14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial

E Robert Greenberg, Garnet L Anderson, Douglas R Morgan, Javier Torres, William D Chey, Luis Eduardo Bravo, Ricardo L Dominguez, Catterina Ferreccio, Rolando Herrero, Eduardo C Lazcano-Ponce, María Mercedes Meza-Montenegro, Rodolfo Peña, Edgar M Peña, Eduardo Salazar-Martínez, Pelayo Correa, María Elena Martínez, Manuel Valdivieso, Gary E Goodman, John J Crowley, Laurence H Baker

Summary

Background **Evidence from Europe, Asia, and North America suggests that standard three-drug regimens of a proton-pump inhibitor plus amoxicillin and clarithromycin are significantly less effective for eradication of *Helicobacter pylori* infection than are 5-day concomitant and 10-day sequential four-drug regimens that include a nitroimidazole. These four-drug regimens also entail fewer antibiotic doses than do three-drug regimens and thus could be suitable for eradication programmes in low-resource settings. Few studies in Latin America have been done, where the burden of *H pylori*-associated diseases is high. We therefore did a randomised trial in Latin America comparing the effectiveness of four-drug regimens given concomitantly or sequentially with that of a standard 14-day regimen of triple therapy.**

Methods **Between September, 2009, and June, 2010, we did a randomised trial of empiric 14-day triple, 5-day concomitant, and 10-day sequential therapies for *H pylori* in seven Latin American sites: Chile, Colombia, Costa Rica, Honduras, Nicaragua, and Mexico (two sites). Participants aged 21–65 years who tested positive for *H pylori* by a urea breath test were randomly assigned by a central computer using a dynamic balancing procedure to: 14 days of lansoprazole, amoxicillin, and clarithromycin (standard therapy); 5 days of lansoprazole, amoxicillin, clarithromycin, and metronidazole (concomitant therapy); or 5 days of lansoprazole and amoxicillin followed by 5 days of lansoprazole, clarithromycin, and metronidazole (sequential therapy). Eradication was assessed by urea breath test 6–8 weeks after randomisation. The trial was not masked. Our primary outcome was probablity of *H pylori* eradication. Our analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, registration number NCT01061437.**

Findings **1463 participants aged 21–65 years were randomly allocated a treatment: 488 were treated with 14-day standard therapy, 489 with 5-day concomitant therapy, and 486 with 10-day sequential therapy. The probability of eradication with standard therapy was 82·2% (401 of 488), which was 8·6% higher (95% adjusted CI 2·6–14·5) than with concomitant therapy (73·6% [360 of 489]) and 5·6% higher (–0·04% to 11·6) than with sequential therapy (76·5% [372 of 486]). Neither four-drug regimen was significantly better than standard triple therapy in any of the seven sites.**

Interpretation **Standard 14-day triple-drug therapy is preferable to 5-day concomitant or 10-day sequential four-drug regimens as empiric therapy for *H pylori* infection in diverse Latin American populations.**

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Introduction

Helicobacter pylori infects most of the world's adult population and is the principal cause of gastric cancer, accounting for an estimated 60% of all cases.[1–3] Gastric cancer is second only to lung cancer as a cause of cancer death worldwide, and almost all of the nearly 1 million cases and 0·75 million deaths each year occur in east Asia and Latin America.[4] Although gastric cancer death rates have fallen in recent decades, the number of deaths has actually increased as a consequence of ageing populations, and gastric cancer is projected to rank among the ten leading global causes of death by 2030.[5,6] *H pylori* is also the main cause of peptic ulcer disease, which accounts for the loss of about 4·6 million disability-adjusted life-years every year worldwide, with most of the burden borne by populations in low-income and middle-income countries.[7] Population-wide eradication programmes seem to offer the most direct approach to reducing the enormous human and economic consequences of *H pylori* infection; however, none has been implemented to date.[8]

Large programmes for *H pylori* eradication require a practical and inexpensive antibiotic regimen that is effective in the specific locale where it will be used. Standard antibiotic regimens for *H pylori* usually entail a proton-pump inhibitor, amoxicillin, and clarithromycin, taken together over 7–14 days.[9–11] However, the effectiveness of these triple-therapy regimens seems to have diminished over time, largely as a result of emerging resistance of the organism to clarithromycin.[12,13] Recent meta-analyses have shown that regimens that add a nitroimidazole (metronidazole or tinidazole) to triple

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SWOG Statistical Center, Cancer Research and Biostatistics, Seattle, WA, USA (E R Greenberg MD, G L Anderson PhD, J J Crowley PhD); **Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (E R Greenberg, G L Anderson, G E Goodman MD); **Division of Gastroenterology, University of North Carolina, Chapel Hill, NC, USA** (D R Morgan MD); **Unidad de Investigación en Enfermedades Infecciosas, Instituto Mexicano del Seguro Social, Mexico City, Mexico** (J Torres PhD); **Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, MI, USA** (W D Chey MD); **Departamento de Patología, Universidad del Valle, Cali, Colombia** (L E Bravo MD); **Hospital Regional de Occidente, Santa Rosa de Copán, Honduras** (R L Dominguez MD); **Departamento de Salud Pública, Pontificia Universidad Católica de Chile, Santiago, Chile** (C Ferreccio MD); **Fundación INCIENSA, San José, Costa Rica** (R Herrero MD); **Screening and Prevention Group, International Agency for Research on Cancer, World Health Organization, Lyon, France** (R Herrero); **Instituto Nacional de Salud Pública, Cuernavaca, Mexico** (E C Lazcano-Ponce MD, E Salazar-Martínez PhD); **Instituto Tecnológico de Sonora, Ciudad Obregón, Mexico** (M M Meza-Montenegro PhD); **Centro de Investigación en Demografía y Salud, León,**

Nicaragua (R Peña PhD, E M Peña MD); **Division of Gastroenterology, Vanderbilt Medical Center, Nashville, TN, USA** (P Correa MD); **Cancer Prevention and Control, University of Arizona Cancer Center, Tuscon, AZ, USA** (M E Martínez PhD); **Division of Hematology/Oncology, University of Michigan Medical School, Ann Arbor, MI, USA** (M Valdivieso MD, L H Baker DO); **and Swedish Cancer Institute, Seattle, WA, USA** (G E Goodman)

Correspondence to: Dr E Robert Greenberg, Cancer Research and Biostatistics, 1730 Minor Ave, Suite 1900, Seattle, WA, USA 98101–1468 **e.r.greenberg@dartmouth.edu**

For more on the **Rome III diagnostic questionnaire** see http://www.theromefoundation.org

therapy and are given either sequentially for 10 days or concomitantly for 5 days are significantly more successful at eradication of *H pylori* infection than are triple-therapy regimens.[14–16] These regimens also require fewer doses of antibiotics and thus might be more affordable in low-resource settings. Almost all the evidence supporting these four-drug regimens comes from Europe and Asia; few data are available from Latin America, a region with some of the world's highest rates of gastric cancer mortality.[17] We therefore undertook a randomised trial in Latin America comparing the effectiveness of four-drug regimens given concomitantly or sequentially with that of a standard 14-day regimen of triple therapy. The trial also provided insights into the feasibility of community-based programmes of *H pylori* eradication.

Methods

Study design and patients

The trial (SWOG S0701) was a randomised trial of empiric 14-day triple, 5-day concomitant, and 10-day sequential therapies for *H pylori* infection in seven Latin American sites: Chile (Santiago), Colombia (Túquerres), Costa Rica (Guanacaste), Honduras (Santa Rosa de Copán), Mexico (Ciudad Obregón and Tapachula), and Nicaragua (León). Between September, 2009, and June, 2010, study research staff recruited potential participants from the general population of adult men and women aged 21–65 years and explained the purpose and eligibility requirements of the study to them. Staff in Colombia, Costa Rica, and Nicaragua selected individuals from a census of households, in Chile they selected potential participants from a list of individuals served by a large public primary care clinic, and in Honduras and Mexico (two sites) they recruited participants by walking house-to-house within the local community or through announcements at primary care clinics.

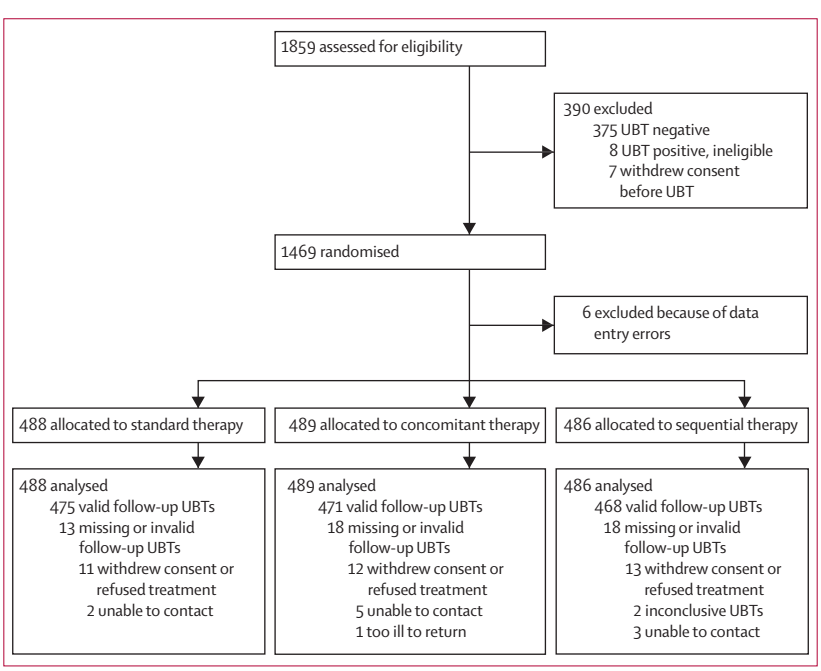

Figure: **Trial profile**
UBT=urea breath test.

Study participants in Tapachula (Mexico), Nicaragua, and Chile were predominantly urban, and those in the other sites were from small, rural communities. Potential participants were deemed ineligible if they had been treated in the past for *H pylori* infection, had serious illnesses that might end their lives before completing the study, or had other disorders that required or precluded treatment with antibiotics or proton-pump inhibitors. They also had to agree to abstain from alcohol use for at least 2 weeks. Those who expressed an interest in participating and gave signed, informed consent then completed an interview regarding socioeconomic characteristics and health history and a detailed gastrointestinal-symptom-history assessment with the validated Spanish language version of the Rome III diagnostic questionnaire for the adult functional gastrointestinal disorders.[18,19] The institutional review boards for each clinical centre and for the SWOG Statistical Center, Seattle, WA, USA approved the study protocol.

Procedures

Participants provided a urea breath test for *H pylori* infection by exhaling into foil balloons before, and 30 min after, consuming a 75 mg dose of ^{13}C-labelled urea with water. Staff at each centre analysed the breath samples using an infrared mass spectrometry device (IRIS, Wagner Analysen Technik, Bremen, Germany) that produced a computer-generated result of positive (change relative to baseline ≥4·0%) or negative (change relative to baseline <2·5%); intermediate values were classified as inconclusive. If a participant reported use of an antibiotic or proton-pump inhibitor within the past 15 days, or if the result from the urea breath test was inconclusive, the test was rescheduled for a later date.

Study staff contacted participants at least once during treatment to encourage adherence and to remind them to return any unused doses at their follow-up visit, which was scheduled to occur 6–8 weeks after randomisation. During follow-up visits, participants completed another interview assessing adherence to therapy, their reasons for missing any doses of the regimens, and the occurrence of any new or worsened medical disorders that led them to seek medical attention. Study staff counted the number of drug doses returned and administered the follow-up urea breath test.

Randomisation and masking

Participants who had a positive urea breath test and met all other eligibility criteria were randomly assigned, in equal proportions, to one of three treatment groups: standard triple therapy of lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg taken twice a day for

14 days; concomitant therapy of lansoprazole 30 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and metronidazole 500 mg taken twice a day for 5 days; or sequential therapy of lansoprazole 30 mg and amoxicillin 1000 mg taken twice a day for 5 days followed by lansoprazole 30 mg, clarithromycin 500 mg, and metronidazole 500 mg taken twice a day for 5 days. Each clinical centre purchased its own supply of the drugs, as generic (off-patent) preparations, from suppliers in country, except the centres in Honduras and Nicaragua, which both used the same supplier in Honduras. The drug suppliers provided quality-control data for the content and dissolution of each drug. Randomisation was implemented centrally through a dynamic balancing procedure at the SWOG Statistical Center to ensure balance within centre by age and sex across the three regimens. Staff at the clinical centres entered data for potentially-eligible, consented individuals into the SWOG Statistical Center computer using a web-based data entry system. If the participants met all eligibility requirements, the computer assigned them to a treatment group and immediately transmitted the treatment assignment to the clinical centre. All participants were randomly assigned in a 1:1:1 ratio within 2 weeks after a positive urea-breath-test result. The trial was not masked.

Statistical analysis

We designed the study to address two primary hypotheses. The first hypothesis was that 5-day concomitant therapy was not inferior to 14-day standard therapy, whereby inferiority was defined as a difference in eradication probability of 5% or greater in favour of standard therapy. We reasoned that the shorter duration and lower cost associated with concomitant therapy would make it preferable to standard therapy if it were not appreciably less effective in eradication of *H pylori* infection. Our second hypothesis was that 10-day sequential therapy would be more effective than 14-day standard therapy, because a four-drug sequential regimen would be preferred over standard three-drug therapy only if it were clearly superior in eradication of *H pylori* infection. Assuming an eradication rate of 80% for standard therapy, 10% missing follow-up urea-breath-test results, and 210 randomised participants per centre (1470 total), each treatment group comparison would have 82% power to detect a difference of 8% or greater, based on a two-sided, 0·025-level test. Although a meta-analysis by Essa and colleagues[16] suggested that concomitant therapy was about 10% better than sequential therapy, if the therapies were actually equivalent the trial would have 46% power to reject the inferiority of concomitant therapy, based on a one-sided, 0·025-level test.

Our primary statistical analyses adhered to the intention-to-treat principle and included all randomised eligible participants, with those without a definitive follow-up urea breath test judged to be treatment failures (urea-breath-test positive). To compare concomitant versus standard therapy, we used a two-sample Z test of the null hypothesis, in which the difference in the estimated probabilities of eradication was 5% or greater

	14-day standard therapy (N=488)	5-day concomitant therapy (N=489)	10-day sequential therapy (N=486)	Total (N=1463)
Centre				
Santiago (Chile)	69 (14%)	70 (14%)	70 (14%)	209 (14%)
Túquerres (Colombia)	71 (15%)	72 (15%)	69 (14%)	212 (15%)
Guanacaste (Costa Rica)	70 (14%)	70 (14%)	70 (14%)	210 (14%)
Copán (Honduras)	70 (14%)	72 (15%)	71 (15%)	213 (15%)
Tapachula (México)	71 (15%)	69 (14%)	70 (14%)	210 (14%)
Obregón (México)	70 (14%)	69 (14%)	71 (15%)	210 (14%)
León (Nicaragua)	67 (14%)	67 (14%)	65 (13%)	199 (14%)
Sex				
Women	287 (59%)	288 (60%)	286 (59%)	861 (59%)
Men	201 (41%)	201 (41%)	200 (41%)	602 (41%)
Age (years)				
20–29	66 (14%)	66 (14%)	91 (19%)	223 (15%)
30–39	137 (28%)	139 (28%)	117 (24%)	393 (27%)
40–49	142 (29%)	117 (24%)	127 (26%)	386 (26%)
≥50	143 (29%)	167 (34%)	151 (31%)	461 (32%)
Years of education				
≤4	88 (18%)	77 (16%)	80 (17%)	245 (17%)
5–8	135 (28%)	166 (34%)	143 (29%)	444 (30%)
9–12	146 (30%)	135 (28%)	136 (28%)	417 (29%)
≥13	71 (15%)	71 (15%)	70 (14%)	212 (14%)
Not reported	48 (10%)	40 (8%)	57 (12%)	145 (10%)
Chronic dyspeptic symptoms				
Present	125 (26%)	121 (25%)	127 (26%)	373 (26%)
Absent	363 (74%)	368 (75%)	359 (74%)	1090 (75%)

Data are n (%).

***Table 1*: Participant characteristics by treatment group**

	Standard therapy (N=475)	Concomitant therapy (N=471)	Sequential therapy (N=470)	Total (N=1416*)
Amount of drugs taken†				
All (100%)	427 (90%)	442 (94%)	437 (93%)	1306 (92%)
Nearly all (>80%)	7 (2%)	0 (0)	2 (<1%)	9 (<1%)
Most (50–80%)	24 (5%)	14 (3%)	21 (4%)	59 (4%)
Less than half (<50%)	10 (2%)	8 (2%)	5 (11%)	23 (2%)
Undetermined (but not all)	7 (2%)	5 (1%)	5 (1%)	17 (1%)
None	0 (0)	2 (<1%)	0 (0)	2 (<1%)
Reasons for not taking all drugs‡				
Concern about having or developing side-effects	41 (9%)	28 (6%)	33 (7%)	102 (7%)
Unrelated illness or injury	3 (1%)	1 (<1%)	5 (1%)	9 (<1%)
Forgot or inconvenient	36 (8%)	25 (5%)	37 (8%)	98 (7%)
Reason not given	0 (0)	3 (<1%)	2 (<1%)	5 (<1%)

Data are n (%). *Includes 1414 participants with a valid follow-up urea breath test and two (from the sequential therapy group) whose urea breath test results were inconclusive. †Based on count of returned drugs and self-report among participants who returned for a follow-up urea breath test. ‡Multiple responses allowed.

***Table 2*: Adherence to treatment of patients that returned for 6-week follow-up, by treatment group**

in favour of the standard regimen, based on a one-sided test of non-inferiority. Comparison of sequential versus standard therapies was based on a two-sample *Z* test for no difference between eradication probabilities. Sensitivity to missing data assumptions was examined by excluding data from participants without a conclusive follow-up urea breath test. To establish how poor adherence could have affected our conclusions, we further restricted the analyses to participants with a definitive urea breath test who had taken at least 80% of their assigned study drugs.

Secondary analyses assessed variability in treatment outcome by sex, age, presence of chronic dyspeptic symptoms, and clinical centre. Tests of interaction were calculated as deviance tests comparing logistic regression models with the treatment group indicators, the designated covariate, and their interaction terms, with those without the interaction terms.

All analyses were done with SAS version 9.2 and R version 2.12.2 statistical software. Bonferroni-adjusted 95% CIs were used to account for the two primary comparisons, and p values less than 0·025 were classed as statistically significant. No corrections for multiplicity were applied to secondary analyses, because they were considered to be exploratory. All p values were two-sided except the test of non-inferiority.

This trial is registered with ClinicalTrials.gov, registration number NCT01061437.

	N	*Helicobacter pylori* eradication	Difference from standard group (adjusted 95% CI for difference)
Intention to treat (N= 1463)			
14-day standard therapy	488	401 (82·2% [78·5 to 85·5])	..
5-day concomitant therapy	489	360 (73·6% [69·5 to 77·5])	8·6% (2·6 to 14·5)
10-day sequential therapy	486	372 (76·5% [72·5 to 80·2])	5·6% (–0·4 to 11·6)
Definitive 6-week UBT (N=1414)			
14-day standard therapy	475	401 (84·4% [80·8 to 87·6])	..
5-day concomitant therapy	471	360 (76·4% [72·3 to 80·2])	8·0% (2·2 to 13·7)
10-day sequential therapy	468	372 (79·4% [75·5 to 83·1])	4·9% (–0·9 to 10·8)
Adherent to therapy (N=1314)			
14-day standard therapy	434	378 (87·1% [83·6 to 90·1])	..
5-day concomitant therapy	442	348 (78·7% [74·6 to 82·5])	8·4% (2·7 to 14·0)
10-day sequential therapy	438	355 (81·1% [77·1 to 84·6])	6·0% (0·3 to 11·8)

Data are number (% [95% CI]) unless otherwise indicated. UBT=urea breath test.

***Table 3:* *Helicobacter pylori* eradication by treatment group for three definitions of analysis population**

	N	*Helicobacter pylori* eradication	Difference from standard group (adjusted 95% CI)	p value for interaction*
Sex	..	..	..	0·91
Women	861	..	..	..
14-day standard	287	234 (81·5%)	..	..
5-day concomitant	288	207 (71·9%)	9·7% (1·8 to 17·5)	..
10-day sequential	286	214 (74·8%)	6·7% (–1·4 to 14·8)	..
Men	602	..	..	
14-day standard	201	167 (83·1%)	..	..
5-day concomitant	201	153 (76·1%)	7·0% (–2·0 to 15·9)	..
10-day sequential	200	158 (79·0%)	4·1% (–5·2 to 13·3)	..
Age	..	..	..	0·21
21–40 years	663	..	..	..
14-day standard	222	182 (82·0%)	..	..
5-day concomitant	220	164 (74·5%)	7·4% (–1·3 to 16·2)	..
10-day sequential	221	160 (72·4%)	9·6% (0·3 to 18·9)	..
41–65 years	800	..	..	..
14-day standard	266	219 (82·3%)	..	..
5-day concomitant	269	196 (72·9%)	9·5% (1·4 to 17·5)	..
10-day sequential	265	212 (80·0%)	2·3% (–5·6 to 10·3)	..
Chronic dyspeptic symptoms	..	..	..	0·38
Absent	1090	..	..	..
14-day standard	363	297 (81·8%)	..	..
5-day concomitant	368	277 (75·3%)	6·5% (–0·2 to 13·3)	..
10-day sequential	359	281 (78·3%)	3·5% (–3·4 to 10·5)	..
Present	373	..	..	..
14-day standard	125	104 (83·2%)	..	..
5-day concomitant	121	83 (68·6%)	14·6% (2·5 to 26·7)	..
10-day sequential	127	91 (71·7%)	11·5% (–0·9 to 24·0)	..

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Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and participated in the decision to submit for publication.

Results

1859 potentially-eligible adults agreed to participate in the study and completed the screening interview and intake questionnaire, but seven withdrew before the urea breath test (figure). The test was positive for 1471 (79%) of 1852 tested participants. Eight patients with a positive test were not randomly assigned because they opted not to be treated, could not be randomly assigned within 2 weeks of their urea breath test, or had a disqualifying factor (eg, pregnancy). Six participants with a negative urea breath test, who were randomly assigned incorrectly because of data entry errors, were withdrawn from the study before receiving treatment, and their data were not included in any of the following analyses. Of the eligible participants who were randomised, 861 (59%) of 1463 were women, 847 (58%) of 1463 were age 40 years or older, and 373 (25%) of 1463 had chronic dyspeptic symptoms as classified by the Rome III criteria. Participant characteristics were balanced between the three treatment groups (table 1). 47 participants did not return for their follow-up urea breath test, and two participants had follow-up tests that were inconclusive after two repeat tests. Thus, we obtained definitive follow-up urea-breath-test results for 1414 (97%) of 1463 of the randomised eligible participants (figure).

Table 2 shows adherence to treatment of patients that returned for 6-week follow-up. 1313 (92%) of

1416 participants who returned for their follow-up visit had taken at least 80% of their assigned drugs, as assessed by pill count and self-report (table 2). Five participants had new, therapy-related symptoms (stomach discomfort, nausea or vomiting, or fatigue or weakness) that led them to seek medical attention; one in the standard treatment group and two each in the concomitant and sequential treatment groups.

In intention-to-treat analyses, the estimated probability of *H pylori* eradication was higher with 14-day standard triple therapy than with 5-day concomitant therapy and 10-day sequential therapy (table 3). The null hypothesis of inferiority of concomitant therapy to standard therapy could not be rejected (one-sided p=0·91); thus, the data are consistent with 5-day concomitant therapy being inferior to 14-day standard therapy. The difference between 10-day sequential therapy and standard therapy was not significant (p=0·04) at the p=0·025 level, but the near statistical significance of this two-sided test suggests that sequential therapy was not as effective as standard therapy. Sensitivity analyses that excluded participants without a definitive follow-up urea breath test and those that were confined to participants who had adhered to the prescribed regimens showed similar patterns of treatment contrasts as the intention-to-treat analysis, but with somewhat higher estimated eradication probabilities (table 3). Secondary analyses examining potential interactions showed no significant interactions between treatment and sex, age, presence of chronic dyspeptic symptoms at baseline, or study centre (table 4). Differences between study sites occurred in the overall probability of eradication in both the intention-to-treat populations (table 4) and the adherent-to-therapy population (webappendix), but nowhere was either four-drug regimen clearly better than standard triple therapy.

	N	*Helicobacter pylori* eradication	Difference from standard group (adjusted 95% CI)	p value for interaction*
(Continued from previous page)				
Study site	..	..	..	0·28
Santiago (Chile)	209	..	..	..
14-day standard	69	59 (85·5%)	..	..
5-day concomitant	70	46 (65·7%)	19·8% (3·9 to 35·7)	..
10-day sequential	70	59 (84·3%)	1·2% (–13·6 to 16·1)	..
Túquerres (Colombia)	212	..	..	..
14-day standard	71	58 (81·7%)	..	..
5-day concomitant	72	58 (80·6%)	1·1% (–13·5 to 15·8)	..
10-day sequential	69	54 (78·3%)	3·4% (–13·2 to 20·0)	..
Guanacaste (Costa Rica)	210	..	..	..
14-day standard	70	61 (87·1%)	..	..
5-day concomitant	70	54 (77·1%)	10·0% (–4·4 to 24·4)	..
10-day sequential	70	63 (90·0%)	–2·9% (–16·3 to 10·6)	..
Copán (Honduras)	213	..	..	..
14-day standard	70	66 (94·3%)	..	..
5-day concomitant	72	62 (86·1%)	8·2% (–2·9 to 19·2)	..
10-day sequential	71	58 (81·7%)	12·6% (–0·8 to 26)	..
Tapachula (México)	210	..	..	..
14-day standard	71	55 (77·5%)	..	..
5-day concomitant	69	50 (72·5%)	5·0% (–11·4 to 21·4)	..
10-day sequential	70	47 (67·1%)	10·4% (–7·9 to 28·5)	..
Ciudad Obregón (México)	210	..	..	..
14-day standard	70	54 (77·1%)	..	..
5-day concomitant	69	47 (68·1%)	9·0% (–7·8 to 25·9)	..
10-day sequential	71	47 (66·2%)	10·9% (–7·4 to 29·2)	..
León (Nicaragua)	199	..	..	..
14-day standard	67	48 (71·6%)	..	..
5-day concomitant	67	43 (64·2%)	7·4% (–10·6 to 25·5)	..
10-day sequential	65	44 (67·7%)	3·9% (–15·5 to 23·4)	..

Subgroup analyses for age, sex, and study site were prespecified; subgroup analyses for chronic dyspeptic symptoms were not. *p value for χ^2 drop-in-deviance test for significance of interaction with treatment regimen in a logistic regression model controlling for main effects of treatment and baseline covariate.

Table 4: **Summary of *Helicobacter pylori* eradication by treatment group and selected baseline characteristics for intention-to-treat population**

Discussion

Our principal outcome measure, the probability of *H pylori* eradication, was higher for 14-day standard triple therapy than for both four-drug regimens, and these results did not vary significantly by age, sex, study site, or history of chronic dyspeptic symptoms. The prevalence of *H pylori* infection in screened participants was high, and nearly all individuals who had a positive urea breath test were randomly assigned into the trial. Participants tended to adhere closely to the protocol by returning for their follow-up urea breath test and taking their prescribed tablets. In the three treatment groups, the difference in adherence and serious side-effects was small.

H pylori presents a major global health challenge, which can probably best be addressed through practical, inexpensive, and population-based interventions in the resource-limited countries where it is most prevalent. From this perspective the size of our trial, technical simplicity, broad geographic coverage within Latin America, community-based population, use of locally sourced generic drugs, and statistically robust findings across important subgroups reflect the realities of a region where diseases associated with *H pylori* are especially burdensome. Our results are important because they challenge those of meta-analyses showing that four-drug regimens (triple therapy plus a nitroimidazole) given concomitantly or sequentially were clearly better than triple therapy,[14–16] and they suggest that findings based primarily on data from Europe and other high-income regions might not be readily generalisable to lower-income countries (panel).

We reported probabilities of *H pylori* eradication of less than 80% with 5-day concomitant and 10-day sequential regimens by the intention-to-treat analysis, whereas meta-analyses had reported probabilities greater than 90% for both.[14–16] Investigators of a trial from Taiwan comparing 10-day regimens of concomitant versus sequential four-drug therapies also reported that both

See Online for webappendix

regimens were more than 90% successful.[20] The estimated effectiveness of our three-drug regimen (82%) in the intention-to-treat analysis was only modestly greater than that reported in the meta-analyses (77–79%).[14–16] Thus, the divergence between our findings and those of the meta-analyses represents the substantially worse performance of the four-drug regimens.

Geographical variations in the pattern of *H pylori* resistance to antibiotics might account for some of the discrepancies between the results. In clinical series from several countries included in our trial, clarithromycin resistance in *H pylori* isolates has been reported to be less prevalent than in Europe, and metronidazole resistance substantially more prevalent (as high as 80%).[21–24] Clarithromycin resistance strongly diminishes the effectiveness of triple therapy, so a better outcome with triple therapy would be expected if the prevalence of resistance in our trial population was actually low.[13,21,25] A high prevalence of resistance to metronidazole in our study population is a plausible, but less certain, explanation for the worse-than-expected success of the four-drug regimens.[25] Results according to antibiotic resistance are available from only two trials of sequential therapy versus triple therapy; the combined data showed that 68 of 71 (96%) patients with metronidazole-resistant organisms were treated successfully with sequential therapy compared with 46 of 59 (78%) treated with triple therapy.[16,26] No comparable data from trials of concomitant versus triple therapy are available. The presence of organisms resistant to both antibiotics would likely cause treatment to fail for all three studied regimens, but data for this topic from Latin America are scarce.

We used a 14-day regimen of triple therapy in our trial, whereas previous trials of the four-drug regimens generally compared them to 7 days or 10 days of triple therapy. In one meta-analysis 14-day triple therapy regimens were slightly, but significantly, superior to those of 7 days or 10 days; thus, longer duration conceivably enhanced the performance of triple therapy in our trial.[27] Success with the four-drug regimens perhaps would also improve with longer duration;[13,20,28] however, this would increase their cost.

We recruited our participants from the general adult population in the community, whereas previous trials studied patients with gastrointestinal symptoms.[14–16] The success of *H pylori* treatment with triple therapy or sequential therapy has not been shown to be affected by a diagnosis of peptic-ulcer disease or dyspepsia, and the superiority of triple therapy over the four-drug regimens in our trial did not vary significantly according to history of chronic dyspeptic symptoms.[14]

Our trial was undertaken in the general population in community settings where it was not feasible to mask the study or to obtain bacterial specimens for antibiotic sensitivity testing. We also obtained generic drugs from a variety of sources and did not have a completely objective way of determining adherence to therapy. Each of these factors is a potential limitation of the trial, but we doubt that any of them represents a serious threat to the validity of our results. Despite the absence of masking, our principal outcome measure (urea breath test) was objectively measured and seems unlikely to be biased. The absence of antibiotic sensitivity data also should not affect study validity, but it does make it more difficult to generalise our results to other regions where sensitivity patterns could be different. Inaccuracies in patient reports of adherence to therapy could have lowered our estimates of treatment effectiveness in the subgroup of participants classified as adherent, but these inaccuracies would not compromise the validity of the main results from our intention-to-treat analyses comparing the relative effectiveness of the three regimens. Lastly, although we cannot guarantee that the locally available generic drugs were of uniform efficacy, differences in treatment response between centres cannot be easily attributed to variable drug quality, since some of the greatest differences were seen between Nicaragua and Honduras, where investigators obtained drugs from the same source.

For individuals with *H pylori* infection in much of Latin America, 14 days of triple therapy is probably the preferred empiric treatment. Nevertheless, the 87% eradication

Panel: Research in context

Systematic review

Consensus groups that represent both global and Latin American perspectives have designated triple-drug regimens of a proton-pump inhibitor plus amoxicillin and clarithromycin taken for 7–14 days as a standard approach for eradicating *Helicobacter pylori*.[10,11] However, the effectiveness of these regimens seems to have diminished to unacceptably low levels over time,[12,13] and recent meta-analyses of clinical trials from Europe and Asia show that four-drug regimens that add metronidazole or tinidazole to triple therapy achieve superior results.[14–16] The reported meta-analyses have not included any trials that were undertaken in Latin America, an area where *H pylori*-associated diseases are common and where wide-scale eradication programmes might be needed. We did a Medline search of all publications up to 2010, with no language restrictions, using the search terms "Helicobacter" in combination with the term for each country in Latin America. No publications of clinical trials that compared 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection were identified.

Interpretation

Our findings showed that in the Latin American populations we studied, by contrast with those for European and some Asian populations, 14-day standard triple therapy is more effective than 5-day concomitant or 10-day sequential four-drug regimens that include metronidazole for eradication of *H pylori*. Thus, effectiveness of *H pylori* eradication regimens in one area might not be as equally effective elsewhere.

success in participants who adhered to the regimen is suboptimum in the clinical setting, and its effectiveness might decrease over time as clarithromycin resistance increases. Improved *H pylori* treatment regimens for Latin American populations could conceivably be designed on the basis of local antibiotic resistance data. However, the small number of published reports of antibiotic resistance in this region generally pertain to *H pylori* isolates obtained from symptomatic patients undergoing endoscopy in urban academic centres, and thus the results might not be applicable to broader populations.[21] In view of the paucity of representative data for resistance, and the daunting technical and financial challenges of obtaining these data, treatment guidelines for Latin America and other regions with limited resources might have to rely primarily on the results of large, simple clinical trials of empiric therapies in the specific populations to which the guidelines would apply. These data could be supplemented by subsequent monitoring of effectiveness in practice over time and by the results of antibiotic-resistance testing in selected patients, when feasible.

We designed our study as a preliminary step towards implementation of programmes of gastric cancer prevention in Latin America. *H pylori*-associated gastric cancer results from a long progression from normal mucosa to invasive cancer.[3,29] The most promising preventive approach seems to be eradication of *H pylori* infection before cancer develops, and several randomised trials have assessed this strategy. The results show that eradication of this infection slows or reverses progression of premalignant histological lesions, but no trial has been large enough to show a definitive cancer-preventive effect.[30,31] Nevertheless, analyses have suggested that *H pylori* eradication programmes would be cost effective over the long term if they prevented only 10% of gastric-cancer deaths; over the short term they would reduce costs of care for peptic ulcers and dyspepsia symptoms.[32–34] Eradication programmes are potentially even more cost effective in regions such as Latin America, where the burden of *H pylori*-associated diseases is high.

Our results suggest that population-wide clinical trials or public health programmes of *H pylori* eradication are feasible in Latin America. Individuals with a positive urea breath test readily agreed to be randomly assigned to antibiotic treatment, and all three regimens of generic drugs resulted in probabilities of eradication comparable to those reported in previous prevention programmes.[31] The 14-day triple-drug regimen had superior results, but the lower cost of the shorter duration regimens might make them acceptable for use in prevention programmes, where resources are particularly scarce. Other considerations, including risks of recrudescence and reinfection after eradication, will also be important.

Contributors

All the authors participated in the design and oversight of the trial and in the interpretation and reporting of results, and have seen and approved the final report. LEB, RLD, CF, RH, MMM-M, RP, and ES-M directed the clinical activities at the study centres. GLA had principal responsibility for the statistical analyses of the data.

Conflicts of interest

DRM has submitted a patent application through the University of North Carolina for a technique using molecular endoscopy to detect cancer in the gastrointestinal tract, and has received funding from Axcan for his participation in a speakers' bureau; he has also received a research grant from AstraZeneca, for a proton-pump inhibitor study in Hispanic populations in the USA, and from Given Imaging, for ongoing efficacy studies of colon endocapsule efficacy. All other authors declare that they have no conflicts of interest.

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