

The burden of *Helicobacter pylori* infection in England and Wales

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SUMMARY

The prevalence of active infection with *Helicobacter pylori* in the general population of England and Wales was estimated using high reactivity for specific IgG in serum ELISA as a marker. A total of 10 118 anonymized residues of serum samples collected in 1986 and 1996 from persons aged 1–84 years were used. Estimated prevalence of active infection varied by region and was highest in London. Prevalence was related to decade of birth and increased from 4.3% in those born during the 1980s to 30% in those born before 1940. An estimated total of 7.5 million people living in England and Wales have an active infection and analysis by decade of birth showed no significant difference between samples collected in 1986 and 1996. These data suggest *H. pylori* infection is becoming less common, is acquired at an early age and is unlikely to be resolved unless suitable antimicrobial treatment is sought.

INTRODUCTION

Humans are the natural hosts of *Helicobacter pylori*, with infection usually occurring early in life [1]. Since its discovery and isolation from the human stomach in 1982 [2], *H. pylori* has been associated with some common gastrointestinal disorders, although many people colonized by the bacteria remain asymptomatic. The diseases attributed to *H. pylori* infection include gastritis, gastric and duodenal ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma and in 1994 *H. pylori* was categorised as a class 1 carcinogen [1, 3, 4]. *H. pylori* infection may be eradicated with appropriate antimicrobial therapy, and reinfection following successful treatment is rare [3]. However, there is some

concern over the development of antibiotic resistant strains of *H. pylori* [1].

High antibody titres to *H. pylori* have been shown to be indicative of an active infection, which fall following eradication of the bacteria [5–7]. However, antibody levels to *H. pylori* remain detectable for years after eradication [5, 8]. ELISA technology for *H. pylori* has been developed and commercial serological kits are widely available [9]. Although the more accurate urea breath tests are becoming more widely used and are replacing ELISA for diagnostic testing [3], ELISA remains the most practical and useful method for large-scale epidemiological surveys.

Previous studies investigating the seroprevalence of *H. pylori*, based on the presence or absence of specific antibody in various samples of the UK population have been carried out [10, 11]. The purpose of this

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study was to estimate for the first time the prevalence of active *H. pylori* infection, as indicated by a high reactivity in serum ELISA for specific IgG, using a collection of serum samples considered the closest approximation available to the general population of England and Wales, representing the complete age range, and collected in 1986/7 and 1996 [12]. Results were analysed by age, decade of birth, sex and region, and compared by year of collection.

METHODS

Samples

In the main study, 10118 serum samples were examined. These came from persons aged 1–84 years and were collected in 1986 and 1996. All were anonymized residues of specimens submitted for microbiological or biochemical testing to Public Health Laboratories in England and Wales, collected as part of the PHLS serological surveillance programme [12]. This collection is used primarily to determine prevalence of antibody to vaccine-preventable infections (e.g. measles, mumps and rubella) in England and Wales, but is also available to investigate the epidemiology of other infectious diseases. Samples from immunocompromised persons and those submitted for testing for antibody to human immunodeficiency virus (HIV) and hepatitis B virus (HBV) were excluded to avoid over-representation of these groups. In total, 4943 (48.9%) sera were from males and 5175 (51.1%) from females. A total of 2971 samples collected in 1986 were provided by Ashford, Leeds and Preston Public Health Laboratories, with 1513 from males and 1458 from females. Those collected in 1996 consisted of 7147 samples provided by 16 Public Health Laboratories and 2 NHS laboratories with 3430 from males and 3717 from females. Of the samples collected in 1986 and 1996, 2506 (84.3%) and 2959 (41.4%) respectively had been screened previously for IgG specific for hepatitis A virus (HAV) [13] (PHLS unpublished data).

A validation panel of 80 sera was used to establish a cut-off level of reactivity in serum ELISA indicative of a current *H. pylori* infection. These were collected in a separate study from cases of suspected *H. pylori* infection (age range 21–77 years), from whom a biopsy sample (principally antral) had also been taken and tested for the presence of the *H. pylori* urease enzyme using the CLO test (Tri-Med Specialities, Inc. USA) to confirm the presence of the organism. The

CLO test has high sensitivity and specificity (> 90% respectively) [14].

Laboratory methods

Sera were tested for IgG antibody to *H. pylori* by ELISA (Premier *H. pylori*, Meridian Diagnostics, Inc.) according to the manufacturer's instructions. Included on each assay plate were duplicates of two negative controls (one 'in-house') and two strong positive controls (one 'in-house'). Results were expressed as the log of the optical density (OD) of each test sample divided by that of the mean 'in-house' strong positive control on that plate. Reactivity in serum ELISA for *H. pylori* specific IgG was therefore defined as:

$$\log_{10}(\text{OD}_{\text{sample}}) - \log_{10}(\text{OD}_{\text{poscontrol}}).$$

A consideration of control samples used showed that this standardization produced the least interassay variation.

Statistical methods

Age, sex and area effects were investigated using 5-year age groups. Samples were also classified according to decade of birth, from those born between 1910 and 1919, to those born during the 1990s. Region was classified as London, North, South West and Wales, or East and South East according to the location of the laboratory providing the sample.

The association between reactivity in ELISA for specific IgG and CLO test result and association between *H. pylori* infection and HAV antibody status was tested using a χ^2 test. Multivariable logistic regression was used to compare the proportion of samples positive by age (or decade of birth), sex, region and survey year.

RESULTS

The distribution of results showing reactivity in serum ELISA for *H. pylori* specific IgG using 80 samples from cases of suspected *H. pylori* infection with a corresponding CLO test result is shown in Figure 1. Of the 80 biopsy samples used, 33 (41%) tested positive by CLO test. Results using these paired samples showed a strong association that was highly significant between a high reactivity in serum ELISA and the presence of urease as detected using the CLO test ($P < 0.001$). On the basis of these results a reactivity ≥ -0.4 was considered to indicate active *H.*

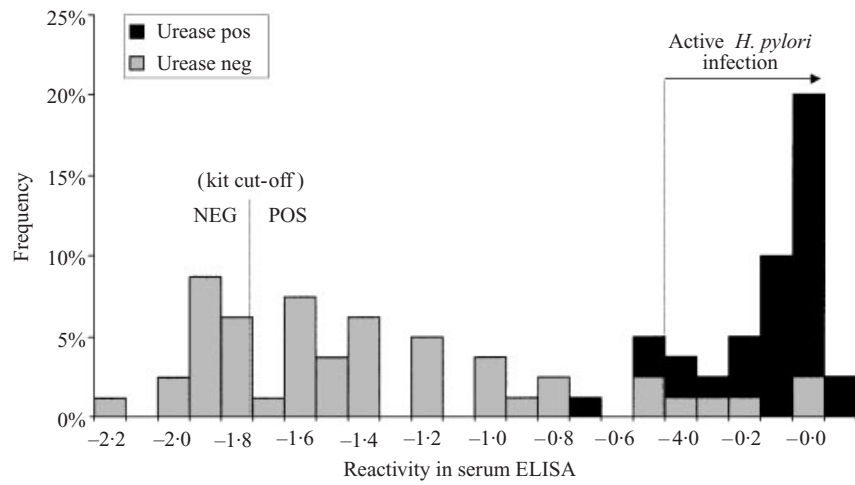


Fig. 1. Reactivity in serum ELISA and CLO test result.

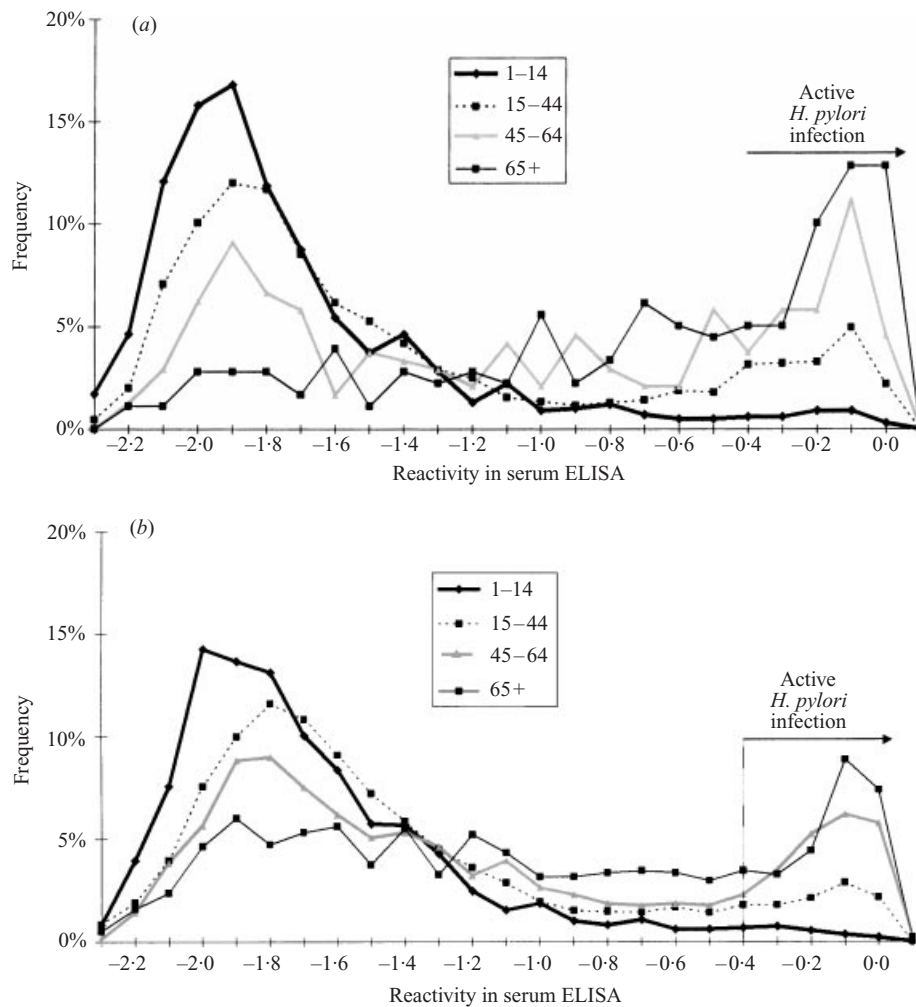


Fig. 2. Distribution of results by age group (samples collected in (a) 1986, (b) 1996).

pylori infection. For brevity, ‘prevalence of active infection’ is taken to mean ‘prevalence of high reactivity of *H. pylori* specific IgG in ELISA, indicative of active infection’. This cut-off gave the

ELISA assay a sensitivity and specificity of 91% (30/33) and 89% (42/47) respectively in comparison to the CLO test. The distribution of reactivity from all samples collected in each year is shown in Figure 2*a, b*.

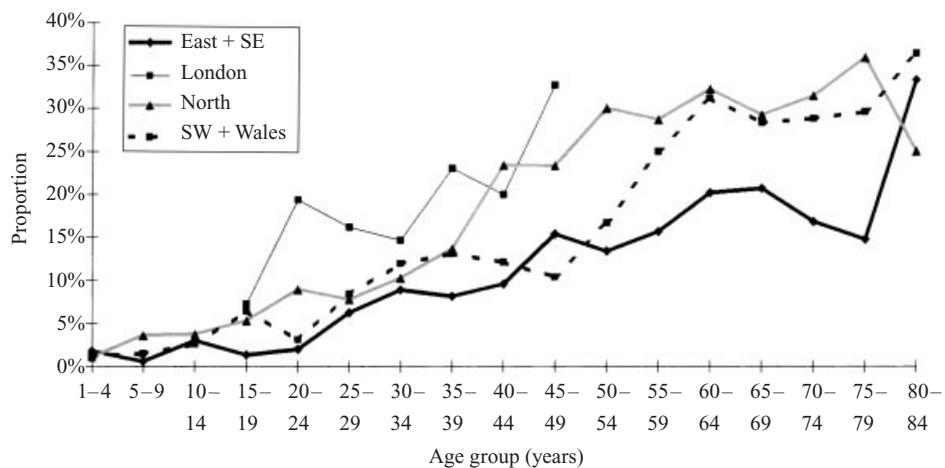


Fig. 3. Active *H. pylori* infection by age and region (samples collected in 1996).

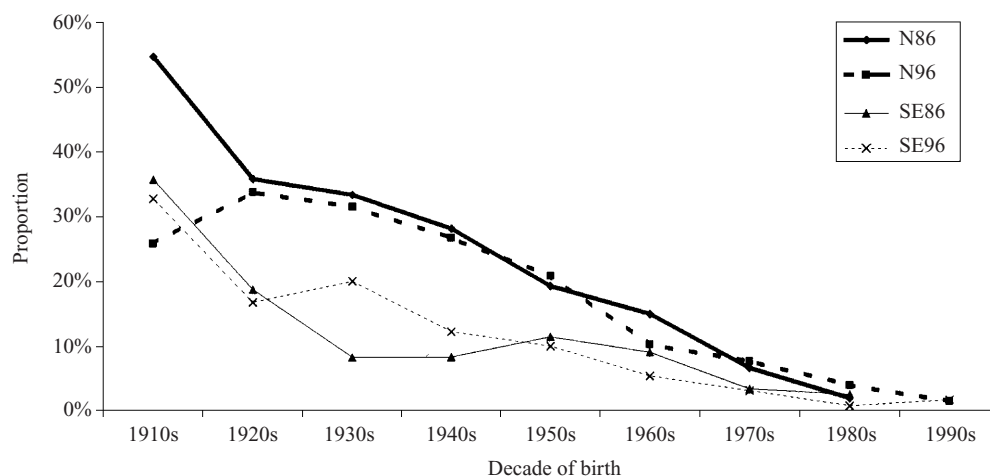


Fig. 4. Active *H. pylori* infection by region (north and south east) and decade of birth.

Samples collected in 1996 were analysed by both age and region (Fig. 3), though only samples from persons aged 15–54 years were available from London. Analysis by region, stratified by age, showed prevalence of active infection to be highest for samples from London, followed by those from the North of England. The East and South-East region showed the lowest prevalence of active infection.

No significant difference in prevalence of active infection between sexes was seen for samples collected in 1986 ($P = 0.6$). An age stratified comparison between sexes for samples collected in 1996 showed a small difference that was significant ($P = 0.002$) with evidence of active infection higher in males (498/3430 [14.5%]) than in females (459/3717 [12.3%]).

Prevalence of active *H. pylori* infection in 1986 and 1996 was compared by region (North and South-East of England only) with age group and decade of birth

(Fig. 4). Of the 2971 samples collected in 1986, 2263 (76%) were from the North of England. The remaining 708 (24%) were from the South-East of which 642 (91%) were obtained from persons aged 1–39 years. Of those samples collected in 1996, 2531/3635 (70%) were from the North of England and 1104/3635 (30%) from the South-East and all age groups were well represented. For each age group, prevalence of active *H. pylori* infection was seen to be lower in samples collected in 1996 than in 1986 ($P < 0.001$). However, analysis by decade of birth showed no overall significant difference in active *H. pylori* infection between samples collected in 1986 and 1996 (Fig. 4) though prevalence was higher in samples collected in 1986 for those born in the 1910s ($P < 0.001$) and the 1960s ($P = 0.018$).

The association between active *H. pylori* infection and HAV seroprevalence was investigated using 5465

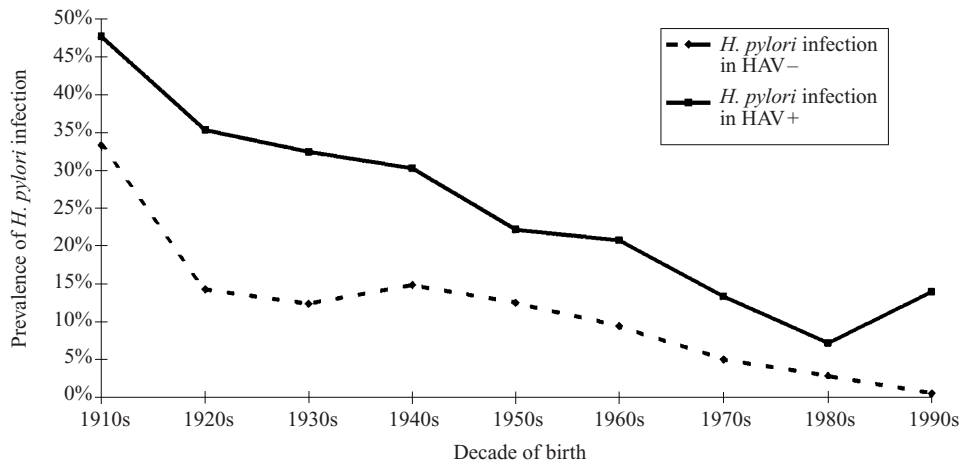


Fig. 5. Active *H. pylori* infection in persons with and without antibody to hepatitis A virus.

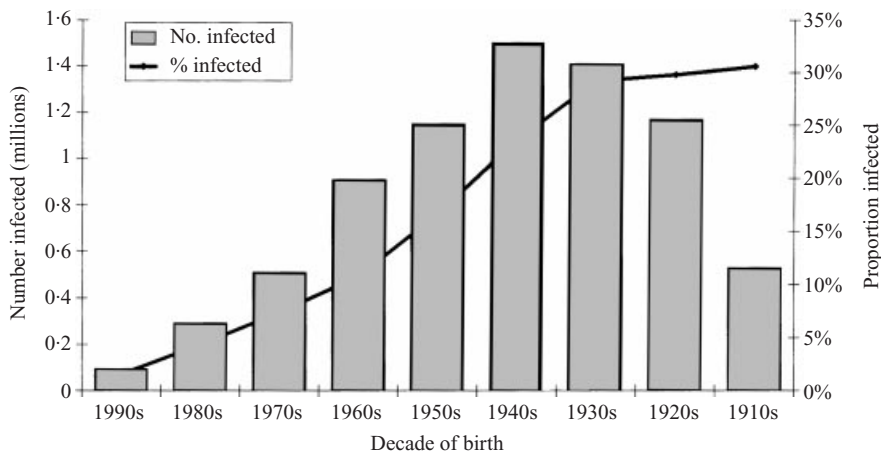


Fig. 6. The population of England and Wales estimated to have an active *H. pylori* infection by decade of birth.

samples screened for both *H. pylori* and HAV IgG (Fig. 5). The prevalence of *H. pylori* infection was higher in samples positive for antibody to HAV ($P < 0.001$), even after adjusting for regional variation.

Estimates of the number of people in England and Wales with an active *H. pylori* infection were calculated using mid-1999 UK population estimates provided by the Office for National Statistics (ONS). For those age groups in London where there were few data available (< 15 years and > 49 years) the proportion with an active *H. pylori* infection was estimated using logistic regression with age and region effects and assuming regional effects were constant across age groups. Using these data, the number of people in England and Wales with an active *H. pylori* infection was estimated as 7.5 million. Analysing by decade of birth (Fig. 6) showed the number of people with infection to peak for those born during the 1940s.

The proportion of people with infection was similar for those born pre-1940 and decreased with decade of birth for those born post-1940 (Fig. 6).

DISCUSSION

This is the first study to investigate the prevalence of active *H. pylori* infection in England and Wales using samples that represent the closest available approximation of the general population across the whole age range. Our data suggest that 14% (7.5 million persons) of the population of England and Wales have an active *H. pylori* infection and those born earlier in the 20th century are more likely to be actively infected.

The subjects tested were not a random sample of the population, but were persons whose serum was submitted to microbiology or biochemistry laboratories for routine diagnostic examination. Given the comprehensive diagnostic service that each offers,

substantial differences between laboratories regarding the reasons for which sera were submitted are unlikely and a comparison between results from each region is justified [12].

The validation study using 80 samples from cases of suspected *H. pylori* infection showed there was a strong association between a high reactivity in serum ELISA for specific IgG and presence of the organism. Since results were to be used to estimate active infection in a population rather than for diagnosis on an individual level, it was appropriate to establish a suitable cut-off for this purpose rather than use that suggested by the kit. A high cut-off was chosen to err on the side of specificity and may not be suitable for the diagnosis of active *H. pylori* in the individual. The cut-off recommended by the Premier ELISA kit to confirm the presence of IgG corresponds to a reactivity of ≥ -1.7 . However, the bi-modal distribution of results suggests that for this study this cut-off is too low and errs on the side of sensitivity at the expense of specificity.

A significant sex difference has been reported in one study where *H. pylori* infection was observed to be more common in males than females in those aged > 25 years [10]. A similar small, but significant, gender difference was found in this study in samples collected in 1996 but not in samples collected in 1986. Gender related differences in prevalence should therefore be investigated further. A higher prevalence in males may indicate that males are either more susceptible to *H. pylori* infection, may be more exposed to the transmission routes of *H. pylori* due to behavioural differences, or that females resolve infection more frequently.

The prevalence of active *H. pylori* infection was shown to vary by region and was highest in the London area, followed by the North of England. An association between HAV antibody and evidence of an active *H. pylori* infection was also found in this study. These two observations may assist in understanding factors affecting transmission of *H. pylori*. The major mode of transmission of *H. pylori* is thought to be by human contact and infection has been shown to cluster within families [15–17]. Other factors known to affect the risk of *H. pylori* infection are childhood living conditions, socioeconomic status and ethnicity [15, 18, 19]. The regional differences observed in prevalence of active *H. pylori* infection may therefore be related to regional variation in levels of household overcrowding and social deprivation, being higher in the North of England and London.

This would also explain the association with HAV seroprevalence since these are also risk factors for HAV infection [20]. An alternative or complementary explanation for these findings is that *H. pylori* infection may be associated with immigrant and ethnic populations, since *H. pylori* and HAV are rare in children in the UK but more common overseas, especially in developing countries [1, 3, 21, 22]. In particular, this may contribute to the high prevalence of *H. pylori* infection observed in the London area. However, previous reports from other countries on an association between *H. pylori* and HAV are conflicting [23–25]. These issues concerning transmission routes and regional differences for *H. pylori* infection could be investigated further. This would require additional information on samples not available for the collection used in this study. Ideally a household study is needed where different regions of the UK are represented and each family member provides a serum sample and information on socioeconomic status, household overcrowding and history of living abroad.

A variety of studies suggest that *H. pylori* infection is acquired at a young age [16–18, 26]. Our data are consistent with the hypothesis that *H. pylori* infection is acquired predominantly in childhood but is becoming less common, possibly as a result of the rising standard of socioeconomic conditions in England and Wales over the last half century. If there is little infection in adults, the lack of difference in the prevalence by decade of birth between samples collected in 1986 and 1996 suggests that there is little resolution of infection. This suggests that few infected persons seek appropriate therapy, possibly because asymptomatic infection is common, and that the immune system alone is not able to eliminate the organism. Effective treatment is most likely to be initiated following the investigation of gastrointestinal disorders that may be related to a *H. pylori* infection.

Our data suggest that *H. pylori* infection is becoming less common, is acquired at an early age and is not resolved unless suitable treatment is sought. The need to provide appropriate therapy depends on the risk of developing serious gastrointestinal disorders, an issue that requires further investigation [27]. The relatively large proportion of the general population of England and Wales with evidence of active infection that could potentially receive antimicrobial treatment raises concern that widespread anti-*H. pylori* therapy could result in antimicrobial resistance in both *H. pylori* and other bacterial pathogens.

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