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Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection

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ABSTRACT

Background: The epidemiology of Helicobacter pylori infection is poorly understood.

Aim: To establish the reported regional and national prevalence of H. pylori infection, stratified by age and gender.

Methods: All relevant English publications from 2000 to 2017 cited by PubMed and Scopus were retrieved using comprehensive combinations of keywords. The overall prevalence of H. pylori was estimated using both random effect and fixed effect meta-analyses, and presented as prevalence rate (% and 95% CI). The analyses were extended by separation into gender and age groups.

Results: A total of 14 056 records were obtained initially. After applying exclusion criteria in several steps, 183 studies were selected. Analysis of 410 879 participants from 73 countries in six continents revealed an overall prevalence of 44.3% (95% CI: 40.9-47.7) worldwide. This rate ranged from 50.8% (95% CI: 46.8-54.7) in developing countries compared with 34.7% (95% CI: 30.2-39.3) in developed countries. The global H. pylori infection rate was 42.7% (95% CI: 39-46.5) in females compared to 46.3% (95% CI: 42.1-50.5) in males. The prevalence in adults (≥18 years) was significantly higher than in children (48.6% [95% CI: 43.8-53.5] vs 32.6% [95% CI: 28.4-36.8], respectively). There was a statistically non-significant decrease in the prevalence in 2009-2016 compared with the 2000-2009 period.

Conclusions: The observed differences between countries appear to be due to economic and social conditions. H. pylori infection can be a benchmark for the socioeconomic and health status of a country. Further studies are suggested to investigate the natural history of the acquisition of H. pylori infection from childhood into adult life.

1. INTRODUCTION

Helicobacter pylori is a gram-negative bacterium that colonizes the human stomach and can lead to chronic gastritis, peptic ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma.[1] About half of the world's population is estimated to be infected with this pathogen. However, the reported infection rates vary between different regions, with greater prevalence in developing countries than in developed countries.[2, 3] It was shown that H. pylori prevalence among European populations is in the region of 20% to 40%.[4] A cross-sectional survey in the USA reported a 25.4% prevalence of the infection in persons aged ≥3 years.[5] In Japan, the prevalence was stated to be near 90% among individuals born before 1950s, but with a subsequent decreasing trend, reaching less than 2% among subjects born after 2000s. This low rate is very important due to the strong association of H. pylori with gastric cancer in the Japanese population.[6] On the other hand, in the Eastern Mediterranean region, an H. pylori prevalence of up to 80% was reported.[7]

Given the association of H. pylori with some important gastrointestinal diseases, and recognising that the pattern of H. pylori infection has potentially changed with improvements in sanitation and exposure to antibiotics, it seems prudent to determine the changing epidemiological characteristics of this pathogen. Such information may facilitate improved clinical practice and management decisions regarding the infection. Two epidemiological reviews have been recently published, but they only cover nationwide reports or specific groups in terms of age and population type.[8, 9] In this study, we conducted an updated systematic review and meta-analysis on the population-based literature to evaluate the prevalence of H. pylori globally, and to report different aspects of geography, age, gender, time trend and diagnostic tests.

2. MATERIALS AND METHODS

2.1. Information sources and search strategy

The authors searched literature published between 1 January 2000 and 31 June 2017 in the databases of PubMed and Scopus. The related terms were searched in the Medical Subject Headings (MeSH) database, and finally, the keywords “Helicobacter pylori” OR “H. pylori” AND “epidemiology” OR “prevalence” OR “incidence” OR “frequency” were selected. The search was limited to Title/Abstract. We also manually searched the reference lists of the included articles for additional relevant sources. Embase is not available in Iran (Elsevier, Amsterdam, the Netherlands).

2.2. Inclusion and exclusion criteria

We included all English-language observational studies reporting the prevalence of H. pylori infection among the general population. Detection of H. pylori could be assessed by any of the following methods: serology (anti-H. pylori IgG antibody), urea breath test, histological examination, bacterial culture, rapid urease test and/or stool antigen test

The exclusion criteria for our study were the following:

1. Reviews, case reports, editorials, guidelines, letter to the editors and abstracts from conferences.
2. Articles not written in English.
3. Experimental studies, clinical trials or animal studies.

4. Duplicate articles or those evaluating the same sample.
5. Hospital-based studies, and surveys including subjects with any disease and complication (eg, gastrointestinal diseases).
6. Case-control studies.
7. Studies conducted on refugees and/or migrants.
8. Studies without the above-mentioned tests for detection of the infection, or those with unusual diagnostic methodology (eg, urine antibody test, molecular method of polymerase chain reaction).
9. Articles with no clear methodology or results.

2.3 Study selection and data extraction

Three authors (MZ, VZ, and FE) independently evaluated the titles and abstracts of the included studies for eligibility. Disagreements were resolved by consensus or through discussion with a fourth author (RA). Full-text of the relevant articles was assessed. The following information was extracted from each study regarding H. pylori prevalence; first author, region of study, study population, study date, diagnostic method, sample age, sample size and prevalence rate. The three reviewers conducted the data extraction. We contacted the authors of the articles when the full-texts were not accessible. Regarding cohort studies, we extracted the data referred at the baseline assessment. When a study was presented in several reports, the one giving more complete detail or with the largest sample size was selected.

2.4 Study outcomes and statistical analysis

For subgroup analysis, we categorized global data into regions based on The United Nations Statistics Division.[10] We analysed H. pylori prevalence separately for males and females. An analysis was also performed separately for children (aged <18 years) and adults (aged ≥18 years). To analyse any time-trend of H. pylori prevalence, the study period was split into 2000-2008 and 2009-2016. Furthermore, the meta-analysis was conducted based on different diagnostic methods wherever the data were available. When a study presented H. pylori prevalence for different regions, periods or diagnostic methods, we considered each report separately for analysis. The extracted data were analysed using stata (StataCorp, College Station, TX, USA) statistical package. Heterogeneity was checked using the I2 index. Random effects model and fixed effects model were chosen when I2 was ≥50% and <50%, respectively. The pooling method was “Weighted Pooling to study size.” To determine a significant difference between two groups, we assessed the coverage of 95% confidence intervals. The map showing worldwide H. pylori prevalence was created using an online service.[11]

3. RESULTS

A total of 14 056 records were initially obtained from searching PubMed and Scopus. After evaluation of titles and abstracts, 9789 studies were excluded due to not being relevant or failing to meet the inclusion criteria. Then, full-text of the articles was reviewed and 53 studies were excluded based on the predefined criteria. Finally, 183 articles were included in this systematic review, of which seven were cohort and others were cross-sectional studies. A summary of the process is

exhibited in a flow diagram according to the PRISMA (Preferred reporting items for systematic review and meta-analysis) guideline [12] (Figure 1).

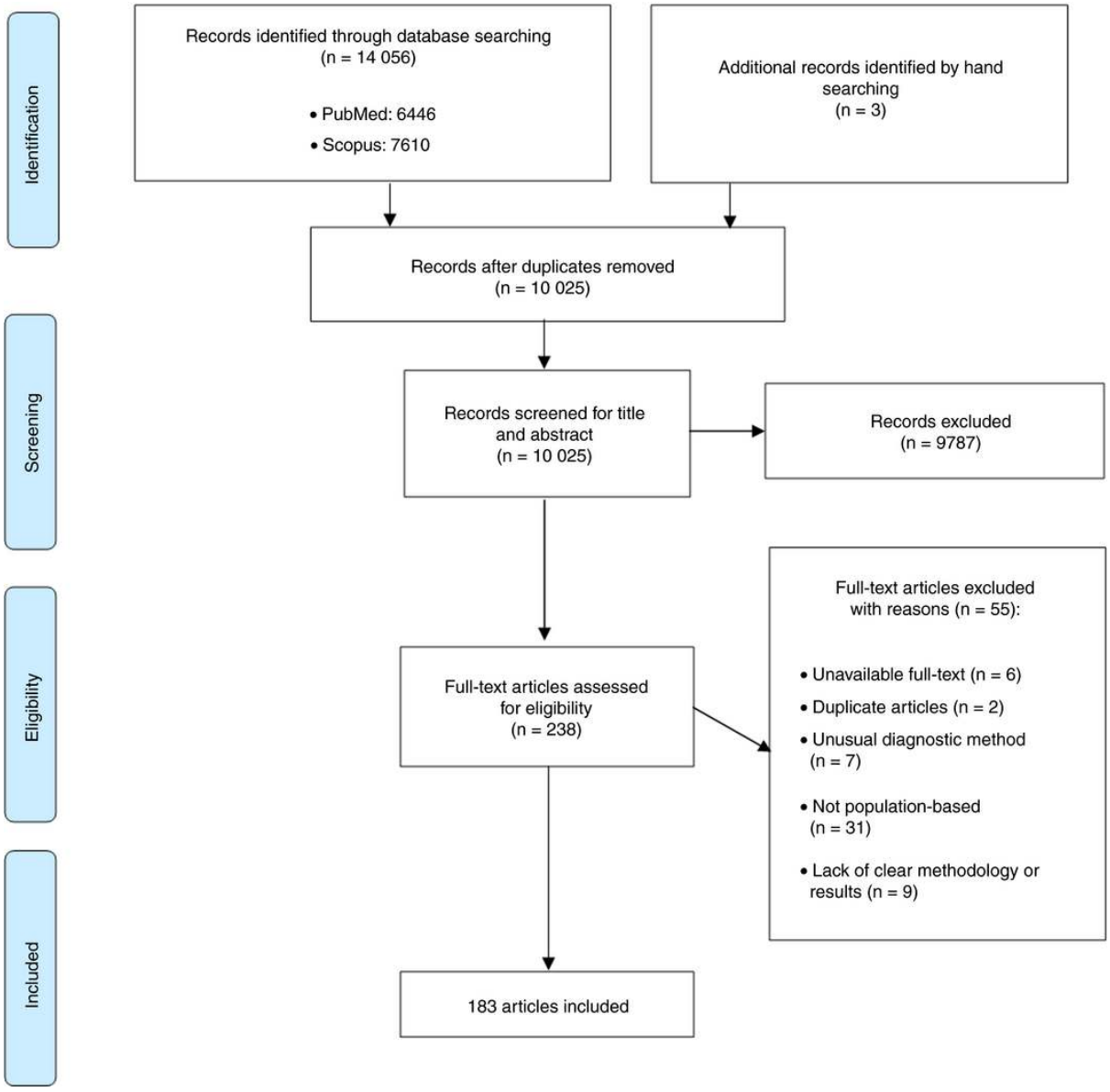

Figure 1: Flow chart of literature selection process

3.1 Continent-based prevalence

Of total 183 studies, 80 reports were found from Asia, followed by 48 from Europe, 25 from Latin America and the Caribbean, 18 from Africa, 11 from Northern America, and three from Oceania (two studies have reported prevalence from more than one continent). Details of included papers are summarized in Table S1.

The studies covered 410 879 participants from 73 countries, among whom the overall prevalence of H. pylori was 44.3% (95% CI: 40.9-47.7). Figure 2 shows the distribution of H. pylori infection across the world. Latin America and the Caribbean had the highest rate of infection in the world (59.3%,

95% CI: 52.9-65.6), by contrast, the lowest infection rate was belonged to Northern America (25.8%, 95% CI: 20.7-36.3). The analysed prevalence rates by continents are shown in Figure 3 and Table S2.

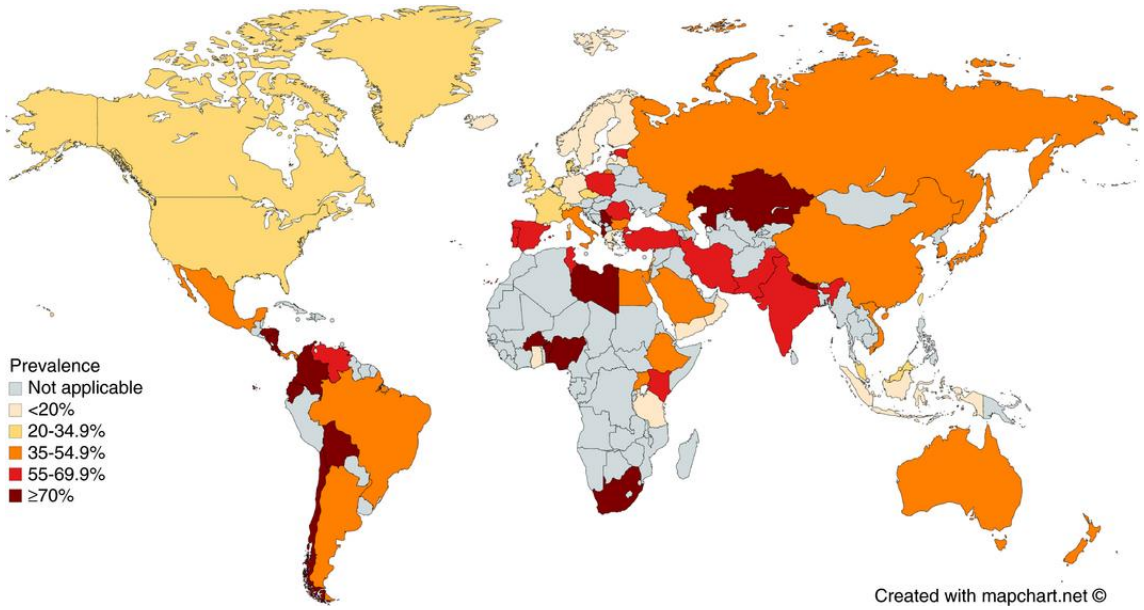

Figure 2: Graphical presentation of prevalence of *Helicobacter pylori* infection across the world

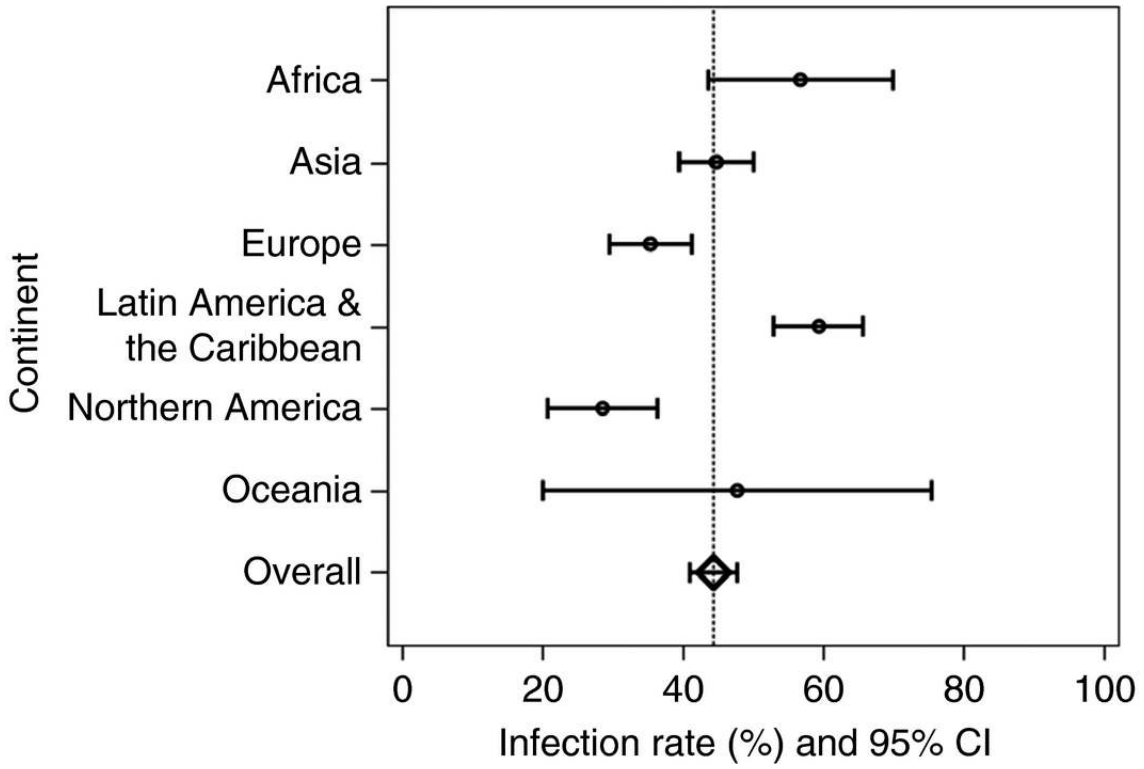

Figure 3: Prevalence of H. pylori infection across six continents. Each data set represents estimated prevalence from pooled analysis of different studies. The reference line represents overall global prevalence (44.3%).

3.2 National prevalence

Pooled estimates of studies revealed a wide range (approximately 10-fold) of H. pylori infection prevalence across countries (Figure 4 and Table S2). The highest and the lowest rates were for Nigeria (89.7%, 95% CI: 86.6-92.8), and Yemen (8.9% in 0-10 year-olds, 95% CI: 6.6-11.2), respectively. Serbia (88.3%, 95% CI: 84.6-92.0), South Africa (86.8%, 95% CI: 83.3-90.3), Nicaragua (83.3%, 95% CI: 78.6-88.0), and Colombia (83.1%, 95% CI: 78.5-87.7) were other nations with the highest rates. Indonesia (10.0%, 95% CI: 0-20.8), Belgium (11.0%, 95% CI: 8.3-13.7), Ghana (14.2%, 95% CI: 9.8-18.6) and Sweden (15.0%, 95% CI: 11.1-18.9) were the nations with the lowest infection rates (Figure 4). Of note, there was high diversity of infection rates in countries with close geographical proximity. The pooled estimates of each country's prevalence came from varying numbers of studies and differing sample sizes. This has been reflected in narrow confidence intervals in some estimates [(ie, 27% (95% CI: 25.4-28.5) for United Kingdom] or wide confidence intervals in other estimates [(ie, 47.1% (95% CI: 5.4-88.8) for Egypt]. The forest plots of the pooled prevalence for countries are presented in Figure S2.

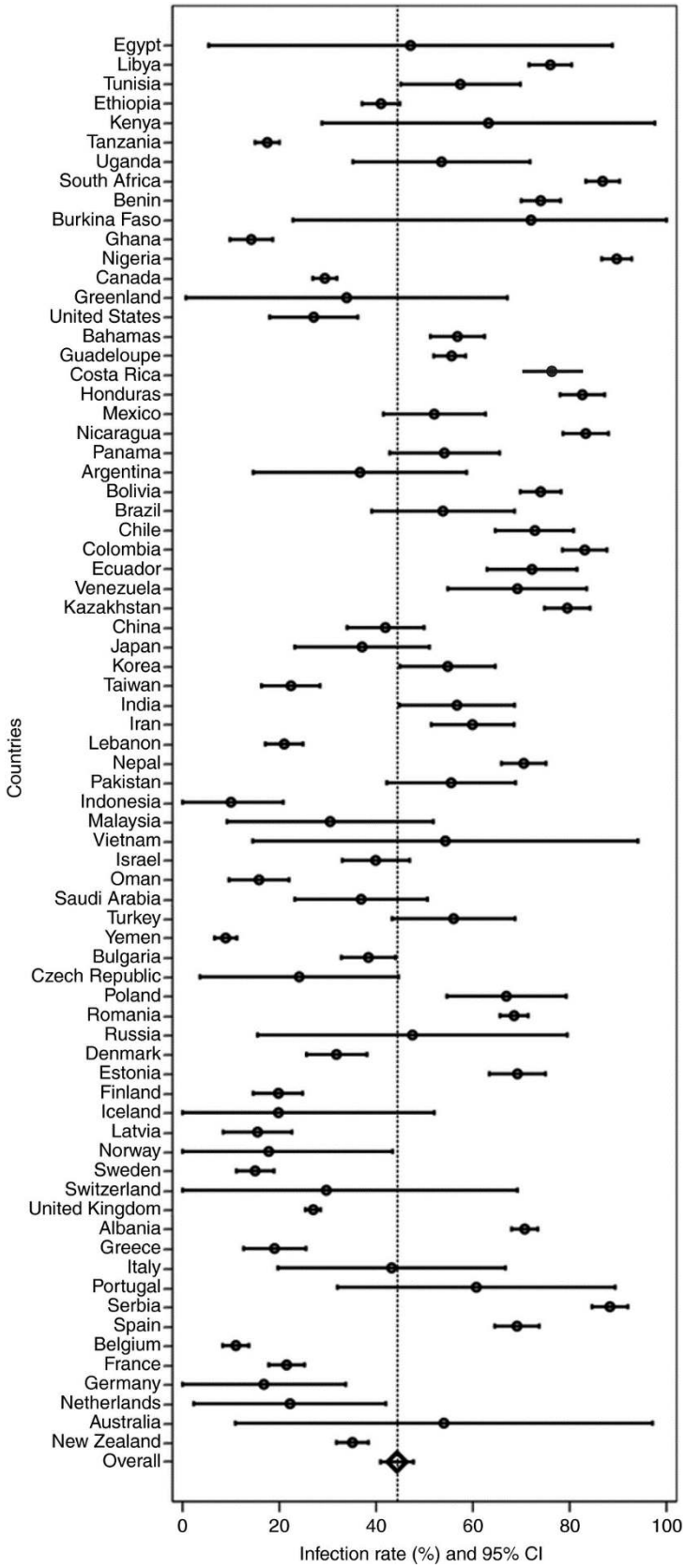

Figure 4: Prevalence of H. pylori infection across 73 countries. Each data set represents estimated prevalence from pooled analysis of different studies. The reference line represents overall global prevalence (44.3%).

3.3 Prevalence in developed vs developing countries

Overall, the infection was more prevalent in developing (50.8%, 95% CI: 46.8-54.7) compared to developed (34.7%, 95% CI: 30.2-39.3) countries (Figure S3).

3.4 Gender and prevalence

Regarding gender, females had a rate of 42.7% (95% CI: 39-46.5) for the infection across the world, in comparison with males who had a rate of 46.3% (95% CI: 42.1-50.5) (Figure 5). The gender gap was greatest in Africa (Male/Female = 1.16), and lowest in Latin America and the Caribbean (Male/Female = 1.03) (Table S4 and Figure S4). Although male predominance of H. pylori infection was evident across all continents, none of the differences reached statistical significance.

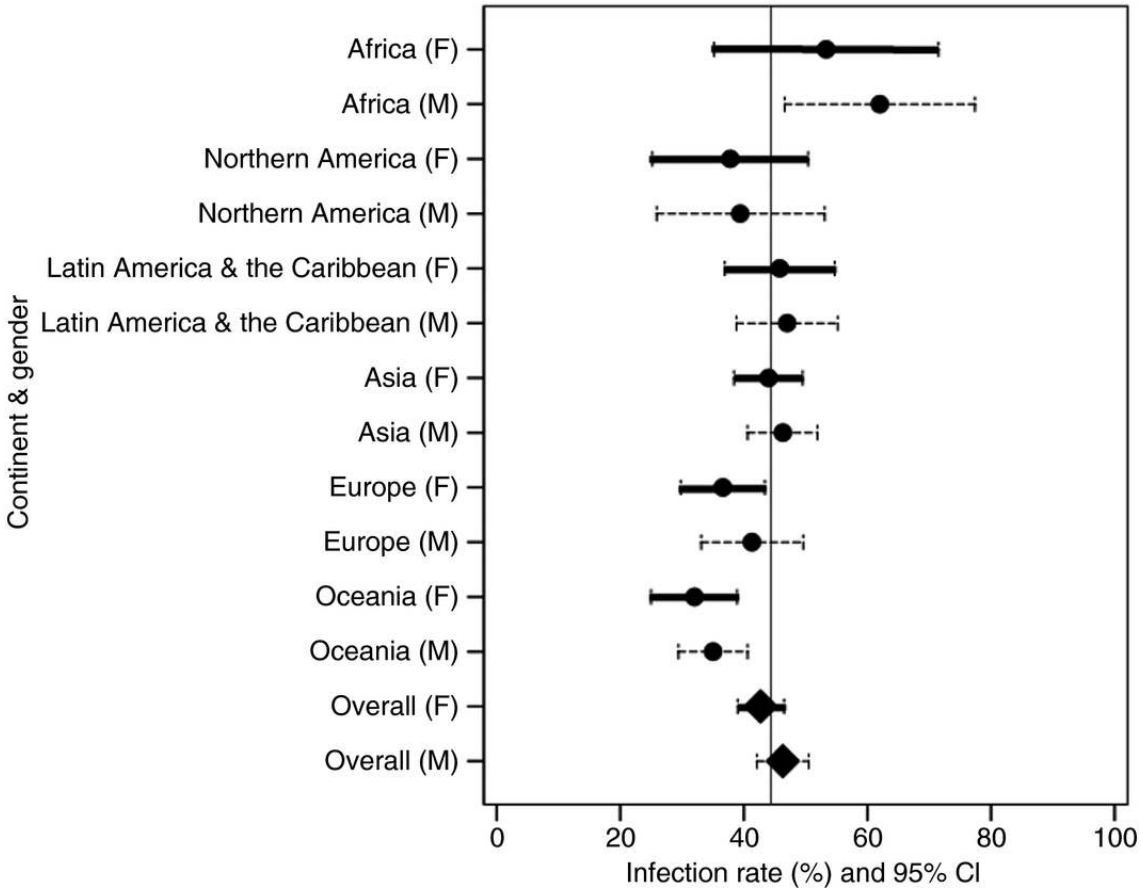

Figure 5: Prevalence of H. pylori infection by gender across six continents. The reference line represents overall global prevalence (44.3%), M, Males; F, Females.

3.5 Age and prevalence

Globally, adults had significantly higher H. pylori infection rates compared to children 48.6% (95% CI: 43.8-53.5) vs 32.6% (95% CI: 28.4-36.8) respectively. When examining the data at continent level, this was statistically significant for Asia, Europe and Oceania (Figure 6, Table S5 and Figure S5).

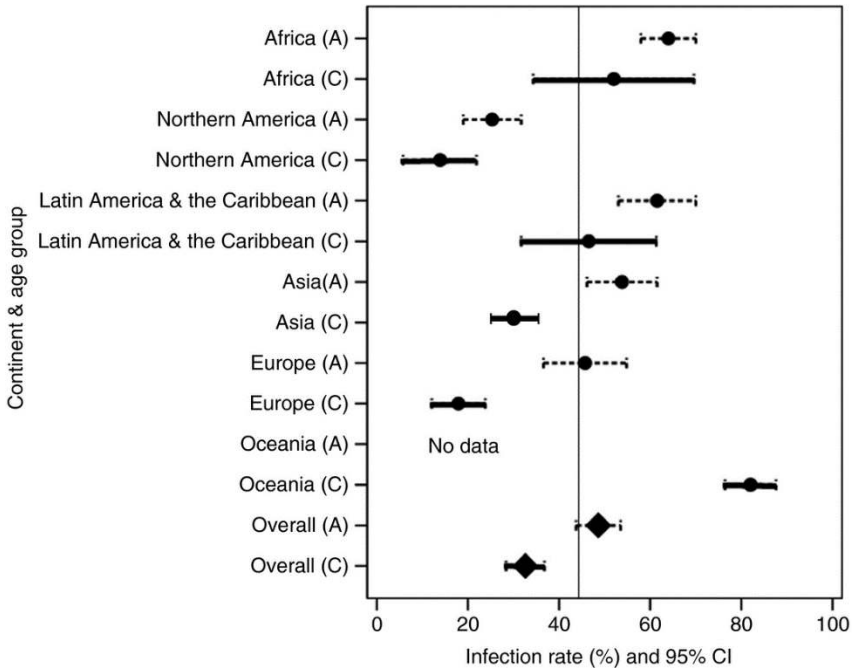

Figure 6: Prevalence of H. pylori infection by age group across six continents. The reference line represents overall global prevalence (44.3%), A, Adults; C, Children.

3.6 Study date and Prevalence

The overall infection rate was 46.8% (95% CI: 40.4-53.3) in studies conducted in the period between 2000-2008, whereas, the rate was 44.9% (95% CI: 37.9-51.9) for those studies performed in 2009-2016 (Figure 7, Table S6 and Figure S6).

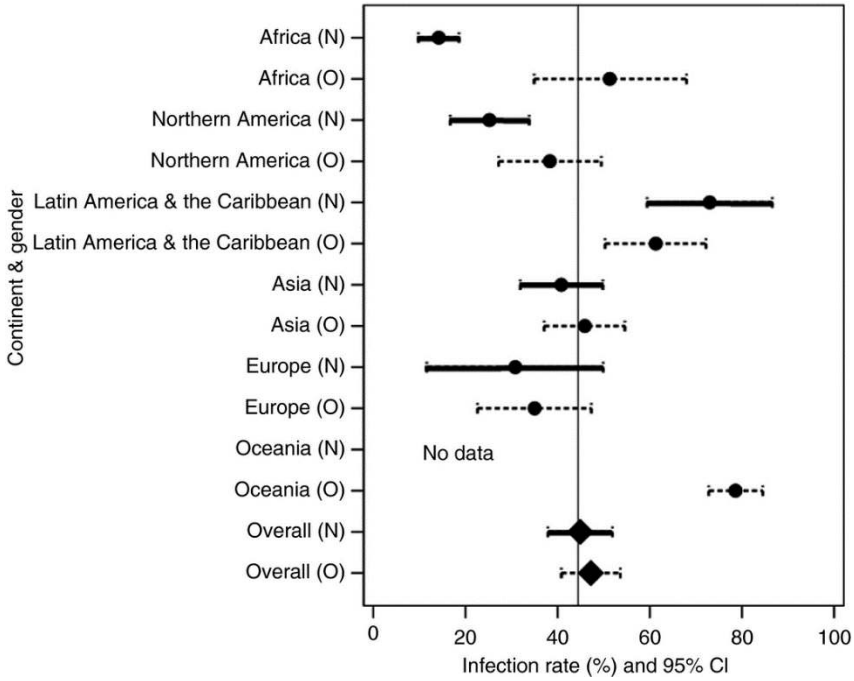

Figure 7: Prevalence of H. pylori infection by study date across six continents. The reference line represents overall global prevalence (44.3%), O, Older group (2000-2008); N, Newer group (2009-2016).

3.7 Diagnostic tests and prevalence

Serology was the most frequent method used as a diagnostic test for H. pylori, (113 articles), followed by urea breath test (41 articles), stool antigen test (31 articles), histology (five articles) and rapid urease test (three articles). We were unable to compare detection rates of two or more tests in same populations, as the number of studies presenting such information was inadequate. The information related to H. pylori prevalence by diagnostic tests is presented in Table S7 and Figure S7.

4. DISCUSSION

The present comprehensive systematic review and meta-analysis revealed a wide difference in the prevalence of H. pylori infection, with an approximately a 10-fold range across the countries of the world. Although there were notable differences between neighbouring countries within a close proximity, a meaningful prevalence pattern can be seen in continent-based findings.

As stated above, the highest and the lowest H. pylori prevalence rates pertained to Latin America and the Caribbean, and Northern America respectively. These results are consistent with previous findings from single to pooled estimates that the infection is seen more frequently in developing countries than in developed countries,[9, 13, 14] as most of the countries in the former group, ie, Latin America and Caribbean, were classified in the developing country list.

There was reasonable homogeneity in the estimated pooled prevalence in those countries within North America, and Latin America/Caribbean, but there were huge variations in country-based prevalence within Asia. This can be observed in the extreme prevalence rates from Kazakhstan (79.5%) and Indonesia (10.0%). Similar findings can be seen from the Europe, with a highest rate from Serbia (88.3%) and lowest rate from Belgium (11.0%).

The wide range of infection rate in those continents could be related to many lifestyle and environmental parameters. The higher socioeconomic status and education levels (of index person and parents) are among the well-established factors protecting against H. pylori,[15-17] Lower H. pylori infection rates in two south-eastern countries, Indonesia and Malaysia, could be explained by other factors, mainly attributed to their dietary factors. Lee et al showed that frequent use of “budu” or local anchovy sauce and “pegaga” (the vegetable Centenella asiatica) were associated with lower risk of H. pylori infection,[18] although the findings have to be supported in larger studies.

In our review, the worldwide infection with H. pylori was significantly more prevalent in adults than in children. This can be explained by either birth cohort effect or accumulated risk of infection by age, as the risk of exposure increases with the age. Detailed analyses of the birth cohort effect would be necessary, if health authorities wish to explore the nature and magnitude of associations between lifestyle changes and H. pylori infection.

The relationship between gender and H. pylori infection has been controversial in previous studies.[19-21] By our analysis, no significant difference was observed between the two genders in worldwide H. pylori prevalence. A recent meta-analysis by Ibrahim et al,[22] showed that infection occurred more frequently in males than in females, both in children and adults. Gender disparity in

H. pylori infection is an intriguing topic, as gastric adenocarcinoma (the most serious consequence of H. pylori infection) shows significant male predominance. In an attempt to explore the nature of the male predominance of gastric cancer in a Scottish population-based study, we showed that there is a 17-year delay in development of cancer in females.[23] The predominance was driven by intestinal subtype of adenocarcinoma, which has a strong link to H. pylori infection. Examining precancerous lesions, there is a significant male predominance in gastric intestinal metaplasia, but not so in atrophic gastritis. Chronic gastritis induced by H. pylori has not shown strong links to either gender. These areas need to be explored deeply, as it may be helpful to health authorities to tailor their preventive measures by taking into consideration gender as a factor.

Each of the methods for confirmation of H. pylori infection has a characteristic sensitivity and specificity which may influence an investigation's outcome. As determined in our review, most of the studies used serology, especially Asian studies. In contrast, most of the surveys from Northern America used the urea breath test. Selecting particular methods for the diagnosis depends on access to the methodologies and/or being cost-effective.

There are a number of limitations in our study. First, the identification stage of the literature review covered all significant medical databases but we had to exclude Embase, due to access restrictions in Iran. While acknowledging this limitation, we believe it had a minimal effect on our literature coverage, as all other major databases have been covered. Second, data analysis was restricted to only 72 countries, mainly due to lack of any published reports from the other nations. Also, in some countries, only one report was available, which is unsatisfactory. Third, high heterogeneity was identified for the pooled estimates, resulting from various factors, such as differences in diagnostic tests, date of study and population age. Finally, as an inherent limitation of all similar meta-analyses, the pooled prevalence in this study would not be a perfect image of actual H. pylori prevalence due to lack of adjusted data in the original studies.

In summary, this systematic review and meta-analysis found a wide variation in H. pylori prevalence across the world, in the country- and continent–based analyses. This study confirms the findings of Hooi et al,[9] that H. pylori infection is a global infection, and it is not resolving spontaneously. More studies should be performed to explore whether variation in prevalence of H. pylori infection does affect the global burden of upper gastrointestinal diseases. The higher infection rates are observed in developing compared with developed regions, and it appears that H. pylori could be considered an additional benchmark for the socioeconomic and health status of a community.

We propose that greater research effort should be applied to understand the exact process of transmission from one human to another. In terms of controlling the H. pylori global infectious disease, stopping the start of infection may be more easy to achieve than eradication. Eradication regimens all fail to achieve 100% success, even in the most sophisticated medical units.

Eradication regimens have little chance of success in the poorer countries of the world. Stopping cross-infection with H. pylori by improved water quality, sanitation, personal hygiene, isolation during the acute stage of infection could be old-fashioned, but of more benefit to the World.

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