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A Serological Survey for Cholera Antibodies in Rural East Pakistan

2. A Comparison of Antibody Titres in the Immunized and Control Populations of a Cholera-vaccine Field-trial Area and the Relation of Antibody Titre to Cholera Case Rate *

W. H. MOSLEY,[1] A. S. BENENSON [2] & R. BARUI

Controlled field trials of a highly antigenic cholera vaccine were held in Matlab Bazar in rural East Pakistan in 1963 and again in 1964. In July–September 1965, a serological survey for cholera antibodies was carried out on a random sample of the field-trial population. This survey revealed that it was possible to demonstrate the effect of a single injection of the cholera vaccine per head on the proportion of the population with detectable vibriocidal and agglutinating antibody 10 and 22 months after injection. More significantly, the reduction in cholera case rate caused by the vaccine could be correlated with the rise in vibriocidal antibody after vaccination, suggesting that the serological response to vaccine in man may be a useful measure of vaccine potency. The survey also indicated that in this endemic cholera area, with a high level of immunity in adults, a single injection of cholera vaccine was in fact a booster dose for the majority of the population. Thus, the results of cholera vaccine field trials in endemic areas cannot be directly extrapolated to predict the effects of the same vaccine in non-endemic areas.

The design of the cholera vaccine field trials conducted in Matlab Bazar, East Pakistan, by the Pakistan–SEATO Cholera Research Laboratory has involved the selection of a defined population, the allocation of cholera vaccine and control vaccine to this population in a random order and the continuous house-to-house surveillance for diarrhoeal illness to detect every cholera case subsequently developing (Oseasohn et al., 1965; Benenson, Mosley et al., 1968). In the first trial, initiated in November 1963, there were 6956 persons who received cholera vaccine and 7098 persons who received the control vaccine; and in the second trial, started in September 1964, there were 8357 persons who received the same cholera vaccine, 8453 who received a control vaccine and 8457 who received purified Ogawa antigen.

In July-October 1965 a random-sample serological survey was conducted among the 5 populations defined above, to determine the antibody pattern in this endemic area, and to determine if there were detectable antibody differences among these vaccine groups. Because of the high " base-line " antibody titres found, the first report in this series (Mosley et al., 1968) [3] presented an examination of the results obtained from the control groups only. This revealed that there was a rise in antibody titre with age, a pattern not found in sera collected from Czechoslovakia, a non-endemic area. This rise in antibody titre with age could be correlated with a fall in the age-specific cholera case rate. In the present report, the antibody titres of the vaccinated populations are

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[1] Chief, Epidemiology Section, Pakistan–SEATO Cholera Research Laboratory.

[2] Formerly Director of the Pakistan–SEATO Cholera Research Laboratory, Dacca, East Pakistan. Present address: Jefferson Medical College, Philadelphia, Pa. 19107, USA.

[3] See the paper on p. 327 of this issue.

TABLE 1. DISTRIBUTION OF THE MATLAB BAZAR VACCINE TRIAL POPULATION, BY AGE AND VACCINE GROUP

Age-group (years)	1963 Trial		1964 Trial		
	Cholera vaccine	Typhoid vaccine	Cholera vaccine	Tetanus toxoid	Ogawa antigen
0–4	1 248	1 288	1 514	1 588	1 573
5–9	1 529	1 546	1 790	1 793	1 731
10–29	2 067	2 110	2 617	2 531	2 662
⩾ 30	2 112	2 154	2 436	2 541	2 491
Total	6 956	7 098	8 357	8 453	8 457

compared with those of the corresponding controls and further observations are made on the relationship of the cholera case rate to antibody levels.

METHODS

The sampling methods are described in detail in the first report (Mosley et al., 1968):[1] using the individual census cards available on the 39 321 persons taking part in the trial, the population was stratified into 5 vaccine-groups and 4 age-groups, and by sex, and a random sample of 50 persons was drawn from each of these 40 strata. The sampling technique used ensured that the 2000 individuals selected represented a cross-section of the entire vaccine-trial population.

Finger-tip blood specimens were collected between 26 July and 6 October 1965 by the methods previously described (Mosley et al., 1968).[1] All specimens submitted to the laboratory were identified only by a code number. The sera were titrated for vibriocidal and agglutinating antibody in random batches of 36, together with known positive controls, at an initial blood dilution of 1 : 20. The microtechniques used in this study have been described in detail elsewhere (Benenson, Saad & Mosley, 1968; Benenson, Saad & Paul, 1968). Vibriocidal titres were determined on all specimens; agglutinating titres on a 65% subsample.

The calculation of geometric mean titres was reduced to an arithmetic averaging process by assigning the value of 0 to titres of less than 1 : 20, 1 to titres of 1 : 20, 2 to titres of 1 : 40, 3 to titres of 1 : 80, 4 to titres of 1 : 160, etc. The levels of significance (P) for the differences between means were calculated using Student's *t*-test.

[1] See the paper on p. 327 of this issue.

RESULTS

Table 1 gives the populations in the vaccine field trials by age and vaccination status. The distribution by sex is not included since sex was not shown to be a factor related to antibody titre or cholera case rate. Blood samples were collected from 1522 (76.1%) of the 2000 persons in the random sample originally chosen from this population. Only 2 individuals refused to give specimens; 24 were dead, and the

TABLE 2. PERCENTAGE OF BLOOD SAMPLES FROM 1963 TRIAL POPULATION WITH AGGLUTINATING TITRES OF 1:20 OR MORE, BY AGE, VACCINE GROUP AND SEROTYPE

Age-group (years)	Cholera vaccine			Typhoid vaccine		
	No. tested	Percentage positive		No. tested	Percentage positive	
		Ogawa	Inaba		Ogawa	Inaba
0–4	47	6.4	6.4	40	0.0	5.0
5–9	24	8.3	12.5	16	0.0	0.0
10–29	48	29.2	22.9	39	17.9	12.8
⩾ 30	32	37.5	34.4	34	14.7	14.7

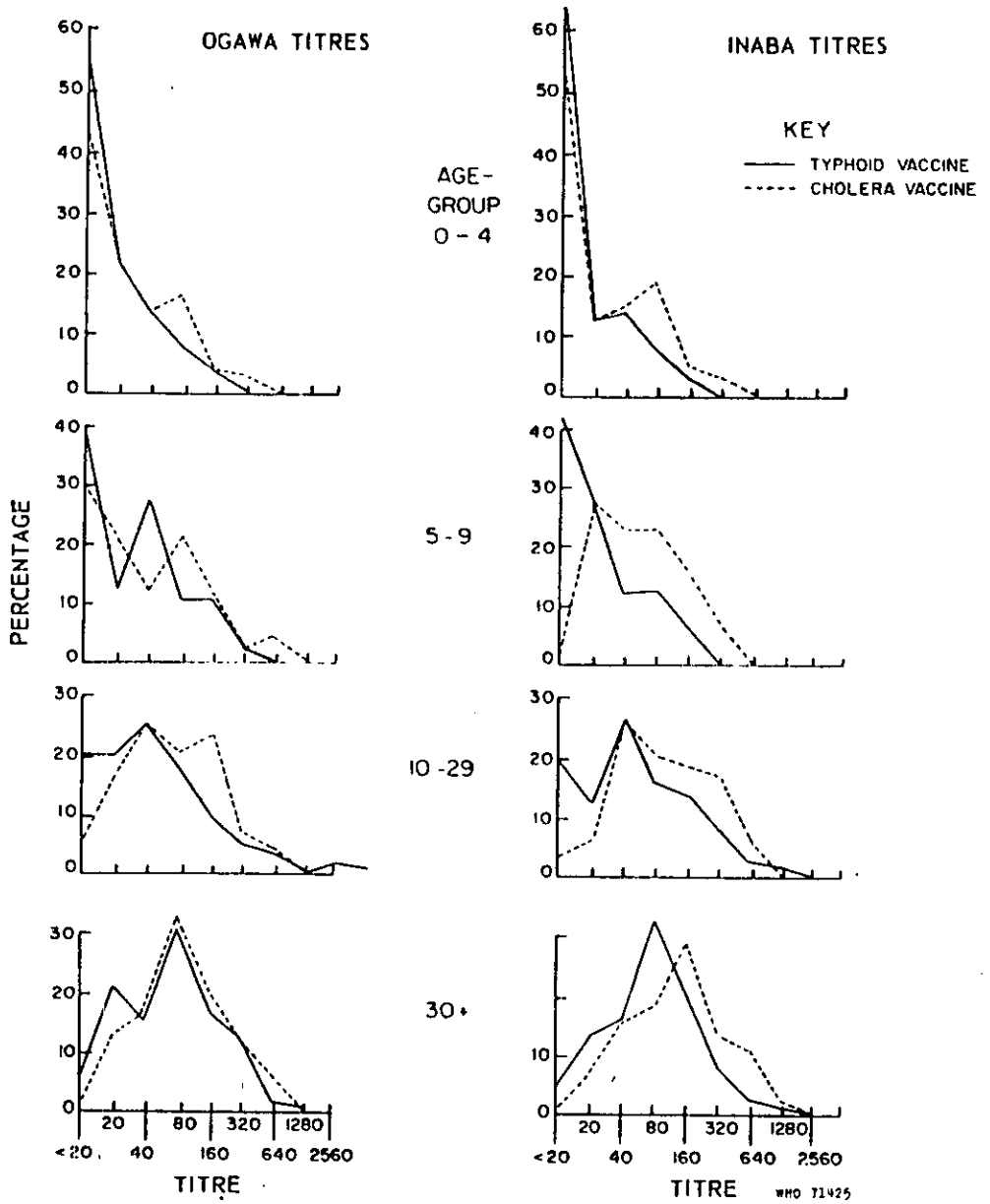
remainder were out of the locality at the time of the survey. The highest percentage of collections was in the 0–4-year age-group (85.2%) while the fewest collections were in the 15–29-year age-group (67.0%), primarily because this group contained a large proportion of young men at work away from Matlab.

1963 trial population

The results for the sample of the populations vaccinated in the 1963 trial will be examined first. Table 2 shows the proportion with agglutinating titres of 1:20 or greater, by age and vaccination status. It will be seen that the cholera vaccine group contained a larger proportion of persons with detectable agglutinating antibody than the corresponding controls, while in both groups there was an increase with age in the proportion of individuals with detectable antibody.

Fig. 1 gives the distribution of the vibriocidal titres found within each age-group, by vaccination status. In both the vaccinated and control populations, there is a shift in the distribution of antibody titres to higher levels with age; but it is evident that within each age-group the vibriocidal titres in the

FIG. 1 PERCENTAGE DISTRIBUTION OF VIBRIOCIDAL TITRES IN 1963 TRIAL POPULATION, BY AGE-GROUP, VACCINE GROUP AND SEROTYPE



vaccinated population are higher than in the controls.

The geometric mean vibriocidal titres calculated from the distributions shown in Fig. 1 are given in Table 3 and Fig. 2. Within each age-group the mean titres are significantly higher in the vaccinated population than in the controls, particularly for the Inaba serotype. Fig. 2 also shows that the marked rise in titre with age results in higher titres in adult controls than in vaccinated children.

The serological survey was conducted between two cholera seasons; the cholera season generally extends from September to June, with an incidence peak in December and January. Thus, in examining the relationship between the antibody titre in the population and the cholera case rate, we combined the incidences for the seasons preceding and following the survey; cholera cases with onset between 10 and 32 months after vaccination are thus compared with the results of the serological survey conducted 22 months after vaccination. Table 4 presents the cholera cases and case rate, by age and vaccine group, for Ogawa and Inaba infections, while Fig. 3 shows the data for Inaba infections. Since there were only a few Ogawa infections, the discussion will be limited to Inaba cholera. There was a 56% reduction in

TABLE 3

GEOMETRIC MEAN VIBRIOCIDAL TITRES IN 1963 TRIAL POPULATION, BY AGE, VACCINE GROUP AND SEROTYPE

Age-group (years)	Cholera vaccine			Typhoid vaccine			Level of significance (P) for differences between vaccines [a]	
	No. tested	Mean titre (95 % confidence interval)		No. tested	Mean titre (95 % confidence interval)			
		Ogawa	Inaba		Ogawa	Inaba	Ogawa	Inaba
0–4	83	23 (19–28)	24 (19–30)	81	18 (14–23)	16 (14–19)	0.05	0.003
5–9	44	37 (26–53)	52 (37–75)	48	28 (20–38)	22 (17–28)	NS	0.0001
10–29	96	64 (51–81)	93 (77–115)	86	43 (34–56)	49 (38–63)	0.02	0.0001
⩾ 30	70	86 (68–110)	129 (100–161)	74	66 (53–81)	75 (60–94)	0.06	0.001
All ages [b]	293	52 (46–59)	72 (63–80)	289	38 (34–43)	38 (34–45)	0.001	0.0001

[a] NS = not significant.
[b] Adjusted for age distribution of original population.

FIG. 2

GEOMETRIC MEAN VIBRIOCIDAL TITRES WITH (95 % CONFIDENCE INTERVAL) IN 1963 TRIAL POPULATION, BY AGE-GROUP, VACCINE GROUP AND SEROTYPE

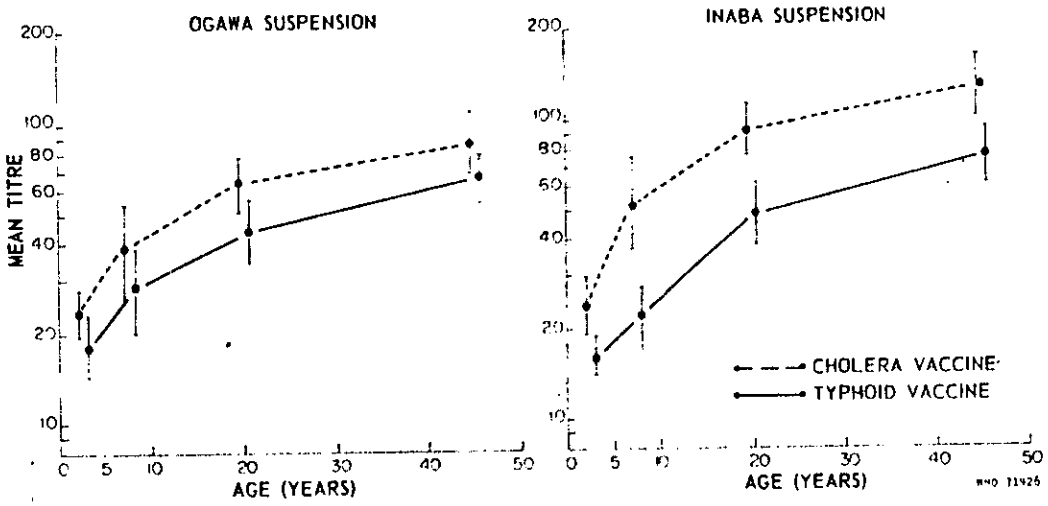
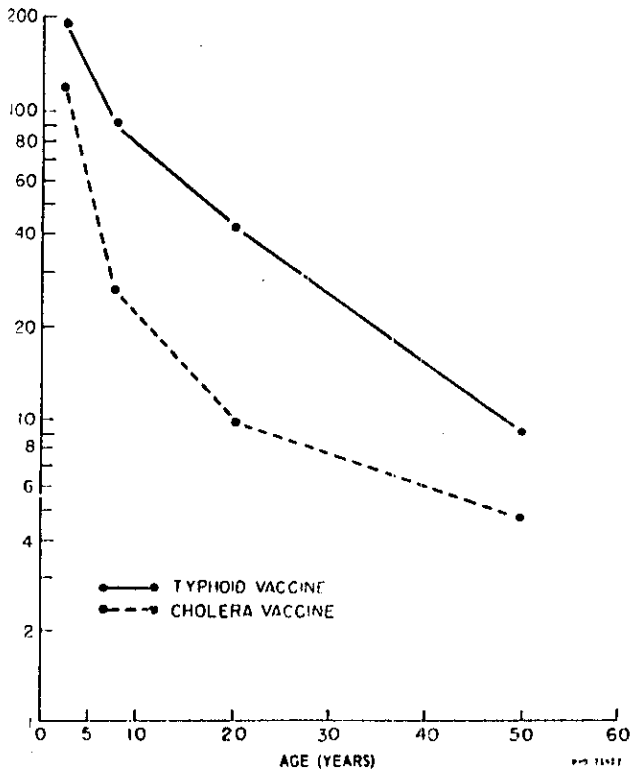


TABLE 4
CHOLERA CASES AND CASE RATES PER 10 000 PERSONS, SEPTEMBER 1964–JUNE 1966, BY AGE AND VACCINATION STATUS DURING THE 1963 TRIAL

Age-group (years)	Cholera vaccine		Typhoid vaccine	
	Cases	Rate per 10 000	Cases	Rate per 10 000
	Inaba cholera			
0–4	15	120.2	25	194.1
5–9	4	26.2	14	90.6
10–29	2	9.7	9	42.7
⩾30	1	4.7	2	9.3
Total	22	31.6	50	70.4
	Ogawa cholera			
0–4	3	24.0	3	23.7
5–9	0	—	3	19.4
10–29	0	—	4	19.0
⩾30	0	—	0	—
Total	3	4.3	10	14.1

FIG. 3
INABA CHOLERA CASE RATE PER 10 000 PERSONS, OCTOBER 1964-JUNE 1966, BY AGE-GROUP AND VACCINATION STATUS IN 1963 TRIAL POPULATION



cholera incidence in the vaccinated as compared with the control population. As Fig. 3 shows, the case rates in the vaccinated population were lower than among the controls in every age-group. Most striking, however, is the 95% reduction in the cholera case rate with age seen both in the vaccinated and control populations. As a result of this, the cholera case rate in vaccinated children is over 10 times higher than that in the adult control population.

The fall in the cholera case rate with age in both the vaccinated and control groups (Fig. 3) and the rise in the mean antibody titre with age (Fig. 2) suggest a relationship between antibody titre and cholera case rate. Fig. 4 illustrates the nearly linear correla-

FIG. 4
RELATIONSHIP BETWEEN INABA CHOLERA CASE RATE AND GEOMETRIC MEAN VIBRIOCIDAL TITRE AGAINST INABA ORGANISMS IN 1963 TRIAL POPULATION, BY VACCINATION STATUS

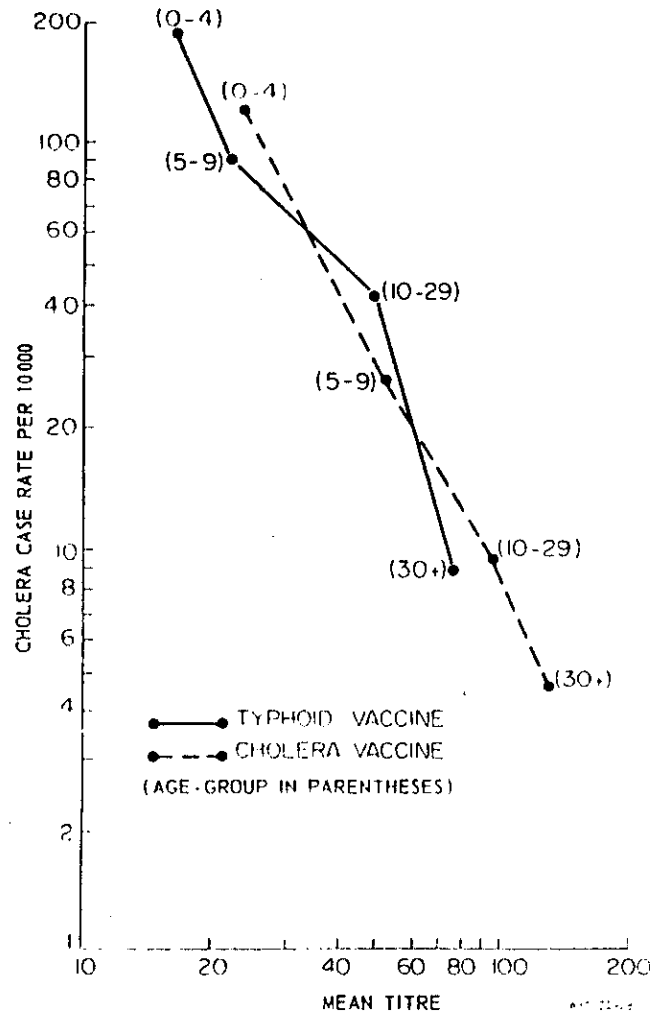


TABLE 5

PERCENTAGE OF BLOOD SAMPLES WITH AGGLUTINATING TITRES OF 1:20 OR MORE IN 1964 TRIAL POPULATION, BY AGE, VACCINE GROUP AND SEROTYPE

Age-group (years)	Cholera vaccine			Tetanus toxoid			Purified Ogawa antigen		
	No. tested	Percentage positive		No. tested	Percentage positive		No. tested	Percentage positive	
		Ogawa	Inaba		Ogawa	Inaba		Ogawa	Inaba
0–4	67	0.0	1.5	65	1.6	0.0	56	5.4	5.4
5–9	41	24.4	14.6	34	2.9	2.9	47	12.8	2.1
10–29	63	47.6	47.6	77	19.5	13.0	55	29.1	16.4
⩾ 30	61	65.6	68.9	56	39.3	33.9	57	40.4	33.3

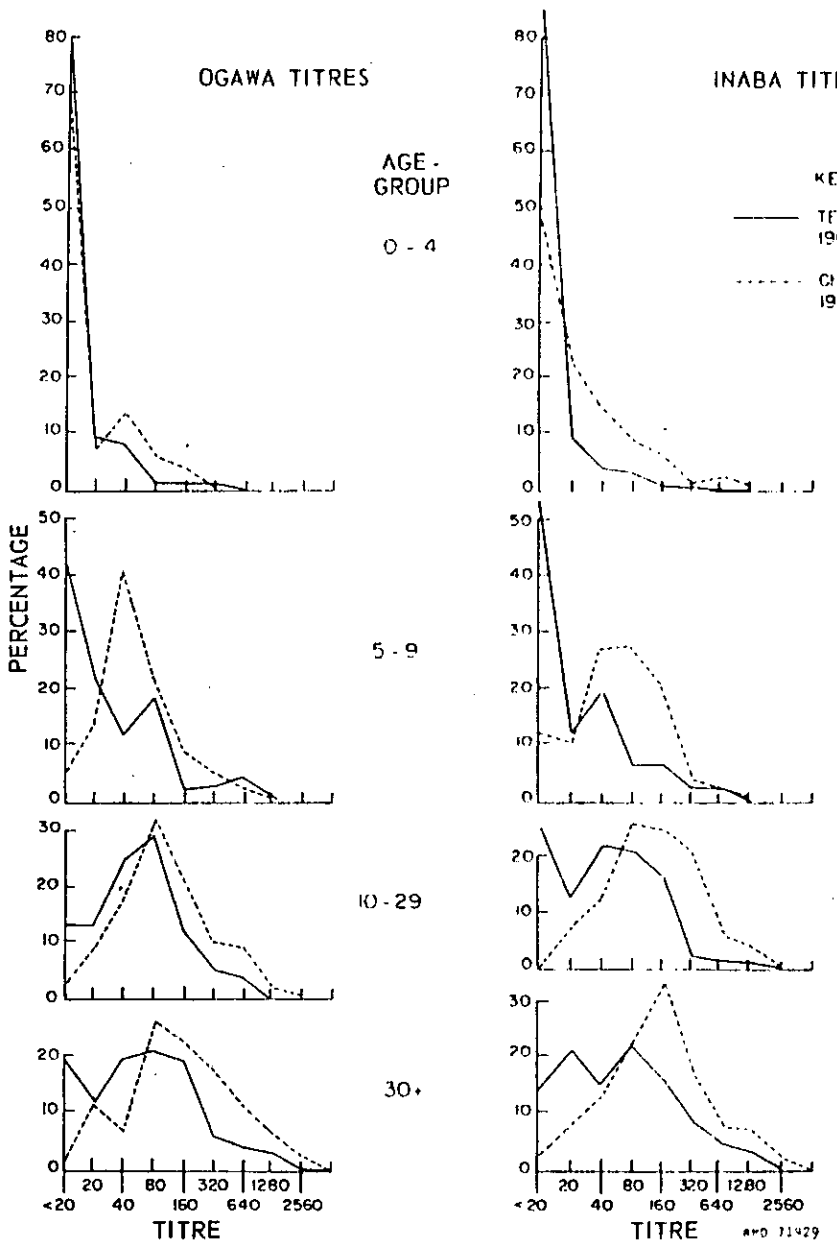


FIG. 5

PERCENTAGE DISTRIBUTION OF VIBRIOCIDAL TITRES IN 1964 TRIAL POPULATION, BY AGE-GROUP, VACCINE GROUP (CHOLERA VACCINE AND TETANUS TOXOID) AND SEROTYPE

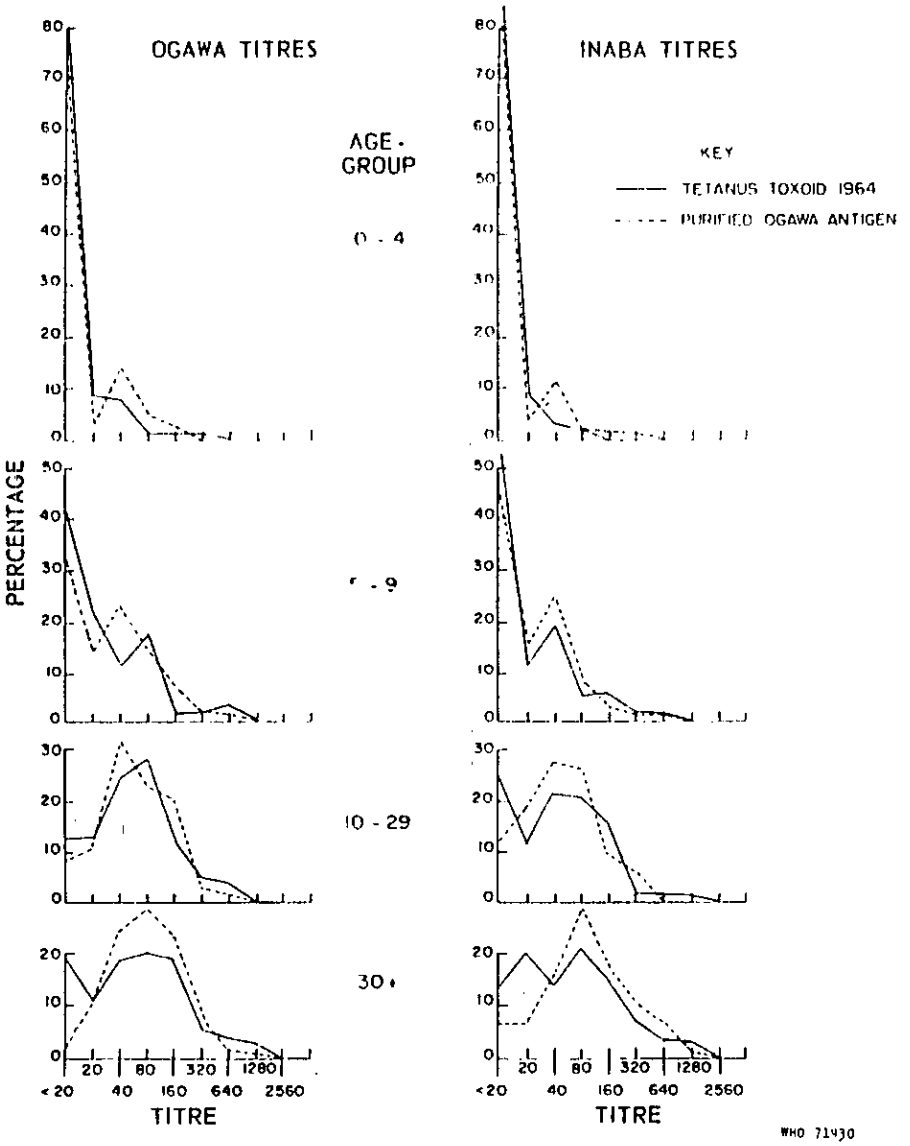
tion between the cholera case rate and the geometric mean titres in each age-group for both the vaccinated and control populations, and the fact that vaccination is associated with lower case rates and correspondingly higher mean titres in each age-group.

1964 trial population

Turning to the samples of the populations that received the cholera vaccine, tetanus toxoid, and purified Ogawa antigen in 1964, we find the distribution of agglutinating titres in Table 5. Again, the cholera-vaccinated population has a higher proportion with detectable agglutinating antibody than the controls, in the age-groups over 4 years. In the group that received the purified Ogawa antigen, however, while agglutinating antibody against Ogawa organisms was found more frequently in the 5–9-year and 10–29-year age-groups, this was not so in the over-30-year age-group. In addition, agglutinating antibody was much less frequent in those receiving the purified Ogawa antigen than in the cholera-vaccinated population.

Fig. 5 shows the distribution of the vibriocidal titres found in the 1964 cholera vaccine group as compared with that for the controls, by age-group. The titres against both Ogawa and Inaba organisms are higher for the vaccinees than for the controls in every age-group. Fig. 6 compares the distribution of the vibriocidal titres found in the population that received the purified Ogawa antigen with that for

FIG. 6
PERCENTAGE DISTRIBUTION OF VIBRIOCIDAL TITRES IN 1964 TRIAL POPULATION, BY AGE-GROUP, VACCINE GROUP (OGAWA ANTIGEN AND TETANUS TOXOID) AND SEROTYPE



the controls. It may be seen that the vaccinated population had only slightly higher titres, in both the Ogawa and Inaba vibriocidal tests.

The geometric mean vibriocidal titres summarized in Table 6 and Fig. 7 again reveal the significant increase in titre in the vaccinated population as compared with the controls. In the population receiving the purified Ogawa antigen, the mean vibriocidal titres were only slightly higher than in the controls. The higher titres were seen in both the Ogawa and Inaba tests. This difference was significant only in the oldest age-group.

The cholera cases occurring in these populations in the season preceding and following the serological survey had onsets between December 1964 and June 1966, i.e., between 1 and 21 months after vaccination, while the serological survey was conducted approximately 9–10 months after vaccination. Again, the cases were predominantly Inaba cholera. Table 7 and Fig. 8 present the cholera cases and case rates, showing that over-all there was a 63% reduction in the Inaba case rate in the vaccinated population as compared with the controls, while the Inaba case rate was reduced by only 23% in the population receiving the purified Ogawa antigen. It is apparent that the purified Ogawa antigen had very little effect in the age-groups below 10 years; on the other hand, in the age-groups over 10 years, though the numbers involved were small, the protection was similar to that provided by the whole-cell cholera vaccine.

The fall in incidence rate with age in the various vaccine-groups showed on the whole a close correlation with the fall in the geometric mean titre with age found in the serological survey, as may be seen from Fig. 9. With the purified Ogawa antigen, there was only a slight reduction in the case rate as compared with the controls, particularly in the youngest age-group; this agrees well with the fact that there was only a slight increase in the antibody titre.

The over-all relationship between the cholera case rates and the geometric mean vibriocidal titres in both the 1963 and 1964 vaccine trials is summarized in Fig. 10. This shows that there was a consistent association between the increase in titre produced by cholera vaccination and the reduction in case rate, as illustrated by the near parallelism of the lines for the two trials. Furthermore, in the 1964 trial, where two different vaccines were used, the relative effectiveness of the two vaccines in reducing the case rate agreed excellently with the relative increase in the antibody titre produced by the two vaccines.

TABLE 6

GEOMETRIC MEAN VIBRIOCIDAL TITRES IN 1964 TRIAL POPULATION, BY AGE, VACCINE GROUP AND SEROTYPE

Age-group (years)	Cholera vaccine			Tetanus toxoid			Purified Ogawa antigen			Level of significance P for differences between vaccines [a]			
	No. tested	Mean titre (95% confidence interval)		No. tested	Mean titre (95% confidence interval)		No. tested	Mean titre (95% confidence interval)		Cholera vaccine vs tetanus toxoid		Purified antigen vs tetanus toxoid	
		Ogawa	Inaba		Ogawa	Inaba		Ogawa	Inaba	Ogawa	Inaba	Ogawa	Inaba
0–4	90	16 (13–18)	21 (16–27)	90	13 (11–15)	12 (9–15)	82	15 (12–17)	14 (12–16)	0.05	0.001	NS	NS
5–9	60	50 (40–62)	56 (44–72)	51	26 (19–36)	22 (17–29)	57	33 (25–41)	24 (18–32)	0.001	0.0001	NS	NS
10–29	85	95 (77–118)	129 (104–160)	101	55 (45–67)	41 (33–51)	91	58 (47–70)	46 (38–55)	0.001	0.0001	NS	NS
⩾ 30	79	134 (103–176)	153 (121–195)	78	58 (44–77)	59 (45–75)	76	76 (62–33)	90 (71–115)	0.0001	0.0001	0.05	0.02
All ages [b]	314	66 (59–73)	82 (72–92)	320	36 (32–40)	32 (28–35)	306	43 (38–48)	33 (35–44)	0.0001	0.0001	0.03	0.005

[a] NS = not significant.
[b] Adjusted for age distribution of original population

FIG. 7

GEOMETRIC MEAN VIBRIOCIDAL TITRES (WITH 95% CONFIDENCE INTERVAL) IN 1964 TRIAL POPULATION, BY AGE-GROUP, VACCINE GROUP AND SEROTYPE

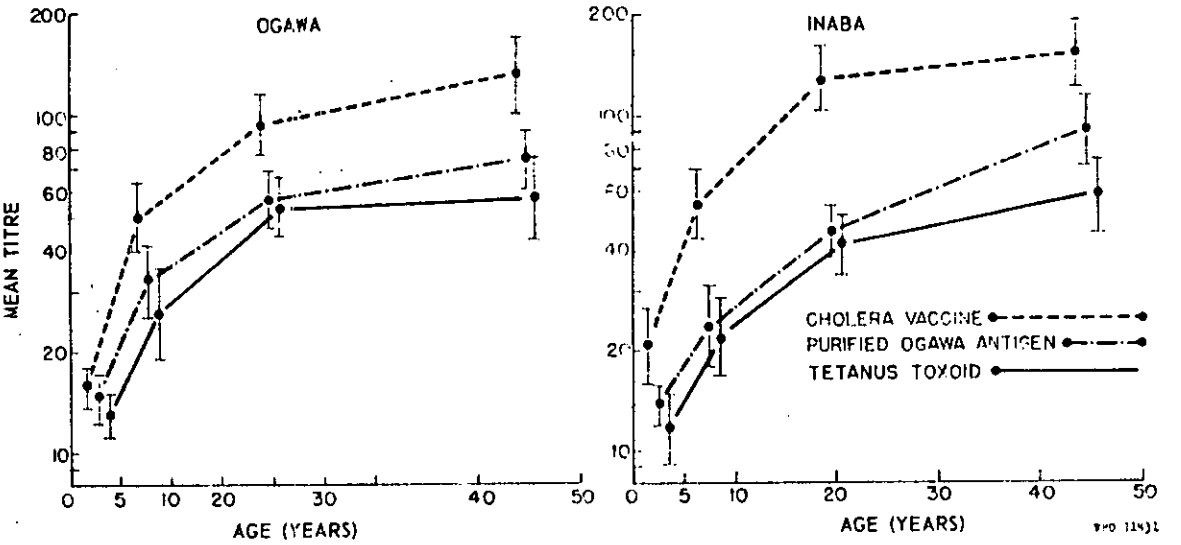


TABLE 7

CHOLERA CASES AND CASE RATES PER 10 000 PERSONS, DECEMBER 1964-JUNE 1966, BY AGE AND VACCINATION STATUS DURING THE 1964 TRIAL

Age-group (years)	Cholera vaccine		Tetanus toxoid		Ogawa antigen	
	Cases	Rate per 10 000	Cases	Rate per 10 000	Cases	Rate per 10 000
Inaba cholera						
0–4	8	52.8	25	151.1	21	133.5
5–9	6	33.5	17	94.8	14	80.9
10–29	3	11.5	7	26.6	4	15.0
⩾ 30	2	8.2	4	15.8	1	4.0
Total	19	22.7	52	61.5	40	47.3
Ogawa cholera						
0–4	1	6.6	3	18.9	1	6.4
5–9	0	—	1	5.8	1	5.8
10–29	0	—	0	—	0	—
⩾ 30	0	—	1	3.9	0	—
Total	1	1.2	5	5.9	2	2.4

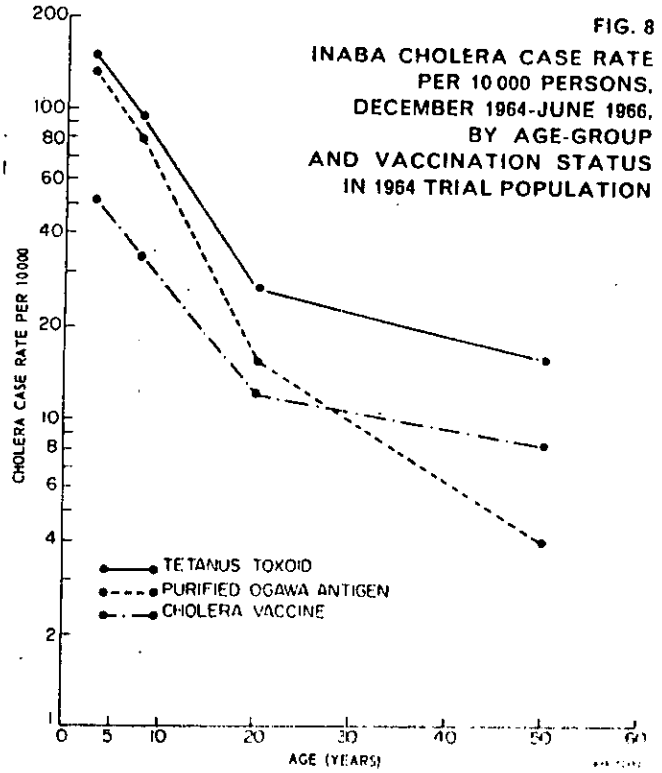


FIG. 8
INABA CHOLERA CASE RATE PER 10 000 PERSONS, DECEMBER 1964-JUNE 1966, BY AGE-GROUP AND VACCINATION STATUS IN 1964 TRIAL POPULATION

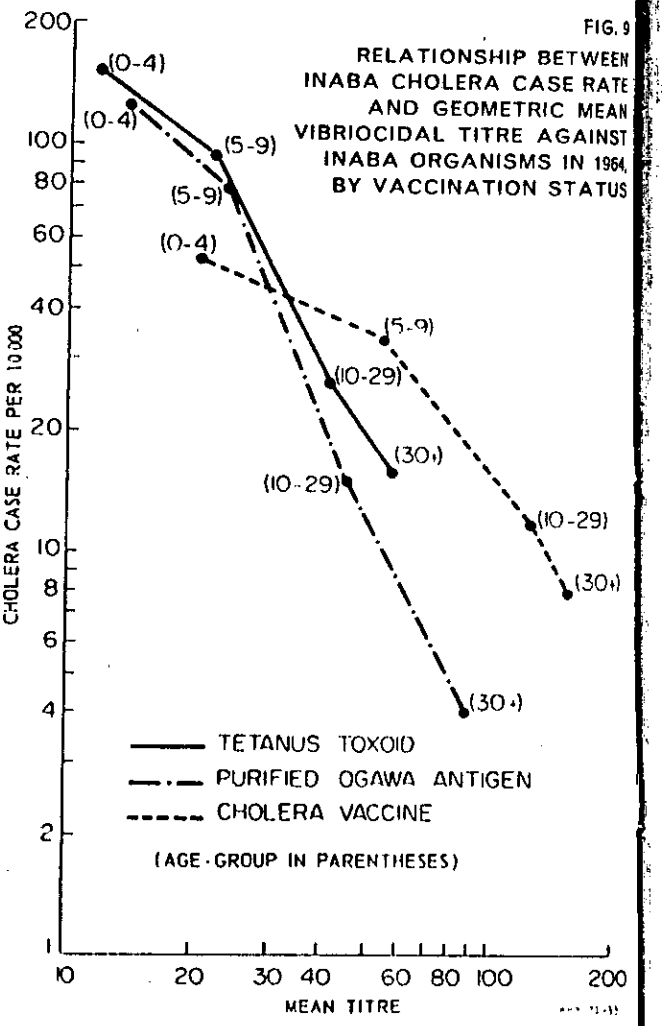


FIG. 9
RELATIONSHIP BETWEEN INABA CHOLERA CASE RATE AND GEOMETRIC MEAN VIBRIOCIDAL TITRE AGAINST INABA ORGANISMS IN 1964, BY VACCINATION STATUS

DISCUSSION

These studies have shown that it is possible to demonstrate the effect of a single injection of cholera vaccine on the antibody titre 10 and 22 months after vaccination. This effect is demonstrable over a relatively high antibody base-line in a population that has had considerable exposure to cholera antigens in the past. Of greater interest than the mere presence of detectable antibody response is the additional evidence supporting the relationship between the level of antibody in the population and level of protection against cholera. This relationship was first demonstrated for the control population of the Matlab vaccine trials, where the fall in case rate with age correlated with the rise in the geometric mean vibriocidal titre (Mosley et al., 1968).[1] While that observation could have been due to a fortuitous association of two variables independently related to age, in this report it has been shown that, when the mean antibody titre within any age-group was increased by vaccination, the fall in case rate corresponded quite well to the relative increase in antibody.

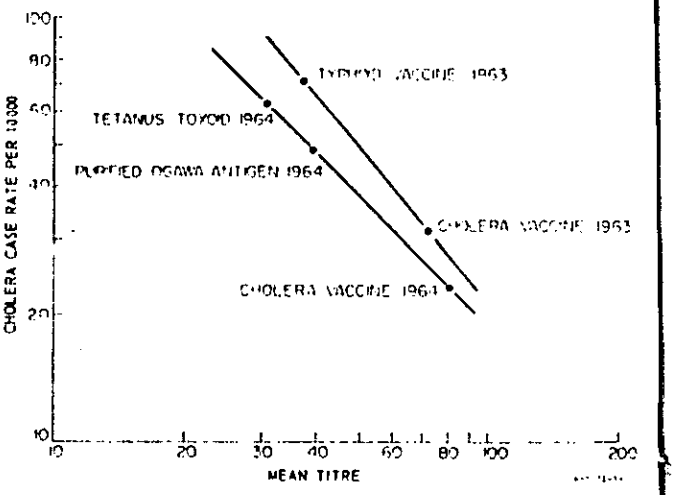


FIG. 10
RELATIONSHIP BETWEEN INABA CHOLERA CASE RATES AND GEOMETRIC MEAN VIBRIOCIDAL TITRES AGAINST INABA ORGANISMS IN THE 1963 AND 1964 TRIAL POPULATIONS

[1] See the paper on p. 327 of this issue.

These studies indicate that in this population a doubling of the mean vibriocidal titre by active vaccination was associated with a 50%–60% reduction in the cholera case rate. This observation, which was made with two quite different types of vaccine, suggests that the serological response in man may be a useful measure of the protective potency of cholera vaccines, for preliminary evaluations.

In this report, most of the discussion has dealt with the vibriocidal antibody, since the vibriocidal test is much more sensitive than the agglutinating test. Also, the tables and figures have specifically related Inaba cholera rates with Inaba antibody titres. In this population, as has generally been observed in man, there was a correlation between the agglutinating and vibriocidal titres, as well as between titres against Ogawa and Inaba organisms. Thus, this study does not indicate which antibody may be protective, or even whether protection is type-specific. In fact, the evidence suggests that the protection is not type-specific, since the purified Ogawa antigen did indeed protect against Inaba cholera, to an extent that paralleled the vibriocidal titre against Inaba organisms, which could represent antibody against a "group" antigen.

The serological survey has raised some practical points regarding vaccine evaluation in an endemic cholera area. It is obvious that the population in these trials, especially the adults, had a relatively high level of immunity prior to the study. Thus, the single injection of cholera vaccine used in these trials can in fact be regarded as a booster dose for the majority of the population. For this reason, it is not possible to extrapolate the results directly to predict the effect of a single injection of this cholera vaccine in a non-endemic area. This can be seen by examining the high cholera case rates in children, even in the vaccinated children, as compared with the adults. This age-group would be more comparable with the completely susceptible population in a non-endemic area. While it is evident that there was a reduction in the cholera case rate in vaccinated children as compared with the control children, the protection given was much lower than that in adults. It is of interest that in both of these trials all children aged from 2 to 12 years received only one-half of the adult dose and the children aged under 2 years only one-fourth of the adult dose. Thus, the segment of the population with the least immunity received the smallest amount of vaccine. This procedure for children may be unnecessary, since recent observations indicate that children have less reaction to cholera vaccine than adults (Benenson, Joseph & Oseasohn, 1968).

Now that the role of active immunization in the prevention of cholera has been established and the present study has suggested a relationship between the level of circulating antibodies and protection from cholera, the next steps in cholera-vaccine development would seem to be a search for the protective antigens of the organism and a study of the immunological response to these antigens in man. In particular, the vaccine should be modified with adjuvants and a study made of various immunization schedules to determine how to produce in man, particularly in children, a uniformly high and persistent serological response. Ultimately, field trials would still be required to establish that these procedures, based on the serological response in man, actually augmented protection from disease.

ACKNOWLEDGEMENTS

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The field survey was co-ordinated by Mr K. M. A. Aziz and Mr S. Islam and valuable assistance was rendered by the entire Matlab Vaccine Trial field staff. The advice and interest of Dr A. D. Langmuir, Communicable Disease Center, Atlanta, Ga., USA, in the development of this study are gratefully acknowledged.

RÉSUMÉ

Ce deuxième article expose et analyse les résultats de l'enquête sérologique menée au Pakistan oriental parmi la population soumise à la vaccination anticholérique et la population témoin.

Cette enquête a révélé qu'il était possible de mettre en évidence l'effet d'une injection unique de vaccin anticholérique sur la proportion de la population présentant des anticorps agglutinants et vibriocides décelables 10 et

22 mois après l'injection. D'une manière encore plus significative, on pourrait mettre en corrélation la protection conférée par le vaccin, entraînant une réduction du taux d'incidence cholérique, et l'augmentation des titres d'anticorps vibriocides qu'il détermine, ce qui amène à penser que la réponse sérologique de l'homme au vaccin peut servir à mesurer son activité. Cette enquête a aussi permis de constater que, dans cette zone d'endémicité cholérique, où le niveau d'immunité chez les adultes est élevé, une injection unique de vaccin anticholérique constituait en fait une dose de rappel pour la plus grande partie de la population. On ne peut donc pas extrapoler directement les résultats des essais de vaccin anticholérique sur la population de zones d'endémicité pour prévoir les effets de ce même vaccin dans les zones de non-endémicité.

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