

***Helicobacter pylori* status in family members as risk factors for infection in children**

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SUMMARY

This study aimed to disentangle the independent contributions of *Helicobacter pylori* infections in mothers, fathers and siblings to the risk for the infection in the 11–13 years age group. Index children from a cross-sectional Stockholm school survey and their family members completed questionnaires and contributed blood samples. *H. pylori* serostatus was determined with an enzyme-linked immunosorbent assay and immunoblot. Fifty-four seropositive and 108 seronegative index children were included and 480 out of 548 family members contributed blood. In multivariate logistic regression modelling, having an infected mother (OR 11·6, 95% CI 2·0–67·9) or at least one infected sibling (OR 8·1, 95% CI 1·8–37·3) were risk factors for index child infection, whilst the influence of infected fathers was non-significant. Birth in high-prevalence countries was an independent risk factor (OR 10·4, 95% CI 3·4–31·3). *H. pylori* infections in mothers and siblings and birth in high-prevalence countries stand out as strong markers of infection risk amongst children in Sweden.

INTRODUCTION

The bacterium *Helicobacter pylori* infects the gastric mucosa of about half of the world's population, rendering it one of the most common human infections [1]. The infection causes gastritis and contributes substantially to the development of peptic ulcer disease and gastric cancer [2, 3]. The sources of *H. pylori* and the mechanisms of acquisition remain poorly understood. Further knowledge about the mode of transmission could be valuable for primary prevention of the infection.

H. pylori transmission is likely to exhibit variation between different settings but some general features

can be discerned. Social and economic development decreases the infection prevalence, reflected in comparisons both between [1] and within countries [4, 5]. Typically, *H. pylori* infection is initiated in early childhood, i.e. before 5 years of age, and once established, may persist throughout decades [4, 6–8]. The infection prevalence increases with age, which in high-income countries can be largely explained by a birth-cohort phenomenon caused by higher incidence rates in the past [6, 8]. The occurrence and relevance of environmental reservoirs are uncertain [5, 6, 9, 10] and person-to-person transmission through contaminated body excretions appears to be the most common way to acquire the infection [11–14].

The family stands out as the most important framework for transmission [11–13, 15–17]. Having an infected mother has been reported to be a significant risk factor for childhood infection, being more

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important than having an infected father [11, 12]. Transmission between siblings has also been postulated based on clustering of the infection in sibships [12, 13]. The outlined transmission patterns are supported by molecular typing of *H. pylori* strains from families [18, 19]. However, epidemiological studies that take all infected family members into consideration are lacking. In the present cross-sectional study, we aimed to disentangle the independent contributions of *H. pylori* infections in mothers, fathers and siblings to the risk for the infection in 11- to 13-year-old index children.

SUBJECTS AND METHODS

Index children

The present cross-sectional study is an extension of a previous serological survey in 11 Stockholm schools, conducted between February and April 1998, investigating risk factors for *H. pylori* infection in children [15]. In the present study, the children from the four schools with the highest *H. pylori* prevalence served as seropositive and seronegative index children, each representing one family. Index children were included in the analyses if at least one household member contributed blood for infection status determination and completed a questionnaire. The local ethics committee approved the study protocol and children and parents gave informed consent.

Exposure assessment

Information about family members was collected between November 1998 and May 1999. Individuals residing in the household at least 14 days per month at the time of the investigation were considered. Parents and children were invited to complete questionnaires and thereafter contribute blood for infection status determination. The questionnaire gathered information about family composition, socioeconomic status (SES), country of birth, breastfeeding, day-care attendance, pet ownership, consumption of antibiotics and other potential risk factors and confounders. The questionnaire was available in eight languages, making it possible for children and parents to respond in the language in which they felt most comfortable.

Infection status determination

The *H. pylori* serostatus of index children and family members was assessed with an in-house

enzyme-linked immunosorbent assay (ELISA) [20, 21]. Subjects with an ELISA value over 0.1 were subsequently tested with immunoblot (HelicoBlot 2.0 and 2.1, Genelabs Diagnostics, Singapore), which defined the final result. The methods had previously been evaluated against the urea breath test in the index children [21]. The sensitivity of the ELISA was 0.98 and the specificity 0.96 for a cut-off value of 0.22 and the HelicoBlot 2.0 had a sensitivity of 0.98 and a specificity of 0.94. Laboratory work was performed blinded to the identity and background of the study subjects.

Statistical methods

Household SES was assigned according to the Swedish socioeconomic classification system into high (white-collar employees) and low (blue-collar workers, unqualified self-employed and unemployed) [22]. The countries of birth were divided into low-*H. pylori* prevalence areas (Western Europe and North America) and high-prevalence areas (Middle East, Turkey, Eastern Europe, Africa, Asia, Latin America and South America) [1, 15]. After excluding index children, family size was classified as 1–2, 3–4 or ≥ 5 family members. The proportion of infected family members of those tested was categorized as 0–33%, 34–66% or $\geq 67\%$. Presence of infected siblings was classified as ‘all siblings seronegative’, ‘at least one seropositive sibling’ or, when there were no other children in the household, as ‘absence of siblings’. Information about siblings was regarded as missing when the sibship was not examined ($n=14$) or only partially examined without identifying any *H. pylori*-infected siblings ($n=11$). The number of antibiotic courses in life was categorized as 0–5 or ≥ 6 .

The data were analysed using the STATA statistical package (version 8.0, Stata Corporation, TX, USA). The associations between *H. pylori* infection in the index children and exposures were estimated by odds ratios (OR) and 95% confidence intervals (CI). Logistic regression models were used to obtain ORs adjusted for the infection status of mothers, fathers and siblings, country of birth of the index child, household SES and antibiotic consumption. Gender and age were considered as potential confounders. Multivariate logistic modelling was also used to investigate potential selection bias in this study. In this case, the dependent variable was participation in the study and data from the school survey were explanatory variables.

RESULTS

Of the 233 children in the previous school survey, 162 participated in the present study with family members' *H. pylori* serostatus and questionnaire information. The participation rate was 54/68 (79%) for seropositive index children and 108/165 (65%) for seronegative index children. Except for the serostatus of the index child, none of the investigated factors (household SES, family size, gender, country of birth of the index children and parents) were associated with participation. In addition to the blood sample in the school survey, all 54 seropositive index children and 93 out of the 108 seronegative index children contributed a second blood sample when family members were sampled. No changes in serostatus were noted in these 147 children over the period of 6–16 months.

Sociodemographic characteristics and *H. pylori* prevalence of the 162 ascertained index children are presented in Table 1. The study subjects were commonly born in or had familial connections to countries outside Western Europe and North America. This observation reflects the sampling scheme which targeted population strata with higher *H. pylori* prevalence than generally found in the low-prevalence native Swedish population [15, 23]. The median age of the index children was 12 years with the range 10–14 years and the majority, 139/162 (86%), were aged 11–13 years.

The 162 index children had 548 family members, of whom 480 (88%) contributed blood samples for *H. pylori* serostatus determination (Table 2). The availability of the serostatus of mothers, fathers and siblings was investigated separately and found to be unrelated to the examined variables (serostatus of the index child, household SES, family size and country of birth). The median age of all siblings and of siblings participating with a blood sample was 10 years with a range of 0–23 years.

A strong familial clustering of *H. pylori* infection was found. The proportion of infected family members was 146/186 (78%) for seropositive index children and 79/294 (27%) for seronegative index children (Table 2). Accordingly, having infected family members was a significant determinant for seropositivity of the index children in the multivariate models. The OR for infection in the index children was 4.8 (95% CI 1.2–19.0) when 34–66% of the family members were infected and 31.6 (95% CI 8.7–115.0) when ≥67% were infected, compared to families where 0–33% of

Table 1. Sociodemographic characteristics and *H. pylori* prevalence of the index children

Variable	All index children		<i>H. pylori</i> infected	
	No.	%	No.	%
All	162	100	54	33
Gender				
Male	82	51	25	30
Female	80	49	29	36
Household SES				
White-collar worker	48	30	7	15
Blue-collar worker, self-employed, unemployed	113	70	47	42
Family size*				
1–2	40	25	9	23
3–4	90	56	25	28
≥5	32	20	20	63
Index child's place of birth				
Low-prevalence area†	113	70	21	19
High-prevalence area‡	49	30	33	67
Mother's place of birth				
Low-prevalence area†	70	43	1	1
High-prevalence area‡	84	52	53	63
Mother not living with family	8	5	0	0
Father's place of birth				
Low-prevalence area†	52	32	1	2
High-prevalence area‡	70	43	39	56
Father not living with family	40	25	14	35

SES, socioeconomic status.

* Excluding the index child.

† Western Europe and North America.

‡ Middle East, Turkey, Eastern Europe, Africa, Asia, Latin America and South America.

the members were infected (Table 3). These estimates indicate a dose–response relation between infection in the index children and an increasing proportion of infected family members. Larger family size *per se* was not a risk factor for infection after adjustment for potential confounders.

Index children born in high-prevalence regions had a higher proportion of infected family members, 112/171 (65%), than index children born in low-prevalence regions, 113/309 (37%). Nevertheless, birth of the index child in a high-prevalence region was an independent risk factor for infection compared to birth in a low-prevalence region (OR 10.4, 95% CI 3.4–31.3) (Table 3). There was a high degree of correlation between infection in parents and their

Table 2. Family members' participation and *H. pylori* serostatus stratified by the serostatus of the index children

Family members	Family members of seropositive index children					Family members of seronegative index children				
	All No.	Serostatus available		Seropositive		All No.	Serostatus available		Seropositive	
		No.	%	No.	%*		No.	%	No.	%*
All†	215	186	87	146	78	333	294	88	79	27
Mothers	54	50	93	47	94	100	98	98	35	36
Fathers	40	35	88	32	91	82	70	85	29	41
Siblings	118	99	84	65	66	150	125	83	14	11

* The denominator is the number of tested family members.

† The row includes four additional adults in the households.

Table 3. Family and index child characteristics as risk factors for *H. pylori* infection in the index children

Variable	<i>H. pylori</i> infected		Adjusted OR*	95% CI
	No./total	%		
Proportion of <i>H. pylori</i> infected family members (%)†‡				
0–33	5/81	6	1.0	
34–66	13/33	39	4.8	1.2–19.0
≥67	36/48	75	31.6	8.7–115.0
Family size‡				
1–2	9/40	23	1.0	
3–4	25/90	28	0.6	0.2–2.1
≥5	20/32	63	1.9	0.4–8.6
Index child's place of birth				
Low-prevalence area§	21/113	19	1.0	
High-prevalence area¶	33/49	67	10.4	3.4–31.3
Household SES				
White-collar worker	7/48	15	1.0	
Blue-collar worker, self-employed, unemployed	47/113	42	2.1	0.6–7.8
Antibiotic courses in life				
0–5	35/99	35	1.0	
≥6	15/58	26	1.3	0.4–3.8

OR, odds ratio; CI, confidence interval; SES, socioeconomic status.

* Adjusted for all variables shown in the table.

† The denominator is the number of tested family members.

‡ Excluding the index child.

§ Western Europe and North America.

¶ Middle East, Turkey, Eastern Europe, Africa, Asia, Latin America and South America.

place of birth. Of parents born in high-prevalence regions, 121/138 (88%) were infected compared to 22/115 (19%) for parents born in low-prevalence regions. The birthplaces of the family members were regarded as surrogates for their infection status and hence were not included in the models which

considered the serostatus of the family members. In the multivariate models, lower SES did not reach statistical significance as a risk factor for infection and higher reported lifetime antibiotic consumption was not associated with a decreased risk for being infected.

Table 4. *H. pylori* serostatus in different categories of family members as risk factors for the infection in the index children

Variable	<i>H. pylori</i> infected		Adjusted	
	No./total	%	OR*	95% CI
Mother				
Seronegative	3/66	5	1.0	
Seropositive	47/82	57	11.6	2.0–67.9
Father				
Seronegative	3/44	7	1.0	
Seropositive	32/61	52	1.4	0.2–9.8
Father not living with family	14/40	35	1.4	0.2–10.8
Siblings				
All siblings seronegative	10/73	14	1.0	
≥1 seropositive sibling	34/44	77	8.1	1.8–37.3
Absence of siblings	5/20	25	5.2	0.7–38.1

OR, odds ratio; CI, confidence interval.

* Adjusted for all variables in the table, household socioeconomic status, index children's place of birth and antibiotic consumption.

H. pylori infection in the mother was a marked risk factor for infection in the index children when the infection status of the other family members was taken into account (OR 11.6, 95% CI 2.0–67.9) (Table 4). In contrast, having an infected father was not an independent predictor for index child infection (OR 1.4, 95% CI 0.2–9.8). Being part of a sibship with at least one identified infected sibling was positively associated with infection in the index children compared to having only uninfected siblings (OR 8.1, 95% CI 1.8–37.3). Having no siblings also tended to be associated with a higher risk of infection relative to having only seronegative siblings (OR 5.2, 95% CI 0.7–38.1). Because infected siblings may be intermediates in transmission from the mother to the index child, the analysis was rerun with siblings omitted from the model to assess the overall effect of the mother. The reduced model yielded an adjusted OR of 18.5 (95% CI 3.8–91.2) for being infected when having a seropositive mother compared to a seronegative one. We were unable to assess interaction between infected mothers and siblings or the role of siblings' ages relative to the index child due to sparse data.

The effect estimates of some household variables seemed to change when the model in Table 4 was

stratified by birth country of the index child. The OR for index children to be infected when having an infected mother increased from 9.7 (95% CI 0.7–138.6) for children born in high-prevalence countries to 22.5 (95% CI 1.4–373.0) for children born in low-prevalence countries. Similarly, the OR for infection in index children who had at least one infected sibling was 2.3 (95% CI 0.3–15.6) for children born in high-prevalence countries and 111.6 (95% CI 2.5–4951.7) for children born in low-prevalence countries. Furthermore, the association between infection in the index children and belonging to a household of low SES corresponded to an OR of 1.1 (95% CI 0.1–8.7) and 15.9 (95% CI 0.8–316.3) for children born in high- and low-prevalence countries respectively.

No associations with index child infection were found for residential crowding (persons per m²), breastfeeding, bed sharing, day-care attendance, pet ownership, travels to the country of birth of the parents, pacifier usage, thumb-sucking and CagA and VacA immunoblot status of family members (data not shown). Gender and age (within the narrow age range of this study) did not confound our estimates.

DISCUSSION

The present cross-sectional investigation of familial *H. pylori* infections as risk factors for seropositivity in index children provides further evidence that having infected family members is highly associated with the infection in children. In accordance with previous studies, the *H. pylori* status of the mother was found to be a strong determinant for childhood infection and more predictive than the status of the father [11, 12]. Data from a Colombian high-prevalence area previously showed that having infected siblings was a predictor of the infection in children, although that study did not control for parental infection status [13]. The importance of both infected siblings and mothers was recently corroborated in a Brazilian high-prevalence community [12]. The present study confirms the presence of infected siblings as an independent risk factor for the infection in children, even when controlling for the infection status of both parents. The findings are substantiated by a previous report of *H. pylori* strain concordance between mothers and offspring and amongst siblings, demonstrated by using bacterial molecular typing in a subset of the currently studied families [18].

Previously described risk factors for *H. pylori* infection such as large family size and residential

crowding (persons per room or persons per m²) may be regarded as proxies for the number of infected family members [6, 10, 13, 15–17, 24]. Accordingly, the positive association between family size and infection in the index children disappeared in our analyses when infected family members were taken into account. The dose–response relation between index child infection and the proportion of seropositive family members may reflect an increased probability of *H. pylori* exposure in families with more infected individuals. However, presence of particularly communicable bacterial strains, behaviours facilitating transmission or shared host genetics contributing susceptibility to infection [25] might also be involved.

Having an infected mother was a major risk factor for index child infection in the present setting. The mother is likely to have introduced the infection to her offspring, because day-care attendance and *H. pylori* prevalence amongst classmates have been refuted as risk factors for the infection in this child population, thus rendering child-to-child transmission outside the family improbable in Sweden [15]. The importance of infected mothers and the lack of a significant contribution from infected fathers possibly reflect how intimate contact potentiates the effect of having seropositive family members. Intimate contact has been proposed to explain some previously described risk factors such as bed sharing [17, 24] and breastfeeding [26], but we were not able to confirm these findings.

Presence of one or more infected siblings was also identified as a strong predictor for infection in the index children. The trend towards increased risk of infection for a child having no siblings present compared to a child having only seronegative siblings is consistent with prior presence of potentially infectious siblings in some of the households. Gastric juice, saliva and diarrhoeal faeces have been postulated as vehicles for *H. pylori* based on culture of the bacterium from these body excretions [14, 27]. Regurgitation, vomiting and diarrhoea are common at a young age and consequently the presence of infected children may boost familial *H. pylori* transmission. The spread of the bacterium may be further promoted by lower gastric acidity of young children and during infective gastroenteritis [27–29].

The number of children in a household has been reported to be a risk factor for *H. pylori* infection in adults, suggesting that children may mediate the infection to their parents [16]. But siblings may also serve as intermediates in transmission from parents to

children. To assess the role of the mother through both the direct and indirect path via siblings, siblings were excluded from the model. Hereby, the effect of having an infected mother tended to increase but the interpretation of this finding is limited by low precision. To clarify the direction of transmission and the sequence of events, studies with repeated measurements are needed.

The finding that birth of the index child in a high-prevalence region was an independent risk factor for infection could be explained by more efficient transmission in high-prevalence countries. There was a strikingly high *H. pylori* prevalence (88%) in the parents from these areas. This high prevalence in parents and the association between index child infection and birth in a high-prevalence region may originate in worse living conditions, poorer sanitation or more frequent gastroenteritis in the country of birth. More contacts with infected individuals in the extended family or community could also contribute to the higher risk of contracting the infection in low-income countries. Furthermore, environmental reservoirs of *H. pylori* such as contaminated water have been suggested in some studies [9, 10, 30], whilst in other circumstances the type of drinking water could not be linked to the infection [5, 6].

The effect of some household variables seemed to be modified by the birth country of the index child. Having an infected mother, infected siblings or belonging to a household of low SES appeared more firmly associated with the infection for index children born in low-prevalence countries than for children born in high-prevalence countries. These tendencies could indicate that *H. pylori* acquisition in high-prevalence countries also depends on additional factors so that the nearest household comes to play a relatively lesser role than in a low-prevalence setting. However, this interpretation is limited by the poor precision and by the fact that current familial constellations and SES probably do not adequately reflect those that the child was exposed to in the country of origin. Furthermore, the mother has been speculated to be a relatively more important infection source than siblings in high-income countries and vice versa in low-income countries [11, 14], but the present stratified analyses could not support this notion.

H. pylori infections are usually persistent in adults but transient infections have been reported in early childhood [4, 7, 31]. Stability of the infection status in older children is supported by the observation that no

changes in serostatus were found for 147 of the index children over 6–16 months. In the family members, the frequency of transient infections and their relevance in transmission are uncertain, but existing knowledge does not give reason to believe that such infections would interfere significantly with the present conclusions.

A primary strength of the present study is that all types of family members were simultaneously assessed for their contributions to the risk of infection in the index children. The high response rate amongst family members (88%) decreases the possibility of bias from non-participation. Accordingly, there was no association between participation and the examined variables (serostatus of the index child, household SES, family size and country of birth) for any of mothers, fathers and siblings. Whilst the participation rate of index children was somewhat lower (79% and 65%), we also found no evidence of selection bias at this stage.

In conclusion, our data provide further evidence that *H. pylori*-infected mothers and siblings are primary determinants for childhood *H. pylori* infection, being consistent with a predominantly mother–child and sib–sib transmission. Moreover, being born in a high-prevalence country was found to be an independent marker of risk for the infection in children living in a low-prevalence country. The present findings constitute a step towards the identification of behavioural, social or possibly environmental factors that explain the mechanisms of transmission and ultimately how societal development restrains *H. pylori* dissemination.

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