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Quadruple therapies show a higher eradication rate compared to standard triple therapy for *Helicobacter pylori* infection within the LEGACy consortium. A multicenter observational study in European and Latin American countries

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Abstract

Introduction: Gastric cancer (GC) is one of the most lethal malignancies worldwide. *Helicobacter pylori* is the primary cause of GC; therefore, its eradication reduces the risk of developing this neoplasia. There is extensive evidence regarding quadruple therapy with relevance to the European population. However, in Latin America, data are scarce. Furthermore, there is limited information about the eradication rates achieved by antibiotic schemes in European and Latin American populations.

Objective: To compare the effectiveness of standard triple therapy (STT), quadruple concomitant therapy (QCT), and bismuth quadruple therapy (QBT) in six centers in Europe and Latin America.

Methods: A retrospective study was carried out based on the LEGACy registry from 2017 to 2022. Data from adult patients recruited in Portugal, Spain, Chile, Mexico, and Paraguay with confirmed *H. pylori* infection who received eradication therapy and confirmatory tests at least 1 month apart were included. Treatment success by

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each scheme was compared using a mixed multilevel Poisson regression, adjusting for patient sex and age, together with country-specific variables, including prevalence of *H. pylori* antibiotic resistance (clarithromycin, metronidazole, and amoxicillin), and *CYP2C19* polymorphisms.

Results: 772 patients were incorporated (64.64% females; mean age of 52.93 years). The total *H. pylori* eradication rates were 75.20% (255/339) with STT, 88.70% (159/178) with QCT, and 91.30% (191/209) with QBT. Both quadruple therapies (QCT-QBT) showed significantly higher eradication rates compared with STT, with an adjusted incidence risk ratio (IRR) of 1.25 (p: <0.05); and 1.24 (p: <0.05), respectively. The antibiotic-resistance prevalence by country, but not the prevalence of *CYP2C19* polymorphism, showed a statistically significant impact on eradication success.

Conclusions: Both QCT and QBT are superior to STT for *H. pylori* eradication when adjusted for country-specific antibiotic resistance and *CYP2C19* polymorphism in a sample of individuals residing in five countries within two continents.

KEYWORDS
combination drug therapies, gastric cancer, *Helicobacter pylori*, quadruple therapy, standard triple therapy

INTRODUCTION

Eradication of *Helicobacter pylori* (*H. pylori*) is relevant for gastroenterologists and primary care physicians because it is an intervention for *H. pylori*-induced gastric ulcers, gastric and duodenal peptic ulcer disease, and gastric mucosa-associated lymphoid tissue (MALT).[1] Also, eradicating *H. pylori* infection reduces the incidence and mortality related to gastric cancer (GC) in high-risk populations, becoming the main intervention for primary prevention of GC in high-risk populations.[2] This is particularly relevant because GC is a major cause of cancer deaths worldwide.[3] The main risk factors related to GC are smoking, high salt intake, and chronic *H. pylori* infection, which has an estimated 50% prevalence worldwide.[4]

H. pylori treatment has evolved significantly through the past decades, moving forward from triple standard therapy (STT), based principally on amoxicillin and clarithromycin to quadruple schemes with or without bismuth.[5] Moreover, recently the antimicrobial stewardship paradigm has been proposed to guide *H. pylori* therapy,[6] for the purpose of avoiding ineffective antimicrobial exposure, reducing the spread of antimicrobial resistance and allowing the design of targeted antibiotic schemes.

In this context, the increase in *H. pylori* antibiotic resistance is a primary cause of treatment failure. In Latin America, a systematic review reported high rates of antibiotic resistance among *H. pylori* infection in naïve patients, especially for clarithromycin.[7] In Europe, a prospective study found high rates of *H. pylori* resistance to both clarithromycin and levofloxacin.[8] Also, there are reported high rates of resistance to clarithromycin, that could reflect the southeastern European situation.[9]

Key summary

Summarise the established knowledge on this subject

- Gastric cancer (GC) ranks among the deadliest malignancies worldwide, with *H. pylori* identified as its primary cause. Eliminating *H. pylori* markedly diminishes the risk of developing GC.
- Treatment for *H. pylori* has evolved, moving from triple standard therapy to quadruple regimens with or without bismuth because of the diminishing effectiveness of previous schemes.
- Limited data exist on eradication rates achieved by antibiotic therapies in European and Latin American populations simultaneously.

What are the significant and/or new findings of this study?

- Our multicentric, observational study showed that quadruple therapies (QT), both quadruple concomitant therapies and quadruple bismuth therapies, have a higher eradication rate than standard triple therapy in European and Latin American countries, being 88%, 91% and 75%, respectively.
- Quadruple bismuth therapy achieved an eradication rate of over 90%, reaching the desired threshold of optimal therapeutic eradication in European and Latin American populations.
- We recommend the use of QT and the discontinuation of STT, because a 75% success rate is unacceptable for an empirical treatment.

Another factor related to the effectiveness of *H. pylori* treatment is the presence of polymorphisms in cytochrome P450-2C19 *(CYP2C19)*, which is an enzyme that regulates the metabolism and bioavailability of proton pump inhibitors (PPIs). A PPI extensive metabolizer classification by *CYP2C19* has a higher risk of treatment failure.[10]

Recently, the Maastricht VI/Florence consensus recommended quadruple bismuth therapy (QBT) as a first-line treatment for *H. pylori* infection among areas with high rates of clarithromycin resistance (>15%),[4] based on the high efficacy (>90%) of this scheme demonstrated by controlled trials.[7–9]

In Europe, triple therapies are mostly used in southeastern and northern Europe (82%–88%).[11] In Turkey, a systematic review by Sezgin and cols in 2019 found that the STT eradication rate to the ITT analyses was 60% (95% CI: 56%-63), in a sub-group the rate for 7 days of treatment was 57% (95% CI: 46%–68%) and for 14 days of treatment was 60% (95% CI: 56%–63%).[12]

Quadruple therapies are preferred in southwestern and central Europe (63%–82%). The results from a study of the Hp-EuReg showed that only bismuth QT lasting at least 10 days or 14-day concomitant treatment were able to achieve over 90% eradication rates.[13,14]

In those areas with high (>15%) clarithromycin resistance, eradication treatment with the 3-in-1 single capsule bismuth quadruple therapy (marketed as Pylera®), the quadruple with bismuth in the classical form (that is administering bismuth, tetracycline and metronidazole separately), and the concomitant therapy with tinidazole are the best options in naive patients.[15]

However, despite the efforts of the Maastricht VI/Florence consensus and other guidelines to standardize the eradication therapies, the "European Registry on *Helicobacter pylori* management" (Hp-EuReg), with ~70,000 patients, has shown that the management of *H. pylori* infection is heterogeneous among countries and clinical recommendations are being slowly implemented.[16,17]

In Latin America, there is limited information regarding the schemes and their eradication rates, particularly for the QT. A recent retrospective study from Chile characterized the most used schemes. QT showed a superior eradication rate compared to STT while maintaining similar tolerance.[18] Evidence relating to eradication in other countries in the region is scarce and no study simultaneously evaluating eradication schemes in both European and Latin American populations.

In this context, this study aimed to compare the effectiveness of STT, quadruple concomitant therapy (QCT) and QBT on *H. pylori* eradication in six centers in Europe and Latin America.

METHODS

Study design and patients

The study was part of "The CELAC and European Consortium for a Personalized Medicine Approach to Gastric Cancer" (LEGACy). Briefly, it is a consortium between institutions from European and Latin American countries that studied outcomes related to GC. The LEGACy study protocol can be found at Schooten et al.[19]

We conducted a retrospective study from January 2008 to October 2022 to analyze the effectiveness of the most frequently indicated eradication schemes for *H. pylori* infection. We considered individual and aggregate variables by country of origin in six LEGACy centers. All participants in Europe (Portugal and Spain) and Latin America (Chile, Mexico, and Paraguay) were adult patients over 18 years old with confirmed active *H. pylori* infection. Only antibiotic naïve *H. pylori* infections were included. Naïve were defined as those with no prior antibiotic treatment directed to *H. pylori*. The availability of a confirmatory test to define treatment success at least 1 month after treatment completion was required to include the participant in the study.

Our analysis included patients receiving one of this eradication schemes:

1. STT: clarithromycin (CLA) + amoxicillin (AMX) + PPI.
2. QCT: 3 antibiotics (either AMX, CLA, metronidazole (MET), levofloxacin (the LEV), and tetracycline (TET) + PPI).
3. *Quadruple bismuth therapy* (QBT): 2 antibiotics (either AMX, MET, the LEV, and TET) + bismuth salt + PPI.

In accordance with the 1975 Helsinki Declaration and following Good Clinical practices, all patients signed an informed consent document before participating in the study. The study protocol was approved by the ethical committees of: University Clinical Hospital of Valencia, Spain (reference number 2018/205), VU University Medical Center Amsterdam (reference number 2019.355, NL 69480.02919), Instituto de Prevision Social, Asuncion-Paraguay (reference number CA N°11–020/19), Instituto Alexander Fleming, Buenos Aires Argentina (Resolution 25 July 2019, and 3 October 2019), Instituto Nacional de Cancerología (INCAN, México (reference number INCAN/CEI/0486/19), University Center of Sao Joao and Medicine Faculty of Porto University, Portugal (reference 100/019), Pontificia Universidad Católica de Chile (reference number 180806007), and Vall d'Hebron University Hospital, Barcelona, Spain (references PR (AG) 387/2019 approved on 29 October 2019, PR (AG)388/2019 approved in 13 December 2019 and PR (AG)419/2019 approved in January 30th).

The trial registration of the LEGACy in ClinicalTrials.gov has the following identifiers: NCT03957031, NCT04015466, NCT04019808.

Data collection and samples collection

To ensure compatibility of data collection methods across centers, the recruitment of individuals and the collection and handling of patient material and data, were standardized by following a handbook "standard operating procedures in all processes in LEGACy".

The data were stored in a centralized database created for the Consortium.

The *H. pylori* infection diagnosis and confirmation of treatment success were made by rapid urease test during the endoscopy, culture testing, Giemsa staining on the histology, $^{C-13}$ urea breath test, or stool antigen tests. For the purposes of this study, each detection method was considered equally effective.

Country aggregated data were used to incorporate statistical models along with *H. pylori* antibiotic resistance profiles and *CYP2C19* polymorphism status. Resistance by country to amoxicillin, clarithromycin, and metronidazole, as well as information on the different *CYP2C19* extensive metabolizer polymorphisms was obtained from published information on the NCBI PubMed database. The search terms ("*Helicobacter pylori*"[Mesh] AND "Drug Resistance, Multiple/drug effects"[Mesh]) OR ("Cytochrome P-450 *CYP2C19*"[Mesh]) AND (Latin America OR Central America OR South America or Argentina OR Chile OR Mexico OR Paraguay OR Spain OR Portugal) were performed in April 2023. To broaden the search, *H. pylori* experts were consulted for the availability of additional information. We selected the most recent data in each country and did not perform any type of meta-analysis.

In the case of Paraguay, given the lack of data in the published literature, the *CYP2C19* rapid metabolizer polymorphism prevalence was obtained directly from a sample ($n = 25$) of Paraguayan LEGACy participants (further details in Table 1). Briefly, genotyping was performed from the DNA extracted from gastric tissue samples using *TaqMan*® assays from the Drug Metabolism Genotyping Assay (Thermofisher Scientifc, USA) to detect *2 (c.681G > A; rs 4,244,285), *3 (c.636G > A; rs 4,986,893) and *17 (−806C > T; rs12248560) variants.

Statistical analysis

The primary outcome was *H. pylori* treatment success eradication rate (i.e., number of patients with successful treatment among all patients treated) and compared between the three treatment schemes (STT vs. QCT vs. QBT). As a secondary analysis, QCT and QBT were grouped as QT and compared with STT.

The descriptive analysis included: mean age, sex proportion, the frequency and eradication rates of the different schemes stratified by center, and the frequency of the antibiotics used stratified by scheme. A 95% confidence interval (CI) was used for categorical variables (Table 2). A $p < 0.05$ was considered statistically significant. (two-sided *p*-values) Proportions in the baseline variables were compared using the Chi-2 test.

A mixed multilevel effect model, specifically a robust mixed multilevel Poisson multivariable regression analysis, grouped by center, was used to compare the different *H. pylori* treatment schemes. Considering the data structure, the independence of observations could not be guaranteed, assuming correlation between the participants belonging to each center, as they are more likely to share common characteristics, such as genetics, clinical settings and socioeconomic context.

Age, sex, prevalence of *H. pylori* resistance by country, and prevalence of *CYP2C19* extensive metabolizer polymorphism by country were considered in the regression models. We built different models as follows:

- *Model 1*: crude (only treatment and outcome).
- *Model 2*: model adjusted by observed variables (sex and age).
- *Model 3*: model adjusted by observed variables (sex and age) and ecological variables (*H. pylori* country-resistance, *CYP2C19* polymorphism).

We made two versions of each model, *Model 1a*, *Model 2a*, and *Model 3a*, to compare STT, QCT, and QBT. The versions *Model* 1b, *Model* 2b and *Model* 3b, are for the comparison of STT versus QT (QCT + QBT).

In our statistical models, we incorporated a random effect for the "center" variable, denoting the specific location of data collection and acknowledging shared characteristics, as we mentioned before. On the other hand, the remaining variables in the model were treated as fixed effects. This distinction ensures that the

TABLE 1 Sample characteristics.

Center	Country	*N*	Sex female % (*N*)	*p*-value (X^2)	Age mean (SD)	*p*-value (ANOVA)
PUC	Chile	210	67.14 (141)	0.87	52.79 (14.49)	<0.001
GENPAT	Paraguay	125	66.60 (82)		49.28 (15.32)	
INCAN	Mexico	82	64.63 (53)		55.83 (17.51)	
IPATIMUP	Portugal	152	62.9 (96)		52.78 (13.31)	
INCLIVA	Spain	143	64.34 (92)		50.50 (15.52)	
VHIO	Spain	60	58.33 (35)		63.01 (13.02)	
Total	-	**772**	**64.64 (499)**		**52.93 (15.57)**	

Note: Individual-level variables: sex and age. Statistical significance was set at $p < 0.05$.

Abbreviations: GENPAT, GenPat Laboratory; INCAN, Instituto Nacional de Cancerología; INCLIVA, Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana; IPATIMUP, Institute of Molecular Pathology and Immunology of the University of Porto; PUC, Pontificia Universidad Católica de Chile; VHIO, Vall d'Hebron Institute of Oncology.

TABLE 2 Aggregate variables, including the *H. pylori* country-resistance and the CYP2C19 rapid metabolizer country prevalence (CYP).

Country	*H. pylori* country-resistance to CLA	*H. pylori* country-resistance to MET	*H. pylori* resistance to AMX	*CYP2C19* rapid metabolizer polymorphism prevalence
Chile	26.0[20]	49.0[21]	2.0[7]	20.5[20]
Paraguay	2.0[22]	32.6[22]	2.6[22]	0.0*
México	12.0[23]	58.6[24]	1.8[24]	14.3[25]
Portugal	48.0[23]	34.4[26]	0.6[27]	28.8[28]
Spain	27.0[23]	30.5[29]	0.2[29]	29.5[30]

Note: The reference where the prevalence was extracted is as superscript next to each value.
Abbreviations: AMX, amoxicillin; CLA, clarithromycin; MET, metronidazole.

TABLE 3 Comparison of effectiveness between quadruple concomitant therapy, quadruple bismuth therapy and triple standard therapy through Poisson multilevel multivariable models.

Variable type	Scheme	RR eradication (95% CI)	*p*-value
Model 1a: Crude (only treatment and outcome)			
Scheme	STT	Reference	-
	QCT	1.18 (1.10–1.27)	<0.001
	QBT	1.21 (1.13–1.30)	<0.001
Model 2a: Model adjusted by observed variables (sex and age)			
Scheme	STT	Reference	-
	QCT	1.17 (1.10–1.26)	<0.001
	QBT	1.21 (1.14–1.29)	<0.001
Variable type	**Scheme**	**IRR eradication (95% CI)**	***p*-value**
Model 3a: Model adjusted by observed variables (sex and age) and ecologic variables (*H. pylori* country-resistance, *CYP2C19* polymorphism)			
Scheme	STT	Reference	-
	QCT	1.25 (1.14–1.37)	<0.001
	QBT	1.24 (1.17–1.32)	<0.001

Note: Statistical significance was set at $p < 0.05$.
Abbreviations: QCT, Quadruple concomitant therapy; QBT, Quadruple bismuth therapy; RR, Relative risk; STT, standard triple therapy; CI 95%, 95% confidence interval.

TABLE 4 Comparison of effectiveness between quadruple therapies and triple standard therapies through Poisson multilevel multivariable models.

Variable type	Variable	RR eradication (95% CI)	*p*-value
Model 1b: Crude (only treatment and outcome)			
Scheme	STT	Reference	-
	QT	1.18 (1.11–1.26)	<0.001
Model 2b: Model adjusted by observed variables (sex and age)			
Scheme	STT	Reference	-
	QT	1.18 (1.11–1.25)	<0.001
Model 3b: Model adjusted by observed variables (sex and age) and ecologic variables (*H. pylori* country-resistance, CYP2C19 polymorphism)			
Scheme	STT	Reference	-
	QT	1.23 (1.15–1.32)	<0.001

Note: Statistical significance was set at $p < 0.05$.
Abbreviations: QT, Quadruple therapy; RR, Relative risk; STT, standard triple therapy; CI 95%, 95% confidence interval.

influence of the "center" variable is captured in a nuanced way, while the other variables contribute as fixed components with constant effects.

Incidence risk ratios (IRR) reported the association between eradication success *versus* failure. Crude and adjusted models were performed as specified in Table 3 and Table 4. For sensitivity analysis, models were executed excluding the cases with the LEV or TET in the QTC schemes and TET in the QBT schemes. The analysis was performed with the statistical software Stata 15 and *R* 4.3.1.

RESULTS

Study population characteristics

The LEGACy registry included 876 patients and were analyzed 726 according to the flowchart (Figure 1). The 64.64% were females, with a mean age of 52.93 ± 15.57 standard deviation (SD). No statistical differences were found in the distribution of males and females between the participating centers ($p = 0.57$), although women accounted for over 60% in almost all recruitment centers. Significant differences were observed regarding age ($p < 0.05$) (Table 1), with the average of age being 49.28 ± 15.32 years in Paraguay (GENPAT) to 63.01 ± 13.02 in a Spanish recruitment center (VHIO) (Table 1).

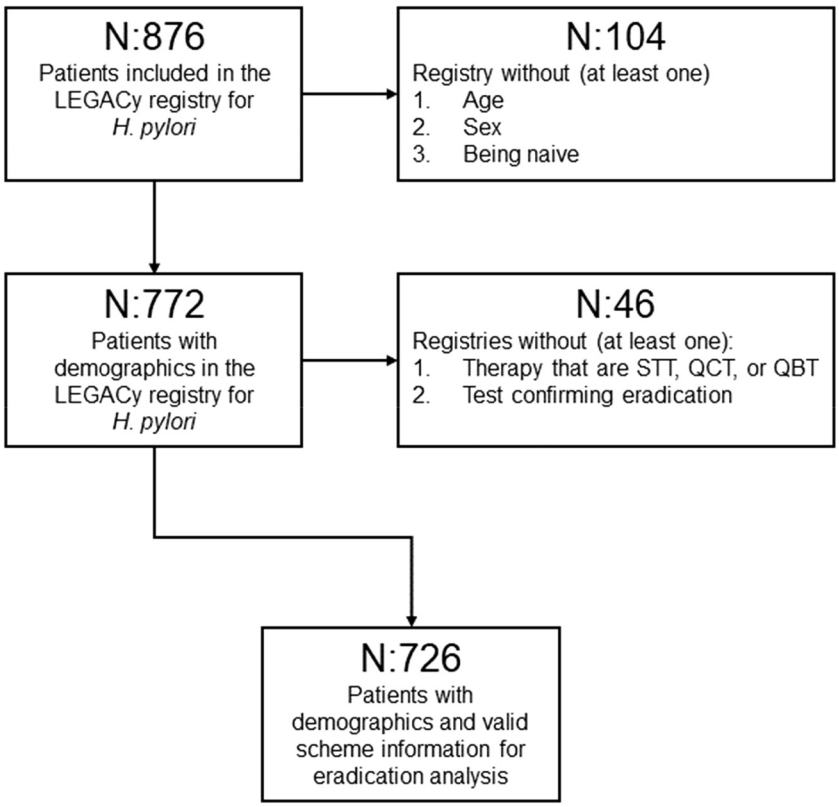

FIGURE 1 Flowchart of the analysis in the LEGACy registry.

Aggregate data by country

The aggregate data selected for use in the statistical models are presented in Table 2. *H. pylori* resistance prevalence ranges from 2% to 48%, 30%–58%, 0.2%–2%, for CLA, MET, AMX, respectively. PPI extensive metabolizers (by *CYP2C19* polymorphism) prevalence ranges from 0% to 29% (Table 2).

H. pylori eradication therapy

In the STT therapy, we found that the antibiotics most used were AMX and CLA, with 98.56% and 98.28%, respectively, followed by LEV (2.29%), MET 0.57% and TET 0.28%. In the QCT, almost all the cases used AMX (99.49%), CLA (99.49%) and MET (100.00%), followed by LEV (0.05%) and TET (0.05%). For QBT, AMX was counted in 19.64%, MET in 98.66%, the LEV 6.81% and TET 80.35%.

The crude *H. pylori* eradication rate was 75.20% (255/339) for STT, 88.70% (159/178) for QCT, and 91.30% (191/209) for QBT, a difference that is statistically significant ($p < 0.05$) in the chi-square test. Furthermore, *H. pylori* eradication rate among QTs was significantly higher compared to STT (90.21% vs. 75.86%; $p < 0.05$). In all centers, QCT and QBT showed higher eradication rates versus STT (Table 5).

Factors associated with eradication rate

In the Poisson regression models, QCT and QBT therapies were independently associated with higher eradication rates compared with STT in all models tested. The fully adjusted *Model 3a* reported an IRR of 1.25 (95%CI: 1.14–1.37) for QCT and an IRR of 1.24 (95%CI: 1.17–1.32) for QBT. Furthermore, grouped QTs showed significant association with treatment success compared with STT, with and IRR 1.23 (95%CI: 1.15–1.32) for the full adjusted *Model* 3b (Table 3).

Analyses of the antibiotic resistance effect showed that higher resistance rates of AMX, CLA and MET were statistically associated with eradication probability in *Model 3a* and *Model* 3b, but with minimal variation, <1% in the successful eradication rates observed in their IRRs. For *Model 3a*, the IRRs for AMX, CLA and MET were 1.005 (95%CI: 1.004–1.007), 1.004 (95%CI: 1.001–1.007) and 1.005 (95%CI: 1.002–1.008). In *Model* 3b, IRR for AMX, CLA and MET were 1.005 (95%CI: 1.004–1.007), 1.004 (95%CI: 1.002–1.006) and 1.005 (95%CI: 1.002–1.007), respectively. No significant association was observed between *CYP2C19* extensive metabolizer prevalence and treatment success.

The coefficients observed in the variance components of the random effects were: 5.09×10^{-31} (95% CI, 4.76×10^{-41}–5.45×10^{-21}) in *Model 1a*, 1.81×10^{-35} (95% CI, 3.41×10^{-38}–9.65×10^{-33}) in *Model 2a*, 4.08×10^{-36} (95% CI, 1.20×10^{-43}–1.39×10^{-28}) in *Model 3a*, 9.69×10^{-33} (95% CI, 1.60×10^{-34}–

TABLE 5 Observed eradication rates per the scheme used, stratified by LEGACy center.

Center	*N* patients recorded	STT eradication rate % (*N*)	QCT eradication rate % (*N*)	QBT eradication rate % (*N*)	Chi-square *p*-value
PUC	210	81.82 (108/132)	91.67 (33/36)	97.62 (41/42)	<0.05
GENPAT	125	74.74 (71/95)	92.86 (26/28)	100.00 (2/2)	0.08
INCAN	56	77.78 (28/36)	100.00 (9/9)	90.91 (10/11)	0.20
IPATIMUP	151	68.00 (17/25)	88.89 (16/18)	94.44 (102/108)	<0.05
INCLIVA	129	54.17 (13/24)	84.42 (65/77)	75.00 (21/28)	<0.05
VHIO	55	66.67 (18/27)	100.00 (10/10)	83.33 (15/18)	0.07
Total	726	75.20 (255/339)	88.70 (159/178)	91.30 (191/209)	<0.05

Note: Statistical significance was set at $p < 0.05$.

Abbreviations: GENPAT, GenPat Laboratory; INCAN, Instituto Nacional de Cancerología; INCLIVA, Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana; IPATIMUP, Institute of Molecular Pathology and Immunology of the University of Porto; PUC, Pontificia Universidad Católica de Chile; VHIO, Vall d'Hebron Institute of Oncology.

5.87×10^{-31}) in *Model* 1b, 5.66×10^{-36} (95% CI, 4.69×10^{-38}–6.84×10^{-34}) in *Model* 2b, 7.16×10^{-32} (95% CI, 2.2×10^{-189}–2.3×10^{126}) in *Model* 3b.

In the sensitivity analysis, the effects in IRRs of eradication had minimal variation, <0.10% in almost all models except *Model 3a*, that had an IRR of 1.24 (95%CI: 1.13–1.36), for QCT in the original model was 1.25 with QCT. In QBT, remained without changes, IRR of 1.24 (95%CI: 1.17–1.31).

DISCUSSION

Our multicentric, observational study showed that QCT and QBT have a higher eradication rate than STT in European and Latin American countries. Notably, all QTs, both with and without bismuth, were independently associated with higher treatment success. However, only QBT achieved an eradication rate over 90%, thus reaching the desired threshold of optimal therapeutic eradication.[6] Notably, through the different models that compared the effectiveness of STT versus QT or STT versus QCT-QBT, the magnitude of the effect persisted with minor variation. Similar results were obtained in the sensitivity analysis, in which negligible differences in the magnitude of the treatment effect were observed when LEV and TET were restricted in QCT and LEV in QBT, that were previsible specially in the STT and QCT schemes because of the high homogeneity in the antibiotics registered on those schemes. The very low coefficients observed in the variance components of the random effects across all models suggest minimal variability in the intercept among centers. This consistency in the intercept across different centers implies that this grouping variable center may not significantly impact the results.

There is a variety in the antibiotics used in the LEGACy centers that may reflect the heterogeneity in prescription reported in previous research in Europe, especially in QBT schemes.[17] This is interesting, because our decision to keep the variability of antibiotics in the main analysis reflects the prescription reality and furthermore may give our results high external validity, showing that the choice - in this case, QTs - of empirical eradication treatment scheme in the studied populations is the main predictor of eradication successfulness. This observation could also encourage a change in the local guidelines in the countries within this consortium.

The high prevalence of resistance to CLA and MET remains a worldwide concern. In the data found for our analysis, CLA resistance prevalence ranged from 2% in Paraguay to 48% in Portugal, metronidazole was above 30% in all centers (Table 2).[7,8,20] The prevalence of *H. pylori* resistance to AMX, CLA and MET were statistically significant in the full adjusted models (*Model 3a and Model* 3b), but with an effect magnitude <1% in the probability of successful eradication change (IRRs in the results section). This result obtained in the analysis is not in concordance with other scientific evidence, which through meta-analysis has reported an odds ratio of 6.97 (95% CI, 5.23–9.28) for failure in patients who had *H. pylori* resistance to CLA.[31] This surely can be explained considering that antibiotic prevalence was not measured at the individual level and was collected from scientific evidence in the literature to adjust the models.

Available susceptibility testing for *H. pylori* is increasing but is it far from having universal access in many countries. Currently, empirical eradication therapy appears to be the best standard of care in the management of *H. pylori* infection, showing that it is possible to reach optimal eradication rates of >90% with an empirical approach, as occurs with QBT. Surveillance efforts such as those performed as part of the Hp-EuReg and Latin-American Registry (Hp-LATAM-Reg)[16] will guide future local recommendations and provide continuous updates by health outcome.

Despite its potential efficacy, QTs are far from perfect. The combination of drugs may undermine patient adherence, a critical factor for *H. pylori* eradication. Furthermore, side effects such as metallic taste, nausea, and gastrointestinal disturbances could also lead to treatment discontinuation.[32] Unfortunately, the LEGACy *H. pylori* clinical registry did not include adherence and therapy side effects, for that reason we cannot make conclusions about these aspects; however, we demonstrate optimal therapy success in a real-world setting where adherence is not always controlled. In that scenario, this study may contribute to reducing the concerns related to adherence and adverse reaction barriers of QTs.

Although in our analysis the prevalence of *CYPC219* rapid metabolizer did not have an impact on the eradication probability, PPIs are known to be crucial for the optimal therapy selection. Gastric acid inhibition, which is altered in the presence of genetic variations in the *CYPC219* gene, is essential for *H. pylori* therapy success.[33] The prevalence >20% of *CYP2C19* rapid metabolizers in all countries encourage the selection of PPIs that reach more profound acid suppression. Novel therapeutic schemes such as the potassium-competitive acid blockers combined with antibiotics may soon be an alternative in some selected cases. Therefore, more studies considering a genetic variable are required, and this is especially relevant in the Latin American population where polymorphism information is still scarce.[5,34]

In terms of the study strengths, the combined data from multiple sites led us to a larger sample size, improving the robustness of our findings. Also, the LEGACy study standardized protocol and data collection tool ensure consistency and accuracy across sites.[19] However, our study has limitations. First, it is an observational study and not a randomized controlled clinical trial, so the observed effect can be biased. In second place, the use of aggregated population data carries the risk of ecological fallacy, as we noted in the antibiotic resistance outcomes. The lack of information regarding the antibiotic and PPI doses could also affect the results and there is no information about the side effects caused by the therapy. The included centers represent only one or two centers per country and thus may not reflect the broader population of each nation or region. Furthermore, as previously mentioned, the observational nature of this study precludes further analysis of the impact of specific antimicrobial resistance and *CYPC219* status on *H. pylori* therapy effectiveness. Future multicentric studies with antibiotic adherence and content, PPI doses and genetic background may help us to understand why eradication does not reach 100%.

In summary, based on our findings of over a 90% eradication rate, we recommend the use of QBT in European and Latin American populations. Considering these data, which complement that of other studies, we suggest that the discontinuation of STT with only a 75% success rate is unacceptable. Our views concur with the Maastricht VI/Florence consensus that recommends bismuth quadruple therapy as a first-line eradication treatment option in areas of high (>15%) or unknown rates of clarithromycin resistance.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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