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Cost-effectiveness of rapid susceptibility testing against second-line drugs for tuberculosis

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Summary

Background—Drug susceptibility testing (DST) against second-line tuberculosis drugs (SLDs) is essential for improving outcomes among multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) cases.

Objective—To evaluate the potential cost-effectiveness of rapid DST for SLDs.

Design—We constructed a decision analysis model of Xpert® MTB/RIF-based TB diagnosis in East and South-East Asia to compare culture-based DST vs. a hypothetical rapid SLD DST system for specimens resistant to rifampin. Our primary outcomes were the effectiveness and incremental cost-effectiveness of a rapid SLD DST assay relative to culture-based DST.

Results—For rapid SLD DST to be more effective than culture-based DST, treating individuals with pre-XDR/XDR-TB with a standardized MDR-TB regimen while awaiting culture-based DST must incur at least 30% excess XDR-TB mortality (100% = treatment with first-line drugs); rapid SLD DST should attain an aggregate sensitivity and specificity for all pre-XDR/XDR mutations of 88% and 96%, respectively. The unit cost of the rapid SLD DST assay must approach that of culture to achieve common thresholds for cost-effectiveness in low-income countries.

Conclusion—Rapid SLD DST has the potential to be cost-effective, but must meet stringent criteria for accuracy and costs, and requires that standardized second-line treatment for pre-XDR/XDR-TB incur substantial excess mortality before the return of culture results.

Keywords

tuberculosis; economic models; drug resistance; diagnostic methods and procedures

Diagnosis of Tuberculosis (TB) is approaching the point of care through such advances as same-day microscopy,¹ Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA)² and ‘fast-

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follower' assays designed for peripheral-level deployment.³ In contrast, drug susceptibility testing (DST) of drugs other than rifampin requires a strong infrastructure. The standard of reference — *Mycobacterium tuberculosis* culture, followed by phenotypic DST — can take months to complete.⁴ During that time, patients with drug-resistant TB are often treated empirically with inappropriate regimens, resulting in avoidable mortality.⁵ Xpert has facilitated rapid DST against rifampin (RMP) in many settings, but patients with RMP resistance still need to wait for culture-based DST against second-line drugs (SLDs).⁶ Molecular assays could provide SLD DST results in days, but a key barrier to the development and deployment of such assays is uncertainty about their cost-effectiveness.⁷ We used decision analysis to examine the performance requirements of a rapid SLD DST assay in terms of accuracy and cost for it to be cost-effective relative to culture.

Methods

Population

We modeled a cohort of adults seeking treatment for bacteriologically confirmed pulmonary TB in the public sector in Asia. A simplified decision tree is shown in Figure 1. We considered a low-income and a middle-income scenario, populated by data from Bangladesh and China, respectively. These countries were selected due to their recent, high-quality data on drug resistance, high TB burdens and health systems (including costs and drug resistance) representative of other high-burden countries where such an assay might be implemented. We estimated the incremental cost-effectiveness ratio (ICER) to compare diagnosis using Xpert, followed by culture-based DST, among RMP-resistant isolates, with an alternative scenario in which a second cartridge is added for rapid SLD DST. Although we report estimates of incremental cost-effectiveness, the analysis was designed primarily to provide guidance on settings where cost-effectiveness is optimized, identify performance targets that must be met to achieve cost-effectiveness and describe data that must be gathered to inform more precise projections.

Ethics approval was not required for this non-human subjects research.

DST algorithms

We evaluated a rapid DST assay for individuals eligible for second-line treatment based on an RMP-resistant Xpert result. It was assumed that the rapid SLD DST assay would be performed only in settings where results would guide treatment (i.e., multiple second-line regimens) and would include DST against fluoroquinolones, second-line aminoglycosides (kanamycin and amikacin) and capreomycin. We assumed that Xpert would be available — at least as a referral test — in all settings where rapid SLD DST would be implemented, and we defined the unit cost of rapid SLD DST as including all necessary labor, consumables, capital expenditures and overheads beyond that needed for Xpert testing. We also assumed that Xpert would be used for patients previously treated for TB (including failure of an initial regimen); individuals with no history of anti-tuberculosis treatment would receive empiric first-line treatment. In the settings studied, human immunodeficiency virus (HIV) associated TB and contacts of known multidrug-resistant TB (MDR-TB) cases comprised a small proportion of TB cases and were therefore ignored. In the reference strategy, Xpert

was followed by culture-based phenotypic DST if the patient was found to be RMP-resistant; in the strategy using rapid SLD DST, culture was replaced by a rapid molecular test for DST against SLDs, as described below.

Model structure and assumptions

We followed individuals diagnosed with TB through treatment attempts that could end in cure, loss to follow-up ('default'), failure or death. We calculated the probability of each outcome based on drug resistance status, DST result, treatment decision, probability of new ('acquired') resistance and probability of treatment completion. For those who were lost to follow-up, we assigned a probability of returning for repeat treatment, with a probability of success similar to that for other previously treated individuals. Those who failed their initial regimen received repeat DST and treatment based on a Markov process, with up to three cycles that included the possibility of acquired drug resistance (Figure 1).

Given the large number of potential combinations that could be entered into this cascade, we focused on four profiles of sequentially broader drug resistance: 1) fully drug-susceptible, 2) isoniazid (INH) mono-resistant, 3) MDR-TB (i.e., resistant to both INH and RMP), and 4) extensively drug-resistant TB (XDR-TB) or pre-XDR-TB (i.e., resistant to INH, RMP and at least one of the drugs — fluoroquinolone or injectable — included in the rapid SLD DST assay). We assumed that fully susceptible strains could acquire INH monoresistance or MDR-TB directly, and that INH-monoresistant strains could acquire RMP resistance sequentially, but that individuals with initially susceptible or INH-monoresistant TB could not acquire XDR/pre-XDR-TB in a single treatment course without first developing MDR-TB. Based on the high probability of acquired resistance to SLDs in the literature,⁸ we assumed that any individual failing treatment for MDR-TB had developed either pre-XDR or XDR-TB.

The main clinical benefit of rapid SLD DST is the more rapid initiation of appropriately tailored treatment in individuals with pre-XDR/XDR-TB, who would otherwise be started on a standard regimen for MDR-TB (e.g., fluoroquinolone, second-generation aminoglycoside, cycloserine, pyrazinamide [PZA] and ethionamide) while awaiting culture-based DST. The main risk of rapid molecular second-line DST is the exclusion of a high-potency second-line agent due to a false-positive resistance result. We modeled the benefits of rapid SLD DST in terms of a reduction in mortality among those receiving drug regimens tailored on the basis of rapid SLD DST results compared to those receiving empiric MDR-TB treatment, followed by treatment adjustments based on conventional DST results that would become available only after delay. We did not consider transmission as part of this model, as data on the relative potential for transmission and risk of acquiring resistance among individuals with pre-XDR/XDR-TB on standardized second-line treatment vs. individualized treatment are not available. We conceptualized this mortality benefit as consisting of two key parameters: 1) the size of the mortality differential between ideal treatment (i.e., guided by appropriate DST) and standardized treatment (e.g., empiric treatment for MDR-TB) among individuals with pre-XDR/XDR-TB, and 2) the proportion of the mortality differential that occurs between the time that such individuals would take to switch to an ideal treatment regimen based on rapid SLD DST and the time they would take

to switch based on culture-based DST results. Given the paucity of data on individual drugs, we describe this rapid DST assay not in terms of accuracy of any one drug, but rather by 'aggregate sensitivity and specificity', defined as the proportion of individuals with (sensitivity) or without (specificity) pre-XDR/XDR-TB who would, if tested using rapid DST, receive tailored treatment, resulting in a differential mortality rate relative to a standardized regimen.

Economic evaluation

We performed an incremental cost-effectiveness analysis from the health care perspective. Our primary outcome was the ICER, measured in units of US dollars (year 2012) per disability-adjusted life-year (DALY) averted. We obtained estimates of unit costs from published empirical costing studies of Xpert,⁹ financial reports to the World Health Organization (WHO),¹⁰ treatment outcomes from WHO notifications,¹¹ published meta-analyses of outcomes in drug-resistant TB patients,^{5,12} prevalence of drug resistance from national surveys in Bangladesh (M Zignol, personal communication) and China,¹³ and disability due to TB from the 2010 Global Burden of Disease study.¹⁴ We measured all costs and DALYs through a time horizon that ended at the termination of the last individual's treatment course; for those who died during this time, we accumulated future DALYs over remaining life expectancy. DALYs were calculated without age weighting. All future costs and outcomes were discounted at 3% per year.¹⁵ We defined 'cost-effectiveness' as cost per DALY averted below willingness-to-pay thresholds of the 2012 per capita gross domestic products (GDPs) of Bangladesh (US\$747) and China (US\$6091) (<http://data.worldbank.org/indicator/NY.GDP.PCAP.CD>) as numerical examples for low- and middle-income countries, respectively (Table 1).

Sensitivity and uncertainty analyses

We performed one-way sensitivity analyses across all model parameters to assess influence on cost-effectiveness, and multiway sensitivity analyses on those parameters found to be the most important. We present multiple sensitivity analyses to show the primary drivers of uncertainty, as this is our primary interest. We also performed a probabilistic uncertainty analysis, but found that uncertainty in most model parameters was too great to inform meaningful distributions.

Results

Using the reference ranges in Table 1, in comparison to Xpert followed by culture-based DST, Xpert followed by rapid SLD DST cost US\$633/DALY averted in the low-income setting and US\$675/DALY averted in the middle-income setting (Table 2). Cost-effectiveness depended on five key parameters (Figure 2), in which variations led to situations where one algorithm was less costly and more effective (i.e., dominant) than the other. Two of these parameters measured assay accuracy, two measured excess mortality among (pre-) XDR-TB patients awaiting culture results, and one indicated the assay cost relative to culture.

For the rapid SLD DST algorithm to be as effective as Xpert followed by culture-based DST in the low-income setting, the assay needed to achieve an aggregate sensitivity (calculated as aggregate measure of ability to appropriately diagnose pre-XDR/XDR-TB) of at least 88%, and a specificity (for all fluoroquinolones and injectables combined) of at least 96%. To achieve cost-effectiveness of less than US\$747/DALY averted (the low-income willingness-to-pay threshold for cost-effectiveness), the assay needed to achieve a sensitivity of 90% and a specificity of 98.5%. In the middle-income setting, where drug-resistant TB was more prevalent, the rapid SLD DST algorithm remained more cost-effective than Xpert followed by culture (at a willingness to pay of US\$6091/DALY averted) as long as the sensitivity was above 90%, even if specificity fell as low as 92%.

The excess mortality incurred from placing someone with (pre-)XDR-TB on standardized MDR-TB treatment while awaiting culture results also strongly influenced the cost-effectiveness of the SLD DST algorithm. We scored excess mortality from 0 (no excess mortality relative to a DST-tailored, e.g., six-drug, regimen) to 1 (equivalent to treatment with RMP, INH, PZA and ethambutol). For the rapid SLD DST algorithm to be as effective as Xpert followed by culture, excess mortality due to standardized SLDs needed to score at least 0.3 on this scale, and at least 30% of the excess mortality needed to occur before culture results became available (Figure 3). Beyond these thresholds, rapid SLD DST was almost universally more cost-effective than Xpert followed by culture, at either willingness-to-pay threshold (i.e., if rapid SLD DST is more effective, it is also generally cost-effective at the thresholds considered).

Finally, the rapid SLD DST algorithm was less costly (costs included labor, equipment, etc., in addition to materials) than Xpert followed by culture in the low-income setting when rapid SLD DST was at least US\$7 cheaper per test than culture (Figure 4). However, as the cost of rapid SLD DST rose, the cost/DALY averted rose rapidly, such that at a cost of \$2 more than culture (i.e., \$45 per test), the assay (relative to Xpert followed by culture) surpassed the willingness-to-pay threshold for cost-effectiveness in the low-income setting (US\$747/DALY averted). The dependence on the cost of assay was weaker in the middle-income setting, with the assay remaining cost-effective at a willingness to pay of US\$6091/DALY averted up to a unit cost of US\$100 per test.

Discussion

This decision analysis explores the conditions under which a rapid DST for TB SLDs (SLD DST) is likely to be more effective and cost-effective than Xpert followed by culture. Our primary findings are as follows: 1) for rapid SLD DST to be more effective than conventional approaches relying on phenotypic culture-based DST, it must have high accuracy (at least 88% aggregate sensitivity and 96% aggregate specificity) for any form of pre-XDR/XDR-TB; 2) standardized treatment of (pre-)XDR-TB using current regimens for MDR-TB while awaiting the results of culture-based DST must lead to considerable excess mortality for rapid molecular DST to be the more effective option; 3) assuming that these two effectiveness conditions are met, a rapid SLD DST assay must also have a unit cost approaching that of culture (with costs for both tests including all additional capital expenditures, labor, referral costs, and the costs of repeat tests in case of indeterminate or

contaminated results) to be cost-effective at a willingness-to-pay threshold of the per-capita gross domestic product of a low-income country.

Our findings may prove valuable to assay developers wishing to know whether a rapid SLD DST assay carries sufficient potential for cost-effectiveness to proceed to later stages of development. They also highlight the uncertainty in projections involving the cost-effectiveness of DST, and provide data that could improve such estimates in the future; for example, results of pooled analyses of early outcomes (mortality as well as pulmonary damage, drug side effects, etc.) among individuals with underlying (pre-) XDR-TB and undergoing treatment with three or four weakly effective agents while awaiting culture results could be very informative. It should be noted that the cost-effectiveness of any SLD DST assay must ultimately be considered in the context of implementation, including the implementation of measures for detecting and containing drug-resistant TB in key institutions (e.g., prisons, hospitals), and maintaining laboratory capacity for culture²² and infrastructure to support patient-centered care.²³

As with any model-based analysis, our study has certain limitations. The data on many of our key parameters were highly uncertain; we therefore adopted the simplest, most data-driven model structure feasible. In doing so, however, we were unable to explore the full breadth of possible testing algorithms (e.g., line-probe assays), drug resistance profiles (e.g., specific SLDs) and patient populations (e.g., HIV-infected individuals or up-front testing of all individuals with presumptive TB²⁴). We therefore highlight detailed sensitivity analyses over point estimates to provide context and guide the interpretation of study results. We measured effectiveness in terms of differential mortality; however, rapid SLD DST may also have other benefits and disadvantages, such as false-negative results, in terms of transmission and acquisition of further drug resistance while on suboptimal treatment. If these benefits outweigh the disadvantages, our estimates of the effectiveness of SLD DST may be conservative. Furthermore, we did not incorporate potential benefits of culture in terms of providing an isolate that could be sequenced (e.g., matched to a known contact) or subjected to further DST in the future, nor did we account for settings where capacity for either culture or individualized DST was not fully available. Results from the public sector in Eastern and South-East Asia may not be generalizable to other world regions—particularly HIV-endemic settings and the private sector—although we have provided sensitivity analyses that may help to understand where setting-specific differences are likely to matter (e.g., costs) and where they do not (e.g., effectiveness criteria in Figure 2).

In summary, we have constructed a decision-analytic framework for evaluating the conditions under which rapid DST for TB SLDs is likely to be effective and cost-effective. We demonstrate that strong performance conditions need to be achieved for such an assay to be more effective than culture; however, in settings where those conditions are met, assays with high aggregate sensitivity/specificity and per-test cost similar to that of culture are likely to be cost-effective in the settings tested here. Studies in routine settings are needed to further elucidate treatment outcomes of patients with drug-resistant TB according to regimen and DST profile. Until such data are available, this modeling framework may inform data collection and assay development efforts to help deliver DST in an effective and cost-effective fashion to patients suffering from drug-resistant TB.

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Figure 1.

The square on the left denotes the decision node, circles chance nodes, and triangles on the right terminal nodes (at which costs and effectiveness are calculated). Wavy lines suggest similar structure to the tree above. The open circles with M symbols denote Markov nodes, with failure and retreatment cases being treated similarly. The asterisk represents the patient population (failure/re-treatment cases with MDR-TB plus additional resistance) who benefit most from the rapid SLD DST assay, as DST is assumed to be performed more quickly, leading to fewer deaths. TB = tuberculosis; DST = drug susceptibility testing; INH = isoniazid; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; RMP = rifampicin; SLD-R = resistance to second-line drugs.

Figure 2.

One-way sensitivity analyses: cost-effectiveness of rapid DST for SLDs in a low-income Asian setting. We varied all model parameters in Table 1 across their respective ranges. Not all parameters are shown; variation of five parameters led to dominance of either rapid SLD DST or Xpert, followed by culture-based DST algorithms (shown below). The sensitivity ranges of these parameters were therefore truncated at the point across which dominance was achieved (i.e., resulting in a negative incremental cost-effectiveness ratio). The next-most influential parameter, the discount rate, is shown for comparison. DST= drug susceptibility testing; SLD = second-line drug; XDR-TB = extensively drug-resistant TB; FLD = first-line drug; TB = tuberculosis; DALY = disability-adjusted life-year; Xpert = Xpert[®] MTB/RIF.

Figure 3.

Effectiveness of rapid SLD DST vs. Xpert followed by culture, according to excess mortality in (pre-)XDR-TB. The y -axis quantifies the excess mortality of individuals with (pre-)XDR-TB who are treated with standard second-line drugs relative to those who are treated with DST-tailored therapy, ranging from 0 (no excess mortality) to 1 (excess mortality equivalent to treatment with first-line drugs). The x -axis describes the proportion of this excess mortality that occurs between the time it takes to use rapid SLD DST to guide therapy vs. culture. The white portion of the graph shows where rapid DST for second-line drugs (90% sensitive and 99% specific) is more effective than Xpert followed by culture; in the vast majority of this section, the cost per DALY averted is less than US\$1000. Results were similar in the middle- and low-income settings; the very thin black region shows where rapid multiplexed DST was more effective in the middle-income setting but less effective in the low-income setting. XDR-TB = extensively drug-resistant tuberculosis; DST = drug susceptibility testing; SLD = second-line drug; DALY = disability-adjusted life-year; Xpert = Xpert[®] MTB/RIF.

Figure 4.

Incremental cost-effectiveness of rapid SLD DST vs. Xpert, followed by culture, according to assay price. In Figures 2 and 3, the cost of rapid DST assay for SLDs was assumed to be US\$43 per test (including equipment, labor and all overheads), equivalent to that of culture (including equipment, labor, overheads, and any additional costs for referral or specimen transport/reporting of results). Assuming that the effectiveness conditions in Figures 2 and 3 can be met, the cost of the assay relative to culture becomes the primary driver of cost-effectiveness, particularly in a low-income setting. Areas with cost-effectiveness of US\$0 represent assays that are both cheaper and more effective than (i.e., dominate) Xpert, followed by culture. DST = drug susceptibility testing; SLD = second-line drug; DALY = disability-adjusted life-year; Xpert = Xpert[®] MTB/RIF.

Table 1
Model parameters

Variable	Value, low-income country [*] % (range) [‡]	Value, middle-income country [†] % (range) [‡]	Reference
Percentage of cases who are drug-resistant			
New cases			
INH-mono-resistant	5 (0–10)	10.3 (8.2–12.4)	13,16
MDR-TB	1.4 (0.7–2.5)	5.7 (4.5–7.0)	11,13
Pre-XDR-TB	0.4 (0–1.4)	1.8 (1.0–2.6)	13
Retreatment cases			
INH-mono-resistant	4.7	5.1	11
INH-mono-resistant	8 (5–11)	12.9 (8.1–17.7)	13,16
MDR-TB total	29 (24–34)	25.6 (21.5–29.8)	11,13
Pre-XDR-TB	6.8 (4–10)	8.5 (6.4–10.6)	15 M Zignol, personal communication
Percentage of treatments resulting in acquired resistance			
Susceptible to MDR-TB	0.2 (0–0.4)		8
Susceptible to INH mono-resistance	0.4 (0–0.8)		8
INH-mono-resistant to MDR-TB, on therapy guided by INH result	1.7 (0.2–3.3)		12
INH-mono-resistant to MDR-TB, on standard FLD therapy	8 (5–11)		8
Percentage of treatments resulting in clinical outcomes			
LTFU, FLDs	2 (0–15)		11
LTFU, SLDs	16 (11–22)		5
Death, susceptible or INH-mono-resistant on FLDs	4 (2–10)		11
Death, standard MDR-TB regimen with no resistance	9 (5–12)		5
Death, (pre-)XDR-TB on tailored regimen	12 (8–16)		17,18
Death, (pre-)XDR-TB on standard MDR-TB regimen	15 (12–21)		Assumption (see Figure 2)
Death, MDR/(pre-)XDR-TB on FLDs	21 (12–39)		5
Percentage of excess (pre-)XDR-TB deaths that occur before culture	33 (17–50)		Assumption (see Figure 2)
Percentage of treatments resulting in cure without relapse			
Susceptible, standard FLD therapy completed	99 (97–100)		11
INH-mono-resistant, tailored therapy completed	99 (97–100)		11
INH-mono-resistant, standard FLD therapy completed	92 (81–99)		12
Susceptible or INH-mono-resistant, lost to follow-up	50 (25–100)		Model assumption
MDR-TB treatment completed, no resistance	92 (80–99)		5
(pre-)XDR-TB treatment completed	86 (70–95)		5
MDR or (pre-)XDR-TB, inadequate regimen completed	51 (0–75)		5

Variable	Value, low-income country [*] % (range) [‡]	Value, middle-income country [†] % (range) [‡]	Reference
MDR or (pre-)XDR-TB, lost to follow-up	0		Model assumption
Recurrence			
Percentage of treatments resulting in recurrence	60 (45–95)		Model assumption [§]
Case fatality if recurrent TB not treated	50 (30–70)		19
Additional parameters			
Sensitivity of Xpert for RMP resistance	94 (87–97)		2
Sensitivity of multiplexed DST for INH monoresistance	84 (76–90)		21
Sensitivity of multiplexed DST for appropriate SLD regimen	90 (80–100)		Model assumption
Specificity of Xpert for RMP resistance	99 (98–100)		2
Specificity of multiplexed DST	99 (98–100)		Model assumption
Life expectancy at age 38 years, years (range)	36 (33–39)		20
Years of disability for SLD treatment, years (range)	0.5 (0–1)		Model assumption
Disability weight for TB	0.331		14
Costs, US\$ (range)			
Price of multiplexed DST assay	43		Assumption: same as culture (see Figure 4)
Cost of FLD treatment, per patient	200 (75–500)	255 (200–1000)	10
Additional cost of ideal regimen for INH-monoresistant TB	125 (50–200)	125 (50–500)	9
Cost of SLD treatment, per patient	9000 (5000–15 000)	13 500 (10 000–20 000)	10
Cost of culture + DST	43 (22–58)	43 (22–58)	9
Cost of Xpert	15 (12–40)	20 (12–40)	9
Discount rate, %/year (range)	3 (0–7)		15

^{*} Data from Bangladesh.

[†] Data from China.

[‡] Unless otherwise indicated in variable column

[§] Matched to the level that would be required for the case-fatality rate of these individuals to equal the countrywide case-fatality rate in Bangladesh.

¹¹ Kept constant between the two countries to improve comparability of results.

INH = isoniazid; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; FLD = first-line drugs; LTFU = loss to follow-up; SLD = second-line drugs; TB = tuberculosis; DST = drug susceptibility testing; Xpert = Xpert[®] MTB/RIF assay.

Table 2

Cost-effectiveness of rapid SLD DST in East/South-East Asia

DST algorithm	Adults with active TB <i>n</i>	Adults with XDR or pre-XDR-TB <i>n</i>	Total cost (2012 US \$) [*]	Incremental cost (2012 US\$)	DALYs [†]	Incremental DALYs averted	Incremental cost-effectiveness ratio (US\$ per DALY averted)
Low-income scenario							
Xpert + culture	1000	7	466 808		1106.0		
Xpert + rapid SLD DST	1000	7	467 071	263	1105.6	0.4	633
Middle-income scenario							
Xpert + culture	1000	21	948 645		1413.2		
Xpert + rapid SLD DST	1000	21	949 549	904	1411.9	1.3	675

^{*} Assuming the same unit cost for culture and rapid SLD DST (US\$43 per test) in both low- and middle-income settings; total costs include costs associated with diagnostic testing as well as treatment and monitoring.

[†] Higher DALYs in the middle-income scenario reflects the higher level of drug resistance assumed in that scenario, with equivalent proportions of treatment success.

DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB; SLD = second-line drug; TB = tuberculosis; DALY = disability-adjusted life-year.