Pathogenicity and Convalescent Excretion of *Campylobacter* in Rural Egyptian Children

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*Campylobacter* infection in developing countries has not received much public health attention because of the observation that infections are not associated with disease beyond the first 6 months of life. A cohort of 397 Egyptian children aged less than 3 years, who were observed twice weekly during 1995–1998, experienced an incidence of 0.6 episodes of *Campylobacter* diarrhea per child-year. A total of 13% of the *Campylobacter* diarrheal episodes were characterized by severe dehydration. Age-specific incidence rates (episodes per year) were 0.9 in infants aged less than 6 months, 1.5 in those 6–12 months, and 0.4 and 0.2 in the second and third years of life, respectively. Convalescent excretion of *Campylobacter* after a diarrheal episode might be enhancing transmission and contributing to this high incidence. Observed risk factors for *Campylobacter* diarrhea were poor hygienic conditions and the presence of animals in the house. Regardless of the child’s age, a first infection by *Campylobacter* was associated with diarrhea (odds ratio = 2.45; 95% confidence interval: 1.61, 3.71); however, subsequent infections were associated with diarrhea only in children aged less than 6 months. This observation that natural infection did not confer protection during the first 6 months of life poses a challenge to vaccine development. *Am J Epidemiol* 2001;154:166–73.

*Campylobacter* species are one of the leading causes of diarrheal illness worldwide with as many as 400 million cases annually (1). The epidemiology of *Campylobacter*-associated diarrhea appears to differ between developed and developing countries. In the developed world, both children and adults are at risk for *Campylobacter* infection, and transmission of the organism has been associated with the consumption of unpasteurized milk, undercooked meats, contaminated water, and travel to *Campylobacter* endemic areas (2–6). In contrast, *Campylobacter* is endemic in the developing world, and infection is usually limited to children, suggesting that a high level of exposure in early life leads to the development of protective immunity (7–9). This is supported further by the finding that, irrespective of symptoms, children aged over 6 months of age in developing countries frequently have comparable rates of *Campylobacter* excretion, and that children have decreasing illness/infection ratios as they age (8–16). Infection rates are much lower in the developed world with reports of 80 cases per 100,000 population in a developed nation compared with up to 40,000 cases per 100,000 per year in children aged less than 5 years from less developed countries (8–10, 17–21). The duration of excretion of *Campylobacter* after infection is also reported to differ between the two settings. The organism is shed for an average of 2–3 weeks after cessation of diarrheal symptoms in cases from the developed world compared with durations as short as 1 week in children from developing areas (9, 21–23).

Poor hygiene and suboptimal water sanitation are often linked to childhood diarrheal illness in less developed settings. Environmental conditions generally vary with season and climate. Additionally, maternal hygiene behaviors relating to child-care practices, such as feeding, hand washing, and cleaning, are influenced by the age of the child and generally change as the child ages. These time-variant behaviors and changing environmental conditions influence the child’s risk of diarrhea. Most of the past reports investigating the epidemiology of *Campylobacter* were based on prevalence studies (11–14). Such studies do not take into consideration the influence of past exposure on current susceptibility and the seasonality of the disease. Another weakness in the literature on *Campylobacter* diarrhea is that the few published community-based cohort studies have used only the baseline characteristics of the population to identify risk factors for the disease rather than re-collecting data on the hygiene conditions in the households at regular intervals throughout the study (8, 10).

Between February 1995 and February 1998, we conducted a community-based longitudinal study of diarrhea in...
rural Egyptian children. Using this resource, the present study was undertaken to study the epidemiology of *Campylobacter* and to identify potential risk factors for *Campylobacter* diarrhea. In addition, we evaluated whether there is an association between excretion of *Campylobacter* and the occurrence of diarrheal symptoms (pathogenicity) and whether there is prolonged shedding of *Campylobacter* after a symptomatic infection.

**MATERIALS AND METHODS**

**Study population**

The study was conducted in the Abu Homos district of the Beheira Governorate in Egypt. Two contiguous villages, identified as 820 and 830, approximately 40 km southeast of Alexandria were selected for the study. Located in the Nile Delta, this district has an agrarian economy with cotton and rice as the main crops.

**Cohort assembly**

After mapping and numbering the houses of the two villages, we conducted a door-to-door census in which demographic characteristics of the families and baseline socioeconomic data were collected. Beginning in February 1995, children under the age of 24 months living in either of the two study villages were eligible for study enrollment. Thereafter, only new births were enrolled into the study until September 1997. Subjects were followed until they were aged 36 months or until February 1998, whichever came first. Written informed consent was obtained from the parent or guardian of each child before enrollment. Human subject guidelines of the US Departments of Defense and of Health and Human Services were followed throughout the study.

**Epidemiologic surveillance**

Beginning in February 1995, all study subjects were visited in their homes twice weekly by trained fieldworkers. At each visit, a history of gastrointestinal symptoms since the last scheduled visit was obtained. If loose or liquid stools were reported, a rectal swab and a stool specimen were obtained and a physician examined the child. For children aged under 1 year, a detailed dietary history with reference to breastfeeding and introduction of supplementary liquids and solids was obtained at each visit. If a visit was missed because of the absence of the child or the caretaker, a revisit was attempted the following day. The surveillance enabled monitoring of deaths and out-migrations, which were censoring events for follow-up. Of the scheduled twice-weekly visits, 95 percent were successfully completed, and rectal swab specimens were obtained from all children who reported having loose or liquid stools at the time of the visit.

Cross-sectional surveys of the cohort were conducted at 2-month intervals over the 3-year period. In these surveys dietary information was collected for all children under surveillance at that point of time. In addition, rectal swabs and stool specimens were collected from the children irrespec-

**Laboratory evaluation**

After collection, rectal swabs were immediately placed in Cary-Blair medium and stored on ice packs along with the stool specimens and transported to the Abu Homos field laboratory where they were refrigerated. The specimens were then transported to Cairo twice each week to the US Naval Medical Research Unit-3 for microbiologic evaluation. Standard microbiologic methods were used to isolate *Salmonella, Shigella*, and *Vibrionaceae* (24). In addition, the swabs were plated on MacConkey’s medium, and five lactose-positive colonies were evaluated for both heat-labile enterotoxin and heat-stable enterotoxin *Escherichia coli*, using GM$_1$ ganglioside enzyme-linked immunosorbent assays (25, 26). For isolation of *Campylobacter*, fecal specimens were inoculated onto modified Skirrow’s medium and incubated at 42°C in a microaerophilic environment (5 percent O$_2$/10 percent CO$_2$) for 48 hours (27). Suspect colonies were evaluated for Gram’s stain morphology, motility, oxidase and catalase reactivity, and sensitivity to nalidixic acid (28). *Campylobacter* isolates were differentiated between *Campylobacter jejuni* (C. *jejuni*) and *Campylobacter coli* (C. *coli*) by hippurate hydrolysis (29). Commercial enzyme-linked immunosorbent assay kits were used to detect rotavirus in the stool specimens (Rotadawn; Meridian Diagnostics, Inc., Cincinnati, Ohio).

**Definition of events**

A “diarrheal day” was defined as passage of three or more loose or liquid stools in any 24-hour period (in addition, for breastfed infants, the mother had to state that the stools were less formed or more liquid than usual) or having at least one loose or liquid stool with the presence of visible blood. A diarrheal episode was defined to begin on the first day of loose or liquid stools after at least 3 consecutive nondiarrheal days. The episode was defined as completed when there were 3 consecutive nondiarrheal days after a diarrheal day. An episode of diarrhea was classified as *Campylobacter*
diarrhea, if Campylobacter was isolated at any time in the entire duration of the episode. Based on the clinical examination, dehydration was classified as “none,” “some,” or “severe” according to World Health Organization criteria (30). A child was considered to be breastfed if breast milk constituted any part of the child’s diet.

Analytical methods

To determine incidence rates we divided the number of episodes by the total person-time at risk. To identify risk factors that were time dependent, we linked all the 2-month and hygiene surveys to the twice-weekly surveillance. The survey information was assumed to be time invariant for the interval between two surveys. Crude relative rates were computed as a ratio of the incidence rates in the presence and absence of the factor under consideration. Incidence rates were compared using the Mantel-Haenszel test statistic for density follow-up studies (31).

Because the follow-up visits for a child are not statistically independent entities, it is necessary to account for the correlation between repeated observations. Generalized estimating equations were used to adjust for nonindependence of the diarrheal episodes for a child (32). We fit Poisson regression models to obtain relative rates adjusted for time-varying covariates and other potential confounding variables. Because the risk of Campylobacter diarrhea increased with age during infancy and subsequently decreased in the second and third years of life, the confounding effect of age was adjusted using a linear spline with knots at 12 and 24 months of age. Follow-up was aggregated over 1-month periods for each child in the models. Adjusted relative rates of diarrheal incidence were obtained by exponentiation of the parameter estimates of the independent variables. Empirical standard error estimates from the generalized estimating equation models were used to calculate the 95 percent confidence intervals of the estimated relative rates.

Case-control studies

To evaluate pathogenicity, a case-control analysis was performed on a subset of the cohort to examine the association between the occurrence of diarrheal symptoms and excretion of Campylobacter. Because a previous infection with Campylobacter alters the risk of acquiring a subsequent infection with the organism, it was necessary to restrict this analysis to newborns enrolled within the first 28 days of birth. Cases were defined as study subjects with diarrhea detected during the twice-weekly surveillance. Controls were defined as children without diarrhea who had cultures performed on fecal samples obtained during the routine 2-month survey visits. Both cases and controls with a prior history of a Campylobacter infection were excluded (either as a case or a control). Because the controls had a single fecal specimen collected at each visit for microbiologic workup, to avoid a bias of selectively detecting Campylobacter more frequently among cases as compared with the controls, only the microbiologic result of the first fecal specimen from each episode was included in the analysis.

A second case-control analysis was conducted to determine whether Campylobacter diarrhea is associated with prolonged convalescent excretion of Campylobacter. To study convalescent excretion, follow-up of Campylobacter diarrheal episodes alone is not sufficient, because it is possible that persistent detection of Campylobacter in the stool may result from intercurrent asymptomatic reinfections with the organism. In this case-control analysis, cases and controls were selected from the 2-month surveys (i.e., both cases and controls were asymptomatic). Cases were children who had no diarrhea but excreted Campylobacter, and controls were children who had no diarrhea and were not excreting Campylobacter. We postulate that, if there is prolonged excretion of Campylobacter after an episode of Campylobacter diarrhea, more cases (asymptomatic and Campylobacter excretors) in the 2-month surveys will have a history of Campylobacter diarrhea compared with the controls (asymptomatic and not excreting Campylobacter). On the other hand, if there was no chronic excretion but significant intercurrent asymptomatic infections after episodes of Campylobacter diarrhea, the odds of having a history of Campylobacter diarrhea for controls would be expected to be the same as the odds of a positive history of Campylobacter diarrhea in cases. A recent history of Campylobacter diarrhea was defined as a diarrheal episode within the past 30 days in which Campylobacter was isolated. Duration since exposure is defined as the duration between the end of the Campylobacter diarrheal episode and the date when the cases and controls were visited. For multiple episodes of Campylobacter diarrhea within the past month, the most recent episode is used to classify the duration since exposure. To eliminate prevalent and incubating infections that could be the cause for the excretion of Campylobacter identified in the 2-month surveys, persons having diarrheal symptoms on the survey day or having a diarrheal episode that started within 3 days following the survey visit were excluded from both the cases and the controls.

For case-control analyses, odds ratios were calculated to assess the association between exposure and case-control status. Proportions were statistically compared using the chi-square test or Fisher’s exact test when the data were sparsely distributed. To estimate adjusted odds ratios we used multiple logistic regression to control for the simultaneous confounding effect of several variables. Because the repeated visits for a child are not independent, we used generalized estimating equations to adjust for the correlation between repeated observations. To test whether pathogenicity or convalescent excretion of Campylobacter varied by age, we examined the statistical significance of an interaction term between exposure and age, entered into the model along with the main effects and confounding variables. Adjusted odd ratios were obtained by exponentiating the parameter estimate for exposure, and 95 percent confidence intervals were calculated from the standard error of the parameter estimate.

All statistical tests were interpreted in a two-tailed manner to estimate p values and confidence intervals. A p value of <0.05 was considered to be statistically significant.
RESULTS

Incidence

Of the 397 children that were enrolled in the study, 211 were enrolled within 28 days of birth. Losses to follow-up resulted from 13 deaths and 10 out-migrations that were detected in the twice-weekly surveillance. Over the 3-year period, there were a total of 3,477 episodes of diarrhea resulting in an incidence of 5.5 episodes of diarrhea per child per year. The diarrheal attack rates were highest during the first year of life with an incidence of 8.1 episodes per child per year as compared with 5.5 and 2.9 episodes per child per year during the second and third years of life, respectively. Enterotoxigenic *E. coli* was the most common pathogen isolated with an incidence of 1.5 episodes per child per year followed by *Campylobacter* with an incidence of 0.6 episodes per child per year. *Campylobacter* incidence rates declined with age from 1.2 to 0.4 to 0.2 episodes per child per year over the first 3 years of life. The incidence rate in the first 6 months of life was 0.9 episodes per child per year, which increased to 1.5 episodes per child per year in the second 6 months of life. Over the 3-year period, 366 episodes of *Campylobacter* diarrhea were detected with isolation rates consistently higher during the warmer months between May and August (figure 1).

Description of cases

Of the 366 episodes of *Campylobacter* diarrhea, 49 (13 percent) were associated with severe dehydration, and 15 (4 percent) were associated with bloody diarrhea. There was no difference in the proportion of severely dehydrated *Campylobacter* episodes across age groups in the first 3 years of life. *Shigella, Salmonella, rotavirus*, or enterotoxigenic *E. coli* was isolated as a copathogen in 133 (36 percent) of the episodes of *Campylobacter* diarrhea. Speciation was performed on 310 of the 366 *Campylobacter* isolates, with 251 (81 percent) being *C. jejuni*, 56 (18 percent) being *C. coli*, and three (1 percent) being mixed infections. Severe dehydration occurred in 29 (12 percent) cases of *C. jejuni* diarrhea compared with 10 (18 percent) of the *C. coli* infections. After excluding episodes with copathogens, we found that severe dehydration occurred in 18 (11 percent) of the *C. jejuni* episodes and four (12 percent) of the *C. coli* episodes.

Risk factors

As shown in table 1, village 830 experienced a higher incidence of *Campylobacter* diarrhea compared with village 820 (relative rate (RR) = 1.29; 95 percent confidence interval (CI): 1.01, 1.67; *p* < 0.05), and the incidence rates between May and August were significantly higher than those of the remaining months (RR = 2.34; 95 percent CI: 1.90, 2.89; *p* < 0.001). Breastfeeding did not appear to alter the risk of *Campylobacter* diarrhea (RR = 0.87; 95 percent CI: 0.64, 1.20), but having a flush toilet in the house was associated with a lower risk of *Campylobacter* illness (RR = 0.38; 95 percent CI: 0.15, 0.96; *p* < 0.05). Mere ownership of livestock or fowl was not associated with an increased

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TABLE 1. Adjusted relative rates for the associations between selected factors and the incidence of Campylobacter diarrhea, Abu Homos, Egypt, 1995–1998

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Characteristic present</th>
<th>Characteristic absent</th>
<th>Crude RR†</th>
<th>RR‡</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Village 830</td>
<td>0.62</td>
<td>0.53</td>
<td>1.18</td>
<td>1.29*</td>
<td>1.01, 1.67</td>
</tr>
<tr>
<td>Male</td>
<td>0.58</td>
<td>0.57</td>
<td>1.02</td>
<td>1.05</td>
<td>0.82, 1.35</td>
</tr>
<tr>
<td>Breastfed</td>
<td>0.88</td>
<td>0.27</td>
<td>3.24***</td>
<td>0.87</td>
<td>0.64, 1.20</td>
</tr>
<tr>
<td>May to August</td>
<td>0.95</td>
<td>0.39</td>
<td>2.42***</td>
<td>2.34***</td>
<td>1.90, 2.89</td>
</tr>
<tr>
<td>Educated mother¶</td>
<td>0.49</td>
<td>0.59</td>
<td>0.84</td>
<td>0.75</td>
<td>0.37, 1.51</td>
</tr>
<tr>
<td>Livestock#</td>
<td>0.56</td>
<td>0.66</td>
<td>0.84</td>
<td>0.86</td>
<td>0.64, 1.16</td>
</tr>
<tr>
<td>Fowl††</td>
<td>0.55</td>
<td>0.72</td>
<td>0.77</td>
<td>0.79</td>
<td>0.55, 1.15</td>
</tr>
<tr>
<td>No crowding§§</td>
<td>0.56</td>
<td>0.60</td>
<td>0.93</td>
<td>1.02</td>
<td>0.79, 1.33</td>
</tr>
<tr>
<td>Flush toilet</td>
<td>0.24</td>
<td>0.59</td>
<td>0.41*</td>
<td>0.38*</td>
<td>0.15, 0.96</td>
</tr>
</tbody>
</table>

Hygiene surveys¶¶

<table>
<thead>
<tr>
<th>Sleeping area</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals present</td>
<td>0.67</td>
<td>0.42</td>
<td>1.59*</td>
<td>1.71</td>
<td>0.93, 3.13</td>
</tr>
<tr>
<td>Feces on floor</td>
<td>0.43</td>
<td>0.45</td>
<td>0.97</td>
<td>0.96</td>
<td>0.59, 1.56</td>
</tr>
<tr>
<td>Uncovered garbage</td>
<td>0.43</td>
<td>0.44</td>
<td>0.96</td>
<td>0.99</td>
<td>0.69, 1.42</td>
</tr>
<tr>
<td>Cooking area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals present</td>
<td>0.53</td>
<td>0.37</td>
<td>1.41*</td>
<td>1.50*</td>
<td>1.02, 2.17</td>
</tr>
<tr>
<td>Feces on floor</td>
<td>0.46</td>
<td>0.42</td>
<td>1.10</td>
<td>1.13</td>
<td>0.73, 1.73</td>
</tr>
<tr>
<td>Uncovered garbage</td>
<td>0.49</td>
<td>0.28</td>
<td>1.75*</td>
<td>2.02**</td>
<td>1.27, 3.20</td>
</tr>
<tr>
<td>Open drainage of latrine##</td>
<td>0.58</td>
<td>0.43</td>
<td>1.36</td>
<td>1.50</td>
<td>0.52, 4.33</td>
</tr>
<tr>
<td>Feces on toilet floor</td>
<td>0.55</td>
<td>0.43</td>
<td>1.27</td>
<td>1.19</td>
<td>0.60, 2.36</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001.
† RR, relative rate; CI, confidence interval.
‡ Relative rate adjusted for age, breastfeeding, village, season, and ownership of flush toilet.
§ Incidence rate, expressed as episodes per child-year.
¶ Mother received formal school education, missing information for one mother.
¶¶ Diarrheal episodes from the second and third years of surveillance.
## Latrine drains to the environment or to an open pit (applies to houses with latrines).
### Flushing of latrines into the environment.
#### Cowardly defined as having five or more persons to a sleeping room.
### Ownership of one or more of the following: goat, sheep, buffalo, cow, ox, rabbit, camel, horse, and/or donkey.
††† Ownership of one or more of the following: chicken, pigeons, and/or ducks.
†† Ownership of one more of the following: television, water heater, electric oven, motorcycle, refrigerator, and/or washing machine.
§§ Crowding defined as five or more persons to a sleeping room.

The risk of Campylobacter diarrhea. The presence of animals in the cooking area was, however, associated with a higher risk of developing Campylobacter diarrhea (RR = 1.50; 95 percent CI: 1.02, 2.17; p < 0.05). Houses where uncovered garbage was present in the cooking areas also had higher rates of Campylobacter diarrhea (RR = 2.02; 95 percent CI: 1.27, 3.20; p < 0.01) (table 1).

Pathogenicity of Campylobacter

In the birth cohort of 211 children, the relative odds of excreting Campylobacter among children having diarrhea compared with children not having diarrhea were 2.45 (95 percent CI: 1.61, 3.71; p < 0.001) (table 2). This association did not change when bacterial copathogens were excluded from the analysis (odds ratio (OR) = 2.18; 95 percent CI: 1.43, 3.32; p < 0.001). Because there was no statistically significant interaction between age and excretion of Campylobacter, this association is consistent for younger and older children. Pathogenicity was not dependent on the infecting species because the association of diarrhea with excretion of C. coli was not different from that of C. jejuni (table 2). Of the 211 children, 122 (58 percent) experienced one or more episodes of Campylobacter diarrhea. In the subgroup of children who had a first episode of Campylobacter diarrhea, pathogenicity of subsequent infections was age dependent. For children having their first episode of Campylobacter diarrhea in the first 6 months of life, a subsequent Campylobacter infection within the first 6 months of life was pathogenic (OR = 5.66; 95 percent CI: 1.20, 26.56; p < 0.05). On the other hand, if a child had a first episode of Campylobacter diarrhea after 6 months of age, then a subsequent infection with Campylobacter was not pathogenic (OR = 1.21; 95 percent CI: 0.69, 2.16).

Convalescent excretion

Having an episode of Campylobacter diarrhea within the past month was associated with an increased odds of excreting Campylobacter asymptptomatically in the subsequent 2-
month survey (OR = 3.41; 95 percent CI: 2.01, 5.79; p < 0.001) (table 3). Age-specific odds ratios for the association were 4.15 (95 percent CI: 2.21, 7.79), 2.51 (95 percent CI: 0.75, 8.38), and 3.05 (95 percent CI: 0.33, 28.42) for the first, second, and third years of life, respectively, which were not statistically different from one another. The duration since exposure also did not alter the association between Campylobacter diarrhea and prolonged excretion of the organism (table 3). For cases with a preceding Campylobacter diarrheal episode, the median duration of asymptomatic Campylobacter excretion was 14 days, with an interquartile range of 10–25 days.

**DISCUSSION**

The overall incidence of Campylobacter diarrhea in this population was 0.6 episodes per person-year, which is the highest incidence rate ever reported from a developing country. This incidence rate is tenfold higher than that reported in a previous cohort study conducted in Bilbeis, Egypt (20), and we are unable to find any obvious reasons to explain this significantly higher incidence rate. We found incidence rates of Campylobacter diarrhea to be as high as 1.5 episodes per child-year in children aged between 6 and 12 months. In hyperendemic settings such as this, the burden of diarrhea associated with Campylobacter is substantial despite the large proportion of asymptomatic excretors. Campylobacter diarrhea could be overlooked as a major public health problem in developing countries because of the notion that infections due to Campylobacter are not pathogenic beyond the first 6 months of life. As a result, insufficient emphasis has been placed on the design and implementation of preventive measures to reduce disease transmission. Our data are at considerable odds with this

**TABLE 3. History of Campylobacter diarrhea in asymptomatic subjects with and without Campylobacter isolated from their fecal specimens collected in the 2-month surveys, Abu Homos, Egypt, 1995–1998**

<table>
<thead>
<tr>
<th>History of Campylobacter diarrhea in past month</th>
<th>Crude OR†</th>
<th>OR‡</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter‡</td>
<td>No. Total %</td>
<td>Campylobacter</td>
<td>No. Total %</td>
</tr>
<tr>
<td>All</td>
<td>19 156 12</td>
<td>91 3,324 3</td>
<td>4.93**</td>
</tr>
<tr>
<td>Duration (days)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>1 156 0.6</td>
<td>7 3,324 0.2</td>
<td>3.37</td>
</tr>
<tr>
<td>7–13</td>
<td>7 156 5</td>
<td>26 3,324 0.8</td>
<td>6.35*</td>
</tr>
<tr>
<td>14–20</td>
<td>4 156 3</td>
<td>23 3,324 0.7</td>
<td>4.10**</td>
</tr>
<tr>
<td>21–30</td>
<td>7 156 5</td>
<td>35 3,324 1</td>
<td>4.72**</td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>2 22 9</td>
<td>14 483 3</td>
<td>3.35</td>
</tr>
<tr>
<td>6–11</td>
<td>13 57 23</td>
<td>36 490 7</td>
<td>3.73**</td>
</tr>
<tr>
<td>12–23</td>
<td>3 46 7</td>
<td>29 1,199 2</td>
<td>2.82</td>
</tr>
<tr>
<td>24–35</td>
<td>1 31 3</td>
<td>12 1,152 1</td>
<td>3.17</td>
</tr>
</tbody>
</table>

* p < 0.01; ** p < 0.001.† OR, odds ratio; CI, confidence interval.‡ Odds ratios adjusted for age, breastfeeding, village, and season.
§ Isolation from asymptomatic subjects in the 2-month surveys.
¶ Duration between history of Campylobacter diarrheal episode and 2-month survey.

tion and suggest the need for a greater focus on the control of *Campylobacter* diarrhea in children.

Similar to other studies from developing areas, our study observed an age-specific decline in the incidence of *Campylobacter* diarrhea, suggesting that there is an age-related acquisition of immunity (9, 14, 19, 23, 33). However, we have shown that first-time infections with *Campylobacter* are pathogenic regardless of the age of the child, suggesting that prior exposure and immunity influence the risk of *Campylobacter* diarrhea for a child. This association was consistent even when we excluded *Campylobacter* infections with bacterial copathogens from the cases and controls, suggesting that pathogenicity observed in older age children is not explained by a co-infection. The observation that *Campylobacter* remains highly pathogenic in the first 6 months of life even in those with a prior symptomatic infection suggests that early infections may not be immunogenic enough to confer protection against subsequent disease. This observation is corroborated by the finding that children aged under 6 months have very poor serologic responses to natural *Campylobacter* infection (33). However, consistent with observations from most developing countries, our study found that infections beyond the first 6 months of life that occur subsequent to a symptomatic infection are not pathogenic. These findings have implications for the use of new *Campylobacter* vaccines in children from less developed settings where the risk of disease is greatest in early life. The vaccine will need to confer immunity in the very young in order to protect children during the period of greatest risk.

We found evidence suggesting that prolonged convalescent excretion of *Campylobacter* lasted for a month after the diarrheal episode. Our results are similar to findings in Thailand, but they differ from the shorter convalescent excretion periods noted in Mexico and Chile (9, 21, 23). Although our study was not designed to examine the role of prolonged convalescent *Campylobacter* excretion in secondary transmission, this is an important area for future investigation.

In vitro studies have demonstrated that *C. coli* are more readily phagocytosed and killed by peritoneal macrophages than *C. jejuni* (34). These findings have raised the possibility that infections due to *C. coli* are not as severe as those caused by *C. jejuni*. Compared with *C. jejuni* infections, *C. coli* infections have less often been found to be associated with bloody diarrhea and symptomatic disease (23). In our study population, we found no difference in the proportion of severe disease in infections resulting from *C. coli* compared with *C. jejuni*. This observation remained consistent even when *Campylobacter* episodes with other copathogens were excluded from the analysis.

Studies that have shown *Campylobacter* diarrhea to be associated with the consumption of contaminated water or foods, ownership of livestock or poultry, or contact with animals have not factored in the time-dependent nature of these environmental conditions (8, 15, 18, 22, 35–39). After incorporating these changing conditions into our analyses, we found that the presence of animals and uncovered garbage in the cooking area is associated with an increased risk of *Campylobacter* diarrhea. In our observations, we did not record the species of animals in the house, so this increased risk could not be associated with specific types of animals. However, we know from the census that more than 80 percent of the enrolled children resided in houses that owned barnyard animals. An observational study conducted in a shantytown in Peru showed that toddlers frequently come into contact with poultry feces that lie within the homes and have an average of 3.9 feces-to-mouth episodes in a 12-hour period (40). This observation, coupled with the fact that the feces from poultry when cultured yielded viable *C. jejuni* for up to 48 hours after deposition, suggests that there is a high risk of *Campylobacter* transmission in environments where there may be frequent human-animal contact. Our findings support the suggestion that it is the presence of the animals themselves and the poor hygienic conditions within the house, as opposed to the mere ownership of animals, that place the child at an increased risk of *Campylobacter* disease.

In conclusion, the high burden of disease resulting from *Campylobacter* infection in this population highlights the need for improved methods for disease control. Improving hygiene-related behaviors and minimizing contact with animals may be recommended, and consideration must be given to the development of safe, effective candidate vaccines that can confer protection in early infancy.

**ACKNOWLEDGMENTS**

Financial support was provided by the Naval Medical Research and Development Command (work unit nos. M00101.HIX.3421 and M00101.PIX.3270), the National Institute of Child Health and Human Development (inter-agency agreement Y1-HD-0026-01), the World Health Organization Global Program for Vaccines and Immunization, and the World Health Organization Control of Diarrhoeal Diseases Programme.

The authors thank Sahar Abd El Samad, Manal El Sayed, and the staff of the Abu Homos Field Research Center for their contributions to field and laboratory work and Dr. Mahmoud Abu El Nasr and Dr. Badriya Z. Morsy of the Egyptian Ministry of Health and Population for their advice and support. In addition, the authors would like to thank Dr. Lawrence Moulton, Johns Hopkins University Bloomberg School of Public Health, for his comments and suggestions.

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