Volume 9 · Supplement 1 · 2004
HELICOBACTER

Epidemiology of *Helicobacter pylori* Infection

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ABSTRACT

This review summarizes key results of epidemiologic studies published in peer-reviewed journals between April 2003 and March 2004. The prevalence of *H. pylori* infection continues to vary strongly between developing countries and developed countries, and according to ethnicity, place of birth and socioeconomic factors among people living in the same country. Intrafamilial spread appears to play a central role in transmission of the infection in both developing and developed countries. The role of *H. pylori* infection in development of noncardia gastric cancer appears to be even much stronger than previously assumed, whereas the lack of an association with cardia cancer and an inverse association with adenocarcinoma of the esophagus could be confirmed. Suggestions for an inverse association of the infection with atopic diseases have recently received further support, whereas evidence concerning the role of the infection (or its eradication) in GERD and a large variety of other extragastric diseases, including cardiovascular disease, remains inconclusive.

Keywords. epidemiology, *Helicobacter pylori*, prevalence, risk factors, transmission.

Current knowledge implies that acquisition of *Helicobacter pylori* seems to occur predominantly in childhood and that once acquired the infection persists life-long in most infected subjects. Although a major role of intrafamilial spread is now beyond controversy, one of the most elusive areas in *H. pylori* research is a definitive knowledge of the transmission pathway from human to human, when transmission occurs and which factors ensure persistence of *H. pylori* infection in some, but not all humans exposed to the pathogen. At the same time, epidemiologic studies continue to make major contributions to a better understanding of the role of the infection (or the lack thereof) for a large variety of gastric and extragastric diseases.

Prevalence, risk factors, acquisition and transmission

It has been well demonstrated that the prevalence of *H. pylori* strongly varies between developing and developed countries, where prevalence among adults is typically around 80–90% and < 40%, respectively. Furthermore, modes and risk factors of transmission, as well as reinfection rates are likely to vary between developing and developed countries [1,2]. For that reason, results of recent studies are presented separately for both groups of countries.

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Developing countries

Apparently socioeconomic factors are important in *H. pylori* epidemiology even within developing, high prevalence countries. Socio-economic factors such as low income, high household density of children, and use of stove for heating were found to be important risk factors for *H. pylori* infection among Turkish preschool and school children [3]. Low socioeconomic level likewise constitutes a main risk factor in asymptomatic Tunisian children [4]. Socioeconomic factors also explain a large proportion of the difference in *H. pylori* prevalence between Mexican and American children living on both sides of the Rio Grande [5]. By contrast, no association of *H. pylori* prevalence and socioeconomic variables was found in a study from rural Zambia [6].

Two independent Taiwanese studies explored the fecal-oral transmission of *H. pylori* and compared it with transmission of hepatitis A virus. They concluded that the fecal-oral route did not seem to play a major role in the transmission of *H. pylori*, and that *H. pylori* and hepatitis A virus may have different transmission routes [7,8]. Furthermore, a recent study in Guatemala compared the prevalence of waterborne pathogens and *H. pylori* in children and concluded that *H. pylori* is unlikely to be transmitted by water in this population [9].

The oral–oral transmission route was evaluated by assessing the presence of *H. pylori* in dental plaque and gastric biopsy samples in a study from Turkey [10]. A strong correlation between dental plaque and gastric biopsy samples' positivity to *H. pylori* was observed. Nevertheless, the role of dental plaque in *H. pylori* transmission remains unclear. Specific treatment achieved eradication of *H. pylori* from the gastric mucosa in 83% of the patients, but was unsuccessful regarding eradication of *H. pylori* from dental plaque.

One of the less conflicting issues in *H. pylori* epidemiology is that transmission occurs in the family setting and acquisition takes place mainly in early childhood [11]. A study of Brazil confirmed previous findings that *H. pylori*-positive mothers are a strong and independent risk factor for *H. pylori* infection of their children (OR 22.7; 95% CI 2.31–223.21) [12]. Another study, also from Brazil, reported no correlation between seropositivity of the mothers and the *H. pylori* status of their children [13], but the number of mothers included in this study (n = 39) was too small to assess this association with adequate power.

Two independent studies from developing countries (Mexico and Peru) reported reinfection rates following *H. pylori* eradication of 3.2% and 7.6% per year, respectively [14,15]. These results might reflect the high exposure to multiple sources of infection soon after *H. pylori* eradication among patients in developing countries. They have to be taken into account in potential strategies to reduce the burden of *H. pylori*-related diseases in developing countries.

Developed countries

Prevalence of *H. pylori* infection in developed countries varies considerably with ethnic background and within each population with age. A seroepidemiologic study recruiting subjects while presenting to a hospital in Germany or in Turkey found an overall seroprevalence of 13.1% in German citizens living in Germany (n = 675), a seroprevalence of 30.4% in the Turkish born people living in Germany (n = 260) and of 44.5% in the Turkish patients recruited and living in Turkey (n = 148) [16].

Grimm and Fischbach [17] investigated 540 pupils aged 7–9 years from Germany by means of ^{13}C-urea breath test and found an overall prevalence of 9.4%. German pupils were less often infected (7.1%) than those of foreign origin (28.2%). The authors found number of household members as well as history of gastric complaints of other family members and of the pupils to be related to *H. pylori* prevalence after adjustment for covariates.

A study from Sweden [18] compared *H. pylori* seroprevalence of 3502 blood donors aged 17 years and over with an age-stratified random sample from the general population. A steady increase from about 10% in the age group 20–29 years up to 40–50% in the subjects 70 years and over was observed. Notably, this increase was not evident in blood donors over age 50. The reason for this difference was unclear, however, the study results point to the limited use of elderly blood donors as proxy for the general population.

The seroprevalence of *H. pylori* in 71 Greenlanders (mean age 39 years) who were living in Denmark was 46.5% and was therefore almost as twice as high as in Caucasian Danes (25.6%, mean age 41 years) [19]. Robertson and colleagues investigated 500 consecutive blood donors from Australia; overall *H. pylori* seroprevalence was 32% and ranged from less than 20% in subjects 21–30 years up to 54% in subjects aged > 60 years [20]. They found no association with ABO blood groups.

Evidence regarding a key role of intrafamilial spread of the infection has further been strengthened by recent studies. A study in 39 families using molecular typing of strains found the same strains in a large proportion of sibs [29 of 35 (81%)]. Mother–offspring strain concordance was observed in 10 of 18 (56%) of the families, whereas father–offspring strain concordance was not occurring. Clustering of siblings strains was also observed in six families where the mother harboured her own strain. Spouses were infected with the same strain in 5 of 23 (22%) of cases, pointing also to a possible relevance of spouse-to-spouse transmission [21].

A comprehensive study conducted in a Canadian First Nations community with a high seroprevalence of about 95% investigated 50 children in an age range up to 17 years who were all *H. pylori* negative at baseline. Sixteen per cent became *H. pylori* positive after 1 year as determined by means of stool testing and all were of positive mothers. PCR analysis revealed that 78% (18/23) of mothers' saliva, 69% (11/16) of the soother water samples and 9% (1/11) of the water samples from infected homes were positive. The authors concluded that their observations support a person-to-person mode of transmission, mainly between mother and child and an oral-oral pathway. Transmission among siblings was considered to be of less importance [22].

A history of drinking well water was a major risk factor for *H. pylori* seroprevalence in a study from Japan in which 41 families were enrolled. RAPD fingerprinting of isolated *H. pylori* strains from families who drank well water and *H. pylori* DNA detected in five wells suggested that waterborne transmission may occur in this population [23].

Poor hygiene in childhood was an important risk factor for *H pylori* seroprevalence in adulthood in another study from Japan, but the low correlation with presence of antibodies against hepatitis A virus (used as a proxy marker for fecal-oral exposure) does not point to a fecal-oral route of transmission of *H. pylori* in this population [24]. Yet another study from Japan [25] also presented evidence against a common transmission pathway of *H pylori* and HAV, which further supports the suggestion that a common fecal-oral pathway seems to be of little relevance in developed counties.

H. pylori associated diseases

Epidemiologic studies have clearly demonstrated a major etiologic role of *H. pylori* for several gastroduoedenal diseases, including gastric ulcer, duodenal ulcer, gastric MALT lymphoma, and distal gastric cancer [26]. Recent studies imply, that this role may even be much stronger than previously thought. By contrast, the role of *H. pylori* for GERD and for a variety of extra gastric diseases is still controversial.

GERD

Perhaps the most conflictive area of *H. pylori* associated diseases is a possible inverse association between *H. pylori* infection and GERD, and a possible promotion of GERD with eradication of the infection. GERD is a major public health issue in developed countries, and it now appears to become a very important disease in developing countries as well [27].

In a study from Spain, the prevalence of *H. pylori* in GERD patients was lower than in the general population [28]. In a study from the Netherlands, GERD occurred significantly more often (33% vs. 9.7%, $P < 0.001$) in ethnical Dutch individuals, who had a low *H. pylori* prevalence (18.5%), than in people of Turkish descent, who had a much higher *H. pylori* prevalence (60.6%) [29]. However, eradication of *H. pylori* among children and adolescents was not associated with increased symptoms of GERD in a study from Israel [30], and *H. pylori* strains obtained from patients with GERD showed similar bacterial virulence attributes as *H. pylori* strains isolated from duodenal ulcer patients [31]. Given the inconsistency of the methodology and the results of studies on the association of *H. pylori* and GERD, it is important to apply more rigorous methodological criteria to finally resolve the question of the role of *H. pylori* in GERD. Several authors have already emphasized this requirement [32,33].

Gastric and esophageal cancer

Although a positive relationship between *H. pylori* infection and noncardia gastric cancer has long been established, previous suggestions that this association may have been strongly underestimated due to false negative classification of infection status among cases who have lost the infection prior to diagnosis have received further strong support: a case-control-study from Germany found much higher odds ratios after application of strict exclusion criteria to minimize this potential bias [34]. This study even suggested that *H. pylori* infection may be a (close to) necessary condition for noncardia gastric cancer. This suggestion is further supported by a cohort study from Japan, in which the only two *H. pylori* negative patients among 45 gastric cancer cases were people with severe chronic atrophic gastritis who might have lost the infection as a result of this condition [35].

The primary question therefore is no longer whether *H. pylori* causes noncardia gastric cancer, but which cofactors determine who of the *H. pylori* infected people are at particular risk for

the development of noncardia gastric cancer. In this context, a proinflammatory cytokine genetic profile [36–38], in addition to lifestyle factors [39] and bacterial virulence factors [40,41], was consistently shown to be of particular relevance by several recent studies [39–41]. The interaction of lifestyle factors, such as tobacco and alcohol consumption with *H. pylori* infection may partly explain the so-called African and Asian enigmas, i.e. low gastric cancer incidence despite high *H. pylori* prevalence, in some Asian and African countries, according to a recent ecological study [39].

On the other side, the evidence of the absence of an association of *H. pylori* infection with gastric cardia adenocarcinoma and the evidence of an inverse relationship with adenocarcinoma of the esophagus has been further strongly corroborated by a large population-based case-control study from Sweden [42]. However, in contrast to previous suggestions, this inverse association does not appear to be due to atrophy-reduced acidity. The same study also found an increased risk for esophageal squamous-cell carcinoma associated with gastric atrophy and infection with CagA positive strains of *H. pylori*.

Other diseases

Results of epidemiologic studies addressing the relationship of *H. pylori* infection with cardiovascular disease (CVD) remain ambiguous. While a recent case-control study from Italy reported a positive association between infection with CagA positive *H. pylori* strains and atherosclerotic stroke as well as carotid plaque instability [43], other epidemiological studies did not confirm an association of *H. pylori* infection with either CVD events [44,45], unstable angina pectoris [46], or endothelial function [47]. A large case-control study from New Zealand found a weak association of *H. pylori* infection with the risk of myocardial infarction which was though attributed to residual confounding [48]. A positive association of an 'infectious burden' (i.e. seropositivity to various infectious agents including *H. pylori*) with CVD was reported in a case-control study from France [49], while no such association was seen in a German case-control study after careful control of a variety of potential confounders and use of a stable reference group [50]. Along with previous results, current evidence does not support a strong independent effect of *H. pylori* infection in the development of cardiovascular disease.

According to a study from Italy conducted in 121 patients with diabetes mellitus (DM) type 1 and 147 matched controls, *H. pylori* infection and CagA-positive strains do not affect metabolic control in DM type 1 patients (however, a subgroup analysis came to the result that halitosis may make a difference) [51].

A study in 76 women and 29 men conducted in France stated that *H. pylori* infection and chronic gastritis, especially atrophic gastritis, are significantly associated with unexplained iron deficiency anaemia [52].

The hypothesis that *H. pylori* infection may reduce the risk of atopic disorders has received further support by two recent large-scale epidemiologic studies: *H. pylori* infection was associated with a 30% reduction in prevalence of each of three assessed atopic disorders (asthma, eczema and allergic rhinitis) among 3244 participants of a prospective, randomized controlled trial of *H. pylori* eradication in Bristol, UK [53], and seropositivity to two or three markers of poor hygiene (*H. pylori*, hepatitis A virus, and *T. gondii*) was associated with a 50% lower prevalence of atopy in the population-based sample of the Copenhagen Allergy study [54].

A recent study of Goodman *et al*. [55] found that women of reproductive age residing along the US-Mexico border have a high prevalence of *H. pylori* and brought back the idea that *H. pylori* may be associated with hyperemesis gravidarum. However, two independent studies did not confirm this suggestion [56,57], and a large scale epidemiologic study from Germany did not find any involvement of *H. pylori* in the generation of gastrointestinal symptoms during pregnancy [58].

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