EPIDEMIOLOGIC PATTERN OF DIARRHOEA CAUSED BY NON-AGGLUTINATING VIBRIO (NAG) AND EF-6 ORGANISMS IN DACCA

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PREFACE

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) is an autonomous, international philanthropic and non-profit centre for research, education and training as well as clinical service. The Centre is derived from the Cholera Research Laboratory (CRL). The activities of the institution are to undertake and promote study, research and dissemination of knowledge in diarrhoeal diseases and directly related subjects of nutrition and fertility with a view to develop improved methods of health care and for the prevention and control of diarrhoeal diseases and improvement of public health programmes with special relevance to developing countries. ICDDR,B issues two types of papers: scientific reports and working papers which demonstrate the type of research activity currently in progress at ICDDR,B. The views expressed in these papers are those of authors and do not necessarily represent views of International Centre for Diarrhoeal Disease Research, Bangladesh. They should not be quoted without the permission of the authors.

ABSTRACT

Diarrhoea due to non-agglutinating vibrio (NAG) has been present in Dacca for a long time. The NAGs and a new organism (EF-6) caused a severe diarrhoea epidemic in Dacca in 1976 and 1977. The most common NAGs detected were groups II, V and VII which were present all the year round with peaks in the spring and postmonsoon seasons, while EF-6 appeared in October and attained its peak in March. NAG diarrhoeas occurred all over the city with a higher incidence in poor areas simulating the distribution of cholera. EF-6 diarrhoeas were also detected in the poor areas. Although NAG and EF-6 infected all age groups the attack rates in males were twice as high as in females and EF-6 more often affected the age group 0-4. The overall secondary attack rates in contacts of NAG groups II, V and VII ranged from 10% to 25%. None in the EF-6 group affected families. Open sources of water were very often contaminated with NAGs. Twenty-five percent of the open sources were infected though there might not be an active case in neighbouring families. About half of the isolates from contacts and water sources were of groups other than the index case. NAGs were commonly found in the environment, but very few EF-6. Water was thought to be the vehicle of transmission.

INTRODUCTION

Diarrhoea caused by non-agglutinating (NAG) or non-cholera vibrio (NCV) has been described by many investigators in the past (Yajnik, B.S. *et al.*, 1954, Nacescu, N. *et al.*, 1974 and Sil, J. *et al.*, 1975, Lindenbaum *et al.*, 1965, and McIntyre *et al.*, 1965).

During 1976, the number of NAGs isolated from diarrhoea cases in Dacca increased several fold. In addition, from October 1976, a vibrio-like bacteria, closely resembling group III NAGs, was isolated from severe diarrhoea cases. Between February and May of 1977, the new organism caused an epidemic of diarrhoeal diseases resembling cholera. This organism fitted characteristics of Heiberg's group III NAGs except in salt requirement, decarboxylase reaction and negative indole reaction (Huq, M.I. *et al.*, 1980). The organism induced accumulation of fluid in ligated rabbit ileal loops and killed mice when injected intraperitoneally. It did not cause a rise in vibriocidal titre. Pending final taxonomy, the CDC has grouped the new organism as EF-6 (personal communication). To characterise epidemiologic patterns of NAGs and EF-6 organisms (Lee, J.V. *et al.*) we studied families affected with the NAGs and the new organisms for 10 days.

METHODOLOGY

February through August 1977, two trained teams conducted a study of the EF-6 and NAG affected families selected from the hospital. On the day following admission of selected index cases, the families were visited.

A family census was done and histories of diarrhoeal illness were obtained. For 10 consecutive days rectal swabs and samples of domestic water were collected and cultured in Monsur's media and triple strength B.P. media respectively using the standard technique (Monsur *et al.*, 1961). On days one and ten, finger stick blood samples were collected for testing the rise in vibriocidal titre (Benenson *et al.*, 1968). Bacteriological characterisation and toxin testing were also done (Huq, M.I. *et al.*, 1980). Symptomatology of the index and contact cases were recorded. For each study family at least one comparable neighbourhood family was taken, to study prevalence.

Retrospective analyses were made to examine past cases from the hospital admission and bacteriological registers. Patients were grouped in Heiberg classi fication (Heiberg, B., 1935). To illustrate seasonality all hospital cases have been used, and for geographical distribution, only cases occurring within known geographical areas have been analysed.

RESULTS

Table 1 shows the number of NAGs isolated during the endemic (1970 through 1975) and the epidemic period (1976 through 1977). During both periods the most prevalent groups were II, V and VII. Only 5 cases of group III NAGs were isolated during the first 6 year period (1970-1975). During the epidemic period (1976 to 1977), there were 403 cases of EF-6, which constituted 58.0 percent of all cases. During the six year endemic period (1970-75) the NAGs peaked in March-April (10.0%) and in October-November (26.1%), as did *Vibrio cholerae* (Figure 1). However, unlike *V.cholerae*, NAGs were isolated throughout the year. NAGs illustrate identical trends of peak occurrence (14.2% and 17.5%) during the epidemic period as well. Figure 2 shows the seasonality of NAGs and EF-6 organisms which were isolated from Dacca and the adjoining suburbs. EF-6 appeared in October, 1976 and attained its peak (34.7%) in March 1977, sharply declined in June and July (2%) and disappeared by December.

The geographical distribution based on the administrative units (Police Stations) has been shown in Figure 3. Over 475 NAGs and 300 EF-6 organisms were isolated in 8 years (1970-1977) from within the municipal area and the rest from outlying areas. The overall annual attack rate in the municipal area per 100,000 population was 3.1 for NAGs and 7.8 for EF-6. These were widely distributed over the entire city.

Table 2 gives the age and sex breakdown of all persons yielding NAGs and EF-6 organisms. EF-6 rates were highest among patients aged 0-4 years (54.8%) and considerably lower in older patients. Both in the case of EF-6 and NAG infections the overall rate was 64% for males and 36% for females.

Table 3 shows age, sex and secondary infection rates among contacts of 30 NAG and 30 EF-6 index study families. In the NAG group, the secondary infection (same organism as the index, isolated from family contact) rates for males and females up to the age of 9 were similar, but among the over-10 age group, males had a considerably higher rate (18.29%) than females (6.8%). Over 15% of contacts had secondary infection, 4.7% were secondary cases (contacts yielding the same organism as the index with diarrhoea) and 10.7% were with inapparent infection. Nearly 5% of all NAG index contacts were infected with other NAGs.

In the EF-6 group there was only one instance of secondary infection. But over 10% of the contacts of EF-6 index cases had infection with NAGs.

Table 4 shows the rates of secondary infection, secondary case and inapparent infection among the contacts of index cases of NAG groups II, V and VII. In all groups of NAGs the infection, inapparent infection and case rates in the age group 5-9 were higher than other age groups (N.S.). The overall infection rate was significantly higher in group V than in group II.

TABLE 1

DISTRIBUTION OF NAG BY GROUPS FROM HOSPITALISED PATIENTS WITH DIARRHOEA (1970 - 1977)

Year	Group I	II	III	IV	V	VI	VII	VIII	Total
1970 - 1975	27	132	5	5	59	0	87	4	319
Percent	8.5	41.4	1.6	1.6	18.5	-	27.2	1.2	100.0
1976-1977	44	91	409*	3	86	2	60	1	696
Percent	6.3	13.0	58.7	.4	12.3	.3	8.6	.1	100.0
Total	71	223	414	8	145	2	147	5	1015
Percent	7.0	22.0	40.7	.8	14.3	.2	14.5	0.5	100.0

* Only 6 NAG Group III, rest EP-6

N.B. Grouping could not be done 64 NAG

Fig I. Seasonality of NAGs (1970-75)
All incidence

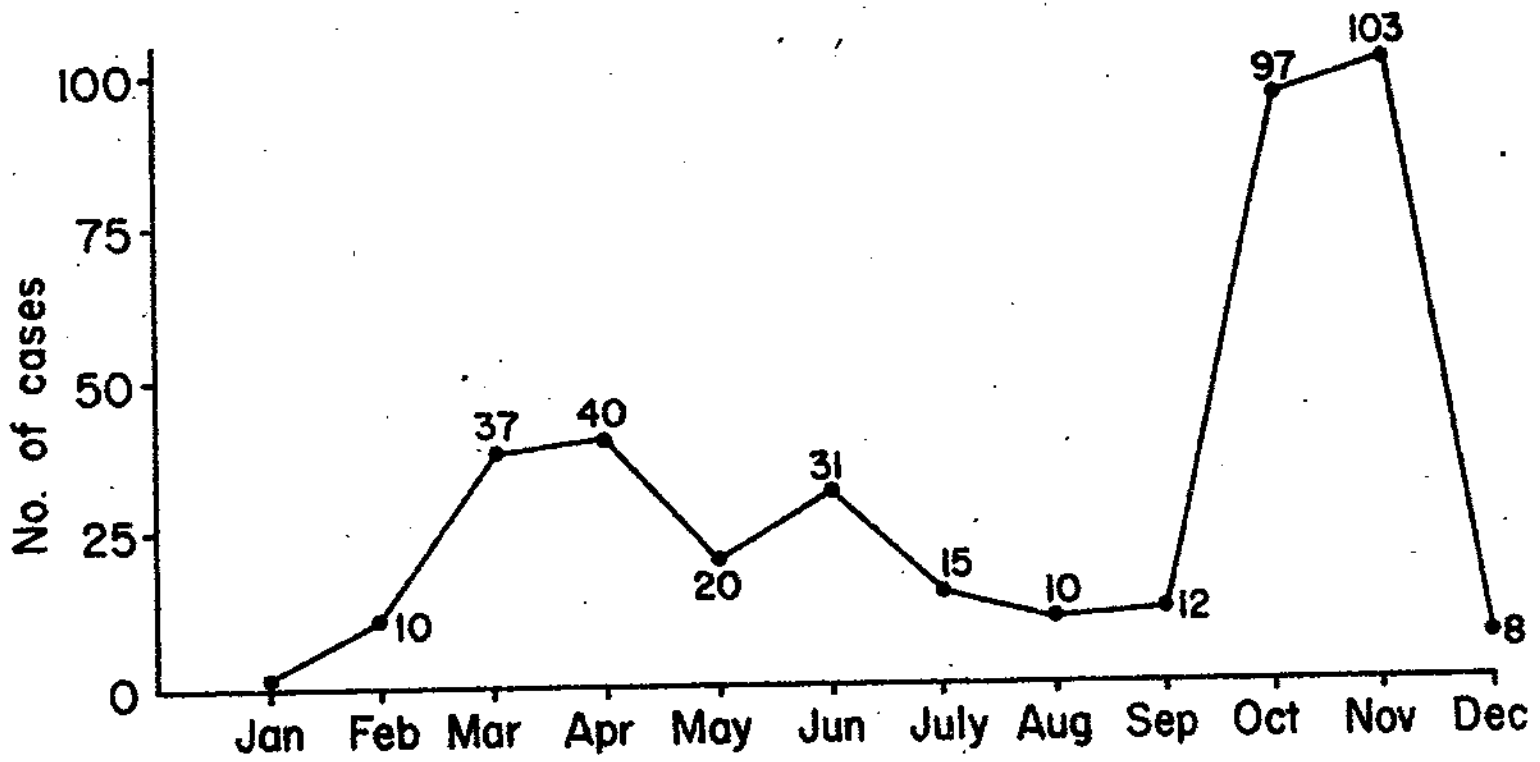

Fig. 2 Seasonal variation of incidence of NAGs and EF-6 associated diarrhoea

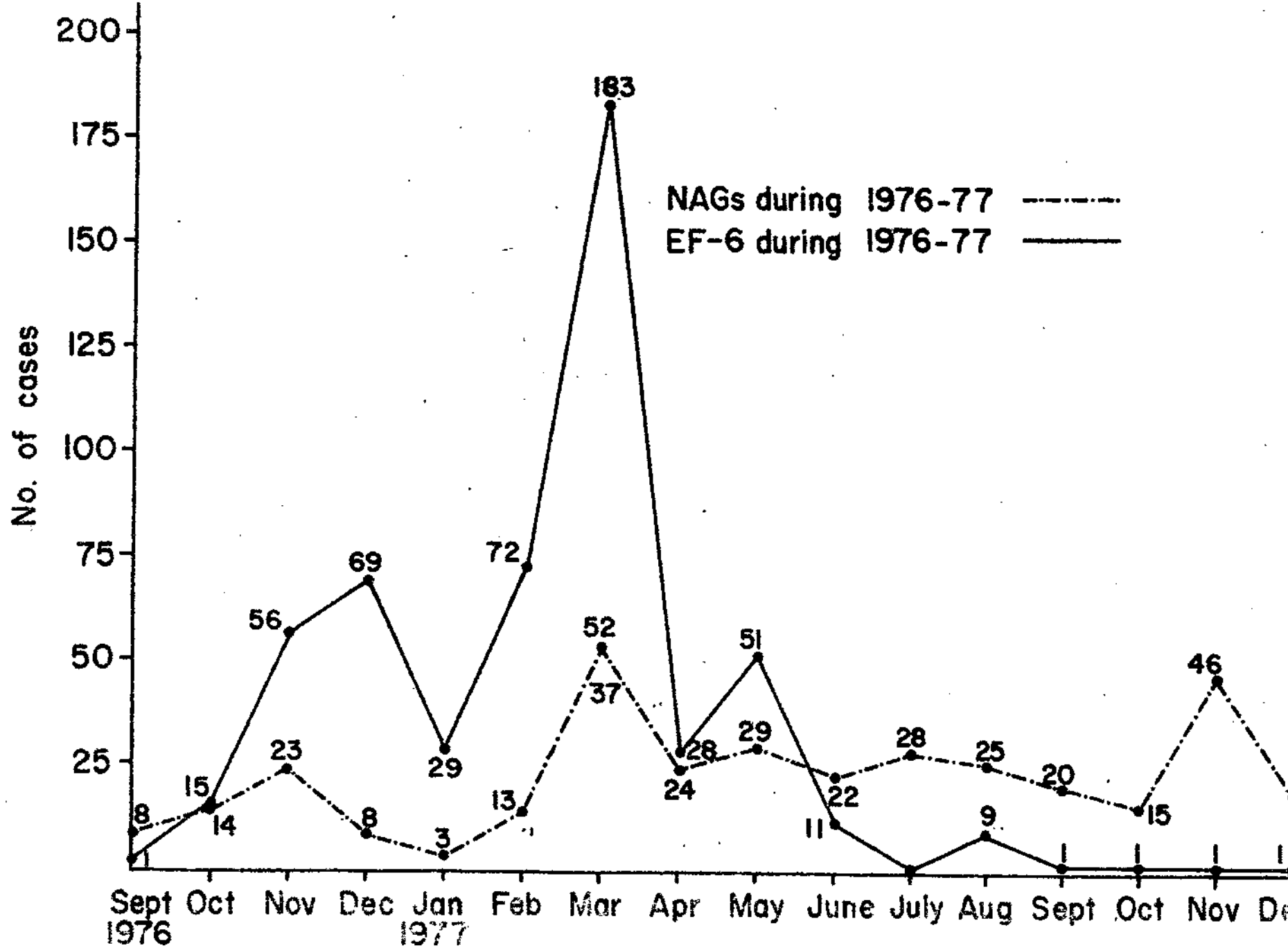

Fig 3 Geographical distribution of NAGs and EF-6 organism (1976-1977)

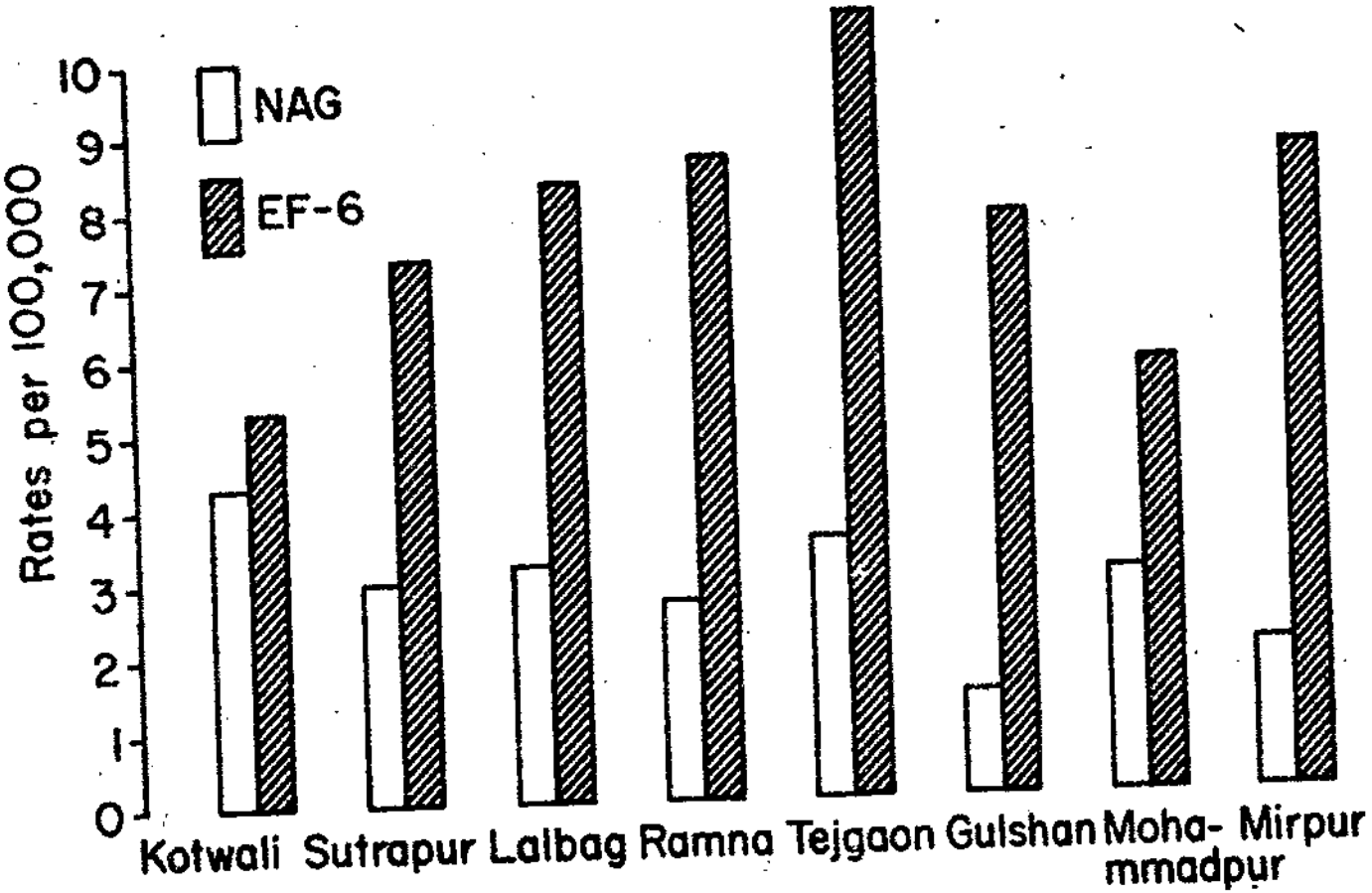

TABLE 2

AGE AND SEX OF PATIENTS HOSPITALISED WITH NAGS AND EF-6 ORGANISMS (1970 - 1977)

	NAG			EF-6 Organisms		
Age	Male	Female	Total	Male	Female	Total
0 - 4	41(6.1)	40(5.9)	12.0[a]	148(36.2)	70(18.6)	54.8[b]
5 - 9	34(5.1)	16(2.4)	7.4	14(3.4)	7(1.7)	5.1
10 - 14	27(4.0)	19(2.8)	6.8	9(2.2)	3(0.7)	2.9
15 - 19	16(2.4)	17(2.5)	4.9	6(1.5)	4(0.97)	2.4
20 - 29	90(13.4)	56(8.3)	21.7	29(7.1)	23(5.6)	12.7
30 - 39	95(14.1)	42(6.3)	20.4	17(4.2)	16(3.9)	8.0
40 - 49	65(9.7)	27(4.0)	13.7	18(4.4)	6(1.5)	5.8
50 - 59	27(4.0)	15(2.3)	6.3	9(2.2)	5(1.2)	3.5
60 +	35(5.2)	10(1.5)	6.7	13(3.2)	6(1.5)	4.6
Total	430(64.0)[c]	242(36.0)[d]	100.0	263(64.3)[c]	146(35.7)[d]	100.0

a vs b = P = < .001

c vs d = P = < .01

TABLE 3

SECONDARY INFECTION AND CASE RATES IN CONTACTS OF NAGS AND EF-6 ASSOCIATED INDEX CASES BY AGE

Age of Index and Contacts	NAGs					EF-6 Organism			
	No. of Contacts from 30 Families	Secondary Infection Rates	Secondary Case Rates	Infection with Other NAGs	Infection: Case Ratio	No. of Contacts from 30 Families	Secondary Infection Rates	Secondary Case Rates	Infection with Other NAGs
0-4 (M+F)	25	4(16.0)	1(4.0)	4(16.0)	4:1	27	0.0	0.0	6(22.2)
5-9 (M+F)	36	8(22.2)	4(11.1)	2(5.6)	2:1	35	0.0	0.0	3(8.6)
10 & over (M)	44	8(18.2)[a]	2(4.5)	1(2.3)	4:1	43	0.0	0.0	4(9.3)
10 & over (F)	44	3(6.8)[b]	0.0	0.0	0.0	49	1(2.0)	0.0	3(6.1)
Total	149	23(15.4)	7(4.7)	7(4.7)	3.3:1	154	1(.64)	0.0	16(10.4)

a vs b $\chi^2 = 1.66$, N.S.

TABLE 4

SECONDARY INFECTION RATES, SECONDARY CASE RATES AND INAPPARENT INFECTION RATES PER 100 IN FAMILY CONTACTS OF CASES WITH GROUPS II, V AND VII NAGS

	NAG Group II				NAG Group V				NAG Group VII			
Age	No. of Contacts	Infection	Case	Inapparent	No. of Contacts	Infection	Case	Inapparent	No. of Contacts	Infection	Case	Inapparent
0 - 4	11	9.1	9.1	-	5	20.0	20.0	0.0	7	14.3	0.0	14.3
5 - 9	18	16.7	11.1	5.6	2	50.0	50.0	0.0	9	33.3	22.2	11.1
10 +	31	6.5	6.5	-	24	25.0	8.3	16.7	26	11.5	0.0	11.5
Total	60	6(10.0)[a]	5(8.3)	1(1.7)	31	8(25.8)[b]	4(12.9)	4(12.9)	42	7(16.7)	2(4.8)	5(11.9)

a vs b = p = <.05

Figure 4 shows the symptomatology associated with NAG and EF-6 hospitalised cases. In the NAG index cases, approximately 80% had watery stools, abdominal pain and vomiting compared to similar symptoms observed in 50-60% of EF-6 index cases. The most common symptoms of *V.parahaemolyticus* infection, i.e., abdominal pain, fever and bloody mucoid stoos (Sarker, B.K. *et al.*, 1976), were identical to the symptomatology associated with NAG infection.

Table 5 shows that the water sample from only one of the 30 EF-6 families was positive for EF-6. EF-6 organisms were isolated from the water of 7 out of 30 NAG-infected families. The water sources of 16.9% of the families had the same isolates as the index case and 73% of the families yielded NAGs different from those as yielded by index cases.

Table 6 shows the sources of water used by the NAG-infected families and the subsequent infection rate in contacts. All samples of the household water of these families were positive for the same groups of NAGs as the index case, where open sources of water were used. In those cases using mixed or closed sources, the recovery rates were lower. The secondary infection rate in the group using closed sources was lower (N.S.).

Table 7 gives the same breakdown for EF-6. No member of this group used an open source of water. There was, however, a difference ($P=<.10$) in the percentage of secondary infection from other NAGs between the users of mixed water sources (12.9%) and the users of closed water sources (5.8%). The EF-6 organism did not appear to infect water as frequently as the NAGs and had no secondary infection.

Table 8 shows whether water sources used by the neighbours of hospitalised NAGs and EF-6 cases also had NAG and EF-6 infections. Although water sources were infected both for index and other groups there was no secondary infection with EF-6 and other groups of NAGs (6%) among the household members.

Table 9 shows the rates of NAGs from the water sources of NAG and EF-6 infected families by types of water sources and groups of indexes. Tank and canal groups show the highest rates of infection compared with closed ones, in both NAG and EF-6 families. Even when all the open sources are combined, the differences persist between the open and closed sources both in cases of NAG ($P=<.01$) and EF-6 groups ($P=<.01$).

Table 10 shows the duration of excretion of NAGs and EF-6 by cases and contacts. The range for the NAG index cases was 1 to 5 days with an average of 1.5 days. Though the range for contacts was the same, the average was twice that of the index cases. This may be due to picking up infected contacts early on. The EF-6 organism excreted only for 1-2 days and the average was 1.3 days.

Fig 4. Clinical Symptomatology of Hospitalised NAG and EF-6 infected cases

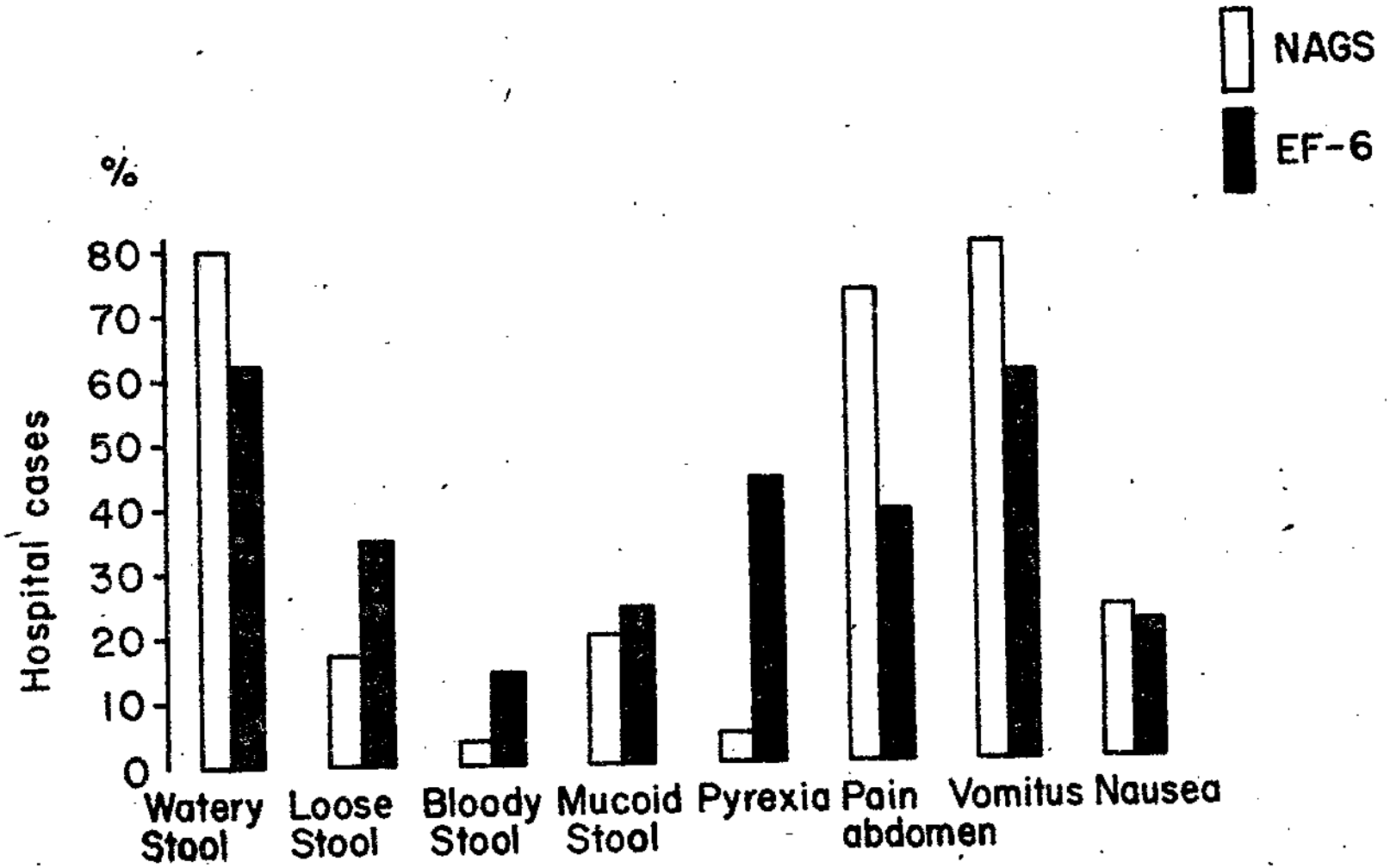

TABLE 5

RATES OF NAGS AND EF-6 ORGANISMS ISOLATED FROM WATER OF STUDY FAMILIES

Index Group	No. of Families	Groups recovered from water							% of Same Group	% of Other Group
		I	II	IV	V	VI	VII	EF-6		
I	1	1							1(100%)	-(0.0%)
II	12	1	7	1	4			4	7(58)	10(83)
V	8	-	2	-	1			1	1(12.5)	3(38)
VII	9	2	3	-	1			2	-(0.0)	8(89.0)
EF-6	30	6	8	1	6		1	1	1(3.4)	22(76.0)
Total	60	10	20	2	12		1	8	10(16.9)	43(72.0)

TABLE 6

NAGS ISOLATED FROM WATER AND SECONDARY INFECTION IN NAG CONTACTS BY SOURCES OF WATER

Sources of Water	No. of Families Used	No. Sources Tested/Infected with Index Group	No. Sources Tested/Infected with Other Group	Contacts Infected with Index Group	Contacts Infected with Other Group
Open source (pond, canal, river, dugwell)	2	2/2 (100%)	2/2 (100%)	10/1 (10%)[c]	-
Mixed source (pond, canal, river, dugwell, tubewell, city supply)	24	3/1 (33%)	4/4 (100%)	106/12 (11.3%)[b]	106/11 (10.4%)
Closed source (tubewell, city supply)	14	14/3 (21%)	14/4 (30%)	71/3 (4.2%)[a]	71/5 (7%)

a vs (b+c) χ^2 = 1.92, N.S.

TABLE 7

EF-6 AND NAGS ISOLATED FROM WATER SOURCES AND INFECTION RATES IN EF-6 FAMILY CONTACTS INFECTED BY SOURCES OF WATER

Sources of Water	No. of Families Used	No. of Sources Tested/No. Infected with Index Group	No. of Sources Tested/No. Infected with Other Group	Percent of Contacts Infected with NAGS
Mixed source (pond, canal, river, dugwell, tubewell, city supply)	12	12/2 (17%)	12/12 (100%)	70/9 (12.9)[a]
Closed source (tubewell, city supply)	18	14/0 (0.0%)	18/5 (28%)	86/4 (5.8)[b]

a vs b $\chi^2 = 2.41$ $P = > 0.10$

TABLE 8

RATES OF WATER SOURCES AND MEMBERS INFECTED IN THE NEIGHBOURING FAMILIES

Neighbours	No. of Families	No. of Sources Tested/No. Infected with Index Group	No. of Sources Tested/No. Infected with Other Group	Members Infected with Index Group	Members Infected with Other Group
NAGs Families	40	40/5 (12.5%)	40/3 (7.5%)	162/1 (0.61%)	162/2 (1.23%)
EF-6 Families	33	33/2 (6.0%)	33/3 (9.0%)	131/0 (0.0%)	131/0 (0.0%)

TABLE 9

ISOLATION OF VIBRIOS FROM NAG AND EF-6 INFECTED FAMILY WATER BY SPECIFIC SOURCES

Sources	NAG Infected Index Families				EF-6 Infected Index Families			
	No. of Samples	Group II	Group V	Total NAGs	No. of Samples	Group II	Group V	Total
Pond/Tank	8	4	4	8(100)	7	1	2	3(43)
Canal/River	9	5	-	5(56) a	5	3	2	5(100) c
Dugwell	6	1	-	1(17)	3	2	-	2(67)
Tubewell	10	-	-	-	7	1	-	1(14)
City supply	9	1	1	2(22) b	17	-	-	- d
Storage jar	32	4	4	8(25)	32	3	3	6(19)
Total	74	15	9	24(32)	69	10	7	17(25)
%	100	20	12	32	(100)	15	10	25

a vs b = χ^2 = 10.50, P = < .01

c vs d = χ^2 = 15.46, P = < .01

TABLE 10

DURATION OF EXCRETION OF NAGS AND EF-6 BY INDEX CASES AND CONTACTS (IN DAYS)

(Hosp.)	Day 1	2	3	4	5	6	7	8	9	10	Mean
Index #	21	8	2	-	1	-	-	-	-	-	1.5 days
NAG Percent	65.6	25.0	6.25	-	3.1	-	-	-	-	-	
Contact #	9	2	4	3	1	-	-	-	-	2	3.0 days
NAG Percent	42.8	9.5	19.0	14.3	4.8	-	-	-	-	9.5	
Index #	41	9	-	-	-	-	-	-	-	-	1.3 days
EF-6 Percent	70.0	30.0	-	-	-	-	-	-	-	-	

DISCUSSION

The association of non-agglutinating vibrio with diarrhoea has been described. But its epidemiologic pattern has not been adequately documented. In CRL, NAGs have been isolated since 1962. The epidemic in late 1976 caused by NAG and EF-6 created renewed interest. The EF-6 organisms had been reported earlier from Britain, Bahrain and Jordan by Lee *et al.* (1978) and from Bangladesh by Khan, M.U. (1979) and Huq, M.I. *et al.* (1980).

Although NAGs are present throughout the year, the infections showed two peaks, almost identical with cholera. EF-6, on the other hand, attained its peak once during March of 1977, and has disappeared since then. It appears that both NAGs and EF-6 organisms were seeded all over the city as was cholera, especially in poorer areas. Socioeconomic status and sanitation might be, like cholera, factors influencing infection due to NAG and EF-6 organisms.

EF-6 (54.8%) and NAG (12.0%) infections were common in children 0-4 years. This may be due to lack of immunity in infants. This deserves further exploration. Cholera rates are similar in male and female except for a higher incidence in adult females. Unlike cholera, both NAGs and EF-6 infections were twice as common in men than in women. The reason has not yet been explained.

The secondary infection and case rates of NAGs were the same as cholera, but the inapparent infection rate (10.7%) was higher. This might be due to the milder nature of NAGs or greater human resistance. Although we were unable to detect development of titre rise from paired blood, the rabbit ileal loop test was positive for toxicity and it killed mice on intraperitoneal injection. Unlike other enterobacterial organisms the EF-6 had no secondary infection in contacts except one case in 30 families. Its recovery from household water was also limited.

It is possible that EF-6 was associated with other pathogens responsible for the diarrhoea epidemic which we could not isolate. We do not know, however, whether an enterovirus, which might have partially altered the character of NAGs, was responsible for the epidemic. In any case, it remains to be proven that EF-6 is a new organism and is a new pathogen capable of causing diarrhoea.

Of the 3 common groups of NAGs, group V had the maximum secondary infection rate, case rate and inapparent infection rate. Group II had the lowest rates and group VII intermediate rates. Families affected with group VII did not yield any group VII NAGs from the household water, though other groups of NAGs were present. This shows that different grades of NAGs are normally present in water and this may not establish infection in the families in all instances.

Rivers and canals had the highest isolation rates (55-100%). One third of all the samples of water from NAG-affected families and one fourth of EF-6-affected families were positive for at least one of the groups of NAGs. From the adjacent families also one fourth to one fifth of all samples were positive for one group of NAG. This shows how frequent the NAGs are in the local environment.

A high percentage of affected index cases of both NAGs and EF-6 had blood in their stools and a rise in temperature. Further study is needed to explore the invasiveness of both NAGs or EF-6 organisms.

This study shows that surface water contains NAG and EF-6 organisms and plays a vital role in their transmission. Water may be contaminated with infected stool or the organisms may multiply in water and people may either be infected after swallowing a heavy dose or repeated small doses as suggested by Spira *et al.* (1980) as a means of contracting cholera. However, the epidemiology of NAG and EF-6 organism will require further study in other parts of the world where these problems are present.

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