Persistent Diarrhea in a Cohort of Israeli Bedouin Infants: Role of Enteric Pathogens and Family and Environmental Factors

Drora Fraser, Ron Dagan, Nurith Porat, Joseph El-On, Soliman Alkrinawi, Richard J. Deckelbaum, and Lechaim Naggan

This study examined the role of enteric pathogens and infant, family, and household characteristics in persistent diarrhea. Bedouin infants from southern Israel were followed from birth to age 18–23 months. During monthly home visits, stool samples were obtained, and feeding practices and history of diarrhea were determined, and at age 3 months, an environmental assessment was done. Diarrhea surveillance was either via a network covering all community health care facilities or via weekly interviews with the mother. None of the enteric pathogens examined, including Cryptosporidium parvum and enteroaggregative Escherichia coli, were associated with persistent diarrhea. In multivariate analyses, age at first diarrheal illness and maternal age and maternal education were independently and significantly associated with the risk of persistent diarrhea. These data suggest that persistent diarrhea is a clinical entity that may be related less to a specific enteric pathogen and more to the health experiences of children and their home environment.

Diarrhea, a major cause of morbidity in children in developing countries [1, 2], is also associated with high health care costs in developed areas [3]. Persistent diarrhea, defined by the World Health Organization as illness beginning as acute diarrhea lasting ≥14 days [4], is associated with retardation of growth, morbidity, and mortality [5, 6] and is a frequent finding in malnourished children [7]. Persistent diarrhea is responsible for 3%–23% of diarrheal illnesses in various locations [8] and has been estimated to be responsible for ∼50% of all child diarrhea deaths in northeast Brazil [9, 10].

Different enteric pathogens are associated with persistent diarrhea. These include rotavirus, Shigella and Campylobacter species, Cryptosporidium parvum, and enteroaggregative Escherichia coli (EAggEC) [11–16]. The results, however, are inconsistent between studies and between populations. For example, while EAggEC were identified more frequently in persistent than in acute diarrhea in India [13], Bangladesh [14], and Mexico [17], in other studies from Bangladesh [15], Peru [16], and in Cambodian refugees [18] these differences were not found. Similarly Cryptosporidium parvum was detected more frequently in persistent diarrhea in Bangladesh [15] and Guinea Bissau [19] but not in Peru [16]. The lack of consistent results regarding the cause of persistent diarrhea by specific enteric agents raises the possibility that other factors associated with the children, their family, or their immediate environment may contribute to the risk of developing persistent diarrhea [20].

The Bedouin people who were the subjects of this study live in the Negev region in southern Israel. This population is in transition from a seminomadic to a settled, semiurban lifestyle. Since the establishment of the State of Israel and the closure of international borders in the area, the Bedouins in Israel who were desert nomads have become more settled and are undergoing a process of urbanization [21]. However, despite recent changes in lifestyle, the rates of hospitalizations for infectious diseases of infants and young children in this population are several fold higher than for the largely urban Jewish population living in the same geographic region and served by the same health care services [22]. Thus, Bedouin infants <1 year old have nearly a 6-fold risk for hospitalizations (odds ratio [OR], 5.6; 95% confidence interval [CI], 4.9–6.4 P < .0001) when compared with Jewish infants; while in the second year of life, the risk is 2-fold (OR, 2.0; 95% CI, 1.6–2.4; P < .0001).
This study examined the role of enteric pathogens as well as infant, family, and household characteristics in persistent diarrhea detected in the community and in infants and young children from a newly urbanized population.

Methods

Study location. This study was conducted between November 1989 and July 1994 in a town 35 km north of Beer-Sheva, the capital of the Negev. The community was chosen because it was the first urban settlement of Bedouin tribes and it has well-developed community preventive and curative health care facilities. The town was first settled in the early 1970s and has grown from 6000 inhabitants in 1976 to 28,000 in 1995 [23]. The population growth is largely due to the birth rate, which is the highest for any population group in Israel [23]. The Negev region in the southern area accounts for more than half the landmass of the country and is a sparsely populated semiarid desert, housing only 7.6% of the Israeli population. The Bedouins constitute about a quarter of the Negev population. The climate is desert-like with a mean annual daily temperature of 20°C and average annual rainfall of ~140 mm.

Intake procedures. From November 1989 to December 1993, infants of families from the town born at the Soroka University Medical Center in Beer-Sheva were enrolled in the study. The medical center is the only tertiary care institution in the area and provides both delivery and postdelivery care. All Jewish and >99% of Bedouin women deliver at this hospital. The study intake was designed to ensure an even distribution of births during the different seasons of the year. A total of 263 healthy infants, birth weight >2500 g, were recruited; however, 12 (4.6%) of the families who signed informed consent could not be located or the home could not be reached on a regular basis, leaving 251 infants in the study.

Routine follow-ups. Throughout the study, monthly home visits were made and questionnaires were completed relating to feeding habits of the infant, his or her health in the preceding month, and health of family members. At age 3 months, an environmental assessment was done that included observations of environmental conditions of the home and yard and the presence of animals. In addition, the physical conditions of the home and availability of water, toilet facilities, and electricity were noted. Other observations included the hygienic condition of the infant, kitchen, home, and yard.

Each month, mothers were asked to place 2 consecutive infant stool specimens in tubes containing phenol-alcohol-formaldehyde (PAF) [24] and another stool sample into a tube without PAF. All tubes were refrigerated until collection within 48 h. Of the samples for collection during routine surveillance, 93.2% were obtained. Mothers who did not have refrigerators (23%) kept the samples in a refrigerator at a relative’s or neighbor’s home. Stool samples were delivered in an icebox to the laboratories at Soroka University Medical Center for testing.

Parasitology studies were done on all routine monthly samples and on diarrhea samples. Bacteriology and rotavirus testing were done on all diarrhea samples and on a random 1 in 4 sample of the monthly routine specimens. Adenovirus and astrovirus were tested only for the first 164 children in the study and were not sought in later samples due to the low yield obtained. Wet smears were used for detection of *Giardia lamblia* cysts. Modified acid-fast staining was used for detection of *C. parvum* oocysts; positive samples were confirmed by immunofluorescent assays (Merifluor cryptosporidium indirect immunofluorescent detection procedure; Meridian Diagnostics, Cincinnati). Because parasitology samples were collected in pairs, detection of *Giardia* or *Cryptosporidium* species in one of the samples was considered a positive result. Stool cultures for *Campylobacter, Shigella,* and *Salmonella* species were done by routine laboratory methods.

For *E. coli,* specimens were inoculated onto MacConkey’s agar and incubated for 18–24 h at 37°C. Five lactose-fermenting colonies were picked, confirmed as *E. coli,* and frozen at −72°C in sheep erythrocytes until DNA extraction was performed. *E. coli* categories were determined by DNA hybridization with radioactive probes prepared as described in Levine et al. [25]. The following *E. coli* categories were examined: EAggEC, diffuse adherent, localized adherent enteropathogenic, enterotoxigenic expressing heat-stable toxin (ETEC-ST), enterotoxigenic expressing heat-labile toxin (ETEC-LT), enterotoxigenic expressing both toxins (ETEC-ST/LT), enterohemorrhagic, and enteroinvasive (EIEC).

Rotavirus, enteric adenoviruses, and astrovirus were examined by an ELISA developed at the Centers for Disease Control (Atlanta) according to methods previously described [26–28]. Only results of stool samples for which parasitology and bacteriology testing were done are included in the present analysis.

Diarrhea morbidity surveillance. From November 1989 to December 1992, diarrhea morbidity was identified via a surveillance network that was established at all health care locations in the study area. Study nurses were stationed at the local primary health care clinics, the local rehydration unit, and at the well infant and mother clinics (Ministry of Health) responsible for the immunization program and for monitoring of growth and development. Mothers of infants in the study were issued special cards with which they identified themselves to study personnel and that enabled faster medical attention. These cards were presented to community clinics associated with the study and to the hospital emergency room. This morbidity surveillance system was supplemented by maternal reports at monthly home visits (method 1). From January 1993 to the end of the study (July 1994), after the primary health care clinic and rehydration unit nurse left the project, morbidity was ascertained weekly by interviewers trained to inquire about diarrhea by a home visit (85% of homes) or by telephone interview (15% of homes; method 2) and by information obtained at the monthly home visits.

All sick infants were examined by health care personnel and, when diarrhea was diagnosed, an episode form was completed. In addition to routine monthly samples, stool samples were also obtained for all diarrhea episodes as soon as they were identified and at 7- to 10-day intervals thereafter, up to 7–10 days after each episode. During diarrhea episodes, 73.0% of the samples that should have been obtained were collected.

Definitions and data analysis. An episode of diarrhea was defined as the passing of unformed stools (watery, mucoid, or bloody) ≥4 times in a 24-h period for infants <1 month old and ≥3 times in a 24-h period for older children. A new episode of diarrhea was preceded by 3 diarrhea-free days. Persistent diarrhea was defined as an episode beginning as acute illness and lasting ≥14 days. A stool sample was defined as “onset” if obtained on any of the first 3 days of symptoms. Routine monthly (non-diarrhea) samples
were defined as samples obtained up to 1 week before a diarrhea episode or those obtained ≥1 week from the last day of diarrhea. Stool samples collected at other times were excluded from the present analysis.

Means were compared using Student’s t test or analysis of variance (for a 3-group comparison) with Scheffe test for a posteriori testing between groups. For contingency table analysis, χ² or Fisher’s exact test was used as appropriate. Rates were compared according to the method outlined by Smith and Morrow [29]. ORs and 95% CIs were computed, and multiple logistic regression was used to determine associations between persistent diarrhea and suspected risk factors. Pearson’s correlation coefficients were computed to determine the association between maternal age and education and environmental factors, feeding practices, and illness parameters.

Results

A total of 234 (93%) of the 251 children starting follow-up are included in this analysis. Most of the children, 192 (82.1%), completed ≥2 years of follow-up; 27 (11.5%) completed 20–22 months and 15 (6.4%) completed 18 or 19 months of follow-up. Total follow-up was 5339 child-months (445 child-years): 29 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes. Of those children, 53 had 1 episode, 20 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes. Of those children, 53 had 1 episode, 20 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes. Of those children, 53 had 1 episode, 20 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes. Of those children, 53 had 1 episode, 20 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes. Of those children, 53 had 1 episode, 20 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes.

Table 1. Number and rates of diarrhea episodes per 100 months of follow-up recorded in the study population by two different surveillance methods (age of the child at onset and length of diarrheal illness).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Method 1</th>
<th>Method 2</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>13.4 (123)</td>
<td>9.2 (38)</td>
<td>12.1 (161)</td>
</tr>
<tr>
<td>6–11</td>
<td>24.6 (235)</td>
<td>20.1 (85)</td>
<td>23.2 (320)</td>
</tr>
<tr>
<td>12–17</td>
<td>18.6 (177)</td>
<td>21.3 (90)</td>
<td>19.4 (267)</td>
</tr>
<tr>
<td>18–23</td>
<td>9.7 (91)</td>
<td>12.5 (40)</td>
<td>10.5 (131)</td>
</tr>
<tr>
<td>All ages</td>
<td>16.6 (626)</td>
<td>16.0 (253)</td>
<td>16.5 (879)</td>
</tr>
<tr>
<td>Length of illness (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–7</td>
<td>9.2 (347)</td>
<td>9.8 (154)</td>
<td>9.4 (501)</td>
</tr>
<tr>
<td>8–13</td>
<td>4.2 (156)</td>
<td>3.9 (62)</td>
<td>4.1 (218)</td>
</tr>
<tr>
<td>≥14</td>
<td>3.3 (123)</td>
<td>2.3 (37)</td>
<td>3.0 (160)</td>
</tr>
</tbody>
</table>

NOTE. Rates were compared to Smith and Morrow [29]. No statistically significant differences were found between the 2 methods for rates of reporting diarrheal illness either by age at onset or by length of illness.

29 had 2, 6 had 3, and 6 children had 4–7 persistent diarrhea episodes.

Although, on average, persistent diarrhea constituted only 18.2% of all diarrhea episodes, 45.2% of all days of illness were from persistent episodes (figure 1), with the highest rates recorded at age ≤3 months. At this age, however, we found no enteric parasites or viruses, ETEC-ST, EIEC, or shigellae. Other enteric agents were detected at lower rates at ≤3 months than at older ages.

The rates at which enteric agents were detected were compared between those for non-diarrhea routine stool samples and stools samples obtained at diarrhea onset (table 2). C. parvum, Campylobacter species, and rotavirus were found more frequently in samples obtained during diarrheal illness. When detection rates of all ETEC-expressing heat-stable toxin colonicies were considered together, they were found significantly more frequently in diarrhea-onset stools (4.5%) than in routine non-diarrhea samples (1.7%; OR, 2.76; 95% CI, 1.03–7.86). In contrast, G. lamblia was more often detected in routine than in diarrhea specimens.

Only 40.3% (509/1262) of routine stools and 35.8% (68/190) of diarrhea-onset stool samples were free of any of the enteric agents tested for in this study. Thus, even in routine, non-diarrhea samples, in 6 of any 10 samples at least 1 enteric agent was detected. In addition, in 33.8% (254/752) of all routine samples positive for an enteric pathogen, ≥2 pathogens were detected. In onset samples, ≥2 pathogens were detected in 30.5% (36/118) of all samples in which an enteric agent was detected.

No significant changes in the direction or magnitude of the difference between routine and onset samples was found when the analysis shown in table 2 was repeated for samples containing only a single pathogen. The exception was for Shigella species where the difference became statistically significant.
Figure 1. Distribution of days ill with persistent diarrhea and persistent diarrhea by age in months.

Age in months

(OR, 15.4; 95% CI, 1.09–430.7; \( P = .037 \)). The statistically significant associations shown in Table 2 were not found because the lower number of observations in the analysis was restricted to samples with single organisms.

In order to define the enteric pathogens associated with persistent diarrhea, the detection rate of enteric agents was determined in samples obtained at the onset of diarrhea according to length of illness (Table 3). None of the enteric pathogens were identified more frequently in persistent diarrhea. All ETEC-ST colonies combined were detected in 9.5% of persistent samples versus in 1.7% in non-diarrhea stools (\( P = .057 \)). *C. parvum* was found significantly more often in episodes that lasted ≤14 days and was detected only in 1 of the 52 sets of samples obtained during persistent illness. Rotavirus and *Campylobacter* species were associated with episodes lasting ≤1 week, while *Campylobacter* species and astrovirus were associated with illness lasting 8–13 days. When the analysis was repeated only for samples in which a single pathogen was detected (66.2% of routine and 69.5% of onset samples), no significant change in the magnitude or direction of the differences between the diarrhea groups and routine samples was found, but the statistical significance of the differences was not retained due to the decreased number of observations. Shigellae were an exception and were significantly associated with diarrhea lasting 8–13 days (\( P = .003 \)).

To investigate the possibility that sequential infections may contribute to the occurrence of persistent diarrhea, we examined persistent episodes for which stool samples were obtained during the first week of illness and at least once during one of the following 2 weeks. In 22.2% (14/63) of those episodes, different enteric pathogens were detected between the first week and subsequent weeks.

Other factors that may contribute to the incidence of persistent diarrhea, such as infant, family, and environmental factors, were also sought. In order to do so, the status of each child was defined according to the longest episode of diarrhea experienced. Ninety-four children experienced ≥1 persistent diarrhea episode. Sixty-six children had ≥1 diarrhea episode lasting 8–13 days and no episodes of persistent illness; 55 children had diarrhea episodes lasting ≤7 days. For 19 children, no diarrheal illness of any length was recorded. All results presented from here on refer to analyses that included each child only once, according to status defined by the longest diarrhea episode experienced by the child.

The mean number of diarrhea episodes experienced, the total days of illness, and the age at the first recorded episode were compared between the groups by the longest episode of diarrhea experienced (Table 4). All comparisons were statistically significant and showed clear trends. Thus, children who during follow-up had ≥1 persistent episode experienced the most diarrhea episodes (mean, 5.8), had the most days of illness (nearly 2 months in total), and had the first episode of diarrhea at the youngest age (mean, 4.7 months) compared with other children.
We assessed the relationship between infant, family, and environmental factors and persistent diarrhea (table 5). While young age at first diarrhea episode and low maternal age and education at enrollment were associated with increased risk for persistent diarrhea, children living in a hut or tent, the presence of an outdoor toilet, and breast-feeding in the second year of life lowered the risk for persistent diarrhea. The associations between dwelling type and maternal education and persistent diarrhea were close to statistical significance ($P < .10$). None of the other variables were associated with $\geq 1$ persistent illness: exposure to animals; physical and hygienic conditions of the dwelling, yard, and kitchen; food and kitchen utensil storage conditions; infant hygiene; weaning before age 3 months; and other family and infant variables, such as infant gender, family size, and birth order.

All of the variables in table 5 were available for stepwise analysis, but as shown in table 6, only age at first diarrhea illness and maternal age and education were independently and significantly associated with the risk of $\geq 1$ persistent diarrhea episode. Maternal education was close to statistical significance ($P = .064$). Since maternal age and education were inversely related (i.e., young mothers had more years of education), the presence of both variables was required in the final model. Increased maternal age or years of maternal education resulted in a lower risk of persistent diarrhea for the child as did a delay in the first diarrhea episode. Thus, for every 10-year increase in maternal age, the risk fell by 46%, and if a mother completed primary school, the risk for persistent diarrhea in her child fell by 44%.

Correlation coefficients were used to examine the association between maternal age and education and other factors. Low maternal education was associated with higher parity ($P < .001$) and lower years of maternal education was associated with increased risk for persistent diarrhea ($P < .001$). The risk for persistent diarrhea was close to statistical significance ($P = .05$) when we examined the relationship between infant, family, and environmental factors and persistent diarrhea (table 5). While young age at first diarrhea episode and low maternal age and education at enrollment were associated with increased risk for persistent diarrhea, children living in a hut or tent, the presence of an outdoor toilet, and breast-feeding in the second year of life lowered the risk for persistent diarrhea. The associations between dwelling type and maternal education and persistent diarrhea were close to statistical significance ($P < .10$). None of the other variables were associated with $\geq 1$ persistent illness: exposure to animals; physical and hygienic conditions of the dwelling, yard, and kitchen; food and kitchen utensil storage conditions; infant hygiene; weaning before age 3 months; and other family and infant variables, such as infant gender, family size, and birth order.

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.001), older age at enrollment (P < .001), more days of diarrhea (P = .036), more diarrhea episodes (P = .031), having an outdoor water supply (P = .010), having an outdoor toilet (P = .009), animal excrement in the yard (P = .001), infant appearing very or moderately dirty (P = .001), and breast-feeding beyond age 1 year (P = .001). Young maternal age at enrollment was also associated with more days of illness with diarrhea (P < .001) and more diarrhea episodes (P = .002) in the follow-up period.

### Discussion

Bedouins residing in southern Israel provide an opportunity to examine factors associated with pediatric persistent diarrhea in a community undergoing urbanization. This study, which followed infants from birth to age 2 years, investigated the associations between specific enteric agents, infant characteristics, family and environmental factors, and persistent diarrhea. While we did not find any association between persistent diarrhea and specific enteric pathogens, we found that the age at which a child experienced the first diarrhea episode and maternal age and education were strongly associated with the risk of persistent diarrhea during the first 2 years of life.

Before age 3 months, persistent diarrhea was responsible for 76% of days of diarrhea illness; persistent diarrhea accounted for 43% of all diarrhea episodes detected. Similar findings of higher rates of detection of persistent diarrhea in the very young have come from India, Bangladesh, and Guatemala [13, 14, 30]. In the very young, much persistent diarrhea (sometimes termed intractable diarrhea of infancy) is believed to result from milk protein intolerance either as a result of exposure to cow’s milk or soy protein or following an infection [31]. In this population, breast-feeding is highly prevalent and continues into the second year of life accompanied, however, in half of the children by supplemental milk-feeding from age 2 months. We examined the prevalence of enteric agents before age 3 months and found that most enteric agents were either nondetectable or were detected at much lower levels than in older children. The low prevalence of enteric agents at this age is probably due to the combined effects of the passive protection young infants have from their mothers and from lower exposure rates. This finding together with the high rates of milk supplementation given at an early age suggest that it is unlikely that a high proportion of persistent diarrhea episodes at this age is due to specific enteric pathogens, and other causes need to be sought.

Our surveillance methods may have underestimated the overall number of episodes of diarrhea in the community, although both (one passive—relying on use of health care services and one active—weekly surveillance) yielded similar rates of diarrhea both by age at onset and by length of episode.

Several enteric agents were detected more frequently in stool samples obtained during diarrheal illness: *C. parvum*, *Campylobacter* species, rotavirus, and *ETEC* expressing heat-stable toxins. These enteric agents have been associated with diarrheal illness in pediatric and adult populations worldwide [15, 19, 32, 33]. In contrast *G. lambia* in this study was found more frequently in non-diarrhea than in diarrhea specimens. Our findings, which are similar to those from Guinea Bissau and Bangladesh [15, 19], question the role of *Giardia* as a pathogen in areas in which diarrhea is endemic [34].

In our search for enteric agents associated with persistent diarrhea, we did not detect higher rates for any of the enteric agents examined. EAggEC, which have been implicated in persistent diarrhea in India [13], Bangladesh [14], and Mexico [17], were detected frequently both in non-diarrhea (26%) and in diarrhea-related samples (20.3%–33.3%). This *E. coli* category was the enteric agent most frequently detected in the Bedouin pediatric population but was unrelated to diarrheal illness. This is consistent with studies in Bangledeshi, Peruvian, and Cambodian refugee children that did not find an association between EAggEC and persistent diarrhea [15, 16, 18]. In our study, DNA probes were used to define the different *E. coli* categories and may contribute to the difference between our findings and those of other studies. In most published studies in which EAggEC were more frequently detected in persistent

### Table 5. Association between selected maternal, infant, and household factors and persistent diarrhea in Bedouin children by univariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first diarrhea episode (months)</td>
<td>−0.2177</td>
<td>0.80</td>
<td>0.74–0.87</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal age at enrollment (years)</td>
<td>−0.0576</td>
<td>0.94</td>
<td>0.91–0.98</td>
<td>.004</td>
</tr>
<tr>
<td>Child breast-fed beyond 1 year of age (1 = yes, 0 = no)</td>
<td>−0.6427</td>
<td>0.53</td>
<td>0.31–0.90</td>
<td>.019</td>
</tr>
<tr>
<td>Outdoor toilet (yes = 1, indoor = 0)</td>
<td>−0.8139</td>
<td>0.44</td>
<td>0.20–0.99</td>
<td>.048</td>
</tr>
<tr>
<td>Living in hut or tent (yes = 1, house = 0)</td>
<td>−1.0658</td>
<td>0.34</td>
<td>0.11–1.06</td>
<td>.064</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td>−0.0531</td>
<td>0.95</td>
<td>0.89–1.01</td>
<td>.088</td>
</tr>
</tbody>
</table>

**NOTE.** OR, odds ratio; CI, confidence interval.

### Table 6. Multivariate logistic regression defining the risk factors associated with persistent diarrhea in Bedouin children.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first diarrhea episode (months)</td>
<td>−0.2155</td>
<td>0.81</td>
<td>0.74–0.88</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal age at enrollment (years)</td>
<td>−0.0627</td>
<td>0.94</td>
<td>0.90–0.98</td>
<td>.006</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td>−0.0699</td>
<td>0.93</td>
<td>0.87–1.00</td>
<td>.064</td>
</tr>
</tbody>
</table>

**NOTE.** OR, odds ratio; CI, confidence interval.
diarrhea than in subjects with acute diarrhea or in controls, the HEp-2 assay was used. However, in one prospective study from Peru in which the HEp-2 assay was used, no association between EAggEC and persistent diarrhea was found [16].

While *C. parvum* was associated with diarrhea in general and with diarrhea episodes lasting <13 days, it was only detected in 1 of the 52 sets of stool samples obtained at the onset of persistent diarrhea. This finding contradicts results from other studies in which this enteric agent was associated with persistent diarrhea [15, 19] but is in agreement with a report that failed to find association between *C. parvum* and persistent diarrhea [16].

Most available data on the role of enteric pathogens in persistent diarrhea are from studies in developing populations. The Bedouins studied differ in that they have access to piped water and to modern preventive and curative medical services. The Bedouin population should be considered as one that is intermediate between developing and developed populations as indicated by their transition from seminomadism to urbanization. Thus, our results may not be directly applicable to developing populations. Nevertheless, our findings add to the knowledge of geographic and intrapopulation differences regarding pathogenicity of various enteric pathogens around the globe. Those differences may be related to density of exposure, host characteristics (e.g., extent of breast-feeding and malnutrition), or to strain differences in different areas. Answers for these geographic differences may be obtained from multipopulation studies with unified protocols and standardized laboratory methods.

Regardless of enteric pathogens, factors associated with the child’s immediate environment and diarrhea experience contribute to the risk of persistent illness. Maternal education and age were both associated with reduced risk for persistent illness in our population and in others. In Zaire, for example, education was strongly and inversely associated with risk of diarrhea [35], while maternal age was inversely related to diarrhea in Cali, Columbia [36]. In a study in Guinea Bissau, fewer mothers of children with diarrhea had attended school than the mothers of controls [19]. Low levels of education and young maternal age were risk factors for persistent diarrhea in Burma and Chile, respectively [37, 38]. Thus, the association between maternal education and age are consistent between different populations around the world.

When the correlations of maternal age and maternal education with other factors were examined in our study, it became apparent that maternal age and education were strongly associated with variables related to living conditions, the overall diarrhea experience of the child during the observation period, household hygiene practices, family size, and breast-feeding practices. We have little doubt that these factors reflect the overall level of knowledge and behavior in the home, including habits that are related to the prevention and treatment of illness, in particular diarrhea. Maternal practices during diarrheal illness were recently shown to affect the length of diarrhea episodes in a study in Kenya [39].

In addition to maternal age and education level, we found that the child’s experience of diarrhea at a young age was the strongest risk factor for persistent diarrhea. The child’s age at first diarrhea episode may act as an indicator for the overall diarrhea experience of the child during the first 2 years of life. Thus, those with first illness at a younger age will accumulate more episodes and more days of illness. Age at first diarrhea episode may also be an expression for the density of exposure and for diarrhea treatment provided. In Italy, early onset of diarrhea was associated with increased incidence of persistent diarrhea in hospitalized children [40], while in Bangladesh, recent diarrhea episodes were associated with persistent diarrhea in a case-control study [41].

An important predictor of persistent diarrhea in developing countries is malnutrition [18, 42, 43]. In our study, anthropometric measures were obtained at the maternal and child health clinic, usually during an immunization visit unrelated to illness. These data therefore cannot be used to investigate the role of undernutrition as a predictor for persistent diarrhea in the present study.

After reviewing the available data, we propose that persistent diarrhea is a clinical entity that may be related less to a specific enteric agent and be more reflective of the health experiences of a given child and the child’s home environment. It is possible that an infectious event initiates this process, resulting in malaise, loss of appetite, and changes in the intestinal mucosa. This leads to loss of fluids and difficulties in nutrient absorption. In the weakened nutritional and immunologic state resulting, one of the explanations for persistent diarrhea raised by Penny [44] may come into play, namely a secondary event or sequential infections may cause the prolonged illness. In populations such as ours, where the background level of exposure to enteric agents is high (60% of non-diarrhea routine samples contained one of the enteric pathogens examined), the probability of secondary events or sequential infections resulting in persistent illness is high as shown by our data. This would be especially true in a home environment in which preventive practices are not practiced. This hypothesis is consistent with data indicating lack of consistent association between specific enteric agents and persistent diarrhea found in different populations and different studies. It is also consistent with data showing associations between caregiver characteristics and persistent illness that have been described in studies worldwide. The caregiver characteristics influence both the degree of exposure the child has to various enteric agents and the modes of treatment undertaken.

In conclusion, shifting attention from the search for a specific enteric agent that causes persistent diarrhea to examining the immediate environment of the children themselves will allow us to gather appropriate data to plan community-based interventions. The aim of these interventions would be to reduce the heavy burden of persistent diarrhea and its consequences in high-risk populations.

References


