carried out in the field trial population prior to, and 3 months and 6 months following, vaccination. The details of this part of the study are covered in the second paper in this series (Mosley et al., 1969).

Statistical analysis

Vaccine effectiveness was estimated by calculating the percentage reduction in the case rate in the vaccinated group compared with the control group.

RESULTS

The total population in the study villages was 111 673. Table 1 shows the population arranged by age and sex. The children under 15 years of age numbered 53 862, or 48.3% of the total. Vaccine was assigned only to this age-group.

TABLE 1
TOTAL POPULATION IN MATLAB VACCINE FIELD TRIAL AREA BY AGE AND SEX

Age-group (years)	Male	Female	Total
0–4	9 913	9 669	19 582
5–9	10 581	10 007	20 588
10–14	7 456	6 236	13 692
15–29	10 387	12 733	23 120
30+	18 782	15 909	34 691
Total	57 119	54 554	111 673

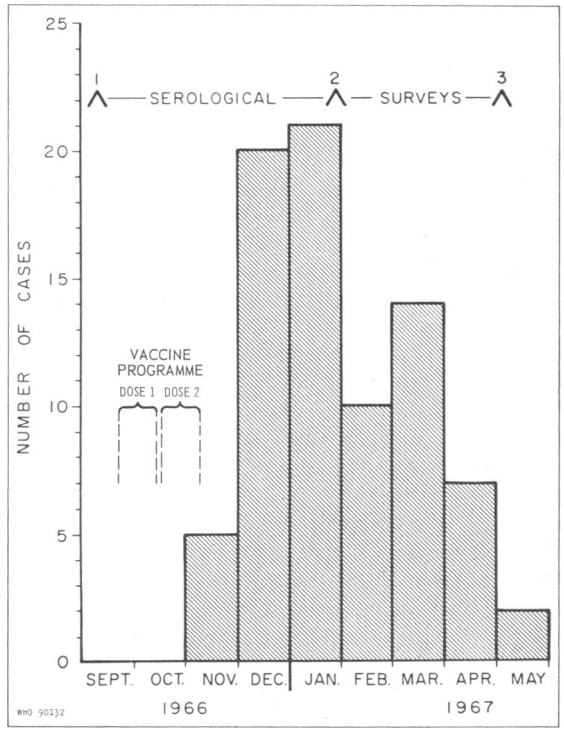
The study population for this field trial includes only those persons who received both assigned injections. The children who received only the first or only the second injection are excluded from this analysis. Table 2 shows the study population arranged by age, sex and vaccine group. Altogether, 39 862 children received both injections, which represents 74.0% of those assigned vaccine. Participation was best in the 0–4-years age-group (77.9%) and least in the 10–14-years age-group (64.2%), mainly because the older boys were away at work. In the study population, 9923 (24.9%) were in vaccine group OO; 10 020 (25.1%) were in vaccine group XO and 19 919 (50%) were in vaccine group XX. As indicated in Table 2, the various groups were essentially identical in their age and sex structure.

The accompanying figure illustrates the time relationships of the vaccine programme to the cholera season. The first cholera cases appeared in November 1966 towards the close of the vaccination campaign, and the season extended to May 1967. There were no cases in the subsequent 6 months. Altogether there were 79 cholera cases in the study population, with 1 death from cholera in vaccine group OO. All but 4 of the cholera cases were caused

TABLE 2
STUDY POPULATION BY AGE, SEX AND VACCINE GROUP

Age-group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
Vaccine OO						
0–4	1 901	19.2	1 892	19.0	3 793	38.2
5–9	1 868	18.8	2 052	20.7	3 920	39.5
10–14	1 010	10.2	1 200	12.1	2 210	22.3
Total	4 779	48.2	5 144	51.8	9 923	100.0
Vaccine XO						
0–4	1 946	19.4	1 872	18.7	3 818	38.1
5–9	1 983	19.8	2 034	20.3	4 017	40.1
10–14	1 022	10.2	1 163	11.6	2 185	21.8
Total	4 951	49.4	5 069	50.6	10 020	100.0
Vaccine XX						
0–4	3 877	19.5	3 759	18.9	7 636	38.3
5–9	3 840	19.3	4 050	20.3	7 890	39.6
10–14	2 019	10.1	2 374	11.9	4 393	22.1
Total	9 736	48.9	10 183	51.1	19 919	100.0

MONTHLY CHOLERA CASES IN THE 1966 VACCINE FIELD TRIAL POPULATION IN RURAL EAST PAKISTAN, SHOWING THE RELATIONSHIP OF SEROLOGICAL SURVEYS AND THE VACCINATION PROGRAMME



by the Inaba serotype of *V. cholerae*. The 4 Ogawa cases occurred in April 1967. No organisms of the El Tor biotype were isolated.

Table 3 shows the pattern of appearance of cholera cases in the hospital and in the field by month of onset in each vaccine group. There were 62 hospitalized cholera cases for an over-all rate of 15.6 per 10 000 persons. There were 28 cases (28.2 per 10 000) in vaccine group OO, 15 cases (15.0 per 10 000) in vaccine group XO and 19 cases (9.5 per 10 000) in vaccine group XX. These differences are highly significant ($P = <0.001$). Only 17 of the acute diarrhoea cases in the study population, which were cultured by field-surveillance personnel, were positive for *V. cholerae*; 16 were mild and did not require hospitalization or intravenous fluids; 1 was an acute diarrhoea death in group OO, which was confirmed as cholera by a positive culture from the clothing of the deceased. The over-all rate for field cases was 4.3 per 10 000. The distribution of field cases in the 3 vaccine groups gave a rate of 7.1 per 10 000 for group OO, 4.0 per 10 000 for group XO and 3.0 per 10 000 for group XX. While these differences are not significant statistically, the distribution of field cases by vaccine group follows the same pattern as the distribution of hospitalized cases.

For comparative purposes, Table 4 gives the hospitalized and field acute non-cholera diarrhoea cases by month for each vaccine group. There were 63 hospitalized non-cholera diarrhoea cases for an over-all rate of 15.8 per 10 000 persons. The case rates by vaccine group range from 15.1 to 17.1 per 10 000 persons with no significant differences. Similarly, 628 acute diarrhoea cases were detected by field surveillance for an over-all rate of 157.5 per 10 000 persons. The rates for each vaccine group ranged from 149.6 to 169.3 per 10 000 persons. Again, there was no significant difference in the acute diarrhoea experience for the various vaccine groups.

TABLE 3

HOSPITALIZED AND FIELD CHOLERA CASES BY MONTHS OF ONSET IN EACH VACCINE GROUP

Vaccine group	Nov.	Dec.	Jan.	Feb.	March	April	May	June	Total	Rate per 10 000
Hospitalized cases [a]										
OO	1	10	9	3	4	1	0	0	28	28.2
XO	2	3	6	2	0	1	1	0	15	15.0
XX	0	4	2	4	4	4	1	0	19	9.5
Total	3	17	17	9	8	6	2	0	62	15.6
Field cases [b]										
OO	2	2	2[c]	0	1	0	0	0	7[c]	7.1
XO	0	0	1	0	2	1	0	0	4	4.0
XX	0	1	1	1	3	0	0	0	6	3.0
Total	2	3	4	1	6	1	0	0	17	4.3

[a] $\chi^2 = 14.9$ (2 degrees of freedom); $P<0.001$.
[b] $\chi^2 = 3.13$ (2 degrees of freedom); P not significant.
[c] Includes 1 cholera death detected by field surveillance.

TABLE 4

HOSPITALIZED AND FIELD ACUTE NON-CHOLERA DIARRHOEA CASES BY MONTH IN EACH VACCINE GROUP

Vaccine group	Nov.	Dec.	Jan.	Feb.	March	April	May	June	Total	Rate per 10 000
Hospitalized cases [a]										
OO	0	1	3	1	2	2	5	3	17	17.1
XO	2	0	3	3	2	3	3	0	16	16.0
XX	1	8	5	1	6	4	2	3	30	15.1
Total	3	9	11	5	10	9	10	6	63	15.8
Field cases [b]										
OO	7	29	30	26	18	19	14	25	168	169.3
XO	11	18	26	20	17	24	16	30	162	161.7
XX	23	43	47	35	29	40	34	47	298	149.6
Total	41	90	103	81	64	83	64	102	628	157.5

[a] $\chi^2 = 0.74$ (2 degrees of freedom); P not significant.
[b] $\chi^2 = 1.81$ (2 degrees of freedom); P not significant.

TABLE 5

CHOLERA CASES AND RATES BY AGE IN EACH VACCINE GROUP, AND VACCINE EFFECTIVENESS

Age-group (year)	Cases			Rate per 10 000			Vaccine effectiveness (%)	
	OO	XO	XX	OO	XO	XX	XO	XX
Hospitalized cases								
0–4	16	13	11	42.2	34.0	14.4		
5–9	7	2	7	17.9	5.0	8.9		
10–14	5	0	1	22.6	—	2.3		
Total	28	15	19	28.2	15.0	9.5		
Field cases								
0–4	5	3	3	13.2	7.9	3.9		
5–9	1	1	3	2.6	2.5	3.8		
10–14	1	0	0	4.5	—	—		
Total	7	4	6	7.1	4.0	3.0		
Total cases								
0–4	21	16	14	55.4	41.9	18.3	24.4	67.0
5–9	8	3	10	20.4	7.5	12.7	78.9	60.5
10–14	6	0	1	27.1	—	2.3		
Total	35	19	25	35.3	19.0	12.6	46.2	64.3

Table 5 gives an analysis of the cholera cases by age for each vaccine group, and the vaccine effectiveness. A single injection of cholera vaccine reduced the cholera case rate by 46% while the 2-injection schedule had an effectiveness of 64%. Examining the case rates and vaccine effectiveness by age, it is evident that a single injection of cholera vaccine resulted in only minimal protection in children under 5 years of age; however, it produced substantial protection in the 5–14-years age-groups. The enhancement in over-all protection produced by the 2-injection schedule was entirely due to the lowering of the case rate in the children under 5 years of age. There were no significant differences in protection produced by a 1- or a 2-dose schedule in the 5–14-years age-groups. It should be noted that, in spite of the protection provided by a 2-dose injection schedule in children under 5 years of age, the case rate in these children remained higher than in children aged 5–9 and 10–14 years receiving a single dose of cholera vaccine.

Table 6 summarizes the cholera case rates and the protection achieved in 3-month periods following the vaccination programme. While the numbers of cases are small for this analysis, the data suggest that a significant level of protection was maintained for only about 3 months, even in the children who received 2 doses of vaccine. The loss of protection seems definite in children under 5 years of age; in older children, the numbers of cases are too small to evaluate any persistence of protection throughout the cholera season.

TABLE 6

CHOLERA CASE RATES, AND PROTECTION IN THE FIRST 3 MONTHS AND LAST 4 MONTHS OF THE CHOLERA SEASON, BY AGE-GROUP

Vaccine group	Age-group 0–4 years			Age-group 5–14 years			All ages		
	Cases	Rate/ 10 000	Protection (%)	Cases	Rate/ 10 000	Protection (%)	Cases	Rate/ 10 000	Protection (%)
November 1966–January 1967									
OO	16	42.2	—	10	16.3	—	26	26.2	—
XO	11	28.8	31.8	1	1.6	90.2	12	12.0	54.2
XX	3	3.9	90.8	5	4.1	74.8	8	4.0	84.7
February 1966–May 1966									
OO	5	13.2	—	4	6.5	—	9	9.1	—
XO	5	13.1	0	2	3.2	50.7	7	7.0	23.1
XX	11	14.4	0	6	4.9	24.6	17	8.5	6.6

Table 7 gives a comparison of the potency in active mouse-protection tests of vaccine X with vaccine CRL used in earlier field trials (Oseasohn et al., 1965; Benenson et al., 1968). On a millilitre basis, vaccine X was considerably less potent than vaccine CRL, especially against Inaba challenge. Since different dose levels were used for the children, however, 0.5 ml of vaccine X should be compared with 0.2 ml of vaccine CRL. At these levels, vaccine X was one-half as potent as vaccine CRL against Ogawa challenge and one-sixth as potent against Inaba challenge. These differences would be reduced by a factor of 2 for those children in the XX group who received 2 0.5-ml doses of vaccine X. Vaccine CRL was administered in a single dose.

TABLE 7

RELATIVE POTENCY IN ACTIVE MOUSE-PROTECTION TESTS OF CHOLERA VACCINES EMPLOYED IN FIELD TRIALS

Vaccine	Serotype challenge	Relative potency [a] per single human dose [b] of:		
		0.5 ml	0.4 ml	0.2 ml
CRL [c]	Ogawa	3.42	2.73	1.37
	Inaba	12.20	9.72	4.86
X	Ogawa	0.62	—	—
	Inaba	0.72	—	—

[a] Based on the Potency of US Reference Cholera Vaccines Ogawa and Inaba; 1.0 ml = 1.0 for both vaccines.

[b] For vaccine CRL, single dose was 0.4 ml for adults, and 0.2 ml for children; for vaccine X, single dose for children was 0.5 ml.

[c] Designated as vaccine B and vaccine R in 1963 and 1964 field trials, respectively.

DISCUSSION

In this study, and in the 1963–64 and 1964–65 cholera vaccine field trials carried out by the PSCRL in the endemic cholera area in rural East Pakistan, several consistent patterns have emerged (Oseasohn et al., 1965; Benenson et al., 1968). In the control populations the cholera case rates were highest in children under 5 years of age and fell sharply with increasing age. Cholera vaccine has had the least effect in children under 5 years, and when protection was achieved, it was short-lived. By contrast, in older children and adults, the 2 whole-cell vaccines tested since 1963 have produced protection of 60%–80% with a single injection and, as the present study indicates, this protection was not enhanced by the 2-dose schedule. It is evident from these observations that a number of factors should be considered in interpreting the results of field trials in the endemic cholera area. Among these are vaccine potency, the injection schedule used, the ages and previous cholera experiences of the population.

The effect of vaccine potency seems to be reflected only in the youngest age-group. The whole-cell vaccine CRL tested in the 1963–64 trial (Oseasohn et al., 1965) and again in the 1964-65 trial (Benenson et al., 1968) was unusually potent on a per-millilitre basis according to the mouse-protection test (Feeley & Pittman, 1965). However, based on the single human doses administered to the youngest age-group, vaccine CRL was approximately twice as potent against Ogawa challenge and 6 times as potent against Inaba challenge as vaccine X. The differences would be reduced by a factor of 2 for those children who received 2 doses (total 1.0 ml) of vaccine X. While the differences in potency against Ogawa challenge were less striking, the greater differences in potency against Inaba challenge were reflected in the results of the field trials in children under 5 years of age. A single dose (0.1 ml–0.2 ml) of vaccine CRL gave 80% and 75% protection in the first cholera seasons following the 1963–64 and 1964–65 trials, respectively. A single dose (0.5 ml) of vaccine X gave only 24% protection in the 1966–67 trial. However, with 2 injections (total 1.0 ml) of vaccine X at an interval of 1 month, the level of protection was raised to 67%, which approximates that obtained from 1 dose (0.2 ml) of vaccine CRL. Therefore, the prophylactic efficacy of these vaccines appears to be related to their potency assayed against Inaba challenge. Since there were only a few Ogawa infections in the study population, there is no basis for evaluating the relationship of laboratory potency and actual field efficacy for this serotype.

The effect of age was important in two respects. In children under 5 years of age, any protection achieved seemed quite transitory. Thus, in spite of the relatively high level of protection produced by the 2-dose schedule (91% in the first 3 months), this appears to have been lost toward the end of the cholera season 4–8 months after injection. There had been a similar loss of effectiveness in children under 5 years of age with the high potency vaccine; during the second cholera season of the 1963–64 trial, the protection in this age-group fell to 37% (Benenson et al., 1968). In older children in this endemic cholera area, there was evidence that the vaccine was

acting as a booster. Thus, while the high potency vaccine gave 75% and 59% protection to children in the 5–14-year age-group in the 1963–64 and 1964–65 trials, respectively, similar results were obtained with vaccine X in 1966–67; 1 dose gave 79% protection and this was not improved by a 2-injection schedule. Data from the 1963–64 study indicate that protection was also more sustained in the older children and adults (Benenson et al., 1968).

The data from the field trials in East Pakistan have conclusively established that cholera vaccine can provide measurable protection against cholera. At the same time, it is clear that the duration of protection provided either by a vaccine of high antigenic concentration or by a 2-dose injection schedule of commercial vaccine is inadequate for practical public health purposes. Further cholera vaccine development will require major modifications in the present vaccine, such as its use with adjuvants, or the exploration of new vaccines and new routes of immunization, for example, a living attenuated oral vaccine or possibly a toxoid preparation.

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RÉSUMÉ

RAPPORT SUR L'ESSAI PRATIQUE D'UN VACCIN ANTICHOLÉRIQUE DANS UNE RÉGION RURALE DU PAKISTAN ORIENTAL (1966-1967): 1. CONCEPTION DE L'ESSAI ET RÉSULTATS ENREGISTRÉS DURANT LA PREMIÈRE ANNÉE

On a procédé en 1966-1967 à un essai pratique contrôlé de vaccin anticholérique pendant la poussée saisonnière de l'affection dans une région rurale du Pakistan Oriental. Le vaccin utilisé était une préparation commerciale contenant par millilitre 4 milliards d'organismes de chacun des sérotypes Ogawa (souche NIH 41) et Inaba (souche NIH 35A3) de *Vibrio cholerae*. De l'anatoxine tétanique et de l'anatoxine diphtérique ont servi de préparation témoin.

L'essai a porté sur un total de 39 862 enfants âgés de 3 mois à 14 ans. On a administré la préparation témoin à 9923 d'entre eux, cependant que 10 020 enfants recevaient une injection et 19 919 deux injections de vaccin anticholérique. Le dépistage des cholériques a été assuré à la fois par les services hospitaliers fonctionnant au centre de la région de l'enquête et par des visites à domicile quotidiennes pour la recherche des cas d'affections diarrhéiques graves. Tous les cas de choléra ont reçu une confirmation bactériologique.

Pendant la poussée saisonnière de choléra qui a sévi au cours des huit mois suivant la vaccination, on a relevé chez les sujets ayant reçu une seule dose de vaccin un taux de protection global de 46%. L'administration de deux doses à un mois d'intervalle a eu pour résultat de protéger 64% des sujets vaccinés. Après la vaccination à dose unique, le taux de protection n'était que de 24% chez les enfants de moins de 5 ans, mais il atteignait 79% dans le groupe d'âge 5-14 ans. Après injection de deux doses de vaccin, la proportion des sujets immunisés a dépassé 60% aussi bien chez les jeunes enfants que chez les enfants plus âgés. La protection conférée par l'administration d'une dose unique ou double de vaccin anticholérique s'est manifestée essentiellement pendant les trois premiers mois suivant la vaccination. Au cours des quatre derniers mois de la poussée saisonnière de choléra, elle s'est complètement dissipée chez les enfants de moins de 5 ans, qu'ils aient reçu une ou deux doses de vaccin.

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