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Immune Response to *Campylobacter jejuni* and *Campylobacter coli* in a Cohort of Children from Birth to 2 Years of Age

PAUL M. V. MARTIN,* JEANINE MATHIOT, JULIENNE IPERO, MICHELINE KIRIMAT, ALAIN J. GEORGES, AND MARIE-CLAUDE GEORGES-COURBOT

Institut Pasteur de Bangui, B.P. 923, Bangui, Central African Republic

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A cohort of 111 children from Bangui, Central African Republic, was surveyed for enteric *Campylobacter* infections from birth to the age of 2 years; stools were examined biweekly in these children until 6 months of age and at least four times per year thereafter until 2 years of age and after each diarrheal episode. Blood samples were obtained at birth and at 3, 6, 9, 12, 18, and 24 months of age. Antibodies against glycine-extracted membrane antigens, purified flagella, and cholera toxin (CT) were assayed by an enzyme-linked immunosorbent assay. The results showed that titers of antibody against the three tested antigens increased in children between 6 and 12 months of age and that nearly all children were immunized by the age of 2 years. A significant fall in anti-flagellum ($P < 0.001$) and anti-glycine extract antigen antibodies ($P < 0.001$) occurred between birth and age 3 months, and children who had *Campylobacter* infections during the first 6 months of life had significantly ($P < 0.02$) less anti-flagellum antibodies at birth than did those who did not have *Campylobacter* infections during that time. Three-month-interval stratification showed that CT antibody titers at birth were significantly lower in children who developed *Campylobacter* infection than in controls ($P = 0.05$). Comparison of the immune response to a single *Campylobacter* episode showed that 46.6% of children with asymptomatic carriage did not respond to CT while only 5% of children with diarrhea-producing infection did not respond to CT ($P < 0.01$), compared with 30% ($P = 0.065$) and 56% ($P < 0.01$), respectively, of the age-matched controls. Antibodies to flagella seem to protect against enteric colonization by *Campylobacter jejuni* and *Campylobacter coli*.

Campylobacter jejuni and *Campylobacter coli* are considered important enteropathogens for children (7, 10), particularly in developing countries (1, 6, 13, 28). However, several investigators, including ourselves, have reported high rates of isolation of these enteropathogens from healthy children in developing countries (3, 9, 16, 17), while symptomless excretion is uncommon in developed countries.

In another study, we described the results obtained from a prospective study of *Campylobacter* infections in a cohort of 111 children monitored from birth to 2 years of age (M. C. Georges-Courbot, A. M. Beraud-Cassel, I. Gouandjika, J. Monges, and A. J. Georges, submitted for publication). We showed a statistically significant association of *Campylobacter* species with diarrhea in children between the ages of 1 and 6 months (16) but not older. Similarly, Calva and co-workers (12) recently showed the same association in a cohort of Mexican children under 5 years of age, with an illness-to-infection ratio of 50% during the first 6 months of life that dropped considerably with age. Moreover, 32% of symptomless Bangladeshi infants had *C. jejuni*, and this proportion declined during childhood (17). Healthy Bangladeshi (4) and Thai (8) children have higher anti-*C. jejuni* antibody titers than healthy age-matched children in the United States. In a recent study of acute diarrheal disease in Thailand, Taylor and co-workers (29) showed that exposure to *Campylobacter* species confers immunity to infection that is associated with a peak in specific serum antibodies but that this exposure does not prevent asymptomatic infection. The data collected in cross-sectional and longitudinal studies in developing countries suggested the development of a protective immunity early in life.

In most studies in Asia (28), America (21), and Europe (18), *C. coli* accounted for ca. 10% of enteric *Campylobacter* isolates, while *C. coli* represented 50% of the strains isolated in the Central African Republic during the present cohort study (Georges-Courbot et al., submitted). We reported previously that children naturally infected with *C. coli* responded to crude antigenic extracts from *Campylobacter* species, to purified flagella from *C. coli*, and to purified cholera toxin (CT) (24). The antibody response of children to *C. coli* resembles the response to *C. jejuni*; this similarity permits the study of a larger number of infections (24). We present here the results of the humoral antibody response to *Campylobacter* species in a cohort of children monitored from birth to 2 years of age. The epidemiological results of this study will be published elsewhere (Georges-Courbot et al., submitted).

MATERIALS AND METHODS

Patients, collection of serum, isolation of *Campylobacter* spp., and culture conditions. Patients, collection of serum, isolation of *Campylobacter* spp., and culture conditions were described in detail in a preceding paper (16). Briefly, 111 children were monitored from birth to age 2 years, and stools were cultured biweekly for *Campylobacter* spp. until patients reached 6 months of age and then were cultured at least four times per year until age 2 years, as well as after each diarrheal episode. Parasitological, bacteriological, and virological investigations were performed by routine standard procedures as previously described (15). For 107 children, i.e., those monitored in the present study, sera were obtained at birth and at 3, 12, 18, and 24 months of age and frozen at −20°C until used. Additional sera, taken at 6 and 9 months of age ($n = 46$ and 30, respectively), were obtained from children in the second half of the cohort, from whom mothers permitted additional samples to be taken.

* Corresponding author.

TABLE 1. Antibodies to *Campylobacter* spp. in children during the first 2 years of life in the city of Bangui, Central African Republic

Antigen	Level of antibodies at age (mo)[a]:						
	Birth (cord blood) (n = 98)	3 (n = 98)	6 (n = 46)	9 (n = 30)	12 (n = 103)	18 (n = 103)	24 (n = 91)
Glycine-extracted antigen	21.2 ± 23.8	9.82 ± 12.5	15.95 ± 20.8	29.1 ± 22.2	41.4 ± 33.2	45 ± 30.5	59.1 ± 34.5
CT	8.2 ± 10.9	8.9 ± 14.1	33 ± 33	57.7 ± 62.5	63.3 ± 42.9	75.5 ± 44.9	76.9 ± 46.3
Flagella	1.045 ± 0.61	0.7 ± 0.62	0.73 ± 0.42	1.047 ± 0.58	1.02 ± 0.52	1.02 ± 0.47	1.08 ± 1.53

[a] Levels of antibodies are given as antibody units (glycine-extracted antigen and CT) (24) or as the optical density at 492 nm as measured by ELISA (flagella). Values are means ± standard deviation.

Heat-labile-enterotoxin-producing enterotoxigenic *Escherichia coli* were tested for the presence of heat-labile enterotoxin by enzyme-linked immunosorbent assay (ELISA), as described previously (15). *Vibrio cholerae* was not detected; no case of cholera has ever been reported in the Central African Republic.

Immune response to glycine-extracted antigen, enterotoxin, and purified flagella. The immune response to glycine-extracted membrane antigens, enterotoxin, and purified flagella was tested by ELISA as described previously (24). Glycine-extracted antigens were kindly provided by H. Lior (Laboratory Center for Disease Control, Ottawa, Ontario, Canada). Purified CT was obtained from Sigma Chemical Co., St. Louis, Mo. Flagella were purified from strain 2500 of *C. coli* by the method of Nachamkin and Hart (27), which we slightly modified (24). Purified flagella were assayed for protein content (23) and were at phase 1 (22) when separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (20). Titers of antibodies against glycine-extracted antigens and CT were assayed by ELISA and expressed in antibody units, calculated as described previously (24), with reference sera as the standard. Anti-flagellum antibody titers, as measured by ELISA, were expressed as the optical density at 492 nm. In all experiments, antibodies were detected by using peroxidase-conjugated anti-human immunoglobulins G, A, and M (Biosys, Compiègne, France). All serum samples were not tested in every assay because of the small volumes of some of the samples available, but this accounted for less than 15% of the serum samples at each sampling time.

RESULTS

Antibody responses of the cohort of children. The antibody responses of children infected by *C. jejuni* or by *C. coli* did not differ. Table 1 shows the general evolution of the antibody response against glycine-extracted membrane antigens, CT, and purified flagella in the cohort of 107 children over the 24-month period. As can be seen in Table 1, the mean levels of antibody against CT were very low at birth, started to increase between the ages of 3 and 6 months, and reached a plateau at the age of 12 months. Table 1 shows a drop in the level of anti-flagellum ($P < 0.001$) and anti-glycine extract ($P < 0.001$) antibodies between birth and 3 months of age and then a sharp increase between 6 and 9 months. It is noteworthy that the average level of anti-flagellum antibodies at birth was the same as that after 9 months. Figure 1 shows the percentage of *Campylobacter* spp. isolated from diarrheic stools in the same cohort of children, in parallel with the level of anti-flagellum antibodies. There is a clear inverse relationship between anti-flagellum and anti-glycine extract antibody titers and the onset of diarrhea due to *C. jejuni* and *C. coli*. This finding prompted us to do 3- and 6-month-interval stratification analysis to compare the means of anti-flagellum, anti-glycine extract, and anti-CT pre-antibody titers in serum samples from children infected with *Campylobacter* spp. with those of children who were not during the first 6 months of life. The stratification of the immunological results in 3-month intervals (Table 2) showed that children who had *Campylobacter* infection or carriage in the first 3 months of their life had significantly less antibodies against CT at birth than did children who did not experience *Campylobacter* infection during the same period of time.

The 6-month-interval stratification showed that there was no difference in the levels of anti-glycine extract antibodies between the groups. The mean level of anti-flagellum antibodies in the 62 children from whom *Campylobacter* spp. were never isolated was 1.149 ± 0.67, while it was 0.859 ± 0.45 for the 36 children who developed *Campylobacter* infection (associated with diarrhea or not) in the first 6 months of life. The difference was significant ($P < 0.02$, $Z = 2.55$). However, the comparison of pre-antibody titer at birth of children who had subsequent asymptomatic *Campylobacter* infection in the first 6 months of life with that of children who had symptomatic infection during this period did not show any statistically significant difference in anti-flagellum antibodies.

Antibody response in patients, carriers, and controls. During the 2-year survey, *Campylobacter* spp. were isolated at

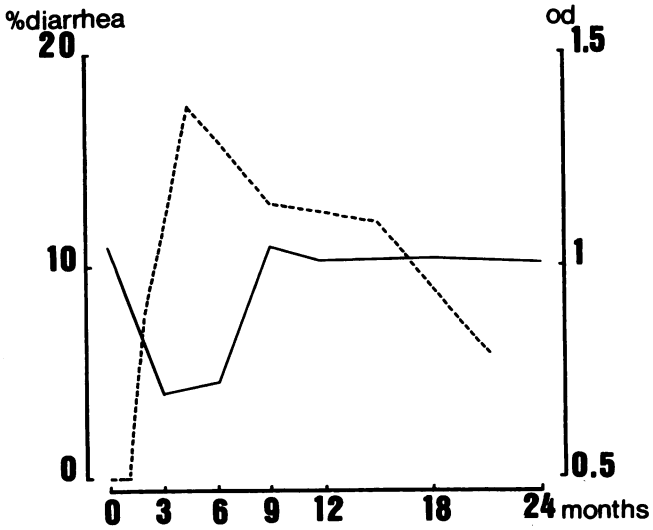

FIG. 1. Evolution of the antibody response against flagella from *Campylobacter* spp. in a cohort of children from birth to 2 years of age. The figure shows the antibody response against purified flagella as measured by ELISA (—) (optical density at 492 nm) and the percentage of diarrheic stools positive for *Campylobacter* spp. (– – –).

TABLE 2. Stratification of the antibody response to glycine-extracted antigen, CT, and flagella 3 months postinfection in children who had been infected with *Campylobacter* spp. (*Campylobacter* group) and in those who had not (non-*Campylobacter* group)

Group	Mean antibody level ± SD[a]					
	At birth			3 mo postinfection		
	Glycine-extracted antigen	CT	Flagella	Glycine-extracted antigen	CT	Flagella
Campylobacter	17.5 ± 12.5 (n = 20)	4.84 ± 5.39* (n = 20)	1.055 ± 0.59 (n = 18)	6.6 ± 5.65** (n = 22)	6.3 ± 6.5 (n = 22)	0.71 ± 0.58 (n = 21)
Non-*Campylobacter*	24.3 ± 27.8 (n = 66)	10.9 ± 13.84* (n = 66)	1.099 ± 0.65 (n = 63)	11.83 ± 14.66** (n = 66)	10.9 ± 16.88 (n = 66)	0.69 ± 0.65 (n = 61)

[a] SD, Standard deviation. Antibody levels are given as antibody units (glycine-extracted antigen and CT) or as the optical density at 492 nm as measured by ELISA (flagella). Data followed by an asterisk differed significantly (P = 0.05); data followed by two asterisks also differed significantly (P = 0.095). All other pairs of data did not differ significantly.

least once from 62 of the 107 children. We separated the children into five groups with respect to *Campylobacter* isolations. Group I (20 patients) consisted of those who suffered diarrhea-associated intestinal *Campylobacter* infection; group II (30 cases: carriers) included those who had diarrhea-free *Campylobacter* infection; group III (33 controls) consisted of those with diarrhea due to either rotavirus or parasites (13 cases) or of unknown origin (20 cases); group IV (15 cases) included those who experienced diarrhea owing to heat-labile-enterotoxin-producing *Escherichia coli*; and group V (8 cases) included those who had diarrhea-free *Campylobacter* infection followed by diarrhea-associated *Campylobacter* infection. Only one child had no diarrhea and yielded no pathogen during the study. In group IV, *Campylobacter* spp. were isolated from four children. Results showed that all five groups had the same general pattern for antibodies directed against glycine extracts and CT. It is noteworthy that anti-CT antibodies reached the same level in all groups. Conversely, the group of children who suffered from *Campylobacter* sp.-associated diarrhea (group I) was better immunized against flagellar antigens from 12 to 24 months of age. The mean anti-flagellum antibody titers were higher in group I (patients) than in group II (asymptomatic carriers) at 12 months (1.38 ± 0.52 and 0.83 ± 0.35, respectively; $P < 0.001$), 18 months (1.48 ± 0.6 and 1.05 ± 0.44, respectively; $P < 0.01$), and 24 months (1.24 ± 0.55 and 0.9 ± 0.5, respectively; $P < 0.05$).

Antibody response before and after intestinal *Campylobacter* infection. The antibody response elicited by *Campylobacter* spp. after diarrhea-associated infection was compared with that elicited after symptomless enteric carriage. Since antibody levels change with patient age, as shown in Table 1, each group was compared with age-matched controls from the same cohort. Paired-matched controls were selected as the first following child in the group of children who suffered diarrhea due to rotavirus or parasites or of unknown origin. Antibody titers before and after *Campylobacter* sp.-associated diarrhea (20 patients) and carriage (30 cases), as compared with those of corresponding controls, are summarized in Table 3. Age differences between patients and carriers partially account for the differences observed. But anti-flagellum antibody levels rose significantly only in the group of patients, while carriage did not elicit a significant antibody response against flagella. Antibodies against CT rose significantly in all groups, but the mean titer in postinfection serum samples from patients was more than twice that observed in carriers and higher than that in age-matched controls (P = 0.06). Moreover, only 1 of 20 (5%) postinfection serum samples from the *Campylobacter* sp.-associated-diarrhea group had an anti-CT antibody titer of ≤20 units, while 14 of 30 (46.6%) samples from the group of carriers (chi-square test, $P < 0.01$) and 30% (Fisher exact test, P = 0.065) and 56% ($P < 0.01$) of samples in the corresponding age-matched controls, respectively, had an anti-CT antibody titer below 20 units.

DISCUSSION

The immune response to *Campylobacter* infection has been remarkably reviewed by Walker et al. (30). Evidence for immunity against *Campylobacter* spp. is abundant. (i) Several immunological studies have strongly suggested that

TABLE 3. Antibody response to *Campylobacter* spp.[a]

Group of children (n)	Antibody response[b] against glycine extract in serum sample		Antibody response[b] against CT in serum sample		Antibody response[c] against flagella in serum sample	
	Preinfection	Postinfection	Preinfection	Postinfection	Preinfection	Postinfection
Patients[d] (20)	23.8 ± 28	39.7 ± 35[e]	24.4 ± 31	73.9 ± 46.5[f]	0.88 ± 0.59	1.65 ± 1.1[g]
Age-matched controls[d] (20)	16.3 ± 20.9	21.7 ± 14.9[e]	20 ± 26	46.8 ± 33.3[h]	0.59 ± 0.36	0.82 ± 0.36[e]
Carriers[i] (30)	8 ± 6.7	22.6 ± 21.4[f]	5.3 ± 6	32.8 ± 28[f]	0.81 ± 0.52	0.95 ± 0.54[e]
Age-matched controls[i] (30)	14.4 ± 20.4	14.4 ± 12.3[e]	9.1 ± 12.8	28.8 ± 33[g]	0.96 ± 0.72	0.6 ± 0.33[e]

[a] Found in children during infection and carriage and in age-matched controls, as measured by ELISA with crude glycine extracts, purified CT, or purified flagella as antigens. Values are means ± standard deviation.
[b] Units calculated with reference to a standard human serum sample (see text for details of calculation).
[c] Optical density at 492 nm.
[d] Mean age in months (range): preinfection, 5.1 (birth to 12); postinfection, 11.25 (3 to 18).
[e] Not significant.
[f] $P < 0.001$.
[g] $P < 0.01$.
[h] $0.02 > P > 0.01$.
[i] Mean age in months (range): preinfection, 2.2 (birth to 3); postinfection, 6.7 (3 to 12).

immunity against *C. jejuni* in children is acquired after infection. A progressive decrease in the illness-to-infection ratio with increasing age has been demonstrated in Bangladesh (17), Peru (2), Mexico (12), and the Central African Republic (Georges-Courbot et al., submitted). (ii) The development of anti-*Campylobacter* sp. antibodies in children frequently exposed to the bacterium in Bangladesh contrasted with the lack of such antibodies in age-matched children from the United States (4). (iii) Multiple exposures to *C. jejuni* of individuals who drink raw milk lead to a high level of anti-*Campylobacter* sp. antibodies and little or no illness as compared with individuals who rarely drink raw milk (5). (iv) Rechallenge experiments with *C. jejuni* among volunteers in the United States (2) and in animal models (11) have demonstrated the development of a protective immunity after the first exposure to the bacterium.

Moreover, in the prospective study conducted in the Central African Republic (16), *Campylobacter* spp. were isolated from nondiarrheic stools, but never from diarrheic stools, in children under 1 month of age, suggesting a protective role of antibodies from their mothers.

In two separate studies of Bangladeshi (4) and Thai (8) children, Blaser and co-workers have shown that immunoglobulin-class-specific responses to *Campylobacter* spp. vary with age. But all three isotypes rose linearly from birth to 2 years of age, while IgG levels then declined and IgM levels plateaued. Cord blood contained only anti-*Campylobacter* sp. IgG (8). Because no children in our cohort were over 2 years old, we used a conjugate which detects simultaneously all three isotypes in order to assay the global immune response of children to *Campylobacter* antigens. It is likely that the fall in anti-glycine extract and anti-flagellum antibodies from birth to 3 months mainly involves the IgG isotype.

The general pattern of evolution of antibodies against CT (Table 1) in the cohort of children shows a lack of antibodies early in life and the development of immunity between 6 and 12 months. The 3-month-interval stratification showed that anti-CT antibody titers at birth could influence the development of subsequent *Campylobacter* infection. Owing to the small number of cases and carriers in our cohort during the first 3 months of life, there was no significant difference within the *Campylobacter* group between patients and carriers. Conversely, anti-flagellum and anti-glycine extract antibody levels are elevated at birth and rapidly decrease. This corresponds to an increase in *Campylobacter* sp.-associated diarrheas. There is clearly an inverse relationship between the level of anti-flagellum antibodies and the percentage of diarrheic stools containing *Campylobacter* species. In our study, the illness-to-infection ratio could be accurately calculated between birth and 6 months and was 0 in the first month, 0.85 from 2 to 3 months, and 0.85 from 4 to 6 months, a pattern which is similar to that detected by Calva and co-workers (12) in Mexican children. Moreover, children who did not have *Campylobacter* infection in the first 6 months of life had significantly more anti-flagellum antibodies at birth than did those who became infected with *Campylobacter* spp., although there was no difference between pre-antibody titers in children who had asymptomatic versus symptomatic *Campylobacter* infection. This strongly suggests that antibodies directed against flagella protect against enteric infection by *Campylobacter* spp. Flagella have been involved in *Campylobacter* pathogenicity, both through bacterial motility (26) and their adhesive properties (25). Consequently, antibodies directed against flagella are likely to limit the colonization of the mucus. In the present study, we detected antibodies against a purified flagellum preparation from *C. coli* and not against homologous flagella; i.e., we assayed anti-flagellum antibodies directed toward common epitopes from *Campylobacter* species. Because the presence of such antibodies at birth seems to prevent infection by *Campylobacter* spp., it is likely that the detected epitopes are located on the surface.

The comparison of serum antibody titers before and after symptom-producing infection or carriage shows that CT is more immunogenic in symptomatic patients than in carriers. Although not a proof, this suggests that *Campylobacter* diarrhea per se is the cause of the anti-CT antibody response. Moreover, about 50% of carriers do not exhibit an antibody response against CT. Whether this reflects the lack of CT production by *Campylobacter* strains during carriage, as suggested by the work of Klipstein et al. (19), or a limited and abbreviated intestinal colonization in carriers remains to be investigated. However, in our study, the mean duration of shedding of *Campylobacter* spp. was the same in patients and in carriers (16). In 7 of 20 patients, there was a preexistent elevation of the level of anti-CT antibodies, indicating either that they were not protecting against the disease or that other pathogenic factors were involved. The significant anti-CT antibody increase in controls suggested that other enterobacteria can elicit a CT-like antibody response. Conversely, carriage does not elicit a significant increase in anti-flagellum antibodies (Table 3), at least not during the course of a single infection, while *Campylobacter* sp.-associated diarrhea does. This supports the role of flagella in *Campylobacter* pathogenicity. Moreover, the significantly higher titers of anti-flagellum antibodies at birth in children who did not develop subsequent *Campylobacter* infection indicate that flagellin is a good candidate for a vaccine.

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