

# Risk of Recurrent *Helicobacter pylori* Infection 1 Year After Initial Eradication Therapy in 7 Latin American Communities

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**G**ASTRIC ADENOCARCINOMA IS the second leading cause of cancer death worldwide.<sup>1</sup> Although gastric cancer rates are declining in some areas, the number of deaths is expected to increase over the coming decades due to growing and aging populations in high-incidence regions such as Latin America and eastern Asia.<sup>2</sup> *Helicobacter pylori* infects more than half of the world's adult population, and chronic infection with this bacterium is the dominant risk factor for gastric cancer, accounting for an estimated two-thirds of all cases globally.<sup>3,4</sup>

**Importance** The long-term effectiveness of *Helicobacter pylori* eradication programs for preventing gastric cancer will depend on recurrence risk and individual and community factors.

**Objective** To estimate risk of *H pylori* recurrence and assess factors associated with successful eradication 1 year after treatment.

**Design, Setting, and Participants** Cohort analysis of 1463 randomized trial participants aged 21 to 65 years from 7 Latin American communities, who were treated for *H pylori* and observed between September 2009 and July 2011.

**Interventions** Randomization to 1 of 3 treatment groups: 14-day lansoprazole, amoxicillin, and clarithromycin (triple therapy); 5-day lansoprazole and amoxicillin followed by 5-day lansoprazole, clarithromycin, and metronidazole (sequential); or 5-day lansoprazole, amoxicillin, clarithromycin, and metronidazole (concomitant). Participants with a positive (13) C-urea breath test (UBT) 6 to 8 weeks posttreatment were offered voluntary re-treatment with 14-day bismuth-based quadruple therapy.

**Measurements** Recurrent infection after a negative posttreatment UBT and factors associated with successful eradication at 1-year follow-up.

**Results** Among participants with UBT-negative results who had a 1-year follow-up UBT (n=1091), 125 tested UBT positive, a recurrence risk of 11.5% (95% CI, 9.6%-13.5%). Recurrence was significantly associated with study site ( $P=.03$ ), nonadherence to initial therapy (adjusted odds ratio [AOR], 2.94; 95% CI, 1.31-6.13;  $P=.01$ ), and children in the household (AOR, 1.17; 95% CI, 1.01-1.35 per child;  $P=.03$ ). Of the 281 with positive posttreatment UBT results, 138 completed re-treatment, of whom 93 tested UBT negative at 1 year. Among the 1340 who had a 1-year UBT, 80.4% (95% CI, 76.4%-83.9%), 79.8% (95% CI, 75.8%-83.5%), and 77.8% (95% CI, 73.6%-81.6%) had UBT-negative results in the triple, sequential, and concomitant groups, respectively ( $P=.61$ ), with 79.3% overall effectiveness (95% CI, 77.1%-81.5%). In a single-treatment course analysis that ignored the effects of re-treatment, the percentage of UBT-negative results at 1 year was 72.4% (95% CI, 69.9%-74.8%) and was significantly associated with study site ( $P<.001$ ), adherence to initial therapy (AOR, 0.26; 95% CI, 0.15-0.42;  $P<.001$ ), male sex (AOR, 1.63; 95% CI, 1.25-2.13;  $P<.001$ ), and age (AOR, 1.14; 95% CI, 1.02-1.27 per decade;  $P=.02$ ). One-year effectiveness among all 1463 enrolled participants, considering all missing UBT results as positive, was 72.7% (95% CI, 70.3%-74.9%).

**Conclusions and Relevance** One year after treatment for *H pylori* infection, recurrence occurred in 11.5% of participants who had negative posttreatment UBT results. Recurrence determinants (ie, nonadherence and demographics) may be as important as specific antibiotic regimen in determining the long-term success of *H pylori* eradication interventions. Study findings are relevant to the feasibility of programs for the primary prevention of gastric cancer in high-incidence regions of Latin America.

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In a randomized trial in Shandong, China, eradication of *H pylori* using amoxicillin and omeprazole reduced gastric cancer incidence by 39% over

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a 15-year period.<sup>5</sup> If results of this and other trials are confirmed,<sup>6-9</sup> focused community eradication programs may offer a promising approach for diminishing the enormous human and economic consequences of this cancer. The feasibility of large-scale programs is uncertain and success in specific populations will depend on the efficacy of the antibiotic regimen used and the risk of recurrent infection following eradication.<sup>10,11</sup>

We observed a cohort of patients enrolled in a randomized trial in 7 community populations in Latin America with moderate to high risk for gastric cancer to compare the short-term effectiveness of 3 regimens in eradicating *H pylori*.<sup>12,13</sup> We previously reported the results of eradication therapy 6 to 8 weeks following randomization.<sup>14</sup> One year after therapy, study participants were retested to determine risk of recurrent infection and to assess factors that influenced eradication effectiveness. We now present the key results of the 1-year follow-up.

## METHODS

The trial sites and methods have been previously reported<sup>14</sup> and were coordinated by SWOG, a federally funded cancer research cooperative group. In brief, men and women aged 21 to 65 years were recruited and screened for eligibility in 7 Latin American communities between September 2009 and June 2010. Potential participants were selected using a census of households (Colombia, Costa Rica, Nicaragua), a large public clinic registry (Chile), or household recruitment (Honduras and 2 sites in Mexico). Eligibility requirements included having no prior treatment for *H pylori* infection and no significant illness (eg, active cancer, other serious chronic illness).<sup>14</sup> We explained the purpose and eligibility requirements of the study to potential participants and those who expressed an interest provided signed informed consent. The institutional review boards for each center and the SWOG statistical center approved the study protocol.<sup>14</sup>

*H pylori* infection was assessed using the (13) C-urea breath test (UBT) with a 75-mg oral dose of 13C-labeled urea, analyzed with infrared mass spectrometry (IRIS, Wagner Analysen Technik). A change in 13C carbon dioxide, relative to a baseline of 4.0% or greater, was considered positive. Serologic markers for the *H pylori* CagA protein (cytotoxin-associated gene A) were assessed by IgG antibodies in the study laboratory in Mexico (J.T.) by previously described methods.<sup>15</sup> Standard instruments were used (including the Rome III Diagnostic Questionnaire for the assessment of baseline dyspepsia symptoms) to assess demographic factors, household conditions, and health history.<sup>16,17</sup>

Individuals who had positive UBT results and met other eligibility criteria were randomly assigned by a central computer to 1 of 3 treatment groups using a web-based dynamic randomization procedure that assured balance of sex, age, and study site across the 3 regimens. The treatments were: (1) triple therapy, given for 14 days of lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg; (2) sequential therapy, given for 5 days of lansoprazole 30 mg and amoxicillin 1000 mg, followed by 5 days of lansoprazole 30 mg, clarithromycin 500 mg, and metronidazole 500 mg; and (3) concomitant therapy, given for 5 days of lansoprazole 30 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and metronidazole 500 mg.<sup>18,19</sup> All medications were taken twice per day. The medications were generic and obtained from certified manufacturers. Treatment assignments were not blinded.

Participant follow-up was scheduled 6 to 8 weeks after randomization to include a UBT and assessment of adverse effects and adherence (defined as having taken  $\geq 80\%$  of each drug of the study regimen).<sup>14</sup> Participants who had UBT-positive results at their follow-up visit were offered a voluntary 14-day re-treatment regimen of standard quadruple therapy with twice-daily lansoprazole 30 mg, with tetracycline 500 mg, metronidazole 500 mg, and bismuth subsalicylate 524 mg (or bismuth subci-

trate 420 mg), each taken 4 times per day.<sup>13,20</sup> The protocol did not specify measures during re-treatment to encourage acceptance or adherence, or to assess adverse effects or re-treatment effectiveness. The 1-year follow-up examination, scheduled between 48 and 52 weeks following randomization for all participants, included a UBT and final questionnaire.

## Statistical Considerations

The trial sample size of 1470 participants was chosen to provide a greater than 80% power to assess the first study aim—whether sequential therapy was superior to triple therapy and whether concomitant therapy was noninferior to triple therapy in terms of eradication success (UBT negativity) at the 6- to 8-week follow-up. This sample size was determined to be sufficient to address the 1-year study goals of estimating recurrence risk and eradication success. Specifically, we assumed a recurrence risk of as much as 10% based on prior studies in Latin America,<sup>21,22</sup> and with projected sample sizes of 1000 and 1400 participants, the estimated probabilities of recurrence and overall effectiveness would have standard errors of 0.95% and 0.80%, respectively. Eradication success or failure was determined by UBT results. The term *infection recurrence* was used to identify participants who had UBT-negative results at the 6- to 8-week visit, but UBT-positive results at the 1-year visit; *H pylori* strain data were not available for differentiating recrudescence (same strain) and true reinfection (new strain).

Statistical analyses considered all participants as belonging to the treatment group to which they were assigned, regardless of adherence to their assigned regimens. Analyses of recurrence risk and treatment outcomes were based on participants who had a conclusive (definite) UBT result at the 1-year visit. Treatment outcome results are also presented using 2 additional approaches: (1) a 1-year intent-to-treat analysis in which participants without a follow-up UBT were considered as treatment failures (UBT posi-

); and (2) a single-treatment course analysis in which the effects of re-treatment were ignored, ie, participants who had UBT-positive results at 6 to 8 weeks that became UBT negative at 1 year were considered still to be UBT positive. A strategy of retesting all participants and re-treating those with positive results shortly after initial eradication therapy may not be a cost-effective cancer prevention strategy,<sup>23</sup> and the single-treatment course analysis represents the 1-year outcome of a strategy without re-treatment.

The 95% CIs for estimates of recurrence risk and treatment success were calculated using the binomial exact method, and *P* values for comparisons among the 3 treatment groups for these outcomes were based on the likelihood ratio  $\chi^2$  test for independence. Univariate and multivariate logistic regression analyses were used to explore associa-

tions between participant characteristics and recurrence risk, initial treatment success, and 1-year treatment success. Multivariate models were adjusted for the effects of age, sex, and study center. *P* values for the standard logistic regression models were based on the Wald  $\chi^2$  test statistic and were 2-sided without adjustment for multiplicity, and values less than .05 were considered statistically significant. Analyses were conducted using SAS version 9.2 and R version 2.12.

**RESULTS**

We identified 1859 adults who agreed to participate, of whom 1844 were potentially eligible with positive UBT results (FIGURE). Exclusions included 375 individuals (20.3%) because of negative UBT results, 7 withdrew consent, and 8 were ineligible on subsequent interviews. Six individuals with nega-

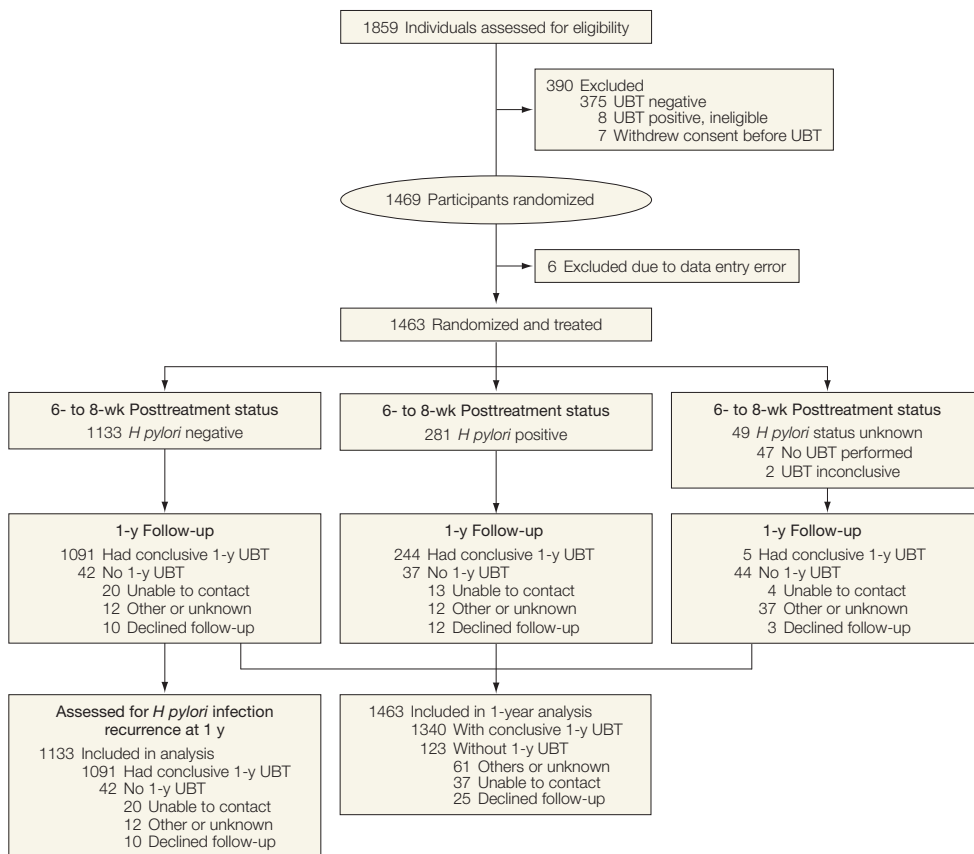
tive UBT results were incorrectly randomized due to data entry error and immediately withdrawn, leaving 1463 participants randomized to receive 1 of the 3 antibiotic regimens.

TABLE 1 shows participants' characteristics according to their treatment assignment and follow-up status: 59% were women, 55% older than 40 years, 84% were *H pylori* CagA positive, and 26% had chronic dyspepsia symptoms. Reported use of alcohol (8%,  $\geq 1$  drink/week) and tobacco (16%,  $\geq 1$  cigarette/d) was relatively infrequent. We obtained a conclusive UBT result at the posttreatment (6- to 8-week) visit from 1414 participants (96.7%) and from 1340 (91.6%) at the 1-year follow-up visit.

**Infection Recurrence**

Of the 1133 participants who were UBT negative following initial treatment, 1091 had a 1-year UBT result, of whom 125

**Figure.** Latin America *Helicobacter pylori* Eradication Trial Profile



had become UBT positive, a recurrence risk of 11.5% (95% CI, 9.6%-13.5%). The recurrence risk ranged from 6.8% in Costa Rica to 18.1% in Colombia. Recurrence at 1 year was significantly associated with study site ( $P=.03$ ), number of children in the household (odds ratio [OR], 1.17; (95% CI, 1.01-1.35 per child;  $P=.03$ ), and nonadherence to therapy (OR, 2.94; 95% CI, 1.31-6.13;  $P=.01$ ), but not with treatment assignment ( $P=.63$ ) (TABLE 2).

**1-Year Outcomes**

In the primary analysis of treatment effectiveness based on the 1340 partici-

pants with definitive 1-year UBT results, the estimated 1-year eradication success rate was 80.4% (95% CI, 76.4%-83.9%) for triple therapy, 79.8% (95% CI, 75.8%-83.5%) for sequential therapy, and 77.8% (73.6%-81.6%) for concomitant therapy ( $P=.61$ ). Overall effectiveness was 79.3% (95% CI, 77.1%-81.5%; TABLE 3). Outcome of treatment effectiveness among study sites ranged from a higher level (87%-90%) in Costa Rica and Honduras to a lower level (71%-76%) in Colombia, Nicaragua, and in Obregón and Tapachula, Mexico. Women 21 to 44 years of age were significantly less likely to

have eradication success at 1 year (72.3%; 95% CI, 68.0%-76.2%) when compared with women 45 to 65 years of age (82.8%; 95% CI, 78.2%-86.8%), and when compared with men who were both younger (82.1%; 95% CI, 77.3%-86.2%) and older (85.6%; 95% CI, 80.5%-89.9%).

Of participants with positive post-treatment UBT results, 244 of 281 returned for a 1-year examination. Of those who returned, 198 (81%) had accepted a prescription for re-treatment quadruple therapy but only 138 (57%) reported that they had completed the regimen; 37 (15%) refused re-

**Table 1.** Participant Characteristics at Enrollment, Posttreatment, and 1-Year Follow-up

	UBT Status, No. (%)						
	Total	Posttreatment (6-8 wk) <sup>a</sup>			1 Year		
		Negative	Positive	Unknown or Inconclusive	Negative	Positive	Unknown or Inconclusive
Total, No.	1463	1133	281	49	1063	277	123
Treatment regimen							
14-d Triple	488 (33.4)	401 (35.4)	74 (26.3)	13 (26.5)	364 (34.2)	89 (32.1)	35 (28.5)
10-d Sequential	486 (33.2)	372 (32.8)	96 (34.2)	18 (36.7)	356 (33.5)	90 (32.5)	40 (32.5)
5-d Concomitant	489 (33.4)	360 (31.8)	111 (39.5)	18 (36.7)	343 (32.3)	98 (35.4)	48 (39.0)
Study site							
Santiago, Chile	209 (14.3)	164 (14.5)	31 (11)	14 (28.6)	145 (13.6)	34 (12.3)	30 (24.4)
Túquerres, Colombia	212 (14.5)	170 (15.0)	41 (14.6)	1 (2.0)	146 (13.7)	59 (21.3)	7 (5.7)
Guanacaste, Costa Rica	210 (14.4)	178 (15.7)	29 (10.3)	3 (6.1)	182 (17.1)	21 (7.6)	7 (5.7)
Copán, Honduras	213 (14.6)	186 (16.4)	25 (8.9)	2 (4.1)	178 (16.7)	26 (9.4)	9 (7.3)
Obregón, México	210 (14.4)	148 (13.1)	55 (19.6)	7 (14.3)	139 (13.1)	52 (18.8)	19 (15.4)
Tápachula, México	210 (14.4)	152 (13.4)	55 (19.6)	3 (6.1)	147 (13.8)	47 (17.0)	16 (13.0)
León, Nicaragua	199 (13.6)	135 (11.9)	45 (16.0)	19 (38.8)	126 (11.9)	38 (13.7)	35 (28.5)
Sex							
Women	861 (58.9)	655 (57.8)	190 (67.6)	16 (32.7)	614 (57.8)	189 (68.2)	58 (47.2)
Men	602 (41.1)	478 (42.2)	91 (32.4)	33 (67.3)	449 (42.2)	88 (31.8)	65 (52.8)
Age, y							
21-29	246 (16.8)	183 (16.2)	52 (18.5)	11 (22.4)	166 (15.6)	54 (19.5)	26 (21.1)
30-39	417 (28.5)	323 (28.5)	89 (31.7)	5 (10.2)	296 (27.8)	96 (34.7)	25 (20.3)
40-49	377 (25.8)	284 (25.1)	80 (28.5)	13 (26.5)	278 (26.2)	66 (23.8)	33 (26.8)
≥50	423 (28.9)	343 (30.3)	60 (21.4)	20 (40.8)	323 (30.4)	61 (22.0)	39 (31.7)
Adherence to initial therapy, pills returned <sup>b</sup>							
<20%	1319 (90.2)	1081 (95.4)	233 (82.9)	5 (10.2)	1017 (95.7)	232 (83.8)	70 (56.9)
≥20%	98 (6.7)	39 (3.4)	43 (15.3)	16 (32.7)	34 (3.2)	41 (14.8)	23 (18.7)
Baseline dyspepsia symptoms <sup>c</sup>							
Present	373 (25.5)	278 (24.5)	86 (30.6)	9 (18.4)	269 (25.3)	85 (30.7)	19 (15.4)
Absent	1090 (74.5)	855 (75.5)	195 (69.4)	40 (81.6)	794 (74.7)	192 (69.3)	104 (84.6)
Posttreatment (6- 8-wk) UBT status							
Negative	1133 (77.4)				966 (90.9)	125 (45.1)	42 (34.1)
Positive	281 (19.2)				93 (8.7)	151 (54.5)	37 (30.1)
Unknown or inconclusive	49 (3.3)				4 (0.4)	1 (0.4)	44 (35.8)

Abbreviation: (13) UBT, C-urea breath test.

<sup>a</sup>The posttreatment UBT was obtained 6 to 8 weeks following treatment initiation.

<sup>b</sup>Adherence was defined as having taken at least 80% of each drug of the study regimen. Adherence was not reported for 46 participants.

<sup>c</sup>Dyspepsia symptoms persisting for at least 6 months as determined by the ROME III questionnaire and accompanying scoring algorithm. The SAS program used to score the questionnaires was obtained from [http://www.romecriteria.org/rome\\_iii\\_sas/](http://www.romecriteria.org/rome_iii_sas/).

treatment. The UBT result had become negative for 38% overall (93/244) and also for 54% of those who reported completing re-treatment (74/138). Of the individuals with UBT-positive results who declined re-

treatment, 4 of 46 had UBT-negative results at 1 year.

In a 1-year analysis that included all 1463 randomized participants, and that considered as treatment failures (UBT positive) the 123 individuals (8.4%) without a UBT result, treatment effectiveness estimates were 74.6% (95% CI, 70.5%-78.4%), 73.3% (95% CI, 69.1%-77.1%), and 70.1% (95% CI, 65.9%-74.2%) for the triple, sequential, and concomitant treatment groups, respectively, or about 7% lower than those in the analysis mentioned previously. (Table 3).

To explore the possible outcomes of a program without the retest and re-treatment component at 6 to 8 weeks, we conducted the single-treatment course analysis that considered as treatment failures the 93 participants whose negative 1-year UBT had been preceded by a positive UBT result at 6 to 8 weeks. Results of this analysis showed an overall effectiveness of 72.4% (95% CI, 69.9%-74.8%; Table 3). Voluntary re-treatment tended to dilute differences in effectiveness among the treatment groups, and removing these effects yielded estimates of 75.5% (95% CI, 71.3%-79.4%), 72.4% (95% CI, 68.0%-76.5%), and 69.2% (95% CI, 64.6%-73.4%) for the triple, sequential, and concomitant therapy groups, respectively ( $P=.11$ ).

**Predictors of Treatment Success**

In the logistic regression models of the posttreatment (6-8 weeks) and the

**Table 2. Helicobacter pylori Recurrence at 1 Year by Participant Characteristics and Treatment Regimen**

	Positive, No./ Total No. (%)	Adjusted	
		OR (95% CI) <sup>a</sup>	P Value <sup>a</sup>
1-year UBT status	125/1091 (11.5)		
Treatment regimen			
14-d Triple	47/389 (12.1)	1 [Reference]	.63
10-d Sequential	36/356 (10.1)	0.82 (0.51-1.30)	
5-d Concomitant	42/346 (12.1)	1.01 (0.64-1.58)	
Study site			
Santiago, Chile	21/154 (13.6)	1.91 (0.95-3.92)	.03
Túquerres, Colombia	30/166 (18.1)	2.45 (1.29-4.80)	
Guanacaste, Costa Rica	12/176 (6.8)	0.83 (0.37-1.81)	
Copán, Honduras	16/181 (8.8)	1 [Reference]	
Obregón, México	19/143 (13.3)	1.56 (0.77-3.21)	
Tápachula, México	14/147 (9.5)	1.13 (0.52-2.40)	
León, Nicaragua	13/124 (10.5)	1.44 (0.65-3.15)	
Sex			
Women	81/633 (12.8)	1 [Reference]	.08
Men	44/458 (9.6)	0.70 (0.46-1.04)	
Age, y <sup>b</sup>			
21-29	22/174 (12.6)	0.88 (0.74-1.04)	.13 <sup>b</sup>
30-39	43/310 (13.9)		
40-49	26/287 (9.4)		
≥50	34/329 (10.3)		
Children in the household <sup>b</sup>			
0	34/332 (10.2)	1.17 (1.01-1.35)	.03 <sup>b</sup>
1-2	64/566 (11.3)		
≥3	27/184 (14.7)		
Adherence, pills returned <sup>c</sup>			
<20%	114/1041 (11)	1 [Reference]	.01
≥20%	10/39 (25.6)	2.94 (1.31-6.13)	

Abbreviations: OR, odds ratio; UBT, (13) C-urea breath test.  
<sup>a</sup>Statistic estimated from a logistic regression model that accounts for age (continuous), sex, and study center. CIs are based on the profile likelihood method. P values are based on the Wald  $\chi^2$  test statistic. Statistics do not include missing values for children in the household (n=9) and adherence (n=11).  
<sup>b</sup>P value corresponds to a logistic regression model in which the association of interest was considered as a continuous variable (for age, per 10 years).  
<sup>c</sup>Adherence was defined as having taken at least 80% of each drug of the study regimen.

**Table 3. Helicobacter pylori Eradication Success at 1 Year by Treatment Regimen and Analytic Approach**

Treatment regimen	Analytic Approach					
	Definitive UBT (n = 1340) <sup>a</sup>		Single-Treatment Course (n = 1340) <sup>b</sup>		1-y ITT (n = 1463) <sup>c</sup>	
	Negative No./ Total No.	% (95% CI) <sup>d</sup>	Negative No./ Total No.	% (95% CI) <sup>d</sup>	Negative No./ Total No.	% (95% CI) <sup>d</sup>
14-d Triple	364/453	80.4 (76.4-83.9)	342/453	75.5 (71.3-79.4)	364/488	74.6 (70.5-78.4)
10-d Sequential	356/446	79.8 (75.8-83.5)	323/446	72.4 (68.0-76.5)	356/486	73.3 (69.1-77.1)
5-d Concomitant	343/441	77.8 (73.6-81.6)	305/441	69.2 (64.6-73.4)	343/489	70.1 (65.9-74.2)
Overall	1063/1340	79.3 (77.1-81.5)	970/1340	72.4 (69.9-74.8)	1063/1463	72.7 (70.3-74.9)

Abbreviations: UBT, (13) C-urea breath test; ITT, intention to treat.  
<sup>a</sup>Analysis includes all participants with a conclusive UBT result at the 1-year visit. P value=.61 based on a  $\chi^2$  test.  
<sup>b</sup>Analysis includes all participants with a conclusive 1-year UBT result and assumes that those with UBT-positive results at 6 to 8 weeks were still positive at 1 year, statistically eliminating the effect of retreatment. P value=.11 based on a  $\chi^2$  test.  
<sup>c</sup>Analysis includes all 1463 randomized participants and assumes that those lost to follow-up and without a 1-year UBT result are UBT positive. P value=.28 based on a  $\chi^2$  test.  
<sup>d</sup>Eradication success is expressed as percent (95% CI). All 95% CIs are exact binomial.

1-year (single-treatment course) outcomes (TABLE 4), significant associations were observed with study site, male sex, older age, and adherence to initial therapy. Having fewer children in the household was associated with the 1-year outcomes but not with 6- to 8-week outcome, while treatment assignment was significantly associated with 6- to 8-week outcome,<sup>14</sup> but not with 1-year outcome. Other factors such as cigarette smoking, alcohol use, water source, sanitation, and baseline chronic dyspepsia were unrelated to outcome (eTable, available at <http://www.jama.com>).

**COMMENT**

In our 1-year follow-up study from this randomized trial in 7 community populations in Latin America, the risk of recurrent *H pylori* infection following apparently successful eradication was 11.5%. Although triple therapy in our initial analyses had appeared to be superior to sequential and concomitant therapies at 6 to 8 weeks, there were only modest and nonsignificant differences in 1-year outcomes among the 3 treatment groups. Triple therapy succeeded in eradicating *H pylori* infection in 84.4% of participants who had a UBT 6 to 8 weeks posttreatment<sup>14</sup> but

its observed efficacy at 1 year was 80.4%, and its success was estimated to be 75.5% if the effects of re-treating participants whose initial treatment had failed were ignored. Significant predictors of successful eradication of *H pylori* infection at 1 year were study site, male sex, older age, and adherence to initial therapy.

**Recurrence of Infection**

The 11.5% 1-year recurrence risk observed in our trial is consistent with prior reports from Latin America and other low- and middle-income regions.<sup>21,24,25</sup> In a review by Gisbert<sup>21</sup> of

**Table 4.** Characteristics Associated With *Helicobacter pylori* Eradication Success Posttreatment and at 1 Year by Single-Treatment Analysis

	Posttreatment (6-8 Week) Success (n = 1414) <sup>a</sup>			1-Year Success Single-Treatment Course Analysis (n = 1340) <sup>b</sup>		
	Negative No./ Total No. (%)	Adjusted OR (95% CI) <sup>c</sup>	P Value <sup>c</sup>	Negative No./ Total No. (%)	Adjusted OR (95% CI) <sup>c</sup>	P Value <sup>c</sup>
Treatment regimen						
14-d Triple	401/475 (84.4)	1 [Reference]	.005	342/453 (75.5)	1 [Reference]	.09
10-d Sequential	372/468 (79.5)	0.70 (0.50-0.98)		323/441 (72.4)	0.84 (0.62-1.14)	
5-d Concomitant	360/471 (76.4)	0.58 (0.41-0.80)		305/446 (69.2)	0.71 (0.53-0.96)	
Study site						
Santiago, Chile	164/195 (84.1)	0.60 (0.33-1.07)	<.001	134/179 (74.9)	0.59 (0.36-0.97)	<.001
Túquerres, Colombia	170/211 (80.6)	0.51 (0.29-0.87)		136/205 (66.3)	0.42 (0.26-0.66)	
Guanacaste, Costa Rica	178/207 (86.0)	0.75 (0.42-1.33)		166/203 (81.8)	0.96 (0.58-1.60)	
Copán, Honduras	186/211 (88.2)	1 [Reference]		165/204 (80.9)	1 [Reference]	
Obregón, México	148/203 (72.9)	0.37 (0.22-0.62)		124/191 (64.9)	0.45 (0.28-0.71)	
Tápachula, México	152/207 (73.4)	0.36 (0.21-0.60)		133/194 (68.6)	0.50 (0.31-0.79)	
León, Nicaragua	135/180 (75.0)	0.33 (0.19-0.57)		112/164 (68.3)	0.41 (0.25-0.67)	
Sex						
Women	655/845 (77.5)	1 [Reference]	.004	553/803 (68.9)	1 [Reference]	.003
Men	478/569 (84.0)	1.53 (1.14-2.05)		417/537 (77.7)	1.63 (1.25-2.13)	
Age, y						
21-29	183/235 (77.9)	1.14 (1.02-1.29)	.03 <sup>d</sup>	155/220 (70.5)	1.14 (1.02-1.27)	.02 <sup>d</sup>
30-39	323/412 (78.4)			268/392 (68.4)		
40-49	284/364 (78.0)			252/344 (73.3)		
≥50	343/403 (85.1)			295/384 (76.8)		
Children in the household						
0	343/411 (83.5)	0.99 (0.89-1.11)	.87 <sup>d</sup>	298/390 (76.4)	0.91 (0.82-1.00)	.05 <sup>d</sup>
1-2	586/745 (78.7)			506/707 (71.6)		
≥3	194/246 (78.9)			157/232 (67.7)		
Adherence, pills returned						
<20%	1081/1314 (82.3)	1 [Reference]	<.001	929/1249 (70.4)	1 [Reference]	<.001
≥20%	39/82 (47.6)	0.23 (0.14-0.37)		30/75 (30.6)	0.26 (0.15-0.42)	

Abbreviations: OR, odds ratio; UBT, (13) C-urea breath test.

<sup>a</sup>Analysis only includes participants with a conclusive UBT result at the 6- to 8-week visit after treatment initiation.

<sup>b</sup>Analysis includes all participants with 1-year UBT results and assumes that those who were UBT positive at 6 to 8 weeks are still positive at 1 year, statistically eliminating the effect of retreatment.

<sup>c</sup>Statistic estimated from a logistic regression model that accounts for age (continuous), sex, and study center. CIs are based on the profile likelihood method. P values are based on the Wald  $\chi^2$  test statistic. Statistics do not include missing values for children in the household (n = 12 at 6 to 8 weeks and n = 11 at 1 year) and adherence (n = 18 at 6 to 8 weeks and n = 16 at 1 year).

<sup>d</sup>In the regression models, the variables age (per 10 y) and number of children in the household were considered as continuous variables.

more than 100 studies, the overall annual recurrence risk ranged from 3.4% (95% CI, 3.1%-3.7%) in high-income countries to 8.7% (95% CI, 8.8%-9.6%) in lower-income countries. In studies from Latin America with at least 50 person-years of follow-up,<sup>22,26-29</sup> the 1-year recurrence risk ranged from 0% to 17.3%.<sup>28,29</sup> In the largest prior study in Latin America, conducted in Colombia, the mean annual recurrence rate over 6 years of cohort follow-up was 5.4%.<sup>22</sup> In our trial, the Colombia site had the highest recurrence risk (18.1%), and notably, the participants were recruited from the same region as in the aforementioned study. A high rate of recurrent infection was also seen in the eradication trial from Shandong,<sup>5</sup> wherein UBT negativity in the group treated with amoxicillin-based treatment declined from 74% at 1 year to 47% by the seventh year.<sup>30</sup> Nonetheless, participants randomized to eradication therapy in the Shandong trial had a statistically significant 39% decrease in gastric cancer incidence over a 14.7-year period of follow-up.<sup>5</sup>

*H pylori* recurrence in the first year following eradication seems likely to represent a mixture of recrudescence infection and reinfection, whereas reinfection dominates in subsequent years and the overall annual risk of recurrence tends to diminish.<sup>22,24,26</sup> We found an association between recurrence with both medication nonadherence and study site (a possible marker of regional antibiotic resistance), suggesting that recrudescence was an important component of 1-year recurrence in the populations in this study.<sup>31</sup> The borderline association between number of children in the household and recurrence suggests that an element of reinfection also occurred during the first year, consistent with previous reports wherein number of children was a risk factor for infection.<sup>32,33</sup> Our finding that women who were between 21 and 44 years old were less likely to have successful 1-year eradication is also consistent with a risk of reinfection mediated through contact with young children. Differences in generic medi-

cations were unlikely to explain site differences because Honduras and Nicaragua used drugs from the same batch and manufacturer in Central America, yet they had disparate 1-year outcomes. Continued cohort follow-up should provide important insights.

### Implications of 1-Year Outcomes

The observed 1-year outcomes of our study represent a mixture of the effects of initial eradication therapy, re-treatment, recurrence, and participant and community characteristics. Although *H pylori* eradication programs may be cost effective, particularly in high-incidence areas,<sup>34-36</sup> retesting and re-treating individuals shortly after initial eradication therapy may not be cost effective, especially when the probability of successful eradication with initial therapy is relatively high and the efficacy of re-treatment is modest.<sup>21</sup> To simulate a program that did not include an early retest and re-treatment stage, we conducted the single-treatment course analysis, which ignored the effects of voluntary re-treatment. Our estimated 75.5% success rate for triple therapy in this analysis was not remarkably better than that for the other 2 regimens tested and the success of all 3 regimens without re-treatment was comparable to what has been reported from prior eradication trials.<sup>5-7,10</sup> Thus, while our data underscore the continued use of 14-day triple therapy in Latin America, from a program perspective they also point to the possible acceptability of a lower-cost regimen (eg, sequential therapy). Assessment of program effectiveness must also consider potential adverse outcomes such as adverse effects of treatment, rare serious events,<sup>37</sup> and the potential contribution to community antimicrobial resistance.<sup>38</sup> In low- and middle-income nations, the incremental effects of an eradication program on resistance are difficult to gauge given the prevalence of unsanitary conditions that facilitate spread of resistant bacteria and the common practice of self-prescription with over-the-counter antibiotics.<sup>39</sup>

In our current study, adherence, study site, sex, and age were significantly associated with the probability of a successful 1-year outcome. From the public health perspective, a “one size fits all” intervention strategy may not be optimal. For example, the fact that age-specific rates of gastric cancer incidence in women lag those of men by 10 to 15 years,<sup>1</sup> coupled with the higher risk of recurrent infection in younger women, suggests that an eradication program could enroll men beginning at age 30 years but delay enrolling women until they reach 40 or 50 years of age. In general, programs will be more effective if tailored to the demographics and community ecology of their target populations.<sup>40</sup>

The feasibility and success of an *H pylori* eradication strategy for preventing gastric cancer focused on specific populations in high-risk regions will depend on the cancer risk in the target population, the prevalence of virulent *H pylori* strains, the probability of success of initial treatment, the risk of recurrent infection, and the per-person program cost of screening and eradication. Eradication programs seem likely to be cost effective if they prevent at least 10% of cancer deaths,<sup>41,42</sup> a threshold that was exceeded in the Shandong Intervention Trial<sup>5</sup> and in a trial from Japan that randomized patients with resected gastric cancer to antibiotics or placebo and observed a statistically significant 64% decrease in risk of metachronous cancers over 3 years of follow-up.<sup>9</sup> A combined analysis of the effects of 5 randomized trials of *H pylori* eradication on gastric cancer incidence<sup>5</sup> reported a pooled relative risk of 0.58 (95% CI, 0.42-0.81).<sup>5</sup>

### Study Strengths and Limitations

Our trial was designed as a public health intervention with a vision toward future programs of *H pylori* eradication in high-risk areas of Latin America. The trial incorporated data from 7 heterogeneous community populations in 6 countries, noninvasive *H pylori* testing with UBT, generic medications purchased locally, and standard antimicro-

crobial regimens. However, this public health approach had inherent limitations. Participants were recruited from the community and the results may not be generalizable to symptomatic patients requiring clinical evaluation. We also did not assess antibiotic resistance or gastric histology. Additionally, re-treatment of UBT-positive participants was voluntary, and thus, efficacy estimates with quadruple therapy are qualified.

## CONCLUSIONS

In this large study in diverse community populations in Latin America, our results indicate that geographic site, demographic factors, adherence to initial therapy, and infection recurrence may be as important as the choice of antibiotic regimen in *H pylori* eradication interventions. Ongoing research initiatives are needed, given the expected increase in the gastric cancer burden in Latin America over the next 2 decades, evidence that *H pylori* infection is the dominant risk factor, and evidence that eradication reduces gastric cancer risk.

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