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Seroprevalence of helicobacter pylori and hepatitis A among children

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Literature review

Helicobacter pylori (H. pylori) is a Gram-negative bacterium which lives in the human stomach and is one of the causes of gastritis, peptic ulcer disease, gastric cancer and primary B-cell gastric lymphoma (1). More than a half of the world population is infected with this bacteria. The prevalence of this infection varies across the regions of the world and depends on age, low socioeconomic status, high population density, poor sanitation and hygiene (2). Many studies have confirmed more frequent occurrence of H. pylori infection in poorly developed countries in comparison to industrialized countries (3).

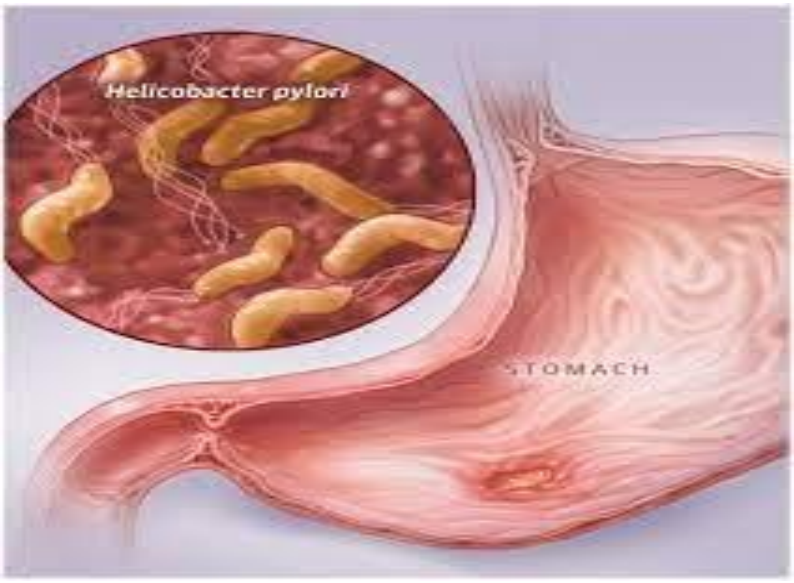

Figure 1. *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) infection is one of the most common human bacterial infection worldwide with about 50% of the global population infected. The prevalence of infection varies both between and within countries in relation to race, ethnicity and geographical area2 such that developed countries have significantly lower rates of *H. pylori* infection than developing countries. This difference has been attributed to differing rates of acquisition of the organism in childhood as well as

sanitation, socio economic and hygiene status of the population3. Most of the infected people develop no clinical symptoms and live their lives with superficial chronic gastritis. However, about 17% of infected subjects will develop peptic ulcers and about 1% will progress to gastric cancer which is the third leading cause of cancer-related deaths in the world, especially in the adult population (4).

The childhood period may be critical for the acquisition of *H. pylori* infection. It is believed that once the organism is acquired, it persists for life unless there is an intervention. However, some authors have reported loss of infection either spontaneously in some rare cases, or as a result of inadvertent exposure to antibiotics.

Documented risk factors for *H. pylori* infection include poverty, poor sanitation, overcrowding and unsafe water source, which are prevalent in most communities (5).

Hepatitis A is a common form of acute viral hepatitis worldwide. Hepatitis A virus (HAV) is transmitted by the fecal–oral route because of ingestion of contaminated food or water or through direct contact with an infectious individual. The spread of the virus is strongly correlated with poor socioeconomic and hygienic conditions. In low-income countries, where access to safe water and sanitation standards are inadequate, HAV is highly endemic, and infections occur almost universally in early childhood (6,7). The risk of disease after acute HAV infection varies by age, and the clinical course in children is usually asymptomatic or mild. By contrast, infected adolescents and adults more frequently develop classic symptoms of hepatitis, including jaundice. The infection induces lifelong protection, with detectable anti-HAV immunoglobulins (Ig)G.

Hepatitis E virus (HEV) has an extensive global distribution and causes epidemics and sporadic cases in many low income countries. In endemic areas, HEV genotypes (gt) 1 and 2 are transmitted by the fecal–oral route, primarily through contaminated drinking water, but person-to-person transmission is uncommon (8). Unlike other hepatitis viruses, large reservoirs of HEV gt 3 and 4 have been recognized in various animal species, such as pigs, rabbits, boar, and deer. These observations suggest zoonotic transmission, which has been well documented in high-income countries, mainly in Europe (7). Hepatitis E virus infection by gt 1 and 2 causes an acute, selflimiting hepatitis, predominantly in young adults. Although the symptoms are generally mild, fulminant infection may occur, especially in pregnant women. In many developed countries, gt 3 and 4 are the dominant circulating HEV and cause acute hepatitis usually in older males and chronic infection in the immunosuppressed. In contrast to HAV, global HEV seroprevalence is less than 10% in children younger than 10 years, and the peak of incidence occurs in young adults aged between 15 and 40 years in many areas endemic for HEV gt 1 and 2 (9).

Helicobacter pylori is a common bacterium that infects the gastric mucosa of nearly half of the human population. Prevalence is higher in developing than in developed countries, and it seems to be related to inadequate sanitation practices, low social class, and overcrowded or high-density living conditions (10). Although the infection is likely to spread from person to person, the precise route of transmission is controversial, as data supporting fecal–oral, oral–oral, gastric–oral, waterborne, and zoonotic transmission have been reported (11).

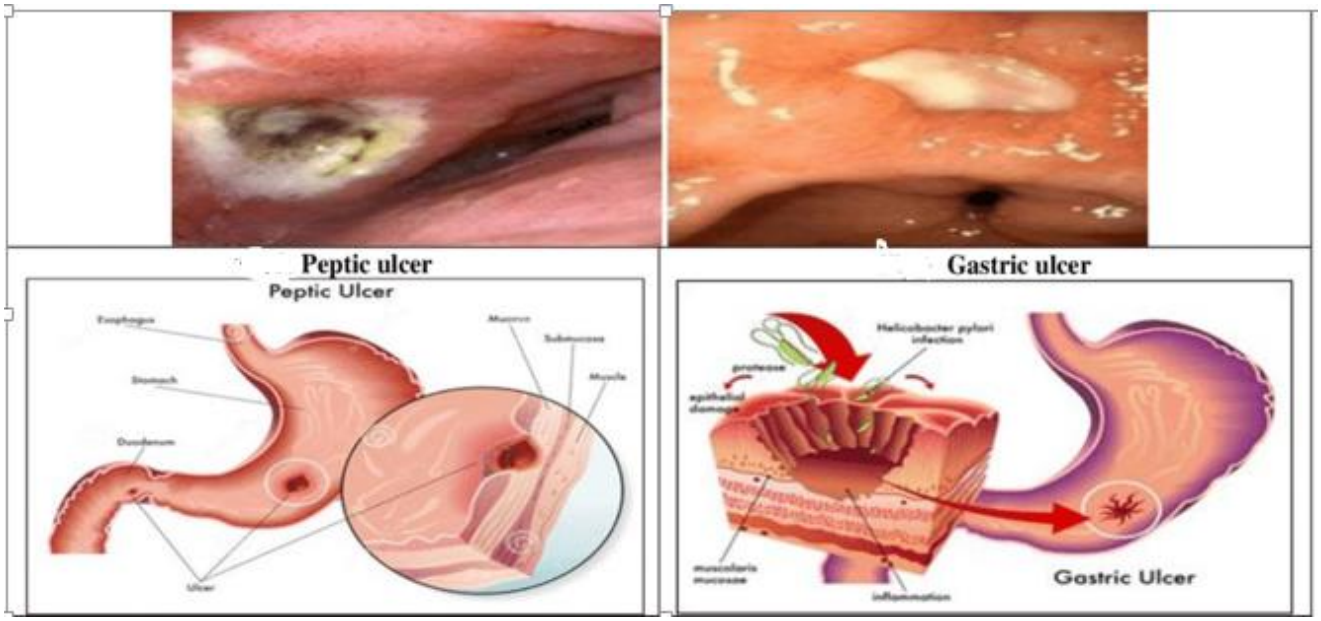

Figure 2. *Helicobacter pylori* in stomach and duodenum

Most of the infections occur in early childhood and, if not treated, persist lifelong. Chronic infection with H. pylori is associated with gastrointestinal tract disorders, ranging from chronic gastritis to gastric adenocarcinoma, gastric lymphoma, and peptic ulcer. In the Bolivian Chaco, a tropical region in the south-east of Bolivia, previous studies showed a high prevalence of HAV, above 90% in the general population. However, a significant decrease in the HAV seroprevalence, from 86.9% to 64.7%,was observed among children aged 1–5 years, during the period 1987–1997 (12,13).

In the second survey, HEV seroprevalence was initially assessed in two areas of the Bolivian Chaco, reporting an overall prevalence of 7.3%, with significantly lower levels in individuals £ 30 years of age.8 In 2006, a further study in the same area showed a similar seroprevalence (6%). However, both these previous results are likely to be significant

underestimates of HEV seroprevalence because of the poor sensitivity of the assays used (14). As far as H. pylori is concerned, in the same population surveyed for HAV and HEV in 1997, the prevalence of specific antibodies was 60.7%.

OTHER STUDIES AND DISCUSSION

The other studies showed that the imbalance of seroprevalence of the infection observed between both communities was accounted for by differences in young children aged 1–5 years (12.5% in Bartolo versus 100% in Ivamirapinta,), whereas in both communities, it was found to be [3] 95% in individuals aged > 10 years. Anti-HAV positivity was strongly associated with increasing age. Stratification by age cohort showed that exposure occurred predominantly in subjects aged up to 10 years, reaching 100% in the second decade of life. No difference was observed in the gender distribution of seropositives (15).

In common with the other infections, H. pylori seroprevalence increased with age in subjects up to the age of 40 years, after which it 'plateaued'. Coinfections. Among 237 individuals with interpretable results, coinfection was found in 166 (70%), including 82 (34.6%) exposed to both HAV and HEV and 53 (22.4%) exposed to all three pathogens. No significant age-corrected associations were found between H. pylori infection and HAV.

in the Bolivian Chaco, the seroprevalence of HAV, HEV, and H. pylori was surveyed, 10 to 20 years after the last assessment in the same area. Hepatitis A virus seroprevalence was 95.1%, with universal exposure after the first decade of life (Figure 3).

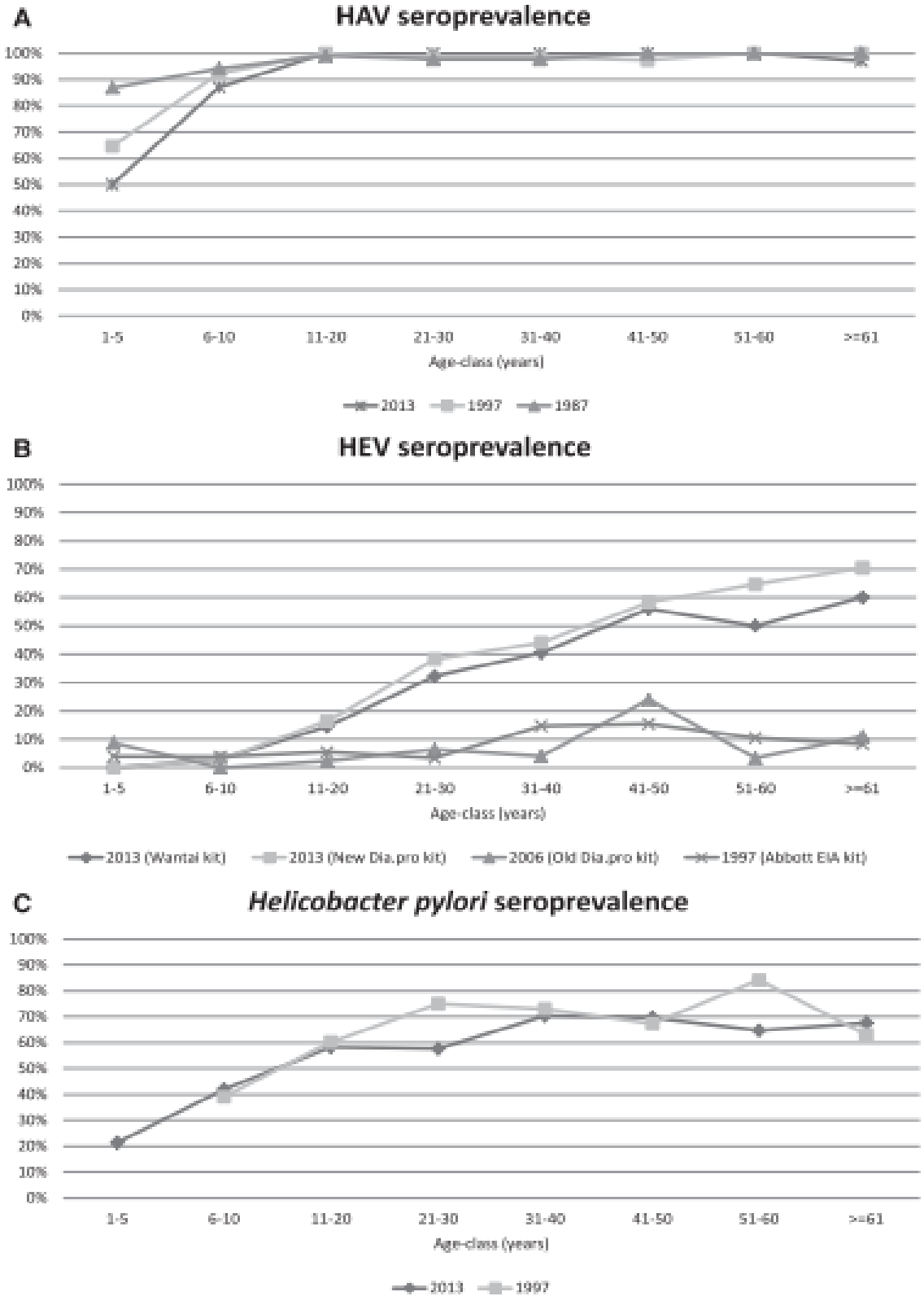

Figure 3. (A–C) Seroprevalence trends of hepatitis A virus (HAV) (A), hepatitis E virus (HEV) (B), and Helicobacter pylori (C) in the human population of rural communities of the Bolivian Chaco: 1987–2013**.**

This finding is unchanged from previous observations in Bolivia and Peru and is in line with World Health Organization (WHO) estimates for Andean Latin American countries, both in rural and urban areas (16,17).

Previously, a significant decrease in HAV seroprevalence among children aged 1–5 was years observed from 1987 to 1997 (from 86.9% to 64.7%). However, in the current study, a decrease in HAV seroprevalence was seen only in the community of Bartolo (1/8, 12.5%) but not in Ivamirapinta (6/6, 100%). This observed difference in prevalence in such very young children between Bartolo and Ivamirapinta does not reflect differences in sanitation between both communities, and it cannot be explained by family or household clustering (data not shown).

These results need to be interpreted with caution, given the low number of children studied in this age cohort. A decline in circulating HAV among children is consistent with reports from many parts of the world, where anti-HAV epidemiology is changing, probably because of improvements in socioeconomic conditions and local health education.10 Since the end of the last century, the prevalence of anti-HAV antibodies has decreased in several Latin American countries, including Argentina, Brazil, Venezuela, Chile, and Uruguay (18,19) As a consequence of the reduction in viral exposure during early childhood, the peak age of infections is shifting to middle childhood or later, resulting in more clinical cases in adolescents and adults and an increased potential for clinically overt outbreaks. In these countries, monitoring of HAV epidemiology, especially in younger age cohorts, is important, as such data will inform preventive intervention strategies, such as vaccination campaigns.

The HEV seroprevalence was found to be an order of magnitude higher, using both newer Dia.pro (34.8%) and the well-validated Wantai kits (30.7%), compared with that reported in previous surveys from Bolivia

and Latin America, including our studies in the Bolivian Chaco (20) (Figure 1B). The finding is not surprising, considering that commercial assays for anti-HEV IgG detection show highly variable performance.16 The use of more sensitive assays has led to a three-times or four-times increase in estimates of HEV seroprevalence, including countries in Asia, where HEV gt 1 is the dominant circulating gt, and Europe, where gt 3 and 4 zoonotic HEV is endemic (21,21).

Of note, in the community of Bartolo,previously surveyed in 2006 using an older version of the commercial ELISA kit Dia.pro, a five to six-times higher prevalence was observed (38% versus 7%)(14). Because no HEV or jaundice outbreaks have been reported in recent years in this area, these discrepancies are likely due to the improved performance of the newer tests, whose reliability is corroborated by the excellent interassay agreement (23). The finding of high HEV seroprevalence in the areas tested, the lack of relationship regarding coinfection with other common fecal–oral pathogens, together with the lack of outbreaks of jaundice/ deaths in pregnant females, and our previous observations of HEV gt 3 in both pigs and humans from the same community suggest that the dominant mode of infection in the areas studied is likely to be zoonotic.

This is congruent with recent studies from several countries in South America, which shows that HEV gt 3 is the dominant circulating gt and that the epidemiology is similar to that seen in locally acquired zoonoticinfections in Europe (24,25). However, previously reported sequencing data on porcine and human strains, detected in the Bartolo community, suggest that the source of human HEV infection is unlikely to be from the local pig population, as there was poor sequence homology between porcine HEV (gt 3i) and human HEV (gt 3e) (26).

The seroprevalence of H. pylori was 58.6%, with an agedependent distribution, reaching a plateau around 70% after the fourth decade of life. Unpublished data (A. Bartoloni) from the same area reported similar results in 1997 (61%) (Figure 1C). Previously, a high H. pylori seroprevalence (44%) was reported among children aged 6 months to 9 years from 17 rural communities in the Santa Cruz Department, Bolivia. This rose to 64% when just considering individuals aged 7–9 years (27).

Two cross-sectional surveys on H. pylori infections in Bolivia, conducted in the city of Sucre and in two villages of the eastern territories using the urea breath test (UBT), reported a prevalence of 74% and 80%, respectively (28,29). The higher prevalence found in the latter studies might be attributed to the higher sensitivity of UBT in comparison with serology. Serological assays for H. pylori cannot distinguish between ongoing and resolved infections because specific IgG persist for months or years after a successful eradication of the bacterium. Likewise, seronegativity does not entirely exclude the possibility of a previous infection (30).

However, it seems likely that the observed prevalence in the current study is a reasonable estimate of the cumulative exposure burden over time, as local access to diagnostic tests and treatment of H. pylori infection are extremely limited. In Bolivia, stomach cancer, which is the main clinical sequela of H. pylori infection, was one of the five most frequently diagnosed cancers, as in many other countries of Latin America and, in 21% of cases it affects people younger than 50 years (31). In the population we studied, no association was found between HAV, HEV, and H. pylori seropositivity when corrected for age. These findings are consistent with the conclusion of a recent systematic review (11).

Although serostatus may not be an accurate marker for this association, our findings suggest that these three infections do not share the same route of transmission. This would fit with current notions of source and routes of infection: HAV is transmitted through the fecal–oral route, with humans as the main reservoir; gt 3 HEV is a porcine zoonosis, most likely due to either consumption of infected pork meat or close contact with infected animals; H. pylori seems to spread through multiple routes, depending on cultural and environmental conditions (11).

Conclusion

This Review provides a comprehensive description of the HAV infection epidemiology across the Europe Union and Eastern Europe Area during the past 40 years. The Review shows that HAV circulation has been decreasing steadily over time in the EU and EEA as a whole, although important differences exist at national and subnational levels, and that a progressively growing part of the EU and EEA population has become susceptible to HAV infection. We show that susceptibility among adults can serve as a more accurate indicator of the epidemiological situation in the EU and EEA than HAV seroprevalence in the population.

The analysis of epidemiological transition patterns has revealed important similarities between countries with similar susceptibility profiles and can be used to predict future developments and to identify what preventive measures are needed to accelerate the progression of countries towards lower endemicity levels. At the same time, the lower rates of infection in the region and the high level of susceptibility of the population is a cause for concern. The increasing susceptibility among the adult population (at risk of more severe disease) poses the risk of increasing incidence of acute symptomatic HAV infection and occurrence of outbreaks due to local circulation of HAV in the EU and EEA area through

common-source food exposures or travellers returning from endemic countries. In conclusion, our review supports the need to reconsider specific prevention and control measures, such as vaccination strategies, to further decrease HAV circulation while providing protection against the infection in the EU and EEA, a heterogeneous region with free movement of people and trade. In the studied population, the low socioeconomic status and poorer sanitary-hygienic condition were found to be the factors predisposing to H. pylori infected in children and in adults.

The place of birth in a rural area, crowded household, lack of running tap water, toilet outside the home, poor economic status, owning domestic pets and working with farm animals, drinking unboiled water, smoking tobacco among youngsters of over 14 years of age, working in the garden or in the field and not washing fruits before consumption predisposed to H. pylori infection in children.

In adults, the prevalence of H. pylori infection depended on the place of birth in a rural area, low family income, elementary education, owning domestic pets, consuming raw meat and highproof alcohol, smoking tobacco, not washing hands after coming home and cleaning teeth only once daily. Improving socioeconomic, sanitary and hygienic conditions as well as educating the society should decrease H. pylori infection prevalence in children and in adults.

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