Epidemiol. Infect. (1997), **119**, 29–34. Printed in the United Kingdom

Helicobacter antibodies in 1973 and 1994 in the adult population of Vammala, Finland

T. U. KOSUNEN,[1]* A. AROMAA,[2] P. KNEKT,[2] A. SALOMAA,[3] H. RAUTELIN,[1] P. LOHI[1] AND O. P. HEINONEN[4]

[1] *Department of Bacteriology and Immunology, University of Helsinki, Helsinki, Finland*
[2] *Social Insurance Institution, Helsinki, and National Public Health Institute, Helsinki, Finland*
[3] *Vammala Health Center, Vammala, Finland*
[4] *Department of Public Health, University of Helsinki, Helsinki, Finland*

(*Accepted 24 February 1997*)

SUMMARY

Changes in *Helicobacter pylori* seroprevalence were studied determining IgG and IgA antibodies of 408 randomly selected adults aged 15–74 years living in Vammala, Finland in 1973 and of 504 similarly selected subjects in 1994. Seroprevalence increased by age at both time points. The age-adjusted seroprevalence rate was clearly lower in 1994 than in 1973 (31 *vs.* 56%, $P = 0{\cdot}001$). Paired serum samples of 224 subjects collected in 1973 and 1994 showed that the antibody status remained unaltered in 92%; 4% seroconverted and 4% seroreverted within the 21 years. The decrease in the seroprevalence rate in the population and the persistence of individual antibody status over two decades support a difference in *H. pylori* infection rates among birth cohorts over time rather than continuous acquisition of new infections with advancing age. Thus the risk of helicobacter infection in Vammala, Finland has been highest in childhood and continuously decreased at least for the last five decades.

INTRODUCTION

Helicobacter pylori, the cause of active chronic gastritis, is a risk factor for peptic ulcer [1, 2] and gastric cancer [3–6]. Persisting serum antibodies against *H. pylori* are characteristic of this chronic infection. Eradication of the infection leads to healing of gastritis and gradual disappearance of the antibodies [7–9]. Many laboratories only use an IgG antibody test, which is positive in more than 90% of culture-positive patients [9, 10]. An IgA antibody test can also be used, but is less sensitive (73%). In combination with the IgG antibody test, it has been positive in a further 2% of culture-positive patients [9]. Thus both antibodies indicate current infection except in recently healed infection, after which antibody titres gradually decline [9]. The higher the original titre, the longer it takes to become negative; usually about a year, but in some cases more than 2 years [11].

Serological data from various parts of the world show that *H. pylori* infection is a disease associated with low living standards, and everywhere the prevalence of *H. pylori* infection increases with age [12]. Seropositivity among Finnish blood donors in Helsinki increased by advancing age about 10% units per 10 years from 10% in 18–25-year-old to 60% in 56–65-year-old donors [13]. Long-term follow-up studies suggest that the age-dependent increase of seropositivity is mainly due to the decreasing rate of childhood infections [14, 15], often referred as a cohort phenomenon. The rate of helicobacter seropositivity has declined in Great Britain since 1969 in birth cohorts of patients with suspected pneumonia, rubella or pyrexia of unknown origin [16]. A similar decline of rates in successive birth cohorts has been postulated after studying healthy controls from

* Author for correspondence.

various studies at various times in Finland [17]. In contrast there is also evidence suggesting a constant rate of new infections at all ages, which could result in a similar age-dependent increase of seropositivity [18].

We determined the prevalence of *H. pylori* antibodies in randomly selected subjects representing the adult population of a community in 1973 and 1994. We also studied individual changes in antibody status over two decades.

MATERIALS AND METHODS

Study design, subjects and samples

A health examination was carried out by the Social Insurance Institution in 1973 in Vammala, a semi-urban community in South-West Finland. A random sample of the adult population was selected by computer from the National Population Register. Altogether 600 subjects were invited by mail and 492 participated. Participation rate was 84% between the ages 15 and 74 years, and it had a range of 65–100% in 5-year age groups. For the present study 408 sera, from 213 females and 195 males, stored at −20 °C were available (Group A).

In 1994 a new random sample of 600 residents of Vammala was selected from the National Population Register. Fifty females and 50 males from each 10-year age group between 15 and 74 years were randomly selected to represent each gender and age stratum. These persons were invited by mail to the local health centre for phlebotomy. Blood samples were obtained from 504 subjects (84% of invited), 262 females and 242 males (Group B). Fourteen subjects belonged also to Group A, i.e. had participated in our 1973 study.

Another blood sample was obtained from 224 (60%) of the 372 invited subjects still alive in 1994 from the original Group A first examined in 1973. Seventy-six (34%) of these samples were from subjects who had moved to other communities.

The informed consent of all the participants was obtained. The study was approved by the Ethical Committee of the University Hospital in Tampere, Finland.

Study area

Vammala was selected as a typical Finnish small community and because the sera obtained in 1973 were available.

Before the serum samples were taken in 1994, local physicians (according to oral inquiries by one of us. A.S.) had not used antimicrobial drugs to treat patients complaining of gastric disorders.

Vammala had a relatively stable population size of about 16000 both in 1973 and 1994; data on movements in and out were not available. According to the national statistics, Finland had experienced a considerable demographic change [19, 20]. In the early 1970s, 22% of the population earned their living from agriculture and 38% from services, in 1994 12 and 54%, respectively. In accordance with the development in the entire country, the level of education of the Vammala population has risen markedly since young age groups in 1994 had achieved a much higher educational level than in 1973.

Investigations

Antibodies to *H. pylori* were measured separately for IgG and IgA by an enzyme immunoassay method [9, 13]. The antigen used was an acid glycine extract from *H. pylori* strain NCTC 11637. The absorbance readings were converted to reciprocals of the end-point titres. The end-point titres were dilutions of the serum at the cut-off level defined by the optical densities of positive reference serum pools at constant dilutions. Separate reference pools were used for immunoglobulins G and A. They were placed on each microtitre plate. Paired serum samples were always tested on the same microtitre plate.

The lower limits of raised titres (expressed as reciprocals) were 700 for IgG and 70 for IgA antibodies. With these limits, the sensitivity and specificity of the tests were 94 and 93% for IgG and 73 and 95% for IgA, respectively, as determined in a separate series of 544 patients whose biopsy samples were cultured and studied histologically for the presence of helicobacters during the same period as this study. Three percent of the infected patients had a raised IgA titre only; thus the sensitivity of combined IgG and IgA tests was 97%.

The overall prevalence rates were adjusted for age by the ordinary linear regression model [21].

RESULTS

Prevalence of antibodies in 1973 and 1994

Age-dependent increases in the prevalence of antibodies (combined results of IgG and IgA tests) were

https://doi.org/10.1017/S0950268897007565 Published online by Cambridge University Press

Table 1. *Prevalence of* H. pylori *antibodies* (*IgG and IgA antibody results combined*) *in the population of Vammala, Finland in 1973 and 1994*

Age (years)	Number studied		Number antibody positive		Seroprevalence rate	
					1973	1994
	1973	1994	1973	1994	% (95% CI)	% (95% CI)
15–24	102	69	39	5	38·2 (28·8–47·7)	7·3 (2·4–16·1)
25–34	97	78	40	7	41·2 (31·3–51·7)	9·0 (3·7–17·6)
35–44	67	87	33	18	49·3 (36·8–61·8)	20·7 (12·8–30·7)
45–54	61	91	35	30	57·4 (44·0–70·0)	33·0 (23·5–43·6)
55–64	43	88	35	59	81·4 (66·6–91·6)	63·6 (56·2–76·7)
65–74	38	91	28	62	73·7 (56·9–86·6)	68·1 (57·5–77·5)
Total	408	504	210	178	56·3* (46·6–56·3)	31·4* (31·1–39·5)

* Age-adjusted, $P = 0{\cdot}001$.

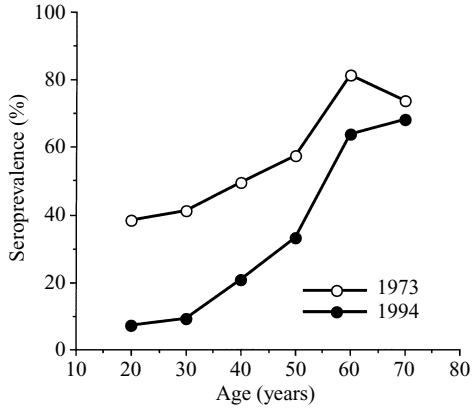

Fig. 1. Prevalence of helicobacter antibodies (IgG and IgA results combined) in the population of Vammala, Finland in 1973 and 1994.

obvious in both cross-sectional samples from the population (Table 1, Fig. 1). In 1994 this increase continued to the oldest of the 10-year groups (65–74 years) studied, but in 1973 the prevalence was highest in a younger age group (55–64 years).

During the 21-year period the prevalence of *H. pylori* antibodies decreased by 24–32% units in all age groups from 15 to 54 years. In older subjects the seroprevalence rates differed less and the 95% confidence intervals overlapped (Table 1, Fig. 1). In 1973, 98% of the seropositive subjects had IgG and 71% IgA antibodies; 2% of them had only IgA antibodies. In 1994 the respective rates were 97, 77 and 3%.

The age adjusted seroprevalence fell from 1973 to 1994 significantly in both female and male populations (Table 2). In 1973, there was a slightly higher rate of seropositivity in males, but in 1994 the reverse was true; the gender differences were not significant.

Restriction of the comparisons to subjects born in Vammala or the neighbouring communities and to specific occupational groups showed that the seroprevalence rates in these subgroups were similar to those in the entire sample in 1973 and 1994 (data not shown).

Persistence or antibodies

Serum samples from 224 subjects belonging to Group A were available for a 21-year follow-up study of the persistence of the antibody status. Of all the subjects, 52% were antibody negative and 40% antibody positive at both time points (Table 3). Only 4% of the initially antibody negative subjects had become antibody positive and 4% of the initially positive ones antibody negative by 1994 (Table 4). The median IgG titre of the 90 subjects who remained seropositive was 3000 in 1973 and 3500 in 1994. Fifty-eight of these 90 subjects (64%) also had an elevated IgA titre in both samples; the median was 175 in 1973 and 220 in 1994.

DISCUSSION

Our population-based findings showed that the prevalence rate of *H. pylori* infection in Vammala, Finland had increased with age and that the age-dependent increase became steeper over two decades. Overall and age-specific rates have decreased dramatically in the last 20 years, new infections in adults have been infrequent, and during a long time period the number of resolving infections has been of the same magnitude as the rate of new infections. In Vammala, the *H. pylori* prevalence rate in adults in the 1970s increased

https://doi.org/10.1017/S0950268897007565 Published online by Cambridge University Press

Table 2. *Prevalence of* H. pylori *antibodies* (*IgG and IgA antibody results combined*) *in adult females and males in Vammala, Finland in 1973 and 1994*

	Number studied		Number antibody positive		Seroprevalence rate (%)*		
Gender	1973	1994	1973	1994	1973	1994	*P*-value
Females	212	260	105	93	52·5	33·4	< 0·001
Males	196	244	105	85	60·7	29·1	< 0·001
Total	408	504	210	178	56·3	31·4	< 0·001

* Age-adjusted.

Table 3. *Individual* H. pylori *IgG antibody status in 224 subjects studied in both 1973 and 1994 in Vammala, Finland*

IgG antibody status			
1973	1994	Number	Proportion (%)
Negative	Negative	117	52·2
Positive	Positive	90	40·2
Negative	Positive	9	4·0
Positive	Negative	8	3·6

Table 4. H. pylori *antibody titres of seroconverters and seroreverters in Vammala, Finland in 1973 and 1994*

Initial age, years	Gender	IgG		IgA	
		1973	1994	1973	1994
Seroconverters					
19	f	50	3000	10	180
24	f	50	12000	5	500
26	f	50	1300	5	10
27	f	50	1600	5	400
31	f	50	2500	5	450
34	f	100	7000	10	100
24	m	50	1200	10	120
24	m	50	3500	5	250
34	m	100	7000	10	100
Seroreverters					
16	f	5000	100	50	10
21	f	1300	100	10	5
28	f	1200	50	10	5
28	f	2200	100	70	10
31	f	2200	100	50	5
19	m	1000	200	20	10
27	m	2000	200	70	20
38	m	5500	100	150	50

at an average of 21% (up to 65 years) with each decade of age. Twenty years later, the average increase per decade was 63% (up to 75 years) primarily due to the lower rate of infection in younger age groups. After 1973 the age-specific rates decreased by an average of 21% per decade of calendar time, and both new and resolved infections had a rate of 2% per 10 years. These results support the idea that the changing incidence of *H. pylori* infections in childhood in successive birth cohorts better explains the changes in prevalence rates, than an increase in incidence of new infections in adulthood. The risk of childhood infections has dropped to about one tenth the risk of 50 years ago.

We studied two random samples and one group of same subjects twice 21 years apart from a population. Precision of the rates estimated in such population studies can suffer from demographic changes in the population, selective participation and non-random deaths during follow-up. The response rates were high, which suggests that the findings correspond well with the occurrence of *H. pylori* infection at the time of examination. Furthermore, when we limited the analysis to persons who have lived their lives without moving and to the most typical local professions, the results remained practically unchanged. Mortality decreased considerably in Finland during the study period and resulted in proportionally smaller older age groups in the 1970s. This was partly treated by adjusting the overall rates for the effect of age by a multivariate method. Crude and age-adjusted rates differed only slightly. Those reasons that may have made people particularly prone to *H. pylori* infection in earlier times (e.g. poverty and poor hygiene), are also related to mortality. Thus, the estimated rates, especially in the older age groups, have to be considered with some caution. Nevertheless, the principal findings of our study were based on large

https://doi.org/10.1017/S0950268897007565 Published online by Cambridge University Press

changes and differences, so that these methodological reservations do not have much importance.

In infected subjects, spontaneous healing, development of advanced atrophy and antibiotics given for any infectious disease, may lead to the disappearance of infection, which will be followed by seroreversion [9]. In this study we could not rule out any of these causes for seroreversion. Nevertheless, the total number of seroreverters was small.

Age-dependent increases in the prevalence *H. pylori* antibodies is a worldwide phenomenon [12]. Earlier data from 1988 from a cross-sectional study of healthy blood donors in Helsinki, Finland showed a clear increase of prevalence by age [13]. Our study is the first in which random samples from a geographically defined population have been used to study changes in the prevalence of *H. pylori* infection over time.

Age-dependent increases in the prevalence rates of antibodies were clear in both samples. The 1994 prevalence distribution resembled that of the Finnish blood donors in 1988, which began at 10% in the youngest donors aged 18–25 years and reached 60% in the oldest group aged 56–65 years [13]. The age distribution of prevalence rates in the 1970s was flatter than in the 1990s, probably because the incidence in childhood changed less many decades ago than recently. The lower rate in the oldest age group in 1973 may be due to selective mortality.

Our data show a clearcut decrease in the age-specific *H. pylori* seropositivity over the last two decades in this population. In the four youngest 10-year age groups the current population has about 25–30% units lower prevalence rates of *H. pylori* antibodies than 20 years earlier. A similar conclusion of decreasing *H. pylori* seropositivity was shown in South Yorkshire, United Kingdom in three successive groups of patients with suspected pneumonia, rubella or pyrexia of unknown origin collected in 1969, 1979 and 1989 [16]. It was also suggested in an earlier study from Finland [17].

Vammala has experienced socio-economic changes comparable to other similar Finnish communities. The standard of living has been rising, the educational level is now much higher than in the 1970s and the occupational structure has shifted away from agriculture to services. A reduction in the infection rate is compatible with the hypothesis that better socio-economic circumstances and improved hygiene have reduced the risk of helicobacter infection [12].

Follow-up data on the *H. pylori* antibodies of the same individuals showed that antibodies persisted in a great majority of those who had them 21 years earlier. This occurred in a population that has not been actively treated with the current combinations of antimicrobial drugs, needed for the eradication of infection. This is in agreement with the results of Jones and colleagues [7], who in 1986 reported that antibody titres remained at the same level in 'a small number' of individuals whose paired sera, taken 8–12 years apart, were available.

A similar number of seroconverters and seroreverters (about 4% for both of them and about the same across the age groups) kept the rate of seropositivity constant. This implies that the rate of seropositivity in each cohort is mainly determined in childhood, as suggested by Parsonnet and colleagues [14]. Data supporting this cohort effect theory have also been reported by Kuipers and colleagues [15]. In a population with a higher rate of new infections in adults, the continuous acquisition theory may be more applicable [18].

The low number of new infections in adults, as indicated by the low number of seroconverters, also implies that reinfections are rare. A programme aimed at the eradication of current infections could remove the most important cause of chronic gastritis and peptic ulcer disease in the population. If carried out early enough in young adults, it could be expected to decrease the risk of intrafamilial infections, which are of particular importance to the epidemiology of helicobacter infection in children [22] and in the long run in the whole population.

Based on serological studies, *H. pylori* infection is also a risk factor for gastric cancer [3–6]. During the time of the decreasing trend in seropositivity for *H. pylori* apparent in the present study, the incidence of gastric cancer has declined according to data collected by the Finnish Cancer Registry. The incidence exceeded 60 per 100000 in males and 35 per 100000 in females in 1953, but had fallen to a quarter in both genders by 1993 [23, 24]. The observed decrease in the prevalence of *H. pylori* infection may have contributed to the reduction in the incidence of gastric cancer.

To conclude, our data mainly support the birth cohort phenomenon as an explanation for the increased occurrence of *H. pylori* infection seen with age. The decreasing incidence rate of childhood infections, has probably been declining for many decades. Further studies will show whether the increasing use of antimicrobials to eradicate helicobacter infection, as currently applied in developed countries, will accelerate the decrease of infection

rates and lead to decreasing numbers of patients suffering from active chronic gastritis, peptic ulcers [25] and gastric malignancies [23, 24, 26].

ACKNOWLEDGEMENT

This work has been financially supported in part by the Yrjö Jahnsson Foundation, Helsinki, Finland, and the Swedish Cancer Foundation, Stockholm, Sweden.

The authors thank Terhi Isomäki, Mari Junnila, Eila Kelo and Pirjo Kosonen for technical help.

The results of this study were partly presented at the Yrjö Jahnsson Foundation IXth Medical Symposium 'Peptic Ulcer and Gastritis – New Infectious Diseases' in Porvoo, Finland, 17–19 August 1994, and at the VIIIth International Workshop on Gastroduodenal Pathology and *Helicobacter pylori* in Edinburgh, Scotland, 7–9 July, 1995.

REFERENCES

1. Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfil Koch's postulates for pyloric campylobacter. Med J Aust 1985; **142**: 436–9.
2. Blaser MJ. *Helicobacter pylori* and the pathogenesis of gastroduodenal inflammation. J Infect Dis 1990; **161**: 626–33.
3. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991; **325**: 1127–31.
4. Nomura A, Stemmermann GN, Chyou P-H, et al. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991; **321**: 1132–6.
5. Forman D, Newell DG, Fullerton F, et al. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. Br Med J 1991; **302**: 1302–5.
6. Aromaa A, Kosunen TU, Knekt P, et al. Circulating anti-*Helicobacter pylori* IgA antibodies and low serum pepsinogen I level are associated with increased risk of gastric cancer. Am J Epidemiol 1996; **144**: 142–9.
7. Jones DM, Eldridge J, Fox AJ, Sethi P, Whorwell PJ. Antibody to the gastric campylobacter-like organism ('*Campylobacter pyloridis*') – clinical correlations and distribution in the normal population. J Med Microbiol 1986; **22**: 57–62.
8. Valle J, Seppälä K, Sipponen P, Kosunen TU. Disappearance of gastritis after eradication of *Helicobacter pylori*: a morphometric study. Scand J Gastroenterol 1991; **26**: 1057–66.
9. Kosunen TU, Seppälä K, Sarna S, Sipponen P. Diagnostic value of decreasing IgG, IgA, and IgM antibody titres after eradication of *Helicobacter pylori*. Lancet 1992; **339**: 893–5.
10. Strauss RM, Wang TC, Kelsey PB, et al. Association of *Helicobacter pylori* infection with dyspeptic symptoms in patients undergoing gastroduodenoscopy. Am J Med 1990; **89**: 464–9.
11. Seppälä K, Sipponen P, Kosunen TU. Do changes in gastritis and serum antibodies reflect successful triple therapy in *Helicobacter pylori* infection? Gastroenterology 1993; **104**: Suppl. A189.
12. Talley NJ, Noack KB. The worldwide prevalence of *Helicobacter pylori*: asymptomatic infection and clinical states associated with infection in adults. In: Goodwin CS, Worsley BW, eds. *Helicobacter pylori*: Biology and clinical practice. Boca Raton, Florida: CRC Press, Inc., 1993: 63–83.
13. Kosunen TU, Höök J, Rautelin HI, Myllylä G. Age dependent increase of *Campylobacter pylori* antibodies in blood donors. Scand J Gastroenterol 1989; **24**: 110–4.
14. Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. Gastroenterology 1992; **102**: 41–6.
15. Kuipers EJ, Peña AS, van Kamp G, et al. Seroconversion for *Helicobacter pylori*. Lancet 1993; **342**: 328–31.
16. Banatvala N, Mayo K, Mégraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and *Helicobacter pylori*. J Infect Dis 1993; **168**: 219–21.
17. Sipponen P, Kosunen TU, Samloff IM, Heinonen OP, Siurala M. Rate of *Helicobacter pylori* aquisition among Finnish adults. A 15-year follow-up. Scand J Gastroenterol 1996; **31**: 229–32.
18. Veldhuyzen van Zanten SJ, Pollak PT, Best LM, Bezanson GS, Marrie T. Increasing prevalence of *Helicobacter pylori* infection with age: continuous risk of infection in adults rather than cohort effect. J Infect Dis 1994; **169**: 434–7.
19. Statistical yearbook of Finland 1974. Helsinki: Central Statistical Office of Finland, 1975.
20. Statistical yearbook of Finland 1994. Helsinki: Central Statistical Office of Finland, 1995.
21. Searle SR. Linear models. New York: Wiley, 1971.
22. Bamford KB, Bickley J, Collins JSA, et al. *Helicobacter pylori*: comparison of DNA fingerprints provides evidence for intrafamiliar infection. Gut 1993; **34**: 1348–50.
23. Pukkala E, Gustavsson N, Teppo L, eds. Atlas of cancer incidence in Finland 1953–1982. (CSF publication No. 37). Helsinki: Cancer Society of Finland, 1987: 20.
24. Finnish Cancer Institute Registry – Institute for Statistical and Epidemiological Cancer Research. Cancer incidence in Finland 1993. (CSF publication No. 56). Helsinki: Cancer Society of Finland, 1995: 16–9.
25. Glise H. Epidemiology in peptic ulcer disease. Current status and future aspects. Scand J Gastroenterol 1990; Suppl **175**: 13–8.
26. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. Epidemiol Rev 1986; **8**: 1–27.