# Incidence of *Helicobacter pylori* Recurrent Infection and Associated Factors in Thailand

Duangporn Thong-Ngam MD*,
Varocha Mahachai MD**, Pinit Kullavanijaya MD**

** Department of Physiology, Faculty of Medicine, Chulalongkorn University*
*** GI unit, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University*

***Objective:*** *To determine the incidence of H. pylori recurrent infection after successful eradication in 4-year follow-up study, and to evaluate the influencing factors for re-infection.*
***Material and Method:*** *Thirty-seven patients (age range 20-74 years; average 49.06 ± 14.03 years) were recruited of which 64.9% were females. The H. pylori infection was proved to be successfully eradicated in all patients. Annually, urea breath test (UBT) was assessed to determine H. pylori status after eradication. Age, sex, eating habit, water drinking, number of children, and treatment regimens against H. pylori were recorded. A breath test was also performed on the patient's spouse.*
***Results:*** *The H. pylori recurrence occurred in 5/37 (13.51%) of patients observed. There were two patients in the first year, one patient each in the second, third, and fourth year. The cumulative re-infection rate was 5.41% at 1-year, 8.11% at 2-year, 10.81% at 3-year, and 13.51% at 4-year. H. pylori infection of spouse was also frequent (80%). Even if the spouse was infected, 88.89% of patients will remain uninfected after 4-years of H. pylori eradication. No influencing factor for infection recurrence was detected.*
***Conclusions:*** *The risk of re-infection after H. pylori eradication was low in Thai patients after 4-year follow up. Annual re-infection rate was 3.38%. No dependent factors were associated with a recurrence.*

***Keywords:*** *H. pylori, Recurrent, Thailand*

***J Med Assoc Thai 2007; 90 (7): 1406-10***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

*Helicobactor pylori (H. pylori)*, a gram-negative spiral-shaped bacterium, has many different clinical outcomes. It has been established as a major etiological agent of chronic gastritis and peptic ulcer disease, which includes duodenal ulcer (DU) and gastric ulcer (GU)[1]. The roles of *H. pylori* infection in gastric adenocarcinoma and mucosal associated lymphoid tissue lymphoma (MALT) are also recognized[2]. Numerous studies have shown that the risk of ulcer recurrence is markedly reduced after successful eradication of *H. pylori*[3]. After successful *H. pylori* eradication, recrudescence or re-infection may happen.

In developed countries with a low prevalence of *H. pylori*, eradication of *H. pylori* is typically associated with a very low risk of infection recurrence rates ranging between 0.5% and 2.0% per year in adults[4-6]. In contrast, in many developing countries where the baseline prevalence of *H. pylori* infection is often as high as 70%-90%, *H. pylori* re-infection rates have reportedly varied substantially from 4.3% to 73%[7,8]. The high recurrence rates have been reported in Peru (73% within 8 months)[9], Korea (12.8%)[10], Brazil (20.7%)[11], Vietnam (23.5%)[12], and Bangladesh (13%)[13]. However, the study from China[14], which also has a high prevalence of *H. pylori* infection, reported that the re-infection was rare (1.08%).

In this present study, the authors wanted to determine the rate of *H. pylori* recurrent after successful eradication in 4-year follow-up study and to evaluate the influencing factors of re-infection in Thailand.

## Material and Method

Thirty-seven patients that were proven to be successfully treated for *H. pylori* infection were recruited

*Correspondence to : Thong-Ngam D, Department of Physiology, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand. Fax. 0-2256-4267, E-mail: thongngam007@yahoo.com*

in this study. Annually, urea breath test was assessed to determine *H. pylori* status after eradication. Patients were divided into two groups: re-infected, if a recurrence of *H. pylori* infection was observed and non-re-infected, if UBT was persistently negative. Each patient was systematically interviewed for demographic characteristics and symptoms. Age, sex, eating habit, water drinking, number of children, relapse of dyspeptic symptoms, and treatment regimens against *H. pylori* were recorded. A breath test was also performed on the patient's spouse. All patients signed an informed consent describing the purpose, possible risks, and benefits of the present study.

### *Urea Breath Test*

$^{14}$C-UBT using the PY test kit and a microcount scintillation counter (Ballard Medical Products) was used to screen for urease activity, as a surrogate marker of *H. pylori* infection. After at least 6 hours of fasting and 2 hours without having smoked tobacco products, participants ingested the PY $^{14}$C-labeled urea capsule with 20 mL of water, followed by an additional 20 mL of water 3 minutes later. After 10 min, a single breath sample was collected by having the participant hold his/her breath for 5-10 seconds then completely fill a Mylar breath collection balloon. The amount of $^{14}$C in the balloon was measured by a scintillation counter. Quantification was reported as DPM. Ranges used for classification of participants were the following: DPM of $< 50$ was negative (uninfected); DPM of 50-200 was indeterminate; and DPM of $\geq 200$ was positive (infected). For purposes of analysis, indeterminate results were repeated and if the same result was obtained, the authors considered the result negative.

### *Statistical analysis*

Chi-square test or Fishers' Exact test was used for qualitative variables and the Student *t*-test for quantitative variables. SPSS software for Windows version 11 (SPSS, Chicago, IL, USA) was then used for processing of data. A p-value of less than 0.05 was considered significant.

## Results

Thirty-seven patients (age range 20-74 years; mean 49.06 $\pm$ 14.03 years) were followed up. There were 35.1% males and 64.9% females. The *H. pylori* recurrence occurred in five (13.51%) patients observed. There were two patients in the first year, one patient in the second year, one patient in the third year, and one patient in the fourth year. The cumulative re-infection rate was 5.41% at 1-year, 8.11% at 2-years, 10.81% at 3-years, and 13.51% at 4-years. *H. pylori* infection of spouses was also frequent (80%). Even if the spouse was infected, 88.89% of patients remained uninfected after 4-years of *H. pylori* eradication. The demographic and clinical characteristics of non-reinfected and re-infected patients are shown in Table 1. No evidence was obtained to indicate that the re-infection rate depended on the age, sex, eating habit, water drinking, number of children, relapse of dyspeptic symptoms, or eradication regimens.

## Discussion

The epidemiology of *H. pylori* infection is different in developed and developing countries. In industrialized countries, *H. pylori* infection is acquired at a fairly constant rate of 2-6% per year with a prevalence of 20-40% in adults. In developing countries, the infection is acquired in early childhood at higher rates, and 70-90% of people are infected by age 20[15,16]. After successful *H. pylori* eradication, recrudescence (recurrence after a clinical but not biological cure) or re-infection (recurrence after a cure but acquiring the infection later) may happen. The re-infection rate of *H. pylori* after successful eradication in Western population ranged between 0.5% and 2.0% per year in adults[5,6].

High recurrence rates have been reported in such developing countries (4.3% to 73%)[9-11,17]. In the present study, the authors reported the annual recurrence rate was 3.38%. Similar to some studies in China and Malaysia that settings of high prevalence of *H. pylori* have demonstrated low rates of recurrence that mirror those in developed countries[14,18].

The use of molecular techniques can distinguish a re-infection (infection by a strain of *H. pylori* that differs from the pre-treatment infection in the same host) from a recrudescence (re-emergence of a strain that genetically matches the pretreatment strain, which thus may not have been fully eradicated). Strains can be isolated using polymerase chain reaction (PCR) or restriction fragment length polymorphism (RFLP) analysis. Hildebrand et al reported that recrudescence of *H. pylori* infection was observed within 3 months after eradication, while beyond 3 months, all patients who showed recurrence of *H. pylori* infection harbored different *H. pylori* strains before and after eradication, thus indicating re-infection using DNA fingerprinting analysis[13]. Okimoto et al compared the strains of *H. pylori* isolated at the time of initial endoscopic examination with those isolated at the time of recurrence using PCR-RFLP analysis. Comparison of isolates from

**Table 1.** Demographic and clinical characteristics of non-reinfected and re-infected patients

| Variables | | Non-reinfected (n = 32) | Re-infected (n = 5) |
|---|---|---|---|
| Age (yrs) (mean ± SE) | | 50.0±2.3 | 43.8±10.3 |
| Gender | Female | 66.7% | 60.0% |
| | Male | 33.3% | 40.0% |
| Treatment regimens | PPI+2 antibiotics | 62.5% | 80.0% |
| | RBC+2 antibiotics | 37.5% | 20.0% |
| Dyspeptic symptom | No symptom | 28.1% | 40.0% |
| | Recurrence-symptom | 71.9% | 60.0% |
| Eating habit | No spicy food | 9.4% | 25.0% |
| | Spicy food | 90.6% | 75.0% |
| Drinking water | Pipe water | 59.4% | 60.0% |
| | Boiled water | 40.6% | 40.0% |
| Number of children | 0 | 46.9% | 40.0% |
| | 1 | 12.5% | 40.0% |
| | 2 | 15.6% | 0% |
| | ≥ 3 | 25.0% | 20.0% |
| Spouse UBT result (n = 10) | Positive | 88.9% | 50.0% |
| | Negative | 11.1% | 50.0% |

No significant difference between non-reinfection and re-infection ($p > 0.05$)

eight patients showed that, at 6 months, three patients were infected with the same strains of *H. pylori* isolated at initial endoscopy and after 12 months, all the patients were infected with different strains[4]. When patients with the same strains were considered to have recrudescence and those with different strains were considered to have re-infection, five of eight patients showed re-infection at 6 months. After 12 months, all the recurrences were re-infection[19]. Since a genetic analysis was not performed in the present study, the authors cannot distinguish between recrudescence and true re-infection.

Limited information exists regarding risk factors for re-infection after cure of *H. pylori* infection. McMahon BJ et al proposed that a history of previous peptic ulcer disease or presence of ulcer at the time of upper endoscopy study were the only risk factors associated with re-infection ($p = 0.01$)[17]. Cheon JH et al reported that the relapse of dyspeptic symptoms was the only factor predictive of *H. pylori* recurrence[20]. Gomerz Rodriguez BJ et al reported re-infection occurred in 9.6% of patients observed, 6.7% (14/208) in the first year, 1.9% (4/208) in the second year, 1% (2/208) in the third, and 0% in the fourth. Risk factors for infection recurrence were younger age and higher values of urea breath test in the multivariate analysis[21]. Feydt-Schmidt A et al reported the re-infection rate in children (aged 9.7-14.9 years) was 2.3% per person per year. There is no evidence that the re-infection rate depends on the age, sex, or nationality of the child[22]. Some factors have been proposed as adjuvant of infection recurrence; such as: impaired immune response, low socioeconomic status, and young age can as a risk factor for infection recurrence[23]. Some studies reported that dental plaque or partner infection was a potential risk factor for *H. pylori* recurrence[24].

In the present study, the authors reported the cumulative re-infection rate was 5.41% at 1-year, 8.11% at 2-year, 10.81% at 3-year, and 13.51% at 4-year. No evidence was obtained to indicate that the re-infection rate depended on age, sex, eating habit, water drinking, relapse of dyspeptic symptoms, and treatment regimens. Moreover, family variables (*H. pylori* status of spouse, number of children living at home) did not correlate with recurrences. Even though *H. pylori* infection of a spouse was also frequent (80%), 88.89% of patients remained uninfected after 4-years of *H. pylori* eradication. Recurrence of *H. pylori* infection seems to be relatively infrequent, even if the patient's spouse is *H. pylori*-positive. The molecular study demonstrated that the strains in re-infected patients and their partners are different, suggesting that the patient's partner does not act as a reservoir for *H. pylori* re-infection[25,26]. In general, UBT should be the first-choice test for detecting *H. pylori* re-infection, since it is a non-invasive method that explores the whole stomach.

In conclusion, we showed that the risk of *H. pylori* re-infection was low in Thailand after a 4-year follow up, although it is a developing country that had a high prevalence of *H. pylori*. The re-infection rate was only 3.38% annually. No dependent factors were associated with a recurrence. The periodic urea breath test to detect re-infection should be followed in each case after successful treatment.

**References**


1. Tytgat GN, Rauws EA. Campylobacter pylori and its role in peptic ulcer disease. Gastroenterol Clin North Am 1990; 19: 183-96.
2. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med 2002; 347: 1175-86.
3. de Boer WA, Tytgat GN. Regular review: treatment of Helicobacter pylori infection. BMJ 2000; 320: 31-4.
4. Okimoto T, Murakami K, Sato R, Miyajima H, Nasu M, Kagawa J, et al. Is the recurrence of Helicobacter pylori infection after eradication therapy resultant from recrudescence or reinfection, in Japan. Helicobacter 2003; 8: 186-91.
5. van der Hulst RW, Rauws EA, Koycu B, Keller JJ, ten Kate FJ, Dankert J, et al. Helicobacter pylori reinfection is virtually absent after successful eradication. J Infect Dis 1997; 176: 196-200.
6. Berstad A, Hatlebakk JG, Wilhelmsen I, Berstad K, Bang CJ, Nysaeter G, et al. Follow-up on 242 patients with peptic ulcer disease one year after eradication of Helicobacter pylori infection. Hepatogastroenterology 1995; 42: 655-9.
7. Soto G, Bautista CT, Roth DE, Gilman RH, Velapatino B, Ogura M, et al. Helicobacter pylori reinfection is common in Peruvian adults after antibiotic eradication therapy. J Infect Dis 2003; 188: 1263-75.
8. Bardhan PK. Epidemiological features of Helicobacter pylori infection in developing countries. Clin Infect Dis 1997; 25: 973-8.
9. Ramirez-Ramos A, Gilman RH, Leon-Barua R, Recavarren-Arce S, Watanabe J, Salazar G, et al. Rapid recurrence of Helicobacter pylori infection in Peruvian patients after successful eradication. Gastrointestinal Physiology Working Group of the Universidad Peruana Cayetano Heredia and The Johns Hopkins University. Clin Infect Dis 1997; 25: 1027-31.
10. Kim N, Lim SH, Lee KH, Jung HC, Song IS, Kim CY. Helicobacter pylori reinfection rate and duodenal ulcer recurrence in Korea. J Clin Gastroenterol 1998; 27: 321-6.
11. Coelho LG, Passos MC, Chausson Y, Costa EL, Maia AF, Brandao MJ, et al. Duodenal ulcer and eradication of Helicobacter pylori in a developing country. An 18-month follow-up study. Scand J Gastroenterol 1992; 27: 362-6.
12. Wheeldon TU, Hoang TT, Phung DC, Bjorkman A, Granstrom M, Sorberg M. Long-term follow-up of Helicobacter pylori eradication therapy in Vietnam: reinfection and clinical outcome. Aliment Pharmacol Ther 2005; 21: 1047-53.
13. Hildebrand P, Bardhan P, Rossi L, Parvin S, Rahman A, Arefin MS, et al. Recrudescence and reinfection with Helicobacter pylori after eradication therapy in Bangladeshi adults. Gastroenterology 2001; 121: 792-8.
14. Mitchell HM, Hu P, Chi Y, Chen MH, Li YY, Hazell SL. A low rate of reinfection following effective therapy against Helicobacter pylori in a developing nation (China). Gastroenterology 1998; 114: 256-61.
15. Hopkins RJ, Vial PA, Ferreccio C, Ovalle J, Prado P, Sotomayor V, et al. Seroprevalence of Helicobacter pylori in Chile: vegetables may serve as one route of transmission. J Infect Dis 1993; 168: 222-6.
16. Zendehdel N, Nasseri-Moghaddam S, Malekzadeh R, Massarrat S, Sotoudeh M, Siavoshi F. Helicobacter pylori reinfection rate 3 years after successful eradication. J Gastroenterol Hepatol 2005; 20: 401-4.
17. McMahon BJ, Bruce MG, Hennessy TW, Bruden DL, Sacco F, Peters H, et al. Reinfection after successful eradication of Helicobacter pylori: a 2-year prospective study in Alaska Natives. Aliment Pharmacol Ther 2006; 23: 1215-23.
18. Goh KL, Navaratnam P, Peh SC. Reinfection and duodenal ulcer relapse in south-east Asian patients following successful Helicobacter pylori eradication: results of a 2-year follow-up. Eur J Gastroenterol Hepatol 1996; 8: 1157-60.
19. Xia HX, Windle HJ, Marshall DG, Smyth CJ, Keane CT, O'Morain CA. Recrudescence of Helicobacter pylori after apparently successful eradication: novel application of randomly amplified polymorphic DNA fingerprinting. Gut 1995; 37: 30-4.
20. Cheon JH, Kim N, Lee DH, Kim JM, Kim JS, Jung HC, et al. Long-term outcomes after Helicobacter pylori eradication with second-line, bismuth-containing quadruple therapy in Korea. Eur J Gastroenterol Hepatol 2006; 18: 515-9.
21. Gomez Rodriguez BJ, Rojas FM, Garcia Montes

MJ, Romero CR, Hergueta DP, Pellicer Bautista FJ, et al. Incidence and factors influencing on Helicobacter pylori infection recurrence. Rev Esp Enferm Dig 2004; 96: 620-3.
22. Feydt-Schmidt A, Kindermann A, Konstantopoulos N, Demmelmair H, Ballauff A, Findeisen A, et al. Reinfection rate in children after successful Helicobacter pylori eradication. Eur J Gastroenterol Hepatol 2002; 14: 1119-23.
23. Aydin A, Ersoz G, Ozutemiz O, Tuncyurek M. Low reinfection rate of Helicobacter pylori infection in Turkey. J Clin Gastroenterol 2000; 30: 337.
24. Anand PS, Nandakumar K, Shenoy KT. Are dental plaque, poor oral hygiene, and periodontal disease associated with Helicobacter pylori infection? J Periodontol 2006; 77: 692-8.
25. Gisbert JP. The recurrence of Helicobacter pylori infection: incidence and variables influencing it. A critical review. Am J Gastroenterol 2005; 100: 2083-99.
26. Gisbert JP, Arata IG, Boixeda D, Barba M, Canton R, Plaza AG, et al. Role of partner's infection in reinfection after Helicobacter pylori eradication. Eur J Gastroenterol Hepatol 2002; 14: 865-71.

## *อุบัติการณ์และปัจจัยสัมพันธ์กับการติดเชื้อซ้ำของเฮลิโคแบคเตอร์ไพลอริในคนไทย*

***ดวงพร ทองงาม, วโรชา มหาชัย, พินิจ กุลละวณิชย์***

***วัตถุประสงค์****: เพื่อศึกษาอุบัติการณ์และปัจจัยการติดเชื้อซ้ำของเฮลิโคแบคเตอร์ ไพลอริในคนไทย หลังการกำจัดเชื้อสำเร็จแล้วโดยติดตามเป็นเวลา 4 ปี*

***วัสดุและวิธีการ****: มีผู้ป่วยเข้าร่วมโครงการทั้งสิ้น 37 คน อายุระหว่าง 20-74 ปี เฉลี่ย 49.06 $\pm$ 14.03 ปี คิดเป็นชาย ร้อยละ 35.1 เป็นหญิงร้อยละ 64.9 เป็นผู้ป่วยที่มาด้วยอาการไม่สบายในท้องและได้รับการวินิจฉัยว่ามีการติดเชื้อเฮลิโคแบคเตอร์ ไพลอริจากการส่องกล้องตรวจทางเดินอาหารส่วนต้น ได้รับการกำจัดเชื้อและพิสูจน์ว่ากำจัดเชื้อสำเร็จแล้วอีก 4 สัปดาห์ต่อมา หลังจากนั้นตรวจติดตามผู้ป่วยกลุ่มนี้โดยการตรวจวัดลมหายใจ $^{14}$C-UBT ปีละครั้ง ทำการบันทึกปัจจัยต่าง ๆ ได้แก่ อายุ เพศ อาการ พฤติกรรมการรับประทานอาหาร น้ำดื่ม จำนวนบุตร สูตรยาที่ใช้กำจัดเชื้อ และทำการตรวจ $^{14}$C-UBT เพื่อดูการติดเชื้อในคู่สมรสด้วย*

***ผลการศึกษา****: พบอุบัติการณ์การติดเชื้อซ้ำของเฮลิโคแบคเตอร์ ไพลอริในคนไทยทั้งสิ้น 5 ใน 37 คน คิดเป็นร้อยละ 13.51 หลังการติดตามเป็นเวลา 4 ปี โดยพบ 2 รายในปีแรก พบ 1 รายในปีที่สอง พบ 1 รายในปีที่สาม และพบอีก 1 รายในปีที่สี่ตามลำดับ คำนวณเป็นอัตราอุบัติการณ์การติดเชื้อสะสมได้ร้อยละ 5.41 ในปีแรก ร้อยละ 8.11 ในสองปี ร้อยละ 10.81 ในสามปี และร้อยละ 13.51 ในสี่ปี พบการติดเชื้อในคู่สมรสร่วมด้วยร้อยละ 80 แม้ว่าจะพบความชุกของการติดเชื้อเฮลิโคแบคเตอร์ ไพลอริสูงในคู่สมรส แต่ร้อยละ 88.89 ของผู้ป่วยก็ยังไม่มีการติดเชื้อซ้ำหลังติดตามไปสี่ปี ไม่พบปัจจัยใดที่สัมพันธ์กับการติดเชื้อซ้ำ*

***สรุป****: อุบัติการณ์การติดเชื้อซ้ำของเฮลิโคแบคเตอร์ ไพลอริในคนไทยพบได้น้อย โดยพบเพียงร้อยละ 3.38 ต่อปี หลังจากกำจัดเชื้อสำเร็จแล้วติดตามการรักษาต่อไปอีกเป็นเวลา 4 ปี ไม่พบปัจจัยที่สัมพันธ์กับการติดเชื้อซ้ำ*