Familial clustering of *Helicobacter pylori* infection: population based study

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Abstract

Objectives To assess the rate of intrafamilial transmission of *Helicobacter pylori* infection in the general population and the role of a family's social background.
Design Population survey.
Setting Campogalliano, a town in northern Italy with about 5000 residents.
Participants 3289 residents, accounting for 416 families.
Main outcome measures Prevalence of *H pylori* infection assessed by presence of IgG antibodies to *H pylori*.
Results The overall prevalence of *H pylori* infection was 58%. Children belonging to families with both parents infected had a significantly higher prevalence of *H pylori* infection (44%) than children from families with only one (30%) or no parents (21%) infected ($P < 0.001$). Multivariate analyses confirmed that children with both parents positive had double the risk of being infected by *H pylori* than those from families in which both parents were negative. Family social status was independently related to infection in children, with those from blue collar or farming families showing an increased risk of infection compared with children of white collars workers (odds ratio 2.02, 95% confidence interval 1.16 to 3.49).
Conclusions *H pylori* infection clusters within families belonging to the same population. Social status may also be a risk factor. This suggests either a person to person transmission or a common source of exposure for *H pylori* infection.

Introduction

Helicobacter pylori is considered the main aetiological agent of the most common form of chronic gastritis in the adult population—type B gastritis. Type B gastritis is localised in the antrum and pylorus, whereas type A gastritis, the classic autoimmune gastritis, mainly occurs in the fundus.[1–3] *H pylori* positive chronic gastritis of the antrum has been found to be closely related to duodenal ulcer[4–7] and can lead to gastric atrophy, a precursor of gastric cancer.[8]

Environmental factors, such as socioeconomic and educational state, seem to affect the prevalence of *H pylori* infection. Infection is consistently higher in Hispanic and black people than in white people and is inversely related to educational level.[9]

The prevalence of *H pylori* infection is higher in close communities[10 11] and in members of family groups[12–25] than in the general population. This may be due to relapses or reinfections between members of the same family.[13] Furthermore, the route of transmission of *H pylori* remains unknown, although most of the evidence supports person to person transmission with colonisation occurring primarily in childhood. Under natural circumstances transmission could be by the oro-oral or faecal-oral routes, but no strong evidence exists to support either route as the primary one, and both may be relevant depending on other factors.[26]

Most studies of transmission of *H pylori* infection within families have been conducted on parents and siblings of children referred for symptoms and not on the general population. To avoid this potential selection bias, we studied part of the population of the Dionysos cohort study[27] to assess whether children of *H pylori* infected parents had a higher infection rate then those from families with uninfected parents.

Participants and methods

Family units were identified within the framework of the Dionysos cohort study, which aimed at assessing the prevalence of chronic liver disease in the general population.[27] All the subjects enrolled into the study gave written formal consent to participate.

For the *H pylori* investigation we studied residents aged 12-65 in Campogalliano, Italy (population 4767), one of two towns in the original Dionysos study. In all, 3289 residents (69%) agreed to participate. Agreement was higher among women (71% *v* 67% of men, NS) and lower among young people, especially those aged 17-35, but not significantly so. Details of the estimation of possible bias in patient accession and the validations of the study have been described.[27]

We obtained a serum sample for evaluation of IgG antibodies to *H pylori* from each participant. Serum samples were stored at −20°C until assessment by enzyme linked immunosorbent assay (ELISA) (Eurohospital Kit, Trieste, Italy). A cut off antibody titre of 10 µg/ml was used to classify subjects as positive or negative, as recommended by the manufacturer (sensitivity

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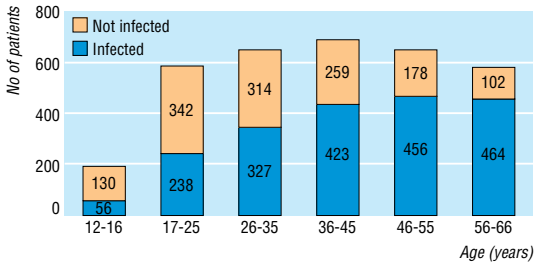

Infection with H pylori *according to age*

Table 1 Distribution of families investigated according to parents' infection with *H pylori*

Parental infection	No (%) of families	No of children
Group 1 (both parents infected)	170 (41)	265
Group 2 (one parent infected)	185 (44)	256
Father infected	94 (23)	133
Mother infected	91 (22)	123
Group 3 (neither parent infected)	61 (15)	80
Total	416 (100)	601

Table 2 Proportion of children infected with *H pylori* according to infection of parents

Parental infection	No (%) of children infected*	95% CI
Group 1 (both parents infected)	116/265 (44)	37.9 to 50.1
Group 2 (one parent infected)	75/256 (30)	24.8 to 36
Father infected	34/133 (25)	17.5 to 32.5
Mother infected	41/123 (33)	24.5 to 41.5
Group 3 (neither parent infected)	17/80 (21)	11.9 to 30.1

*Significant trend (χ^2 test, P<0.001).

96%, specificity 93%).[28] The same IgG antibody assay has been recently used in another multicentre Italian study and showed a sensitivity of 98% and specificity of 78% when compared with a single Giemsa stained histology specimen.[29] To test assay reliability we analysed about 1 in 40 samples twice, with the laboratory blinded to the previous result. Selection for repeat assay was weighted in order to overrepresent samples close to the 10 μg/ml threshold.

The following information was available for each of the 3289 participants: age, sex, family status (father, mother, child, other), and occupation. A family unit was defined as a husband and a wife with at least one child, all living in the same household.

The number of families was 416, representing 1433 of the 3289 cases analysed (43.6%). The median number of members for each family was 3 (range 3-6). Families were divided into three groups according to parents' *H pylori* test results: group 1 included families in which both parents were positive; group 2 families in which either the father or mother was positive; and group 3 those with neither parent positive. In addition, families were grouped into three categories according to father's occupation: "white collar" (when occupation was represented by any type of intellectual work), "blue collar" (including factory employees, shop assistant, and domestic workers), and farmers.

Table 3 Infection with *H pylori* among children according to father's job

Father's job	No of families	No (%) of children infected with *H pylori*	95% CI
White collar worker	66	19/91 (21)*	12.5 to 29.5
Blue collar worker	237	124/331 (37)	31.7 to 42.3
Farmer	87	52/128 (41)	32.3 to 49.7
Total	390†	195/550 (35)	—

*P <0.005 compared with other groups.
†Father's job not available for 26 families.

Statistical analysis

We assessed the extent to which differences in proportions were due to chance alone using the χ^2 test, and P values below 0.05 were considered significant. We used two approaches to explore the relative weight of specific covariates on a child's likelihood of being *H pylori* positive. Firstly, we used a multivariate logistic model with children as the unit of analysis and their own characteristics (age and sex) as well as those of their families (census, infection of their relatives) as the dependent variables.[30] The associations between children's *H pylori* test result (positive *v* negative) and individual covariates were expressed as odds ratios with 95% confidence intervals. However, the weakness of such an approach is that individual children may belong to same family, thus violating the assumption of independence of observations.

Therefore, we also used a model with individual families as the unit of analysis. In this model, the effect of parents' serological state was assessed within families with the same number of children, comparing the number of children positive according to the presence of one, two, or no parents positive for *H pylori*. Statistical analyses were performed with the SPSS/PC statistical package.

Results

The overall prevalence of *H pylori* infection in the town of Campogalliano was 59.7%, increasing with age (from 30% in those aged 12-16 to 82% in those aged 56-66) with a typical cohort effect (figure). The prevalence of *H pylori* infection was similar among families with less than four people (60%, 800/1337) and those with more than four people living in the same household (57%, 55/96). The prevalence of *H pylori* infection in the 1433 participants belonging to the 416 families analysed, accounting for 186 children, was 51.2% (734), with 41% of families having both parents infected and 44% one parent (table 1). The prevalence of *H pylori* infection in children increased with increasing numbers of parents infected (table 2).

Based on fathers' occupation, 66 families could be defined as white collar (91 children), 237 as blue collar (331 children), and 87 as farmers (128 children). Among parents, *H pylori* prevalence was related to occupation, the proportion of fathers testing positive being 55% (36) among white collar workers, 60% (142) in blue collar workers, and 74%[64] in farmers (χ^2 for trend 6.44, P = 0.01) with no significant difference with sex. The trend with husband's occupation was not significant for women (prevalences 58%[38], 62% (147), and 75%[65] respectively; χ^2 for trend 3.59, P = 0.059). White collar families had a significantly lower (21%) proportion of infected children compared with the other two groups (table 3).

Table 4 shows the multivariate analysis assessing the relation between infection in parents and that in

children (after children's age, sex, and family social status were corrected for). Children from families in which both parents were *H pylori* positive had over twice the risk of being *H pylori* positive (odds ratio 2.48, 95% confidence interval 1.35 to 4.52) compared with those from families in which neither parent was positive. The risk was also higher for children belonging to families with one positive parent, although the difference was not significant (P = 0.27). Children with fathers who were blue collar workers or farmers showed a significant increase in the risk of being *H pylori* positive compared with those from white collar families (P < 0.05).

These findings were confirmed when families were used as the unit of analysis (table 5). The number of positive children increased according to the number of positive parents consistently within families with the same number of children. Overall, after number of children was adjusted for, families in which one or both of the parents was positive had a significant increase in the risk of having at least one positive child (2.07, 1.32 to 3.24 for one parent; 2.71, 1.39 to 5.26 for two parents) compared with those with both parents negative.

Discussion

Our large epidemiological study of the distribution of *H pylori* prevalence among families used a different approach from that used in other studies addressing the same topic. It was designed as a population study, and all the consenting residents of a small town were involved, thus avoiding the biases that previous studies on selected series could have had. We studied all the consenting families in one community, representing a valuable sample (66%) of the entire population. Infection of children could be related directly to parents' positivity and family's social background.

The overall prevalence of *H pylori* infection differed according to age, and within children aged 12-16 years the prevalence of infection was similar to that found in a population based study performed in San Marino,[31] an area not far from Campogalliano, but different from other reported values. The prevalence of *H pylori* infection in children was, for example, 40% in Saudi Arabia,[32] 60% in India,[33] and only 10-15% in the United States.[34] This is probably related both to the different age groups considered (5-10 years, 3-10 years, and 3-5 years, in the three countries), and to the different conditions that the children live in.

Table 4 Results of logistic regression analysis assessing relation between infection of parents and likelihood of children being positive for *H pylori* adjusted for children's age, sex, and family social environment

Variable	Odds ratio	95% CI	P value
1 parent infected *v* no parent	1.47	0.81 to 2.70	0.27
2 parents infected *v* no parent	2.48	1.35 to 4.52	0.016
Blue collar workers and farmers *v* white collar workers	2.02	1.16 to 3.50	0.02
Age (continuous variable)	1.06	1.02 to 1.09	0.001
Sex (male reference category)	0.76	0.53 to 1.09	0.18

In our study the prevalence of *H pylori* infection in children was higher if the social conditions were lower. *H pylori* prevalence was significantly higher (P < 0.005) among children of farmers than among children of blue and white collar families. Moreover, children living in white collar families had a lower risk of being positive for *H pylori*. These findings confirm the results of a study by Malaty and Graham which showed a strong inverse correlation between childhood social class and *H pylori* infection.[35] However, we found no correlation between occupancy rates and *H pylori* infection, and this is consistent with the fact that the hygiene conditions of families belonging to the same community should be similar.

Finally, we found that children living in families in which both parents were infected had a significantly higher rate of infection than children with only one or no parents infected. These findings suggest close personal contact of family members living in the same households and support an oro-oral or faecal-oral route of transmission for *H pylori*, as shown by other authors.[36 37]

Although the prevalence of *H pylori* infection in children with two positive parents was lower than that reported by Drumm et al (probably because they studied a selected series),[9] it was similar to that found in two other studies.[24 38] Malaty et al studied family clustering of *H pylori* infections in families of healthy asymptomatic volunteers and showed that *H pylori* infection was higher among children with a positive parent (mother or father) than among those whose parents were negative (50% *v* 5% respectively).[24] Offspring of infected index cases were more likely to be infected than those of uninfected index cases, regardless of whether the infected case was the mother or father. The second study evaluated mothers, fathers, and siblings of index children separately and concluded that mothers of *H pylori* infected children were more likely to be positive.[38]

Table 5 *H pylori* infection in children according to parents' infection and number of children in family

	No (%) of infected children				
No of children in family	0	1	2	>2	Total
1:					
Both parents negative	32 (74)	11 (26)			43
1 parent positive	96 (77)	29 (23)			125
Both parents positive	53 (60)	36 (40)			89
2:					
Both parents negative	12 (71)	4 (24)	1 (6)		17
1 parent positive	26 (51)	18 (35)	7 (14)		51
Both parents positive	27 (37)	28 (38)	18 (25)		73
>2:					
Both parents negative	1 (100)	0	0	0	1
1 parent positive	2 (22)	3 (33)	1 (11)	3 (33)	9
Both parents positive	0	3 (38)	2 (25)	3 (38)	8
Total	249	132	29	6	416

Key messages

- The route of transmission of *H pylori* is still unknown and most studies have been on selected groups
- In this population based study the prevalence of *H pylori* infection in children was related to parents' infection
- Children whose fathers were blue collar workers or farmers' families had a significantly increased risk of *H pylori* infection compared with children of white collar workers.
- These findings support person to person transmission of *H pylori* infection
- Further research is needed to assess the role of housing, dietary habits, and other lifestyle factors

The strong association between infection in mothers and their children may be explained by a greater chance of person to person contact between them within a family. We also found that the prevalence of *H pylori* infection among children was higher when the mother, rather then the father, was infected (33% *v* 25%).

In conclusion, our findings confirm, in an open population, a relation between *H pylori* infection in children and parents and that social environment has a role in spreading the infection. Although the association between parental and children's infection supports the hypothesis of a person to person, probably oro-oral, transmission of infection, the effect of social environment raises the need for further research to assess whether aspects of lifestyle (housing, dietary habits, etc) could have a role.

Contributors: SB, the principal investigator of the Fondo per lo Studio delle Malattie del Fegato, had the original idea for the Dionysos study, coordinated this part of the study, and participated in data analysis and writing and editing the paper. PD, MF, EG, FB, and CT had the original idea for this part of the study, discussed core ideas, designed the protocol, and participated in the discussion of the results and writing the paper. GS, ALR, and FM participated in the execution of the study, particularly blood and data collection and data documentation. ARDB and LV performed IgG assay and quality control of the study. RG participated in discussing and writing the paper and performed all the statistical analyses. SB is the study guarantor.

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Commentary: *Helicobacter pylori*—the story so far

Mike Thomson

The past 10-15 years has seen an almost unprecedented interest in the pathogenic ability of *Helicobacter pylori*. This is perhaps because it is the main cause of gastritis, responsible for up to 80% of gastric and 95% of duodenal ulcers,[1] and is implicated in the pathogenesis of gastric adenocarcinoma and mucosa associated lymphoid tissue lymphoma.[2] The importance of this bacterium was not appreciated until 1983, although it had been recognised in the gastric mucosa nearly a century ago. Initially research concentrated on classification, in vitro culture, and histopathology. The bacterium was first called *Campylobacter pyloridis*, but was subsequently differentiated from campylobacter by, among other properties, the presence of multiple flagellae. A new genus (helicobacter) was devised in 1989. Since then many different strains have been identified with variable virulence—for example, those carrying the cagA gene cause a greater gastric inflammatory response.

However, the gastroenterology community required some persuasion about the pathogenic importance of *H pylori*, and one of the important milestones for this was the demonstration of the acute ulcerogenic effects of infection with the organism after self administration in 1985.[3] Then in 1988 the observation that eradication of *H pylori* diminished the rate of ulcer recurrence tipped the argument in favour of pathogenicity.[4] Evidence for non-gastrointestinal effects, such as risk for cardiovascular disease, remains limited and inconclusive.

Infection is now accepted to occur in childhood, most rapidly under 5 years,[5] and the decreasing rate of acquisition over recent decades may account for an apparent birth cohort effect. Low socioeconomic status and overcrowding are associated with a higher prevalence,[6] and Dominici et al's study adds to the evidence pointing to intrafamilial spread, which may be by the oro-oral or faeco-oral route.

Sensitive and specific diagnostic tests have been developed. Some rely on the urease producing properties of the organism—for example, the Clo test, which is a colorimetric assay requiring a gastric biopsy and the urea breath test using ^{13}C and ^{14}C labelled urea which is then exhaled as labelled carbon dioxide (this is useful to ensure eradication). Serological tests are increasingly used in primary care but do not give any indication of associated disease.

Eradication of the bacterium was first reported to cure duodenal ulceration in 1987,[7] and many studies have confirmed this.[4] Gastric ulcer relapse is also substantially reduced by eradication regimens.[8] Regimens involve triple therapy with a proton pump antagonist and two antibiotics (for example, amoxicillin and metronidazole or clarithromycin) for 1 or 2 weeks. However, evolution of antibiotic resistance is increasingly important. Regimens based on ranitidine bismuth subcitrate have also been investigated.

In 1994, *H pylori* was defined as a grade 1 carcinogen, and it was recommended that all patients with gastric or duodenal ulceration and *H pylori* infection should be given an eradication regimen.[9] In 1997, a European consensus group suggested that all patients with gastritis, peptic ulcer, gastric adenocarcinoma, and mucosa associated lymphoid tissue lymphoma associated with *H pylori* be treated with a triple drug therapy including a proton pump antagonist.[10] Although treatment was also recommended for non-ulcer dyspepsia, a recent prospective study strongly suggests that there is no basis for this.[11] Similarly, eradication regimens in children with recurrent abdominal pain rarely result in improvement.[12]

More recently, physical and genetic maps have been made of the entire *H pylori* genome, and these have shown the organism's high genetic variability. This information has led to better understanding of pathogenicity, virulence factors, and host-pathogen interactions—for example, severe inflammation and duodenal ulceration occurs in 89% of infections with vacA s1a strains but only 20% with vac s2 strains.

Research into vaccination remains active as the organism is good at evading the host immune response. Efforts have focused on the urease component, and in animals mucosal adjuvants, such as cholera toxin, have shown some success. In humans, mucosal routes of vaccination have reduced gastric mucosal density of *H pylori* but have not produced a serological response.

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Endpiece

Training

The three qualities necessary for training:
Great faith
Great doubt
Great effort

The Little Zen Companion,
Workman Publishers, New York, 1994

Submitted by Dorothy Bell-Hall, Doncaster