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24-week, all-oral regimens for pulmonary rifampicin-resistant tuberculosis in TB-PRACTECAL trial sites: an economic evaluation

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Summary

Background New 6-month rifampicin-resistant tuberculosis treatment regimens containing bedaquiline, pretomanid, and linezolid (BPaL) with or without moxifloxacin or clofazimine, could improve treatment efficacy, safety, and tolerability, and free up resources within the health system. Following a change to WHO rifampicin-resistant tuberculosis treatment guidelines, countries are facing difficult decisions about when and how to incorporate new drug regimens into national guidelines. We aimed to assess the probability of BPaL-based regimens being cost-saving using data collected in the TB-PRACTECAL trial.

Methods This economic evaluation using a cost-utility analysis was embedded in five TB-PRACTECAL trial sites in Belarus, Uzbekistan, and South Africa. Between Nov 19, 2020, and Sept 27, 2022, we collected detailed primary unit cost data in six hospitals and four ambulatory health facilities and collected data on patient-incurred costs from 73 trial participants. The primary efficacy endpoint of the main trial, a composite of unfavourable outcomes (death, disease recurrence, treatment failure, early discontinuation of therapy, withdrawal, or loss to follow-up) and clinically important safety outcomes by 72 weeks of follow-up were incorporated into the analysis. Societal perspective cost data and effect outcome data were input into a Markov model to estimate the cost per disability-adjusted life-year (DALY) averted by BPaL-based regimens compared with the standard of care over a 20-year time horizon. We conducted a range of univariate and probabilistic sensitivity analyses to test our findings.

Findings BPaL-based regimens averted a mean of 1·28 DALYs and saved a mean of US$14 868 (SD 291) per person from the provider perspective compared with standard-of-care regimens over 20 years. Patient-incurred costs were reduced by a mean of $172 (SD 0·84) in BPaL-based regimen groups compared with standard of care. The main cost drivers for both providers and patients were inpatient bed-days; the duration of the inpatient period varied across countries. Varying a range of model parameters affected the degree of cost savings but did not change the finding that BPaL-based regimens are cost-saving compared with standard of care.

Interpretation This trial-based evidence adds to consistent indications from modelling studies that BPaL-based regimens are cost-saving for both the patient and health system. Urgent implementation of BPaL-based regimens in countries with a high burden of tuberculosis could improve treatment of rifampicin-resistant tuberculosis, reduce pill burden, and free up desperately needed resources within the health system.

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Introduction

Tuberculosis that is resistant to antimicrobial drugs is a global concern. Despite recent advances in treatment options, treatment of rifampicin-resistant tuberculosis remains an ongoing challenge. 2024 estimates suggest that only two in five people with rifampicin-resistant tuberculosis globally are started on an appropriate treatment regimen.[1] Of these, only 68% have treatment success.

WHO treatment guidelines for rifampicin-resistant tuberculosis were updated in 2019 to include long, all-oral regimens and shorter, 9-month treatment regimens. In late 2022, these guidelines were updated again to include a conditional recommendation for 6-month, all-oral regimens including bedaquiline, pretomanid, and linezolid (BPaL) with or without the addition of moxifloxacin.[2] This recommendation was informed by promising findings from two clinical trials (ZeNix[3] and TB-PRACTECAL[4]) evaluating the safety and efficacy of drug regimens containing bedaquiline and pretomanid for the treatment of patients with pulmonary rifampicin-resistant tuberculosis. Results from TB-PRACTECAL showed that all three investigative trial groups had better efficacy and safety than the control group.[4]

Research in context

Evidence before this study

Treatment options for tuberculosis that is resistant to rifampicin are rapidly changing. New 6-month regimens containing bedaquiline, pretomanid, and linezolid (BPaL), with or without moxifloxacin or clofazimine, could improve treatment outcomes and reduce pill burden for patients, and free up resources within the health system. TB-PRACTECAL was the first multicountry, randomised, controlled, open label, phase 2/3 trial to evaluate the safety and efficacy of drug regimens containing bedaquiline and pretomanid for the treatment of patients with pulmonary rifampicin-resistant tuberculosis. We searched PubMed for studies published in any language between Jan 1, 2006, and May 8, 2024, using the following search terms: ([bedaquiline AND pretomanid AND linezolid] OR BPaL OR BPaLM OR BPaLC) AND (cost-effectiveness OR cost OR budget impact). We found six modelling studies evaluating the cost-effectiveness and budget impact of regimens based on BPaL for treatment of multidrug-resistant tuberculosis. These modelling studies suggest that BPaL is more effective and less costly than the previous standard of care.

Added value of this study

To our knowledge, this is the first within-trial cost-utility analysis of 6-month BPaL-based regimens for treating rifampicin-resistant tuberculosis using real-world cost and effect data. This cost-utility analysis estimated the incremental cost per disability-adjusted life-year averted by three BPaL-based regimens as implemented in the TB-PRACTECAL trial (BPaL, BPaL plus moxifloxacin, and BPaL plus clofazimine) compared with the current standard of care in each of the trial countries (South Africa, Belarus, and Uzbekistan). We found that all three regimens improve health outcomes and reduce costs compared with the standard-of-care regimens in the trial. Varying parameters in sensitivity analysis changed the degree of cost savings but did not affect our conclusion.

Implications of all the available evidence

These results suggest that programmatic uptake of BPaL-based regimens will be cost saving from both provider and patient perspectives, adding strength to the WHO recommendations including BPaL or BPaL plus moxifloxacin as preferred regimens for the treatment of rifampicin-resistant tuberculosis.

As BPaL-based regimens are recommended for treating rifampicin-resistant tuberculosis, and in the context of persisting high costs for newer drugs, countries are facing difficult decisions about when and how to incorporate new drug regimens into national guidelines. The economic impact of new regimens will be a key consideration in their uptake. We aimed to carry out an economic evaluation substudy of the TB-PRACTECAL randomised control trial. To our knowledge, this is the first within-trial cost-utility analysis of 6-month BPaL-based regimens for treating rifampicin-resistant tuberculosis using real-world cost and effect data.

See Online for appendix 1

Methods

Study design and participants

TB-PRACTECAL was an open-label, phase 2/3, multicentre, randomised, controlled, non-inferiority trial with recruitment from Jan 16, 2017, to March 18, 2021. The design of the TB-PRACTECAL trial is described in detail elsewhere.[5] In brief, the trial evaluated three investigational regimens for rifampicin-resistant tuberculosis. The all-oral 24-week regimens consisted of a backbone of bedaquiline (400 mg daily for 2 weeks followed by 200 mg three times per week for 22 weeks), pretomanid (200 mg daily), and tapered-dose linezolid (600 mg daily for 16 weeks then 300 mg daily for 8 weeks), with or without the addition of moxifloxacin (400 mg; BPaLM) or clofazimine (50–100 mg; BPaLC), against the locally accepted standard of care. Individuals aged 15 years or older with microbially proven rifampicin-resistant pulmonary tuberculosis were eligible for recruitment. The trial was terminated early for benefit in accordance with a recommendation from the independent data and safety monitoring board.[5]

Due to changes in global treatment guidelines for rifampicin-resistant tuberculosis, the locally accepted standard of care changed throughout the course of the trial. Most participants in the standard-of-care group received an all-oral regimen (102 [71%] of 143); regimens received over the course of the trial are shown in appendix 1 (p 1).

This planned economic evaluation substudy was embedded in five TB-PRACTECAL trial sites in Belarus, Uzbekistan, and South Africa. A cost-utility analysis was selected to enable trade-off decisions across different disease areas. Cost-utility of investigative regimens was estimated from a societal perspective, using primary cost data linked to a Markov model. The population for the economic evaluation included study participants who had been randomly assigned and received at least one dose of trial medication, and excluded people who did not have microbiologically proven rifampicin-resistant tuberculosis. We further excluded six participants from the standard-of-care group who crossed over to the BPaLM regimen after trial termination.

The economic evaluation was conducted in line with the health economic analysis protocol.[6] The main trial and economic evaluation substudy were approved by the London School of Hygiene & Tropical Medicine and Médecins Sans Frontières institutional ethics boards as well as local ethics committees and national regulatory authorities in the countries where the trial was conducted. The study was designed and implemented with extensive engagement of communities and patients in each trial

site.[7] We followed recommendations from the CHEERS 2022 statement;[8] a completed CHEERS checklist is in appendix 1 (p 16). Written informed consent was obtained from all participants.

Model design and data collection

Efficacy outcomes were defined in the main trial at 72 weeks after randomisation as: treatment completion or cure, treatment failure, death, early discontinuation, and lost to follow-up after treatment completion. A summary of outcomes for the population included in the economic substudy is shown in table 1. To capture long-term outcomes in the overall trial population, we constructed a Markov model structured to represent progression of the trial cohort through different health states and activities over a time horizon of 20 years (figure 1). The structure of the Markov model was developed following review of the existing literature that used Markov models to estimate the cost-effectiveness of shortened tuberculosis treatment regimens.[9–12] Patients entered the model with active rifampicin-resistant tuberculosis at the point of treatment initiation. At the end of each month, patients could transition to the next month of treatment, lost to follow-up, treatment failure, early discontinuation, or death. Early discontinuation and treatment failure were treated as moving from the assigned regimen to a rescue regimen equivalent to the longer standard-of-care treatment regimen in the country. Outcomes for rescue regimens were estimated from the most recent country-level data.[16] We used the mean actual time to complete treatment to estimate transition probabilities for treatment completion or cure, death, treatment failure, and treatment discontinuation. This was 24 weeks in BPaL-based treatment groups, and 68 weeks in the standard-of-care group (table 2). Loss to follow-up and recurrence after treatment completion were estimated for all participants at 72 weeks. Loss to follow-up was defined as a patient missing appointments after completing treatment and not being traceable until the end of the expected follow-up period; we conservatively assumed that these patients were not durably cured in the base case and tested this assumption in a sensitivity analysis. We assumed a further risk of recurrence in the first 4 years after treatment completion, and an increased risk of recurrence for participants with HIV. Treatment re-entry after recurrence followed national tuberculosis treatment coverage rates. We did not model any potential reduction of onward transmission of tuberculosis due to the short treatment period of 24 weeks. At model entry, age was assumed to be 35 years, which was the mean age of TB-PRACTECAL participants.[5] Key model parameters are listed in table 2. Country-specific parameters used to derive parameters for the model population are listed in appendix 1 (p 2).

Monthly participant and provider costs were incurred for each patient-month spent in each activity state in the model. These costs were parameterised by site using detailed primary cost data. Hospitalisation was a protocol requirement early in the study; most trial participants were hospitalised for an initial period and then treated as outpatients for the remainder of their episode. Ambulatory treatment from day 1 became available later in the study. We distinguished all costs incurred in the inpatient versus outpatient phases of treatment. The duration of the inpatient phase varied by study site, from 1 week in South Africa to 12 weeks in Tashkent.

	Standard-of-care group (n=137)	BPaLM group (n=138*)	BPaLC group (n=115)	BPaL group (n=111)
No unfavourable outcome	81 (59%)	121 (88%)	88 (77%)	96 (87%)
Unfavourable outcome: deaths	5 (4%)	0	1 (1%)	1 (1%)
Unfavourable outcome: early discontinuation	50 (37%)	11 (8%)	11 (10%)	11 (10%)
Adherence issues	11 (8%)	1 (1%)	4 (3%)	3 (3%)
Adverse event	23 (17%)	7 (5%)	6 (5%)	5 (5%)
Not meeting inclusion criteria or meeting exclusion criteria	2 (1%)	1 (1%)	1 (1%)	2 (2%)
Withdrew consent while still on treatment	11 (8%)	1 (1%)	0	1 (1%)
Other reason	3 (2%)	1 (1%)	0	0
Unfavourable outcome: treatment failure	0	0	1 (1%)	0
Unfavourable outcome: lost to follow-up after treatment completion	1 (1%)	4 (3%)	9 (8%)	0
Recurrence after treatment completion	0	1 (1%)	5 (4%)	3 (3%)

Data are n (%). BPaL=bedaquiline, pretomanid, and tapered-dose linezolid. BPaLC=bedaquiline, pretomanid, and tapered-dose linezolid, plus clofazimine. BPaLM=bedaquiline, pretomanid, and tapered-dose linezolid, plus moxifloxacin. *One patient in the BPaLM group had a non-assessable outcome and was not included in this analysis.

Table 1: **Trial outcomes in the economic evaluation population**

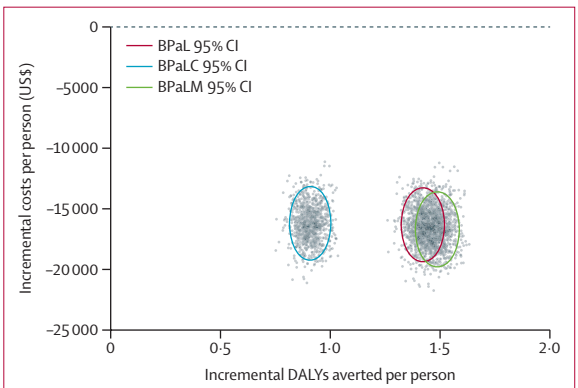


Figure 1: **Incremental cost-utility plane in the Markov model design**
Costs are shown in US dollars. BPaL=bedaquiline, pretomanid, and tapered-dose linezolid. BPaLC=bedaquiline, pretomanid, and tapered-dose linezolid, plus clofazimine. BPaLM=bedaquiline, pretomanid, and tapered-dose linezolid, plus moxifloxacin. DALYs=disability-adjusted life-years.

Participant costs

Collection of cost estimates from the patient perspective began on Nov 19, 2020. Three questionnaires were used to estimate patient-incurred costs and were administered to 52 participants in the intervention groups (BPaL n=13, BPaLC n=12, and BPaLM n=27) and 21 participants in the

	Value	SE	PSA distribution	Reference
Discount rate for costs and outcomes	3·00%	NA	NA	Wilkinson et al (2016)[13]
Annual risk of relapse in year 1 after treatment	2·80%	0·40%	Normal	Marx et al (2014)[14]
Annual risk of relapse in year 2 after treatment	1·00%	0·30%	Normal	Marx et al (2014)[14]
Annual risk of relapse in year 3 after treatment	0·40%	0·20%	Normal	Marx et al (2014)[14]
Annual risk of relapse in year 4 after treatment	0·30%	0·20%	Normal	Marx et al (2014)[14]
Hazard ratio for relapse, HIV-positive	2·4	NA	NA	Naidoo et al (2018)[15]
Return to care after relapse or recurrence	70%	NA	NA	WHO (2022)[16]
Return to care after loss to follow-up	28%	3%	Normal	WHO (2022)[16]
Access to end-of-life care	100%	NA	NA	Assumption
Monthly probability of death for untreated tuberculosis	6·86%	0·69%	β	Franke et al (2008)[17]
Monthly probability of death for end-of-life care	6·86%	0·69%	β	Franke et al (2008)[17]
Actual time to treatment completion in the BPaLM group, weeks	24	NA	NA	TB-PRACTECAL trial result
Actual time to treatment completion in the BPaLC group, weeks	24	NA	NA	TB-PRACTECAL trial result
Actual time to treatment completion in the BPaL group, weeks	24	NA	NA	TB-PRACTECAL trial result
Actual time to treatment completion in the standard-of-care group, weeks	68	NA	NA	TB-PRACTECAL trial result
Proportion of patients in the standard-of-care group on short standard-of-care regimen	37%	NA	NA	TB-PRACTECAL trial result
Proportion of patients in the standard-of-care group on long standard-of-care regimen	63%	NA	NA	TB-PRACTECAL trial result
Rescue regimen outcomes				
Treatment success	70%	NA	NA	WHO (2022)[16]
Died	15%	NA	NA	WHO (2022)[16]
Treatment failure	5%	NA	NA	WHO (2022)[16]
Lost to follow-up	11%	NA	NA	WHO (2022)[16]

BPaL=bedaquiline, pretomanid, and tapered-dose linezolid. BPaLC=bedaquiline, pretomanid, and tapered-dose linezolid, plus clofazimine. BPaLM=bedaquiline, pretomanid, and tapered-dose linezolid, plus moxifloxacin. NA=not applicable. PSA=probabilistic sensitivity analysis.

Table 2: **Model parameters**

control group. The first questionnaire was conducted at recruitment and estimated costs incurred from the onset of symptoms until the start of treatment (n=40). The second and third questionnaires were conducted at 24 weeks (n=53) and 48 weeks (n=70), and were designed to estimate costs incurred during treatment.

Patient costs included out-of-pocket medical expenses (consultation fees and payments for medicines or diagnostics), non-medical expenses (travel, food, special foods and dietary supplements, and interest on loans), and indirect costs (equivalent to the opportunity cost of time spent seeking care). We collected data on costs incurred at the trial site and any other health-care providers, including public health facilities, private clinics, traditional healers, pharmacies, and ambulance services. Most respondents could not report their individual or household incomes, so we estimated the opportunity costs of time using the equivalent average monthly earnings by occupation from International Labour Organization databases.[18] Weekly participant-incurred costs were summarised by site, regimen, and inpatient versus outpatient phase of treatment for inclusion in the Markov model.

Catastrophic cost is defined by WHO as a financial burden above 20% of the household income due to treatment of tuberculosis disease.[19] We estimated catastrophic costs due to tuberculosis incurred by participant households, including any costs incurred before trial enrolment, defined as total participant-incurred costs amounting to more than 20% of annual household income. Due to delays in obtaining ethics approval for patient cost estimation, only 35 patients completed all three questionnaires. Given this small sample size and high variation in patient cost data, we limited our estimation of catastrophic costs to a complete case analysis.

Provider costs

Between Nov 3, 2021, and Sept 27, 2022, we collected the economic, trial-based costs of each service from the provider perspective using an adapted tool for estimating the costs of tuberculosis services.[20] We used a combined bottom-up and top-down approach to derive the costs of outpatient visits, inpatient bed-days, telephone or video consultations, and home visits. Data were collected for five trial sites, including one hospital and one Ministry of Health dispensary in Belarus, two THINK-led sites operating in parallel with public hospitals in South Africa, and three hospitals and three ambulatory facilities in Uzbekistan. Because laboratory and radiology tests were largely decentralised, it was not possible to collect primary data for most of these tests; we therefore derived costs from a combination of sources: Médecins Sans Frontières records, the Value TB study,[21] and micro-costing of

blood sample collection and ophthalmological examination within study sites.

The cost per service output was obtained by multiplying the quantity of each capital input (building, equipment and furniture, vehicles, and training) and recurrent input (staff, supplies, maintenance, utilities, fuel, food, and other recurrent inputs) by its corresponding value. Resource quantities were obtained remotely via telephone and video interviews, self-completed timesheets, data extraction of facility and government documents, and from the TB-PRACTECAL trial database. Resource prices were extracted from study facilities, government or study reports, invoices, or other financial documents. Overhead costs were calculated based on allocation of service use (for building, vehicle, and fuel), building space (for utilities and capital maintenance) or inpatient bed-days (for inpatient food and supplements) for patients in the TB-PRACTECAL trial.

Quantities of outpatient visits and inpatient bed-days for adverse events were estimated using experience from the TB-PRACTECAL trial. Costs of tradeable goods related to treating adverse events (including laboratory tests, investigations, medications, and fluids) were estimated from the literature.[22] Patients who were lost to follow-up were assumed to incur costs of one lost to follow-up tracing call or home visit per month until death or return to care. Costs of death were estimated as the cost of body disposal.[23]

Drug prices were sourced from the Global Drug Facility (GDF) Catalogue for all countries.[24] Drug quantities were estimated using weighted proportions of trial participants receiving each drug, using standard recommended dose for an adult weighing 51–70 kg.

All costs were estimated in 2021 US dollars and capital costs were discounted at a rate of 3% in the base case.[13] All primary cost data were collected in 2021 local currency units, then converted into 2021 US dollars (US$1=BYN2·53, ZAR14·31, or UZS10 600·24). Costs from secondary data sources were inflated to 2021 US dollars using the US Consumer Price Index.[25]

Outcomes

We used disability-adjusted life-years (DALYs) as our primary measure of effectiveness for the incremental cost-utility analysis. DALYs were more appropriate than quality-adjusted life-years (QALYs) for policy decisions in the trial countries because there are no validated value sets for EQ-5D surveys in the trial countries, limiting the validity of any estimate of QALYs. DALYs were estimated as the sum of years of life lost (YLLs) and years of life lived with disability (YLDs). We estimated YLLs using the weighted mean life expectancy at death across the trial population.[26] We estimated YLDs using disability weights for each health state, sourced from the most recent Global Burden of Disease study;[27] all disability weights are specified in appendix 1 (p 3). Following evidence that there is a lifelong health burden after tuberculosis, even in patients with treatment success, we used a disability weight of 0·053 for patients after tuberculosis cure in the base case.[28] We used expert opinion to map symptoms for adverse events grade 3 and above using the Médecins Sans Frontières Tuberculosis severity grading scale[29] to equivalent health states where adverse events were not specified in the Global Burden of Disease database. We used a multiplicative model to generate a combined disability weight for patients with tuberculosis symptoms and adverse events.[30] All outcomes were discounted at 3% in the base case to reflect time preference.[13]

Uncertainty and sensitivity analysis

We conducted a series of univariate sensitivity analyses to evaluate the impact of changing specific key parameters in the analysis. We varied parameters for which there was no empirical measure of real-world variation by plus or minus 20%, including risk of recurrence after treatment completion, costs of drugs, costs of health services, and costs of treating adverse events. We shortened the time horizon for the analysis to 18 months, capturing only costs and outcomes incurred during the trial period. We varied the discount rate from 0% to the maximum real interest rate for all study countries in the past five years (9·8%[31]). Because the lost to follow-up rates at 72 weeks varied across trial groups, we applied the rates at 108 weeks to our analysis and also tested our assumption that all participants who were lost to follow-up after treatment completion were not cured by recoding all treatment completions as treatment success. Finally, we explored the impact of changes in the standard-of-care regimen throughout the trial period by changing costs of all standard-of-care regimens to match shorter, post-2019 standard-of-care regimens.

Parameter uncertainty was assessed in a probabilistic sensitivity analysis, varying all parameters over 1000 simulations. Unit costs were varied using a γ distribution, and all DALY weights were varied following a β distribution.

All analyses were conducted using Stata (version 18).

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

The total and incremental costs and DALYs incurred in each treatment group over the 20-year time horizon of the Markov model are reported in table 3. The three BPaL-based regimens averted a mean of 1·28 DALYs and saved a mean of $172 (SD 0·84) from the patient perspective and $14 868 (SD 291) from the provider perspective compared with standard-of-care regimens. The largest cost savings were seen during the treatment episode. Substantial savings were also seen for rescue treatment following treatment failure or discontinuation, arising

	Standard-of-care group	BPaLM group	BPaLC group	BPaL group
Mean total costs per patient over model time horizon	$31 485	$16 434	$16 982	$16 862
Patient-incurred costs	$495	$324	$322	$323
Provider-incurred costs	$30 990	$16 110	$16 660	$16 539
Tuberculosis drugs costs (initial regimen)	$1688	$740	$825	$707
Non-drugs costs* (initial regimen)	$19 631	$12 448	$12 260	$12 369
Costs of rescue treatment	$9671	$2922	$3575	$3462
Costs of lost to follow-up tracing	$7	$4	$8	$2
Costs of adverse event treatment	$583	$286	$178	$188
Costs of end-of-life care	$897	$272	$333	$322
Costs of death	$11	$5	$8	$6
Mean total DALYs per patient over model time horizon	3·84	2·35	2·93	2·42
Years of life lost	2·55	1·27	1·87	1·34
Years of life lived with disability	1·30	1·08	1·06	1·08
Mean incremental costs per patient	NA	−$15 050	−$14 503	−$14 623
Mean incremental DALYs averted per patient	NA	1·49	0·91	1·42

All costs are in 2021 US dollars. BPaL=bedaquiline, pretomanid, and tapered-dose linezolid. BPaLC=bedaquiline, pretomanid, and tapered-dose linezolid, plus clofazimine. BPaLM=bedaquiline, pretomanid, and tapered-dose linezolid, plus moxifloxacin. DALYs=disability-adjusted life-years. NA=not applicable. *Includes costs of outpatient visits, inpatient bed-days, home visits, telephone calls, and laboratory tests.

Table 3: **Mean total costs and cost-utility model outputs, by treatment group**

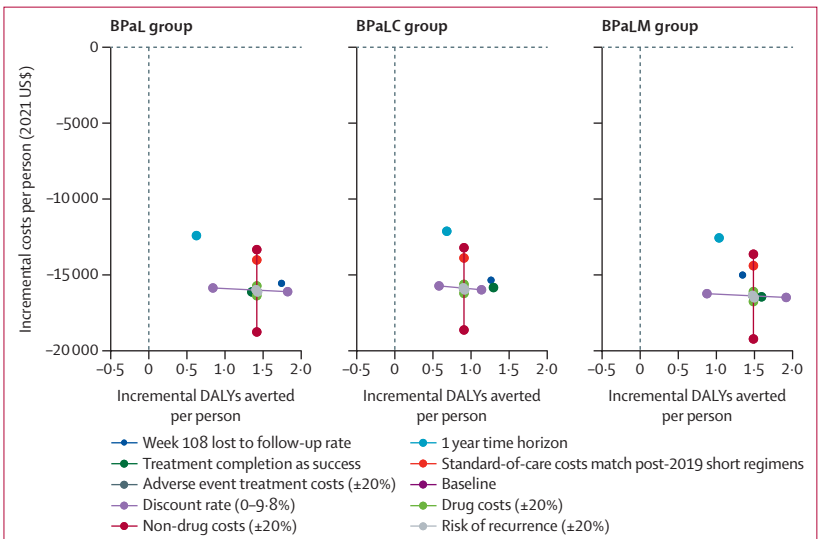


Figure 2: **Probabilistic sensitivity analysis results**
BPaL=bedaquiline, pretomanid, and tapered-dose linezolid. BPaLC=bedaquiline, pretomanid, and tapered-dose linezolid, plus clofazimine. BPaLM=bedaquiline, pretomanid, and tapered-dose linezolid, plus moxifloxacin. DALYs=disability-adjusted life-years.

from the comparatively large number of early discontinuations in the standard-of-care group (table 1).

The total provider-incurred costs during the treatment episode are shown in appendix 1 (pp 4–11). Total costs per treatment episode were higher in Minsk and Nukus, and lower in Tashkent and the facilities in KwaZulu-Natal, South Africa, particularly for the long standard-of-care regimen. Most savings were reduced outpatient visits, inpatient bed-days, home visits, telephone calls, and laboratory and radiology tests (appendix 1 p 8). Minsk and South Africa provided more community-level care (video-observed therapy) and Minsk provided drug delivery, whereas outpatient visits for follow-up were more common in Nukus and Tashkent (appendix 1 pp 8–9). All sites conducted regular laboratory and radiology tests with trial participants to ensure regimen safety as per protocol. Costs for inpatient bed-days were highest in Minsk, driven by large building space allocated to PRACTECAL activities (appendix 1 pp 6–7).

Patients at all sites incurred direct and indirect costs before the start of treatment (appendix 1 pp 10–11). Mean patient-incurred costs during the treatment episode were higher for patients in the standard-of-care group compared with patients in BPaL-based regimen groups, except in Nukus (appendix 1 pp 10–11). The main driver of patient-incurred costs was the duration of the inpatient period (appendix 1 p 10). Slightly more patients in the standard-of-care group than in the BPaL-based regimen groups incurred catastrophic costs (appendix 1 pp 14–15); however, sample sizes were too small to conclude any differences in catastrophic costs based on regimen.

In our probabilistic sensitivity analysis, all model iterations for all BPaL-based regimens showed substantial cost savings and averted DALYs compared with standard-of-care regimens (figure 2). Cost savings for BPaL-based regimens varied from $11 095 to $21 724. The number of DALYs averted by BPaL-based regimens compared with standard-of-care varied from 0·77 to 1·64.

Results of our univariate sensitivity analysis are shown in appendix 1 (p 12). Varying the time horizon of analysis, costs of standard-of-care treatment, choice of discount rate, lost to follow-up rates, and estimates of non-drug costs (including costs of outpatient visits, inpatient bed-days, home visits, telephone calls, and laboratory tests) had an effect on the degree of cost savings but did not affect the overall finding that all BPaL-based regimens are cost-saving compared with the standard of care.

Discussion

This economic evaluation substudy embedded in the TB-PRACTECAL trial found that all three BPaL-based investigative regimens were highly cost-saving and more effective compared with the standard of care. To our knowledge, this is the first study to use real-world cost and effect data to compare BPaL-based regimens against the standard of care regimens in different countries, and substantiates findings from previous modelling analyses suggesting that BPaL-based regimens can provide substantial savings for countries with a high burden of rifampicin-resistant tuberculosis while simultaneously improving health outcomes, and can therefore be considered the dominant treatment approach.[9–12] The

number of DALYs averted varied across regimens in line with the efficacy of the respective regimens.

We found BPaL-based regimens saved a mean of $14868 from the provider perspective compared with standard-of-care regimens over 20 years. These costs were parameterised using detailed unit cost data reflecting actual care provided in each of the three countries. Whether these savings can be realised at the national level, and any additional budget impact of adopting BPaL-based regimens, will depend on the degree to which resources freed up by these regimens (such as staff time) can easily be repurposed to other services. The pace and degree of uptake of these regimens will also depend on barriers to adoption outside of cost.[32]

The generalisability of our results might be limited because within-trial cost and effect estimates might not reflect real-world implementation of the regimens. The trial was patient-centred, with assistance in adherence to treatment adapted to patient circumstances. Study sites provided intensive follow-up and adherence support to participants throughout their treatment episode, and the quantity of services provided to TB-PRACTECAL participants might have been higher than a patient would receive through the national health system. Our estimate of cost savings is therefore higher than that estimated in previous modelling studies.[10–12] Previous modelling analyses using cost and standard-of-care outcome estimates that were more reflective of real-world treatment scenarios showed that BPaL-based regimens remained highly likely to be cost-saving.[9–12,33,34]

Patient-incurred costs were reduced by a mean of $172 in BPaL-based regimen groups, equivalent to a 35% reduction compared with standard-of-care. Due to small sample sizes, we were unable to assess whether these savings were enough to reduce the incidence of catastrophic costs for households affected by tuberculosis. Patients in some trial sites incurred high costs before treatment was started, suggesting that improved case-finding and early initiation of appropriate treatment regimens are important in addition to shortened treatment regimens. Patients in all treatment groups also incurred high indirect costs during their inpatient phase; shifting to a more decentralised treatment approach with reduced inpatient time would be likely to reduce indirect costs to patients.

Our sensitivity analysis showed that varying drug prices by plus or minus 20% had minimal impact on the incremental cost of BPaL-based regimens, partly because many participants in the standard-of-care group were also on regimens including bedaquiline. In this trial setting, all sites were able to purchase bedaquiline at the rate available through the GDF ($340 per bottle of 188 doses). The 2023 announcement that the manufacturer will not pursue patents for bedaquiline in countries with a high tuberculosis burden is a welcome development in tuberculosis drug pricing.[35] Both pretomanid and linezolid have had price reductions in recent years facilitated by the GDF, improving affordability of regimens containing these drugs.

A strength of this analysis is in the detail of the unit cost data collection for most services. There were also several limitations. We were limited in our ability to collect detailed unit costs for laboratory and radiology tests, and therefore used secondary data to fill gaps for these services. Although laboratory and radiology tests made up large proportions of overall provider-incurred costs during the treatment episode, our sensitivity analysis showed that varying these costs did not have a large effect on our overall estimate of cost savings. The sensitivity analysis also showed there was no effect on the overall outcome when the lost to follow-up rates were varied across trial groups; however, no further analysis on the lost to follow-up costs and rates was possible because costs were estimated by site, whereas effects were measured overall for the trial population. Therefore, it was not possible to assign weights to each individual for an inverse probability weighting or other ad hoc analysis.

Recurrence in our trial population was very low despite a lengthy follow-up period; however, there is some concern that long-term use of BPaL-based regimens could contribute to the emergence of drug resistance.[36] Our analysis is limited in that it does not incorporate any transmission effect and therefore doesn't include any long-term emergence of resistance to new drugs or reduced transmission of tuberculosis arising from shortened treatment regimens. A 2024 modelling analysis found that BPaLM remained cost-effective in settings with the proportion of people with rifampicin-resistant tuberculosis that was resistant to fluoroquinolones varying from 0% to 40%,[33] and that BPaLM might result in a small, non-significant reduction in total QALYs compared with the standard of care at lower levels of initial fluoroquinolone resistance. Further research on the emergence of resistance would improve the ability of policy makers to optimise clinical care based on their context.

Our estimation of patient-incurred costs was limited by small patient numbers, as well as delayed recruitment, early termination of the trial, and the decision to continue only one investigational group to stage 2. Challenges posed by the COVID-19 pandemic delayed transition to stage 2, and more than expected information was obtained on BPaLC and BPaL, allowing some assessment of these promising regimens. Methods of data collection also needed to be adapted for the COVID-19 pandemic. Nevertheless, we were unable to estimate the effect of BPaL-based regimens on catastrophic costs. Due to small sample sizes, we were also unable to estimate any distributional effects across different individuals—for example, by socioeconomic status, HIV status, or gender—although the wider trial found no major difference between these subgroups.[4] Further studies should also consider powering for analysis by HIV status,

which could be important in some settings. The trial was not powered to estimate trial outcomes individually by country.

This within-trial cost-utility analysis provides robust evidence that BPaL-based regimens to treat rifampicin-resistant tuberculosis are more effective and cost-saving than the current standard of care. The choice to use a cost-utility methodology allows policy makers to consider the potential benefits of adopting BPaL-based regimens using a generic measure, in this case DALYs, and enables comparison across different health-care interventions. Every year, nearly half a million people are affected by rifampicin-resistant tuberculosis and cost is frequently cited as a barrier to treatment uptake. People with rifampicin-resistant tuberculosis urgently need improved access to better treatment options, and we recommend roll-out of these improved regimens as quickly as possible in settings with a high tuberculosis burden.

Contributors

SS and B-TN conceived the study. B-TN, CB, EK, and IM led the sponsor project management team. SS and YVL led cost data collection and conducted analysis. RM, VS, ZT, IL, and MR were site principal investigators and responsible for participant recruitment and data collection. MPS, RU, GMN, IB, NP, NS, PJ, PSA, SM, and TA assisted with cost data collection and cleaning. MD and KF conducted statistical analysis. SS and YVL accessed and verified the data. The first draft of the report was drafted by SS, YVL, and CB. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors for this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

See Online for appendix 2

Declaration of interests

B-TN, CB, EK, PJ, SM, IM, TA, PSA, and NS were employees of Médecins Sans Frontières during the trial. SS, YVL, MPS, MD, and KF received salary funding paid to the London School of Hygiene & Tropical Medicine. MR was a member of the BPAL Community Access Program data monitoring committee and a member of the BEAT Tuberculosis data monitoring committee. All other authors declare no competing interests.

Data sharing

The sponsor of this trial (Médecins Sans Frontières) intends to make all data publicly available along with related trial documentation. Main trial data are available on the TB-PACTS data sharing platform on request. Data collection tools for the patient cost data are available online from the London School of Hygiene & Tropical Medicine Data Compass on request. De-identified provider and patient-perspective cost data will be made available on the London School of Hygiene & Tropical Medicine Data Compass platform in early 2025.

For the **TB-PACTS platform** see https://c-path.org/tools-platforms/tb-pacts/

For the **Data Compass** see https://datacompass.lshtm.ac.uk/id/eprint/1799/

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