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Report of the 1966–67 cholera vaccine trial in rural East Pakistan *

4. Five years of observation with a practical assessment of the role of a cholera vaccine in cholera control programmes

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A controlled cholera vaccine field trial was carried out in rural East Pakistan to determine the efficacy of a cholera vaccine of average antigenic potency when used in a continuing programme with annual reimmunizations. A cohort of 40 000 children aged 0–14 years was equally divided into a control group and 3 vaccine groups. Inoculations of vaccine were given annually for 3 years just before the start of the cholera season, and follow-up continued for 2 additional years. The results indicate that there was increasing protection with reimmunization, reaching a maximum with 3 doses. One dose produced 43 % protection, 2 doses 64 %, 3 doses 81 %, and 4 doses 76 %. Protection was more sustained after reimmunization; being 50 % and 39 %, 1 and 2 years after the fourth injection, respectively. Serological surveys suggested a general parallel in the antibody response to vaccine and the level of protection achieved; however, the levels of vibriocidal antibody titres could not be related directly to levels of protection. The overall protection achieved with the 3-year programme of annual reimmunizations was 55 % for the group receiving one inoculation annually, and 65 % for the group receiving 2 inoculations in the first year followed by annual reimmunizations. When the costs and effectiveness of annual vaccine programmes are compared with those for cholera treatment centres, it becomes clear that the cholera vaccines now available are not appropriate alternatives to treatment in routine cholera control programmes.

The controlled vaccine field trials carried out since 1963 in East Pakistan (now Bangladesh) have been directed mainly towards measuring the maximum level and duration of protection of specific vaccine preparations (Benenson et al., 1968a; Mosley et al., 1969a, 1970; Oseasohn et al., 1965). In those studies, a single or a divided dose of vaccine was administered, and observations for effectiveness were reported for one or two cholera seasons. The various vaccines tested showed a peak effectiveness ranging from 47 % to 93 %; characteristically, this diminished rapidly within 3–6 months after inoculation, particularly in young children.

The 1966–67 vaccine field trial was designed to go beyond the limited investigation of vaccine efficacy to explore the usefulness of a cholera vaccine of average antigenic potency when applied in a continuing programme with annual reimmunizations. This study was carried out in a cohort of approximately 40 000 children aged 0–14 years who were followed prospectively for a period of years. The participants were equally divided into

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a control group and 3 vaccine groups. Injections were given annually for the first 3 years, and follow-up was continued for an additional 2 years. A total of 11 serological surveys were made during the course of these studies to relate the immune response to vaccine effectiveness.

The results, given in this report, indicate that while a single dose of cholera vaccine of average antigenic potency gave only 46% protection, reimmunization gave increasing protection. Two doses increased the protection to 64%, and annual reimmunizations with 3–4 doses increased the protection to 76–81%. Protection was significantly more sustained in the groups receiving annual reimmunizations in comparison with a group not reimmunized after the first year; however, the level of sustained protection was low, ranging from 28% to 39% 2 years after the last inoculation. Serological studies indicated that the serum antibody responses broadly paralleled the protective efficacy of the vaccine; however, titres in specific groups could not be related directly to levels of protection.

METHODS

A detailed description of the design of the field trial is given in the first paper in this series (Mosley et al., 1969a).

Vaccines

The cholera vaccine used was prepared by a commercial manufacturer in the USA. This bivalent vaccine contained 4 000 million organisms per ml each of the Ogawa (NIH 41) and Inaba (NIH 35A3) serotypes. The organisms were grown on agar, suspended in saline, and killed and preserved with 0.5% phenol. Potency assays by the mouse protection test (Feeley & Pittman, 1962; Pittman & Feeley, 1963) and a human antigenicity test on the lot of vaccine used in 1966 are described elsewhere (Mosley et al., 1971). For the 1967 and 1968 vaccine programmes, additional lots of vaccine from the same manufacturer, meeting the same specifications, were used.

The control preparation was "Tetanus and Diphtheria Toxoids (for adult use)". The cholera vaccine was designated vaccine X, and the control, vaccine O.

Assignment and administration of vaccines

The field trials were carried out in 132 villages in the Matlab area in Comilla District. After the entire population had been numbered, census books were prepared, and all children aged 0–14 years were assigned in strict alternation to one of four vaccine groups according to the series of inoculations to be given: (1) group OOOO (2) group XOXX; (3) group XXOO; (4) group XXXX. The first two inoculations in each group were given at an interval of 1 month in 1966, the third inoculation was given in 1967, and the fourth in 1968. The immunization programmes each year were carried out in the months of September and October, just before the expected cholera season.

The vaccine doses of 0.5 ml were administered to all participants by means foot-operated jet injectors.[1] Separate jet injectors were used for the cholera and the control vaccines. (The vaccine procedure was modified in 1968 because of a time limitation imposed by a concurrent field trial. The vaccinators were instructed that in the event of the malfunctioning of an injector, the same injector could be used for both vaccines after the cylinder had been cleaned with distilled water. Subsequent serological surveys revealed, however, that in spite of this precaution about 10% of the participants in the control group showed a significant rise in vibriocidal titre as a result of contaminating cholera vaccine in the inoculation. A detailed analysis of the field trial results excluding villages where this procedure was followed did not reveal any detectable effect on the estimates of vaccine effectiveness.)

Serological surveys

Random-sample serological surveys were carried out prior to, and two or three times following, each vaccination programme in the first 3 years, and once in the fourth year. Fingertip blood was collected, and vibriocidal titres for Inaba organisms were determined by the microtechnique of Benenson et al. (1968b). Details of the survey methods have been given previously (Mosley et al., 1969b).

Surveillance for cases

Surveillance for cholera cases was carried out by field workers who visited every family daily. Rectal swab cultures were obtained from all severe cases of acute diarrhoea detected in the

[1] Ped-O-Jet, manufactured by the Scientific Equipment Manufacturing Corporation, Lodi, N.J., USA.

field. All cases of diarrhoea requiring treatment were taken by speedboat ambulance to a centrally located field hospital. The methods of intravenous and oral treatment used are described in detail elsewhere (Cash et al., 1970; Rahman, 1969).

Bacteriological methods

Rectal swab cultures for cholera were made on admission for all cases of diarrhoea seen at the hospital. The swabs were plated on Monsur's agar and gelatin agar, both before and after enrichment, and the cultures were examined for *Vibrio cholerae* according to techniques previously described (Monsur, 1963). Rectal swabs obtained by field staff were placed directly in liquid transport media (Monsur, 1963) and plated after overnight incubation on Monsur's and gelatin agar. *V. cholerae* were identified by the agglutination of suspicious colonies in specific absorbed antisera. Only those cases of diarrhoea that had a culture positive for *V. cholerae* were classified as cholera.

RESULTS

The total number of children in the study villages at the time of the census in 1966 was 53 862. In the first year 39 862 (74%) received both assigned inoculations. In 1967, 38 546 (96.6% of this cohort) received the assigned reinoculation. In 1968, 37 827 (95.9% of the reinoculated group) received the fourth injection. As indicated in Table 1, the participants were distributed equally among the 4 vaccine groups. It should be noted that throughout this report, age refers to the age of the cohort at the time of the census (1966); thus in 1970, for example, children in the 0–4-year age group were actually 4–8 years old.

Table 2 summarizes the cholera experience in each of the 4 vaccine groups by month from November 1966 to the end of February 1971. Also indicated in Table 2 are the months when the vaccine programmes and the serological surveys were carried out. The vaccine programmes were timed to precede the usual winter cholera season so that maximum effectiveness would be observed. Significant winter epidemics occurred in the first, third, fourth, and fifth years of observation. The winter epidemics extended into the summer in the first and fourth years, and there were small distinct summer outbreaks in the second and third years.

Table 1. Number of vaccine recipients, by age and vaccine group, 1966–68

Vaccine group			Age (years)	Year		
1966	1967	1968		1966	1967	1968
0–0	0	0	0–4	3 793	3 671	3 590
			5–14	6 130	5 957	5 876
			total	9 923	9 628	9 466
X–O	X	X	0–4	3 818	3 656	3 578
			5–14	6 202	5 980	5 892
			total	10 020	9 636	9 470
X–X	O	O	0–4	3 833	3 689	3 609
			5–14	6 177	5 994	5 894
			total	10 010	9 683	9 503
X–X	X	X	0–4	3 803	3 669	3 562
			5–14	6 106	5 930	5 826
			total	9 909	9 599	9 388
all groups				39 862	38 546	37 827

Table 3 gives the cholera case rates by age and vaccine group for each epidemic year. The estimated vaccine effectiveness, calculated as the percentage reduction in case rates of the vaccinated groups in comparison with the control group, is also indicated. In the first year, all three vaccinated groups showed significant protection. Groups XXOO and XXXX, both of which received 2 doses of vaccine in the first year, were better protected (63% and 66%) than group XOXX (46%). This 40% improvement in protection by the second dose was mainly the result of increased protection in the 0–4-year age group. (A detailed analysis of the first year's results has already been reported by Mosley et al. (1969a).) There were too few cases for any conclusions to be drawn regarding effectiveness in the second year.

In the 1968–69 cholera season, the groups receiving third or fourth inoculations of cholera

Table 2. Cholera cases by vaccine group and month, 1966–71 [a]

Vaccine group	Month												Total	Rate per 10 000
	A	S	O	N	D	J	F	M	A	M	J	J		
						1966–67								
	(S)[b]	(V)[c]	(V)			(S)				(S)				
OO	—	—	—	3	12	11	3	5	1*	—	—	—	35	35.3
XO	—	—	—	2	3	7	2	2	2	1	—	—	19	19.0
XX	—	—	—	—	4	1	3	1	2**	1	—	—	12	12.0
XX	—	—	—	—	1	2	2	6	2*	—	—	—	13	13.1
						1967–68								
	(S)	(V)		(S)		(S)								
OOO	—	—	—	—	2	1	—	—	2	3	2	—	10	10.4
XOX	—	—	—	—	2	—	—	—	—	3	2	—	7	7.3
XXO	—	—	—	—	1	—	—	—	—	6	—	—	7	7.2
XXX	—	—	—	—	—	—	—	—	3	1	—	1	5	5.2
						1968–69								
	(S)	(V)	(S)		(S)	(S)								
OOOO	—	2	1	5	8	3	—	—	1*	1*	—	—	21	22.2
XOXX	—	—	1	—	—	1	—	—	2**	—	—	—	4	4.2
XXOO	—	1	2	5	5	6	—	1	—	2	—	—	22	23.2
XXXX	—	—	—	3	—	1	—	—	1	—	—	—	5	5.3
						1969–70								
						(S)								
OOOO	—	—	2**	—	18*	4	2	3	3	—	—	—	32	33.8
XOXX	—	—	—	1*	19*	2	—	—	1	—	—	—	23	24.2
XXOO	—	—	—	4*	17	5	—	1	1	—	2	—	30	31.6
XXXX	—	—	—	—	9	4	2	—	1	—	—	—	16	17.0
						1970–71								
OOOO	—	—	—	3	12***	10**	—						25	26.4
XOXX	—	2	—	3	9**	3*	1						18	19.0
XXOO	—	—	—	2	14***	7	—						23	24.2
XXXX	—	1	—	4	9*	1	—						15	16.0

[a] Each asterisk indicates an Ogawa case; all other cases were Inaba.
[b] Time of serological survey.
[c] Time of vaccine programme.

vaccine (XOXX and XXXX) showed an increased level of protection (81% and 76%, respectively) in comparison with the results from 1 and 2 doses in the first year. In group XOXX, this third reimmunization resulted in a 75% increase in the protective efficacy as compared with the effectiveness of 2 doses. There was no difference in the level of protection between the groups that received the third and fourth doses. Group XXOO, which was given no further inoculations

Table 3. Cholera cases, case rates,[a] and protection [b] by vaccine group and age, 1966–71

Vaccine group	Age (years)	1966–67			1967–68			1968–69			1969–70			1970–71		
		No.	Rate	Protection	No.	Rate	Protection	No.	Rate	Protection	No.	Rate	Protection	No.	Rate	Protection
OOOO	0–4	21	55.4		5	13.6		11	30.6		22	61.3		16	44.5	
	5–14	14	22.8		5	8.4		10	17.0		10	17.0		9	15.3	
	total	35	35.3		10	10.4		21	22.2		32	33.8		25	26.4	
XOXX	0–4	16	41.9		7	19.1		2	5.6		14	39.1		13	36.3	
	5–14	3	4.8		0	0.0		2	3.4		9	15.3		5	8.5	
	total	19	19.0	46	7	7.3	—[c]	4	4.2	81	23	24.2	28	18	19.0	28
XXOO	0–4	5	13.0		5	13.6		21	58.2		21	58.2		17	47.2	
	5–14	7	11.3		2	3.3		1	1.7		9	15.3		6	10.2	
	total	12	12.0	66	7	7.2	—[c]	22	23.2	0	30	31.6	6	23	24.2	8
XXXX	0–4	9	23.7		4	10.9		2	5.6		11	30.9		7	19.6	
	5–14	4	6.6		1	1.7		3	5.1		5	8.6		8	13.7	
	total	13	13.1	63	5	5.2	—[c]	5	5.3	76	16	17.0	50	15	16.0	39

[a] Rate per 10 000 persons.
[b] Percentage reduction in case rate in comparison with the control group.
[c] Insufficient cases to estimate protection.

of cholera vaccine, showed no residual protection in the 1968–69 cholera season.

In the fourth and fifth years, when no further inoculations of cholera vaccine were given, there was a decline in protection in groups XOXX and XXXX. Group XXXX showed 50% protection in 1969–70, and 39% in 1970–71; group XOXX showed 28% protection in both years. Significantly, both these groups had some residual protection 2 years after the last inoculation of cholera vaccine. This is in contrast to group XXOO, which showed no residual protection in 1968–69, and continued to have case rates similar to those of the control group in the fourth and fifth years of observation.

An overall summary of the effectiveness of the 3-year immunization programme is given in Table 4. In children receiving 1 inoculation of cholera vaccine annually (group XOXX), the protection achieved was 55%. Protection varied substantially with age; in the 0–4-year cohort the protection rate was only 32%, while in the older children it averaged 83%. In the children receiving 2 inoculations of cholera vaccine the first year, followed by annual boosters (group XXXX), the protection rate was 65%. The improvement in protection resulted mainly from the effect of the more intensive immunization programme on the 0–4-year age group. The additional dose of cholera vaccine in the first year did not improve protection in the older children.

For comparative purposes, the case rates in each vaccine group of noncholera diarrhoea treated at the hospital were analysed. For the 4 years from November 1966 to the end of June 1970, noncholera diarrhoea occurred with approximately equal frequency in all four vaccine groups. The cumulative numbers of cases were: group OOOO, 255; group XOXX, 254; group XXOO, 248; group XXXX, 223.

The geometric mean vibriocidal titres against Inaba organisms are given in Table 5 by vaccine

Table 4. Summary of the cholera cases, case rates, and protection during the 3-year immunization programme at Matlab, 1966–69

Vaccine group	Age (years)	Person-years of observation	Cumulative cases, 1966–69	Rate [a]	Protection [b]
OOOO	0-4	11 054	37	33.4	
	5-14	17 963	29	16.1	
	total	29 017	66	22.7	
XOXX	0-4	11 052	25	22.6	32
	5-14	18 074	5	2.8	83
	total	29 126	30	10.3	55
XXXX	0-4	11 034	15	13.6	59
	5-14	17 862	8	4.5	72
	total	28 896	23	8.0	65

[a] Per 10 000 person-years.

[b] Percentage reduction in case rate in comparison with group OOOO.

group and age for each of the 11 serological surveys. In the first year, different groups of children were selected for each of the three surveys. In the second and third years, serial bleedings were taken from the same sample. Only a single bleeding was carried out in the fourth year. The sample size averaged 2–2.5 % of each vaccine group.

Several general patterns in the antibody response of these children to cholera vaccine are evident. Most notable is the lack of a typical anamnestic response to repeated inoculations. In fact, there was actually a smaller rise in titre from the baseline following each successive reimmunization. This is evident from a comparison of the August and January surveys for each of the 3 years when cholera vaccine was given. (It should be noted that the January surveys were the only post-inoculation surveys to be made at comparable intervals after inoculation in all three years.)

Although the reinoculations did not induce a typical anamnestic response, the reinoculated groups did develop progressively higher titres that were directly related to the number of doses.

Table 5. Reciprocal geometric mean vibriocidal titres by vaccine group and age, 1966–70

Vaccine group	Age	1966–67			1967–68			1968–69				1970
		Aug.	Jan.	May	Aug.	Nov.	Jan.	Aug.	Oct.	Dec.	Jan.	Jan.
OOOO	0–4	11	21	13	18	22	22	20	36	26	25	22
	5–14	21	35	24	33	39	38	35	55	49	46	52
	total	16	28	19	26	32	30	27	45	37	35	38
XOXX	0–4	12	40	21	26	124	58	29	490	80	70	60
	5–14	21	112	50	66	172	128	97	443	194	167	137
	total	16	74	35	45	150	92	62	460	139	121	96
XXOO	0–4	11	59	28	29	31	29	28	55	38	32	34
	5–14	23	118	69	91	86	80	64	76	71	70	99
	total	16	88	48	54	54	50	47	68	56	53	53
XXXX	0–4	(same as XXOO in 1966–67)			38	177	82	38	540	117	104	54
	5–14				83	229	147	114	417	202	185	157
	total				61	202	117	71	465	159	144	104

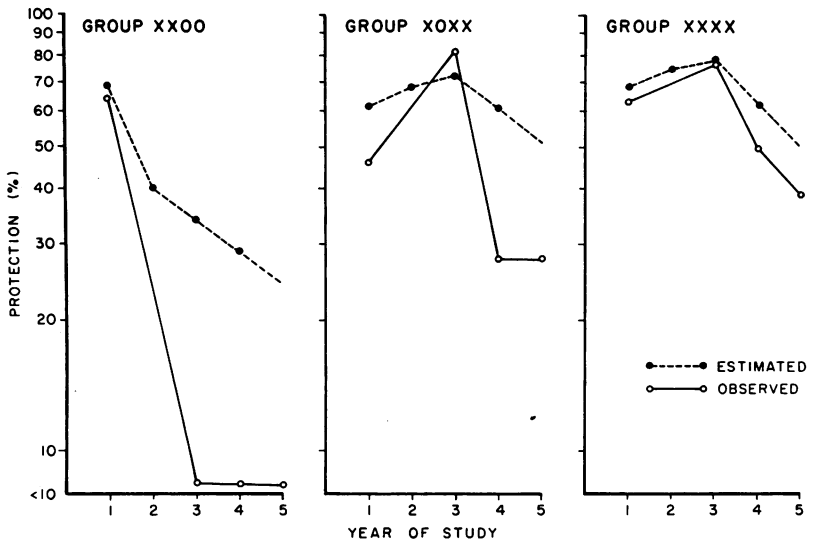

Fig. 1. Comparison of the level of protection observed in the field trials with the level estimated in the January serological surveys for the 5 years of observation, by vaccine group.

The reciprocal titres in group XOXX in January following the first, second, and third inoculations were 74, 92, and 121, respectively, while the titres in group XXXX following the second, third, and fourth inoculations were 88, 117, and 144. It is clear that for both groups the titres following the second inoculation (92 and 88) and the third inoculation (117 and 121) are almost identical, even though the inoculations were given in different years. Considering the progression of titres over the entire series of 4 inoculations, it can be estimated that each immunization boosted the titres found in the January bleedings by about 25%. Multiple reinoculations also resulted in a somewhat more sustained antibody response.

Previous investigations have suggested that vibriocidal titres may be useful as a measure of immunity to cholera (Mosley et al., 1968a, 1968b, 1969b). The relationship between the antibody response and protection was examined in this study by using the vibriocidal titres found in the January surveys each year as an average for the level of immunity over the cholera season and calculating an "expected" protection for each vaccine group, a 50% protection rate being assumed for every 2-fold elevation of titre in the vaccinated groups as compared with the control group (Mosley et al., 1969b). The expected protection for each year is shown in comparison with the observed level (from Table 3) in Fig. 1. This comparison indicated that although in some instances the serologically estimated "immunity" roughly paralleled the protection observed it was not a reliable guide for estimating protection.

DISCUSSION

These studies have confirmed and extended previous observations indicating that cholera vaccine field trials in this endemic cholera area must be evaluated as a dynamic interaction of several variables, only one of which is vaccine potency. Other important variables are the age of the recipient, the immunization schedule, the previous experience of the population with cholera antigens (from vaccine or natural infection), and the time interval from inoculation to infection (Mosley et al., 1969a, 1971). Unfortunately, some of these variables are interdependent so that the primary factors influencing the results remain undefined.

The serological surveys have proved to be useful in interpreting the results of the field trials (Mosley et al., 1968b, 1969b). In the study with reimmunizations over a 3-year period, the magnitude and patterns of vibriocidal antibody responses in general ran parallel to vaccine efficacy. Repeated inoculations resulted in a progressive rise in titres in the reimmunized groups

and also more sustained titres paralleling the observed increase in protection, and the sustained protection seen in the reimmunized groups. In spite of these correlations it is now clear that the level of vibriocidal antibody cannot be used as a direct measure of the level of immunity in cholera. This is because of the problem of non-specific vibriocidal antibodies induced by other bacteria (Gangarosa et al., 1970), and because of the failure to distinguish type-specific vibriocidal antibodies induced by the two serotypes of *V. cholerae* (Mosley et al., 1970, 1971). The lack of a consistent relationship of titre to protection is evident in this study.

This study, attempting more than the simple assessment of the relative efficacy of a vaccine, has examined the practical efficacy of an immunization programme, using a cholera vaccine that meets international standards of acceptability, and is comparable with cholera vaccines in general use throughout the world. The results indicate that vaccine efficacy in very young children can be significantly improved by reimmunization, either by giving a series of 2 inoculations initially, or by reimmunizing annually. In older children, an initial 2-inoculation schedule did not improve the protective efficacy although annual reimmunizations were necessary to maintain the level of protection. Even though reimmunizations did result in a significant increase in protection, a maximum level of about 80% was reached with 3 doses, and a fourth inoculation caused no improvement.

Repeated annual reimmunizations did appear to result in rather more sustained protection in comparison with the group that received inoculations in the first year only. Unfortunately, because of an interaction with the effect of aging in the cohort, it is impossible to determine whether this more sustained response was actually the result of repeated inoculations. In any event, the residual protective efficacy of 28–39% after 2 years cannot be considered of any practical value.

The overall protective effect of the 3-year immunization programme in these children was relatively poor. In the group receiving 1 dose annually, immediately preceding the cholera season for maximum effect, the protection was only 55%; more significantly, in the 0–4-year age group, the vaccine programme was almost ineffective. Giving the younger children 2 inoculations of cholera vaccine in the first year enhanced the overall protective efficacy of the group to 65%. This was a significant improvement, but such a schedule is rather impracticable on a mass basis in rural Bangladesh.

The results of this investigation support the conclusion drawn from earlier trials, that cholera vaccines available at present are not satisfactory for general public health use because of their limited period of effectiveness, particularly in contrast to the simplicity and effectiveness of treatment. A simple cost analysis reinforces this conclusion. In this study, group XOXX received 29 126 inoculations of cholera vaccine during the first 3 years. This programme prevented an estimated 36 cases of cholera, based on the number of cases in the control group. Thus 810 inoculations were required to prevent 1 case of cholera. At a cost of about US$0.06[1] per injection, i.e., the cost of the cholera vaccine and administration expenses in Bangladesh (M. Khan, personal communication) this amounts to approximately US$45[1] to prevent 1 case of cholera but even after this effort, an almost equal number of cases (30) requiring treatment occurred in the group. In group XXXX, 38 805 cholera inoculations were given, preventing an estimated 43 cases. In this group, 900 inoculations at an estimated cost of US$52[1] were necessary to prevent 1 case, but 23 cases of cholera requiring treatment occurred among recipients of the vaccine.

The cost and effectiveness of immunization programmes can be compared with the cost and effectiveness of the cholera treatment centre serving this population. For the 12 months from 1 July 1969 to 30 June 1970, the P-SCRL Matlab field hospital, which serves an estimated population of 750 000, treated 1 743 cases of cholera. There were 4 deaths, i.e., a case fatality rate of 0.2%. The total annual cost of this facility, including the operation of 14 speedboat ambulances, was approximately US$60 000.[1] A determining factor in the cost of treatment was the use of oral maintenance therapy after intravenous rehydration (Cash et al., 1970), which saved over 27 000 litres of intravenous fluid, resulting in savings of ever US$20.000[1]. The approximate cost of treatment per cholera case in this opera-

[1] Based on an exchange rate of Rs 4.76 to US$1 at the end of 1970.

tion was US$34.[1] The cost per patient is actually much less, and the benefits are much greater, when it is considered that 6 432 non-cholera cases of diarrhoea were also treated during the same period.

These calculations indicate that an immunization programme or a cholera treatment centre serving a given population would cost about the same annually. An immunization programme involves a logistic disadvantage in having to be carried out for the entire population within a period of 1–2 months immediately before the expected cholera season in order to have a significant effect. Even if that were feasible, and even if 100 % coverage could be achieved every year, about 50 % of the expected cholera cases (and deaths, in the absence of treatment facilities) would still occur. The treatment centre, on the other hand, can be almost 100 % effective throughout the year in saving the lives of cholera victims, and will also serve an even larger group of patients suffering from other diarrhoeal diseases. Thus, it becomes evident that until a substantially improved cholera vaccine that does not require annual reimmunizations is developed, cholera vaccines are not appropriate alternatives to the establishment of treatment facilities as a routine part of cholera control measures.

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RÉSUMÉ

RAPPORT SUR L'ESSAI DE VACCIN ANTICHOLÉRIQUE MENÉ EN 1966/67 DANS UNE RÉGION RURALE DU PAKISTAN ORIENTAL: 4. RÉSULTATS APRÈS 5 ANS D'OBSERVATION ET ÉVALUATION PRATIQUE DU RÔLE D'UN VACCIN ANTICHOLÉRIQUE DANS LES PROGRAMMES DE LUTTE CONTRE LE CHOLÉRA

En 1966/67, un essai pratique de vaccin anticholérique a eu lieu dans 132 villages du Pakistan oriental (actuellement Bangladesh). Il s'agissait de déterminer l'efficacité d'un vaccin d'activité antigénique moyenne administré dans le cadre d'un programme continu d'immunisation comportant des revaccinations annuelles. Les 40 000 enfants choisis pour cet essai, âgés de 0 à 14 ans, ont été répartis en 4 groupes égaux (3 groupes vaccinés et un groupe témoin). Les vaccinations ont été faites annuellement pendant 3 ans immédiatement avant le début de la saison épidémique du choléra et la surveillance a été poursuivie ensuite pendant 2 ans.

Les résultats montrent que la protection contre l'infection cholérique est renforcée par les revaccinations et atteint une valeur maximale après 3 doses. Les taux obtenus ont été de 43 % après 1 dose, 64 % après 2 doses, 81 % après 3 doses et 76 % après 4 doses. Chez les sujets ayant subi la série complète de vaccinations, des taux de protection de 50 % et 39 % ont été observés respectivement 1 et 2 ans après la 4e injection. L'enquête sérologique a montré en général une corrélation entre la réponse immunitaire postvaccinale et le taux de protection, mais l'absence de rapport direct entre les titres d'anticorps vibriocides et le niveau de protection conféré. Le taux global de protection, pour l'ensemble des 3 années du programme, s'est élevé à 55 % dans le groupe ayant reçu une dose annuelle de vaccin et à 65 % dans le groupe ayant subi 2 vaccinations la 1re année et revacciné annuellement.

Pour une population donnée, le coût d'un programme de vaccination est du même ordre de grandeur que celui du fonctionnement d'un centre de traitement pour cholériques. Compte tenu des avantages qu'offre ce dernier et de l'efficacité relative des vaccins anticholériques actuels, la vaccination ne peut remplacer le traitement en tant que mesure de routine dans la lutte anticholérique.

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