Published in final edited form as:
Am J Gastroenterol. 2014 April ; 109(4): 485–495. doi:10.1038/ajg.2014.24.

The Problem of *Helicobacter pylori* Resistance to Antibiotics: A Systematic Review in Latin America

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Abstract

OBJECTIVES—Latin America has a high prevalence of *Helicobacter pylori* infection and associated diseases, including gastric cancer. Antibiotic therapy can eradicate the bacterial infection and decrease associated morbidity and mortality. To tailor recommendations for optimal treatments, we summarized published literature and calculated region- and country-specific prevalences of antibiotic resistance.

METHODS—Searches of PubMed and regional databases for observational studies evaluating *H. pylori* antibiotic resistance yielded a total of 59 independent studies (56 in adults, 2 in children, and 1 in both groups) published up to October 2013 regarding *H. pylori* isolates collected between 1988 and 2011. Study-specific prevalences of primary resistance to commonly prescribed

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SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

CONFLICT OF INTEREST

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Specific author contributions: Study concept and design: M.C.C., A.G. and C.S.R; acquisition of data: A.G., C.A.C., and T.H.; statistical analysis: M.C.C.; drafting of the manuscript: M.C.C. and C.S.R.; critical revision of the manuscript for important intellectual content: all authors.

Potential competing interests: The authors declare no conflict of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the United States National Cancer Institute and/or the United States Centers for Disease Control and Prevention.

antibiotics were summarized using random-effects models. Between-study heterogeneity was assessed by meta-regression. As a sensitivity analysis, we extended our research to studies of patients with prior *H. pylori*-eradication therapy.

RESULTS—Summary prevalences of antimicrobial primary resistance among adults varied by antibiotic, including 12% for clarithromycin (n = 35 studies), 53% for metronidazole (n = 34), 4% for amoxicillin (n = 28), 6% for tetracycline (n = 20), 3% for furazolidone (n = 6), 15% for fluoroquinolones (n = 5), and 8% for dual clarithromycin and metronidazole (n = 10). Resistance prevalence varied significantly by country, but not by year of sample collection. Analyses including studies of patients with prior therapy yielded similar estimates. Pediatric reports were too few to be summarized by meta-analysis.

CONCLUSIONS—Resistance to first-line anti- *H. pylori* antibiotics is high in Latin American populations. In some countries, the empirical use of clarithromycin without susceptibility testing may not be appropriate. These findings stress the need for appropriate surveillance programs, improved antimicrobial regulations, and increased public awareness.

INTRODUCTION

Chronic *Helicobacter pylori* infection is causally related to serious benign and malignant upper gastrointestinal diseases, including peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer (1). Conversely, eradication of *H. pylori* is associated with ulcer healing (2), regression of mucosa-associated associated lymphoid tissue lymphoma (3), and decreased cancer risk (4). Successful treatment for *H. pylori* infection requires multidrug regimens, which are frequently based on clarithromycin as the central component. Eradication rates vary with level of antibiotic resistance (5,6), and, according to one guideline (7), the use of clarithromycin without susceptibility testing is not recommended in populations with more than 15–20% prevalence of resistant isolates.

Many Latin American countries have a high burden of *H. pylori* infection (8,9) and associated diseases, particularly gastric cancer (10). This geographic region also has multiple avenues of unfettered access to antibiotics, including self-medication, unnecessary prescriptions, and lax regulation of sales (11). In order to guide treatment choice and tailor eradication strategies for Latin American populations, we summarized the published literature on *H. pylori* antibiotic resistance in the region.

METHODS

Review methods and reporting were performed according to the PRISMA guidelines (12).

Search strategy and selection criteria

The literature databases PubMed (United States National Library of Medicine, Bethesda, MD), LILACS (Latin America and the Caribbean Literature on Health Sciences; http://lilacs.bvsalud.org/en), and SciELO (Scientific Electronic Library Online; http://www.scielo.org) were searched for observational studies evaluating *H. pylori* antibiotic resistance in the 20 countries comprising Latin America, as defined by the United Nations

Educational Scientific and Cultural Organization (13), published in any language up to 31 October 2013.

To identify studies in PubMed, the following search strategy was used: *Helicobacter pylori*, and antimicrobial resistance or antibiotic resistance or " Drug Resistance, Microbial " [Mesh] or " Microbial Sensitivity Tests " [Mesh] and Latin America or Central America or South America or Argentina or Aruba or Bolivia or Brazil or Colombia or Costa Rica or Cuba or Chile, or Dominican Republic or Ecuador or El Salvador or Guatemala or Honduras or Mexico or Nicaragua or Panama or Paraguay or Peru or Uruguay or Venezuela. Analogous strategies were used to search the other two databases.

Two investigators (C.A.C. and T.H.-G.) independently reviewed titles and abstracts for selection of potentially relevant articles; any disagreement was resolved by consulting a third reviewer (A.G.). Full-text articles were retrieved for potential inclusion if data on resistance to at least one antibiotic were reported. Citations of retrieved articles were reviewed for studies that may have been missed or were absent from our database queries.

The following information was abstracted from each selected article: first author, year of publication, study location (country), year of sample collection, participant age (range or mean), prior antibiotic treatment for *H. pylori*, number of patients, histologic diagnoses, number of samples (gastric biopsies or *H. pylori* isolates), prevalence of antibiotic resistance, and method of resistance assessment (agar dilution, E-test, disk diffusion, or detection of point mutations by polymerase chain reaction). To ensure comparability across studies, we contacted the corresponding authors to enquire about missing data on prior antibiotic treatment for *H. pylori*. In all, 20 of the 21 authors contacted provided unpublished information. We also obtained additional unpublished data for 11 studies on year of sample collection and potentially overlapping sample sets.

In order to assess quality (risk of bias) of the included studies, we evaluated the following characteristics: (1) representativeness of the patients; (2) consecutive or random selection for inclusion; (3) adequacy of description of patient characteristics (e.g., demographics, year of sample collection, histologic diagnoses, and so on); (4) accounting of study flow (e.g., percentage of not consenting, percentage of failed cultures, percentage of inconclusive results, and so on); and (5) validity of testing methodology. Each domain was coded individually as " + " (i.e., low risk of bias), " − " (i.e., high risk of bias), or "?" (i.e., unclear).

Statistical analysis

All of our analyses were restricted to adults. We used random-effects models (14) to summarize double arcsine – transformed (15) prevalences of primary resistance to antibiotics, for which more than five articles were identified. Summary prevalences and corresponding 95% confidence intervals (CIs) were calculated by back-transformation. Study-specific results are presented for antibiotics reported in two to four articles, but antibiotics reported in a single study were not summarized. Given their similar antimicrobial activity, data on levofloxacin and ciprofloxacin resistance were combined. Between-study heterogeneity was assessed for statistical significance using the *Q* test and quantified with

the I^2 statistic as low (<25%), moderate (25–50%), or high (>50%) (16). If moderate or high heterogeneity was identified for a given antibiotic, meta-regression models were used to examine the extent to which country, year of sample collection (1988–1995, 1996–2000, 2001–2005, or 2006–2011), or test method may be explanatory. For one study that reported antibiotic resistance by anatomic subsite of sample collection (i.e., antrum or corpus), we used a random-effects model to estimate the overall prevalence. For 15 articles that did not state when samples were collected, year of collection was imputed as being 4 years prior to publication on the basis of the median difference between sample collection and publication year for the remaining articles. Sensitivity analyses were performed by including studies that evaluated secondary resistance (i.e., with prior antibiotic treatment for *H. pylori*) as well as those that did not specify prior antibiotic exposure.

For each of the evaluated antibiotics, publication bias was investigated by visual inspection of Begg's funnel plots (17) and was formally tested using Egger's regression asymmetry method (18). Meta-analyses were performed with Stata version 11 (Stata-Corp, College Station, TX, USA) using a combination of published macros (19). A *P* value of less than 0.05 was considered statistically significant for all tests, except the heterogeneity and Egger tests for which a *P* value less than 0.10 was considered significant. All statistical tests were two-sided.

RESULTS

Literature search and description of studies

The literature searches identified a total of 201 articles: 106 from PubMed, 49 from LILACS, and 46 from SciELO (Figure 1). After excluding 146 irrelevant or duplicate publications, 55 full-text articles were retrieved for further evaluation; 9 additional publications were identified from citations of these articles. Five articles were excluded because the respective authors had other publications involving the same antibiotic in larger, but overlapping, samples. Thus, a total of 59 articles (38 written in English and 21 in Spanish) reporting on samples collected between 1988 and 2011 for assessing resistance to clarithromycin, metronidazole, amoxicillin, tetracycline, furazolidone, levofloxacin, and/or ciprofloxacin were included in this analysis (Supplementary Table online). Other antibiotics that were reported in single studies and therefore were not summarized included azithromycin, trovafloxacin, ampicillin, and doxycycline.

Fifty-six studies reported on adults, two only on children and one had both population groups. A total of 14 studies were conducted in Brazil, 11 in Colombia, 9 in Mexico, 5 in Chile, 5 in Argentina, 3 in Peru, 3 in Cuba, 3 in Costa Rica, 2 in Venezuela, 2 in Ecuador, 1 in Paraguay, and 1 in Uruguay. The total sample size ranged from 15 to 395 *H. pylori* isolates. In all, 6 studies included samples collected during the period 1988–1995, 20 during 1996–2000, 17 during 2001–2005, and 16 during 2006–2011. Forty-eight (81%) studies evaluated resistance by either agar dilution or E-test. Regarding the type of resistance, 50 (85%) studies evaluated only primary resistance, 8 (13%) included secondary resistance, and 1 (2%) did not specify this information.

Assessment of study quality

In general, the reviewed studies included a representative spectrum of patients and used valid methods to assess resistance (Table 1). There were some deficiencies with regard to the reporting of sampling strategy and patient characteristics. Nevertheless, based on the information for sample collection period, it seems likely that most studies used consecutive or random selection.

Summary estimates of resistance in adults

Clarithromycin—Thirty-five studies examined primary resistance to clarithromycin. Study-specific prevalences ranged from 0% to 60% (Supplementary Figure S1). The overall summary prevalence was 12%, with high between-study heterogeneity (Table 2). Peru (50%, *n* = 1) reported the highest prevalence, where as Paraguay (2%, *n* = 1) reported the lowest. Pre valences did not differ significantly by period of collection (Table 2). Furthermore, prevalence estimates did not vary significantly by test method (*P*= 0.9): the estimates were 13% (*n* = 16) for agar dilution, 12% (*n* = 14) for E-test, 14% (*n* = 4) for disk diffusion, and 8% (*n* = 1) for PCR. The summary prevalence including studies evaluating secondary (*n* = 7) resistance was 12% (95% CI, 9–16%; *n* = 42).

Metronidazole—Prevalences of primary resistance to metronidazole were reported in 34 studies. Study-specific prevalences ranged from 12.5% to 95% (Supplementary Figure S2). The summary prevalence was 53% with high heterogeneity among studies (Table 2). The highest resistance was reported in Colombia (83%, *n* = 4; Table 3), whereas the lowest was reported in Argentina (30%, *n* = 3). Prevalences did not differ significantly by period of collection (Table 2). Furthermore, prevalence estimates did not vary significantly by test method (*P* = 0.3): the estimates were 44% for agar dilution (*n* = 13), 57% (*n* = 16) for E-test, 62% (*n* = 3) for disk diffusion, and 59% (*n* =2) for PCR. The summary prevalence including studies evaluating secondary (*n* = 5) or unspecified (*n* = 1) resistance was 56% (95% CI, 49–63%; *n* = 40).

Amoxicillin—Twenty-eight studies examined primary resistance to amoxicillin. Study-specific prevalences ranged from 0% to 39%. The summary prevalence was 4%, with high heterogeneity among the studies (Table 2). The highest resistance was reported in Brazil (15%, *n* = 5; Table 3). Prevalence did not differ significantly by period of collection (Table 2). Furthermore, prevalence estimates did not vary significantly by test method (*P* = 0.5): the estimates were 6% (*n* =14) for agar dilution, 3% (*n* =12) for E-test, and 3% (*n* =2) for disk diffusion. The summary prevalence including studies evaluating secondary (*n* = 5) or unspecified (*n* = 1) resistance was 4% (95% CI, 2–8%; *n* = 34).

Tetracycline—Primary resistance to tetracycline was evaluated in 20 studies. Study-specific prevalences ranged from 0% to 86%. The summary prevalence was 6% with high between-study heterogeneity (Table 2). The highest resistance was reported in Colombia (86%, *n* = 1; Table 3). Prevalence did not differ significantly by period of collection (Table 2). However, prevalence estimates varied significantly by test method (*P*= 0.0002): the estimates were 6% (*n* = 9) for agar dilution, 1% (*n* = 7) for E-test, 86% (*n* = 1) for disk

diffusion, and 10% (n =3) for PCR. The summary prevalence including studies evaluating secondary (n = 3) or unspecified (n = 1) resistance was 7% (95% CI, 2–14%; n = 24).

Furazolidone—Primary resistance to furazolidone was studied only in Brazil (n = 6), with study-specific prevalences ranging from 0% to 14%. The summary prevalence was 3% with high heterogeneity across studies (Table 2). Prevalences did not differ significantly by period of collection (Table 2). All studies used agar dilution to assess resistance.

Fluoroquinolones—Five studies provided results about primary resistance to levofloxacin or ciprofloxacin (Supplementary Table) with study-specific prevalences ranging from 4% to 37%. The summary prevalence was 15% with high heterogeneity across studies (Table 2). Four studies used E-test to assess resistance (11%; 95% CI, 4–19%). The summary prevalence including studies evaluating secondary (n = 1) or unspecified (n = 1) resistance was 15% (95% CI, 7–25%; n = 7).

Clarithromycin and metronidazole—Dual primary resistance to clarithromycin and metronidazole was examined in 10 studies. Study-specific prevalences ranged from 0% to 18%. The summary prevalence was 8% with high heterogeneity among studies (Table 2). The highest resistance was reported in Mexico (13%, n = 4; Table 3), whereas the lowest was reported in Paraguay (2%, n = 1). Prevalences did not differ significantly by period of collection (Table 2). The summary prevalence including studies evaluating secondary resistance (n = 3) was 7% (95% CI, 4–10; n = 13).

Pediatric studies

As compared with adults, higher prevalences were observed in the three studies in children (Supplementary Table) for resistance to clarithromycin (ranging from 19% to 27%) and dual resistance to clarithromycin and metronidazole (18%), whereas lower prevalences were reported for metronidazole (ranging from 13% to 78%), tetracycline (0%), and furazolidone (0%). No pediatric data were available for resistance to fluoroquinolones.

Publication bias

For studies in adults, the P values for Egger's test were equal or greater than 0.10 for all antibiotics (Table 2). Funnel plots confirmed symmetric distributions.

DISCUSSION

Antibiotic resistance patterns of *H. pylori* may predict the effi-cacy of current antibiotic regimens and may suggest new treatment strategies. Our study represents the first systematic effort to review and synthesize available data in Latin America. Our analysis indicates that *H. pylori* resistance to first-line antibiotics is high in some countries, which may contribute to high rates of treatment failure in this region.

Three-drug regimens including a proton pump inhibitor (PPI), clarithromycin, and either metronidazole or amoxicillin have been widely recommended as a first choice for *H. pylori* eradication with success rates of around 80% (7,20). However, this approach has decreased the efficacy of antibiotics in individuals with antibiotic-resistant strains (5,21,22). In the

presence of clarithromycin or metronidazole resistance, the success rate of a PPI – clarithromycin–metronidazole regimen is significantly reduced by 35% and 18%, respectively. The decrease in success is 66% in case of clarithromycin resistance if the treatment contains PPI – clarithromycin – amoxicillin (5,23). Alternative first-line regimens include bismuth-containing quadruple, sequential, concomitant quadruple, and hybrid therapies (24).

According to the fourth edition of the European Maastricht Consensus (7), PPI clarithromycin – containing triple therapy without prior susceptibility testing should be abandoned in a given region when the local clarithromycin resistance rate is more than 15–20%. Levels within or above this range have already been reported in some European and Asian countries (25–28). Similarly, although the overall prevalence in Latin America (13%) was below this threshold, our meta-analysis suggests that empirical use of clarithromycin may not be appropriate in Peru, and perhaps in Colombia.

Levofloxacin is frequently substituted for clarithromycin in second-line treatment regimens for *H. pylori* infections. Given its broad spectrum of antibacterial activity, resistance to this agent may evolve rapidly. The overall prevalence of fluoroquinolone resistance in Latin America is higher than the overall levofloxacin resistance rates reported for Europe (14.1%) (25) and Asia (11.6%) (26). Urinary tract *Escherichia coli* isolates in Latin America also have a high prevalence of this resistance (29). Levofloxacin should not be used for first-line therapy of *H. pylori* infections. This antibiotic should only be considered for patients with clarithromycin-resistant isolates and for retreatment of patients who failed first-line clarithromycin-based therapies (7).

Regarding metronidazole, our meta-analysis found that resistance in Latin American populations was high and stable over the study period without remarkable trends within individual countries. Although concerns have been raised regarding lack of reproducibility of metronidazole testing for individual diagnosis (30,31), the trend of low, medium, or high prevalences provides useful information at a population level (32). In contrast to clarithromycin, metronidazole resistance is not of great clinical relevance, as it can be overcome by increasing the length of treatment or by adding bismuth to the regimen (33).

The relatively low overall prevalence of amoxicillin resistance in Latin America is similar to that of other regions (25). Thus, inclusion of this antibiotic in empiric eradication regimens is still appropriate worldwide.

In some areas, local variation in *H. pylori* antibiotic resistance is associated with the use of the same antibiotic in the general population (25,34). On the basis of retail sales data, total per capita consumption of antibiotics in Latin America was found to have increased by nearly 10% between 1997 and 2007 (35). The 10-year sales trends for macrolide, lincosamide, and streptogramin antibiotics showed large increases in Peru, Brazil, and Argentina but relatively little change, or even decreases, in Uruguay, Mexico, and Colombia. In 2007, the countries with highest per capita consumption of macrolides (including clarithromycin) and related antibiotics were Venezuela, Argentina, and Chile. Fluoroquinolone use, including levofloxacin, significantly increased throughout the region,

with the highest consumption for 2007 recorded in the same three countries. The patterns in these retail data do not seem to correlate with the variation in prevalence of antimicrobial resistance, but further efforts should be directed to better monitor local and national antibiotic consumption.

Between-study heterogeneity was high in all meta-analyses and could not be explained by variation in country, period of sample collection, and test method. In previous studies, both patient (e.g., sex (36), age (25), and diagnosis (37)) and bacterial (e.g., cagA positivity (38,39)) characteristics have been associated with antibiotic resistance, and could therefore influence heterogeneity. Unfortunately, we did not have detailed data to assess such variation.

The majority of studies evaluated resistance by either agar dilution or E-test, which are both considered to be highly accurate and equivalently valid testing methodologies (40). Although in general we found no variation by testing method, studies using disk diffusion tended to provide higher resistance estimates. Nevertheless, these findings should be interpreted cautiously, as they were not based on studies directly comparing the techniques on the same *H. pylori* isolates.

The data we summarized mainly represent convenience samples of adults from 12 of the 20 Latin American countries. Most patients were recruited in specialized medical centers, with uncertain relevance to the appropriate target population for *H. pylori* eradication in Latin America. Also, there were only three reports regarding bacterial isolates from children. All the reviewed studies were at least moderate in quality with low risk of contributing bias to our systematic analysis. We found no evidence of publication bias.

Apart from antibiotic resistance, other determinants of eradication success include smoking, medication adherence, and host genetic variation. Smokers have a twofold increased risk of eradication failure (41). Poor adherence with the medication regimen is inversely associated with the probability of therapeutic success (42,43). Carriage of alleles encoding active cytochrome P450 2C19 isoenzymes is associated with increased PPI metabolism and diminished pharmacologic effect; these genotypes are common in Latin American populations (44,45). Success rates could be improved by strategies to reduce smoking and enhance adherence (e.g., counseling regarding medication side effects and risk of antibiotic resistance with treatment failure).

Surveillance systems for *H. pylori* antimicrobial resistance have proven useful for informing practitioners about empirical choices for treatment (25,36). Organized surveillance efforts in Latin American countries therefore warrant serious consideration. These systems could be set up using already established networks currently monitoring antibiotic resistance to other bacteria, such as the World Health Organization Collaborating Centre for Surveillance of Antimicrobial Resistance (WHONET), the Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA), the Alliance for the Prudent Use of Antibiotics (APUA), and the SENTRY antimicrobial surveillance program.

In conclusion, our meta-analysis demonstrated high *H. pylori* resistance to first-line antibiotics in Latin American countries. This finding stresses the need for appropriate

surveillance programs, improved institutional and governmental antimicrobial regulations, and increased public awareness and knowledge. Implementation of safe and effective eradication regimens can help alleviate the burden of *H. pylori* -related diseases, and in particular, to reduce the high incidence of gastric cancer in this region.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We are grateful to the following colleagues who provided unpublished information: Drs Adalucy Alvarez Aldana, Universidad Tecnológica de Pereira, Colombia; Guadalupe Ayala Aguilar, Instituto Nacional de Salud Pública, México; Douglas E. Berg, University California San Diego, United States; Mariana Catalano, Universidad de Buenos Aires, Argentina; Yvette Debets-Ossenkopp, Vrije Universiteit, The Netherlands; Mercedes Figueroa Macca, Universidad del Valle, Colombia; Beatriz Gutierrez, Instituto de Oncología y Radiobiología, Cuba; Rafael Llanes, Instituto de Medicina Tropical Pedro Kourí, Cuba; Rosario Morales-Espinosa, Universidad Autónoma de México, México; Diana Ortiz, Universidad Central de Venezuela, Venezuela; Laura Otth Rademacher, Universidad Austral de Chile, Chile; José Pedrazzoli Jr, Universidade São Francisco, Brazil; Orlando Reyes, Centro Nacional de Investigaciones Científicas, Cuba; Patricia Rivera Moya, Hospital Nacional de Niños, Costa Rica; Claude Andre Solari, Instituto Oswaldo Cruz, Brazil; Márcia Aparecida Sperança, Universidade Federal do ABC, Brazil; Alba E. Vega, Universidad Nacional de San Luis, Argentina. We also thank Olga Mejia from the Revista Colombiana de Gastroenterología and Dr Juan Carlos Maldonado from the Revista de la Facultad de Ciencias Médicas, Universidad Central del Ecuador for their assistance in gathering articles for our systematic review.

Financial support: This work was supported by the Intramural Research Program of the United States National Institutes of Health, National Cancer Institute.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Latin America has a high burden of *Helicobacter pylori* infection and associated diseases, particularly gastric cancer.
- ✓ Current *H. pylori* treatments have unacceptably high rates of failure.
- ✓ *H. pylori* resistance may decrease antibiotic efficacy, requiring alteration of eradication regimens.

WHAT IS NEW HERE

- ✓ Our meta-analysis found that primary resistance to first-line antibiotics is high in Latin America. In particular, empirical use of clarithromycin as the core antibiotic in *H. pylori* eradication regimens may already be an obsolete strategy for some countries.
- ✓ Better data on antibiotic resistance patterns are needed to improve region- and country-specific *H. pylori*-treatment strategies.
- ✓ This study represents the first systematic effort to review and synthesize available information on *H. pylori* antibiotic resistance in Latin America.

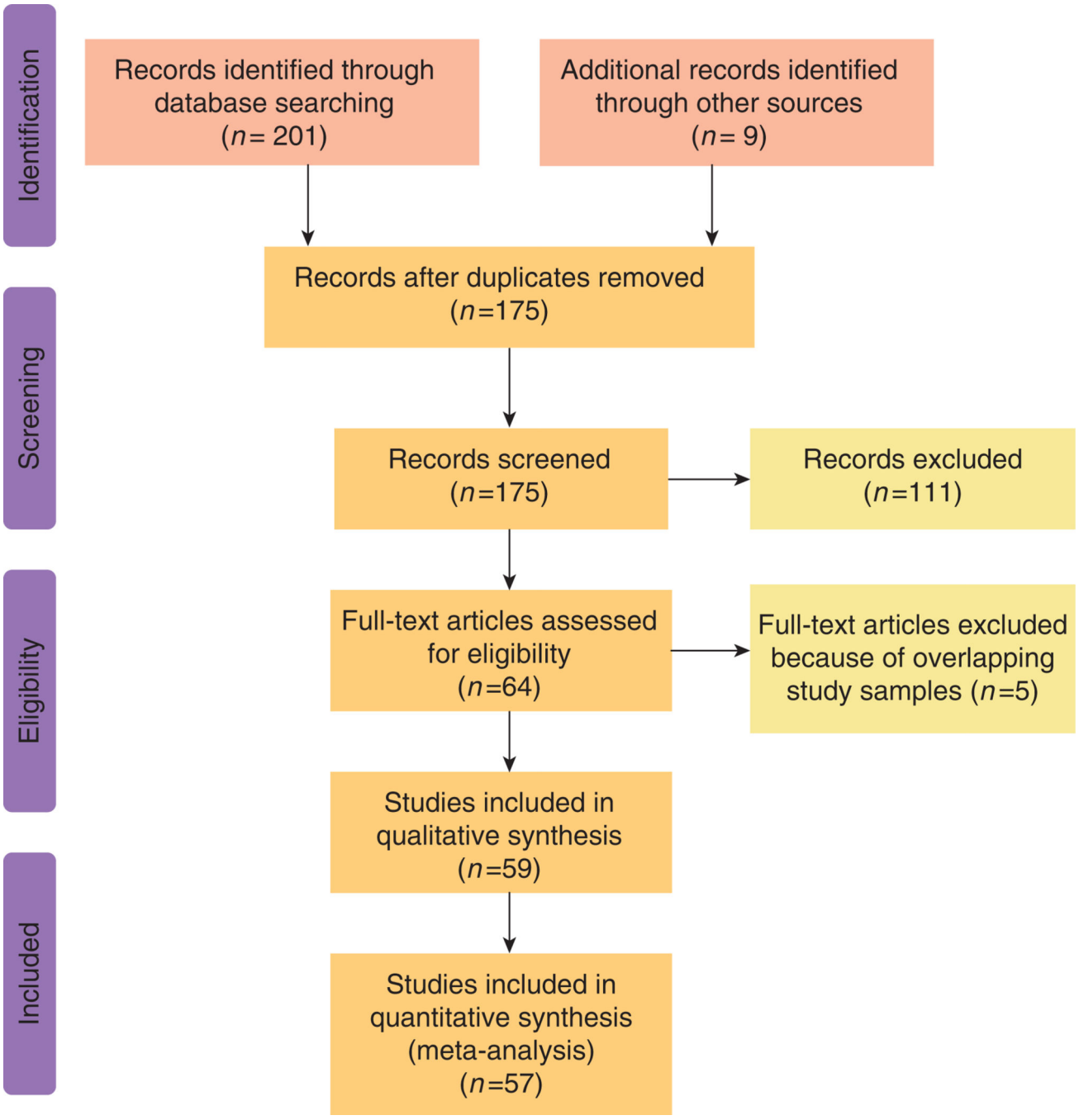

Figure 1.
Flow diagram of the literature search.

Table 1

Methodological assessment of risk of bias

Authors	Representativeness	Consecutive or random selection	Adequate description of patient characteristics	Accounting of study flow	Validity of testing methodology
Argentina					
Vega *et al.* (1)	+	?	Except collection time	+	+
Matteo *et al.*[a] (2)	?	?	Except age and diagnosis	+	+
Stege *et al.*[b] (3)	?	?	Except age	+	+
Matteo *et al.*[a] (4)	?	?	Except age and diagnosis	+	+
Antelo *et al.* (5)	+	+	Except collection time	+	+
Brazil					
Ogata *et al.* (6)	+	+	+	+	+
Suzuki *et al.*[a] (7)	+	+	+	+	+
Eisig *et al.* (8)	+	?	Except collection time	+	+
Lins *et al.* (9)	+	+	+	+	+
Garcia *et al.* (10)	+	+	+	+	+
Eisig *et al.* (11)	+	?	Except collection time	+	−
Godoy *et al.*[a] (12)	+	?	Except collection time	+	+
Magalhaes Queiroz *et al.* (13)	+	+	Except collection time	+	+
Prazeres Magalhães *et al.* (14)	?	?	Except collection time and age	+	+
Ecclissato *et al.* (15)	?	+	Except collection time	+	+
Mendonça *et al.* (16)	+	+	Except collection time	+	+
van Doorn *et al.* (17)	?	?	Missing collection time, age and diagnosis	−	+
Salazar *et al.*[a] (18)	+	?	Except age	+	+
Queiroz *et al.*[b] (19)	?	?	Except collection time	−	+
Chile					
Otth *et al.*[a] (20)	+	?	+	+	+
Toledo *et al.* (21)	+	?	Except age and diagnosis	+	+

Authors	Representativeness	Consecutive or random selection	Adequate description of patient characteristics	Accounting of study flow	Validity of testing methodology
Soto *et al.*[a] (22)	?	?	−	?	+
Vallejos *et al.* (23)	+	?	+	+	+
González *et al.*[a] (24)	+	?	Except age	+	−
Colombia					
Bustamante-Rengifo *et al.* (25)	+	?	+	+	+
Figueroa *et al.*[a] (26)	+	?	+	+	+
Trespalacios *et al.*[a] (27)	+	?	+	+	+
Trespalacios *et al.* (28)	+	?	+	+	+
Henao *et al.* (29)	+	?	+	+	+
Henao-Riveros *et al.* (30)	+	?	+	+	−
Alvarez *et al.*[a] (31)	+	−	Except age	+	+
Alvarez *et al.*[a] (32).	+	−	Except age	−	+
Yepes *et al* (33)	+	+	+	+	−
Isaza *et al.* (34)	?	?	+	+	+
Gutierrez *et al.*[a] (35)	+	?	+	+	+
Costa Rica					
Lang *et al.* (36)	+	?	+	+	+
Rivas *et al.* (37)	+	?	Missing collection time, age and diagnosis	+	+
Quintana-Guzmán *et al.* (38)	+	?	Missing collection time, resistance type, age and diagnosis	+	−
Cuba					
Reyes-Zamora *et al.*[a] (39)	+	?	Except age	+	+
Llanes *et al.*[a] (40)	+	+	+	+	+
Gutiérrez *et al.*[a] (41)	+	?	Except age	+	+
Ecuador					
Zurita *et al.* (42)	+	?	+	+	+
Debets-Ossenkopp *et al.*[a] (43)	+	?	Except age	+	+

Authors	Representativeness	Consecutive or random selection	Adequate description of patient characteristics	Accounting of study flow	Validity of testing methodology
Mexico					
Ayala *et al.*[a] (44)	+	?	Except diagnosis	+	+
Garza-Gonzalez *et al.* (45)	+	?	+	+	+
Morales-Espinosa *et al.*[a] (46)	?	?	Except age	+	+
Chihu *et al.*[a] (47)	+	−	+	+	+
Garza-Gonzalez *et al.* (48)	+	?	+	+	+
Dehesa *et al.* (49)	+	?	Except collection time	+	+
Torres *et al.* (50)	+	?	+	+	+
Dehesa *et al.* (51)	?	?	+	+	+
Lopez-Vidal *et al.* (52)	+	−	Except age	+	+
Paraguay					
Fariña *et al.* (53)	+	?	+	+	+
Peru					
Mochizuki-Tamayo *et al.* (54)	+	+	+	+	+
Berg *et al.*[a] (55)	+	?	+	+	−
Vasquez *et al.*[a] (56)	?	?	Except collection time and age	+	+
Uruguay					
Torres-Debat *et al.* (57)	+	−	Except diagnosis	+	+
Venezuela					
Ortiz *et al.*[a] (58)	+	?	+	+	+
Urrestarazu *et al.*[a] (59)	+	?	+	+	+

+, low; −, high; ?, unclear.

Reference numbers correspond to online Supplementary Information.

[a]Supplemented with unpublished data provided by personal communication.

[b]Letter to the Editor.

Table 2

Overall and period-specific summary prevalences of *H. pylori* antibiotic resistance among adults in Latin America

Antibiotic	No. of studies	Summary prevalence of resistance (95% CI), %	P_Q for heterogeneity	I^2 for heterogeneity, %	$P_{Egger's}$ for publication bias
Clarithromycin					
Primary	*35*	*12 (9–16)*	*< 0.001*	*89.7*	*0.11*
Study period (P *trend: 0.46*[a])					
1988–1995	1	50	—	—	
1996–2000	15	10 (6–15)	< 0.001	86.0	
2001–2005	10	13 (5–23)	< 0.001	93.4	
2006–2011	9	13 (8–20)	< 0.001	88.3	
All studies	*42*	*12 (9–16)*	*< 0.001*	*88.7*	*0.10*
Study period (P *trend: 0.47*[a])					
1988–1995	1	50	—	—	
1996–2000	19	11 (7–15)	< 0.001	85.1	
2001–2005	12	12 (5–21)	< 0.001	92.8	
2006–2011	10	14 (9–20)	< 0.001	86.8	
Metronidazole					
Primary	*34*	*53 (46–60)*	*< 0.001*	*92.0*	*0.85*
Study period (P *trend: 0.22)*					
1988–1995	5	65 (57–72)	0.593	0	
1996–2000	14	54 (44–63)	< 0.001	90.9	
2001–2005	9	47 (30–64)	< 0.001	93.3	
2006–2011	6	50 (29–71)	< 0.001	95.7	
All studies	*40*	*56 (49–63)*	*< 0.001*	*92.6*	*0.57*
Study period (P *trend: 0.15)*					
1988–1995	6	71 (57–83)	< 0.001	78.4	
1996–2000	17	55 (47–63)	< 0.001	89.7	
2001–2005	11	54 (39–70)	< 0.001	94.1	
2006–2011	6	50 (29–71)	< 0.001	95.7	

Antibiotic	No. of studies	Summary prevalence of resistance (95% CI), %	P_Q for heterogeneity	I^2 for heterogeneity, %	$P_{Egger's}$ for publication bias
Amoxicillin					
Primary	*28*	*4 (2–8)*	*< 0.001*	*93.4*	*0.69*
Study period (P *trend: 0.78)*					
1988–1995	2	1 (0–3)	0.862	0	
1996–2000	11	7 (1–17)	< 0.001	95.6	
2001–2005	8	3 (1–8)	< 0.001	79.7	
2006–2011	7	4 (0–9)	< 0.001	92.6	
All studies	*34*	*4 (2–8)*	*< 0.001*	*92.8*	*0.74*
Study period (P *trend: 0.35)*					
1988–1995	3	10 (2–51)	< 0.001	96.6	
1996–2000	14	5 (1–12)	< 0.001	94.8	
2001–2005	10	3 (1–6)	< 0.001	75.2	
2006–2011	7	4 (0–9)	< 0.001	92.6	
Tetracycline					
Primary	*20*	*6 (2–14)*	*< 0.001*	*96.4*	*0.13*
Study period (P *trend: 0.61)*					
1988–1995	2	1 (0–5)	0.855	0	
1996–2000	7	5 (1–11)	< 0.001	84.9	
2001–2005	6	13 (0–47)	< 0.001	98.8	
2006–2011	5	5 (0–15)	< 0.001	92.6	
All studies	*24*	*7 (2–14)*	*< 0.001*	*96.6*	*0.10*
Study period (P *trend: 0.62)*					
1988–1995	3	18 (7–83)	< 0.001	97.9	
1996–2000	8	4 (1–9)	< 0.001	83.7	
2001–2005	8	8 (0–30)	< 0.001	98.3	
2006–2011	5	5 (0–15)	< 0.001	92.6	
Furazolidone					
Primary	*6*	*3 (0–9)*	*< 0.001*	*85.4*	*0.31*
Study period (P *trend: NA)*					

Antibiotic	No. of studies	Summary prevalence of resistance (95% CI), %	P_Q for heterogeneity	I^2 for heterogeneity, %	$P_{Egger's}$ for publication bias
1988–1995	1	0	—	—	
1996–2000	4	6 (1–14)	< 0.001	88.2	
2006–2011	1	0	—	—	
Levofloxacin or ciprofloxacin					
Primary	*5*	*15 (6–28)*	*< 0.001*	*91.8*	*0.94*
Study period (P *trend: NA)*					
2001–2005	1	4	—	—	
2006–2011	4	19 (7–34)	< 0.001	91.6	
All studies		*15 (7–25)*	*< 0.001*	*88.6*	*0.93*
Study period (P *trend: 0.39)*					
1988–1995	1	7	—	—	
2001–2005	2	12 (0–35)	0.002	89.2	
2006–2011	4	19 (7–34)	< 0.001	91.6	
Clarithromycin and Metronidazole					
Primary	*10*	*8 (5–12)*	*< 0.001*	*74.6*	*0.34*
Study period (P *trend: 0.35)*					
1996–2000	6	10 (5–16)	< 0.001	81.6	
2001–2005	3	5 (3–9)	0.33	9.8	
2006–2011	1	5	—	—	
All studies	*13*	*7 (4–10)*	*< 0.001*	*73.0*	*0.15*
Study period (P *trend: 0.39)*					
1996–2000	8	8 (4–13)	< 0.001	78.7	
2001–2005	4	4 (2–7)	0.360	6.6	
2006–2011	1	5	—	—	

CI, confidence interval; NA, not applicable.

[a]Excluding the period 1988–1995.

Table 3

Country-specific summary prevalences of *H. pylori* antibiotic resistance among adults in Latin America

Country	Clarithromycin		Metronidazole		Amoxicillin		Tetracycline		Furazolidone		Clarithromycin and metronidazole	
	No. of studies	Resistance, % (95% CI)	No. of studies	Resistance, % (95% CI)	No. of studies	Resistance, % (95% CI)	No. of studies	Resistance, % (95% CI)	No. of studies	Resistance, % (95% CI)	No. of studies	Resistance, % (95% CI)
Primary												
Argentina	3	14 (3–31)	3	30 (20–42)	3	0 (0–1)	1	NA				
Brazil	7	11 (6–18)	7	54 (47–61)	5	15 (2–36)	5	2 (0–9)	6	3 (0–9)	2	5 (1–11)
Chile	3	9 (2–21)	4	31 (16–49)	3	2 (0–5)	3	14 (0–45)			2	7 (4–12)
Colombia	7	18 (7–31)	4	83 (73–90)	5	7 (2–14)	1	NA				
Costa Rica	2	6 (3–11)	2	42 (34–50)	2	3 (0–11)	2	6 (2–38)				
Mexico	7	13 (7–20)	7	60 (47–72)	6	4 (0–13)	3	2 (0–9)			4	13 (6–21)
Peru	1	NA	2	66 (51–79)			1	NA				
Venezuela	2	8 (3–16)	2	59 (41–77)	2	0 (0–4)	2	5 (1–13)			1	NA
All studies												
Argentina	3	14 (3–31)	3	30 (20–42)	3	0 (0–1)	1	NA				
Brazil	9	14 (8–21)	7	54 (47–61)	5	15 (2–36)	5	2 (0–9)	6	3 (0–9)	2	5 (1–11)
Chile	3	9 (2–21)	4	31 (16–49)	3	2 (0–5)	3	14 (0–45)			2	7 (4–12)
Colombia	8	16 (7–28)	5	83 (76–89)	6	6 (2–12)	2	33 (0–98)			1	NA
Costa Rica	2	6 (3–11)	3	63 (27–92)	3	13 (0–46)	3	26 (0–82)				
Cuba	2	6 (1–16)	2	68 (30–95)	1	NA	2	5 (0–26)				
Ecuador	2	9 (3–17)	2	66 (32–92)	2	0 (0–4)	1	NA			1	NA
Mexico	8	12 (7–19)	8	59 (48–70)	7	3 (0–11)	3	2 (0–9)			5	11 (6–18)
Peru	1	NA	2	66 (51–79)			1	NA				
Venezuela	2	8 (3–16)	2	59 (41–77)	2	0 (0–4)	2	5 (1–13)			1	NA

CI, confidence interval; NA, not applicable.

Summary prevalences not presented for single studies from Paraguay and from Uruguay.