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Assessing the cost-effectiveness of the new treatment BPaLM/BPaL for Multi-drug resistant, rifampicin resistant, tuberculosis (MDR-RR-TB) as compared to the mixed standard of care Bedaquiline containing regimen under the National Tuberculosis Elimination Programme (NTEP)

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Submitted by
Regional Resource Centre for HTAIn
ICMR-National Institute for Research in Tuberculosis
No. 1, Sathyamoorthy Road, Chetpet, Chennai

Assessing the cost-effectiveness of the new treatment BPaLM/BPal for multi-drug resistant, rifampicin resistant, Tuberculosis (MDR-RR-TB) as compared to the mixed standard of care Bedaquiline-containing regimen under the National Tuberculosis Elimination Programme (NTEP)

Study Team

Principal Investigator: Dr. M Muniyandi, Scientist-D, Dept. of Health Economics

Coordinator : Dr. Padmapriyadarsini C, Director, ICMR-NIRT

Co-Investigator: Dr. Karikalan, Scientist C, Dept. of Socio Behavioural Research

Dr..Kavitha Rajsekar, Scientist-E, ICMR, Dept. of Health Research, Ministry of Health and Family Welfare, New Delhi

Dr. Kirti Tyagi, Technical Expert: healthcare priority setting PGIMER, Chandigarh

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SUMMARY

Current options for treating tuberculosis (TB) that is resistant to rifampicin (RR-TB) are few, also regimens are often long and poorly tolerated. Following recent evidence from the TB PRACTECAL trial, countries are considering programmatic uptake of 6-month, all-oral treatment regimen, BPaLM. We conducted an economic evaluation to assess whether the introduction of BPaLM/BPaL regimen under National Tuberculosis Elimination Programme (NTEP) for the treatment of MDR/RR-TB is a cost-effective strategy. We used a Markov model to estimate the incremental cost-effectiveness of two regimens containing Bedaquiline, Pretomanid and Linezolid (BPaL) with and without moxifloxacin (BPaLM). These two regimens are compared with the current mix of (Longer regimen – 4% and shorter regimen – 96%) standard of care (SOC) regimen to treat MDR/RR-TB from the health system perspective. We estimated the total costs and quality-adjusted life years (QALYs) for life time horizon. Costs and QALYs were discounted at 3% in the base case analysis. Probability Sensitivity Analysis (PSA) was used to assess the impact of parameter uncertainty on Incremental Cost Effectiveness Ratio (ICER) values. Our findings indicate that BPaL is cost saving and BPaLM is cost effective compared to that of the current mix of (Longer regimen 4% and shorter regimen 96%) standard of care (SOC) regimen. Probability sensitivity analysis showed that when compared to SOC BPaLM and BPaL were more costly and more effective 92% and 89% of the simulations respectively. In Cost Threshold Analysis (CTA), BPaL was found to be cost saving if the price is reduced to 29% than the current price and BPaLM was found to be cost saving if the price is reduced to 33% than the current price. Evidence suggests to consider programmatic uptake of BPaL and BPaLM.

I. INTRODUCTION

Tuberculosis (TB) drug resistance is a global public health concern as it threatens the progress made in TB care and control. Drug-resistant TB is a growing public health concern since it requires more complex treatment than drug-sensitive TB and incurs more cost.[1] Multidrug resistant TB (MDR-TB) is a type of TB that is resistant to at least two first-line anti-TB drugs ie., Isoniazid and Rifampicin. Pre-XDR-TB is TB in which resistance to Rifampicin (MDR/RR-TB) and any fluoroquinolone are detected.[2] Extensively Drug Resistant Tuberculosis (XDR-TB) TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (Group A drugs are the most potent group of drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise levofloxacin, moxifloxacin, bedaquiline and linezolid).[3] Treatment and management of drug-resistant TB is costly to the health system and patients (with high hospitalisation rates for long periods and high drug costs). Available treatments are also difficult for patients to use due to the complex and significant side effects and adverse events as well as the number of drugs prescribed, often including a combination of injectables and oral medications.[2, 4]

India with an annual incidence of 2.6 million TB cases is striving to accelerate the incorporation of evidence based new interventions in its NTEP to achieve the TB elimination goal by 2025. The estimated incidence of MDR/RR-TB in 2021 for the country was 119,000 (93,000-145,000).[5] Several new initiatives have been undertaken to control TB more efficiently and shortening of TB treatment duration is considered an important strategy to achieve the TB elimination Goals.

In Bangladesh, where a 9-month shorter regimen resulted in a treatment success rate of 87.9%.[6] Similar assenting experiments were then conducted by Cameroon and Niger, with the treatment success rates of over 89% in each country.[7] The first randomised controlled trial study on the short-term therapy of MDR-TB was released in 2019 by A.J. Nunn et al.[8] The standardized shorter regimen of 9–11 months (composed of 7 drugs) with a treatment success rate of 78.8% was proved to be non-inferior to the long-term program recommended by the World Health Organization (WHO) in 2011.[9] WHO released and updated guidelines for MDR-TB in 2018 that introduced shorter regimen as an option for patients who have not been previously treated for more than one month with second-line medicines or have no evidence of resistance to fluoroquinolones and second-line injectable drugs after reviewing the results of the STREAM study and other observational studies.[7,10] The findings of the Nix TB trial were reported by Conradie F et al, in 2020 where three-drug regimen given orally to patients with XDR-TB for 26 weeks, consisting of Bedaquiline, Pretomanid, and Linezolid (BPaL).[11] A total of 109 patients participated in the trial, and at the end of the therapy, 98 patients (90%) had a favourable outcome, suggesting that the combination of Bedaquiline, Pretomanid, and Linezolid led to a favourable outcome in a significant number of patients who were fluoroquinolone resistant. Zenix TB trial was reported by Conradie F et al[12], in 2022. In the Zenix trial, a total of 181 participants were enrolled, a total of 84 to 93% of the participants across all four bedaquiline–pretomanid– linezolid treatment groups had a favorable outcome. The overall risk–benefit ratio favored the group that received the three-drug regimen with linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer linezolid dose modifications. TB-PRACTECAL evaluated the safety and efficacy of all oral regimens (24 weeks) for the treatment of MDR-RR TB containing BPaL plus moxifloxacin (BPaLM) which highlighted that it was both BPaLM was both noninferior to

the accepted standard care with respect to primary composite outcomes of 89% and 52% of the patients respectively, had a favourable outcome. Considering the evidences from the above clinical trials, in December 2022, WHO recommended (i) a 6-month treatment regimen composed of Bedaquiline, Pretomanid, Linezolid (600 mg), and Moxifloxacin (BPaLM) regimen in place of the 9-month or longer (18-month) regimens in MDR/RR-TB patients, (ii) the use of the 9-month all-oral regimen rather than longer (18-months) regimen is suggested in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

In an ongoing pragmatic clinical trial in India, 403 pre-XDR-TB or treatment interrupters or non-responders to treatment among MDR-TB patients are treated with BPaL regimen. This present economic evaluation study we try to estimate the cost-effectiveness of a BPaL/ BPaLM regimen for rifampicin resistant tuberculosis (RR-TB) patients as compared to current mix of (Longer regimen – 4% and shorter regimen – 96%) standard of care (SOC) regimen based on the existing evidences. This study finding will be useful for policymakers to implement shorter regimen over longer regimen in the Indian health system.

II. RESEARCH QUESTION

Does phase-wise introduction of BPaLM/BPaL regimen under the NTEP for treatment of MDR/RR-TB would be a cost-effective strategy.

III. OBJECTIVE

1. To estimate the cost and effectiveness of BPaLM/BPaL regimen for drug resistant tuberculosis (MDR/RR-TB).
2. To estimate the incremental cost incurred from BPaLM/BPaL regimen in comparison with the current mix of (Longer regimen – 4% and shorter regimen – 96%) standard of care (SOC) regimen.
3. To estimate the incremental cost effectiveness ratio and quality adjusted life years (QALYs) gained due to roll out of BPaLM/BPaL regimen.

IV. METHODOLOGY

IV.1 Study Perspective

A hybrid economic model involving a Markov model was conducted to analyse the cost-effectiveness of the shorter regimen for RR-TB in comparison to the BPaLM/BPaL regimen. The economic evaluation model was conducted primarily from the Health System perspective, which includes cost incurred by the health system in the NTEP program.

IV.2 Study Population

The study was conducted taking into consideration individuals with microbiologically confirmed RR-TB aged more than 14 years irrespective of Fluoroquinolones resistance. Individuals with less than 1-month previous exposure to Bedaquiline, Linezolid and Pretomanid or Delamanid.

IV.3 PICO

Population	Individuals with microbiologically RR-TB aged more than 14 years. Individuals with less than 1-month previous exposure to Bedaquiline, Linezolid, Pretomanid or Delamanid.
Intervention	6 months BPaLM/BPaL regimen
Comparator	Current mix of (longer– 4% and shorter– 96%) standard of care (SOC) regimen containing oral Bedaquiline-containing MDR/RR-TB regimen
Outcome	QALYs gained, incremental cost, Incremental Cost Effectiveness Ratio (ICER) by roll out of BPaLM/ BPaL treatment under the NTEP.

IV.4 Intervention and Comparator

The present model compares the costs and outcomes of a BPaLM/BPaL regimen as compared to shorter regimen for RR-TB patients at public health facilities. Currently, all notified MDR/RR-TB patients are treated for a period of current mix of (longer regimen – 4% and shorter regimen – 96%) standard of care (SOC) regimen under NTEP. BPaL regimen consist of Bedaquiline at a dose of 400 mg once daily for 2 weeks followed by 200mg three times a week for 24 weeks, plus Pretomanid at a dose of 200mg daily for 26 weeks and linezolid at a dose of 1200mg daily for up to 26 weeks. BPaLM regimen consist of BPaL plus Moxifloxacin. Shorter standard of care contains Bedaquiline, Levofloxacin/Moxifloxacin, Clofazimine, Ethionamide, Ethambutol, Isoniazid (high dose) and Pyrazinamide for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive or culture positive at the end of the fourth month), followed by 5 months of treatment with

Levofloxacin/Moxifloxacin, Clofazimine, Ethambutol and Pyrazinamide. Bedaquiline use in this regimen is for 6 months.

IV.5 Time Horizon

Incremental costs from the provider perspective and quality-adjusted life years (QALYs) averted were modelled over life time horizon. A global discount rate of 3% was incorporated for both the cost and consequences. The full course of the treatment period was considered, to model the cost and outcomes of all the regimens. The average age of TB patients was assumed from the literature and the life expectancy at that age was used. Life expectancy and all-cause mortality was calculated based on the average age of the cohort using the standard life table of India. This model characterizes the health state of the MDR/RR-TB patients. In addition, the quality of life for patients was taken into consideration.

Table 1. Treatment intervention for adult new smear-positive drug-resistant TB

Strategies	Drugs	Regimen	Duration	Population
Intervention-BPaL	Bedaquiline (Bdq) Pretomanid (Pa) Linezolid (Lzd)	(6-9) Bdq Pa Lzd	6-months	Adult aged ≥14 years smear positive MDR/ RR-TB Individuals
Intervention-BPaLM	Bedaquiline (Bdq) Pretomanid (Pa) Linezolid (Lzd) Moxifloaxacin(M)	(6-9) Bdq Pa Lzd M	6-months	Adult aged ≥14 years smear positive MDR/ RR-TB Individuals
Comparator (SOC)	Bedaquiline (Bdq) Levofloxacin (Lfx) Clofazimine (Cfz) Pyrazinamide(Z) Ethambutol(E) Isoniazid(Hh)	(4-6) BdqLfx, Cfz, Z, E, Hh, Eto	9-11 months and longer 18- 21 months current mix of (Longer	Adult aged ≥14 years smear positiveMDR/ RR-TB individuals

	Ethionamide(Eto)		regimen – 4% and shorter regimen – 96%) standard of care (SOC) regimen	

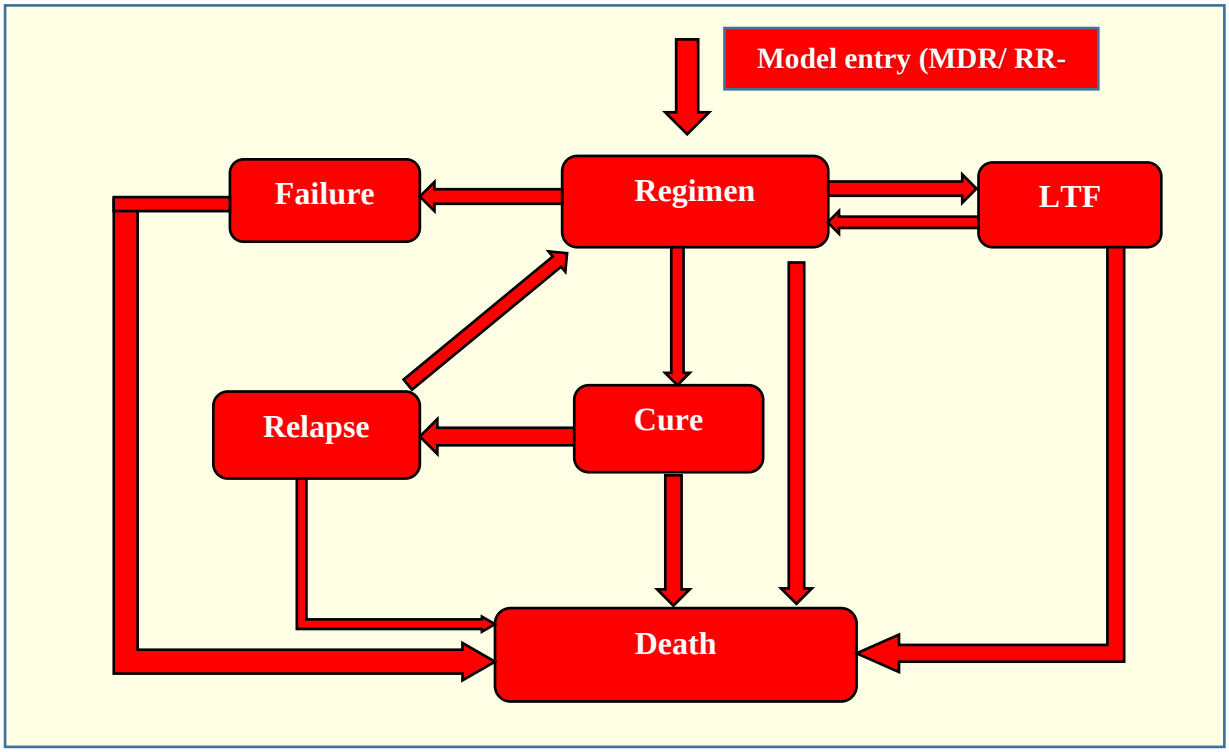
IV.6 Model structure

We used an economic model involving Markov modelling from a provider perspective for this economic evaluation. In the current modelling work, we focused on assessing the impact of SOC regimen (current mix of longer– 4% and shorter– 96%) standard of care (SOC) regimen with the proposed BPaL and BPaLM regimen for MDR/RR-TB treatment regimen based on a hypothetical cohort of TB patients undergoing treatment in the public health facilities.

A hypothetical cohort of 1,00,000 patients were assumed to enter the model with active MDR/RR-TB at the point of treatment initiation. At model entry, mean age was assumed to be 35, the average age of BPaL, BPaLM participants individuals entered the Markov model and was gone through different health states in respect to transition probabilities. A total of five health states included cure, failure, lost-to-follow-up, death, and TB recurrence.[1] Treatment duration depended on the treatment regimen; we assumed the standardized BPaL/ BPaLM containing regimens lasted 26-39 weeks, the standard short SOC regimen lasted for 39-47 weeks in shorter oral regimen and 78 – 86 weeks in longer oral regimen. Patients who were lost-to-follow-up (LTFU) before treatment completion had a chance of re-entering treatment each month in the first two years from the start of treatment. Patients successfully completing treatment had a chance of experiencing recurrence in the

first four years following treatment completion; recurrence was not included in the model. Patients who had recurrence of TB had a chance of re-entering treatment following national TB treatment coverage rates. We did not model any potential reduction of onward transmission of TB due to a shorter treatment period.

Figure 1. Markov model for different health states and possible transitions



Source: Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. PLOS Glob Public Health 2022 2(12): e0001337.

IV.7 Model Input Parameters

The key input parameters for the model includes age specific life expectancy and all-cause mortality. The life table technique was used to calculate age-specific life expectancy and all-cause mortality.[13] The key parameters which were included in the model are: demographic,[2,11,12] TB treatment outcomes,[2,11,14] recurrence of TB,[2,11,13] treatment outcome of LTF,[3,13] treatment outcome of failures,[13] treatment outcome of recurrence,[13,4] and quality of life of different patients[15,16] (Table-2).

IV.8 Cost data

Treatment costs were estimated from a providers perspective using a combination of MDR treatment guidelines, previously published estimates of prices and expert opinion from the central TB division.[17] The costs for treatment regimens such as pre and post treatment investigation cost were also collected from the literature.[3] The medication costs of all the regimen was collected from the central TB division.[17] Staff and patient incentives was collected from the NTEP 2023 report.[18]

IV.9 Effectiveness data

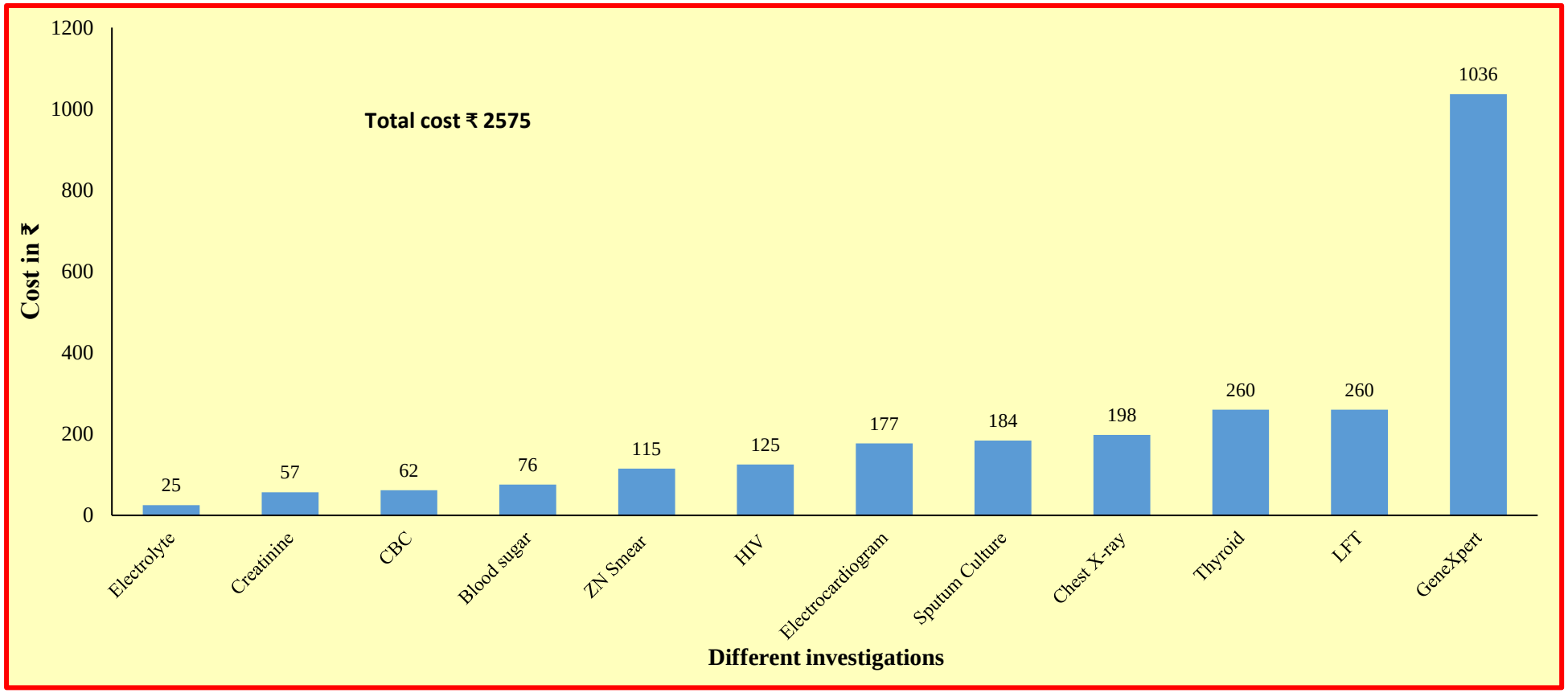
The clinical outcomes of the BPaLM/BPaL was collected from clinical trial results. Whereas for shorter SOC regimen was collected from the published literature.[2,11] The study used quality of life scores from an Indian study that used 36 items short form survey (SF-36) for cured TB patients.[19] The quality of life scores for lost-to-follow-up, and failure were utilized based on the scores published from Nigeria.[15] The utility value of well-being was measured on a scale of 0 to 1; where a score of zero represents death and one indicates perfect health. Quality of life score was be considered same for all the shorter regimens included in the study.

Table 2. Input parameters used for cost-effectiveness analysis

Variable	Parameter	SOC	BPaL	BPaLM	Distribution	References
Demographic values	Start age in years	35	35	35	Normal	Conradie F, et al. Nyang'wa BT, et al.
	Cohort population	100000	100000	100000	NA	Assumption
	Life expectancy at age 35	39	39	39	NA	SRS
Mortality	All cause mortality	0.01	0.01	0.01	Beta	SRS
	Mortality among LTF	0.0004	0.0004	0.0004	Beta	Dhamnetiya D, et al.
	Mortality among failures	0.0004	0.0004	0.0004	Beta	Dhamnetiya D, et al.
	Mortality from recurrence	0.0004	0.0004	0.0004	Beta	Dhamnetiya D, et al.
Treatment outcomes	Cure	0.74	0.92	0.96^{2}	Beta	Conradie F, et al., Nyang'wa BT, et al. Ndjeka N et al.
	Lost-to-follow-up (LTF)	0.09	0	0.04	Beta	
	Failure	0.005	0	0	Beta	
	Death	0.17	0.06	0	Beta	
Recurrence		0.001	0.02	0	Beta	Conradie F, et al., Nyang'wa BT, et al. Ndjeka N et al.
Treatment outcome of LTF	Remain LTF	0.06	0.06	0.06	Beta	Ndjeka N et al.
	Back to regimen	0.28	0.28	0.28	Beta	Sweeney, et al.
Treatment outcome of failures	Remains failure	0.01	0.01	0.01	Beta	Ndjeka N et al.

Variable	Parameter	SOC	BPaL	BPaLM	Distribution	References
Treatment outcome of Recurrence	Back to regimen	0.01	0.75	0.75	Beta	Ndjeka N et al. Gomez GB, et al.
Quality of life	Cure	0.87	0.87	0.87	Beta	Muniyandi M, et al.
	LTF	0.62	0.62	0.62	Beta	Chikaodinaka AA, et al.
	Failure	0.62	0.62	0.62	Beta	Chikaodinaka AA, et al.
Costs in Indian rupees	Nutritional support to patients	4500	3000	3000	Gamma	NTEP 2023 report
	Incentives to treatment supporter	5000	5000	5000	Gamma	NTEP 2023 report
	Medicine cost	24784	37279	39738	Gamma	Central TB division
Discount Rate	Discount rate Cost	0.03	0.03	0.03	Beta	Haacker M, et al. [20]
	Discount rate QALY	0.03	0.03	0.03	Beta	Haacker M, et al.
	Discount rate life year	0.03	0.03	0.03	Beta	Haacker M, et al.
Willingness to pay threshold	Willingness to pay threshold (GDP per capita)	141265	141265	141265	NA	Kazibwe J, et al. [21]

Table 3. Cost for different investigations



Source: Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. PLOS Glob Public Health 2022 2(12): e0001337

V.10 Model Outcome Parameters

The outcomes of the model are expressed in terms of QALYs, overall cost incurred by the cohort for all the regimens. Further, ICER value was calculated based on the incremental cost and incremental QALYs.

IV.11 Cost Effectiveness Analysis

Cost-effectiveness of shorter regimens was assessed by calculating the incremental cost effectiveness ratio (ICER) between the shorter regimen and the longer regimen. The difference in costs and QALYs of the proposed strategy and the current strategy was used to calculate ICER using the following formula.

$$\text{ICER} = \frac{\text{(Cost of proposed strategies (BPaL/ BPaLM)) - (Cost of current strategies (SOC))}}{\text{(QALY by proposed strategies (BPaL/ BPaLM)) – (QALY by strategies (SOC))}}$$

ICER was compared with Cost Effectiveness Thresholds (CET) value to conclude whether the intervention is good to implement or not. CET is determined by one time of the GDP per capita of the county.

IV.12 Sensitivity Analysis

The robustness of the model was assessed through sensitivity analysis by varying the input parameters between 20% above or below normal values. One Way Sensitivity Analysis (OWSA) was used to find out the variations of input parameter effects on model outcomes. The uncertainty in outcome variables and their effect on ICER was illustrated in the Tornado diagram. Probabilistic Sensitivity Analysis (PSA) using 1000 iterations of Monte Carlo simulations with 95% confidential intervals was used to validate the model. The resulting ICER

values were plotted in a scatter plot. The Cost Effectiveness Acceptability Curve (CEAC) was drawn to indicate the model's probabilistic response to different cost-effectiveness thresholds.

V. RESULT

V.1 Cost Effectiveness

The Table-4 depicts discounted and undiscounted total cost and also QALY, cost incurred by the all the regimens for MDR/RR-TB patients.

Table 4. Base Case Results

Here, we have carried out the analysis by giving different distribution of cohort in SOC. BPaL is found to be cost saving compared to SOC in all the cases and BPaLM is found to be cost effective. The analysis are as follows:

Discounted Cost/ QALY: Mix* of short and long SOC regimens vs 6-month regimen (BPaLM)					
Longer regimen – 4% and shorter regimen – 96%	Longer regimen – 10% and shorter regimen – 90%	Longer regimen – 20% and shorter regimen – 80%	Longer regimen – 30% and shorter regimen – 70%	Longer regimen – 40% and shorter regimen – 60%	Longer regimen – 50% and shorter regimen – 50%
1752	**1596**	**1339**	**1085**	**833**	**584**

Discounted Cost/ QALY: Mix* of short and long SOC regimens vs 6-month regimen (BPaL)					
Longer regimen – 4% and shorter regimen – 96%	Longer regimen – 10% and shorter regimen – 90%	Longer regimen – 20% and shorter regimen – 80%	Longer regimen – 30% and shorter regimen – 70%	Longer regimen – 40% and shorter regimen – 60%	Longer regimen – 50% and shorter regimen – 50%
-588	**-820**	**-1201**	**-1576**	**-1945**	**-2309**

*Mix distribution (Longer regimen 4% and shorter regimen 96%) adopted from Sweeney et al. Longer regimen (18-20months and shorter regimen 9-11 month SOC)

Cost and outcomes for longer regimen (18-20 month regime) taken from TB programme data.

The findings highlight that when compared to the current Longer regimen – 4% and shorter regimen – 96% SOC regimen, we need to spend ₹1752 and there is a cost saving of ₹588 more for BPaLM and BPaL respectively to gain one QALY.

V.3 Probability Sensitivity Analysis

The PSA showed that the joint incremental cost and effectiveness analysis of BPaLM and mixed SOC shows that 94% simulations were more costly and more effective. It was found that 94% of ICER iterations are lying in the north-east quadrant and 6.1% of ICER iterations are lying in the north-west quadrant. In 94% iterations are depicting more costly and more effective.

Figure 2. Cost Effectiveness Plane of BPaLM and mixed SOC and PSA Joint incremental cost and QALY

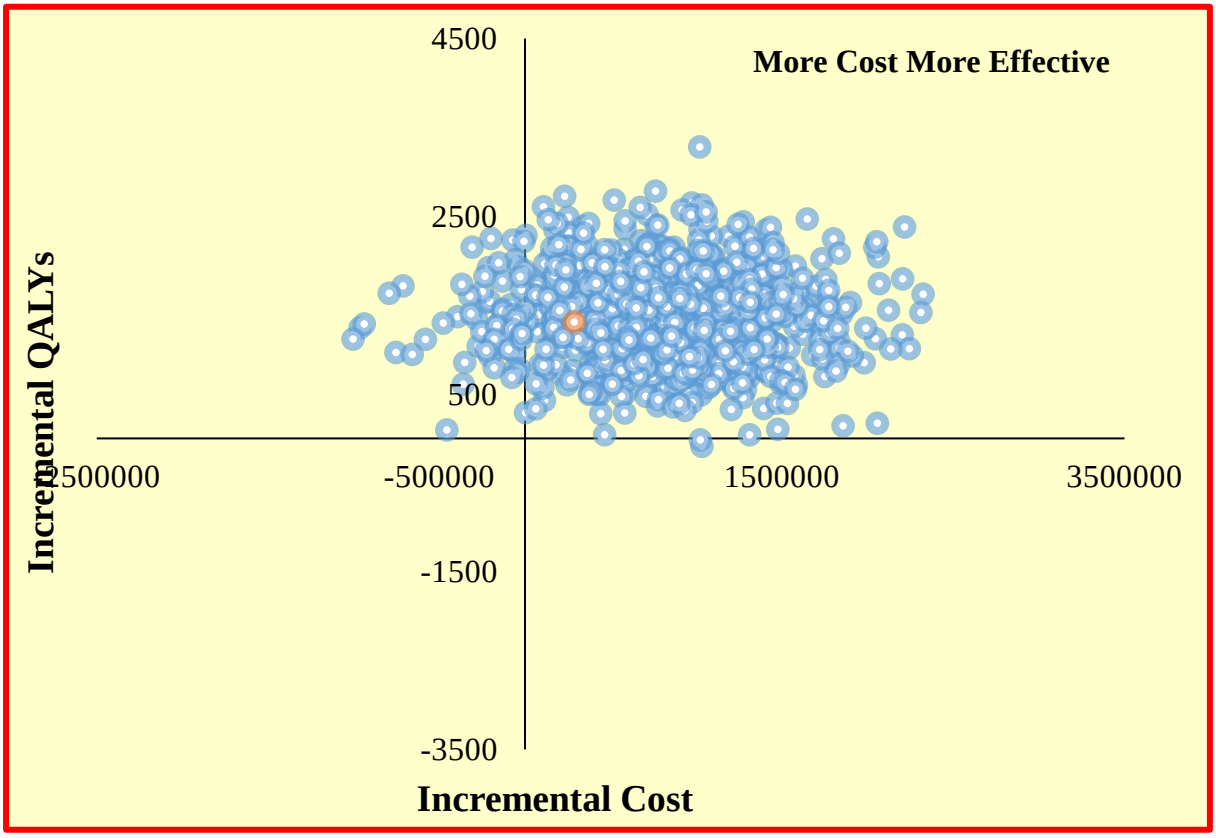


Table 6. CE plane quadrants distribution (mixed SOC and BPaLM)

CE plane quadrant (Q)	Simulations (%)
North-East Q: Needs evaluation	0.937
North-West Q: Dominated	0.061
South-West Q: Needs evaluation	0
South-East Q: Dominant	0.002

For BPaL and the PSA of joint incremental cost-effectiveness analysis shows that 66% simulations were less costly and more effective. It was found that 19.1% of ICER iterations are lying in the north-east quadrant, 3.4% of ICER iterations are lying in the North West quadrant, 11.5% of ICER iterations are lying in the south west quadrant and 66% of ICER iterations are lying in the south east quadrant. In 66% iterations are depicting less costly and more effective.

Figure 3. Cost Effectiveness Plane of BPaL and mixed SOC and PSA Joint incremental cost and QALY

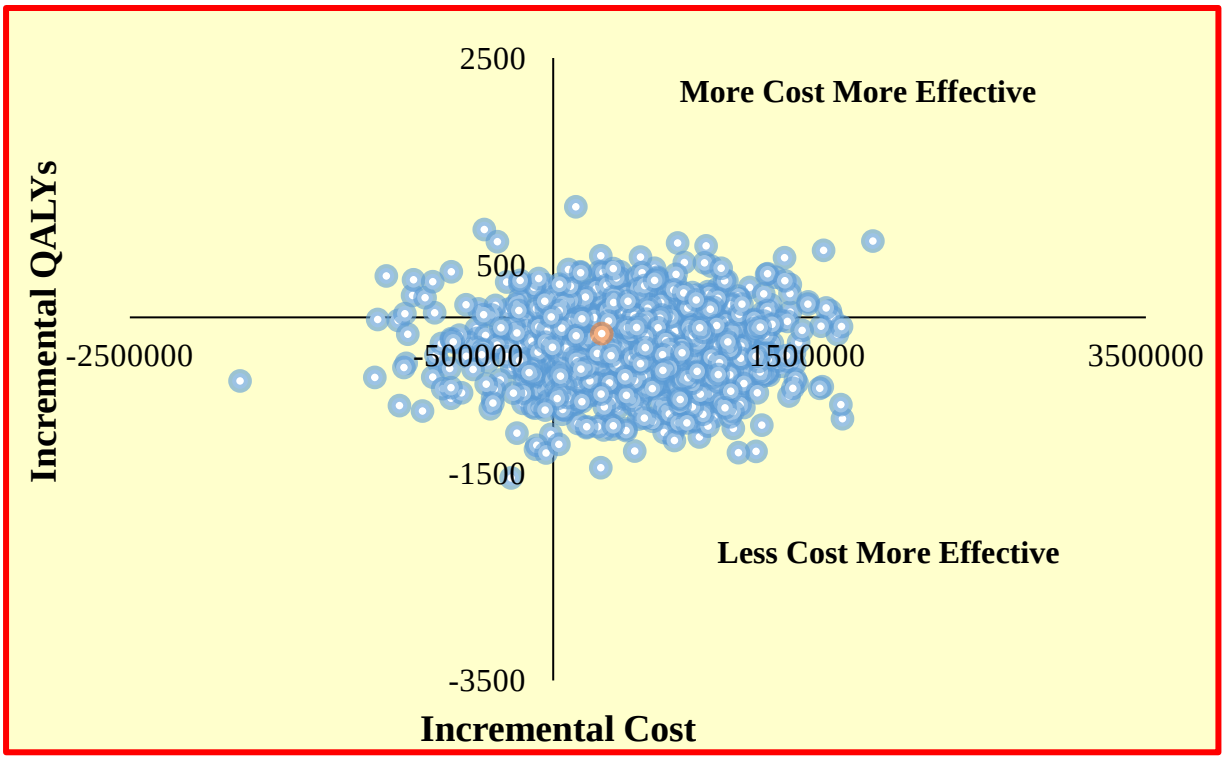


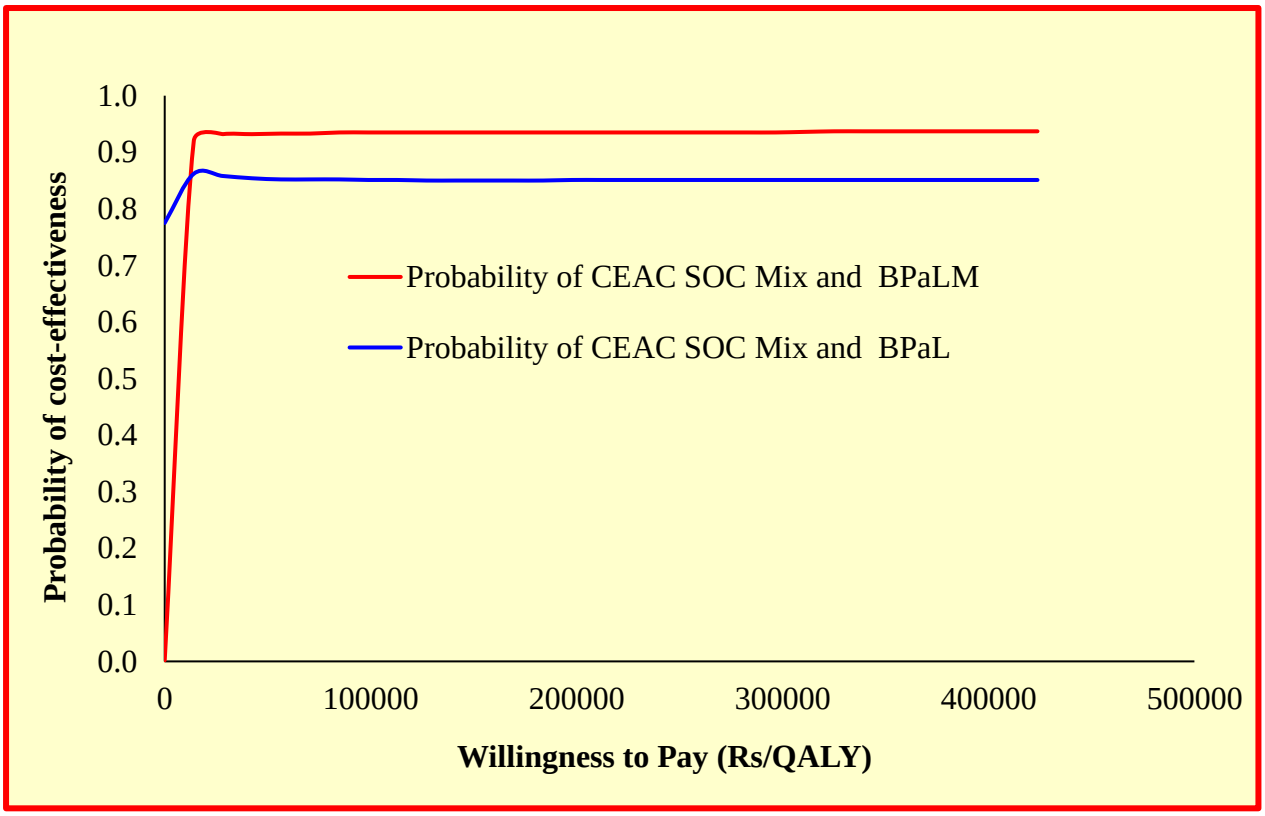
Table 8. CE plane quadrants distribution mixed SOC and BPaL)

CE plane quadrant (Q)	Simulations (%)
North-East Q: Needs evaluation	0.191
North-West Q: Dominated	0.034
South-West Q: Needs evaluation	0.115
South-East Q: Dominant	0.66

V.4 Cost Effectiveness Acceptability Curve

The cost effectiveness acceptability curve highlights that the implementation of BPaLM had a 92% and BPaL had 86% of being an economically dominant strategy as compared to implementation of mixed SOC for treating MDR TB patients (Figure-5).

Figure 5. Cost Effectiveness Acceptability Curve



V.5 One Way Sensitivity Analysis

One Way Sensitivity Analysis (OWSA) was performed for 6-month regimen (BPaL) and mixed SOC. Tornado plot was used to illustrate the one-way sensitivity analysis to understand how changes in the input parameters will affect the ICER. Here LTF of BPaLM, failure rate of SOC, recurrence of SOC are mainly influencing the ICER value. The length of the bar indicates, how much the respective parameter is affecting the ICER value.

Figure 5. Tornado Digram for BPaLM and mixed SOC

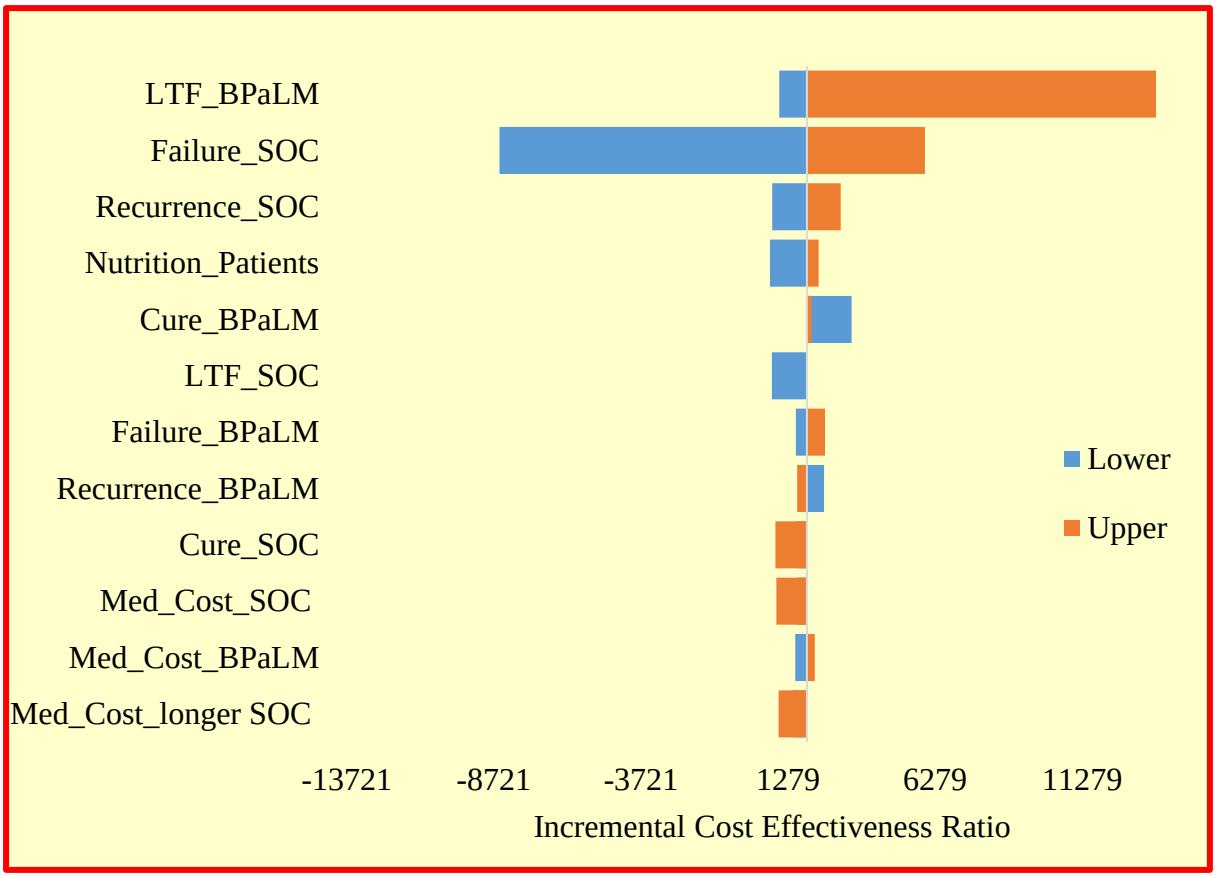
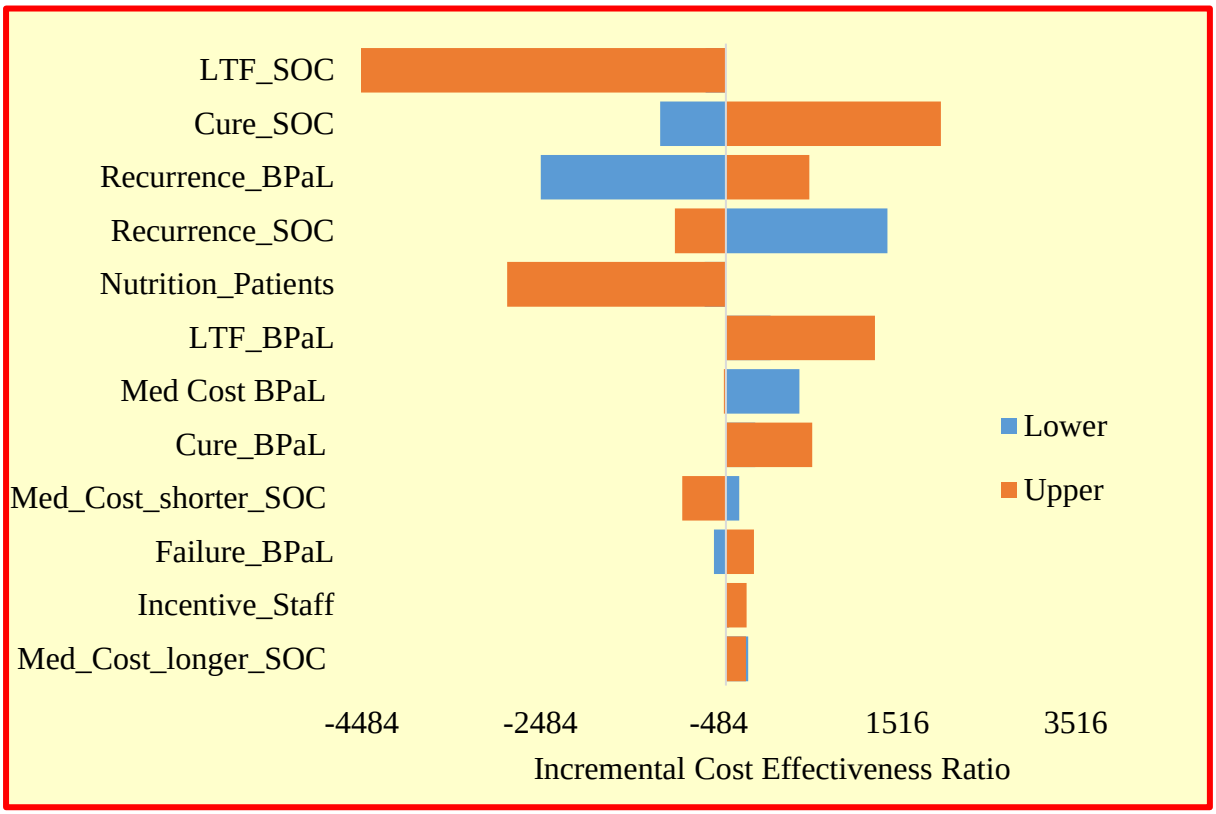
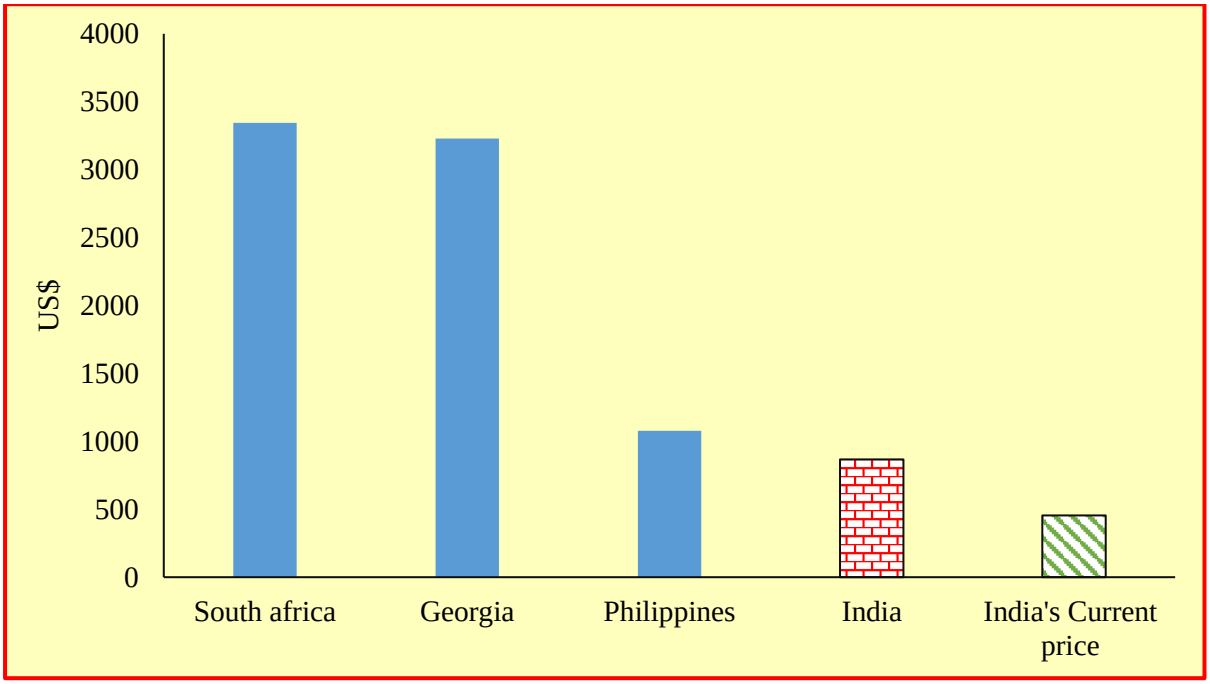


Figure 6. Tornado Digram for BPaL and mixed SOC



One Way Sensitivity Analysis for 6-month regimen (BPaL) and mixed SOC regimens was performed to know which parameter affects the ICER and it was found that LTF of SOC due to SOC regimen, cure rate of SOC, recurrence rate due to BPaL regimen and SOC regimen and nutritional support to patients per month cost was influencing the ICER significantly in base case value. Here, when the LTF due to SOC is low, the ICER value is also low which is cost saving. When the nutritional support cost for patients is high, the ICER value is low (less-cost more-effective). Similarly, when the cure rate of SOC is low, we get positive ICER value (more-cost more-effective).

Figure 7. Total cost per person of BPaL regimen in different countries

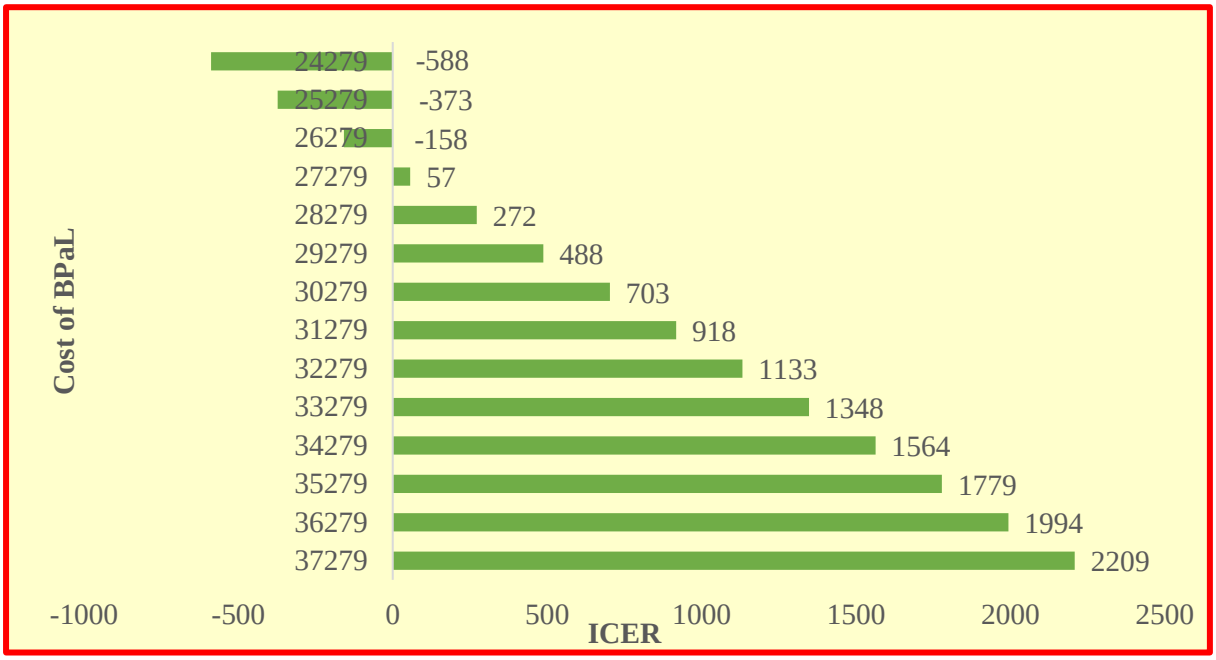


While comparing the total cost per person for BPaL regimen in different countries, it was found to be higher in South Africa followed by Georgia and Philippines. India's current price was low as compared to other countries.

Cost Threshold Analysis (CTA)

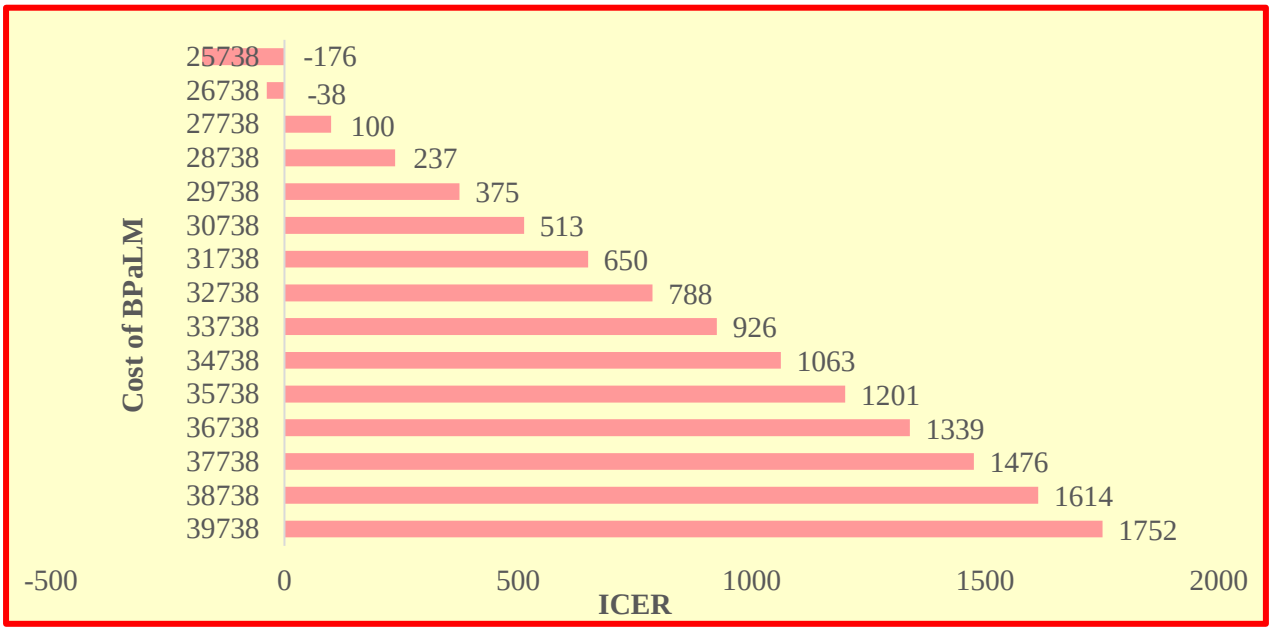
The cost of the regimen plays an important role in determining the ICER value, therefore one way sensitivity cost threshold analysis was performed.

Figure 7. Cost threshold analysis for BPaL vs mixed SOC



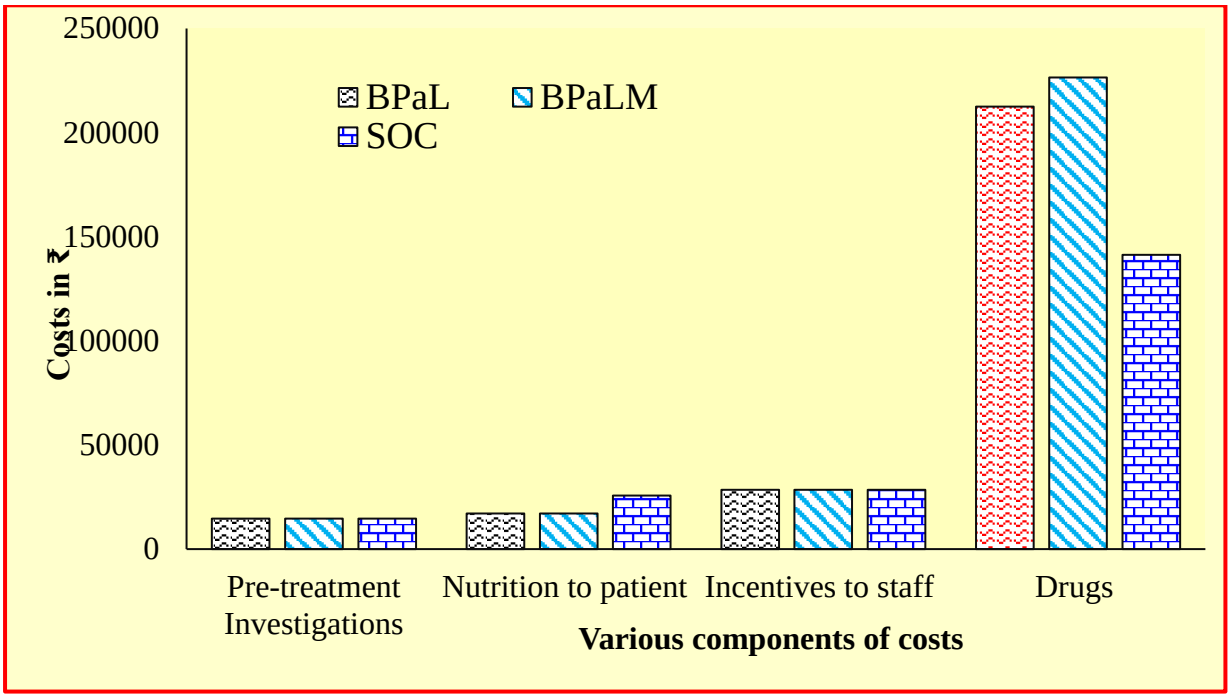
The cost threshold analysis shows that, if the price decreases, the ICER value is also decreasing simultaneously. We can see that the ICER value changes to negative when the price is 29% less than the regimen's initial cost, which was 37,279. This demonstrates clearly that BPaL would save money if the price was 29% cheaper than the initial pricing.

Figure 8. Cost threshold analysis for BPaLM vs mixed SOC



Cost threshold analysis was performed for the regimen BPaLM vs mixed SOC regimen. According to this cost threshold analysis, the ICER value similarly reduces in parallel with a falling price. We can see that the ICER value changes from positive to negative when the price is 33% less than the original regimen cost, which is 39,738. This clearly shows that BPaLM would be cost-saving when the price is 33% cheaper than the original price.

Table 10. Various componets of costs in BPaLM, BPaL and SOC



Total cost for BPaLM is most expensive as compared to other regimens and SOC is less costly. Patient incentive is higher in SOC due to longer duration of treatment period.

Limitations of the study

Current study have not considered the costs of Diagnostics, follow – up investigation, patient visits, ADR management and staff incentives. Current study does not include 18-20 month standard of care regimen as we have considered mixed standard of care regimen. 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 trail are published. If ADR is similar for both regimens, further analysis is required. Implications of MDR – TB are also likely to be affecting the wide community. We have not considered that in our model. Adverse effects of Linezolid are comparatively higher than the other drugs, we have not considered them in our model.

Conclusion

As countries consider shifting their current treatment strategy to shortened all oral regimens, it is critical that India's TB programmes consider how best to repurpose these savings. Investment in reducing lost-to-follow-up through improving patient support, expanding TB case finding efforts, or improving TB prevention efforts in countries with high TB prevalence could further country progress towards End TB targets, moving us closer to a world without TB.

Recommendation

- There is now consistent evidence that the 6 month Bedaquiline regimens are likely to be cost-effective. Programmatic uptake of these regimens could improve treatment success rate for RR-TB and free up resources for investment in other areas of TB programme.
- We estimated the incremental cost-effectiveness of implementing BPaLM and BPaL regimens with a health systems perspective, as compared with mixed SOC. The findings of the current analysis highlight that when compared to the mixed SOC regimen, the health system needs to spend ₹1856 and ₹2374 more for BPaLM and BPaL respectively to gain one QALY.
- The current interventions BPaL and BPaLM are more effective and more costly than the mixed SOC. Reduction in price of the drugs by up to 29% for BPaL and 33% for BPaLM will make the regime cost saving treatment strategy. Therefore, additional budget will not be required and the health system costs will be less, saving on present cost.

- Multi Drug-resistant TB has high externality. Providing an effective treatment, such as BPal and BPaLM, as a result, longer SOCs treatment regimen may be avoided, thereby proving to be cost saving strategy. However, due to lack of data, this has not been included in the study.
- Programmatic uptake of these regimens could improve treatment success rate for MDR/RR-TB. Implementation should be done cautiously keeping a look out for adverse drug reactions and mortality issues.

VII. Review of Literature

Table 11. Clinical Trial Evidences

Study	Sample size	Study Design	Conclusion	Reference
TB PRACTECAL trial **An open-label, phase 2–3, multicenter, randomized, controlled, noninferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant TB.**	N=301 Patients in Belarus, South Africa, and Uzbekistan who were 15 years of age or older and had rifampin- resistant pulmonary tuberculosis were enrolled.	In stage 2 of the trial, a 24-week regimen of Bedaquiline, Pretomanid, Linezolid, and moxifloxacin (BPaLM) was compared with a 9-to-20-month standard-care regimen.	In patients with rifampin-resistant pulmonary tuberculosis, a 24-week, all-oral regimen was noninferior to the accepted standard-care treatment, and it had a better safety profile.	Nyang'wa *et. al*., 2022 [2]
ZeNix trial **A partially blind, randomized trial that enrolled participants with pulmonary exten- sively drug-resistant (XDR) tuberculosis, pre-XDR**	N=181 Participants with extensively drug-resistant (XDR) tuberculosis (i.e., resistant to rifampin, a fluoroquinolone, and an aminoglycoside), pre-	Randomly assigned the participants to receive Bedaquiline for 26 weeks (200 mg daily for 8 weeks, then 100 mg daily for 18 weeks), Pretomanid (200 mg daily for 26	A total of 84 to 93% of the participants across all four bedaquiline–pretomanid– linezolid treatment groups had a favorable outcome. The overall risk–benefit ratio favored the group that received the three-drug regimen with	Conradie *et. al*., 2022[11]

tuberculosis, or rifampin-resistant tuberculosis	XDR tuber- culosis (i.e., resistant to rifampin and to either a fluoroquinolone or an aminogly- coside), or rifampin-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects.	weeks), and daily linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks. The primary end point in the modified intention- to-treat population was the incidence of an unfavorable outcome, defined as treat- ment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. Safety was also evaluated.	linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer linezolid dose modifications.	

Table 12. Cost-effectiveness studies

Study title	PICO	Results	Reference
Cost-effectiveness of Bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines	**Design** Cost-effectiveness analysis using Markov cohort model. **Setting** South Africa, Georgia and the Philippines. **Participants** XDR-TB and multidrug-resistant tuberculosis (MDR-TB) failure and treatment intolerant patients. **Interventions** BPaL regimen. **Primary and secondary outcome measures** (1) Incremental cost per disability-adjusted life years averted by using BPaL against standard of care at the Global Drug Facility list price. (2) The potential maximum price at which the BPaL regimen could become cost neutral.	**Results** BPaL for XDR-TB is likely to be cost saving in all study settings when pretomanid is priced at the Global Drug Facility list price. The magnitude of these savings depends on the prevalence of XDR-TB in the country and can amount, over 5 years, to approximately US$ 3 million in South Africa, US$ 200 000 and US$ 60 000 in Georgia and the Philippines, respectively. In South Africa, related future costs of antiretroviral treatment (ART) due to survival of more patients following treatment with BPaL reduced the magnitude of expected savings to approximately US$ 1 million. Overall, when BPaL is introduced to a wider population, including MDR-TB treatment failure and treatment intolerant, we observe increased savings and clinical benefits. The potential threshold price at which the probability of the introduction of BPaL becoming cost neutral begins to increase is higher in Georgia and the Philippines (US$ 3650 and US$	Gomez et.al. 2021[4]

Study title	PICO	Results	Reference
		3800, respectively) compared with South Africa (US$ 500) including ART costs. **Conclusions** Our results estimate that BPaL can be a cost-saving addition to the local TB programmes in varied programmatic settings.	
Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis	**Population**: all patients with RR-TB in four countries with a range of characteristics potentially relevant to global decision-making context, including burden of MDR/RR-TB, burden of HIV among people with TB, and current mix of long vs. short SOC regimens for MDR-TB **Interventions and comparators** The TB-PRACTECAL trial evaluated three six-month treatment regimens; arm 3 included bedaquiline, pretomanid and tapered-dose linezolid (600mg daily for 16	BPaL was the most cost-saving regimen in all countries, saving $112-$1,173 per person. BPaLM was the preferred regimen at a willingness to pay per DALY of 0.5 GDP per capita in all settings. Our findings indicate BPaL-based regimens are likely to be cost-saving and more effective than the current standard of care in a range of settings. Countries should consider programmatic uptake of BPaL-based regimens.	Sweeney *et. al.*, 2022 [3]

Study title	PICO	Results	Reference
	weeks then 300mg daily for the remaining 8 weeks) (BPaL). Arm 1 included the BPaL backbone with addition of moxifloxacin (400mg) (BPaLM); arm 2 included the BPaL backbone with addition of clofazimine (50-100mg) (BPaLC). Each TB-PRACTECAL regimen was compared with the current mix of SOC regimens, which was estimated from the reported number of patients enrolled on short vs. long MDR-TB regimens in data underlying the most recent Global TB Report		
Budgetary impact of using BPaL for treating extensively drug resistant tuberculosis	**Population:** 908 projected number of patients with XDR-TB who were anticipated to start using BPaL during 2020–2024. **Interventions and comparators:**	BPaL regimen can be highly cost-saving compared with conventional regimens to treat patients with XDR-TB	Christiaan Mulder et al.,[22]

Study title	PICO	Results	Reference
	costs and budget impact concerning the use and introduction of BPaL regimen to the conventional regimens in each country to treat patients with XDR-TB Conventional regimens included bedaquiline and linezolid with four to six additional anti-TB drugs administered over at least 20 months		
Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients	188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria	Overall acceptability for BPaL was high, especially patient friendliness was often rated as acceptable (93%, 124/133). In contrast, patient friendliness of the ITR was rated as acceptable by 45%. Stakeholders appreciated that BPaL would reduce workload and financial burden on the health care system	S. E. J. van de Berg et al.,[23]
Lifesaving, cost-saving: Innovative simplified regimens for drug-resistant tuberculosis		The cost of implementing BPaLM/BPaL regimens, even without accounting for patient-incurred costs, is potentially 40–90% less expensive when compared with current regimens, despite containing two innovative new drugs (bedaquiline and pretomanid). In addition to the cost savings,	Aastha Gupta et al.,[24]

Study title	PICO	Results	Reference
		the BPaLM/BPaL regimens significantly reduce the pill burden and economic hardship for patients, simplifying administration and improving the patient experience	

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