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Original Article

Cost-effectiveness of BPaL/BPaLM as compared to mixed standard of care bedaquiline containing regimen for MDR/RR-TB

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***Background & objectives*: Current options for treating tuberculosis (TB) that is resistant to rifampicin (RR-TB) are limited and available regimens are often lengthy and poorly tolerated. However, following recent evidence from the TB PRACTECAL trial, countries are considering programmatic adoption of six-month, all-oral treatment regimen such as bedaquiline, pretomanid, linezolid (BPaL) and BPaL with moxifloxacin (BPaLM). We conducted an economic evaluation to assess whether the introduction of BPaL/BPaLM regimen under National Tuberculosis Elimination Programme (NTEP) for the treatment of multi-drug resistant (MDR)/RR-TB is a cost-effective strategy. The idea was to estimate the incremental cost incurred from BPaL/BPaLM regimen in comparison with the current mix of standard of care (SoC) regimen.**

***Methods*: We used an economic model comprising a Markov analysis. The study estimated the incremental costs, life years gained and quality adjusted life years (QALYs) gained by the introduction of BPaL/BPaLM regimen for MDR/RR-TB patients. A scenario analysis for different proportions of shorter and longer SoC regimen compared with BPaL/BPaLM was also done. Cost threshold analysis was done to assess the ideal cost at which the drug BPaL/BPaLM turns into cost-saving. Budget impact analysis was conducted to assess the financial implications of adopting BPaL/BPaLM compared to mix SoC, supporting informed decision-making alongside cost-effectiveness analysis for one year.**

***Results*: The base case analysis showed the total discounted costs by health system perspective for the BPaL, BPaLM and the current mixed SoC were INR 2515, INR 2644 and INR 2630 million, respectively. The ICER for BPaL was INR -379 which indicates that we have to spend INR 379 less per patient for BPaL than the mixed SoC to gain one QALY. The ICER for BPaLM was INR 37 which indicates that we have to spend INR 37 additionally per patient for BPaLM than the mixed SoC to gain one QALY.**

***Interpretation & conclusions*: Our findings indicate that BPaL based regimens are likely to be cost-saving and more effective than the current mixed SoC in a range of settings. Countries should consider programmatic uptake of BPaL based regimens to treat MDR/RR-TB.**

Key words Bedaquiline - cost-effectiveness analysis - linezolid - pretomanid - standard of care - tuberculosis - Tuberculosis, multidrug-resistant - quality-adjusted life years

Drug-resistant tuberculosis (TB) is a major public health concern globally, undermining the advances achieved in TB prevention and treatment. It presents a rising public health threat as managing drug-resistant (DR) TB is more complicated than treating drug-sensitive (DS) TB, leading to higher treatment costs and increased complexity[1]. Multi-drug resistant TB (MDR-TB) refers to a form of TB that does not respond to at least two of the first line primary anti TB drugs, namely rifampicin and isoniazid. Pre-extensively drug-resistant TB (XDR-TB) is the TB which shows resistance to rifampicin (MDR/RR-TB) and any fluoroquinolone are detected[2]. XDR-TB is caused due to *Mycobacterium tuberculosis* strains that meet the criteria for MDR/RR-TB and exhibit resistance to at least one Group-A drugs and any fluoroquinolone. The Group-A drugs include moxifloxacin, levofloxacin, bedaquiline and linezolid. These are the most effective second line drugs used to treat MDR-TB with longer duration[3]. The treatment and management of drug resistant-TB are expensive for both the healthcare system and patients, due to extended hospitalisation periods and the higher cost of medications. The available treatments are challenging for patients to follow because of the complexity, significant side effects and adverse events, along with the large number of prescribed medications, which often include a mix of injectable and oral drugs[2,4].

With an annual incidence of more than two million cases, India needs to implement novel evidence-based interventions. The estimated incidence of MDR/RR-TB for India was 119, 000 (93,000-145,000)[5] for the year 2021. Numerous efforts have been made to reduce treatment duration which is a significant strategy to achieve TB elimination. A nine-month shorter regimen demonstrated an 87.9 per cent treatment success rate in Bangladesh[6]. Comparable supportive experiments were subsequently carried out in Cameroon and Niger, both achieving treatment success rates exceeding 89 per cent[7]. In 2019, the first randomised controlled trial reported on examining short-term treatment for MDR-TB[8]. The standardised shorter regimen, which consisted of seven drugs, and lasted 9-11 months, had a 78.8 per cent treatment success rate and was determined to be non-inferior to the long term programme that the World Health Organization (WHO) recommended in 2011[9].

The updated WHO guidelines in 2018 for MDR-TB, introduced shorter regimen as an option for treating patients.[10] These were given to patients who have not received second-line medications for more than one month or showing a lack of evidence on resistance to second line injectable drugs and fluoroquinolones. This was updated based on the findings of observational studies and the STREAM study[7,10]. The findings of the Nix TB trial, reported by Conradie *et al*[11], in 2020 where three-drug regimen were given orally to patients with XDR-TB for 26 wk, consisting of bedaquiline, pretomanid, and linezolid (BPaL)[11]. Out of the 109 patients who took part in the clinical trial, 98 patients (90%) had favorable outcomes at the end of treatment, suggesting that the combination of bedaquiline, pretomanid and linezolid led to a favourable outcome in a significant number of patients who were fluoroquinolone resistant. In the Zenix trial, a total of 181 participants were enrolled, a total of 84 to 93 per cent of participants in all four groups receiving treatment with different drug dosages of bedaquiline, pretomanid and linezolid experienced favourable outcomes[12]. The group of patients who got treated with three-drug regimens including linezolid at a dose of 600 mg for 26 wk had an overall favourable risk: benefit ratio. A few of these patients required modifications to the linezolid dosage due to lower incidence of adverse events. The safety and efficacy of all oral regimens (24 wk) including BPaL and moxifloxacin (BPaLM) for the treatment of MDR/RR-TB were assessed by the TB PRACTECAL study, which demonstrated that BPaLM treatment was successful and had a better profile than standard of care (SoC)[13]. In December 2022, the WHO recommended (*i*) a six-month treatment regimen consisting of bedaquiline, pretomanid, linezolid (600mg), and moxifloxacin (BPaLM) as an alternative to shorter (9-month) or longer (18-month) regimens for patients with MDR/RR-TB, taking into account the evidence from the above mentioned clinical trials; and (*ii*) using the nine-month shorter all-oral regimen instead of the 18-month longer regimen for MDR/RR-TB patients whom fluoroquinolone resistance had been ruled out[10].Though the clinical effectiveness of BPaL/BPaLM has been thoroughly established, a critical gap remains in the information regarding the economic evaluation of these regimens. This void in understanding the cost-effectiveness of BPaL based treatments compared to existing SoC regimens underscores the need for comprehensive analysis. Our study endeavours to address this gap by evaluating the economic implications of implementing BPaL based regimens, aiming to provide essential insights that complement the demonstrated clinical efficacy of these innovative treatments in managing DR-TB. In this present economic evaluation study, we estimated the cost-effectiveness of a BPaL/BPaLM regimen for MDR/RR-TB patients as compared to current mix of

(longer 58% and shorter 42%) SoC regimen based on the existing evidences.

Materials & Methods

This study was a secondary analysis of cost data of BPaL, BPaLM and current mix of SoC regimens, undertaken by the department of Health Research, Ministry of Health and Family Welfare, Government of India, New Delhi, India. The ICMR-National Institute for Research in Tuberculosis manuscript review committee and research integrity committee approved this manuscript. We also received waiver of concern from the Institutional Ethics Committee approval, since secondary data from published literature was used for this study. The study was carried out by the researchers in accordance with the consolidated health economic evaluation reporting standards (CHEERS) statement, which is the appropriate reporting standard globally (Supplementary Table I).

Study setting: In India, 119,000 MDR/RR-TB cases have been estimated for 2021. In 2022 compared to 2021, there were 32 per cent more MDR/RR-TB patients notified by National Tuberculosis Elimination Programme (NTEP)[14]. MDR/RR-TB diagnosis and therapy have seen substantial change in the last few decades. However, there are still a number of challenges hindering optimal disease management.

Increasing resistance to WHO-recommended Group-A and Group-B medications, the high rates of catastrophic costs experienced by patients with MDR/RR-TB, the wide variations in private providers' involvement in TB treatment, and the lack of private sector engagement are the most urgent problems.

The most pressing issues include: (*i*) increasing resistance levels to WHO recommended Group-A and Group-B drugs, (*ii*) substantial catastrophic costs facing individuals with MDR/RR-TB, (*iii*) lack of steady participation of private providers in TB management and (*iv*) insufficient private sector engagement. These challenges are further compounded due to inadequate national investment in health. Nonetheless, India has the potential to guide the global battle against MDR/RR-TB[15]. Given that India carries a significant portion of the global TB burden, achieving success in the country which would greatly influence global TB control efforts. In order to achieve the TB elimination goal, there is a need for the implementation of rapid diagnostic tools and newer drugs that can cure MDR/RR-TB and accelerate the step towards 'End-TB' goal.

In India, under the National Tuberculosis Elimination Programme, all notified MDR/RR-TB patients were taking treatment with the existing mixed SoC regimen, in which 58 per cent of patients placed on the longer regimen (18-20 months) and 42 per cent were treated with the shorter regimen (9-11 months).

Study design: We used Markov model for this economic evaluation. Our study centred on evaluating the effects of two treatment regimens (*i*) BPaL and (*ii*) BPaLM compared with a mixed SoC regimen which is in current practice. We conducted this assessment using MDR/RR-TB patients aged over 14 yr, regardless of their fluoroquinolones resistance status. Specifically, we included individuals who had been exposed to bedaquiline, linezolid, pretomanid or delamanid for less than one month in the past.

Study perspective: Using a health system perspective, this cost-effective analysis solely took into account the expenses incurred by the health system, including the costs of patient incentives, nutritional assistance and regimens (shorter SoC, Longer SoC, BPaL and BPaLM).The costs for pre investigations such as smear examination by Ziehl-Neelsen smear microscopy, CBNAAT, solid sputum culture, ECG, HIV rapid test, full haemogram, electrolyte, creatinine, blood sugar, thyroid stimulating hormone test, chest X-ray and liver function test were also added.

Intervention and comparator: In the current study, a comparison was made between the costs and outcomes of BPaL/BPaLM regimens with the current strategy of treating MDR/RR-TB which is a mixed SoC regimen in the NTEP (Table I).

Intervention: The BPaL regimen (6-9 months) consisted of bedaquiline, pretomanid and linezolid; while the BPaLM regimen (6-9 months) included BPaL along with moxifloxacin.

Comparator: The comparator was the currently used mixed SoC regimen for treating MDR/RR-TB following the National Tuberculosis Elimination Programme guidelines[16]. The shorter SoC regimen included levofloxacine, bedaquiline, clofazimine, ethambutol, ethionamide and pyrazinamide. The regimen comprised of a 4-months initial phase extendable to 6-months and a 5-months continuation phase for a total duration of 9 to 11-months. Bedaquiline was administered for 6-months. The longer SoC regimen included

Table I. Treatment intervention for adult new smear-positive drug-resistant TB

Strategies	Drugs	Regimen	Duration	Population
Intervention-1 BPaL	Bedaquiline (Bdq) Pretomanid (Pa) Linezolid (Lzd)	(6-9) Bdq Pa Lzd	6-9 months	Adult aged >14 yr smear positive MDR/ RR-TB Individuals
Intervention-2 BPaLM	Bedaquiline (Bdq) Pretomanid (Pa) Linezolid (Lzd) Moxifloaxacin (M)	(6-9) Bdq Pa Lzd M	6-9 months	Adult aged >14 yr smear positive MDR/ RR-TB Individuals
Comparator Mixed standard of care	Bedaquiline (Bdq) Levofloxacin (Lfx) Clofazimine (Cfz) Pyrazinamide(Z) Ethambutol(E) Isoniazid(Hh) Ethionamide(Eto)	(4-6) Bdq, Lfx, Cfz, Z, E, Hh, Eto/ (5) Lfx, Cfz, Z, E	9-11 months	Adult aged >14 yr smear positive MDR/ RR-TB individuals
	Levofloxacin(Lfx) Bedaquiline(Bdq) Clofazimine (Cfz) Linezolid(Lzd) Cycloserine(Cs)	(18-20) Lfx, $Bdq_{(6\ month\ or\ longer)}$, Lzd, Cfz, Cs	18-20 months	Adult aged >14 yr smear positive MDR/ RR-TB individuals

levofloxacin, bedaquiline, clofazimine, linezolid and cycloserine and was administered for 18-20 months.

Time horizon: Costs and outcomes of the two comparative regimens were modelled using a life time horizon. Based on the literature, the average age of a TB patients was 32 yr[17], and life expectancy at that age was utilised. Both costs and outcomes were adjusted by three per cent discount rate[18]. The population's health status was defined by the model, which tracked it until it was either cured or death.

Description of model: A cohort of 48,563 MDR/ RR-TB patients was monitored by the model[19].The model considered TB treatment outcomes between the two regimens. Regardless of their fluoroquinolones resistance status, we only took into consideration individuals over the age of 14 yr who accessed the government health facilities every two weeks for treatment. Specifically, we included individuals who had been exposed to bedaquiline, linezolid, pretomanid or delamanid for less than one month in the past. Table II describes the demographic characteristics of the TB patients. Disease recurrence was considered in transition health state. Treatment related mortality was also taken into account. Life years and QALYs obtained by patients receiving two distinct regimens were the model outcomes. The analyses were performed using a Microsoft Excel spreadsheet.

Markov model: The Markov model considered five health states of TB treatment outcomes (Figure). Based on specific probabilities, each patient moved to a different health condition after a year.

Model input parameters: The important model input parameters include demographic values, treatment outcomes attributable to the regimen BPaL, BPaLM and mixed SoC, transition probabilities and various costs of the health system data. The detailed information on the collected input parameters are given in table II. It also included life expectancy and all-cause mortality which was used from the SRS based life table (2012-2016)[20].

Cost data: MDR/RR-TB treatment guidelines, previously published prices and expert opinions were used to estimate treatment costs from a provider perspective. Costs related to treatment regimens such as cost of full course of the treatment regimen, nutritional support to patients, incentives to treatment supporters were provided by Central TB Division (CTD) through personal communication. Medication costs for all regimens were also provided by CTD. Pre-treatment investigation costs were taken from the published literature[2].

Effectiveness data: The clinical outcomes of the BPaL and BPaLM regimens including recurrence were sourced from randomised control trials[11,13,21-24], the

Table II. Input parameters used for cost-effectiveness analysis of the BPaL/BPaLM regimen as compared to mix of standard of care regimen

	Input Parameters	Base case	Lower	Upper	Distribution	Source
Demographic values	Average age of TB patient	32	26	38	Normal	17
	Life expectancy at age 32	44	44	44	NA	20
	Cohort population	48563	48563	48563	NA	19
Standard of care-shorter (42%)	Cure	0.71	0.568	0.852	Beta	14,25
	TB Recurrence	0.029	0.023	0.034	Beta	2
	Lost-to-follow-up	0.11	0.083	0.138	Beta	14,25
	Failure	0.02	0.088	0.132	Beta	14,25
	Death	0.15	0.016	0.024	Beta	14,25
Standard of care-longer (58%)	Cure	0.65	0.52	0.78	Beta	13,14,21,25
	TB Recurrence	0.029	0.023	0.034	Beta	2
	Lost-to-follow-up	0.06	0.045	0.075	Beta	13,14,21,25
	Failure	0.01	0.048	0.072	Beta	13,14,21,25
	Death	0.13	0.104	0.156	Beta	13,14,21,25
BPaL	Cure	0.84	0.672	1	Beta	11,13,21,22,23,24
	TB Recurrence	0.04	0.032	0.048	Beta	11,13,21
	Lost-to-follow-up	0.04	0.032	0.048	Beta	11,13,21,22,23
	Failure	0.018	0.014	0.022	Beta	13,21,22,23
	Death	0.04	0.032	0.048	Beta	11,13,21,22,23
BPaLM	Cure	0.87	0.696	1	Beta	13,21,22
	TB Recurrence	0.01	0.008	0.012	Beta	13,21
	Lost-to-follow-up	0.04	0.032	0.048	Beta	13,21,22
	Failure	0	0	0	Beta	13,21,22
	Death	0	0	0	Beta	13,21,22
Transition probabilities	Cure to all cause mortality	0.01	0.008	0.012	Beta	2
	Recurrence to all cause mortality	0.01	0.008	0.012	Beta	2
	Recurrence to death	0.0004	0.0003	0.0005	Beta	2
	Lost-to-follow-up to regimen	0.3	0.24	0.36	Beta	2
	Lost-to-follow-up to all cause mortality	0.01	0.008	0.012	Beta	2
	Lost-to-follow-up to death	0.0004	0.0003	0.0005	Beta	2
	Failure to all cause mortality	0.01	0.008	0.012	Beta	2
	Failure to death	0.0004	0.0003	0.0005	Beta	2
Mortality	All cause mortality	0.01	0.008	0.012	Beta	20
Utility	Cure	0.87	0.696	1	Beta	26,27
	TB Recurrence	0.62	0.496	0.744	Beta	26,27
	Lost-to-follow-up	0.62	0.496	0.744	Beta	26,27
	Failure	0.62	0.496	0.744	Beta	26,27
Cost	Drug cost for shorter standard of care	24784	19827	29741	Gamma	CTD
	Drug cost for longer standard of care	43013	34410	51616	Gamma	CTD
	Drug cost for BPaL	37279	19423	29135	Gamma	CTD
	Drug cost for BPaLM	39738	31790	47686	Gamma	CTD
	Nutritional support to patients per month	500	400	600	Gamma	CTD
	Honorarium to treatment supporter	5000	4000	6000	Gamma	CTD

Contd...

	Input Parameters	Base case	Lower	Upper	Distribution	Source
Investigations	CBNAAT	1036	829	1243	Gamma	2
	Ziehl-Neelsen smear microscopy	115	92	138	Gamma	2
	Solid sputum culture	184	147	221	Gamma	2
	Electrocardiogram	177	142	213	Gamma	2
	HIV rapid test	125	100	150	Gamma	2
	Full haemogram	62	50	75	Gamma	2
	Electrolyte	25	20	30	Gamma	2
	Creatinine	57	45	68	Gamma	2
	Blood sugar	76	60	91	Gamma	2
	Thyroid-stimulating hormone test	260	208	312	Gamma	2
	Chest X-ray (digital)	198	158	237	Gamma	2
	Liver function test	260	208	312	Gamma	2
Discount Rate	Discount rate	0.03	0.03	0.03	NA	18
Willingness to pay threshold	One time GDP per capita (in INR)	115746	115746	115746	NA	28

BPaL, bedaquiline, pretomanid, linezolid; BPaLM, bedaquiline, pretomanid, linezolid, moxifloaxacin; CTD, Central TB Division; CBNAAT, cartridge-based nucleic acid amplification test; GDP, gross domestic product

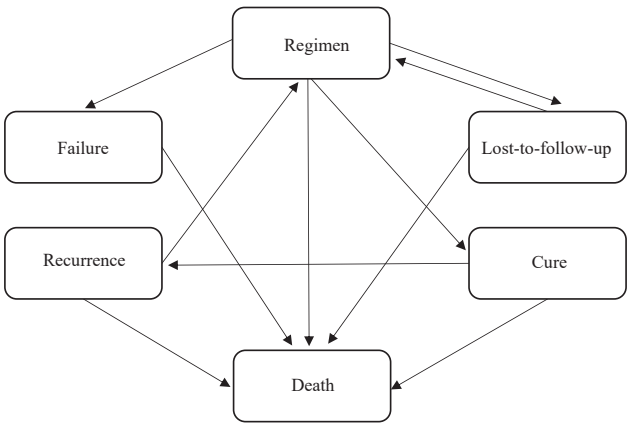

Figure. Markov model of the sequence of possible TB treatment outcomes and health states.

Nix-TB and TB-PRACTECAL trials. The Nix-TB trial was done at three sites in South Africa among 109 patients. The use of oral, bedaquiline, pretomanid and linezolid was examined. The intention-to-treat analysis showed that 90 per cent favourable outcome, which is similar to that obtained with the SoC for DS-TB (isoniazid, rifampicin, pyrazinamide and ethambutol). The TB-PRACTECAL trial was done in Belarus, South Africa and Uzbekistan during 2017 to 2021 with four comparator groups. One was the SoC group and other three are BPaL groups such as BPaL, BPaLC and BPaLM. This multi country randomised controlled trial showed that treatment with BPaLM was more effective and had a better safety profile than SoC. BPaLC and BPaL were also highly efficacious. Treatment outcomes of SoC by shorter and longer regimen were collected from the TB control Programme as well as published literature[13,14,21,25]. The collected treatment outcomes of BPaL, BPaLM and the SoC were pooled using meta-analysis. The primary parameters of the model were demographic information and TB treatment outcomes, including cure, failure, lost-to-follow-up and death. Information on the recurrence of SoC regimen was collected from the published literature[2]. Data on the quality of life for cured and other outcomes of TB patients were collected from the published literature[26,27].

Model outcome parameters: The model outcomes were presented in the form of life years, QALYs and the total cost incurred by the population for all the regimens. Life years were estimated by multiplying the number of patients by their respective remaining life expectancy. QALYs were derived by multiplying life years by the utility score of quality of life related with each health state. In this study, utility scores were obtained directly from the published sources used for our model parameters. These utility values were applied to estimate the QALYs for each treatment regimen. Using the cost of regimens and the corresponding QALYs estimated from model, we calculated the incremental cost effectiveness ratio (ICER) calculated to compare alternatives.

Table III. Summary table for BPaL/BPaLM compared with mixed standard of care regimen

Undiscounted					
Strategy	Total (in million)		Incremental (in million)		ICER
	Cost (INR)	QALY	Cost (INR)	QALY	Cost/QALY
BPaLM	4887	2.48	27	0.52	51
BPaL	4648	2.32	-212	0.36	-579
Mix standard of care	4860	1.96	-	-	-
Discounted					
BPaLM	2644	2.01	14	0.38	37
BPaL	2515	1.93	-115	0.30	-379
Mix standard of care	2630	1.63	-	-	-

QALY, quality adjusted life years; ICER, incremental cost effectiveness ratio

Willingness to pay: Cost-effectiveness of the proposed regimens was assessed by comparing the willingness to pay (WTP) criterion, which is the one time GDP per capita (INR 1,15,746) for the year 2022-2023[28].

Sensitivity analysis: We generated 1,000 input sets by uniformly sampling from reasonable ranges for the input parameters. By varying the input parameters by 20 per cent above or below their typical values, sensitivity analysis was used to assess the model's robustness. Model results were examined in relation to change in input parameters using one-way sensitivity analysis (OWSA). A tornado diagram was used to illustrate the uncertainty in the outcome factors and how it affected the incremental cost effectiveness ratio. Further, the model was validated using Microsoft Excel through Probability Sensitivity Analysis (PSA) utilising 1,000 Monte Carlo simulation iterations that included 95 per cent confidence intervals (CI). A cost-effectiveness acceptability curve (CEAC) was developed to illustrate the model's probabilistic response to various cost-effectiveness threshold and the resulting ICER values were displayed in a scatter plot.

Cost threshold analysis: The price of the BPaL and BPaLM was taken from the CTD. However, the cost-effectiveness was mostly determined by the price at which the drugs were procured. We assessed the threshold prices at which BPaL and BPaLM would become most cost-saving treatment options.

Budget impact analysis (BIA): This economic evaluation calculated the financial effects of switching from mixed SoC to BPaL/BPaLM. Cost-effectiveness analysis was supplemented with BIA to help make well informed decisions. The budget estimates were based on current unit costs of drugs and service delivery within the National Tuberculosis Elimination Programme.

Results

Base case analysis: The base case analysis for the population of 48,563 showed that the total discounted costs by health system perspective for the BPaL, BPaLM and the current mixed SoC regimen were INR 2515, INR 2644 and INR 2630 million, respectively while the total undiscounted costs acquired were INR 4648, INR 4887 and INR 4860 million for the same, respectively. It was observed that the cost for the drug was higher for BPaLM regimen as against BPaL and mixed SoC. The human resources cost, diagnostic, nutritional support, incentives to treatment supporters were considered same for both intervention regimens. In terms of effectiveness, QALY gained by BPaLM regimen is higher than the BPaL and mixed SoC (2.01 *vs.* 1.93 *vs.* 1.63 million) (Table III).

Incremental cost-effectiveness ratio (ICER): The ICER was calculated by the estimated incremental cost and incremental QALYs. When BPaL was compared with the mixed SoC regimen, the ICER was INR -379 which indicated that (the intervention is less cost and more effective) we have to spend INR 379 less per patient for BPaL than the mixed SoC to gain one additional QALY. When BPaLM was compared with the mixed SoC regimen, the ICER was INR 37 which indicates that (the intervention is more cost and more effective) we have to spend INR 37 additionally per patient for BPaLM than the mixed SoC to gain one QALY (Table III). The cost-effectiveness plane illustrates the ICER values (Supplementary Fig. 1).

Table IV. Incremental cost effectiveness ratios for different proportions of longer and shorter standard of care regimen

Discounted incremental cost effectiveness ratio (BPaLM)											
Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short
58%	42%	10%	90%	20%	80%	30%	70%	40%	60%	50%	50%
37		1521		1212		904		594		285	
Discounted incremental cost effectiveness ratio (BPaL)											
Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short
58%	42%	10%	90%	20%	80%	30%	70%	40%	60%	50%	50%
-379		1507		1115		723		330		-64	

Table V. Budget Impact analysis for BPaL/BPaLM

Regimen	Budget (in million)
BPaLM	2443
BPaL	2324
Mixed SoC (shorter-42%/longer-58%)	2430
Budget impact (BPaLM *vs*. Mix standard of care)	13
Budget impact (BPaL *vs*. Mix standard of care)	-106

Scenario analysis: We carried out multiple scenario analyses by altering the proportion of patients receiving each regimen ranging from the current distribution of 58 per cent on the longer *vs*. 42 per cent on the shorter regimens to 50 per cent in longer regimen *vs.* 50 per cent in shorter regimen. These alternative mixes were compared against the BPaL and BPaLM regimens. The corresponding ICER values for each scenario were calculated and summarised in table IV. The ICER for the proportion of mixed SoC 10 per cent *vs*. 90 per cent calculated for BPaLM and BPaL was INR 1521 and INR 1507, respectively. When the mixed SoC proportion was adjusted to 50:50 ratio, the estimated ICER for BPaLM and BPaL were INR 285 and INR -64, respectively. As the proportion of longer regimen was increased in the mixed SoC, BPaLM regimen turned more cost-effective and BPaL regimen turned more cost-saving.

One way sensitivity analysis (OWSA): The OWSA for the BPaLM regimen revealed that factors such as health-related quality of life utility score of BPaLM cure, medicine cost of BPaLM, medicine cost for longer SoC and health related quality of life utility score of shorter SoC cure had a substantial impact on the ICER value (Supplementary Fig. 2A). Similarly, the OWSA for the BPaL regimen revealed that factors such as the health related quality of life utility score of BPaL cure, medicine cost for longer SoC medicine cost of BPaL and health related quality of life utility score of shorter SoC cure had a significant influence on the ICER value (Supplementary Fig. 2B).

Probability sensitivity analysis (PSA): The PSA indicated that when joined incremental cost and effectiveness was considered and measured in QALY, BPaLM was found to be cost-effective in 48.3 per cent and cost-saving in 45.5 per cent of the iterations as shown in supplementary figure 3A. The PSA results indicated that the joint incremental cost and effectiveness, measured in QALY favored BPaL as being cost-saving in 61 per cent and cost-effective in 30.3 per cent of the iterations, as illustrated in supplementary figure 3B. Additionally, the CEAC showed that, across a range of cost-effectiveness thresholds, the 6-month BPaL regimen had a 91 per cent change of being an economically dominant strategy when compared to the mixed SoC regimen, as displayed in supplementary figure 3C.

Cost threshold analysis (CTA): The cost threshold analysis showed that BPaLM turns to be cost-saving when the cost is decreased from INR 39738 to INR 39438 (Supplementary Fig. 4). This indicates that BPaLM turns to be cost-saving if the drug cost is reduced by approximately one per cent.

Budget impact analysis: Table V shows the additional budget required for implementation of BPaL or BPaLM regimen to treat MDR/RR-TB patients in India. If BPaLM regimen is implemented, health system needs to invest around INR 13 million additionally per year. Whereas for the BPaL regimen, health system needs to invest INR 106 million lesser than the current investment.

Discussion

The findings of this study shed light on the cost-effectiveness of two prominent regimens such as BPaL and BPaLM as compared to mixed SoC regimen

incorporating bedaquiline in the treatment of MDR/RR-TB. Our analysis provided evidence that for treating MDR/RR-TB with BPaL, the health system has to spend INR 379 lesser per patient to gain one additional QALY than the mixed SoC regimen. Whereas, for BPaLM health system has to spend INR 37 additionally per patient to gain one additional QALY than the mixed SoC regimen. Notably, the BPaL and BPaLM regimens exhibited commendable efficacy in terms of higher cure rates and shorter treatment duration.

The current study evaluated the cost-effectiveness of BPaL and BPaLM with the current mixed SoC regimen. Two previously published modelling studies used data from the Nix trial to do an economic evaluation of Bedaquiline based regimen for patients with treatment intolerant or non-responsive to MDR-TB and pre-XDR-TB[29,4]. It was reported that BPaL was cost-saving for this population in Georgia, the Philippines and South Africa[4]. These findings were influenced by assumptions about loss-to-follow-up and drug prices. Adoption of the BPaL regimen resulted in a 15–32 per cent decline in the current expenditure associated with XDR-TB in Indonesia, Kyrgyzstan and Nigeria[29]. These conclusions about the economic benefits of BPaL based regimens align with our results. Our study findings align with the other study findings that BPaL was the cost-saving regimen in all countries[4]. The current study finding showed that BPaL based regimen was more economical and efficient than the current SoC in a range of settings. The programmatic adoption of BPaL based regimen should be considered by countries with high burden of TB and low resource settings like India.

The other important finding from this study was that the sensitivity analysis found health related quality of life utility score for patients cured of TB by BPaL/BPaLM is a factor impacting the cost-effectiveness of the treatment strategy for MDR/RR-TB patients. There is an indirect association between health-related quality of life utility score for cured patients and ICER value. It indicates that if the health-related quality of life utility score is decreasing, the ICER value is increasing. Thus, with the decreased health related quality of life utility score we need to spend more cost to gain one QALY. The other important factor that affected the ICER are the medication costs of the regimens. Our findings show that the medical costs of the regimen influence the ICER and are corroborated by the findings of cost-effectiveness studies conducted in other countries[29].

A study conducted in UK revealed that programmatic acceptance of these regimens could enhance treatment success rates for RR-TB and also showed that bedaquiline-based regimens are likely to be cost-saving at current price of the regimen[2]. A study from China also reported that BPaL regimen was cost-saving[30]. The anticipated cost savings associated with the BPaL regimen primarily stem from reduced expenses for drug acquisition, outpatient clinic visits and laboratory follow ups. Additionally, the BPaL regimen contributes to cost savings by decreasing health service utilisation, as it lowers the number of unfavourable treatment outcomes that require addressing treatment failures and reduces costs related to mortality due to TB.

Thus, the BPaL based regimen is a promising and highly effective treatment option that offers a shortened duration for patients diagnosed with RR-TB. Therefore, despite its higher initial expenses, BPaL/BPaLM may help alleviate the burden of MDR/RR-TB by reducing transmission rates, preventing recurrent infections and enhancing overall societal well-being. The current study underscores the balance between treatment costs and long-term benefits in managing MDR/RR-TB. While the cost of implementing the BPaL and BPaLM regimens may initially appear high, their considerable clinical effectiveness prompts consideration through negotiated procurement. The superior efficacy demonstrated by these treatments in managing MDR/RR-TB suggests that negotiating prices through bulk purchases could potentially offset the higher upfront expenses. The high clinical effectiveness warrants exploration of strategies like negotiated bulk buying to make these treatments more economically viable and accessible for managing MDR/RR-TB on a larger scale.

Current study did not consider the costs of diagnostics, follow up investigation, patient visits, adverse drug reactions management and staff incentives. High cure rate and manageable adverse events which has been considered in this model is based on the interim analysis of 118 patients in different arms of ongoing pragmatic trial. However, the study is subject to be revised once Phase-I results from the Indian trial are published (*https://clinicaltrials.gov/study/NCT05040126*). The current analysis focused only the health system perspective. Further studies needed for focusing societal perspective which include both patient and health system costs. Future research can also focus on conducting a prospective cost analysis alongside a clinical trial or real-world

implementation, which would allow validation of the modelled estimates.

Our findings indicate that BPaL based regimens are not only more effective but also likely to be cost saving compared to the current mixed SoC across various settings. To treat MDR/RR-TB, countries should think about implementing BPaL based regimens on a programmatic basis. The outcomes of this study contribute valuable insights into the decision-making process for healthcare policymakers, urging a balance between costs and long term benefits to optimise patient outcomes. It is crucial that the India TB programme assesses how best use these finding to implement policy changes their current treatment strategy to shorter regimens.

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