Determinants of ethnic or geographical differences in infectivity and transmissibility of *Helicobacter pylori*

Carlo A Fallone MD FRCPC

CA Fallone. Determinants of ethnic or geographical differences in infectivity and transmissibility of *Helicobacter pylori*. Can J Gastroenterol 1999;13(3):251-255. The prevalence of *Helicobacter pylori* infection is variable in different countries. There are two distinct patterns of *H pylori* prevalence with respect to age depending on the geographical region studied. The first pattern is widespread infection early in childhood with elevated prevalence rates of close to 80% throughout adulthood, and the second is increasing prevalence with age. This variability in pattern suggests a difference in infectivity or transmissibility of *H pylori* infection. Potential determinants of these differences are reviewed including environmental, bacterial and host factors. The most important determinant is likely socioeconomic class, which affects living conditions and sanitation, thus altering exposure to the bacterium. Host factors also play a role, perhaps via host receptors for *H pylori*. Bacterial factors may also contribute, although compelling evidence is lacking.

Key Words: *Epidemiology*, Helicobacter pylori, *Human leukocyte antigen*, *Transmission*

Facteurs ethniques ou géographiques liés à l'infectivité et à la transmissibilité d'*Helicobacter pylori*

RÉSUMÉ : La prévalence des infections à *Helicobacter pylori* varie d'un pays à l'autre. On note deux modes distincts de prévalence d'*H. pylori* en ce qui a trait à l'âge, selon la région étudiée. Le premier tableau est une infection étendue en bas âge, avec taux de prévalence élevé, à près de 80 % tout au long de la vie adulte, et le second est un accroissement de la prévalence avec l'âge. Cette variabilité du mode de présentation suggère une différence quant à l'infectivité ou à la transmissibilité de l'infection à *H. pylori*. Les facteurs potentiels de ces différences sont passés en revue, notamment les facteurs liés à l'environnement et à l'hôte et les facteurs bactériens. Le facteur le plus déterminant est probablement le statut socioéconomique qui affecte les conditions de vie et d'hygiène et altère ainsi l'exposition à la bactérie. Les facteurs liés à l'hôte jouent également un rôle, probablement par le biais des récepteurs de *H. pylori* chez l'hôte. Les facteurs bactériens peuvent aussi contribuer, bien que l'on ne dispose pour l'instant d'aucune preuve concluante à cet effet.

Helicobacter pylori is now recognized as an important pathogen in the development of duodenal ulcer disease, gastric ulcer disease and chronic antral gastritis. It also plays a prominent role in the development of gastric malignancies such as mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma (1). Although the majority of infected individuals do not develop the above diseases, *H pylori* is probably the most common human infection worldwide. It is present in approximately 40% of persons in the developed world and close to 90% of people in the developing world (2). The determinants of these geographical or ethnic differences in *H pylori* prevalence rates are the topic of the present review. Socioeconomic, bacterial and host factors will be considered in turn.

WHAT ARE THE GEOGRAPHICAL OR ETHNIC DIFFERENCES?

Pounder and Ng (3) reviewed the prevalence of *H pylori* infection in different countries. The prevalence of this infection with respect to age follows one of two patterns depending on the country examined. The first pattern is high prevalence during childhood (Figure 1). In countries

McGill University Health Centre, McGill University, Montreal, Quebec
Correspondence and reprints: Dr CA Fallone, GI Division, R2.28, Royal Victoria Hospital, 687 Pine Avenue West, Montreal,

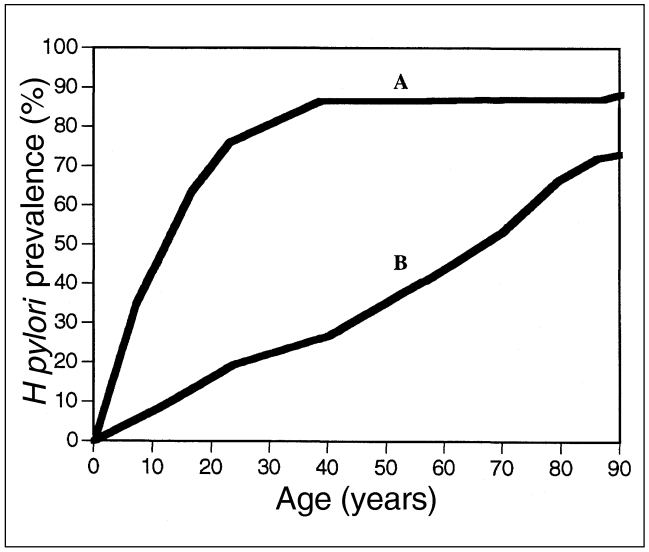

Figure 1) *The pattern of* Helicobacter pylori *prevalence rates with respect to age seen in developing (A) and developed (B) countries*

where the first pattern is present, a large proportion of the population is infected early in life so that by adulthood close to 80% of the population is infected with *H pylori*. The prevalence remains at this level for all older age groups. Populations from developing countries tend to have this pattern of *H pylori* prevalence. Examples include Algeria (4), where 43% of children younger than nine years of age are infected compared with 92% of those in the fifth decade of life; Ivory Coast (4), where 54% of those younger than nine years of age and 70% to 80% of adults are seropositive for *H pylori*; Vietnam (4), where although only 13% of children younger than age nine years are positive, 43% are positive before age 20 years and 50% to 80% are infected in adulthood; Thailand (5), where 17.5% of children five to nine years of age, 55% of those from 20 to 29 years of age and 75% of those in the fifth decade of life are positive; Saudi Arabia (6), where 40% of those in Riyadh between five and 10 years of age and 70% of those more than 20 years of age are infected; Peru (7,8), where close to 50% to 70% of children younger than 10 years of age are infected; Chile (9,10), where 60% to 70% of people younger than 20 years of age are infected; Brazil (11), with a 64% infection rate in those aged 15 to 18 years of age; and South Africa (12), where 60% of those younger than 10 years of age and 94% of those younger than 30 years of age are positive regardless of whether they are from rural or urban parts of South Africa. Interestingly, the Caucasians of South Africa do not have elevated rates throughout adulthood but rather show increasing rates with age, more in keeping with the pattern demonstrated in industrialized countries discussed below. This correlates with the higher socioeconomic status found in this population compared with that of other South Africans.

The second pattern of prevalence with respect to age seems to be present in more developed countries, or populations with higher socioeconomic status or better community sanitation. These populations show an increasing prevalence of *H pylori* infection throughout life, with significantly lower prevalence rates in those younger than 20 years of age compared with populations following the first pattern. In addition, prevalence rates generally do not exceed 60% until the sixth or seventh decade of life (Figure 1). Examples include France (4), with rates below 20% in those younger than 20 years of age and below 40% in those in their sixth decade of life. The rate is only 7.3% in children aged two to 14 years in Belgium (13). Finland (14) has similar results, with 10% of 18- to 25-year-olds infected, but 60% of 56- to 65-year-olds infected. Studies from the United Kingdom (15-18) also demonstrate age-related rates from less than 35% in those younger than 30 years to 50% to 67% in those in their sixth decade of life. In the United States (19), results also follow this pattern with 10% of those 18 to 29 years of age infected compared with 47% of those in their seventh decade. Social class seems to play a role because the poorer Black populations residing in Houston had rates of 70% compared with 34% in the richer Caucasian populations in the same city (20). However, the pattern followed is still that of increasing rates throughout life for both Caucasians and Blacks. In Canada, rates also increase with age at approximately 1% per year, with rates of 21% in 20- to 29-year-olds compared with 47% in 60- to 69-year-olds (21).

WHY ARE THERE GEOGRAPHICAL DIFFERENCES?

That the variations in *H pylori* prevalence rates found among countries seem to parallel the socioeconomic status of these countries suggests that the reason for these differences is related to increased exposure to the organism. Lower socioeconomic status may result in poorer sanitation, overcrowding and contamination of water supplies, which, in turn, would lead to further person to person transmission of this infection via either a fecal-oral or gastric-oral mode. This type of transmission would be more favourable in developing countries and thereby would result in higher rates of infection in the young population of these countries. Because *H pylori* tends to remain present in gastric tissue unless specifically treated, the infection remains for life and the prevalence of infection remains high throughout adulthood. Approximately 10% to 20% of the population will never become infected, either because their living environment somehow protects them from exposure to *H pylori* or because they possess host factors that prevent bacterial colonization.

In the developed world, living conditions are such that both fecal-oral and gastric-oral spread of pathogens are decreased. Therefore, fewer children are infected. The higher rate of infection as one ages, as opposed to a tapering rate after the second decade, has a few potential explanations. It is possible that new infections continue as one ages. Continued acquisition with age is supported by a study by Veldhuyzen van Zanten et al (21), who found

that approximately 1% of the adult population of eastern Canada per year converted from seronegative to seropositive. The 'cohort effect' is another possibility. Individuals who are currently more than 50 years of age had a childhood environment before World War II that was not as hygienic as the present environment. There was more domestic crowding, and hot water could not always be supplied. Hence, these individuals had a higher rate of infection in childhood, and, because infection is longstanding, the prevalence in these individuals is higher than that of the the latest generation of children. This is also seen in Japan (22), where the prevalence of infection increased at approximately 1% per year for people born after 1950, but, in those born prior to 1950, the prevalence is substantially higher (70% to 80%). These changes parallel the dramatic improvement in socioeconomic status observed in Japan during the same time period. In addition, a study by Roosendaal et al (23) determined the presence of *H pylori* antibodies in Dutch children aged six to eight years and aged 12 to 15 years from blood collected in 1978 and 1993. They found that, during 1978 to 1993, the *H pylori* infection rate dropped from 23% to 11% in those aged 12 to 15 years and from 19% to 9% in those aged six to eight years. This confirms a continuing decline of *H pylori* infection rate in children of a developed country and suggests a persistent birth cohort effect.

FACTORS KNOWN TO INCREASE INFECTIVITY AND TRANSMISSIBILITY

Consistently, it has been found that a variety of factors related to lower socioeconomic status are associated with an increased prevalence of *H pylori* infection. These include lower education level of parents, poor water supply, poverty and domestic crowding. The EUROGAST study (24), for example, involved serological determination of *H pylori* status in 3000 subjects from 17 populations in 13 countries. This study found an infection rate of 62% in subjects with only primary school education compared with 47% in subjects with secondary education and 34% in subjects with postsecondary education. Malaty and Graham (25) estimated social class during childhood from parents' education level, parental occupation and family income and found that each variable was inversely related to *H pylori* prevalence. The lowest socioeconomic class had an 85% prevalence of *H pylori* infection compared with 52% in the middle class rating and 11% in the higher class levels. Staat et al (26) performed serology on more than 2500 subjects from the United States and also found an association with low education level of the head of household (odds ratio [OR] 1.8), crowding (OR 5.6), poverty (OR 1.5) and being non-Caucasian (OR 2.6).

Lower socioeconomic status, likely because of its associated overcrowding and poor living conditions, can lead to increased exposure to the bacterium and a higher *H pylori* infection rate in developing countries. This must be a major determinant of the geographical differences observed in the prevalence of *H pylori* infection.

OTHER POTENTIAL DETERMINANTS

Bacterial factors: Although exposure to *H pylori* is necessary for infection to occur, other factors may contribute in facilitating or preventing infection. These factors may be bacterial or host in origin. It is known, for example, that urease-deficient organisms are unable to infect the host (27,28). It is also known that there is enormous diversity in the genetic composition of *H pylori* , both in DNA sequence and in gene order (29-32). Whether such diversity can account for different degrees of infectivity or transmissibility among strains has not been investigated. Whether this diversity contributes to the different prevalence of this infection in different geographical regions also is not clear. Hook-Nikanne et al (33) examined isolates obtained from infected subjects in Africa, the People's Republic of China, Japan, Peru, Thailand and the United States and found no obvious geographical pattern by protein bonding with the use of gel electrophoresis. Göttke et al (34) also found no significant differences using phylogenetic analysis of the DNA sequence and directed restriction enzyme analysis of the *flaA* and *vacA* genes of isolates obtained from Berlin, Germany, and Montreal, Quebec.

However, when Miehlke et al (35) compared the *cagA* gene in isolates obtained from Korea with those from Houston, Texas, variability was noted. Polymerase chain reaction (PCR) was used to amplify the *cagA* gene with two different primer sets. With the first set, they identified the PCR amplicon for *cagA* in 98% of *H pylori* isolates from Korea and 88% of those from Houston. In contrast, with the second set of primers, the PCR product was found in only 2% of Korean strains compared with 88% of Houston isolates. This suggests that allelic variations exist in the *H pylori* genome that are geographically distributed.

Pan et al (36) found similar variability when using two sets of primers for *cagA* to test *H pylori* isolates from Chinese patients compared with Dutch patients. Perez-Perez et al (37) also found variation in antibody titres to *cagA* in serum obtained from patients of different countries, with rates higher in Peru and Thailand (82% and 79%, respectively) than in Canada (42%), Holland (39%), China (38%) and New Zealand (28%). This demonstrates some geographical variation, but the pattern does not seem to parallel the prevalence of infection in these patients, particularly in China where one would expect a high degree of infectivity. Variability in the *vacA* gene has also been demonstrated in different countries (38), but no clear-cut pattern has emerged that would explain a difference in infectivity in these countries.

Hence, although geographical variability of *H pylori* may play a role in the infectivity or transmissibility of the infection, thus contributing to different rates in different populations, there is no compelling evidence that this is, in fact, the case.

Host factors: In the United States, Malaty and Graham (39) found that Hispanics have a lower rate of *H pylori* infection than Blacks despite attendance at the same daycare centres. This suggests that host factors may play a role in

the acquisition of infection. In a cross-sectional survey of 1060 consecutive patients presenting with dyspepsia in Malaysia, Goh (40) found that ethnicity (in particular, being Indian) is an independent risk factor for *H pylori* infection (OR 4.9 [95% CI 3.2 to 7.5]). Although this may suggest an inherent ethnic or genetic predisposition to infection, the association may also be due to varying sociocultural practices that are responsible for transmission of the infection. Consistent with the former of these two possibilities are the results of an analysis of the Swedish Twin Registry, which consists of 25,000 twin pairs (41). There was a greater concordance for *H pylori* antibodies in monozygotic twins than in dizygotic twins (probandwise concordance of 81% versus 63%, respectively), even when the analysis was limited only to twins who were reared apart after a young age. This strongly suggests that the host does play a role in the acquisition of *H pylori* infection. Differences in the host from different ethnic or geographical origins may, therefore, contribute to the variable prevalence rates seen in different regions of the world.

One mechanism by which the host may contribute to the degree of infectivity or transmissibility is through the presence of *H pylori* receptors. *H pylori* demonstrates marked tissue tropism, binding solely to gastric or gastric-like (gastric metaplasia) epithelium, suggesting the presence of receptors to which the organism specifically binds (42,43). Boren et al (44,45) described a potential receptor as the Lewis b antigen. This antigen, which binds to *H pylori*, is found in reduced frequency in patients with blood groups A and B compared with those with blood group O. This finding fits nicely with the observation that duodenal ulcer patients have a higher frequency of O blood group than patients without duodenal ulcer (46). However, clinical studies fail to confirm this association between ABO and Lewis blood group antigens and *H pylori* infection rates (47,48).

Other potential receptors that have been found to bind in vitro to *H pylori* include carbohydrates for hemagglutinins (49,50), phosphatidylethanolamine (51) and the basement membrane laminin (52). Again, there have been no studies to assess whether these receptors can account for differences in *H pylori* prevalence rates seen in different geographical regions.

Some associations have been discovered between the presence of *H pylori* infection and human leukocyte antigens (HLA), although the precise significance of these observations is still not clear. In particular, HLA DR (53-55) and HLA DQA1*0301 (56) are increased in those infected with *H pylori*. Whether this association occurs as a result of induction of this particular class of inflammatory cells by *H pylori* or whether they are associated with increased susceptibility to infection is not clear. *H pylori* may bind to major histocompatability complex class II molecules on the gastric epithelium to promote colonization (57).

CONCLUSIONS

The infectivity and transmissibility of *H pylori* are such that two types of prevalence patterns predominate. The first type is widespread infection occurring at an early age with high prevalence rates persisting throughout adulthood. This pattern is found in developing countries. In developed countries, the pattern is increasing prevalence with age. Clearly, the most important determinant of these geographical differences is socioeconomic status, which affects living conditions and sanitation, thus altering exposure to the bacterium. Host factors also play a role in acquisition of infection, perhaps via the existence of variations in the expression of *H pylori* receptors. Other factors, including bacterial diversity, may contribute to the geographical and ethnic differences in the infectivity and transmissibility of *H pylori*, but they remain to be proven.

REFERENCES

1. Hunt R, Thomson ABR. Canadian *Helicobacter pylori* consensus conference. Canadian Association of Gastroenterology. Can J Gastroenterol 1998;12:31-41.
2. Marshall BJ. *Helicobacter pylori*. Am J Gastroenterol 1994;89:S116-8.
3. Pounder RE, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. Aliment Pharmacol Ther 1995;9(Suppl 2):33-9.
4. Megraud F, Brassens-Rabbe MP, Denis F, Belbouri A, Hoa DQ. Seroepidemiology of *Campylobacter pylori* infection in various populations. J Clin Microbiol 1989;27:1870-3.
5. Perez-Perez GI, Taylor DN, Bodhidatta L, et al. Seroprevalence of *Helicobacter pylori* infections in Thailand. J Infect Dis 1990;161:1237-41.
6. Al-Moagel MA, Evans DG, Abdulghani ME, et al. Prevalence of *Helicobacter* (formerly *Campylobacter*) *pylori* infection in Saudi Arabia, and comparison of those with and without upper gastrointestinal symptoms. Am J Gastroenterol 1990;85:944-8.
7. Klein PD, Graham DY, Gaillour A, Opekun AR, Smith EO. Water source as risk factor for *Helicobacter pylori* infection in Peruvian children. Gastrointestinal Physiology Working Group. Lancet 1991;337:1503-6.
8. Klein PD, Gilman RH, Leon-Barua R, Diaz F, Smith EO, Graham DY. The epidemiology of *Helicobacter pylori* infection in Peruvian children between 6 and 30 months of age. Am J Gastroenterol 1994;89:2196-200.
9. Russell RG, Wasserman SS, O'Donnoghue JM, et al. Serologic response to *Helicobacter pylori* among children and teenagers in Northern Chile. Am J Trop Med Hyg 1993;49:189-91.
10. Hopkins RJ, Vial PA, Ferreccio C, et al. Seroprevalence of *Helicobacter pylori* in Chile: vegetables may serve as one route of transmission. J Infect Dis 1993;168:222-6.
11. Oliveira AMR, Queiroz DMM, Rocha GA, Mendes EN. Seroprevalence of *Helicobacter pylori* in children of low socioeconomic level in Belo Horizonte, Brazil. Am J Gastroenterol 1994;89:2201-4.
12. Sather MA, Simjee AE, Wittenberg DF, et al. Seroprevalence of *Helicobacter pylori* infection in Natal/KwaZulu, South Africa. Eur J Gastroenterol Hepatol 1994;6:37-41.
13. Blecker U, Hauser B, Lanciers S, Peeters S, Suys B, Vandenplas Y. The prevalence of *Helicobacter pylori*-positive serology in asymptomatic children. J Pediatr Gastroenterol Nutr 1993;16:252-6.
14. Kosunen TU, Höök J, Rautelin HI, Myllylä G. Age-dependent

increase in *Campylobacter pylori* antibodies in blood donors. Scand J Gastroenterol 1989;24:110-4.
15. Sitas F, Forman D, Yarnell YWG, et al. *Helicobacter pylori* infection rates in relation to age and social class in a population of Welsh men. Gut 1991;32:25-8.
16. Mendall MA, Coggin PM, Molineaux N, et al. Childhood living conditions and *Helicobacter pylori* seropositivity in adult life. Lancet 1992;339:896-7.
17. Whitaker CJ, Dubiel AJ, Galpin OP. Social and geographic risk factors in *Helicobacter pylori* infection. Epidemiol Infect 1993;111:63-70.
18. Webb PM, Knight T, Greaves S, et al. Relation between infection with *Helicobacter pylori* and living conditions in childhood: evidence of person to person transmission in early life. Br Med J 1994;308:750-3.
19. Dooley CP, Cohen H, Fitzgibbons Pl, et al. Prevalence of *Helicobacter pylori* infection and histologic gastritis in asymptomatic persons. N Engl J Med 1989;321:1562-6.
20. Graham DY, Malaty HM, Evans DG, Evans DJ, Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. Gastroenterology 1991;100:1495-501.
21. Veldhuyzen van Zanten SJO, Pollak PT, Best LM, Bezanson GS, Marrie T. Increasing prevalence of *Helicobacter pylori* infection with age: continuous risk of infection in adults rather than cohort effect. J Infect Dis 1994;169:434-7.
22. Asaka M, Kimura T, Kudo M, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology 1992;102:760-5.
23. Roosendaal R, Kuipers EJ, Buitenwerf J, et al. *Helicobacter pylori* and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. Am J Gastroenterol 1997;92:1480-2.
24. Epidemiology of and risk factors for *Helicobacter pylori* infection among 3194 asymptomatic subjects in 17 populations. The EUROGAST Study Group. Gut 1993;34:1672-6.
25. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. Gut 1994;35:742-5.
26. Staat MA, Kruszon-Moran D, McQuillan GM, Kaslow RA. A population-based serologic survey of *Helicobacter pylori* infection in children and adolescents in the United States. J Infect Dis 1996;174:1120-3.
27. Tsuda M, Hkarita M, Mizote T, Morshed MG, Okita K, Nakazawa T. Essential role of *Helicobacter pylori* urease in gastric colonization: definite proof using a urease-negative mutant constructed by gene replacement. Eur J Gastroenterol Hepatol 1994;6:S49-52.
28. Eaton KA, Brooks CL, Morgan DR, Krakowka S. Essential role of urease in pathogenesis of gastritis induced by *Helicobacter pylori* in gnotobiotic piglets. Infect Immun 1991;59:2470-5.
29. Fallone CA, Barkun AN, Göttke MU, Beech RN. A review of the possible bacterial determinants of clinical outcome in *Helicobacter pylori* infection. Can J Microbiol 1998;44:201-10.
30. Beech RN, Göttke MU, Groody JM, Loo V, Fallone CA, Barkun AN. Utility of *vac*A DNA as a genetic marker for virulence in *Helicobacter pylori*. Gastroenterology 1996;110:A63. (Abst)
31. Taylor DE, Featon M, Chang N, Salama SM. Construction of a *Helicobacter pylori* genome map and demonstration of diversity at the genome level. J Bacteriol 1992;174:6800-6.
32. Jiang Q, Hiratsuka K, Taylor DE. Variability of gene order in different *Helicobacter pylori* strains contributes to genome diversity. Mol Microbiol 1996;20:833-42.
33. Hook-Nikanne J, Perez-Perez GI, Blaser MJ. Antigen characterization of *Helicobacter pylori* strains from different parts of the world. Clin Diagn Lab Immunol 1997;4:592-7.
34. Göttke M, Fallone C, Trautmann M, et al. Genetic relationship among *Helicobacter pylori* strains from Central Europe and North America. Can J Gastroenterol 1997;11:44A. (Abst)
35. Miehlke S, Kibler K, Kim JG, et al. Allelic variation in the *cagA* gene of *Helicobacter pylori* obtained from Korea compared to the United States. Am J Gastroenterol 1996;91:1322-5.
36. Pan ZJ, van der Hulst RW, Feller M, et al. Equally high prevalences of infection with *cagA*-positive *Helicobacter pylori* in Chinese patients with peptic ulcer disease and those with chronic gastritis-associated dyspepsia. J Clin Microbiol 1997;35:1344-7.
37. Perez-Perez GI, Bhat N, Gaensbauer J, et al. Country-specific constancy by age in *cagA*+ proportion of *Helicobacter pylori* infections. Int J Cancer 1997;72:453-6.
38. van Doorn LJ, Figueiredo C, Megraud F, Blaser MJ, Quint W. Geographic distribution of *Helicobacter pylori vac*A genetic types. Gastroenterology 1998;114:A320-1. (Abst)
39. Malaty HM, Graham DY. *Helicobacter pylori* infection in pre-school and school age children: effect of race and environment. Gastroenterology 1998;114:A211. (Abst)
40. Goh KL. Prevalence of and risk factors for *Helicobacter pylori* infection in a multiracial dyspeptic Malaysian population undergoing endoscopy. J Gastroenterol Hepatol 1997;12:S29-35.
41. Malaty HM, Engstrand L, Pederson NL, Graham DY. *Helicobacter pylori* infection: genetic and environmental influences: a study of twins. Ann Intern Med 1994;120:982-6.
42. Solnick JV, Tompkins LS. *Helicobacter pylori* and gastroduodenal disease: pathogenesis and host-parasite interaction. Infect Agents Dis 1993;1:294-309.
43. Logan RPH. Adherence of *Helicobacter pylori*. Aliment Pharmacol Ther 1996;10(Suppl 1):3-15.
44. Boren T, Falk P, Roth KA, Larson G, Normark S. Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. Science 1993;262:1892-5.
45. Boren T, Normark S, Falk P. *Helicobacter pylori*: molecular basis for host recognition and bacterial adherence. Trends Microbiol 1994;2:221-8.
46. Aird I, Bewtall HH, Mehigan JA, Roberts JAP. The blood groups in relation to peptic ulceration and carcinoma of the colon, rectum, breast, and bronchus. Br Med J 1954;ii:315-21.
47. Niv Y, Fraser G, Delpre G, et al. *Helicobacter pylori* infection and blood groups. Am J Gastroenterol 1996;91:101-4.
48. Umlauft F, Keeffe EB, Offner F, et al. *Helicobacter pylori* infection and blood group antigens: lack of clinical association. Am J Gastroenterol 1996;91:2135-8.
49. Evans DJ, Evans DJ Jr, Moulds JJ, Graham DY. *N*-Acetylneuraminyllactose-binding fibrillar hemagglutinin of *Campylobacter pylori*: a putative colonization factor antigen. Infect Immun 1988;56:2896-906.
50. Wadstrom T, Guruge J, Wel S, Aleijung P, Ljungh A. *Helicobacter pylori* hemagglutinins – possible gut mucosa adhesions. In: Malfertheiner P, Ditschuneit H, eds. *Helicobacter pylori*, Gastritis and Peptic Ulcer. Berlin: Springer-Verlag, 1990:96-103.
51. Lingwood CA, Law H, Pellizzari A, Sherman P, Drumm B. Gastric glycerolipid as a receptor for *Campylobacter pylori*. Lancet 1989;11:238-41.
52. Plotrowski J, Morita M, Slomiany A, Slomiany BL. Inhibition of gastric mucosal laminin receptor by *Helicobacter pylori* lipopolysaccharide. Effect of ebrotidine. Biochem Int 1992;271:131-8.
53. Wee A, Teh M, Kang JY. Association of *Helicobacter pylori* with HLA-DR antigen expression in gastritis. J Clin Pathol 1992;45:30-3.
54. Chiba M, Ishii N, Ishioka T, et al. Topographic study of *Helicobacter pylori* and HLA-DR antigen expression on gastric epithelium. J Gastroenterol 1995;30:149-55.
55. Ihan A, Krizman I, Ferlan-Marolt V, Tepez B, Gubina M. HLA-DR expression on CD8 lymphocytes from gastric mucosa in urease-positive and urease-negative gastritis. FEMS Immunol Med Microbiol 1995;10:295-9.
56. Azuma T, Konishi J, Tanaka Y, et al. Contribution of HLA-DQA gene to host's response against *Helicobacter pylori*. Lancet 1993;343:542-3.
57. Fan XJ, Gunasena H, Gonzales M, et al. *Helicobacter pylori* urease binds to class II MHC molecules on gastric epithelial cells to initiate apoptosis. Gastroenterology 1998;114:A118. (Abst)