

Primary Resistance Pattern of *Helicobacter pylori* to Antibiotics in Adult Population: A Systematic Review

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Gebremicheal

Gebreslassie Kasahun ¹

Gebre Teklemariam Demoz ²

Desilu Mahari Desta ³

¹Pharmacoepidemiology and Social Pharmacy Unit, School of Pharmacy, College of Health Science, Aksum University, Aksum, Ethiopia; ²Clinical Pharmacy Unit, School of Pharmacy, College of Health Science, Aksum University, Aksum, Ethiopia; ³Clinical Pharmacy Unit, School of Pharmacy, College of Health Science, Mekelle University, Mekelle, Ethiopia

Background: *Helicobacter pylori* is a spiral-shaped gram-negative bacteria associated with peptic ulcer, gastritis and gastric cancer. The global burden and occurrence of *H. pylori* infection remains prevalent and worldwide. Despite this, the trend of the bacterial resistance is not recently studied which can help in the adoption of global, regional and local prevention strategies.

Objective: The aim of the study was to systematically review the existing published literature that presents the estimate of *H. pylori* antibiotic resistance.

Methods: A protocol was primarily registered in PROSPERO International prospective register of systematic reviews and has given a registration number CRD42017068710. It was registered after checking whether there was similar study being conducted. A database search (PubMed/Medline and Google scholar) was used to collect relevant articles. A standardized form was prepared for the extraction of relevant data from studies which fulfilled the eligibility criteria. A National Institute for Health research (NIH)-based quality assessment tool was utilized to assess the quality of studies included in the study.

Results: Our searching process has retrieved a total of 288 publications which later resulted in 38 articles for full-text review. Among the 38 articles reviewed in full text, 14 studies were included which fulfilled the inclusion criteria. *H. pylori*-pooled overall prevalence rate of antibiotic resistance was found to be 4.55% (95% confidence interval (CI): 3.96–5.22%) to amoxicillin, 27.22% (95% CI: 25.89–28.58%) to clarithromycin, 39.66% (95% CI: 38.20–41.15%) to metronidazole, and 22.48% (95% CI: 21.24–23.76%) to levofloxacin.

Conclusion: The primary antibiotic resistance pattern of *H. pylori* is increasing worldwide. Thus, implementation of local drug susceptibility surveillance program, rational prescribing and use of antibiotics are necessary.

Keywords: *H. pylori*, primary antibiotics resistance, drug resistance, systematic review

Background

Helicobacter pylori is a spiral-shaped gram-negative bacteria which colonize the gastric or intestinal mucosa of humans and induce histologic inflammation.^{1,2} It is associated with peptic ulcer, gastritis and cancer.^{2,3} The infection of *H. pylori* remains a prevalent and worldwide chronic disease. It causes more than 90% and 80% of duodenal and gastric ulcers, respectively.^{1,4} This shows the world population is highly infected with *H. pylori*. About one-third of the adult population residing in Northern Europe and Northern America were found infected with *H. pylori*. Moreover, above 50% of population living in Southern and Eastern

Correspondence: Gebremicheal
Gebreslassie Kasahun
Tel +251-914 586 170
Email gebremicheal.kassahun@gmail.com

Europe, South America and Asia were infected with *H. pylori*. This was over pronounced in immigrants coming from countries with higher prevalence of *H. pylori*.⁵

Worldwide, various eradication strategies are proposed for the treatment of *H. pylori* infection including triple therapy, sequential therapy, concomitant therapy, quadruple therapy and hybrid therapy.^{6,7} The Maastricht IV Florence Consensus report overemphasized, eradication of *H. pylori* infection produces a long-term relief of dyspepsia. However, a long-term treatment with proton pump inhibitors is associated with the development of a corpus-predominant gastritis which accelerates to the development of atrophic gastritis.⁸

Antibiotic resistance is nowadays the challenging issue in the treatment of bacterial infections. It is still continuing as global public health threat specifically in most of the major microbial pathogens.^{9,10} Similar to other bacterial resistances, *H. pylori* drug resistance is also the main factor affecting the efficacy of current treatment regimens.¹¹ Various resistance mechanisms are described earlier however, point mutation on the surface of bacterial chromosome is described as the main causes of treatment failure due to drug resistance.¹²

H. pylori resistance to antibiotics is the major cause of treatment failure.¹³ Patients with sensitive isolates of clarithromycin (CLR) isolates have shown 100% eradication compared to none of patients with CLR resistant isolates.¹⁴ This indicates CLR resistance was responsible for the treatment failure. In addition to this, there are different mechanisms of resistance the bacteria can remain unharmed. These includes redox intracellular potential, pump efflux systems and membrane permeability for medications including to CLR, metronidazole (MTR), Quinolones, amoxicillin (AMX) and tetracycline.¹⁵ Prolonged hospitalization and use of antibiotics without prescription were also indicated as major reasons for the increased incidence of bacterial resistance.¹⁶

In vitro antibiotic susceptibility tests of *H. pylori* need standard culture because it is a relatively fastidious and slow-growing microaerophilic microorganism.¹⁷ Antibiotic susceptibility test helps in the proper prescribing and use of medications, and increase patient treatment outcome. Despite this, the trend of bacterial resistance is not yet recently studied which helps in the adoption of appropriate global and regional prevention strategies. Therefore, the purpose of this review was to systematically review and analyze existing published literature that presents estimates of primary antibiotic resistance of *H. pylori* in adult population.

Methods

Search Strategy

Before beginning of the study, the recent publication of the research question was checked to prevent over duplication in PROSPERO International prospective register of systematic reviews and had registered with a registration number; CRD42017068710. A comprehensive systematic search was done using searching key terms; *H. pylori* antibiotic resistance, amoxicillin, clarithromycin, metronidazole, and levofloxacin adding Boolean terms OR, AND, and NOT to gather relevant articles of a consecutive three years (2015 to 2017). A search engines; PubMed/Medline and Google scholar were used to collect relevant literature ([Supp 1 record identification](#)).

Eligibility Criteria

Studies conducted in adult age group greater than eighteen, bacteria confirmed on endoscopic observation/diagnosis from gastric/duodenal biopsy, previously never taken *H. pylori* treatment, *H. pylori* infection without gastric/duodenal cancer, had no prior 2-weeks history of acid secretion inhibitors drug intake (proton pump inhibitors or H₂-blockers), had not undergone gastric surgery and published in English language between 2015 and 2017 were the eligibility criteria for inclusion in the study.

Selection and Extraction of Data

Data were extracted using a standardized pre-prepared table to collect similar evidence from each literature. The evidence extracted includes: author/s name and year of the study, study area or country, number of study participants, study period and prevalence estimate of antibiotic resistance. This was based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement for reporting systematic reviews and meta-analyses of studies flow chart ([Figure 1](#)).¹⁸

Statistical Analysis

An initial extraction and estimation of pooled prevalence using Wilson method of double arcsine transformations were done to estimate a confidence interval for a proportion of studies in Excel.¹⁹ A pooled overall prevalence rate was estimated with 95% confidence interval (CI). This was interpreted and compared among countries and continents.

Quality Assessment

Two reviewers (GGK and GTD) carried out the initial screening of the citations retrieved in the searches based

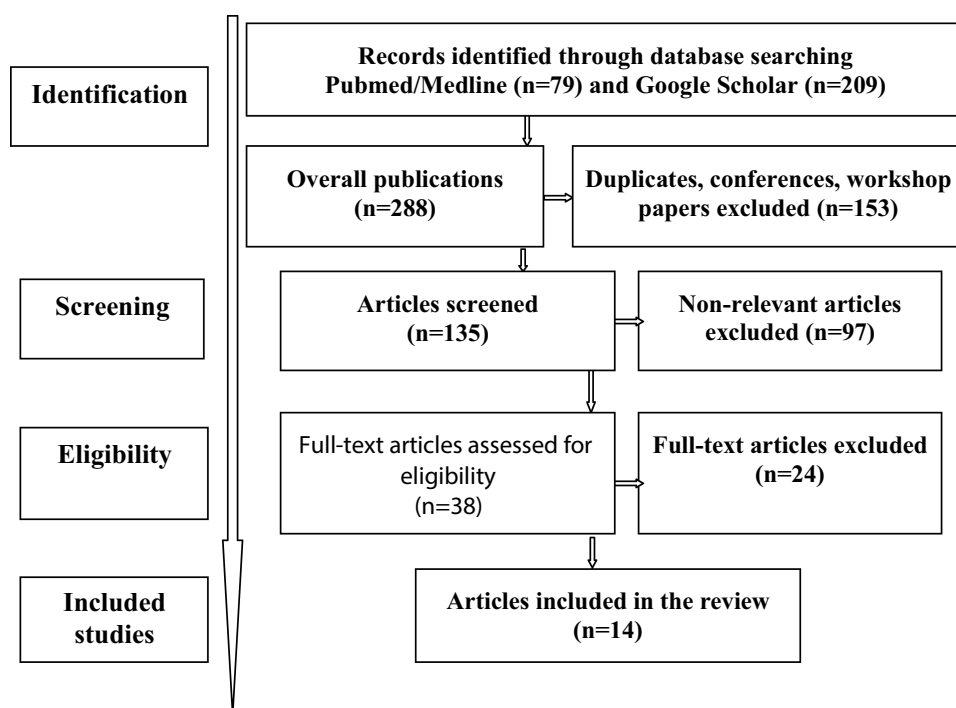


Figure 1 PRISMA flow chart representation showing the overall searching and article selection process of a study *Helicobacter pylori* primary resistance pattern to antibiotics. **Note:** Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. <https://doi.org/10.1371/journal.pmed.1000097>.¹⁸

on titles and abstracts followed by a full-text assessment of any article identified as being potentially eligible. Any discrepancies during the assessment had resolved by the team. Both reviewers have made a methodological quality assessment on the included eligible studies. The National Institute for Health research (NIH) based Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to assess the methodological quality of studies included in the systematic review rating; good = 2, fair = 1 and poor (cannot be determined, not reported or not applicable) = 0.²⁰

Results

Search results

Our searching process has retrieved a total of 288 publications which later resulted in 38 articles for full-text review. Among 38 articles reviewed in full text, 14 studies have been included for the study which fulfilled the inclusion criteria.^{21,24–36} The selection and screening process is presented in detail (see Figure 1).

Characteristics of Studies

Primary Resistance to Amoxicillin

Among patients (n=4218) previously never taken the treatment regimen, no resistance was reported in Europe and

North America for AMX. In contrast to this, higher resistance rate was reported from Africa (17.7%). Asian and Latin American studies also reported comparable resistance pattern of 3.9% and 4.4%, respectively. A study conducted in Egypt, among 46 study participants almost half of them were non-susceptible to AMX. Similar to this, a study conducted in Nigeria and Peru reported one-third of *H. pylori* positive patients were non-susceptible. But, no resistances were seen in Morocco, Poland, Turkey, America, Canada and Nepal.

Primary Resistance to Clarithromycin

Clarithromycin (CLR) is a Macrolide derivative used in the treatment of *H. pylori* eradication. CLR resistance has shown an association in predicting treatment failure of *H. pylori* eradication therapy.²² Comparable resistance rate was reported in Europe (31.3%) and Asia (30.9%) respectively. Within this the bacterial non-susceptibility rate was reported as 26.7% in Africa. Low rate of resistance was obtained in North America (18.5%) and South America (19.4) in comparison to other continents. Above half patients were non-susceptible in Poland, Egypt and China. *H. pylori* resistance of CLR has significantly increased in 2009–10 and 2013–14 as a study reported from china.²¹

Primary Resistance to Metronidazole

Metronidazole (MTR) is an alternative for penicillin-allergic candidates during *H. pylori* eradication therapy.⁸ Almost half of Asian patients were non-susceptible (48.9%) to MTR-based *H. pylori* treatment and higher rate of resistance was reported in Nigeria, Nepal, China, Peru and Poland with a prevalence rate of 99.1%, 88.1%, 66.8%, 61.8% and 56.7%, respectively.

Primary Resistance to Levofloxacin

It is a promising Fluoroquinolones derivative used in the eradication of *H. pylori* infection.²³ However, a substantial prevalence of resistance was observed especially in North America and Asia; 29.2% and 29.9%, respectively. In addition to this, indispensable primary resistance rate was reported in other continents; Europe (13.0%), South America (7.2%), and Africa (5.7%) in descending order.

Primary Dual and Multiple Antibiotic Resistances

A higher multiple antibiotic resistance rate was reported from Turkey (n=98) CLR-MTR-LVX 18.1% and out of 110 American *H. pylori* positive patients, 1.8% were resistant for CLR-MTR-LVX and for CLR-MTR, 5.5% for CLR-LVX and MTR-LVX.²³ In Poland among 67 participants 32.5%, 1.5%, and 4.5% individuals were non-susceptible for CLR-MTR, CLR-LVX and MTR-LVX, respectively.²⁵ Above the multiple drug resistance, a higher dual resistance rate was also seen in Turkey (n=98); 45.4% and 27.2% to CLR-MTR and to CLR-LVX resistance rate were reported, respectively.²³ In

addition, dual resistance pattern of 1.8% was reported to MTR/CLR in Singapore. About 10.5% (n=76) of Peruvian patients were resistant for AMX/CLR which are parts of the standard triple therapy regimen (Table 1).

Overall Resistance

From a total of 14 studies retrieved with a total of 4218 study participants of *H. pylori* positive patients, the overall pooled primary resistance was found; 4.55% at 95% CI: 3.96–5.22% for AMX, 27.22% at 95% CI: 25.89–28.58% for CLR, 39.66% at 95% CI: 38.20–41.15% for MTR, and 22.48% at 95% CI: 21.24–23.76% for LVX. These studies were from different continents including from Europe, North America, South America, Asia and Africa. These studies had used different methods of testing antibiotic susceptibility (Table 2).

Discussion

The treatment success of *H. pylori* eradication achieved by first-line treatment with a proton pump inhibitor, CLR and AMX have decreased to 70–85% due to increasing CLR resistance.⁶ Unlike De Francesco et al¹⁵ consideration where improved knowledge in drug resistance strategies can result in better infection control, the safe and effective way of bacterial infection prevention and control seems difficult to touch.

The present study found higher resistance rate of CLR recorded in Europe, Asia and Africa. In addition, highest rate of non-susceptibility was seen in Asia for MTR and LVX. Concurrent to this, other worldwide systematic review

Table 1 Primary Resistance Pattern of *Helicobacter pylori* to Antibiotics Across Different Countries 2015–2017

Author(s) and Year	Country	No. of Participants (n)	Study Period	Prevalence of Primary Antibiotic Resistance			
				AMX	CLR	MTR	LVX
Zhang et al 2015 ²¹	China	375	2009–10	0.067(0.0478–0.0996)	0.399(0.3517–0.4504)	0.668(0.6202–0.7150)	0.345(0.3003–0.3962)
Zhang et al 2015 ²¹	China	950	2013–14	0.044(0.0329–0.0592)	0.526(0.4945–0.5579)	0.638(0.6079–0.6689)	0.548(0.5166–0.5798)
Caliskan et al 2015 ²⁴	Turkey	98	2012–13	0	0.367(0.2786–0.4661)	0.355(0.2693–0.4557)	0.295(0.2146–0.3926)
Ferenc et al 2017 ²⁵	Poland	67	2011–13	0	0.552(0.4336–0.6652)	0.567(0.4481–0.6790)	0.059(0.0235–0.1437)
Ang et al 2016 ²⁶	Singapore	170	2012–14	0.041(0.0201–0.0825)	0.171(0.1215–0.2343)	0.482(0.4085–0.5570)	0.147(0.1016–0.2081)
Boehnke et al 2017 ²⁷	Peru	76	2011–13	0.329(0.2338–0.4406)	0.355(0.2570–0.4674)	0.618(0.5060–0.7194)	0.539(0.4282–0.6469)
Tamayo et al 2017 ²⁸	Spain	91	2014–15	NA	0.077(0.0378–0.1504)	NA	NA
Shiota et al 2015 ²⁹	America	110	2009–13	0	0.145(0.0916–0.2233)	0.173(0.1135–0.2541)	0.291(0.2142–0.3817)
Eng et al 2015 ³⁰	Canada	20	2012–13	0	0.40(0.2188–0.6134)	0.35(0.1812–0.5671)	0.30(0.1455–0.5190)
Sanches et al 2016 ³¹	Brazil	490	2012–15	NA	0.169(0.1388–0.2051)	NA	NA
Miftahussurur et al 2016 ³²	Nepal	42	2012	0	0.214(0.1171–0.3594)	0.881(0.7500–0.9481)	0.429(0.2912–0.5779)
Liou et al 2015 ³³	Taiwan	1395	2000–12	0.023(0.0169–0.0330)	0.112(0.0970–0.1302)	0.257(0.2351–0.2809)	0.088(0.0744–0.1042)
Bouihat et al 2016 ³⁴	Morocco	177	2014	0	0.254(0.1958–0.3231)	0.401(0.3318–0.4747)	0.107(0.0698–0.1616)
Zaki et al 2016 ³⁵	Egypt	46	2014–15	0.478(0.3412–0.6186)	0.608(0.4646–0.7361)	0.217(0.1226–0.3557)	NA
Harrison et al 2017 ³⁶	Nigeria	111	2010–13	0.333(0.2525–0.4253)	0.144(0.0907–0.2214)	0.991(0.9507–0.9984)	NA

Abbreviations: AMX, amoxicillin; CLR, clarithromycin; LVX, levofloxacin; MTR, metronidazole; NA, not analyzed.

Table 2 Overall Primary Resistance Pattern of *Helicobacter pylori* to Antibiotics in Adult Population Across Different Continents 2015–2017

Country	No. of Participants	Overall Prevalence of Primary Antibiotic Resistance			
		AMX	CLR	MTR	LVX
Europe	256	0	0.3125(0.2588–0.3717)	0.2852(0.2333–0.3433)	0.1289(0.0933–0.1755)
North America	130	0	0.1850(0.1273–0.2600)	0.2000(0.1403–0.2769)	0.2923(0.2210–0.3756)
South America	566	0.0442(0.0301–0.0644)	0.1943(0.1639–0.2290)	0.0830(0.0630–0.1087)	0.0724(0.0538–0.0968)
Asia	2732	0.0395(0.0328–0.0478)	0.3093(0.2922–0.3269)	0.4890(0.4703–0.5078)	0.2990(0.2822–0.3165)
Africa	334	0.1766(0.1395–0.2212)	0.2665(0.2219–0.3163)	0.5719(0.5183–0.6238)	0.0569(0.0367–0.0871)
Overall	4218	0.0455(0.0396–0.0522)	0.2722(0.2589–0.2858)	0.3966(0.3820–0.4115)	0.2248(0.2124–0.2376)

reported, the overall rate of *H. pylori* antibiotic resistance was found 11.2% to AMX, 17.2% to CLR, 26.7% to MTR, and 16.2% to LVX. The prevalence rate of CLR, MTR and LVX resistance was significantly increased from Europe to Asia, Northern America and Africa.¹³ This might be due to irrational use of antibiotics. Similarly, other study also addressed the rate of *H. pylori* antibiotic resistance were 14.7% to AMX, 19.7% to CLR, 47.2% to MTR, and 18.9% to LVX. The prevalence rate of MTR and AMX resistance was higher in Africa, while CLR and LVX resistance was higher in North America and Asia, respectively.³⁷ Compared to these studies, the primary resistance rate towards CLR substantially increased from 17.2%¹³ 19.7%³⁷ to 27.2%. LVX resistance was also increased from 16.2%¹³ to 22.5%. Despite the over consumption of AMX and MTR the frequency of non-susceptibility rate of these antibiotics was found decreased. This was in contrary to previous studies.^{13,37} This might be due to the recent implementation of antimicrobial stewardship and rational antimicrobial practice awareness creation.³⁸ However, even in the recent implementation of the programs the other above mentioned antibiotics resistance rate is substantially increased which necessities other studies to be undertaken.

Country specific systematic review studies reported 16.0%, 22.4%, 61.6%, and 5.3% in Iran;³⁹ 9.7%, 24.8%, 33.7%, and 23.8% in Turkey;³⁸ 4%, 12%, and 53% in Latin America (no for LVX);⁴¹ 3.1%, 28.9%, 63.8%, and 28.0%, in China⁴² to AMX, CLR, MTR and LVX, respectively. The resistance pattern for MTR and LVX was diffused and higher especially to MTR. AMX resistance in Latin America and China was comparable however Turkish and Iranian reviews reported double and almost four times higher from the present study.^{39–42} This shows the antibiotic susceptibility pattern of *H. pylori* could not be predicted arbitrary in any country mandating that implementation of local drug

susceptibility surveillance program and appropriate or rational prescribing and use of antibiotics is necessary.

Individual and dual antibiotic resistance significantly influences the successful eradication of the bacterial infection. The Maastricht V 2016 guideline report articulates resistance to CLR affect the efficacy of both sequential and triple treatment methods and resistance to MTR affects the treatment success by sequential therapy. Moreover, the report also had reported resistance to CLR and MTR affects the efficacy of sequential, hybrid and concomitant therapy of *H. pylori* eradication treatment protocols. According to this empirical triple therapy is discouraged. When the resistance of *H. pylori* is greater than 15% towards CLR at the specified area the treatment should be based on susceptibility pattern to other antibacterials.⁴³

Multi-resistant strains of *H. pylori* result in life-long infection that might lead to death.^{44,45} With the reserved treatment alternatives,^{43,46} a study conducted by Olleik et al on temporin-SH and its analogs resulted in good activity against resistant strains of *H. pylori* which should be taken as promising treatment alternatives for the eradication of resistant *H. pylori* infection.⁴⁷

Appropriate surveillance programs, improved antimicrobial regulations and increased public awareness to region-specific resistance rate of *H. pylori* isolates are possible mechanisms of prevention for *H. pylori* associated drug resistance.^{41,48,49} Therefore, drug susceptibility result of these antibiotics is necessary to select the appropriate drug for the successful eradication of the infection. This fosters rational drug prescribing practice improve patient treatment outcome and avoid unnecessary medical and nonmedical expenditure.

Conclusion

The primary antibiotic resistance of *H. pylori* is increasing worldwide. The overall resistance rate was found to be 4.55% at 95% CI (3.96–5.22) for amoxicillin; 27.22% at 95% CI (25.89–28.58) for clarithromycin; 39.66% at 95%

CI (38.20–41.15) for metronidazole; and 22.48% at 95% CI (21.24–23.76) for levofloxacin. The antibiotic susceptibility pattern of the *H. pylori* could not be predicted arbitrary in any country mandating that implementation of local drug susceptibility surveillance program and appropriate or rational prescribing and use of antibiotics as necessary.

Abbreviations

AMX, amoxicillin; CLR, clarithromycin; *H. pylori*, *Helicobacter pylori*; LVX, levofloxacin; MTR, metronidazole; NHS, National Institute for Health research.

Data Sharing Statement

The datasets used for this study should be accessed from the corresponding author on reasonable request.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare they have no conflicts of interest in this work.

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