# *Helicobacter Pylori* INFECTION AND GASTRIC CANCER WORLDWIDE: THAILAND DISTRIBUTION AND BURDEN DISEASE

**Taweesak Tongtawee[1,2*], Theeraya Simawaranon[1], and Wareeporn Wattanawongdon[1]**

*Received: December 28, 2016; Revised: August 11, 2017; Accepted: August 15, 2017*

## Abstract

**A high prevalence of *Helicobacter pylori* (*H. pylori*) infection has been reported in many areas in the world, especially in countries with low-income economies, including India, Bangladesh, Pakistan, and Thailand. The prevalence of the *H. pylori* infection varies between different geographic locations. There is a strong association with the incidence of gastric cancer (GC) in many countries such as Japan. However, the risk of GC development in Thailand is relatively low compared with other Asian countries. This phenomenon is referred to as the "Thailand enigma". This review focuses on epidemiologic data describing the prevalence of *H. pylori* infection in other ethnic populations. The aim of this mini-review was to find studies relating to the high prevalence of the *H. pylori* infection link between incidences of GC in different ethnic groups, particularly in Thailand. We discuss the enigma correlation of *H. pylori* infection and the incidence of GC in the Thai population. Establishing a review between *H. pylori* prevalence and the incidence of GC may lead to insights into individual and population-based GC prevention strategies.**

**Keywords: *Helicobacter pylori*, gastric cancer, prevalence, incidence rate**

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[1] *Department of Surgery, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima, 30000, Thailand. Tel.: 0-81901-0891; E-mail: taweesak.t@sut.ac.th*
[2] *Suranaree University of Technology Hospital, Nakhon Ratchasima, 30000, Thailand.*
[*] *Corresponding author*

## Introduction

*Helicobacter pylori* (*H. Pylori*) infection is an important exogenous cause for gastric cancer (GC) and it is the most important etiological agent in the pathogenesis of GC. After the bacteria enters the stomach, at least 3 steps are required for *H. pylori* pathogenesis; establishing successful colonization, evading the host's immune surveillance, and invading into the gastric mucosa (Sheu *et al.*, 2010). Several specific host genes are involved in response to the *H. pylori* colonization, immune escape, and mucosal injury in the stomach, with the carcinogenesis process of GC progressing stepwise from normal stomach, inflammation, and precancerous conditions to carcinoma (Correa, 1992). These processes are characterized by marked ethnic diversity. The host genetic and environmental factors play a crucial role in the transitional steps; normal mucosal/ superficial gastritis, atrophic gastritis (AG), and carcinoma transition (He *et al.*, 2013). Therefore, *H. pylori*-related gastritis appears to play a role in modulating the risk of the development of gastric carcinogenesis. There are several pieces of evidence for the role *H. pylori* in GC, such as cohorts for which nested case-control studies have shown that *H. pylori* infection increases the risk of GC significantly, both of the intestinal and diffuse subtypes, and meta-analysis studies have shown that *H. pylori* infection increases GC development (Moss, 2017). Thus, establishing a review between the prevalence of *H. pylori* and the incidence of GC may lead to insights into individual and population-based GC prevention strategies.

The aim of this mini-review was to find studies of the high prevalence of the *H. pylori* infection link between incidences of GC in different ethnic groups and to focus on epidemiologic data that have emerged over the last 26 years describing the prevalence of *H. pylori* infection in the worldwide population, particularly in Thailand. We discuss the enigma of the correlation between *H. pylori* infection and the incidence of GC in the Thai population.

## Methods

The data of this mini-review article were found in searches of the Medline and PubMed databases in terms of the global prevalence of *H. pylori* infection to verify the incidence and prevalence rate in different geographic locations. The literature was searched for articles in the period from 1991-2017. The criteria for exclusion of studies were the following: (1) studies not involving humans (e.g., animal models or in vitro), (2) studies with data not related to the prevalence of *H. pylori* or which addressed other outcomes (e.g., mathematical models), (3) non-eligible publication types, such as review articles (except systematic reviews), comments, guidelines, case reports or editorials, and (4) studies with data not related to the prevalence of *H. pylori* or which addressed other outcomes (e.g., mathematical models). Twenty-eight articles were selected which matched the aim of the review. To maximize the diagnostic accuracy of the review, 5 different methods were used for the diagnosis of *H. pylori* infection, including the stool antigen test (SAT), rapid urease test (RUT), urea breath test (UBT), culture, histology, immunohistochemistry, and serology.

## Results and Discussion

### Global Prevalence of *H. pylori* infection

The prevalence of *H. pylori* infection varies between different geographic locations. *H. pylori* infection was found to be more frequent in countries with low-income economies, such as India, Bangladesh, Pakistan, and Thailand (Graham *et al.*, 1991; Thiede *et al.*, 1997; Lunet and Barros, 2003), whereas in countries and regions of Asia with more highly developed economies, such as Korea, Japan, China, and Singapore, a lower rate of *H. pylori* infection is seen (Miwa *et al.*, 2002). A recent study from Uganda about the roles of geographic location, education, and water sources (Baingana *et al*., 2014) shows that the prevalence of *H. pylori* infection was very different according to the region considered (18.2–60.5%). A low prevalence of infection can be found in areas of low economic status. A recent study from Chile on pregnant women found an association between the infection status of *H. pylori* and hyperemesis (Poveda *et al*., 2014). A report from Bolivia found a very high prevalence of infection (80%) despite the inclusion of children (Sivapalasingam *et al*., 2014). Among the studies from Asia, a recent study from China on patients over 60 years of age showed that there was a high rate of *H. pylori* infection (83.4%) (Zhang *et al*., 2014). Another recent study on the prevalence of *H. pylori* infection by year of birth and geographic area in Japan in 2014 showed that the overall prevalence of *H. pylori* infection was 37.6% in women and 43.2% in men. It was concluded that the prevalence of *H. pylori* infection increases with age and exhibits geographic variations in Japan and that there had been a striking decrease in the prevalence of *H. pylori* infection, especially in the younger Japanese population (Ueda *et al*., 2014). In Taiwan, there was a report that the overall prevalence of *H. pylori* infection was 72.1%, and there was no significant difference between genders (Chen *et al*., 2014). South Asia and Southeast Asia are enigmatic areas for GC because they are low risk regions with a high prevalence of *H. pylori* infection. The infection rate of *H. pylori* in Pakistan was reported as about 62%, and there was no difference in the distribution of *H. pylori* infection in relation to age, sex, and site of malignancy (Yakoob *et al*., 2017). In Myanmar, the overall prevalence of *H. pylori* infection was 48.0%. There was no relationship between age and the infection rate (Myint *et al*., 2015). In Thailand, the prevalence of *H. pylori* infection in the South region (14.4%) was the lowest compared with the Northeast (60.6%), North (46.9%), and Central (39.0%) regions (all $p<0.001$). The Northeast region of Thailand shows the highest rate of *H. pylori* infection (Uchida *et al*., 2015). Studies from Butare, Rwanda and Ethiopia reported a high prevalence of *H. pylori* infection (70%) (Abebaw *et al*., 2014; Walker *et al*., 2014, respectively). From a cross-sectional population study in Germany in 2014, it was reported that *H. pylori* seroprevalence (positivity for at least 3 antigens) was 48% and increased with age from 12% in children <15 years to 69% in females and 90% in males >65 years. It was concluded that *H. pylori* antibody response accumulates qualitatively and quantitatively with age (Michel *et al*., 2014). A study of 518 subjects from Italy concluded that *H. pylori* infection is highly dynamic with a wide range of spontaneous clearances. It is easily cleared in the first decades of life, more recent years, less crowded homes, and males (Luzza *et al*., 2014). Multicenter epidemiological studies from Poland on 6565 subjects (3307 adults and 3258 children) concluded that improvement of socioeconomic status, sanitary and hygienic conditions, and the education of society might decrease the prevalence of *H. pylori* infection in children and in adults (Laszewicz *et al.,* 2014). The study for *H. pylori* infection in young women in a multi-ethnic European city concluded that *H. pylori* remains highly prevalent in migrant communities, which may constitute target groups for screening and eradication to prevent *H. pylori*-related diseases (den Hollander *et al*., 2013). A study of the prevalence of H. pylori between different ethnic groups living in a Western city showed that the highest prevalence of *H. pylori* and CagA was found in the children of non-Dutch ethnicities, and that the decreased colonization rates were uniform across all ethnic groups (den Hollander *et al*., 2015). A systemic review about the prevalence of *H. pylori* infection worldwide in 2014 showed that the prevalence was higher in Central/South America and Asia, and at least two-fold higher in countries with a high GC incidence (Peleteiro *et al*., 2014). Another systematic review focused on studies performed among the healthy population in Iran and the countries of the Eastern Mediterranean region. It was concluded that the prevalence of *H. pylori* is still high in the healthy asymptomatic population (70% or more) (Eshraghian, 2014). The prevalence of *H. pylori* infection of some countries worldwide is shown in Table 1.

## Gastric Cancer in Thailand

*H. pylori* is classified by the World Health Organization as a type I carcinogen, and its infection is strongly associated with the incidence of GC. However, the incidence of GC seems to be low despite the high rate of infection that exists. Several studies have been reported of geographical 'enigmas' (i.e., African, Asian, Indian, and Costa Rican enigmas) based on perceptions that the outcomes that were expected were not achieved in a particular population or region (Miwa *et al*., 2002; Singh and Ghoshal, 2006). Thailand is an area with an enigmatic situation. A recent report from Thailand by Uchida *et al*. (2015) showed that, among the number of males (30-32.8%) of 1546 cases, there was a 45.9% overall prevalence of *H. pylori* infection. The prevalence of *H. pylori* infection in the South region of Thailand (14.4%) was the lowest compared

**Table 1. Prevalence of *H. pylori* infection in some countries worldwide**

| Countries | Study design | Cases | Study duration | Infection rate (%) | Diagnostic test |
|---|---|---|---|---|---|
| Africa | | | | | |
| Uganda | Cross-sectional | 447 | 2005–2008 | 45.2 | SAT |
| Ethiopia | Cross-section of dyspeptic patients | 209 | 2013 | 72.2 | Serology |
| Rwanda | Endoscopy of patients in Butare | 825 | 2011–2012 | 75.3 | RUT |
| Asia | | | | | |
| China | Randomized cluster sampling of aged people | 2006 | 2010 | 83.4 | Serology |
| Japan | Cross-sectional | 14716 | 1997–2013 | 39.9 | Serology or SAT or UBT |
| Myanmar | Prospective study of dyspeptic patients in Yangon and Mandalay | 252 | 2012 | 48 | Culture, Serology, Histology, UBT immunohistochemistry |
| Pakistan | Cross-sectional | 394 | 2000-2016 | 62 | Serology, SAT, UBT |
| Taiwan | Cross-sectional | 796 | 2008 | 72.1 | UBT |
| Thailand | Cross-sectional | 1546 | 2008-2013 | 45.9 | Serology |
| America | | | | | |
| Chile | Pregnant women in 13 municipalities | 274 | 2005 | 68.6 | Serology |
| Bolivia | Two rural villages | 1065 | 2000 | 80 | UBT |
| Europe | | | | | |
| Italy | Village in Calabria | 518 | 2002 | 71.6 | UBT |
| Poland | National survey | 3307 | 2002–2003 | 84.2 | Serology |

SAT: stool antigen test; UBT: urea breath test with the Northeast (60.6%), North (46.9%), and Central (39.0%) regions. The Northeast region of Thailand shows the highest rate of *H. pylori* infection (all $p<0.001$). In contrast, for the prevalence of infection, from a recent report from the Thai National Cancer Institute (Imsamran *et al*., 2015), the incidence of GC is 3.5 mean annual age-standardized rate (ASR) per 100000. From this result, Thailand is an area with an enigmatic situation, but the reason is unclear. The prevalence of *H. pylori* infection and incident of GC is shown in Table 2.

The prevalence of *H. pylori* infection remains high in various parts of the country, especially in Northeast Thailand, as shown in Figures 1 and 2. The authors also investigated the prevalence of *H. pylori* infection in other regions in Thailand over recent years (Table 3). Even though the prevalence of *H. pylori* infection was 58% for an individual province, Chonburi, for a past period (2000-2002) (Mitipat *et al*., 2005), between 2008-2013 there was a variation in the prevalence of *H. pylori* infection in different regions from 34.1-51.2% suggesting that it might be related to a variation in nutrient consumption. and improved hygiene.

### *Helicobacter pylori*-related gastritis Patients in Thai Population

The GC rate in males is higher as a previous study reported differences in the incidence of GC and the ASR of GC in Thailand. The incidence rate of 6.45 for men is higher than the rate of 4.35 for women in the North region and it is 1.9 for men and 1.4 for women in the South region. The study also attributed other environmental risk factors that influence GC including consumption of salt and nitrates (Mitacek *et al*., 2008). All *H. pylori*-positive patients revealed a difference of range or mean age in nationwide *H. pylori* infection among the studies (Table 3). However, Uchida *et al*. (2015) found that 1546 gastritis patients with *H. pylori* infection exhibited a percentage of *H. pylori* infection

**Table 2. The prevalence of *H. pylori* infection and incidence of gastric cancer in Thailand**

| Region | Province | Cases (1546) | Sex (Male) | *H. pylori*-positive (710) | % Prevalence | Incidence (mean annual ASR per 100000) |
|---|---|---|---|---|---|---|
| **North** | **Total** | **482** | **144 (30%)** | **226** | **46.9** | **4.58** |
| | Nakhon Sawan | 139 | 39 | 56 | 40.3 | |
| | Tak | 129 | 45 | 53 | 41.1 | |
| | Lampang | 112 | 30 | 66 | 58.9 | |
| | Phitsanulok | 89 | 26 | 44 | 49.4 | |
| | Lamphun | 13 | 4 | 7 | 53.8 | |
| **Northeast** | **Total** | **541** | **173 (32%)** | **328** | **60.6** | **2.68** |
| | Khon Kaen | 135 | 45 | 82 | 60.7 | |
| | Chaiyaphum | 122 | 34 | 72 | 59 | |
| | Ubon Rachathanee | 120 | 36 | 81 | 67.5 | |
| | Nakhon Ratchasima (Pak Thong Chai district) | 90 | 31 | 48 | 53.3 | |
| | Roi Et | 74 | 27 | 45 | 60.8 | |
| **Central** | **Total** | **328** | **100 (30.5%)** | **128** | **39** | **3.1** |
| | Lopburi | 116 | 34 | 48 | 41.4 | |
| | Bangkok | 99 | 35 | 30 | 30.3 | |
| | Prachuap Khiri Khan | 60 | 20 | 24 | 40 | |
| | Ayutthaya | 42 | 9 | 23 | 54.8 | |
| | Chonburi | 11 | 2 | 3 | 27.3 | |
| **South** | **Total** | **195** | **64 (32.8%)** | **28** | **14.4** | **2.25** |
| | Nakhon Si Thammarat | 98 | 35 | 11 | 11.2 | |
| | Songkhla | 97 | 29 | 17 | 17.5 | |

that was similar in the age groups of the study population; this consisted of 62 patients aged ≤ 29 years (43.5%), 221 patients aged 30-39 years (45.7%), 448 patients aged 40-49 years (49.3%), 460 patients aged 50-59 years (47%), and 355 patients aged ≥60 years (41%) (Table 4). The prevalence of *H. pylori* infection was 43.5% in young patients (aged ≤ 29 years) indicating the fact that *H. pylori* infection occurs earlier in life and with a higher frequency in developing countries (Goh *et al.*, 2011).

## Correlation of *H. pylori* Infection and Gastric Cancer

Currently, it has been accepted since 1994 that *H. pylori* infection is a causative agent of the GC carcinogen (International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans, 1994). Several studies have shown the contribution of *H. pylori* infection and GC development. Uemura *et al.* (2001) reported that GC developed in patients with *H. pylori* infection (2.9%) and in none of the uninfected patients. In their study, Miyahara *et al.* (2007) showed that nearly 60% of intestinal-type GC are associated with *H. pylori* infection). A positive correlation was found between *H. pylori* infection rates and GC prevalence in Japan, Korea, China, and Singapore (Miwa *et al.*, 2002).

However, there is low correlation between areas with high *H. pylori* infection

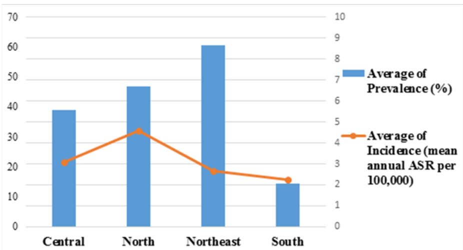


**Figure 1. The correlation of *H. pylori* infection and incidence of gastric cancer in Thailand**

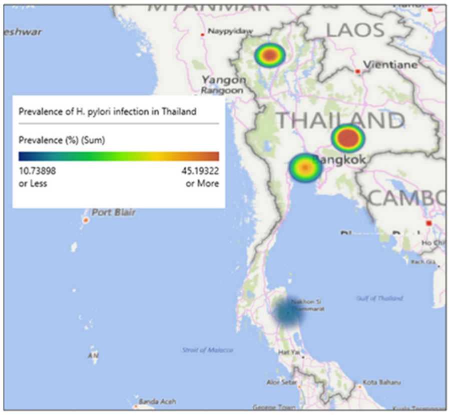


**Figure 2. The prevalence of *H. pylori* infection in Thailand from 2008-2013**

**Table 3. The prevalence of nationwide *H. pylori* infection in Thailand**

| Regions | Year | Cases | Range or mean age | Prevalence of *H. pylori* infection (%) | Method | References |
|---|---|---|---|---|---|---|
| Tak | 2013 | 291 | 46.7 | 149 (51.2) | Culture, Urease test | Vilaichone *et al.* (2016) |
| Nationwide | 2008-2013 | 1546 | 2960 | 710 (45.9) | Histochemical and immunohistochemical methods | Uchida *et al.* (2015) |
| Thai individuals | 2007-2008 | 179 | 51.3 | 78 (43.6) | Antigen detection | Hirai *et al.* (2010) |
| Nationwide | 2004-2012 | 3964 | 51.1 | 1350 (34.1) | Urease test | Vilaichone *et al.* (2013) |
| Nationwide | 2002 | 230 | 56.7 | 98 (42.6) | Culture | Vilaichone *et al.* (2004) |
| Nationwide | 2003 | 3776 | 30-60 | 1718 (48.2) | Histology | Atisook *et al.* (2003) |

**Table 4. The prevalence of *H. pylori* infection related to age in the North, Northeast, Central, and South of Thailand (2008-2013)**

| Group of age | Total | *H. pylori* infection (%) |
|---|---|---|
| ≤29 years | 62 | 27 (43.5) |
| 30-39 | 221 | 101 (45.7) |
| 40-49 | 448 | 221 (49.3) |
| 50-59 | 460 | 216 (47) |
| ≥60 | 355 | 145 (41) |

rates and those with a high prevalence of GC. In African countries, 91% of their populations were infected with *H. pylori*, but there was a very low prevalence of GC (Fock, 2014). A similar pattern has been reported in under-developed countries in Asia such as Myanmar, Pakistan, and Thailand (Myint *et al*., 2015; Uchida *et al*., 2015; Yakoob *et al*., 2017). In Thailand, especially in the Northeast region, *H. pylori*-infected patients were investigated for the correlation between the *H. pylori* infection and GC. Only 1% of the *H. pylori*-infected patients also were infected with GC (Tongtawee *et al*., 2015; 2016). Moreover, GC is associated with H. pylori infection and, when a comparison is made, GC is present in H. pylori-infected patients (2.64%) and uninfected patients (0.65%) (Tongtawee *et al*., 2016). These results support the hypothesis of gastritis in the Thai population thought to represent the enigma.

## Conclusions

GC is one of the common cancers, especially in Asian countries. Many studies have suggested the relationship between *H. pylori* infection and GC. Data from recent studies show that the incidence of GC in Thailand is rather low despite the high prevalence of *H. pylori*. This phenomenon is referred to as the "Thailand enigma". *H. pylori* infection seems to be less frequent in the population in the South region as compared to the Northeast, North and Central regions. The highest prevalence rate of *H. pylori* infection was found in the Northeast region and remains a major health problem in this area. Variations in *H. pylori* infection have been documented in different parts of Thailand and this might be related to variations in nutrient consumption. However, the mechanism underlying the enigma with respect to *H. pylori* infection has not been defined, especially at the genetic level. The host's genetic makeup and dietary and environmental factors might explain this enigma.

## Acknowledgments

The authors would like to acknowledge a grant from Suranaree University of Technology Research and Development Fund.

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