Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries*

Sima Huilan,[1] Lu Guang Zhen,[1] M.M. Mathan,[2] M.M. Mathew,[2] J. Olarte,[3] R. Espejo,[3] Khin Maung U,[4] M.A. Ghafoor,[5] M.A. Khan,[5] Z. Sami,[5] & R.G. Sutton[6]

A 2-year etiological survey of acute diarrhoea in children aged 0–35 months who were attending treatment facilities was carried out using a standardized protocol in five hospitals in China, India, Mexico, Myanmar, and Pakistan. A total of 3640 cases of diarrhoea and 3279 age- and sex-matched controls were studied; about 60% of the patients were aged less than 1 year and 60% were male. An enteric pathogen was detected in 68% of the cases and in 30% of the controls. In all the study centres, the pathogens most strongly associated with disease were rotavirus (16% of cases, 2% of controls), Shigella *spp. (11% of cases, 1% of controls) and enterotoxigenic* Escherichia coli *(16% of cases, 5% of controls). Rotavirus was commonest among 6–11-month-olds, accounting for 20% of all cases in this age group; 71% of all rotavirus episodes occurred during the first year of life.* Shigella *spp. were commonest among those aged 12–23 months and 24–35 months, accounting for 22% and 27% of the cases, respectively. The proportion of cases that yielded no pathogen was inversely related to age, being highest (41%) among infants below 6 months of age and lowest (19%) among those aged 24–35 months. These results suggest that microbe-specific intervention strategies for the control of childhood diarrhoeal diseases in developing countries should focus on rotavirus,* Shigella *spp. and enterotoxigenic* E. coli.

Introduction

Knowledge of the etiology of acute diarrhoea is relevant for planning diarrhoeal disease control strategies, especially vaccine development. The possibilities for the etiological diagnosis of diarrhoea were greatly enhanced in the 1970s through a series of advances, the most important of which were the discovery of rotaviruses and *Campylobacter jejuni*, the discovery and development of diagnostic tests for enterotoxigenic *Escherichia coli* (ETEC), and the detection by electron microscopy of several noncultivable enteric viruses. With improved diagnostic methods, it became possible to detect an etiological agent in 70–75% of acute cases of diarrhoea in children treated at hospitals in developed countries (*4*, *13*). In comparable etiological surveys in developing countries, the rate of positive identification of microorganisms has been slightly lower, and compared with viruses the role of bacterial agents has been greater (*1–3*, *5–12*). Moreover, in developing countries it has been recognized that enteric pathogens can frequently be encountered also in healthy children, making it more difficult to determine their true etiological role in causing diarrhoea (*5*, *6*). Furthermore, in developing countries it is not uncommon to isolate more than one enteric pathogen from the same child (*1*, *3*, *5*, *6–8*, *10*).

To define more carefully and compare the etiology of acute diarrhoea in young children in different areas of the world, the WHO Diarrhoeal Diseases Control (CDD) Programme initiated and supported a multicentre study in five developing countries. Standardized protocols for sampling patients and controls and for the laboratory procedures were used to allow comparison between sites

* The following persons also contributed to this study: Shi Ou Sheng, Xie Mei Wen, Duan Shu Cheng, Xia Lu Di, and Wang Shun Lin (Shanghai); S.M. Pereira, T. Raghupathi, C. Kirubakaran, C. Prabhakaran, D.P. Rajan, R. Martin and V.I. Mathan (Vellore); A. Zamora, E. Galindo, C. Soler, and M. del Carmen Bezualdo (Mexico); and Nyunt Nyunt Wai, Myo Khin, Thane Toe, Daw Tin Aye, Daw Mar Mar Nyein, Phyu Phyi Win, Mi Mi Khin, Kyaw Moe, Kyi Kyi Khin, Soe Thein, May La Lin, Daw Khin, and Than Nu (Yangon).

[1] Shanghai Hygiene and Anti-epidemic Centre, Shanghai, China.

[2] Wellcome Research Unit, Christian Medical College Hospital, Vellore, India.

[3] Laboratory of Intestinal Bacteriology, Hospital Infantil de Mexico "Federico Gomez" and Instituto de Investigaciones Biomedicas, UNAM, Mexico DF, Mexico.

[4] Clinical Research Division, Department of Medical Research, Yangon, Myanmar.

[5] Public Health Division, National Institute of Health, Islamabad, Pakistan.

[6] Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to this author.

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and permit more general conclusions to be drawn. This article summarizes the main results from the study.

Methods

The hospitals and laboratories outlined below participated in the study.

- Shanghai, China: Shanghai Hygiene and Anti-epidemic Centre, and the Shanghai Children's Hospital.
- Vellore, India: Wellcome Research Unit of the Christian Medical College Hospital.
- Mexico City, Mexico: Hospital Infantil de Mexico "Federico Gomez".
- Yangon, Myanmar: Department of Medical Research and the Yangon Children's Hospital.
- Islamabad and Rawalpindi, Pakistan: National Institute of Health (Islamabad), and the Rawalpindi General Hospital and Holy Family Hospital (Rawalpindi).

The standardized protocol, which is summarized below, was developed by the CDD Programme's Scientific Working Groups on Bacterial Enteric Infections and Viral Diarrhoea. All participating laboratories had prior experience in microbiological studies of enteric infections; in some instances assistance was provided to establish specific diagnostic tests at the study site. Although each study lasted 2 years, not all centres participated at the same time. The first study (in Myanmar) began in February 1982, and the last (in Pakistan) in October 1985.

Selection of cases

The patients were children aged 0–35 months who were seeking treatment for diarrhoea at the outpatient clinics of the participating hospitals. According to the original study protocol, children with a history of acute diarrhoea (an increase in the number or volume of stools) that lasted for 72 hours or less and clinical evidence of dehydration were eligible for the study. In practice, however, dehydration was not recorded, and most of the children probably were not clinically dehydrated. Also included were children with a history of blood or mucus in stools and a temperature of at least 38.5 °C. Children were excluded if they had an associated complicating illness or had received an antibiotic or antiparasitic drug within the preceding 10 days.

Cases were selected each week for 104 consecutive weeks. Based on records from previous years, a month-by-month sampling proportion was determined that took into account normal seasonal variations in disease incidence. The objective was to sample 5–12 cases per week throughout the study period, with the exact number varying according to the seasonal incidence of diarrhoea so that the proportion of total cases sampled each month remained nearly constant. Provided children met the case definition given above, their age, sex and type of diarrhoea (watery or dysenteric) were not considered when they were selected for the study; thus, the cases studied reflected the proportions actually seen for each age group, sex and type of diarrhoea.

Each child admitted to the study was matched with a control—a healthy child from the same geographical area and of the same sex, age (± 30 days for those aged 1–11 months and ± 60 days for others), socioeconomic status, and ethnic group, who had not had diarrhoea within the previous month.

A questionnaire was completed for each patient, giving details of the clinical history, pre-illness feeding practice, household environment, and demographic information (age, sex, and ethnic group). Most of the patients were from an urban/periurban environment, except in Vellore, where the study was carried out in a periurban/rural environment.

Laboratory procedures

The laboratory procedures have been described elsewhere.[a]

At least 5 ml (5 g) of faeces was collected from each patient within 1 hour of admission. Rectal swabs were used with dysenteric patients or controls if stools could not readily be obtained. Specimens were brought to the laboratory and divided for immediate culture and examination (2 g) and for virological studies (1 g diluted 1 : 5 in phosphate-buffered saline). A spare specimen (2 g) was stored frozen (−70 °C) for future use.

A portion of each stool was examined microscopically for trophozoites (*Entamoeba histolytica*) and cysts (*Giardia lamblia* and *E. histolytica*). *Cryptosporidium* spp. were not routinely sought, since the importance of these pathogens was not recognized when the protocol was developed.

For bacteriological examination the following media were inoculated: selenite broth (salmonella enrichment), alkaline peptone water (*Vibrio cholerae* enrichment), McConkey agar (22 °C for *Yersinia enterocolitica*; 37 °C for *E. coli*, *Shigella* spp. and *Salmonella* spp.), TCBS agar (*V. cholerae*), and Butzler's or Skirrow's medium (Campylobacter). Additional selective media for *Salmonella* spp. and *Shigella* spp. were inoculated as desired by the participating laboratory.

[a] *Manual for laboratory investigation of acute enteric infections*. WHO unpublished document CDD/83.3.Rev.1. Requests for single copies should be addressed to Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

Preliminary identification of suspicious colonies was carried out using standard biochemical tests. After preliminary identification of *E. coli* was completed, enterotoxin production was demonstrated using the Biken test or, in Mexico, using the Y-1 adrenal cell assay, for heat-labile toxin (LT), and the suckling mouse assay for heat-stable toxin (ST). Enteropathogenic *E. coli* (EPEC) were tentatively identified by serogrouping with O-antigen antisera[b] using both slide and tube agglutination techniques. Enteroinvasive *E. coli* (EIEC) were studied by testing two colonies (including atypical lactose-negative strains) for invasiveness using the Sereny test. Isolates of *V. cholerae* 01 were serotyped.

All stools were examined by electron microscopy for rotavirus, Norwalk-agent-like particles, and adenovirus. Initially, negatively-stained specimens were screened for all virus particles. This was followed by immune electron microscopy using pooled sera from indigenous donors. In addition, most samples were tested for rotavirus antigen using an enzyme-linked immunosorbent assay (ELISA) provided by the WHO Collaborating Centre for Human Rotavirus, Birmingham, England.

Results

A total of 3640 cases and 3279 controls were investigated; this represents approximately 10% of the total number of diarrhoea cases seen in the five centres during the 2-year study (Table 1). Throughout their respective study periods, no centre recognized unusual epidemics that would have distorted the findings.

Table 1: **Distribution of cases of diarrhoea in the five study sites**

Study site	No. of diarrhoea cases	No. admitted into the study	
		Cases	Controls
China	6192	594 (10)[a]	562
India	5862	916 (16)	587
Mexico	6376	559 (9)	559
Myanmar	NA[b]	813	813
Pakistan	9438	758 (8)	758

[a] Figures in parentheses are percentages of the total number of diarrhoea cases in each site.
[b] NA = not available.

The age distribution of cases was generally similar in all five centres (Table 2); however, the proportion of cases aged 0–5 months was greater in Mexico (40%) than Myanmar (16%), while the proportion of children aged 12–23 months was greatest in Myanmar (43%) and least in Mexico (22%). Overall, about 60% of the patients were aged less than 12 months, 30% were aged 12–23 months, and less than 10% were aged 24–35 months.

Table 2: **Distribution of diarrhoea cases, by age and sex in the study sites**

Study site	% of cases in age group (months):				Sex distribution (all ages)	
	0–5	6–11	12–23	24–35	Males (%)	Females (%)
China[a]	28	31	32	6	63	37
India	33	28	30	9	61	39
Mexico	40	35	22	3	57	43
Myanmar	16	31	43	10	59	41
Pakistan	27	38	28	7	56	44
All sites	28	32	32	7	60	40

[a] Age was not reported for 2% of cases.

In all the study centres approximately 60% of all cases were boys (Table 2). Two centres (Shanghai and Vellore) determined the correlation of sex with the diarrhoeal etiological agent. In both instances, males predominated for all agents except isolates of *Shigella* spp. from Shanghai, which were detected equally frequently from males and females.

An enteric pathogen was detected in 68% of diarrhoea cases, with a bacterial agent being detected in 48%, a viral agent in 23%, and *G. lamblia* in 3% of cases; these included cases from which more than one pathogen was isolated. More than one enteric pathogen was found in at least 20% of diarrhoea episodes in Mexico City, Shanghai, and Vellore, but in only about 5% in Islamabad and Yangon. An enteric pathogen was detected in approximately 30% of healthy controls, the highest prevalence being 49% in Vellore.

The only agents that were consistently and substantially more prevalent in cases than in controls were rotavirus, *Shigella* spp. and ETEC (Table 3 and Table 4). The prevalence of EPEC was relatively high in controls, and, with the exception of Islamabad, nearly equal to that in cases. *Salmonellae* spp. were more frequently detected in cases than controls in Islamabad and Shanghai, but not at the other study sites. *C. jejuni* was clearly more prevalent in cases than controls in Islamabad, Mexico and Shanghai, but not in Vellore or Yangon. Mixed infections were detected approximately three times more frequently in cases than controls. *G. lamblia* and *E. histolytica* were seldom found in the study cases (Table 4).

[b] Difco Laboratories, Detroit, MI, USA.

Table 3: **Distribution of bacterial agents detected in children aged under 3 years with diarrhoea and in healthy controls in the five study sites[a]**

	% of individuals from whom the agent shown was detected:											
	Escherichia coli (ETEC)		*E. coli* (EPEC)		*Salmonella* spp.		*Shigella* spp.		*Vibrio cholerae* 01		*Campylobacter jejuni*	
Study site	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
China	6	2	3	3	5	2	18	0.4	0	0	17	2
India	14	7	9	7	4	6	20	3	2	0.2	15	14
Mexico	17	7	10	9	4	3	11	1	0	0	15	10
Myanmar	26	7	8	5	1	1	3	1	0.5	0	2	2
Pakistan	17	4	14	8	3	0.3	6	1	2	0.8	10	5
All sites	16	5	9	6	3	2	11	1	1	0.2	11	7

[a] In some instances two or more agents were isolated from the same individual. ETEC = enterotoxigenic *E. coli*; EPEC = enteropathogenic *E. coli*.

Table 4: **Distribution of viral and parasitic agents detected in children aged under 3 years with diarrhoea and in healthy controls in the five study sites[a]**

	% of individuals from whom the agent shown was detected:									
	Rotavirus		Adenovirus		Norwalk-like agent		*Giardia lamblia*		*Entamoeba histolytica*	
Study site	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
China	13	1	2	1	3	4	0.2	0	0	0
India	18	1	6	2	3	2	7	7	0.1	0.2
Mexico	13	2	3	1	5	2	5	1	0.7	0
Myanmar	22	1	—[b]	—[b]	—[b]	—[b]	0.1	0.1	0	0
Pakistan	14	4	6	3	2	1	3	3	0.6	0.4
All sites	16	2	4	2	3	2	3	3	0.3	0.1

[a] In some instances two or more agents were isolated from the same individual.
[b] Not stated.

The effect of age on the prevalence of specific pathogens was evaluated by determining the rate of isolation of a specific pathogen (or no pathogen) from children within defined age groups, e.g., the proportion of diarrhoeic children aged 6–11 months who were positive for rotavirus; and by determining the distribution by age group of all isolates of specific agents, e.g., the proportion of all rotavirus isolates from diarrhoeic children aged 6–11 months. Table 5 summarizes these data from four of the study centres for children aged 0–5, 6–11, 12–23, and 24–35 months; no data are shown for the fifth centre, Yangon, which reported age-specific data on etiology for only 0–11-month-olds and 12–35-month-olds. Nevertheless, the general pattern in Yangon, was similar to that in the other centres. The three commonest enteropathogens isolated from 0–5-month-olds were rotavirus, ETEC, and *C. jejuni*. The data for 0–6-month-olds from these study sites were further analysed by monthly age groups (Table 6).

Table 5: **Age-specific isolation rates for the major enteropathogens in four of the study sites[a]**

Entero-pathogen	% of cases that were positive for specific pathogens in different age groups (months)			
	0–5	6–11	12–23	24–35
Rotavirus	13 (28)[b]	20 (43)	12 (25)	12 (5)
ETEC[c]	11 (26)	14 (34)	15 (31)	18 (9)
Campylobacter jejuni	11 (26)	14 (34)	16 (33)	17 (8)
Shigella spp.	5 (12)	10 (26)	22 (49)	27 (14)
None detected	41 (44)	25 (28)	25 (24)	19 (4)

[a] Yangon was excluded, as noted in the text.
[b] Figures in parentheses show the % of all isolates of specific pathogens, by age group.
[c] Enterotoxigenic *Escherichia coli*.

The main results from the analysis of the age-specific data are summarized below.

- Rotavirus was the most frequently detected pathogen in diarrhoea episodes during the first year of life, and most episodes that were rotavirus-positive (71%)

Table 6: **Combined data for four of the study sites on the detection of rotavirus, ETEC and campylobacter from cases and controls in the first 6 months of life**[a]

	Data from cases in age group (days):						
	0–29	30–59	60–89	90–119	120–149	150–179	Total
Rotavirus							
No. of isolates	5 (3)[b]	10 (4)	24 (6)	20 (4)	26 (2)	33 (1)	118 (20)
% of cases in age group 0–5 months	4	9	20	17	22	28	100
ETEC							
No. of isolates	7 (3)	7 (5)	16 (16)	22 (8)	21 (14)	27 (10)	100 (56)
% of cases in age group 0–5 months	7	7	16	22	21	27	100
Campylobacter							
No. of isolates	5 (2)	13 (5)	25 (9)	13 (7)	25 (10)	24 (11)	105 (44)
% of cases in age group 0–5 months	5	12	24	12	24	29	100

[a] ETEC = enterotoxigenic *Escherichia coli*.
[b] Figures in parentheses refer to data from controls.

also occurred during the first year of life (Table 5). The highest incidence of rotavirus was among 6–11-month-olds, for whom it was detected in 20% of all diarrhoea cases. A total of 28% of all rotavirus-associated cases occurred among under-6-month-olds (Table 5), 87% of these being in infants aged 60–179 days.

- Most isolates of *Shigella* spp. were from cases aged 6–23 months and these were the most frequently isolated pathogens in diarrhoeic children aged 12–35 months (Table 5). These findings were observed in all study centres and were most striking where the proportion of cases with shigellosis was highest—Shanghai, Vellore, and Mexico. *Shigella* spp. were rarely isolated from controls (29 isolations from over 3000 healthy control children).
- ETECs were detected at a relatively constant rate throughout the first 3 years of life. In three of the five centres they were, with *Shigella* spp., the agent most frequently isolated from children over 1 year of age. A total of 76% of ETEC strains from cases that were typed produced only ST, 23% only LT, and 10% both ST and LT. In less than 5% of cases, strains that produced only ST and only LT were found in the same patient. A predominance of strains producing only ST was observed in all centres. Among controls, 36% of ETEC produced only LT and 57% only ST; and 7% produced both toxins. Altogether, 26% of cases with ETEC were infants aged less than 6 months; however, ETEC was also common among control infants in this age group.
- *C. jejuni* was isolated at a relatively constant rate throughout the first 3 years of life. The rate of isolation in Yangon (2% of cases) was much lower than that in the other centres. A total of 26% of *C. jejuni* isolates from cases were from infants aged 0–5 months (data from four centres excluding Yangon). The difference in the isolation rates of *C. jejuni* between cases and controls was greater for this age group than that for older children.

Table 5 also shows the age distribution of diarrhoea cases whose etiology was undetermined. The proportion of such cases was highest among the youngest children, i.e., those aged less than 6 months, and this occurred in all the study centres. For this age group, 41% of all cases were of undetermined etiology, whereas for those aged 12–35 months only 19% of cases did not yield a potential pathogen.

Information on clinical findings was not consistently collated for each case in terms of specific etiology or the age of the child. However, the observations outlined below could be made about the clinical features of cases.

—Only 1.8% of cases presented with severe dehydration, and these were due mostly to rotavirus, *V. cholerae* 01, or ETEC.

—Stools from more than 80% of the patients were described as "loose"; watery diarrhoea occurred in less than 20% of cases. Watery diarrhoea was recorded in 8% of cases in Myanmar, 13% in Pakistan, and 32% in Mexico City. Apart from the few cases of cholera, watery diarrhoea was most frequently associated with rotavirus (27–36% of cases), ETEC (25–37%), and campylobacter (24–29%).

—Overall, visible faecal blood was reported in approximately 20% of cases, ranging from 4% in Myanmar to 29% in Mexico. As expected, it was most frequently associated with illness caused by *Shigella* spp. (45–67% of cases) and campylobacter (35–37%). Blood was rarely observed for illness caused by rotavirus, ETEC, or *V. cholerae* 01.

—Vomiting was reported as "relatively rare" among Indian cases, but was recorded for 43% of cases in Mexico and 51% in Myanmar. In Pakistan and Mexico, vomiting was reported in 61% and 69% of rotavirus-associated cases, respectively.

Discussion

We have focused on the clinical features and etiology of acute diarrhoea in young children seen at the five participating centres, and have attempted to draw broad conclusions where possible. This approach appears justified because the data were collected from a large number of patients using the same study protocol. The findings at each centre were similar with regard to the age and sex distribution of the diarrhoea cases and the overall etiological pattern. While some regional differences in the etiology of diarrhoea occurred, they were minor relative to the general pattern found and also with respect to other comparable studies in developing countries (*1–3, 5–12*). On the other hand, it should be recognized that this multicentre study was geographically limited, particularly because no centre from Africa or South America was included.

The results show that by using appropriate methodology it is possible to detect a potential microbial cause in nearly 70% of children with acute diarrhoea or dysentery who attend a treatment centre in developing countries; this proportion is similar to that in developed countries, although the distribution of individual agents is different (*4, 13*). It should nevertheless be borne in mind that 30% of cases could not be attributed to a specific microbial agent. The highest proportion of such cases at all sites involved infants aged less than 6 months; further studies are required to more fully determine the causes of acute diarrhoea in this age group.

In all the participating centres the high rate of isolation of identifiable enteric pathogens from healthy control children emphasizes the need for caution in interpreting the results of stool cultures for individual cases. The agents with the highest case: control ratios for isolation rates were rotavirus and *Shigella* spp., followed by ETEC; on the basis of this study, only these three could unequivocally be regarded as important causes of childhood diarrhoea in all five centres. Campylobacter was associated with diarrhoea in some study sites, but mainly among 0–5-month-olds.

Rotavirus was detected in 16% of the cases; this is a lower proportion than that found in surveys of hospitalized children in developing countries (median, 35%), but higher than that in community-based longitudinal surveys in developing countries (8–10%) (*15*). The higher proportion of rotavirus cases in hospital-based studies is consistent with the finding, confirmed by the present study, that rotavirus diarrhoea is of above-average severity. The lower proportion of rotavirus cases found in this study compared with other hospital-based surveys probably reflects the relative mildness of diarrhoea among the participating children, many of whom were not hospitalized, but treated as outpatients.

The present study also confirmed that in developing countries rotavirus is a significant pathogen among infants aged 2–5 months; in contrast, in developed countries few episodes of rotavirus diarrhoea involve this age group (*15*). This finding clearly has implications for research towards a rotavirus vaccine: a candidate rotavirus vaccine for use in developing countries should be efficacious in infants aged 1–2 months. This requirement has been considered in designing trials of such vaccines supported by the WHO Diarrhoeal Diseases Control Programme (*14*).

The second most important etiological agent in this study (*Shigella* spp.) was the most common pathogen in children over 1 year of age. Accordingly, *Shigella* spp. (particularly the *S. dysenteriae* and *S. flexneri* serotypes) should also be regarded as a priority target for vaccine development, especially since dysenteric illness is not treated primarily with oral rehydration salts, but usually requires antimicrobial therapy. ETEC may also be regarded as a candidate for vaccine development on the basis of this study. Campylobacter emerged as a significant pathogen, mainly among under-6-month-olds. Further studies are needed to assess the role of novel diarrhoea viruses in developing countries; the present study, however, failed to demonstrate any significant role for viruses (other than rotavirus) that were detectable by electron microscopy. *G. lamblia* and *E. histolytica* were not important causes of parasitic diarrhoea among young children in the study; the role of *Cryptosporidium* spp. was not investigated.

In summary, the major findings of this large multicentre study were as follows:

—over 60% of cases of acute diarrhoea involving children under 3 years of age were among 0–11-month-olds;

—about 60% of the patients were male; and

—rotavirus, *Shigella* spp. and ETEC were the most important causative agents.

While *V. cholerae* was an uncommon etiological agent, it is an important cause of severe dehydration in endemic areas. As targets for vaccine development, priority should be given to rotavirus, *Shigella* spp., ETEC and *V. cholerae*. For the greatest benefit, candidate vaccines should be efficacious in young infants.

Résumé

Etiologie de la diarrhée aiguë de l'enfant dans les pays en développement: une étude multicentrique dans cinq pays

On a mené pendant 2 ans, au moyen d'un protocole normalisé, une enquête sur l'étiologie de la diarrhée aiguë chez des enfants âgés de 0 à 35 mois amenés pour consultation dans cinq hôpitaux situés en Chine, en Inde, au Mexique, au Myanmar et au Pakistan. Au total, 3640 cas de diarrhée et 3279 témoins appariés selon l'âge et le sexe ont été étudiés; environ 60% des malades avaient moins d'un an et 60% étaient des garçons. Un germe entérique a été décelé chez 68% des malades et chez 30% des témoins. Les germes les plus souvent associés à la diarrhée aiguë dans tous les centres étaient les rotavirus (16% des cas, 2% des témoins), *Shigella* sp. (11% des cas, 1% des témoins) et *Escherichia coli* entérotoxinogène (16% des cas, 5% des temoins). Chez les 6–11 mois, ce sont les rotavirus qui étaient les plus courants, représentant 20% de tous les cas dans ce groupe d'âge; 71% de tous les épisodes de diarrhée à rotavirus sont survenus chez les moins d'un an. Chez les 12–23 mois et les 24–35 mois, *Shigella* sp. était le germe le plus courant, représentant respectivement 22% et 27% des cas. Le nombre de cas dans lesquels aucun germe n'a été décelé est inversement proportionnel à l'âge: maximal (41%) chez les nourrissons de moins de 6 mois, il devient minimal (19%) chez les 24–35 mois. Ces résultats indiquent que pour lutter contre les diarrhées infantiles dans les pays en développement, les stratégies d'intervention devraient être axées sur les rotavirus, *Shigella* sp. et *Escherichia coli* entérotoxinogène.

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