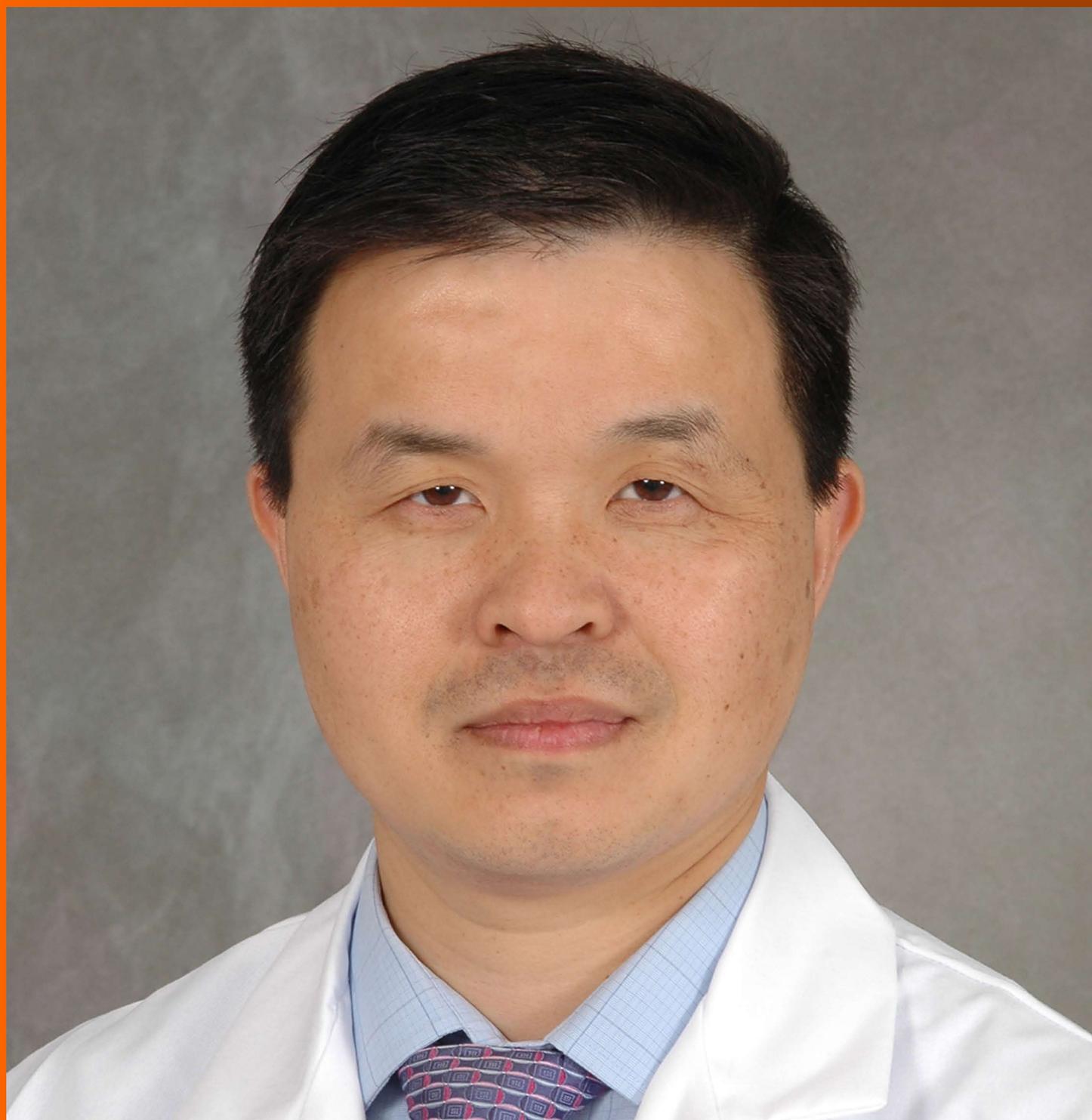


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World Journal of Gastrointestinal Oncology (World J Gastrointest Oncol, WJGO, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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***Helicobacter pylori* recurrence after eradication in Latin America: Implications for gastric cancer prevention**

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Abstract

AIM

To estimate *Helicobacter pylori* (*H. pylori*) recurrence rate in Latin America, a region with a significant *H. pylori* prevalence and gastric cancer burden.

METHODS

PubMed, LILACS, SciELO, Cochrane databases and abstracts from relevant meetings were reviewed. Information collected included: Participants' characteristics, recruitment strategy, diagnostic modality, treatment arms, follow-up and recurrence rates. Recurrence was calculated using 100-patients-year rates, and data were pooled using a random effects model. The I^2 statistic assessed between study heterogeneity. Meta-regression analyses evaluated for effect modifying variables.

RESULTS

Literature search yielded 163 articles. Twelve studies involving 4848 patients from 9 countries met inclusion criteria. Four hundred and thirty-two reinfections were recorded in 5487 person-years of follow-up. Pooled analysis showed a recurrence rate of 7.9 cases per 100 person-years (95%CI: 5.3-10.5). Meta-regression revealed that neither the antibiotic schema, a second antibiotic course, nor the diagnostic modality had an impact on the observed risk of recurrence. The recurrence rate in the first year after treatment, predominantly recrudescence,

was 11.2 (6.1-16.4) per 100 patient years. Recurrence in subsequent years, was only 6.2 (3.8-8.7).

CONCLUSION

H. pylori recurrence rates in Latin America are significant, and with geographic variability, yet are acceptable based upon the current literature for consideration of large scale intervention trials. Further research in Latin America is warranted to evaluate the efficacy, cost-effectiveness, and potential adverse outcomes of proposed eradication programs.

Key words: Gastric cancer; Reinfection; Hispanic; *Helicobacter pylori*; Latin America

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Core tip: Latin America has a high burden of gastric cancer mortality, with significant geographical variability, which offers the opportunity for prevention trials and interventions. Recent trials and meta-analysis show that *Helicobacter pylori* (*H. pylori*) eradication reduces the risk of gastric adenocarcinoma. *H. pylori* reinfection rates in Latin America are similar to those seen in Asian trials. Recurrent cases occur mostly within the first year suggesting treatment failure (re-growth), not reinfection. These findings were not significantly modified by diagnostic modality, the antibiotics selected, retreatment, or the time check for eradication success. Eradication programs are a potentially attractive strategy for gastric cancer prevention in Latin America.

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INTRODUCTION

Gastric cancer is the third most common cause of cancer mortality globally, and the leading infection-associated cancer^[1,2]. Of the 989000 gastric cancer cases in the world in 2008, 78% (770000) were estimated to be attributed to *Helicobacter pylori* (*H. pylori*) chronic infection^[3]. Gastric cancer has a marked geographic variability^[4,5]. Latin America has a particularly high burden of prevalent *H. pylori* infection and gastric cancer incidence and mortality^[6-8]. Estimated age-standardized mortality rates for males per 100000 are elevated in Honduras (22.3), Costa Rica (16.8), Peru (18.2), Chile (15.0), and Ecuador (20.7)^[5,9]. A concentration of incident gastric cancer is observed in the mountainous regions along the Pacific littoral, including in lower incidence countries (e.g., Mexico), which may offer the opportunity for focused prevention trials and interventions^[5].

Recent trials and a meta-analysis suggest that

screening and eradication of *H. pylori* can reduce the risk of gastric cancer^[10,11]. The Shangdong Intervention Trial, the largest randomized clinical trial to date, had a 53% *H. pylori* cumulative recurrence rate at 7 years, yet demonstrated a significant reduction in gastric cancer at 14.8 years (OR = 0.6, 95%CI: 0.4-0.9)^[10]. Trial participants were principally middle-aged Asian adults, and the generalizability of results to other populations is uncertain^[12]. Two subsequent meta-analyses confirmed the findings, while noting that the results were primarily driven by trials conducted in Asia^[11,13]. The International Agency for Cancer Research (IARC) has recently called for the design and study of large scale interventions for gastric cancer prevention in high incidence regions of the world, including Latin America^[12].

The *H. pylori* infection recurrence rate after eradication therapy is the critical determinant of the efficacy of an *H. pylori* eradication program designed to reduce the burden of gastric cancer. This review aims to estimate the reinfection rate of *H. pylori* after completion of antibiotic treatment in Latin America based upon existing literature. We present overall recurrence rates which includes both recrudescence (also called re-growth: Same strain, dominant in the first year after eradication) and reinfection (new strain, dominant in subsequent years), as the majority of studies do not genotype *H. pylori* strains.

MATERIALS AND METHODS

Review methods and reporting were performed according to the PRISMA guidelines^[14]. Literature databases PubMed (United States National Library of Medicine), LILACS (Latin America and the Caribbean Literature on Health Sciences), SciELO (Scientific Electronic Library Online) and Cochrane (the Cochrane Collaboration) were included as well as the abstracts from three major gastroenterology and infectious disease meetings [Digestive Disease Week (DDW), American College of Gastroenterology Scientific Meeting (ACG), and ID Week (IDW)]. Studies evaluating *H. pylori* reinfection in the 20 countries comprising Latin America, as defined by the United Nations Educational Scientific and Cultural Organization^[15], published in any language up to November 1st 2014 were included.

The search was performed in PubMed using the following sequence: *H. pylori* (MeSH term) AND [Recurrence (MeSH) or Recrudescence (MeSH) or Reinfection (not MeSH term)] AND (MeSH terms Latin America or Central America or South America or Argentina 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 Puerto Rico or Uruguay or Venezuela). No other filters or limits were used. Analogous strategies were used to search the other two databases and the meetings' abstracts. Three additional meta-analyses relevant to the study were reviewed for further references^[16-18].

Information coding

Three investigators (Juan E Corral, Corey W Dye and

Douglas R Morgan) independently reviewed titles and abstracts for selection of potentially relevant articles. For journal manuscripts, full text articles were retrieved for further review. Titles that could not be associated with an abstract were excluded from review. A priori, studies with a sample smaller than 50 patient-years (PYs) and studies reporting same populations as other previously registered were excluded from meta-analysis. Citations of retrieved articles were reviewed for studies that may have been missed or were absent from our database queries. Authors were not contacted to provide additional information.

The following information was abstracted from each article: Year of publication, first author, country, information regarding participants (age, recruitment strategy), treatment arms (number of arms, medications used and duration in each arm), follow-up details (duration, intervals of appointment), diagnostic modality and recurrence rates. The interval of possible recurrence started with the last day of antibiotic regimen treatment, and ended with the day of follow-up *H. pylori* diagnostic testing; the last day of treatment was chosen to optimally account for eradication regimens of varying duration. In a given study, if there was more than one follow-up *H. pylori* diagnostic test for recurrence, each testing result was documented independently. The earliest time interval to consider infection recurrence and to be included in the review was 6 mo.

The quality of data (risk of bias) was assessed recording 5 variables, using the same methodology as Camargo *et al.*^[17] Antibiotic strategy was recorded in detail (medications and length of treatment) and was also scored as an ordinal variable [0 = only one antibiotic without a proton pump inhibitor (PPI), ranitidine or bismuth; 1 = either one antibiotic and a PPI or two antibiotics but no PPI (ranitidine or bismuth allowed); 2 = includes two antibiotics and a PPI (regardless of scheme, for example, triple, quadruple, sequential)].

Statistical analysis

All treatment arms in each study were reviewed individually. Cases were allocated in two groups: The patients that received antibiotics and those that received either placebo or an antacid medication (PPI, H2 blocker or bismuth) but without antibiotics. Only antibiotic arms were included in meta-analysis. The number of patients with a negative test immediately after treatment (range 4-8 wk after antibiotic course) were recorded for the intention to eradicate analysis. The patients compliant with subsequent *H. pylori* testing were analyzed for our main analysis, and per our protocol, in this group, the patients lost to follow-up between eradication test (post antibiotics) and subsequent testing were not included. We also documented whether a second antibiotic course was offered for those patients with persistent infection or not.

We used a random-effects model to summarize recurrence rates. Summary reinfection rates and corresponding

95% CIs were calculated using the Poisson distribution. Forest plot graphs were created with 95% CIs. Given the relevance of differentiating between recrudescence (re-growth) and reinfection, subgroup analysis was performed for studies that looked for *H. pylori* recurrence at one year or less (< 53 wk cutoff) and those with longer follow-up^[16]. Pooled recurrence rates were calculated for different points in time for Latin America, starting at the first six months after completing antibiotics and for all subsequent years where data was available.

A secondary analysis was conducted with four additional comparisons: Recurrence 3 years after eradication, recurrence in studies enrolling children compared to studies restricted to adults, antibiotics regimens with high (> 75%) or low (\leq 75%) eradication success, and studies that assessed recurrence with endoscopy and biopsy compared to other diagnostic methods.

Meta-regression analyses were performed to evaluate for five effect modifying variables: Study population (community volunteers, patients with duodenal ulcers, dyspepsia, or intestinal metaplasia), *H. pylori* diagnostic modality (with or without urea breath test), quality of antibiotic treatment (0 to 2 points), possibility of a second antibiotic course, and length of follow-up (in years). Between-study heterogeneity was quantified using the I^2 statistic. Finally, publication bias was investigated by visual inspection of funnel plots. All statistical analyses were performed with Stata version SE 11.2 (Stata-Corp, College Station, TX, United States). The study plan and results were reviewed by a biomedical statistician (Robertino Mera).

RESULTS

The literature search resulted in 164 articles from the following sources: PubMed (104), LILACS (40), SciELO (20), and Cochrane (0) (Figure 1). Four abstracts were considered relevant from our review of conference reports (ACG 1, DDW 3, IDW 0). Two additional articles were identified after screening the references of manuscripts found in first review. After excluding 139 irrelevant or duplicate publications, 25 full text articles were retrieved for further evaluation, of which 7 were excluded because of incomplete data or duplicate samples and six additional per protocol for their small sample size (< 50 person-years of follow-up).

In summary, 12 studies from 9 countries met criteria for inclusion, which were published between 1991 and 2014 (Table 1). Ten studies included only adults, and an additional 2 studies included both adults and children. Eleven manuscripts were written in English and one in Spanish. Time to evaluate *H. pylori* eradication success ranged from 4 to 13 wk after last day of antibiotics (3 studies reported percentage of successful treatment "after randomization" without further details). Follow-up ranged from 6 mo to 16 years. These twelve studies encompassed 4848 patients [4685 patients received a treatment regimen that included antibiotics, 163 were

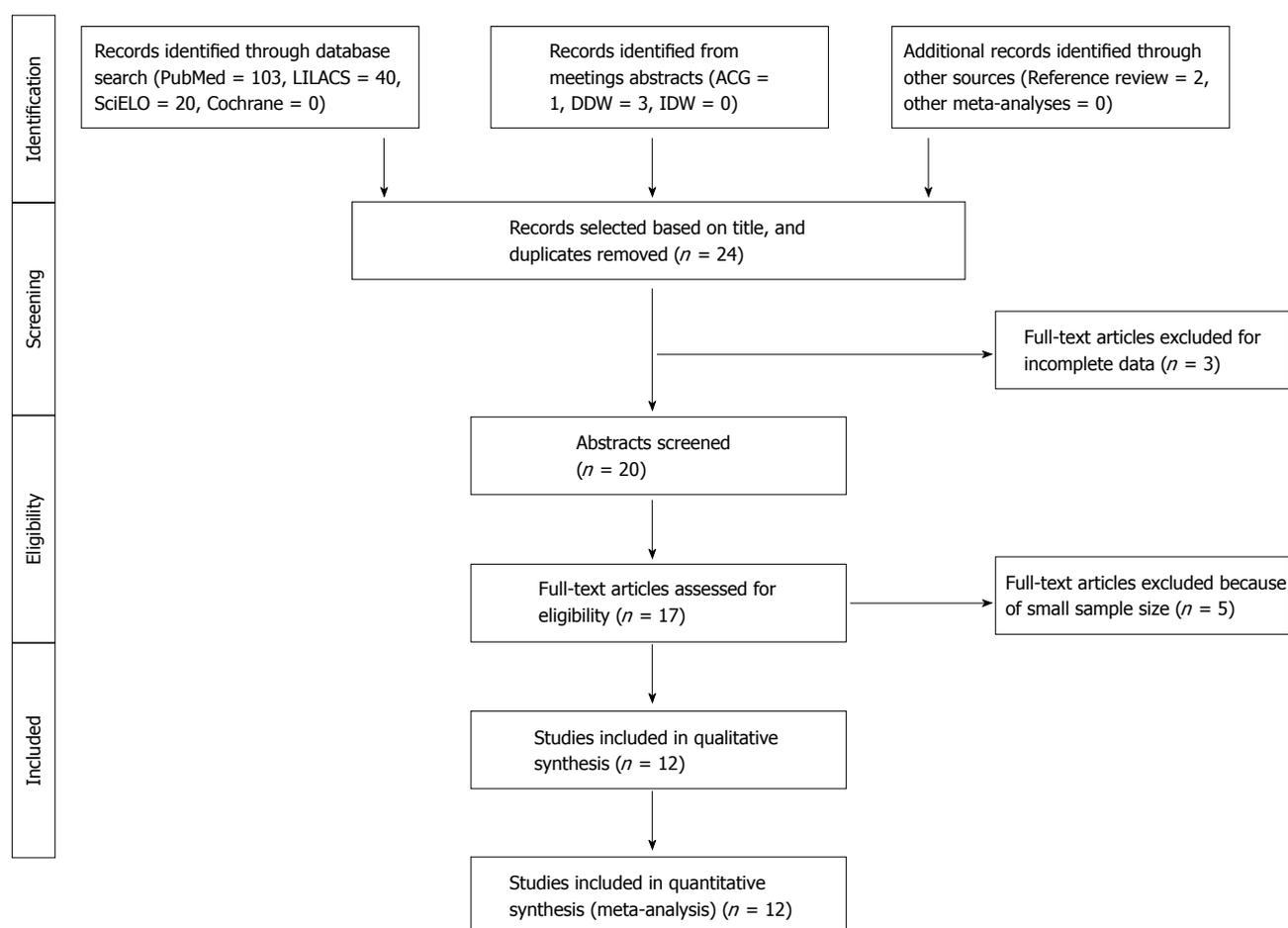


Figure 1 Latin America *Helicobacter pylori* recurrence: Study selection flow diagram (PRISMA 2009). DDW: Digestive Disease Week; ACG: American College of Gastroenterology Scientific Meeting; IDW: ID Week.

assigned to a placebo group or other treatment arm without antibiotics (only anti-acids)]. In these studies, the mean eradication rate after initial treatment was 72.2%, with a range of 30.2% to 100%. Reinfection rates ranged from 1.8% to 85.4%. In total, there were 432 reinfection events recorded in 5487 PYs follow-up in patients with sufficient data to calculate recurrence rates. Of the 4848 patients, 2172 (44.8%) did not complete follow-up diagnostic testing (Table 2).

Pooled analysis showed an overall recurrence rate of 7.9 cases per 100 PYs (95%CI: 5.3-10.5) (Figure 2). Analysis on an intention to eradicate basis (those with a negative test immediately after treatment) had a recurrence rate of 7.1 (4.7-9.6) per 100 PYs. The recurrence rate in the first year after treatment, postulated to be predominantly recrudescence, was 11.2 (6.1-16.4) per 100 PYs (all 12 studies included), while recurrence in subsequent years, an estimate of reinfection, was 6.2 (3.8-8.7) per 100 PYs. The cumulative reinfection rate at the 5 and 7 year time points were 36.2 and 48.6 per 100 PYs, respectively. Recurrence rates from different countries were combined for the first 6 years, 12 and 16 years (only one study had follow-up beyond 5 years^[19]). Recurrence rate were

higher in the first six months and decreased afterwards. Data from year 4 and 5 were combined as they had few PY follow-up (132 and 98, respectively). After the first year, reinfection rates ranged from 3.4 per 100 PYs in year 2 to 6.3 per 100 PYs in the combined 4-5 year period (Figure 3).

In a secondary analysis, the reinfection rate was lower when using a 3-year time cutoff; with an estimated rate of 3.8 (95%CI: 1.6-6.1) cases per 100 PYs. Recurrence rates were two times higher in studies that enrolled children compared to those that only enrolled adults 12.3 (95%CI: 9.6-14.9) vs 6.9 (95%CI: 4.2-9.6) cases per 100 PYs. There was no significant difference in recurrence rates among trials with high or low initial eradication success [7.8 (95%CI: 3.4-12.3) vs 8.4 (95%CI: 4.6-12.1), respectively]. Recurrence rates were higher in studies that evaluated eradication by endoscopy, 11.6 (95%CI: 9.9-13.3), compared to those that used non-invasive diagnostic methods, 6.6 (95%CI: 4.0-9.1).

Meta-regression

In the meta-regression, neither the study population, the method used to detect *H. pylori*, the initial antibiotic

Table 1 Characteristics of eradication trials included in Latin America

Ref.	Year	Country	Patients enrolled or randomized	Mean age \pm SD (age range)	Patient population	Treatment arm(s)	Antibiotic duration (d)	Second antibiotic treatment	Eradication success rate	Waiting time (wk)	Diagnostic method(s)	Follow-up, yr	Study design and quality ¹¹⁷
Morgan <i>et al</i> ^[22]	2013	6 countries ^a	1463	(21-65)	Community populations	3 options: PPI + A + C PPI + A/M PPI + A + C + M	Variable: 14 5/5 5	PPI + M + Bis + Tetra ^b	Total 77.4% 82.20% 76.50% 73.60%	6-8	13C, CagA IgG	1	5
Silva <i>et al</i> ^[34]	2010	Brazil	150	46.7 (16-85)	Duodenal ulcer	PPI + A + C	7	PPI + Tetra + Furazolidone	92.50%	13	14C, H (RUT, PCR)	5	3
Mesquita <i>et al</i> ^[35]	2005	Brazil	50	49 \pm 14 (> 18)	Duodenal ulcer	H2 + Bis + C	14	NA	100%	13	H (RUT, H and E)	3	2
Coelho <i>et al</i> ^[36]	1991	Brazil	48	40.4 (adults)	Duodenal ulcer	A + M + Furaz	5	NA	60.40%	8.5	14C	1.5	2
Rollan <i>et al</i> ^[37]	2000	Chile	111	38 (16-75)	Duodenal ulcer	2 options: H2 + A + M PPI + A + Tinidazole	14 14	Cross-over	Total 75.7% 79% 73%	4-6	14C, H (RUT, Warthin-S, PCR)	3	3
Figueroa <i>et al</i> ^[38]	1996	Chile	57	49.1 (16-65)	Duodenal ulcer	PPI + A + M + Bis	28	NA	80.70%	4	H (RUT, Gram, Clt)	1	5
Novoa-Reyes <i>et al</i> ^[39]	2014	Peru	140	48.9 \pm 12.3 (18-85)	Non-ulcer dyspepsia	PPI + A + C	10	NA	72.10%	4	14C, H (H and E)	2	3
Soto <i>et al</i> ^[40]	2003	Peru	235	37 \pm 8.7 (18-55)	Non-ulcer dyspepsia	PPI + A + C	14	NA	85.50%	4	14C, H (Warthin-S, Clt)	1.5	5
Leal-Herrera <i>et al</i> ^[41]	2003	Mexico	467	(> 5) ^c	Non-ulcer dyspepsia	PPI + A + C	14	NA	30.20%	4-6	14C, H (Giemsa, Clt, PCR), Serology	2	4
Mohar <i>et al</i> ^[42]	2002	Mexico	131	51.4 \pm 9.3 (> 40)	Healthy volunteers	PPI + A + C	7	NA	76.30%	6	H (H and E, Elisa), CagA IgG	1	4
Sivapalasingam <i>et al</i> ^[43]	2014	Bolivia	848	(> 6 mo) ^d	Community populations	PPI + A + C	10	"Triple therapy"	64.00%	6	13C, CagA IgG	1	3
Mera <i>et al</i> ^[19,44]	2005	Colombia	976	50.8 (29-69)	Intestinal metaplasia	Variable (the majority A + M + Bis)	14	NA	51.60%	156	13C, H (H and E, Steiner)	16	5

^aSix countries were Colombia, Costa Rica, Nicaragua, Chile, Honduras, and 2 sites in Mexico (Sonora and Chiapas); ^bVoluntary treatment; ^c66.7% were > 30 years old; ^d41.2% were > 15 years old. PPI: Proton pump inhibitor; A: Amoxicillin; C: Clarithromycin; H2: H2 Blockers; Bis: Bismuth; Furaz: Furazolidone; C: Urea breath test; H: Histology; RUT: Rapid urea test; Clt: Culture.

strategy, the use of a second antibiotic course, nor the length of follow up had a significant impact on the observed risk of reinfection. As anticipated, the recurrence rates decreased after the first year by 40%, but this was not statistically significant after including all five variables ($P = 0.6$).

Assessment of bias and heterogeneity

Risk of bias according to Camargo scale ranged from 2 to 5 points. Even though reviewed studies used various

methods to assess *H. pylori* recurrence, 10 (83%) used at least two different methods, including 9 (75%) that used urea breath tests. Most studies lost points because of sampling techniques or because they failed to describe salient patient characteristics. The I^2 for the model was 90% and adjusted R2 was -38.8%. Funnel plot showed asymmetry towards higher recurrence rates, with a lack of missing studies with low sample size (high SD) where the rates are lower. The top of the funnel plot demonstrated a low risk for publication bias.

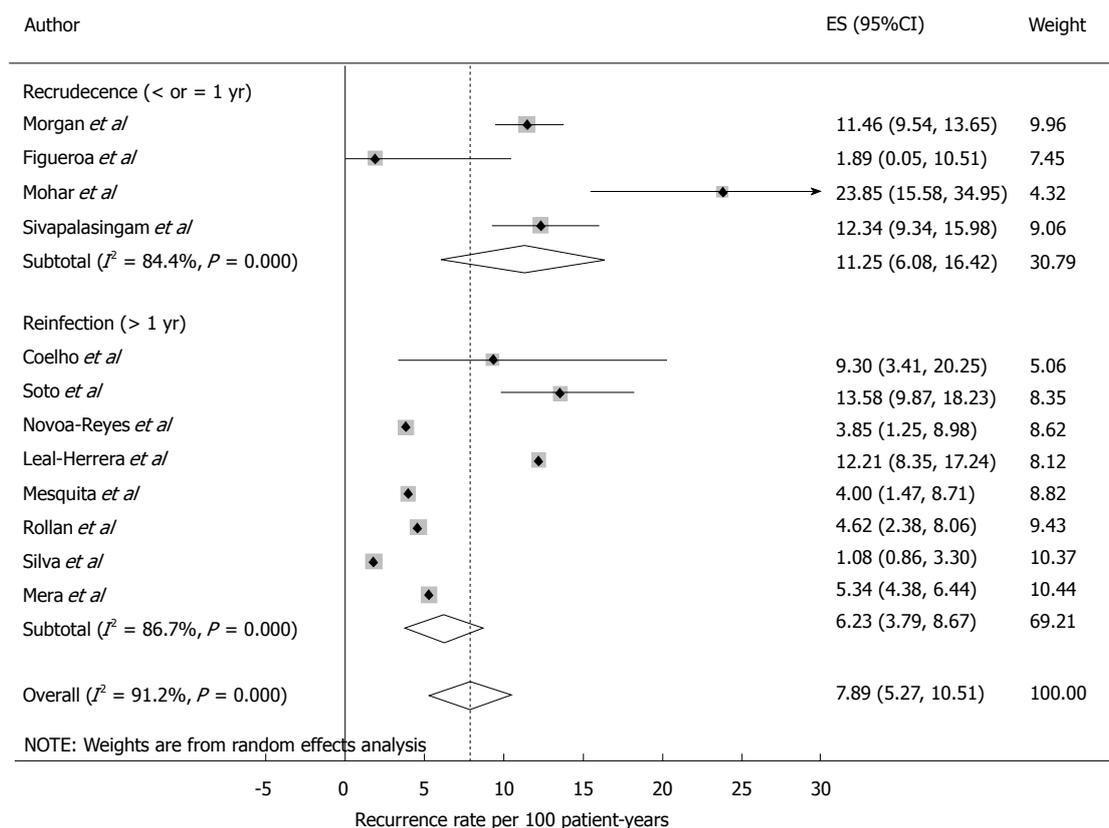


Figure 2 Forest plot of *Helicobacter pylori* recurrence rates in Latin America.

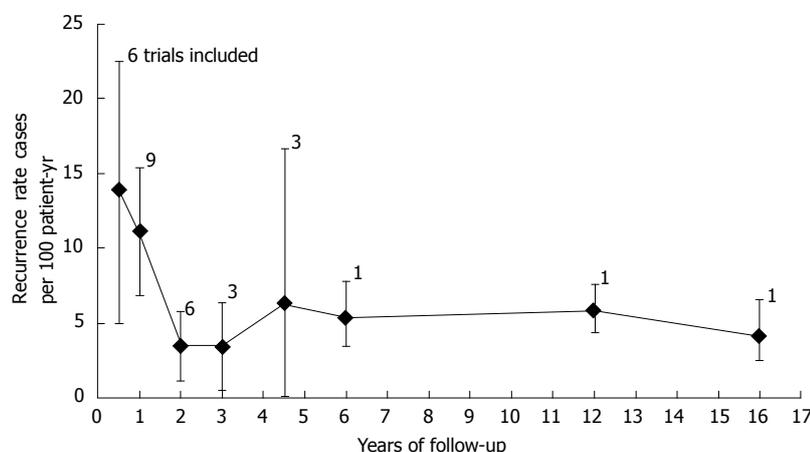


Figure 3 Yearly trends of *Helicobacter pylori* recurrence after eradication treatment in Latin America.

DISCUSSION

H. pylori recurrence after eradication is a critical determinant of the efficacy of potential gastric cancer prevention programs utilizing antibiotic treatment. This measure may be more important than the choice of initial antibiotic regimen and bacterial resistance rates, and is likely to differ by global region^[19-21]. Latin America populations have high colonization rates of *H. pylori*, as well as a significant burden of gastric adenocarcinoma. Our meta-analysis estimates a recurrence rate of 7.9 cases per 100 PYs in Latin America, 11.2 in year-one

and 6.2 in subsequent years. This overall rate is higher than the estimated global recurrence rate of 4.5 (95%CI: 4.2-4.8), but significantly lower than that reported for resource-limited nations 8.7 (7.8-9.6) and 13.0 (6.0-21.0) observed in two independent meta-analyses^[16,18].

Is there a maximum *H. pylori* infection recurrence threshold for potential intervention programs? In the Shangdong trial reported by Ma *et al*^[10] with healthy volunteers in East Asia, *H. pylori* eradication significantly reduced incident gastric cancer compared to placebo after 14.8 years of follow up [OR 0.6 (0.4-0.9), $P = 0.3$]. These results have been supported by recent

Table 2 Estimated *Helicobacter pylori* recurrence rates in Latin America studies

Ref.	Patients that received antibiotics	Patients present at f/u appointment	Recurrent cases total	Crude reinfection rate ¹	Follow-up (yr)	Year patients (present at f-u appointment)	Recurrence rate per 100 PY (95%CI)
Morgan <i>et al</i> ^[22]	1133	1091	125	11.46	1	1091	11.46 (9.54-13.65)
Silva <i>et al</i> ^[34]	147	112	10	8.98	5	557	1.80 (0.86-3.30)
Mesquita <i>et al</i> ^[35]	50	50	6	12.00	3	150	4.00 (1.47-8.71)
Coelho <i>et al</i> ^[36]	29	43	6	13.95	1.5	64.5	9.30 (3.41-20.25)
Rollan <i>et al</i> ^[37]	84	96	12	12.50	3	260	4.62 (2.39-8.06)
Figueroa <i>et al</i> ^[38]	47	53	1	1.89	1	53	1.89 (0.05-10.52)
Novoa-Reyes <i>et al</i> ^[39]	101	65	5	7.69	2	130	3.85 (1.25-8.98)
Soto <i>et al</i> ^[40]	201	216	44	20.37	1.5	324	13.58 (9.87-18.23)
Leal-Herrera <i>et al</i> ^[41]	141	131	32	24.43	2	262	12.21 (8.35-17.24)
Mohar <i>et al</i> ^[42]	183	109	26	23.85	1	109	23.85 (15.58-34.95)
Sivapalasingam <i>et al</i> ^[43]	543	462	57	12.34	1	462	12.34 (9.34-15.98)
Mera <i>et al</i> ^[19,44]	679	126	108	85.37	16	2024	5.34 (4.38-6.44)
Total	3338	2554	432	16.92		5487	7.89 (5.27-10.51)

¹Crude reinfection rate: Recurrent cases total/Patients present at follow-up appointment.

Table 3 Implementation of *Helicobacter pylori* eradication programs for gastric cancer prevention in Latin America

Components	Challenges and considerations	Implementation approaches
Public policy	Lack of awareness among the Ministries of Health, stakeholders, and the public	Large scale education campaigns for cancer and gastric cancer Joint initiatives with international stakeholders: WHO, IARC, PAHO, UICC, NCI, and CDC
Economic investment	Cost of <i>H. pylori</i> eradication program	Conduct CEAs at the country and regional level. The CEAs may differ for HICs and LMICs
Program design	Economics of growing gastric cancer burden Uncertainties and regional variation for target age, screening approach, treatment regimen, and follow-up	Pilot-test eradication campaigns and perform community implementation trials Adapt evidence from cost-effectiveness models and available epidemiologic data. Incorporate screening into existing public health practices (<i>e.g.</i> , cervical cancer)
Appropriate technologies	Technical difficulties in <i>H. pylori</i> testing Consistent eradication confirmation norms Management of high risk patients	Develop economic, point-of-care <i>H. pylori</i> testing Coordinate endoscopy protocols for high risk patients (<i>e.g.</i> , premalignant lesions) Implement information networks to coordinate eradication programs, health centers, and endoscopy centers
Adherence measures	Poor compliance with <i>H. pylori</i> eradication regimen, leading to treatment failure and increased infection recrudescence	Consider medication side effect profiles Pre-regimen counseling for common side effects Consider adherence measures, usual (<i>e.g.</i> , direct observed therapy), or novel (<i>e.g.</i> , cell phone contact)
<i>H. pylori</i> recurrence	Elevated reinfection rate may affect program efficacy and feasibility	Improve living conditions to reduce potential environmental sources of reinfection Consider the family or the village as the intervention target
Potential overall program risks and unknowns	Alteration of the human microbiome Induction of antibiotic resistance Potential increased risk for certain diseases (<i>e.g.</i> , allergic diseases, esophageal cancers) Unknown role(s) of <i>H. pylori</i> as a component of the human microbiome: Commensal and pathogen, which may be strain and/or age dependent	<i>H. pylori</i> eradication programs should be considered investigational, with use of rigorous methodology and long term surveillance Monitoring of antibiotic resistance and microbiome profiles Global antibiotic stewardship programs (<i>e.g.</i> , OTC antibiotic use, veterinary use)
Parallel research agendas	Incorporate evolving approaches and technologies	Develop novel biomarkers for host risk and <i>H. pylori</i> virulence Develop biomarkers for premalignant lesions (<i>e.g.</i> , intestinal metaplasia) to facilitate endoscopy surveillance Incorporate endoscopy technologies, including advanced imaging and low-cost approaches
<i>H. pylori</i> Vaccination	Unknown long-term effectiveness and side effects Lack of data showing impact in clinical outcomes	Evaluate long-term (> 3 yr) effectiveness in other centers, populations and countries ^[23] Complete regulatory evaluations, collect additional safety data and approval by national agencies. Phase IV studies

WHO: World Health Organization; IARC: International Agency for Research on Cancer; PAHO: Pan American Health Organization; UICC: Union for International Cancer Control; NCI: National Cancer Institute; CDC: Centers for Disease Control and Prevention; HIC: High income country; LMIC: Low/middle income country; OTC: Over the counter; CEAs: Cost-effectiveness analyses; *H. pylori*: *Helicobacter pylori*.

meta-analyses^[11]. In the Shangdong study, omeprazole and amoxicillin comprised both the treatment and the retreatment regimen, and only 47% of subjects were *H. pylori* negative at the 7-year post-eradication point. In general terms, this may suggest a 50% threshold at the 5 to 7 year time point as a minimum eradication efficacy target. Our estimated 5-year and 7-year reinfection rates in the current meta-analysis are lower or at least similar to the 7-year reinfection rate observed in the Shangdong study: 36.2% and 48.6%, vs 53%, respectively. Thus, *H. pylori* screening and eradication in asymptomatic populations may be an attractive strategy for gastric cancer prevention in Latin America. Further research to evaluate feasibility, cost-effectiveness, acceptance, and adverse consequences of eradication programs in the region is needed. For example, the 1-year recurrence analysis in the large 6-country *H. pylori* eradication trial in Latin America suggested that potential programs may need to be tailored based upon region, gender and age of the participants^[22]. Uncertainties about *H. pylori* screening and treatment have to be answered and significant challenges are foreseen before such programs can be implemented at a population level (Table 3).

H. pylori infection recurrence represents the combination of recrudescence and reinfection, and different strategies may be required to effectively reduce these component rates. Recrudescence or re-growth, usually occurs during the first year after treatment at a rate primarily driven by antibiotic treatment failure, in the setting of a false negative test immediately after treatment. This common scenario may be difficult to distinguish from reinfection with the same strain from a family member in the same household. Reinfection, is the principal component of recurrence after the first year, and persists at a lower but steady state. Molecular analysis comparing pre- and post-treatment strains of patients have shown that 80% of recurrent cases are genetically identical, whereas differing strains were found in only a minority of the cases^[23]. This suggests that the majority of initial recurrent cases are a product of treatment failure, or reinfection with a strain common to close contacts or family members. In this meta-analysis, recurrence rates significantly decreased after the first year and remained stable in subsequent intervals, ranging from 3.4% to 5.8% per 100 PYs.

Strategies aiming to reduce these two types of recurrence should be different. The first scenario requires a clinical approach where cost-effective antibiotic selection and medication compliance measures are crucial, whereas the second involves a broader public health strategy. Reducing reinfection rate is complex as it involves improving living conditions and reducing potential environmental sources of reinfection, including consideration of interventions at the family or the village levels, and possibly vaccination^[24]. In this approach, children become a challenging target group with higher therapeutic failure and higher reinfection as seen in most studies (including this meta-analysis)^[25-27].

Our results are significantly influenced by two trials:

The study by Morgan *et al.*^[22] as the largest trial with 1463 PYs follow up, and the study by Mera *et al.*^[19] as the cohort with the longest follow-up time. The Mera study was the only cohort followed for more than 5 years; subjects with preneoplastic gastric lesions were enrolled from a geographically circumscribed region of Colombia, and thus, the results may not be generalizable to the remainder of Latin America. Of note, the Caribbean was not represented, where the higher African ancestry, different diets and other environmental exposures may affect generalization. In this review, we observed geographic variability in *H. pylori* recurrence rates, as had been previously described^[22]. This likely represented both regional *H. pylori* ecology differences, as well as socioeconomic differences in the study populations. Improved socioeconomic status in subsequent birth cohorts may help explain lower acquisition rates. For example, Chile and Peru are countries with divergent development rates, yet similar ethnography and comparable *H. pylori* prevalence rates-lower reinfection rates are observed in Chile^[16,28]. One likely explanation is that in Chile, the generation ≥ 40 years who contracted *H. pylori* in their childhood and remains colonized, coexists with younger generations that have grown in improved living conditions with reduced *H. pylori* prevalence. This paradox of high prevalence but low reinfection rates has been previously described in Japanese patients with peptic ulcer disease^[29].

In our meta-regression analysis, the findings were not significantly modified by any of the evaluated factors: Study population, *H. pylori* diagnostic modality, the antibiotic strategy selected, retreatment (a second antibiotic course), or the time interval to check for *H. pylori* eradication success. Antibiotic selection varied among different studies, but half of them used the standard triple therapy regimen. This 14-d regimen has been proven to be superior to sequential and concomitant therapy in Latin America post-eradication time, but not at the 1-year time point^[22,30]. Diagnostic modalities were appropriate, and 8 out of 12 studies used two methods to diagnose *H. pylori*, wherein one of them was the urea breath test^[31]. Studies that used endoscopy-based diagnostic methods noted higher recurrence rates, which may be an incidental finding, related to occasional iatrogenic infection, or reflect the improved sensitivity of this approach^[32]. One limitation of this analysis was the study designs which were not able to differentiate whether cases were secondary to reinfection or recrudescence by molecular fingerprinting. Finally, heterogeneity was significant and there is a possibility of publication bias^[33]. The Forrest plot suggested missing studies with low sample size (wide standard deviation) wherein the recurrence rates may be lower, with the exception of the Peru study, but this is attributed to the inclusion criteria of at least 50 PYs of follow-up.

Conclusion

The meta-analysis of studies in Latin America suggests that the *H. pylori* recurrence rate in the first year is

11.2 (95%CI: 6.1-16.4) per 100 person-years, and 6.2 (95%CI: 3.8-8.7) per 100 person-years in subsequent years, or approximately 50% at 7 years. Overall, the reinfection rates are lower than initially reported, making *H. pylori* screening and eradication a reasonable strategy for gastric cancer prevention programs in Latin America, within the context of well-designed clinical trials^[18]. Further research is needed to evaluate the feasibility, cost-effectiveness, and the potential adverse outcomes (e.g., microbiome effects, antibiotic resistance) of eradication programs, while in parallel, to explore novel biomarkers and eradication strategies.

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COMMENTS

Background

Recent trials and systematic reviews suggest that *Helicobacter pylori* (*H. pylori*) eradication may reduce the risk of gastric adenocarcinoma if the 5 to 7-year recurrence rate is less than 50%.

Research frontiers

There is limited evidence of *H. pylori* recurrence after treatment outside of Asia.

Innovations and breakthroughs

The authors' estimated 5-year and 7-year recurrence rates are similar to the recurrence rates observed in the literature, including the Shangdong study. Recurrent cases occur mostly within the first year suggesting treatment failure.

Applications

H. pylori screening and eradication in asymptomatic populations with chronic gastritis may be an attractive strategy for gastric cancer prevention in Latin America. Further research is needed to evaluate the feasibility, cost-effectiveness, and the potential adverse outcomes (e.g., microbiome effects, antibiotic resistance and stewardship) of eradication programs in the region.

Peer-review

This manuscript is well written and clinically interesting. Results are presented clearly and conclusions are supported by results.

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