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Second line drug susceptibility testing to inform the treatment of rifampin-resistant tuberculosis: a quantitative perspective

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Abstract

Treatment failure and resistance amplification are common among patients with rifampin-resistant tuberculosis (TB). Drug susceptibility testing (DST) for second-line drugs is recommended for these patients, but logistical difficulties have impeded widespread implementation of second-line DST in many settings. To provide a quantitative perspective on the decision to scale up second-line DST, we synthesize literature on the prevalence of second-line drug resistance, the expected clinical and epidemiologic benefits of using second-line DST to ensure that patients with rifampin-resistant TB receive effective regimens, and the costs of implementing (or not implementing) second-line DST for all individuals diagnosed with rifampin-resistant TB. We conclude that, in most settings, second-line DST could substantially improve treatment outcomes for patients with rifampin-resistant TB, reduce transmission of drug-resistant TB, prevent amplification of drug resistance, and be affordable or even cost-saving. Given the large investment made in each patient treated for rifampin-resistant TB, these payoffs would come at relatively small incremental cost. These anticipated benefits likely justify addressing the real challenges faced in implementing second-line DST in most high-burden settings.

Keywords

Drug resistance; diagnostics; regimen selection; treatment outcomes; cost effectiveness

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Introduction

Each year, more than half a million new cases of rifampin-resistant tuberculosis – including multidrug-resistant tuberculosis (MDR TB, resistant to rifampin and isoniazid) – occur worldwide. These strains are exceedingly difficult to treat; the per-patient cost of treatment exceeds the per-capita gross domestic product in most countries, and only half of treated patients are successfully cured.¹ As tests that detect rifampin resistance are scaled up globally,² the number of patients diagnosed with rifampin-resistant TB is growing dramatically. Unfortunately, despite the large investment made in each rifampin-resistant TB patient treated, the majority of these patients still receive suboptimal therapy.

In countries with surveillance data, 9.5% of MDR TB cases also had resistance to the two most important classes of second-line TB drugs [fluoroquinolones and second-line injectable drugs (SLIs)] – or extensively drug resistant (XDR) TB – in 2015,¹ and many more have resistance to other combinations of the drugs in the regimens typically used to treat rifampin-resistant TB.^{3,4} This drug resistance is associated with worse treatment outcomes,⁵ and DST to second-line drugs has therefore been recommended for all rifampin-resistant TB patients “where possible”.⁶

Uptake of second-line DST remains limited by economic and logistical challenges, however. Second-line DST costs more than other TB diagnostics^{7,8} and requires specialized laboratory facilities and expertise⁹ as well as infrastructure to transport specimens and relay results. Accurate, rapid assays for fluoroquinolones and SLIs are now available,^{10,11} but for most other drugs used to treat rifampin-resistant TB, the only well-established methods are growth-based, phenotypic assays – which take weeks or months to complete and require stringent biosafety containment procedures.^{12,13} Moreover, developing individualized regimens on the basis of second-line DST can be logistically challenging (for example, to maintain continuous drug supplies¹⁴) and expensive.¹⁵ In light of these challenges, many high-burden countries opt not to maintain capacity for routine second-line DST. Even for fluoroquinolones and SLIs – the easiest second-line drugs to test – susceptibility results were reported for only 36% of MDR TB patients in 2015.¹

Although standardized treatment regimens for rifampin-resistant TB can cure many patients, regimens containing ineffective drugs reduce the probability of success,⁵ expose patients to toxicity without benefit, amplify drug resistance,¹⁶ and waste resources. The only way to reliably prevent these outcomes is to verify susceptibility to any drug being used. In this commentary, we review and synthesize data regarding the expected return on investment in second-line DST for all patients with rifampin-resistant TB – from clinical, public-health, and economic perspectives.

The clinical impact of second-line resistance

Guidelines for treatment of rifampin-resistant TB recommend at least five effective TB medicines, including, when possible, a newer-generation fluoroquinolone, an SLI, and pyrazinamide.⁶ Each of the five drugs in such a regimen makes an important contribution. In meta-analyses of observational data, susceptibility to the fluoroquinolone was associated

with a three-fold increase in the adjusted odds of treatment success of a conventional MDR TB regimen,¹⁷ and an effective SLI¹⁷ and pyrazinamide^{17,18} each increased success roughly two-fold. Beyond these three critical drugs, each additional effective agent still adds value: inclusion of 5 effective drugs rather than 4, and of 6 effective drugs rather than 5, further improves treatment response,¹⁸ and six effective drugs add benefit even in XDR TB.⁵ Knowing that treatment response improves with each effective agent, ensuring that patients with rifampin-resistant TB receive an adequate number of effective drugs should be a high priority; susceptibility to empiric regimens should only be assumed when resistance to each component is rare in the underlying population.

Unfortunately, among patients with rifampin-resistant TB, resistance to second-line drugs is highly prevalent. As detailed in Table 1 for several illustrative settings with population-based data, resistance to a fluoroquinolone, SLI, and/or pyrazinamide is typically present in half of rifampin-resistant TB cases; this number can approach 90% in some settings such as Eastern Europe. The prevalence of resistance to other commonly-used agents, including ethionamide/prothionamide,⁵ cycloserine/terizidone,⁵ ethambutol,¹⁶ and high-dose isoniazid^{19,20} is also substantial. Therefore, without routine use of second-line DST, using five agents in a standardized regimen is likely to result in therapy with four or fewer truly effective drugs – and thus in poorer clinical outcomes. Although there are settings where second-line resistance is rare,^{21–23} in most cases, the prevalence of additional resistance in rifampin-resistant TB has expanded to the point that regimens with 5 effective drugs cannot be reliably constructed without the use of second-line DST.⁶ Furthermore, two recently approved novel agents (bedaquiline and delamanid) offer unprecedented potential to effectively treat such patients when second-line resistance is identified.^{24,25} Thus, the clinical value of second-line DST is greater now than ever before.

Public health consequences of missed second-line resistance

From a public health standpoint, treating large numbers of patients for rifampin-resistant TB without accounting for second-line drug resistance introduces concerning long-term risks. Specifically, at the population level, ineffective treatment prolongs the window of potential transmission and increases the risk that transmitted strains will carry additional drug resistance.

These population-level dynamics can be understood in terms of the effective reproduction number R_{eff} , which describes the average number of secondary infectious TB cases generated per infectious index case. This quantity has four components: (1) the duration of infectiousness for the index case, (2) the rate at which respiratory contacts sufficient for transmission are made, (3) the probability that such contact results in infection, and (4) the probability that an infection progresses to active (infectious) TB. The value of R_{eff} determines whether an epidemic is in advance ($R_{\text{eff}} > 1$) or retreat ($R_{\text{eff}} < 1$). While the data are far from complete, global estimates suggest that the incidence of rifampin-resistant TB is roughly constant (though with wide geographic variation), suggesting a value of R_{eff} near 1.¹ Since the frequency of contact and probability of transmission are difficult to alter, and therapies to prevent progression among those infected with rifampin-resistant strains are not well established, reducing the duration of infectiousness is critical in order to reduce the

effective reproduction number of rifampin-resistant TB below 1. Since patients with MDR TB who receive ineffective therapy likely remain at least partially infectious,²⁶ rapidly initiating effective treatment is our best weapon to reduce the duration of infectiousness, and thus R_{eff} , for rifampin-resistant TB.

Not only can ineffective regimens allow for additional transmission of rifampin-resistant TB, but the selective pressure of treatment may result in transmission of increasingly resistant strains.²⁷ Studies of serial sputum isolates have revealed high rates of acquired drug resistance during treatment of rifampin-resistant TB, especially among those who already have some second-line drug resistance at baseline; of patients with baseline resistance to 3 or more second-line drugs without meeting XDR criteria in one multi-center study, 44% acquired XDR during treatment.²⁸ In some settings, the compounding of drug resistance during ineffective treatment has led to outbreaks of extremely difficult-to-treat disease.^{29,30} Regimens with at least five – as opposed to even three or four – effective drugs are associated with substantial reductions in acquired drug resistance.¹⁶ Given the likelihood that novel regimens of the foreseeable future (e.g. those containing nitroimidazoles^{31,32} or bedaquiline³³) will continue to include conventional drugs such as fluoroquinolones and pyrazinamide, minimizing the transmission of isolates resistant to these agents is an important public health goal – a goal that will be more difficult to achieve without wider use of second-line DST.

Economic considerations

While the clinical and public health benefits of second-line DST may not be controversial, there remains concern that these benefits do not justify the additional cost and logistical challenges of performing routine second-line DST. In settings where resources are clearly constrained, these costs (around \$100 per patient³⁴) and feasibility barriers (such as the need to maintain laboratory expertise) cannot be ignored. They should be understood, however, within the full context of TB and MDR/rifampin-resistant TB treatment programs, including the total costs of treatment and of other diagnostics such as Xpert MTB/RIF, as illustrated in Figure 1. At an average of more than \$6000, per-patient costs of care for rifampin-resistant TB exceed those of drug-susceptible TB more than tenfold in low-income countries.¹ Patients' out-of-pocket expenses are frequently devastating as well.^{35,36} Second-line DST – at about 2% of the total cost to treat a patient with rifampin-resistant TB^{8,34} – represents a relatively small budgetary outlay, one that likely will be recovered. For example, if performing second-line DST on 50 patients with known rifampin-resistant TB can reduce the amount spent on ineffective TB therapy by only one treatment course (likely a substantial underestimate), then second-line DST could be cost-neutral to a rifampin-resistant TB treatment program. Of course, diagnostics are not the only cost involved in individualizing therapy, as switching to effective drugs may add to regimen cost. Yet even substitutions such as clofazamine,³² bedaquiline, and/or newly-generic linezolid,³⁷ are likely to cost no more than a few hundred dollars per patient when averaged over a rifampin-resistant TB cohort,³⁸ and such proactive regimen changes can avoid fruitless investment in standard therapy for patients who are unlikely to benefit from it.⁵ In the short term, implementing DST will require substantial up-front investment, especially in laboratory and sputum transport infrastructure. But given the frequency at which therapy with standardized

regimens is ineffective, this investment could pay for itself by reducing rifampin-resistant TB treatment costs within as little as two years. Given the benefits to patients and populations of routine second-line DST, this is an investment arguably worth making.

Implementation challenges, options, and strategies

If second-line DST is to become the norm in programmatic management of MDR/rifampin-resistant TB, it is important to understand the inherent challenges. An initial challenge is simply deciding which drugs to evaluate and by what methods. Currently, rapid molecular testing is limited to line probe assays for fluoroquinolones and SLIs, as well as for first-line drugs such as isoniazid that may have a role in treating some patients with rifampin-resistant TB;¹¹ the use of line probe assays for these two key second-line drug classes was endorsed by WHO in 2016.³⁹ Phenotypic DST currently provides more complete and accurate results,¹¹ but phenotypic results typically remain unavailable during the initial months of treatment. Therefore, local epidemiology, drug availability, resources, and existing infrastructure should guide the choice of diagnostic algorithms. Options may include line probe assay screening for fluoroquinolone and SLI susceptibility, with follow-up phenotypic testing for those found to have resistance; up-front phenotypic DST, perhaps in conjunction with high-intensity regimens designed to de-escalate once susceptibilities are confirmed; or both line-probe assay and phenotypic DST in order to maximize rapidity and depth of results in settings of highest resistance prevalence. Regardless of the second-line DST algorithm chosen, clinical, laboratory, pharmacy, and ancillary capacity will be required; this capacity includes physicians who can review results of testing and tailor regimens accordingly, guidance for interpreting (discordant) results, laboratory staff with continuing training to maintain proficiency, maintenance of a continuous supply of multiple drugs, and networks to transport specimens and results between clinics and centralized laboratories.

Overcoming these challenges is a difficult task, especially in settings with already very limited infrastructure. The optimal implementation strategy will vary by locale, but a number of settings and programs illustrate possible components of an approach to second-line drug resistance in the steps they have taken to build laboratory capacity, develop clinical diagnostic infrastructure, harness novel drugs, and curb recognized drug-resistant TB epidemics (Table 2). Where second-line DST has been successfully implemented in conjunction with effective treatment regimens and broader public health efforts (e.g., infection control, intensified case finding), drug-resistant TB epidemics from New York City⁴⁰ to Tomsk Oblast, Russia,^{41–43} have declined within a few years. Any initial investment required to implement second-line DST is likely to pay off quickly, as treating patients with ineffective regimens represents an enormous waste of resources – and most importantly, exposes patients to very real toxicity with little clinical benefit. Moreover, to some extent, programs must address DST challenges regardless of whether they implement up-front DST for all patients with rifampin-resistant TB. Patients who are not cured will require assessment for drug resistance, and many will require retreatment with alternative drugs. With the recent introduction of a 9-month regimen for rifampin-resistant TB,⁴⁴ second-line DST will also be able to rapidly identify appropriate candidates for this simpler, cheaper, and potentially more effective regimen. Tailoring regimens based on DST at the start of treatment (before additional acquisition of resistance occurs) may be no more

difficult, on average, than managing retreatments of highly drug-resistant disease – and will result in better outcomes for patients.

Conclusion

Treatment of rifampin-resistant TB is already expensive and complex. Although places exist where second-line drug resistance is relatively rare, the use of standard regimens for rifampin-resistant TB in most settings will result in the use of at least one ineffective drug in the majority of cases. When treatment costs thousands of dollars per patient and carries grave clinical toxicities, it is essential that we optimize the probability that those treatment regimens will work. Second-line DST has the capacity to increase the number of effective drugs in each regimen – an intervention demonstrated to improve treatment outcomes in patients and likely to reduce transmission and acquisition of further resistance in populations. Implementing second-line DST presents real logistical challenges but has the potential to be cost-saving in the long run as the (unnecessary) cost of ineffective treatment is reduced. From a quantitative perspective – but also from the perspective of patients – incorporating second-line DST into the routine care of rifampin-resistant TB seems a justifiable investment to make.

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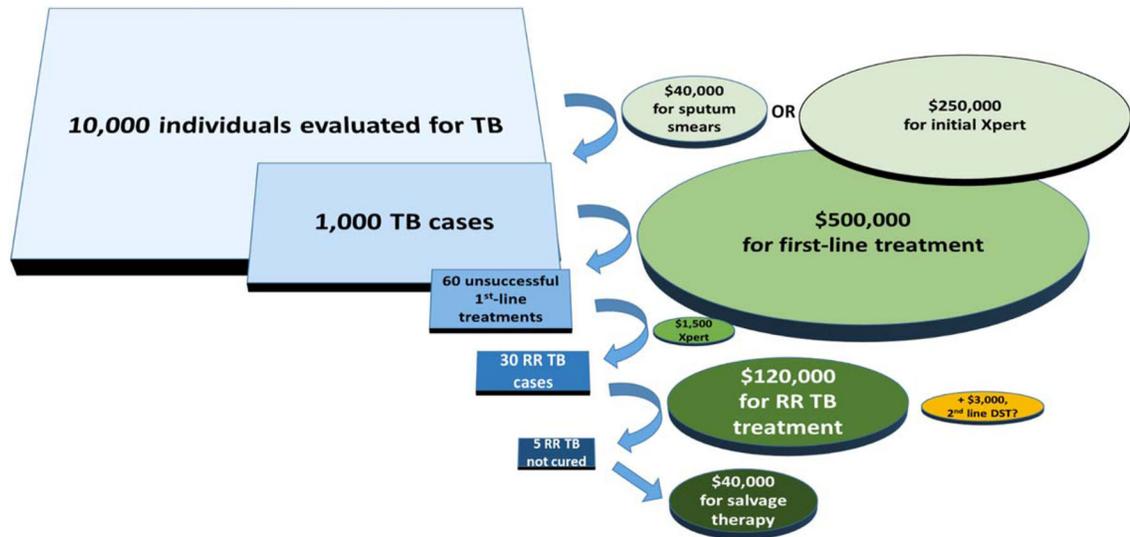


Figure 1. Rifampin-resistant tuberculosis (RR TB) patients and spending in context

By applying estimated outcomes and costs for a high-burden, low-income setting, we compare expenditures on overall and drug-resistant TB diagnostics and treatment in a hypothetical cohort of 10,000 individuals evaluated for TB, using sputum smear or Xpert MTB/RIF as the initial diagnostic test. Assumptions about procedures and outcomes include: initial TB diagnosis by sputum smear, 2 smears (or one Xpert) collected per suspect, 10 suspects per TB case,^{57,58} 3% prevalence of rifampin-resistant TB among TB cases (near the global average),¹ 6% failure or relapse after first-line treatment,^{1,59} rifampin susceptibility testing (e.g. by Xpert) after unsuccessful first-line therapy (if initial diagnosis is by smear), and 15% failure or relapse after treatment for rifampin-resistant TB.⁶⁰ Cost estimates are in US dollars and include \$2 per smear,³⁴ \$500 per first-line treatment,¹ \$25 per Xpert,³⁴ \$4000 per initial MDR TB treatment,¹ \$8,000 per salvage regimen, and \$100 per rifampin-resistant case for second-line DST (second-line line probe assay plus culture and phenotypic second-line DST, including fixed costs, in a low-income, high-burden setting)³⁴. The yellow oval shows the relatively small cost of performing second-line DST for all individuals diagnosed with rifampin resistance, relative to total TB and rifampin-resistant TB spending. Note that secondary drug-resistant cases – an added potential cost of ineffective treatment for rifampin-resistant TB – are not included in this figure.

Prevalence of resistance to drugs used in treatment of rifampin-resistant TB, in illustrative high-burden settings

Table 1

	China	South Africa	Pakistan	Belarus (Minsk city)
Fluoroquinolone (FQ) resistance				
Ofloxacin	25% ⁴⁵	12–18% ³	22% ³	31% ³
Moxifloxacin at 0.5 µg/mL		8–12% ³	14% ³	27% ³
Moxifloxacin at 2 µg/mL		0–4% ³	1.4% ³	9% ³
Second-line injectable (SLI) resistance^a	15% ⁴⁵	12% ⁴⁶	1% ^{47,48}	27% ⁴⁹
FQ and SLI resistance	8% ⁴⁵	7–10% ^{16,46}	1% ^{47,48}	14% ⁴⁹
Pyrazinamide (PZA) resistance	43% ⁵⁰	39–49% ³	38% ³	81% ³
FQ, SLI and/or PZA resistance	56%	52%	47%	89%
Susceptible to all 3 classes^b	44%	48%	53%	11%

^aEstimates in Pakistan are based on limited data in non-population-based samples, with testing of only some SLIs.

^bThis estimate assumes 60% PZA resistance among FQ and/or SLI resistant isolates in China, South Africa, and Pakistan^{5,16} and 81% resistance among FQ and/or SLI resistant isolates in Belarus. Reported FQ and PZA prevalences from two regions in South Africa are averaged.

Table 2 Expanding capacity for the response to drug-resistant TB: Examples from high burden countries

Areas of focus	Examples	Steps taken
Establishment of a biosafety level 3 reference laboratory	Uganda ⁵¹	A successful lab in another low-income country provided standard operating procedures and trained key personnel. National university and international research partnerships increase the sustainability of laboratory funding and expertise.
Creation of a national TB diagnostic program (including second-line DST)	Peru ⁵²	Decentralized first-line DST was combined with centralized second-line DST. Computerized laboratory information systems and provider training reduced transport and reporting delays.
Expansion of TB diagnostic technologies (line probe assays, culture-based DST) also applicable to second-line DST	EXPAND TB partnership (multiple low-income countries) ⁵³	International partners assisted with initial laboratory start-up and technology. Domestic sources provide long-term funding; local political commitment is essential.
Increased use of novel agents for treatment of drug-resistant TB	South Africa ^{54,55}	Genotypic second-line DST and clear treatment guidelines are allowing rapid scale-up of bedaquiline +/- linezolid for pre-XDR and XDR TB.
Scale up of bedaquiline and delamanid for treatment of drug-resistant TB	endTB Project ⁵⁶	This combined implementation project and effectiveness study aims to accelerate importation, financing, and clinical use of novel drugs in participating countries; routine use of some form of second-line DST is required in participating countries.
Comprehensive management of drug-resistant TB including aggressive case detection, individualized regimens, and social support	Tomsk Oblast, Russia ^{41,43}	Second-line DST and aggressive individualized regimens with at least 5 effective drugs resulted in high rates of durable treatment success. These measures were followed by stabilization of a large and growing MDR TB epidemic.