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Health System Costs of Treating Latent Tuberculosis Infection With Four Months of Rifampin Versus Nine Months of Isoniazid in Different Settings

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Background: Four months of rifampin treatment for latent tuberculosis infection is safer, has superior treatment completion rates, and is as effective as 9 months of isoniazid. However, daily medication costs are higher for a 4-month rifampin regimen than a 9-month isoniazid regimen.

Objective: To compare health care use and associated costs of 4 months of rifampin and 9 months of isoniazid.

Design: Health system cost comparison using all health care activities recorded during 2 randomized clinical trials. (Clinical Trials.gov: NCT00931736 and NCT00170209)

Setting: High-income countries (Australia, Canada, Saudi Arabia, and South Korea), middle-income countries (Brazil and Indonesia), and African countries (Benin, Ghana, and Guinea).

Participants: Adults and children with clinical or epidemiologic factors associated with increased risk for developing tuberculosis that warranted treatment for latent tuberculosis infection.

Measurements: Health system costs per participant.

Results: A total of 6012 adults and 829 children were included. In both adults and children, greater health system use and higher costs were observed with 9 months of isoniazid than with 4 months of rifampin. In adults, the ratios of costs of 4 months of rifampin versus 9 months of isoniazid were 0.76 (95% CI, 0.70 to 0.82) in high-income countries, 0.90 (CI, 0.85 to 0.96) in middle-income countries, and 0.80 (CI, 0.78 to 0.81) in African countries. Similar findings were observed in the pediatric population.

Limitation: Costs may have been overestimated because the trial protocol required a minimum number of follow-up visits, although fewer than recommended by many authoritative guidelines.

Conclusion: A 4-month rifampin regimen was safer and less expensive than 9 months of isoniazid in all settings. This regimen could be adopted by tuberculosis programs in many countries as first-line therapy for latent tuberculosis infection.

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An estimated one quarter of the global population has latent tuberculosis infection (1). These 1.7 billion people serve as the reservoir for new active tuberculosis cases, given that 10% are likely to develop the disease if untreated (1). The End TB Strategy aims for a reduction of 90% in the incidence of tuberculosis by 2035 and elimination of the disease by 2050. According to mathematical modeling projections (2), these targets will not be reached solely by treating active tuberculosis cases; prevention through treatment of latent tuberculosis infection among those at high risk for developing tuberculosis must also be addressed (2).

Latent tuberculosis infection treatment is not new. Since the 1960s, many studies have shown that monotherapy with isoniazid for 6 to 12 months can reduce the risk for developing active tuberculosis by 60% to 90% (3). However, the long treatment duration and the fear of adverse events limit the acceptance and completion of latent tuberculosis infection treatment (4, 5).

In recent years, shorter, safer, and better-tolerated rifamycin-containing regimens for latent tuberculosis infection have been evaluated in trials (6). We have completed 2 multicenter randomized clinical trials comparing 4 months of rifampin with 9 months of isoniazid (7, 8). In these trials, 4 months of rifampin was noninferior for tuberculosis prevention, and the completion rate was significantly higher in adults and children. Grade 3 to 5 adverse events attributable to 4 months of rifampin were not observed among children and were significantly less frequent than with 9 months of isoniazid in adults.

A 4-month rifampin regimen therefore seems to offer important advantages over a 9-month isoniazid regimen. However, for the adoption of new treatment regimens, policymakers in many countries also require economic evaluations. In this study, we compared health care use and associated costs between participants who received 4 months of rifampin versus 9 months of isoniazid in the aforementioned trials.

Methods

Study Design, Population, and Data Gathering

The design, study populations, interventions, methods, and end points for the randomized clinical trials in adults (aged ≥18 years) and children (aged 0 to 17 years) are described in detail elsewhere (7, 8). Briefly, the pediatric study was conducted in Australia, Benin, Brazil, Canada, Ghana, Guinea, and Indonesia, and the adult study was conducted in these countries plus

Saudi Arabia and South Korea. Eligible participants had a documented positive result on a tuberculin skin test or interferon-γ release assay, a clinical or epidemiologic risk factor associated with increased risk for developing active tuberculosis, and a recommendation for latent tuberculosis infection treatment from their treating physician (7). Children younger than 5 years who had a household contact with active tuberculosis were eligible, regardless of their tuberculin skin test result (8). Per protocol, participants had a baseline evaluation that included a medical visit, chest radiography, and blood tests (aspartate aminotransferase, alanine aminotransferase, bilirubin, and complete blood count). In the first month, it was recommended that all participants repeat the blood tests. Follow-up visits during treatment occurred monthly for the first 2 months and at least every 8 weeks thereafter. Thus, the minimum number of trial-related follow-up visits was 3 for the group receiving 4 months of rifampin and 5 for the group receiving 9 months of isoniazid (7, 8).

Costs

Using clinical information prospectively recorded during the 2 randomized clinical trials, we tabulated all health care use by participants. We included all activities related to initial medical evaluation, study drugs, routine follow-up visits (including assessments of adherence and potential adverse events), and evaluation and management of possible adverse events or active tuberculosis. All health care services received by each participant during the 2 trials were valuated, including those not mandated by the trial protocols.

Testing included imaging studies (such as chest radiography and computed tomography); blood tests to ascertain renal and liver function; and microbiologic testing, particularly acid-fast bacteria smear and mycobacterial culture of sputum samples.

We estimated direct costs from the perspective of the health care system. For all sites, we obtained local unit costs for the 5 most common tests performed during the study: liver aminotransferase and bilirubin tests, complete blood count, chest radiography, tuberculosis microbiological tests, and testing for HIV antibodies (**Table 1**). The costs of routine follow-up visits and the per diem hospitalization costs for all sites were taken from the World Health Organization's CHOosing Interventions that are Cost Effective tool (WHO CHOICE tool) (9) (**Table 1**; **Appendix Table 1**, available at Annals.org). Prices of latent tuberculosis drugs were taken from the price list of the Global Drug Facility (10) for Indonesia, Ghana, Benin, and Guinea. For Australia, Brazil, Canada, and Saudi Arabia, we used the true cost paid by the Minister of Health or hospitals to the manufacturers or distributors. In South Korea, we used the price from the National Health Insurance Service, which has a co-shared system: 70% of the medication cost is paid by the government, and 30% is charged to the patient.

This approach provided estimated costs for 85% of all activities performed. To estimate the remaining costs of specific tests for which we did not have information from all sites and for types of visits that were not listed in the WHO CHOICE tool, we extrapolated from costs obtained in Canada, which were available for all tests and activities in the study. The extrapolation that was used when local cost information was not available can be summarized as follows: cost of test or visit *Z* at non-Canadian site = [cost of test *Z* in Canada] × [cost of similar test at a non-Canadian site / cost of similar test in Canada].

For the initial evaluation, telephone contacts, home visits, and medical and specialist consultations, the ratio of the unit cost for the specific type of visit in Canada divided by the unit cost for a follow-up visit in Canada was multiplied by the WHO CHOICE cost for a follow-up visit in each country.

Information on costs of other tests in Brazil was available from the Brazilian National Reimbursement Table, a national public source database (**Appendix Table 1**) (11). In Canada, this information was available from the price list based on fees set by the Canadian Interim Federal Health Program because these represent the actual cost of health tests and services in Canada (12).

When needed, visit costs were adjusted using local inflation indices and converted to U.S. dollars using purchasing power parity exchange indices (13). Costs for all other trade items (including tests and latent tuberculosis drugs) were converted using direct exchange rates. All costs are expressed in 2017 U.S. dollars (14).

Statistical Analysis

Cost Comparison Analysis

For each study participant, the number of times each health care service was used was multiplied by the unit cost of the activity. These individual costs were then summed to provide a total cost per participant. This was used to calculate the total and mean cost for participants who met different study end points. We calculated a ratio of mean costs per participant randomly assigned to 4 months of rifampin divided by the mean cost per participant assigned to 9 months of isoniazid to provide a summary estimate of the relative costs for the 2 regimens. The resulting 95% CIs were calculated using the number in the group and the mean and SD of the costs for each subgroup using the package "mratios" in R (15, 16). This package allows the comparison of means between groups performing a *t* test for those ratios. Confidence intervals that did not cross 1.0 were considered statistically significant (equivalent to a *P* value <0.05). We explored the distributions of costs per country and the domestic product per capita of the countries in 2017 (17) and conducted stratified cost comparisons per groups of countries. Groups were defined as follows: high-income countries included Australia, Canada, Saudi Arabia, and South Korea; middle-income countries included Brazil and Indonesia; and African countries included Benin, Ghana, and Guinea. The cost comparison analysis was performed separately for all adults and children included in the modified intention-to-treat analysis (the study

population remaining after prespecified postrandomization exclusions). The protocol is available at www.mcgill.ca/tb/projects.

Sensitivity Analysis

Considering that 6 months of isoniazid is the most commonly prescribed regimen for latent tuberculosis infection in many settings, we performed a sensitivity analysis comparing costs for 4 months of rifampin versus 6 months of isoniazid. For this analysis, we censored all health services used more than 213 days after randomization (180 days plus 18% of extra time) in the group receiving 9 months of isoniazid. We defined this extra time after inspecting the distribution of the treatment duration among participants who completed latent tuberculosis infection treatment in the group receiving 9 months of isoniazid, with a target duration of 270 days. As presented in the Appendix Figure (available at Annals.org), the normal distribution in both populations (adults and children) ranged from 210 to 320 days (18% of extra time). The 18% was multiplied by 180 (ideal duration of 6 months of isoniazid) to give an upper range of 213 days, which was used as the maximum limit to censor the data for 6 months of isoniazid use.

Predictors of Costs

To assess individual predictors of cost, including study regimens, we performed univariable and multivariable regression analyses in the adult and pediatric populations together. For these analyses, we included only participants who completed therapy or had an adverse event that led to discontinuation of treatment because we felt that providers and decision makers would want to understand predictors of costs rather than predictors of noncompletion. Because participants who decided to stop treatment early had substantially lower costs, analysis that included this group inevitably detected predictors of this behavior.

Table 1. Summary of Unit Costs for the Main Health Services Used During the Study*

Service	Unit Cost, *US $*								
	Canada	**Australia**	**South Korea**	**Saudi Arabia**	**Brazil**	**Indonesia**	**Ghana**	**Benin**	**Guinea**
Visits									
Baseline visit†	190.69	202.29	131.49	305.27	11.20	49.67	8.24	13.25	11.68
Follow-up visit‡	75.44	82.80	51.99	120.77	4.43	19.65	3.26	5.24	4.62
Home visit†	129.81	142.48	89.46	207.82	7.62	33.81	–	9.02	7.95
Telephone contacts†	10.41	11.43	7.18	16.67	0.61	2.71	0.46	0.72	0.64
Blood tests§									
Complete blood count	1.49	12.75	3.34	31.47	1.29	4.33	6.90	6.57	7.97
Aspartate aminotransferase	0.87	7.30	1.50	14.16	0.63	0.87	8.43	4.68	4.97
Alanine aminotransferase	0.87	7.30	1.50	15.74	0.63	0.87	8.43	4.68	4.97
Bilirubin	0.87	7.30	1.50	14.16	0.63	0.87	8.43	8.42	4.97
HIV test	22.96	11.76	3.31	47.21	3.13	3.97	9.19	3.74	3.94
AFB smear microscopy§	11.79	32.33	3.03	188.83	1.32	1.08	6.05	0.86	0.55
Chest radiography§	16.63	26.58	5.18	47.21	2.98	8.29	8.96	11.17	12.42
LTBI drugs (costs per pill)‖									
Rifampin, 600 mg	–	–	0.22	–	–	–	–	–	–
Rifampin, 300 mg	0.18	0.14	–	0.38	0.10	0.10	0.10	0.10	0.10
Rifampin, 150 mg	0.18	–	–	–	–	0.06	0.06	0.06	0.06
Isoniazid, 100 mg	0.53	0.03	0.01	0.03	0.01	0.07	0.07	0.07	0.07
Isoniazid, 300 mg	0.49	–	–	0.05	–¶	0.02	0.02	–¶	–¶

AFB = acid-fast bacteria; LTBI = latent tuberculosis infection.
* Costs for visits were first inflated to 2017 values in the local currency and then converted to U.S. dollars using purchasing power parity (13). Costs for blood tests, imaging studies, and drugs were first inflated to 2017 values in the local currency and then converted to U.S. dollars using direct currency exchange (14).
† Extrapolated costs (see the Methods section of the text).
‡ Costs for follow-up visits at all sites were taken from the World Health Organization's CHOICE (CHOosing Interventions that are Cost Effective) database (9).
§ Sources for test costs were as follows: Canada: Interim Federal Health program (amount reimbursed by government); Australia: Medical Benefits Scheme Handbook (price list; amount reimbursed by government); South Korea: Health Insurance Review and Assessment Service (price list; amount reimbursed to laboratory by third-party health insurance); Saudi Arabia: Ministry of National Guard, Health Affairs (price list; amount paid by non-Saudi residents); Brazil: Tabela de Procedimentos e Medicamento do Sistema Único de Saúde (price list; amount reimbursed by government); Indonesia: price list, public laboratory, amount charged to the patient; Ghana: Komfo Anokye Teaching Hospital (price list; amount charged to the patient); Benin: National TB Program (price list; amount charged to the patient); Guinea: L'hopital National Ignace Deen (price list; amount charged to the patient).
‖ Sources for drug costs were as follows: Canada: McGill University Health Centre (price of drugs from wholesale distributor); Australia: New South Wales Ministry of Health (amount paid by the hospital); South Korea: Korean National Health Insurance Service price list (70% reimbursed by government, 30% paid by patients); Saudi Arabia: Ministry of National Guard, Health Affairs (amount paid to the manufacturer/distributor); Brazil: amount paid by the Brazilian Ministry of Health to the manufacturer/distributor; Indonesia, Guinea, Benin, and Ghana: price list of the Global Drug Facility (10).
¶ Brazil, Benin, and Guinea use only the 100-mg formulation.

Table 2. Estimated Total and Mean Per-Participant Costs in the MITT Population, by LTBI Regimen and Group of Countries*

Service	Adults			Children		
	Mean Costs (SD), *US $*		Ratio of Mean Costs per MITT Patient (95% CI)	Mean Costs (SD), *US $*		Ratio of Mean Costs per MITT Patient (95% CI)
	Rifampin (4 mo)	Isoniazid (9 mo)		Rifampin (4 mo)	Isoniazid (9 mo)	
Australia, Canada, Saudi Arabia, and South Korea†						
Patients, *n*	952	927		20	12	
Drugs (isoniazid or rifampin only)	31.9 (17.3)	57.9 (58.2)	0.55	30.3 (14.1)	75.7 (42.3)	0.40
Follow-up visits‡	209.6 (112.5)	314.3 (192.9)	0.67	258.2 (89.4)	364.0 (135.6)	0.71
Follow-up tests and procedures§	42.9 (35.5)	58.5 (58.1)	0.73	24.7 (15.7)	17.7 (8.6)	1.39
AE care‖	15.2 (192.4)	48.02 (724.9)	0.31 (0.05–11.6)	–	–	–
Total costs						
All patients/events¶	549.1 (277.4)	725.4 (791.8)	**0.76 (0.70–0.82)**	559.3 (107.8)	685.7 (179.3)	**0.82 (0.69–0.98)**
Patients who completed treatment**	585.7 (204.8)	871.9 (944.5)	**0.67 (0.61–0.74)**	614.3 (66.3)	873.6 (87.9)	**0.70 (0.63–0.79)**
Brazil and Indonesia						
Patients, *n*	864	879		139	127	
Drugs (isoniazid or rifampin only)	19.4 (8.2)	4.8 (2.9)	4.04	14.1 (7.9)	11.3 (13.6)	1.24
Follow-up visits	33.7 (26.8)	56.7 (50.5)	0.59	40.3 (29.2)	79.1 (57.8)	0.51
Follow-up tests and procedures	7.4 (6.6)	8.0 (10.9)	0.93	3.5 (1.8)	3.7 (1.5)	0.94
AE care	0.6 (8.3)	2.6 (34.3)	0.23 (0.02–1.92)	–††	–††	–††
Total costs						
All patients/events	103.6 (53.6)	114.8 (80.9)	**0.90 (0.85–0.96)**	104.2 (55.8)	142.1 (88.3)	**0.73 (0.64–0.85)**
Patients who completed treatment‡‡	114.0 (50.9)	134.9 (74.9)	**0.85 (0.80–0.90)**	117.4 (50.9)	161.7 (92.9)	**0.73 (0.63–0.85)**
Benin, Ghana, and Guinea						
Patients, *n*	1027	1183		263	258	
Drugs (isoniazid or rifampin only)	21.1 (6.9)	35.8 (23.6)	0.60	18.5 (5.7)	39.8 (18.9)	0.46
Follow-up visits	16.5 (6.3)	28.5 (15.7)	0.59	17.7 (4.4)	34.6 (13.5)	0.51
Follow-up tests and procedures	23.4 (15.7)	23.3 (11.0)	1.00	0.9 (0.2)	0.9 (0.2)	1.00
AE care	0.3 (3.5)	1.7 (13.3)	**0.18 (0.06–0.38)**	–§§	–§§	–§§
Total costs						
All patients/events	112.1 (21.6)	140.5 (44.1)	**0.80 (0.78–0.81)**	86.4 (9.1)	124.8 (30.6)	**0.69 (0.67–0.72)**
Patients who completed treatment‖‖	119.3 (9.6)	161.2 (25.9)	**0.74 (0.73–0.75)**	87.9 (7.2)	134.5 (22.1)	**0.65 (0.64–0.67)**

AE = adverse event; LTBI = latent tuberculosis infection; MITT = modified intention-to-treat.
* Boldface indicates statistical significance. Baseline costs are not shown because there was no cost difference between regimens. However, baseline costs were included in total costs.
† Children from only Australia and Canada were included in the MITT population.
‡ Includes outpatient (clinic) visits, home visits, and telephone calls.
§ Includes blood tests, imaging studies, microbiological tests, and procedures.
‖ Patients investigated for suspected drug-related AEs; includes visits, blood tests, imaging studies, medical procedures, and hospitalizations.
¶ Sum of baseline, follow-up, and AE care costs.
** 740 and 568 adults completed treatment in the rifampin and isoniazid groups, respectively. 14 and 5 children completed treatment in the rifampin and isoniazid groups, respectively.
†† Only 1 child was investigated for a suspected drug-related AE, and the study drug was stopped. There were no costs due to AEs.
‡‡ 628 and 537 adults completed treatment in the rifampin and isoniazid groups, respectively. 106 and 87 children completed treatment in the rifampin and isoniazid groups, respectively.
§§ Only 1 child was investigated for a suspected drug-related AE, and the study drug was stopped. There were no costs due to AEs.
‖‖ 1008 and 779 adults completed treatment in the rifampin and isoniazid groups, respectively. 245 and 222 children completed treatment in the rifampin and isoniazid groups, respectively.

Given that total health system costs vary by country, even after adjustment based on purchasing power parity, the country where the participant was treated could be a key predictor. We therefore applied 1 set of unit costs for the entire population, which was taken from the price list from the Interim Federal Health Program of the Canadian government (12). These costs were then log-transformed. We performed univariate analyses to identify potentially important predictors, using a cutoff *P* value of 0.2 or less. Age, sex, treatment regimen, and occurrence of any adverse event that led to treatment discontinuation were prespecified covariates for the multivariate analysis. We back-transformed the parameter estimates from the multivariable regression, which should be interpreted as cost ratios. Interaction terms were added to explore the association between occurrence of any adverse event and setting. Because our main interest was the absolute difference in costs between 4 months of rifampin and 9 months of isoniazid, we used the NLESTIMATE macro in SAS (18) to convert parameter estimates of ratios to a difference in costs in U.S. dollars. We also performed 2 sensitivity analyses, using the same rules to select variables and including age, sex, regimen, and occurrence of any adverse events, plus interaction terms between site and adverse event. In the first, we standardized unit costs using Canadian costs but used linear regression without log transformation. In the second, we used the unit

costs from each country (that is, we did not standardize using the Canadian costs); these were log-transformed, and the multivariable regression parameter estimates were then back-transformed. Countries were added as fixed effects. We used the NLESTIMATE macro to convert ratios to cost differences.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute), or R, version 3.5.3 (R Project for Statistical Computing).

Ethics

The 2 trials were approved by the Research Ethics Board of the McGill University Health Centre Research Institute and by the responsible local ethics committees at each site.

Role of the Funding Source

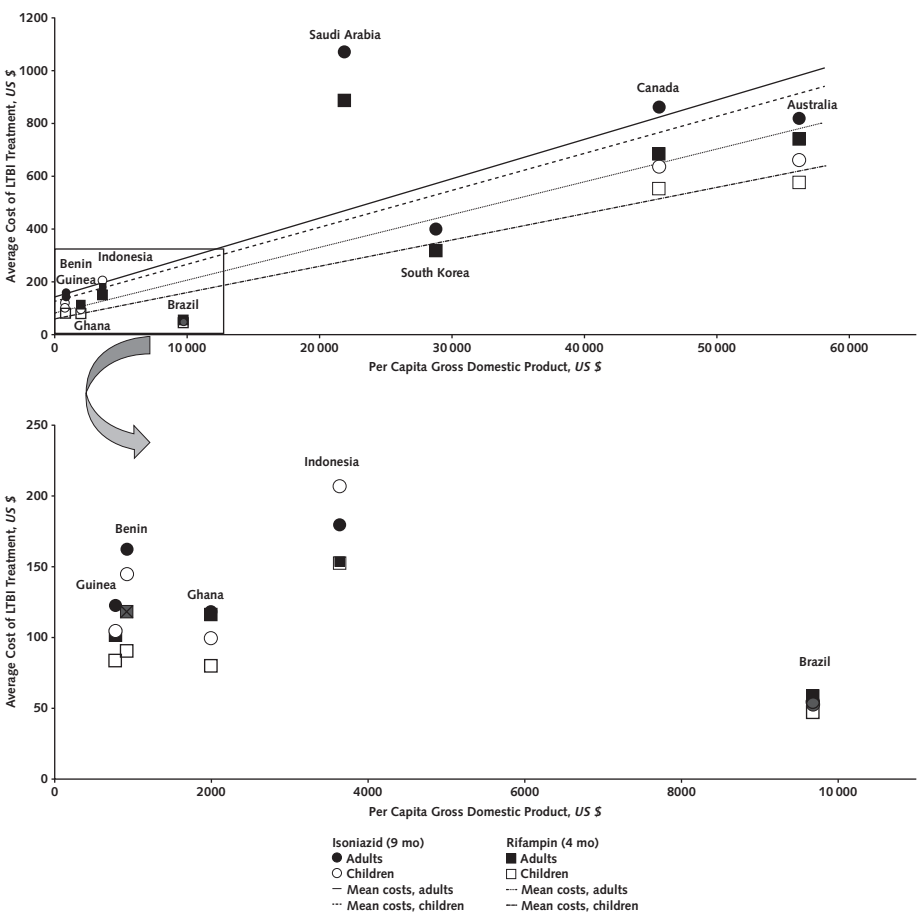
The 2 trials were supported by the Canadian Institutes of Health Research (MOP-111080 and MCT-94831). The funding sources had no role in study design; collection, analysis, or interpretation of the data; writing of the article; or the decision to submit the manuscript for publication.

RESULTS

A total of 6012 adults and 829 children were included in the modified intention-to-treat analysis, of whom 40% and 64%, respectively, were from African countries. The treatment completion rate was 71% among adults and 82% among children. A total of 229 adverse events that led to treatment discontinuation were observed in adult participants, of which 54% occurred in high-income countries (**Appendix Table 2**, available at Annals.org). The most common health care activities during the routine follow-up were visits and blood tests (**Appendix Tables 3** and **4**, available at Annals.org).

Participants at African sites had more follow-up visits than those at other sites, and participants from high-income countries had more blood tests (**Appendix Tables 3** and **4**). With regard to the health care activities during adverse event care, in the adult population, the group receiving 9 months of isoniazid had twice as many visits as the group receiving 4 months of rifampin and 4 times as many blood tests. Baseline health care activities were similar regardless of the latent tubercu-

Figure 1. Relationship of gross domestic product with treatment costs for 4 months of rifampin and 9 months of isoniazid among adults and children in all settings (*top*) and low- and middle-income settings (*bottom*).



LTBI = latent tuberculosis infection.

Table 3. Sensitivity Analysis Comparing Costs of 6 Months of Isoniazid and 4 Months of Rifampin in Adults and Children*

Service	Adults			Children		
	Mean Costs (SD), *US $*		Ratio of Mean Costs per MITT Patient (95% CI)	Mean Costs (SD), *US $*		Ratio of Mean Costs per MITT Patient (95% CI)
	Rifampin (4 mo)	Isoniazid (6 mo)		Rifampin (4 mo)	Isoniazid (6 mo)	
Australia, Canada, Saudi Arabia, and South Korea†						
Patients, *n*	952	927		20	12	
Drugs (isoniazid or rifampin only)	31.9 (17.3)	41.4 (39.9)	0.77	30.3 (14.1)	50.6 (30.3)	0.59
Follow-up visits‡	209.6 (112.5)	252.4 (137.0)	0.83	258.2 (89.4)	291.9 (99.2)	0.88
Follow-up tests and procedures§	42.9 (35.5)	47.7 (44.6)	0.89	24.7 (15.7)	14.8 (3.2)	1.66
AE care‖	15.2 (192.4)	46.9 (724.8)	0.32	–	–	–
Total costs¶	549.1 (277.4)	635.2 (763.3)	**0.86 (0.80–0.94)**	559.3 (107.8)	585.5 (125.1)	0.96 (0.82–1.12)
Brazil and Indonesia						
Patients, *n*	864	879		139	127	
Drugs (isoniazid or rifampin only)	19.4 (8.2)	3.5 (2.0)	5.54	14.10 (7.9)	7.7 (9.2)	1.83
Follow-up visits	33.7 (26.8)	44.2 (34.6)	0.76	40.3 (29.2)	57.3 (38.2)	0.70
Follow-up tests and procedures	7.4 (6.6)	7.9 (10.7)	0.99	3.5 (1.8)	3.5 (1.4)	0.92
AE care	0.6 (8.3)	2.5 (34.2)	0.24	–	–	–
Total costs	103.6 (53.6)	100.7 (68.4)	1.03 (0.97–1.09)	104.2 (55.8)	116.5 (66.6)	0.89 (0.78–1.02)
Benin, Ghana, and Guinea						
Patients, *n*	1027	1183		263	258	
Drugs (isoniazid or rifampin only)	21.1 (6.9)	26.4 (16.2)	0.80	18.5 (5.7)	26.6 (12.0)	0.69
Follow-up visits	16.5 (6.3)	21.9 (9.7)	0.75	17.7 (4.4)	25.3 (8.7)	0.69
Follow-up tests and procedures	23.4 (15.7)	23.2 (10.9)	1.00	0.9 (0.2)	0.9 (0.2)	1.00
AE care	0.3 (3.5)	1.3 (12.3)	0.23	–	–	–
Total costs	112.1 (21.6)	124.1 (33.1)	**0.90 (0.88–0.93)**	86.4 (9.1)	102.3 (19.8)	**0.84 (0.82–0.87)**

AE = adverse event; MITT = modified intention-to-treat.
* Boldface indicates statistical significance. Baseline costs are not shown because there was no cost difference between regimens. However, baseline costs were included in total costs.
† Children from only Australia and Canada were included in the MITT population.
‡ Includes outpatient (clinic) visits, home visits, and telephone calls.
§ Includes blood tests, imaging studies, microbiological tests, and procedures.
‖ Patients investigated for suspected drug-related AEs; includes visits, blood tests, imaging studies, medical procedures, and hospitalizations.
¶ Sum of all costs.

losis infection regimen; this largely reflected the randomization, given that these tests were performed before the participants were randomly assigned.

Total costs among adults in the modified intention-to-treat population were significantly lower in the group receiving 4 months of rifampin than in those receiving 9 months of isoniazid in all settings (Table 2). The highest costs per participant were in high-income countries, with costs of $549.1 in the group receiving 4 months of rifampin and $725.4 in those receiving 9 months of isoniazid (mean ratio, 0.76 [95% CI, 0.70 to 0.82]). The cost per participant at the African sites was $112.1 in the rifampin group and $140.5 in the isoniazid group, and the cost ratio was similar to that in high-income countries (mean ratio, 0.80 [CI, 0.78 to 0.81]). Costs for adverse event care were also lower in the group receiving rifampin in all 3 settings, although this reached statistical significance in African countries only (Table 2). Similar findings were observed in the pediatric population. The total costs were significantly lower for 4 months of rifampin than for 9 months of isoniazid (Table 2). The mean ratio of the total costs was 0.82 (CI, 0.69 to 0.98) in high-income countries and 0.69 (CI, 0.67 to 0.72) in African countries. Adults receiving 4 months of rifampin had lower costs in all countries except Ghana and Brazil, where costs were similar for the 2 regimens (Figure 1). For the pediatric population, in all countries, the rifampin regimen was less expensive.

The most frequent cost components were visits during routine follow-up, latent tuberculosis infection drugs, blood tests, and adverse events (Table 2). In high- and middle-income countries, routine follow-up visits accounted for 30% to 50% of expenditures in both regimens (Table 2), and in African countries, the visits accounted for 15% in the rifampin group and 21% in the isoniazid group. The daily pill cost for rifampin and isoniazid varied among sites according to the formulation used. For most sites, the unit cost was higher for rifampin than for isoniazid (Table 1). In middle-income and African countries, rifampin pills accounted for 20% of the total costs. In African countries, the use of the 100-mg isoniazid pill, which is more expensive than the 300-mg pill (Table 1), also increased costs in the isoniazid group. In African countries, blood tests and other follow-up examinations and procedures accounted for nearly 20% of total costs in both regimens. In the sensitivity analysis, the cost of 4 months of rifampin remained lower than the cost of 6 months of isoniazid in most settings in both adult and pediatric populations. The differences were statistically significant in high-income and African countries (Table 3).

When 1 set of unit costs was applied to the entire modified intention-to-treat population, the overall cost distribution was similar between children and adults, with rifampin being less expensive for most participants (**Figure 2**). In multivariate analysis, after adjustment for other covariates, the total health system costs for the rifampin regimen were $340 (CI, $330 to $350) less than for the isoniazid regimen, a relative savings of 38% (**Table 4**). Diabetes, alcohol intake, country, and an abnormal complete blood count before treatment or after 1 month were also associated with higher costs (**Table 4**). Occurrence of adverse events was associated with higher costs in middle-income countries and lower costs in African countries (**Table 4**). The main components that drove costs in patients who had an adverse event and stopped use of the drug in middle-income countries were more blood tests and days of hospitalization (data not shown). In the 2 sensitivity analyses (**Appendix Tables 5** to **7**, available at Annals.org), predictors of costs were similar, and after adjustment for individual participant characteristics, 4 months of rifampin remained less expensive than 9 months of isoniazid.

Discussion

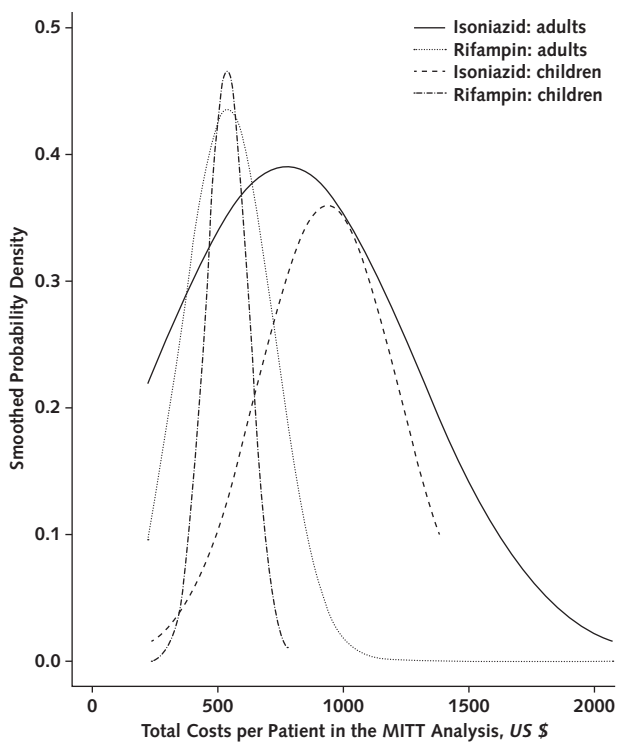
Two multicenter randomized clinical trials indicated that latent tuberculosis infection treatment with 4 months of rifampin resulted in less health service use and significantly lower costs than 9 months of isoniazid for both adults and children. These trials included participants from diverse treatment settings in 9 countries.

Our study has several strengths. Generalizability should be enhanced by the large and diverse population included in our analyses, from different settings and with multiple indications for latent tuberculosis infection treatment (contacts, HIV, or other immunosuppressive conditions). We tabulated every health service used, including tests and visits by each study participant, unlike other economic studies of latent tuberculosis infection treatment (19–21), which relied on assumptions about health care use based on guidelines that do not always reflect actual practices. For 85% of these activities, we were able to obtain precise costs for each site, and for the remaining activities, costs were available from 1 high-income and 1 middle-income setting.

Our study also had limitations. The use of data derived from clinical trials may have resulted in overestimation of follow-up costs because the study protocol required a minimum number of follow-up visits. However, many authoritative guidelines suggest monthly follow-up visits (22–24), so the protocol did not request more than what is currently done in daily practice. Extrapolation of costs for about 15% of activities from a single setting (Canadian sites) may have introduced inaccuracy into our findings. However, the extrapolation occurred with equal frequency in both study groups (16% of health care activities tabulated in the rifampin group and 14% in the isoniazid group). In addition, we did not estimate costs from the participants' perspectives. However, participant costs should have been lower among patients receiving 4 months of rifampin because they had fewer visits, which are associated with indirect (time) costs and out-of-pocket expenditures (25, 26).

Sites provided different sources for direct costs of tests and other activities: Some reported what is reimbursed by the Ministry of Health or a third-party payer (such as health insurance providers), whereas others reported what is charged to participants. This limitation might overestimate or underestimate costs at different sites but reflects the challenge of estimating true costs in 9 different health systems with very different management practices. Because randomization was stratified by site, the numbers in each group were balanced at each site, so this problem applies equally to both treatment groups. We also observed, using information from sites and the Global Drug Facility (10), that the prices of latent tuberculosis infection drugs can vary substantially depending on the formulation (100 or 300 mg of isoniazid) and can change considerably over time. This affected our estimates, especially in children, in whom different combinations and formulations were used. Although the overall study population was large, the number of children enrolled in high-income settings was small, potentially limiting the generalizability of our findings for pediatric populations in high-income countries.

Figure 2. Distribution of costs among all participants included in the MITT analysis, with a standard set of costs (Canadian costs) applied to the entire population (adults [*n* = 6012] and children [*n* = 829]).



MITT = modified intention-to-treat.

Table 4. Independent Predictors of Costs*

Variable	Participants, *n* (%)	Cost Ratio (95% CI)	
		Unadjusted	Adjusted†
Intercept (interpreted as base costs)	–	–	917 (900 to 934)
4 mo of rifampin (9 mo of isoniazid = reference)	2816 (55)	–	–
Cost difference (2017 U.S. dollars)‡	–	–	**−340 (−350 to −330)**
Cost ratio	–	**0.63 (0.62 to 0.64)**	**0.62 (0.61 to 0.63)**
Age (continuous, per additional year)	5168	**0.9993 (0.9988 to 0.9998)**	0.9997 (0.9993 to 1.000)
Male sex (female = reference)	2176 (42)	**1.03 (1.01 to 1.04)**	1.01 (1.00 to 1.03)
Obese or overweight BMI (normal or underweight = reference)§	1964 (38)	0.99 (0.97 to 1.01)	–
Ever-smoker (never-smoker = reference)	1033 (20)	**0.95 (0.93 to 0.98)**	**0.98 (0.96 to 0.99)**
Alcohol intake ever (never = reference)	1481 (29)	**1.02 (1.01 to 1.03)**	**1.02 (1.01 to 1.03)**
Had symptoms or physical examination at baseline (normal = reference)	826 (16)	0.97 (0.95 to 1.00)	1.01 (0.99 to 1.02)
Comorbidity			
None	4649 (90)	Reference	**Reference**
HIV	230 (4)	1.01 (0.96 to 1.04)	1.00 (0.97 to 1.02)
Diabetes mellitus	136 (3)	1.02 (0.97 to 1.06)	**1.04 (1.01 to 1.07)**
Other immunosuppression‖	153 (3)	**0.95 (0.90 to 0.99)**	0.98 (0.95 to 1.01)
Abnormal LFT result at baseline or first month (normal = reference)¶	1196 (23)	1.02 (1.00 to 1.05)	0.99 (0.98 to 1.00)
Abnormal CBC at baseline and first month (normal = reference)**	1489 (29)	**1.02 (1.01 to 1.04)**	**1.02 (1.01 to 1.03)**
Region			
Canada, Australia, Saudi Arabia, South Korea	1451 (21)	**Reference**	**Reference**
Brazil, Indonesia	1398 (30)	**0.95 (0.93 to 0.97)**	**0.94 (0.92 to 0.95)**
Benin, Ghana, Guinea	2319 (45)	**1.06 (1.04 to 1.08)**	**1.05 (1.03 to 1.06)**
Had grade 1 to 5 AE (reference = no)	229 (4)	**0.89 (0.85 to 0.92)**	**0.83 (0.80 to 0.86)**
Interaction terms (AE and region)††			
Had AE (Brazil, Indonesia)	–	–	**1.18 (1.10 to 1.26)**
Had AE (Benin, Ghana, Guinea)	–	–	**0.82 (0.78 to 0.87)**

AE = adverse event; BMI = body mass index; CBC = complete blood count; LFT = liver function test.
* All costs are standardized to Canadian costs and log-transformed for analysis of ratios and 95% CIs. The analysis includes patients who completed treatment or stopped because of AEs but not those who decided to discontinue treatment early. Boldface indicates statistical significance.
† The model was adjusted for sex, age, treatment regimen, occurrence of any adverse event that led to treatment discontinuation, and other covariates that had a *P* value ≤0.2 in the unadjusted model.
‡ The NLESTIMATE macro in SAS was used to convert parameter estimates of ratios to differences in costs.
§ Information was missing for 4 children.
¶ Combined results of aspartate aminotransferase and alanine aminotransferase. Information was missing for 8 patients.
** Combined results of leukocyte and platelet counts. Information was missing for 15 patients.
†† All patients who had a grade 1 to 5 AE and permanently stopped use of the medication, including 5 who died (4 of these deaths were not related to the study drug).

Despite these limitations, this study adds to growing evidence of the benefits of 4 months of rifampin as one of the primary choices for latent tuberculosis treatment. The improved safety and acceptability (based on higher completion rates) and noninferior efficacy have been well established in prior publications (6–8, 27–29). We also identified another important benefit: lower cost of 4 months of rifampin compared with either 6 or 9 months of isoniazid in low-, middle-, and high-income settings. Taken together, this evidence supports the recent guidelines from the U.S. Centers for Disease Control and Prevention, which strongly recommend 4 months of rifampin as a primary regimen for treatment of latent tuberculosis infection (30).

Although daily costs of rifampin were higher in most settings, overall health care system use (visits, blood tests, and adverse event care) was lower in this trial compared with 9 months of isoniazid. Implementation of a regimen should consider not only drug procurement costs but also overall health system costs, including treatment and follow-up. Therefore, the higher costs of the pills should not prevent the adoption of 4 months of rifampin by tuberculosis programs in resource-limited settings.

In conclusion, 4 months of rifampin is a safe, effective, and more affordable regimen compared with isoniazid monotherapy regimens. Tuberculosis programs in all countries should consider adoption of the 4-month rifampin regimen as a first-line therapy for latent tuberculosis infection.

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Data Sharing Statement: The following data will be made available beginning 16 June 2020: deidentified participant data and data dictionary (contact Dr. Menzies; e-mail, dick.menzies@mcgill.ca). Data related to the 2 randomized clinical trials (including cost information) will be available once all secondary analyses are complete, upon written request and provision of a statistical analysis plan to Dr. Menzies. The following supporting documents will be made available beginning 16 June 2020: full protocol of the 2 randomized clinical trials (www.mcgill.ca/tb/files/tb/protocol_version_6_biomarker-peds_july_6th_2011_1.pdf).

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Appendix Table 1. Detailed Unit Costs in Canada and Brazil for Less Common Study Activities*

Activity	Canada†	Brazil‡
Visits		
Neurologist appointment	98.15	5.76
Emergency department visit	87.60	–
Infectious diseases specialist appointment	74.90	–
Gastroenterologist appointment	62.53	–
Hematologist appointment	47.47	–
Dermatologist appointment	39.67	–
Family physician appointment	62.09	–
Pathologist examination	350.52	–
Orthopedist appointment	54.26	–
Rheumatologist appointment	104.96	–
Otolaryngologist appointment	44.39	–
Psychiatrist appointment	98.15	–
Hospitalizations (per diem)	770.53	34.86
Blood tests		
Blood sample drawing fees	12.41	2.08
Complete blood count	1.49	1.29
Aspartate aminotransferase	0.87	0.63
Alanine aminotransferase	0.87	0.63
Bilirubin	0.87	0.63
International normalized ratio	1.37	2.66
γ-Glutamyl transferase	0.87	1.1
Sodium	0.87	0.58
Potassium	0.87	0.58
Chloride	0.87	–
Bicarbonate	0.99	–
Amylase	0.87	0.71
Glucose	0.87	0.58
Erythrocyte sedimentation rate	2.11	–
Smac 17§	14.83	–
Smac 7§	6.11	–
Iron profile	5.59	–
Vitamin B	3.11	–
Folate	4.22	–
Lipase	1.49	0.71
Creatinine	0.87	0.58
Urea	0.87	0.58
Phosphorus	0.87	–
Hemoglobin electrophoresis	16.14	–
Albumin	0.87	0.36
Total protein	0.87	0.36
C-reactive protein	9.92	0.86
Follicle-stimulating hormone	3.23	–
Luteinizing hormone	3.23	–
Thyroid-stimulating hormone	1.99	2.81
Triiodothyronine	3.35	2.74
Thyroxine	2.23	2.73
Thyroglobulin	11.17	–
Phosphatase alkaline	0.87	0.63
Lactate dehydrogenase	0.87	–
Cardiac enzymes	1.99	–
Uric acid	0.87	–
Hemoglobin A_{1c}	3.46	–
Isoniazid drug level	145.16	–
Microsome antibody	3.04	–
QuantiFERON-TB gold in tube	39.72	–
Helicobacter pylori antibody	7.69	–
Protein electrophoresis	6.09	–
IgE	7.2	–
CD4 count	45.88	–
HIV viral load	38.47	–
Human chorionic gonadotropin	5.34	2.46
Prostate-specific antigen	4.72	–
Hepatitis A serologic testing	11.17	5.81
Hepatitis B serologic testing	11.67	5.81
Hepatitis C serologic testing	8.94	5.81
HIV	22.96	3.13

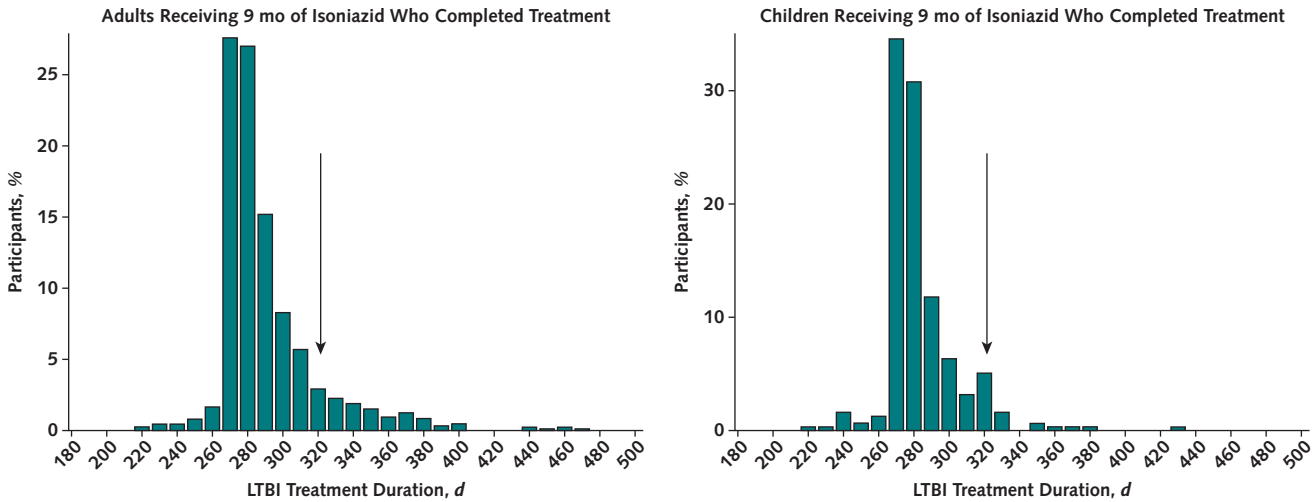
Continued on following page

Appendix Table 1–Continued

Activity	Canada†	Brazil‡
Venereal Disease Research Laboratory test	4.85	–
Reticulocyte count	2.73	–
Cholesterol profile	5.59	–
Vitamin D	8.81	–
Rheumatoid factor	7.94	–
Complement 4	5.83	–
Complement 3	5.83	–
Imaging studies		
Chest radiography	16.63	2.98
Chest computed tomography	43.62	42.74
Chest + abdomen computed tomography	65.44	–
Fluoroscopy	32.72	–
Positron emission tomography	226.27	–
Thyroid ultrasound	32.72	–
Joint radiography	16.63	–
Limb radiography	28.36	11.89
Abdominal ultrasound	54.53	–
Pelvic ultrasound	43.62	–
Thoracic echocardiogram	98.15	–
Transesophageal echocardiogram	50.09	–
Electroencephalogram	–	3.55
Brain magnetic resonance imaging	-	84.21
Brain computed tomography	43.62	30.53
Tuberculosis microbiological tests		
Acid-fast bacteria	11.79	1.32
Culture	49.02	5.94
GeneXpert	–	15.21
Other microbiological tests		
Ova and parasites test	16.51	0.52
Urinalysis	1.49	1.16
Urine culture	2.11	–
Procedures		
Induced sputum	56.97	1.46
Pulmonary function test	15.8	–
Gastroscopy	60.06	–
Cholecystectomy	515.2	–
Leg amputation	330.93	–
Embolectomy	550.89	–
Skin biopsy	10.94	–
Methacholine test	284.3	–

* Costs are in 2017 U.S. dollars and were used to extrapolate the costs for other sites (see the Methods section of the text).
† Data from reference 12.
‡ Data from reference 11.
§ Panel of 7 or 17 biochemical tests.

Appendix Figure. Distribution of treatment duration, in days, among adults (*left*) and children (*right*) receiving 9 months of isoniazid who completed LTBI treatment.



This figure was used to guide the sensitivity analysis for 6 mo of isoniazid. The arrow in each graph points to when the distribution appears to change from normal to skewed. This value (320 d) was used to estimate a maximum upper range for 9 mo of isoniazid due to normal variability of duration. The distance from the ideal (270 d) was considered the upper-range variability, and the ratio (320 − 270 = 50 / 270 = 0.18) was multiplied by 180 (ideal duration of isoniazid regimen) to give an upper range of 213 d, which was used as the maximum limit to censor the data for the analysis of 6 mo of isoniazid. LTBI = latent tuberculosis infection.

Appendix Table 2. Characteristics and Outcomes of Adults and Children in the MITT Population, by LTBI Regimen and Group of Countries

Characteristic or Outcome	Adults		Children	
	Rifampin (4 mo)	Isoniazid (9 mo)	Rifampin (4 mo)	Isoniazid (9 mo)
Australia, Canada, Saudi Arabia, and South Korea*				
Participants, *n*	952	927	20	12
Mean age (SD), *y*	41.2 (13.6)	41.4 (13.6)	10.35 (5.86)	11.25 (3.49)
Female, *n (%)*	529 (56)	505 (54)	8 (40)	9 (75)
Outcomes, *n (%)*				
Completed therapy	740 (78)	568 (61)	14 (70)	5 (42)
Stopped because of adverse event	41 (4)	83 (9)	–	–
Stopped because of active tuberculosis	0 (0)	0 (0)	–	–
Stopped because of participant decision	171 (18)	276 (30)	6 (30)	7 (59)
Brazil and Indonesia				
Participants, *n*	864	879	139	127
Mean age (SD), *y*	41.3 (13.5)	40.2 (13.4)	8.68 (4.70)	9.29 (5.03)
Female, *n (%)*	546 (63)	526 (60)	69 (50)	71 (51)
Outcomes, *n (%)*				
Completed therapy	628 (73)	537 (62)	106 (76)	87 (69)
Stopped because of adverse event	16 (2)	23 (3)	0	1 (0)†
Stopped because of active tuberculosis	1 (0)	1 (0)	0	0
Stopped because of participant decision	219 (25)	318 (36)	33 (24)	39 (31)
Benin, Ghana, and Guinea				
Participants, *n*	1207	1183	263	268
Mean age (SD), *y*	33.9 (13.4)	34.9 (13.5)	9.47 (4.53)	9.54 (4.62)
Female, *n (%)*	740 (61)	706 (60)	130 (49)	130 (49)
Outcomes, *n (%)*				
Completed therapy	1008 (84)	779 (66)	245 (93)	222 (83)
Stopped because of adverse event	17 (1)	47‡ (3)	1‡§	0
Stopped because of active tuberculosis	0 (0)	0 (0)	0	0
Stopped because of participant decision	182 (15)	357 (30)	17 (7)	46 (17)

LTBI = latent tuberculosis infection; MITT = modified intention-to-treat.
* Pediatric study included only participants from Australia and Canada.
† Adverse event not related to the study drug.
‡ Four deaths, 3 of which were not related to the study drug.
§ Death not related to the study drug.

Appendix Table 3. Clinical Activities for Adults in the MITT Population, by LTBI Regimen and Group of Countries

Activities	Rifampin (4 mo)		Isoniazid (9 mo)	
	Total Activities, *n*	Mean Activities per MITT Patient (SD), *n*	Total Activities, *n*	Mean Activities per MITT Patient (SD), *n*
Australia, Canada, Saudi Arabia, and South Korea				
Patients, *n*	952	–	927	–
Baseline evaluation				
Visits*	952	1	927	1
Blood tests†	4653	4.9 (0.2)	4482	4.8 (0.6)
Imaging studies‡	977	1.0 (0.2)	962	1.0 (0.2)
Tuberculosis microbiological tests§	974	1.0 (2.2)	899	0.9 (2.2)
Follow-up during treatment‖				
Visits¶	2490	3.1 (1.3)	4315	4.60 (2.5)
Blood tests**	7699	8.1 (5.5)	9729	10.50 (8.3)
Imaging studies††	137	0.1 (0.4)	132	0.14 (0.4)
Tuberculosis microbiological tests‡‡	6	0.006 (0.1)	11	0.011 (0.1)
Other microbiological tests§§	5	0.005 (0.1)	14	0.02 (0.2)
Procedures‖ ‖	3	0.003 (0.1)	6	0.006 (0.1)
Adverse events during treatment¶¶				
Visits***	96	0.1 (0.5)	210	0.2 (0.9)
Blood tests†	266	0.3 (1.8)	756	0.8 (3.7)
Imaging studies††	5	0.005 (0.1)	20	0.02 (0.2)
Microbiological tests†††	0	–	1	0.001 (0.03)
Tuberculosis microbiological tests‡‡‡	0	–	1	0.001 (0.03)
Procedures§§§	0	–	4	0.004 (0.1)
Specialist consultations‖ ‖ ‖	12	0.01 (0.2)	12	0.01 (0.2)
Hospitalization days	12	0.01 (0.2)	39	0.04 (0.9)
Totals (4 most common activities)				
Visits	3988	4.2 (1.4)	5452	5.9 (2.5)
Blood tests	12 618	13.3 (5.8)	14 967	16.1 (9.1)
Imaging studies	1119	1.2 (0.4)	1114	1.2 (0.4)
Tuberculosis microbiological tests	980	1.0 (2.2)	911	1.0 (2.2)
Brazil and Indonesia				
Patients, *n*	864	–	879	–
Baseline evaluation				
Visits	864	1 (0)	879	1 (0)
Blood tests	4308	5.0 (0.2)	4381	5.0 (0.2)
Imaging studies	872	1.00 (0.1)	889	1.00 (0.1)
Tuberculosis microbiological tests	55	0.06 (0.5)	42	0.04 (0.5)
Follow-up during treatment				
Visits	2495	2.9 (1.1)	4179	4.8 (2.43)
Blood tests	3884	4.5 (2.4)	4201	4.8 (2.98)
Imaging studies	4	0.004 (0.1)	12	0.01 (0.31)
Tuberculosis microbiological tests	6	0.006 (0.1)	25	0.03 (0.55)
Other microbiological tests	0	–	0	–
Procedures	0	–	1	0.001 (0.03)
Adverse events during treatment				
Visits	30	0.03 (0.5)	30	0.03 (0.3)
Blood tests	91	0.1 (1.04)	374	0.4 (3.3)
Imaging studies	1	0.001 (0.03)	7	0.007 (0.1)
Microbiological tests	1	0.001 (0.03)	2	0.003 (0.05)
Tuberculosis microbiological tests	0	–	0	–
Procedures	0	–	0	–
Specialist consultations	0	–	8	0.009 (0.2)
Hospitalization days	0	–	12	0.01 (0.3)
Totals (4 most common activities)				
Visits	3389	3.9 (1.1)	5088	5.8 (2.4)
Blood tests	8283	9.6 (2.6)	8956	10.2 (4.7)
Imaging studies	877	1.0 (0.2)	908	1.0 (0.3)
Tuberculosis microbiological tests	61	0.07 (0.6)	67	0.07 (0.7)
Benin, Ghana, and Guinea				
Patients, *n*	1207	–	1183	–
Baseline evaluation				
Visits	1207	1	1183	1
Blood tests	6559	5.4 (0.7)	6446	5.4 (0.7)
Imaging studies	1207	1.0 (0)	1183	1.0 (0)
Tuberculosis microbiological tests	36	0.03 (0.3)	88	0.07 (0.5)

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Appendix Table 3–Continued

Activities	Rifampin (4 mo)		Isoniazid (9 mo)	
	Total Activities, *n*	Mean Activities per MITT Patient (SD), *n*	Total Activities, *n*	Mean Activities per MITT Patient (SD), *n*
Follow-up during treatment				
Visits	4262	3.5 (1.2)	7219	6.1 (3.0)
Blood tests	5420	4.5 (1.8)	5252	4.4 (1.9)
Imaging studies	0	–	4	0.003 (0.05)
Tuberculosis microbiological tests	0	–	0	–
Other microbiological tests	0	–	0	–
Procedures	0	–	0	–
Adverse events during treatment				
Visits	18	0.01 (0.2)	61	0.05 (0.3)
Blood tests	26	0.02 (0.3)	158	0.1 (1.6)
Imaging studies	1	0.0008 (0.03)	15	0.01 (0.1)
Microbiological tests	0	–	2	0.001 (0.04)
Tuberculosis microbiological tests	0	–	0	–
Procedures	0	–	0	–
Specialist consultations	0	–	4	0.003 (0.1)
Hospitalization days	0	–	1	0.0008 (0.03)
Totals (4 most common activities)				
Visits	5487	4.5 (1.2)	8463	7.2 (3.0)
Blood tests	12 005	9.9 (2.1)	11 856	10.0 (2.7)
Imaging studies	1208	1.0 (0.2)	1202	1.0 (0.2)
Tuberculosis microbiological tests	36	0.03 (0.3)	88	0.074 (0.5)

LTBI = latent tuberculosis infection; MITT = modified intention-to-treat.
* All patients had 1 baseline evaluation (patient visit).
† Includes complete blood count, liver function tests (aspartate aminotransferase, alanine aminotransferase, and bilirubin), and blood sample collection.
‡ All patients had 1 chest radiography. Occasionally, other tests were requested by the physician, including computed tomography and positron emission tomography.
§ Acid-fast bacteria smear microscopy or mycobacterial culture.
‖ Includes activities only during follow-up, excluding adverse event care. Two patients had active tuberculosis diagnosed during LTBI treatment, and the activities related to tuberculosis diagnosis were included in the follow-up.
¶ Includes outpatient (clinic) visits, home visits, and telephone calls.
** Includes complete blood count, liver function tests (aspartate aminotransferase, alanine aminotransferase, and bilirubin), biochemical tests (e.g., pancreatic enzymes, thyroid markers, pregnancy tests, glucose, C-reactive protein, erythrocyte sedimentation rate, vitamin B, folic acid, urea, and creatinine), electrolytes (sodium, potassium, magnesium, and chloride), and serologic tests (HIV; hepatitis A, B, and C; and syphilis). Few patients had QuantiFERON-TB Gold In-Tube requested by the treating physician, regardless of the tuberculin skin test results at baseline.
†† Includes chest radiography, computed tomography (brain, chest, and abdomen), ultrasonography (abdomen, breast, and pelvis), brain magnetic resonance imaging, echocardiography, electroencephalography, and electrocardiography.
‡‡ Includes Xpert MTB-Rif, acid-fast bacteria smear microscopy, and tuberculosis culture.
§§ Includes urine culture, urinalysis, and ova and parasites test.
‖ ‖ Includes induced sputum, gastroscopy, skin biopsy, and methacholine test.
¶¶ Patients investigated for suspected drug-related adverse event.
*** Includes outpatient (clinic) visits, home visits, telephone calls, and emergency department visits.
††† Urine culture, urinalysis, and ova and parasites test.
‡‡‡ Acid-fast bacteria smear microscopy and *Mycobacterium tuberculosis* culture.
§§§ Includes cholecystectomy, leg amputation, embolectomy, and biopsy.
‖ ‖ ‖ Includes infectious diseases specialist, otolaryngologist, orthopedist, hematologist, rheumatologist, gynecologist, dermatologist, orthopedist, gastroenterologist, and pathologist.

Appendix Table 4. Clinical Activities for Children in the MITT Population, by LTBI Regimen and Group of Countries

Activities	Rifampin (4 mo)		Isoniazid (9 mo)	
	Total Activities, *n*	Mean Activities per MITT Patient (SD), *n*	Total Activities, *n*	Mean Activities per MITT Patient (SD), *n*
Australia and Canada				
Patients, *n*	20	–	12	–
Baseline evaluation				
Visits*	20	1.00 (0)	12	1.0 (0)
Blood tests†	86	4.3 (1.34)	58	4.8 (0.39)
Imaging studies‡	20	1.00 (0)	12	1 (0)
Tuberculosis microbiological tests§	6	0.3 (1.34)	0	–
Follow-up during treatment‖				
Visits¶	67	3.4 (1.2)	60	5.0 (1.7)
Blood tests**	110	5.5 (5.7)	44	3.7 (3.9)
Imaging studies††	6	0.3 (0.5)	2	0.2 (0.4)
Microbiological tests‡‡	0	–	0	–
Adverse events during treatment				
Visits	0	–	0	–
Blood tests	0	–	0	–
Totals (most common activities)				
Visits	87	4.4 (1.2)	72	6.0 (1.7)
Blood tests	196	9.8 (6.2)	102	8.5 (4.0)
Imaging studies	26	1.3 (0.5)	14	1.2 (0.4)
Brazil and Indonesia				
Patients, *n*	139	–	127	–
Baseline evaluation				
Visits	139	1.0 (0)	127	1.0 (0)
Blood tests	684	4.9 (0.5)	635	5.0 (0)
Imaging studies	140	1.0 (0)	127	1.0 (0)
Tuberculosis microbiological tests	2	0.01 (0.2)	5	0.03 (0.3)
Follow-up during treatment				
Visits	425	3.1 (1.2)	765	6.0 (2.6)
Blood tests	183	1.3 (1.1)	177	1.4 (1.2)
Imaging studies	0	–	7	0.05 (0.3)
Microbiological tests	1	0.007 (0.08)	3	0.02 (0.2)
Adverse events during treatment§§				
Visits‖ ‖	0	–	1	0.007 (0.1)
Blood tests¶¶	0	–	1	0.007 (0.1)
Totals (most common activities)				
Visits	564	4.1 (1.6)	893	7.0 (2.6)
Blood tests	867	6.2 (1.2)	813	6.4 (1.2)
Imaging studies	140	1.0 (0.1)	134	1.1 (0.3)
Benin, Ghana, and Guinea				
Patients, *n*	263	–	268	–
Baseline evaluation				
Visits	263	1.0 (0)	268	1.0 (0)
Blood tests	1309	4.9 (0.26)	1340	5.0 (0)
Imaging studies	263	1.0 (0)	268	1.0 (0)
Tuberculosis microbiological tests	14	0.05 (0.32)	2.00	0.007 (0.1)
Follow-up during treatment				
Visits	1005	3.8 (1.52)	1999	7.5 (2.4)
Blood tests	448	1.7 (1.52)	440	1.6 (1.5)
Imaging studies	0	–	0	–
Microbiological tests	0	–	0	–
Adverse events during treatment				
Visits	0	–	0	–
Blood tests	0	–	0	–
Totals (most common activities)				
Visits	1268	4.8 (0.63)	2267	8.5 (2.43)
Blood tests	1757	6.7 (1.6)	1780	6.6 (1.5)
Imaging studies	263	1.0 (0)	268	1.0 (0)

LTBI = latent tuberculosis infection; MITT = modified intention-to-treat analysis.
* All patients had 1 baseline evaluation (patient visit).
† Includes complete blood count and liver function tests (aspartate aminotransferase, alanine aminotransferase, and bilirubin).
‡ All patients had 1 chest radiography. Occasionally, other tests were requested by the physician, including computed tomography.
§ Acid-fast bacteria smear microscopy or mycobacterial culture.
‖ Includes activities only during follow-up, excluding adverse event care.
¶ Includes outpatient (clinic) visits, home visits, and telephone calls.
** Includes complete blood count, liver function tests (aspartate aminotransferase, alanine aminotransferase, and bilirubin), biochemical tests (urea, creatinine, and hemoglobin electrophoresis), and serologic tests (HIV; hepatitis A, B, and C; and syphilis).
†† Chest radiography.
‡‡ Urine culture, urinalysis, and ova and parasites test.
§§ Only 1 patient was investigated for a suspected drug-related adverse event, and the study drug was stopped.
‖ ‖ Outpatient visit.
¶¶ Pregnancy test.

Appendix Table 5. Independent Predictors of Costs: Sensitivity Analysis 1 (Unit Costs Standardized Using Canadian Costs; Linear Regression Without Log Transformation)*

Variable	Patients, *n (%)*	Estimated Costs (95% CI), *US $*	
		Unadjusted	**Adjusted†**
Intercept (interpreted as base costs)	–		957 (920 to 994)
4 mo of rifampin (9 mo of isoniazid = reference)	2816 (55)	**−357 (−377 to −338)**	**−362 (−383 to −343)**
Age (continuous, per additional year)	5168	−0.20 (−0.88 to 0.45)	−0.30 (−0.96 to 0.36)
Male sex (female = reference)	2176 (42)	**30 (7 to 52)**	−12 (−33 to 8)
Obese or overweight BMI (normal or underweight = reference)‡	1964 (38)	1 (−21 to 24)	–
Ever-smoker (never-smoker = reference)	1033 (20)	−14 (−42 to 13)	–
Alcohol intake ever (never = reference)	1481 (29)	16 (−8 to 41)	1 (−21 to 24)
Had symptoms or physical examination at baseline (normal = reference)	826 (16)	−18 (−48 to 12)	–
Comorbidity			
None	4649 (90)	Reference	**Reference**
HIV	230 (4)	31 (−22 to 84)	17 (−31 to 66)
Diabetes mellitus	136 (3)	26 (−39 to 97)	41 (−22 to 104)
Other immunosuppression§	153 (3)	**79 (13 to 143)**	97 (37 to 156)
Abnormal LFT result at baseline or first month (normal = reference)‖	1196 (23)	4 (−22 to 29)	–
Abnormal CBC at baseline and first month (normal = reference)¶	1489 (29)	22 (−3 to 46)	**28 (4 to 53)**
Region			
Canada/Australia/Saudi Arabia/South Korea	1451 (21)	Reference	Reference
Brazil/Indonesia	1398 (30)	**−57 (−87 to −27)**	**−62 (−91 to −34)**
Benin/Ghana/Guinea	2319 (45)	20 (−6 to 46)	18 (−10 to 47)
Had grade 1 to 5 adverse event (no = reference)**	229 (4)	25 (−28 to 78)	−26 (−93 to 41)
Interaction terms (adverse event and region)			
Had adverse event (Brazil, Indonesia)	–	–	**165 (33 to 297)**
Had adverse event (Benin, Ghana, Guinea)	–	–	**−222 (−333 to −110)**

BMI = body mass index; CBC = complete blood count; LFT = liver function test.
* Includes patients who completed treatment or stopped because of adverse events but not those who decided to discontinue treatment early. Boldface indicates statistical significance.
† The model was adjusted for sex, age, treatment regimen, occurrence of any adverse event that led to treatment discontinuation, and other covariates that had a *P* value ≤0.2 in the unadjusted model.
‡ Information was missing for 4 children.
§ Includes patients who were medically immunosuppressed and/or used recreational drugs.
‖ Combined results of aspartate aminotransferase and alanine aminotransferase. Information was missing for 8 patients.
¶ Combined results of leukocyte and platelet counts. Information was missing for 15 patients.
** All patients who had a grade 1 to 5 adverse event and permanently stopped use of the medication, including 5 who died (4 of these deaths were not related to the study drug).

Appendix Table 6. Independent Predictors of Costs: Sensitivity Analysis 2 (Country-Specific Costs, With Log Transformation for Analysis of Ratios and 95% CIs)*

Variable	Patients, *n (%)*	Cost Ratio (95% CI)	
		Unadjusted	Adjusted†
Intercept (interpreted as base costs)	–	–	824 (806 to 841)
4 mo of rifampin (9 mo of isoniazid = reference)	2816 (55)	–	–
Cost difference‡	–	–	**−202 (−211 to −193)**
Cost ratio	–	**0.77 (0.74 to 0.81)**	**0.77 (0.76 to 0.78)**
Age (continuous, per additional year)	5168	**1.012 (1.010 to 1.013)**	**1.002 (1.001 to 1.003)**
Male sex (female = reference)	2176 (42)	**1.07 (1.02 to 1.12)**	0.99 (0.98 to 1.00)
Obese or overweight BMI (normal or underweight = reference)§	1964 (38)	0.98 (0.93 to 1.02)	–
Ever-smoker (never-smoker = reference)	1033 (20)	**1.24 (1.17 to 1.31)**	1.00 (0.99 to 1.02)
Alcohol intake ever (never = reference)	1481 (29)	**1.39 (1.32 to 1.46)**	**1.02 (1.01 to 1.03)**
Had symptoms or physical examination at baseline (normal = reference)	826 (16)	1.00 (0.94 to 1.06)	–
Comorbidity			
None	4649 (90)	–	–
HIV	230 (4)	**0.50 (0.45 to 0.56)**	0.99 (0.96 to 1.01)
Diabetes mellitus	136 (3)	**1.57 (1.37 to 1.81)**	1.02 (0.99 to 1.05)
Other immunosuppression‖	153 (3)	**1.75 (1.53 to 2.00)**	0.99 (0.97 to 1.02)
Abnormal LFT result at baseline or first month (normal = reference)¶	1196 (23)	**0.92 (0.87 to 0.97)**	**1.03 (1.02 to 1.04)**
Abnormal CBC at baseline and first month (normal = reference)**	1489 (29)	**0.73 (0.69 to 0.77)**	**1.03 (1.02 to 1.05)**
Country			
Canada	848 (16)	Reference	Reference
Australia	160 (3)	0.98 (0.94 to 1.02)	**0.97 (0.94 to 1.00)**
Benin	1173 (23)	**0.18 (0.17 to 0.19)**	**0.178 (0.175 to 0.181)**
Brazil	684 (13)	**0.082 (0.079 to 0.083)**	**0.079 (0.077 to 0.081)**
Ghana	435 (8)	**0.14 (0.13 to 0.15)**	**0.14 (0.13 to 0.15)**
Guinea	711 (14)	**0.16 (0.15 to 0.17)**	**0.16 (0.15 to 0.162)**
Indonesia	714 (14)	**0.24 (0.23 to 0.25)**	**0.234 (0.230 to 0.236)**
South Korea	402 (8)	**0.49 (0.48 to 0.51)**	**0.47 (0.46 to 0.48)**
Saudi Arabia	41 (1)	**1.42 (1.32 to 1.53)**	**1.41 (1.33 to 1.50)**
Had grade 1 to 5 adverse event (no = reference)††	229 (4)	**1.60 (1.43 to 1.79)**	**0.72 (0.70 to 0.75)**
Interactions (adverse event and country)			
Had adverse event (Australia)	–	–	**1.45 (1.28 to 1.65)**
Had adverse event (Benin)	–	–	**1.35 (1.27 to 1.44)**
Had adverse event (Brazil)	–	–	**1.52 (1.38 to 1.67)**
Had adverse event (Ghana)	–	–	**1.72 (1.34 to 2.22)**
Had adverse event (Guinea)	–	–	**0.81 (0.73 to 0.90)**
Had adverse event (Indonesia)	–	–	**1.38 (1.27 to 1.51)**
Had adverse event (South Korea)	–	–	**1.84 (1.68 to 2.02)**
Had adverse event (Saudi Arabia)	–	–	**1.63 (1.26 to 2.12)**

BMI = body mass index; CBC = complete blood count; LFT = liver function test.
* Includes patients who completed treatment or stopped because of adverse events but not those who decided to discontinue treatment early. Boldface indicates statistical significance.
† The model was adjusted for sex, age, treatment regimen, occurrence of any adverse event that led to treatment discontinuation, and other covariates that had a *P* value ≤0.2 in the unadjusted model.
‡ The NLESTIMATE macro in SAS was used to convert parameter estimates of ratios to differences in costs.
§ Information was missing for 4 children.
‖ Includes patients who were medically immunosuppressed and/or used recreational drugs.
¶ Combined results of aspartate aminotransferase and alanine aminotransferase. Information was missing for 8 patients.
** Combined results of leukocyte and platelet counts. Information was missing for 15 patients.
†† All patients who had a grade 1 to 5 adverse event and permanently stopped use of the medication, including 5 who died (4 of these deaths were not related to the study drug).

Appendix Table 7. Comparison of Three Methods for Modeling Costs*

Variable	Adjusted Costs (95% CIs) From Model 1 (Appendix Table 5) (Canadian Costs; Linear Regression), *US $*	Adjusted Cost Ratio (95% CI)	
		Model 2 (Table 4) (Canadian Costs; Log-Transformed)	Model 3 (Appendix Table 6) (Country-Specific Costs; Log-Transformed)
Intercept (interpreted as base costs)	957 (920 to 994)	917 (900 to 934)	824 (806 to 841)
4 mo of rifampin (9 mo of isoniazid = reference)			
Cost difference (2017 U.S. dollars)	**−362 (−383 to −343)**	**−340 (−350 to −330)**	**−202 (−211 to −193)**
Cost ratio	–†	**0.62 (0.61 to 0.63)**	**0.77 (0.76 to 0.78)**
Age (continuous, per additional year)	−0.30 (−0.96 to 0.36)	0.9997 (0.9993 to 1.000)	**1.002 (1.001 to 1.003)**
Male sex (female = reference)	−12 (−33 to 8)	1.01 (1.00 to 1.03)	0.99 (0.98 to 1.00)
Ever-smoker (never-smoker = reference)	–‡	**0.98 (0.96 to 0.99)**	1.00 (0.99 to 1.02)
Alcohol intake ever (never = reference)	1 (−21 to 24)	**1.02 (1.01 to 1.03)**	**1.02 (1.01 to 1.03)**
Had symptoms or physical examination at baseline (normal = reference)	–‡	1.01 (0.99 to 1.02)	–‡
Comorbidity			
None	**Reference**	**Reference**	–
HIV	17 (−31 to 66)	1.00 (0.97 to 1.02)	0.99 (0.96 to 1.01)
Diabetes mellitus	41 (−22 to 104)	**1.04 (1.01 to 1.07)**	1.02 (0.99 to 1.05)
Other immunosuppression	**97 (37 to 156)**	0.98 (0.95 to 1.01)	0.99 (0.97 to 1.02)
Abnormal LFT result at baseline or first month (normal = reference)	–‡	0.99 (0.98 to 1.01)	**1.03 (1.02 to 1.04)**
Abnormal CBC at baseline and first month (normal = reference)	**28 (4 to 53)**	**1.02 (1.01 to 1.03)**	**1.03 (1.02 to 1.05)**
Region			
Canada/Australia/Saudi Arabia/South Korea	**Reference**	**Reference**	–†
Brazil/Indonesia	**−62 (−91 to −34)**	**0.94 (0.92 to 0.95)**	–†
Benin/Ghana/Guinea	18 (−10 to 47)	**1.05 (1.03 to 1.06)**	–†
Had adverse event (no = reference)§	−26 (−93 to 41)	**0.83 (0.80 to 0.86)**	**0.72 (0.70 to 0.75)**
Interaction of adverse event and region			
Had adverse event (Brazil, Indonesia)	**165 (33 to 297)**	**1.18 (1.10 to 1.26)**	–†
Had adverse event (Benin, Ghana, Guinea)	**−222 (−333 to −110)**	**0.82 (0.78 to 0.87)**	–†
Country			
Canada	–†	–†	Reference
Australia	–†	–†	0.97 (0.94 to 1.00)
Benin	–†	–†	**0.178 (0.175 to 0.181)**
Brazil	–†	–†	**0.079 (0.077 to 0.081)**
Ghana	–†	–†	**0.14 (0.13 to 0.15)**
Guinea	–†	–†	**0.16 (0.15 to 0.162)**
Indonesia	–†	–†	**0.234 (0.230 to 0.236)**
South Korea	–†	–†	**0.47 (0.46 to 0.48)**
Saudi Arabia	–†	–†	**1.41 (1.33 to 1.50)**
Interaction of adverse event and country			
Had adverse event (Australia)	–	–	**1.45 (1.28 to 1.65)**
Had adverse event (Benin)	–	–	**1.35 (1.27 to 1.44)**
Had adverse event (Brazil)	–	–	**1.52 (1.38 to 1.67)**
Had adverse event (Ghana)	–	–	**1.72 (1.34 to 2.22)**
Had adverse event (Guinea)	–	–	**0.81 (0.73 to 0.90)**
Had adverse event (Indonesia)	–	–	**1.38 (1.27 to 1.51)**
Had adverse event (South Korea)	–	–	**1.84 (1.68 to 2.02)**
Had adverse event (Saudi Arabia)	–	–	**1.63 (1.26 to 2.12)**

CBC = complete blood count; LFT = liver function test.
* Boldface indicates statistical significance.
† Not analyzed in the model.
‡ Not included in the multivariate analyses because *P* value was >0.2 in the univariate model.
§ All patients who had a grade 1 to 5 adverse event and permanently stopped use of the medication, including 5 who died (4 of these deaths were not related to the study drug).