Intestinal Helminthiasis in Colombian Children Promotes a Th2 Response to *Helicobacter pylori*: Possible Implications for Gastric Carcinogenesis

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Abstract

Background: **Colombians living in coastal Tumaco have a lower incidence of *Helicobacter pylori*–associated gastric cancer compared with residents of Pasto in the high Andes. Considering the risk for *H. pylori* disease seems affected by features of bacterial virulence and host polymorphisms, other poorly understood influences, such as concurrent helminthiasis, may also be important.**
Methods: **Fecal samples from 211 children were tested for parasites and sera from another cohort of 159 children and 92 adults were tested for IgE and *H. pylori*–specific IgG.**
Results: **Most individuals (95%) from both areas were *H. pylori* seropositive, with a predominant response of IgG1 followed by IgG2 and low IgG3 and IgG4 antibodies. Compared with Pasto children, Tumaco children were more commonly infected with helminths ($P = 0.000$), had higher serum IgE levels ($P < 0.03$), and had higher Th2-associated IgG1 responses to *H. pylori* ($P < 0.0002$). Other IgG isotype responses all increased with age but were not significantly different between children and adults from either area.**
Conclusions: **These results suggest that intestinal helminthiasis in children promotes Th2-polarizing responses to *H. pylori* and may decrease gastric cancer risk in these individuals later in life. Concurrent helminthiasis may alter inflammatory responses to *H. pylori* and thus affect the progression of gastritis to gastric atrophy, dysplasia, and cancer.** (Cancer Epidemiol Biomarkers Prev 2005; 14(6):1464–9)

Introduction

Children are at highest risk for infection with *Helicobacter pylori* and the prevalence of infection can approach 100% in select human populations, particularly those of low socioeconomic status (1, 2). *H. pylori* infection likely occurs via transmission from parents to children or between children. Acquisition may be more common in social settings, such as daycare centers, when sanitation is difficult to control (3, 4). *H. pylori*–associated gastritis is usually subclinical, but after decades of chronic infection, a small percentage of infected individuals develop gastric atrophy with increased risk of gastric adenocarcinoma (5). Epidemiologic evidence suggests that a variety of factors affect the relative risk for *H. pylori* infection to initiate or promote precancerous lesions that can lead to significant clinical sequelae.

Polymorphisms in genes coding for host factors, such as mucins (6), and proinflammatory and anti-inflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-1β, IL-8, and IL-10 have been associated with more severe gastritis and an increased risk for precancerous lesions of the stomach, including intestinal metaplasia, glandular atrophy, and gastric cancer (7-12). In addition to apparent genetic predisposition, some humans may be at increased risk for gastric cancer due to colonization with *H. pylori* strains that express virulence factors, such as the cag pathogenicity island and the vacA toxin and BabA2 adhesion molecules that bind with high affinity to blood group antigens expressed in the human stomach (13). Once infected, environmental influences, such as antioxidant levels in diet, have been suggested to affect progression of disease (14). Additional risk factors affecting the outcome of *H. pylori* infection include unexplained geographic differences in the incidence of gastric cancer even after controlling for factors, such as age at first exposure to *H. pylori* (15) and immunologic differences in the response to the chronic infection (16).

Gastric atrophy, intestinal metaplasia, and gastric cancer have been associated with a vigorous Th1 immune response to *H. pylori* (17). Although IgG subclass responses provide indirect evidence of T helper cell function (18), there have been limited studies of the potential association between *H. pylori*–associated clinical disease and IgG subclass responses to the infection, particularly in children (19-21). Children infected with *H. pylori* may develop a predominantly Th2-associated IgG1 response to *H. pylori* (20), particularly if living in undeveloped areas (21), which contrasts with the Th1-associated IgG2 responses observed in adults (22). Children are also commonly infected with intestinal helminths when climate and poor sanitation favor the life cycle and transmission of parasites. These observations suggest that Th2-polarizing helminthic infections in childhood could promote the Th2 response to *H. pylori* and is supported by studies indicating helminth infections inhibit Th1-promoted responses to unrelated antigens (23-25).

This study evaluated the relationship between childhood parasitism and seroconversion to *H. pylori* in children and adults residing in geographically distinct areas of Colombia known to differ in gastric cancer risk despite similar

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prevalence of *H. pylori* infection (15). The Colombian population centers of Pasto and Tuquerres are in the high Andes, and inhabitants historically have a high rate of gastric cancer and precancerous lesions associated with *H. pylori* infection (26). In contrast, the area of Tumaco is on the Pacific Coast at sea level, and adults infected with *H. pylori* have a low gastric cancer rate. A survey for intestinal parasites in Colombian children indicated that children living in these geographically distinct population centers differed significantly in the occurrence of enteric parasitism, particularly helminthiasis. These findings led to additional investigation to determine if Th2-polarizing helminthic infections in childhood, known to induce immunoregulatory mediators, such as IL-10 and transforming growth factor-β (24), may enhance Th2 responses to *H. pylori* as reflected in higher IgG1 responses measured by ELISA. Our results indicate that intestinal helminthiasis in childhood may be an epidemiologic factor influencing the chronic course of *Helicobacter*-associated clinical disease and therefore has possible implications for gastric carcinogenesis.

Materials and Methods

Study Populations. The children studied were ages 1 to 6 years and in general good health. Feces were collected for intestinal parasite screening, and sera were obtained for ELISA as part of two independent health assessments. Samples could not be paired by individual for logistic reasons, but sample sizes were sufficiently large to be statistically representative of each population center (see below). The children were from five daycare centers in rural Colombia. The centers are sponsored by the Colombian Institute of Family Welfare and accept only children of low socioeconomic strata whose parents work mostly in blue-collar jobs. Pasto and Tuquerres are in the high-altitude Andes mountains and the population has a very high rate of gastric cancer and precancerous lesions in resident adults. We reported previously that the risk of gastric cancer is several times greater in Pasto than in Tumaco. The relative frequency of multifocal atrophic gastritis (with or without intestinal metaplasia or dysplasia) was considerably higher in Pasto (90.5%) than in Tumaco (36.5%; ref. 26). Residents of Pasto and Tuquerres are predominantly mestizos of Spanish-Amerindian ancestry and are mostly agricultural worker families. Stool samples were collected from 101 children from two rural villages around Pasto. Sera from 105 children and 39 adults (ages 38-68 years) from Pasto and the nearby town of Tuquerres were obtained. Individuals from a third site (Tumaco), located on the Pacific Coast at sea level, were also surveyed. Adults living in Tumaco have a very low rate of gastric cancer but, similar to Pasto and Tuquerres, have a high prevalence of *H. pylori* infection. They are predominantly of African-Spanish ancestry and are employed primarily by the fishing industry. Stool and serum samples were collected from 110 and 54 children (ages 1-6 years), respectively, and sera were collected from 53 adults (ages 31-84 years). Informed consent was obtained from all adult participants and from parents of all children who were sampled, and sample use was approved by the Massachusetts Institute of Technology Committee on Use of Human Experimental Subjects.

Diagnosis of Intestinal Parasites in Children. Two aliquots of each stool sample were emulsified in 10% neutral formalin for direct examination and concentration. A third aliquot sample was immersed in Schaudinn solution (27) for staining with H&E. The samples were transported to Cali and examined by parasitologists from the Microbiology Department of Universidad del Valle. The identification of the parasites was made morphologically following the guidelines of the American Society of Parasitology (28).

ELISA for IgG and IgG Subclass Responses to *H. pylori* Antigens. Sera were tested by ELISA for serum IgG and each of the four IgG subclasses (IgG1, IgG2, IgG3, and IgG4). The antigen was a sonicate mix prepared from three clinical isolates of *H. pylori* from Colombia (NQ295, NQ1725, and NQ1886). Pellets were resuspended in sterile PBS and sonicated on ice (Artek Sonic Dismembranator, Artek Systems, Farmingdale, NY). Sonication was for four cycles of 30 seconds on, 30 seconds off at a duty cycle of 50% and power applied slowly to 60 W. Antigen was coated on Immulon II plates (Thermo Labsystems, Franklin, MA) at a concentration of 1 μg/mL (IgG) or 10 μg/mL (IgG subclasses) and sera were diluted 1:1,000. Biotinylated secondary antibodies included goat anti-human IgG, mouse anti-human IgG1 (clone 4E3), anti-IgG2 (clone 31-7-4), anti-IgG3 (clone HP6050), and anti-IgG4 (clone HP6023; all from Southern Biotechnology Associates, Birmingham, AL). Incubation with extravidin peroxidase (Sigma, St. Louis, MO) was followed by 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid), diammonium salt (ABTS) substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD) for color development. Absorbance development at 405/562λ was recorded by an ELISA plate reader (Dynatech MR7000, Dynatech Laboratories, Inc., Chantilly, VA).

Three positive and three negative control sera were obtained from patients from Narino, Colombia whose *H. pylori* status was confirmed by gastric biopsy at the Laboratorio Clinico, Hospital Universitario (Cali, Colombia). Sera from these patients were strongly *H. pylori* positive or negative using a commercially available ELISA (Pylori-Stat, BioWhittaker, Walkersville, MD) that has been independently evaluated for sensitivity and specificity (29). These sera were evaluated using checkerboard titration to determine optimum conditions for ELISA reagents (as described above) to discriminate between positive and negative results. These six control sera were used on each ELISA plate used to test the unknown samples and the absorbance values obtained were used to normalize data between plates. Samples were judged seropositive if the IgG absorbance values exceeded the mean and 3 SDs of the absorbance values obtained for the known negative samples on each respective plate.

ELISA for Total Serum IgE. Immulon II plates were coated overnight at 4°C with goat anti-human IgE (Sigma) at 10 μg/mL in physiologic saline (PBS). Wells were blocked for 1 hour at 37°C with 2% bovine serum albumen in PBS and samples were applied at a dilution of 1:100 for 2 hours at room temperature. An IgE standard of 8,927 IU/mL (Immunology Consultants, Newberg, OR) was diluted to create a seven-point standard curve with the lowest limit of detection at 25 IU/mL. Biotinylated mouse anti-human IgE was used as a secondary antibody at 1:1,000 with incubation for 1 hour at 37°C. Incubation with extravidin peroxidase followed by ABTS substrate and absorbance measurement were done as described for the serum IgG assays.

Statistical analysis. Parasitology results were analyzed by χ^2 analysis and serology by the Student's *t* test.

Results

Intestinal Parasitism. The survey for intestinal parasitism in children living in the regions of Pasto and Tumaco revealed infection with a variety of protozoa and helminths (Table 1). Compared with children living in the high Andes region of Pasto, children living at sea level in Tumaco had significantly greater infection rates with giardia (*Giardia duodenalis*; $P = 0.002$), whipworms (*Trichuris trichiura*; $P = 0.000$), and roundworms (*Ascaris lumbrocoides*; $P = 0.028$). Only the nonpathogenic protozoan *Entamoeba coli* (30) was

Table 1. Parasite species detected in fecal samples from Colombian children residing at sea level in Tumaco or in the Pasto region of the high Andes

Parasites	Pasto* (n = 101)	Tumaco† (n = 110)	P‡
	Prevalence n (%)		
Protozoa			
Entamoeba histolytica	26 (26)	28 (26)	NS
Entamoeba hartmanni	1 (1)	1 (1)	NS
Entamoeba coli	39 (39)	26 (24)	0.014
Endolimax nana	27 (27)	32 (29)	NS
Iodamoeba buetschlii	2 (2)	8 (7)	NS
Giardia duodenalis	19 (19)	41 (37)	0.002
Chilomastix mesnili	14 (14)	9 (8)	NS
Blastocystis hominis	27 (27)	36 (33)	NS
Helminths			
Ascaris lumbrocoides	22 (22)	38 (35)	0.028
Trichuris trichiura	8 (8)	47 (43)	0.000
Uncinarias	0	1 (1)	NS
Strongyloides stercoralis	0	1 (1)	NS
Enterobius vermicularis	0	2 (2)	NS
Rodentolepsis diminuta	0	1 (1)	NS
Rodentolepsis nana	0	4 (4)	NS

*Pasto is in the Colombian Andes, and residents have a high risk for developing gastric cancer.
†Tumaco is a region located at sea level on the Colombian coast and whose residents have a low rate of gastric cancer.
‡Ps for difference from χ^2 analysis.

more common in fecal samples obtained from children living in the high Andes population (P = 0.014). Strongyles (*Strongyloides stercoralis*), pinworms (*Enterobius vermicularis*), and tapeworms (*Rodentolepsis nana* and *Rodentolepsis diminuta*) were found in more limited numbers; however, all of these helminths were detected in samples obtained from individuals living in the Tumaco seacoast area and none were found in children residing in the Andes.

The overall prevalence of parasitic infection was significantly higher in Tumaco than in Pasto (93% versus 76%; P = 0.001; Table 2). Protozoal infections were more prevalent in Pasto than in Tumaco (84% versus 72%; P = 0.046). Regional differences were more marked for helminthiasis: 54% in Tumaco children versus 25% in Pasto (P = 0.000). Coinfections with protozoa and helminths were common in both populations of children; 21% of the children in Pasto were coinfected with protozoa and helminths, and in Tumaco where helminth infections were significantly higher, 45% of children were coinfected.

ELISA for Total Serum IgE. Serum IgE was significantly higher in children and adults living in coastal Tumaco compared with populations sampled of the same age range living in the Pasto region of the Andes (P < 0.03 and P < 0.001, respectively; Fig. 1). The IgE levels of sera sampled from children residing in Pasto were low in comparison with the moderate levels of serum IgE in the sera obtained from adults living in the same region (P < 0.02). In contrast, serum IgE levels were high in Tumaco children by age 6 years and were similarly elevated in adults living in Tumaco. Elevated IgE levels most likely reflect a high rate of parasitism.

Table 2. Prevalence of protozoan, helminth, and parasitic coinfections in Colombian children residing at sea level in Tumaco or in the Pasto region of the high Andes

Parasites	Geographic area		P*
	Pasto (n = 101), n (%)	Tumaco (n = 110), n (%)	
No parasitic infection	24 (24)	8 (7)	
With parasitic infection	77 (76)	102 (93)	0.001
Protozoa only	52 (51)	43 (39)	
Helminths only	4 (4)	10 (9)	
Coinfection	21 (21)	49 (45)	
All protozoa	73 (72)	92 (84)	0.046
All helminths	25 (25)	59 (54)	0.000

*Ps for difference from χ^2 analysis.

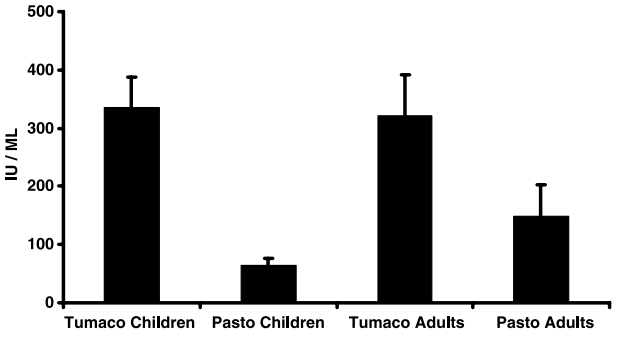

Figure 1. Total serum IgE (IU) in children and adults residing at sea level in Tumaco or in the Pasto region of the high Andes. Serum IgE was significantly higher in children and adults living in Tumaco (P < 0.03 and P < 0.001, respectively). IgE increased from low to moderate levels with age in people living in the Andes (P < 0.02) but peaked early at high levels in children living at sea level and remained elevated through adult life. *Columns,* mean ELISA absorbance (compared using Student's t test); *bars,* SE.

ELISA for IgG and IgG Subclass Responses to *H. pylori* Antigens. Based on statistical analysis of ELISA results from known negative sera, 239 of 251 serum samples from residents of both geographic areas were positive for IgG to *H. pylori*. Twelve sera were seronegative and included one 52-year-old female and 11 children (7 males/5 females; mean age, 2.7 years) equally distributed from both geographic regions. Seronegative children were 1 year younger on average than seropositive children (mean age, 3.7 years; P < 0.001) and seropositive adults from both regions were similar in mean age (54 years in Pasto/Tuquerres and 57 years in Tumaco; P = 0.09). The high rate of seroconversion to *H. pylori* (95%)

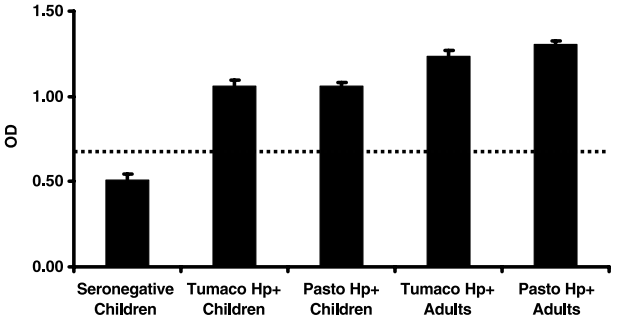

Figure 2. Serum IgG to *H. pylori* in children and adults residing at sea level in Tumaco or in the Pasto region of the high Andes. Ninety-five percent of the population seroconverted to *H. pylori* (*Hp*+). Serum IgG to *H. pylori* increased with age (P < 0.001), but levels of IgG specific for *H. pylori* were not different between groups of children (P = 0.43) or adults (P = 0.11) based on geographic region. *Columns,* mean ELISA absorbance (*OD*; compared using Student's t test); *bars,* SE. Only one adult sample was seronegative (absorbance value of 0.43; data not shown). *Dotted line,* cutoff value used for evaluating seroconversion (mean absorbance ± 3 SDs of established seronegative sera).

was evident in all age ranges, although IgG levels increased with age (Fig. 2; $P < 0.001$). There were no significant differences in levels of serum IgG to *H. pylori* between groups of seropositive children ($P = 0.43$) and seropositive adults ($P = 0.11$) based on geographic region. Th2-associated IgG1 levels against *H. pylori* antigens were highest followed by Th1-associated IgG2 responses and low levels of IgG3 and IgG4 antibodies (Fig. 3). Children from Tumaco who were seropositive for *H. pylori* developed higher Th2-associated IgG1 responses to *H. pylori* compared with children from Pasto ($P < 0.0002$). Other IgG isotype responses (IgG2, IgG3, and IgG4) to *H. pylori* were increased in older individuals but were not significantly different between groups of children or adults sampled from the two geographically distinct areas.

Discussion

Children living in rural Colombia acquire *H. pylori* infection at a very early age and prevalence dramatically increases during the first 4 years of life (15). In addition to evidence that rates of *H. pylori* seroconversion are very high in Colombian children, this study shows that intestinal parasites were also very common in Colombian children, particularly those living near sea level where environmental conditions favor the life cycle and transmission of parasites to children. Infection with most of the protozoan species detected was similar between children from Tumaco and Pasto. The only known pathogenic protozoan that was more commonly detected in feces from Tumaco children was *G. duodenalis*. Although these children were asymptomatic, *G. duodenalis* can cause significant diarrhea (30). *Entamoeba coli* was detected more frequently in children from the Pasto region, although *E. coli* is considered nonpathogenic (30). The increased prevalence of helminth infections detected by fecal screening is more clinically relevant and was supported by elevated IgE levels, indicative of enhanced systemic Th2 responses to helminth infections in humans (31). Notably, Tumaco children with higher prevalence of helminthiasis also had greater Th2-associated IgG1 antibody responses to *H. pylori*. These results support the hypothesis that the lower risk for gastric cancer in these individuals later in life may result from helminth-promoted Th2-polarizing systemic immune responses that are initiated in childhood.

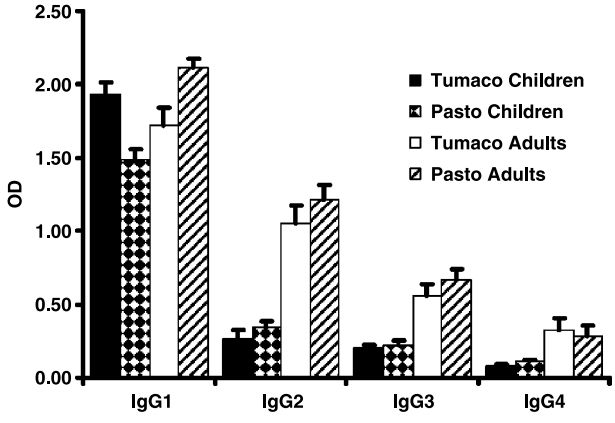

Figure 3. IgG subclass responses to *H. pylori* antigens in children and adults residing at sea level in Tumaco or in the Pasto region of the high Andes. IgG subclass responses were analyzed by age and geographic origin in 239 children and adults who were seropositive to *H. pylori* by ELISA for IgG. Th2-associated IgG1 responses were higher in children living near sea level (Tumaco) compared with children living in the high Andes (Pasto region; $P < 0.0002$) and was associated with higher concurrent helminthiasis in Tumaco children. *Columns,* mean ELISA absorbance (compared using Student's *t* test); *bars,* SE.

Innate and acquired immunity have been shown to be important in clearance of protozoal mucosal infections in mouse models, but the comparative importance of B-cell– and T cell–mediated immunity in human infections is less clear (32). However, polarization of the immune response toward a Th2 bias by helminth infections is well established (33) and may bias inflammatory responses to other pathogens acquired by children, such as *H. pylori*, through induction of Th2 associated cytokines, such as IL-10 and transforming growth factor-β. Modulation of the immune response to *H. pylori* infection toward an anti-inflammatory Th2-like profile would be consistent with the ''hygiene hypothesis''; immune stimulation with microbial and parasitic infections early in life drives induction of immunoregulatory lymphocytes and production of anti-inflammatory cytokines that prevent immune hyperreactivity states, such as allergy and autoimmune diseases (34). Indeed, in Italian children who had access to modern health care and were unlikely to be infected with parasites, *H. pylori* infection was associated with organ-specific autoantibodies, including parietal cell autoantibodies associated with atrophic gastritis, in comparison with uninfected children (35). The results of our study also are consistent with the amelioration of gastric atrophy in the *Helicobacter* gastritis model in mice coinfected with *Helicobacter felis* and *Heligmosomoides polygyrus*, a murine intestinal nematode (25). Reduction in the risk for gastric atrophy in mice dually infected with *Helicobacter* and the nematode was supported by a shift in the Th1-biased response to *H. felis* toward a Th2-like phenotype of gastritis. Concurrent nematode infection enhanced tissue expression of anti-inflammatory IL-4, IL-10, and transforming growth factor-β cytokines, which were offset by lower expression of proinflammatory IFN-γ, tumor necrosis factor-α, IL1-β, and the Th1-associated chemokines of IP-10, RANTES, and macrophage inflammatory protein-1β (25).

Sera from Colombian children and adults living in Tumaco contained significantly high levels of IgE, which was associated with greater childhood parasitism, in particular, intestinal helminths. Serum IgE is a polyclonal response that has been associated with antigen-specific and nonspecific immune stimulation (36). In developed countries, elevated IgE is most commonly associated with allergies (37), and in developing tropical areas, such as Tumaco, elevated IgE is most commonly associated with parasitism (23). In addition to promoting IgE levels in serum and tissues, a variety of helminth infections have been shown to induce Th2-polarized cytokine responses (23, 38), which may afford protection from reinfection (33). The variety of intestinal parasites found in the Colombian children confirms that helminth infection is common and coinfection with multiple species occurs. Fecal samples from adults were not tested, but others have shown persistence of intestinal parasites in 62% of adults living in poor socioeconomic conditions (39). Persistence of parasitic infections into adulthood may explain the long-term elevation of serum IgE and age-associated increase of predominantly IgG1 antibodies to *H. pylori* in the sera from adults living in both Tumaco and Pasto.

The samples collected from these asymptomatic individuals were limited to feces and sera and were obtained from sample sets collected as part of two independent health assessments. Definitive proof of *H. pylori* infection, characterization of infecting strains, and histologic evaluation of gastritis and associated secondary changes were not possible. To test the association between parasites in children and potential polarization of the host immune response to *H. pylori*, we assayed feces for parasites and serum for IgG responses to *H. pylori* as noninvasive and sensitive methods to screen for parasitic and *H. pylori* infections. These assays have been used to estimate prevalence of *H. pylori* in defined populations (40),

and as others have reported (19, 22, 41), we developed an antigen-specific ELISA for *H. pylori* because the accuracy of commercial kits for serologic screening for *H. pylori* infection in children has been questioned (42). Furthermore, commercial kits for measurement of IgG subclass responses to *H. pylori* are not available. We used an antigen mixture consisting of three clinical isolates from Colombian patients to increase the sensitivity of the *H. pylori* ELISA, as regional differences in sensitivity and specificity of *H. pylori* antibody assays have been suggested by others (41, 43).

Consistent with our findings of 95% seroconversion to *H. pylori* in the residents sampled from the Pasto and Tumaco regions, the prevalence of seroconversion to *H. pylori* was reported to be 93% of the adult population of Pasto (2). A prior study using the [^{13}C]urea breath test reported similarly high prevalence of *H. pylori* infection in children ages 1 to 6 years living in Pasto (58.6%) and Tumaco (59.7%; ref. 15). Infection was shown to increase with age in both Pasto and Tumaco; therefore, the age of acquisition of *H. pylori* after age 1 year did not seem to be a primary factor responsible for the differences in the rates of gastric cancer incidence in adults. Other identified differences that may have significance were the presence (Pasto) or absence (Tumaco) of public sewers, variation in diet (grains in Pasto; seafood in Tumaco), and genotypic heterogeneity of *H. pylori*. In both areas, *H. pylori* infection was associated with stunted growth in children, and sharing a bed seemed to increase the transmission rate between siblings. These findings and the results of our study are supported by other epidemiologic surveys that have reported overall seroprevalence of IgG to *H. pylori* to be inversely related to socioeconomic status in Mexico (44) and to be quite high (92%) in the indigenous peoples of South America with >80% seroconversion in children by age 3 years (45).

The propensity for adults of high socioeconomic status to produce greater Th1-associated IgG2 responses to *H. pylori* is consistent with the hygiene hypothesis (34). The asymptomatic Colombian children we evaluated had significant helminth infections and developed Th2-associated IgG1 responses to *H. pylori* that predominated over IgG2, IgG3, and IgG4 subclasses. The IgG1 response seemed to be promoted by concurrent helminthiasis and this polarization of the IgG subclass response continued through adulthood. These results are consistent with a comparison made between *H. pylori*–infected symptomatic children and adults from Soweto, Africa and Australia and Germany (21). An IgG1 predominant response was observed in 81% of Sowetan adults and 90% of children compared with 4.7% of Australians and 4.4% of Germans, providing evidence that immunoglobulin responses to *H. pylori* infection differ between subjects living in Africa and individuals from developed countries. Relatively low IgG3 responses to *H. pylori* in the Colombian children contrasts with IgG3 responses in *H. pylori*–infected Polish children (19) and Australian adults (22) who were associated with peptic ulcer disease, chronicity of antral gastritis, and *H. pylori* colonization density (19). These differences may be related to parasitism or other potential factors that were not similarly evaluated across all three studies. Finally, the IgG4 response to *H. pylori* measured in the Colombian sera increased with age but was low and not dissimilar between individuals from Tumaco and Pasto. Others have also reported IgG4 responses to *H. pylori* (19, 22), but to our knowledge, IgG4 has not been reported as a biomarker for gastric pathology associated with chronic *H. pylori* infection.

The epidemiologic data we present support the hypothesis that childhood parasitism concurrent with *H. pylori* infection could affect the risk for *H. pylori*–associated gastric cancer. Intestinal parasitic infections and associated elevated IgE levels were associated with a reduced *H. pylori* prevalence in adults, but not children, living in Mexico (39), suggesting that intestinal parasites could affect persistence of *H. pylori* colonization in adults by unknown mechanisms. Coinfection with high levels of ascarids and whipworms has been shown to deplete parasite-specific cellular responses and reduce Th1 cytokine responses to both parasite-specific antigens and nonspecific mitogens in young adult Brazilians (23). These authors hypothesized that Th2 responses of elevated IL-10 and IL-13 were likely to promote protective immunity in controlling the persistent parasite burden while minimizing immune-mediated tissue damage. Parasites may potentially induce antigen-specific and nonspecific regulatory T cells, and parasite-released immunomodulators may be adjuvants for Th2-related responses or otherwise alter functions of antigen-presenting cells (24).

The interaction among parasite, bacterial pathogen, and host is no doubt subject to variable outcomes under the influence of many potential factors that are increasingly appreciated for their potential effect on clinical disease. Mouse models to elucidate mechanisms (25, 46) have to date supported the suggestion that childhood parasitism, particularly intestinal helminthiasis, promotes Th2-polarizing immune responses to *H. pylori* infection and may be a significant factor decreasing the risk of gastric cancer later in life.

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