Unexpected Decrease with Age of *Helicobacter pylori* Seroprevalence among Swedish Blood Donors

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Blood donors are often used as proxies for the general population in studies of *Helicobacter pylori* epidemiology. Our aim was to test if the age-specific seroprevalence rates among blood donors match with the corresponding rates in a random population sample. This descriptive study was based on sera obtained from 3,502 blood donors representing all Swedish counties and cities. An age-stratified random population sample of 1,030 from Stockholm County served as comparison. Sera were analyzed by an in-house enzyme-linked immunosorbent assay for *H. pylori* immunoglobulin G antibodies. In the population sample, we found the expected increase with age in the seroprevalence of *H. pylori* infection. This was true also among young blood donors, while the prevalence-by-age curve showed a deflection downward among blood donors who are ≥ 50 years of age. In this age group, the probability of being seropositive was reduced by 73% (95% confidence interval [CI], 63 to 81%) relative to the population sample. Overall, the adjusted odds ratio for *H. pylori* seropositivity among blood donors was decreased by 43% (95% CI, 28 to 55%). Thus, it appears that blood donors who are *H. pylori* seropositive selectively disappear from the blood donor cohort. We speculate that *H. pylori*-seropositive blood donors may tolerate repeated bleedings less well than do noninfected individuals and/or that the general well-being among those who are infected may be somewhat impaired. Our unexpected observation indicates that blood donors may be less suitable as proxies for the general population in analytic studies of *H. pylori* infection and that the underlying cause needs further study.

Helicobacter pylori is accepted as a principal cause of non-autoimmune chronic gastritis (10). Moreover, eradication of *H. pylori* prevents recurrence of peptic ulcers (14), and evidence for a causal role in gastric cancer is accumulating (11, 17, 30).

H. pylori infections are mainly acquired in early childhood (13). In developing countries, the seroprevalence of the infection is higher than in developed countries, where it rises gradually with age (12, 23). This latter phenomenon is considered to reflect a birth cohort effect. Hence, the higher infection prevalence in older individuals represents higher childhood infection rates in these birth cohorts rather than acquisition during adult life (1, 9).

In European epidemiological studies, blood donors are often used to represent the general population since all European countries have unpaid donors (34, 36). The appropriateness of this assumption has not been rigorously tested for *H. pylori* seroprevalence.

We took advantage of a large nationwide sample of blood donors, drawn for the purpose of investigating the seroprevalence of *Borrelia burgdorferi* infection in different parts of Sweden (28), to study also the age-specific seroprevalence of *H. pylori* infection, presuming that the blood donors were representative for the general population. We then compared the seroprevalence pattern among blood donors with that in a population control series consisting of sera from a representative sample of the adult population of Stockholm County.

MATERIALS AND METHODS

Subjects. (i) Blood donors. Sera were collected from unpaid blood donors from all 25 counties and metropolitan districts of Sweden. Representativity was achieved by including all consecutive blood donors from day 1 until all the predetermined sample size had been attained. All samples were collected during the same period, i.e., from September to December of 1995. The sample size was predetermined at 30:100,000 inhabitants or at least 100 samples from each county or district. A total of 3,502 samples were obtained. Each sample represented 10 to 12 ml of blood or 4 to 5 ml of serum. Each sample was accompanied by information on the county of donation and on the age and gender of the donor. No further information on the donors was available, and the identity of the donors was erased from the records sent to the laboratory.

(ii) General population. A stratified random sample of 1,863 individual was drawn from the computerized and continuously updated population register of Stockholm County. The primary purpose was to measure the effect of a diphtheria vaccination campaign. In total, 1,087 of the selected subjects (58.3%) volunteered for the ensuing blood sampling in 1998 to 1999 (8). Participation rates were 60% among women and 49% among men. Among subjects older than 45 years, the participation rates were 70 and 62% for women and men, respectively. Selected subjects were sent two letters of invitation to participate, and a follow-up telephone interview with some of the nonparticipants indicated that the main reasons for nonparticipation (in order of decreasing importance) were as follows: (i) unwillingness to participate, (ii) unavailability, in some cases due to traveling abroad, (iii) disease or impediment that prohibited participation, and (iv) death between selection and blood sample. No further information on the control population was available.

ELISA for immunoglobulin G antibodies. This in-house enzyme-linked immunosorbent assay (ELISA) used sonicated *H. pylori* antigen, based on culture of seven clinical isolates and the NCTC 11438 strain (3). The wells of the 96-well microplates were coated at a concentration of 7 μg/ml. Sera were diluted in 1:1,000 and were tested in duplicate. Serum dilutions were made in phosphate-buffered saline (PBS), first 1:100 in PBS only and then 1:10 in PBS containing 70 mg of sonicated *Campylobacter jejuni* antigen/ml (five clinical isolates) to remove cross-reacting antibodies. Alkaline-phosphate conjugated anti-human immunoglobulin G (Euro Diagnostica, Malmö, Sweden) was used to detect bound antibodies. An optical density at 405 nm of 0.36 was used as a cutoff and had been established in a clinical material of 83 *H. pylori* culture-positive patients and 45 patients negative by microscopy, culture, and rapid urease test (3). The ELISA

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TABLE 1. Characteristics of blood donors and
stockholm population sample

Characteristic	No. of blood donors (% of total)	No. of individuals in Stockholm population sample (% of total)
n	3,502	1,030
Gender		
Men	2,194 (63)	418 (41)
Women	1,299 (37)	608 (59)
Age (yr)		
17–19	32 (1)	0 (0)
20–29	197 (6)	143 (14)
30–39	473 (13)	168 (17)
40–49	905 (26)	190 (19)
50–59	964 (28)	206 (20)
60–69	689 (20)	152 (15)
70–79	231 (7)	121 (12)
≥80	0 (0)	33 (3)
Health care region		
South	605 (17)	0 (0)
West	664 (19)	0 (0)
Southeast	352 (10)	0 (0)
Stockholm/Gotland	659 (19)	1,030 (100)
Central Sweden	773 (22)	0 (0)
North	449 (13)	0 (0)
***H. pylori* status**		
Positive	620 (18)	261 (25)
Negative	2,882 (82)	767 (75)

was found to have a sensitivity of 100% (83 of 83) and a specificity of 96% (43 of 45), established in the aforementioned 83 *H. pylori* culture-positive Swedes and 45 seronegative individuals (3).

Statistical methods. First, the seroprevalence rates among blood donors and population controls were compared in 10-year age strata by using Mantel-Haenszel pooled estimates. Since blood donors and population controls represented only partly overlapping geographical areas (blood donors came from all over Sweden, while population controls came exclusively from Stockholm), we examined the importance of county and health care region in multivariate logistic regression models restricted to blood donors only. In these models, we adjusted for age (in 10-year age categories) and gender. We then fitted multivariate logistic regression models where the effect of blood donor status was estimated while controlling for age, gender, and place of residence (large cities versus other parts of Sweden). In order to avoid confounding by geographical area of residence, a further round of analyses were restricted to blood donors and population controls from Stockholm. Effect modification by age was evaluated through stratified analyses (17 to 49 and >50 years) and by introducing a term for interaction (blood donor status times age category) in the full model. We used the Logistic procedure in the SAS 6.12 statistical package (the SAS Institute, Cary, N.C.).

RESULTS

A total of 4,532 blood samples were analyzed among 3,502 blood donors (mean age ± standard deviation, 50.5 ± 12.9 years) and 1,030 population control subjects (mean age, 49.9 ± 16.7 years). Characteristics of the two study groups are given in Table 1. The mean (± standard deviation) anti-*H. pylori* antibody optical densities among blood donors and population controls were 0.30 (±0.40) and 0.36 (±0.45), respectively. The corresponding median values were 0.14 and 0.13.

Bar charts of seroprevalence rates by age category revealed two different patterns for blood donors and population controls (Fig. 1). While the seroprevalence increased with age in the youngest age groups both among blood donors and in the
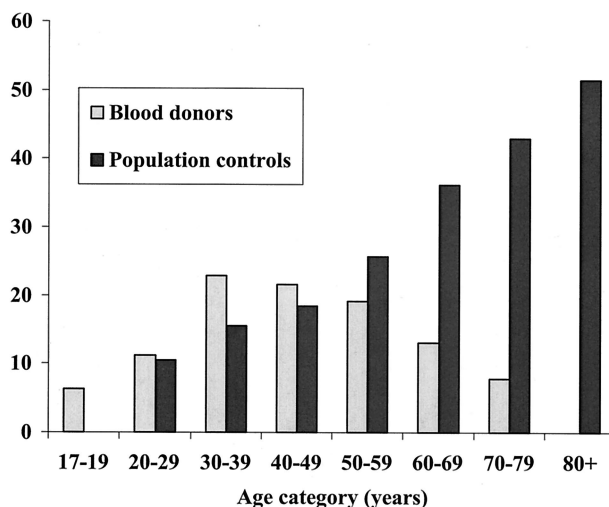

FIG. 1. Prevalence (%) of antibodies to *H. pylori* by age among blood donors and in a population sample.

population sample (albeit the rates were somewhat higher among the former), the curve for the blood donors deflected after ages 40 to 49. After that age, the seroprevalence fell with age. In the population sample, on the other hand, the seroprevalence increased monotonically with age throughout the whole age range. This difference was highly significant; the Mantel-Haenszel pooled-odds ratio for being seropositive among blood donors was 0.65 (95% confidence interval, 0.55 to 0.77), relative to the population sample (*P* = 0.001).

Since blood donors and population controls represented populations that overlapped only in Stockholm, we examined the importance of geographical area of residence in a multivariate logistic regression model with adjustment for age and

TABLE 2. Multivariate analysis of the effects of gender, age, and geographical area of residence on the likelihood of being *H. pylori* seropositive[b]

Determinant	No. of positive donors/total (%)	Odds ratio[a]	95% CI
Gender			
Men	412/2,192 (19)	1	Reference
Women	207/1,298 (16)	0.85	0.70–1.02
Age (yr)			
17–19	2/32 (6)	0.24	0.06–1.02
20–29	22/197 (11)	0.48	0.30–0.77
30–39	108/473 (23)	1.08	0.82–1.41
40–49	195/905 (22)	1	Reference
50–59	184/964 (19)	0.86	0.69–1.08
60–69	90/689 (13)	0.55	0.42–0.72
70–79	18/231 (8)	0.31	0.19–0.51
Health care region			
South	117/605 (19)	1	Reference
West	114/664 (17)	0.91	0.68–1.22
Southeast	63/352 (18)	0.91	0.65–1.28
Stockholm/Gotland	111/659 (17)	0.93	0.69–1.24
Central Sweden	120/773 (16)	0.78	0.59–1.04
North	95/449 (21)	1.22	0.90–1.67

[a] Mutually adjusted for other variables in table.
[b] The analysis is restricted to blood donors only. All estimates are mutually adjusted.

TABLE 3. Adjusted odds ratios for being *H. pylori* seropositive, overall and in analyses stratified by age

| Study group | Data for: | | | | | |
| | Donors of all ages | | Donors aged 17–49 yr | | Donors aged ≥50 yr | |
	OR[a]	95% CI	OR	95% CI	OR	95% CI
Entire country						
Population control	1	Reference	1	Reference	1	Reference
Blood donors	0.57	0.45–0.72	1.48	1.02–2.13	0.27	0.19–0.37
Stockholmers						
Population control	1	Reference	1	Reference	1	Reference
Blood donors	0.57	0.44–0.76	1.47	0.98–2.20	0.26	0.18–0.39

[a] Odds ratio adjusted for gender, age (in 10-year classes), and place of residence (big cities versus rest of Sweden).

gender. This analysis was restricted to blood donors only. Table 2 shows that the area of residence was of minor importance for the risk of being seropositive. Although the odds ratio for seropositivity tended to be somewhat lower in central Sweden and somewhat higher in northern Sweden, none of the estimates attained statistical significance. We also observed an almost statistically significant gender difference in *H. pylori* seroprevalence. The odds ratio for being seropositive was 0.85 (95% confidence interval [CI], 0.70 to 1.02) among women relative to men. A similar difference was seen also in the population sample. There, the odds ratio among women was 0.77 (95% CI, 0.57 to 1.04).

Finally, we estimated the odds ratio for *H. pylori* seropositivity associated with blood donor status, relative to the population sample. In these multivariate analyses, performed on the entire material (both blood donors and population controls), the estimates were adjusted for gender, age (in 10-year classes), and place of residence (cities of >500,000 inhabitants versus the rest of Sweden). Overall, the adjusted odds ratio for *H. pylori* seropositivity among blood donors was decreased by 43% (95% CI, 28 to 55%), relative to population controls (Table 3, first section, left column). In stratified analyses, it was revealed that the effect of blood donor status was modified by age (Table 3, first section, columns 2 and 3). In the age stratum of 17 to 49 years, blood donor status was associated with a 48% (95% CI, 2 to 113%) increased risk of *H. pylori* seropositivity, although this increase was only of borderline significance. Among subjects who were ≥ 50 years of age, the risk of being seropositive for blood donors was reduced by 73% (95% CI, 63 to 81%), relative to the risk in the population sample. This latter interaction was highly statistically significant (*P* = 0.0001). In order to ensure against confounding by place of residence, we repeated the analyses in the subset of 513 blood donors and 1,030 population controls living in Stockholm. The results were almost identical to those obtained in the entire material (Table 3, second section).

DISCUSSION

The most salient finding in our cross-sectional data was a paradoxical drop in *H. pylori* seroprevalence with age among Swedish blood donors over the age of 50 years, who thus markedly differ from the general population with the same age and gender. The seroprevalence among younger blood donors,

on the other hand, was close to, or even somewhat higher than, the age-specific seroprevalence in the general population.

Other studies conducted among blood donors in developed countries have usually not revealed a decline in *H. pylori* seroprevalence similar to the one observed by us (5, 7, 15, 20, 26, 33–36). A closer inspection of the previous data, however, unveils lower-than-expected seroprevalence rates above the age of 50 in several studies, (5, 34, 36), but few of them included subjects who were older than 60. In the ages below 60, the deviant pattern was less clear also in our study. An Italian study (31) that included older blood donors found the same seroprevalence pattern as in our study.

The most simplistic explanation for our findings is that blood donations on a regular basis favor disappearance of the infection. This appears biologically implausible, although empirical data are lacking. Removal of antibodies in blood donors could be another possibility but has not been found for other infections. The sample showed no corresponding decrease in the prevalence of antibodies to *B. burgdorferi* (28).

A biased distribution in socioeconomic background would result in a biased *H. pylori* prevalence but not in a decline with age (12, 23). A successive shift over time in the socioeconomic status of newly recruited blood donors, from low to high, would theoretically lead to lower prevalence rates with increasing age of the donors. However, the prevalence gradient across successive birth cohorts is likely to be steeper than that across socioeconomic strata. Thus, a shift in the socioeconomic status distribution, if any, would probably not have more than marginal impact on the birth cohort effect, the latter resulting in increasing prevalence rates with age. This argument will also counter another possible variant of selection bias, namely, that only socioeconomically privileged blood donors will remain active after age 50. We therefore tentatively refute this explanation, too.

A third alternative explanation would be that subjects who remain active blood donors for the longest time are those with rare and coveted blood groups and that some of these blood groups may be associated with a lower risk of *H. pylori* colonization. Published data, however, consistently refute any important associations between blood group and *H. pylori* prevalence (16, 19, 21, 22, 24, 27). Therefore, this explanation is unlikely.

The fourth, and in our view most probable, explanation is that infected individuals are preferentially removed from the blood donor cohort as they get older. There could be several possible reasons for this selective removal: one would remove them if they are likelier than noninfected individuals to develop laboratory test abnormalities that result in active exclusion. *H. pylori* could potentially affect iron metabolism by causing ulcer-related occult bleeding or impaired absorption of nonheme iron or by scavenging heme iron or ferritin (2, 6). Low serum iron and/or ferritin values occur more frequently in infected than in noninfected adults (4, 25, 29). It is conceivable that the *H. pylori*-induced interference with normal iron metabolism will become clinically overt more readily in blood donors than in people without similar blood losses. *H. pylori* also seems to be a causative agent in the development of adult vitamin B_{12} deficiency (18). However, this reason does not hold up, since few blood donors develop persistent anemia and few are excluded for that reason (J. Lundahl, Department of Clin-

ical Immunology and Transfusion Medicine, Karolinska Hospital, personal communication).

The most common reason for exclusion among older Swedish blood donors is that they themselves decide to stop giving blood. The reason why is not fully understood, but we hypothesize that *H. pylori*-infected subjects may feel less well after donations than do noninfected blood donors and that the recovery time may be prolonged. Moreover, if *H. pylori* infection is causally or noncausally linked to other severe diseases such as coronary heart disease, then these diseases will also contribute to a selective disappearance of infected individuals from the blood donor category.

Our study confirmed the previously reported gender difference (32) with a tendency towards higher *H. pylori* prevalence in men than in women, both among blood donors and in the population sample. Although not quite reaching statistical significance, women had an approximately 20% lower probability of being infected than did men. A recent meta-analysis (32) showed that only in two studies out of six was the *H. pylori* seroprevalence higher in women than in men and that the summary odds ratio for seropositivity among men, relative to women, was 1.2 (95% CI, 1.02 to 1.4). Interestingly, the gender difference has not been seen in children, an observation also confirmed in our recent study of 10- to 12-year-old Swedish schoolchildren (13). The reasons behind the gender difference among adults is unlikely to be due to a preferential eradication treatment in men since screening and eradication, at the time of the drawing of study samples, were little practiced in Sweden. The gender difference may account in part for the increased incidence of *H. pylori*-related diseases (peptic ulcer and stomach cancer) among men in later decades of life (32).

Strengths of our study include representativity of our sample vis-à-vis Swedish blood donors. As an indication of this representativity, the sample showed the expected geographical variation as well as age- and sex-dependent variability in *B. burgdorferi* seroprevalence (28). Another strength is our truly population-based comparison sample. The low participation rate may raise concerns about possible selection bias. The control population did, however, show exactly the expected cohort effect described in numerous studies from developed countries (12, 23). Also, in the age groups where our important findings were made (>45 years), the participation rate (66%) was acceptable.

In conclusion, our data, supported by findings in other studies, are consistent with a falling prevalence of *H. pylori* infection with age among elderly blood donors. The reasons for this paradoxical decrease remain conjectural, but the most reasonable explanation is that *H. pylori*-positive subjects are preferentially removed from the blood donor cohort. Since active exclusions due to persistent anemia are uncommon, our results imply that elderly individuals infected with *H. pylori* may tolerate repeated bleedings less well than do noninfected individuals and/or that the general well-being among those who are infected may be somewhat impaired. This observation ought to prompt more studies of the role of *H. pylori* in the general health status of elderly people. And our findings emphasize the dangers of using blood donor data in lieu of epidemiological sound, population-based observations.

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