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Helicobacter pylori infection in children: should it be carefully assessed?

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Abstract. – The prevalence of *H. pylori* infection, mainly acquired during childhood and may be persisting throughout life, has been found high in developing countries; this high prevalence is related to low socioeconomic status. The persistence of bacterium exposure is related to gastritis and other severe complications including peptic ulcer, lymphoma MALT and gastric cancer, which are rarely present in the pediatric age due to a lower inflammatory and immunological response. Virulence factors, host gastric mucosal factors, and the natural environment of patients are associated with the clinical outcome of *H. pylori* infection. The main bacterial virulence factors include adhesins (BabA, SabA), vacuolating cytotoxin VacA, and the products of the cag pathogenicity island (cag PAI). There are geographic differences between cagA, vacA status and *H. pylori* related diseases. The main criteria to evaluate *H. pylori* infection in children are gastrointestinal and extra gastrointestinal manifestations related to *H. pylori* infection, familial history of gastric cancer, peptic ulcer, lymphoma MALT, symptomatic children living in high prevalence regions, and immigrant or adopted children in developed countries. Early detection of *H. pylori* and its virulence factors, in addition to effective methods of eradication associated with prevention programs, may lead to the decrease of *H. pylori* incidence and gastritis, especially in endemic high-risk regions. The early assessment in children may prevent further severe complications in adulthood.

Key Words:
H. pylori infection, World prevalence of *H. pylori* infection in children, Prevalence map, Virulence factors H. pylori, cagA, Immune response in children.

Introduction

Since the discovery of *Helicobacter pylori* (*H. pylori*) by Barry Marshal and Robin Warren in 1984[1], the infection by *H. pylori* became one of the most common in the world with great differences between and within countries. The epidemiology of *H. pylori* has been changing over the last decades with a progressive decline in developed countries where the incidence is about (20%-30%), but the immigrant population harbors a high prevalence similar to their original country[2]. On the other hand, the prevalence is still over 50% in most of the developing countries and it is closely related to a higher risk conditions to acquire the infection. The main factors for *H. pylori* infection are low socioeconomic status measured also as low family income, inverse association between educational level, crowded homes, and having contaminated sources of drinking water[2-4].

The transmission of *H. pylori* infection is still unclear. *H. pylori* has been isolated from human gastrointestinal tract, including saliva and stools, suggesting that oral-oral and fecal-oral routes as the main transmission pathway[5]. The infection is acquired through interpersonal and intrafamilial spread, especially if the mother and grandmother are infected[4].

The role of environmental transmission such as drinking contaminated water, remains as a possible route, yet the main problem is the inability to routinely isolate the species from water samples by conventional microbiological culture techniques. In addition, zoonotic transmission by dogs, cats, sheep and flies, has been published but not fully demonstrated; as well as iatrogenic transmission by endoscopic procedures has been proposed[6]. Since 1994, *H. pylori* has been classified as Class I category for gastric cancer by the International Agency for Research on Cancer[7]. Consequently, screening and treating infected patients is the main objective to prevent and eradicate this high risk factor for gastric adenocarcinoma especially when *H. pylori* hosts virulence factors[8]. Therefore, assessing children in high prevalence regions of *H. pylori* infection is determinant for the prevention of the related complications.

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Epidemiology: H. pylori World Prevalence Infection in Children

It is important to emphasize that the prevalence of *H. pylori* infection depends on the detection method used by different tests and the colonization status.

Some reports in children from Africa, Asia and Europe have documented a variable prevalence related to the socioeconomic status. In Africa, for example, data of prevalence in children varies from 40% to 80%, in Bangladesh from 50% to 60%, in India 22%, in Taiwan 12%, in Australia 15%, and in Turkey 50%. In Hong Kong, the prevalence in adolescents is 13%. In some countries in the American Continent data reported is as follows: Canada 7%, Guatemala and Mexico 30%-50%, Brazil 30%, and Chile 36%[9].

Venezuela has a high prevalence of *H. pylori* infection in children (30%-80%) with variations due to the socioeconomic conditions of different regions. Data shows children living in rural area with a prevalence of 67% by serology[10]. In another study in children with low socio economical status done by Urea Breath Test (UBT) with C^{13} the prevalence was 75%-82%[11]. In the Venezuelan indigenous children of the etnia Warao located in different geographic regions of the country the prevalence established by stool antigen varied from 10% to 90%[12,13]. In big cities of Venezuela in symptomatic children attending different clinical centers, the prevalence was 30% in private centers and 50% in public hospitals[14,15].

The infection is mostly acquired during childhood[16] and it persists lifelong increasing the prevalence with age[17]. Complications as gastritis, peptic ulcer disease, and chronic pathological changes in gastric mucosa may predispose the development of gastric cancer in adults[18].

The world prevalence of *H. pylori* infection in children (0-18 years) by different diagnosis methods (serology, stool antigens, histology, and urea breath test) is represented in Figure 1 according to the last 5 years (2010-2015) data reported in PubMed; this search was done by entering key words such as "*Helicobacter pylori*," "prevalence," and "infection in children." It is important to mention that in countries with no data reported the last prevalence data published was included[19-152]. In countries where we found more than one publication, the average of the data reported was calculated.

The purpose of this map is to illustrate the global prevalence, and it does not intended to represent specific rates by country, since the data published is varied, limited and does not allow standardized criteria for statistical analysis.

Virulence Factors of H. pylori, Implications to Carcinogenesis Risk

Virulence factors, gastric mucosal factors of host, and natural environmental factors are associated with the clinical outcome of *H. pylori* infection. The main bacterial virulence factors in-

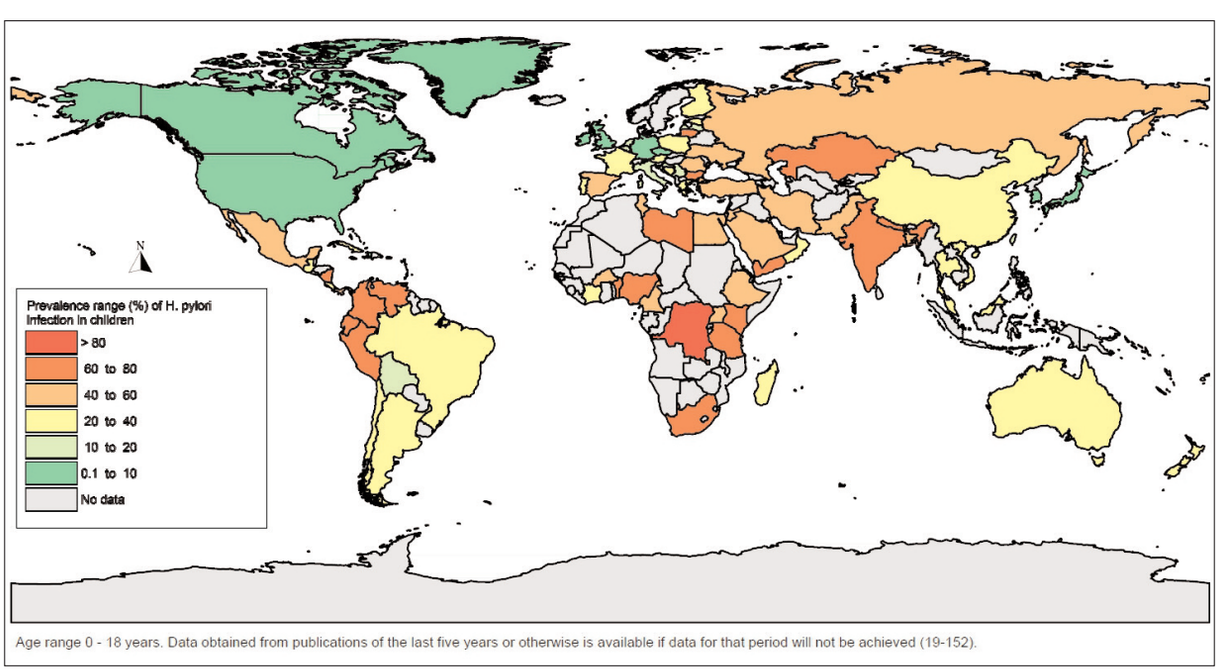

Figure 1. Prevalence of *Helicobacter pylori* infection in children by country.

clude adhesins (BabA, SabA), vacuolating cytotoxin VacA, and the products of the *cag* pathogenicity island (*cag*PAI). There are geographic differences between *cagA*, *vacA* status and *H. pylori* related diseases. In western countries, infection with *vacA* s1 strain is more common in patients with peptic ulcer than in those with chronic gastritis. However, in Asian countries, the association between *vacA* diversity and clinical outcome is not well established[153].

CagA, encoded by the *cagA* gene is the most investigated virulence factor. The *cagA* PAI-encoded type IV secretory system allows the inoculation of *H. pylori* peptidoglycan into the gastric epithelial cells where it encounters the intracellular pattern-recognition molecule Nod1 leading to induction of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) mediated proinflammatory-signaling cascade[154].

cagA-positive isolates are strongly associated with gastric carcinoma, as well as more severe gastritis and peptic ulceration[155]. It is a controvertial issue the relationship between *cagA*-positive status and its association with clinical outcome, and it is not fully understood in Asian countries where the majority of the *H. pylori* strains are *cagA*-positive with low risk of complications probably related to environmental or dietetic factors[156,157]. However, in Malaysia it has been reported that *H. pylori cagA*-negative isolates may induce persistent infection like *cagA*-positive does[158].

Another important virulence factor of *H. pylori* is the vacuolating cytotoxin A gene (*vacA*) which is present in all *H. pylori* strains and it induces vacuolation of epithelial cells[159]. The *vacA* gene includes two variable parts: the signal sequence (s1 and s2) and two types of mid region (m1 and m2). Cytotoxin production and virulence are higher in the s1/m1 subtypes than in the s1/m2 subtypes and lower in the s2/m2 subtypes[160,161]. Recently, another cytotoxic associated virulence factor intermediate polymorphic region (i) of *vacA* has been reported[162]. BabA is an adhesion molecule that mediates the attachment of *H. pylori* to Lewis b blood group antigens on human gastric epithelial cells. Three *bab* alleles have been identified: *babA1*, *babA2*, and *babB* and only the *babA2* gene product is necessary for Lewis b binding activity[163]. Studies[164] in western countries have shown that 70% of *H. pylori* strains associated with increased virulence were typed as *babA2*.

Moreover, the triple-positive phenotype (*babA2, cagA*, and *vacA* s1) was detected at a higher frequency in isolates from patients with ulcers and adenocarcinomas; this detection might be useful as markers of high-risk patients in western countries[164]. The *iceA* gene is induced by contact with epithelium and has two main allelic variants: *iceA1* and *iceA2*. The presence of *iceA1* allele is associated with peptic ulcer disease in western countries[165].

OipA is a proinflammatory response inducing protein associated with high *H. pylori* density and more severe neutrophil infiltration. OipA mediates adherence of *H. pylori* to gastric epithelial cells and it contributes to the pathogenesis of gastroduodenal diseases[166].

The integrity of the gastric mucosa is mainly affected by the interaction of virulence products (VacA y CagA) with the proteins of the intercellular unions altering the stability of the complex E-cadnerin/β-catenin with consequences of structure, functional modification and cellular transformation[167]. Wagih et al evaluated the relation between RUNX3, E-cadherin and β-catenin in chronic gastritis associated with *cagA*-positive *H. pylori* infection and reported that loss of RUNX3 (Runt-related transcription factor 3), E-cadherin and β-catenin were considered early events in the cascade of gastric carcinoma development. RUNX3 but neither E-cadherin nor β-catenin, was related to cagA positive *H. pylori* strains. Loss of RUNX3 was associated with decreased E-cadherin expression and E-cadherin and β-catenin were related to each other[168].

Few reports in children prevalence of *cagA* have been published in the world. One study evaluated the diversity of the *cagA*, *cagE*, *babA2*, and *vacA* genes in *H. pylori* strains isolated in pediatric patients. The relation between these genes and gastric pathologies was found in 93 patients out of whom 32 were positive for infection. A total of 160 *H. pylori* strains were analyzed where 91% and 83% of the strains had the *cagA* and *cagE* genes respectively[169].

The prevalence of *cagA* in children varies in different countries. In Polish children and adolescents with gastrointestinal disease it was reported 60.8%[170]. More recently in another group from Poland it was found 50%[121]. In children and adolescents from southern Brazil, Oliveira et al[171] reported 29.6%, and Braga et al[172] reported 75% in asymptomatic children from a high-risk gastric cancer area in northeastern Brazil. Gambia reported 61%[173] and Iran 46.5%[87]. Another study[88] from Iran reported a high prevalence of 72.7% by PCR from culture isolated. Mendoza et al[105] from Mexico found by CagA positive serology in

73.8% and 91% by genotypic strain analysis[106]. Ozbey et al[143] from eastern Turkey reported 61.2%. O'Ryan et al[174] in Chile reported 60%.

In Venezuela, we found a high prevalence (73%) of *H. pylori* infection in symptomatic children with recurrent abdominal pain associated to *H. pylori* infection from a public hospital in Caracas. Within the *H. pylori* positive patients the genotyping by PCR was 73% for *cagA*, and 85% were *vacA* s1m1[14]. Also in some patients the coexistence of different *H. pylori* strains was found, and which may represent an important consequence in persistence of the infection[12,175,176]. Multiple paths in the network suggest that reticulate events, such as recombination or reinfection have contributed to the observed genotypic diversity[106].

The sequences of pathological changes by *H. pylori* infection in the gastric mucosa are bacterial colonization, progressive inflammation, glandular atrophy and intestinal metaplasia. Atrophy and intestinal metaplasia can be considered as precancerous lesions for gastric cancer[18]. Although its role in the development of gastric cancer is still obscure, the proposed mechanisms are induction of chronic inflammation associated with epigenetic alterations in oncogenes, tumor suppressor genes, cell cycle regulators, and cell adhesion molecules by the bacterium[177].

H. pylori initially targets the innate immune response by signaling through pattern recognition receptors, such as Toll-like receptors, mainly TLR 4, TLR5 and TLR9 at the gastric epithelial cells level[178,179]. In infected adults the neutrophil-activating protein of *H. pylori* polarizes Th1 cells stimulating IL-12 and IL-23 secretion from neutrophils and macrophages and promoting the release of IL-1β, IL-8 e IFN-γ. Th1 cytokines, such as IFN-γ and TNF-α, can increase the release of pro-inflammatory cytokines and augment apoptosis induced by *H. pylori*[180,181]. This mechanism of programmed cell death plays an important role in regulating the number of epithelial cells in the gastrointestinal tract as well as in the control and proliferation of cancer cells, so it is suggested that acceleration of apoptosis plays an important role in *H. pylori* mediated pathogenesis[182,183]. Furthermore, IL-17 expressing Th17 cells are important in the proinflammatory immune response to *H. pylori*. Th17 cells produce IL-17, IL-21, and IL-22 cytokines. *H. pylori* infected macrophages produce IL-6, IL-23, and TGF-β which are required for Th17 cell development and maintenance[184,185]. It has been suggested the role of IL-6 and miRNA in the *H. pylori* infection; Cheng et al reported that the overexpression of IL6 is induced by *H. pylori* (*cagA*+) infection, however, the up-regulated miR-155 and miR-146b decreases the overexpression of IL6 in *cagA* positive *H. pylori* infected human gastric adenocarcinoma cell line[186]. T*regs* are also implicated in the pathogenesis of *H. pylori* infection. TGF-β and IL-18 are responsible for T*reg* development[185]. *H. pylori* specific T*regs* suppress memory T cell responses that prolong the infection[184] and the inflammatory reaction driven by IL-17, thus favoring bacterial persistence[187]. Antimicrobial defense of macrophages is nitric oxide (NO) dependent. *H. pylori's* arginase enzyme can compete with macrophages for the inducible nitric oxide synthase (iNOS) substrate L-arginine so that host NO production is impaired; this leads to enhance bacterial survival. The VacA protein prevents the fusion of phagosomes with lysosomes needed for phagocytosis which is an evasion mechanism of the *H. pylori* to avoid phagocytosis. In addition, the CagA protein translocation inside the gastric epithelial cell induces changes in signaling transduction pathway after phosphorylation EPIYA motifs inducing production of proinflammatory cytokines[188]. A central mediator in the expression of these cytokines/chemokines is the NF-kB, a transcription factor that is the convergent point for multiple pathways activated by *H. pylori*. The overall effects of *cag*PAI translocated products in the sequential activation of the IKK complex, JNK, p38 kinase, NF-kB, and AP-1 in gastric epithelial cells have also been reported[167,189].

The role of B cells in the host response to *H. pylori* has been suggested[185]. Immunoglobulin (Ig) G and IgA antibody release from B cells in response to *H. pylori* may be involved in protective immunity; however, it has been reported that B cell activation and survival may have implications for MALT lymphoma development[184].

Few studies evaluating parameters of the immune response in children (except for antibody determination) have been performed, but recently a great interest in this field has aroused.

The persistence of *H. pylori* colonization is critical for the development of complications and represents the strongest risk factor for gastric adenocarcinoma and MALT lymphoma[184]. Consequently, the clinical manifestations of *H. pylori* infection complications occur predominantly in adults than in children. Gastric inflammation in children colonized by *H. pylori* differs from adults by a reduction in polymorphonuclear and mononuclear cell infiltration decreasing the inci-

dence of gastroduodenal ulceration in comparison to adults[168,190]. In addition, the precancerous mucosal lesions of atrophy and metaplasia are absent or markedly reduced in *H. pylori* infected children[191-195]. For this reason, it is not surprising that gastric adenocarcinoma has not been reported in children and the association between precancerous lesions in the gastric mucosa and gastric cancer in adults is related to the persistence of *H. pylori* infection for decades.

The immune response in children compared to infected adults is characterized by a lower IFN-γ secretion in the stomach and a lower infiltration by IFN-γ secreting cells[196,197]. Freire de Melo et al[36] demonstrated that the gastric concentrations of Th1 cytokines were lower in infected children than in adults; the Th1 associated cytokines increase progressively in the gastric mucosa of infected children achieving similar concentrations reported in adults. This was observed when those infected children were between 14 and 18 years old and when the IL-12p70 was evaluated and after 19 years of age when the IFN-γ was evaluated. Bontems et al[195] demonstrated additional evidences that the gastric mucosal recruitment of neutrophils of CD3+ and of CD8+ cells is lower in infected children in comparison to infected adults. The lower activation status of NF-kB transcription factor in children may be either a direct consequence of the lesser mucosal recruitment of neutrophils of CD3+ and CD8+ cells or more probably of the existence of an overall more subtle inflammatory innate host defense in children.

Regulatory T-cell rather than Th17 cell response to *H. pylori* infection predominates in children[36,169]. This evidence suggests that a weaker immune response could protect the child from more severe gastro duodenal damages due to the infection.

Several authors have reported a reduction of gastric inflammation and Th1 responses with reciprocal increases in the number of regulatory T cells (T*regs*) and the level of T*reg* cytokines (TGF-β and IL-10) in infected children. Gastric TGF-β in infected children localized predominantly in mucosal CD25+Foxp3+ cells indicates T*regs* were the primary source of the TGF-β. Moreover, the authors reported that the reduced gastritis in *H. pylori* infected children was accompanied by reductions in neutrophil infiltration, Th17 cell numbers, and IL-17-specific mRNA and protein levels compared to infected adults[190]. The reduced Th17 responses in children were accompanied by reciprocal increases in the number of T*reg* cells and the level of IL-10 in the gastric mucosa[190] similar to the reciprocal relationship between Th1 and T*reg* responses in children. The increased gastric T*reg* response in infected children exceeded that of uninfected children[169,190,198].

T*regs* play a fundamental role in the maintenance of immunological tolerance[199,200]. The contribution of gastric T*regs* to establishing tolerance to *H. pylori* begins during early childhood infection. Similar to the role of intestinal DCs in initiating the T*reg* response in the intestinal mucosa[201] gastric DCs likely initiate the accumulation of T*regs* in the gastric mucosa through a complex series of cellular events. T*regs* potently down regulate effectors T cells to maintain mucosal homeostasis and limit tissue damage through the secretion of immunosuppressive cytokines[202,203]. At sites of infection and inflammation, the T*reg* cytokines IL-10 and TGF-β suppress effector T cell proliferation and cytokine release limiting the tissue-destructive consequences of the inflammation. The reciprocal relationship between T*reg* responses and Th1 and Th17 responses in the gastric mucosa of *H. pylori* infected children[204,205] is consistent with the ability of gastric T*regs* to suppress *H. pylori* induced T cell proliferation, IFN-γ and IL-17 production, and *H. pylori* specific memory CD4+ T cells[206,207]. Th1 response to *H. pylori* infection varies according to the age and seems to have determinant implications in the *H. pylori* infection outcomes. Therefore, the consequence of a strong gastric T*reg* response during childhood *H. pylori* infection is a dampened effector cell response to the bacteria diminishing the inflammatory damage; thus, resulting in tolerance to the bacteria and persistence of the infection in adulthood[169].

Eventhough the infection is acquired early in life, the associated diseases will develop mainly in adulthood and probably the nature of the immune response and the diverse inflammatory mediators present in the gastric mucosa in childhood can be determinant factors for the final infection's outcome in adulthood. For this reason, it is important to evaluate carefully each case of infection in children in order to prevent the development of severe gastric diseases associated with *H. pylori* infection in adults.

Accordingly, in countries with a high prevalence of *H. pylori* and gastric cancer, non-cardia gastric adenocarcinoma is associated with the acquisition of the bacteria during childhood permit-

ting prolonged infection rather than the acquisition of the infection in adulthood[208].

In contrast to adults, *H. pylori* induced inflammation in children has received little investigative attention; however, the biology of the pediatric response to infection may uncover cellular events that promote tolerance to the bacteria and persistence of the associated inflammation. Table I shows a summary of the gastric inflammatory response to *H. pylori* in children compared with the response of infected adults.

Understanding the immunobiological basis for the reduced inflammatory response in *H. pylori* infected children, particularly in comparison to that of infected adults, is critical for identifying mechanisms by which the host suppresses the neoplastic potential of *H. pylori* infection in children[169].

Why should children be assessed?

H. pylori is mainly acquired during childhood and it may persist throughout life[83]. The proportion of infected children increases with age and by the age of 10 most children in developing countries are infected by *H. pylori*[2].

Since *H. pylori* has pro-carcinogenic activities due to maintenance of a chronic inflammation in the gastric mucosa and by direct action of its virulence factors (*vacA* and *cagA*)[180], *H. pylori* cannot be considered as symbiotic bacteria but rather a part of the pathobiont with ability to induce chronic inflammation and immunologic response[209].

H. pylori has to be diagnosed and eliminated in individuals tending to develop duodenal and stomach ulcers in order to prevent further major diseases development like MALT lymphoma and gastric adenocarcinoma[210]. The criteria to asses and treat patients with *H. pylori* infection are different in children and adults.

Who should be assessed?

The main criteria to assess children with *H. pylori* infection are:

- Gastro intestinal and extra gastrointestinal manifestations related to *H. pylori* infection and parasite co-infection.
- Familial history of gastric cancer, peptic ulcer and lymphoma MALT.
- Symptomatic children living in high prevalence regions and immigrant or adopted children in developed countries.

Children with Gastrointestinal Manifestations

Recurrent abdominal pain in the epigastric region is the main gastrointestinal symptom in children with or without gastro esophageal reflux sensation, nausea and emesis[60,83]. In our experience, recurrent abdominal pain in the upper hemi abdomen is the predominant complaint (73%) in children with *H. pylori* infection[14]. The association of *H. pylori* infection with parasites, *Giardia duodenalis,* is widely known to be high in developing countries. It is not routinely looked for al-

Table I. *H. pylori* infection: differences between children and adults.

	Children	Adults
Bacterial factor		
Colonization, virulence factor and bacterial genotype	Similar	Similar
Immune factors		
T reg cells and responses	Increased but not maintained in adulthood	Decreased
Th1 response	Low	Increased
TH2 response	Increased	Decreased
Th 17 response	Decreased	Increased
Inflammation		
Polymorphonuclear and mononuclear cell infiltration	Low	High
Th17 cell number IL-17 specific mRNA and protein level	Decreased	Increased
Clinical complications		
Gastric and duodenal ulcer	Lower	Higher
Precancerous lesions	Absent	Present
Gastric cancer	Absent	Present
Extra gastrointestinal manifestations	Ferropenic anemic and growth retardation	Chronic idiopathic thrombocytopenic purpura, and diabetes mellitus
Trombocytopenic idiopatic purpura	Absent	Present

though both infectious agents share the same transmission route and its association may be responsible for the symptoms like emesis, diarrhea, and abdominal pain[211].

Data of investigations in Venezuela done by our research team and other data found in some other developing countries, parasitic co-infection has been described especially with *G. duodenalis*[13]. The co-infection was researched in Venezuelan children in duodenal aspirate during the endoscopic procedure in a public hospital[212]. In another study[213], in 253 Venezuelan children with recurrent abdominal pain who underwent upper endoscopy and biopsies 63% had *H. pylori* and 51% co-infection with *G. duodenalis*.

In Turkey, the frequency and relationship of *H. pylori* infection and giardiasis in 98 children and 88 healthy controls with recurrent abdominal pain were assessed by serology and stool antigen. The frequency of co-infection of *H. pylori* and giardiasis in the patient group was 22.4% compared to 6.8% in the control group ($p = 0.002$)[214].

Another recent study from Turkey by Ugras et al[215] reported a lower co-infection rate in 138 children; results show 97% positive for *H. pylori* by histopathology, stool samples revealed 2% for Giardiasis, and 6% for *Blastocystis hominis*. In Ugandian children Ankarklev et al[216] analyzed *H. pylori* antigen and *G. duodenalis* in 427 asymptomatic children; *H. pylori* infection was present in 44.3% and *G. duodenalis* in 20.1%. This study showed the presence of *H. pylori* as a associated risk factor for *G. duodenalis* infection with threefold higher risk of concomitant *G. duodenalis* and *H. pylori* infections compared to no concomitant *G. duodenlis* infection.

H. pylori and intestinal parasites are frequent among individuals living in low socioeconomical countries. This co-existence has a negative effect in the development and in the iron levels in children, being these two effects very important public health issues[215]. Therefore, these parasites should be eliminated in children with *H. pylori* infection. On the other hand, gastroenterologists dealing with adult patients rarely seek for parasites because the main objective is to seek for malignant lesions, but parasites should be also removed especially in patients who live in endemic areas. Knowing the association of infectious agents, *H. pylori* and *G. duodenalis,* is important to select an adequate treatment which will include the eradication of *H. pylori* and antiparasitic infections.

H. pylori Infection and Extra Gastrointestinal Manifestation

The extra gastrointestinal manifestations are not frequent in children and the main reported associations of *H. pylori* with extra gastric disorders in children are iron deficiency anemia (IDA) and growth retardation, but chronic idiopathic thrombocytopenic purpura, asthma, allergic disorders, and diabetes mellitus reported in adults have poor support in pediatrics. Large and well controlled trials are needed among symptomatic and asymptomatic children[217]. The guidelines on *H. pylori* infection in children from ESPGHAN and NASPGHAN in 2011 recommended that children with IDA should be tested for *H. pylori* infection. They also stated that there is lack of evidence to associate *H. pylori* infection with otitis media, upper respiratory tract infections, periodontal diseases, food allergy, short stature, and idiopathic thrombocytopenic purpura[218].

Symptomatic Children with Familial History of Gastric Cancer, Peptic Ulcer and Lymphoma MALT

Symptomatic children with first grade familiar history of gastric cancer, peptic ulcer or lymphoma MALT should be assessed and treated because the intrafamilial transmission is a predisposition to get an infection of *H. pylori* with a high pathogenic strain.

Symptomatic Children Living in High Prevalence Regions and Immigrant or Adopted Children in Developed Countries

It is well known from epidemiological studies, that prevalence of *H. pylori* infection is high in developing countries, so symptomatic children, immigrant children, and adopted children coming from high-risk area should be assessed.

Miller et al[219] analyzed *H. pylori* antibodies from 226 unselected children from eighteen countries who were evaluated in the International Adoption Clinic at New England Medical Center; they reported higher values (31%) compared to the local country prevalence. They concluded that internationally adopted children have a high incidence of exposure to *H. pylori*; furthermore, they found that co-infection with intestinal parasites was more common among children seropositive for anti-*H. pylori* antibodies.

Conclusions

The prevalence of *H. pylori* infection in children is minor to that in adults and it may persist for lifelong inducing mucosal gastric pathologies that might result in cancer in adult life. Early detection of *H. pylori* and its virulence factors with an effective eradication and at the same time associated with prevention programs may lead to a decrease in *H. pylori* incidence and gastritis especially in endemic high-risk regions.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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