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Cholera Reinfection in Man

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As long ago as 1884 [1], it was observed that a person could have clinically apparent cholera more than once. Others have reported similar observations [2–5]. In all instances, the diagnosis of a second attack of cholera was made on clinical grounds, and in no case was the diagnosis confirmed by bacteriologic isolation of *Vibrio cholerae* in both the first and second episodes of disease. This report describes 14 individuals in whom documented reinfection *V. cholerae* has occurred.

Methods

Since 1962, the Pakistan-SEATO Cholera Research Laboratory has maintained a hospital in Dacca, East Pakistan, for the treatment of cholera. In 1963, the laboratory began a field operation in Matlab Thana, a rural area 30 miles southeast of Dacca, for the purpose of conducting controlled field trials of cholera vaccine.

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The field trial area, described in detail elsewhere [6–10], consisted initially of 23 villages with a total population of 27,629. Each person was assigned a census number, each family was given an identifying card containing all the census numbers of that family, and all census numbers from any particular village were entered in separate master census books, maintained by the laboratory staff. By 1970, the field trial was expanded to include over 225,000 people in 234 villages.

Surveillance for diarrhea is maintained by daily house-to-house visits. A person with severe diarrhea is taken by speedboat ambulance to the laboratory's Matlab hospital for treatment and for bacteriologic confirmation of the diagnosis [11]. To ensure accurate identification, the patient's census number is used on all hospital, bacteriologic, and serologic records. In the first 7 years of the program, over 8,300 hospital admissions and over 11,000 outpatients have been treated. Not all patients had cholera, and over half were from outside the study area. Various epidemiologic studies have detected additional persons with cholera infection associated with mild symptoms requiring no medical attention (mild diarrhea) or with no symptoms at all [12, 13].

Infections were divided into four categories: hospitalized patients who required intravenous fluids; outpatients who were less ill, but needed medical attention; individuals with mild diarrhea detected by surveillance in the field; and persons with no symptoms who were usually family contacts of hospitalized cases.

Results

From December, 1963, to March, 1970, 14 persons with two documented cholera infections have been identified (table 1). Thirteen lived in the Matlab surveillance area, and one (patient 14) came from a congested area in Dacca city where a small community study was underway. The 13 patients in Matlab came from nine different villages, with four from a single village (patients 1, 2, 3, 4), and two from another village (patients

Table 1. Line listing of patients with cholera reinfection, Matlab, 1963–1970

Patient	Age at onset (years)	Sex	Vaccination history*	Dates of onset	Clinical status	Bacteriologic result	Vibriocidal result† Acute Og/In	Vibriocidal result† Convalescent Og/In	Interval between infections (months)
1	4	F	1963	12/18/64	Mild diarrhea	Classical Inaba	N.A.‡	N.A.	49
	8		1966, 1967, 1968	1/28/69	No symptoms	Classical Inaba	N.A.	N.A.	
2	4	F	...	1/1/65	Hospital	Classical Inaba	N.A.	N.A.	12
	5		...	1/12/66	Hospital	Classical Inaba	160/80	N.A.	
3	3	F	...	1/12/66	Hospital	Classical Inaba	80/40	N.A.	11
	4		...	12/21/66	Hospital	Classical Inaba	80/40	>2,560/>2,560	
4	5	M	1966 (two)	11/8/68	Hospital	Classical Inaba	<20/<20	N.A.	12
	6		...	11/29/69	Hospital	Classical Inaba	40/40	2,560/>2,560	
5	3	M	...	12/26/64	Hospital	Classical Inaba	N.A.	N.A.	60
	8		1966 (two)	12/19/69	Hospital	Classical Inaba	80/160	N.A.	
6	2	M	1964	1/11/66	Mild diarrhea	Classical Inaba	N.A.	N.A.	39
	5		1966	4/17/69	No symptoms	Classical Inaba	N.A.	N.A.	
7	19	F	...	12/31/66	Hospital	Classical Inaba	20/20	N.A.	22
	21		...	10/22/68	Hospital	Classical Inaba	80/80	320/320	
8	8	M	1968§	11/25/68	No symptoms	Classical Inaba	N.A.	N.A.	13
	9		1969§	12/18/69	Hospital	Classical Inaba	640/80	1,280/>2,560	
9	15	M	1966 (two)	5/5/69	No symptoms	Classical Ogawa	N.A.	N.A.	6
	15		...	11/28/69	Hospital	Classical Inaba	160/160	640/>2,560	
10	12	M	1963, 1966	5/7/69	No symptoms	Classical Ogawa	N.A.	N.A.	6
	12		...	11/26/69	Hospital	Classical Inaba	40/40	160/320	
11	4	F	1963	1/9/64	Mild diarrhea	Classical Ogawa	N.A.	N.A.	29
	6		...	6/17/66	Hospital	Classical Inaba	320/160	N.A.	
12	5	F	...	12/13/64	Mild diarrhea	El Tor Ogawa	N.A.	N.A.	1½
	5		...	1/22/65	No symptoms	Classical Inaba	N.A.	N.A.	
13	6	F	...	4/12/69	Outpatient	Classical Inaba	N.A.	N.A.	7
	7		...	11/30/69	No symptoms	El Tor Ogawa	80/160	160/320	
14	10	M	...	1/21/64	Hospital	Classical Ogawa	N.A.	N.A.	3
	10		...	4/10/64	No symptoms	Classical Inaba	N.A.	N.A.	

* Year of cholera vaccination with bivalent vaccine containing killed Inaba and Ogawa organisms; (two) = 2 doses.

† Expressed as reciprocal of titer.

‡ N.A. = not available.

§ Monovalent Ogawa vaccine.

9, 10). Two families had two reinfections in each (patients 2 and 3, 9 and 10). The mean age at the initial infection was 7.1 years, the median age 5.0 years and the range 2–19 years. There were seven males and seven females.

From eight individuals the same organism, i.e., classical biotype and Inaba serotype, was isolated during both episodes of infection. From the remaining six persons, classical Inaba vibrios were isolated during one episode and either classical Ogawa or El Tor Ogawa organisms during the other.

The mean interval between infections was 19.3 months (range 1½ to 60 months). The average interval for those individuals from whom the same type of organism was isolated on both occasions was 27.3 months (range 11–60 months), whereas it was 8.8 months (range 1½ to 29 months) in those from whom different types of *V. cholerae* were recovered.

Ten of 14 persons required hospitalization. Five were hospitalized during both infections, one during the first infection, and four during the second infection. All five patients who were hospitalized during both infections harbored classical Inaba vibrios on each occasion.

A review of the clinical records did not reveal any amelioration of symptoms in those whose second infection required hospitalization. For example, on her second hospital admission, patient 7 arrived comatose, pulseless, and without detectable blood pressure within 8 hr of onset of disease. All 14 patients survived, since adequate therapy with fluid and electrolytes was administered promptly.

In all but one instance (patient 13), blood for serologic testing was obtained only from hospitalized patients. Serum was tested for vibriocidal antibody against Inaba and Ogawa antigens by a method described previously [14]. Detectable antibody was present in all nine admission specimens obtained from individuals hospitalized during the second infection. The mean titers of antibody to Ogawa and Inaba in this group were 1:118 and 1:80, respectively. The mean Ogawa and Inaba titers of the acute-phase sera, obtained from three patients during their first infection, were 1:25 and 1:20, respectively. Six hospitalized persons submitted both acute and 10-day convalescent specimens. All six sets of sera demonstrated a significant (4-fold or greater) rise in titer. A serum pair from one additional person (patient 13), who was asymptomatic during her second infection, showed no appreciable increase in antibody titer.

Eight of the patients had received cholera vaccine as a part of the field trial being carried out in the Matlab area. Seven had received two or more injections prior to their second episode of infection; yet five required hospitalization during their second infection.

From data accumulated in the field trial, it was possible to estimate the incidence of infection with both Inaba and Ogawa cholera (table 2). During the seven years of the program, 889 Inaba infections and 103 Ogawa infections were detected in

Table 2. Rates of cholera infection, Matlab, 1963–1970

Year	Village population	No. of infections			Infection rate (%)		
		Inaba	Ogawa	Total	Inaba	Ogawa	Total
1963–64*	57,778†	104	11	115	0.18	0.02	0.20
1964–65	58,761	203	37	240	0.35	0.06	0.41
1965–66	59,759	87	...	87	0.15	...	0.15
1966–67	60,774	94	11	105	0.15	0.02	0.17
1967–68	61,809	51	...	51	0.08	...	0.08
1968–69	62,860	137	17	154	0.21	0.03	0.24
1969–70‡	63,929	213	27	240	0.34	0.04	0.38
Total	60,810§	889	103	992	1.46 (0.21/year)	0.17 (0.02/year)	1.63 (0.23/year)

* Beginning on December 1, 1963.

† Includes villages not under census until following year, and whose 1963–64 population was estimated on basis of annual growth rate of entire vaccine trial area.

‡ Ending on March 5, 1970.

§ Average population.

Table 3. Cholera reinfection rates, Matlab, 1963–1969

Type of initial infection	Cumulative initial infections 1963–1969	No. of reinfections		Rate of reinfection (%)	
		Inaba	Ogawa	Inaba	Ogawa
Inaba	676	6	...	0.89 (0.15/year)	...
Ogawa ...	76	4	...	5.26 (0.88/year)	...
Total ..	752	10	...	1.33 (0.22/year)	...

* An additional four reinfections occurred in other areas not under surveillance until 1966 or later.

56 villages. The cumulative rates of infection were 1.46% and 0.17%, respectively, with average annual rates of 0.21% and 0.02%, respectively. The total rate of infection was 1.63%, or an annual rate of 0.23%.

The incidence of reinfection was estimated similarly for both types of cholera, by use of the cumulative totals of Inaba and Ogawa infections for the first 6 years of observation as the denominators (table 3). Ten of the 14 reinfections occurred in the 56 villages for which data were available from the start of the program, and all 10 were due to the classical Inaba vibrio. The total rate of reinfection of 1.33% (0.22% annually) was quite similar to that of the rate of initial infection. However, the average annual incidence of reinfection with Inaba was much greater in those individuals whose first infection had been due to Ogawa than in those who had been infected initially with the same biotype [0.88% vs. 0.15% ($P < .01$)].

Discussion

As noted in the introduction, instances of reinfection with clinical cholera have been described almost a century ago. The infrequency of such reinfection was emphasized, and no diagnosis was confirmed by means of bacteriologic isolation of *V. cholerae*. Almost all second infections occurred in later epidemics of cholera and not during the same epidemic. For this reason, several authors postulated that cholera induced a specific immunity, which gradually waned leaving the individual susceptible to reinfection after a period of time. The lack of bacteriologic facilities prevented confirmation of the clinical diagnosis and completely excluded from consideration those people whose infection was not associated with fully developed symptoms of cholera.

In order to detect even a reasonable fraction of all infections and thus form the basis for discovery of subsequent reinfections, a broad, long-term surveillance program, in which all persons are readily and accurately identified, is essential. Such a program has now documented 14 instances of reinfection. Of the 28 total infections, 22 were due to classical Inaba vibrios, an observation consistent with the predominant role of this organism throughout the vaccine trial area.

Nine people required hospitalization during the second infection, six of them within 13 months after the first infection. That a large proportion of the total could develop disabling, and potentially fatal, disease within such a short period is disturbing, since it implies that the natural immunity derived from previous infection is quite short-lived.

Reinfection with heterologous organisms was associated with a substantially reduced interval between infections, an association implying a relative inability of Ogawa infection to stimulate appreciable cross-protection. This theory is supported by the greater incidence in the study area of reinfection with heterologous organisms and by the results of the 1968–1969 trial of cholera vaccine. Monovalent Ogawa vaccine, administered during that trial, failed to protect individuals significantly against Inaba cholera [9]. Because of the paucity of cases of Ogawa cholera in the area, it is not possible to conclude that the same lack of cross-protection is applicable after initial infection or vaccination with Inaba organisms.

Seven individuals in the present study had received 2 or more injections of cholera vaccine before their second infection, an observation that emphasizes the limited efficacy of present vaccines [8]. From these observations, it may be concluded that for a cholera vaccine to be effective, it will need to stimulate substantially greater immunity than is produced by vaccines currently available as well as by the natural disease. These conclusions are particularly relevant to the development of an attenuated, live, oral vaccine, which presumably would only mimic the natural disease.

There was no evidence tending to implicate any immunologic deficiency. Six persons submitted

paired sera, and all demonstrated a brisk antibody response to infection. Although vibriocidal antibody reflects primarily activity of IgM globulin [15] and thus only a portion of the body's immune mechanism, it would seem quite unlikely that second, and possibly subsequent, infections could be attributed to an immunologic defect.

Serologic surveys in the areas endemic for cholera in rural East Pakistan have indicated that the population rapidly acquires vibriocidal antibodies with increasing age. Approximately 50% of the population has acquired a detectable titer by age 10. The achievement of such a level would require an average annual rate of infection of about 5%, if a single infection provided lasting immunity [16].

Since McCormack et al. have shown that 80% of cholera cases of all ages have lost their initial increases in vibriocidal titer within 3 months after recovery [17], it is evident that the annual rate of infection must be greater than 5% and that reinfection occurs commonly. Direct evidence of such a high rate of infection has been documented by extensive bacteriologic and serologic studies in one village in which the rate of infection during the epidemic of 1968–1969 was 31% for 2–3-year-old children [13].

Whether the incidence of reinfection was greater or less than that of the initial infection could not be determined precisely since the denominator data, on the basis of which the rates were calculated, were relatively crude. For instance, the population at actual risk of the first infection may have been considerably smaller than the total village population because of variation in exposure to sources of infection. Actually, both rates would have been substantially higher if more thorough surveillance had been possible. It is clear that in endemic cholera areas the risk of infection does decrease with age, as the population gradually acquires specific immunity [16]. We feel it reasonable to conclude, however, that the risk of reinfection is probably only slightly less than the risk of initial infection.

Summary

Fourteen documented instances of reinfection with *Vibrio cholerae* in man are reported. They were recognized during the course of surveillance of a rural population in East Pakistan, where field trials of cholera vaccine were being conducted. The duration of immunity derived from cholera infection is short, especially in persons whose subsequent reinfection is due to heterologous organisms. The risk of reinfection with *V. cholerae* is probably only slightly less than the risk of initial infection. The relatively high frequency of reinfection indicates that an effective cholera vaccine will need to stimulate greater immunity than does the natural disease.

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