BMC Medicine

RESEARCH

Open Access

Optimizing drug-resistant tuberculosis diagnosis: cost-effectiveness of rapid molecular and phenotypic assays in South Africa

Ginenus Fekadu[1,2*], Tadesse Tolossa[3,4], Lan Gao[3], Habteyes Hailu Tola[5,6], Tesfaye Regassa Feyissa[7], Lianping Yang[8,9,10], Shanquan Chen[11], Nathorn Chaiyakunapruk[12,13], Elias Asfaw[14,15], Martin Siegel[16] and Wai Kit Ming[2,17*]

Abstract

Background Timely detection of drug-resistant tuberculosis (DR-TB) is essential for effective treatment and preventing poor outcomes. Rapid molecular diagnostics are promising alternatives to conventional phenotypic drug susceptibility testing (pDST), offering faster and more accessible detection of resistance. This study evaluated the cost-effectiveness of rapid molecular assays, alone or combined with pDST, for detecting resistance to isoniazid, rifampicin, and fluoroquinolones from a South African healthcare provider perspective.

Methods A decision-analytic model was developed to simulate TB-related outcomes for a hypothetical cohort of microbiologically confirmed TB patients. Nine diagnostic strategies were evaluated: pDST alone; four rapid molecular tests (line probe assays [LPAs], Xpert MTB/RIF [Xpert] followed by Xpert MTB/XDR [Xpert XDR], Xpert MTB/RIF Ultra [Xpert Ultra] followed by Xpert XDR, and targeted next-generation sequencing [tNGS]); and combinations pairing each molecular test with pDST. Outcomes included early treatment rates, mortality, direct medical costs, disability-adjusted life-years (DALYs), and incremental cost-effectiveness ratios (ICERs). Base-case, sensitivity, and scenario analyses were performed.

Results In the base-case analysis, 'Xpert followed by Xpert XDR + pDST' was the preferred cost-effective strategy, with an ICER of USD 6,554/DALY averted—below South Africa's GDP per capita threshold. While 'tNGS + pDST' yielded the greatest health benefits—lowest DALYs (1.9877), highest early treatment rate (995.54/1,000 tested), and lowest mortality (90.22/1000 tested)—its ICER (USD 25,918/DALY averted) exceeded three times the GDP per capita, rendering it not cost-effective. Sensitivity analyses highlighted the impact of diagnostic accuracy and treatment timing on cost-effectiveness outcomes. Probabilistic sensitivity analysis showed 'tNGS + pDST' had the highest probability of being cost-effective when the willingness-to-pay threshold exceeded USD 10,500/DALY averted. Diagnostic replacement scenario analysis revealed that tNGS alone could be a cost-effective alternative (ICER = USD 1712 per DALY averted) when pDST was unavailable. An extended two-year time horizon analysis confirmed base-case robustness.

*Correspondence:
Ginenus Fekadu
take828pharm@gmail.com
Wai Kit Ming
wkming2@cityu.edu.hk
Full list of author information is available at the end of the article

Conclusions Combining rapid molecular diagnostics with pDST offers a cost-effective and clinically beneficial approach for DR-TB detection in high-burden settings. The Xpert-based strategy provides an optimal balance of diagnostic yield, early treatment, and economic efficiency in South Africa. tNGS represents a feasible alternative in settings where pDST is inaccessible, warranting further evaluation for broader implementation.

Keywords Tuberculosis, Drug resistance, Rapid molecular diagnostics, Phenotypic testing, Cost-effectiveness, High-burden settings

Background

Drug-resistant tuberculosis (DR-TB) remains a critical global health challenge, accounting for nearly one-third of deaths attributed to antimicrobial resistance [1, 2]. In 2023, approximately 400,000 cases of multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) were reported globally, yet only about 40% were diagnosed and initiated on treatment [1, 3]. The rising burden of DR-TB threatens progress toward the World Health Organization's (WHO) End TB Strategy, with projections estimating that over the next 35 years, up to 75 million people could be affected, costing the global economy $16.7 trillion [4, 5].

South Africa, a high-burden country, reported 13,000 MDR/RR-TB cases in 2023, of which only 6,799 were laboratory-confirmed [1]. TB-related mortality remains high at 21%, underscoring the urgent need for improved diagnostic and treatment strategies. Despite having a robust regulatory framework and comprehensive clinical data, only 47% of newly diagnosed TB cases in South Africa received WHO-recommended rapid molecular testing in 2023, contributing to a treatment success rate of just 62% for MDR/RR-TB [1, 3].

Accurate and timely detection of DR-TB is essential for effective management and control [4, 6]. The WHO recommends universal access to drug susceptibility testing (DST), including rapid testing for resistance to rifampicin (RIF), isoniazid (INH), and fluoroquinolones (FQs) [3, 7]. However, routine DST remains limited in many high-burden settings due to financial, technical, and infrastructural constraints [3]. Conventional phenotypic DST (pDST), while considered the gold standard, is hindered by long turnaround times, biohazard risks, and operational complexity [6, 8].

Recent advancements in nucleic acid amplification tests have significantly improved the speed and accessibility of DR-TB diagnosis [3, 9]. Polymerase chain reaction-based assays such as Xpert MTB/RIF (Xpert), Xpert MTB/RIF Ultra (Xpert Ultra), and Xpert MTB/XDR (Xpert XDR) enable rapid detection of *Mycobacterium tuberculosis* and resistance to first- and second-line drugs within hours [3, 10]. Line probe assays (LPAs), which are based on reverse hybridization DNA strip technology—including GenoType MTBDRplus and MTBDRsl—offer mutation-specific resistance profiling for first- and second-line drugs [11, 12]. Targeted next-generation sequencing (tNGS), which uses high-throughput sequencing, such as the Deeplex-MycTB assay, provides comprehensive resistance detection without the need for culture and has recently been endorsed by WHO as a follow-on test [3, 13].

While rapid molecular diagnostics have been increasingly adopted, the cost-effectiveness of combining these assays with pDST, and the comparative evaluation of newer tests such as tNGS against established molecular diagnostics, remains underexplored in high-burden settings. Therefore, this study aimed to evaluate the cost-effectiveness of rapid molecular assays, alone and in combination with pDST, for detecting resistance to INH, RIF, and FQs in TB patients, from the perspective of healthcare providers in South Africa.

Methods

Model design

This economic evaluation was conducted in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (Additional file 1: CHEERS Checklist) [14]. A decision-analytic model was developed to simulate TB-related clinical and economic outcomes for a hypothetical cohort of microbiologically confirmed TB patients undergoing drug resistance testing, from the perspective of healthcare providers in South Africa (Fig. 1).

The model evaluated nine diagnostic strategies: pDST alone; four rapid molecular tests (LPAs, Xpert, followed by Xpert XDR, Xpert Ultra followed by Xpert XDR, and tNGS), and four combination strategies pairing each molecular test with pDST. A one-year time horizon was used to capture key outcomes, including direct medical costs, disability-adjusted life-years (DALYs), TB-related mortality, and the number of patients receiving early treatment.

The pDST-alone strategy was included as a reference comparator to benchmark the incremental value of rapid molecular diagnostics against the conventional phenotypic approach. The nine strategies represent a spectrum of diagnostic pathways—from phenotype-only baseline to molecular-only replacements, and combinations that

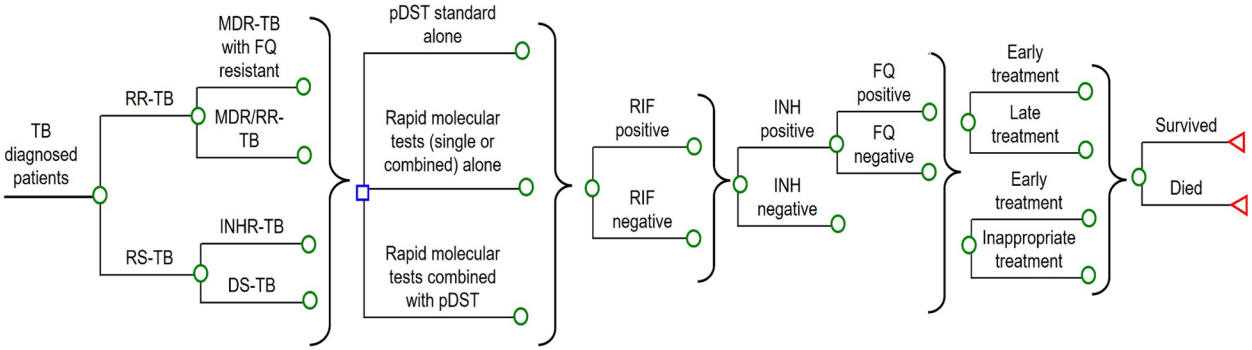

Fig. 1 Simplified schematic of the decision–analytic model used to simulate diagnostic pathways, treatment outcomes, and cost-effectiveness for TB patients

reflect the stepped diagnostic algorithms recommended by WHO and national guidelines [3, 15].

The base-case model assumed ideal test completion rates and diagnostic yield for all assays, including culture-dependent tests. Patients were categorized as either rifampicin-resistant (RR-TB) or rifampicin-susceptible (RS-TB), with further stratification based on FQ and INH resistance profiles. Treatment initiation was classified as early (based on positive test results), late (following false-negative results corrected by pDST), or inappropriate (due to undetected resistance) [1, 3].

Patients receiving late treatment were initially placed on an inappropriate regimen due to false-negative molecular results. Upon receipt of pDST confirmation, treatment was corrected. These patients incurred an elevated mortality risk during the delay, though not as high as those who never received appropriate treatment. Mortality differences were modeled based solely on the timing of correct diagnosis, assuming that once patients were correctly diagnosed, they completed treatment successfully.

The model adhered to the WHO definitions of TB detailed in Additional file 2: Table S1 [2, 16]**.** Treatment regimens were assigned according to South African and WHO guidelines [2, 15–17]. Pre-extensively drug-resistant TB (pre-XDR-TB) cases received bedaquiline, pretomanid, and linezolid (BPaL); MDR/RR-TB cases received bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM); INH-resistant TB (INHR-TB) cases received rifampicin, ethambutol, pyrazinamide, and levofloxacin; and drug-susceptible TB (DS-TB) cases received a standard first-line regimen consisting of an intensive phase of two months with rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by a four-month continuation phase with rifampicin and isoniazid.

In the pDST-only strategy, patients were tested using culture-based methods [3]. All patients initially received first-line treatment, which was subsequently adjusted based on pDST results. In the rapid molecular test strategies, sputum samples were tested using the respective assays: LPAs included GenoType MTBDRplus (for RIF and INH) and MTBDRsl (for FQ); Xpert and Xpert Ultra detected RIF resistance, followed by Xpert XDR for INH and FQ resistance; and tNGS (Deeplex Myc-TB) simultaneously detected resistance to RIF, INH, and FQ. Patients with positive results received early treatment, while those with false-negative results received inappropriate regimens.

For combination strategies, sputum samples were tested in parallel using rapid molecular assays and pDST. Rapid test results guided initial treatment decisions, with pDST results used for confirmation and adjustment. Patients with false-negative molecular results received late treatment upon pDST confirmation, while those with false-positive results received unnecessary second-line treatment until pDST ruled out resistance, after which treatment was reverted to first-line regimens.

Clinical inputs

All model input parameters are detailed in Table 1 and Additional file 2:Table S2. A comprehensive literature search was conducted using Medline (2000–2024), publicly available data from the WHO, and reports from the South African Department of Health. Search terms included "tuberculosis," "drug-resistant tuberculosis," "diagnosis," "testing," "phenotypic drug susceptibility testing," "rapid molecular assays," "line probe assays," "Xpert MTB/RIF," "Xpert MTB/RIF Ultra," "Xpert MTB/XDR," and "targeted next-generation sequencing." Studies were selected based on the following criteria: (1) published in English, (2) involving adult patients with microbiologically confirmed TB, and (3) reporting diagnostic performance or treatment outcomes. Systematic reviews and meta-analyses were prioritized. Where multiple sources were available, base-case values were calculated as

Table 1 Model input parameters

Parameters	Base-case value	Range for sensitivity analysis	Distribution	Reference
Clinical inputs				
Prevalence/proportion				
MDR/RR-TB	7.50%	2.80–20.72%	Beta	[18, 19]
RIF-resistant INH-susceptible TB	17.19%	1.70–37.00%	Beta	[18, 20, 21]
INH-resistant RIF-susceptible TB (INHR-TB)	9.30%	7.40–17.70%	Beta	[20, 21]
FQ-resistant TB	10.92%	4.90–20.10%	Beta	[1, 18]
Sensitivity to drug resistance				
Xpert for RIF	95.65%	90.00–98.10%	Beta	[22, 23]
Xpert Ultra for RIF	94.50%	87.00–97.90%	Beta	[22, 23]
LPA for RIF	96.35%	95.00–97.50%	Beta	[11, 12]
LPA for INH	90.60%	88.20–93.00%	Beta	[11, 12]
LPA for FQ	86.20%	79.20–93.00%	Beta	[3]
Xpert XDR for INH	94.20%	87.50–97.40%	Beta	[3, 10]
Xpert XDR for FQ	93.15%	88.10–96.20%	Beta	[3, 10]
tNGS for RIF	98.70%	97.20–100.00%	Beta	[3]
tNGS for INH	95.80%	92.80–98.70%	Beta	[3]
tNGS for FQ	95.60%	92.40–98.70%	Beta	[3]
Specificity to drug resistance				
Xpert for RIF	98.40%	97.20–99.60%	Beta	[22, 23]
Xpert Ultra for RIF	99.05%	97.70–100.00%	Beta	[22, 23]
LPA for RIF	98.90%	98.00–99.20%	Beta	[11, 12]
LPA for INH	99.10%	98.00–99.50%	Beta	[11, 12]
LPA for FQ	98.60%	95.70–99.50%	Beta	[3]
Xpert XDR for INH	98.25%	92.60–99.70%	Beta	[3, 10]
Xpert XDR for FQ	98.15%	90.80–99.60%	Beta	[3, 10]
tNGS for RIF	81.00%	69.50–92.50%	Beta	[3]
tNGS for INH	97.00%	95.10–98.90%	Beta	[3]
tNGS for FQ	96.30%	93.20–99.50%	Beta	[3]
Clinical outcomes				
Mortality rate among DS-TB patients	8.61%	6.89–10.33%	Beta	[24, 25]
Mortality rate among MDR/RR-TB patients without FQ resistance	13.46%	10.77–16.15%	Beta	[26]
Mortality rate among MDR/RR-TB patients with FQ resistance	16.79%	13.43–20.19%	Beta	[26]
Mortality rate from TB without appropriate treatment	50.00%	40.00–60.00%	Beta	[1, 25]
HR of mortality with late TB treatment	1.53	1.07–2.96	Lognormal	[27, 28]
Utility inputs				
Utility				
DS-TB/INHR-TB treatment	0.69	0.57–0.77	Triangular	[36, 37]
MDR/RR-TB treatment	0.51	0.39–0.73	Triangular	[36, 37]
Age-specific utility				[35]
18–65 years	0.92	—		
> 65 years	0.84	—		
TB patient age (years)	35	23–51	Triangular	[34]
Cost inputs (USD)				
Cost per test				
pDST	62	47–86	Gamma	[40, 43, 46]
LPAs	55	43–70	Gamma	[40, 42–44]
Xpert	34	27–40	Gamma	[40, 42, 43]
Xpert Ultra	34	27–40	Gamma	[40, 42–44]

Table 1 (continued)

Parameters	Base-case value	Range for sensitivity analysis	Distribution	Reference
Xpert XDR	41	34–47	Gamma	[40, 42–44]
tNGS	157	118–257	Gamma	[3, 48]
Cost per case				
DS-TB treatment	467	327–560	Gamma	[54], Additional file 2: Table S2
INHR-TB treatment	486	389–583	Gamma	[54], Additional file 2: Table S2
MDR/RR-TB with FQ-resistant TB treatment	1,742	1394–2,090	Gamma	[54], Additional file 2: Table S2
MDR/RR-TB with FQ-susceptible TB treatment	1,773	1,418–2,128	Gamma	[54], Additional file 2: Table S2
MDR/RR-TB with longer individualized treatment	4,098	3,278–4,918	Gamma	[54], Additional file 2: Table S2
TB-related mortality	5,722	4,933–6,843	Gamma	[43, 46]

Summary of clinical, diagnostic, utility, and cost parameters used in the decision-analytic model, including base-case values, sensitivity ranges, probability distributions, and references. These inputs were derived from systematic reviews, national surveillance data, WHO reports, and cost-analysis studies. Where multiple sources were available, base-case values were calculated as weighted averages, and sensitivity ranges were defined by the upper and lower bounds of reported data. Distributions are provided for probabilistic analysis. DS-TB: drug-susceptible tuberculosis; FQ: fluoroquinolone; HR: hazard ratio; INH: isoniazid; INHR-TB: isoniazid-resistant tuberculosis; LPAs: line probe assays; MDR/RR-TB: multidrug-resistant or rifampicin-resistant; tNGS: targeted next-generation sequencing; pDST: phenotypic drug susceptibility testing; RIF: rifampicin; TB: tuberculosis; Xpert: Xpert MTB/RIF; Xpert Ultra: Xpert MTB/RIF Ultra; Xpert XDR: Xpert MTB/XDR. LPAs include GenoType MTBDR plus (RIF and INH) and GenoType MTBDRs (FQs), whereas the tNGS evaluated in this study is Deeplex Myc-TB. The treatment of MDRR/RR, with or without FQ resistance, followed the current WHO-recommended priority regimen of a shorter oral course

weighted averages, and sensitivity analysis ranges were derived from the upper and lower bounds of the reported data.

The estimated prevalence of RR-TB among TB patients in South Africa was 7.50%, based on national surveillance data and retrospective analyses [18, 19]. The proportion of INH-susceptible RR-TB was 17.19%, while INH-resistant rifampicin-susceptible TB (INHR-TB) accounted for 9.30% of cases [18, 20, 21]. FQ resistance among MDR/RR-TB patients was estimated at 10.92% [1, 18].

Diagnostic accuracy parameters for the Xpert and Xpert Ultra assays in detecting RIF resistance were obtained from two large systematic reviews involving 3,500 and 42,091 participants [22, 23]. The sensitivity and specificity of LPAs for detecting RIF and INH resistance were derived from meta-analyses comprising 21,225 and 182,448 samples [11, 12], while FQ resistance detection was based on a separate meta-analysis of 1,771 participants [3].

For the Xpert XDR assay, sensitivity and specificity values for INH and FQ resistance were extracted from systematic reviews of multinational studies involving 1,605 and 1,228 participants, respectively [3, 10]. Diagnostic performance data for tNGS were obtained from a systematic review of 12 studies encompassing 1,440 participants [3].

Mortality rates were estimated at 8.61% for DS-TB, 13.46% for MDR/RR-TB without FQ resistance, and 16.79% for MDR/RR-TB with FQ resistance, based on national reports and cohort studies in South Africa [24–26]. A 50% mortality rate was assumed for patients who did not receive appropriate treatment, in line with WHO data and retrospective analyses [1, 25]. A hazard ratio (HR) for mortality associated with late versus early treatment was estimated at 1.53 (95% CI: 1.07–2.96), based on multinational cohort studies reporting annualized HR estimates [27–29].

Health utility inputs

The effectiveness of each diagnostic strategy was assessed using TB-related DALYs, which quantify the burden of disease by combining years of healthy life lost due to morbidity-related disability and premature mortality [30, 31]. DALYs attributable to TB morbidity among surviving patients were estimated based on the duration spent in the TB disease state and the corresponding loss in health utility. This utility loss was calculated as the difference between the utility value associated with the TB state and the age-specific utility of a healthy individual. DALYs resulting from TB-related mortality were estimated using age-specific health utility values and the number of life-years lost due to premature death [30, 31].

Age-specific life expectancy data were obtained from WHO life tables for South Africa [32]. The base-case age of TB patients was set at 35 years, based on clinical trials and retrospective cohort studies conducted in South Africa [33, 34]. According to WHO data, the remaining life expectancy for a 35-year-old in South Africa is approximately 36 years [32]. Age-specific health utility values were derived from published studies on health-related quality of life [35].

Due to the absence of South Africa-specific utility data, base-case utility values for DS-TB and DR-TB treatment were sourced from systematic reviews and

cross-sectional studies [36, 37]. These studies used standardized EQ-5D methods and included large patient cohorts. In the absence of local data, it is acceptable to transfer and adopt health state valuations (utilities) from other settings after adjustment for appropriate national value sets, such as age-specific life expectancy [38, 39].

To account for the time value of health benefits, DALYs associated with TB-related mortality were discounted to the year 2024 at an annual rate of 3%.

Cost inputs

The cost analysis was conducted from the perspective of healthcare providers in South Africa. Key cost components included diagnostic testing (pDST, LPAs, Xpert, Xpert Ultra, Xpert XDR, and tNGS), TB treatment, and TB-related mortality. Treatment costs were stratified by resistance profile (DS-TB, INHR-TB, and MDR/RR-TB with or without FQ resistance) and calculated based on the diagnostic outcome.

Diagnostic accuracy determined the treatment pathway: accurate results led to appropriate early treatment, while false-negative results incurred costs from both initial inappropriate and later corrected regimens. False-positive results led to unnecessary second-line treatment until pDST confirmation. These treatment costs were included in the total direct medical costs for each strategy.

Cost parameters were sourced from peer-reviewed literature, the Stop TB Partnership diagnostic and medicines catalogs, and publicly available data from the South African Department of Health (Table 1). The unit costs of the diagnostic tests included consumables, equipment, staffing, and overhead costs (where available). Per-test costs of pDST, LPA, Xpert, Xpert Ultra, and Xpert XDR were derived from the Stop TB Partnership's diagnostic products catalog and cost-analyses studies on TB diagnostics in South Africa [40–47]. The cost of tNGS was estimated using data from an empirical cost analysis and a feasibility study evaluating its implementation in the South African context [3, 48].

Treatment costs per TB case included outpatient clinic visits, drug regimens, imaging (e.g., electrocardiograms, chest X-rays, audiograms), and laboratory investigations (e.g., smear microscopy, culture, liver, renal, and thyroid function tests, electrolytes, complete blood count, and HIV screening), as detailed in Additional file 2:Table S2 [40–43, 46, 47, 49–53]. Drug regimen costs were obtained from the Stop TB Partnership Medicines Catalog [54], while clinical service costs were aligned with national and WHO guidelines for TB treatment [2, 15].

TB-related mortality costs were estimated based on inpatient treatment cost analyses conducted in South Africa [43, 46, 55]. All cost estimates were adjusted to 2024 U.S. dollar values using an exchange rate of USD 1.00 = ZAR 18.733 [56] and the South African Consumer Price Index (CPI) for health services, where applicable [57].

Cost-effectiveness, sensitivity, and scenario analyses

All analyses were conducted using TreeAge Pro 2024 (TreeAge Software Inc., Williamstown, MA, USA) and Excel 365 (Microsoft Corporation, Redmond, WA, USA). Diagnostic strategies were compared incrementally, with the incremental cost-effectiveness ratio (ICER) calculated as the change in cost divided by the change in DALYs averted (ICER = ΔCost/ΔDALYs). Strategies were considered dominated and excluded from further analysis if they resulted in higher DALYs at a higher cost or had an ICER greater than that of a more effective alternative. After eliminating dominated strategies, ICERs were recalculated for the remaining options relative to the next less costly strategy.

A strategy was deemed cost-effective if it resulted in lower DALYs at a lower cost or if it achieved lower DALYs at a higher cost with an ICER below the willingness-to-pay (WTP) threshold [58, 59]. According to WHO guidelines, an intervention is considered highly cost-effective if its ICER is below the gross domestic product (GDP) per capita, cost-effective if the ICER falls between one and three times the GDP per capita, and not cost-effective if it exceeds three times the GDP per capita [60]. For this study, South Africa's GDP per capita in 2022 (USD 6767) was used as the primary WTP threshold, with a range of USD 6767 to USD 20,301 applied to evaluate cost-effectiveness [3].

One-way sensitivity analyses were performed for all model parameters using the ranges specified in Table 1. These ranges were based on 95% confidence intervals or the high and low values reported in the literature. Where such data were unavailable, a ± 20% variation from the base-case value was applied. This analysis assessed the robustness of the base-case findings and identified influential parameters affecting the ICER, which were visualized using tornado diagrams. Threshold analyses were also conducted by varying key parameters across extended ranges to determine the conditions under which a diagnostic strategy would become cost-effective.

Probabilistic sensitivity analysis was performed using Monte Carlo simulation with 10,000 iterations. In each iteration, model input values were randomly sampled from their respective probability distributions to capture joint uncertainty. The resulting incremental costs and DALYs averted were summarized with 95% confidence intervals and visualized using scatterplots. Cost-effectiveness acceptability curves (CEACs) were generated to estimate the probability of each strategy being accepted

as cost-effective across a range of WTP thresholds, from USD 0 to USD 20,301 per DALY averted [60, 61]. This range includes both the traditional 1–3 × GDP per capita thresholds and a locally derived benchmark of approximately USD 3015 per DALY averted, based on estimates by Edoka et al. [62].

Two scenario analyses were conducted to evaluate the robustness and policy relevance of our findings.

First, diagnostic replacement scenario analysis assessed the feasibility of replacing pDST with rapid molecular diagnostics, in light of recent WHO recommendations [3] that conditionally support the use of rapid molecular tests when parallel phenotypic and genotypic testing is not feasible. Five diagnostic strategies were compared: pDST alone, LPA, 'Xpert followed by Xpert XDR', 'Xpert Ultra followed by Xpert XDR', and tNGS.

Second, the extended time horizon scenario analysis evaluated the impact of extending the model time horizon from 1 to 2 years, reflecting the longer treatment duration for patients receiving the individualized 18-month regimen per South Africa's 2023 DR-TB guidelines [15]. Approximately 30% of DR-TB patients were assumed to receive this regimen [63, 64]. All cost and health outcome inputs—including treatment costs and DALYs—were adjusted accordingly. ICERs were recalculated for each strategy, and sensitivity analysis was performed to assess consistency in cost-effectiveness rankings across time horizons.

Results

Base-case analysis

Among the nine diagnostic strategies evaluated, five were dominated and excluded from further cost-effectiveness analysis (Table 2 (a-b)). The remaining four non-dominated strategies were: 'LPA alone', 'LPA combined with pDST', 'Xpert followed by Xpert XDR combined with pDST', and 'tNGS combined with pDST'. The expected costs and DALYs averted for all testing strategies are depicted in Additional file 2: Fig. S1.

Compared to 'LPA alone', the 'LPA + pDST' strategy averted 0.0843 DALYs at an additional cost of USD 38, resulting in an ICER of USD 447 per DALY averted. When compared with 'LPA + pDST', the 'Xpert followed by Xpert XDR + pDST' strategy averted 0.0034 DALYs at an incremental cost of USD 22, yielding an ICER of USD 6,554 per DALY averted—below South Africa's GDP per capita threshold. This makes 'Xpert followed by Xpert XDR + pDST' the preferred cost-effective strategy. Although the 'tNGS + pDST' strategy achieved the lowest DALYs (1.9877), the highest early treatment rate (995.54 per 1000 tested), and the lowest TB-related mortality (90.22 per 1,000 tested), its ICER of USD 25,918 per DALY averted exceeded three times South Africa's GDP per capita, rendering it not cost-effective.

One-way sensitivity analysis

One-way sensitivity analysis revealed 40 threshold parameters that could alter the base-case findings across WTP thresholds of 1–3 × GDP per capita (Additional file 2:Table S3). Over half of these parameters influenced outcomes at the one-time GDP threshold. Variations in these parameters increased the likelihood of three strategies emerging as cost-effective: 'LPA + pDST', 'Xpert Ultra followed by Xpert XDR + pDST', and 'tNGS + pDST'. Notably, 'LPA + pDST' emerged as the preferred strategy under 25 of the 40 threshold variations.

The top 10 influential parameters affecting ICERs are illustrated in the tornado diagrams (Fig. 2a–c). The comparison between 'Xpert followed by Xpert XDR + pDST' and 'LPA + pDST' was most sensitive to the sensitivity of Xpert XDR for INH resistance, the sensitivity of Xpert for RIF resistance, and HR for mortality associated with late TB treatment. Extended sensitivity analysis showed that 'tNGS + pDST' became cost-effective when the HR for late treatment (base-case = 1.53) exceeded 1.69, 2.02, and 3.02 at WTP thresholds of 3 ×, 2 ×, and 1 × GDP per capita, respectively (Additional file 2:Fig. S2).

Probabilistic sensitivity analysis (PSA)

PSA was conducted using 10,000 Monte Carlo simulations. Scatter plots (Fig. 3a–c) illustrate the incremental cost and DALYs averted for each undominated strategy compared to the next less costly alternative.

Compared to 'LPA alone', 'LPA + pDST' incurred an incremental cost of USD 38 (95% CI: USD 37–39) and averted 0.0833 DALYs (95% CI: 0.0830–0.0837), with 99.92% of simulations showing ICERs below the GDP per capita threshold (cost-saving in 28.79% of simulations and incurred higher costs in 71.13%). Compared to 'LPA + pDST', 'Xpert followed by Xpert XDR + pDST' averted 0.0039 DALYs (95% CI: 0.0035–0.0042) at an additional cost of USD 21 (95% CI: USD 20–23), and was cost-saving in 33.31% of simulations. It was identified as cost-effective in 50.77% of simulations at the GDP per capita threshold and in 71.61% at 3 × GDP per capita. Compared to 'Xpert followed by Xpert XDR + pDST', 'tNGS + pDST' averted 0.0070 DALYs (95% CI: 0.0064–0.0077) at an incremental cost of USD 154 (95% CI: USD 150–157), and was cost-effective in 29.14% and 50.36% of simulations at 1 × and 3 × GDP, respectively.

CEACs (Fig. 4) demonstrated that 'LPA + pDST' had the highest probability of being cost-effective at WTP thresholds between USD 237.5 and USD 7,887.5 per DALY averted, peaking at 28.95% at the GDP per capita. At the locally derived WTP threshold of USD 3,015 per

Table 2 Base-case results

a. Full base-case results, including dominated strategies

Testing strategy	TB patients received early treatment (per 1,000 tested)	TB-related mortality (per 1,000 tested)	Direct cost (USD)	Incremental cost (USD)	DALYs	DALY averted	ICER (USD/DALY)
LPAs	987.83	94.74	1,171	-	2.0812	-	
Xpert Ultra followed by Xpert XDR	990.15	93.77	1,182	12	2.0610	0.0202	571 (dominated)
Xpert followed by Xpert XDR	991.03	93.44	1,190	8	2.0543	0.0067	1150 (dominated)
pDST	838.98	99.36	1,197	7	2.1814	−0.1271	−54 (dominated)
LPAs + pDST	987.83	90.66	1,208	38	1.9969	0.0843	447
Xpert Ultra followed by Xpert XDR + pDST	990.15	90.56	1,228	20	1.9949	0.0020	9,729 (dominated)
Xpert followed by Xpert XDR + pDST	991.03	90.50	1,231	22	1.9935	0.0034	6,554
tNGS + pDST	995.54	90.22	1,383	153	1.9877	0.0059	25,918
tNGS	995.54	91.72	1,476	92	2.0185	--0.0309	−2,994 (dominated)

b. Cost-effectiveness comparison excluding dominated strategies

Testing strategy	Total direct cost (USD)	Incremental cost (USD)	DALYs	DALY averted	ICER (USD/DALY)
LPAs	1,171	-	2.0812	-	-
LPAs + pDST	1,208	38	1.9969	0.0843	447
Xpert followed by Xpert XDR + pDST	1,231	22	1.9935	0.0034	6,554
tNGS + pDST	1,383	153	1.9877	0.0059	25,918

Comparative outcomes of the nine diagnostic strategies evaluated, including early treatment rates, TB-related mortality, direct costs, DALYs, incremental costs, DALYs averted, and ICERs. Dominated strategies are excluded from the final cost-effectiveness comparison. *DALY* disability-adjusted life years, *ICER* incremental cost-effectiveness ratio, *LPA* line probe assays, *pDST* phenotypic drug susceptibility testing, *TB* tuberculosis, *tNGS* targeted next-generation sequencing, *Xpert Ultra* Xpert MTB/RIF Ultra, *Xpert XDR* Xpert MTB/XDR, *Xpert* Xpert MTB/RIF, *ICER* incremental cost/DALY averted (compared with the next less costly strategy)

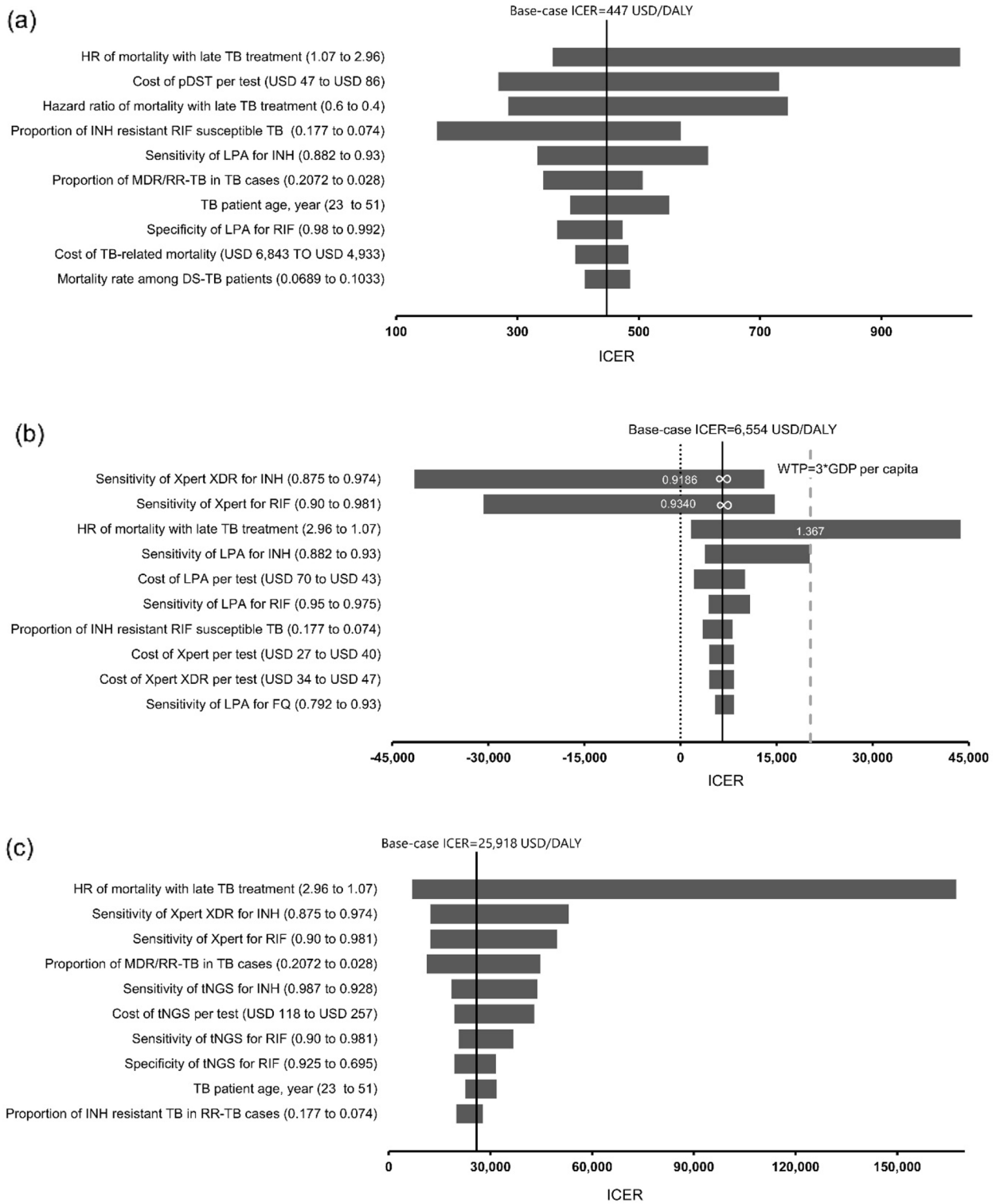

Fig. 2 Tornado diagram of influential factors identified in one-way sensitivity analysis of the ICERs of **a** 'LPAs + pDST' versus LPA, **b** 'Xpert followed by Xpert XDR + pDST' versus 'LPAs + pDST', and **c** 'tNGS + pDST' versus 'Xpert followed by Xpert XDR + pDST'

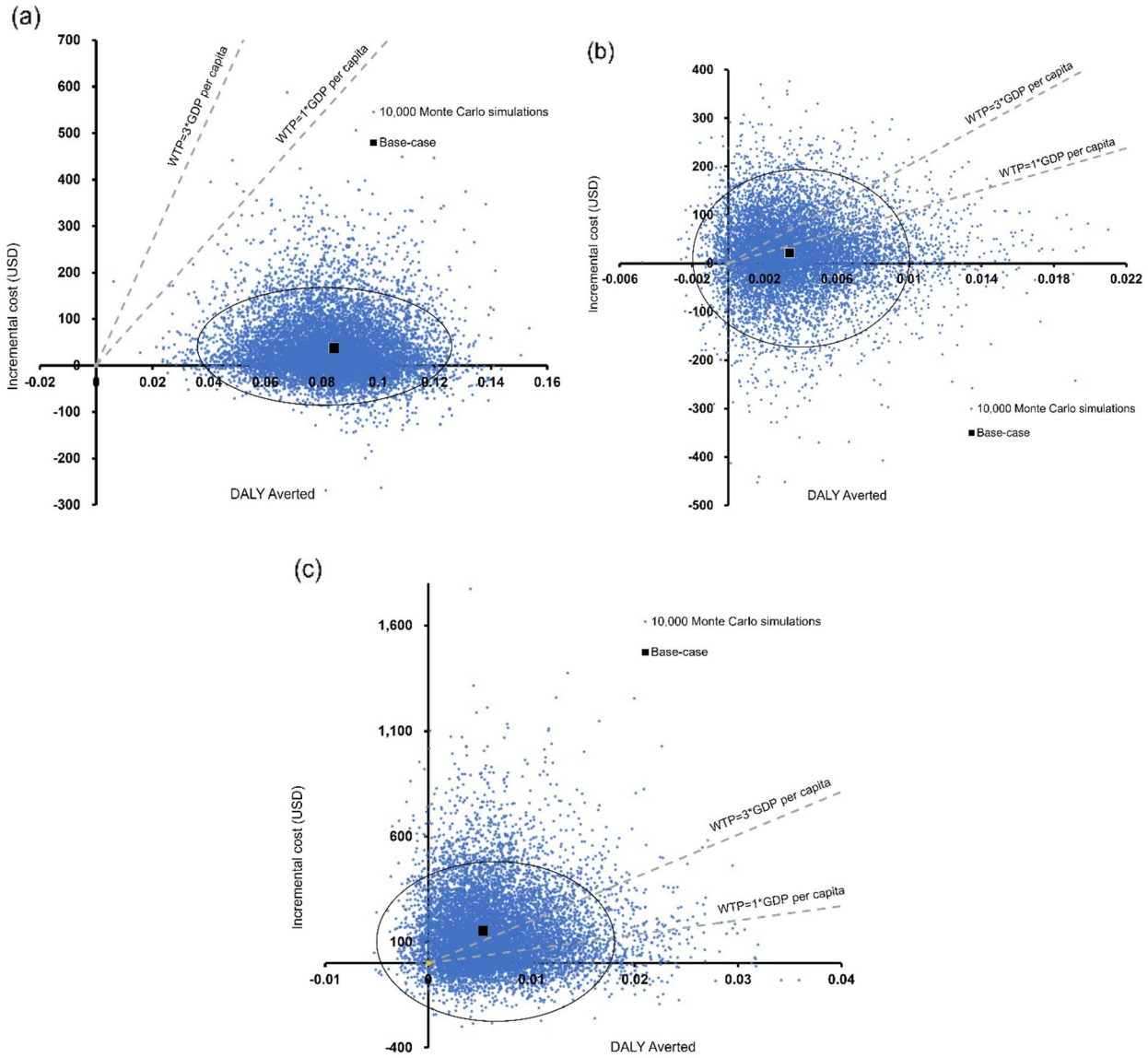

Fig. 3 Scatter plot of the incremental cost against DALY averted by **a** 'LPAs + pDST' versus LPAs, **b** 'Xpert followed by Xpert XDR + pDST' versus 'LPAs + pDST', and **c** 'tNGS + pDST' versus 'Xpert followed by Xpert XDR + pDST' in 10,000 Monte Carlo simulations

DALY averted, the 'LPA + pDST' strategy had an acceptance probability of 36.35%. 'Xpert followed by Xpert XDR + pDST' became the preferred strategy between USD 7,887.5 and USD 10,500, while 'tNGS + pDST' had the highest probability of being cost-effective above USD 10,500, reaching over 45% at 3 × GDP per capita (USD 20,301).

Scenario analysis

Diagnostic replacement scenario analysis

This scenario compared five diagnostic strategies to evaluate the feasibility of replacing pDST with rapid molecular diagnostics. The results showed that tNGS alone could be a viable alternative when pDST is unavailable, with an ICER of USD 1,712 per DALY averted—below South Africa's GDP per capita threshold. These findings support the conditional WHO recommendation for molecular diagnostics in settings where phenotypic testing is not feasible (Additional file 2:Appendix S1, Tables S4–S5, Figs. S3–S5).

Extended time horizon scenario analysis

Extending the model horizon to 2 years increased absolute costs and DALYs across all strategies. However, the relative

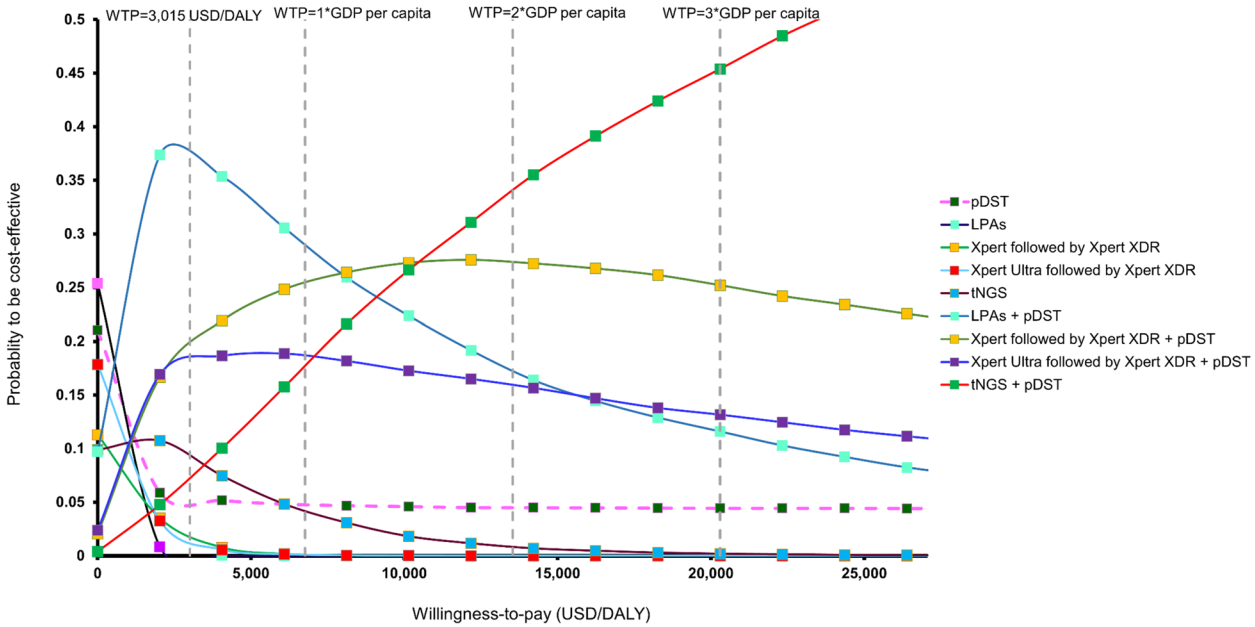

Fig. 4 Cost-effectiveness acceptability curves showing the probability of each diagnostic strategy for RIF, INH, and FQ resistance detection being cost-effective across a range of WTP thresholds

cost-effectiveness rankings remained unchanged. The'Xpert followed by Xpert XDR+pDST' strategy remained the preferred cost-effective option (ICER = USD 6,736/DALY), while'tNGS+pDST' remained not cost-effective (ICER= USD 29,950/DALY). Probabilistic sensitivity analysis confirmed these findings, with low acceptance probabilities for tNGS even at higher WTP thresholds (Additional file 2:Appendix S1, Tables S6–S7, Figs. S6–S8).

Discussion

This study evaluated the cost-effectiveness of rapid molecular assays, with or without pDST, for detecting DR-TB in a high-burden setting. The base-case analysis revealed that the combination of Xpert MTB/RIF followed by Xpert MTB/XDR with pDST was the preferred cost-effective strategy, with an ICER of USD 6,554 per DALY averted—below South Africa's GDP per capita threshold. Although tNGS+pDST yielded the greatest health benefits—including the lowest DALYs (1.9877), highest early treatment initiation rate (995.54 per 1,000 tested), and lowest TB-related mortality (90.22 per 1,000 tested)—its ICER of USD 25,918 per DALY averted exceeded three times the GDP per capita, rendering it not cost-effective under WTP assumptions.

To address concerns about the short time horizon, a two-year scenario analysis was conducted. While absolute costs and DALYs increased across all strategies, the relative cost-effectiveness rankings remained unchanged, confirming the robustness of the base-case findings. The extended horizon reinforced that the diagnostic impact on early treatment initiation and mortality risk is most critical within the first year, validating the use of a one-year horizon for short-term diagnostic evaluations.

Sensitivity analyses highlighted the influence of key diagnostic and clinical parameters. One-way sensitivity analysis identified 40 threshold parameters that could alter the base-case findings. The most influential factors for the 'Xpert followed by Xpert XDR+pDST' strategy were the sensitivity of Xpert XDR for INH resistance, the sensitivity of Xpert for RIF resistance, and the HR for mortality associated with delayed treatment. The HR for late treatment (base-case: 1.53) had a particularly strong impact on the ICER of the tNGS+pDST strategy, given its role in reducing DALYs through earlier treatment initiation. PSA confirmed that tNGS+pDST had the highest probability of being cost-effective when the WTP threshold exceeded USD 10,500 per DALY averted.

To further assess the policy relevance and feasibility of diagnostic strategies in resource-constrained settings, we conducted a diagnostic replacement scenario analysis. This scenario was designed to reflect real-world conditions where concurrent phenotypic and molecular testing may not be feasible, as acknowledged in recent WHO recommendations [3]. The results demonstrated that tNGS alone could serve as a viable and cost-effective alternative when pDST is unavailable, with an ICER of USD 1,712 per DALY averted—below South Africa's GDP per capita threshold. Within this framework, Xpert

followed by Xpert XDR remained a less costly and highly effective option, offering a practical balance between diagnostic yield and affordability. These findings support the conditional use of molecular diagnostics as standalone tools in resource-limited settings and highlight the potential of tNGS for broader implementation where laboratory infrastructure is constrained.

Previous economic evaluations of rapid molecular diagnostics in high-burden settings have primarily focused on Xpert and LPAs compared to pDST [47, 65, 66]. Cost analysis studies in India, Moldova, and South Africa reported that LPAs were faster but more expensive than pDST [47], while in China, LPAs were significantly more affordable [65]. In Brazil, Xpert was found to be the least costly and most efficient option, making it a dominant strategy [66]. A WHO-commissioned analysis of tNGS as an initial DST for all TB-confirmed cases in Georgia, India, and South Africa found it to be cost-effective in Georgia alone (ICER = USD 9,261 per DALY) at three times the GDP per capita threshold [3]. However, that study did not account for the impact of early treatment initiation or compare multiple diagnostic strategies. In contrast, our scenario analysis incorporated early treatment effects and demonstrated that tNGS could be a cost-effective replacement for pDST.

Our inclusion of pDST-alone and combination strategies reflects both historical benchmarks and real-world diagnostic pathways. While pDST-alone is not policy-relevant in South Africa, it serves as a theoretical baseline to assess the added value of molecular diagnostics. The combination strategies model the stepped approach recommended by WHO, where molecular tests are used for initial screening and pDST is applied for confirmation or further resistance profiling [3]. This is particularly important for drugs not covered by molecular assays and for managing complex resistance patterns. This comprehensive framework allows evaluation of whether the operational advantages of molecular-only strategies outweigh the broader resistance profiling offered by combined approaches in high-burden settings.

While we used the 1–3 × GDP per capita thresholds for comparability with global health economic evaluations, we also considered a locally derived WTP threshold from Edoka et al. [62], estimated at USD 3,015 per DALY averted. This alternative benchmark provides a more context-specific lens for interpreting cost-effectiveness in South Africa. At this threshold, the 'LPA + pDST' strategy had the highest probability of acceptance, while 'Xpert followed by Xpert XDR + pDST' became more favorable as the WTP increased.

Compared to pDST, rapid molecular tests offer faster turnaround, improved accessibility, and fewer biosafety concerns. These advantages facilitate the timely initiation of appropriate treatment, improving clinical outcomes and potentially reducing the burden of ineffective therapy, adverse drug reactions, and further resistance development [3, 9]. However, limitations such as incomplete resistance detection, false-negative results, and higher implementation costs must be considered [3]. Notably, tNGS's relatively lower specificity for RIF resistance (81%) may lead to false-positive results and overtreatment, as it can detect mutations of uncertain significance not confirmed by pDST [3].

From a health economics perspective, integrating rapid molecular assays with pDST represents a complementary and cost-effective strategy for enhancing DR-TB diagnosis. This approach can improve case detection, expedite treatment initiation, reduce inappropriate therapy costs, and enable personalized treatment plans. This synergistic approach leverages the strengths of both molecular and phenotypic testing, offering comprehensive resistance profiling and improved diagnostic accuracy. In South Africa, the GeneXpert system remains the cornerstone of TB diagnosis [15, 48]. When RIF resistance is detected via Xpert or Xpert Ultra, the same sample is automatically tested with Xpert XDR for additional resistance markers. Culture confirmation and pDST follow thereafter [15, 48].

Despite its advantages, widespread adoption of tNGS faces challenges, including technical complexity, infrastructure requirements, supply chain limitations, and higher upfront costs [67]. These barriers may hinder its feasibility in resource-limited settings. However, as tNGS technology matures and scales, reductions in cost and improvements in turnaround time are anticipated. These advancements may enhance the cost-effectiveness of tNGS-based strategies, particularly in decentralized or low-resource environments. Periodic re-evaluation of tNGS is warranted as the technology landscape evolves.

Although combining tNGS with pDST improved resistance detection and facilitated earlier treatment, it did not reduce resource utilization compared to the Xpert-based strategy [48]. The decision-analytic model developed in this study is adaptable for use in other settings. By incorporating region-specific clinical and economic inputs, policymakers and clinicians can tailor the model to optimize resource allocation for DR-TB diagnosis. Furthermore, the framework allows for updates as new diagnostic assays with varying performance characteristics become available, guiding future research and development in diagnostic pathology and clinical chemistry.

Strengths and limitations of the study

A key strength of this study lies in its comprehensive evaluation of multiple diagnostic strategies for detecting DR-TB, enabling the identification of optimal and

cost-effective approaches across a range of clinical and policy-relevant scenarios. The inclusion of both molecular-only and combination strategies, as well as a diagnostic replacement scenario, allows for nuanced comparisons that reflect real-world implementation pathways.

The diagnostic accuracy estimates were derived from systematic reviews and meta-analyses of recent evidence, ensuring methodological rigor. The model also integrated probability estimates, cost inputs, and epidemiological data specific to South Africa, enhancing contextual relevance and applicability. This alignment with national TB guidelines and WHO recommendations strengthens the policy relevance of the findings and supports their potential utility in informing strategic decisions in high-burden settings.

Furthermore, the study employed extensive sensitivity and scenario analyses to explore uncertainty and test the robustness of results under varying assumptions. These analyses included both global and locally derived WTP thresholds, providing a more context-specific lens for interpreting cost-effectiveness in South Africa.

This study has several limitations that should be considered when interpreting the findings.

First, the analysis was conducted from the healthcare system perspective and did not account for broader societal costs, such as out-of-pocket expenses incurred by patients or indirect costs related to productivity losses. Additionally, infrastructure and operational costs associated with implementing advanced diagnostics—such as the GeneXpert platform and NGS—were excluded. These omissions may lead to an underestimation of the true economic and implementation impact of the evaluated strategies, particularly in resource-limited settings.

Second, the model focused exclusively on bacteriologically confirmed general TB patients and did not include special populations such as individuals living with HIV, who may derive greater benefit from specific diagnostics like Xpert Ultra and Xpert XDR due to the high HIV/MDR-TB co-infection burden in South Africa. Moreover, the model did not incorporate LTFU or adverse events, which are important factors influencing treatment effectiveness and costs. Excluding these factors may underestimate the real-world benefits of rapid diagnostics, especially in settings where treatment adherence and adverse drug reactions significantly affect outcomes.

Third, the model assumed ideal test completion rates and did not explicitly account for test failure or incomplete diagnostic yield. Assays such as pDST, second-line LPAs, and tNGS may not produce results in all cases due to culture requirements or low bacterial load. While sensitivity analyses explored variability in test performance, future models should incorporate test feasibility more explicitly to better reflect real-world implementation challenges.

Fourth, the model assumed a constant HR for mortality associated with late treatment initiation. While this simplification was necessary due to the decision tree structure and the lack of time-specific data, it may not fully capture the dynamic nature of TB progression and treatment delays. Similarly, the use of a one-year time horizon may truncate the long-term benefits of strategies that reduce mortality, potentially underestimating the cost-effectiveness of highly sensitive diagnostics such as tNGS. However, the extended two-year horizon scenario analysis supports the robustness of the findings. Future studies employing lifetime horizons and time-dependent models could provide a more comprehensive assessment.

Fifth, the model did not incorporate TB transmission dynamics, which likely underestimates the population-level benefits and cost-effectiveness of faster, more sensitive diagnostic strategies such as tNGS and Xpert-based algorithms. These diagnostics can reduce community transmission through earlier initiation of appropriate treatment. Future modeling efforts should incorporate transmission dynamics to better capture the broader public health impact of rapid diagnostics, particularly in high-burden settings.

Sixth, due to the absence of South Africa-specific TB treatment utility data, health utility values were adapted from Thai studies and adjusted using South Africa's age-specific life expectancy. While this approach introduces uncertainty, sensitivity analyses confirmed minimal impact on ICER rankings, suggesting that the base-case results are robust. Nonetheless, future studies should consider collecting country-specific utility data to improve precision in DALY estimation.

Finally, the absence of an officially endorsed WTP threshold in South Africa introduces uncertainty in interpreting cost-effectiveness results. While the study applied the widely used $1–3\times$GDP per capita rule, it also considered a locally derived threshold. Consequently, the comparative ranking of strategies is robust within our parameter ranges, but budget impact and population effects may differ in programmatic settings with varying HIV prevalence, test completion rates, and infrastructure constraints. Future research should aim to establish context-specific WTP benchmarks to guide national decision-making more accurately. Additionally, future studies should prioritize collaborative partnerships with South African researchers, clinicians, and program managers to enhance local relevance and impact.

Conclusions

This study demonstrates that the combined use of rapid molecular diagnostics—specifically Xpert MTB/RIF followed by Xpert MTB/XDR—alongside confirmatory pDST is the preferred cost-effective strategy for detecting DR-TB in high-burden settings such as South Africa. This approach offers a favorable balance between diagnostic accuracy, early treatment initiation, and economic efficiency, with ICER below the national GDP per capita threshold.

Although tNGS combined with pDST yielded the greatest health benefits in terms of DALYs averted and mortality reduction, its higher cost rendered it not cost-effective under standard WTP thresholds. However, scenario analysis revealed that tNGS alone may serve as a viable and cost-effective alternative when pDST is unavailable or infeasible, particularly in settings with limited laboratory capacity.

The inclusion of a two-year extended time horizon scenario further confirmed the robustness of the base-case findings, demonstrating that the relative cost-effectiveness rankings remained stable even when accounting for longer treatment durations. These results underscore the importance of early and accurate diagnosis in improving TB outcomes and optimizing resource allocation in high-burden, resource-constrained environments.

Abbreviations

DALY	Disability-adjusted life year
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-susceptible tuberculosis
FQ/FQs	Fluoroquinolones
GDP	Gross domestic product
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
INH	Isoniazid
INHR–TB	Isoniazid-resistant tuberculosis
LPAs	Line probe assays
MDR/RR-TB	Multidrug-resistant/rifampicin-resistant tuberculosis
MTB	Mycobacterium tuberculosis
NAATs	Nucleic acid amplification tests
pDST	Phenotypic drug susceptibility testing
PSA	Probabilistic sensitivity analysis
RIF	Rifampicin
RR-TB	Rifampicin-resistant tuberculosis
RS–TB	Rifampicin-susceptible tuberculosis
TB	Tuberculosis
tNGS	Targeted next-generation sequencing
WHO	World Health Organization
WTP	Willingness to pay
XDR-TB	Extensively drug-resistant tuberculosis
Xpert	Xpert MTB/RIF
Xpert Ultra	Xpert MTB/RIF Ultra
Xpert XDR	Xpert MTB/XDR

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-026-04693-3.

Additional file 1. CHEERS Checklist for health-economic evaluations.

Additional file 2. Appendix S1, Tables S1–S7, and Figs. S1–S8. Appendix S1: Scenario analyses results. Table S1: WHO-based TB definitions. Table S2: Unit costs for TB clinical services and diagnostic tests. Table S3: Threshold values of influential parameters affecting cost-effectiveness in the main analysis. Table S4: Base-case results for the diagnostic replacement scenario. Table S5: Threshold values for the diagnostic replacement scenario. Table S6: Base-case resultsfor the extended two-year horizon scenario. Table S7: Probabilities of costs, effectiveness, and cost-effectiveness in the extended horizon scenario. Fig. S1: Base-case cost-effectiveness plot for nine diagnostic strategies. Fig. S2: ICER of 'tNGS + pDST' vs. 'Xpert → Xpert XDR + pDST' across hazard ratios for late TB treatment. Fig. S3: Tornado diagrams—diagnostic replacement scenario. Fig. S4: Scatter plots—diagnostic replacement scenario. Fig. S5: Cost-effectiveness acceptability curves—diagnostic replacement scenario across WTP thresholds. Fig. S6: Tornado diagrams—extended time horizon scenario. Fig. S7: Scatter plots—extended time horizon scenario. Fig. S8: Cost-effectiveness acceptability curves—extended time horizon for nine strategies.

Acknowledgements

None.

Authors' contributions

GF conceived and designed the study. GF, TT, and HHT developed the model structure and selected input parameters. GF, HHT, and TRF retrieved and validated data estimates. GF, TT, NC, EA, MS, and WKM conducted the cost-effectiveness analysis and interpreted results. WKM supervised statistical analyses and overall project coordination. GF, TT, HHT, and TRF drafted the initial manuscript. LY, SC, LG, NC, EA, MS, and WKM critically reviewed and revised subsequent drafts. All authors had full access to the data, contributed to the final manuscript, and approved its submission. All authors read and approved the final manuscript.

Funding

None.

Data availability

All model input parameters—including epidemiological data, diagnostic test accuracy values, cost estimates, and health utilities—are fully reported in the manuscript (Table 1) and Additional file 2 (Table S2), with corresponding references provided. These data were derived exclusively from publicly available sources, including WHO reports, South African national surveillance and guideline documents, the National Health Laboratory Service, the Stop TB Partnership diagnostics and medicines catalogs, and peer-reviewed literature cited in the References. No new datasets were generated or analyzed, and all data supporting the findings of this study are included within the article and its supplementary files.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a decision-analytic cost-effectiveness modeling study based exclusively on published, publicly available, aggregated, and de-identified data obtained from scientific literature and public health reports. It did not involve direct interaction with human participants, nor did it involve access to individual-level patient data or identifiable records. Therefore, institutional ethics approval and informed consent were not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]School of Pharmacy, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia. [2]Department of Infectious Diseases and Public Health, Jockey Club College of Veterinary Medicine and Life Sciences, City University of Hong Kong, Kowloon, Hong Kong. [3]Deakin Health Economics, School

of Health and Social Development, Institute for Health Transformation, Deakin University, Victoria, Australia. [4]School of Public Health, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia. [5]Department of Public Health, College of Health Sciences, Salale University, Fitche, Ethiopia. [6]Department of Epidemiology and Biostatistics, School of Public Health, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda. [7]Deakin Rural Health, School of Medicine, Faculty of Health, Deakin University, Victoria, Australia. [8]School of Public Health, Sun Yat-Sen University, Guangzhou, China. [9]Institute for Global Health and Development, Peking University, Beijing, China. [10]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. [11]International Centre for Evidence in Disability, Faculty of Epidemiology and Population Health, London, School of Hygiene & Tropical Medicine, London, UK. [12]Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT, USA. [13]IDEAS Center, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT, USA. [14]Department of Economics, School of Accounting, Economics, and Finance (SAEF), University of KwaZulu Natal, Durban, South Africa. [15]Health Economics and Financing Division, Africa Centres for Disease Control and Prevention (Africa CDC), Addis Ababa, Ethiopia. [16]Chair of General Economics, Health Economics and Econometrics, University of Greifswald, Greifswald, Germany. [17]Institute of Global Governance and Innovation for a Shared Future, City University of Hong Kong, Kowloon, Hong Kong.

Received: 11 August 2025 Accepted: 3 February 2026
Published online: 09 February 2026

References

1. World Health Organization. Global Tuberculosis Report 2024. Geneva: World Health Organization; 2024.
2. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. WHO; 2022.
3. World Health Organization. WHO consolidated guidelines on tuberculosis: module 3: Diagnosis: Rapid diagnostics for tuberculosis detection. Geneva: WHO; 2024.
4. Yusoof KA, García JI, Schami A, Garcia-Vilanova A, Kelley HV, Wang S-H, et al. Tuberculosis phenotypic and genotypic drug susceptibility testing and immunodiagnostics: a review. Front Immunol. 2022;13:870768.
5. Zweynert A. Drug-resistant TB threatens to kill 75 million people by 2050, Cost $16.7 Trillion. London: Reuters; 2022. https://www.reuters.com/article/business/healthcare-pharmaceuticals/drug-resistant-tb-threatens-to-kill-75-million-people-by-2050-cost-167-trilli-idUSKBN0MK004/.
6. Naidoo K, Perumal R, Ngema SL, Shunmugam L, Somboro AM. Rapid diagnosis of drug-resistant tuberculosis–opportunities and challenges. Pathogens. 2023;13(1):27.
7. World Health Organization. WHO standard: universal access to rapid tuberculosis diagnostics. WHO; 2023.
8. Xie YL, Chakravorty S, Armstrong DT, Hall SL, Via LE, Song T, et al. Evaluation of a rapid molecular drug-susceptibility test for tuberculosis. N Engl J Med. 2017;377(11):1043–54.
9. Nandlal L, Perumal R, Naidoo K. Rapid molecular assays for the diagnosis of drug-resistant tuberculosis. Infect Drug Resist. 2022. https://doi.org/10.2147/idr.s381643.
10. Pillay S, Steingart KR, Davies GR, Chaplin M, De Vos M, Schumacher SG, et al. Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin. Cochrane Database Syst Rev. 2022;5(5):Cd014841.
11. Lin M, Chen YW, Li YR, Long LJ, Qi LY, Cui TT, et al. Systematic evaluation of line probe assays for the diagnosis of tuberculosis and drug-resistant tuberculosis. Clin Chim Acta. 2022;533:183–218.
12. Nathavitharana RR, Cudahy PG, Schumacher SG, Steingart KR, Pai M, Denkinger CM. Accuracy of line probe assays for the diagnosis of pulmonary and multidrug-resistant tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2017;49(1):1601075.
13. Liu A, Liu S, Lv K, Zhu Q, Wen J, Li J, et al. Rapid detection of multidrug resistance in tuberculosis using nanopore-based targeted next-generation sequencing: a multicenter, double-blind study. Front Microbiol. 2024;15:1349715.
14. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs A, Carswell C, et al. CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. Value Health. 2022;25(1):3–9.
15. Department of Health - South Africa. Clinical management of rifampicin-resistant tuberculosis: updated clinical reference guide 2023. https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf.
16. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. Geneva: WHO; 2022.
17. Department of Health-South Africa. South African National TB Guidelines - Adults: National Department of Health; 2017. https://www.knowledgehub.org.za/system/files/elibdownloads/2022-09/TB%20Adult_2017.pdf.
18. Mvelase NR, Balakrishna Y, Lutchminarain K, Mlisana K. Evolving rifampicin and isoniazid mono-resistance in a high multidrug-resistant and extensively drug-resistant tuberculosis region: a retrospective data analysis. BMJ Open. 2019;9(11):e031663.
19. Department of Health- South Africa. Annual report 2022/2023 South Africa: National Department of Health, Republic of South Africa; 2023. www.gov.za/sites/default/files/gcis_document/202310/health-annual-report.pdf.
20. National Institute for Communicable Disease (NICD). South African Tuberculosis Drug Resistance Survey 2012–14: Division of the National Health Laboratory Service; 2017. https://www.nicd.ac.za/assets/files/K-12750%20NICD%20National%20Survey%20Report_Dev_V11-LR.pdf.
21. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87.
22. Horne DJ, Kohli M, Zifodya JS, Schiller I, Dendukuri N, Tollefson D, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019;6(6):Cd009593.
23. Zifodya JS, Kreniske JS, Schiller I, Kohli M, Dendukuri N, Schumacher SG, et al. Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis. Cochrane Database Syst Rev. 2021;2(2):CD009593.
24. Department of Health- South Africa. Annual report 2021/2022 South Africa: National Department of Health, Republic of South Africa; 2022. https://www.gov.za/sites/default/files/gcis_document/202210/healthannualreport202122.pdf.
25. Osman M, van Schalkwyk C, Naidoo P, Seddon JA, Dunbar R, Dlamini SS, et al. Mortality during tuberculosis treatment in South Africa using an 8-year analysis of the national tuberculosis treatment register. Sci Rep. 2021;11(1):1–10.
26. Pai H, Ndjeka N, Mbuagbaw L, Kaniga K, Birmingham E, Mao G, et al. Bedaquiline safety, efficacy, utilization and emergence of resistance following treatment of multidrug-resistant tuberculosis patients in South Africa: a retrospective cohort analysis. BMC Infect Dis. 2022;22(1):870.
27. Kraef C, Bentzon A, Panteleev A, Skrahina A, Bolokadze N, Tetradov S, et al. Delayed diagnosis of tuberculosis in persons living with HIV in Eastern Europe: associated factors and effect on mortality—a multicentre prospective cohort study. BMC Infect Dis. 2021;21(1):1–12.
28. Xie Y, Han J, Yu W, Wu J, Li X, Chen H. Survival analysis of risk factors for mortality in a cohort of patients with tuberculosis. Can Respir J. 2020;2020:1654653.
29. Lui G, Wong RYK, Li F, Lee MKP, Lai RWM, Li TCM, et al. High mortality in adults hospitalized for active tuberculosis in a low HIV prevalence setting. PLoS One. 2014;9(3):e92077.
30. Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bull World Health Organ. 1994;72(3):429.
31. World Health Organization. WHO methods and data sources for global burden of disease estimates 2000-2019. WHO; 2020.
32. World Health Organization. Global Health Observatory data repository. Life tables by country_South Africa. Geneva: WHO; 2020.
33. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893–902.

34. Mendelsohn SC, Fiore-Gartland A, Awany D, Mulenga H, Mbandi SK, Tameris M, et al. Clinical predictors of pulmonary tuberculosis among South African adults with HIV. Eclin Med. 2022;45:101328.
35. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses - using national measures to create condition-specific values. Med Care. 1998;36(6):778–92.
36. Kittikraisak W, Kingkaew P, Teerawattananon Y, Yothasamut J, Natesuwan S, Manosuthi W, et al. Health related quality of life among patients with tuberculosis and HIV in Thailand. PLoS One. 2012;7(1):e29775.
37. Park H-Y, Cheon H-B, Choi SH, Kwon J-W. Health-related quality of life based on EQ-5D utility score in patients with tuberculosis: a systematic review. Front Pharmacol. 2021;12:659675.
38. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report. Value Health. 2009;12(4):409–18.
39. Knies S, Evers SMAA, Candel MJJM, Severens JL, Ament AJHA. Utilities of the EQ-5D. Pharmacoeconomics. 2009;27(9):767–79.
40. Shah M, Chihota V, Coetzee G, Churchyard G, Dorman SE. Comparison of laboratory costs of rapid molecular tests and conventional diagnostics for detection of tuberculosis and drug-resistant tuberculosis in South Africa. BMC Infect Dis. 2013;13(1):1–7.
41. TB Diagnostics Market Analysis Consortium. Market assessment of tuberculosis diagnostics in South Africa, 2012-2013. Int J Tuberc Lung Dis. 2015;19(2):216–22.
42. Pooran A, Pieterson E, Davids M, Theron G, Dheda K. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? PLoS One. 2013;8(1):e54587.
43. Cox H, Ramma L, Wilkinson L, Azevedo V, Sinanovic E. Cost per patient of treatment for rifampicin-resistant tuberculosis in a community-based programme in Khayelitsha, South Africa. Trop Med Int Health. 2015;20(10):1337–45.
44. Stop TB Partnership. Diagnostics, medical devices & other health products catalog Geneva. WHO; 2024.
45. African Society for Laboratory Medicine (ASLM). Molecular Diagnostic Pricing Database: ASLM; 2023. https://aslm.org/diagnostic-pricing-database/.
46. Sinanovic E, Ramma L, Vassall A, Azevedo V, Wilkinson L, Ndjeka N, et al. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. Int J Tuberc Lung Dis. 2015;19(2):172–8.
47. Groessl EJ, Ganiats TG, Hillery N, Trollip A, Jackson RL, Catanzaro DG, et al. Cost analysis of rapid diagnostics for drug-resistant tuberculosis. BMC Infect Dis. 2018;18(1):102.
48. Bagratee TJ, Studholme DJ. Targeted genome sequencing for tuberculosis drug susceptibility testing in South Africa: a proposed diagnostic pipeline. Access Microbiol. 2024;6(2):000740.
49. Department of Health South Africa. Uniform patient fee schedule: Department of Health; 2022. http://www.health.gov.za/uniform-patient-fee-schedule/.
50. Menzies NA, Cohen T, Lin H-H, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. PLoS Med. 2012;9(11):e1001347.
51. Mpobela Agnarson A, Wang XC, Potluri R, Bhandari H, Dhir A, Kambili C, et al. Long-term impact of the adoption of bedaquiline-containing regimens on the burden of drug-resistant tuberculosis in China. BMC Infect Dis. 2020;20(1):113.
52. South Africa National Health Laboratory Service. NHLS State Price 2018 https://paediatrics.org.za/wp-content/uploads/2023/05/NHLS-State-Price-List-2018.pdf.
53. Lister Clinic_South Africa. Pathology / laboratory test prices for cash clients 2018. https://listerclinic.com/affordable-pathology-laboratory-tests/downloadable-price-list-pathology-lab-tests-2018-08-24-version-9/.
54. Stop TB Partnership Global Drug Facility. Medicines Catalog Geneva. WHO; 2024.
55. Janson J, Marais F, Mehtar S, Baltussen R. Costs and process of in-patient tuberculosis management at a central academic hospital, Cape Town, South Africa. Public Health Action. 2012;2(3):61–5.
56. United Nations. UN Operational Rates of Exchange 2024 [Available from: https://treasury.un.org.
57. Statistics South Africa. Statistical Release P0141 Consumer Price Index Pretoria;2024. https://www.statssa.gov.za/publications/P0141/P0141February2024.pdf.
58. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford university press; 2015.
59. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation: Oxford University Press, Oxford; 2006. https://global.oup.com/academic/product/decision-modelling-for-health-economic-evaluation-9780198526629?cc=et&lang=en&.
60. World Health Organization. The world health report 2002: reducing risks, promoting healthy life. Geneva: WHO; 2002.
61. Fekadu G, Wang Y, You JH. Standard diagnostics with and without urine-based lipoarabinomannan testing for tuberculosis disease in HIV-infected patients in a high-burden setting–a cost-effectiveness analysis. PLoS One. 2023;18(7):e0288605.
62. Edoka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. Health Policy Plan. 2020;35(5):546–55.
63. Stadler JAM, Kuhlin J, Molloy SF, Mtwa N, Hayes C, Maartens G, et al. Treatment outcomes with an oral short course regimen for rifampicin-resistant tuberculosis in a high HIV prevalence, programmatic setting in South Africa. Clin Infect Dis. 2025;81(4):e153–62.
64. Tack I, Dumicho A, Ohler L, Shigayeva A, Bulti AB, White K, et al. Safety and effectiveness of an all-oral, bedaquiline-based, shorter treatment regimen for rifampicin-resistant tuberculosis in high human immunodeficiency virus (HIV) burden rural South Africa: a retrospective cohort analysis. Clin Infect Dis. 2021;73(9):e3563–71.
65. Li Q, Xia H, Ou X, Zhao B, Pang Y, Zhao Y. Cost comparison analysis of line probe assay and conventional drug susceptibility testing for diagnosis of drug resistance of *Mycobacteria tuberculosis*. Chin J Antitubercul. 2013;35(3):187–90.
66. Silva SCA, Vater MC, Ramalho DMdP, Almeida INd, Miranda SSd, Kritski A. Cost-effectiveness of Xpert® MTB/RIF in the diagnosis of tuberculosis: pragmatic study. Rev Soc Bras Med Trop. 2021;54:e07552020.
67. de Araujo L, Cabibbe AM, Mhuulu L, Ruswa N, Dreyer V, Diergaardt A, et al. Implementation of targeted next-generation sequencing for the diagnosis of drug-resistant tuberculosis in low-resource settings: a programmatic model, challenges, and initial outcomes. Front Public Health. 2023;11:1204064.

Publisher's Note