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Two-Year Survey of Etiologic Agents of Diarrheal Disease at San Lazaro Hospital, Manila, Republic of the Philippines

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The prevalence of bacterial pathogens and rotavirus in 2,908 patients with diarrhea who were admitted to San Lazaro Hospital in Manila in 1983 and 1984 was determined. One or more enteric pathogens were isolated or detected in samples from 1,698 (58.4%) patients. Isolation rates for the various enteropathogens were as follows: rotavirus, 30.6%; *Shigella* spp., 11.6%; *Salmonella* spp., 9.2%; enterotoxigenic *Escherichia coli* (1983 only), 7.8%; *Vibrio cholerae* biotype eltor, 3.8%; non-O1 *V. cholerae*, 2.8%; *Vibrio parahaemolyticus*, 1.7%; other *Vibrio* spp., 1.1%; *Campylobacter jejuni*, 3.0%; *Aeromonas hydrophila*, 1.3%; and *Plesiomonas shigelloides* 1.1%. *Giardia lamblia* and *Entamoeba histolytica* were detected in 0.6 and 0.1%, respectively, of stool samples examined. Determination of the etiologic role of isolates was complicated by one or more of the following factors: (i) isolation of multiple enteric pathogens (302 cases); (ii) isolation of *Salmonella* spp., enterotoxigenic *E. coli*, and *C. jejuni* from a similar proportion of asymptomatic control patients and patients with diarrhea; and (iii) isolation of a high proportion of certain pathogens (especially *Salmonella* spp.) only from enrichment broth, suggesting infection with a small number of organisms. Isolation of *V. cholerae* eltor was seasonal, with the majority of cases occurring in the rainy months. In addition, the number of patients with diarrhea increased with the onset of the monsoon rains and peaked during the months of maximum rainfall. Rotavirus infection occurred in both children and adults throughout the year and was the most frequently identified cause of diarrhea in children under 5 years of age. *Shigella* spp. were the most common agents of diarrhea in adults.

Diarrheal disease continues to be a global health problem, particularly among young children in developing nations. As recently as 1976, it was estimated that between 5×10^6 and 18×10^6 people, mostly children, die each year as a direct result of this disease (18, 19). In addition, it is not uncommon for 50% of tourists to the Third World to develop traveler's diarrhea (7, 9, 11, 27).

A number of microorganisms are now known to cause diarrheal illness (10, 14, 22). Some of these, including *Salmonella*, *Shigella*, and *Vibrio* spp., are well recognized enteric pathogens. Rotavirus, *Campylobacter* spp., and enterotoxigenic *Escherichia coli* (ETEC) also have been identified as important causes. Recently, certain strains of *Aeromonas hydrophila* and *Plesiomonas shigelloides* have been associated causally by some investigators (1, 16, 23). Despite the addition of these "new" diarrheal pathogens, most studies have determined the etiology in only 50% (or fewer) of patients with diarrhea (8, 9, 20). Assignment of a causal role to an isolated pathogen is further complicated when multiple enteric pathogens are isolated from the same patient or when the rate of isolation of potential pathogens from asymptomatic control patients is high (7, 15).

The present survey was undertaken prospectively as part of a continuing study of the infectious diarrhea problem in the Philippine Islands. Throughout 1983 and 1984, patients admitted with diarrheal disease to San Lazaro Hospital, Manila, Republic of the Philippines, the largest infectious-disease hospital in the country, were studied to determine the etiology of their illnesses. Suspected etiological agents were detected among diarrhea patients and asymptomatic controls. In addition, differences in the incidence of enteric pathogens by season, climatic conditions, and age and sex of patients were determined.

MATERIALS AND METHODS

Specimens. Diarrhea was defined as the passage of three or more liquid or loose stools in a 24-h period in association with nausea, vomiting, or fever. Approximately 90% of the patients in the study had passed numerous watery or liquid stools. Specimens were collected on Monday through Friday twice daily at set times from all patients admitted with diarrheal illness since the previous collection period. Hospital policy emphasized treatment of diarrhea with rehydration alone until culture results were obtained, and so antibiotic treatment following admission was not a factor. Self-treatment prior to admission cannot be completely excluded. The sample population represented approximately 15% of the total number of patients treated for gastroenteritis at the hospital. The actual percentage of diarrhea patients studied is unknown, since hospital records did not make a distinction between gastroenteritis and diarrhea. Specimens were also collected from persons admitted with other illnesses who denied having had diarrhea within the previous 2 weeks. Approximately one control patient was studied for every five diarrhea patients. The age and sex distribution of the control group was approximately proportional to that of the group of patients with diarrhea. Whenever possible, both fresh fecal

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TABLE 1. Age and sex distribution of diarrheal and control study groups

Age group	Patients (n = 2,908)		Controls (n = 576)	
	No. of males	No. of females	No. of males	No. of females
0–5 mo	191	142	33	14
6–11 mo	536	378	77	44
12–23 mo	460	332	143	96
2–4 yr	224	136	32	13
5–9 yr	79	31	21	22
10–19 yr	49	40	10	7
20–29 yr	58	63	14	16
30–39 yr	27	34	5	10
40–49 yr	16	19	1	3
50 yr	30	63	7	8
Total	1,670	1,238	343	233

material and rectal swabs were collected; otherwise only a rectal swab was obtained. Most patients, who were residents of the Metro Manila area, were from low-income groups; the vast majority (70%) were children under the age of 2 years.

Isolation and identification of enteric pathogens. Fecal specimens and rectal swabs were cultured by standard bacteriological methods for *Salmonella* spp., *Shigella* spp., *Vibrio* spp., *Campylobacter jejuni*, *E. coli*, *A. hydrophila*, *P. shigelloides*, and *Yersinia enterocolitica* (12, 17, 25, 26). Selective enrichment for *Salmonella* and *Shigella* spp. was performed with Selenite-F and Hajna (GN) broth. Alkaline peptone water was used for enrichment for *Vibrio* spp. Direct and enrichment cultures were plated onto MacConkey, xylose-lysine-desoxycholate, thiosulfate-citrate-bile salts-sucrose, Hektoen enteric, and *Yersinia* selective agars as appropriate. *Campylobacter* blood agar (Campy-BAP), formulated by the method of Blaser et al., was used for the isolation of *C. jejuni* (4). Campy-BAP plates were incubated in polyethylene bags under an atmosphere of 5% oxygen, 10% CO_2 and 85% nitrogen at 42°C for 48 h. *C. jejuni* was identified by previously described methods (12). Ten colonies resembling *E. coli* on MacConkey agar were inoculated into Mueller-Hinton agar slants and sent to the Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, for testing for the production of heat-labile and heat-stable enterotoxins by the Y-1 adrenal cell and suckling mouse assays (6, 21). Specimens were stored at −20°C for subsequent rotavirus antigen detection by the Rotazyme enzyme immunoassay method (Abbott Laboratories, North Chicago, Ill). Fresh fecal specimens were submitted for ovum and parasite examination by concentrated wet and direct-smear preparations for all patients who submitted stool samples.

Antimicrobial susceptibility testing. Bacterial isolates from diarrheal specimens were tested for susceptibility to as many as 24 antimicrobial drugs. All susceptibility testing was performed by a modification of the method of Bauer et al. (3).

Statistical analysis. Associations were determined by chi-square distribution analyses with Yates correction for continuity at the 5% level of significance.

RESULTS

One or more enteric pathogens were isolated from or detected in samples from 1,698 (58.4%) of 2,908 patients admitted to San Lazaro Hospital in 1983 and 1984. Pathogens were also isolated from samples from 98 (17.0%) of 576 patients admitted to the hospital for reasons other than diarrheal illness. Two to four (multiple) isolates were obtained from samples from 302 (10.4%) ill patients and 2 (0.3%) controls.

The patient and control populations are presented in Table 1. Although it was not possible to precisely match controls for age and sex, investigators did attempt to study a number of controls in proportion to the number of patients in the various groups. Note that the distributions are similar and in both cases reflect the approximate overall distribution of gastroenteritis patients seen at San Lazaro Hospital.

Table 2 shows the overall prevalence rates of the various pathogens detected from both the group of patients with diarrhea and the control group. Additionally, *Giardia lamblia* was detected in 6 and *Entamoeba histolytica* was detected in 1 of 1,064 diarrheal stool samples. The predominance of rotavirus is clearly a reflection of the age of the patients: 70% were under the age of 2 years. The importance of rotavirus in these patients is emphasized in Fig. 1, which shows the percent isolation by age group.

The overall isolation rate of *Salmonella* spp. was somewhat higher from patients with diarrhea than from controls (9.2 versus 6.1%; $0.025 > P > 0.01$). *Salmonella* group B also was isolated more often from patients with diarrhea than from controls ($0.005 > P > 0.001$). However, there was no significant difference between patients and controls for other *Salmonella* serogroups.

Figure 2 shows the seasonality of diarrhea in terms of total cases of gastroenteritis seen at San Lazaro Hospital (data provided by the hospital) and in terms of the percent isolation rates of *V. cholerae* eltor, rotavirus, *Salmonella* spp., and *Shigella* spp. *V. cholerae* was usually isolated during the rainy months. *Shigella* infections occurred during the months of greatest rainfall in 1983 but not in 1984. The highest incidence of diarrheal disease occurred during the months of maximum rainfall.

Table 3 shows antimicrobial resistance patterns of bacterial pathogens on the basis of percentage of isolates resistant to drugs tested. Multiple drug resistance occurred in all genera.

DISCUSSION

The weather in 1983 was not typical for the Philippines. Drought conditions prevailed early in the year, and the rainy season, which usually begins in late May, was delayed by almost 2 months. In 1984 there was a typical rainy period from May to October, with only one dry period in early September. The peak incidence of diarrhea corresponded to peak rainfall. Only *V. cholerae* eltor, however, showed any obvious seasonal increase in prevalence during both years. In some countries (e.g., Bangladesh and Thailand), the peak incidence of diarrhea occurs during the dry months of the year (15, 24). This difference may be the result of environmental differences, particularly with respect to storage and distribution of potable water.

Assignment of an etiologic role in specific cases of diarrhea was particularly difficult for *Salmonella* spp., ETEC, *C. jejuni*, and *A. hydrophila*. Factors which served to complicate the analysis included the following: (i) isolations of more than one potential pathogen from the same specimen (10.4% of cases studied); (ii) isolation of these organisms from control specimens at rates approaching those of isolation from specimens from patients with diarrhea; and (iii) a high isolation rate of *Salmonella* spp. (60% of total isolates)

TABLE 2. Prevalence of etiologic agents of diarrhea in patients at San Lazaro Hospital in 1983 and 1984

Organism isolated	No. of isolates from diarrhea patients (% of total)		No. of isolates from controls (% of total)		Significance of isolation (patients vs controls)
	1983 (n = 1,021)	1984 (n = 1,887)	1983 (n = 201)	1984 (n = 375)	
Rotavirus	276 (27.0)	613 (32.5)	12 (6.0)	20 (5.3)	$P < 0.001$
Salmonella spp.	120 (11.8)	147 (7.8)	16 (8.0)	19 (5.1)	$0.025 > P > 0.01$
Shigella spp.	101 (9.9)[a]	235 (12.5)	1 (0.5)	6 (1.6)	$P < 0.001$
ETEC	80 (7.8)	28 (1.5)[b]	9 (4.5)	1 (0.3)[b]	$0.25 > P > 0.10$[c]
V. cholerae eltor	42 (4.1)	68 (3.6)	0	2 (0.5)	$P < 0.001$
Non-O1 *V. cholerae*	40 (3.9)	40 (2.1)	0	1 (0.3)	$P < 0.001$
V. parahaemolyticus	16 (1.6)	33 (1.7)	0	0	$0.005 > P > 0.001$
Other *Vibrio* spp.[d]	7 (0.7)	24 (1.3)	0	1 (0.3)	$0.10 > P > 0.05$
C. jejuni	37 (3.6)	51 (2.7)	4 (2.0)	3 (0.8)	$0.025 > P > 0.01$
A. hydrophila	18 (1.8)	21 (1.1)	1 (0.5)	1 (0.3)	$0.10 > P > 0.05$
P. shigelloides	13 (1.3)	18 (1.0)	0	1 (0.3)	$0.10 > P > 0.05$

[a] Includes two dual isolates counted as one each in calculation of isolation rate.
[b] Not tested in patients less than 10 years old after March 1984.
[c] Calculated with 1983 data only.
[d] Includes *V. fluvialis*, *V. mimicus*, and *V. alginolyticus*.

only after enrichment in Selenite-F broth. The above factors combined could lead to a gross overestimation of the relative importance of any or all of the above bacteria as a cause of disease. These results suggest that future research into the questions of quantitative association of microorganisms and diarrheal disease, synergism between pathogens, and serological response to infections may be required to establish the etiology for some pathogens.

On the other hand, *Shigella* spp., *Vibrio* spp., and rotavirus were more often isolated from patients with diarrhea than from controls. The detection of these pathogens implies a higher degree of certainty that these causative agents are of etiologic importance. Non-O1 *V. cholerae*, once thought to be a nonpathogen but later found to produce two antigenically distinct enterotoxins (13), was also isolated more often from patients with diarrhea than from controls ($P < 0.001$).

A. hydrophila has been considered to be a possible etiologic agent of diarrhea. Studies have shown that certain strains are able to produce enterotoxins (1, 5, 16). However, no clear indication that the bacterium can cause diarrhea in humans has been forthcoming. Probably, the pathogenic potential of this organism depends on strain differences in much the same fashion as for pathogenic isolates of *E. coli*. During this research, *A. hydrophila* was associated with the isolation of other pathogens in 29 of 39 (74.4%) cases. This suggests that this bacterium is not an important cause of diarrhea in this study population.

The recovery rate of *Salmonella* spp. from patients with diarrhea (9.2%) and controls (6.1%) was similar. However, when the isolates were examined by serogroup, only *Salmonella* group B was isolated more often from patients with diarrhea than from controls (5.2 versus 2.3%; $0.005 > P > 0.001$). No significant differences were seen for other serogroups. Approximately 60% of *Salmonella* isolates were obtained only after enrichment. This indicates that only small numbers of organisms were present in the specimens and thereby complicates the determination of an etiologic role. It is unclear that enrichment for this organism in a highly endemic population provides any useful diagnostic

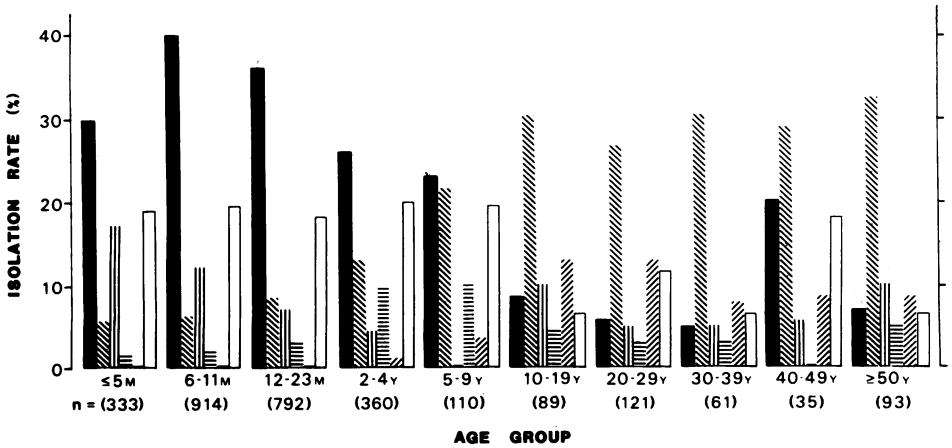

FIG. 1. Isolation rate of enteric pathogens on the basis of age group of patients. Pathogens isolated at a rate of 10% or greater from any single age group are presented individually. All others including ETEC, other *Vibrio* spp., *C. jejuni*, *A. hydrophila*, and *P. shigelloides* are included together as a single grouping. Multiple isolations of two or more pathogens from the same patient are separated into components, and no attempt to assign etiologic importance to any particular agent is made. Abbreviations: M, months; Y, years. Symbols: ■, rotavirus; ▨, *Shigella* spp.; ▥, *Salmonella* spp.; ▤, *V. cholerae* eltor; ▩, *V. parahaemolyticus*; □, other.

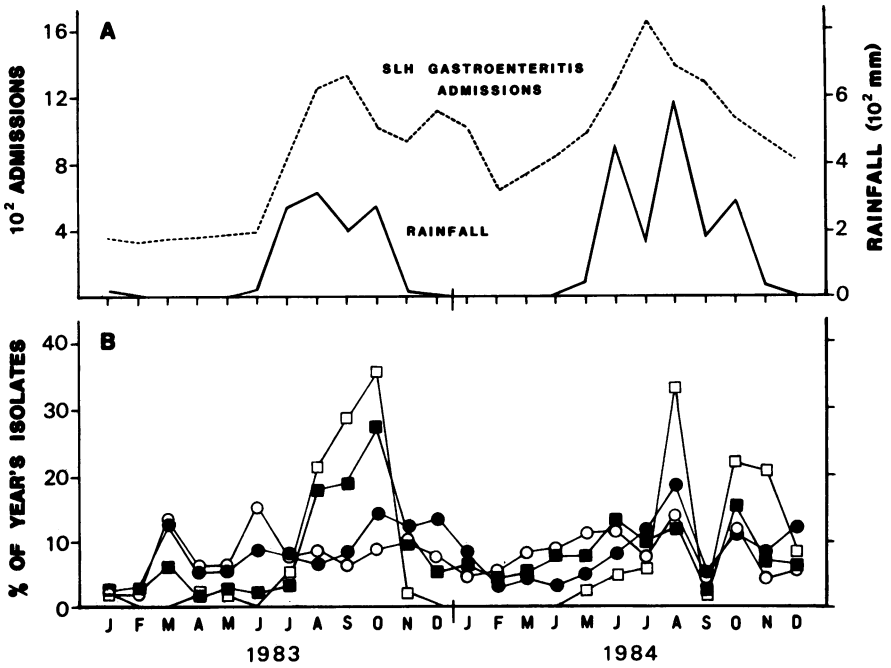

FIG. 2. Seasonality of isolation of etiologic agents of diarrheal disease. (A) Comparison of the number of patients with gastroenteritis admitted to San Lazaro Hospital during 1983 and 1984 with the rainfall during that period. Admission and rainfall data were provided by San Lazaro Hospital and the Philippine Atmospheric Geophysical Astronomical Services Administration, respectively. (B) Isolation by month of rotavirus (●), *Salmonella* spp. (○), *Shigella* spp. (■), and *V. cholerae* eltor (□). Isolations are shown as a percentage of yearly isolations of each organism to normalize for differences in the total number of patients seen between the 2 years.

information. Because antibiotic treatment of *Salmonella* infection increases the time during which these organisms are excreted (2) and because over-the-counter sale of antibiotics is common, it should not be surprising that a large segment of the population carries the pathogen.

The prevalence of enteric pathogens in adults was different from that in children (Fig. 1). Diarrhea in adults was most often caused by *Shigella* spp. This may have been due to the tendency of this organism to cause severe diarrhea, thus making infected individuals more likely to seek medical attention. Other pathogens of importance in adults were *V. parahaemolyticus* (rarely isolated from children under 5 years old) and, to a lesser extent, *Salmonella* spp. Children under 5 years old were most often infected with rotavirus followed by *Salmonella* spp. and ETEC (both isolated at an overall rate of near 10%). The rate of isolation of *Salmonella* spp. declined with increasing age of the patients, while that of ETEC remained approximately constant. Additionally, the monthly isolation rate of ETEC remained constant at about 10% for the first 15 months of the survey period, when testing in patients under the age of 10 years was stopped owing to limited availability of the service. The 5- to 9-year-old group of patients was infected with agents both common to children and adults, although the isolation of *Salmonella* spp. from patients in this group was low. *V. cholerae* eltor was an important cause of diarrhea in all except the youngest infants. *V. cholerae* increased in importance as a cause of diarrheal disease during the months of heaviest rainfall.

TABLE 3. Antimicrobial resistance patterns of bacterial pathogens during 1983 and 1984 from patients with diarrhea

Organism (no. of isolates)	% of isolates resistant to[a]:																
	CC	E	K	S	TE	AM	C	GM	N	NA	PB	CB	CF	FM	NB	OL	SXT
Shigella spp. (338)	98	9	2	78	59	57	25	1	3	1	0	57	2	1	97	76	3
Salmonella spp. (268)	100	87	47	62	54	59	57	5	39	5	1	57	10	19	100	99	39
V. cholerae eltor (110)	100	9	0	7	1	0	3	0	1	1	100	7	1	3	18	58	3
Non-O1 *V. cholerae* (81)	100	1	0	43	5	32	6	0	0	1	31	27	4	1	52	78	26
V. parahaemolyticus (47)	89	2	0	11	0	57	0	0	4	0	15	72	94	0	13	45	0
Other *Vibrio* spp. (30)	97	27	0	40	23	80	13	0	0	3	0	37	63	0	97	87	37
ETEC (103)	NT[b]	NT	5	59	39	59	38	0	5	NT	NT	NT	2	NT	NT	NT	9
C. jejuni[c] (54)	7	6	0	26	9	19	0	0	0	0	0	4	100	0	93	7	52
A. hydrophila (37)	100	8	5	38	22	57	16	0	0	5	0	46	65	5	78	84	24
P. shigelloides (33)	94	3	6	58	42	24	0	0	3	3	0	76	0	0	85	88	0

[a] Abbreviations: CC, clindamycin; E, erythromycin; K, kanamycin; S, streptomycin; TE, tetracycline; AM, ampicillin; C, chloramphenicol; GM, gentamicin; N, neomycin; NA, naladixic acid; PB, polymyxin B; CB, carbenicillin; CF, cephalothin; FM, nitrofurantoin; NB, novobiocin; OL, oleandomycin; SXT, trimethoprim-sulfamethoxazole.

[b] NT, Not tested.

[c] Resistance patterns to additional drugs tested were as follows: oxacillin, 94%; cefoxitin, 93%; methicillin, 93%; vancomycin, 98%; amikacin, 0%; colistin, 9%; tobramycin, 2%; and penicillin, 100%.

Patients from 40 to 49 years of age, most of whom were women, were infected with rotavirus and other bacterial pathogens common to children. This presumably occurred as a result of their close contact with young children.

Multiple antimicrobial resistance was common for all bacterial pathogens tested (Table 3). In general, isolates of *Salmonella* spp. were the most drug resistant (to as many as 15 to 17 drugs tested), but all genera showed multiple resistance to some degree. Again, the ready availability of antibiotics is the likely explanation for this observation. Furthermore, the use of nonprescription antibiotics may have had some effect on the prevalence of the bacterial pathogens reported herein, since reliable data for the exclusion of self-treated individuals were not available.

No etiologic agent was identified in over 40% of patients with diarrhea. Studies to further define the etiology in these cases are needed.

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