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## Infection, diarrhea, and dysentery caused by *Shigella* species and *Campylobacter jejuni* among Guatemalan rural children

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To examine the factors that may influence the outcome of infections by *Shigella* spp. and *Campylobacter jejuni* we followed for 24 consecutive months 321 rural Guatemala children 0 to 35 months old. Home visits were made to determine child morbidity patterns with emphasis on diarrhea and dysentery. Fecal samples for mi-

crobiologic studies were obtained from the participants when they were ill and during healthy periods. *Shigella* spp. were isolated from 9.8 and 4.0% of ill and healthy children, respectively; the figures for *C. jejuni* were 12.1% and 8.1%. *Shigella flexneri* 1, 2 and 6 and *Shigella sonnei* accounted for 70% of all *Shigella* isolates. Twenty-four percent of *Shigella* spp. and 7% of *C. jejuni* infections resulted in dysentery. *Shigella dysenteriae* and *Shigella flexneri* were more likely to induce dysentery than the other species. The incidence of dysentery was 0.84 of 100 child weeks. Age, gender, nutritional status and feeding habits of the children did not affect

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Key words: Diarrhea, dysentery, *Shigella* spp., *Campylobacter jejuni*, Guatemalan children.

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the outcome of *Shigella* infection. Fat consumption favored the development of dysentery caused by *C. jejuni*. The development of dysentery seems to be associated with microbial factors and not with host variables, although specific *Shigella* serotype protection against symptomatic infection may be functional for prolonged periods after natural exposure.

## INTRODUCTION

Diarrheal diseases are a major health problem among children of underprivileged areas of the world.<sup>1</sup> The use of oral rehydration therapy has contributed to decrease diarrhea fatality rates,<sup>2</sup> but mortality associated with dysentery and with persistent episodes of gastroenteritis continues to be high.<sup>3, 4</sup> Although multiple pathogens may induce dysentery, the majority of cases are associated with *Shigella* species and with *Campylobacter jejuni*.<sup>5, 6</sup> Nevertheless not all infections by these pathogens result in dysentery; a proportion of infected individuals remain asymptomatic and others develop nondysenteric diarrhea.<sup>7</sup> With the purpose of better understanding the factors that determine the outcome of infections by *Shigella* and *C. jejuni*, we studied the occurrence of dysentery and its association with those bacteria among rural children of Guatemala.

## METHODS

The study was done in Santa María de Jesús, a rural community in the central highlands of Guatemala.<sup>8</sup> A census carried out by our field team showed that, at the time of recruitment, there were 920 children aged 0 to 29 months living in 815 of the 1978 local households. Each of the families was assigned a number and, considering a 20% dropout rate, 180 were randomly chosen for recruitment; 171 families agreed to participate. Among these the youngest child was selected for the study, representing 18.6% of all eligible children present in the community. Additionally 162 parents of the 316 live births that occurred in Santa María de Jesús in the following 10 months were also approached for participation and 150 (47.5% of all deliveries) gave consent. In total 321 children, each from a different family, were kept under surveillance for 24 consecutive months or until they reached their third birthday by twice-a-week home visits. During these visits field personnel investigated the occurrence of diarrhea, bloody diarrhea, dysentery and associated

signs and symptoms and collected information on dietary habits, medical treatments and anthropometry (weight and height) among the participants.<sup>8</sup> Fecal specimens for microbiologic studies were obtained from the individuals when they were ill and, monthly on a routine basis, when they had been free from diarrhea for at least three consecutive weeks.

Representative samples of fecal material were inoculated into Cary-Blair transport medium within 1 hour after collection and placed at 4°C. Every afternoon the specimens were transported to the Institute of Nutrition of Central America and Panama's central laboratories in ice chests. Once in the laboratory the specimens were streaked onto SS, XLD, McConkey and Butzler Virion agar plates for isolation of *Shigella* species and *C. jejuni*. Other bacterial, viral and parasitic enteropathogens were isolated and/or identified as described by using biochemical and serologic procedures.<sup>9</sup>

Diarrhea was defined as the passing of three or more nonformed or liquid stools in a 24-h period. Diarrhea accompanied by the excretion of blood and mucus was considered dysentery. Incidence of both diarrhea and dysentery were calculated as number of episodes of either diarrhea or dysentery divided by the number of child weeks at risk (number of weeks of observation minus the number of weeks ill). Nutritional status was expressed as Z score, i.e. the number of standard deviations from the mean of the NCHS reference curve.<sup>10</sup> Children with *Shigella*-associated dysentery were given appropriate treatment with antibiotics, according to the susceptibility of the isolate. All diarrheal diseases were managed with oral rehydration therapy.

Statistical analyses were done by comparing proportions using the chi square test.<sup>11</sup>

## RESULTS

There were 2332 episodes of diarrhea among the 321 children studied, for an incidence of 13.5/100 child weeks. The incidence of dysentery was 0.84/100 child weeks (Table 1). Of the 152 documented dysenteric illnesses, 99 (66%) presented as such during the first 3 days of symptoms; 25 (16%) were not associated with the excretion of blood and mucus until the second week of disease.

Dysentery was more common in the 12- to 23-month age range (Table 1), although the highest proportion of episodes of dysentery was observed after 18 months

TABLE 1. Age-specific incidence\* of diarrhea and dysentery Santa María de Jesús

Illness	Age (Months)					Total
	0-5	6-11	12-17	18-23	24-35	
Diarrhea	13.6	15.0	17.6	14.0	10.1	13.5
Dysentery	0.6	0.8	1.0	1.1	0.8	0.8

\* Per 100 child weeks at risk,  $P = 0.002$ .

TABLE 2. Proportion\* of episodes of dysentery, in relation to age and gender: Santa Maria de Jesús

Sex	Age (Months)					
	0-5	6-11	12-17	18-23	24-35	Total
Males	3.4	5.1	5.5	8.7	10.2	6.5
Females	6.5	6.4	7.1	8.2	6.3	6.8
Both	5.7	5.7	6.3	8.5	8.2	6.7

\* Percent.

of life (Table 2). There was no difference in the overall rates of dysentery for males and females, 0.82 and 0.87, respectively; the age-specific incidence did vary among boys and girls (Fig. 1). The differential in rates was determined by the proportion of diarrheal illnesses that were associated with blood and mucus (Table 2).

The isolation rates of *Shigella* and *C. jejuni* from sick children were higher than those from asymptomatic individuals: 9.8 and 4.0, respectively, for *Shigella* and 12.1 and 8.1, respectively, for *C. jejuni* ( $P < 0.001$  in both cases). The isolation rates of both enteropathogens and their association with the monthly incidence of dysentery in the population studies are depicted in Fig. 2A. *Shigella* infections were more common during April (Fig. 2B), the warmest month of the year, whereas *C. jejuni* was isolated preferentially in June and September (Fig. 2C), during the rainy season (May to October).

The pattern of age-specific isolation rates was different for the two enteropathogens, as summarized in Table 3. *C. jejuni* was detected with higher frequency from younger individuals while *Shigella* was detected preferentially in the older ones.

Excretion of *Shigella* was proven in 126 (39%) of the 321 study children; 65 individuals (52% of the *Shigella* excretors) had only 1 infection during their follow-up, 44 (35%) had 2 infections, 10 (8%) had 3, 3 (2%) had 4 and 3 had 5. Overall we documented 223 infections caused by *Shigella* in 207 instances; 73 (35%) of them were asymptomatic, 85 (41%) were watery diarrhea and 49 (24%) were dysenteric.

In the case of *C. jejuni* there were 178 (55%) infected

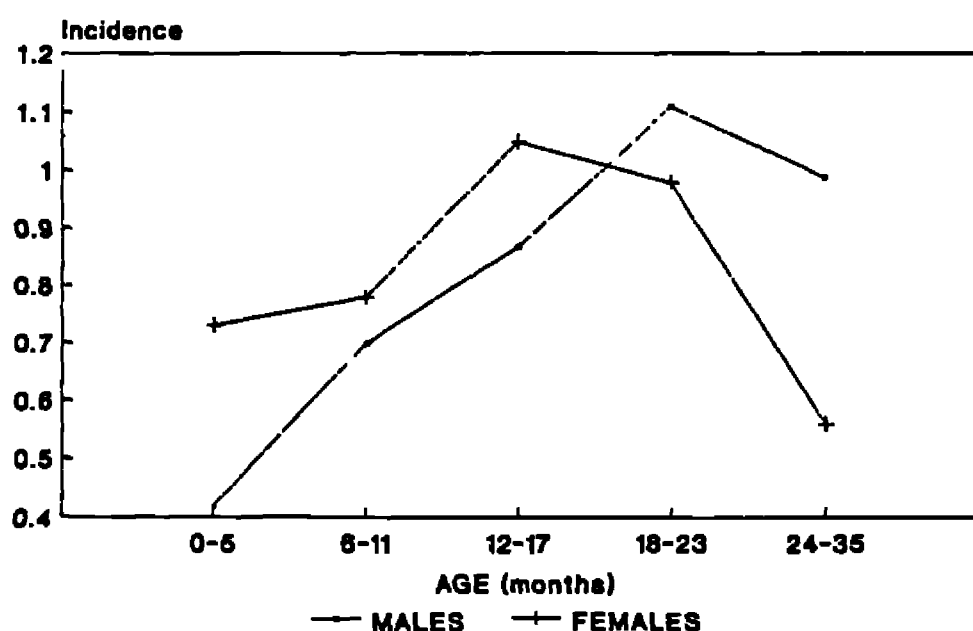
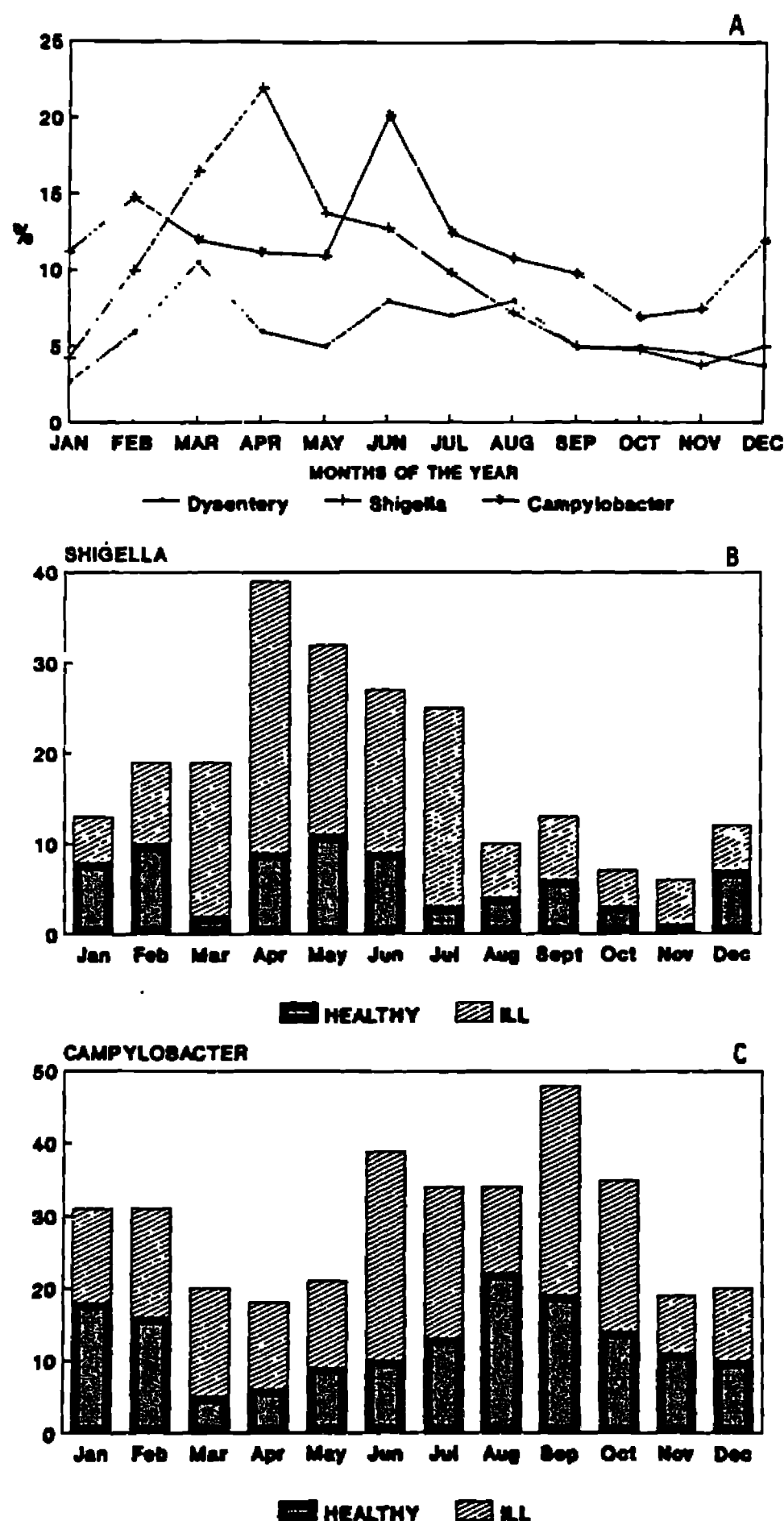


FIG. 1. Age-specific incidence of dysentery, according to gender.

FIG. 2. Monthly incidence of dysentery and monthly isolation rates of *Shigella* and *C. jejuni* (A). Monthly number of isolates of *Shigella* (B) and *C. jejuni* (C).

subjects; 99 (56%) had 1 infection, 49 (27%) had 2 infections, 15 (8%) had 3, 7 (4%) had 4, 6 (3%) had 5 and 2 individuals had 6 and 7. In contrast to *Shigella* only 21 (7%) of the 313 *C. jejuni* infections resulted in dysentery, whereas 148 (47%) were asymptomatic

TABLE 3. Age-specific isolation rates of *Shigella* and *Campylobacter jejuni* from sick children: Santa María de Jesús

Bacteria	Age (Months)						P
	0-5	6-11	12-17	18-23	24-35	Total	
<i>Shigella</i>	2.6	7.0	9.4	15.0	17.1	9.8	<0.001
<i>Campylobacter jejuni</i>	6.3	17.1	13.2	13.2	9.0	12.1	<0.001

and 144 (46%) were diarrhea. Seventeen cases had mixed infections with *Shigella* and *C. jejuni*.

We were able to isolate 17 different serotypes of *Shigella* (two *Shigella dysenteriae* strains were not typed), with *Shigella flexneri* 6, *Shigella flexneri* 1, *Shigella sonnei* and *Shigella flexneri* 2 accounting for 70% of all isolates (Table 4). The relative importance of 4 serotypes varied from the first to the second year of the study (Table 5).

There were 20 cases of repeated infections with the same *Shigella* serotype; the time intervals between them ranged from 1 to 9 months. Five of the initial infections resulted in dysenteric illness and 9 were diarrhea; illness was the outcome in only 7 of the subsequent homologous-type infections ( $P = 0.027$ , Table 6). In 6 of these latter 7 episodes of diarrhea, the children were coinfecting with other potential enteric pathogens.

Loss of appetite was seen in about 50% of the episodes of disease; tiredness and fever were commonly associated with illness (Table 7); Although *Shigella* induced vomiting in more cases than *C. jejuni*, dehydration was seen in only about 10% of cases. The individuals infected with *C. jejuni* who developed dys-

TABLE 6. Outcome of repeated infections by homologous *Shigella* serotypes: Santa María de Jesús

$P = 0.027$ .

Infection	Outcome		
	Dysentery	Diarrhea	Healthy
First	5 (25)*	9 (45)	6 (30)
Second	0	7 (35)†	13 (65)

\* Numbers in parentheses, percent.

† Six cases coinfecting with (1) *Giardia*, (2) *Giardia* and enteropathogenic *Escherichia coli*, (3) *Giardia*, (4) enteroadherent *Escherichia coli* and *Rotavirus*, (5) *Giardia*, and (6) enterotoxigenic *Escherichia coli* and *Giardia*.

entery were more likely to present decreased activity ( $P = 0.010$ ) and fever ( $P = 0.025$ ) than those who developed watery diarrhea.

Age did not play an important role in the outcome of symptomatic infections (Fig. 3). Nevertheless among those infected with *Shigella sonnei*, children who developed illness were younger than those who did not ( $P = 0.0205$ , Table 8). Nutritional status, estimated as adequacy of weight for age, weight for height or height for age, did not influence the outcome of infection (Tables 9 and 10).

Consumption of animal and vegetal proteins, carbohydrates or fiber during the week before infection did not affect its outcome. Children who developed dysentery after infection with *C. jejuni* were more likely to consume fat than those whose infections were either asymptomatic or watery ( $P = 0.021$ ). Children with symptomatic infections by either *Shigella* or *C. jejuni*, however, consumed poorer diets during the first 3 postinfection days compared to those individuals who remained healthy (Figs. 4 and 5).

*S. dysenteriae* and *S. flexneri* were more likely to induce dysentery (42% of symptomatic infections) than *Shigella boydii* and *S. sonnei* (19% of symptomatic infections,  $P = 0.028$ , Fig. 6).

## DISCUSSION

Diarrhea is highly prevalent in the population of Santa María de Jesús with 7 to 8 episodes/child/year, during the first 3 years of life. Seven percent of those illnesses are dysentery, associated primarily with *Shi-*

TABLE 4. Serotypes of *Shigella* spp. isolated from children in Santa María de Jesús

Serotype	Outcome			
	Healthy	Diarrhea	Dysentery	Total
<i>Shigella dysenteriae</i> 1	0	0	1	1 (0.4)*
<i>Shigella dysenteriae</i> 2	6	6	7	19 (8.5)
<i>Shigella dysenteriae</i> 3	0	3	1	4 (1.8)
<i>Shigella dysenteriae</i> 4	2	0	0	2 (0.9)
<i>Shigella dysenteriae</i> 6	0	1	0	1 (0.4)
<i>Shigella flexneri</i> 1	16	16	14	46 (20.6)
<i>Shigella flexneri</i> 2	6	6	9	21 (9.5)
<i>Shigella flexneri</i> 3	3	9	6	18 (8.1)
<i>Shigella flexneri</i> 6	17	23	10	50 (22.4)
<i>Shigella boydii</i> 1	1	0	1	2 (0.9)
<i>Shigella boydii</i> 2	4	3	1	8 (3.6)
<i>Shigella boydii</i> 7	0	1	0	1 (0.4)
<i>Shigella boydii</i> 9	0	1	0	1 (0.4)
<i>Shigella boydii</i> 10	0	3	0	3 (1.4)
<i>Shigella boydii</i> 11	0	3	0	3 (1.4)
<i>Shigella boydii</i> 14	1	1	0	2 (0.9)
<i>Shigella sonnei</i>	16	18	5	39 (17.5)

\* Numbers in parentheses, percent. Two *Shigella dysenteriae* strains were not typed.

TABLE 5. Isolates of the most prevalent *Shigella* serotypes by year of study: Santa María de Jesús

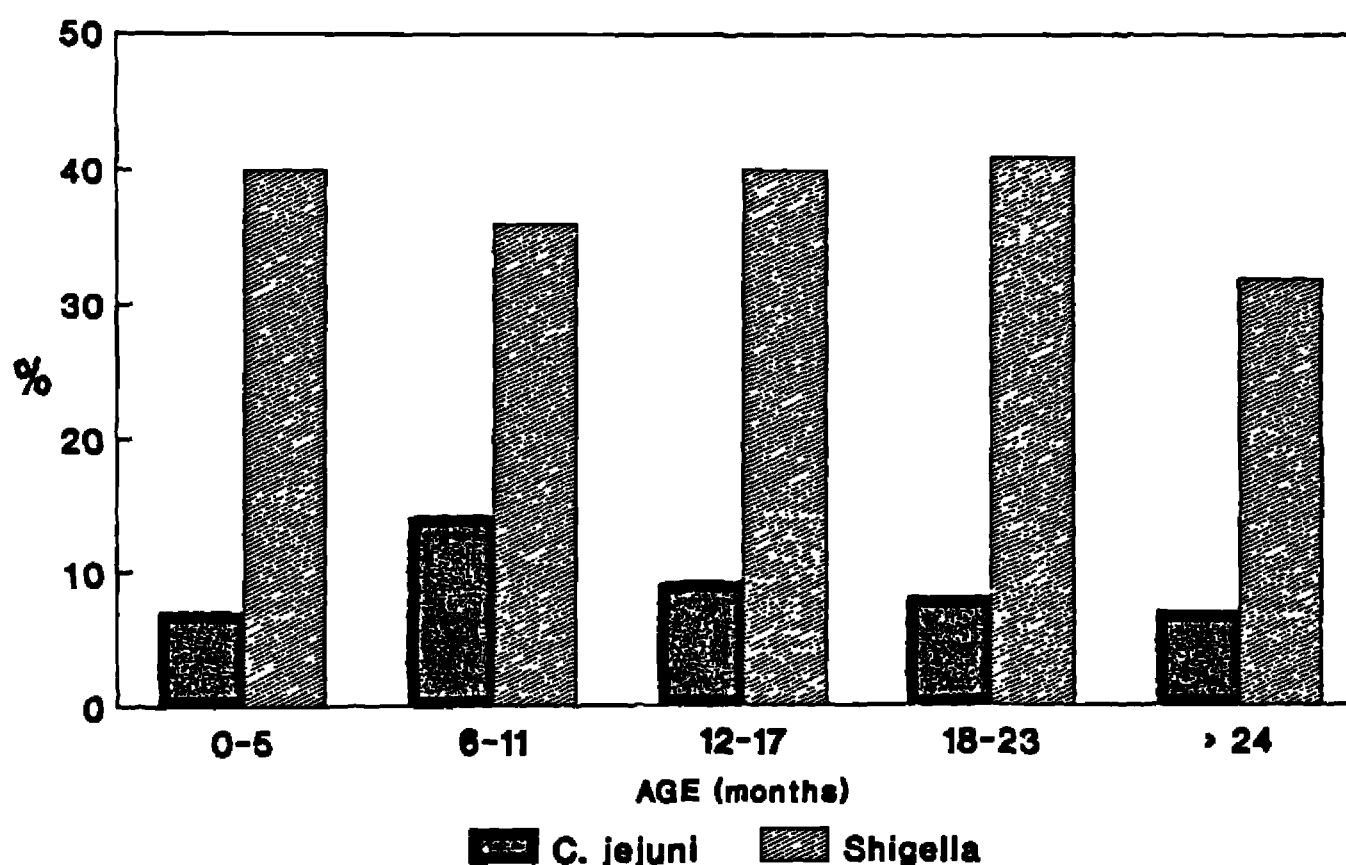
Year	N	Serotype				All
		<i>Shigella flexneri</i> 1	<i>Shigella flexneri</i> 2	<i>Shigella flexneri</i> 6	<i>Shigella sonnei</i>	
1	113	32 (28.3)*	10 (8.8)	21 (18.6)	16 (14.2)	79 (69.9)
2	110	14 (12.7)	11 (10.0)	29 (26.4)	23 (20.9)	77 (70.0)
	223	46 (20.6)	21 (9.5)	50 (22.4)	39 (17.5)	156 (70.0)

\* Numbers in parentheses, percent of line.

TABLE 7. Signs and symptoms associated with diarrhea and dysentery in *Shigella* and *Campylobacter jejuni* infections: Santa María de Jesús

Sign/Symptom	<i>Shigella</i>		<i>P</i>	<i>Campylobacter jejuni</i>		<i>P</i>
	Diarrhea	Dysentery		Diarrhea	Dysentery	
Fever	26 (30)*	11 (22)	0.310	35 (24)	10 (48)	0.025
Vomiting	21 (25)	9 (18)	0.397	9 (7)	1 (5)	0.874
Dehydration	8 (9)	6 (12)	0.606	13 (9)	1 (5)	0.512
Tiredness	27 (32)	19 (39)	0.410	31 (22)	10 (48)	0.010
Loss of appetite	46 (54)	22 (45)	0.304	59 (41)	12 (57)	0.162

\* Numbers in parentheses, percent of cases.

FIG. 3. Outcome of *Shigella* and *C. jejuni* infections, in relation to age.TABLE 8. Age (median)\* of *Shigella* spp.-infected children: Santa María de Jesús

Species	Outcome			<i>P</i>
	Healthy	Diarrhea	Dysentery	
<i>Shigella dysenteriae</i>	26.1	18.9	17.1	0.5957
<i>Shigella flexneri</i>	22.3	20.9	21.9	0.6373
<i>Shigella boydii</i>	24.2	17.9	20.8	0.4402
<i>Shigella sonnei</i>	24.9	13.2	17.0	0.0205

\* Months.

TABLE 9. Outcome of *Shigella* infections in relation to nutritional status (weight-for-age): Santa María de Jesús

Outcome	Nutritional Status		
	Severe deficiency	Mild deficiency	Normal
Healthy	53 (73)*	16 (22)	4 (6)
Diarrhea	55 (68)	18 (23)	7 (9)
Dysentery	34 (71)	12 (25)	2 (4)

\* Numbers in parentheses, percent; *P* = 0.831.TABLE 10. Outcome of *Campylobacter jejuni* infections in relation to nutritional status (weight-for-age): Santa María de Jesús

Outcome	Nutritional Status		
	Severe deficiency	Mild deficiency	Normal
Healthy	87 (59)*	35 (24)	26 (17)
Diarrhea	77 (56)	38 (28)	22 (16)
Dysentery	13 (72)	3 (16)	2 (11)

\* Numbers in parentheses, percent; *P* = 0.707.

*gella* spp., although *C. jejuni* contributed with 28% of dysenteric episodes of known etiology. Cohort studies in Chile<sup>12</sup> have shown that, in children less than 5 years of age from a transitional community with lower diarrhea incidence than in Santa María de Jesús, dysentery also represents 7% of all diarrhea episodes.

It is important to emphasize that, in our study subjects, one-third of dysenteries did not start as such, but as watery diarrhea. In rural settings when families consult for child diarrhea early during the episode, appropriate fluid repletion and feeding should be advised. Additionally continued monitoring of the characteristics of the stools is recommended in order to detect as early as possible, the excretion of blood and mucus, should it occur. Experimental infections of humans with *Shigella* indicate that dysentery is commonly preceded by watery diarrhea.<sup>13</sup>

We isolated *Shigella* from 9.8% of illnesses, a figure that is identical to that reported by Mata<sup>14</sup> after following, from 1964 to 1969, a cohort of 45 children of another rural community of Guatemala, Santa María Cauque. Thirty years ago rural Guatemalan children were mainly infected by *S. flexneri* 4, *S. flexneri* 6 and *S. dysenteriae* 2. Although there were isolates that belonged to 15 different serotypes, *S. flexneri* contributed with 71% of the strains, a figure that is similar to the 61% reported here by us, but

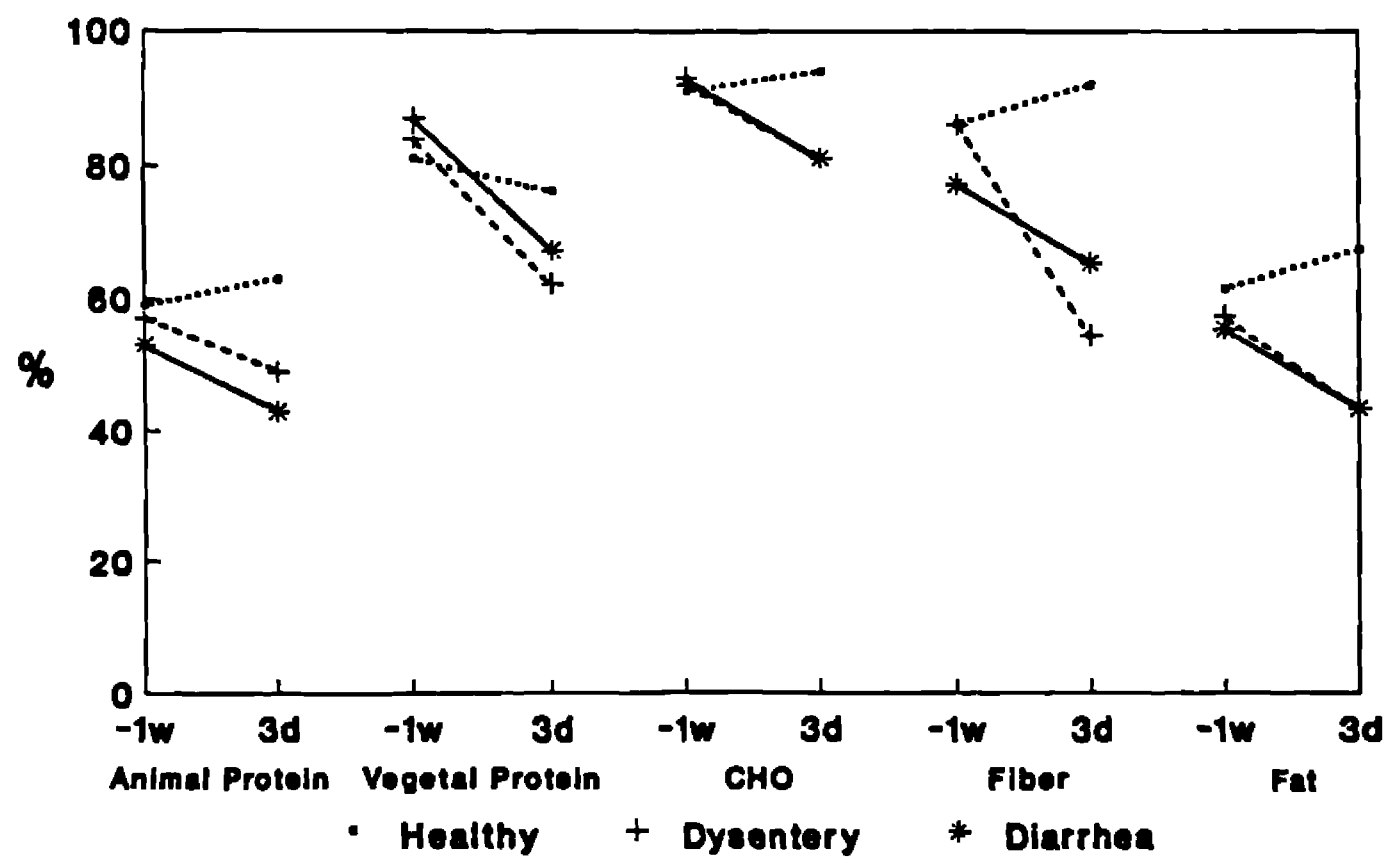


FIG. 4. Nutrient consumption (%) 1 week before and 1 to 3 days after infection with *Shigella*, in relation to outcome.

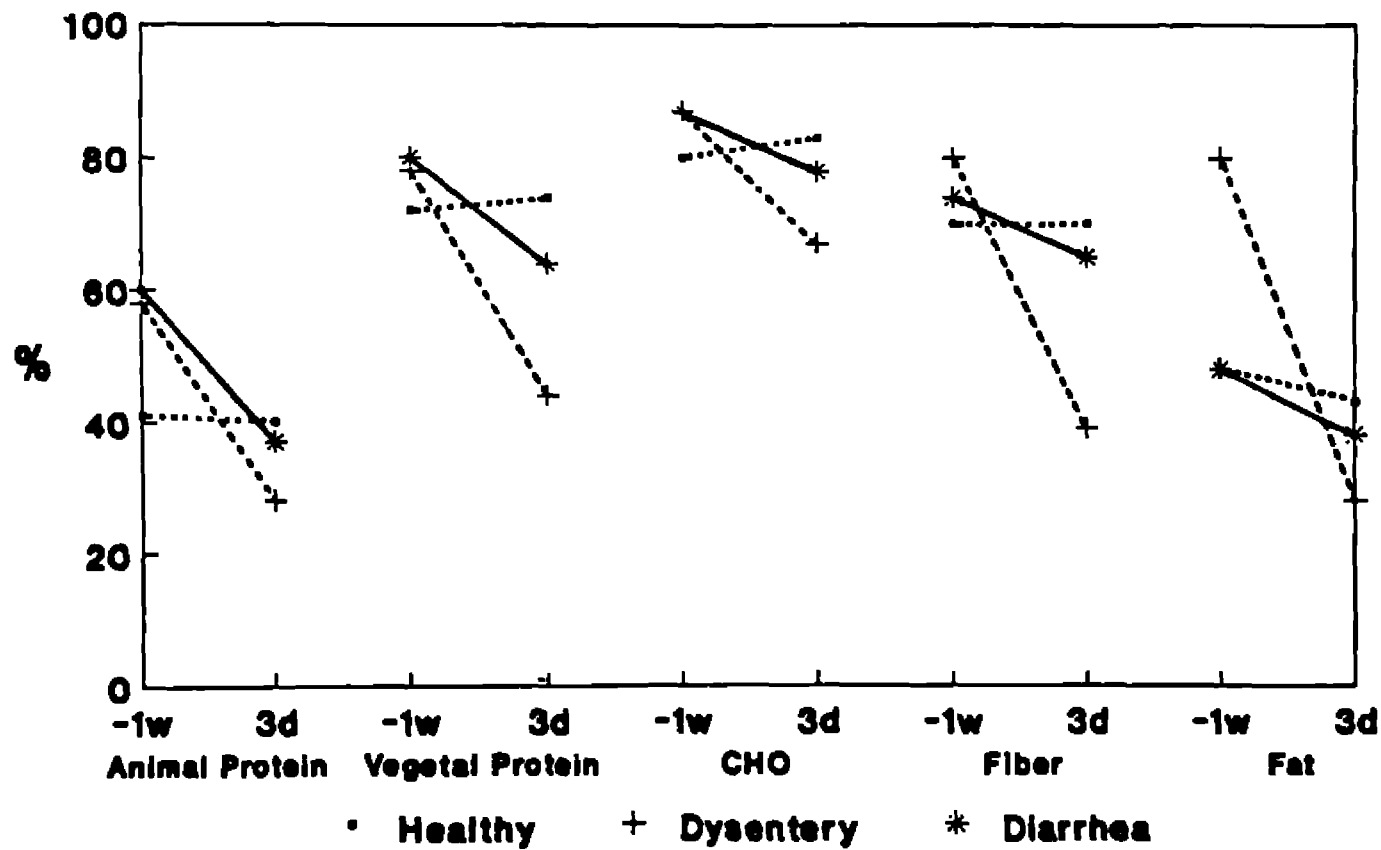


FIG. 5. Nutrient consumption (%) 1 week before and 1 to 3 days after infection with *C. jejuni*, in relation to outcome.

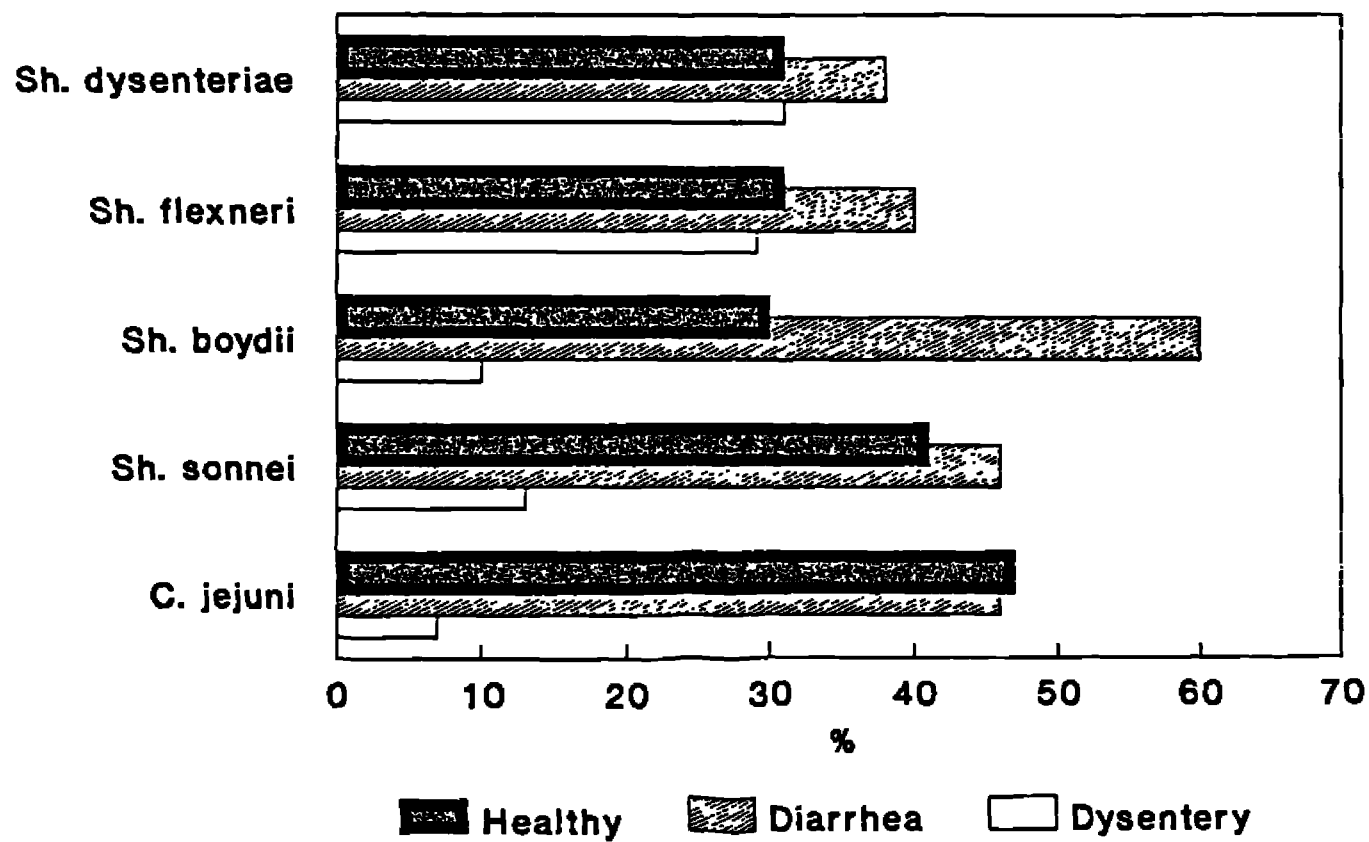


FIG. 6. Outcome of infections by the different species of *Shigella*.



higher than the one reported from Chile, 50%.<sup>12</sup> We isolated *Shigella* strains of 17 serotypes but again 3 serotypes (*S. flexneri* 6, *S. flexneri* 1 and *S. sonnei*) accounted for 61% of all isolates, and 4 serotypes, with the addition of *S. flexneri* 2, contributed 70%. This information supports the findings of Ferreccio et al.<sup>12</sup> who reported that two *flexneri* serotypes, 2a and 6, and *S. sonnei* were responsible for 80% of cases of shigellosis in their Chilean community and provides further evidence that preventive measures tailored to curtail the transmission of few *Shigella* serotypes would have an important impact on *Shigella* morbidity. Furthermore the majority of the *Shigella* isolates in hospitalized patients of Bangladesh,<sup>15</sup> Thailand<sup>16</sup> and Saudi Arabia<sup>17</sup> were also of the *flexneri* group.

The level of fecal contamination in rural Guatemala favors the persistence and transmission of enteric pathogens, such as *Shigella*. In Chile<sup>12</sup> 27% of the cohort children excreted *Shigellae*, compared with 39% in Santa María de Jesús; furthermore only 14 (14%) of the infected Chilean individuals suffered repeated infections whereas in Santa María de Jesús 59 (47%) did; of the individuals infected with *C. jejuni*, 44% had 2 or more infections. The high prevalence of repeated or multiple infections by different enteric pathogens could minimize the protective effect of specific preventive measures, such as vaccination, as indicated by the fact that recurrent infections were symptomatic when the individuals were coinfecting with other enteric pathogens in addition to *Shigella*. These findings underscore the need for comprehensive strategies to improve hygienic conditions of underprivileged communities of the developing world in order to reduce diarrheal morbidity.

We supported the participating families in terms of health education and provision of oral rehydration salts and antibiotics, factors that may have contributed to better case management. Despite this children who were infected with either *Shigella* or *C. jejuni* and who became sick tended to consume poorer diets than during the times when they were healthy (Figs. 4 and 5), suggesting that food withdrawal by child caretakers may still be a problem in the community and that food education measures may be useful in reducing the negative effects of diarrhea. On the other hand loss of appetite was reported in about 50% of sick individuals so that, even if food is offered to the child, intake may be reduced as reported recently by Rahman et al.<sup>18</sup> specifically for *Shigella*-associated dysentery.

Although the incidence of dysentery as well as the proportion of diarrheal episodes that were accompanied by the excretion of blood and mucus increased with age, the risk of developing dysentery after infection with either *Shigella* spp. or *C. jejuni* did not vary with age (Fig. 3), as it did not with nutritional status which deteriorates after the third semester of life. Age was important only in the case of *S. sonnei* infections;

ill subjects were younger than those who remained asymptomatic (Table 8). This observation may be explained by the development of specific immunity against the only serotype of *S. sonnei* and is supported by our findings of specific protection against symptomatic infection, especially dysentery, in repeated infections mainly of the *flexneri* serotypes (Table 6). The same explanation may be applicable to the *C. jejuni* situation, because we documented most of the infections during the first year of life. Passive immunity provided by breast milk may also affect the proportion of asymptomatic infections.<sup>19, 20</sup>

Dietary habits did not influence the outcome of *Shigella* infections. Fat consumption the week before infection was associated with *C. jejuni* dysentery. It may be that fat favors bacterial multiplication in contaminated foods or in the human intestine, as suggested for other microorganisms.<sup>21, 22</sup> This observation deserves further studies.

In conclusion we could not identify inherent host factors that play a determining role in the outcome of *Shigella* and *C. jejuni* infections. Because serotype-specific immunity seems to be important in limiting the expression of *Shigella* infections and, with the small number of *Shigella* serotypes responsible for the majority of dysentery cases, vaccination would seem to be an appropriate alternative. Nevertheless a holistic approach that includes improving water supplies, waste disposal and health education is necessary to reduce diarrheal morbidity among underprivileged communities where diarrhea patterns have not changed in the last 30 years. Meanwhile we consider that the surveillance of dysentery, of its associated etiologies and of their antibiotic susceptibility patterns continues to be important for better application of preventive measures and management algorithms, especially for areas of the world where diagnostic facilities are limited or nonexistent.

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## Announcements

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**Fourteenth Annual National Pediatric Infectious Disease Seminar, April 7 to 9, 1994** preceded by a Symposium on Management of Common Infections in Practice (April 6), Hyatt Regency Embarcadero Hotel, San Francisco, CA. Organized by John D. Nelson, MD, and George H. McCracken Jr, MD, The University of Texas Southwestern Medical Center at Dallas. Faculty: Ann Arvin, MD, Steven B. Black, MD, John S. Bradley, MD, Stephen Chartrand, MD, Heinz F. Eichenwald, MD, Charles M. Ginsburg, MD, George H. McCracken Jr, MD, John D. Nelson, MD, Georges Peter, MD, Eugene D. Shapiro, MD, Jane D. Siegel, MD, Diane W. Wara, MD.

20 CME credits (5 for Symposium, 15 for Seminar). Tuition for Seminar \$390 (\$275 for Residents, Fellows, allied health professionals and clinical pharmacists), no fee for symposium. Contact Department of Continuing Education, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75235-9059. Tel (214) 648-2166, FAX (214) 648-2317.

### 1994 PEDIATRIC INFECTIOUS DISEASES EXAMINATION

The American Board of Pediatrics (ABP) will administer the first Certifying Examination in Pediatric Infectious Diseases on Tuesday, November 15, 1994.

For new applicants, regular registration begins February 1, 1994, and extends through March 31, 1994. The current subspecialty application fee (\$1185) is reviewed annually and is subject to increase. The application fee must accompany the completed application and be postmarked by March 31, 1994. Requests for applications received before February 1, 1994, will be held on file and application material will be sent on February 1. However, any qualified new candidate who does not receive the material by mid-February should request it from the ABP. Late registration begins April 1, 1994. The current subspecialty late registration fee (\$1410, which includes a \$225 nonrefundable late fee) is reviewed annually and is subject to increase. The final deadline for applications is April 30, 1994. Applications postmarked after this date will not be accepted for the 1994 examination. Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Infectious Diseases. Please contact the ABP for eligibility requirements. Please direct inquiries to: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1651. Telephone: (919) 929-0461, Facsimile: (919) 929-9255.