Critical Reviews in Oncology / Hematology 134 (2019) 22–30

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Helicobacter pylori: History and facts in Peru

Indira Tirado-Hurtado[a], Cristian Carlos[b], Luciana Lancho[b], Alejandro Alfaro[b], Richard Ponce[c], Luis J. Schwarz[a], Layonel Torres[d], Michael Ayudant[e], Joseph A. Pinto[a,*], Williams Fajardo[b]

[a] Unidad de Investigación Básica y Traslacional, Oncosalud - AUNA, Lima, Peru
[b] Hospital Nacional Dos de Mayo, Lima, Peru
[c] Instituto de Alta Investigación, Universidad de Tarapacá, Arica, Chile
[d] Escuela Profesional de Medicina Humana, Universidad Privada San Juan Bautista, Lima, Peru
[e] Unidad de Investigación, Hospital San José, Callao, Peru

ARTICLE INFO

Keywords:
Helicobacter pylori
Gastric cancer
Public health
Epidemiology
Antibiotic therapy

ABSTRACT

Helicobacter pylori (*H. pylori*) is a cosmopolite bacteria and the main responsible for the high burden of gastric cancer in developing countries, such as Peru. In this review, we describe some historical facts in the *H. Pylori* discovery, the first researches of this bacterium in Peru, as well as its epidemiology, clinical characteristics, diagnosis, treatments, and outcomes. Our literature and review of real-life data suggest that several efforts should be conducted in our country to deal with antibiotic-resistance and lack of adherence to treatment in order to reduce our incidence of gastric cancer.

1. Background

Helicobacter pylori (H. pylori) is a gram-negative, spiral-shaped bacteria that grow in the mucus layer that lines the inside of the human stomach. It has coexisted with humans for thousands of years and currently is one of the most common bacterial infections (Kusters et al., 2006; Mitchell Hazel, 2001). This bacterium causes acute and chronic gastric inflammation resulting in progressive damage of the gastric mucosa; thus, it has been associated with a number of important upper gastrointestinal conditions that include chronic gastritis, peptic ulcer, distal gastric adenocarcinomas, and gastric lymphomas (Kamangar et al., 2011; Sanders and Peura, 2002; Sjomina et al., 2017).

The outcome of a specific disease due to *H. pylori* infection depends on several factors such as bacterial genotype, host physiology and dietary habits (Go and Graham, 1994; Labigne and de Reuse, 1996). *H. pylori* infection can be detected by various tests (Wang et al., 2015) and, in many cases, it can be treated successfully with antibiotics (Chey et al., 2017). However, the increase in pharmacologic resistance is starting to affect treatment efficacy and disease eradication (Boehnke et al., 2017a; Kusters et al., 2006).

Gastric cancer is an important public health problem, mainly in developing countries. Infection by *H. pylori* is the most important risk factor for gastric cancer development, responsible for almost 90% of these cases worldwide and approximately 5% of the total of all cancers (Plummer et al., 2015).

Therefore, a better understanding of epidemiology and pathogenesis of *H. pylori* is mandatory to improve diagnostic, prevention and therapeutic strategies. This review focuses on *H. pylori* infection in Peru, emphasizing clinical and molecular characteristics.

2. Discovery of *H. pylori* and its history in Peru

By the late 19th and early 20th centuries, the use of the microscope described the role of bacteria, yeast, and fungi in diseases pathogenesis. Nevertheless, at that time it was still unclear whether a specific organism or the abnormal accumulation of organisms in the stomach was the cause of gastric diseases (Kidd and Modlin, 1998). Several researchers reported the presence of a spiral bacteria in the stomachs of humans, some in coexistence with peptic ulcer or gastric cancer (Palmer, 1954).

Robin Warren, a pathologist at the Royal Perth Hospital (Australia), had observed for many years that spiral-shaped gastric bacteria were a common finding in fresh samples obtained by endoscopy of patients with gastritis. However, even though he was convinced that these bacteria was strongly associated with gastric diseases, he had not discussed it extensively with the scientific community at that time, because of the prevailed dogma that acidity was the cause of peptic ulcer disease (Kidd and Modlin, 1998; Pajares and Gisbert, 2006). Warren worked alone until 1982, when Barry Marshall, a medical resident who was looking for a research project, convinced Warren to investigate

* Corresponding author at: Unidad de Investigación Básica y Traslacional, Oncosalud – AUNA, Av. Guardia Civil 571, San Borja, Lima - 41, Peru.
E-mail address: jpinto@gecoperu.org (J.A. Pinto).

https://doi.org/10.1016/j.critrevonc.2018.12.005
Received 20 September 2018; Accepted 17 December 2018
1040-8428/

with him (Moss, 2013). In 1983, together they succeeded in isolating and cultivating these bacteria, which they called *Campylobacter pyloridis*. Years later they were called *Campylobacter pylori*, and since 1989, *Helicobacter pylori* (Marshall and Warren, 1984; Warren and Marshall, 1983). Late, autoingestion experiments showed that these bacteria can colonize the human stomach, thus inducing inflammation of the gastric mucosa (Marshall et al., 1985; Morris et al., 1991; Morris and Nicholson, 1987).

In 1994, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) classified *H. pylori* as a Group 1 carcinogen ("Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994," 1994Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June, 1994"Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994," 1994), despite some contradictory results at that time. A few years later, Tomb et al. (Tomb et al., 1997) completed the sequencing of the *H. pylori* genome, which consist of 1 667 867 base pairs (bp). Although Warren and Marshall did not investigate directly the role of *H. pylori* in gastric cancer, they were aware of the relationship between these entities (Warren and Marshall, 1983). For the discovery of *H. pylori* and its role in gastric diseases, they received the Nobel Prize in Physiology or Medicine in 2005 (Julie Parsonnet, 2005).

Since then, the colonization of *H. pylori* in the stomach has been increasingly accepted as an important cause of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and also associated with other extra-digestive diseases, such as iron-deficiency anemia, idiopathic thrombocytopenic purpura, cardiovascular diseases, hepatobiliary diseases, and diabetes mellitus, among others (J. Parsonnet et al., 1994; Roesler et al., 2014).

In Peru, the first suspicions of the existence of the *H. pylori* began in 1983 from the creation of a new method to measure gastric secretion without intubation, by which it was found that the majority of dyspeptic patients had hypochlorhydria or low normal levels of acidity. This led to the suspicion of a high prevalence of chronic atrophic gastritis in Peruvian dyspeptic patients as a cause of the hypochlorhydria tendency (León et al., 1991). Coincidentally, shortly after Gilman, Spira and Black, professors of the Department of International Health of the University of Johns Hopkins (Baltimore, U.S.A.) brought to Peru the news of a newly discovered bacteria, the *H. pylori* (León-Barúa, 1985). Encouraged by these findings, Raúl León-Barúa promoted the formation of a multidisciplinary group to investigate the role of this bacterium in gastroduodenal diseases. The group was called "Gastrointestinal Physiology Working Group of Cayetano Heredia and the Johns Hopkins Universities" (León et al., 1991). This group identified the *H. pylori* by invasive and non-invasive methods, being the latter cataloged as one of the most simple and precise methods (correct diagnosis in about 85% of cases) (Gilman et al., 1986). They proposed that the most appropriate name for the bacteria should be *Campylobacter gasteri*, but this proposal was not taken into account (León-Barúa et al., 1987a; León-Barúa et al., 1987b).

In the following years, this research group reported many results of their study. They informed that the relationship between *H. pylori* and certain gastroduodenal pathologies (active chronic gastritis, gastric cancer, active duodenitis, and duodenal peptic ulcer) in Peru was similar to other countries (León et al., 1991; Ramírez-Ramos, 1988). With respect to the forms of treatment against *H. pylori* infection, the group argued that one of the most effective medications was bismuth in its various compounds (especially subnitrate and subsalicylate); as well as, the nitrofurans (especially the furazolidone) (Gilman et al., 1987; Morgan et al., 1988). In addition, they also tried combined treatments such as bismuth with one or more antimicrobials (León-Barúa et al., 1991, 1990). Until that moment they could not find a totally efficient form of treatment since in most cases they only achieved the temporary elimination of the infection. All these results have been changing over time.

3. Epidemiology of *H. pylori*

H. pylori infection is ubiquitous and affects approximately half of the humans worldwide, both men and women equally; however, it shows significant differences in the prevalence of infection both within and between countries (Mitchell Hazel, 2001; Percival and Williams, 2014). In general, the prevalence of *H. pylori* infection in developing countries is higher than in developed countries (Bardhan, 1997;Graham et al., 1991; Guillermo I. Perez-Perez et al., 2004). Several studies have shown low socioeconomic level to be associated with an increased prevalence of *H. pylori* infection, in particular in relation to living conditions during childhood (Malaty and Graham, 1994; Malaty Hoda et al., 2002). Socioeconomic level includes factors such as level of hygiene, environmental sanitation, the density of living, and educational opportunities (Mitchell Hazel, 2001); and its importance in childhood has been demonstrated even in studies in monozygotic twins reared separately, showing that twins with *H. pylori* infection were reared in homes under poorer socioeconomic conditions than those of their unaffected cotwins (Malaty et al., 1998).

It is generally argued that *H. pylori* infection is acquired mainly in childhood, and it has been shown that around 10 years old, more than 50% of children around the world carry this bacteria (Pounder and Ng, 1995). Epidemiological data support that the prevalence of this infection in children less than 10 years old is higher in developing countries than in developed countries (approximately 13–60% compared to 0–5%). However, above this age, there is a slow increase in prevalence in both groups (0.5–2% per year) (al-Moagel et al., 1990;Graham et al., 1991;Mitchell et al., 1992;Perez-Perez et al., 1990). The change in the prevalence of *H. pylori* infection among the group of young and older subjects reflects that the population becomes part of a different cohort, in which there are gradual improvements such as medical care, sanitation, and/or living conditions (Banatvala et al., 1993; Cullen et al., 1993; Replogle et al., 1996; Sipponen, 1995).

In 2017, through a systematic review and a meta-analysis, Hooi et al. (Hooi et al., 2017) reported the prevalence of *H. pylori* infection of different countries over different time periods. Regions with the highest prevalence were Africa (70.1%), South America (69.4%), and Western Asia (66.6%); in contrast, regions with the lowest prevalence were Oceania (24.4%), Western Europe (34.3%), and Northern America (37.1%). In addition, by analyzing the prevalence of *H. pylori* infection through two periods of time (1970–1999 and 2000–2016), it was obtained that the prevalence after 2000 was lower than before in Europe (48.8% before 2000 vs. 39.8% after 2000), Northern America (42.7% before 2000 vs. 26.6% after 2000), and Oceania (26.6% before 2000 vs. to 18.7% after 2000). In contrast, the prevalence was similar in Asia (53.6% before 2000 vs 54.3% after 2000), and Latin America and the Caribbean (62.8% before 2000 vs 60.2% after 2000). The prevalence has been decreasing mainly due to the improvement in the standard of living, as well as, the better methods of eradication that have been implemented (especially in developed countries) (Graham, 2014; Hooi et al., 2017; Nagy et al., 2016). After extrapolation to the 2015 world population, Hooi et al. reported that approximately 4.4 billion individuals worldwide would be positive for *H. pylori* (Hooi et al., 2017).

In Peru, there is not yet a complete study of the prevalence of *H. pylori*, but several reports have been made in the last three decades, mainly from the Gastrointestinal Physiology Working Group. In the late 1980s, one of the studies of this research group reported that the frequency of *H. pylori* infection was similar in dyspeptic patients from different places of the country and with different socioeconomic levels (A Ramírez-Ramos et al., 1987a, 1987a, 1987b). However, in 1990, they reported that women with high socioeconomic status showed lower frequencies of infection; and also a seroepidemiologic survey of children demonstrated that infection begins in the first years of life,

predominantly in families from lower socioeconomic levels (The Gastrointestinal Physiology Working Group, 1990).

A few years later, the same research group reported higher infection rates of *H. pylori* in dyspeptic patients from different geographic regions of the country (the coast, the Highlights of the Andes Mountains, and the Amazon jungle), where men had rates approximately 10% higher than for women in the same zone. In addition, higher rates were found in people from high altitude areas compared to those people living at sea level (The Gastrointestinal Physiology Working Group of the Cayetano Heredia and the Johns Hopkins University, 1992).

On the other hand, since it is known that *H. pylori* infection is very frequent in Japan (Asaka et al., 1992), the same research group also decided to investigate a possible racial predisposition to contract the infection. However, no differences were found between the prevalence of the Peruvian population and the Japanese colony resident in our country, both belonging to the same socioeconomic level. A similar study conducted in 2002, but with a larger number of participants, confirmed that there was still no evidence that a certain race is more susceptible to acquire this infection (Alberto Ramírez-Ramos et al., 2002).

Through a study conducted in the period 1985–2002, Ramirez et al. observed a decrease in the prevalence of *H. pylori* in a Peruvian population, residents in Lima, from medium and high socioeconomic levels with chronic active gastritis (from 83.3% to 58.7%; $p < 0.001$), duodenal ulcer (from 89.5% to 71.9%; $p = 0.004$) and gastric ulcer (from 84.8% to 77.3%; $p = 0.36$). This finding was particularly important since until that moment this phenomenon had been described only in developed countries. This result generated some hypotheses such as, for example, that during this period of time there was an improvement in water potability (generally accessible only to people with medium and high socioeconomic status), which in turn could have cause a decrease in reinfection rates. Likewise, this could also be due to an increased consumption of antibiotics in this population (Alberto Ramírez-Ramos et al., 2003). In 2017, Pareja-Cruz et al. (Pareja Cruz et al., 2017) calculated a similar prevalence (63.6%) in adult populations of Lima through a rapid test called H. pylori Ab Combo Rapid Test CE from CTK Biotech, without finding differences between gender and age.

4. Transmission and sources of *H. pylori*

Since the niche of *H. pylori* is the human stomach, it is suggested that ingestion would be the most likely route to acquire the bacteria and through a common environmental source (Mitchell Hazel, 2001). It is believed that new infections occur as a direct result of human to human, through an oral-oral, gastro-oral, fecal-oral route, or combination of any of them. This bacteria has been detected in saliva, vomit, gastric reflux and feces, but there is no conclusive evidence of predominance of transmission through any of these products (Allaker et al., 2002; Ferguson et al., 1999, 1993; Kabir, 2004; Leung et al., 1999; J. Parsonnet et al., 1999).

In particular, animals and water have been considered as potential sources of *H. pylori* infection (Mitchell Hazel, 2001). However, it should be noted that this bacteria has been isolated on rare occasions from domestic and commercial animals (Brown et al., 2001; Dore et al., 2001). It has been found in domestic cats and non-human primates; nevertheless, contact between humans and these animals is rare, so it is unlikely that they have an important role in the transmission of this bacteria (Handt et al., 1994, 1997). The domestic housefly was also considered a potential reservoir and vector for the transmission of *H. pylori*; but it could not be isolated from houseflies (Osato et al., 1998).

Water is considered an important source of transmission of several diseases, both acute and chronic, being one of the latter caused by *H. pylori* infection (Bartram and Cairncross, 2010; World Health Organization, 2013). However, water is not a suitable medium for the growth of *H. pylori*, since it does not have enough nutrients and may contain chemical disinfectants that inhibit the growth of bacteria. The presence of *H. pylori* in water is mainly due to fecal contamination, but it should be noted that it has also been detected worldwide in surface water, well water, drinking water and seawater through the application of molecular techniques (Araujo Boira, 2015).

On the other hand, several studies have also shown that this bacterium can survive in water through its ability to form biofilms, structures that would provide a stable environment under stress conditions; as well as, a concentration mechanism for the subsequent detachment of a group of infectious cells. The biofilms can be adhered to some surface or swimming freely in the liquid medium (planktonic phase), in the latter the bacteria are in a reversible state of "viable, but not cultivable", main reason for its low detection rate by standard methods of culture (Gião et al., 2008; Percival and Thomas, 2009).

Many communities, especially from developing countries, have lack access to reliable sources of drinking water or sanitation services, so they have to consume water from nearby sources such as rivers and streams on a daily basis, or depend on municipal water wells ("WHO | Water for life," 2005). That is why many individuals from these communities are more likely to suffer various gastrointestinal problems, some of which may be related to *H. pylori* (Aziz et al., 2015; Engstrand, 2001; Fogarty et al., 1995).

5. Water as the main source of transmission of *H. pylori* in Peru

Epidemiological studies have shown an association between the prevalence of *H. pylori* infection and water-related sources (Aziz et al., 2015). In Peru, probably the most important route of infection is fecal-oral through contaminated water (Klein et al., 1991; Mai et al., 1989). Klein et al. (Klein et al., 1991) published one of the first reports in the world that suggested water as a source of *H. pylori* infection. They used the urea breath test to examine the *H. pylori* infection in 407 Peruvian children (the probable stage in which individuals become infected) from Lima, obtaining a prevalence of 48%. This result was related to their socioeconomic level, prevalence was higher among children from low-income families (56%) than among those from high-income families (32%); and related to their water supply, children whose homes had external water sources are three times more likely to be infected than children whose homes had internal water sources.

Some years later, Hulten et al. (Hulten et al., 1996) detected *H. pylori* DNA in 46% (11/24) of drinking water samples collected from these same communities, even though most of the samples analyzed came from water provided by the municipality of Lima. These findings were consistent with the report of Ramirez et al. (Ramírez et al., 2004), where they found *H. pylori* in the water from the Atarjea treatment plant, which supplies drinking water to the entire city of Lima since 1956 and whose main source is the Rimac River (Hitos históricos - sedapal.com.pe, 2018), so the population that uses water from this plant would have a higher risk of becoming infected with *H. pylori*.

In 2015, the Instituto Nacional de Estadística e Informática (INEI) presented the document "Perú: Evolución de los Indicadores de los Objetivos de Desarrollo del Milenio al 2015", in which it was shown that Peru continues making great efforts to increase the coverage of drinking water and sanitation services. In urban areas, coverage of drinking water services increased from 85.3% in 2002 to 92.2% in 2015; however, the coverage was still limited in rural areas, from 39.9% in 2002 to 64.9% in 2015. According to the socioeconomic condition, substantial differences were observed, reflecting the high level of inequality of income. In addition, in terms of drinking water, there is a need to improve coverage, the quality of the water delivered and its effective disinfection, as well as reduce the problems of interruption of supply and levels of loss (INEI. Instituto Nacional de Estadística e Informática, 2017).

On the other hand, the proportion of the population with access to improved sanitation services has risen in the country, both in urban and rural areas. In 2002, 60.0% of the country's population, 79.8% in urban areas and 15.5% in rural areas accessed this service; and by 2015,

access reached 78.3% of the country's population, 88.4% of the urban area, and 45.4% of the rural area. According to the socioeconomic level, there is low coverage in the poorest stratum in the treatment of urban wastewater, which is the main cause of serious pollution problems. Although it is true that the socioeconomic level could condition the lack of basic sanitation and therefore favor possible contamination of drinking water; at present we are aware that there is also the possibility that the water that reaches households may already be contaminated, causing a *H. pylori* infection, mainly in children (INEI. Instituto Nacional de Estadística e Informática, 2017).

In recent years, several studies have been carried out in the Lima population, providing evidence of the presence of *H. pylori* DNA in the drinking water. One of them was published by Valdivieso et al. (Valdivieso et al., 2016), in which they detected *H. pylori* in 59% (109/185) of the biopsies analyzed by histology, belonging to individuals living in high (69.5%) and low (35%) risk districts of Lima. Likewise, they evaluated these positive samples again through quantitative polymerase chain reaction (qPCR), obtaining that 97% (106/109) of gastric biopsies, 48.2% (42/87) of their sources of drinking water, and 36% (18/50) of water biofilm samples were positive.

In 2017, a thesis work evaluated the prevalence of *H. pylori* in drinking water consumed by patients diagnosed with gastric cancer and *H. pylori* infection. All the patients lived in Lima and were treated at the Instituto Nacional de Enfermedades Neoplásicas (INEN) during the period 2015 - 2016. Of the 84 water samples evaluated, he reported a prevalence of *H. pylori* of 11.90% (10/84), with at least one positive result in one of the two colonization factors evaluated (ureA and hspA), 6 of them being located in areas designated as human settlements (Bernabé-Monsalve, 2017). A related study at the INEN, obtained a similar result. The water samples analyzed for *H. pylori* colonization factors in the patient's homes were positive in 13.46% (7/56), despite the fact that the most of the sources of supply were drinking water (76.9%) and consumption of boiled water (74.8%) (Custodio-Zegarra, 2017).

A recent study collected drinking water for one year from a single faucet of a district of Lima, and through qPCR analysis, they obtained that 20.3% (49/241) of these samples was contaminated with *H. pylori*. This work demonstrated that there is a continuous contamination of the water supply in this district, suggesting that this could also be happening in other districts of Lima (Boehnke et al., 2018).

6. Epidemiology of gastric cancer

According to GLOBOCAN 2018, gastric cancer is the fifth most common cancer worldwide (1,133,701 new cases per 100,000 inhabitants); with the highest incidences in Eastern Asia, Central and Eastern Europe, and Latin America and the Caribbean, occurring mainly in developed countries. The age-standardized rate (ASR) is high in men than in women, ranging from 4.7 Eastern Africa to 32.1 in Eastern Asia for 100,000 men and from 2.6 in Southern Africa to 13.2 in Eastern Asia for 100,000 women. Likewise, it is the fifth most lethal cancer in both sexes worldwide (782,685 deaths each year). The highest mortality rates are in Eastern Asia (23.0 per 100,000 in men and 9.4 per 100,000 in women) and the lowest in North America (2.4 and 1.3, respectively) (Bray et al., 2018).

In Latin America and the Caribbean, both the incidence and mortality of gastric cancer are very varied between countries, and even between men and women. In men, the highest incidence has been reported in Chile (26.9) and the lowest in Guyana (3.7); while the highest mortality has been reported in Chile (17.9) and the lowest in Puerto Rico (3.8). In women, the highest incidence has been reported in Guatemala (14.2) and the lowest in El Salvador (2.0); while the highest mortality has been reported in Guatemala (17.1) and the lowest in Barbados (1.8) (Bray et al., 2018). Furthermore, a work performed by Recavarren-Arce et al. reported that some of the highest mortality rates are in the Andes from Venezuela to Chile and in Sierra Madre from southern Mexico to Costa Rica, supporting that these gastric cancer rates would be related to altitude and other factors related to this, such as geographical barriers, host genetics, bacteria, diet, smoking, and environmental factors. For example in Peru, people with gastric cancer have more severe gastric lesions in La Oroya (a city located at 3700 m above sea level) than patients from Lima (a city located at sea level) (Recavarren-Arce et al., 2005).

Between 1970 and 2007, the incidence and mortality of gastric cancer decreased in nearly all populations, mainly in European and Asian countries, among which Japan is one of the countries that shows the greatest reduction in both cases. In contrast, in the same period of time, both the incidence and mortality in Oceania and America also decreased but remained relatively stable, except for Costa Rica and Colombia (Bray et al., 2018; Plummer et al., 2015). The decrease in both the incidence and mortality of gastric cancer may be due to the decrease in the prevalence of *H. pylori* infection, as well as, to improvements in sanitation and preservation of foods and changes in habits such as the decrease of tobacco smoking (Di Sibio et al., 2016). However, Latin America and the Caribbean still report some of the highest rates in the world. It has been estimated that by 2040, Latin America will increase its burden by approximately 90% (128,656 new cases and 102,463 deaths) (Bray et al., 2018).

In Peru, the ASR incidence of gastric cancer is 16.1 per 100,000 inhabitants. It is the second most common cancer in men (19.3) and the third one in women (13.4) (Bray et al., 2018); likewise, the mortality rate is high in both men (14.5) and women (11.3). Callao, Huanuco, Ayacucho, Huancavelica and Apurímac are the five departments with the most registered cases of gastric cancer, being four of them (Huanuco, Ayacucho, Huancavelica and Apurímac) regions with high poverty rates (33.3–36.8%) (INEI. Instituto Nacional de Estadística e Informática, 2018; Ramos-Muños and Venegas-Ojeda, 2013). The highest mortality rates (greater than 20.3) have been reported in Huanuco, Huancavelica and Pasco, departments with high levels of poverty and living in the highlands, with rates up to six to seven times higher than other departments (Piñeros et al., 2017; Ramos-Muños and Venegas-Ojeda, 2013). These results are consistent with the fact that the incidence and mortality of gastric cancer are greater among low socio-economic groups and populations who reside at high altitudes (Recavarren-Arce et al., 2005; Torres et al., 2013).

Data from the Registry of Cancer of Metropolitan Lima (Instituto Nacional de Enfermedades Neoplásicas, 2016) shows a decrease in the gastric cancer incidence from 34.35 per 100,000 males in the period 1968–1970 to 21.22 in the period 2010–2012. In the same way, incidence in women has decreased from 19.28 to 13.79 in the same periods. Interestingly, is seen a lower incidence in gastric cancer in districts whose population had higher incomes and better sanitary infrastructure (San Isidro, Miraflores, La Molina) in contrast to districts with lower incomes (San Juan de Lurigancho, El Agustino, Villa El Salvador). On the other hand, ASR incidence of gastric cancer in the affiliates population of Oncosalud-AUNA (a private pre-payment system with approximately one million affiliates), mainly from the A and B socioeconomic sectors, is dramatically lower than the incidence reported to Metropolitan Lima or Peru (Fig. 1).

7. *H. pylori* infection as a major risk factor for gastric cancer

The variation in the incidence and mortality rates of gastric cancer are the result of differences in the distribution of factors associated with the disease across the world. The main risk factors that make a person more likely to develop gastric cancer are low socioeconomic status, habits such as smoking or drinking alcohol, dietary factors (consumption of total fruits, total vegetables, green vegetables, chili pepper, total meat, processed or salted meat, red meat, fish, and others), human genetic variations (*IL1B-31C, IL1B-511 T, IL1RN*2, TNFA-308 A, TP53* codon 72 Arg and *GSTM1* null), *H. pylori* infection, Epstein-Barr virus infection, and personal characteristics (body mass index, ethnicity,

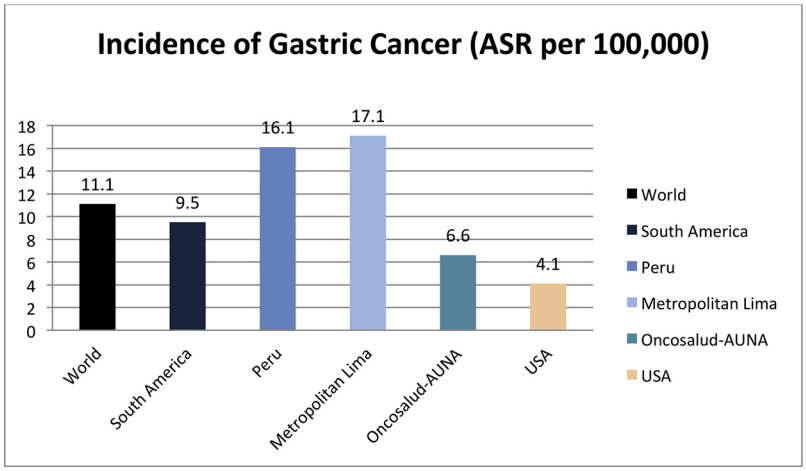

Fig. 1. Comparison of gastric cancer incidence in different scenarios: Worldwide (GLOBOCAN 2018), South America (GLOBOCAN 2018), Peru (GLOBOCAN 2018), Metropolitan-Lima (Registry of Cancer of Metropolitan Lima), USA (GLOBOCAN 2018) and in a Peruvian Private Institute (Oncosalud-AUNA). The gastric cancer incidence in Oncosalud-AUNA cohort was estimated with 1,478,858.9 individuals - years of follow-up.

place of birth, family history of gastric cancer) (Bonequi et al., 2013).

Currently, *H. pylori* is considered the most important risk factor for the development of gastric cancer. Despite the colonization of *H. pylori* is not a disease by itself, it is a condition that increases the risk of developing important upper gastrointestinal conditions (Parsonnet et al., 1994; Roesler et al., 2014) since induces an acute and chronic inflammatory reaction in gastric mucosa. In most people, this bacterium does not cause any symptoms; however, a prolonged inflammatory reaction contributes to the malignant transformation of the epithelium (Kamangar et al., 2011; Sanders and Peura, 2002).

Several studies have shown that approximately 90% of cases of gastric cancer are attributed to *H. pylori*; however, it is important to note that gastric carcinogenesis cannot be explained only by *H. pylori* infection, since only a small percentage (2–5%) of individuals infected with this bacterium develop this malignancy (Pinto-Santini and Salama, 2005). For example, in Latin America and the Caribbean, where there is a high prevalence of *H. pylori* infection (greater than 65%) (Parkin, 2006), it has been reported a high incidence of gastric cancer (8.7 new cases per 100,000 inhabitants). In contrast, in Africa, where a high prevalence of this bacterium is also reported (greater than 70%), there are few cases of gastric cancer (less than 4.5) (Hooi et al., 2017).

The intensity of damage that *H. pylori* could cause will depend on the host, the environment, and the strain of the bacteria (Kabir, 2009). In regard to the host, its genotype plays an important role in the clinical outcome, as well as, the anatomical distribution where the bacteria colonize. Some studies have reported that individuals carrying polymorphisms in the inflammation-related cytokine genes *IL-1B*, *IL-1RN*, *IL-16* and *TNF-α*, as well as, in *TLR4* gene, generate more inflammation in response to *H. pylori* infection, which increase the risk of developing gastric cancer (El-Omar et al., 2001; Kamangar et al., 2006; Machado et al., 2003; Qin et al., 2014). Furthermore, *H. pylori* infection is more associated with non-cardia (approximately 90% of cases) than cardia gastric cancer (Plummer et al., 2016).

Concerning to environmental factors, several studies have shown that tobacco smoking and diet plays an important role; the high intake of salted, pickled, or smoked foods, dried fish and meat, alcohol and refined carbohydrates significantly increases the risk of developing gastric cancer because they can generate carcinogens. In contrast, fiber, fruits, and fresh vegetables have a protective effect against gastric cancer thanks to their high concentrations of antioxidant substances (Shu et al., 2013).

H. pylori has a high genetic diversity, which is attributed to its high rate of mutation and intraspecies genetic recombination. Its strains from unrelated individuals are not only different in the sequences of individual genes but also differ in gene content and chromosomal organization (Cover, 2016). Many studies have shown that there are geographical differences between strains of *H. pylori,* mainly due to human migrations over time from Africa to different parts of the world. These differences could be a potential factor that helps explain the variation in the incidence of *H. pylori*-associated diseases in various parts of the world (Falush et al., 2003; Linz et al., 2007).

The main difference between strains is whether or not they are carriers of the cytotoxin-associated gene pathogenicity island (*cag* PAI), a region of 40 kb that encodes the cagA oncoprotein and components of the type IV secretion system. This system delivers cagA to the cytosol of the gastric epithelial cells, it is subsequently phosphorylated by host cell kinases and interacts with multiple targets, profoundly altering host cellular functions (Cover, 2016; Olbermann et al., 2010). Due to the effect cagA causes, this has been extensively studied, demonstrating that individuals carrying *cag* PAI have an increased risk of developing severe gastrointestinal diseases such as gastric cancer (Blaser et al., 1995; Plummer et al., 2007; Yong et al., 2015). Another widely studied virulence factor is vacA, which is present in all strains of *H. pylori* but has a different effect on their hosts depending on their structure. Strains type s1/i1/m1 of vacA are associated with a higher risk of gastric cancer or premalignant lesions; and this is possibly due to its high capacity to injure gastric epithelial cells, alter parietal cell function and gastric acidification, and interfere with immune cell function (Cover, 2016; Roesler et al., 2014). In summary, several studies have reported that the risk of gastric cancer increases in people infected with *cag* PAI-positive strains containing s1/i1/m1 of *vacA, babA, homB,* type I *hopQ,* and in frame *oipA* alleles (Cover, 2016).

In East Asia, where the highest incidences of gastric cancer are reported, almost all strains of *H. pylori* are *cag* PAI-positive, type s1 *vacA*, and carriers of the other specific markers already mentioned, which could be one of the factors that contribute to the high rate of gastric cancer in that region. In contrast, in the USA and Western Europe (4.1 and 5.8 new cases per 100,000 inhabitants, respectively) are commonly found *cag* PAI-negative strains containing alleles type s2 *vacA* and lacking *babA* (Bray et al., 2018; Cover, 2016). On the other hand, in Peru, where gastric cancer is the most common cancer and cause of cancer death in both sexes (Bray et al., 2018), more than 90% of the *H. pylori* strains in Lima are carriers of the *cagA* gene (Soto et al., 2003).

Some studies carried out in 2017 at the INEN show the high prevalence of *H. pylori* in patients with gastric cancer. One of these studies reported that 54.76% (46/84) of this population had *H. pylori* according to pathological study; while with molecular evaluation it was found that 94% (79/84) were positive for this bacterium (Bernabé-Monsalve, 2017). A related study reported that 84.7% (122/144) of patients with gastric cancer were positive for the presence of *H. pylori*. In addition, these cases presented at least one of the virulence factors: 79.9% positive for both cagA and vacAs, and 77.8% for vacAm; as well as they presented the colonization factors: 65.3% positive for ureA, 83.3% for hspA, and 84.7% for both of these factors (Custodio-Zegarra, 2017).

8. Diagnosis of *H. pylori* infection

Since the discovery of *H. pylori* in 1983, several diagnostic tests for the detection of this bacterium have been developed; each of them with some advantages and disadvantages. These tests are generally classified as invasive and non-invasive, and usually, the combination of more than one of them gives an accurate and satisfactory diagnosis (Ricci et al., 2007).

Invasive tests are very useful because the bacterium is detected directly and, therefore, they are highly sensitive and specific (greater than 90%). They are performed through endoscopy biopsy followed by any of these options: 1) histology by staining with Giemsa, Warthin-Starry, Waysson, and others; considered as "gold standard" in routine hospital diagnostics; 2) culture, which is the most specific method (100%) although not very sensitive; moreover it has the advantage of being able to perform antibiotic sensitivity tests; 3) rapid urease test, which is very fast but sometimes requires an additional test for confirmation because it gives false positives; and 4) molecular tests including in-situ hybridization and the polymerase chain reaction (PCR), which detect *H. pylori* when is undetectable by other methods due to low bacterial density, and also they allow the simultaneous detection of specific mutations that lead to resistance to antibiotics and virulence factors; however, it is recommended to use it for research purposes because they are expensive and technically demanding, and also highly sensitive (generate false positives due to detection of non-pylori Helicobacters) (Patel et al., 2014; Ricci et al., 2007).

Despite the several advantages offered by invasive tests, they are expensive and generally applicable only to tertiary level laboratories. Because of this, non-invasive tests emerged, which also have a high sensitivity and specificity (some greater than 90%). They include 1) serological tests (ELISA, latex agglutination and western blot) that detect IgG antibodies in serum, urine and saliva; and can be performed by most hospital or clinic laboratories; however, they are not useful as markers of infection activity, so they are mainly used for epidemiological studies; 2) the urea breath test, where patients ingest urea labeled with ^{13}C or ^{14}C, is very useful, fast and reliable to evaluate the eradication of the bacteria; but it has limited use because of its high cost; and 3) stool antigen tests, enzyme immunoassay (EIA) and immunochromatography (ICA), which are less expensive than the urea breath test, and they are used for the initial diagnosis of the bacteria and for the assessment of eradication therapy, especially in children and post gastric surgery patients (Patel et al., 2014; Ricci et al., 2007).

In Peru, one of the first invasive tests used was performed by Gilman et al. in 1986, by rubbing the gastric mucosa with a brush for cytology and staining it with Gram reagent. Also, they cultured the bacteria in Butzler or Skirrow media. This method was cataloged in that time as one of the most simple and precise, with an approximate specificity of 85% (Gilman et al., 1986; A Ramírez-Ramos, 1988). Currently, all the tests mentioned above are available in this country, used both for diagnosis and for research; however, it is important to note that since in Peru we have a high incidence of gastric cancer, it is recommended that chronic dyspeptic patients undergo an endoscopy as the first diagnostic test (Ramirez-Ramos et al., 2003).

9. Treatment of *H. pylori* infection

There are many schemes for treating *H. pylori* infection; however, an optimal treatment has not been defined, and usually, a combination of several antibiotics along with a proton pump inhibitor (PPI) is used to eradicate the infection. Before choosing a treatment regimen for *H. pylori*, patients should always be asked if they have previously received antibiotic treatment; and this information must be incorporated into the decision-making process (Chey et al., 2017).

For the first line therapies, clarithromycin triple therapy includes PPI plus two antibiotics, clarithromycin and amoxicillin for 14 days, or metronidazole as an alternative to amoxicillin in patients with allergy to penicillin; however, the last one is not a Food and Drug Administration (FDA)-approved treatment regimen. This therapy should be recommended to patients with no previous history of macrolide exposure and if the rate of resistance to local clarithromycin is low (less than 15%) because it can generate greater resistance (Chey et al., 2017). Potent acid suppression with PPI or VON (vonoprazan, a new suppressor of acid secretion that works by competitive inhibition of potassium channels) can help overcome, although only partially, the antimicrobial resistance of the bacterium (Murakami et al., 2016).

Bismuth quadruple therapy should be strongly considered as the initial treatment choice if a patient has previously been treated with macrolides for any reason or in regions where the rate of clarithromycin resistance is high. This therapy consists in a PPI or histamine-2 receptor antagonist plus bismuth and the antibiotics tetracycline and metronidazole for 10–14 days (Chey et al., 2017). A meta-analysis study suggests that clarithromycin triple and bismuth quadruple therapies had similar efficacy, compliance, and tolerability (Luther et al., 2010). The compounds prescribed separately are not an FDA- approved treatment regimen; but pylera, a combination of all these compounds administrated for 10 days, is an FDA-approved treatment regimen. Quadruple therapy without bismuth includes a PPI and three antibiotics, amoxicillin, clarithromycin, and nitroimidazole (metronidazole or tinidazole), either in concomitant therapy (the four compounds administered together for 3–10 days) or in sequential therapy (PPI plus amoxicillin for 5–7 days, followed by a PPI plus clarithromycin and a nitroimidazole for an additional 5–7 days) (Chey et al., 2017).

Other suggested first-line therapies options are hybrid therapy (PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days), levofloxacin triple therapy (PPI, levofloxacin, and amoxicillin for 10–14 days), levofloxacin sequential (PPI and amoxicillin for 5–7 days followed by a PPI, amoxicillin, levofloxacin and a nitroimidazole for 5–7 days), and LOAD (levofloxacin, PPI, nitazoxanide and doxycycline for 7–10 days). All these therapies are not approved for the FDA (Chey et al., 2017).

All these multi-drug therapies have the objective of eradicate *H. pylori* and prevent gastric cancer; however, this can only be achieved if there is adherence to treatment (take the medication according to the dose and time indicated by the physician). The lack of adherence to treatment causes treatment failures in antibiotic-sensitive patients and in the subsequent development of antibiotic resistance. The main causes of adherence to treatment are: the complexity and side effects of treatment, treatment efficacy, therapy duration, cost of the medications, motivation of the physician towards the patient and cultural factors of the patient (O'Connor et al., 2009).

In 2017, Boehnke et al. demonstrate a high incidence of primary *H. pylori* antibiotic resistance in Lima to antibiotics used in the standard triple therapy. They reported 32.9% (25/76) resistance to amoxicillin, 29.7% (34/118) to clarithromycin, 3.7% (3/81) to tetracycline, 44.4% (76/171) to levofloxacin, 59.1% (101/171) to metronidazole, and 46.1% (35/76) to rifampicin. This would mean that in Peru there is a response to the treatment of *H. pylori* infection lower than expected, causing that the total eradication of this bacterium in this country to be more challenging (Boehnke et al., 2017b).

Unfortunately, in the routine in the public setting in Peru, 13.5% of patients diagnosed with *H. Pylori* infection are not treated, while in patients receiving therapy, 21.7% are refractory to the first-line treatment and 32.5% are lost in follow-up. This data shows that ~70% of our patients diagnosed with *H. Pylori* in the public setting have a high-risk to a further gastric cancer (Table 1).

10. Conclusions

Although there are greatest advances in the understanding of the molecular biology of gastric cancer and its relationship with the *H. Pylori*, we have to face to great challenges to improve the primary attention of patients infected with this bacterium in Peru in order to

Table 1
Patterns of treatment of patients infected with *H. pylori* in the public setting in Peru.

	n	%
Patients with *H. Pylori* infection		
Yes	96	42.5
No	130	57.5
Patients receiving therapy		
Yes	83	86.4
No	13	13.5
First-line therapy		
PPI + Amoxicillin + Clarithromycin	83	100
Response to therapy		
H. pylori erradicated	38	45.8
Refractary	18	21.7
Lost in follow-up	27	32.5

*All patients diagnosed with dyspeptic syndrome that undergo biopsy (n = 226) at the Hospital San José of Callao, period 2015. Abbreviations: PPI, proton pump inhibitor.

reduce our high burden of gastric cancer that affects mainly to poor patients.

References

Allaker, R.P., Young, K.A., Hardie, J.M., Domizio, P., Meadows, N.J., 2002. Prevalence of helicobacter pylori at oral and gastrointestinal sites in children: evidence for possible oral-to-oral transmission. J. Med. Microbiol. 51 (4), 312–317. https://doi.org/10.1099/0022-1317-51-4-312.

al-Moagel, M.A., Evans, D.G., Abdulghani, M.E., Adam, E., Evans, D.J., Malaty, H.M., Graham, D.Y., 1990. Prevalence of Helicobacter (formerly Campylobacter) pylori infection in Saudia Arabia, and comparison of those with and without upper gastrointestinal symptoms. Am. J. Gastroenterol. 85 (8), 944–948.

Araujo Boira, H., 2015. Helicobacter Pylori [Text]. Retrieved from(January 15)). http://www.waterpathogens.org/book/helicobacter-pylori.

Asaka, M., Kimura, T., Kudo, M., Takeda, H., Mitani, S., Miyazaki, T., et al., 1992. Relationship of Helicobacter pylori to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology 102 (3), 760–766.

Aziz, R.K., Khalifa, M.M., Sharaf, R.R., 2015. Contaminated water as a source of Helicobacter pylori infection: a review. J. Adv. Res. 6 (4), 539–547. https://doi.org/10.1016/j.jare.2013.07.007.

Banatvala, N., Mayo, K., Megraud, F., Jennings, R., Deeks, J.J., Feldman, R.A., 1993. The cohort effect and Helicobacter pylori. J. Infect. Dis. 168 (1), 219–221.

Bardhan, P.K., 1997. Epidemiological features of Helicobacter pylori infection in developing countries. Clin. Infect. Dis. 25 (5), 973–978.

Bartram, J., Cairncross, S., 2010. Hygiene, sanitation, and water: forgotten foundations of health. PLoS Med. 7 (11), e1000367. https://doi.org/10.1371/journal.pmed.1000367.

Bernabé-Monsalve, L., 2017. Prevalencia De Helicobacter pylori En El Agua De Consumo Humano De Pacientes Diagnosticados Con Cáncer Gástrico Helicobacter pylori Positivo En El Instituto Nacional De Enfermedades Neoplásicas 2015–2016. Universidad Nacional Mayor de San Marcos, Lima-Perú.

Blaser, M.J., Perez-Perez, G.I., Kleanthous, H., Cover, T.L., Peek, R.M., Chyou, P.H., et al., 1995. Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res. 55 (10), 2111–2115.

Boehnke, K.F., Valdivieso, M., Bussalleu, A., Sexton, R., Thompson, K.C., Osorio, S., et al., 2017a. Antibiotic resistance among Helicobacter pylori clinical isolates in Lima, Peru. Infect. Drug Resist. 10, 85–90. https://doi.org/10.2147/IDR.S123798.

Boehnke, K.F., Valdivieso, M., Bussalleu, A., Sexton, R., Thompson, K.C., Osorio, S., et al., 2017b. Antibiotic resistance among Helicobacter pylori clinical isolates in Lima, Peru. Infect. Drug Resist. 10, 85–90. https://doi.org/10.2147/IDR.S123798.

Boehnke, K.F., Brewster, R.K., Sánchez, B.N., Valdivieso, M., Bussalleu, A., Guevara, M., et al., 2018. An assessment of drinking water contamination with Helicobacter pylori in Lima, Peru. Helicobacter 23 (2), e12462. https://doi.org/10.1111/hel.12462.

Bonequi, P., Meneses-González, F., Correa, P., Rabkin, C.S., Camargo, M.C., 2013. Risk factors for gastric cancer in Latin America: a meta-analysis. Cancer Causes Control CCC 24 (2), 217–231. https://doi.org/10.1007/s10552-012-0110-z.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R., Torre, L., Jemal, A., 2018. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin Forthcoming.

Brown, L.M., Thomas, T.L., Ma, J.L., Chang, Y.S., You, W.C., Liu, W.D., et al., 2001. Helicobacter pylori infection in rural China: exposure to domestic animals during childhood and adulthood. Scand. J. Infect. Dis. 33 (9), 686–691.

Chey, W.D., Leontiadis, G.I., Howden, C.W., Moss, S.F., 2017. ACG clinical guideline: treatment of Helicobacter pylori infection. Am. J. Gastroenterol. 112 (2), 212–239. https://doi.org/10.1038/ajg.2016.563.

Cover, T.L., 2016. Helicobacter pylori diversity and gastric Cancer risk. MBio 7 (1), e01869–01815. https://doi.org/10.1128/mBio.01869-15.

Cullen, D.J., Collins, B.J., Christiansen, K.J., Epis, J., Warren, J.R., Surveyor, I., Cullen, K.J., 1993. When is Helicobacter pylori infection acquired? Gut 34 (12), 1681–1682.

Custodio-Zegarra, D., 2017. Prevalencia de la infección de la bacteria Helicobacter pylori en pacientes diagnosticados con adenocarcinoma gástrico en el Instituto Nacional de Enfermedades Neoplásicas (INEN). Universidad Ricardo Palma, Lima, Perú.

Di Sibio, A., Abriata, G., Forman, D., Sierra, M.S., 2016. Female breast cancer in central and South America. Cancer Epidemiol. 44 (Suppl. 1), S110–S120. https://doi.org/10.1016/j.canep.2016.08.010.

Dore, M.P., Sepulveda, A.R., El-Zimaity, H., Yamaoka, Y., Osato, M.S., Mototsugu, K., et al., 2001. Isolation of Helicobacter pylori from sheep-implications for transmission to humans. Am. J. Gastroenterol. 96 (5), 1396–1401. https://doi.org/10.1111/j.1572-0241.2001.03772.x.

El-Omar, E.M., Carrington, M., Chow, W.H., McColl, K.E., Bream, J.H., Young, H.A., et al., 2001. The role of interleukin-1 polymorphisms in the pathogenesis of gastric cancer. Nature 412 (6842), 99. https://doi.org/10.1038/35083631.

Engstrand, L., 2001. Helicobacter in water and waterborne routes of transmission. Symposium Series (Society for Applied Microbiology). pp. 80S–84S 30.

Falush, D., Wirth, T., Linz, B., Pritchard, J.K., Stephens, M., Kidd, M., et al., 2003. Traces of human migrations in Helicobacter pylori populations. Science (New York N.Y.) 299 (5612), 1582–1585. https://doi.org/10.1126/science.1080857.

Ferguson, D.A., Li, C., Patel, N.R., Mayberry, W.R., Chi, D.S., Thomas, E., 1993. Isolation of Helicobacter pylori from saliva. J. Clin. Microbiol. 31 (10), 2802–2804.

Ferguson, D.A., Jiang, C., Chi, D.S., Laffan, J.J., Li, C., Thomas, E., 1999. Evaluation of two string tests for obtaining gastric juice for culture, nested-PCR detection, and combined single- and double-stranded conformational polymorphism discrimination of Helicobacter pylori. Dig. Dis. Sci. 44 (10), 2056–2062.

Fogarty, J., Thornton, L., Hayes, C., Laffoy, M., O'Flanagan, D., Devlin, J., Corcoran, R., 1995. Illness in a community associated with an episode of water contamination with sewage. Epidemiol. Infect. 114 (2), 289–295.

Gião, M.S., Azevedo, N.F., Wilks, S.A., Vieira, M.J., Keevil, C.W., 2008. Persistence of Helicobacter pylori in heterotrophic drinking-water biofilms. Appl. Environ. Microbiol. 74 (19), 5898–5904. https://doi.org/10.1128/AEM.00827-08.

Gilman, R., León-Barúa, R., Cok, J., Ramírez-Ramos, A., Recavarren-Arce, S., Spira, W., et al., 1986. Rapid identification of pyloric Campylobacter in Peruvians with gastritis. The gastrointestinal physiology working group. Dig. Dis. Sci. 31 (10), 1089–1094.

Gilman, R., León-Barúa, R., Ramírez-Ramos, A., Morgan, D., Recavarren, S., Spira, W., et al., 1987. Efficacy of nitrofurans in the treatment of antral gastritis associated with Campylobacter pyloridis. Gastroenterology 92, 1405.

Go, M.F., Graham, D.Y., 1994. How does Helicobacter pylori cause duodenal ulcer disease: the bug, the host, or both? J. Gastroenterol. Hepatol. 9 (Suppl 1), S8–10.

Graham, David Y., 2014. History of Helicobacter pylori, duodenal ulcer, gastric ulcer and gastric cancer. World J. Gastroenterol. 20 (18), 5191–5204. https://doi.org/10.3748/wjg.v20.i18.5191.

Graham, D.Y., Adam, E., Reddy, G.T., Agarwal, J.P., Agarwal, R., Evans, D.J., et al., 1991. Seroepidemiology of Helicobacter pylori infection in India. Comparison of developing and developed countries. Dig. Dis. Sci. 36 (8), 1084–1088.

Handt, L.K., Fox, J.G., Dewhirst, F.E., Fraser, G.J., Paster, B.J., Yan, L.L., et al., 1994. Helicobacter pylori isolated from the domestic cat: public health implications. Infect. Immun. 62 (6), 2367–2374.

Handt, L.K., Fox, J.G., Yan, L.L., Shen, Z., Pouch, W.J., Ngai, D., et al., 1997. Diagnosis of Helicobacter pylori infection in a colony of rhesus monkeys (Macaca mulatta). J. Clin. Microbiol. 35 (1), 165–168.

Hitos históricos - sedapal.com.pe. (n.d.). Retrieved from http://www.sedapal.com.pe/hitos-historicos.

Hooi, J.K.Y., Lai, W.Y., Ng, W.K., Suen, M.M.Y., Underwood, F.E., Tanyingoh, D., et al., 2017. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology 153 (2), 420–429. https://doi.org/10.1053/j.gastro.2017.04.022.

Hulten, K., Han, S.W., Enroth, H., Klein, P.D., Opekun, A.R., Gilman, R.H., et al., 1996. Helicobacter pylori in the drinking water in Peru. Gastroenterology 110 (4), 1031–1035.

INEI. Instituto Nacional de Estadística e Informática, 2017. Perú: Evolución de los Indicadores de los Objetivos de Desarrollo del Milenio al 2015.

INEI. Instituto Nacional de Estadística e Informática, 2018. Evolución de la pobreza monetaria 2007-2017. Informe Técnico 2018 (April). .

Instituto Nacional de Enfermedades Neoplásicas, 2016. Registro de cáncer de Lima Metropolitana. Incidencia y mortalidad 2010-2012, vol. 5 Lima-Perú.

Kabir, S., 2004. Detection of Helicobacter pylori DNA in feces and saliva by polymerase chain reaction: a review. Helicobacter 9 (2), 115–123. https://doi.org/10.1111/j.1083-4389.2004.00207.x.

Kabir, S., 2009. Effect of Helicobacter pylori eradication on incidence of gastric cancer in human and animal models: underlying biochemical and molecular events. Helicobacter 14 (3), 159–171. https://doi.org/10.1111/j.1523-5378.2009.00677.x.

Kamangar, F., Cheng, C., Abnet, C.C., Rabkin, C.S., 2006. Interleukin-1B polymorphisms and gastric cancer risk–a meta-analysis. Cancer Epidemiol. Biomark. Prevent. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prevent. Oncol. 15 (10), 1920–1928. https://doi.org/10.1158/1055-9965.EPI-06-0267.

Kamangar, F., Sheikhattari, P., Mohebtash, M., 2011. Helicobacter pylori and its effects on human health and disease. Arch. Iran. Med. 14 (3), 192–199. https://doi.org/011143/AIM.0010.

Kidd, M., Modlin, I.M., 1998. A century of Helicobacter pylori: paradigms lost-paradigms regained. Digestion 59 (1), 1–15. https://doi.org/10.1159/000007461.

Klein, P.D., Graham, D.Y., Gaillour, A., Opekun, A.R., Smith, E.O., 1991. Water source as risk factor for Helicobacter pylori infection in Peruvian children. Gastrointestinal

Physiology Working Group. Lancet (London, England) 337 (8756), 1503–1506.
Kusters, J.G., van Vliet, A.H.M., Kuipers, E.J., 2006. Pathogenesis of Helicobacter pylori infection. Clin. Microbiol. Rev. 19 (3), 449–490. https://doi.org/10.1128/CMR.00054-05.
Labigne, A., de Reuse, H., 1996. Determinants of Helicobacter pylori pathogenicity. Infect. Agents Dis. 5 (4), 191–202.
León, R., Recavarren, S., Ramírez, A., 1991. El aporte peruano a la investigación sobre Helicobacter pylori. Rev. Med. Hered. 2 (4) Retrieved from. http://www.upch.edu.pe/vrinve/dugic/revistas/index.php/RMH/article/view/348.
León-Barúa, R., 1985. El Campylobacter pilórico y la patología esófago-gastro-duodenal. Acta Gastroent. Lat. Am. 15, 129–131.
León-Barúa, R., Recavarren-Arce, S., Spira, W., Ramírez-Ramos, A., Gilman, R., Watanabe, J., Cok, J., 1987a. Topology of Campylobacter pylori gastric infection and histopathologic lesions. Am. J. Gastroenterol. 82, 938.
León-Barúa, R., Spira, W., Ramírez-Ramos, A., Gilman, R., Recavarren-Arce, S., Watanabe, J., Cok, J., 1987b. Campylobacter pyloridis: a complete misnomer. Gastroenterology 92, 1501.
León-Barúa, R., Berendson, R., Rodríguez, C., Gilman, R., Recavarren, S., Cok, J., 1990. Study on the effects of oral bismuth and oxytetracycline on the gastric histology and secretory function of patients with Campylobacter pylori-associated advanced lesions of the gastric mucosa. Gastroenterology 98, A19.
León-Barúa, R., Berendson, R., Rodriguez, C., Gilman, R.H., Recavarren, S., Cok, J., 1991. Improvement in gastric secretion by the inclusion of tetracyclines in therapeutic schedules for Helicobacter pylori-associated active chronic gastritis. Am. J. Gastroenterol. 86 (7), 925–927.
Leung, W.K., Siu, K.L., Kwok, C.K., Chan, S.Y., Sung, R., Sung, J.J., 1999. Isolation of Helicobacter pylori from vomitus in children and its implication in gastro-oral transmission. Am. J. Gastroenterol. 94 (10), 2881–2884. https://doi.org/10.1111/j.1572-0241.1999.01431.x.
Linz, B., Balloux, F., Moodley, Y., Manica, A., Liu, H., Roumagnac, P., et al., 2007. An African origin for the intimate association between humans and Helicobacter pylori. Nature 445 (7130), 915–918. https://doi.org/10.1038/nature05562.
Luther, J., Higgins, P.D.R., Schoenfeld, P.S., Moayyedi, P., Vakil, N., Chey, W.D., 2010. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: systematic review and meta-analysis of efficacy and tolerability. Am. J. Gastroenterol. 105 (1), 65–73. https://doi.org/10.1038/ajg.2009.508.
Machado, J.C., Figueiredo, C., Canedo, P., Pharoah, P., Carvalho, R., Nabais, S., et al., 2003. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. Gastroenterology 125 (2), 364–371.
Mai, U., Borsch, G., Opeferkuch, W., 1989. Route of infection in Capylobacter pylori (CP) disease. Gastroenterology 96, A314.
Malaty, H.M., Graham, D.Y., 1994. Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection. Gut 35 (6), 742–745.
Malaty, H.M., Graham, D.Y., Isaksson, I., Engstrand, L., Pedersen, N.L., 1998. Co-twin study of the effect of environment and dietary elements on acquisition of Helicobacter pylori infection. Am. J. Epidemiol. 148 (8), 793–797.
Malaty Hoda, M., El-Kasabany, A., Graham, D.Y., Miller, C.C., Reddy, S.G., Srinivasan, S.R., et al., 2002. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. Lancet (London, England) 359 (9310), 931–935. https://doi.org/10.1016/S0140-6736(02)08025-X.
Marshall, B.J., Warren, J.R., 1984. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet (London, England) 1 (8390), 1311–1315.
Marshall, B.J., Armstrong, J.A., McGechie, D.B., Glancy, R.J., 1985. Attempt to fulfil Koch's postulates for pyloric Campylobacter. Med. J. Aust. 142 (8), 436–439.
Mitchell, H.M., Li, Y.Y., Hu, P.J., Liu, Q., Chen, M., Du, G.G., et al., 1992. Epidemiology of Helicobacter pylori in southern China: identification of early childhood as the critical period for acquisition. J. Infect. Dis. 166 (1), 149–153.
Mitchell Hazel, M., 2001. Epidemiology of infection. In: Mobley, H.L., Mendz, G.L., Hazell, S.L. (Eds.), Helicobacter Pylori: Physiology and Genetics. ASM Press, Washington (DC) Retrieved from. http://www.ncbi.nlm.nih.gov/books/NBK2421/.
Morgan, D., Kraft, W., Bender, M., Pearson, A., 1988. Nitrofurans in the treatment of gastritis associated with Campylobacter pylori. The Gastrointestinal Physiology Working Group of Cayetano Heredia and the Johns Hopkins Universities. Gastroenterology 95 (5), 1178–1184.
Morris, A., Nicholson, G., 1987. Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric pH. Am. J. Gastroenterol. 82 (3), 192–199.
Morris, A.J., Ali, M.R., Nicholson, G.I., Perez-Perez, G.I., Blaser, M.J., 1991. Long-term follow-up of voluntary ingestion of Helicobacter pylori. Ann. Intern. Med. 114 (8), 662–663.
Moss, S.F., 2013. The rediscovery of H. Pylori bacteria in the gastric mucosa by Robin Warren, and implications of this finding for human biology and disease. Dig. Dis. Sci. 58 (11), 3072–3078. https://doi.org/10.1007/s10620-013-2863-y.
Murakami, K., Sakurai, Y., Shiino, M., Funao, N., Nishimura, A., Asaka, M., 2016. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study. Gut 65 (9), 1439–1446. https://doi.org/10.1136/gutjnl-2015-311304.
Nagy, P., Johansson, S., Molloy-Bland, M., 2016. Systematic review of time trends in the prevalence of Helicobacter pylori infection in China and the USA. Gut Pathog. 8, 8. https://doi.org/10.1186/s13099-016-0091-7.
O'Connor, J.P.A., Taneike, I., O'Morain, C., 2009. Improving compliance with Helicobacter pylori eradication therapy: when and how? Ther. Adv. Gastroenterol. 2 (5), 273–279. https://doi.org/10.1177/1756283X09337342.
Olbermann, P., Josenhans, C., Moodley, Y., Uhr, M., Stamer, C., Vauterin, M., et al., 2010. A global overview of the genetic and functional diversity in the Helicobacter pylori cag pathogenicity island. PLoS Genet. 6 (8), e1001069. https://doi.org/10.1371/journal.pgen.1001069.
Osato, M.S., Ayub, K., Le, H.H., Reddy, R., Graham, D.Y., 1998. Houseflies are an unlikely reservoir or vector for Helicobacter pylori. J. Clin. Microbiol. 36 (9), 2786–2788.
Pajares, J.M., Gisbert, J.P., 2006. Helicobacter pylori: su descubrimiento e importancia en la medicina. Revista Española de Enfermedades Digestivas 98 (10), 770–785.
Palmer, E.D., 1954. Investigation of the gastric mucosa spirochetes of the human. Gastroenterology 27 (2), 218–220.
Pareja Cruz, A., Mejía, N., Javier, P., García, P., Francisco, J., 2017. Seroprevalencia de infección por Helicobacter pylori en población adulta de Lima, perú 2017. Horizonte Médico 17 (2), 55–58. https://doi.org/10.24265/horizmed.2017.v17n2.8.
Parkin, D.M., 2006. The global health burden of infection-associated cancers in the year 2002. Int. J. Cancer 118 (12), 3030–3044. https://doi.org/10.1002/ijc.21731.
Parsonnet, Julie, 2005. Clinician-discoverers–Marshall, Warren, and H. Pylori. N. Engl. J. Med. 353 (23), 2421–2423. https://doi.org/10.1056/NEJMp058270.
Parsonnet, J., Hansen, S., Rodriguez, L., Gelb, A.B., Warnke, R.A., Jellum, E., et al., 1994. Helicobacter pylori infection and gastric lymphoma. N. Engl. J. Med. 330 (18), 1267–1271. https://doi.org/10.1056/NEJM199405053301803.
Parsonnet, J., Shmuely, H., Haggerty, T., 1999. Fecal and oral shedding of Helicobacter pylori from healthy infected adults. JAMA 282 (23), 2240–2245.
Patel, S.K., Pratap, C.B., Jain, A.K., Gulati, A.K., Nath, G., 2014. Diagnosis of Helicobacter pylori: what should be the gold standard? World J. Gastroenterol. WJG 20 (36), 12847–12859. https://doi.org/10.3748/wjg.v20.i36.12847.
Percival, S.L., Thomas, J.G., 2009. Transmission of Helicobacter pylori and the role of water and biofilms. J. Water Health 7 (3), 469–477. https://doi.org/10.2166/wh.2009.070.
Percival, S.L., Williams, D.W., 2014. Chapter seven - helicobacter pylori. In: Percival, S.L., Yates, M.V., Williams, D.W., Chalmers, R.M., Gray, N.F. (Eds.), Microbiology of Waterborne Diseases (Second Edition). Academic Press, London, pp. 119–154. https://doi.org/10.1016/B978-0-12-415846-7.00007-X.
Perez-Perez, G.I., Taylor, D.N., Bodhidatta, L., Wongsrichanalai, J., Baze, W.B., Dunn, B.E., et al., 1990. Seroprevalence of Helicobacter pylori infections in Thailand. J. Infect. Dis. 161 (6), 1237–1241.
Perez-Perez, Guillermo I., Rothenbacher, D., Brenner, H., 2004. Epidemiology of Helicobacter pylori infection. Helicobacter 9 (Suppl 1), 1–6. https://doi.org/10.1111/j.1083-4389.2004.00248.x.
Piñeros, M., Ramos, W., Antoni, S., Abriata, G., Medina, L.E., Miranda, J.J., et al., 2017. Cancer patterns, trends, and transitions in Peru: a regional perspective. Lancet Oncol. 18 (10), e573–e586. https://doi.org/10.1016/S1470-2045(17)30377-7.
Pinto-Santini, D., Salama, N.R., 2005. The biology of Helicobacter pylori infection, a major risk factor for gastric adenocarcinoma. Cancer Epidemiol. Biomark. Prevent. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prevent. Oncol. 14 (8), 1853–1858. https://doi.org/10.1158/1055-9965.EPI-04-0784.
Plummer, M., van Doorn, L.-J., Franceschi, S., Kleter, B., Canzian, F., Vivas, J., et al., 2007. Helicobacter pylori cytotoxin-associated genotype and gastric precancerous lesions. J. Natl. Cancer Inst. 99 (17), 1328–1334. https://doi.org/10.1093/jnci/djm120.
Plummer, M., Franceschi, S., Vignat, J., Forman, D., de Martel, C., 2015. Global burden of gastric cancer attributable to Helicobacter pylori. Int. J. Cancer 136 (2), 487–490. https://doi.org/10.1002/ijc.28999.
Plummer, M., de Martel, C., Vignat, J., Ferlay, J., Bray, F., Franceschi, S., 2016. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob. Health 4 (9), e609–616. https://doi.org/10.1016/S2214-109X(16)30143-7.
Pounder, R.E., Ng, D., 1995. The prevalence of Helicobacter pylori infection in different countries. Aliment. Pharmacol. Ther. 9 (Suppl 2), 33–39.
Qin, X., Peng, Q., Lao, X., Chen, Z., Lu, Y., Lao, X., et al., 2014. The association of interleukin-16 gene polymorphisms with IL-16 serum levels and risk of nasopharyngeal carcinoma in a Chinese population. Tumour Biol. J. Int. Soc. Oncodevelop. Biol. Med. 35 (3), 1917–1924. https://doi.org/10.1007/s13277-013-1257-2.
Ramírez, R.A., Chinga, A.E., Mendoza, R.D., 2004. Variación de la prevalencia del H. Pylori y su relación con los niveles de cloro en el agua de la Atarjea, Lima, Perú: Período 1985-2002. Revista de Gastroenterología Del Perú 24 (3), 223–229.
Ramirez-Ramos, A., Leey-Casella, J., Mendoza-Requena, D., Guerra-Valencia, J., 2003. Helicobacter pylori. Epidemiología-Diagnóstico-Tratamiento. Consensos Mundiales-Experiencia en el Perú. 42(1). Retrieved from. DIAGNÓSTICO. http://www.fihu-diagnostico.org.pe/revista/numeros/2003/enefeb03/23-37.html.
Ramírez-Ramos, A., 1988. Campylobacter pylori y enfermedades gastroduodenales. Campylobacter pylori y patología gastroduodenal, first edition. pp. 72–95 Lima-Perú: Santa Ana.
Ramírez-Ramos, A., Hurtado, O., Rodríguez, C., León-Barúa, R., Garrido-Klinge, G., Recavarren-Arce, S., et al., 1987a. Campylobacter pylori in different socioeconomic groups in Perú. Am. J. Gastroenterol. 82, 935.
Ramírez-Ramos, Alberto, Hurtado-Muñoz, O., Rodríguez-Ulloa, C., Garrido-Klinge, G., Recavarren-Arce, S., Gilman, R., et al., 1987b. Campylobacter pilórico y nivel socio-económico. Acta Gastroenterol. Latinoam. 17 (1), 35–42.
Ramírez-Ramos, Alberto, Mendoza-Requena, D., Leey-Casella, J., Guerra-Valencia, J., 2002. Estudio del Helicobacter pylori en el Perú. Revista Peruana de Medicina Experimental y Salud Publica 19 (4), 209–214.
Ramírez-Ramos, Alberto, Chinga-Alayo, E., Mendoza-Requena, D., Leey-Casella, J., Castro, S., Cristina, M., Otoya, C., 2003. Variación de la prevalencia del H. pylori en el Perú período (1985-2002), en una población de nivel socioeconómico medio y alto. Revista de Gastroenterología Del Perú 23 (2), 92–98.
Ramos-Muños, W., Venegas-Ojeda, D., 2013. Análisis de la Situación del Cáncer en el Perú 2013. Lima: Dirección General de Epidemiología, Ministerio de la Salud.
Recavarren-Arce, S., Ramirez-Ramos, A., Gilman, R.H., Chinga-Alayo, E., Watanabe-Yamamoto, J., Rodriguez-Ulloa, C., et al., 2005. Severe gastritis in the Peruvian Andes. Histopathology 46 (4), 374–379. https://doi.org/10.1111/j.1365-2559.2005.

02102.x.
Replogle, M.L., Kasumi, W., Ishikawa, K.B., Yang, S.F., Juji, T., Miki, K., et al., 1996. Increased risk of Helicobacter pylori associated with birth in wartime and post-war Japan. Int. J. Epidemiol. 25 (1), 210–214.
Ricci, C., Holton, J., Vaira, D., 2007. Diagnosis of Helicobacter pylori: invasive and non-invasive tests. Best Pract. Res. Clin. Gastroenterol. 21 (2), 299–313. https://doi.org/10.1016/j.bpg.2006.11.002.
Roesler, B.M., Rabelo-Gonçalves, E.M.A., Zeitune, J.M.R., 2014. Virulence factors of Helicobacter pylori: a review. Clin. Med. Insights Gastroenterol. 7, 9–17. https://doi.org/10.4137/CGast.S13760.
Sanders, M.K., Peura, D.A., 2002. Helicobacter pylori-associated diseases. Curr. Gastroenterol. Rep. 4 (6), 448–454.
Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994, 1994. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 61. pp. 1–241.
Shu, L., Wang, X.-Q., Wang, S.-F., Wang, S., Mu, M., Zhao, Y., et al., 2013. Dietary patterns and stomach cancer: a meta-analysis. Nutr. Cancer 65 (8), 1105–1115. https://doi.org/10.1080/01635581.2013.828086.
Sipponen, P., 1995. Helicobacter pylori: a cohort phenomenon. Am. J. Surg. Pathol. 19 (Suppl 1), S30–36.
Sjomina, O., Heluwaert, F., Moussata, D., Leja, M., 2017. Helicobacter pylori infection and nonmalignant diseases. Helicobacter 22 (Suppl 1). https://doi.org/10.1111/hel.12408.
Soto, G., Bautista, C.T., Roth, D.E., Gilman, R.H., Velapatiño, B., Ogura, M., et al., 2003. Helicobacter pylori reinfection is common in Peruvian adults after antibiotic eradication therapy. J. Infect. Dis. 188 (9), 1263–1275. https://doi.org/10.1086/379046.
The Gastrointestinal Physiology Working Group, 1990. Helicobacter pylori and gastritis in Peruvian patients: relationship to socioeconomic level, age, and sex. Am. J. Gastroenterol. 85 (7), 819–823.
The Gastrointestinal Physiology Working Group of the Cayetano Heredia and the Johns Hopkins University, 1992. Ecology of Helicobacter pylori in Peru: infection rates in coastal, high altitude, and jungle communities. Gut 33 (5), 604–605.
Tomb, J.-F., White, O., Kerlavage, A.R., Clayton, R.A., Sutton, G.G., Fleischmann, R.D., et al., 1997. The complete genome sequence of the gastric pathogen *Helicobacter pylori*. Nature 388 (6642), 539–547. https://doi.org/10.1038/41483.
Torres, J., Correa, P., Ferreccio, C., Hernandez-Suarez, G., Herrero, R., Cavazza-Porro, M., et al., 2013. Gastric cancer incidence and mortality is associated with altitude in the mountainous regions of Pacific Latin America. Cancer Causes Control: CCC 24 (2), 249–256. https://doi.org/10.1007/s10552-012-0114-8.
Valdivieso, M., Bussalleu, A., Sexton, R., Boehnke, K., Osorio, S., Novoa Reyes, I., 2016. Clinical, epidemiologic, and genomic studies (SWOG S1119) of Helicobacter pylori in Lima, Peru. Role Contam. Water 3 (2), 52–63.
Wang, Y.-K., Kuo, F.-C., Liu, C.-J., Wu, M.-C., Shih, H.-Y., Wang, S.S., et al., 2015. Diagnosis of Helicobacter pylori infection: current options and developments. World J. Gastroenterol. WJG 21 (40), 11221–11235. https://doi.org/10.3748/wjg.v21.i40.11221.
Warren, J.R., Marshall, B., 1983. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet (London, England) 1 (8336), 1273–1275.
WHO | Water for life, 2005. Making It Happen. Retrieved from. http://www.who.int/water_sanitation_health/publications/jmp2005/en/.
World Health Organization, 2013. Research priorities for the environment, agriculture and infectious diseases of poverty. World Health Organ. Tech. Rep. Ser. i–xiii (976), 1–125.
Yong, X., Tang, B., Li, B.-S., Xie, R., Hu, C.-J., Luo, G., et al., 2015. Helicobacter pylori virulence factor CagA promotes tumorigenesis of gastric cancer via multiple signaling pathways. Cell Commun. Signal. 13, 30. https://doi.org/10.1186/s12964-015-0111-0.