**Letter to the Editor**

**Immunoglobulin G Subclass Responses to *Helicobacter pylori* Vary with Age in Populations with Different Levels of Risk of Gastric Carcinoma**

*Helicobacter pylori* infects one-half of the world’s population, leading to peptic ulcer in up to 15% of adult cases, and increases the risk of gastric adenocarcinoma by 2.3- to 9-fold (11). Colonization induces an intense immune response in the human host which rarely leads to clearance of the organism but which is linked to disease expression (3, 4).

Childhood *H. pylori* infection is common in developing countries. In The Gambia, 85% of children are colonized by 30 months of age (12). Despite this, gastric cancer is uncommon in West Africa (8). It has been suggested that the host immune response to *H. pylori* infection in an African population differs from that observed in subjects from developed countries, although it is unclear whether this reflects changes in host response at all stages of infection (10). We investigated whether circulating *H. pylori*-specific immunoglobulin G2 (IgG2) and IgG1 levels, as markers of mucosal Th1 and Th2 responses, respectively (1), were similar between Gambian and United Kingdom adults and children. Sustained differences in mucosal Th1/Th2 bias against *H. pylori* might explain a low prevalence of adult disease in a population with a very high early prevalence of colonization.

Four groups of subjects were recruited after appropriate ethical approval and consent, comprising adults and children with *H. pylori* infection from the United Kingdom and from The Gambia. Thirty-four United Kingdom children 4 to 14 years of age (mean age, 11 years) with *H. pylori* infection confirmed by endoscopy (hematoxylin and eosin [H+E] stain and Giemsa stain; urease positive) were studied. *H. pylori* was successfully cultured from all subjects in this group. A group of 56 Gambian children (2 to 5 years of age), of whom 19 had *H. pylori* infection confirmed by endoscopy (H+E and Giemsa, but cultures not undertaken) were recruited, while the remaining 37 did not undergo endoscopy but were IgG seropositive. One hundred sixty-three seropositive United Kingdom adults aged 50 years and 30 adult Gambians (25 to 70 years) with infection confirmed by endoscopy (H+E and Giemsa stain and urease positive) were studied. *H. pylori* was successfully cultured from all subjects in this group. A group of 56 Gambian children (2 to 5 years of age), of whom 19 had *H. pylori* infection confirmed by endoscopy (H+E and Giemsa, but cultures not undertaken) were recruited, while the remaining 37 did not undergo endoscopy but were IgG seropositive. One hundred sixty-three seropositive United Kingdom adults aged 50 years and 30 adult Gambians (25 to 70 years) with infection confirmed by endoscopy (H+E and Giemsa stain and urease positive) were studied. *H. pylori* was successfully cultured from all subjects in this group. A group of 56 Gambian children (2 to 5 years of age), of whom 19 had *H. pylori* infection confirmed by endoscopy (H+E and Giemsa, but cultures not undertaken) were recruited, while the remaining 37 did not undergo endoscopy but were IgG seropositive. One hundred sixty-three seropositive United Kingdom adults aged 50 years and 30 adult Gambians (25 to 70 years) with infection confirmed by endoscopy (H+E and Giemsa stain and urease positive) were studied. *H. pylori* was successfully cultured from all subjects in this group. A group of 56 Gambian children (2 to 5 years of age), of whom 19 had *H. pylori* infection confirmed by endoscopy (H+E and Giemsa, but cultures not undertaken) were recruited, while the remaining 37 did not undergo endoscopy but were IgG seropositive.

Individual *H. pylori* IgG2/IgG1 ratios emphasize the difference in IgG subclass production between groups. A Kruskal-Wallis test suggested significant variation in the responses in the four populations (*P* < 0.0001). The response in the United Kingdom adult population was significantly higher than in the other three populations (*P* < 0.0001). The median IgG2/IgG1

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**TABLE 1. Titers of *H. pylori* IgG1 and IgG2**

| Immunoglobulin | UK uninfected children (n = 35) | UK children (n = 35) | Gambian children (n = 56) | UK adults (n = 163) | Gambian adults (n = 30) |
|---------------|---------------------------------|----------------------|--------------------------|---------------------|------------------------|
| IgG1 ‡4 × 10^−5 (8 × 10^−6–2 × 10^−4) | 3.9 (1.5–11.8) | 4.37 (1.6–11.9) | 4.07 (1.7–32.5) | 6.5 (2.4–13.1) |
| IgG2 †1 × 10^−3 (7.3 × 10^−4–2 × 10^−3) | 1.3 (0.8–10.9) | 1.95 (0.9–16.7) | 99.46 (5.0–17.9) | 1.3 (0.9–10.2) |

* Mann-Whitney U test. Symbols: †, *P* < 0.0001 for all between-group comparisons; ‡, *P* < 0.0001 for all between-group comparisons. UK. United Kingdom.
ratio for United Kingdom and Gambian children and Gambian adults demonstrated an IgG1-biased response, whereas United Kingdom adults demonstrated a log-fold increase in the same ratio with a predominantly IgG2-biased response (Fig. 1).

We have observed that United Kingdom adults produce high \textit{H. pylori}-specific IgG2 levels (indicating a Th1 reaction to \textit{H. pylori}), whereas Gambian adults and children and United Kingdom children produce predominantly IgG1 (indicating a Th2 response). These data suggest that Gambians, who are challenged with \textit{H. pylori} infection in childhood, maintain the Th2 response throughout life, whereas United Kingdom adults appear to convert to a Th1 response.

European children may mount a gastric mucosal Th1 response to \textit{H. pylori} (7), similar to adults (2). However, we have measured an apparent systemic Th2 response. This discrepancy between the mucosal and systemic responses may be explained by local regulatory responses, such as bystander suppression, mediated by transforming growth factor beta. Such a mechanism can selectively suppress local cell-mediated inflammation (6), encouraging a Th2 bias. This process, however, requires a continual mucosal challenge, which is not sustained in United Kingdom children, allowing a Th1 phenotype to develop. This Th1 bias may be associated with gastric carcinogenesis (3).

The bias in IgG2 production in United Kingdom adults is consistent with the hypothesis that a shift in polarity of T-helper-cell responses in chronic \textit{H. pylori} infection could provide an explanation for the apparent difference in prevalence of \textit{H. pylori}-associated gastric carcinoma between West African and European populations. These results require confirmation with direct studies of gastric mucosa in these four groups of subjects. The factors involved in the reversal of T-helper-cell polarity in United Kingdom children to one that leads to gastric cancer are unknown but are likely to include bacterial factors, host genetics, and coexistent enteropathy (5).

Conventional vaccines have failed to eradicate \textit{H. pylori}, but this study highlights differences in immune responses associated with populations with high and low risks of gastric cancer. Identifying those factors that lead to a reversal of the African phenotype to the cancer-prone United Kingdom phenotype could allow immunomodulation to achieve the elusive goal of preventing \textit{H. pylori}-associated gastric cancer.

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**FIG. 1.** Box plot of log\textsubscript{10} IgG2/IgG1 titer ratios in United Kingdom (UK) and Gambian adults and children.
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