Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines

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ABSTRACT

Objectives Patients with highly resistant tuberculosis have few treatment options. Bedaquiline, pretomanid and linezolid regimen (BPaL) is a new regimen shown to have favourable outcomes after six months. We present an economic evaluation of introducing BPaL against the extensively drug-resistant tuberculosis (XDR-TB) standard of care in three epidemiological settings.

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$ 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.

INTRODUCTION

Patients with extensively drug-resistant tuberculosis (XDR-TB) and those who have failed or are intolerant to their multidrug-resistant tuberculosis (MDR-TB) treatment have few treatment options, low cure rates and high mortality.1 Treatment and management of such patients is costly to the health system and patients (with high hospitalisation rates for long periods and high drug costs).2 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, depending on the setting.3 Use of new drug pretomanid in the bedaquiline, pretomanid and linezolid (BPaL) regimen was approved by the US Food and Drug Administration (FDA) under the Limited Population pathway for Antibacterial and antifungal Drugs pathway in 2019 and conditionally approved by the European Medical Agency (EMA) and Drugs Controller General of
India, among others (Democratic Republic of the Congo, Georgia, South Africa, Tajikistan, Turkmenistan, Uzbekistan and Zimbabwe to date). It was also prequalified by WHO. The BPaL regimen was also endorsed for use under operational research conditions by the WHO. This regimen consists of three drugs, is shorter in duration compared with standard therapy and is administered orally. The BPaL regimen was shown to lead to favourable outcomes after 6 months in a high percentage of patients with highly drug-resistant forms of tuberculosis in an open-label, single-group study at three South African sites in the Nix-TB trial. There were associated side effects observed, primarily due to the high dose of linezolid studied. The long-term follow-up of this study recently showed sustained efficacy. An alternative dosing scheme was explored in the phase III ZeNix trial. The results of ZeNix were presented in July 2021 at the International AIDS Conference. They demonstrated that BPaL remains effective in patients with XDR-TB and those who have failed or are intolerant to their MDR-TB treatment with either reduced dosage or duration of the linezolid component of the regimen in sites across Georgia, Moldova, Russia and South Africa. With the maintenance of efficacy, there was a decrease in linezolid-associated side effects.

Following these empirical results, countries may consider the health benefits and economic trade-offs of including this regimen in national recommendations. To date, a series of economic evaluations looking at the addition of bedaquiline to MDR treatment regimens for the treatment of adult patients with pulmonary MDR-TB and/or XDR-TB have been published. However, there has been no economic evaluation of a shorter, all-oral treatment regimen, consisting of three drugs with minimal pre-existing resistance, such as BPaL. We present here an economic evaluation of introducing BPaL for use in XDR-TB against the local standard of care. We consider the eligible population with and without MDR-TB failure or intolerant patients in three epidemiological settings.

METHODS
We developed a Markov cohort model to estimate cost and benefits of BPaL for treatment of a cohort of diagnosed patients with XDR-TB (with and without the inclusion of MDR-TB failure and intolerant patients) in three settings adopting a lifetime horizon and a health sector perspective. We parameterised this model with a combination of publicly available and aggregated cost and health outcome data by setting. Because we used only secondary data sources without any identifiable information and publicly available, this study was exempt from submission to ethics committee. We chose a Markov cohort model, as opposed to a decision tree, to be able to model both disease and treatment processes where timing of events and repeat events are important. In such a modelling framework, the impact of transmission on the wider population has been excluded, which may underestimate health impact. The model schematic is provided in online supplemental figure S1.

Our main analytical outcomes are (1) the incremental costs and disability-adjusted life years (DALYs) averted of using BPaL against the context-specific standard of care at the Global Drug Facility list price and (2) the potential maximum drug price at which BPaL could be considered cost saving in three epidemiological settings.

Population and setting
The primary population modelled is patients with XDR-TB. We also explored in a separate scenario the inclusion of those patients who have failed or are intolerant to their MDR-TB treatments, as this is part of the approved label by the US FDA andEMA. XDR-TB is defined as resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to MDR-TB, defined as resistance to two first-line TB drugs,isoniazid and rifampicin. MDR-TB treatment failure is defined as non-responsiveness to MDR-TB treatment at 6 months (lack of sputum conversion by the end of the intensive phase) and intolerance is defined as the inability to continue a second-line drug regimen due to a documented intolerance to para-aminosalicylic acid, ethionamide, aminoglycosides or fluoroquinolones. We chose to separate these two scenarios because those patients who have failed an MDR-TB regimen containing bedaquiline may not be considered eligible for BPaL without further drug sensitivity testing and considering that the definition of XDR-TB has been recently updated as to include MDR-TB that is resistant to a fluoroquinolone and at least one of bedaquiline or linezolid (or both). We performed the analysis for three countries chosen to represent a range of epidemiological settings across two dimensions: prevalence of MDR-TB and HIV coinfection (epidemiological profiles introduced in online supplemental table S1). These are drivers of observed differences in both burden and mortality from XDR-TB. In South Africa, we observe a high burden of both MDR/XDR-TB and HIV; in Georgia, there is high burden of MDR/XDR-TB but a lower HIV burden; while in the Philippines, there is a low incidence of XDR-TB and HIV.

Intervention, comparator and outcomes
The intervention considered is a shortened (6 months), all-oral regimen for treatment of patients with XDR-TB, including BPaL, see figure 1. This duration can be extended to 9 months in the case of no sputum conversion after 4 months of treatment. We modelled the published prescription recommendations for pretomanid as well as current guidance for monitoring of bedaquiline and linezolid in the definition of tests and visits schedules. We characterised the comparator using standardised recommendations for XDR-TB regimens (18 months) that may be modified based on drug sensitivity testing results. Routine clinical practice as defined in current national guidelines and validated with local expert
opinion in each setting is the comparator. Comparators by setting are detailed in figure 1.

Partial lung resection for patients with XDR-TB is not included for either the intervention or comparator as, after assessing a recent review of the evidence, it was not recommended.30

We used information from the Nix-TB study, an open-label single-arm study, to inform clinical efficacy of the intervention (ClinicalTrials.gov reference: NCT02333799).9 The Nix-TB study aimed to evaluate the efficacy, safety, tolerability and pharmacokinetics of BPaL after six to 6–9 months of treatment in XDR-TB or treatment intolerant or non-responsive MDR-TB. It had a total of 109 patients enrolled. After 6-month follow-up from the end of treatment, it showed that 90% (95% CI, 83 to 95) of participants had a favourable outcome. Side effects included peripheral neuropathy in 81% of patients and myelosuppression in 48%. All these were manageable and led often to dose reductions or interruptions of linezolid treatment. The occurrence of these side effects led to further investigation on how to optimise the linezolid dose. In the ZeNix trial (ClinicalTrials.gov reference: NCT03086486),12 the efficacy observed in Nix-TB was confirmed with less side effects, from 84% to 93% depending on the linezolid dosage across the four arms of the trial.

For state transitions in the Markov cohort model beyond the trial time period and the effectiveness of the comparator, we use national secondary data. Expert elicitation was used where no data were available, for example, estimating the extent to which patients return to care after default. Cure in the standard of care has been defined as reported treatment completed, as recommended by national policies. A patient is classified as having completed treatment if there is no evidence of failure and three or more consecutive negative cultures taken at least 30 days apart after the intensive phase. In the Nix-TB trial, cure was defined as no evidence of infection 6 months after end of treatment.9 Failure is a lack of conversion by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative at the end of the intensive phase. Patients can die at any time and while being in any state. The number of DALYs averted was the measure of quality and length of life chosen to assess health outcomes. DALYs averted are suitable for comparisons across economic evaluations in low-income and middle-income countries consistent with the recommendations of the International Decision Support Initiative Reference Case for Economic Evaluation.31 DALYs averted were calculated as the sum of the present value of future years of life lost through TB mortality and the present value of years adjusted for disability caused by TB using the standard formula.32 Disability weights were sourced from the Global Burden of Disease study in 201733 and are presented in table 1.

Costs
We used cost estimates from the literature and local consultations and guidelines to build disaggregated unit costs for the intervention and comparator (ie, drugs, visits, tests). We did not collect new data but obtained data from the Global Health Costing Consortium database and from VALUE TB (a multicountry TB costing study funded by the Bill and Melinda Gates Foundation).34,35 Unrelated costs and the costs of comorbidities have been excluded, except for costs related to HIV in South Africa, which have a significant impact on the intervention in this setting and are presented separately. All costs are presented in 2018 US$, after conversion from other currencies per standard recommendations.36 Parameters and assumptions made are presented in tables 1 and 2.

We modelled treatment outcomes for 5 years but capture all costs and consequences relevant to the economic evaluation until death. We followed international conventions and discounted both cost and effects at 3% for our main analysis.31

Uncertainty and sensitivity analysis
Uncertainty has been explored using deterministic and probabilistic sensitivity analyses. A deterministic sensitivity analysis is presented to evaluate the main drivers of the results, both in terms of cost savings and DALYs averted. We conducted a sensitivity analysis around discounting assumptions in addition to other parameters.
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The probabilistic sensitivity analysis was done by running the model 10 000 times while sampling from the parameter’s distributions. We present these analyses for two outcomes. First, for the incremental cost per DALY averted of using BPaL against standard of care at the Global Drug Facility list price, we plotted the cost-effectiveness planes by country, illustrating the uncertainty in both costs estimates and DALYs averted. Second, for the potential maximum price at which the BPaL regimen could still be considered cost saving, we present threshold price estimates as curves, plotting the probability of the regimen being cost saving as a function of drug price.

**Patient and public involvement**

There was no direct involvement of patients or the public in this health economics modelling study.

### Table 1  Input parameters for cost-effectiveness analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>South Africa</th>
<th>Georgia</th>
<th>The Philippines</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR intolerant/failure</td>
<td>10% of all patients with MDR-TB</td>
<td>Assumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV prevalence (n=56/109)*</td>
<td>51%</td>
<td>–</td>
<td>–</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 (range 17–60)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment outcomes†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cent completed at 18 mo, SoC</td>
<td>0.73 (0.031)</td>
<td>0.585</td>
<td>0.64–0.73</td>
<td>45–48</td>
</tr>
<tr>
<td>Per cent failure at 18 mo, SoC</td>
<td>0.045 (0.015)</td>
<td>0.073</td>
<td>0.045 (0.015)</td>
<td>45 47 48</td>
</tr>
<tr>
<td>Per cent LTFU at 18 mo, SoC</td>
<td>0.10 (0.021)</td>
<td>0.219</td>
<td>0.15–0.20</td>
<td>45 47 48</td>
</tr>
<tr>
<td>Per cent completed/cure at 6 mo, BPaL</td>
<td>0.90 (0.83–0.95)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cent death, BPaL (n=7/109)</td>
<td>0.064 (0.026)</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Per cent LTFU at 6 mo, BPaL</td>
<td>0.04 (0.021)</td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Outcomes after treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of relapse‡</td>
<td>2836 (2131–3693)</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cent return to care after relapse, SoC and BPaL</td>
<td>0.75 (±20%)</td>
<td>Assumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cent return to care after LTFU, SoC and BPaL</td>
<td>0.20 (±20%)</td>
<td>Assumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival after treatment failure, mo (LTFU/relapse/palliative), SoC and BPaL</td>
<td>19.84 (4.16–26.04)</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR-TB/MDR-TB, without HIV infection</td>
<td>0.333 (0.224–0.454)</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR-TB/MDR-TB, with HIV infection</td>
<td>0.408 (0.274–0.549)</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS receiving ART without TB</td>
<td>0.078 (0.052–0.111)</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All HIV-positive patients are assumed to be on/started on ART.
†Transformed to a rate (per mo) assumed constant.
‡Incidence risk of relapse per 100 000 successfully treated.

ART, antiretroviral treatment; BPaL, bedaquiline, pretomanid and linezolid; LFTU, loss to follow-up; MDR-TB, multidrug-resistant tuberculosis; mo, months; n, number; SoC, standard of care; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

### Table 2  Input cost estimates for cost-effectiveness analyses (US$2018 per month)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>South Africa</th>
<th>Georgia</th>
<th>The Philippines</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of care (intensive phase)</td>
<td>558.9 (drugs)</td>
<td>424.6 (drugs)</td>
<td>424.6 (drugs)</td>
<td>35 51–55</td>
</tr>
<tr>
<td></td>
<td>64.9 (delivery)</td>
<td>25.0 (delivery)</td>
<td>30.1 (delivery)</td>
<td></td>
</tr>
<tr>
<td>Standard of care (continuation phase)</td>
<td>208.9 (drugs)</td>
<td>74.58 (drugs)</td>
<td>74.58 (drugs)</td>
<td>35 51–55</td>
</tr>
<tr>
<td></td>
<td>30.1 (delivery)</td>
<td>14.0 (delivery)</td>
<td>13.7 (delivery)</td>
<td></td>
</tr>
<tr>
<td>BPaL</td>
<td>296.4 (drugs)</td>
<td>214.0 (drugs)</td>
<td>214.0 (drugs)</td>
<td>35 51–55</td>
</tr>
<tr>
<td></td>
<td>65.3 (delivery)</td>
<td>31.0 (delivery)</td>
<td>38.3 (delivery)</td>
<td></td>
</tr>
<tr>
<td>Palliative care*</td>
<td>428.1</td>
<td>330.9</td>
<td>328.0</td>
<td>56</td>
</tr>
<tr>
<td>Antiretroviral treatment</td>
<td>249.2</td>
<td>–</td>
<td>–</td>
<td>57</td>
</tr>
</tbody>
</table>

*Average of 10% hospice inpatient unit; 40% community care and 50% no care.

BPaL, bedaquiline, pretomanid and linezolid.
RESULTS
Costs, effectiveness and cost-effectiveness

When assessing the potential cost and effectiveness of introducing BPaL for the treatment of XDR-TB against the current standard of care, we observe that in all three settings this regimen has the potential to be cost saving at the current Global Drug Facility list price (ie, US$ 364 per treatment course for pretomanid). Results are presented in table 3. These savings are a function of the cost of care and the magnitude of XDR-TB burden. Savings following the introduction of BPaL are more important in settings with more expensive current standard of care or a higher burden of XDR-TB. Consequently, cost savings are estimated greater in South Africa and Georgia than in the Philippines.

The magnitude of the potential savings increased when the clinical indication for BPaL was modelled to include those patients who are MDR-TB treatment intolerant or MDR-TB treatment failures. In a setting such as South Africa, where changes in treatment guidelines for TB may have significant cost consequences across both TB and HIV programmes, we have included both TB costs and costs due to continuous antiretroviral treatment (ART) following principles of good practice in economic evaluation. As a result, the savings in this high HIV prevalence setting are reduced once we consider the increase in lifetime ART costs (following more patients surviving the TB episode and needing ART for more years of life). Even with this conservative assumption, BPaL introduction in a setting such as South Africa continues to be estimated as cost saving. These additional (HIV-related) costs are not significant in low HIV settings such as Georgia or the Philippines.

In addition to the main results in terms of incremental costs and DALYs averted, we also present several sensitivity analyses. All deterministic sensitivity analyses can be found in online supplemental tables S2–S4 and online supplemental figures S2–S8. In general, a programme’s performance in terms of rates of loss to follow-up or mortality during treatment will drive the value for money of introducing BPaL. For example, in South Africa, we observe that our costs results are most sensitive to variations in assumptions regarding the performance of the TB programme. BPaL introduction ceases to be cost saving in scenarios where we assume a long term under-performance of the standard of care (such as higher mortality rates at 18 months or a higher rate of loss to follow-up at 18 months) compared with the base case assumptions. In Georgia and the Philippines, our cost results are robust to the assumptions tested with BPaL introduction remaining cost saving across sensitivity analyses. Effectiveness results are sensitive to changes in assumptions for mortality and loss to follow-up for both BPaL and standard of care across settings. A threshold analysis explores the probability of introducing BPaL becoming cost neutral (ie, not cost saving) as a function of possible prices (figure 2). This is based on the results from the probabilistic sensitivity analyses, which can be found in the online supplemental file. We observed that 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$ 3800, respectively) compared with South Africa (US$ 500).

DISCUSSION

BPaL for treatment of XDR-TB is likely to be cost saving in the study settings at the proposed price. In settings such as South Africa, related future costs like those from the HIV programme (ART costs) may reduce the magnitude of expected savings to the health service. BPaL treatment is estimated to avert more deaths in patients with XDR-TB compared to the current standard of care. The reduction of expected savings relates to these patients requiring lifelong ART.

Cost savings from the introduction of the BPaL regimen are higher in settings with a more expensive current standard of care. Consequently, the threshold price at which BPaL becomes cost neutral is higher in less expensive settings: US$ 3650 and US$ 3800 for Georgia and the Philippines, respectively, and US$ 500 for South Africa for our base case of only patients with XDR-TB, after factoring in incremental cost of ART. It is worth noting that this threshold price is not the price at which the introduction of such regimen will still be considered cost-effective, it indicates an increasing probability of a price being cost neutral.

The impact of BPaL on costs and DALYs averted depends on the programmatic performance of the standard of care. A standard of care with lower loss to follow-up or mortality rates than currently assumed will decrease the value for money of introducing BPaL. Overall, when BPaL is introduced to a larger patient population (including MDR-TB treatment failure and treatment intolerant), we observe an increase in the incremental benefits, that is, an increase in deaths averted and in DALYs averted. The increase in benefits observed is due to both the shortening of the regimen (principal driver of cost savings) and the better curative performance in clinical trials compared with the current standard of care.

In this assessment, we established a conservative baseline. We are likely to have underestimated secondary benefits, particularly in terms of transmission averted. We assessed standard of care scenarios that are less expensive (with more community/outpatient treatment) than previously observed, which is an emerging treatment norm. A standard of care including more hospitalisation time in all these settings would result in higher savings following the introduction of BPaL. In addition, our analysis was restricted to a health service perspective. Costs incurred by patients and their households have been shown to be a significant burden to society. In limiting the perspective to the health service, we aimed to be conservative in the analysis of cost savings and its relationship to price.

Table 3  Health outcomes and total costs estimate by country

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Deaths in 5 years</th>
<th>Total TB-related costs (US$2018)</th>
<th>Total ART-related costs (US$2018)</th>
<th>Incremental (all) cost (US$2018)</th>
<th>Total DALYs</th>
<th>Total DALYs averted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>South Africa</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BPaL</td>
<td>118 (117–118)</td>
<td>1 859 461 (1 857 374–1 861 548)</td>
<td>15 446 196 (15 347 992–15 544 400)</td>
<td>–1 053 237 (–1 030 204 to −1 076 20)</td>
<td>7486</td>
<td>(7393–7578)</td>
</tr>
<tr>
<td><strong>Georgia</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>BPaL</td>
<td>7 (7–7)</td>
<td>83 775 (83 706–83 845)</td>
<td>–</td>
<td>−198 905 (−199 210 to −198 600)</td>
<td>396</td>
<td>(390–402)</td>
</tr>
<tr>
<td>BPaL</td>
<td>13 (13–13)</td>
<td>141 489 (141 370–141 608)</td>
<td>–</td>
<td>−336 950 (−337 480 to −336 420)</td>
<td>661</td>
<td>(651–672)</td>
</tr>
<tr>
<td><strong>The Philippines</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Cohort: XDR-TB only SoC</td>
<td>5 (5–5)</td>
<td>84 327 (84 240–84 413)</td>
<td>–</td>
<td>–</td>
<td>268</td>
<td>(264–272)</td>
</tr>
<tr>
<td>BPaL</td>
<td>2 (2–2)</td>
<td>26 357 (26 330–26 384)</td>
<td>–</td>
<td>−57 970 (−57 881 to −58 058)</td>
<td>119</td>
<td>(118–121)</td>
</tr>
<tr>
<td>Cohort: XDR-TB and MDR-TB intolerant/failure</td>
<td>221 (220–221)</td>
<td>3 704 919 (3 701 227–3 708 611)</td>
<td>–</td>
<td>–</td>
<td>11 890</td>
<td>(11 714–12 066)</td>
</tr>
<tr>
<td>BPaL</td>
<td>104 (103–104)</td>
<td>1 158 821 (1 157 611–1 160 032)</td>
<td>–</td>
<td>−2 546 098 (−2 542 254 to –2 549 942)</td>
<td>5316</td>
<td>(5231–5400)</td>
</tr>
</tbody>
</table>

ART, antiretroviral treatment; BPaL, bedaquiline, pretomanid and linezolid; DALYs, disability-adjusted life years; MDR-TB, multidrug-resistant tuberculosis; SoC, standard of care; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.
However, in doing so, we may have underestimated the value of this regimen to society. Finally, we did not consider costs and/or effects of introducing this new technology in the countries. The introduction of a new technology implies fixed costs of training, changes in guidance and changes in systems, among others. This omission may have led to an underestimation of the BPaL costs.

This study has important limitations. First, this study was based on efficacy estimates from a small study (n=109) without a randomised control group. During this clinical study, both bedaquiline and linezolid were increasingly used as part of the standard of care to treat both MDR-TB and XDR-TB (all the patients received bedaquiline and 81% also received linezolid), as reflected in our comparator arm. Previous evidence has shown that while bedaquiline had a low incidence of adverse events leading to permanent drug discontinuation, linezolid had a high incidence. In the Nix-TB study, a high percentage of patients had adverse events related to linezolid during the study. However, all eight patients who had the regimen interrupted for adverse events resumed and completed the full 26 weeks of treatment. Due to both the small sample size and the use of linezolid in both comparator groups, we were not able to quantify the impact on DALYs or costs of adverse events. However, the efficacy results of the Nix-TB study have been recently confirmed in a phase III trial, the ZeNix study which included other settings. This linezolid dose optimisation trial also demonstrated that the linezolid dose and/or duration of the regimen will likely reduce, which will potentially make our results an underestimate of savings. Finally, cost parameter values were estimated from guidelines and verified against empirically measured recent estimates from a multinational and standardised costing study, improving the comparability of the results across settings. This comparison showed that our estimates were lower than those empirically measured. The implication being that the cost savings presented here could be considered as conservative.

CONCLUSIONS
The optimisation of MDR/XDR-TB regimens is a priority in global health. Our study is the first model to explore the costs and benefits of introducing an all-oral shorter treatment regimen for XDR-TB treatment using data from recent trials. Other economic evaluations alongside clinical trials are expected to be published soon looking at other shorter combinations, including the PRACTECAL trial which has published positive initial data.

In November 2019, the WHO reviewed clinical data available for Nix-TB following the recommendation from the FDA and concluded that more research was needed before the programmatic implementation of the regimen worldwide could be recommended. Currently, WHO guidelines endorse the use of the BPaL regimen under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones. At the time of writing, operations research had commenced in six countries and expected to start in another five/six countries by late 2021. This operational research will be useful for countries to further assess costs and benefits of introducing BPaL. Until then, our results point to BPaL being an efficient and needed addition to the local TB programmes in varied programmatic settings.
the model parameterisation, analysis and manuscript editing. SM, SC-S, SJ, DE and MeS contributed to the analysis and manuscript editing. AV contributed to the study design, model development, analysis and manuscript editing. All authors have read and approved the final version of the manuscript. GBG is the guarantor of the paper.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. The data used in the paper are based on the sources described in the main text and supplementary material and on summarised and published available data from the Nix-TB trial.

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