CHAPTER I

INTRODUCTION

Helicobacter pylori is a gram-negative, spiral shaped microaerophilic bacterium that colonizes in the gastric mucosa in humans (1). *H. pylori* infects more than half of the world population but the geographical prevalence varies greatly (2). Higher infection rates occur in developing countries, where 80 % of middle - aged adults are infected comparing with infection rates of only 20 to 50 % in developed countries (3, 4). Worldwide, the occurrence of *H. pylori* infection increases with age, and specific ethnic groups are also at greater risk (5-8). *H. pylori* is an important human pathogen that causes chronic gastritis. It is also associated with development of atrophic gastritis, mucosa - associated lymphoid tissue (MALT) lymphoma and increased risk of gastric carcinoma (9-15).

The biological factors that influence the clinical outcome of *H. pylori* infection have been extensively studied. Apart from immunological factors in the host, the bacterial virulence determinants in *H. pylori* strains are likely to play crucial roles (16). All clinical isolates of *H. pylori* produce a number of virulence factors that are essential for the colonization of the stomach and survival in this hostile environment. The best-known virulence factors are the urease, which is supposed to play an important role in the neutralization of gastric acid secretion (17). The flagella, which are essential for swimming through the mucous layer (18, 19). The superoxide dismutase (20) and several molecules that are involved in specific adhesion to the superficial epithelial cells of the stomach (21). In addition to the above factors that are produced by all strains, some factors are produced by only a subset of clinical isolates. Approximately 60 % of *H. pylori* strains contain the cytotoxin associated (*cagA*) gene, located at the right end of the cag pathogenicity island 40 Kb genome regions, encodes the Cag A protein which varies in molecular mass between 120 and 140 kDa (22, 23). The presence of gene *cagA* can be considered as a marker for this genomic pathogenicity island. The role of Cag A protein is a type - IV secretion apparatus translocates the Cag A protein into the host epithelial cell. Cag A protein is phosphorylated

and binds to an SHP-2 tyrosine phosphatase, leading to a growth factor - like cellular response and cytokine production by the host cell (24). Once colonization of the gastric mucosa has taken place, the immunogenic properties of *H. pylori* induce an inflammatory reaction with neutrophilic gastritis that ultimately results in the clinical manifestations of the infection. This process is mediated by increasing the production of Interleukin 8 by gastric epithelial cell related to gastric inflammation and gastroduodenal diseases (25, 26). A number of studies in Western countries have confirmed that infection with *cagA* positive strains is associated with more severe gastritis and a higher prevalence of peptic ulceration and gastric carcinoma (27-29). In contrast, study in Asia demonstrates equally high prevalence of *cagA* positive strains in patients with peptic ulcer, gastric cancer and non- ulcer dyspepsia. Overall the data support the notion that infection with *cagA* positive strains increases the risk but does not predict the presence of clinical outcome (30-36).

Another virulence factor, produced by appoximately 50 % the *H. pylori* strains, is a cytotoxin that induces the formation of vacuoles in the human epithelial cell *in vitro* and that leads to cell death (37-39). This toxin is encoded by the *vacA* gene, which is present in virtually all *H. pylori* strain (40, 41) and comprises two variable parts. (38, 42). The N-terminal signal (s) region occurs as either an s1a, s1b, s1c or s2 allele. The middle (m) region is present as an m1, m1a, m1b or m2 allele.

The *vacA* s and m regions appear to have different clinical relevance (43). The *vacA* s1a strains are associated with greater antral mucosal neutrophil and lymphocyte infiltrates than type s1b or s2 strains. Duodenal ulcer disease appears to be more prevalent in patients infected or colonized with type s1a strains than in patients colonized with type s1b and s2 strains. The *vacA* type m1 strains are associated with greater gastric epithelial damage than type m2 strains. In contrast, previous studies in Japan demonstrated that no association between the gene *vacA* and clinical outcome (35).

A novel gene has been discovered recently, designated *iceA* (induced by contact with epithelium). There are two main allelic variants of the gene : *iceA1* and *iceA2*. The expression

of *iceA1* is up-regulated on contact between *H. pylori* and human epithelial cell, and may associate with peptic ulcer disease (44, 45). However, previous studies demonstrated that no significant association between the gene *iceA* and clinical outcome(34, 35). In addition, previous studies demonstrated that mixed *iceA* genotype had wide range of prevalence 15% in the Netherlands, 22% in Columbia and 40% in South Africa (35, 44, 46).

Because of this diversity of reports associating the virulence genes with the clinical outcome from different geographic regions, it is important to analyze the association between genes *cagA, vacA* and *iceA* of *H. pylori* and clinical outcome in Thai setting. The aim of the present study is to examine the prevalences of *cagA*, *vacA* and *iceA* genes of *H. pylori* isolated from patients with peptic ulcer comparing to those with non-ulcer dyspepsia and determine the association of this genes with clinical outcomes in Thai population. This study may contribute to the identification of peptic ulcer susceptible genes and to development of new prognostic markers based on genotypes. and to development of new treatment and prevention. In addition, it will provide the prevalence of *cagA, vacA* and *iceA* genes in *H. pylori* isolates of Thai population which is a basic knowledge for study in the future.