

Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial



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Summary

Background The STREAM stage 2 trial assessed two bedaquiline-containing regimens for rifampicin-resistant tuberculosis: a 9-month all-oral regimen and a 6-month regimen containing an injectable drug for the first 2 months. We did a within-trial economic evaluation of these regimens.

Methods STREAM stage 2 was an international, phase 3, non-inferiority randomised trial in which participants with rifampicin-resistant tuberculosis were randomly assigned (1:2:2) to the 2011 WHO regimen (terminated early), a 9-month injectable-containing regimen (control regimen), a 9-month all-oral regimen with bedaquiline (oral regimen), or a 6-month regimen with bedaquiline and an injectable for the first 2 months (6-month regimen). We prospectively collected direct and indirect costs and health-related quality of life data from trial participants until week 76 of follow-up. Cost-effectiveness of the oral and 6-month regimens versus control was estimated in four countries (oral regimen) and two countries (6-month regimen), using health-related quality of life for cost-utility analysis and trial efficacy for cost-effectiveness analysis. This trial is registered with ISRCTN, ISRCTN18148631.

Findings 300 participants were included in the economic analyses (Ethiopia, 61; India, 142; Moldova, 51; Uganda, 46). In the cost-utility analysis, the oral regimen was not cost-effective in Ethiopia, India, Moldova, and Uganda from either a provider or societal perspective. In Moldova, the oral regimen was dominant from a societal perspective. In the cost-effectiveness analysis, the oral regimen was likely to be cost-effective from a provider perspective at willingness-to-pay thresholds per additional favourable outcome of more than US\$4500 in Ethiopia, \$1900 in India, \$3950 in Moldova, and \$7900 in Uganda, and from a societal perspective at thresholds of more than \$15 900 in Ethiopia, \$3150 in India, and \$4350 in Uganda, while in Moldova the oral regimen was dominant. In Ethiopia and India, the 6-month regimen would cost tuberculosis programmes and participants less than the control regimen and was highly likely to be cost-effective in both cost-utility analysis and cost-effectiveness analysis. Reducing the bedaquiline price from \$1.81 to \$1.00 per tablet made the oral regimen cost-effective in the provider-perspective cost-utility analysis in India and dominate over the control regimen in the provider-perspective cost-effectiveness analysis in India.

Interpretation At current costs, the oral bedaquiline-containing regimen for rifampicin-resistant tuberculosis is unlikely to be cost-effective in many low-income and middle-income countries. The 6-month regimen represents a cost-effective alternative if injectable use for 2 months is acceptable.

Funding USAID and Janssen Research & Development.

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Introduction

Tuberculosis that is resistant to rifampicin, with or without resistance to other first-line antituberculosis drugs, continues to be a global public health threat. Current treatment for rifampicin-resistant tuberculosis requires a drug regimen lasting a minimum of 9 months, and up to 20 months, although this is expected to be reduced to 6 months in the forthcoming WHO guidelines.¹ Treatment

of rifampicin-resistant tuberculosis costs patients and health providers more than treatment of drug-susceptible tuberculosis, and has a lower success rate (59% vs 86%).^{2,3} The WHO clinical recommendations^{1,4} do not include directly measured comparative economic data.

STREAM stage 2 is a multicountry randomised controlled trial assessing two new bedaquiline-containing treatment regimens for rifampicin-resistant

Lancet Glob Health 2022

Published Online
December 21, 2022
[https://doi.org/10.1016/S2214-109X\(22\)00498-3](https://doi.org/10.1016/S2214-109X(22)00498-3)

See Online/Comment
[https://doi.org/10.1016/S2214-109X\(22\)00519-8](https://doi.org/10.1016/S2214-109X(22)00519-8)

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See [Online](#) for appendix

Research in context

Evidence before this study

In 2020, WHO recommended a short, all-oral treatment regimen for rifampicin-resistant tuberculosis. However, the guidelines were published before availability of directly measured economic data comparing all-oral to existing treatment regimens, relying instead on modelling work, which indicated that an all-oral regimen had the possibility to achieve improved treatment outcomes and reduce lifelong disability, while also enabling patients to return to employment sooner than an injectable-containing regimen. In making their 2020 recommendation, the WHO Guideline Development Group rated the overall certainty of evidence “very low”, and acknowledged that implementing the all-oral shorter regimen does not automatically and immediately eliminate or reduce costs. Several modelling studies using data from the first bedaquiline trial have suggested that an oral regimen would decrease costs and increase quality-adjusted life-years gained, but no study has directly collected efficacy outcomes, patient-reported costs, or quality of life data. Given the economic impact of rifampicin-resistant tuberculosis, the global policy goals of financial protection and elimination of catastrophic costs for patients with tuberculosis, and the resource constraints facing health providers in countries where rifampicin-resistant tuberculosis is a substantial challenge, there was a clear need for additional, robust evidence on the economics of shorter treatment regimens, to support health programmes considering these new strategies. We searched PubMed for within-trial economic evaluations published from Jan 1, 2016, to June 16, 2022, with the terms “trial” AND “tuberculosis” AND “rifampicin resistance” OR “rifampicin-resistance” OR “rifampin resistance” OR “rifampin-resistance” OR “MDR” OR “multidrug” OR “multi-drug” OR “MDR-TB” OR “RR-TB” AND “economic evaluation” OR “cost-effectiveness” OR “cost-utility” OR “QALY” OR “cost”, with no language or article type restrictions. This search yielded 71 results; studies that were not randomised clinical trials were excluded, leaving just one

study, the STREAM stage 1 economic evaluation, which did not compare bedaquiline-containing regimens.

Added value of this study

The STREAM stage 2 economic evaluation uses a within-trial and multicountry approach, offering detailed analyses and comparisons of the provider and participant costs, as well as participant quality of life data over the treatment duration and for 36 weeks (for the oral and control regimens) and 48 weeks (for the 6-month regimen) after treatment completion. The results show that a 9-month, oral, bedaquiline-containing regimen is unlikely to be either cost-saving or cost-effective compared with a 9-month regimen that includes daily injections for the first 4 months. Although the oral regimen had superior clinical outcomes, the participant-reported quality of life data were not significantly different across the two intervention groups. Moreover, participants in both groups had similar levels of catastrophic health-related costs. A 6-month, bedaquiline-based regimen is a cost-effective alternative if daily injections for 2 months are acceptable for patients, clinicians, and policy makers.

Implications of all the available evidence

Our findings provide robust evidence on the cost-utility and cost-effectiveness of two new rifampicin-resistant tuberculosis regimens. The data on likely costs, potential savings, and patient-reported outcomes can be used to guide uptake and implementation of regimens by national tuberculosis programmes. Results suggest that provider costs, including drug costs, will need to be reduced to enable cost-effective delivery of 9-month bedaquiline-based regimens; otherwise, providers will need to allocate additional resources for treating rifampicin-resistant tuberculosis. The results also provide crucial information for use in designing financial protection packages for patients.

tuberculosis versus a 9-month control previously evaluated in STREAM stage 1.⁵ Both STREAM stage 1 and STREAM stage 2 included within-trial economic evaluations, to support global policy recommendations and decisions by tuberculosis programmes on the best rifampicin-resistant tuberculosis regimen for their health system and health financing context. The STREAM stage 2 economic study was done (with minor modifications, see appendix pp 11–12) in line with the health economic analysis plan published elsewhere.⁶

This study was done in Ethiopia, India, Moldova, and Uganda and presents the costs and cost-effectiveness associated with the oral, 6-month, and control regimens of STREAM stage 2. We present participant costs, catastrophic costs, and provider costs for each regimen and explore associated cost drivers. We separately compared the oral and 6-month regimens versus the control regimen in two economic evaluations, initially

from the provider perspective and separately from the societal perspective. The primary economic evaluation is a cost-utility analysis using health-related quality of life data, collected from participants during the treatment duration and follow-up period, as the outcome. The secondary evaluation is a cost-effectiveness analysis using the efficacy outcome (favourable or unfavourable) from the clinical trial.⁶

Methods

Study design and participants

The clinical trial design has been described in detail elsewhere.⁷ In brief, STREAM stage 2 was an international, multicentre, non-inferiority randomised controlled trial done in 13 hospital clinics in seven countries (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda). The Union Ethics Advisory Group was the global ethics committee. Ethical approvals were also obtained

from national and institutional ethics committees of participating sites. At recruitment, participants aged 15 years or older (where approved, otherwise 18 years or older) with rifampicin-resistant tuberculosis without fluoroquinolone or aminoglycoside resistance were randomly assigned (1:2:2:2) by a web-based randomisation system to a 20-month injectable-containing regimen (WHO-recommended regimen from 2011 to 2018), a 9-month injectable-containing regimen (moxifloxacin, clofazimine, ethambutol, and pyrazinamide for 40 weeks, with kanamycin, high-dose isoniazid, and prothionamide given for the 16-week intensive phase; control regimen) recommended by WHO from 2016 when STREAM stage 2 began to 2020, a 9-month all-oral regimen with bedaquiline (identical to control, except that bedaquiline for 40 weeks replaced kanamycin and levofloxacin replaced moxifloxacin; oral regimen), or a 6-month regimen with bedaquiline and an injectable for the first 2 months (bedaquiline, clofazimine, pyrazinamide, and levofloxacin for 28 weeks, with high-dose isoniazid with kanamycin for an 8-week intensive phase; 6-month regimen). Randomisation to the 20-month and 6-month regimens ceased early at most sites.⁷

The primary trial objective was to determine whether the proportion of participants in the modified intention-to-treat population with a favourable efficacy outcome at week 76 in the oral regimen group was non-inferior to that in the control group. Assessment of the 6-month regimen versus control was a secondary objective. The modified intention-to-treat population was defined as all randomly assigned participants with a positive culture for *Mycobacterium tuberculosis* at screening or randomisation, apart from participants with isolates obtained before randomisation who were subsequently found to be susceptible to rifampicin or resistant to both fluoroquinolones and second-line injectable drugs on phenotypic drug-susceptibility testing. Treatment for rifampicin-resistant tuberculosis was administered free at the point of care for all patients (as it would be under programmatic conditions), in publicly funded health facilities.

Health economic data were collected from four of the seven countries in STREAM stage 2: Ethiopia, India, Moldova, and Uganda. All participants who fulfilled the inclusion criteria as outlined in the trial protocol,⁷ were older than 18 years, provided written informed consent, and responded to the health economic questionnaires at least once were included in the health economic study.

The analyses presented here cover the period from randomisation until week 76 of follow-up. This time horizon captures 36 weeks (for the oral and control regimens) and 48 weeks (for the 6-month regimen) of data after completion of tuberculosis treatment. We contend that this time horizon is sufficiently long to capture any important between-group differences in treatment outcomes, survival, serious adverse events, and therefore

health-related quality of life, that would be likely to have an effect beyond 76 weeks. Further details are provided in the appendix (p 10) and Discussion section.

Procedures

Participant costs were collected between June 20, 2016, and July 29, 2021, using an adapted STOP TB Partnership questionnaire, administered in the local language of each site during the scheduled trial follow-up visits.⁸ Data on both medical spending (consultation fees, administration fees, and drugs) and non-medical spending (food and transport) were collected at baseline and then every 12 weeks until week 60 and finally at week 76. For further details see appendix (p 8).

We used bottom-up and top-down methods to collect provider costs.⁹ Duration of hospital stay, medication use, and social support payments were collected for each participant; consumable costs were obtained from aggregate data using activity-based costing and allocated to individual participants using a suitable proxy. Site-specific tuberculosis care activities (eg, patient management processes), their timing, and resources used were determined from interviews with clinical and managerial staff at each site. Laboratory tests were assumed to follow the trial's assessment schedule for each regimen.⁷ Individual participant care records for each serious adverse event were used to identify and cost the number and type of tests done, examination duration, and consumables used.

Health-related quality of life responses, used for the cost-utility analyses, were collected every 12 weeks from week 0 until week 60 and at week 76, using the EQ-5D-5L form translated into the local language at each site.¹⁰ Participants were asked to rate their health on five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Missing responses were multiple imputed. If a participant died during follow-up, we assumed that their responses were 5 for each dimension (ie, worst possible health state) since their last interview until last follow-up visit at week 76.

The efficacy outcome used for cost-effectiveness analyses was the pooled (all seven trial countries) primary endpoint of favourable outcome at 76 weeks.⁷ Favourable status was defined as a culture negative for *M tuberculosis* at week 76 and on the previous visit, with no intervening positive culture or previous unfavourable outcome. Unfavourable outcomes were the initiation of bedaquiline, kanamycin, linezolid, or two or more other drugs if they were not included in the assigned regimen; treatment extension beyond the permitted duration; death from any cause; a positive culture from one of the two most recent specimens; or no week 76 visit.

Cost data

Direct cost per participant was estimated by multiplying the cost of each directly observed treatment or assessment

visit by the number of visits. Guardian costs were assumed to equal the participant's non-medical direct costs and, for participants who indicated they required a guardian to accompany them during treatment, these were included in the total visit cost. Supplementary food expenditure (eg, on additional fruits, meat, and energy drinks) was reported separately.

Indirect costs were estimated using the output approach, by subtracting the self-reported (every 12 weeks) individual income from all sources, including social support, during tuberculosis treatment from the participants' self-reported pre-tuberculosis income, pro-rata for the 76 weeks of follow-up.¹¹ If participants reported that their guardian lost income, this was assumed to be equivalent to the participant's income loss.

Missing values in participants' responses for participant (and guardian) costs incurred for directly observed treatment and assessment visits (transport and food), lost income, and supplementary food expenditure were imputed using chained imputation models using a predictive mean matching algorithm.¹² All participant costs were estimated from treatment start until week 76 of follow-up or participants' last visit if they discontinued early or died. We considered total participant costs to be catastrophic if they exceeded 20% of annual individual income, approximating (for a combination of pragmatic reasons, see appendix p 8) to the WHO definition that uses household income.¹³

Inpatient hotel costs were calculated by dividing the total annual expenditure on hotel costs by the number of annual inpatient stay days, for each institution. Data were obtained from public hospital records where possible, with data from private hospitals or market prices used where hospital records were not available (see appendix p 7). To this cost, we added the staff costs. Outpatient visit costs were calculated by multiplying the quantity of each resource used as reported in clinical staff interviews (laboratory tests, staff time, consumables, etc) by their unit cost.

We used treatment logs to calculate medication intake for each participant. Total number of pills taken was multiplied by the Global Drug Facility unit cost (highest price available) for each drug to estimate regimen medication costs.¹⁴ If a participant was transferred to a salvage regimen anytime during the 76-week follow-up period, total salvage regimen costs (ie, even if extending beyond 76 weeks) were included in the respective trial group costs.

Social support costs were calculated by multiplying the country-specific amount by the outpatient duration or treatment duration as per country norms. Research costs (eg, payments received for attending trial-related visits) were excluded from participant and provider costs.

Where serious adverse events were related to either rifampicin-resistant tuberculosis or its treatment (assessment made independently by two clinicians, see appendix p 7), serious adverse event management costs

were included in the analysis. Each resource used (staff, tests, and consumables) was multiplied by its unit cost from hospital records and, when not available, from the local private facilities. We focused on serious adverse events rather than adverse events because many adverse events were minor and had relatively few cost implications, and because there was a practical limit in collecting resource use data. Safety results showed that adverse events were equally distributed across the regimens and a sensitivity analysis was done to assess the effect of including an assumed cost of adverse events on our conclusions. Other sensitivity analyses are described in subsequent subsections. All costs were adjusted to 2021 prices using country-specific consumer price indexes and converted to US\$.^{15,16}

Cost-utility analysis and cost-effectiveness analysis

EQ-5D-5L responses were converted into health-utility scores using the EuroQol validated tariff from the geographically nearest available country (Indonesia for India; Ethiopia for Ethiopia and Uganda; and Poland for Moldova).⁶ Quality-adjusted life-years (QALYs) gained were calculated using the area under the curve approach and were used as an outcome for the cost-utility analysis (see appendix pp 8–9). Since baseline QALY measures can be prognostic of outcomes that are independent of treatment allocation,¹⁷ we tested for between-group differences, planning to adjust before analysis if p value for the difference was less than or equal to 0.1.

Pooled (all seven trial countries) efficacy outcomes were used in the cost-effectiveness analysis because these were powered to show the non-inferiority of the oral regimen to the control regimen, whereas country-specific estimates were not. For both the cost-utility and cost-effectiveness analyses, we calculated the incremental cost-effectiveness ratio (ICER), by dividing the between-group difference in mean total cost by the between-group difference in mean effect.

Uncertainty is presented using cost-effectiveness acceptability curves, which plot the ICER as a function of probability of cost-effectiveness against plausible willingness-to-pay (WTP) thresholds between US\$0 and \$20 000.¹⁸ Cost-effectiveness acceptability curves were produced via bootstrapping, where we resampled 1000 estimates of mean costs and effects for each regimen.¹⁷ The probability of being cost-effective was considered high if more than or equal to 80%. Cost-utility and cost-effectiveness analyses were done from the provider perspective and then from the societal perspective, by adding total participant costs to the provider costs.

Where one regimen was dominant (ie, cost less and delivered better outcomes), we report the dominant regimen. Where the intervention (oral or 6-month regimen) costs more and delivered better or similar outcomes than the control, we report the ICER and WTP threshold value where the cost-effectiveness acceptability

curve has an 80% probability of being cost-effective. To aid interpretation, WTP values in the cost-utility analysis are compared with the upper bound of published purchasing power parity adjusted cost per QALY-gained thresholds of \$696 in Ethiopia, \$2781 in India, \$2400 in Moldova, and \$725 in Uganda.¹⁹

Sensitivity and statistical analyses

All analyses were performed in Stata version 15.1. Participant costs are presented as means with their 95% CIs and p values. A difference was considered significant at the 95% significance level ($p \leq 0.05$). Deterministic sensitivity analyses were done on the following set of input parameters: bedaquiline costs, inclusion of adverse event costs, and the site-specific clinical efficacy outcome. Complete case analysis was done by excluding participants with incomplete responses. Some participant data were collected retrospectively in India and Uganda because of delayed in-country approvals. A sensitivity analysis excluding retrospectively collected data was done to identify the potential impact of recall bias. We also tested whether a change in the catastrophic expenditure threshold would affect the results. This trial is registered with ISRCTN, ISRCTN18148631.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, except that Janssen Pharmaceuticals provided a consultancy service upon request of the sponsor in relation to bedaquiline, the eligibility criteria, safety investigations, and the pharmacokinetic component to fulfil the regulatory requirements of the trial.

Results

All except two participants enrolled in the clinical trial in the four countries provided written informed consent and health economic data. Only eight participants in Moldova and nine participants in Uganda were assigned to the 6-month regimen group; because this did not allow for meaningful comparison, analysis of the 6-month regimen was not done in these two countries. 300 participants were included in the economic analyses (Ethiopia, 61; India, 142; Moldova, 51; Uganda, 46). Participant characteristics and socioeconomic status at baseline are detailed in table 1.

Participant total direct costs were lower in the oral regimen group than in the control regimen group across all countries, apart from Uganda. Within direct costs, supplementary food was the main cost driver, with participants in the control regimen group spending more on supplements than those in the oral regimen group in Ethiopia, India, and Moldova, with the opposite finding in Uganda (tables 2, 3). Indirect participant costs were lower in the oral regimen group than the control group in Moldova and Uganda, and higher in the oral regimen group than the control group in Ethiopia and India. Total participant costs were lower in the oral regimen group than the control group in Moldova and Uganda, and higher in the oral regimen group than the control group in Ethiopia and India. Supplementary food expenditure was the main direct cost driver in the 6-month regimen group. Participants in the 6-month regimen group spent less on direct costs than those in the control group in both Ethiopia and India; the difference was statistically significant in India. Indirect participant costs were also lower for participants in the 6-month regimen group than in the control group in both countries. The proportion of

	Ethiopia				India				Moldova*			Uganda†		
	Control (n=21)	Oral (n=20)	6-month (n=20)	Total (n=61)	Control (n=46)	Oral (n=48)	6-month (n=48)	Total (n=142)‡	Control (n=25)	Oral (n=26)	Total (n=51)	Control (n=22)	Oral (n=24)	Total (n=46)‡
Sex														
Male	10 (48%)	11 (55%)	9 (45%)	30 (49%)	29 (63%)	16 (33%)	35 (73%)	80 (56%)	20 (80%)	19 (73%)	39 (76%)	13 (59%)	14 (58%)	27 (59%)
Female	11 (52%)	9 (45%)	11 (55%)	31 (51%)	17 (37%)	32 (67%)	13 (27%)	62 (44%)	5 (20%)	7 (27%)	12 (24%)	9 (41%)	10 (42%)	19 (41%)
Age (years)	29 (8.3)	31 (10.1)	28 (7.9)	29 (8.8)	35 (12.6)	38 (12.1)	36 (13.7)	36 (12.8)	40 (11.4)	38 (10.2)	39 (10.7)	35 (9.9)	33 (10.6)	34 (10.3)
HIV positive	0	2 (10%)	1 (5%)	3 (5%)	0	0	0	0	0	0	0	8 (36%)	9 (38%)	17 (37%)
Highest education level														
Illiterate	2 (10%)	2 (10%)	3 (15%)	7 (11%)	7 (15%)	9 (19%)	8 (17%)	24 (17%)	0	0	0	1 (5%)	0	1 (2%)
Primary	4 (19%)	4 (20%)	5 (25%)	13 (21%)	11 (24%)	19 (40%)	9 (19%)	39 (27%)	3 (12%)	2 (8%)	5 (10%)	11 (50%)	10 (42%)	21 (46%)
Secondary	7 (33%)	7 (35%)	8 (40%)	22 (36%)	21 (46%)	18 (38%)	22 (46%)	61 (43%)	19 (76%)	20 (77%)	39 (76%)	6 (27%)	12 (50%)	18 (39%)
Graduate	8 (38%)	7 (35%)	4 (20%)	19 (31%)	7 (15%)	2 (4%)	9 (19%)	18 (13%)	3 (12%)	4 (15%)	7 (14%)	4 (18%)	2 (8%)	6 (13%)
Primary income earner	8 (38%)	10 (50%)	11 (55%)	29 (48%)	18 (39%)	25 (52%)	23 (48%)	66 (46%)	17 (68%)	13 (50%)	30 (59%)	14 (64%)	16 (67%)	30 (65%)

Data are n (%) or mean (SD). *Only eight participants were assigned to the 6-month regimen group; because this did not allow for meaningful comparison, no analysis of the 6-month regimen was done in Moldova. †Only nine participants were assigned to the 6-month regimen group; because this did not allow for meaningful comparison, no analysis of the 6-month regimen was done in Uganda. ‡Total number of participants included in India and Uganda is lower than the number of participants included in the clinical analysis. For logistical reasons, data collection for the health economic component was delayed in India and by the time we started participant interviews, one participant in the control group had died. In Uganda, one participant in the oral regimen group was younger than 18 years at the time of the interview, and thus excluded from our analysis.

Table 1: Participant characteristics and socioeconomic status at baseline

	Ethiopia						India					
	Control, mean*	Control, %†	Oral, mean*	Oral, %†	6-month, mean*	6-month, %†	Control, mean*	Control, %†	Oral, mean*	Oral, %†	6-month, mean*	6-month, %†
Direct costs (US\$)												
Directly observed treatment cost‡	2.5 (0.37–4.53)	0.2%	2.2 (0.44–3.89)	0.1%	2.3 (0.39–4.25)	0.3%	11.6 (7.46–14.91)	0.8%	11.6 (7.64–15.13)	0.8%	8.6 (6.82–10.40)	0.7%
Assessment visit cost	19.8 (12.16–25.77)	1.2%	20.3 (14.12–26.39)	0.9%	39.6 (0.64–78.52)	4.4%	52.1 (42.22–61.99)	3.6%	56.2 (45.52–66.88)	3.9%	37.1 (30.70–43.40)	2.9%
Guardian cost	0.3 (0.00–0.73)	0	0.6 (0.00–1.21)	0	0.3 (0.00–0.66)	0	4.4 (1.56–7.22)	0.3%	4.1 (1.93–6.28)	0.3%	2.3 (0.96–3.65)	0.2%
Supplementary food	155.4 (71.52–239.27)	9.8%	133.0 (72.22–192.26)	5.9%	95.9 (31.80–160.01)	10.7%	224.2 (191.51–256.93)	15.7%	199.9 (167.60–232.20)	13.8%	186.4 (158.12–214.63)	14.4%
Total direct costs (US\$)	178.0 (85.76–262.55)	11.2%	156.1 (89.51–216.69)	6.9%	138.1 (37.43–234.09)	15.5%	292.3 (2.48–80.312.64)	20.5%	271.8 (233.08–287.34)	18.7%	234.3 (196.44–255.02)	18.1%
Total indirect costs (US\$)	1408.9 (110.32–2702.64)	88.8%	2091.7 (891.34–3292.15)	93.1%	755.6 (420.31–1090.83)	84.5%	1135.5 (811.68–1459.19)	79.5%	1179.9 (823.10–1536.58)	81.3%	1059.2 (656.28–1462.20)	81.9%
Total participant cost (US\$)	1586.9	100%	2247.8	100%	893.7	100%	1427.8	100%	1451.7	100%	1293.6	100%
Incurred catastrophic costs (n)	17	81.0%	19	95.0%	18	90.0%	41	89.1%	40	83.3%	40	83.3%
p value (oral or 6-month costs vs control costs)												
Direct costs	NA	NA	0.68	NA	0.54	NA	NA	NA	0.33	NA	0.0098\$	NA
Indirect costs	NA	NA	0.43	NA	0.33	NA	NA	NA	0.84	NA	0.77	NA

Table 2: Participant direct, indirect, total, and catastrophic costs for each regimen (baseline to week 76), in Ethiopia and India

participants facing catastrophic costs within the trial was high (81% or more) in all regimen groups and countries (tables 2, 3).

Total provider cost was higher in the oral regimen group than the control group in all countries (figure 1; appendix pp 16–17; for unit costs used see appendix pp 18–22). The difference in mean total cost per participant in the oral and control regimen groups (oral minus control) was \$538.1 (95% CI 419.5–656.8, $p < 0.0001$) in Ethiopia, \$205.9 (102.0–309.1, $p < 0.0001$) in India, \$234.0 (187.0–653.7, $p = 0.27$) in Moldova, and \$725.4 (336.7–1113.3, $p = 0.00070$) in Uganda. There were some provider cost savings in outpatient visit and staff cost categories in the oral regimen group compared with the control group, but these did not offset the higher regimen medication costs in the oral regimen group. Moreover, in terms of monitoring tests, the major cost drivers were laboratory tests required for monitoring both oral and injectable-containing regimens; the injectable-regimen-specific monitoring tests were not a major cost driver (appendix pp 11, 20–21). In the clinical trial, there were more participants reporting hearing loss as a serious adverse event in the control group than in the oral regimen group. Hearing loss serious adverse events were estimated to cost \$34.6 per participant, so the oral regimen would still be costlier (appendix p 10). A full course of bedaquiline in the oral regimen group accounted for 15% of total provider cost in Ethiopia, 26% in India, 15% in Moldova, and 9% in Uganda (appendix pp 16–17). Duration of inpatient stay varied widely across the four countries (from 10.7 days to 125.0 days) and regimens (30 days to 59 days) with correspondingly variable inpatient stay costs (appendix p 22). Total provider cost was lower in the 6-month regimen group than the control group in both Ethiopia and India. The difference in mean total cost per participant treated (6-month minus control) was -\$291.0 (95% CI -189.6 to -391.9, $p < 0.0001$) in Ethiopia and -\$47.7 (-135.9 to 38.7, $p = 0.27$) in India. Outpatient visit, staff, and monitoring test costs were lower, while regimen medication costs were higher, in the 6-month regimen group versus the control regimen group (appendix pp 16–17).

Mean incremental QALYs were not adjusted for baseline differences, because no such differences were found.²⁰ Compared with the control regimen, the oral regimen was associated with more mean QALYs over the 76 weeks of follow-up in Moldova (0.92 vs 0.96, $p = 0.28$), fewer QALYs in India (0.76 vs 0.74, $p = 0.72$) and Uganda (0.73 vs 0.69, $p = 0.19$), and the same QALYs in Ethiopia (0.90 vs 0.90, $p = 0.69$). Compared with the control regimen, the 6-month regimen resulted in the same QALYs in Ethiopia (0.90 vs 0.90, $p = 0.75$) and more QALYs in India (0.76 vs 0.79, $p = 0.29$; table 4). Across all trial sites, a pooled favourable outcome was achieved by 162 (83%) of 196 participants in the oral regimen group, 122 (91%) of 134 participants in the 6-month regimen group,

	Moldova				Uganda			
	Control, mean*	Control, %†	Oral, mean*	Oral, %†	Control, mean*	Control, %†	Oral, mean*	Oral, %†
Direct costs (US\$)								
Directly observed treatment cost‡	4.3 (1.67–7.01)	0	4.0 (0.00–8.12)	0.1%	6.1 (3.27–8.86)	0.2%	11.0 (7.17–14.80)	0.5%
Assessment visit cost	62.7 (35.25–90.10)	0.5%	72.8 (52.64–92.90)	1.0%	104.1 (85.55–122.66)§	3.7%	117.0 (102.26–131.81)§	5.4%
Guardian cost	0	0	0	0	0.9 (0.00–2.00)	0	1.6 (0.00–4.06)	0.1%
Supplementary food	75.4 (36.41–114.34)	0.6%	39.7 (0.00–79.66)	0.6%	101.2 (81.26–121.06)	3.6%	117.6 (78.82–156.31)	5.4%
Total direct costs (US\$)	142.3 (100.90–183.87)	1.2%	116.4 (72.77–160.14)	1.6%	212.2 (187.35–224.86)	7.6%	247.3 (197.99–274.47)	11.4%
Total indirect costs (US\$)	11 516.3 (6069.33–16 963.18)	98.8%	6 942.7 (3817.36–10 068.14)	98.4%	2 575.3 (1641.32–3 509.40)	92.4%	1 928.9 (942.26–2 915.61)	88.6%
Total participant cost (US\$)	11 658.6	100%	7 059.1	100%	2 787.5	100%	2 176.2	100%
Incurring catastrophic costs (n)	23	92.0%	25	96.2%	21	95.5%	20	83.3%
p value (oral or 6-month costs vs control costs)								
Direct costs	NA	NA	0.38	NA	NA	NA	0.16	NA
Indirect costs	NA	NA	0.14	NA	NA	NA	0.30	NA

NA=not applicable. *Data are mean (95% CI), apart from in rows showing incurred catastrophic costs (number) and p values. †As a percentage of total costs. ‡Costs of directly observed treatment comprised transport and food, and for a very small number of participants (n=12) in India, a fee to get the injectable treatment at private facilities during weekends when public facilities were closed. For the rest of the participants treatment was free. §Because recruitment catchment area was extended towards the end of the trial, more participants in the all-oral group were living further from the hospital, having to use a means of transport for attending participant follow-up visits, on average, for an additional 12 minutes compared with the control group. Because this difference was not related to the treatment allocation, we used pooled mean transport costs for both regimens to calculate total assessment visit costs. The difference in cost is given by the different number of visits and food purchases on the day.

Table 3: Participant direct, indirect, total, and catastrophic costs for each regimen (baseline to week 76), in Moldova and Uganda

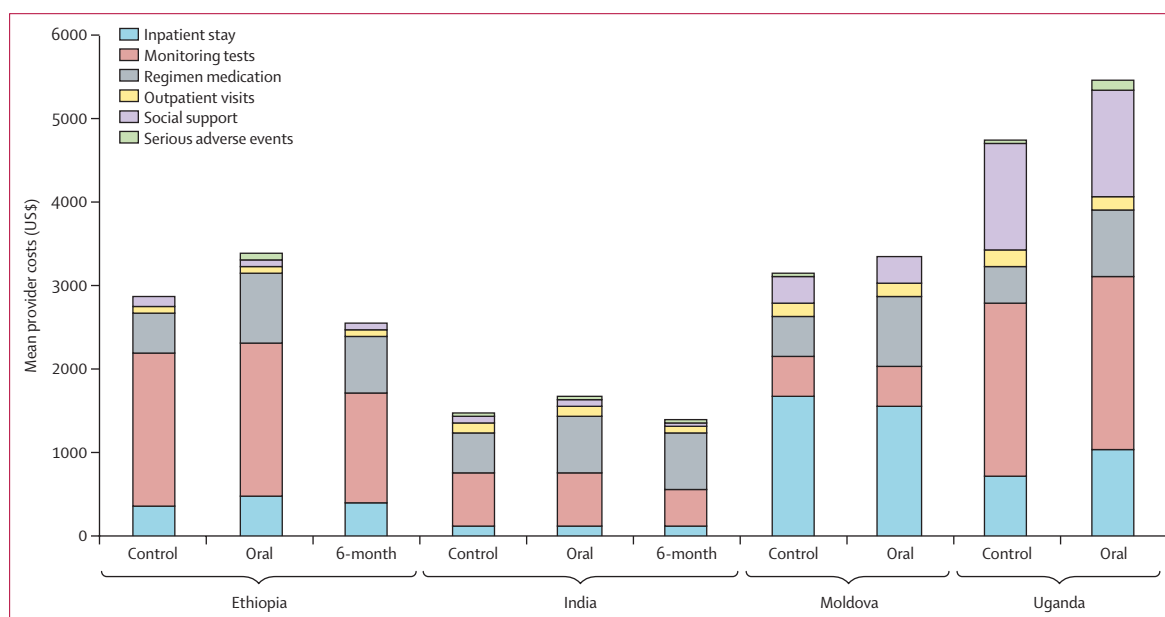


Figure 1: Mean provider costs by regimen, cost category, and country

and 133 (71%) of 187 participants in the control regimen group. The oral regimen was superior in efficacy to the control regimen.⁷

From the provider perspective, the oral regimen resulted in higher provider costs and the same or lower QALYs in Ethiopia, India, and Uganda, meaning that it is not cost-effective, and the control regimen dominates (table 4 and figure 2A). In Moldova, the oral regimen cost

more and resulted in more QALYs; however, the ICER (\$5965) exceeds the upper bound of the Moldovan WTP threshold of \$2400 per QALY, and the cost-effectiveness acceptability curve does not meet the 80% threshold within the WTP range tested, thus suggesting that the oral regimen is not cost-effective in Moldova (table 4 and figure 2A). Adoption of a societal perspective does not change the results for Ethiopia, India, and Uganda,

	Total costs by perspective (US\$) and QALYs				Interpretation	
	Provider	Participant	Societal	QALYs	Provider	Societal
Ethiopia						
Oral	3378.1	2247.8	5625.9	0.8981
6-month	2549.0	893.7	3442.7	0.9002
Control	2876.6	1586.9	4463.5	0.9050
Difference: control vs oral	501.5	660.9	1162.4	-0.0068	Control dominant (costs less and yields more QALYs)	Control dominant (costs less and yields more QALYs)
Difference: control vs 6-month	-327.6	-693.2	-1020.8	-0.0047	6-month costs less and yields slightly fewer QALYs; ICER vs WTP: \$68 530.6 vs \$686, 6-month is considered cost-effective because the magnitude of the cost-saving is large, whereas the magnitude of the QALY reduction is very small (bottom-left quadrant of the cost-effectiveness plane)	6-month costs less and yields slightly fewer QALYs; ICER vs WTP: \$205 818.5 vs \$686, 6-month is considered cost-effective because the magnitude of the cost-saving is large, whereas the magnitude of the QALY reduction is very small (bottom-left quadrant of the cost-effectiveness plane)
India						
Oral	1628.0	1451.7	3079.7	0.7439
6-month	1374.7	1293.6	2668.0	0.7932
Control	1422.1	1427.8	2849.9	0.7644
Difference: control vs oral	205.9	23.9	229.8	-0.0205	Control dominant (costs less and yields more QALYs)	Control dominant (costs less and yields more QALYs)
Difference: control vs 6-month	-47.4	-134.2	-181.9	0.0288	6-month dominant (costs less and yields more QALYs)	6-month dominant (costs less and yields more QALYs)
Moldova						
Oral	3362.9	7059.1	10 422.0	0.9627
Control	3128.9	11 658.6	14 787.5	0.9235
Difference: control vs oral	234.0	-4599.5	-4365.5	0.0392	Oral costs more and yields more QALYs; ICER vs WTP: \$5965.5 vs \$2400, hence oral unlikely to be cost-effective	Oral dominant (costs less and yields more QALYs)
Uganda						
Oral	5437.9	2176.2	7614.1	0.6937
Control	4712.5	2787.5	7500.0	0.7343
Difference: control vs oral	-725.4	-611.3	-114.1	-0.0406	Control dominant (costs less and yields more QALYs)	Control dominant (costs less and yields more QALYs)

ICER=incremental cost-effectiveness ratio. QALYs=quality-adjusted life-years. WTP=willingness-to-pay.

Table 4: Provider costs, QALYs, ICERs, and interpretation against WTP threshold by country, regimen, and perspective

because the oral regimen still results in higher costs and the same or lower QALYs than the control regimen in these countries (table 4 and figure 2C). However, in Moldova, the oral regimen results in lower societal costs (because of substantially lower participant costs) and higher QALYs, making the oral regimen dominant and cost-effective (table 4 and figure 2C).

From the provider-perspective cost-effectiveness analysis, the oral regimen has a high (80%) probability of being cost-effective compared with the control regimen if the WTP thresholds for each additional favourable outcome are more than \$4500 in Ethiopia, more than \$1900 in India, more than \$3950 in Moldova, and more than \$7900 in Uganda (figure 2B). From a societal perspective, the WTP thresholds must exceed \$15 900 in Ethiopia, \$3150 in India, and \$4350 in Uganda for the oral regimen to have a high probability of being cost-effective (figure 2D). In Moldova, the oral regimen results in lower costs and additional favourable outcomes versus the control regimen, so it is dominant and cost-effective.

In Ethiopia, the 6-month regimen had lower provider and societal costs and very similar QALYs versus the

control regimen. There is a high probability that the 6-month regimen is cost-effective against published Ethiopian threshold estimates of \$686 per QALY. In India, the 6-month regimen also resulted in lower provider and societal costs, and higher QALYs, making it dominant and cost-effective (table 4, figure 3A, C). The 6-month regimen had more favourable outcomes than the control regimen in both Ethiopia and India, making the 6-month regimen dominant and cost-effective from both perspectives (figure 3B, D).

Results were sensitive to the cost of bedaquiline. A reduction in the price per 200 mg pill from \$1.81 to \$1.00 (appendix pp 25–26) would make the oral regimen cost-effective in India (ICER \$1018 < WTP threshold \$2781) and Moldova (ICER \$517 < WTP threshold \$2400) from a provider-perspective cost-utility analysis. Making the same change to bedaquiline pricing, the cost-effectiveness analysis shows that the oral regimen would dominate the control regimen in India from a provider perspective and have a high probability of being cost-effective from a societal perspective. The oral regimen would also have a high probability of being cost-effective in Moldova from the provider perspective (and become

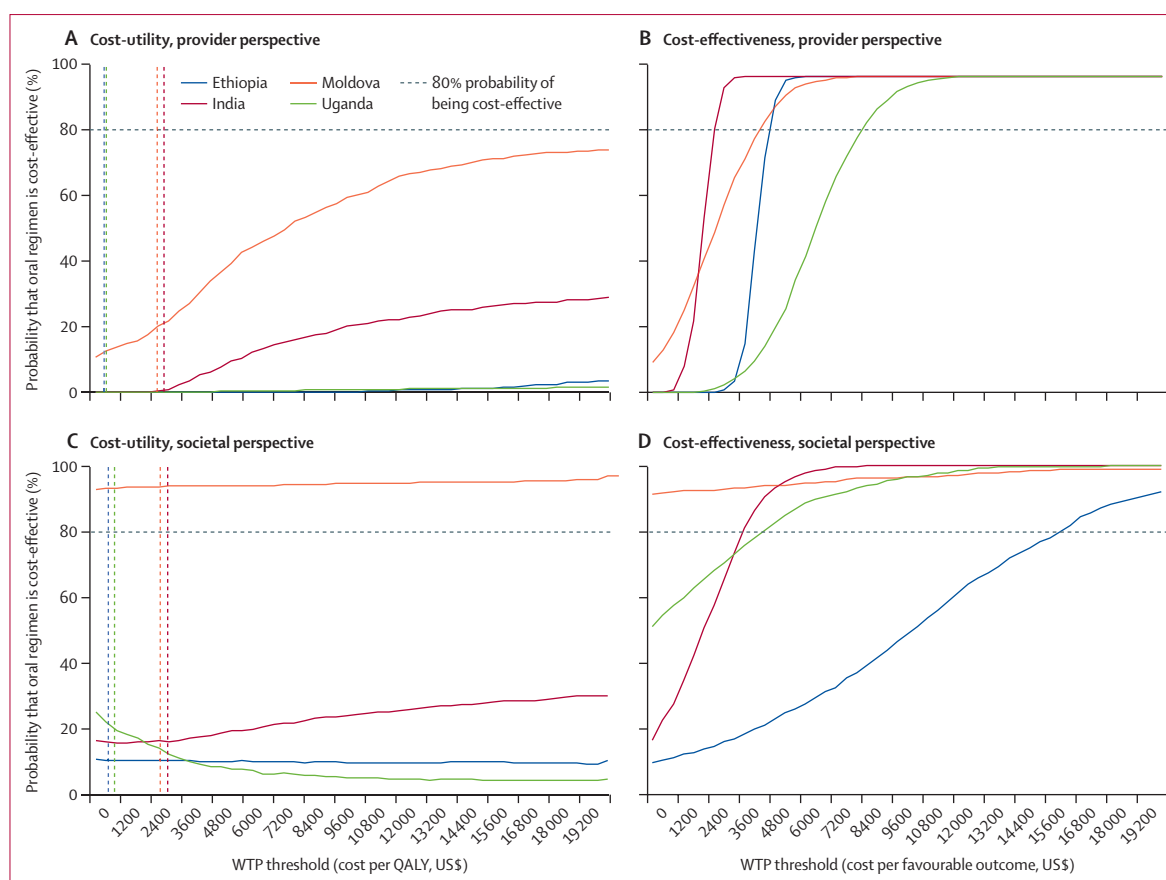


Figure 2: Cost-effectiveness acceptability curves from the economic evaluation of the oral regimen versus control regimen

The solid lines plot country-specific cost-effectiveness or cost-utility probabilities as derived from our 1000 bootstrapped estimates of mean incremental costs and effects for the oral regimen compared with the control regimen. To aid interpretation, the horizontal dashed black line on each panel illustrates our (arbitrary) threshold of 80% that we deem a high probability of being cost-effective. In the cost-utility analysis panels (A and C), empirically derived, country-level WTP per QALY thresholds from the literature¹⁹ are shown using vertical-dashed blue (Ethiopia, US\$686 per QALY), red (India, \$2781 per QALY), orange (Moldova, \$2400 per QALY), and green (Uganda \$725 per QALY). Decision makers may have their own thresholds for both uncertainty and WTP. In the cost-effectiveness analysis panels (B and D), since favourable outcome as used in this study is not a standard health outcome, there are no available published thresholds to present, and instead we report the value where the cost-effectiveness estimates cross the 80% probability threshold. (A) The probability does not exceed 80% in any country for any WTP per QALY threshold, hence the oral regimen is not cost-effective. (B) The probability exceeds 80% for WTP per additional favourable outcome thresholds of more than \$4500 in Ethiopia, more than \$1900 in India, more than \$3950 in Moldova, and more than \$7900 in Uganda. (C) The probability exceeds 80% in Moldova for all WTP per QALY thresholds, hence the oral regimen is considered cost-effective. In Ethiopia, India, or Uganda, the probability does not exceed 80% for any WTP per QALY threshold, hence the oral regimen is not cost-effective. (D) The probability exceeds 80% for WTP per additional favourable outcome thresholds of more than \$15 900 in Ethiopia, more than \$3150 in India, and more than \$4350 in Uganda. In Moldova, the probability exceeds 80% for all WTP thresholds. WTP=willingness-to-pay. QALY=quality-adjusted life-year.

more attractive). The 6-month regimen would be even more attractive in relation to the WTP thresholds (appendix pp 25–26).

When the country-specific efficacy outcome (instead of the pooled estimates) was used in the provider-perspective cost-effectiveness analysis, the ICERs decreased in India, Moldova, and Uganda, suggesting that the oral regimen became more attractive than in the base case. In the societal-perspective analysis, the oral regimen remained dominant in Moldova, while the ICERs decreased in Uganda and increased in India. In Ethiopia, from either perspective, the ICERs increased, making the oral regimen less attractive than in the base case (appendix pp 25–26). The 6-month regimen would

continue being dominant (and cost-effective) in both Ethiopia and India.

The proportion of participants who provided complete data was 48 (79%) of 61 in Ethiopia, 139 (98%) of 142 in India, 51 (100%) of 51 in Moldova, and 43 (93%) of 46 in Uganda. Using complete case analysis, the mean cost per participant increased overall, but this had no effect on the cost-utility conclusions (appendix pp 25–26). Results remained robust to exclusion of retrospectively collected data in India and Uganda, and an increase of up to \$150 per participant to treat adverse events (while mean cost per participant to treat a serious adverse event was \$18). A high proportion of participants (69% or higher) still had catastrophic costs when the catastrophic

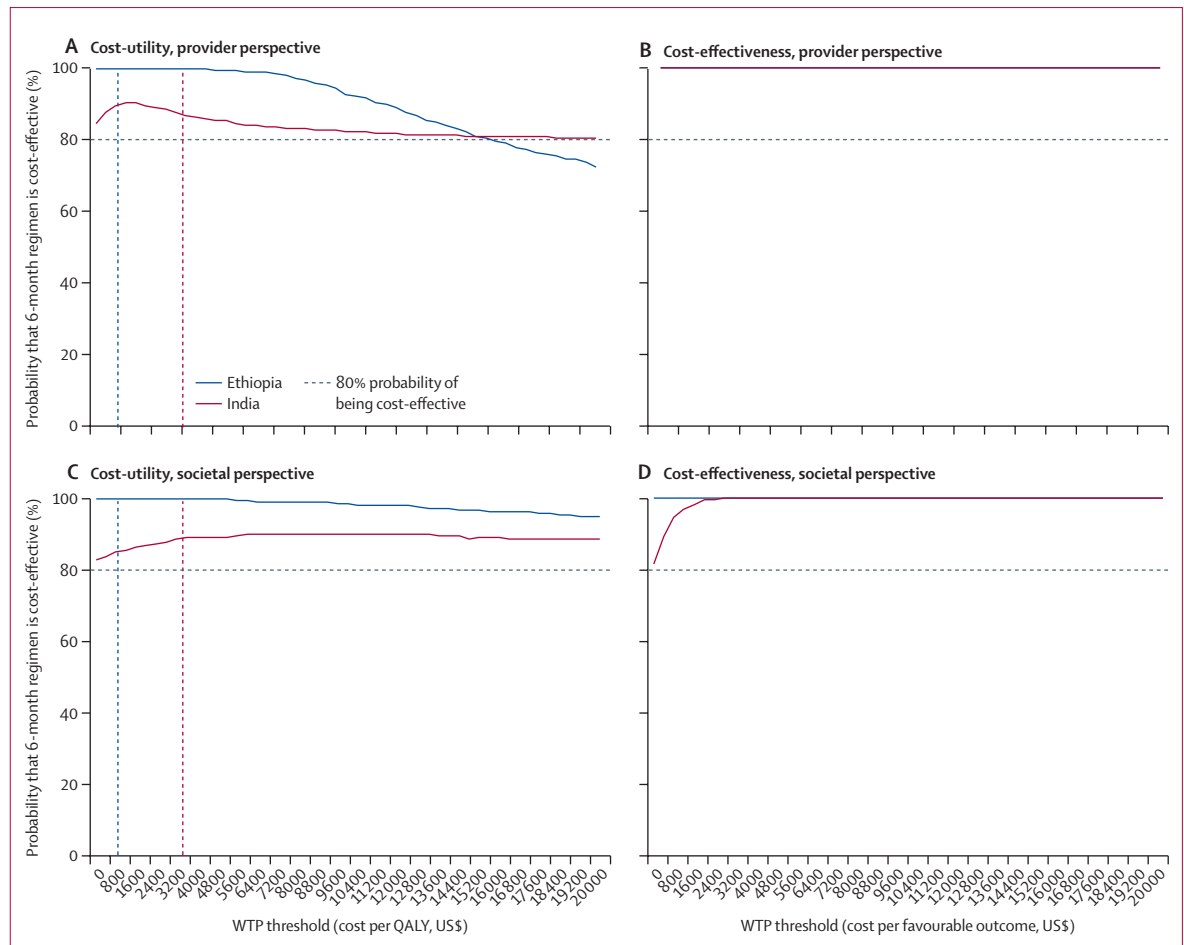


Figure 3: Cost-effectiveness acceptability curves from the economic evaluation of the 6-month regimen versus control regimen

The solid lines plot country-specific (insufficient data for comparison in Moldova and Uganda) cost-effectiveness or cost-utility probabilities as derived from our 1000 bootstrapped estimates of mean incremental costs and effects for the 6-month regimen compared with the control regimen. To aid interpretation, the horizontal dashed black line on each panel illustrates our (arbitrary) threshold of 80%, which we deem a high probability of being cost-effective. Decision makers may have their own threshold. In the cost-utility analysis panels (A and C), empirically derived, country-level WTP per QALY thresholds from the literature¹⁹ are shown using vertical-dashed blue (Ethiopia, US\$686 per QALY) and red (India, \$2781 per QALY). Decision makers may have their own thresholds for both uncertainty and WTP. In the cost-effectiveness analysis panels (B and D), since favourable outcome as used in this study is not a standard health outcome, there are no available published thresholds to present and instead, we report the value where the cost-effectiveness estimates cross the 80% probability threshold. (A, C) In Ethiopia, the probability exceeds 80% at the empirical WTP per QALY threshold of \$686 and up to \$15 600, hence the 6-month regimen is cost-effective within that WTP range. In India, the probability exceeds 80% at the empirical WTP per QALY threshold of \$2781 and up to more than \$20 000, hence the 6-month regimen is cost-effective within that WTP range. (B, D) In Ethiopia and India, the probability exceeds 80% for all WTP per additional favourable outcome threshold values, hence the 6-month regimen is cost-effective. Note, in B, lines are directly on top of each other, so only one can be seen. WTP=willingness-to-pay. QALY=quality-adjusted life-year.

expenditure threshold was increased from 20% to 60% of participants' individual income (appendix pp 27–28).

Discussion

This within-trial economic evaluation compared an oral regimen for the treatment of rifampicin-resistant tuberculosis, as recommended by WHO in 2020, with an injectable-containing regimen (control) in widespread use when STREAM stage 2 began in 2016. The results of the provider-perspective cost-utility analysis showed that the ICERs exceeded realistic WTP per additional QALY thresholds in all countries. These findings were upheld in the societal-perspective analysis, except in Moldova, where the oral regimen was cost-effective from a societal

perspective. The trial endpoint (favourable outcome) used in the cost-effectiveness analysis is difficult to interpret because of the absence of any revealed WTP data on it, and difficult to meaningfully compare with other outcomes (because of practical challenges in calculating the costs and consequences of favourable or unfavourable outcome). Nevertheless, it seems unlikely that country tuberculosis programmes would be willing to pay the amounts estimated by our bootstrap analysis (ie, for the oral regimen to have a probability $\geq 80\%$ of being cost-effective), which ranged from \$1900 to \$7900 per additional favourable outcome. In the two countries (Ethiopia and India) for which we had data to make a comparison, we found that treating rifampicin-resistant

tuberculosis with the 6-month regimen is highly likely to be cost-effective, regardless of economic evaluation method or perspective.

Bedaquiline costs were an important cost driver in the oral regimen, accounting for 15% of total provider costs in Ethiopia and Moldova, 26% in India, and 9% in Uganda. Importantly, sensitivity analyses showed that a reduction in bedaquiline costs would make the oral regimen cost-effective in India and Moldova (though not in Ethiopia and Uganda) in the provider-perspective cost-utility analysis, and highly likely to be cost-effective in Moldova and dominant in India in the provider-perspective cost-effectiveness analysis. For the 6-month regimen, the bedaquiline costs were offset because the shorter treatment duration resulted in lower provider costs overall.

Although the empirically derived WTP per QALY threshold estimates used (from 2013) might be different today,¹⁹ both sets of economic evaluation results were presented together with the cost-effectiveness acceptability curves to allow for interpretation across a range of possible thresholds. Decision makers are encouraged to consider their outcomes of interest (QALYs or improved efficacy), WTP, and how sure they want to be about the decision, alongside additional factors (not captured within this economic evaluation), such as patient and community perceptions about injectables, to make context-specific decisions on which regimens to implement within a transparent decision-making process.^{21,22}

Given the importance of patient-centred care in tuberculosis, a key strength of the STREAM trial is that we collected health-related quality of life data directly from participants in receipt of different regimens, whereas most previous studies have used disability-adjusted life-years or QALY estimates from the literature. This difference compromises our ability to compare our empirical results directly with other economic evaluations; however, our conclusions contrast with most existing studies, which suggest that all-oral regimens are cost-effective or cost-saving when compared with an injectable regimen of the same duration,^{23,24} for the reasons discussed later in this report.

Most previous studies used data from a phase 2b trial, which showed that addition of bedaquiline to an existing treatment regimen for rifampicin-resistant tuberculosis reduced the median time to culture conversion and increased the rate of culture conversion (ie, clinical cure) at 24 weeks compared with the addition of placebo (79% vs 58%, difference 21%).²⁵ Provider and patient costs were then modelled, based on these outcomes, with the proportion of patients achieving culture conversion strongly influencing economic findings. A systematic review indicated that these and other inputs, such as a lower number of patients reporting adverse events, were responsible for the reduced treatment and patient costs in the bedaquiline-containing group. Within STREAM,

we measured the median time to culture conversion, and found no significant differences between regimens; moreover, the difference in the percentage of participants achieving a favourable outcome in control versus oral regimen groups was substantially lower in STREAM (11%) than in the phase 2b trial (21%).^{7,25} We also observed how these clinical outcomes affected costs. Regarding adverse events, in STREAM, there was no suggestion of between-group differences in the proportion of participants who had a serious adverse event, treatment-related serious adverse event, or grade 3 or 4 adverse events.⁷

WHO recommends mainly outpatient rather than inpatient care for patients with rifampicin-resistant tuberculosis, and this model was followed in all our trial sites apart from Moldova.²⁶ Unlike the control regimen, the oral regimen does not require administration of injectable drugs for 112 days, and thus would potentially be more suited to outpatient-based delivery than the control regimen, with potential economic savings and benefits to providers and patients. However, we found that duration of inpatient stay was influenced by the need to monitor severely ill patients and that sites chose their duration of inpatient care according to local circumstances, rather than regimen allocation, suggesting that these economic benefits would not necessarily arise.

Modelling carried out for the WHO 2020 guidelines suggested that injectable-containing regimens carried the additional costs of managing injectable-related adverse events, which would potentially be reduced when moving to an oral regimen, improving cost-effectiveness.⁴ However, we showed that within the monitoring tests, the major cost drivers were laboratory tests required for monitoring both oral and injectable-containing regimens (sputum smear and culture, liver function tests, lactate dehydrogenase, and pancreatic amylase) and that the injectable-regimen-specific monitoring costs (audiometry and renal function) were not a major cost driver.

Ending the tuberculosis epidemic requires the implementation of socioeconomic interventions. Two findings from our study will be useful in designing social protection packages for patients with tuberculosis. First, despite provision of social support payments for all participants, the majority on all regimens had catastrophic costs. Second, supplementary food expenditure was an important participant cost driver. Although supervising clinicians offered the same advice to all participants, those in the control regimen group reported higher supplementary food expenditure across all countries, apart from Uganda, where this is being investigated qualitatively.

Time horizon is crucial in economic evaluations. An insufficiently long time horizon might fail to capture outcomes accurately and lead to biased results; however, modelling a longer time horizon beyond the trial's measured endpoints increases assumptions and uncertainty, indicating a trade-off. The results reported

here cover the period from randomisation to week 76, which includes a 36-week follow-up beyond the treatment end date for the oral and control regimens, and 48-week follow-up for the 6-month regimen. We contend that this time horizon is sufficiently long to have captured any non-trivial between-group differences in costs, treatment outcomes, or treatment-related serious adverse events that would affect patients' health-related quality of life or survival or death rates in the longer term, with one possible exception being hearing loss. Exploring this event from the provider perspective showed that managing the additional hearing loss in the control group would not change our conclusions. We recognise that this analysis does not capture the wider effects of hearing loss on ability to work (and therefore participants' economic outcomes) and plan to conduct further analysis of longer-term costs and outcomes (positive and negative [eg, from serious adverse events]) on participants once follow-up data to week 132 are available. A further potential limitation in relation to hearing loss is that the literature suggests that EQ-5D-3L performs poorly in conditions involving hearing disorders.²⁷ Although we used the (likely more sensitive) EQ-5D-5L, it remains possible that this questionnaire might not have fully captured the benefits of an oral regimen. We have also not included the effect of permanent disability on income beyond week 76. To model this would have required country-specific data on the state of labour markets and levels of participation by individuals after treatment completion who have been in receipt of the alternative treatment regimen, and this was beyond the scope of the current analysis.

Transferability of findings from within-trial economic evaluation, and trials in general, can be challenging. For example, in this study, participants' visits for trial monitoring might have been more frequent than under programmatic conditions, especially for visits after treatment completion, potentially increasing direct costs. However, the number of visits was balanced across trial groups and participant costs for attending the trial assessment visits are less than 5% of the total participant cost, so this is unlikely to have affected the conclusions. Given the trial setting, it is possible that clinicians noted the early signs of some adverse events before evolution into serious adverse events, thus underestimating provider costs expected under routine conditions. Again, this would be balanced across groups. We have tried, wherever possible, to approximate usual care in our analysis, and thus we included trial regimen costs, salvage regimen costs, and additional medication costs that would occur outside the trial setting. In some cases, we used private rather than public facility costs to calculate provider costs; although this is unlikely to affect between-group comparisons, it might overestimate total costs, hence readers are invited to consider the detailed unit costs presented in relation to their own context.

In a May 2022 rapid communication, WHO announced that forthcoming guidelines will include recommendations for programmatic use of a 6-month all-oral regimen and a 9-month all-oral regimen for rifampicin-resistant tuberculosis.¹ Economic evaluation data from clinical trials on these regimens are not in the public domain, but both regimens contain bedaquiline and new drugs (eg, pretomanid), requiring providers to carefully consider these costs when planning implementation.

Rifampicin-resistant tuberculosis is a disease that affects approximately 500 000 people per year. Our results provide robust evidence on the cost-utility and cost-effectiveness of two new rifampicin-resistant tuberculosis regimens under trial conditions and aim to guide uptake and implementation of regimens in-country by providing crucial information on the potential costs, savings, and patient-reported outcomes. These results (and their limitations) indicate that further work is needed to enable cost-effective delivery of 9-month bedaquiline-based regimens, and that the 6-month bedaquiline-based regimen represents a cost-effective alternative—if injectable use for 2 months is acceptable for patients, providers, and policy makers. The results also provide crucial information for use in designing financial protection packages for patients, at a time when the world has recently missed the 2020 milestone of 0% tuberculosis-affected households facing catastrophic costs.

Contributors

LR made a substantial contribution to the conception and design, organisation, and conduct of the study. She supervised data collection in all countries, contributed to data collection, and carried out data cleaning, analysis, and interpretation. She designed the figures and tables, produced the first draft of the manuscript, and incorporated critical feedback and revisions from coauthors. JJM made a substantial contribution to study conception and design, analysis, and interpretation. He also helped with the conduct of the study and critiqued the manuscript for important intellectual content. EMT helped with the conduct of the study in Uganda, interpretation of the overall results, and critiqued the manuscript for important intellectual content. MM, JN, MG, VV, PB, and RD supervised participant data collection and provider costing data at their respective sites in Chennai, Uganda, Ethiopia, Moldova, Delhi, and Ahmedabad, and provided their input when needed. MM also critiqued the manuscript for important intellectual content. AKBa, DM, GN, RS, AKBh, ET, and BK were the principal investigators of the health economic analysis sites and were involved in trial data collection. AKBa, DM, GN, and ET critiqued the manuscript for important intellectual content. SKM is the co-chief investigator of the clinical trial. She made data from the clinical trial available to us, classified the serious adverse events for the health economic analysis, and critiqued the manuscript for important intellectual content. AJN is the co-chief investigator of the clinical trial. He made data from the clinical trial available to us and critiqued the manuscript for important intellectual content. GB contributed to the data interpretation and critiqued the manuscript for important intellectual content. She also helped with the project administration. IDR together with SBS conceived and planned the presented study and were the investigators with most responsibility for securing funding. They both critiqued the manuscript for important intellectual content. SBS made a substantial contribution to the organisation, conduct, and supervision of the study and to data analysis and interpretation. He contributed to drafting the manuscript. EW contributed substantially to the study design, supervised data collection, and contributed substantively to the analysis, data interpretation, and writing of this

manuscript and critiqued it for important intellectual content. All authors have read and approved the final version of the manuscript for submission. MG accessed and verified the data in Ethiopia, MM in India, VV in Moldova, and JN in Uganda. LR accessed and verified the data across all sites. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

LR reports consulting fees from GSK (paid to institution) and support for attending trial-related meetings from Janssen Research & Development and the US Agency for International Development (USAID; paid to institution). JJM reports support for attending meetings or travel from the Liverpool School of Tropical Medicine. EMT reports consulting fees from GSK (paid to institution) and support for attending meetings from USAID (paid to institution). MM, PB, RD, GN, AKBh, BK, SKM, AJN, GB, IDR, and EW report support for attending trial-related meetings from Janssen Research & Development and USAID (paid to institution). ET reports support for attending meetings from USAID (paid to institution). SBS reports a research grant on tuberculosis research (paid to institution) from the UK Foreign & Commonwealth Development Office, support for attending trial-related meetings from Janssen Research & Development and USAID (paid to institution), and is co-chair of the Scientific Working Group on Implementation Research for the Tropical Disease Research Foundation (unpaid). All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available no later than 12 months after the end of the trial via the TBFACT data repository (<https://c-path.org/programs/tb-facts/>). We will provide deidentified participant data, data dictionary, study protocol, a set of blank case record forms, and the informed consent form.

Acknowledgments

STREAM stage 1 was funded by USAID through the Cooperative Agreement GHN-A-00-08-0004-00. Stage 2 of STREAM was jointly funded by USAID and Janssen Research & Development. Additional funding for STREAM was provided by the Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement, which is also part of the EDCTP2 programme supported by the EU.

References

- WHO. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization, 2022.
- Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J* 2014; **43**: 1763–75.
- WHO. Global tuberculosis report 2021. Geneva: World Health Organization, 2021.
- WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment. Drug-resistant tuberculosis treatment. Geneva: World Health Organization, 2020.
- Nunn AJ, Phillips PP, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; **380**: 1201–13.
- Rosu L, Madan J, Worrall E, Tomeny E, Squire B. Economic evaluation protocol of a short, all-oral bedaquiline-containing regimen for the treatment of rifampicin-resistant tuberculosis from the STREAM trial. *BMJ Open* 2020; **10**: e042390.
- Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet* 2022; **400**: 1858–68.
- Tuberculosis Coalition for Technical Assistance. Tool to estimate patients' costs. The Hague and Washington, DC: Tuberculosis Coalition for Technical Assistance and United States Agency for International Development, 2008.
- Hendriks ME, Kundu P, Boers AC, et al. Step-by-step guideline for disease-specific costing studies in low- and middle-income countries: a mixed methodology. *Global Health Action* 2014; **7**: 23573.
- EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208.
- WHO. Tuberculosis patient cost surveys: a handbook. Geneva: World Health Organization, 2017.
- Royston P. Multiple imputations of missing values. *Stata J* 2004; **4**: 227–41.
- WHO. 6.2 National surveys of costs faced by TB patients and their households. <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/uhc-tb-determinants/6-2-national-surveys-of-costs-faced-by-tb-patients-and-their-households> (accessed July 14, 2022).
- Stop TB Partnership. GDF medicines catalogue, 2021. <https://www.stoptb.org/global-drug-facility-gdf/gdf-product-catalog> (accessed July 1, 2022).
- International Monetary Fund. World economic outlook database. March, 2022. <https://data.imf.org/?sk=4FFB52B2-3653-409A-B471-D47B46D904B5> (accessed May 23, 2022).
- Oanda. Currency converter. <https://www.oanda.com/currency-converter/en/> (accessed April 7, 2022).
- Willan AR, Briggs AH. Statistical analysis of cost-effectiveness data. Chichester, UK: John Wiley & Sons, 2006.
- Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ* 2004; **13**: 405–15.
- Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016; **19**: 929–35.
- Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005; **14**: 487–96.
- Bertram MY, Lauer JA, De Joncheere K, et al. Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ* 2016; **94**: 925–30.
- Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost effectiveness in low- and middle-income countries a review of the debates surrounding decision rules. *Pharmacoeconomics* 2009; **27**: 903–17.
- Schnippel K, Firnhaber C, Conradie F, Ndjeka N, Sinanovic E. Incremental cost effectiveness of bedaquiline for the treatment of rifampicin-resistant tuberculosis in South Africa: model-based analysis. *Appl Health Econ Health Policy* 2018; **16**: 43–54.
- Wolfson LJ, Walker A, Hettle R, et al. Cost-effectiveness of adding bedaquiline to drug regimens for the treatment of multidrug-resistant tuberculosis in the UK. *PLoS One* 2015; **10**: e0120763.
- Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371**: 723–32.
- WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization, 2014.
- Yang Y, Longworth L, Brazier J. An assessment of validity and responsiveness of generic measures of health-related quality of life in hearing impairment. *Qual Life Res* 2013; **22**: 2813–28.