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***Helicobacter pylori* Infection – A Boon or a Bane: Lessons from Studies in a Low-Prevalence Population**

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Abstract

Helicobacter pylori (*H. pylori*) infection is etiologically associated with gastric cancer and peptic ulcer diseases which are both important public health burdens which could be largely eliminated by *H. pylori* eradication. However, some investigators urge caution based on the hypothesis that eradication of *H. pylori* may result in an increase in the incidence of gastroesophageal reflux disease, esophageal adenocarcinoma, and childhood asthma. The ethnic Malays of northeastern Peninsular Malaysia have long had a low prevalence of *H. pylori* infection and, as expected, the incidence of gastric cancer and its precursor lesions is exceptionally low. The availability of a population with a low *H. pylori* prevalence and generally poor sanitation allows separation of *H. pylori* from the hygiene hypothesis and direct testing of whether absence of *H. pylori* is associated with untoward consequence. Contrary to predictions, in Malays, erosive esophagitis, Barrett's esophagus, distal esophageal cancers, and childhood asthma are all of low incidence. This suggests that *H. pylori* is not protective rather the presence of *H. pylori* infection is likely a surrogate for poor hygiene and not an important source of antigens involved in the hygiene hypothesis. *Helicobacter pylori* in Malays is related to transmission from *H. pylori*-infected non-Malay immigrants. The factors responsible for low *H. pylori* acquisition, transmission, and burden of *H. pylori* infection in Malays remain unclear and likely involves a combination of environmental, host (gene polymorphisms), and strain virulence factors. Based on evidence from this population, absence of *H. pylori* infection is more likely to be boon than a bane.

Keywords

Causes; consequences; *Helicobacter pylori*; low prevalence; Malays; Malaysia

The prevalence of *Helicobacter pylori* infection varies globally from one geographical region to another with a greater prevalence generally being reported from developing countries [1,2]. South-East Asia is a cultural-diverse region rich with multiple ethnicities and indigenous communities. One of the larger ethnic groups is the Malays (*Melayu*) who are a member of the Austronesian family, largely populating the Peninsular Malaysia, Sumatra, and Borneo. In the first half of the 20th century, it was noted that peptic ulcer and gastric

cancer were rare in the ethnic Malays but not in the Chinese or Indian populations living in this region [3]. With the discovery of *H. pylori* being the etiological agent underlying gastric cancer, the ethnic Malays were also reported to have a low prevalence of *H. pylori* infection besides a low gastric cancer rate [4–6].

The population of the northeastern region of Peninsular Malaysia (state of Kelantan – Fig. 1) consists of 90% ethnic Malays and, over many centuries, has had minimal to no interactions with populations from the nearby Indonesian archipelago or with more recent migrants. A population genotyping study indicates that the Malays from this region are genetically distinctive from Malays of other parts of the Peninsular [7]. Despite the fact that the region (i.e., state of Kelantan) is among the lowest in coverage of clean water and sanitation facilities in the country [8], this unique Malay population has a prevalence of *H. pylori* infection that is probably the lowest in the world [9]. Studying this population may provide important insights to public health problems related to *H. pylori* infection especially in gastric cancer prevention.

The reasons for the exceptionally low prevalence of *H. pylori* are intriguing and remain elusive [10]. One postulation is that this Malay population may have passed through bottlenecks in which its founding population was uninfected. Another possibility is that local practices or environmental factors may limit transmission or inhibit the infection. Unidentified genetic or host factors intrinsic to this population may also result in them being less susceptible to *H. pylori* infection or cancer as a whole.

Studying this unique population also provides some insights into answering the contentious issue on whether eliminating *H. pylori* infection has potentially detrimental effects? While *H. pylori* infection is known to be etiologically associated with dire consequences including peptic ulcer disease and gastric cancer among others, its absence has been postulated to be causative in the rise of other morbidities including gastroesophageal reflux disease, distal esophageal cancers, and childhood asthma [11].

This review examines the evidence from available studies conducted on the Malay population in northeastern Peninsular Malaysia in an attempt to shed some light on this issue and also discusses the potential reasons for the exceptionally low prevalence of *H. pylori* infection.

Unique Epidemiology of *H. pylori* Infection in Malaysia

Within different regions of Peninsular Malaysia, the reported prevalence of *H. pylori* among the ethnic Malays differs and this is reflected by its local population demographics and the mixing of Malays with other immigrant ethnics (Table 1). In the northeastern region of Peninsular Malaysia where the population consists of 90% Malays, *H. pylori* seroprevalence rate has been reported to be 4.2% among 496 blood donors and 4.8% among 921 subjects attending health a screening clinic [9]. This contrasts with the 11.9% prevalence rate among blood donors in the Klang valley (city of Kuala Lumpur), where the population consists of 30% Malays [4]. More recently, among asymptomatic blood donors from northwestern region of the Peninsular which consists of 20% Malays in its demographics, the reported rate was 15.2% in the Malays, and this was no different from other ethnics residing within the area (Chinese 14% and Indians 12.8%) [12].

Interestingly, the prevalence of *H. pylori* infection among both Chinese and Indian immigrant populations in the state of Kelantan is lower than that of the larger cities (14.5% in Kelantan compared with 23.5% in Kuala Lumpur) [4,9]. Additionally, the prevalence rate among a group of recent immigrants from Kampuchea currently living in northeastern Peninsular Malaysia was 72.5%, as expected but the prevalence among local-born

Kampucheans was only 25.9% [13]. The seroprevalence among the Orang Asli, the aboriginal community, residing in the state of Kelantan has been reported to be only 19% [14]. This is in contrast with the 37.7% prevalence among the indigenous aboriginal Penan community of East Malaysia (North Borneo) [15]. The seroprevalence rate among household members of Malay individuals initially identified to be *H. pylori* positive at endoscopy was found to be only 7.6% and was not significantly higher than the 2.9% infection rate among household members of an uninfected control group [13].

The extraordinarily low rates of *H. pylori* infection among the Malays in Kelantan were observed not only in the general population but also among patients with gastroduodenal erosive lesions demonstrated by endoscopy (Table 1). The *H. pylori* infection rate reported from gastric biopsies was 20% in duodenal ulcer, 21.2% in gastric ulcer, 16.7% in duodenal erosion, and 17.1% in gastric erosion [16]. The incidence of peptic ulcer perforations within the region from 1991 to 1992 was only 1.5 per 100,000 person-years [9,17]. Another study from the northwestern region of Peninsular Malaysia revealed infection rates of 32.1, 10.4, 20.0, and 16.2% in ulcer, gastritis, duodenitis, and nonulcer dyspepsia, respectively, with the Malays having a prevalence of only 5.8% [18]. In a survey from Kuala Lumpur involving 1060 dyspeptic patients undergoing endoscopy in 1994–1995, the *H. pylori* infection rates were 16.4, 48.5, and 61.5% among Malay, Chinese, and Indians, respectively. [19].

Consequences of Low *H. pylori* Infection: Good or Bad?

Gastric Cancer and its Precancerous Lesions

The incidence of gastric cancer according to the Malaysian National Cancer Registry for the period between 2003 and 2005 was 2.2 of 100,000 among the Malays and was lower than in the Chinese (11.3 of 100,000), and Indians (11.9 of 100,000; Table 2) [20]. A similar pattern is also seen in the Singapore Cancer Registry albeit at relatively higher rates, but a much lower rate is seen among populations in Indonesia [21] who ethnically and linguistically have much in common with the Malays. The incidence of gastric cancer in northeastern region versus northwestern region was 1.5 of 100,000 versus 3.2 of 100,000 among Malay men and 0.9 of 100,000 versus 1.8 of 100,000 among Malay women [6,22–24]. Multiple logistic regression analysis from a study in Singapore identified Chinese race, *H. pylori* infection, low level of education, smoking, and high intake of salted fish and vegetables as being risk factors for gastric cancer [25]. There has been a marked decline in the incidence of gastric cancer in the Western populations following the end of World War II with a similar trend being observed in Asia recently [26,27]. Besides eradication of *H. pylori* infection with increased use of antibiotics, a change in diet with reduced consumption of salted and preserved foods from widespread use of refrigeration, increasing level of education, and improvement in hygiene also contributed to this decline [28,29]. The low prevalence of gastric cancer and *H. pylori* among the Malays has existed even before the two World Wars. The low force of transmission among household members and the low reservoir of infection among the Malays in northeastern Peninsular Malaysia suggest that environmental factors other than that related directly to sanitation and hygiene and/or host genetic factors intrinsic to Malays protect them from *H. pylori* and consequently gastric cancer.

Atrophic gastritis and intestinal metaplasia are considered as precancerous lesions in the “Correa” cascade of gastric cancer genesis [30]. Studies from China and Japan have reported high prevalence rates of atrophic gastritis and intestinal metaplasia of up to 80% largely due to a high rate of *H. pylori* infection in these regions acquired since childhood [31]. In a survey of 234 subjects undergoing upper endoscopy in a tertiary hospital from the state of Kelantan, the overall reported rate of atrophic gastritis was 42.3% (99 of 234) and that of intestinal metaplasia was 7.7% (14 of 234). Notably, intestinal metaplasia was only present

in 1.4% (2 of 146) of Malay subjects (Table 2) [32]. This observed low rate of atrophic gastritis and intestinal metaplasia is a result of the low *H. pylori* infection in the study population of only 6.8%. The low force of transmission of infection since childhood in this population is likely to account for this low frequency of gastric precancerous lesions. In the same study [32], with multivariable analysis, the risk of intestinal metaplasia was only significant in the presence of *H. pylori* infection. This and other studies infer that if there is a low existence of *H. pylori* infection since early life provided by early and continuing eradication strategies, these precancerous lesions are potentially preventable [33].

Esophageal Cancer, Barrett's Esophagus, and Erosive Esophagitis

There is an increasing prevalence of esophageal cancer in particular adenocarcinoma of the distal esophagus being reported in Western populations and more recently in Asia [34,35]. This has been thought to be related to increasing obesity, gastroesophageal reflux disease, and a declining prevalence of *H. pylori* infection [36,37]. The role and evidence for *H. pylori* involvement in the etiology of esophageal cancer remain controversial. The Malays from the Singapore Cancer Registry have the lowest reported incidence for this cancer (1.7 of 100,000 in males and 0.6 of 100,000 in females) when compared with the Chinese or the Indians [21]. This is also the case among Malays in Kelantan among whom the age-standardized incidence was 1.6 of 100,000 in males and 2.2 of 100,000 in females, respectively (Table 2) [38]. This suggests that a low presence of *H. pylori* alone is unlikely to be the pivotal factor accounting for the recently observed rise in adenocarcinoma in some populations. The low incidence of esophageal cancer in the Malays may be partly related to the low consumption of alcohol due to their Islamic faith, and it is interesting to note that a similarly low incidence of squamous cell carcinoma has been reported from Egypt and Jordan [39]. It is intriguing that the incidence of squamous cell carcinoma is relatively higher among Malay women in Kelantan as compared with the Malays in Singapore or indeed in many other parts of the world. This may be partially attributed to the habit of smoking unfiltered tobacco and chewing betel quid among older Malay women in Kelantan.

There is an increasing prevalence of gastroesophageal reflux disease and Barrett's esophagus being reported in Asia, a disease thought to be uncommon until the recent decades [40,41]. Successful eradication of *H. pylori* infection is thought to cause a rise in acid reflux disease [42]. While eradication of *H. pylori* will likely increase the average acid secretion in areas where corpus gastritis is common, the ability to secrete acid is only one factor in the development of gastroesophageal reflux disease [43,44]. If simply absence of *H. pylori* was the critical variable, ethnic Malays would be expected to have a high prevalence of gastroesophageal reflux disease and its complications as they have a very low prevalence of *H. pylori* infection. In a retrospective analysis involving 1895 consecutive patients undergoing upper endoscopy between 2005 and 2007 in a tertiary hospital in Kelantan, only 3.7% (71 of 1895) of patients had confirmed erosive esophagitis and 0.8% (15 of 1895) had Barrett's esophagus (Table 2) [45]. The reported rates for erosive esophagitis and Barrett's esophagus are much higher among patients undergoing endoscopy from the northwestern (esophagitis 6.1% and Barrett's 6.2%) and central western belt (esophagitis 13.4% and Barrett's 2.0%) of Peninsular Malaysia (Table 2) [46,47]. The low observed rate of esophagitis and Barrett's esophagus despite the low rate of *H. pylori* infection seen among the Malays does not support the notion that the absence of *H. pylori* infection plays more than a minor role as a risk factor for both diseases. A recent meta-analysis also showed no convincing association between *H. pylori* eradication and the development of gastroesophageal reflux disease [48].

Childhood Asthma

Some studies have suggested an inverse relationship exists between *H. pylori* seropositivity and asthma, while more recent meta-analyses have cast doubts regarding this claim [49–51]. It has been proposed that an early exposure to *H. pylori* infection in life may cause immunological changes that protect against the development of asthma. This is in keeping with the “hygiene hypothesis” and suggests that *H. pylori* bacterium contains critical antigens that trigger a protective immune response. A survey among schoolchildren in the state of Kelantan revealed that the prevalence of wheezing at any time in the preceding 12 months was 5.4% among children 6–7 years old and 5.7% among children 13–14 years old (Table 2) [52]. Such low rates of asthma among young children in Kelantan in the setting of low *H. pylori* infection do not support the inverse relationship hypothesis and an important protective effect specifically of exposure to *H. pylori* antigens. It is rather more consistent with the notion that *H. pylori* infection in some populations is simply a marker for poor hygiene.

Origin of Low *H. pylori* Infection Among Malays in Kelantan

Environmental and Dietary Factors

In a case–control study involving 161 Malay subjects (79 tested positive for *H. pylori* or “cases” and 82 tested negative for *H. pylori* or “controls”) born and residing in Kelantan, a validated questionnaire was employed to identify sociocultural and dietary factors that might explain the low *H. pylori* prevalence seen [53]. As previously reported, poor household hygiene and sanitation practices were found to increase the risk of *H. pylori* infection among the Malays. These practices with a link to water supply included the use of well water (odd ratio; OR = 3.4, 95% confidence interval; CI: 1.8–6.5), use of pit latrine (OR = 2.8, 95% CI: 1.5–5.3), and infrequent hand wash practices with toilet use (OR = 3.5, 95% CI: 1.1–11.3). There is valid evidence that the *H. pylori* bacterium can survive and contaminate local water supply [54–56]. Some dietary factors were found to be associated with increased risk of infection including the use of chili, preserved vegetables, coconut oil, and coffee, and some were significantly protective including consumption of “budu” (OR = 0.3, 95% CI: 0.1–0.7), “pegaga or *centenella asiatica*” (OR = 0.3, 95% CI: 0.1–0.7), and tea (OR = 0.02, 95% CI: 0.01–0.07) [53].

“Budú” is a local food sauce made from fermented anchovies (*Stolophorus* genera) allowing growth of lactic acid-producing bacteria. Budu may have a probiotic effect that blunts the growth of *H. pylori* bacterium with regular use. “Pegaga” or *centenella asiatica* contains asiaticoside which has antiulcer, antioxidant, and anti-inflammatory effects. The antioxidant property of asiaticoside may also have antimicrobial effect toward *H. pylori*. Tea contains catechins in which in vitro studies have demonstrated antimicrobial properties [57]. However, tea is widely consumed in the Indian subcontinent, Japan, and China where the prevalence of *H. pylori* infection is extremely high casting doubts on its importance. It has been suggested that cloves of which Malaysia and Indonesia produce more than 70% of the world’s crop may protect against *H. pylori* but this was not found to be a protective factor in the study [53].

While regular use of foods with antimicrobial properties may confer protection against *H. pylori*, this may not be the pivotal factor as other low-prevalence populations do not favor these foods. It is possible that genetic or other intrinsic host factors coexist that reduce susceptibility to infection or it could be a combination of genetic, host, and dietary factors that explain the exceptionally low infection rate among the Malays from Kelantan.

Host Factors – Lessons from Gene Polymorphisms

The host can express genetic polymorphisms which may result in them being susceptible to or protected against disease phenotypes associated with *H. pylori* infection. Often, a common disease is associated with a number of causative alleles (single nucleotide polymorphisms or SNPs), and genome-wide association studies are now commonly employed to detect these SNPs [58]. Recently, *ATG16L1* (autophagy gene) polymorphism has been found to increase susceptibility to *H. pylori* infection in the European population [59]. Genetic polymorphism of *NOD1* in *H. pylori*-infected individuals was found to be associated with gastritis in Koreans [60], gastric cancer in the Chinese [61], and erosive esophagitis in the Japanese [62]. In Malay population from the northeastern Peninsular Malaysia, polymorphism in the deleted in colorectal cancer (*DCC*) gene (rs10502974) had been associated with *H. pylori* infection in a case-control study [63]. The *DCC* gene is a tumor suppressor gene and is known to be involved in colorectal carcinogenesis and more recently, aberrant methylation of this gene was also observed in the course of gastric carcinogenesis [64,65]. While this finding requires further validation studies, it suggests that a minority of Malay population from this region might be genetically susceptible to *H. pylori* infection.

The host may also express protective gene variants against *H. pylori* infection resulting in reduced susceptibility to its disease phenotypes. Among the Chinese population, gene polymorphism of DNA methyltransferase-1 (DNMT-1), an enzyme important in genomic methylation patterns in mammalian cells, has been recently found to be associated with a reduced risk of *H. pylori* infection [66]. Urokinase plasminogen activator has an important role in tumor invasion, and its homozygous genotype is observed to be associated with reduction in *H. pylori* infection among the Japanese [67]. Gene polymorphisms in native Malays from the state of Kelantan who were negative for *H. pylori* infection had been compared with immigrant populations to determine whether protective variants are present [68]. Using fixation index (F_{ST}) calculation and comparing highly differentiated SNPs between the Malays in Kelantan and Han Chinese and South Indians of the HUGO Pan-Asian SNP consortium study, the protective gene variants found among the Malays included *C7orf10*, *TSTD2*, *SMG7*, and *XPA*. These genes encode enzymes involved in metabolism of compounds which are inhibitory to the survival of *H. pylori* bacterium as well as proteins that allow detection and repair of aberrant genomes [68]. These genes may serve as potential genetic markers for *H. pylori* infection, and further gene expression studies are needed to validate the findings.

Strain Virulence Factors

Two studies comparing the genetics of *H. pylori* strains obtained from members of the three major ethnic groups resident in Malaysia support the notion that *H. pylori* was introduced into the Malays from the immigrant Han Chinese and South Indian populations [69,70]. The virulence genotype of *H. pylori* strain is different among the recent immigrant Chinese (East Asian *cagA*) and Indian (Western *cagA*) populations, but the native Malays showed a mixture of both [71]. Among the variants in size of 3' region of *cagA* gene, type A strain (621–651 base pairs) is commonly found among the Chinese and type B strain (732–735 base pairs) is common among the Malays and Indians [72]. The expression of less virulence genotypes among the Malays may provide protection against gastroduodenal diseases and gastric cancer. At present, there are no studies on the virulence genotype of *H. pylori* strain among ethnic Malays from the northeastern region of Peninsular Malaysia.

Conclusion: Low or Absence of *H. pylori* Infection is More Likely a Boon Than a Bane

Epidemiological studies have identified populations with an exceptionally low prevalence but not total absence of *H. pylori* infection including Malays and possibly inhabitants of Pemba Island in Zanzibar [73]. *Helicobacter pylori* in Malays is related to transmission from *H. pylori*-infected non-Malay immigrants. The causes for low prevalence of *H. pylori* infection in Malays remain unclear and likely involve a combination of environmental, host (gene polymorphisms), and strain virulence factors. Ethnic Malays are largely spared the burdens associated with *H. pylori* infection as gastric cancer and gastroduodenal ulcer diseases are uncommon. However, the postulated increase in erosive esophagitis, Barrett's esophagus, esophageal adenocarcinoma, and childhood asthma for which *H. pylori* has been postulated to have a protective role is also rare. The Malay population of northeastern Peninsular Malaysia provided an opportunity to test whether these associations proposed to be due to removal of protective effects of *H. pylori* infection were causative or unrelated. The pathophysiology of gastroesophageal reflux disease is related to alterations in the gastroesophageal barrier functions and acid secretion; *H. pylori* infection only affects acid secretion and may be associated with increased or decreased secretion. In contrast, childhood asthma and allergic diseases are thought to relate to the initial exposure of the immune system to environmental antigens (the hygiene hypothesis), and the experience in Malays tends to absolve *H. pylori* from any role as a protective antigen and suggests rather that it is a surrogate marker for the presence of poor household hygiene. These data clearly come on the side of *H. pylori* being an important human pathogen and its eradication will be a boon with no evidence to support significant untoward effects associated with eradication (i.e., the absence of *H. pylori* infection is more likely to be boon than a bane).

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Figure 1.
Map of Peninsular Malaysia showing the northeastern region (State of Kelantan).

Table 1 Epidemiology of *Helicobacter pylori* infection in Malaysia

Authors	References	Year	Region	Ethnic (% in region)	Sample size	Prevalence in studied ethnic (%)
Serology studies						
Uyub et al.	[9]	1994	Northeastern Peninsular	Malays (90%)	496 (blood donors) 921 (health screen)	4.2 (blood donors) 4.8 (health screen)
Goh and Parasakthi	[4]	2001	Central Peninsular	Malays (30%)	548	11.9
Sasidharan and Uyub	[12]	2009	Northwestern Peninsular	Malays (20%)	760	15.2
Huang et al.	[15]	2004	Borneo	Penans	295	37.7
Raj et al.	[13]	2008	Northeastern Peninsular	Kampuchians	51 (immigrant) 27 (native)	72.5 (immigrant) 25.9 (native)
Rahim et al.	[14]	2010	Northeastern Peninsular	Orang Asli	480	19
Endoscopy studies						
Raj et al.	[16]	2001	Northeastern Peninsular	Malays (90%)	124	7
Goh	[19]	1997	Central Peninsular	Malays (30%)	1060	16.4
Sasidharan et al.	[18]	2008	Northwestern Peninsular	Malays (20%)	697	5.8

Table 2 Consequences of *Helicobacter pylori* infection among ethnic Malays in Malaysia

Authors	References	Year	Region in Peninsular Malaysia	Diseases	Prevalence (%)	Incidence (adjusted rate per 100,000 population)
Malaysian National Cancer Registry	[20]	2003–5	All (including Borneo)	Gastric cancer	–	2.2
Radzi and Raj	[24]	2000	Northeastern	Gastric cancer	–	1.2
Yeh et al.	[32]	2009	Northeastern	Atrophic gastritis, intestinal metaplasia	42.3, 7.7	–
Lee et al.	[38]	2011	Northeastern	Esophageal cancer	–	1.9
Lee et al.	[45]	2011	Northeastern	Erosive esophagitis, Barrett's esophagus	3.7, 0.8	–
Rajendra et al.	[46]	2004	Northwestern	Erosive esophagitis, Barrett's esophagus	6.1, 6.2	–
Rosaida and Goh	[47]	2004	Central	Erosive esophagitis, Barrett's esophagus	13.4, 2.0	–
Raj et al.	[52]	2009	Northeastern	Childhood asthma	5.4 (6–7 years), 5.7 (13–14 years)	–