

## Rapid drug susceptibility testing and treatment outcomes for multidrug-resistant tuberculosis in Peru

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### SUMMARY

**SETTING:** The detection of multidrug-resistant tuberculosis (MDR-TB) using rapid drug susceptibility testing (DST) has increased steadily in recent years in Peru, from 9216 tests in 2010 to 27 021 tests in 2015. Research examining the impact of rapid DST on treatment outcomes is required.

**OBJECTIVE:** To evaluate the association between rapid DST use (nitrate reductase assay, microscopic observation drug susceptibility assay [MODS] and GenoType<sup>®</sup> MTBDR<sup>plus</sup>) and treatment outcomes and mortality in MDR-TB patients in Peru.

**DESIGN:** Retrospective cohort study of patients diagnosed with pulmonary MDR-TB between 2010 and 2013 (with treatment outcomes up to December 2015) using the electronic registry of the Peruvian National TB Programme.

**RESULTS:** A total of 2671 MDR-TB patients were included; the median age was 27 years, 2.8% were co-infected with the human immunodeficiency virus. Use of rapid DST was associated with a 40% increase in the adjusted odds of treatment success (aOR 1.40, 95%CI 1.19–1.64) and a 54% reduction in mortality (aOR 0.46, 95%CI 0.33–0.64). Higher treatment success rates were driven by MODS and GenoType<sup>®</sup> MTBDR<sup>plus</sup> testing (aORs for unsuccessful outcomes respectively 0.68 and 0.66).

**CONCLUSION:** The use of rapid DST (MODS and MTBDR<sup>plus</sup>) to diagnose MDR-TB was associated with a reduction in the odds of death and a substantial increase in the odds of treatment success.

**KEY WORDS:** outcomes; death; rapid DST; Peru; operational research

WHILE MOST TUBERCULOSIS (TB) cases can be cured, the disease remains one of the biggest infectious disease threats worldwide. In 2015, there were an estimated 10.4 million new TB cases, 1.4 million of whom died. In addition, of the estimated 580 000 multidrug-resistant TB (MDR-TB; defined as resistance to at least isoniazid and rifampicin) cases worldwide, only about 20% were detected and reported, and only 52% of MDR-TB patients had a successful treatment outcome.<sup>1,2</sup>

Peru has the highest number of MDR-TB patients in the Americas Region.<sup>3</sup> Although the Lima and Callao Regions have only one third of the country's population, they account for 59% of patients with susceptible TB, 70% of those with MDR-TB and 73% of those with extensively drug-resistant TB (XDR-TB; defined as MDR-TB plus resistance to at least one fluoroquinolone and at least one of the second-line injectables).<sup>4</sup> Treatment and care of MDR- and XDR-TB leads to increased health care costs, which must be borne by Peru's Ministry of

Health (MoH), and leads to economic losses for patients and their families, adversely affecting their quality of life.<sup>5,6</sup>

Early diagnosis, including universal access to drug susceptibility testing (DST), is one of the key components of the End TB Strategy championed by the World Health Organization (WHO) as part of its new Global TB Strategy post-2015.<sup>2</sup> However, almost one decade before the End TB Strategy, the Peruvian MoH introduced rapid DST in line with WHO-recommended policies:<sup>7,8</sup> the nitrate reductase assay (NRA) was introduced in 2006 for all sputum smear-positive patients,<sup>9</sup> in 2008 the microscopic observation drug susceptibility assay (MODS) was made universally accessible in those regions where it was implemented, regardless of smear status,<sup>10</sup> and in 2010 the GenoType<sup>®</sup> MTBDR<sup>plus</sup> test (Hain Lifescience, Nehren, Germany) was initially used for patients with positive microscopy results and MDR-TB risk factors, but was subsequently made universally accessible, as set down in the 2013 technical

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guidelines.<sup>11</sup> These tests are used to directly detect MDR-TB from sputum samples with negative or positive microscopy (MODS) and positive microscopy (NRA and MTBDR*plus*), as well as from culture-positive samples.<sup>10,11</sup>

As a result, rapid DST diagnosis increased steadily in recent years in Peru, from 9216 tests in 2010 to 27 021 tests in 2015.<sup>12</sup> However, their implementation has not been homogeneous. During the study period, populations will have been served either by a regional laboratory implementing rapid DST using MODS, NRA or MTBDR*plus*, or by a laboratory earmarked for future upgrading to rapid DST, but only providing conventional DST using the agar proportion method (APM) during the study period following referral of patients who were initially culture-positive when tested locally. The sequence of implementation in laboratories and selection of the rapid DST method to be used was driven principally by the testing capacity of regional laboratories with appropriate biosafety measures.<sup>13</sup>

Few studies have explored the association between routine rapid DST use and treatment outcomes and mortality in MDR-TB patients.<sup>14,15</sup> NRA use in Peru has been shown to reduce the time to treatment initiation,<sup>16</sup> while use of MTBDR*plus* in Georgia has been associated with reduced time to both MDR-TB treatment initiation and culture conversion.

Use of Xpert<sup>®</sup> MTB/RIF (Cepheid, Sunnyvale, CA, USA) in primary health care facilities in South Africa and Brazil has provided further evidence of the association between rapid DST use and reduced time to treatment initiation.<sup>14,17</sup> No systematic evaluation examining the association between the introduction of rapid DST and treatment success and reduction in mortality in MDR-TB patients has been conducted in Peru. Using routine data from available laboratory records, as well as data on MDR-TB and XDR-TB treatment, the aim of the present study was to assess the association between rapid DST use and treatment outcome and death in MDR-TB patients in Peru from 2010 to 2015.

## MATERIALS AND METHODS

This operational research study consisted of a retrospective analysis of data obtained from the electronic records of patients classified as having MDR-TB in Peru's National Resistant Tuberculosis Registry (*Registro Nacional de Tuberculosis Resistente*, RNTR) under the National TB Programme (NTP), and laboratory records (laboratory information system, Netlab<sup>®</sup>)<sup>18</sup> at the Peruvian National Institute of Health (NIH).<sup>19</sup> The RNTR was established in 2006 and is the electronic database routinely used by the MDR-TB Technical Unit of the Peruvian NTP for monitoring and evaluation of patients diagnosed with MDR-TB. Data are entered by NTP

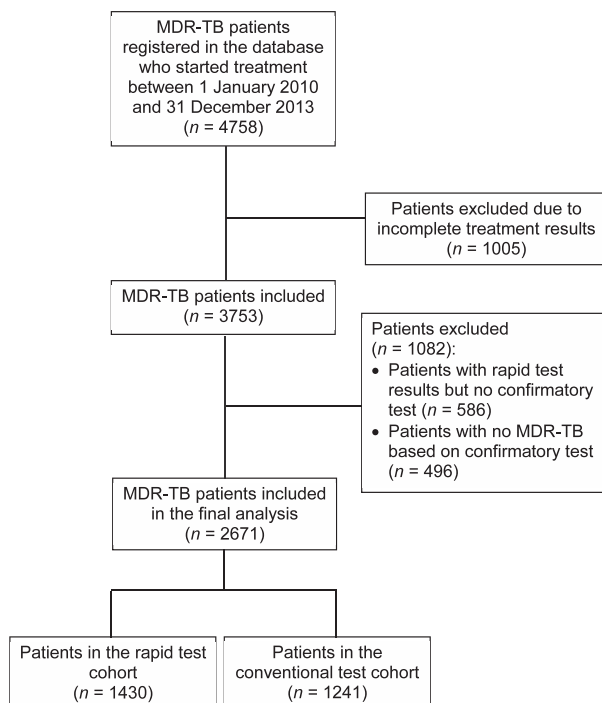
data entry staff and checked and validated every week by the RNTR engineer by cross-checking random electronic entries with corresponding hard-copy source data.

The study sample comprised two cohorts of patients diagnosed with pulmonary MDR-TB from January 2010 to December 2013 with a documented treatment outcome in the RNTR up to 31 December 2015. Patients were diagnosed using either 1) conventional DST only by the Middlebrook 7H10 APM with results from the National TB Reference Laboratory (NRL) of the Peruvian NIH; or 2) rapid DST (NRA, MODS, MTBDR*plus*) with confirmatory APM testing by the NRL. Patients with an initial MDR-TB diagnosis on rapid DST that was not confirmed using subsequent APM testing were excluded from the study.

Conventional DST was carried out at the Peruvian NIH TB NRL, which is overseen for external quality assurance by a supranational reference laboratory. Rapid DST was performed at the regional reference laboratories of the national TB laboratory network and at the NIH TB NRL. The RNTR includes a treatment outcome for each patient. However, as this is an operational registry and not specifically designed for research, this information is not always available; records of patients with no available treatment outcome in the RNTR were excluded from this analysis. Definitions used for each treatment outcome were in accordance with WHO guidelines at the time of data entry into the database. Time to MDR-TB treatment initiation and MDR-TB treatment outcome were the study endpoints, with rapid DST or APM DST alone being the exposures of primary interest.

Demographic and clinical information was collected, including year of MDR-TB diagnosis, sex, age, human immunodeficiency virus (HIV) status and geographical location. MDR-TB treatment success was defined as a composite of 'cured' cases at hospital discharge and 'completed treatment' status,<sup>19</sup> which provided the number of patients with successful treatment outcomes among patients diagnosed using rapid DST vs. APM testing. The treatment success rate among patients diagnosed using rapid DST was compared with that of patients diagnosed using APM with proportional Z test. As a secondary analysis to propose a predictive model, a dependent variable was created: success = 1 and no success = 0. Variables with  $P < 0.2$  were entered into the multivariate logistic regression model, for which odds ratios (ORs) and 95% confidence intervals (CIs) were reported; variables with  $P < 0.05$  were considered significant. Results from the cohort diagnosed using rapid DST were compared with those from the cohort diagnosed using APM.

The research protocol was approved by the Ethics Advisory Group of the International Union Against



**Figure 1** MDR-TB patient registry, inclusion and exclusion from the study. Respectively 968, 786 and 717 patients were tested using NRA, LPA and MODS (some by more than one), 715, 601 and 536 of whom also had a corresponding APM (reference laboratory) result and were thus eligible for inclusion. For patients undergoing testing by multiple rapid DST methods, only the first available test result was used in this analysis, reflecting the clinical action that ensued. MDR-TB = multidrug-resistant tuberculosis; NRA = nitrate reductase assay; LPA = line-probe assay; MODS = microscopic observation drug susceptibility assay; APM = agar proportion method; DST = drug susceptibility testing.

Tuberculosis and Lung Disease, Paris, France, and the ethics committee of the Hospital Nacional Hipólito Unanue, Lima.

## RESULTS

Data from 4758 MDR-TB patients were registered between January 2010 and December 2013. A total of 2087 patient records were excluded for the reasons shown in Figure 1, leaving 2671 MDR-TB patients who were confirmed by the TB NRL and included in the analysis. The patients came from all regions of the country, with a high proportion from the Lima-Callao Region (75.3%). The male:female ratio was 1.8:1; median age was 27 years (interquartile range [IQR] 21–37); 93.4% of patients were screened for HIV, of which 71 (2.8%) were HIV co-infected.

### Cohorts

Clinical and epidemiological patient characteristics in the rapid DST cohort ( $n = 1430$ ) and APM cohort ( $n = 1241$ ) were similar (Table 1), except that a larger proportion of the rapid DST cohort were from Lima-

**Table 1** General characteristics of MDR-TB patient cohorts in Peru, 2010–2013

	Rapid DST cohort* ( $n = 1430$ ) $n$ (%)	APM cohort† ( $n = 1241$ ) $n$ (%)	$P$ value‡
Year of MDR-TB diagnosis			
2010	234 (16.4)	388 (31.3)	<0.001
2011	279 (19.5)	367 (29.6)	
2012	471 (32.9)	261 (21.0)	
2013	446 (31.2)	225 (18.1)	
Sex			
Female	490 (34.3)	449 (36.2)	0.288
Male	940 (65.7)	792 (63.8)	
Age group, years			
<15	56 (3.9)	42 (3.4)	0.194
≥15 and <35	973 (68.0)	829 (66.9)	
≥35 and <55	313 (21.9)	266 (21.5)	
≥55	89 (6.2)	103 (8.1)	
HIV infection status			
No	1319 (92.2)	1104 (88.9)	0.940§
Yes	39 (2.7)	32 (2.6)	
Unknown	72 (5.1)	105 (8.5)	0.002¶
Place of origin			
Provinces	248 (17.3)	412 (33.2)	<0.001
Capital	1182 (82.7)	829 (66.8)	

\* Nitrate reductase assay or MODS or GenoType® MTBDRplus.

† Conventional DST (proportion method in Middlebrook 7H10 agar).

‡ Calculated using the  $\chi^2$  test.

§ Only includes patients with HIV test results.

¶ Includes patients with and without HIV test results.

MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; APM = agar proportion method; HIV = human immunodeficiency virus; MODS = microscopic observation drug susceptibility assay.

Callao and were diagnosed and treated in the latter part of the study period.

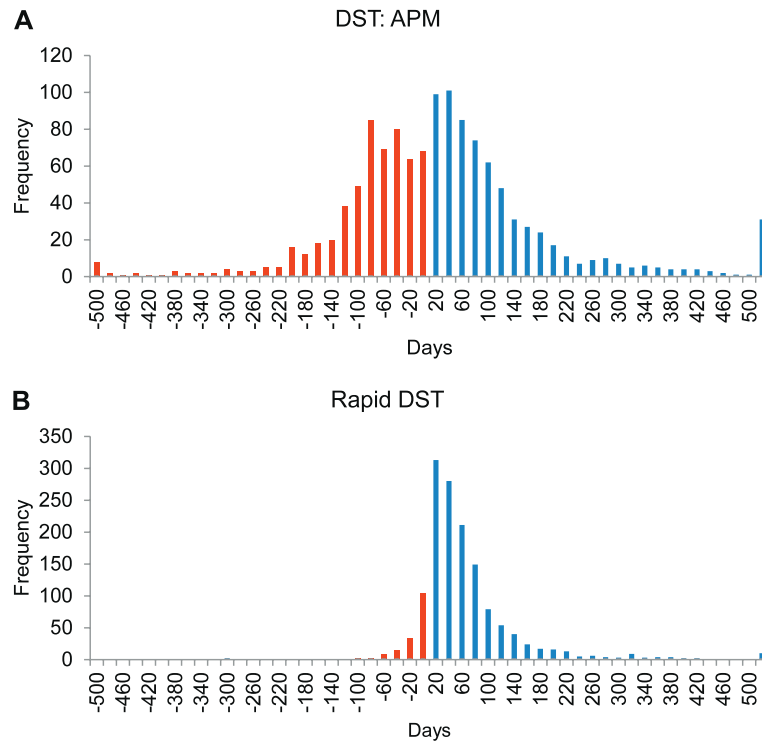
### Time to treatment initiation

Patients in the rapid DST cohort were less likely than those with only conventional APM testing to initiate MDR-TB treatment before the DST results became available (5.2% vs. 39.9% respectively, Figure 2). The median time to treatment initiation from availability of DST results in those initiating treatment after DST was available was respectively 21 days ( $n = 1355$ ) and 110 days ( $n = 746$ ) for the rapid and APM cohorts.

### Treatment outcomes

Table 2 shows the treatment outcomes based on year of treatment initiation and availability of rapid DST results. The results 'cured' and 'completed treatment' were combined to obtain the treatment success rate. Reasons for 'unsuccessful treatment', combined and separated by year, are given in the same table.

Table 2 shows that, year on year, patients for whom the diagnosis of MDR-TB was made using rapid DST had a higher treatment success rate than those diagnosed using slower, conventional methods, increasing to almost 65%, an increase of 10.8% in treatment success, by 2013 ( $Z$  test for comparison of proportions 0.64 vs. 0.56,  $P < 0.001$ ). This difference



**Figure 2** Frequency distribution of time elapsed between DST result availability and MDR-TB treatment initiation. Patients who started empirical treatment pending the DST result are shown in red. DST = drug susceptibility testing; APM = agar proportion method; MDR-TB = multidrug-resistant tuberculosis. This image can be viewed online in colour at <http://www.ingentaconnect.com/content/iuatld/ijtld/2018/00000022/000000011/art00017>

was largely driven by lower rates of adverse outcomes death and treatment failure.

#### Predictors of treatment success

On multivariate analysis, male sex (adjusted OR [aOR] for treatment success 0.58, 95%CI 0.49–0.69) and increasing age (aOR 0.79, 95%CI 0.70–0.89) were associated with unsuccessful treatment. Use of rapid DST increased the odds of treatment success by 40% (OR 1.4, 95%CI 1.19–1.64). HIV infection status did not affect the model (Table 3). Greater treatment success in the rapid DST cohort was attributable to the effect of MODS (aOR for unsuccessful outcome 0.68, 95%CI 0.54–0.86) and MTBDR*plus* (aOR for unsuccessful outcome 0.66, 95%CI 0.53–0.87). No significant differences were seen in unsuccessful treatment outcomes between conventional DST and NRA use (aOR for unsuccessful outcome 0.87, 95%CI 0.70–1.07,  $P = 0.2$ ).

#### Predictors of death

On bivariate and multivariate analysis, HIV infection (aOR 1.10, 95%CI 1.04–1.16) and older age (aOR 2.00, 95%CI 1.64–2.44) were associated with death, while sex was not (Table 4). The odds of death were significantly greater among patients from regions outside Lima/Callao (aOR 1.63, 95%CI 1.12–2.36). Both later years of treatment initiation (aOR 0.80,

95%CI 0.69–0.92) and the use of rapid DST (aOR 0.46, 95%CI 0.33–0.64) were independently associated with a significant reduction (20% and 54%, respectively) in the odds of death as the outcome of MDR-TB treatment.

#### Impact of confirmatory DST on the effect of rapid DST

Overall, 1082 patients registered as receiving treatment for MDR-TB were excluded from the analysis (Figure 1). For 496 of these, i.e., 10.4% of all patients treated with second-line drugs by the NTP during this period (496/4758), APM DST did not indicate MDR-TB, likely reflecting empirical treatment preceding the availability of DST results. MDR-TB treatment was initiated in 586 patients based on the results of one of the three rapid DST tests; however, confirmatory testing using APM at the NRL was not performed. To examine if the performance or non-performance of confirmatory testing introduced bias, we analysed whether successful treatment outcomes or death were associated with the performance of APM DST for each of the rapid DST methods. In the case of MODS and MTBDR*plus* (but not for NRA), the proportion of patients with successful treatment outcomes was lower, while the proportion of deaths was higher among those who did not undergo APM testing (Table 5).

**Table 2** MDR-TB treatment outcome by DST method and year of treatment initiation

	2010		2011		2012		2013		Total	
	Rapid DST* (n = 234) %	APM† (n = 388) %	Rapid DST (n = 279) %	APM (n = 367) %	Rapid DST (n = 471) %	APM (n = 261) %	Rapid DST (n = 446) %	APM (n = 225) %	Rapid DST n (%)	APM n (%)
Cured	62.0	57.5	47.3	45.0	25.3	24.9	30.7	23.6	533 (37.3)	506 (40.8)
Treatment completed	2.1	2.6	12.2	9.5	39.5	29.9	33.9	30.2	376 (26.3)	191 (15.4)
Failure	9.4	8.5	5.0	5.7	1.9	3.4	5.4	2.2	69 (4.8)	68 (5.5)
Death	7.7	11.1	4.7	11.7	4.2	7.7	3.1	8.9	65 (4.5)	126 (10.2)
Lost to follow-up	18.8	20.4	30.8	28.1	29.1	34.1	26.9	35.1	387 (27.1)	350 (28.2)
Treatment success	64.1	60.1	59.5	54.5	64.8	54.8	64.6	53.8	909 (63.6)	697 (56.2)
Unsuccessful treatment	35.9	39.9	40.5	45.5	35.2	45.2	35.4	46.2	521 (36.4)	544 (43.8)
Total	100	100	100	100	100	100	100	100	1430 (100)	1241 (100)

\* Nitrate reductase assay or MODS or GenoType® MTBDRplus.

† Conventional DST (proportion method in Middlebrook 7H10 agar).

MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; APM = agar proportion method; MODS = microscopic observation drug susceptibility assay.

## DISCUSSION

The key finding of the present study was that use of rapid DST in MDR-TB treatment was associated with a 40% increase in treatment success and a 54% reduction in the odds of death during MDR-TB treatment, regardless of the age, sex, place of residence or HIV status of the patient. This is the first evidence to suggest that choice of a diagnostic strategy may impact and improve final treatment outcomes in MDR-TB treatment, independently of potential confounders, including temporal trends.

The assumption that reduced time to treatment initiation leads to improved treatment outcomes had been difficult to prove until now. These data appear to substantiate this assertion for the first time.

It has been shown previously that the time to treatment initiation is significantly reduced upon introduction of rapid DST in Peru, in the case of both the NRA<sup>16</sup> and MODS.<sup>15,20</sup> In Georgia, use of MTBDRplus has been shown to be associated with significant clinical improvement, and a reduced time to MDR-TB treatment initiation and culture conversion.<sup>21</sup> The data presented here demonstrate that

**Table 3** Predictors of MDR-TB treatment success

	Unsuccessful treatment outcome n (%)	Successful treatment outcome n (%)	Bivariate analysis OR (95%CI)	P value	Multivariate analysis* aOR (95%CI)	P value
Rapid MDR-TB test						
No	544 (43.9)	697 (56.1)	1 (Reference)	0.000	1 (Reference)	<0.001
Yes (all)	521 (36.4)	909 (63.6)	1.37 (1.17–1.59)		1.40 (1.19–1.64)	
NRA					0.87 (0.70–1.07)	
MODS					0.68 (0.54–0.86)	
Genotype MTBDRplus					0.66 (0.53–0.87)	
Year of MDR-TB diagnosis <sup>†</sup>						
2010	239 (38.4)	383 (61.6)	1 (Reference)	0.721	—	
2011	280 (43.3)	366 (56.7)				
2012	284 (38.8)	448 (61.2)				
2013	262 (39.1)	409 (61.0)	1.01 (0.94–1.09)			
Sex						
Female	299 (31.8)	640 (68.2)	1 (Reference)	0.000	1 (Reference)	<0.001
Male	766 (44.2)	966 (55.8)	0.59 (0.50–0.70)		0.58 (0.49–0.69)	
Age group, years <sup>†</sup>						
<15	24 (24.5)	74 (75.5)	1 (Reference)	0.000	1 (Reference)	<0.001
≥15–<35	686 (38.1)	1116 (61.9)				
≥35–<55	274 (47.3)	305 (52.7)				
≥55	81 (42.2)	111 (57.8)	0.79 (0.71–0.90)		0.79 (0.70–0.89)	
HIV infection status						
No	948 (39.1)	1475 (60.9)	1 (Reference)	0.099	—	
Yes	37 (52.1)	34 (47.9)	0.97 (0.94–1.01)			
Place of origin						
Provinces	273 (41.4)	387 (58.6)	1 (Reference)	0.367	—	
Capital	792 (39.4)	1219 (60.6)	1.09 (0.91–1.30)			

\* This model only includes variables independently associated with treatment success (cured, completed treatment).

† OR increase for each category

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; NRA = nitrate reductase assay; MODS = microscopic observation drug susceptibility assay; HIV = human immunodeficiency virus.

**Table 4** Factors associated with death in MDR-TB patients

Characteristics	Bivariate analysis OR (95%CI)	Multivariate analysis* aOR (95%CI)
Rapid MDR-TB test		
No	1 (Reference)	1 (Reference)
Yes (all)	0.42 (0.30–0.57)	0.46 (0.33–0.64)
NRA		0.56 (0.37–0.84)
MODS		0.39 (0.23–0.65)
GenoType® MTBDRplus		0.32 (0.19–0.53)
Year of MDR-TB diagnosis <sup>†</sup>		
2010	1 (Reference)	1 (Reference)
2011		
2012		
2013	0.77 (0.67–0.88)	0.80 (0.69–0.92)
Sex		
Female	1 (Reference)	–
Male	1.14 (0.83–1.56)	
Age group, years <sup>†</sup>		
<15	1 (Reference)	1 (Reference)
≥15–<35		
≥35–<55		
≥55	1.96 (1.61–2.39)	2.00 (1.64–2.44)
HIV infection status		
No	1 (Reference)	1 (Reference)
Yes	1.09 (1.04–1.15)	1.10 (1.04–1.16)
Place of origin		
Provinces	1 (Reference)	1 (Reference)
Capital	1.18 (0.83–1.68)	1.63 (1.12–2.36)

\* This model only includes variables independently associated with treatment success (cured, completed treatment).

<sup>†</sup> OR increase for each category.

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; NRA = nitrate reductase assay; MODS = microscopic observation drug susceptibility assay; HIV = human immunodeficiency virus.

introduction of rapid DST has contributed to improved outcomes in MDR-TB patients in Peru.

Although logic would suggest that the sooner adequate MDR-TB treatment is started, the better the treatment outcome will be, conclusive evidence has been hard to find. A systematic literature review conducted in 2016 could not identify a single study with an adequate methodology to demonstrate an impact upon MDR-TB treatment outcomes based on early treatment initiation vs. delayed treatment initiation.<sup>15</sup> The methodology used in the present study fulfils the search criteria of the earlier review in showing improved patient-centred outcomes with the use of rapid DST. However, widespread empirical treatment led to a result in which half of patients who only had conventional DST were already receiving MDR-TB treatment before receiving an appropriate microbiological diagnosis. The availability of a laboratory service offering rapid DST may have encouraged providers to await laboratory confirmation of drug resistance rather than initiate empirical treatment, which would explain the different distributions of the time to treatment initiation. Empirical anti-tuberculosis treatment also partially explains another important evidence gap: despite large-scale implementation driven by the WHO and other international agencies as well as widespread research, conclusive evidence showing that Xpert use has an epidemiological impact on TB or MDR-TB transmis-

sion remains elusive. Due to the introduction of the three rapid DST methods reported here, Xpert has not seen substantial uptake in Peru, and was therefore not included in this analysis.

Another important observation is that the availability of a rapid assay alone is not sufficient, as this is only one component to be considered when assessing its impact on individual patients and on the community. The use of these tests outside established algorithms and the gap between diagnosis and treatment initiation may reduce the impact of the test. Conversely, the use of interventions that close this gap would be expected to further enhance the impact of rapid DST. In Peru, universal access to rapid MODS or MTBDRplus DST remains an aspiration that has not yet been fully achieved, although NRA implementation is no longer national policy. It is not inconceivable that health centres served by laboratories offering rapid DST provide better care for TB patients, leading to improved outcomes (and perhaps better completion of the RNTR, with patient exclusion being less likely); had it been feasible, a time-series analysis might have been able to shed light on this parameter. However, for some regions, rapid DST became available to health centres only during the latter part of the study period; if availability of rapid DST did enhance patient care, this will have been attributable both to the quick availability of actionable clinical information (the

**Table 5** Association between APM DST and treatment outcomes and death

	Treatment outcome			P value*
	Success	No success	Total n (%)	
NRA				
APM				
Yes	479	236	715 (67.0)	0.64
No	165	88	253 (65.2)	
MODS				
APM				
Yes	383	153	536 (71.5)	0.004
No	108	73	181 (59.7)	
Genotype MTBDR <sub>plus</sub>				
APM				
Yes	416	185	601 (69.2)	0.016
No	110	75	185 (59.5)	
	Death			P value*
	Yes	No	Total n (%)	
NRA				
APM	Total			
Yes	46	669	715 (6.4)	0.77
No	18	235	253 (7.1)	
MODS				
APM				
Yes	27	509	536 (5.0)	0.008
No	20	161	181 (11.0)	
Genotype MTBDR <sub>plus</sub>				
APM				
Yes	30	571	601 (5.0)	0.023
No	18	167	185 (9.7)	

\* Derived from Fisher's exact test.

APM = agar proportion method; DST = drug susceptibility testing; NRA = nitrate reductase assay; MODS = microscopic observation drug susceptibility assay.

DST result) and the action taken by providers in using it. Both are crucial for evaluating impact.

The retrospective nature of the study and the use of routinely stored electronic records allowed data from a large sample of programmatically managed patients to be analysed. However, there are challenges and limitations with using programme data. One drawback to this design is the lack of certain variables that were not routinely collected, such as admission status, diabetes status, previous history of anti-tuberculosis treatment and certain demographic data. It should be noted that individuals with no registered treatment outcome or no confirmatory conventional DST result in the database were excluded to optimise the validity of the analysis; this resulted in a loss of data from respectively 21% and 23% of potential subjects. This raises two concerns: the risk of selection bias and the quality of routine data registration and entry within the NTP. Of the 2687 patients excluded, 28% did not have a confirmatory test for rapid DST indicating MDR-TB. As confirmatory testing is part of the NTP algorithm, and while a small proportion may represent technical failures in the laboratory, this percentage suggests a management failure leading to a significant gap that

requires improvements in the health care system; clearly, these patients could not be included in the analysis. Furthermore, 24% of excluded patients had APM testing that did not indicate MDR-TB. This included patients treated empirically for MDR-TB based on epidemiological risk assessment (e.g., treatment failure, known MDR-TB contact) in whom APM DST subsequently demonstrated drug susceptibility, and some patients (likely to be a minority) for whom the APM DST result was discordant with an earlier rapid DST result. The available data set did not permit breakdown into these two categories, although the approximately 10% of all patients who received empirical treatment that turned out to be unnecessary on later testing reflects the proportion anticipated; DST discordance should ordinarily lead to an analysis of discrepancies based on a third test as part of ongoing quality assurance and improvement. Moreover, as in the previous scenario, these patients should be excluded to avoid bias in the results. Perhaps surprisingly, the failure to perform APM testing was associated with lower rates of treatment success and higher rates of death among those apparently benefiting from rapid DST. Patients might not undergo APM testing because the local health care provider is overstretched and does not prioritise seeking a follow-up sample (necessary for GenoType MTBDR, although not for MODS or NRA, which both yield a primary isolate), because the culture becomes contaminated, or because the patient is lost to follow-up before a second sample can be obtained; some of these factors may also be associated with worse treatment outcomes. Further prospective studies are needed to better understand the mechanisms underlying this observation.

Finally, among excluded patients, 48% did not have treatment outcome data available in the register. This finding shows another systemic failure of recording that needs to be addressed, while reminding clinical service providers of the importance of having reliable routine data. However, there are no reasons to believe that this lack of information would be any more common in patients with or without rapid DST, suggesting that the possibility of significant bias arising from their exclusion would be minimal.

This was a nationwide operational study spanning a 5-year period from 2010 to 2015. Based on the extensive coverage and the amount of data included, the results provide an important and relevant message. Temporal changes in MDR-TB management clearly contribute; however, on multivariate analysis, the highly positive effect of rapid DST use was independent of the year of treatment.

In summary, in a country with high rates of MDR-TB, rapid DST implementation as a routine test was associated with a significant and important increase in the odds of treatment success and a major reduction in the odds of death as an MDR-TB

treatment outcome. These results reinforce the policy of universal access to rapid DST in Peru; other countries should explore rapid DST implementation in the NTP to improve MDR-TB patient health care.

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## RÉSUMÉ

**CONTEXTE :** La détection de *Mycobacterium tuberculosis* multirésistant (TB-MDR) grâce à un test de pharmacosensibilité rapide (DST) a constamment augmenté au cours des dernières années au Pérou (de 9216 tests en 2010 à 27 021 tests en 2015) ; la démonstration de l'impact sur les résultats centrés sur le patient est requise.

**OBJECTIF :** Evaluer l'association entre utilisation du DST rapide (test de nitrate réductase, observation microscopique des milieux de culture [MODS] et GenoType® MTBDR*plus*) et le résultat du traitement et le décès chez les patients TB-MDR au Pérou.

**SCHEMA :** Etude rétrospective de cohorte utilisant le registre électronique du programme national TB des patients ayant eu un diagnostic de TB-MDR pulmonaire (2010–2013), avec les résultats du traitement jusqu'à décembre 2015.

**RÉSULTATS :** Ont été inclus 2671 patients TB-MDR, d'âge médian 27 ans, 2,8% avec une co-infection au virus de l'immunodéficience humaine. L'utilisation du DST rapide a été associée à une augmentation de 40% des chances de succès du traitement (OR ajusté [ORa] 1,40 ; IC95% 1,19–1,64) et une réduction de 54% des décès (ORa 0,46 ; IC95% 0,33–0,64). L'amélioration du succès du traitement a été obtenue grâce à l'effet des tests MODS et MTBDR*plus* (ORa pour un résultat négatif de 0,68 et 0,66, respectivement).

**CONCLUSION :** L'introduction du DST rapide (MODS et MTBDR*plus*) pour le diagnostic de TB-MDR a été associée à une réduction des risques de décès et à une augmentation significative des chances de succès du traitement.

## RESUMEN

**MARCO DE REFERENCIA:** La detección de *Mycobacterium tuberculosis* multidrogorresistente (TB-MDR) mediante pruebas rápidas de susceptibilidad a las drogas (DST) ha aumentado constantemente en los últimos años en el Perú (de 9216 pruebas en 2010 a 27 021 en 2015), siendo necesario demostrar su impacto sobre los resultados centrados en el paciente.

**OBJETIVO:** Evaluar la asociación entre el uso de DST (ensayo de nitrato reductasa, ensayo de evaluación de la sensibilidad a fármacos mediante observación microscópica [MODS] y GenoType® MTBDR*plus*) y el resultado del tratamiento y la muerte en pacientes con TB-MDR en el Perú.

**METODO:** Estudio retrospectivo de cohortes utilizando el registro electrónico del Programa Nacional de TB de pacientes diagnosticados con TB-MDR pulmonar (2010–2013), con resultados de tratamiento hasta diciembre de 2015.

**RESULTADOS:** Fueron incluidos 2671 pacientes con TB-MDR, los cuales tuvieron una mediana de edad de 27 años y 2,8% con coinfección por virus de la inmunodeficiencia humana. El uso de DST rápida se asoció con un aumento del 40% en las probabilidades de éxito del tratamiento (OR ajustado [ORa] 1,40; IC95% 1,19–1,64) y una reducción del 54% en el resultado de la muerte del tratamiento (ORa 0,46; IC95% 0,33–0,64). Beneficios en el éxito del tratamiento fue impulsado por el efecto de las pruebas MODS y MTBDR*plus* (ORa para el resultado sin éxito fue de 0,68 y 0,66, respectivamente).

**CONCLUSIÓN:** La introducción de DST rápida (MODS y MTBDR*plus*) para el diagnóstico de TB-MDR se asoció con una reducción en las probabilidades de muerte y un gran aumento en las probabilidades de éxito del tratamiento.