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Review

An overview of pathogenesis and epidemiology of *Helicobacter pylori* infection

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Helicobacter pylori **induces chronic gastritis, the strongest known risk factor for peptic ulcer disease, distal gastric cancer and a number of extra gastric related morbidity. More than 50% of the world's population is infected with this organism lifelong without effective bacterial eradication. Clinical sequelae are dependent upon bacterial virulence factors and host genetic diversity, particularly within immune response genes. The organism is able to evade the harsh acidic environment in the gastric mucosa and host immune response by elaborating a number of factors that aid in the achievement of its persistent colonization.** ***H. pylori*** **possess numerous virulence proteins (*cagA, vacA* and *iceA*) and enzymes (urease, catalase, lipase, phospholipase and proteases) with substantial genotypic diversity, which engenders differential host inflammatory responses that influence the pathologic outcome. The hallmark of** ***H. pylori*** **infection is a marked inflammatory response with the infiltration of various immune cells into the infected gastric mucosa; with a polarized Th1 immune response which further attracts inflammatory cells to the gastric mucosa leading to damage. Knowledge on** ***H. pylori*** **reservoirs and transmission remains elusive. However, studies have described the gastro-oral, oral-oral and faecal-oral as possible routes of acquisition and transmission. This paper provides an understanding of** ***H. pylori*** **persistence and pathogenesis as well as its route of transmission.**

Key words: *Helicobacter pylori*, pathogencity, virulence factors, epidemiology, risk factors, immune evasion.

INTRODUCTION

The human gastrointestinal tract is colonized by an abundance of bacteria, which are in constant interaction with the epithelial lining usually leading to an intricate balance between tolerance and immunological response (Mbulaiteye et al., 2006; Rasmus et al., 2007). There is ample evidence that the abundant presence of bacteria thus play a role in the maintenance of human health, as well as in the induction of chronic inflammatory diseases of the gastrointestinal tract (Kuipers and Michetti, 2005).

Helicobacter pylori, the principal species of the genus *Helicobacter,* is a common human pathogen that is responsible for a variety of gastro–duodenal pathologies in the developed and developing world (Perez-Perez et al., 1991; Abdulrasheed, 2005). *H. pylori* is a small, curved, highly motile, gram-negative bacillus which is recognized as a chronic colonizer of the human stomach; and known to be one of the most genetically diverse of bacterial species (Ndip et al., 2003; McNulty et al., 2004; Hovey et al., 2007; Talekhan et al., 2008). It has been implicated as the major cause of various diseases since its Nobel-prize-winning discovery by Warren and Marshall in 1982 (Warren and Marshall, 1983; Dixon, 1991; Parsonnet et al., 1991; Ndip et al., 2003). It is closely associated with adenocarcinoma of the distal stomach, mucosa-associated lymphoid tissue (MALT) lymphoma and primary gastric non-Hodgkin's lymphoma as well as a number of extra gastric diseases (Permin and Andersen, 2005) A number of factors have been implicated in the pathogenesis of *H. pylori* infection. The risk of disease involves specific interactions between the pathogen and host, which, in turn, are dependent upon strain-specific bacterial factors and/or inflammatory responses governed by host genetic diversity (Peek, 2005; Rasmus et al., 2007). A comprehensive understan-ding of how *H. pylori* infection causes gastritis, peptic ulcer or gastric cancer is very important in the prognosis

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and management of infection.

The prevalence of *H. pylori* infection varies widely according to geographical area, patient age and socio-economic status (Graham et al., 1991; Segal et al., 2001). Rates of isolation range between 70 - 90% in developing countries and 25 - 50% in developed countries (Logan and Walker, 2002; Tay et al., 2009). In various regions of sub-Saharan Africa, for example, 61 - 100% of the population may harbour the pathogen (Holcombe, 1992; Asrat et al., 2004). Although there is geographical and socio-demographic variation in the prevalence of human infection with the organism (Mukhopadhyay et al., 2000; Ndip et al., 2004; Asrat et al., 2004), prevalence has been reported to be discordant with the incidence of morbidity caused by the infection. In Africa, for example, the prevalence of infection is very high but the incidence of gastric carcinoma and other *H. pylori*-associated morbidities is relatively low (Ahmed et al., 2007). This apparent anomaly has been termed the 'African enigma' (Holcombe, 1992; Tanih et al*.,* 2009).

The principal reservoir of *H. pylori* is man, but there have been descriptions of infection spread by means of water or uncooked vegetables contaminated with sewage and a host of other factors (Feldman et al., 1998; Dube et al., 2009a). The role of domestic animals in the spread of infection still remains unclear (Fox et al., 1995) . The putative routes of transmission of the organism have been reported to be faecal-oral, oral-oral, and gastric-oral (Brown*,* 2000).

This review appraises the factors and or mechanisms that govern *H. pylori* pathogenesis and epidemiology.

PATHOGENESIS OF *H. PYLORI* INFECTION

Virulence proteins

The role of *H. pylori* in gastroduodenal diseases has been firmly established. Infection by the organism is presumed to be from the gastric antrum and then extending down to the corpus after extensive mucosal damage (Akada et al., 2003). Intense research into *H. pylori* has lead to the discovery of virulence factors such as *vacA, cagA* and other proteins like *iceA*. These proteins have revealed many aspects of the relationships between this bacterium, the gastric mucosal surface, and the induction of disease (van Doorn et al., 1998; Smith et al*.,* 2002). Disease outcome is the result of the intricate, ongoing interplay between environmental, bacterial, and host factors. Strain-to-strain genetic variability in bacterial virulence factors does not only affect the ability of the organism to colonize and cause disease but also affects inflammation and gastric acid output (Figueiredo et al., 2002; Kuster et al., 2006).

The vacuolating cytotoxin, *vacA*, is a protein complex which is present in about 50% of all *H. pylori* strains (Haas, 2002). *vacA* leads to the formation of acidic vacuoles in epithelial cells and consequently to their death following infection and colonization of an *H. pylori* strains carrying the gene. *IceA* is a novel gene signaling*:* induced by contact with epithelium. There are two main allelic variants of the gene*: iceA1* and *iceA2* (van Doorn et al., 1999; Wong et al., 2001; Smith et al., 2002). The function of *iceA* is not yet clear but there is significant homology to a type II restriction endonuclease. The expression of *iceA1* is up-regulated following contact between *H. pylori* and human epithelial cells and may be associated with peptic ulcer and other gastric related diseases (van Doorn et al*.,* 1999; Arents et al., 2001).

The well-characterized *H. pylori* virulence determinant is the *cagA* gene (Ally et al*.,* 1999; Andreson, 2002). Although all *H. pylori* strains induce gastritis, *cagA*+ strains significantly augment the risk for severe gastritis, peptic ulcer disease, and distal gastric cancer compared to that incurred by *cagA*− strains. A combination of these genotypes is responsible for prolong and severe risk of disease associated with *H. pylori* infection (Atherton et al., 1995; Asrat et al*.,* 2004).

Initial infection by highly pathogenic strains possessing a cluster of genes known as the *cag* pathogenicity island result in altered expression of several genes associated with glycan biosynthesis, especially 3GlcNAc T5, a GlcNAc transferase required for the biosynthesis of Lewis antigens (Marcos et al., 2008). Resultant over-expression of 3GlcNAc T5 in human gastric carcinoma cell lines lead to increased sialyl-Lewis x expression, a specific kind of sugar molecule that these cells display on their surface as a flag to attract immune cells to the infection site (Nagorni, 2000; Bor-Shyang et al., 2006; Marcos et al., 2008).

While the *rocF* gene is not essential for the initiation of an infection, it encodes arginase, an enzyme responsible for the hydrolysis of L-arginine to L-ornithine and urea. Unavoidable, arginase allows the bacterium to evade host immune response by competing with macrophage iNOS for L-arginine. Due to bacterial cell deficiency in arginine synthesizing enzymes, this organism exploits the host's arginine to maintain the nitrogen balance (Hovey et al., 2007).

Gastric colonization

H. pylori have been shown to employ multiple mechanisms to antagonize, impair, or subvert host responses (Ernst et al., 2006). The stomach is protected by a mucosal barrier that prevents gastric secretions and other destructive agents from injuring the epithelial and deeper layers of the stomach wall (Radosz-Komoniewska et al., 2005). The integrity of the mucosal layer is maintained by tight cellular junctions and the presence of a protective mucus layer. Prostaglandin is derived from the cell membrane lipids and serves as a chemical messenger that protects the stomach lining by improving

blood flow, increasing bicarbonate secretion, and enhancing mucus production (Porth, 2002).

Controversy still persists on the duration of the relationship between *H. pylori* and humans considering how this pathogen has adapted to having a complete life in the human stomach (Scott et al., 2007). However, co-evolution of *H. pylori* with humans over thousands of years has effectively refined the interactions that occur between bacterial and host factors, transmission between hosts, survival during acidic stress within hosts, and avoidance of immune response (Blaser, 1997; Scott et al., 2007) . Gastric acidity and peristaltic muscle movement of the alimentary canal have the potential to preclude bacterial colonization of the human stomach.

H. pylori have evolved several mechanisms to evade primary host defences such as acidity and peristalsis in order to establish persistent infection within the stomach. The organism elaborates a number of enzymes of which urease is one of the most important (Malcolm et al., 2004; Peek, 2005) . Urease is conserved among all known *Helicobacter species* and is a necessary factor for the establishment of chronic infection *with* the organism. Two major subunits of this enzyme have been identified (*ureA* and *ureB*). This accessory protein, catalyses the cleaving of urea into ammonia and hydrogen carbonate, achieving a local neutralization of the acid pH in the cytoplasm and on the periplasm (Tanahashi et al., 2000; Peek, 2005; Suarez et al., 2006). Thus, the pathogen can successfully survive in the gastric lumen (pH 1 - 2) for a short time before it penetrates into the bicarbonate-buffered mucus layer of the gastric mucosa, its real habitat (Benanti and Chivers, 2009). The mucus layer has a pH gradient reaching from the epithelial cell surface (pH 7) to the lumen (pH 2), and the pathogen reacts chemotactically to this gradient (Haas, 2002).

Isolates that lack the ability to produce urease correspondingly fail to colonize rodent models indicating the importance of this conserved enzyme (Peek, 2005). In addition to urea that can be bacterial derived or obtained from the host (Hovey et al., 2007), other enzymes such as catalase and oxidase are produced (Kusters et al., 2006).

Motility within the gastric mucosal is aided by five or six polar flagella that are comprised of two major structural subunits: *flaA* and *flaB*. The genes encoding these two flagellar components are located at distant sites on the *H. pylori* chromosome and are transcriptionally regulated by different promoters (O Toole et al*.,* 2000). Similar to urease production, motility is required for persistent infection, and recent data have shown that a component of the flagellar secretion apparatus, which regulates flagellar biosynthesis, also regulates urease activity (Peek, 2005). They are coupled by the *FlbA* gene.

Other very important virulence factors are adhesins, which allows binding of the bacterium to the gastric cells. Many different molecules such as *SabA, OipA, AlpA*, and *AlpB*, show adhesion activity, including the BabA2 outer membrane protein, which is encoded by the *bab* (blood group antigen binding) genes (Maeda and Mentis, 2007). The BabA2 protein can bind fucosylated polysaccharides, which are blood antigens known as Lewis blood antigens (Ilver et al., 1998; Sheu et al., 2003). These antigens have been found both on the surface of the mucous membrane and in *H. pylori* lipopolysaccharide.

Inter-species and intra-species entero-coexistence has been highlighted in several studies, with competitive exclusion failing to take its toll (Gibson et al., 1998; Nagorni, 2000; Akada et al., 2003; Fritz et al., 2006; Samie et al., 2007). Coexistence is enhanced by failure of competitive exclusion by *H. pylori* strains suggesting that different strains occupy different gastro-mucosal micro-niches (Akada et al., 2003). The organism has the capacity for horizontal gene exchange hence enabling genetic variability within the population. In addition, it shows competency in the uptake of DNA from other *H. pylori* cells (Blaser and Artherton, 2004; Schwarz et al., 2008). The profound diversity exhibited by this organism can play an influential role in the survival of the population in its niche. Flexibility or adaptability in this population, allows for maximised use of resources in a variety of niches and the size or availability of these gastro-mucosal micro- niches is affected by host genotype and age or physiology (Blaser and Artherton, 2004).

Avoidance of the immune response

If a bacterial species is to persistently colonize its host, its most formidable challenge is to evade immune clearance. *H. pylori* evade immune clearance including the harsh environment in the gastric mucosa, and elicit systemic and mucosal immune responses which, however, are unable to clear the infection (Suarez et al., 2006). Multiple lines of evidence suggest that the immune response contributes to the pathogenesis associated with the infection (Suarez et al., 2006).

Instead of killing the colonizing bacteria, the immune response may lead to destruction of epithelial cells and thinning of the mucosal lining leading to increased mucosal contact with luminal acid (Fan et al., 1998; Beswick et al., 2005). This process is first associated with up- regulation of various genes that are associated with the innate immune system including various Toll-like receptors; complement factor C3, lactoferrin, and bactericidal/permeability-increasing protein. The Toll-like receptor induction in particular occurs through the bacterial LPS. Signaling pathways utilized by these receptors all appear to eventuate in NF- B activation and proinflammatory gene expression (Peek, 2005). Another mechanism through which *H. pylori* may persist is by limiting the bactericidal effects of proinflammatory molecules, such as nitric oxide. The organism has evolved strategies to avoid global activation of this system (Permin and Andersen, 2005; Peek, 2005; Ernes et al., 2006).

Both natural and acquired specific immune responses

to the organism are elicited at gastric mucosal level. Response to gastro duodenal infection by the organism is characterized by mucosal infiltration of lymphocytes, plasma cells, neutrophils and monocytes. Those infected with the organism have been reported to have elevated titres of IgG and IgA antibodies directed at membrane proteins (MP), flagelin, urease, lipopolysaccharide (LPS), adhesin A (HpaA) as well as IgM- and IgA-producing cells in biopsies from the antral region of the patients' stomaches. These suggest that the infection induces a large recruitment of immune cells into the gastric mucosa, particularly IgA-producing cells (Mattson et al., 1998).

The inflammatory process is further characterized by the production of various cytokines such as IL-2, IL-3, IL-12, as well as IFN- (Harris et al., 1996; Kuipers and Michetti, 2005). Colonisation unavoidably stimulates nuclear factor-kappa B (NF-kappa B) activation and interleukin-8 (IL-8) expression in gastric epithelial cells (Kim et al., 2003; Lundgren et al., 2003). Toll-like receptor 2 (TLR2) and 5 (TLR5) recognize *H. pylori* and initiate signalling pathways that result in enhanced activation of NF B; IL-8 is secreted by the host cells to attract components of the innate and adaptive immune systems to the site of infection. This polarises the immune response towards a Th1 response, further attracting inflammatory cells and T-lymphocytes (Harris et al., 1996; Kim et al., 2003; Lundgren et al., 2003; Yamasaki et al., 2004; Suarez et al., 2006). An effective CD4+ T -cell response is essential to clear *H. pylori*, however this organism has been shown to inhibit CD4+T-cell proliferation and arresting IL-2 cell-cycle progression resulting in avoidance of clearance thereby staging an infection (Gebert et al., 2003; Sundrud et al., 2004; Rasmus et al., 2007).

However, some infection with *H. pylori* elicits a Th2 instead of Th1-dominant immune response to thwart their elimination and could plausibly modulate *H. pylori*-induced immune response towards one less damaging to the gastric mucosa (protective). This response results in the elaboration of pro-inflammatory cytokines such as IL-4, IL-5 and IL-10 (Rasmus et al., 2007). It has been suggested that persons living in high *H. pylori*-prevalence areas with low gastric- cancer incidence like in Africa might have Th2-type dominant *H. pylori*-specific responses (Mbulaiteye et al., 2006).

Besides presenting *H. pylori* antigens to the specific T cells recruited into the gastric antrum, antigen presenting cells release several cytokines, such as IL-1, IL-6, TNF- and IL-12, whose local concentration strongly influence the developing specific T-cell response (Harris et al., 1996; Yamasaki et al., 2004). Other than inhabiting superficial glycoprotein-rich mucosal niche meant to protect stomach cells from the secreted acids in the stomach cavity, a micro-distance from inflamed glandular cells (Mahdavi et al., 2002; Delport et al., 2006), the organism also avoids recognition by producing specific bacterial factors that stimulate selective expression of host genes and also by inducing an ineffective T-cell response. Genetic diversity of this organism also plays a paramount role in its persistence (Mahdavi et al., 2002).

In uncomplicated chronic gastritis and gastric MALTomas, most of gastric *H. pylori*-induced specific T cells have been reported to elaborate the secretion of both Th1- and Th2-type cytokines (Yamasaki et al., 2004; Rasmus et al., 2007). Existing data suggest that host gastric immune response to *H. pylori* can influence the clinical picture and that gastroduodenal disease may be an immunopathological consequence of a Th1-polarized response to some *H. pylori* antigens, whereas exhaustive and deregulated *H. pylori* -induced T cell-dependent B-cell activation may support the onset of low-grade gastric B-cell lymphoma (De Jong and Enbald, 2008).

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Gastritis

Gastritis refers to inflammation of the gastric mucosa. There are many causes of gastritis; most of which can be grouped as acute or chronic gastritis. Chronic infection with *H. pylori* can lead to gastric atrophy and intestinal metaplasia (Kuipers et al., 1995) . Acute gastritis refers to the transient inflammation of the gastric mucosa (Kuipers et al., 1995). It is most commonly associated with local irritants such as bacterial endotoxins, caffeine, alcohol, and aspirin (http//www.tjclarko.com/d_ulcers.htm, Furuta and Delchier, 2009). Depending on the severity of the disorder, the mucosal response may vary from moderate oedema and hyperaemia to haemorrhagic erosion of the gastric mucosa (Porth, 2002). Clinical manifestations of acute gastritis include heartburn or sour stomach, transient gastric distress, which may lead to vomiting and, in more severe situations, to bleeding and hematemesis. Acute gastritis is usually a self-limiting disorder; complete regeneration and healing usually occur within several days (Porth, 2002).

Chronic gastritis is characterized by the absence of grossly visible erosions and the presence of chronic inflammatory changes leading eventually to atrophy of the glandular epithelium of the stomach (Kuipers et al., 1995). The changes may become dysplastic and possibly transform into carcinoma. *H. pylori* and a number of factors such as chronic alcohol abuse, cigarette smoking, and chronic use of non steroid anti-inflammatory drugs (NSAIDs) may contribute to the development of the disease (Palmer et al., 2002; Furuta and Delchier, 2009). There are four major types of chronic gastritis: *H. pylori* gastritis, autoimmune gastritis, multifocal atrophic gastritis and chemical gastritis (Porth, 2002; Ernst et al.,

2006; Furuta and Delchier, 2009). *H. pylori* gastritis is a chronic inflammatory disease of the antrum and body of

the stomach. It is the most common type of chronic non-erosive gastritis in the United States.

Peptic ulcer disease

Since the early 1980s, there has been a radical shift in thinking regarding the cause of peptic ulcer. No longer is peptic ulcer thought to result from a genetic predisposition, stress, or dietary indiscretions (http//www.tjclarko.com/d_ulcers.htm). Much of the familial aggregation of peptic ulcer whose development was formerly linked to genetic factors is now thought to be due to intra-familial infection with *H. pylori* rather than genetic susceptibilities (van Doorn et al., 1999; Smith et al., 2002; Porth, 2002; Ndip et al., 2008) . The most common forms of peptic ulcer are duodenal and gastric ulcers (van Doorn et al., 1999; Figueiredo et al., 2002). It has been documented that virtually all persons with duodenal ulcer and 70% of those with gastric ulcer have *H. pylori* infection. However, two other forms of gastric ulcers, Zollinger -Ellison syndrome and stress ulcers have different causes (Porth, 2002).

Peptic ulcer disease, with its remissions and exacerbations, represent a public health problem (Smith et al., 2002). It has been documented that approximately 10% of the population have or will develop peptic ulcer (Porth, 2002). Duodenal ulcers occur five times more commonly than gastric ulcers; it occurs at any age and frequently is seen in early adulthood. Gastric ulcers turn to affect the older age group, with a peak incidence between 55 and 70 years of age. Both types of ulcers affect men three to four times more frequently than women (Porth, 2002).

Peptic ulcer can affect one or all layers of the stomach or duodenum. It may penetrate only the mucosal surface, or it may extend into the smooth muscle layer. Occasionally, an ulcer may penetrate the outer wall of the stomach or duodenum; with spontaneous remissions and exacerbations being common. The second most common cause of peptic ulcer is NSAID and aspirin use (Porth, 2002; Furuta and Delchier, 2009). There is a 10 - 20% prevalence of gastric ulcers and 2 - 5% prevalence of duodenal ulcers among chronic NSAID users. Aspirin appears to be the most ulcerogenic of NSAIDs. Ulcer development in NSAID user is dose dependent, but some risk occurs even with aspirin doses of 325 mg/day (http//www.tjclarko.com/d_ulcers.htm, McQuaid, 2001; Furuta and Delchier, 2009). The pathogenesis of NSAID-induced ulcers is thought to involve mucosal injury and inhibition of prostaglandin synthesis. In contrast to peptic ulcer from other causes, NSAID-induced gastric injury is often without symptoms, and life-threatening complications can occur.

Clinical manifestations of peptic ulcer include discomfort and pain. The pain, which is burning, gnawing, or cramp-like, is usually rhythmic and frequently occurs when the stomach is empty - between meals and at 1 or 2 O'clock in the morning. The pain is usually located over a small area near the midline of the epigastrium near the xiphoid, and may radiate below the costal margins, into the back, or, rarely, to the right shoulder (Furuta and Delchier, 2009). Superficial and deep epigastric tenderness and voluntary muscle guarding may occur with more extensive lesions. An additional characteristic of ulcer pain is periodicity. The pains turn to recur at intervals of weeks or months. During an exacerbation, it occurs daily for a period of several weeks and then remits until the next recurrence. Characteristically, the pain is relieved by food or antacids (Porth, 2002).

Complications of peptic ulcers include haemorrhage, obstruction, and perforation. Haemorrhage is caused by bleeding from granulation tissue or from erosion of an ulcer into an artery or vein. It occurs in up to 10 - 20% of persons with the condition (Graham et al., 1993; McQuaid, 2001). Evidence of bleeding may consist of hematemesis or melena. Bleeding may be sudden, severe, and without warning, or it may be insidious, producing only occult blood in stool. Up to 20% of persons with bleeding ulcers have no antecedent symptoms of pain; this is particularly true with person's receiving NSAIDs. Acute haemorrhage leads to a sudden onset of weakness, dizziness, thirst, cold and moist skin, the desire to defecate, and the passage of loose, tarry, or even red stools and coffee-ground emesis. Signs of circulatory shock develop depending on the amount of blood lost (Graham et al., 1993).

Obstruction of blood flow is caused by oedema, spasm, or contraction of scar tissue and interference with the free passage of gastric contents through the pylorus or adjacent areas. There is feeling of epigastric fullness and heaviness after meals. With severe obstruction, there is vomiting of undigested food. Perforation occurs when an ulcer erodes through all the layers of the stomach or duodenum wall. Perforation develops in approximately 5% of persons with peptic ulcers usually from the anterior wall of the stomach or duodenum (McQuaid, 2001). With perforation, gastrointestinal contents enter the peritoneum and cause peritonitis, or penetrate adjacent structures such as the pancreas. Radiation of pain into the back, severe night distress, and inadequate pain relief from eating foods or taking antacids in persons with a long history of peptic ulcer may signify perforation (Graham et al., 1993).

Gastric carcinoma

Infection with *H. pylori* appears to serve as a cofactor in some types of gastric carcinomas (Wotherspoon, 1998). Although its incidence has decreased during the past 50 years, stomach cancer is the seventh most frequent cause of cancer mortality in the United States. In 2001, it was estimated that approximately 21,700 Americans

were diagnosed with stomach cancer and 12,800 died of the disease (Porth, 2002). The disease is much more common in other countries and regions, principally Japan, Central Europe, the Scandinavian countries, South and Central America, Soviet Union, China, and Korea; and is the major cause of cancer death worldwide (Porth, 2002). Among factors that increase the risk of gastric cancer is genetic predisposition, carcinogenic factors in diet (e.g., *N*-nitroso compounds and benzopyrene found in smoked and preserved foods), autoimmune gastritis, and gastric adenomas or polyps (Ernst et al., 2006; Furuta and Delchier, 2009).

Virtually all tumours are adenocarcinomas arising from mucus-secreting cells in the base of the gastric crypts. Most develop upon a background of chronic atrophic gastritis with intestinal metaplasia and dysplasia. Stomach cancers are either 'intestinal', arising from areas of intestinal metaplasia with histological features reminiscent of intestinal epithelium, or 'diffuse', arising from normal gastric mucosa (Palmer et al., 2002). Intestinal carcinomas are more common, and arise against a background of chronic mucosal injury. Diffuse cancers tend to be poorly differentiated and occur in young patients. Between 50 and 60% of gastric cancers occur in the pyloric region or adjacent to the antrum (Furuta and Delchier, 2008). Compared with a benign ulcer, which has smooth margins and concentrically shaped, gastric cancers tend to be larger, irregularly shaped, and have irregular margins. Unfortunately, stomach cancers often are asymptomatic until late in their course. Symptoms, when they do occur, are usually vague and include indigestion, anorexia, weight loss, vague epigastric pain, vomiting and an abdominal mass (Porth, 2002).

Gastric lymphoma

H. pylori are closely associated with the development of a low-grade lymphoma ('MALToma') (Wotherspoon, 1998). Lymphoid tissue is not found in the normal stomach but lymphoid aggregates develop in the presence of *H. pylori* infection (Seymour et al., 1997). Superficial MALTomas may be cured by *H. pylori* eradication (Palmer et al., 2002). Primary gastric lymphoma comprises about 3-6% of all the gastric malignancies (Wotherspoon, 1998). The stomach is however, the most common site for extranodal non-Hodgkin's lymphoma and 60% of all primary gastrointestinal lymphomas occur at this site. The clinical presentation is similar to that of gastric cancer and endoscopically the tumour appears as a polypoid or ulcerating mass.

EPIDEMIOLOGY AND ANTICIPATED MODES OF TRANSMISSION

Trends in Prevalence

H. pylori have a computed high prevalence worldwide. Several studies have highlighted inconsistencies between the prevalence rates for *Helicobacter* and disease. In industrialized countries there is generally a low prevalence and yet a relatively high prevalence of gastric cancer. On the other hand, some countries with high *Helicobacter* prevalence rates have low gastric cancer prevalence. The prevalence of *H. pylori* infection though declining in the developed world (Graham et al., 1991; Segal et al., 2001) still varies widely by geographic area, age, race, and socioeconomic status (Malcolm et al., 2004).

It is not possible to ascertain when infection occurs clinically hence most of the information on the rates of *H. pylori* in geographically and demographically diverse populations are drawn from seroprevalence studies. Retrospective seroepidemiological studies have shown a cohort effect consistent with the hypothesis that infection is mainly acquired in early childhood (Logan and Walker, 2002; Thomas et al., 2004). In a rural village of Linqu Country, Shandong Province, China, a study of 98 children found that nearly 70% of those aged 5- 6 years were infected with the organism, a rate similar to that reported for adults in that area, suggesting that most infection takes place early in childhood (Dale et al., 1998).

Infection with this organism is relatively common in Africa (Asrat et al., 2004; Ndip et al., 2004; 2008; Dube et al., 2009b) and the organism is the main cause of at least 90% of duodenal ulcers and 70% of gastric ulcers (Ndip et al., 2008; Tanih et al., 2010) . Studies conducted in various parts of Africa have revealed high sero-prevalence of infection (61-100%) which differs from country to country and between different racial groups within each country (Holcombe, 1992). Childhood acquisition is the rule with more than 50% of all children in Africa being infected by the age of 10 years, with prevalence rising to 80% in adults (Segal et al., 2001).

More recent reports also show a wide variation of infection rates, with anti-*H. pylori* IgG antibodies reported in 85.6% in 215 dyspeptic individuals in Ethiopia. Kidd et al. (1999) documented a prevalence of 25 and 97% in Uganda and Ghana respectively. Nabwera et al. (2000) in their study observed a high prevalence among Kenyan children aged between 3 - 5 years, indicating that most children in the study area were infected before they reached their third birthday. In Mozambique, Carrilho et al. (2009) reported a high prevalence of 94.5% while in Cameroon Ndip et al. (2008) equally documented a high prevalence of 92.2% in their study population. In Ethiopia, a prevalence of 93% was found in a study by Henriksen et al. (1999) on patients with peptic ulcer disease. In the Democratic Republic of Congo, a seroprevalence of 62.4% was delineated among the study participants (Longo-Mbenza et al., 2007).

H. pylori infection also appears to be common in South Africa; Pelsar et al. (1997) documented a high prevalence (67 - 84%) of *H. pylori* antibodies in children in Bloemfontein, while Mosane et al. (2004) also reported *H. pylori* IgG antibodies in South African mothers and their

children. Recently, Samie et al. (2007) described a prevalence of 50.6% in their study in Venda, North of South Africa. In a recent study of asymptomatic individuals in the Eastern Cape Province, *H. pylori* antigenemia was observed in 86.8% in the stools of our study subjects (Dube et al., 2009b).

In the Western world a number of studies have also reported a high prevalence of the organism in children (Thomas et al., 2004). The difference in the rate of childhood acquisition of infection is probably responsible for the differences seen, in the prevalence of infection, between developed and developing countries (Segal et al., 2001) . The prevalence of infection and the incidence of gastric cancer are higher in Asia, South America, and the Caribbean than in Europe and the United States (Segal et al., 2001).

A study carried out in Guatemala revealed the presence of this organism in about 58% of the participants' enrolled (Dowsett et al., 1999). Ghose et al. (2005) in Venezuela also found a high prevalence of the organism [121/127(95.3%)] in their study population. Prevalence of infection has been reported to be higher among blacks than Caucasians in the United States (Hisada et al., 2001). A study which enrolled a Hispanic population reported a prevalence of about 79% (Dehesa et al., 1991). The epidemiology of *H. pylori* infection in the Caribbean islands remains an important concern for public health investigation because of the high prevalence of this infection and its association with gastric cancer. In Jamaica a high prevalence of 70% has been described (Hisada et al., 2001).

Plausible factors exacerbating spread

The prevalence of *H. pylori* has been reported to be high in African Americans, Hispanic, Asian and Native American populations with similar infection rates in males and females (Dehesa et al., 1991). Until recently, it has been difficult to assess accurately the incidence (or route) of infection because of the inaccuracy and cost of detecting (non-invasively) *H. pylori* in young children. Primary acquisition in adults, or re- infection after successful eradication, does occur but is less common, with an annual incidence of 0.3-0.7% in developed countries and 6-14% in developing countries (Logan and Walker, 2002).

The generally high prevalences of human infection seen in Africa and the world at large are an indication that effective public -health interventions need to be developed; while the variations seen in the prevalence of infection between and among populations may point to the fact that parameters such as age, cultural back-ground, genetic predisposition, socio - economic status and environmental factors all play a role in the acquisition and transmission of *H. pylori* (Graham et al., 1991; Segal et al., 2001; Chong et al., 2008; Dube et al., 2009b).

A number of authors have emphasized the role of other factors such as smoking, alcohol consumption, occupa-tional exposure, waterborne exposures, hygienic practices, density/crowding, social factors and family history of gastric disease (Ogihara et al., 2000; Brown et al., 2000; Iso et al., 2005). Within countries, there may be a similarly wide variation in prevalence between the more affluent urban populations and the resource-poor rural populations. A lack of proper sensitization, good drinking water and poor diet seem to play a role in the high prevalence of infection (Dale et al., 1998; Ndip et al., 2004; Dube et al., 2009b).

There appears to be a substantial reservoir of *H. pylori* aside from the human stomach. Animals, e.g. cats, monkeys etc harbour organisms that resemble *H. pylori* (Dubois et al., 1994) but under particular circumstances (Fox et al., 1995) . These animals could be reservoirs for human infection. Although possibly important in some circumstances, neither a zoonotic reservoir nor food appears to be significantly involved in acquisition of *H. pylori*. Thus the major question of transmission is how *H. pylori* move from the stomach of one person to that of another.

MODES OF TRANSMISSION

Although epidemiologic studies have addressed a variety of factors such as bacterial, host genetic and environmental factors to delineate the causative links of *H. pylori* infection; knowledge of reservoirs and transmission modes remain poor (Thomas et al., 2004; Asrat et al., 2004; Ndip et al., 2004). However, some routes have been described (Tanih et al., 2008).

Gastro-oral routes

With human being the only known reservoir of infection, it is likely that in developed countries *H. pylori* is picked up from siblings, other children, or parents predominantly via the gastro-oral route (Brown et al., 2000). The organism has been recovered from vomitus after specific culture based approaches on selective media (Leung et al., 1999; Ndip et al., 2003)

Iatrogenic transmission

Iatrogenic transmission is the mode, in which tubes, endoscopes or specimens in contact with the gastric mucosa from one person are introduced to another person (Akamatsu et al., 1996). Adequate sterilization and disinfection of endoscopes has reduced the incidence of transmission (Tytgat, 1995). Endoscopists, especially those who do not wear protective clothing during procedures, are occupationally exposed

(Sobala et al., 1991; Kikuchi and Dore, 2005) . This is however the least common form of transmission.

Faecal-oral transmission

Faecal-oral transmission appears to be the most important route of transmission (Tanih et al., 2008). Albeit being isolated from the faeces of young children infected with the organism (Thomas et al., 2004), faecal isolation is not common; this could indicate that shedding is intermittent (Mackay et al., 2003). Faecally contaminated water may be a source of infection (Klein et al., 1991; Dube et al., 2009a) but the organism proves difficult to be isolated from water. Food-borne transmission and unclean hands have also been substantiated (Kersulyte et al., 1999) . *Helicobacter* seropositivity increased with consumption of uncooked vegetables in Chile which was perhaps related to contaminated water used on the vegetables (Hopkins et al., 1993).

Oral-oral transmission

Oral-oral transmission has been identified in African women who feed their children with premasticated foods (Me´graud, 1995). Premastication of food was common in Burkino Faso families with both mother and child sero-positive for *H. pylori* when compared to frequencies in families with a sero-positive mother and a sero-negative child (Aditya et al., 2009). There is evidence of intrafamilial transmission; in which poor living conditions has been shown to increase the risk of infection (Aguemon et al., 2005). Although dental plaque has been proposed to be a possible route of transmission (Majmudar et al., 1990; Desai et al., 1991) this has failed in other studies (Bernander et al., 2003).

Sexual transmission

There is no identified association of infection with sexual transmission (Perez- Perez et al., 1991) and such transmission, if it occurs, must be uncommon.

CONCLUSION

The data presented in this review demonstrates the importance of the interactions between virulence factors of *H. pylori* and host cells, and the consequences that follow interplay between the bacterium and cells of the immune system. *Helicobacter* infections induce inflammation and stimulate an ineffective immune response. Alteration of epithelial cell growth and en-hanced apoptosis play a role in disease manifesttations; failure of mucosal adaptation, ulceration, and abnormal repair may predispose to malignancy. However, many questions still remain unanswered on *H. pylori* epidemiology; further studies are therefore required to gain a better understanding of the transmission pathway of this notorious pathogen.

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