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Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis

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ABSTRACT

Introduction Bedaquiline, pretomanid and linezolid (BPaL) is a new all oral, 6-month regimen comprised of bedaquiline, the new drug pretomanid and linezolid, endorsed by the WHO for use under operational research conditions in patients with extensively drug-resistant tuberculosis (XDR-TB). We quantified per-patient treatment costs and the 5-year budgetary impact of introducing BPaL in Indonesia, Kyrgyzstan and Nigeria.

Methods Per-patient treatment cost of BPaL regimen was compared head-to-head with the conventional XDR-TB treatment regimen for respective countries based on cost estimates primarily assessed using microcosting method and expected frequency of each TB service. The 5-year budget impact of gradual introduction of BPaL against the status quo was assessed using a Markov model that represented patient's treatment management and outcome pathways.

Results The cost per patient completing treatment with BPaL was US$7142 in Indonesia, US$4782 in Kyrgyzstan and US$7152 in Nigeria – 57%, 78% and 68% lower than the conventional regimens in the respective countries. A gradual adoption of the BPaL regimen over 5 years would result in an 5-year average national TB service budget reduction of 17% (US$128 780) in XDR-TB treatment-related expenditure in Indonesia, 15% (US$700 247) in Kyrgyzstan and 32% (US$1 543 047) in Nigeria.

Conclusion Our study demonstrates that the BPaL regimen can be highly cost-saving compared with the conventional regimens to treat patients with XDR-TB in high drug-resistant TB burden settings. This supports the rapid adoption of the BPaL regimen to address the significant programmatic and clinical challenges in managing patients with XDR-TB in high DR-TB burden countries.

Key questions

What is already known?

- Conventional treatment for extensively drug-resistant tuberculosis (XDR-TB) is highly costly to both the health systems and to the patients—posing significant challenges in treatment adherence and ultimately treatment outcomes.
- A 6-month novel regimen (bedaquiline, pretomanid and linezolid; BPaL) containing three oral medications—pretomanid, bedaquiline and linezolid—developed by the Global Alliance for TB Drug Development (TB Alliance) received regulatory approval from the United States Food and Drug Administration in 2019, and the WHO announced it recommends its use under operational research conditions.
- We found no study estimating the potential cost trade-offs and budget impact of introducing BPaL alongside the continued use of the conventional XDR-TB treatment regimens.

What are the new findings?

- Our study is the first study to empirically assess costs of health service components for patients with XDR-TB and quantify the budget impact of switching to the BPaL regimen in three geographically diverse high drug-resistant TB burden countries.
- On a per-patient basis, the BPaL regimen can be two-to-five fold cheaper to treat patients with XDR-TB compared with the conventional regimens.
- Gradual adoption of BPaL would result in an average reduction of between 15% and 32% in budgets required to manage patients with XDR-TB.

What do the new findings imply?

- Our study demonstrates that the BPaL regimen can be highly cost-saving compared with conventional regimens to treat patients with XDR-TB.
- Our study supports the rapid adoption of the BPaL regimen in countries fighting against a high drug-resistant TB burden.

INTRODUCTION

The increasing burden of drug-resistant tuberculosis (TB) is a significant public health concern. Particularly, the problem of providing appropriate treatment to those with extensively drug-resistant TB (XDR-TB)—defined for the purpose of this study as patients with multidrug resistant TB (MDR-TB), whose TB strains are also

resistant to at least one fluoroquinolone and a second-line injectable agent—is alarming. The global number of reported XDR-TB patients increased to 12 350 in 2019 compared with 10 800 in 2017.[1] This number likely still reflects a substantial underestimate given the need for advanced drug susceptibility testing. Although XDR-TB treatment coverage has improved, treatment completion rates remain low at 39% with a considerable proportion of patients with XDR-TB dying (26%), failing treatment (18%) or lost to follow-up (LTFU) (18%).[2] In addition, high costs and long treatment duration associated with the conventional XDR treatment regimens may pose financial challenges for both the National TB Programmes (NTPs) and patients with XDR-TB. As such, these financial burdens can impede the progress towards the 2030 end TB targets.[3]

The low treatment success is attributable to the complexity and challenges associated with the conventional XDR-TB treatment regimens. A typical XDR-TB treatment lasts at least 20 months requiring lengthy hospitalisation during the intensive phase and use of at least seven drugs, including 6 months daily administration of injectable drugs that may result in patients experiencing adverse events.[4 5] Likewise, conventional XDR-TB treatment is highly costly to both the health systems and to the patients—both out-of-pocket and in productivity losses—posing significant challenges in treatment adherence and ultimately treatment outcomes.[6–8] Given these concerns, promising trial results of a 6-month novel regimen (bedaquiline, pretomanid and linezolid; BPaL) containing three oral medications—pretomanid, bedaquiline and linezolid—developed by the Global Alliance for TB Drug Development (TB Alliance) provides a hopeful outlook in managing patients with XDR-TB.[9] The results of the Nix-TB clinical trial evaluating the BPaL regimen showed 89% treatment efficacy in patients with XDR-TB and 92% in patients who had MDR-TB treatment intolerance (to regimens available in South Africa 2015–2017) or failed MDR-TB treatment, with insignificant differences in adverse events to other regimens containing linezolid.[10 11] Furthermore, the BPaL regimen proved to be equally effective in both HIV-negative patients and people living with HIV on antiretroviral therapy.[11]

In August 2019, BPaL received regulatory approval from the United States Food and Drug Administration and the WHO announced it recommends its use under operational research conditions.[10 12] In 2020, the regimen was granted conditional marketing authorisation by European Medicines Agency. Given favourable clinical trial outcomes and regulatory approvals for its wide use, it is equally important to understand the potential cost trade-offs and budget impact of introducing BPaL alongside the continued use of the conventional XDR-TB treatment regimens in various epidemiologic and operational settings.[13] We conducted empiric cost and budget impact analyses from a health service provider perspective of introducing the BPaL regimen alongside the use of conventional regimens for XDR-TB treatment in three high MDR-TB burden countries.

METHODS

Study overview

This study was conducted in Indonesia, Kyrgyzstan and Nigeria, which are among the 30 high-burden countries for MDR-TB.[14] The number of laboratory-confirmed patients with XDR-TB in these countries was 33, 109 and 16, respectively, in 2019.[1] We collected the projected number of patients with XDR-TB who were anticipated to start using BPaL during 2020–2024 from a separate study (submitted for publication), in which we conducted semistructured interviews with NTPs in the three countries to gather in-depth information on country targets and planned regimens for DR-TB treatment (table 1).

We compared 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 (online supplemental table S1). For the BPaL regimen, we assumed a duration of 6 months for the full course of treatment.

Cost analysis

We first conducted a landscape analysis, in close collaboration with the NTP staff, to identify key health services and utilisation frequencies necessary to assess empiric unit cost estimates and per-patient costs to treat patients with XDR-TB in the respective countries. Health service costs were primarily assessed based on the bottom-up costing method, multiplying empirically measured direct and indirect use of resources by unit prices/cost estimates necessary to complete each service process (online supplemental tableS2). For resource use and cost data that were not possible to empirically collect at each study site, we reviewed literature (including estimates from World Health Organization Choosing Interventions that are Cost-Effective (WHO-CHOICE)), price catalogues, financial records service utilisation statistics (online supplemental Cost Analysis). These costs were estimated using top-down method, where estimated service-specific total costs were divided by service use/volume.[15] Capital costs including buildings, equipment, vehicles and furniture were annualised using a discount rate reflecting the economics in each country (5% in Kyrgyzstan, 3% in Indonesia and Nigeria) and the standard assumption of respective useful life for each capital good.[15 16] All costs were assessed as 2019 US$ adjusted for inflation for cost data available in years other than 2019.[13 17 18] Cost data collected in local currency were converted to the 2019 US$ estimates using the Oanda currency converter.[19] All cost data were collected using a modified version of a validated Excel-based tool developed by the Management Sciences for Health for the USAID-funded, TB CARE 1 project, led by KNCV.[20]

Table 1 Model parameters

	Conventional regimen*			Source	BPaL*			Source
Treatment parameters probabilities	%				%			
LTFU while on treatment	18.6			(25)	1.4			(11)
Permanently discontinuing treatment due to adverse events	14.1			(23)	14.1			(23)
Dying during treatment	11.8			(25)	8.5			(11)
Dying after LTFU (monthly)	2.7			(22)	2.7			(22)
Dying after permanently discontinuing treatment	11.8			(25)	8.5			(11)
Resuming treatment after LTFU	16.4			(22)	16.4			(22)
Hospitalisation after permanently discontinuing treatment	10			(24)	10			(24)
Switching to conventional regimen after permanently discontinuing BPaL	NA				50			Assumption
Treatment completion	58			Derived from model	78			Derived from model
Natural cure if LTFU or permanently discontinuing treatment	21			Derived from model	13			Derived from model
	Conventional regimen			**Source**	**BPaL**			**Source**
	Indonesia	Kyrgyzstan	Nigeria		Indonesia	Kyrgyzstan	Nigeria	
Cost parameters US$								
Average monthly drug costs	378.90	541.93	298.12	Online supplemental table S2	534.50	186.84	191.39	Online supplemental table S2
Average monthly treatment management costs	173.41	126.76	453.95	Online supplemental table S2	225.32	188.92	493.38	Online supplemental table S2
Cohort parameters								
Annual XDR-TB patients treated with regimen—nr (%)								
2020	58 (100)	167 (100)	250 (100)	Gupta *et al* (submitted)	0 (0)	0 (0)	0 (0)	Gupta *et al*. (submitted)
2021	61 (100)	175 (100)	275 (100)	Gupta *et al* (submitted)	0 (0)	0 (0)	0 (0)	Gupta *et al*. (submitted)
2022	32 (50)	184 (100)	138 (50)	Gupta *et al*. (submitted)	32 (50)	0 (0)	138 (50)	Gupta *et al*. (submitted)
2023	33 (50)	135 (70)	75 (25)	Gupta *et al*. (submitted)	33 (50)	58 (30)	225 (75)	Gupta *et al*. (submitted)
2024	34 (50)	78 (38%)	88 (25)	Gupta *et al*. (submitted)	34 (50)	125 (62)	263 (75)	Gupta *et al*. (submitted)

*Assumed similar probabilities across the three countries.
BPaL, bedaquiline, pretomanid and linezolid; LTFU, lost to follow-up; XDR-TB, extensively drug-resistant tuberculosis.

Perpatient costs in treating and monitoring patients with XDR-TB for each regimen were assessed assuming full adherence to the national guideline and algorithm in each country. These estimates were calculated based on identified frequency or quantities of key health services and medical commodities (eg, drugs) consumed by one patient with XDR-TB throughout the entire TB care cascade from the point when the patient was initiated on treatment. Each health service utilisation frequency was then multiplied by service unit cost to arrive at the total per-patient cost. Costs of drugs were categorised into intensive and continuation treatment phases. Prices of TB drugs for Kyrgyzstan and Nigeria were based on the Global Drug Facility (GDF) Medicines Catalog from November 2018.[21] In Indonesia, the GDF catalogue was used for imipenem/cilastatin, whereas the prices of all other drugs except for pretomanid were extracted from the national e-catalogue, which is the NTP procurement

database. For pretomanid, we included the price of US$364 for the entire 6-month BPaL treatment course, as listed on the GDF catalogue in October 2019. Treatment management costs included costs of inpatient days, outpatient consultations (including directly observed therapy (DOT), home visits and other patient support), safety monitoring investigations and follow-up testing for treatment monitoring.

Budget impact analysis

We built a Markov model that represents different states of patient with XDR-TB care and outcomes, starting from the point of treatment initiation (eg, initial diagnostic process costs not included), in introducing the BPaL regimen alongside the conventional regimen with one full cycle representing 1 month (online supplemental figure S1, a simplified visual model representation). Patient outcomes and costs were tallied over a total of 60 cycles to represent budget years over 2020–2024. At the end of each cycle, patients can transition to the following states: (1) next month of XDR-TB treatment, (2) LTFU, (3) treatment discontinuation due to adverse events, (4) death, (5) treatment completion or (6) natural cure (table 1). For patients with LTFU, irrespective of the state, we assumed that 16.4% would return to care and undergo the entire duration of their initial regimen and, therefore, incurred costs, irrespective of their treatment regimen.[22] We assumed that 14.1% of the patients would experience major adverse events requiring discontinuation of XDR-TB treatment,[23] out of those, 10% would incur 1 day of hospitalisation costs due to myelosuppression, irrespective of the treatment regimen.[24] For patients permanently discontinuing BPaL due to adverse events, we assumed that 50% would be switched to the conventional regimen and incur drug costs for the full duration of that regimen on top of the initial BPaL regimen costs. The remainder of the patients who permanently discontinued treatment either die or naturally cure (table 1).[25]

For each country, the annual and 5-year costs were calculated by multiplying the expected number of patients by cumulative service utilisation and costs of XDR-TB care for respective regimen tallied for each stage state over 12 and 60 model cycles. Annual and 5-year net budget impact was assessed by comparing the current budget scenario, in which all patients with XDR-TB are initiated on the conventional regimens against the scenario, in which BPaL would be gradually introduced over the 5-year period. Costs and outcomes were tracked for all patients initiating on XDR-TB treatment within the 5-year period until they reached one of the treatment outcome states.

Sensitivity analysis

We conducted one-way sensitivity analyses of key parameters to determine the robustness of our model results regarding the average cost per BPaL treatment completed and the average net budget impact. We varied: (1) the timeline of introducing BPaL (±1 year), (2) the population eligible for the BPaL regimen (±20%), (3) reducing the dosage of linezolid with 50% in the BPaL regimen as being studied in the ZeNix trial[26] and (4) reducing the frequency of outpatient consultations to weekly instead of daily.

Ethical statement

This manuscript structure follows the Consolidated Health Economic Evaluation Reporting Standards statement checklist which is based on the format of the CONSORT statement checklist.[27]

Patient and public involvement

The National Tuberculosis Programs of all countries endorsed this study. No patient was involved in generating the research questions or the outcomes measures, nor were they involved in designing the study, or developing the models. No patient was consulted on interpretation or writing up the results. The results will be disseminated to the National Tuberculosis Programs. There are no plans to disseminate the results to patients or the community.

RESULTS

Cost per patient treated

Unit costs, types and service utilisation frequencies of key health services necessary for XDR-TB care varied across the three countries assessed in our study (online supplemental table S2). The cost per patient treated when fully adherent with the BPaL regimen was US$4559 in Indonesia, US$2255 in Kyrgyzstan and US$4109 in Nigeria (figure 1). In Indonesia, drugs constituted 70% of the total cost of the BPaL regimen, versus 49% in Kyrgyzstan and 27% in Nigeria. In Kyrgyzstan, hospitalisation constituted 24% of the total cost of the BPaL regimen, and in Nigeria outpatient consultations 51%. The cost per patient treated with the respective conventional regimens was US$11 046 in

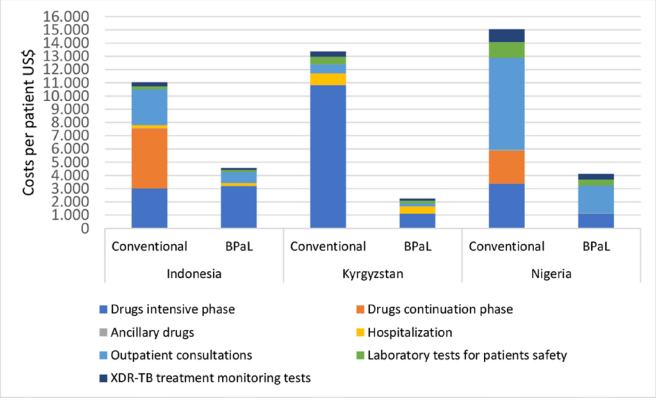

Figure 1 The drug and treatment management costs (in US$) per XDR-TB patient 100% adhering to the conventional regimens and BPaL by country. BPaL, bedaquiline, pretomanid and linezolid; XDR-TB, extensively drug-resistant tuberculosis.

Table 2 Annual costs and cost per treatment completed by treatment regimen Indonesia, 1000 US$

	Year					
	2020	2021	2022	2023	2024*	Average
Indonesia						
Current budget scenario						
All conventional regimen	260.1	493.6	549.8	570.2	913.3	
New budget scenario						
Conventional regimen	260.1	493.6	406.5	301.8	456.7	
BPaL	0	0	127.2	159.9	195.0	
Cost sum	260.1	493.6	533.7	461.7	651.6	
Net budget impact (%)	0 (0)	0 (0)	−16,1 (-3)	−108.5 (-19)	−261.7 (-29)	−128.8 (-17)
Cost per treatment completed						
Conventional regimen	NA	35.2	11.8	10.6	9.3	16.7
BPaL	NA	NA	10.2	6.3	5.0	7.1
Kyrgyzstan						
Current budget scenario						
All conventional regimen	876.7	1702.9	1902.7	1997.8	3320.7	
New budget scenario						
Conventional regimen	876.7	1702.9	1902.7	1686.9	1688.9	
BPaL	0	0	0	141.6	400.6	
Cost sum	876.7	1702.9	1902.7	1828.6	2089.5	
Net budget impact (%)	0 (0)	0 (0)	0 (0)	−169.2 (-8)	−1231.2 (−37)	−700.2 (−15)
Cost per treatment completed						
Conventional regimen	NA	42.2	19.3	16.3	9.1	21.7
BPaL	NA	NA	NA	6.2	3.3	4.8
Nigeria						
Current budget scenario						
All conventional regimen	1620.3	3018.1	3319.9	3499.0	6125.1	
New budget scenario						
Conventional regimen	1620.3	3018.1	2421.1	1365.5	1578.7	
BPaL	0	0	517.6	978.3	1453.6	
Cost sum	1620.3	3018.1	2938.8	2343.8	3032.3	
Net budget impact (%)	0	0	−381.2 (−11)	−1155.1 (−33)	−3092.8 (−50)	−1543.0 (−32)
Cost per treatment completed						
Conventional regimen	NA	49.9	16.0	10.8	11.2	22.0
BPaL	NA	NA	9.6	6.9	5.0	7.2

BPaL, bedaquiline, pretomanid and linezolid.

Indonesia, US$13 374 in Kyrgyzstan and US$15 042 in Nigeria (figure 1). For Indonesia and Kyrgyzstan, drugs constituted the largest percentage of the total cost of the conventional regimen (68% and 81%, respectively), whereas in Nigeria, outpatient consultation was the largest cost relatively with 46%.

Cost per treatment completed

The cost per treatment completed among patients treated with BPaL was on average US$7142 in Indonesia, US$4782 in Kyrgyzstan and US$7152 in Nigeria (table 2). These costs were 57%, 78% and 68% lower, respectively, when compared with the cost of completing treatment with conventional regimens, US$16 732 in Indonesia, US$21 714 in Kyrgyzstan and US$22 021 in Nigeria (table 2). In our sensitivity analysis, reducing the dosage of linezolid with 50% reduced the average cost per BPaL treatment completed to US$6026 (−16%) in Indonesia, to US$4517 (−6%) in Kyrgyzstan, and to US$6900 (−4%) in Nigeria (figure 2A, online supplemental figures S2A and figure S3A). Reducing DOT to weekly visits reduced the average cost per BPaL

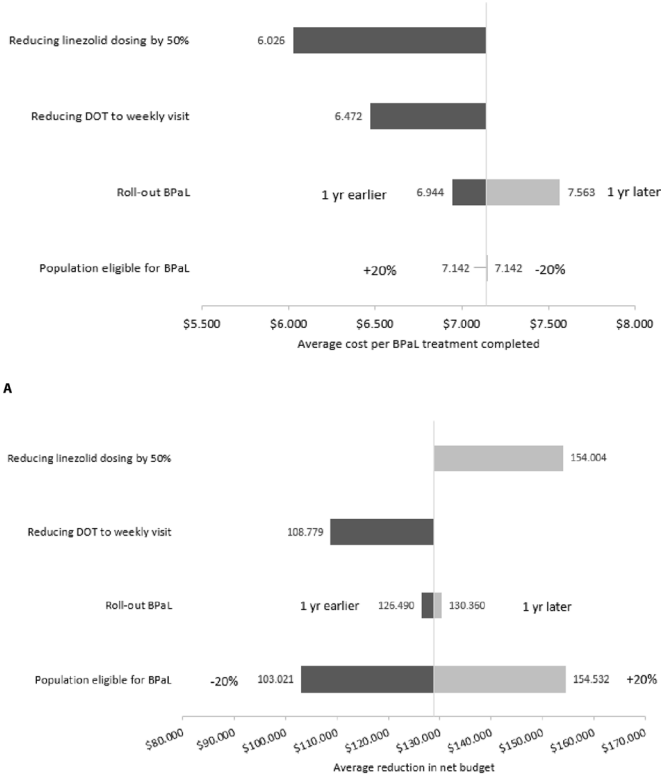

Figure 2 (A) One-way sensitivity analysis for the average cost per BPaL treatment completed in Indonesia. (B) One-way sensitivity analysis for the average reduction in the net budget in Indonesia. BPaL, bedaquiline, pretomanid and linezolid.

treatment completed to US$5387 (–25%) in Nigeria, to US$6472 (–9%) in Indonesia and to US$4661 (–3%) in Kyrgyzstan (figure 2A, online supplemental figure S2A and figure S3A).

Budget impact

Adoption of the BPaL regimen would result in an average reduction in XDR-TB-related expenditure of US$128 780 (17%) in Indonesia, US$700 247 (15%) in Kyrgyzstan and US$1 543 047 (32%) in Nigeria (table 2). In our sensitivity analysis, we found that accelerating the uptake of BPaL with 1 year would reduce the average costs in Kyrgyzstan to US$763 412 (additional 9% reduction) but would have little impact in Indonesia and Nigeria (figure 2B, online supplemental figure S2B and figure S3B). Likewise, delaying the uptake with 1 year in Kyrgyzstan would lower the reduction to US$466 621 (33% higher expenditure) but would have little impact in Indonesia and Nigeria. Reducing the dosage of linezolid with 50% resulted in an average reduction of US$154 004 (20% additional reduction) in Indonesia, but had little impact in the other countries.

DISCUSSION

To our knowledge, this is the first study to empirically assess costs of health service components for XDR-TB and quantify the budget impact of switching to the recently FDA-approved pretomanid-containing BPaL regimen in three geographically diverse high DR-TB burden countries. On a perpatient basis, the BPaL regimen can be two-to-five fold cheaper to treat patients with XDR-TB compared with the conventional regimens, assuming full adherence to the respective care paths outlined in the respective NTP guidelines. We showed that gradual adoption of BPaL would result in an average reduction of between 15% and 32% in budgets required to manage patients with XDR-TB in the respective countries.

Of all the health systems service components, BPaL drug costs constituted the largest contributor to the overall cost-savings. Across the three countries included in this study, using BPaL would result in at least 57% (and as high as 90%) reduction in per-patient drug costs compared with the current regimens to treat XDR-TB. This was primarily due to a reduction in the number of drug types and shortened duration of treatment for the BPaL regimen compared with conventional regimens. Furthermore, procurement prices of key drugs used to treat XDR-TB largely contributed to the difference in cost-savings across the three countries. For example, the unit cost used for one tablet of bedaquiline was US$5.71 in Indonesia, which is more than two times as high as the price charged through GDF. Similarly, the unit cost of one tablet of linezolid was US$6.39, which is more than five times higher than the price charged through GDF. In Indonesia, it is anticipated that these key drugs for XDR-TB treatment will be not procured through GDF for the foreseeable future. Likewise, Indonesia had highest per-patient cost of XDR-TB treatment using BPaL (US$4559), resulting in lowest absolute cost-savings compared with other countries

Another notable contributing factor to the cost-savings associated with the BPaL regimen was the reduction in health service utilisation required to manage treatment of patients with XDR-TB. If the BPaL regimen would be used in the three countries, we anticipate that the number of visits to clinics for outpatient consultation, number and types of patient safety and treatment monitoring tests would be dramatically reduced due to simplified standardised drug regimen and a 14-month reduction in treatment duration compared with the conventional XDR-TB treatment course. Furthermore, if factoring in programmatic (eg, simplified procurement and supply chain management) and operational (decentralisation of XDR-TB treatment) benefits of the simplified and standardised treatment regimen, we expect that the economic case for adopting BPaL regimen would become more favourable.

In our sensitivity analyses, we showed that the average costs per BPaL treatment completed in Indonesia were most sensitive to halving the dosage of linezolid, which showed to be efficacious and more tolerable in the ZeNIX trial.[26] Prescribing BPaL to the other WHO-recommended patient populations, patients who are either unable to tolerate or failed MDR-TB treatment would increase

the reduction in the net budget (figure 2B). Increasing the speed of BPaL roll-out would reduce the XDR-TB-related expenditure, particularly when the proportion of patients with XDR-TB being enrolled on BPaL would increase over the years.

Our findings should be interpreted in light of the following limitations. First, because the BPaL regimen is a novel regimen that has not yet been widely adopted or studied in large scale, we primarily relied on the data available from the Nix trial to populate the BPaL treatment parameters in the model. Some parameter values in the model may, therefore, have been optimistic in a simplified model structure that may not fully capture the complexities of the XDR-TB patient care. For example, in our study, we used 1.4% LTFU rates of BPaL regimen as reported in the Nix trial. In reality, LTFU rates may be higher, and this would result in higher cost estimate per patient completing BPaL treatment, reducing the overall cost-savings associated with the introduction of BPaL regimen. Second, while we accounted for the impact of adverse events on treatment outcomes and overall treatment costs, we assumed types of adverse events, and management of adverse events would be similar between the two regimens (eg, 10% of the patients would require hospitalisation due to myelosuppression for both regimens). As such, we did not assess costs specific to managing adverse events, resulting from respective XDR-TB treatment. If frequency and types of adverse events associated with the programmatic use of BPaL regimen are higher compared with the conventional regimen, we expect that the overall cost-savings for BPaL regimen will also subsequently be reduced. While uncertainties around these parameters did not impact our overall cost-saving and budget impact estimates for BPaL, 'real-world' cost implications may be more significant on overall costs associated with the introduction and use of BPaL regimen. These factors are being evaluated in on-going operational research projects in various settings by the TB Alliance and KNCV.

Second, the overall cost and budget estimates for BPaL introduction were estimated based on the anticipated number of patients who will be initiated on the BPaL regimen in the respective years between 2020 and 2024 in each country. As our study was done prior to the FDA approval, we took a conservative approach in estimating these numbers with the key stakeholders from the NTP in the respective countries. Likewise, if countries take more rigorous and inclusive approach to introducing the BPaL regimen, we expect that the overall cost-savings and budget impact be greater than what was projected in our analyses. Third, in our budget impact analyses, we did not consider initial diagnostic costs and the costs associated with the implementation when transitioning to the novel regimen. While we expect that initial diagnostic process will not change for the decision to initiate patients BPaL, if the diagnostic process becomes simplified for BPaL, this would further favour adoption of BPaL regimen. Furthermore, while we expect that the costs associated with the implementation of the new regimen are an important factor, if the regimen can be scaled-up and maintained for the longer term, these costs will be marginalised.[28] However, these implementation costs will vary considerably depending on the operational conditions, training needs, coverage and speed of implementation to the lower levels of health systems. Therefore, we encourage future studies to thoroughly investigate programmatic and implementation costs for introducing new treatment regimens for TB.[28] Finally, as our analyses were restricted to the health service provider perspective, we did not factor potential patient benefits and cost that could result from the simplified treatment regimen for XDR-TB. We encourage future studies to empirically assess patient perspective costs and benefits of simplified standardised regimens for DR-TB.[11]

CONCLUSION

Our study demonstrates that the BPaL regimen can be highly cost-saving compared with conventional regimens to treat patients with XDR-TB. While further evidence on costs from the patient perspective would provide an important complementary evidence to our work, findings from our study support the rapid adoption of the BPaL regimen in countries fighting against a high drug-resistant TB burden with limited health system capacity.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Table S1. Treatment regimens

	Conventional regimen Indonesia	**Conventional regimen Kyrgyzstan**	**Conventional regimen Nigeria**	**BPaL**
Intensive phase	Bedaquiline Clofazimine Ethionamide Cycloserine Linezolid Ethambutol Pyrazinamide Isoniazid (high dose) Pyridoxin	Bedaquiline Clofazimine Cycloserine Imipenem-Cilastatin Amoxicillin-Clavulanic acid Linezolid Pyridoxin	Bedaquiline Clofazimine Delamanid Isoniazid (high dose) Linezolid PAS-(H)-4-(S)-30 Pyrazinamide Pyridoxin	Bedaquiline Pretomanid Linezolid Pyridoxin
Continuation phase	Ethionamide Cycloserine Linezolid Clofazimine Ethambutol Pyrazinamide Isoniazid (high dose) Pyridoxin	(no different continuation phase regimen)	Bedaquiline Clofazimine Linezolid PAS-(H)-4-(S)-30 Pyrazinamide Pyridoxin	
Duration of intensive phase	6 months	Not applicable	6 months	Not applicable
Total duration	20 months	20 months	20 months	6 months

Table S2. Unit costs of the cost components and the quantities of use for the current regimens and BPaL for treating XDR-TB in Indonesia, Kyrgyzstan, and Nigeria.

	Unit costs (USD, 2017)			Quantities of use				Source Unit costs Indonesia/Kyrgyzstan/Nigeria
	Indonesia	Kyrgyzstan	Nigeria	Conventional XDR-TB regimen			BPaL [I] (Indonesia), [K] (Kyrgyzstan), [N] (Nigeria)	
				Indonesia	Kyrgyzstan	Nigeria		
Drugs								
Intensive phase								
Bedaquiline 100 mg	5.71	2.16	2.16	188	356	188	200	national e catalogue / GDF Nov 2018 / GDF Nov 2018
Clofazimine 100 mg	1.13	1.00	1.00	540	600	180	0	national e catalogue / GDF Nov 2018 / GDF Nov 2018
Cycloserine 250 mg	0.19	0.23	NA	540	1,800	-	0	national e catalogue / GDF Nov 2018
Delamanid 50 mg	NA	NA	2.77	0	0	720	0	GDF Nov 2018
Ethambutol 400 mg	0.03	NA	NA	540	0	0	0	national e catalogue /
Ethionamide 250 mg	0.08	NA	NA	540	0	0	0	national e catalogue /
Imipenem-Cilastatin 500 mg/500 mg	NA	3.40	NA	0	2,400	0	0	GDF Nov 2018
Amoxicillin-Clavulanic acid 250 mg/ 125 mg	NA	0.12	NA	0	1,200	0	0	GDF Nov 2018
Isoniazid 300 mg	0.03	NA	0.02	360	0	900	0	national e catalogue / GDF Nov 2018
Linezolid 600 mg	6.39	1.20	1.20	180	600	180	265	national e catalogue / GDF Nov 2018 / GDF Nov 2018
PAS-(H)-4-(S)-30	NA	NA	1.46	0	0	360	0	GDF Nov 2018
Pyrazinamide 400 mg	0.02	NA	NA	720	0	0	0	national e catalogue
Pyrazinamide 500 mg	NA	NA	0.06	0	0	540	0	GDF Nov 2018
Pretomanid 200 mg	2.00	2.00	2.00	0	0	0	182	TB Alliance 2019[a]
Continuation phase*								
Bedaquiline 100 mg	NA	NA	2.16	0	0	156	0	national e catalogue / GDF Nov 2018
Clofazimine 100 mg	1.13	NA	1.00	1,260	0	420	0	national e catalogue / GDF Nov 2018
Cycloserine 250 mg	0.19	NA	NA	1,260	0	0	0	national e catalogue
Ethambutol 400 mg	0.03	NA	NA	1,260	0	0	0	national e catalogue

Ethionamide 250 mg	0.08	NA	NA	1,260	0	0	0	national e catalogue
Isoniazid 300 mg	0.03	NA	NA	840	0	0	0	national e catalogue
Linezolid 600 mg	6.39	NA	1.07	420	0	420	0	national e catalogue / GDF Nov 2018
PAS-(Na)-4-(S)-30	NA	NA	1.36	0	0	840	0	GDF Nov 2018
Pyrazinamide 400 mg	0.02	NA	NA	1,680	0	0	0	national e catalogue
Pyrazinamide 500 mg	NA	NA	0.06	0	0	1,260	0	GDF Nov 2018
Ancillary drugs								
Pyridoxine 50 mg	NA	NA	0.10	0	0	1,200	$0^{I,K}$, 360^{N}	Private pharmacy
Pyridoxine 100 mg	0.04	0.03	NA	600	600	0	$180^{I,K}$, 0^{N}	national e catalogue / GDF Nov 2018
Treatment management								
Hospitalization day	212.05	17.91	81.08	1	49	0	1^{I}, 30^{K}, 0^{N}	National insurance / microcosting / literature(1)
Consultation at hospital	NA	2.93	8.42	0	21	1	0^{I}, 9^{K}, 1^{N}	Microcosting / WHO CHOICE
Consultation at health center	1.45	NA	5.75	19	0	20	9^{I}, 0^{K}, 8^{N}	Microcosting / microcosting / WHO CHOICE
DOT at health center	2.69	0.55	6.78	600	550	600	149^{K}, $180^{I,N}$	Microcosting / microcosting / literature(1)
DOTS at hospital	NA	1.51	NA	0	1	0	0^{I}, 1^{K}, 0^{N}	Microcosting
Home visit	NA	1.60	119.35	0	20	20	0^{I}, $6^{K,N}$	Microcosting / literature(1)
Patient support per month	53.68	14.75	16.50	20	20	20	6	NTP / microcosting / top down KNCV
Laboratory tests for patients safety								
ECG	7.63	2.95	16.50	8	22	22	8	Microcosting / Fee at private labs / fee at private lab
Audiometry	13.03	6.05	8.25	1	9	9	0	Fee at private hospitals / Fee at private labs / top down KNCV
Color vision testing	5.80	NA	NA	1	0	0	1^{I}, $0^{K,N}$	Fee at private and public hospitals
Complete blood counts	4.77	4.87	9.90	1	22	22	12	Microcosting / Fee at private labs / fee at private lab
HIV rapid test	NA	NA	3.30	0	0	3	0	fee at private lab

Liver function tests	4.61	16.96	16.50	7	14	14	7	Microcosting / Fee at private labs / fee at private lab
Pregnancy test	NA	NA	3.30	0	0	0.29	0[I,K], 0.29[N]	fee at private lab
Serum creatinine	2.48	3.98	9.90	1	7	7	1	Microcosting / Fee at private labs / fee at private lab
Serum glucose	1.81	2.95	3.30	1	1	1	1	microcosting Fee at private labs / fee at private lab
Thyroid stimulating hormone	17.89	12.68	33.00	4	4	4	0	Fee at private lab / Fee at private labs / fee at private lab
Amylase	NA	NA	16.13	0	0	1	0[I,K], 1[N]	fee at private lab
Lipase	7.07	6.49	32.27	0	1	1	1	Microcosting / Fee at private labs / fee at private lab
Serum albumin	1.88	3.69	4.84	0	0	1	1	Microcosting / Fee at private labs / fee at private lab
Serum potassium	5.94	2.51	6.45	6	7	7	1	Fee at private lab / Fee at private labs / fee at private lab
Hepatitis B Ag	NA	NA	3.30	0	0	1	0[I,K], 1[N]	fee at private lab
Hepatitis C Ag	NA	NA	6.45	0	0	1	0[I,K], 1[N]	fee at private lab
XDR-TB treatment monitoring test								
Smear	1.92	5.45	9.45	13	21	21	7	Microcosting / microcosting / literature(1)
Liquid culture	20.46	NA	NA	13	0	0	6[I], 0[K,N]	Fee at public lab
Solid culture	NA	20.67	54.69	0	13	13	0[I], 6[K,N]	Microcosting / literature(1)
CXR	4.76	2.97	9.90	5	4	5	2	Microcosting / Fee at private labs / top down KNCV

*In Kyrgyzstan no distinction was made between intensive and continuation phase

NA: Not applicable

[a]Applicable to all countries

Cost analysis

The unit costs for inpatient days were calculated using a top-down method for Kyrgyzstan, based on the annual financial report of the national TB hospital and the statistics on inpatient days of TB patients. In Nigeria, the inpatient costs were extracted from the earlier costing study and inflated to the actual cost in USD for 2017 (1). In Indonesia, the costs for inpatient days referred to the standard tariff under National Health Insurance scheme, given that most TB patients are covered by the government. This included the costs for administration, buildings, catering, cleaning, radiology, pharmacy (without the cost of drugs), consumables, laundry, maintenance, security, staff, transportation, and other costs. The unit costs for outpatient consultations included costs for consumables, overhead, staff, transportation allowance, other supplies, and direct personnel costs and were obtained empirically in Kyrgyzstan in the three health facilities mentioned above, and in Indonesia and Nigeria from recent costing studies (Indonesian findings being prepared for publication) (1).

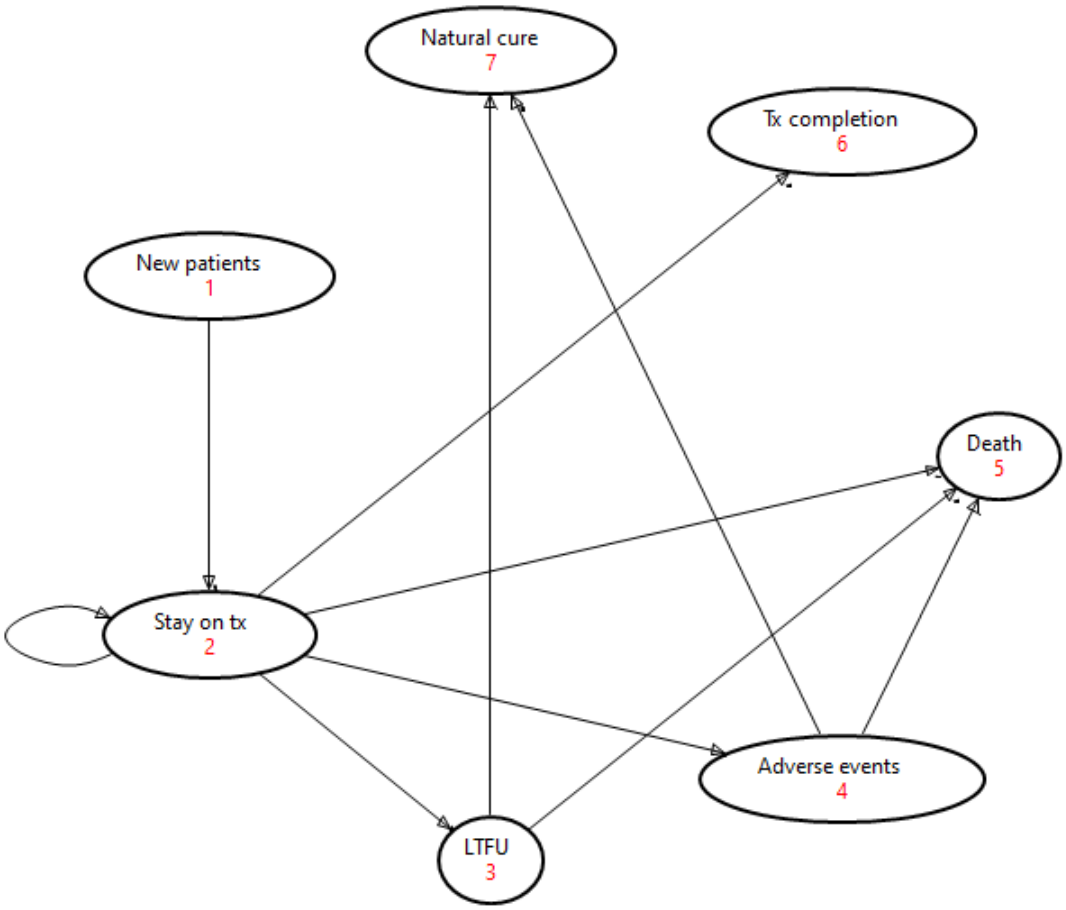

Figure S1. Design of the Markov model for the conventional regimen and the BPaL regimen. For patients on the BPaL regimen who permanently discontinued treatment we assumed that 50% would be switched to the conventional regimen.

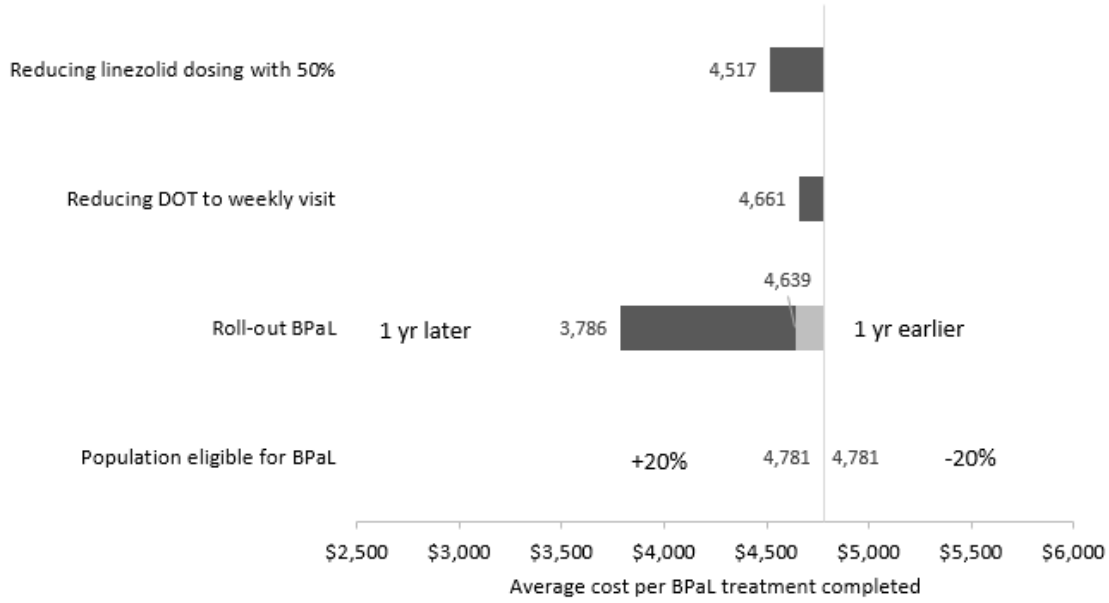

Figure S2A. One-way sensitivity analysis for the average cost per BPaL treatment completed in Kyrgyzstan

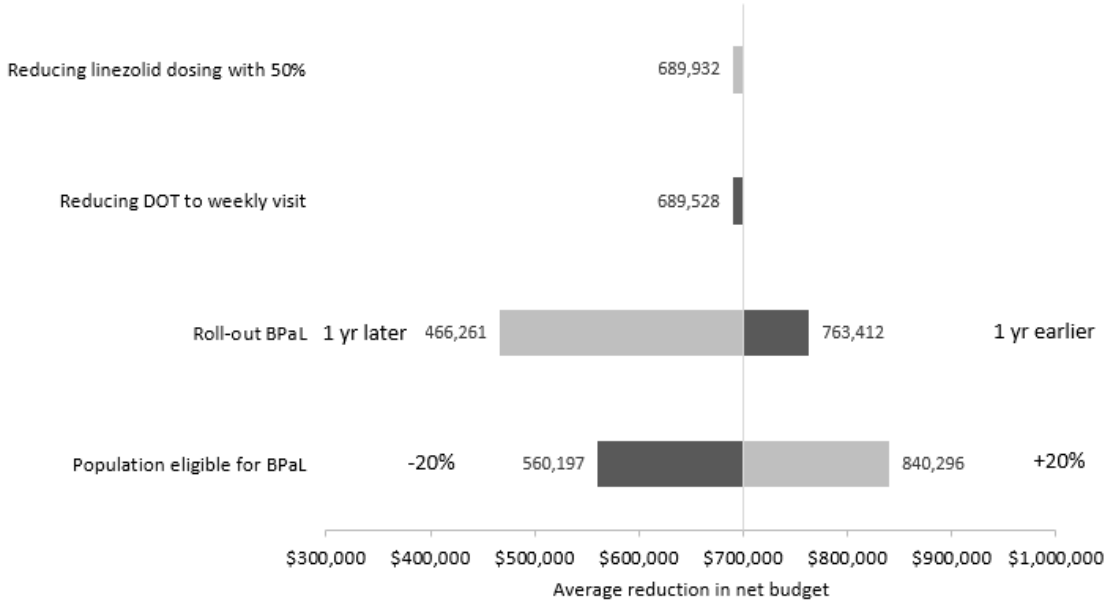

Figure S2B. One-way sensitivity analysis for the average reduction in the net budget in Kyrgyzstan

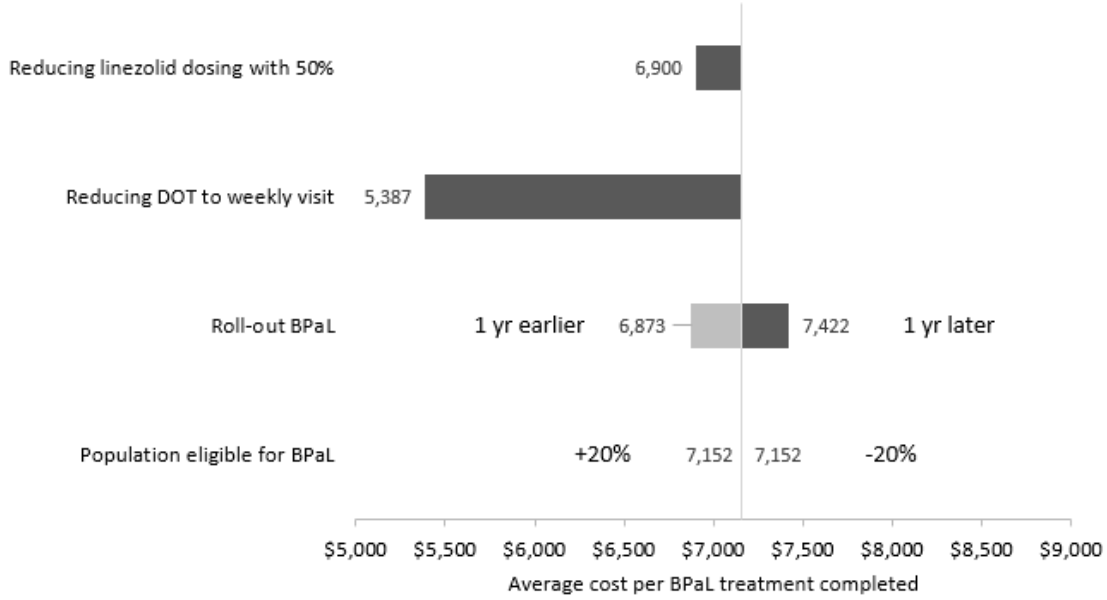

Figure S3A. One-way sensitivity analysis for the average cost per BPaL treatment completed in Nigeria

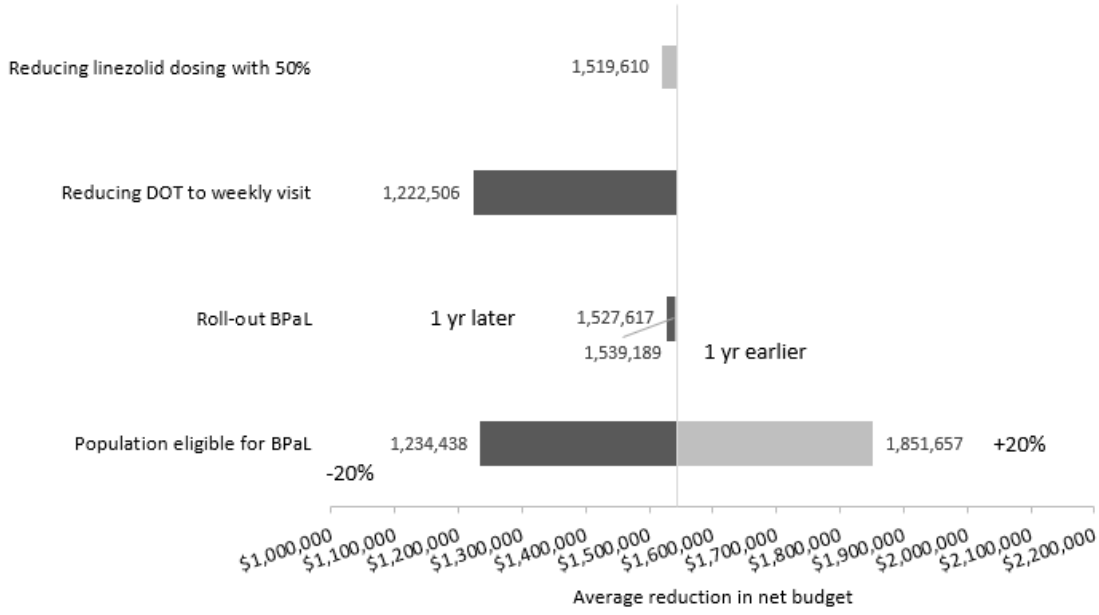

Figure S3B. One-way sensitivity analysis for the average reduction in the net budget in Nigeria

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