

***Helicobacter pylori* infection in a low prevalence population – what can we learn?**

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Helicobacter pylori (*H. pylori*) infection is etiologically associated with gastric cancer and peptic ulcer diseases which are both important public health burdens and 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 north-eastern 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. *H. 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. 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.

Keywords *Helicobacter pylori*; Malays

1. Introduction

South-East Asia is a cultural-diverse region rich with multiple ethnics 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 [1]. 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 [2]. With the discovery of *Helicobacter pylori* (*H. pylori*) in 1982, subsequent studies identified and confirmed the low prevalence of *H. pylori* infection among the ethnic Malays as compared to the Chinese and Indians living in the same region in Peninsular Malaysia, and this was termed racial cohort phenomenon [3-5].

The ethnic Malays from the north-eastern region of Peninsular Malaysia (state of Kelantan), comprising 90% of its demography, have probably the lowest reported prevalence of *H. pylori* in the world besides the Pemba Island in Zanzibar [6, 7]. Over many centuries, the ethnic Malays from this region have had minimal to no interactions with populations from the nearby Indonesian archipelago or with more recent migrants. This is supported from a population genotyping study which indicated that the Malays from this region were genetically distinctive from Malays of other parts of the Peninsular [8]. The prevalence of *H. pylori* is epidemiologically linked to poor hygiene and sanitation, however, the region (i.e., state of Kelantan) is among the lowest in coverage of clean water and sanitation facilities in the country [9]. The surprising finding of an exceptionally low prevalence of *H. pylori* in this population, therefore, merits further investigations.

What possible reasons which may explain this phenomenon? [10, 11] 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. The evidence for the above hypotheses will be examined in subsequent sections.

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.

The current review examines the evidence from published studies on this unique Malay population from the north-eastern region of Peninsular Malaysia in an attempt to shed some light on the above highlighted issues.

2. Epidemiology evidence of low *H. pylori* prevalence in the Malays

The prevalence of *H. pylori* differs between different regions of the Peninsular, and is reflected by the regions' local population mix of Malays with other immigrant ethnics (Table 1).

Table 1 Epidemiology of *Helicobacter pylori* infection in Malaysia

Authors	Region	Ethnic (% in region)	Sample size	Prevalence in studied ethnic (%)
Serology studies				
Uyub AM et al.	North-eastern Peninsular	Malays (90%)	496 (blood donors), 921 (health screen)	4.2 (blood donors), 4.8 (health screen)
Goh KL et al.	Central Peninsular	Malays (30%)	548	11.9
Sasidharan S et al.	North-western Peninsular	Malays (20%)	760	15.2
Huang SS et al.	Borneo	Penans	295	37.7
Raj SM et al.	North-eastern Peninsular	Kampuchean	51 (immigrant), 27 (native)	72.5 (immigrant), 25.9 (native)
Rahim AA et al.	North-eastern Peninsular	Orang Asli	480	19.0
Endoscopy studies				
Raj SM et al.	North-eastern Peninsular	Malays (90%)	124	7.0
Goh KL et al.	Central Peninsular	Malays (30%)	1060	16.4
Sasidharan S et al.	North-western Peninsular	Malays (20%)	697	5.8

The *H. pylori* sero-prevalence rate in the north-eastern region has been reported to be only 4.2% among blood donors [5] and this is in contrast with 11.9% among blood donors in the Klang valley where the population consists of 30% Malays [4] and 15.2% among blood donors in the north-western region of the Peninsular where the population consists of 20% Malays (Table 1) [12]. The difference in sero-prevalence rate between regions is explained by transmission from *H. pylori*-infected non-Malay immigrants to the local non-infected Malays. The seroprevalence among the Orang Asli; the aborigines residing in the state of Kelantan, has been reported to be only 19% [13], in contrast with the 37.7% prevalence amongst the indigenous aboriginal Penan community of East Malaysia (North Borneo) (Table 1) [14]. Endoscopy-based studies indicated that *H. pylori* infection was present in 7% of Malays from the north-eastern region [15], 5.8% of Malays in the north-western region [16] but 16.4% of Malays in the central region of the Peninsular [17] (Table 1).

3. Consequences of low *H. pylori* prevalence in the Malays

3.1. Upper gastrointestinal cancers and its precancerous lesions

The incidence of gastric cancer according to the Malaysian National Cancer Registry for the period between 2003-05 was 2.2/100,000 among the Malays and was lower compared to the Chinese (11.3/100,000) and Indians (11.9/100,000) (Table 2) [18]. 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% and that of intestinal metaplasia was 7.7% (Table 2) [19]. Notably, in the study, intestinal metaplasia was only present in 1.4% of Malay subjects. The low rate of atrophic gastritis and intestinal metaplasia among the Malays in this study was a result of low *H. pylori* infection of only 6.8% [19].

Table 2 Consequences of *Helicobacter pylori* infection in the Malays

Authors	Region in Peninsular Malaysia	Diseases	Prevalence (%)	Incidence (adjusted rate per 100,000 population)
Malaysian National Cancer Registry	All (including Borneo)	Gastric cancer	-	2.2
Radzi M, Raj SM	North-eastern	Gastric cancer	-	1.2
Yeh LY et al.	North-eastern	Atrophic gastritis, intestinal metaplasia	42.3, 7.7	-
Lee YY et al.	North-eastern	Esophageal cancer	-	1.9
Lee YY et al.	North-eastern	Erosive esophagitis, Barrett's esophagus	3.7, 0.8	-
Rajendra et al.	North-western	Erosive esophagitis, Barrett's esophagus	6.1, 6.2	-
Rosaida MS et al.	Central	Erosive esophagitis, Barrett's esophagus	13.4, 2.0	-
Raj SM et al.	North-eastern	Childhood asthma	5.4 (6-7 years), 5.7 (13-14 years)	-
Mahadeva S et al.	Central (urban, rural)	Uninvestigated dyspepsia (Rome II)	12.8, 14.6	-
Mahadeva S et al.	Central	Clinically significant endoscopic findings	6.8	-
Wahab N et al.	North-eastern	Functional dyspepsia (Rome III)	11.9	-
Lee YY et al.	North-eastern	Irritable bowel syndrome (Rome III)	10.9	-

In contrary to beliefs of some investigator, based on the hypothesis that eradication of *H. pylori* may result in an increase in the incidence of gastroesophageal reflux disease and therefore esophageal cancer, the age-standardized incidence for esophageal cancer among ethnic Malays from Kelantan was only 1.6/100,000 in males and 2.2/100,000 in females (Table 2) [20]. Likewise, in a retrospective study involving 1,895 consecutive patients undergoing upper endoscopy between 2005 and 2007 in a tertiary hospital in Kelantan, only 0.8% of patients had Barrett's esophagus (Table 2) [21]. The reported rates for Barrett's esophagus were much higher among patients undergoing endoscopy from the north-western region and the Klang valley of Peninsular Malaysia being 6.2% and 2.0% respectively [21].

3.2. Gastroduodenal diseases and erosive esophagitis

Early studies from Malaysia indicate that peptic ulcers and incidence of perforated ulcers were less common among the Malays, as compared to the Chinese and Indians [22]. Similarly, non-erosive reflux disease and erosive esophagitis have remained uncommon in the Malay population, despite a rising trend being observed elsewhere in the world (Table 2) [23]. In a recent report, clinically significant endoscopic findings were found in 26.4% of Malaysian adults (6.8% in Malays) with uninvestigated dyspepsia, of which peptic ulcer disease was found to be more prevalent in the Chinese population and erosive esophagitis in the Indians, but both diseases were less common among the Malays [24].

3.3. Functional gastrointestinal disorders

Uninvestigated dyspepsia, based upon Rome II criteria, is found in 12.8% and 14.6% of Malays in the urban and rural communities respectively [25, 26]. Due to a low prevalence of *H. pylori* infection among the Malays, organic causes of dyspepsia are also of low prevalence. The role of *H. pylori* infection in functional dyspepsia (FD) has remained unclear [27]. If *H. pylori* infection is contributory to FD, then population with low prevalence of *H. pylori* infection would have reported lesser dyspeptic symptoms, which is apparently not, among the ethnic Malays. Within a primary setting, 11.9% of Malays from the north-eastern region of Peninsular Malaysia fulfilled the Rome III criteria for FD [28]. This study indicates that FD is more common among the Malays than one would have expected despite the extremely low prevalence of *H. pylori* in this population. In the same study, a positive married status (odds ratio 8.1) and positive psychosocial alarm symptoms (odds ratio 3.8) were independent risk factors being associated with FD, which suggests that *H. pylori* infection is rather a surrogate factor of FD and psychological factors are likely more important in its pathogenesis.

In actual practice, FD can overlap with gastroesophageal reflux disease and irritable bowel syndrome (IBS), especially in the context of Asia, where patients with IBS tend to report upper abdominal symptoms [29]. Of 221 Malays recruited within the hospital compound (relatives, visitors) from the state of Kelantan, IBS was reported in 10.9% based upon Rome III criteria [30]. Red flags but not psychosocial alarms were commonly reported among subjects with IBS, and it was an independent predictor of IBS after multivariate analysis [30]. Previous reports indicate that red flags have low yield for organic diseases after being investigated [31], and this was confirmed in our study subjects with investigated IBS [32], rather its presence is a surrogate for IBS but not diagnostic.

3.4. Childhood asthma

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 [33] (Table 2). Such low rates of asthma among young children in Kelantan in the setting of low *H. pylori* infection do not support the hygiene hypothesis rather it is more consistent with the notion that *H. pylori* infection in some populations is simply a marker for poor hygiene [34].

4. Reasons for low prevalence of *H. pylori* infection in the Malays

The causes for low prevalence of *H. pylori* infection in Malays have remained unclear and likely to involve a combination of environmental, host (gene polymorphisms) and strain virulence 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”) from the state of Kelantan, some dietary factors were found to reduce the risk of infection including frequent use of “budu”, “pegaga or *centenella asiatica*” and tea [35].

Unidentified genetic or host factors intrinsic to this population may also result in them being less or have increased susceptibility to *H. pylori* infection or cancer as a whole. In a recent study, protective gene variants were found among ethnic Malays residing in Kelantan including *C7orf10*, *TSTD2*, *SMG7* and *XPA* [36]. 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. Instead, polymorphism in the Deleted in Colorectal Cancer (*DCC*) gene (rs10502974) is found to be associated with increased risk of *H. pylori* infection in the Malays [37]. Also, in Malays susceptible to *H. pylori* infection, certain gene variants are found to be associated with gastric precancerous lesions, and these gene variants included rs9315542 (*UFMI* gene), rs6878265 (*THBS4* gene), rs1042194 (*CYP2C19* gene) and rs10505799 (*MGST1* gene) which are associated with atrophic gastritis, complete intestinal metaplasia, incomplete metaplasia with foci of dysplasia and only dysplasia, respectively [38]. These genes, once validated in subsequent studies, may serve as potential markers for *H. pylori* infection and its associated precancerous lesions.

The virulence genotype of *H. pylori* strain is shown to be different among the recent immigrant Chinese (East Asian *cagA*) and Indian (Western *cagA*) populations but the native Malays showed a mixture of both [39]. Furthermore, 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 [40]. These strain virulence studies support the notion that *H. pylori* bacterium is introduced into the Malays from the immigrant Han Chinese and South Indian populations.

How is then, the *H. pylori* bacterium, being transmitted into the Malays from other immigrants? The answer is still unknown, but it appears that water may be important. Poor household hygiene and sanitation practices with links to water are found to increase the risk of *H. pylori* infection among susceptible Malays, and these practices included the use of well water (odds ratio 3.4), use of pit latrine (odds ratio 2.8) and infrequent hand wash after toilet use (odds ratio 3.5) [35]. There is valid evidence that the *H. pylori* bacterium can survive and contaminate local water supply [41-42].

5. Conclusion

So what can we learn from the Malays, a population with an exceptionally low prevalence of *H. pylori* infection? (Figure 1) Organic causes of dyspepsia, in particular, peptic ulcer disease and gastric cancer, both being important public health burdens in the Asia Pacific, are uncommon, these clearly come on the side of *H. pylori* being an important human pathogen and its eradication will be advantageous. Furthermore, 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 are also rare. The causes for low prevalence of *H. pylori* infection in the Malays are likely a result of combination of factors including environmental, gene polymorphisms and strain virulence. *H. pylori* in Malays, is related to transmission from *H. pylori* infected non-Malay immigrants, during their early or more recent contacts with the Indians and Chinese immigrants, and is likely to transmit through unhygienic water practices in susceptible Malays.

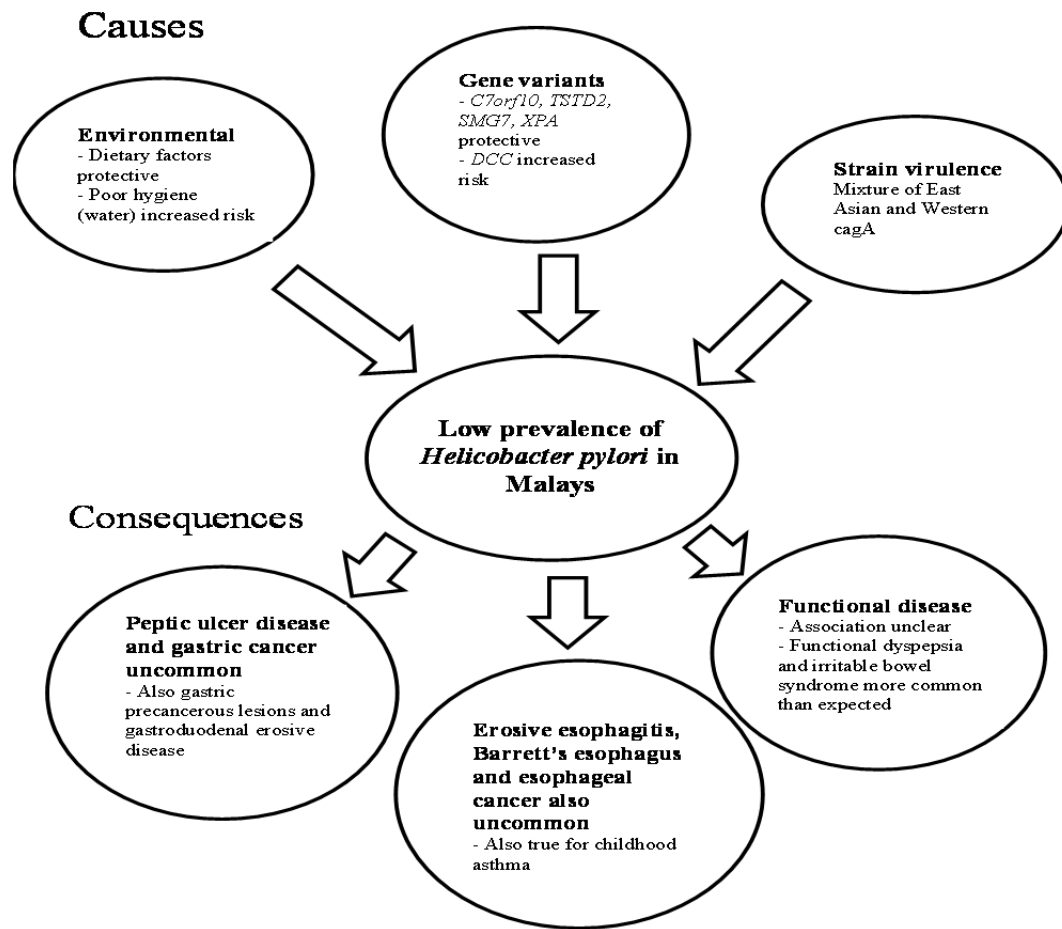


Fig. 1 Causes and consequences of low *H. pylori* prevalence in the Malays

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