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REVIEW ARTICLE

Helicobacter pylori occurrence and transmission: A family affair?

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Abstract
About half of the world's population is estimated to be infected with Helicobacter pylori, a gastric bacterium that contributes to the development of peptic ulcer disease and gastric cancer. H. pylori is more prevalent in low-income areas of the world and social and economic development decreases the prevalence as reflected in comparisons both within and between countries. The infection is typically acquired in early childhood and once established commonly persists throughout life unless treated. Person-to-person transmission within the family appears to be the predominant mode of transmission, particularly from mothers to children and among siblings, indicating that intimate contact is important. The route of transmission is uncertain, but the gastro-oral, oral-oral and faecal-oral routes are likely possibilities. Hence, gastroenteritis may facilitate dissemination of the infection. The community and environment may play additional roles for H. pylori transmission in some (low-income) settings. Furthermore, host and bacterial factors may modify the probabilities of acquisition and persistence of the infection. The understanding of H. pylori occurrence and transmission is of practical importance if future study deems prevention of the infection desirable in some high-prevalence populations. The present paper reviews aspects of H. pylori occurrence and transmission with an emphasis on household factors.

Introduction

Helicobacter pylori may have accompanied humans throughout the existence of our species and molecular typing has uncovered signs of historic and prehistoric human migrations in the bacterial genome [1,2]. Spiral-shaped, Gram-negative bacilli were observed in human gastric mucosa already a century ago, but were not ascribed any significance until the 1980s when Warren and Marshall cultured the bacterium that later was to be designated H. pylori [3]. Approximately half of the world's population is estimated to be infected, which renders H. pylori one of the most common bacterial pathogens in humans.

The association between H. pylori infection and chronic gastritis was recognized early [3]. This usually asymptomatic gastritis has later been confirmed to be present in virtually all infected individuals. A crucial role of the infection in peptic ulcer disease has been firmly established, which has enabled a paradigm shift in the treatment of the 6–20% of infected individuals that develop peptic ulcer disease [4,5]. Accumulating data have also corroborated an association between H. pylori infection and gastric cancer, which develops in a small percentage of infected individuals [6–8]. The role of H. pylori in the above mentioned conditions is supported by eradication of the infection resulting in abolition of gastritis [9], healing of ulcers, prevention of ulcer recurrence [10] and possibly arrested cancer development [8,11–13]. Furthermore, the infection has been found to be somewhat implicated in functional dyspepsia [14] and numerous studies have explored associations between the infection and a variety of extragastric conditions. For the latter, however, cumulative evidence is often inconclusive with an exception possibly being an association with iron deficiency anaemia [15,16].

The high prevalence of H. pylori in many parts of the world accentuates the public health importance of any association between the infection and disease. This may be particularly noteworthy for associations

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that are of modest strength or involve relatively benign conditions, as these associations may otherwise tend to be neglected. Importantly, H. pylori-associated disease may be prevented by eradication of the infection with antibiotics or by limiting the acquisition or persistence of the infection by other means. To devise future intervention with the aim to limit the burden of the infection, understanding the transmission and persistence of H. pylori could contribute essential information.

H. pylori prevalence and incidence

There are several methods to diagnose H. pylori infection, including serology, urea breath test, stool antigen test and invasive endoscopy-based methods such as culture, histology and rapid urease test of gastric biopsies [17,18]. The diagnostic accuracies vary depending on the method and the population and should preferably be evaluated for the population in which the test is to be applied. To avoid bias when investigating H. pylori prevalence, incidence and associated risk factors, the study design should also be taken into account. Population-based studies are usually more suitable than convenience-based samples when studying the occurrence and natural history of the infection. Furthermore, longitudinal studies are preferred over cross-sectional, because the latter cannot disentangle effects on acquisition from effects on persistence and also have an inherent uncertainty as for the direction of causality.

Association with low socioeconomic status

There are considerable differences in H. pylori occurrence between high- and low-income countries and the prevalence in child populations ranges from below 10% to over 80%, respectively (Table I) [18]. H. pylori infection is also associated with low socioeconomic status within countries [19–21]. An early study from 1991 demonstrated this concept in the United States, where a significantly lower prevalence of the infection was found in Caucasians (34%) compared to African-Americans (70%) and this discrepancy was interpreted as a reflection of the different socioeconomic backgrounds of the groups [19]. This finding was more recently further investigated in a follow-up study of a 1970s bi-racial birth cohort consisting of 224 1–3-y-olds followed to young adulthood [21]. The study revealed a 3-fold higher seroconversion rate for African-Americans compared to Caucasians, but also a higher seroreversion rate for the Caucasian youngsters, which amounted to an H. pylori prevalence of over 40% for African-Americans and under 10% for Caucasians at 19–23 y of age.

The specific socioeconomic factors that explain the declining H. pylori prevalence in high-income countries may include improved sanitation [22,23], increased antibiotic consumption [24,25], fewer episodes of gastroenteritis [26] and less frequent close contacts with infected individuals in the community [27]. However, this understanding is partly based on theory as existing data are often inconclusive or even contradictory. The discrepancies may be attributed to real variations between settings or methodological imperfections, notably confounding by other socioeconomic descriptors.

Acquisition typically in early childhood

High acquisition rates of H. pylori have been reported early in life, i.e. before the age of 5 y, from both low- and high-income parts of the world [21,24,28,29]. The importance of childhood acquisition is supported by studies of adults, in whom childhood living conditions predicted infection in adulthood [23,30]. One of the first longitudinal studies of H. pylori infection in children used repeated urea breath tests in 56 Peruvian children aged 6–30 months. The authors noted not only a high prevalence of infection (74% at entry), but also, for the first time, frequent apparently spontaneous elimination and reinfection [31]. Annual incidence rates of over 20% have been reported in early childhood from Bolivia [32] and the border area between Mexico and the United States [29]. The latter study also found that about 80% of childhood infections had been cleared by 2 y of age and concluded that incidence estimates are likely to be underestimated unless this high rate of clearance is taken into account [29]. This pattern of a high annual incidence and repeated H. pylori acquisition explains the rapidly increasing prevalence seen before the age of 5 y in many parts of the world (Table I).

The lower H. pylori prevalence in high-income countries can be attributed to a usually somewhat lower incidence, but also to a high rate of clearance of the infection. In a seroepidemiological study of 201 Swedish children monitored from 6 months to 11 y of age, the highest incidence was found between 18 and 24 months (13 new infections per 100 person-y) [28]. This finding supports that H. pylori infection occurs primarily in early childhood, also in a low-prevalence country. However, 80% of the early infections were transient, leaving only 3% of the 11-y-olds infected. Similarly, in a 1-y prospective study of 1–4-y-old children of Turkish descent in Germany, an annual incidence of 7% was found among previously uninfected children, while 35% of the infected children cleared the infection during

Table I. H. pylori prevalence by age in different populations.

Country (reference)	Study population	Age (y)	Size (*n*)	H. pylori prevalence (%)
Benin [37]	General population	2–5	44	68
		6–9	75	79
		10–13	60	68
		14–15	20	75
		16–24	44	80
		25–34	77	74
		35–44	85	79
		45–54	19	74
		55–74	22	55
Mexico [38]	General population	1–4	527	25
		5–9	1809	43
		10–14	1854	55
		15–19	1418	65
		20–29	1944	77
		30–39	1423	81
		40–49	954	84
		50–59	723	86
		60–69	506	89
		70–	447	79
Korea [20]	General population,	1–19	62	12
	upper socioeconomic class	20–	67	74
	General population,	1–19	168	25
	middle socioeconomic class	20–	75	73
	General population,	1–19	17	41
	lower socioeconomic class	20–	24	83
Germany [108]	General population,	5–7	874	5
	German descent	25–45	825	25
	General population,	5–7	118	44
	Turkish descent [a]	25–45	106	86
Sweden [36]	General population	20–29	143	10
		30–39	168	15
		40–49	190	18
		50–59	206	26
		60–69	152	36
		70–79	121	43
		80–	33	52

[a] Turkish immigrants and their children.

follow-up [33]. Among children of preschool and school ages, moderate incidence rates have been reported from high-income parts of the world [28,34], while higher rates have been described in low-income countries [32]. These findings are supported by the observation that reinfection after successful H. pylori eradication was rare among Irish children older than 5 y (2% per person per y) [35].

Occurrence in adulthood – birth-cohort phenomenon and sustained acquisition

H. pylori prevalence is generally found to increase with age, reaching 20–50% in adult populations in Europe and North America and higher in countries with a history of poor socioeconomic conditions [19,20,36–39] (Table I). The first studies with longitudinally collected sera from people of different ages were interpreted to reflect a birth cohort phenomenon of H. pylori infection [40,41]. This means that most of the detected infections would have been acquired in childhood and that the observed increasing prevalence with age reflected a decreasing risk of childhood infection due to improved socioeconomic conditions over the decades.

H. pylori infection may, however, be acquired also in adulthood. The seroconversion rates are about 0.5–1% per annum in high-income countries with slightly higher seroreversion rates [34,42,43]. In low-income countries, the rates of seroconversion tend to be higher [42] and annual reinfection rates after H. pylori eradication have been reported to be as high as 13–24% in some low-income communities [44,45], thus being comparable to the incidence in childhood. One study from such a high-prevalence setting in Peru found cumulative

recurrence rates of 17% and 30%, 12 and 18 months after successful eradication, respectively [46].

Determinants and mechanisms of H. pylori acquisition

An obvious necessary cause for acquiring H. pylori infection is exposure to the bacterium. Additionally, host and bacterial factors may modify the probabilities of acquisition and persistence of the infection (Table II). In the absence of consistent and verified environmental reservoirs, a predominantly person-to-person transmission has been postulated. This notion was initially based primarily on the clustering of the infection in families [47] and to some extent on a higher prevalence in institutionalized individuals [48] and subsequent research has taken these findings further.

Intrafamilial clustering of the infection

The family stands out as the most important framework for transmission, and a child's risk of being infected is associated with having infected family members [49–52]. Family size and residential crowding (persons per room or per square metre) are frequently described as risk factors for H. pylori infection and may be regarded as proxies for the number of infected family members [50,52]. Likewise, having familial connections to high-prevalence regions is associated with infection in children living in low-prevalence areas [39,53]. It is less well studied how the transmission dynamics are affected by migration from high- to low-prevalence countries, but a decreasing prevalence in successive generations of immigrants indicates a reduction of acquisition or persistence [54]. The familial clustering of H. pylori infection is likely to reflect that family members are infection sources, although another shared source could theoretically contribute to the observed clustering. Furthermore, shared host genetics contributing susceptibility to infection, behaviours facilitating transmission and a presence of particularly infectious strains may contribute to the observed clustering.

Importance of infected family members

Several reports indicate that having an H. pylori infected mother is a more prominent risk factor for childhood infection than having an infected father [49,51–53]. In a seroepidemiological study of 162 index children and their 480 family members in Sweden, having an infected mother was a strong independent risk factor for index child infection, while the influence of infected fathers was not significant after adjustment for other risk factors and confounders [52]. Comparable results have been reported from a rural community in Brazil [49]. The importance of infected mothers, and the lack of a major contribution from infected fathers, probably reflects that intimate contact plays an important role in the transmission.

Clustering of H. pylori infection in sibships further suggests transmission between siblings [49,50,52]. In a Colombian study based on urea breath tests in 684 2–9-y-olds, having older infected siblings was suggested to be more important for a child's infection status than having younger infected siblings [50]. A narrower age gap to the next older infected sibling also seemed to increase the risk of infection. However, the study did not control for parental infection status. When this adjustment was accomplished in a Brazilian study, the presence of

Table II. Overview of possible determinants of H. pylori infection.

Determinant	References
Necessary cause: Exposure to the bacterium	
Living in or originating from high-prevalence areas	[18,39,52–54]
Infected family members and large family size	[22,23,30,49–52,88]
Infected contacts in the community	[27]
Environmental reservoirs	[22,64]
Behaviour and other factors increasing the exposure: Intimate contact, gastroenteritis, poor sanitary facilities	[30,49,51,52,60,61,88]
Component cause: Host factors	
Expression of receptors	[77,79,82]
Host defences: Gastric acid secretion, immune responses	[83–85,90]
Other factors affecting the gastric milieu: Young age	[21,24,28]
Component cause: Bacterial factors	
Protected localization: Motility, adhesion, internalization	[77,80,81,92,94,109]
Withstanding host defences: Urease activity, immune evasion	[93,98–102]
Adaptive evolution	[75–77]

infected siblings remained as an independent predictor for childhood infection [49]. Also, in the recent study from Sweden, infected siblings remained as a strong risk factor for index child infection after adjustment for parental infection status [52].

The mother is probably a key source for introducing the infection among her children, based on the higher infection prevalence in the parental generation. In high-income societies with a relatively low H. pylori prevalence there is at present no clear alternative from where the children could acquire the infection. For example, day-care attendance and a high H. pylori prevalence in classmates did not predict the infection status of Swedish children [53]. However, the situation may be different in instances where poor sanitary facilities and frequent close contacts with infected individuals in the extended family or community may favour transmission. A higher H. pylori prevalence was, for example, found among children who attended day-care centres in urban Sardinia compared to those who never attended [27].

Some evidence supports H. pylori acquisition in adulthood from an infected spouse, which is in line with some remaining risk for becoming infected after childhood [55]. In addition, having more children has been described as a risk factor for infection in adults, which possibly indicates that children may serve as mediators of transmission within families [23]. The high rates of reinfection after eradication in adults reported from high-prevalence regions are of unknown aetiology, but infected family members are likely sources [44–46]. A lesser role played by factors outside the family is supported by the finding that travelling to high-prevalence areas, although not directly comparable to permanent residence, has not been found to increase the risk of becoming infected in adulthood [56].

The transmission patterns outlined above are corroborated by studies using H. pylori molecular typing. Unrelated individuals harbour distinct H. pylori isolates, while clonal isolates can be discerned within families, occasionally in combination with clonal variants [57,58]. In a molecular typing study encompassing 104 members from 39 families, siblings were frequently infected with the same strains (29 of 36 siblings) [58]. This finding could in many cases be explained by acquisition of the mother's strain since mothers and offspring exhibited strain concordance in 10 of 18 families. Furthermore, no father-offspring strain concordance was observed in 8 families, while spouses were infected with the same strains in 5 of 23 couples.

Transmission routes

Possible H. pylori transmission routes are gastro-oral, faecal-oral, oral-oral or a combination of all, but firm evidence is scarce. H. pylori has been cultured from vomitus, diarrhoeal stools and saliva, demonstrating that the bacterium is potentially transmissible by these routes [26,59]. Vomitus in particular appears to harbour viable bacteria and even air in the vicinity of a vomiting study subject can be H. pylori positive by culture [26]. In line with this observation is a study which found a weak association between vomiting in siblings and childhood infection [60]. An elevated incidence of H. pylori infection has also been reported after outbreaks of gastroenteritis among institutionalized children in France [61]. It is largely unknown whether the transmissibility of the infection is influenced by bacterial virulence or the symptoms experienced by a minority of infected individuals. However, acute H. pylori infection has been associated with symptoms such as vomiting and diarrhoea, which may promote transmission [62,63].

Close contacts within families plausibly facilitate exposure to bacteria through contaminated body excretions, being in agreement with familial transmission. Regurgitation, vomiting and diarrhoea are common in childhood and thus, children may boost familial H. pylori transmission after the bacterium has been introduced into a child. Following this line of reasoning, it is appealing to envisage a model in which societal development involves a decreasing frequency of gastroenteritis and an improved sanitary standard, thereby contributing to the declining H. pylori prevalence in high-income parts of the world.

Transient or persistent survival of H. pylori in environmental reservoirs has been hypothesized to promote the spread of the infection. For example, contaminated water has been proposed as a reservoir for H. pylori based on epidemiological findings [22,64], but there are conflicting results [20,32,37]. One of the first studies that pointed to the possibility of environmental transmission was a Peruvian study, which found that children whose homes had external compared to internal water supply were 3 times as likely to be infected [64]. Bacterial DNA can be detected in environmental water samples by PCR [65]; however, such findings may very well represent non-viable bacteria and H. pylori culture of environmental water samples has rarely been successful [66]. This indicates that H. pylori cannot survive for long outside its gastric niche, which is supported by the relatively limited metabolic and regulatory potential of the bacterium [67], thus arguing against environmental

transmission. Hepatitis A is spread through the faecal-oral route and correlations between antibodies against hepatitis A and H. pylori could possibly indicate a common mode of transmission. However, a number of studies have not been able to confirm this hypothesis [68,69] and more conclusive evidence has to be sought elsewhere. Moreover, H. pylori has been suggested to possess zoonotic potential, but these theories have not received wide acceptance [70–72]. Interestingly, different ethnic groups in the same geographical area have been found to harbour distinguishable bacterial strains, a finding which may argue against significant infection sources in the environment or community [1,2].

Host and bacterial factors

H. pylori strains differ in their ability to establish and maintain an infection in a given host, which can be attributed to host and bacterial factors and their compatibility [73–77]. The transient infections in childhood may reflect instances where the bacterium is not optimally suited for the new host and adaptation is not feasible or rapid enough, leading to the host succeeding in clearing the infection [21,28,29,31].

Host genetics have been indicated to be involved in susceptibility to H. pylori infection based on higher infection concordance rates in monozygotic (81%) than in dizygotic (63%) twin pairs [78]. Expression of blood group antigens that mediate bacterial adherence to the gastric mucosa may be involved in host susceptibility to the infection [79–81]. There are indications that H. pylori strains have adapted their binding affinities in accordance with the blood group antigen expression of different human populations [77]. Furthermore, individuals that excrete receptors in body fluids, offering removable binding sites that can compete with tissue-bound receptors, have been reported to have a lower risk of being infected [82]. Factors of the immune system may also be involved in determining predisposition to H. pylori infection. This notion is supported by studies that have described specific human leukocyte antigen alleles [83,84] and a cytokine receptor polymorphism [85] to be associated with the infection.

The immune system is commonly unable to eradicate the infection and the reported high rates of reinfection after eradication may speak against a significant protective role of natural immunity [44–46]. Breastfeeding has been speculated to provide children with passive immunological protection against early infection [86,87]. However, such protection, if any, should be of limited importance after weaning, as supported by negative findings [27,32,88]. One study even reported that breastfeeding resulted in a higher risk of infection, which may be explained by the intimate contact between the mother and the breastfed child [89]. A lower gastric acid secretion in childhood and during infective gastroenteritis may also promote the spread of the bacterium, as indicated by a study using a murine model system [90].

H. pylori has to overcome numerous barriers to successfully establish an infection in an individual: 1) exit from an infected individual; 2) transient survival outside the gastric niche; 3) introduction into a new host; 4) colonization of the new gastric mucosa; and 5) maintenance of the colonization. The bacterium has developed a repertoire of functions for survival in the harsh gastric niche, including acid tolerance, motility, adherence, adaptive evolution and immune evasion [67,91]. These features are all involved in the interplay between the host and the bacterium and, if disrupted, the colonization and adherence capabilities of the bacterium may be impaired [80,81,92–94]. H. pylori is an exceptionally genetically diverse bacterial species, which may contribute to adaptation to newly infected individuals and to persistence of the infection despite a changing gastric environment over the years [75–77,95,96]. Genes related to DNA metabolism and surface structures appear to be especially variable, which probably illustrates the importance of genome variability in H. pylori and that surface structures exposed to the host undergo antigenic variation [91,97]. Furthermore, the bacterium has developed means to evade both the innate and adaptive immune responses, for example by being relatively inert in interactions with the Toll-like receptors [98,99], by inhibiting the activation of T-lymphocytes [100,101] and by modifying the nature of the immune response [102].

Prevention

Management of H. pylori infection benefits from knowledge about who will develop disease. This is reflected in current treatment guidelines that recommend eradication therapy in some patient groups at high risk for H. pylori-associated disease [17,103,104]. Such groups for instance include persons with atrophic gastritis and first degree relatives of gastric cancer patients, who are at high risk of developing gastric cancer. Persons using non-steroidal anti-inflammatory drugs, which is an independent risk factor for peptic ulcer disease, may also be offered H. pylori eradication. Some studies have targeted high-risk groups to study the effects of eradication therapy with somewhat encouraging results. Anti-H. pylori treatment has been reported

to result in regression of cancer precursor lesions [11,13] and there are indications that eradication treatment may protect against gastric cancer [8,12]. A randomized trial in a Chinese population found that eradication did not affect the overall gastric cancer incidence over the observation period of 7.5 y, but the incidence was reduced in an infected subgroup without precancerous lesions at entry [12].

More widespread and indiscriminate eradication of H. pylori infection has also been proposed as an approach to limit the burden of H. pylori-associated disease. The appropriateness of such a large-scale and crude intervention has been questioned, especially as the infection is benign in the majority of cases and the full spectrum of consequences of eradication is uncertain. The argumentation has been further fuelled by the finding that H. pylori infection appears to protect against oesophageal adenocarcinoma [105,106]. Moreover, routine triple-agent therapy is beyond the financial reach of many low-income nations, but also for high-income societies a test-and-treat approach would be costly. Large-scale treatment approaches would also promote the emergence of antibiotic resistance of H. pylori and other bacterial species, which would be a critical problem.

An alternative approach could be to target the acquisition or persistence of H. pylori, while limiting the use of antimicrobials. Antibiotic treatment or general socioeconomic advances are likely to play central roles to eliminate the infection, with or without specific intentions. Nevertheless, understanding and interfering with the acquisition or persistence may become useful supplemental strategies in prevention of the morbidity associated with the infection. This is probably especially true for some (low-income) populations, where effective antibiotic regimens may be impaired by high cost, poor compliance, antibiotic resistance and high reinfection rates. Preventing the establishment of infection is an often successful and central approach in public health interventions against a variety of infections. There have been considerable efforts to develop protective or therapeutic vaccines against H. pylori, but despite some promising results, further work is needed to bring about effective and safe candidates for humans [107]. There is a lack of studies that investigate prevention of the infection by limiting the transmission, which may be explained by there being no apparent and simple prevention strategy at present. This may be attributed to the seemingly multifaceted nature of H. pylori acquisition, intertwined with activities of everyday life. Better understanding of H. pylori acquisition and persistence, as well as of the consequences of eradication, is needed before practical and effective intervention strategies can be devised and tested.

Concluding remarks

The association between H. pylori infection and low socioeconomic status and the identification of early childhood and the household as the typical time and place of acquisition are important pieces of epidemiological knowledge. The finding that transmission appears to occur primarily between mothers and offspring and among siblings fits into a scheme where close contact is important for transmission. Probable mechanisms of transmission have been postulated and partially tested based on this information. Further longitudinal studies coupled with experimental investigations are needed to clarify the mechanisms of acquisition and persistence, the sequence of familial transmission events and possible roles of alternative infection sources. Comparable studies could be performed in low- and high-income countries to elucidate how the transmission and natural history of H. pylori infection relate to the declining prevalence in high-income countries. Such investigations could provide clues about behavioural, social or possibly environmental factors that explain how societal development restrains dissemination of the infection. These insights may be essential if future study deems it appropriate to develop intervention strategies aimed at accelerating the disappearance of H. pylori infection in high-prevalence populations.

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