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Managing multidrug-resistant tuberculosis in South Africa: a budget impact analysis

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SUMMARY

SETTING: In South Africa prior to 2016, the standard treatment regimen for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) was 24 months long and required daily injectable aminoglycoside (IA) treatment during the first 6 months. Recent evidence supports the replacement of IA with well-tolerated oral bedaquiline (BDQ) and a shortened 9–12 month regimen.

DESIGN: Using a Markov model, we analyzed the 5-year budgetary impact and cost per successful treatment outcome of four regimens: 1) IA long-course, 2) oral long-course, 3) IA short-course, and 4) oral short-course. We used the South African MDR/RR-TB case register (2013–2015) to assess treatment outcomes for the then-standard IA long-course. Data on the improvement in outcomes for BDQ-based regimens were based on the literature. Costs were estimated from the provider perspective using costs incurred to provide decentralized treatment for MDR-TB at a Johannesburg hospital.

RESULTS: Based on our analysis, by 2023, the cost/successful outcome for the four regimens was respectively 1) US$7374, 2) US$7860, 3) US$5149, and 4) US$4922. The annual total cost of each regimen was US$37 million, US$43 million, US$26 million, and US$28 million.

CONCLUSION: Despite the high cost of BDQ, a BDQ-based shortened regimen for the treatment of MDR/RR-TB will result in improved treatment outcomes and cost savings for South Africa.

KEY WORDS: MDR-TB; bedaquiline; cost; cost-effectiveness; TB

DESPITE ADVANCES IN CONTROLLING TB in South Africa and globally, TB remains the leading cause of death from a single infectious organism,[1] and pathogen resistance to standard first-line medications is both widespread and expanding. According to the WHO, there were 558 000 incident cases of rifampicin-resistant and multidrug-resistant tuberculosis (MDR/RR-TB) globally in 2017. Only 25% of these cases were detected and initiated on treatment. Of the 15 986 cases of laboratory-confirmed MDR/RR-TB South Africa had during this period, only 10 259 patients were started on treatment. Outcomes for MDR/RR-TB treatment remain poor, with only 55% of patients achieving treatment success.[1]

Fortunately, there have been significant recent advancements in the treatment of MDR/RR-TB. Until 2016, the standard regimen for treating MDR/RR-TB was 18–24 months long and included daily injectable aminoglycoside (IA) treatment for the first 6 months ('IA long-course'). This regimen has significant side effects, including IA-related irreversible hearing loss, and has generated poor treatment outcomes, with high rates of death and loss to follow-up.[2] Following promising early results from observational studies using regimens lasting 12 months or less, the WHO endorsed an IA-containing shortened treatment regimen of just 9–12 months in May 2016 ('IA short-course').[3–7]

In 2018, the WHO released updated interim guidelines for the treatment of MDR/RR-TB which revised its ranking of medications for MDR/RR-TB based on effectiveness.[6–8] The new 'Group A' medicines to be prioritized included levofloxacin/moxifloxacin, bedaquiline (BDQ), and linezolid (LZD) (all oral medications), while IA were demoted to 'Group C' status, to be included only when better options are unavailable. There are now two regimen options endorsed by the WHO: an all-oral, 18–20 month regimen ('oral long-course') and the previously endorsed 9–12 month IA short-course. In June 2018, the South African National Department of Health (NDOH) made a decision to make BDQ routinely available to all MDR/RR-TB patients.[5,6] South Africa subsequently became the first country to

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Table 1 Model parameters

Parameters	Regimen 1 (IA long-course) %	Regimen 2 (oral long-course) %	Regimen 3 (IA short-course) %	Regimen 4 (oral short-course) %	Source
Treatment parameters					
Average treatment duration, months	21	19	10	10	
Total mortality rate	24.1	11.8	24.1	11.8	(5)
Total LTFU rate	20.3	20.3	20.3	20.3	(9)
Relapse rate	2.3	2.3	5.1	5.1	(20)
Treatment success rate	42.8	49.3	42.8	49.3	(5)
Treatment failure rate	3.4	3.4	2.2.	2.2	(9)
Ototoxicity rate	Month 1: 8.7; Month 2: 8.7	NA	Month 1: 8.7; Month 2: 8.7	NA	(10)
Proportion meeting eligibility criteria	100	100	79	79	(9)
Cost parameters, US$					
Cost of administering daily injectable per visit	3.58	NA	3.58	NA	(12)
Cost of audiometry during injectable phase	61.84	NA	54.96	NA	(12)
Monthly cost of the injectable	26.25	NA	26.36	NA	(12)(16)
Monthly cost of linezolid	NA	78.62	NA	78.62	(16)
Monthly cost of bedaquiline	NA	Month 1: 150.00; Months 2–6: 53.00	NA	Months 1–2: 150.00; Months 3–6: 53.00	(16)

IA = injectable aminoglycoside; LTFU = loss to follow-up; NA = not available.

recommend an injection-free, oral short-course (9–12 month) regimen ('oral short-course').[6] The new shortened oral regimen has the potential to eliminate hearing loss as a side effect of treatment, improve outcomes by decreasing loss to follow-up and mortality, and reduce treatment costs incurred by the government.[4,5]

In this study, we compared four treatment regimens: the previous IA long-course (regimen 1); the WHO-recommended oral long-course (regimen 2); IA short-course (regimen 3); and South Africa's oral short-course (regimen 4). We carried out a budget impact analysis to estimate the cost per patient with a successful DR-TB treatment outcome and the expected budget impact of changes in treatment regimens on MDR/RR-TB expenditure in South Africa.

STUDY POPULATION AND METHODS

Study population

We analysed the Electronic Drug-Resistant Tuberculosis Register (EDRWeb) data from all adult patients who initiated second-line treatment between 1 January 2013 and 31 December 2015. EDRWeb, the national electronic case register for DR-TB patients, is a reporting database containing patient-level information from facility TB registers. This system has been implemented across all South African provinces in at least 22 facilities providing DR-TB treatment. Although not all sites are currently included in the EDRWeb, it is the most comprehensive database of the DR-TB population and treatment outcomes available. The 2013–2015 initiation interval allowed for at least 24 months of follow-up after treatment initiation by the data extraction date of 20 February 2018. Assumptions regarding treatment outcomes were derived from EDRWeb and the literature (Table 1).

Treatment regimens

We modelled the following four regimen scenarios (See Supplementary Text S1, Table S1).

1 A long-course 18–24-month regimen including a daily IA, which was the standard of care during the 2013–2015 period of observation[6] (regimen 1, IA long-course)
2 The WHO's newly recommended 18–20 month injectable-free regimen (regimen 2, oral long-course)
3 The WHO's newly recommended short 9–12 month regimen including a daily IA (regimen 3, IA short-course)
4 South Africa's new short 9–12 month injectable-free regimen (regimen 4, oral short-course).

Outcomes

For each regimen, we estimated the likelihood, by month, of mortality, loss to follow-up and treatment failure rates as defined in Table S2 (see Supplementary Data). The treatment outcomes recorded were mutually exclusive and defined according to national and international guidelines (Table 2).[7,8]

Model design and assumptions

We built a Markov model that estimated the number of patients at different stages of the MDR/RR-TB treatment cycle to calculate the costs and outcomes of treatment over five budget years (2019/2020–2023/2024) for each regimen. The model allowed for the movement of patients through different treatment stages and tracked MDR/RR-TB patients from treatment initiation to treatment outcome. The

Table 2 Treatment outcome definitions

Outcome	Description
Cured	Patients who have no evidence of failure AND three or more consecutive culture samples taken at least 30 days apart are negative after the intensive phase
Treatment completed	Patients who complete treatment but do not meet the criteria to be classified as cured or as treatment failure
Treatment success	Sum of patients who are either cured or have completed treatment
Treatment failed	Patients whose treatment is terminated or a permanent regimen change of at least two anti-tuberculosis drugs is required because (i) lack of conversion by the end of the intensive phase (max 8 months), (ii) bacteriological reversion in the continuation phase after conversion to negative, (iii) drug susceptibility testing indicate additional acquired resistance to fluoroquinolones or second-line injectable drugs, and (iv) adverse drug reactions
Lost to follow-up	Patients who miss >2 consecutive months of treatment
Died	Includes all-cause mortality during the course of treatment
Not evaluated	Patient for whom no treatment outcome is assigned (this includes cases 'transferred out' to another treatment unit and those whose treatment outcome is unknown)

proportion of patients who qualified for regimens 3 and 4 (the short-courses) was estimated from EDRWeb based on the exclusion criteria outlined in South African and WHO guidelines.[3,6] We used durations of 18–20 months for regimen 2 (oral long-course) and 9–12 months for the shortened regimens.[6]

In the model, patients could transition at monthly intervals to either the next month of treatment, be lost to care, fail treatment, or have died (Figure 1, a simplified visual model representation). Table S2 (see Supplementary Data) specifies the transition rates between disease states in the model.

Data

Treatment outcomes, total mortality, and treatment success rates for patients on an IA long-course were sourced from EDRWeb and those on an IA short-course or an oral long-course were sourced from literature.[5,9,10] The treatment outcomes for oral short-course therapy in operational settings is currently unknown. We have extrapolated from the results of the STREAM (Standard Treatment Regimen of Anti-Tuberculosis drugs for patients with MDR-TB) trial and have assumed that they will be similar to that of oral long-course.[11] EDRWeb provided patients' demographic characteristics, treatment regimen details, treatment outcomes, adverse events, and HIV information. Monthly mortality rates were estimated from EDRWeb records, and then proportionally inflated to reflect total mortality rates reported by Schnippel and colleagues.[5] We used the total mortality rate reported in their analysis as it was supplemented with data from the South African national vital register, a more accurate record of deaths. Relapse rates were allowed for by reducing

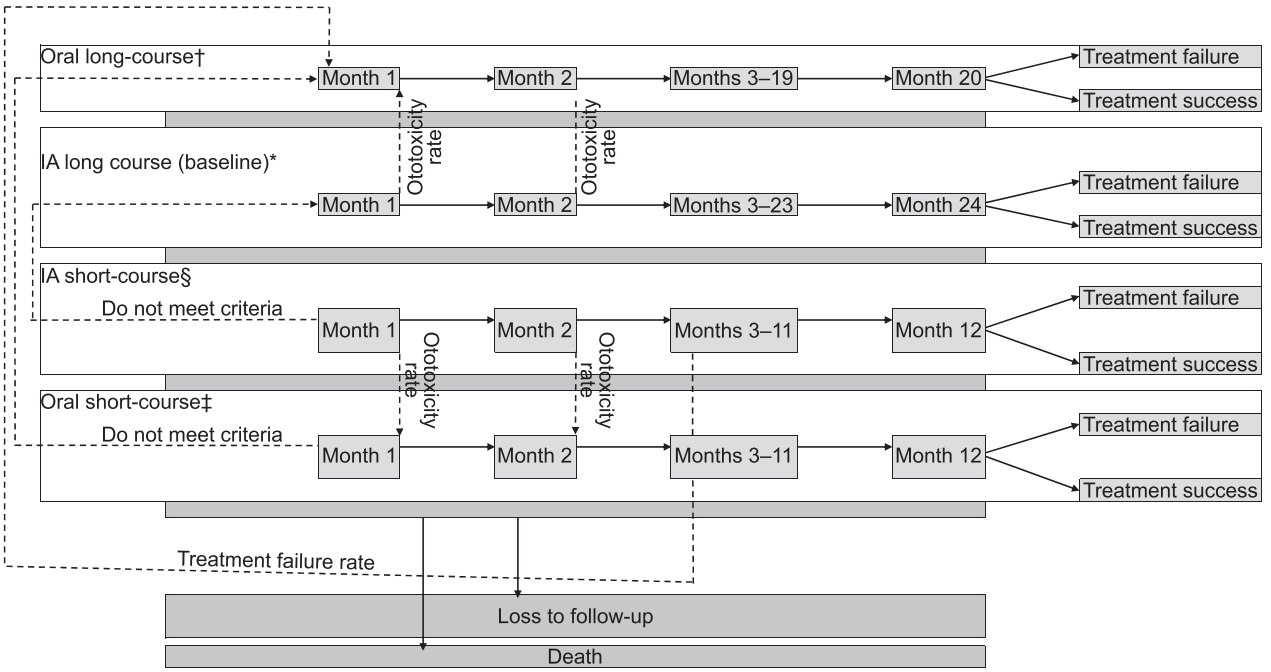

Figure 1 Structure of the Markov model. * IA long-course (baseline) = 18–24 month regimen with 6-month IA. † Oral long-course = 18–20 month regimen with BDQ as a substitute for IA. § IA short-course = 9–12 month regimen with 6-month IA. ‡ Oral short-course = 9–12 month regimen with BDQ as a substitute for IA. IA = injectable aminoglycoside; BDQ = bedaquiline.

the proportion of successful treatments for each regimen.[12]

Cost data were drawn from a micro-costing study in 2017 of 127 MDR/RR-TB patients at an outpatient DR-TB treatment facility at Helen Joseph Hospital in Johannesburg, South Africa.[13] Treatment costs included personnel, consumables, overheads, and equipment. The cost of audiometry included personnel costs, a KUDUwave (eMoyoDotNet, Johannesburg, South Africa) device, and consumables. The cost of the intramuscular administration of the IA included staff costs, overheads, and consumables. The costs of all laboratory tests were obtained from the 2017 National Health Laboratory Service price list.[14] At baseline, it was assumed that patients had tests for pregnancy for women of childbearing potential, creatinine urea and electrolytes, full blood count, HIV, liver function and a chest X-ray. As per guidelines, recommended monthly laboratory evaluations included sputum microscopy and TB culture.[15] Monthly audiometry and urea and electrolyte tests were conducted during the injectable phase. The cost of the chest X-ray was obtained from the 2017 Uniform Patient Fee Schedule (UPFS).[16] Drug costs were obtained from September 2018 government tender prices,[17] except for clofazimine which was based on a price quote made to the SA National Department of Health by Equity Pharmaceuticals (Centurion, South Africa).

Cost and budget impact analysis

We first estimated the resources used by disease state, as well as the cost of each resource.[13] We then calculated the cost per patient by multiplying all resources utilized by the unit cost per resource by person-time spent in a disease state. To calculate the cost per successfully treated patient, the total cost of all patients who started treatment was divided by the total number of successful outcomes (cured and completed). Where appropriate, costs were adjusted for inflation using the South African Consumer Price index.[18] Costs were presented in 2018 US dollars (US$1 = ZAR13.07, the average exchange rate between January 2017 and May 2018) and estimated from the perspective of the South African National TB Programme.

For the budget impact analysis, total expenditure was calculated by multiplying the expected number of individuals in each stage of treatment (e.g., month one of treatment as shown in Figure 1) by the respective costs of providing that treatment. Total budget is calculated per fiscal year for the coming five years (2019/2020–2023/2024) for the entire treatment population.

Sensitivity analysis

To determine the robustness of our model results, we conducted one-way sensitivity analyses of key parameters to see how they affected the cost/successful outcome in 2023. The key parameters varied included the number patients initiating treatment, improvement in the number of successful treatments as a result of a switch to an oral-based regimen, the possibility of additional improvement as a result of moving to a shortened regimen, cost of BDQ, the dosage of LZD, and the TB focal point clinic costs.

Ethics

The study protocol was approved by the Human Research Ethics Committee (Medical), of the University the Witwatersrand, Johannesburg, South Africa (#M171158) on 6 July 2018. The study used programmatic data, and a waiver of informed consent was granted to retrospectively review these records.

RESULTS

Study population

On average, 11 485 drug-resistant (DR-TB) adults per annum registered on the EDRWeb between 2013 and 2015, 73% of whom were HIV-positive. Eight per cent of these patients were excluded from our analysis because they were diagnosed with extensively drug-resistant TB. Of the remaining patients, 79% met the eligibility criteria for an oral short-course.

Cost per patient treated

In the first year, cost per patient treated was US$4020 under regimen 1, US$4146 for regimen 2, US$1811 for regimen 3 and US$1889 for regimen 4. For all the regimens, drugs comprised the largest percentage of total cost (35–64%) followed by staff costs. Staff costs, overheads, and consumables were approximately 14% higher for the IA-based regimens than for the corresponding oral regimens because of the labour-intensive process (Figure 2, Table S3–S5).

Impact on total MDR/RR-TB costs and cost per successful treatment

By 2023, an estimated annual 4958, 5662, 4962, 5615 patients will be successfully treated under the four regimens respectively (Table 3). The cost per successful outcome of regimen 1 in 2023 is expected to be US$7396. Introducing BDQ to long-course treatment results in a 5% increase in the cost per successful outcome (US$7739). While IA is less expensive than BDQ, staff and health facility overhead costs are incurred for daily IA injections, offsetting the higher price of BDQ. Improvement in BDQ treatment outcomes contributed to a lower cost per successful treatment by year 4 for regimen 4.

Budget impact analysis

Adoption of an oral short-course will result in a 23–25% reduction in MDR/RR-TB-related expenditure

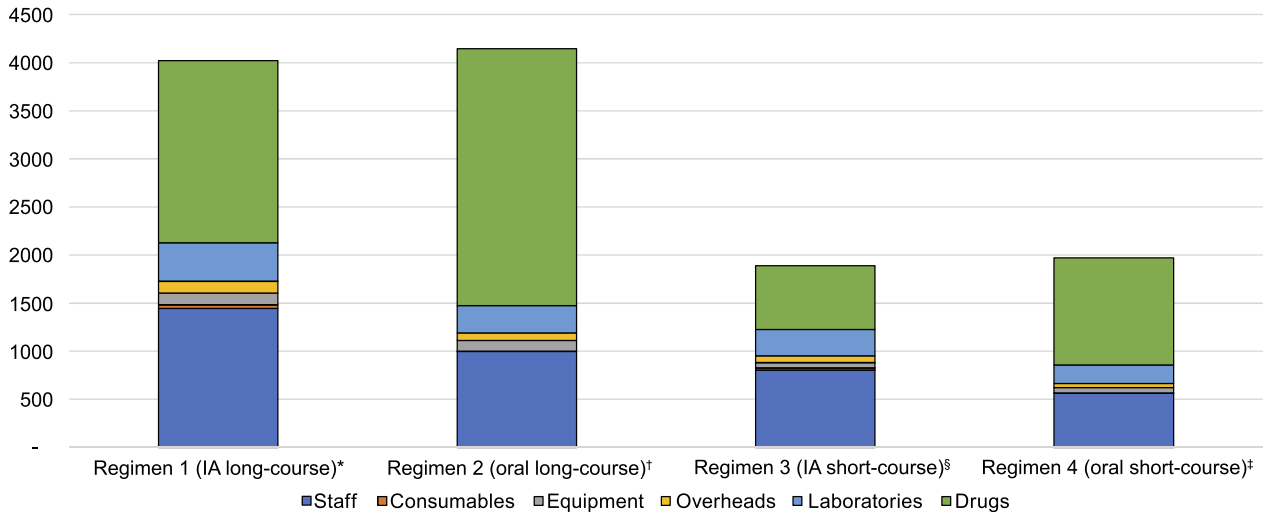

Figure 2 Cost per patient treated by regimen. * IA long-course (baseline) = 18–24 month regimen with 6-month IA. † Oral long-course = 18–20 month regimen with BDQ as a substitute for IA. § IA short-course = 9–12 month regimen with 6-month IA. ‡ Oral short-course = 9–12 month regimen with BDQ as a substitute for IA. IA = injectable aminoglycoside; BDQ = bedaquiline.

in the coming 5 years compared to the IA long-course, US$28 million compared to US$37 million in 2023/2024 (Table 3). Compared to the oral long-course (US$44 million), the oral short-course is expected to result in a 36–37% reduction in MDR/RR-TB related expenditure (US$28 million).

Sensitivity analysis

In our one-way sensitivity analyses, the cost per successful outcome of the oral short-course regimen is most sensitive to improvement in the BDQ treatment success rate. Improving treatment success by 5% decreased the cost per successful outcome from US$4910 to US$4726; decreasing it by 5% increased the cost per successful outcome to US$5109 (Figure 3). A decline or improvement of shortened regimen treatment outcomes by ±5% resulted in a 4% change in the cost/successful outcome. Assuming a 7% year-on-year increase or decrease in the number of patients initiating treatment would have little (<1%) impact on the cost per successful treatment (Figure 3, Supplementary Figure S1).

Table 3 Total cost and cost per successful treatment of standard and shortened MDR/RR-TB treatment with and without the use of BDQ*

	Annual number of successful treatments in 2023				
	2019/2020	2020/2021	2021/2022	2022/2023	2023/2024
Regimen 1 (IA long-course)			4958		
Regimen 2 (oral long-course)			5662		
Regimen 3 (IA short-course)			4962		
Regimen 4 (oral short-course)			5615		
Cost per successful treatment, $US					
Regimen 1 (IA long-course)	6730	6780	6975	7180	7396
Regimen 2 (oral long-course)	7157	7292	7433	7582	7739
% change over baseline	6%	8%	7%	6%	5%
Regimen 3 (IA short-course)	4535	4642	4790	4946	5111
% change over baseline	−33%	−32%	−31%	−31%	−31%
Regimen 4 (oral short-course)	4506	4594	4694	4799	4910
% change over baseline	−33%	−32%	−33%	−33%	−34%
Annual costs, million $US					
Regimen 1 (IA long-course)	33.37	33.62	34.59	35.60	36.67
Regimen 2 (oral long-course)	40.53	41.29	42.09	42.93	43.82
% change over baseline	21%	23%	22%	21%	19%
Regimen 3 (IA short-course)	22.35	23.03	23.77	24.54	25.36
% change over baseline	−33%	−31%	−31%	−31%	−31%
Regimen 4 (oral short-course)	25.23	25.79	26.35	26.94	27.57
% change over baseline	−24%	−23%	−24%	−24%	−25%

* IA long-course (baseline) = 24-month regimen with 6-month IA; oral long-course = 18–20 month regimen with BDQ as a substitute for IA; oral short-course = 9–12 month regimen with BDQ as a substitute for IA; IA short-course = 9–12 month regimen with 6-month IA.
MDR/RR-TB = multidrug-resistant/rifampicin-resistant tuberculosis; BDQ = bedaquiline; IA = injectable aminoglycoside.

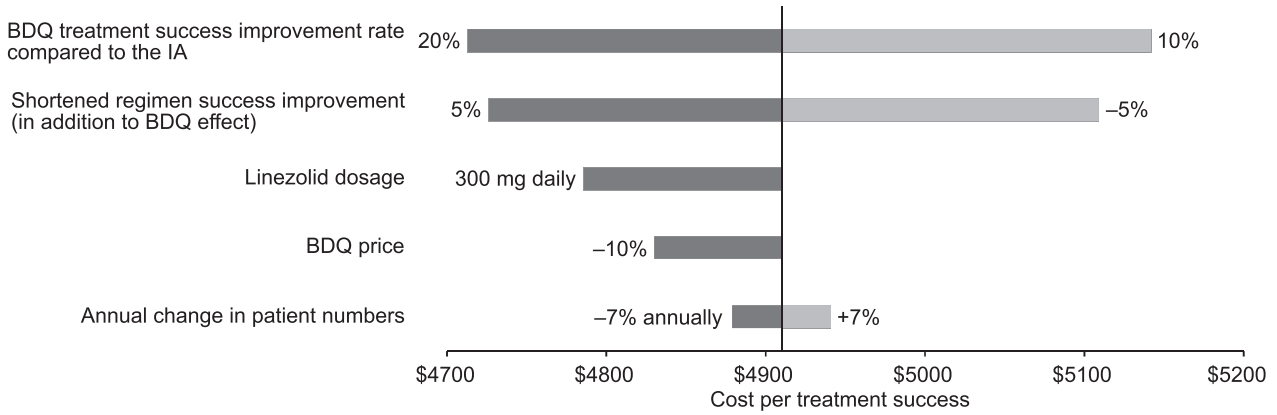

Figure 3 One-way sensitivity analysis for the oral short course. Cost per successful treatment as estimated in year 2023 for the oral short-course. BDQ = bedaquiline; IA = injectable aminoglycoside.

DISCUSSION

South Africa was the first country to recommend an oral short-course for the treatment of MDR/RR-TB, which is in contrast to current WHO guidelines which recommend either a short IA-based regimen or a long BDQ-based oral regimen.[6] Assuming that the switch to BDQ-based oral regimens is associated with improved outcomes and reduced mortality (as demonstrated in recent retrospective cohort studies), we predict that the switch to an oral long-course regimen for all patients with MDR/RR-TB would result in a cost increase of 19–21% over the period of 5 years, whereas the introduction of an oral short-course would result in at least 22% in cost savings starting in year 1.[4,5,19] While a short IA-based regimen is predicted to cost less than a short oral regimen, it is also expected to generate fewer treatment successes.

To date, there have been just two studies that have reported the cost of MDR/RR-TB in South Africa.[20,21] One estimated that the national cost of the IA long-course MDR/RR-TB treatment regimen was US$5804 (adjusted to 2018 $US).[20] This cost is slightly less than ours, likely due to that study's lower cost for injectable administration at a different facility. In sensitivity analyses, using that study's cost estimate did not change our conclusions (Figure S2).[13] Others have estimated that the cost per successfully treated MDR/RR-TB patient in South Africa was US$7930 (in 2018 $US), comparable to our analysis of an IA long-course regimen.[12] Both of these studies focused on the IA long-course regimen, which is rapidly being replaced by the oral and/or short-course regimens.

To our knowledge, this is the first study that quantifies the budget impact of switching to new oral regimens. The model uses parameters based on the South African MDR/RR-TB treatment cohort and provides accurate estimates that are applicable to high HIV-prevalence, low-middle-income settings.

There are a number of limitations to our analysis. First, the impact of a shortened oral regimen on treatment outcomes is unknown. There may be a combined impact on treatment outcomes of a regimen that is both oral and shortened, which we did not allow for in our model.[11,22] As a result, we may have overestimated the cost per successful treatment of this regimen, which would then become even more competitive. Second, the cost data from a single clinic in Johannesburg may not be representative of treatment facility costs across South Africa. We did, however, use treatment guidelines that are nationally applicable for drug and laboratory costs. In a sensitivity analysis, when assuming a 10% change in costs, the cost per successful outcome did not vary substantially between the four regimens (Supplementary Figure S1). Third, our model assumed a fixed number of patients initiating treatment annually. The number of patients treated annually for MDR/RR-TB treatment more than doubled between 2011 and 2015 from 5643 to 12 527 as a result of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) implementation for the diagnosis of rifampicin resistance and decentralization of DR-TB services.[9] However, numbers have since fallen to 10 259 in 2017.[1,9] Predicting the future number of patients treated for MDR/RR-TB is outside the scope of this analysis and depends on a variety of factors including diagnostics improvement, linkage to care and transmission.

CONCLUSIONS

Based on our analysis, the oral short-course regimen for MDR/RR-TB is superior to the IA long-course regimen with respect to total costs of the MDR/RR-TB programme. Should the shortened regimen result in improved treatment outcomes, this regimen will result in the lowest cost per treatment success compared to the other regimens analysed. This is the case even despite the price of BDQ. We believe that the results of our study are applicable to other

low and middle-income countries with high HIV co-infection and MDR/RR-TB burden. Moving to a BDQ-based shortened regimen for the treatment of MDR/RR-TB will result in improved treatment outcomes and in cost savings to the South African National TB Programme.

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RÉSUMÉ

CONTEXTE : Jusqu'à 2016, le protocole standard de traitement de la tuberculose multirésistante et résistante à la rifampicine (MDR/RR-TB) en Afrique du Sud durait 24 mois et nécessitait l'administration quotidienne d'aminosides injectables (IA) pendant les 6 premiers mois. Des preuves récentes sont en faveur du remplacement des IA par de la bédaquiline (BDQ) orale si bien tolérée et d'un protocole raccourci de 9–12 mois.
SCHÉMA : Grâce à un modèle de Markov, nous avons analysé l'impact budgétaire sur 5 ans et le coût par traitement réussi de quatre protocoles: 1) IA longue durée, 2) oral longue durée, 3) IA protocole court, et 4) oral protocole court. Nous avons utilisé le registre des cas de MDR/RR-TB d'Afrique du Sud (2013–2015) afin d'évaluer les résultats du traitement du protocole standard de ces années c'est-à-dire le protocole IA long cours. L'amélioration des résultats des protocoles basés sur la BDQ a été extraite de la littérature. Les coûts ont été estimés du point de vue du prestataire de soins à partir des coûts liés à la fourniture d'un traitement décentralisé de MDR-TB dans un hôpital de Johannesburg.
RÉSULTATS : D'ici 2023, le coût/traitement réussi des quatre protocoles a été de 1) US$7374 ; 2) US$7860 ; 3) US$5149, et (4) US$4922. Le coût total annuel de chaque protocole a été de US$37 millions, US$43 millions, US$26 millions, et US$28 millions, respectivement.
CONCLUSION : Malgré le coût élevé de la BDQ, un protocole raccourci basé sur la BDQ pour le traitement de la MDR/RR-TB va aboutir à un meilleur résultat et à des économies pour l'Afrique du Sud.

RESUMEN

MARCO DE REFERENCIA: Antes del 2016, la duración del esquema corriente de tratamiento de la tuberculosis multirresistente y la tuberculosis resistente a rifampicina (MDR/RR-TB) en Suráfrica era 24 meses y exigía la administración diaria de un aminoglucósido inyectable (IA) durante los primeros 6 meses. La evidencia reciente respalda el reemplazo del IA por la bedaquilina (BDQ) oral, que es bien tolerada, y un esquema acortado de 9–12 meses.
MÉTODO: En un modelo Markov se analizó el impacto sobre el presupuesto a 5 años y el costo por desenlace terapéutico exitoso de cuatro pautas terapéuticas, a saber: 1) esquema largo con IA; 2) esquema largo por vía oral; 3) esquema corto con IA; y 4) esquema corto por vía oral. Se utilizó el registro surafricano de casos de MDR/RR-TB (2013–2015) a fin de evaluar los desenlaces terapéuticos del esquema largo con IA, que hasta ese momento era el tratamiento corriente. La información sobre los mejores desenlaces logrados con esquemas basados en BDQ se obtuvo de publicaciones científicas. Se estimaron los costos desde la perspectiva del proveedor de atención, a partir de los costos generados por la administración descentralizada del tratamiento de la MDR-TB en un hospital de Johannesburgo.
RESULTADOS: Hacia el 2023, el costo de un desenlace terapéutico exitoso con los esquemas mencionados arriba sería como sigue: 1) US$7374; 2) US$7860; 3) US$5149 y 4) US$4922. El costo total anual de cada esquema en dólares sería 37 millones, 43 millones, 26 millones y 28 millones, respectivamente.
CONCLUSIÓN: Pese al alto costo de la BDQ, el tratamiento de la MDR/RR-TB con un esquema acortado basado en BDQ daría lugar a mejores desenlaces terapéuticos y ahorraría costos en Suráfrica.