

New Study: Helicobacter Species as a Potential Zoonotic Infectious Carcinogen : A Review**Arnaot May Ramzey, Independent Medical Researcher, Germany****Corresponding author; drmayramzey@yahoo.com****Doi: <https://doi.org/10.37940/AJVS.2020.13.1.1>**

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<http://creativecommons.org/licenses/by/4.0/>.**Abstract**

In 1983 two Australian doctors discovered a spiral bacterium in human stomach which was called *Campylobacter pylori* (or *pyloridis*) to be re-named (*Helicobacter pylori*) in 1990. Carried by half the global population it was first believed exclusive to Human causing chronic gastritis, peptic and duodenal ulcer, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. This discovery revolutionized peptic ulcer treatment with antibiotics instead of surgery. *H.pylori* is the only bacterial agent classified as Class 1 carcinogen.

In 1997 genetic advances allowed genome sequencing and detailed research particularly on genomic pathogenesis. Genome printing methods revealed that *H.pylori* was transmitted from domesticated animals to pre stone-age man probably of African ancestry.

New non-*pylori* *Helicobacter* species were found in farm, small, wild, and non-human primate animals. Some cause chronic gastritis and vomiting, occasionally lymphocytic gastric tissue proliferation and cancer. Some animal and avian species are contagious to human, sometimes sharing genomic similarities with *H.pylori*.

There are currently about 35 *Helicobacter* species. In pathogenic strains, certain genes function as virulence factors making proteins responsible for chronic inflammatory reactions and carcinogenesis in variable degrees. This is called (genomic polymorphism), it create diverse species and strains with variable degrees of pathogenicity. Genomic heterogeneity is the result of *Helicobacter* adaptation in various environmental, geographic, and host circumstances. *Helicobacter* strains with diverse virulence may exist in different ethnic and geographic groups. Both *H.pylori* in human and non-*pylori* species in animal may co-exist mixed in one host. Sheep is believed the reservoir for *H.pylori* and *H.canis*.

Keywords: *Helicobacter*, Zoonosis, Veterinary, Infection, Carcinogenesis.**اهمية البكتريا اللولبية كوابائيات معدية ومسرطنة قوية الاحتمال****الخلاصة**

في عام 1983 اكتشف طبيبين استراليين بكتريا لولبية الشكل في المعدة البشرية سميت (الكامبيلوبكتريا البوابية) لتعاد تسميتها عام 1990 الى (اللولبية البوابية) نسبة الى شكلها وتواجدها في بوابة المعدة. يحمل هذه البكتريا حوالي نصف سكان العالم واعتقد بانها متخصصة بالبشر. تسبب الالتهابات المعوية المزمنة وقرحة المعدة والاثنى عشر، كذلك سرطانات المعدة ولمفوما الخلايا اللمفية في انسجتها المخاطية (مالت). غيرالاكتشاف علاج قرحة المعدة جذريا من الجراحة الى المضادات الحيوية. وهي البكتريا الوحيدة المبوبة كعامل مسرطن من النوع الاول.

بعد تقدم التقنيات الوراثية حلل التسلسل الجيني للولبية المعوية عام 1997 وتفاصيل الجينوم وقابليته المرضية. وظهرت الطبعات الوراثية ان اصولها الجينية تعود الى انسان ما قبل العصر الحجري وانها انتقلت اليه لأول مرة في افريقيا من الحيوانات المدجنة .

ثم اكتشفت انواع جديدة من اللولبيات في الحيوانات الحقلية والصغيرة والوحشية وفي القروود تسبب التهابات المعدة والتقيؤ المزمنين واحيانا تكاثر النسيج اللمفاوي المعدي والسرطان, ويمكن لبعضها الانتقال من الحيوانات والطيور الى الانسان , بينما يتشابه البعض في الصفات الجينية مع النوع البوابي فيه.

هناك حاليا حوالي 35 نوعا من اللولبيات. وفي الانواع المرضية جينات معينة تعمل كعوامل حيوية مسؤولة عن التفاعلات الالتهابية المزمنة والتسرطن بدرجات متفاوتة اي (تعدد الاشكال الجينية). ومن هذا تنشأ انواع وعترات متغايرة الحيوية والقدرات المرضية. نتج تباين الجينوم عن مرونته وقابليته للتأقلم تحت مختلف الظروف البيئية والجغرافية ومع اختلافات المضيف. وقد توجد اللولبية البوابية متمازجة مع لولبيات حيوانية اخرى في مضيف واحد. كما يعتقد ان الخراف تعمل كحامل لكل من اللولبيات البوابية والكلبية.

هذه الدراسة تسلط الاضواء على اهمية اللولبيات بانواعها كعوامل معدية ومسرطنة تنتقل من الحيوان واهمية الجينوم المرن في التأقلم مع المضيف الجديد . وتقتصر خصوصا في العراق بعض التوصيات الوقائية بصدد العادات الغذائية والاجتماعية المتعلقة بالموضوع بينما تستطلع الاحتمالات المستقبلية المهمة لاجراء البحوث بهذا الصدد.

Introduction

In 1983 the Australian doctors Warren and Marshal discovered a spiral-shaped flagellated mobile bacterium slipping on mucosal surfaces of gastric antrum avoiding the fundus region having adapted to live in highly acidic environment similar to *Proteus* species which adapted to live in the urinary (1). The new micro-organism was called *Campylobacter pyloridis* (2) (or *C. pylori*) (3) first as related to family *Campylobacteraceae*. In 1990 the new genus *Helicobacter* was established and the bacterium re-named *Helicobacter pylori* (*Helicos* = spiral in Greek) first believed to be exclusive to human (4).

Microscopically, *H. pylori* is a Gram negative rod that may change into coccoid following antibiotic treatment. As a (microaerophile) it is capable of living with small quantities of air helped by a Hydrogenase enzyme, a Urease enzyme helps neutralizing the highly acidic gastric surrounding by breaking urea into ammonia creating an alkaline environment around the microbe (5).

Despite that 80% of infections are asymptomatic, *H. pylori* in human is found primarily responsible for chronic gastritis and peptic ulcer, which revolutionized treatment with antibiotics instead of surgery. Some strains may induce duodenal ulcer (6,7). others may cause hepatitis in mice (8), and are suspected to be responsible for chronic

active hepatitis and hepatocellular carcinoma in human (9). Chronic infection may lead to gastric adenocarcinoma, an important worldwide morbidity or gastric mucosa-associated lymphoid tissue (MALT) lymphoma, the reason the International Agency for Research on Cancer (IARC) listed *H.pylori* as the only potent bacterial carcinogen (Class I) (10). Following the advances in genetics and molecular biology, *H.pylori* genome was deciphered and sequenced in 1997 (11). Genetic printing revealed that like *Mycobacterium* species, *H.pylori* was first transmitted to human in Africa from domesticated animals (possibly sheep or cattle ancestry) before the Neolithic (stone) ages (12). Historically, genetic adaptation to changing environmental circumstances, geographic locations, and host communities was helped by a polymorphic genome and flexible virulence (motifs) (13),(14). This way, several species and strains with variable virulence and therefore pathogenicities constantly developed having adapted in certain communities. Using the so-called (molecular finger printing) bacterial migrations and adaptations can be traced back to African ancestors (15). Genomic similarities indicate that the Spanish carried the bacterium to South American Peruvians, and the Europeans back to Africa, both are now high incidence areas (16).

Nowadays, about 4.4 billion people i.e. approximately half the global population are carriers (17). The incidence and pattern of pathogenicity varies widely with geographic location, age, race, ethnicity and bacterial strain (18,19,20,21). Other factors may play a role like low socio-economic classes, crowds, hygiene (polluted or badly prepared food and water), sharing food utensils, some religious ceremonies (7), public health awareness and medical treatment options (22).

The mechanism of transmission is thought to be via oro-oral or faeco-oral routes. *H. pylori* DNA was detected in vomitus, saliva, dental plaque, gastric juice, and faeces. Food and waterborne transmission, probably due to fecal contamination, may be an important source of infection (23). This is of zoonotic significance as fecal-polluted water and badly prepared animal meats may allow *Helicobacter* into the food chain.

Infection is acquired early life, incidence increases with age. In Iraq 28% of 6 years old in Duhok are seropositive (24). Parent transmission is possible, a Turkish study found 69% seropositive mothers of infected children compared to 8% mothers of uninfected children (25). Breast feeding does not provide immunity, however, acute infection in children can be eliminated spontaneously without chronically establishing, and within the family, siblings are the highest risk of transmission followed by mothers then grandmothers (15). This area deserves more studies.

In the Middle East strain diversities exists among Iraq, Iran, and Turkey, *H. pylori* carrier rates varies from as high as 62-91.7% in Iran, Turkey, Egypt and UAE, to as low as 51% in Saudi Arabia and 44% in Jordan, also depending on the diagnostic methods used (25). In Iraq, 77% in Arabic areas between 15-68 years (26) and 78 % in Kurdish areas were found seropositive, of whom 85% were above 30 years (27).

Certain *H. pylori* genes functions as virulence factors i.e. responsible for pathogenicity. The (Cytotoxine -associated Gene A) (*cagA*) encodes gastric cells bacterial adherence proteins and stimulate the immune system via Cytokines, Chemokines, Interleukines and Tumor Necrotic Factor Alpha (TNF- α), causing inflammatory reactions and later ulceration and cancer. The (Vacuolating cytotoxin gene) (*vac*) proteins induces lymphocytic proliferation and apoptosis (28). The *BabA2* gene proteins may be associated with peptic ulcer disease, gastric atrophy and premalignant proliferation (29). The lately described duodenal ulcer promoting gene A (*dupA*) is associated with duodenal ulcer (30).

Not all virulent factor genes are equally active in all strains, this is due to genome *polymorphism*, e.g. the number of Tyrosine phosphorylation motifs (TPM) in *cagA* gene which determines its virulence and pathogenicity may vary in different ethnic groups or geographic locations (20).

In animals, spiral organisms were discovered in stomach of dogs, cats and other species since the nineteenth century and remained obscure until recent genetic identification as *Helicobacter* species, some are commensals, others are animals and sometimes human pathogens and may share genomic similarities with *H. pylori* (31). The most important shared species are: *H. heilmannii*, *H. bizzozeronii*, *H. salomonis*, others species of zoonotic significance may include *H. felis* and *H. canis* in small animals, *H. bovis*, *H. bilis*, and *H. trogonum* in ruminants, *H. suis* in swine, *H. pullorum* and *H. canadensis* in birds, *Helicobacter* species are also found in ferrets, wild animals and non-human primates (31,32).

H. pylori has also been isolated from milk in sheep, cow, camel, pig, goat and even dogs and may enter the food chain this way (33,34). The role of other farm animals is not fully explored

yet Sheep are believed to be the reservoir for contagious human and dog *Helicobacter* species (32, 34).

Cats may harbor *H. pylori* mixed with feline and other *Helicobacter* species, the incidence is extremely low, such as pet or stray cats should not be considered a public health threat to human, on the other side, *H.pylori* in cats was hypothesized as responsible for the high incidence of feline lymphoma (35).

Accordingly, *Helicobacter* infections are grouped into: *H. pylori* species (HPS) infections and non-*H.pylori* species (NHPS) infections with significant cross transmission between the two as mixtures of human and non-human species can be found on both sides (31). The fact that contagious animal species are found in dogs, cats, swine, sheep, and poultry, imply significant zoonotic importance. There are currently about 35 known species of genus *Helicobacter* and more are regularly discovered.

Materials and methods

Data and references were obtained from PMD and Google Scholar as well other professional websites with the appropriate search words.

Results and discussion

H. pylori species infection

I. a. Incidence and prevalence of *H. pylori*

H. pylori infection is associated with chronic gastritis and a high risk of developing peptic ulcer, duodenal ulcer, gastric adenocarcinoma and gastric (MALT) lymphoma. In 2015 it was estimated that half the global population are carriers.

The incidence varies geographically, ethnically, and with age, socio-economic state and hygienic measures. It is higher in low socio-economic areas improving with better hygiene, e.g. in the

U.S. it is low in whites 35.6% and high in indigenous Alaskans 76.0 %, in Australia it is 24.6% in whites and 74.8% in the indigenous population. The incidence is decreasing in the west due to public health awareness and medical treatment options (23).

The highest prevalences are in Africa (70.1%), South America (69.4%), and Western Asia (66.6%), the lowest are in Oceania (24.4%), Western Europe (34.3%), and North America (37.1%) (17).

In the Middle East, *H.pylori* carrier incidence is high in Egypt (91.7 % seropositive) and Kuwait (66-96.6% depending on the method used), low in Saudi Arabia (51% seropositive) and Jordan (44% PCR positive gastric biopsies of symptomatic patients), while in Turkey the overall prevalence among 25-64 years was 77.5%, and in Iran the incidence above 40 years of age was 62-90% depending on the area (25). In Iraq 77-78% are seropositive (26,27).

Despite multi-factorial etiology the prevalence of gastric cancer corresponds to that of childhood *H.pylori* infection (36). Regional variations exist between Iraq, Iran and Turkey, e.g. in Southern Iran as high as 98% of 2 years old children were fecal Antigen positive, compared to only 40% aged 7-12 years in North Iran, and in Turkey *H.pylori* positivity varied with area and increased with age, estimated to be 60% on average, however, 60.3% of children with recurrent abdominal pain were found positive compared to 20.8% in symptomless children (25). In Iraq, 28% of children average 6 years age in Duhok were seropositive regardless of parents education (24).

The Heterogenic Virulence and Pathogenesis of *H.pylori*

The presence of certain genes as virulence factors in different *H. pylori* strains greatly increase the risk of disease. The most important genes are; (*cagA*) and its intermediate pathogenicity island

(s1,m1 and i1 allele regions), the active forms of (*vacA*) gene, the (*babA2*) gene, and the duodenal ulcer promoting gene A (*dupA*) described as associated with duodenal ulceration while protective against gastric cancer (30) .

H. pylori virulence and pathogenesis varies geographically due to gene heterogeneity which is also determined by ethnicity (19,37,38,20). In Iraq for example, the frequencies of (*vacA*) s1 and m1 allele regions and (*cagA*) positive genotypes were found to be higher in the non-Semitic inhabitants of the North (e.g. Kurds) than the Semitic inhabitants of the South (e.g. Arabs) (37). The distribution of virulence genes in Iraqis was 66.6% *cagA* gene, 30% *dup* gene, 93.3% *vacA* type s1, 26.6% *vacA* type i1, and 23.3% *vacA* type m1 genes (39).

Iraqi *H.pylori* strain virulence are also variable, in a Kurdish study on 154 gastric biopsies 75% were found *H. pylori* positive of which, 72.7% *cagA* positive (82% of peptic ulcer patients) and 18.8% *dupA* positive (21). In an Arabic study on 42 fecal samples, 73.8% were *H.pylori* antigen positive, of which, only 38.7% were *cagA* positive and 25.8% *vacA* positive (40). Comparative strain studies using the same methods and sample size are still lacking in Iraq.

CagA gene has repeat tyrosine phosphorylation motifs (TPM) sequence which varies with geographical area and ethnicity in different species or strains (37). The number of motifs determines gene virulence and the degree and pattern of the inflammatory disease process. High virulence corresponds to the presence of three or more motifs particularly in the so-called intermediate gene zone (s and m), and associates with cancer risk, while two are associated with gastric atrophy (19). This may be due to variable sizes of encoded protein molecule and therefore pathogenicity in similar virulence genes carried by different strains according to location and ethnicity (14).

In Iraq, unlike peptic ulcer, gastric atrophy and cancer are relatively rare despite early *H. pylori* infection, compared for example to Iran and Turkey. However gastric cancer occupies the eighth place among top ten malignancies in Iraq comprising 3.1% of total malignancies and causing 5.2% deaths annually (41). This was explained pathologically as due to the antral (rather than fundal) inflammatory pattern and the very low incidence (about 3%) of gastric atrophy (39). Genetically however, only 29% of *cagA* positive peptic ulcer patients are 3TPM positive (42).

The (*vacA*) gene is also a mosaic of heterogenic alleles in various strains which explains the variable toxicity degrees of its encoded cytotoxic proteins (43).

The presence of (*dupA*) gene is associated with duodenal ulcers in Iraq but not Iran (37). However, *dupA*-negative *H.pylori* strains were found to associate with pre-malignant lesions in Iran (44).

(*BabA2*) is usually associated with preneoplastic lymphocytic infiltration (29), and can be used as a marker for peptic ulcer risk in (North) Iraq followed by (*cagA*) (21,42).

***H.pylori* as zoonosis**

H. pylori was found in gastric biopsies of 97.6 % of polish mountain shepherds and 86% of their family members together with significantly higher *cagA* encoded proteins like plasma gastrin, interleukin-8 and tumor necrosis factor- α , compared to controls without sheep contact where *H. pylori* was found in only 65 % of subjects. In goats, it was found in milk only, not in gastric biopsies (34). In another study, *H. pylori* was found in 82% of human gastric biopsies, 16% of sheep, and 3% of cows but not in goats indicating a cross transmission between sheep, goats and other animals. In sheep strains *vacA* gene polymorphism was comparable to that of human, sheep are therefore believed to be the

ancestral host of human *H. pylori* (33).

Cats has been implicated as a potential reservoir for *H. pylori* human infection, this is so uncommon however and does not constitute a real health threat (35).

Non-H.pylori species infection as zoonosis

Non-H.pylori species normally found in other mammals and birds were also detected in human clinical specimens. The most common zoonotic animal strains are *H. heilmannii*, *bizzozeronii*, and *salomonis* known to colonize animal gastric mucosa causing gastritis and peptic ulcer which may be manifested as chronic vomiting specially in dogs and cats (32).

Helicobacter heilmannii

H. heilmannii (previously *Gastrospirillum hominis*) is the dominant micro-organism in gastric mucosa of pigs, cats, dogs and primates (31). It was first identified in human gastric antrum by Dent et al 1987 (45). Compared to *H. pylori* it is associated with a milder chronic gastritis with low incidence of <0.3%, as well as peptic and duodenal ulcers, diffuse gastric carcinoma and (MALT) lymphoma which rate (3.4%) is surprisingly high in human. 80% of *H. heilmannii* (type1) infection in patients are acquired from dogs, cats, or pigs (46).

The zoonotic risk of *H.heilmannii* posed by dogs and cats is likely to be small due to low prevalence ranging from 0.5% in developed countries to 1.2 - 6.2 % in East European and Asian countries, only one case is reported of a 12-year old boy with chronic *H.heilmannii* gastritis contracted from his pet dog (31). Human infection by more than one *H.heilmannii* strain closely related to animal strains is possible (47).

Other non-H.pylori species in animals

Three species resembling *H.heilmannii* has been isolated from dogs or cats: *H. felis*, *H bizzozeronii*, and *H.salomonis*.

H. bizzozeronii can be detected in 0.17-2.3% of gastric biopsies of human patients with gastric symptoms, a human strain of *H.bizzozeronii* type CIII-1 was isolated and sequenced in 2008 (48).

H.hepaticus and *H. bilis* may cause liver disease in addition to gastric symptoms in animals (9), *H trogontum* induces abortion in sheep (31). The last two species display carcinogenic potential in animals and harbor numerous virulence genes which may cause disease in humans (49).

H.canis has been associated with hepato- biliary and gastrointestinal disease in dogs, cats, and human. In one case a 78-year-old man with diffuse gastric large B cell lymphoma developed persistent *H.canis* bacteremia while on chemotherapy. Sheep were identified as reservoirs for *H. canis* (50).

H. cinaedi is associated with gastroenteritis in primates and human and was reported to infect immunocompromised patients infected with Human Immunodeficiency Virus (HIV)(31).

Non-pylori Helicobacter species in birds

H.pullorum infect poultry and cause hepatobiliary disease and gastroenteritis in both chicken and human, it has been cultured from chicken liver and caeca, and from a diarrhoeic psittacine bird kept as a pet, as well as human faeces, the prevalence in broilers of laying hens and the majority of turkeys was found to be 100% (31).

H. canadensis closely resembles *H. pullorum* and is widely distributed in nature and can be disseminated by wild birds polluting water or may enter the food chain through poorly cooked wild birds meat, it is known to cause enteropathies in birds and was isolated from a patient with enteritis, its zoonotic significance is still unclear (31).

Summary Conclusions and Recommendations

The zoonotic significance of *Helicobacter* species particularly *H.pylori* is of emerging importance. Several important issues are yet to be addressed.

H.pylori was transmitted to human at ancient times from domesticated farm animals ancestry. Since then, it adapted as a human pathogen. Other *Helicobacter* species adapted are pathogens in small and farm animal as well as poultry and wild birds. Cross infection and mixed species and strains can still be found on both sides.

As a human pathogen *H.pylori* can be responsible for dyspeptic symptoms, chronic gastritis, gastric and duodenal ulcers as well as gastric atrophy, adenocarcinoma and (MALT) lymphoma. The incidence and pattern of these complaints is a function of species and strain pathogenicity which varies with the geographic location, ethnicity, race, age as well as other factors. This diversity is a result of virulence genomic polymorphism and heterogeneity which allows adaptability and cross cohabitation.

Virulence factors are gene (segments) encoding for functional proteins of various pathogenic potencies depending on the strain, e.g. the number of phosphorylation motifs in *cagA* virulence gene determines the degree and pattern of immunomodulation and the inflammatory process, i.e. the presence of three or more motifs associates with cancer risk, while only two motifs associate with gastric atrophy. In addition, allele variations in the intermediate *cagA* so-called pathogenicity island also play an important role.

Similarly, the base sequencing of *vac* virulence gene is a *mosaic* which varies with strain.

It is therefore important to determine the pattern and sequence of each virulence factor in each *H. pylori* strain at each geographic and even regional location and in ethnic group as the pathogenicity pattern may differ.

In Iraqi *H. pylori* virulence gene factors were found to differ between the southern Arabs and the northern Kurds. These in turn are different from other strains in neighboring geographic locations like Turkey and Iran, e.g. *H.pylori* stomach cancer is less common in Iraq compared to Turkey and West Iran (37). In addition, the Iraqi Kurdish strain has an active *babA2* virulence factor expressing duodenal ulcer pathogenic proteins (42). Such important findings are not fully explored yet while little is known about other Iraqi *Helicobacter* animal species and strains

The mechanism of transmission deserves more attention. *H. pylori* infection is mostly acquired in childhood leading to gastric atrophy and later cancer. Evidence of salivary and parental transmission has been found and requires more investigation. Meanwhile, habitual children kissing by family members should not be recommended.

There is evidence that this pathogen can establish in food chain compromising food safety and health. Of specific importance is the finding that sheep may act as a reservoir for both *H. pylori* in human and *H.canis* in dogs. While there is high incidence and symptomatic infection in shepherds and their family, and indications of transient *H. pylori* transmission to goats without infection (34). The significance of sheep contact to other risk groups e.g. farmers and veterinarians and to other animals like dogs and other farm animals has not been well investigated. Food borne transmission can be another potential mechanism for *H.pylori* infection. Food habits in Iraq allow the consumption of cooked sheep stomach as a delicacy (Pacha). The importance of such tradition in transmitting *H. pylori* infection during preparation and consumption is unexplored. Similarly, the habit of consuming wild birds particularly in south Iraq. *H.pylori* was isolated from polluted water resources in Basrah (51).

Prior contact with farm and pet animals has attracted attention as a risk of *H. pylori* transmission. Little is known about the zoonotic significance of non-*H. pylori* species to humans or other animals. Pathogenicity and clinical manifestations are still to be explored. As emerging zoonosis, there is evidence that non-*H. pylori* species are able to cause gastritis, enteritis, peptic and duodenal ulcer, colitis, hepatitis, and MALT lymphoma in both human and animals. These bacterial species can therefore be considered as potential research models to study pathogenesis, carcinogenesis and therapy from both medical and veterinary perspectives..

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