Longitudinal Analysis of Serological Responses of Adults to *Helicobacter pylori* Antigens

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Because *Helicobacter pylori* persist for decades in the human stomach, the aim of this study was to examine the long-term course of *H. pylori*-specific serum immunoglobulin G (IgG) responses with respect to subclass and antigenic target. We studied paired serum samples obtained in 1973 and in 1994 in Vammala, Finland, from 64 healthy *H. pylori*-positive adults and from other healthy control subjects. *H. pylori* serum immunoglobulin A, IgG, and IgG subclass responses were determined by antigen-specific enzyme-linked immunosorbent assays. *H. pylori*-specific IgG1 and IgG4 subtype responses from 47 subjects were similar in 1973 and 1994, but not when compared with unrelated persons. *H. pylori*-specific IgG1:IgG4 ratios among the participants varied >1000-fold; however, 57 (89.1%) of 64 subjects had an IgG1:IgG4 ratio >1.0, consistent with a predominant IgG1 (Th1) response. Furthermore, ratios in individual hosts were stable over the 21-year period (P < .001). The immune response to heat shock protein HspA was unchanged in 49 (77%) of the 64 subjects tested; of the 15 whose serostatus changed, all seroconverted and were significantly younger than those whose status did not change. These findings indicate that *H. pylori*-specific antibody responses are host-specific with IgG1:IgG4 ratios stable over 21 years, IgG1 responses predominating, and HspA seroconversion with aging.

*Helicobacter pylori* colonizes the gastric mucous layers of much of the world’s population [1, 2]. *H. pylori* colonization is clinically unapparent, despite histological evidence of host responses, such as chronic gastritis [3]; it is a risk factor for the development of peptic ulceration, gastric MALT-lymphoma, and noncardiac gastric cancer [3–5] yet may protect against other illnesses [6]. *H. pylori* infection persists for decades and often for life [1, 2]. Its ability to persist occurs through a long-standing dynamic equilibrium between microbe and host [6], influenced by many factors, including the adaptive immune responses [7]. However, after an initial transience, bacterial persistence suggests that the immune responses are ineffective at microbe elimination, resulting in the establishment of host colonization [8, 9].

*H. pylori* strains may carry the cag genomic island, which encodes a type IV secretion system, including the CagA protein [10]. Persons carrying such strains produce serum immunoglobulin G (IgG) antibodies to the CagA protein [11]. Patients colonized with *H. pylori* develop strong serologic responses to *H. pylori*-specific antigens [12]. In contrast, only 30%–40% of colonized persons develop antibodies to a highly conserved 13kDa *H. pylori* heat shock protein (HspA) [13], a response that appears to be age-associated [14, 15].

The adaptive immune responses in *H. pylori*-colonized persons involve both T and B lymphocytes [12] and may be considered as being polarized by the commitment of naive T cells to undergo Th1 or Th2 re-
sponses. Th1-dominated responses affect local immune effectors including interleukin 2 (IL-2), interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α) [16, 17], whereas Th2 responses involve interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 6 (IL-6) [7, 18]. Host B cells are activated by both Th1 and Th2 cells by means of specific cytokines, and responses involving IgG1, IgG2, IgG3, and IgG4 [19] predominate systemically. IgG1 and IgG4 are considered markers of Th1 and Th2 responses, respectively [20, 21]. The influence of environmental factors such as parasitic infections [22], host factors including aging, and presence of H. pylori in the differentiation and regulation of T-cell responses remains uncertain [23].

We studied antigen-specific serum immunoglobulin levels over a 21-year period in a group of healthy adults. Our goal was to assess HspA immune responses and the stability of H. pylori–specific IgG1 and IgG4 over decades of colonization.

**SUBJECTS AND METHODS**

**Subjects.** Based on a population of 16,000 inhabitants, 408 healthy subjects in Vammala were selected at random from Finland’s National Population Register during both 1973 and 1994 [24]. Individuals who had participated in the initial 1973 study and were still alive in 1994 were invited to reparticipate; a total of 224 (54.9%) persons agreed.

We selected 64 adults who were persistently H. pylori seropositive in 1973 and 1994, as previously determined [24, 25], and from whom paired serum samples were available. The subjects included 29 men and 35 women. We also selected 25 subjects known to be H. pylori seronegative in both 1973 and 1994 to serve as negative control subjects for assay standardization and to determine background levels of immune responses to specific antigens. In total, 89 (39.7%) of the 224 original subjects sampled at both times were included in these studies. We studied 47 of the 64 subjects because a sufficiently large serum sample was available from each to perform all of the assays for IgG subclasses in duplicate. Subjects were classified as younger (n = 22; age, 16.6–28 years [median, 24.7 years]) or older (n = 25; age, 31.3–58.2 years [median, 46.4 years]); we chose these two groups to examine whether antibody kinetics differed in younger or older adults. As controls, we used serum from 1994 from 37 H. pylori–seropositive subjects (median age, 53.6 years); serum samples from a subset of 24 of these subjects who were seropositive in all 3 of the IgG and immunoglobulin A (IgA) H. pylori and IgG CagA assays were used as controls in particular studies.

The selection of subjects who were consistently positive was necessary to determine the HspA status, which is only possible in H. pylori–positive subjects, and to determine variations in IgG subclasses that are only possible in persons with detectable H. pylori–specific IgG responses at both time points. Among the overall population of 221 subjects assessed in 1973 and 1994, only 12 (5.4%) subjects changed H. pylori status, as reported elsewhere [25]. As such, the effect of our selection is minimal.

**Serum antibodies to H. pylori antigens.** Antibody responses were determined by antigen-specific enzyme-linked immunosorbent assays (ELISAs), including acid-glycine extract [24, 26], H. pylori CagA antigen [11, 25], and H. pylori HspA [13, 14]. Serum samples were considered CagA positivity if the optical density ratio (ODR) was >0.35, as described elsewhere [25] (see the Appendix, which appears only in the electronic edition of the Journal).

**IgG subclass determinations.** ELISAs of IgG1 and IgG4 subclasses to H. pylori antigens were performed on samples obtained from 47 subjects for whom a sufficiently large serum sample was available for complete determinations in duplicate [27].

**Statistical analysis.** A Student t test analysis assuming equal variance was performed; P < .05 was considered significant in all comparisons using SPSS software (SPSS Inc). The χ² analysis was also performed for dichotomous variables using EPI-INFO 2005 software (version 3.3.2; Centers for Disease Control and Prevention). Correlation analysis between results in 1973 and 1994 was performed, and linear regression coefficients and P values were calculated using SPSS software.

**RESULTS**

**Interhost variation in humoral responses to H. pylori antigens.** In our population of 64 H. pylori–seropositive subjects, all had IgG responses to H. pylori in both 1973 and 1994, by definition. Persistent IgA and CagA positivity was observed in 42 (65.6%) and 55 (85.9%) of these subjects in 1994. In 1973, there was no difference in age or sex between the 22 IgA-negative subjects and the 42 persistently IgA-positive subjects, but there was a significantly lower ODR in CagA (0.46 vs 0.71; P < .005) and in IgG titer (2450 vs 5460; P < .005). The positive responses of hosts ranged from reciprocal titers of 700–25,000 for IgG and 70–1000 for IgA, and ODRs of 0.36–1.52 for CagA (Figure 1). The ranges observed were similar in 1973 and 1994, and in 24 unrelated persons who were used as a control group. These data indicate considerable interhost variation in serological responses with all 3 assays, even among adults who were persistently positive.

**Stability of IgG and IgA responses to H. pylori antigens in individual hosts.** We assessed stability of the serological responses in individual persons over a 21-year time period. Among the 64 subjects who were H. pylori seropositive in both 1973 and 1994 [24, 25], the IgG responses to H. pylori whole cell antigens were extremely stable during the 21-year period (mean Δlog titer variation in titer, 0.23 ± 0.15) (Table 1). As a control, we compared the 1973 levels with the 1994 levels in unrelated positive persons, which showed significantly greater var-
Figure 1. Stability of *Helicobacter pylori*–specific and CagA-specific immune responses over 21 years. A, Log10 *H. pylori*–specific reciprocal immunoglobulin G (IgG) titers in 64 subjects in 1973 and 1994, and comparison with 1994 values in 24 control subjects. B, Log10 *H. pylori*–specific reciprocal immunoglobulin A (IgA) titers in 42 subjects and 24 control subjects. C, CagA IgG in 55 subjects and 24 control subjects. Data are median value ± interquartile range (IQR); circles represent values >90th or <10th percentile. In each panel, the number of subjects reflects those with a positive result of the specified assay in both 1973 and 1994; 24 subjects were positive in all 3 assays in both years and were matched with 24 similarly aged control subjects in 1994.

Stability of serum IgG subtypes over 21 years. We asked whether age of subjects correlated with the immune response levels observed. There were no significant differences in IgG1 or IgG4 levels, or in the IgG1:IgG4 ratio for the 1973 and 1994 serum samples from the younger subject group (mean age, 23.9 ± 3.7 years) or the older subject group (mean age, 45.2 ± 8.2 years) (Table 2). We then addressed whether in individual hosts, the specific IgG1, IgG4, and ratio values were stable over the 21-year period. For the 47 subjects tested, *H. pylori*–specific IgG1 and IgG4 levels in 1973 and 1994 were remarkably similar (Table 2 and Figure 2). However, great variation in the magnitude of the IgG1:IgG4 ratios among the 47 *H. pylori*–positive subjects was observed. Nine subjects had extremely high or low ratios (≥11.0 or ≤0.1) at at least 1 of the 2 time points. In each of these 9 cases, values did not change direction of dominance between 1973 and 1994. Eliminating the data for these 9 subjects with low values (IgG1, n = 8; IgG4, n = 1) confirmed a stable and host-specific response over the 21-year observation period (Table 2). Even with their inter-individual variation (0.41 ± 0.27 log10; *P* < .001). In the 42 persistently IgA-positive subjects, there was also a low level of variation in the titers from 1973 to 1994 (0.20 ± 0.17), in comparison to the variation with unrelated persons (Table 1). Over the 21-year period, the level of anti-CagA antibodies were also relatively stable, varying only by 24.1% ± 15.7%. For the paired samples over the 21-year period, the IgA and IgG responses to the *H. pylori* whole cell and CagA antigens in individual hosts were highly correlated (*r* = 0.59, 0.68, and 0.70, respectively; all *P* < .001). In contrast, immune responses to the same antigens compared with the test group of 24 unrelated individuals in 1994 showed little relationship, as expected. From these data, we conclude that among individuals with paired samples, immune responses to *H. pylori* antigens were significantly stable and host-specific over the 21-year observation period.

**IgG subclass-specific responses to *H. pylori* antigens.** A subset of 47 persistently IgG-seropositive subjects was used for analysis of IgG subclass responses. Of these subjects, 34 (72.5%) were also persistently positive for α–*H. pylori* IgA and 46 (97.9%) were persistently positive for α–CagA antibodies. Serum IgG1:α–*H. pylori* concentrations ranged from 0.09 to 101.7 ng/mL in 1973 and from 2.2 to 129.6 ng/mL in 1994 (Table 2 and Figure 2). Thus, there was substantial interindividual variation (≥3 log10), but most values were within a narrower range (Table 2 and Figure 2). IgG4 values ranged from 0.1 to 73.0 in 1973 and from 0.2 to 73.3 ng/mL in 1994, also a nearly 3 log10 range (Table 2). However, despite these wide ranges, >50% of the subjects varied within a <1 log10 range (Table 2), and across the population, the median IgG1:IgG4 ratio was ~2.0. However, the log10 IgG1:IgG4 ratio of individual test subjects ranged from −1.98 to 1.79 in 1973, and from −0.66 to 1.38 in 1994, showing >2 log10 interindividual variation (Table 2). The 37 control participants obtained in 1994 showed comparable levels of variation in subclass responses to the *H. pylori* antigens. Thus, the IgG1 and IgG4 subclass responses to *H. pylori* whole cell antigens also showed extensive interindividual variation.
Conclusion, median IgG1:IgG4 ratios were uniform within the groups. We observed higher IgG4 values in the control subjects, with a consequent decrease in the IgG1:IgG4 ratio; however, these were not significantly different from the paired samples. Stability of serum IgG subtypes over the 21-year period was examined by regression analysis for the paired 1973 and 1994 samples. Our *H. pylori* hypothesis is that there would be correlation, indicative of a stable immunologic response, and we found highly significant R values (Table 3). As controls, we compared the 1973 serum sample (serum sample 1) with a 1994 serum sample from an unrelated person (unpaired serum samples). As expected, the IgG subtype responses for the unpaired samples showed no correlation. From the strong correlation in the paired serum samples (but not in unpaired specimens), we concluded that there is indeed substantial stability. The IgG1 and the IgG4 specific responses to the *H. pylori* whole cell antigens in individual hosts were also weakly (r = 0.24) but significantly (P = .02) correlated. These results indicate that the IgG1 and IgG4 levels and their ratios are host-specific and remained relatively stable over 21 years in *H. pylori*-positive adult subjects.

**Polarity of the Th immune responses.** In 1973, a Th1-dominant immune response (level of IgG1>IgG4) was observed in 34 (80.9%) of the 42 subjects with clear-cut responses (mean age ± SD, 35.9 ± 12.8 years) (Table 4). Th2 was dominant in 8 (19%) (mean age ± SD, 37.0 ± 13.3 years), and 5 others had essentially equivalent (borderline) levels (Table 4). Over the next 21 years, 31 (73.2%) of the 42 with clear-cut responses continued to have a response in the same direction, 8 (19.0%) had a changed direction of response, and 3 (7.1%) had responses that became borderline. Of the 13 subjects who had a Th2-dominant or borderline response in 1973, 6 (46.1%) converted to a Th1 response (in 1973, 3 subjects had borderline responses and 3 had Th2-dominant responses). Thus, by 1994, 32 (74.4%) of 43 definable persons (mean age, 55.6 ± 12.4) had Th1–predominant responses, 11 had Th2-dominant responses (mean age, 52.8 ± 12.4), and 4 were borderline. Three (37.5%) of 8 subjects who had Th2-dominant responses in 1973

### Table 1. Variation in *Helicobacter pylori*-Specific and CagA-Specific Immune Responses in Study Subjects, over a 21-Year Period

<table>
<thead>
<tr>
<th>Assay</th>
<th>No. of subjects</th>
<th>Paired samples</th>
<th>Control subjects</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Absolute log₁₀ variation in titer or % variation</td>
<td>P value</td>
</tr>
<tr>
<td><em>H. pylori</em> IgG</td>
<td>64</td>
<td>0.23 ± 0.15&lt;sup&gt;d&lt;/sup&gt; NS</td>
<td></td>
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<tr>
<td><em>H. pylori</em> IgA</td>
<td>42</td>
<td>0.20 ± 0.17&lt;sup&gt;d&lt;/sup&gt; &lt;.001</td>
<td></td>
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<tr>
<td>CagA IgG</td>
<td>55</td>
<td>24.1 ± 15&lt;sup&gt;d&lt;/sup&gt; .002</td>
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</table>

**NOTE.** Only those subjects who were seropositive in the indicated assay in both 1973 and 1994 are included. IgA, immunoglobulin A; IgG, immunoglobulin G; NS, no specimen analyzed; SD, standard deviation.

<sup>a</sup> P values determined using Student t test; NS, P > .05.

<sup>b</sup> Single 1994 sample from an unrelated *H. pylori*-positive subject; P values compared with samples from 24 subjects in 1973.

<sup>c</sup> Measured as reciprocal titer.

<sup>d</sup> Variation measured as absolute difference between the 2 studied samples and shown as mean ± standard deviation (SD) log₁₀ value.

<sup>e</sup> Variation measured as absolute percent difference between the 2 studied samples and shown as mean ± SD.

### Table 2. *Helicobacter pylori*-specific IgG Subclass Concentrations, in Study Patients in 1973 and 1994

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Age in 1994, years</th>
<th>Concentration, ng/mL, median (IQR)</th>
<th>IgG1:IgG4 ratio</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IgG1</td>
<td>IgG4</td>
</tr>
<tr>
<td>All (paired)</td>
<td>47</td>
<td>56.3 ± 12.5</td>
<td>17.4 (9.0–32.1)</td>
<td>9.5 (2.4–14.7)</td>
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<tr>
<td>Younger</td>
<td>22</td>
<td>44.9 ± 3.7</td>
<td>15.8 (8.8–35.3)</td>
<td>9.7 (2.3–15.1)</td>
</tr>
<tr>
<td>Older</td>
<td>26</td>
<td>66.2 ± 8.2</td>
<td>17.5 (8.9–28.6)</td>
<td>9.5 (2.6–15.1)</td>
</tr>
<tr>
<td>Control subjects&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
<td>51.4 ± 5.2</td>
<td>NS</td>
<td>NA</td>
</tr>
</tbody>
</table>

**NOTE.** IgG, immunoglobulin G; IQR, interquartile range; NA, not applicable; NS, no specimen analyzed.

<sup>a</sup> Single 1994 sample from an unrelated *H. pylori*-positive subject.
had a change in the direction of response in 1994, compared with only 5 (14.7%) of 34 persons who had Th1-dominant responses in 1973 (P = .01, FET). Nevertheless, the proportions of subjects with Th1 and Th2 immune responses were about the same at the 2 time points, 21 years apart. The magnitude of the Th1 and Th2 ratios in 1973 and 1994 (Table 4) show clear distinctions for the majority of hosts.

**Stability of IgG-specific responses to HspA antigens.** We next examined host responses to *H. pylori* HspA, a conserved antigen to which only a fraction of *H. pylori*–positive subjects respond [15–17]. Over the 21-year period, 49 (76.6%) of the 64 study subjects had stable HspA immune response status, either persistently HspA positive (29 subjects [45.3%]) or HspA negative (20 subjects [31.3%]) (Table 5). Over the 21 years, there were 15 seroconversions (negative to positive), and no seroreversions (P < .001). In 1973, the 29 seropositive subjects were older (62.5 ± 12.2) than the 35 seronegative subjects (mean age ± SD, 52.0 ± 11.1 years; P = .005). The mean age (SD) of the persons who had seroconverted by 1994 was almost identical to that of the persons who remained seronegative (mean age ± SD, 52.5 ± 9.9 years vs 51.6 ± 12.2 years; Table 5). In 1994, the 44 seropositive subjects were significantly older than the 20 who remained seronegative (mean age, 59.1 ± 12.3 vs 51.6 ± 12.2 years; P = .03). Among the 37 control subjects, the 25 HspA-seropositive subjects were also significantly older in 1994 than the 12 seronegative subjects, results that confirm the association of HspA seropositivity with host age [14, 15]. Thus, with adult aging, there is a strong tendency toward increasing HspA seroresponsiveness, with no seroreversion observed.

**Association of HspA status and immune responses to other H. pylori antigens.** Because responses to HspA are acquired over the course of *H. pylori* colonization, we asked whether there was any relationship between a subject’s seropositivity for HspA and their IgG and IgA immune responses against either *H. pylori* whole cell or CagA antigens. No associations between subject HspA status and IgG responses to CagA or IgA responses to *H. pylori* whole cell antigens were found. However, the persistently HspA-negative (serofast-negative) subjects had significantly lower IgG immune responses to *H. pylori* whole cell antigens than did those subjects who had HspA seroconversion and those who had stable positive responses (serofast-positive) to HspA (data not shown). There were not significant differences in the Th1:Th2 ratios in the hosts according to their HspA serostatus in 1973 or in 1994 (data not shown).

**DISCUSSION**

The equilibrium between host and microbe that allows *H. pylori* to persist in the human gastrointestinal system for several decades must depend on a variety of host, bacterial, and environmental factors [28]; however the bacterium’s ability to evade eradication by the host immune response is central to this capacity [7, 29]. We sought to examine subjects who were unequivocally *H. pylori* positive for a long period of time, without having to factor in any losses of *H. pylori* resulting from specific treatment. Thus, the present study focused on *H. pylori*–colonized adults from a community-wide survey who had not been treated with antibiotics to eradicate *H. pylori* and who were stably positive for *H. pylori*–specific serum antibodies over a 21-year interval. With this well-characterized [24–26] group of subjects representing a sample of the normal population, we could ascertain the stability and broad characteristics of their immune responses.

Overall, we found stability in the IgG values and IgG1 and IgG4 subclass values over the study period. We also observed that despite evidence of heterogeneity in CagA proteins [30], the immunological responses to CagA were also largely stable during the 21-year interval [25]. Cross-sectional and longitudinal studies that examined *H. pylori* seroprevalence across age groups have indicated the stability of positivity [24, 31], but the exact relationships had not been dissected. Other studies have documented CagA as a strongly immunogenic protein and showed a significant relationship between IgG1 and CagA antibody levels in patients with gastric cancer [32].

Characterization of adaptive immune responses to *H. pylori* in humans is essential to permit determining whether such responses contribute to the development of disease or its prevention [6], as well as identifying the bacterial constituents that evoke the responses. The immune responses to *H. pylori* in most individuals have been considered to be skewed toward Th1 [3, 12, 33–34], and the predominant responses have been in IgG1 and IgG2 [32, 35], as in other chronic infections [36]. Studying the immune responses to *H. pylori* in asymptomatic persons is a better way to understand the natural history of the interactions than focusing on symptomatic persons with altered gastric physiology [37] who present for endoscopy [27, 38].

IgG1, the predominant IgG subclass in humans [19], is considered a serologic marker of Th1 responses [20, 39]. An IgG1 (Th1) predominance in the *H. pylori* immune response has

Table 3. Relationship of the Immunoglobulin G (IgG) Subclass Responses over 21 Years for the Paired Samples, in Comparison to Unpaired Samples

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has been observed in children [40]. We confirmed that IgG1 production is predominantly stimulated, and that the immunoglobulin subclass levels were relatively stable during a 21-year interval. IgG4, part of B-cell responses to chronic infections [41], does not form large immune complexes and therefore induces inflammation less often [41]. Host immune responses with non-complement-fixing IgG isotypes, such as IgG4 in humans [39], are considered markers for Th2 responses [21, 39]. That levels of \textit{H. pylori}–specific IgG4 in the studied population were stable during the 21-year interval, independent of age, provides evidence for ongoing Th2 responses in adults. As in the chronic Mycobacterial infections—tuberculosis and leprosy—persistent IgG1 and IgG4 responses often are both present [36].

We also showed that \textit{H. pylori} antigen-specific IgG subclass responses occur in different proportions to those observed for total IgG subclasses, in which the IgG1:IgG4 ratio usually varies between 10:1 and 20:1 [42]. In contrast, in schistosomiasis, specific IgG1:IgG4 ratios are 2:1 or 5:1 [43], and in patients with tuberculosis, the ratio of IgG1:IgG4 responses to the Hsp65kDa heat shock protein is essentially at unity [44]. These examples indicate that specific IgG1:IgG4 ratios are not fixed but reflect the nature of the immunologic response to the microbial antigen in question.

Overall, examination of \textit{H. pylori} colonization over 21 years shows that there are both Th1 and Th2 host responses with Th1 dominance in most adult hosts, but Th2 predominance in a small proportion (~10%). The data also suggest that by the time in adulthood that adaptive immune responses have become established, the direction of adaptive immunity (Th1 or Th2 dominance) to this organism is largely but not completely stable.

Prior cross-sectional studies have shown increasing serologic recognition of HspA in older \textit{H. pylori}–positive hosts [14, 15]. In this longitudinal study, we showed that HspA status is generally stable but that there is a unidirectional trend toward seroconversion with aging. Thus, of 35 healthy subjects who were seronegative for both \textit{H. pylori} and HspA and were in their early 30s in 1973, 15 (42.8%) seroconverted over the 21-year period. This phenomenon indicates that there is a maturing of the immune response to \textit{H. pylori} with age, even in persons who presumably had already been colonized by the organism for decades. This contrasts with the general stability of responses to \textit{H. pylori} whole cell and CagA antigens and should be explored further to understand its immunological and possible clinical significance. The HspA protein is produced by a well-conserved and probably essential \textit{H. pylori} gene, \textit{hspA} [13]. Whether the age-related increased responses represent increases in bacterial expression of the protein or loss of tolerance to a conserved antigen is not known. However, the association of seroconversion with lower immune responses to other \textit{H. pylori} antigens at baseline suggests that the phenomenon is mediated primarily at the host level rather than by changing bacterial antigenic expression. An age-related increase in the number of responders and in titers for \textit{H. pylori} specific IgA has been reported by Salomaa-Rasanen et al [45].

This study is limited by several factors. The population studied is from a small community in a developed country in which the prevalence of \textit{H. pylori} colonization now is relatively low [24]. However, when subjects acquired \textit{H. pylori} in the early to mid-20th century, \textit{H. pylori} was highly prevalent in Finland [24, 46]. In addition, only adults were studied, and only 3 antigens were tested. However, the antigens are representative of broad categories. We examined IgG and IgA responses to \textit{H. pylori}.
pylori whole cell antigens, and IgG responses to a strain-specific antigen (CagA), and to a conserved but host-specific antigen (HspA) [13]. Nevertheless, considering a relatively homogenous population, as in this Finnish village, aids analysis, and H. pylori prevalence results are consistent with studies of other Western adult populations [47, 48]. Although the sample was moderate in size, the study design was able to demonstrate stability of antibodies over a 21-year period, as we have documented using other measurements in another study of this same population [25]. In addition, in this population, nearly all subjects (85.9%) also had IgG responses to CagA, whereas fewer subjects (65.6%) had IgA responses to whole cell antigen, consistent with the notion that IgG responses to H. pylori antigens are more universal than are IgA responses [49]. The fact that nearly all those who had a positive result of the IgG CagA assay or the IgA H. pylori assay in 1973 also had a positive result in 1994 also indicates the stability of the responses. Finally, while immune responses in adults may be relevant to the development of H. pylori–associated diseases, such as peptic ulceration or gastric cancer, important questions need to be resolved about the development of α- H. pylori responses in childhood, which may be critical to understanding gastric physiology [50]. The methodologies reported in studies of adults might be useful for parallel longitudinal studies of children.

References


