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Assessing the Effect of Decentralization of Laboratory Diagnosis for Drug-resistant Tuberculosis in Kenya

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Abstract

Setting—Drug susceptibility testing (DST) is recommended in Kenya to identify multidrug-resistant tuberculosis (MDR-TB) in persons registered for retreatment of tuberculosis (TB). DST is performed at a central laboratory with a two-step growth-based process and a regional laboratory with a simultaneous molecular- and growth-based process.

Objective—To compare proportions of retreatment cases that underwent DST and turnaround times for hospitals referring to the central versus regional laboratory.

Design—Cases were persons registered for retreatment of TB during January 1, 2012 to December 31, 2013. Records were reviewed at 11 hospitals and 7 hospitals referring to the regional and central laboratories, respectively.

Results—Overall, 238/432 (55%) and 88/355 (25%) of cases at hospitals referring to the regional and central laboratories, respectively, underwent DST. The mean time from case registration to receipt of DST results and initiation of MDR-TB treatment was faster for hospitals referring to the regional laboratory. Specimen transport, specimen testing, and receipt of DST results at hospitals were shorter for the regional laboratory ($p < 0.05$).

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Conclusion—Testing was faster and more complete at hospitals referring to the regional laboratory. The low proportions of cases receiving DST warrant a comprehensive review of detection of MDR-TB in Kenya.

Keywords

Decentralization; laboratory testing; drug-resistant tuberculosis

Introduction

Previous treatment for tuberculosis (TB) is one predictor of drug resistance, including multidrug-resistance, which is defined as resistance to at least isoniazid and rifampicin[1]. Rapid diagnosis of and treatment initiation for drug-resistant TB is essential to improve outcomes and reduce transmission[2]. The World Health Organization (WHO) recommends rapid drug susceptibility testing (DST) over conventional testing for patients who might have multidrug-resistant TB (MDR-TB), such as those who have been previously treated[3]. Cepheid GeneXpert MTB/RIF is one recommended test that rapidly identifies *Mycobacterium tuberculosis* in sputum specimens and detects resistance to rifampicin (a marker for MDR), which helps health workers decide whether to initiate treatment for MDR-TB without delay[4].

WHO groups Kenya with the 22 countries with a high-burden of TB and estimates that there were 2,780 cases of MDR-TB in Kenya in 2013[5]. In contrast, only 254 cases of MDR-TB were reported nationally in 2013 by the Division of Leprosy, Tuberculosis, and Lung Disease (DLTLD) at the Kenyan Ministry of Health (MOH)[6]. This discrepancy between the WHO estimated cases and the DLTLD reported cases suggests that MDR-TB may be underdiagnosed, that the WHO figure is an overestimate, or a combination of these.

Consistent with WHO guidance, in Kenya DST is recommended for all retreatment TB cases, defined as persons returning to treatment after relapse, failure, or a two month period of non-adherence to a prior episode of TB treatment[7]. DLTLD reported that DST was performed for more than 80% of retreatment cases in both 2011 and 2012[8]. The Central Reference Laboratory (CRL) in Nairobi was the main institution for DST until January 2012, when the MOH established a regional reference laboratory in Kisian operated by the Kenya Medical Research Institute and the U.S. Centers for Disease Control and Prevention (KEMRI/CDC). Starting in 2012, clinics and hospitals providing treatment of TB in Nyanza province in Western Kenya submitted specimens for mycobacteriology to KEMRI/CDC instead of CRL[8]. Clinics and hospitals providing TB treatment in regions other than Nyanza continued to submit specimens to CRL for DST. Specimens submitted to CRL were tested by isolation of mycobacteria on solid media followed by DST on Mycobacterial Growth Indicator Tubes (MGIT), while specimens submitted to KEMRI/CDC were tested simultaneously with GeneXpert and DST on MGIT.

The objective of this study was to compare testing sequences of hospitals referring to the regional laboratory with testing sequences for hospitals referring to the central laboratory by (1) describing specimen submission, specimen processing, and DST reporting, (2) calculating the proportion of cases of retreatment TB tested for drug resistance, (3)

estimating the time in each event in the testing sequence, and (4) among retreatment cases that were found to be MDR-TB, determining the time from registering as retreatment cases to starting treatment for MDR-TB.

Methods

The study population was persons who were registered as retreatment cases of TB between January 1, 2012 and December 31, 2013. Hospitals referring to the regional reference laboratory were selected using data from the KEMRI/CDC laboratory data management system. To focus on hospitals with greatest need for efficient testing and reporting, 9 hospitals in counties in Nyanza province with at least 10 specimens submitted for DST and one specimen with rifampicin resistance, the hospital with the highest number of rifampicin-resistant specimens, and the hospital with highest number of specimens negative for rifampicin resistance were selected. To represent hospitals referring to the central laboratory, 7 hospitals in counties adjacent to Nyanza province with at least 100 reported TB cases in 2012 were selected. The selected hospitals represented a broad geographic area in western Kenya (Figure 1).

Laboratory managers at KEMRI/CDC were interviewed in person to gather information about techniques used for DST and processes for reporting DST results to hospitals. Facility TB managers at hospitals were asked during site visits to describe how records are kept for sputum collection and DST results. For retreatment cases identified as MDR-TB by DST, district TB coordinators were asked via phone or in person to describe the process by which DST results are used to initiate MDR-TB treatment.

Three data sources were reviewed: facility TB registers, laboratory DST reports, and district MDR-TB registers. Facility TB registers were examined to find the retreatment cases that met criteria for the study population. Records from facility TB registers were linked to laboratory reports by name, age, and case registration number. Cases that could not be linked to a laboratory report were classified as not having been tested. Retreatment cases with a laboratory report indicating resistance to rifampicin by Cepheid GeneXpert (Sunnyvale, CA) or resistance to isoniazid and rifampicin by culture were classified as MDR-TB and were linked to cases recorded in district MDR-TB registers.

From the three data sources, six dates were obtained. Two dates were abstracted from facility TB registers: the date a retreatment case was registered and the earliest date DST results were received from the laboratory in electronic or paper format. The treatment start date for MDR-TB was obtained from the district MDR-TB register. Three dates were abstracted from laboratory DST reports: the date that a specimen was collected at the hospital, the date that a specimen was processed at the laboratory, and the date that DST results were recorded at the laboratory. For retreatment cases that were linked to laboratory reports, the earliest date of completion of a test for DST (i.e., GeneXpert or DST on MGIT) was used.

From these six dates, the time in five events was calculated. Four sequential events were: (1) from case registration to specimen collection at the hospital, (2) from specimen collection at

the hospital to specimen processing at the laboratory, (3) from specimen processing at the laboratory to recording of DST results at the laboratory, and (4) from the recording of DST results at the laboratory to the receipt of DST report at the hospital. The date of registration as a retreatment case at the hospital and the date of starting MDR-TB treatment were used to estimate the time for a fifth event (Figure 2).

The Wilcoxon rank-sum test was used to test for statistical differences in the time in each event in the testing sequence for DST by laboratory. The total time from case registration to receipt of DST results at a hospital was estimated by summing mean times for each event in the testing sequence. All analyses were conducted in R version 3.0.1 (R Core Team, Vienna, Austria).

Both CDC and the Kenyan MOH reviewed the study plan and determined that it was part of routine programmatic activities and did not require oversight from an institutional review board. All names and personal identifiers were kept confidential.

Results

Observations and interviews revealed that the sequence from specimen collection to reporting of DST results consists of the following steps:

1. Case data including registration date, patient information, clinical details, laboratory results, and outcomes were recorded for retreatment cases at hospitals on facility TB registers.
2. Specimens were collected at hospitals and were submitted to a reference laboratory (CRL or KEMRI/CDC). No standardized register was used to record dates for specimen collection and submission to the laboratory for DST.
3. Results for specimens received, processed, and tested at the reference laboratories were recorded in databases. The completeness and quality of data stored in these databases were not evaluated. Both laboratories reported DST results as paper copies to hospitals via courier. KEMRI/CDC also sent electronic copies via email to facility TB managers.
4. DST results were received by facility TB managers at hospitals and were stored in a single binder. Some facility TB managers recorded DST results in the “remarks” section of the facility TB register. No standardized field or register was used for recording the date that a DST report was received.

During the study period, 432 cases (range 7–75) were registered at hospitals referring to the regional laboratory, and 355 (12–129) at hospitals referring to the central laboratory (Table 1). Overall, 55% (range 26%–76%) of cases at hospitals referring to the regional laboratory and 25% (2%–83%) of cases at hospitals referring to the central laboratory underwent DST. Among hospitals referring to the central laboratory, those with smaller numbers of registered cases appeared to have higher proportions of cases tested for drug resistance. In total, 326/787 (41.4%) of retreatment cases underwent DST.

The time in several events in the testing sequence differed by reference laboratory coverage (Table 2). There was no statistically significant difference in the number of days from case registration to specimen collection between hospitals referring to the central laboratory versus regional laboratory. However, hospitals referring to the regional laboratory demonstrated statistically significantly shorter number of days from specimen collection at the hospital to specimen processing at the laboratory, specimen processing at the laboratory to preparation of report of DST results at the laboratory, and preparation of report at the laboratory to receipt of report at hospital ($p < 0.05$). On average, the overall time from registration as a retreatment case to receipt of DST results at hospitals referring to the regional laboratory was 36 days compared to 240 days at hospitals referring to the central laboratory (Figure 3).

Of retreatment cases with DST results, 9/238 (3.8%) and 1/88 (1.1%) at hospitals referring to regional and central laboratories, respectively, had MDR-TB. The mean number of days before MDR-TB treatment was started was 68 for hospitals referring to the regional laboratory and 302 for hospitals referring to the central laboratory.

Discussion

This assessment demonstrates that hospitals referring to the regional laboratory more commonly tested retreatment cases for drug resistance than hospitals referring to the central laboratory. Additionally, the overall time required for testing retreatment cases for drug resistance was shorter for hospitals referring to the regional versus central laboratory after accounting for differences in DST techniques used at each respective laboratory. Due to rapid testing and reduced transit of specimen and DST results between laboratories and hospitals, decentralization of DST is helpful for shortening the time from registration as a retreatment case to starting MDR-TB treatment when indicated by laboratory testing.

Hospitals referring to the reference laboratory compared to the central laboratory had shorter times for transit of specimens and test results, which may be explained by differences in the proximity of hospitals and the laboratory. KEMRI/CDC is located in Kisian in western Kenya, while CRL is based in Nairobi in central Kenya. Because hospitals in this assessment were in western Kenya, specimens and laboratory reports would need to travel a shorter distance between hospitals and KEMRI/CDC compared to hospitals and CRL. These results confirm that bringing testing closer to patients and TB treatment centers reduces the overall time for DST. However, geographic differences would not explain the large differences in turnaround times at the other events in the process.

The difference in time for specimen processing to recording of DST results at the laboratory is likely due to differences in the tests conducted for drug resistance. At KEMRI/CDC, GeneXpert and growth-based DST are both used to identify presence of mycobacteria and resistance to rifampicin. At CRL, in contrast, specimens were analyzed with only growth-based DST at the time of this evaluation. GeneXpert results at KEMRI/CDC are typically available in two hours[9] and are reported within two days, while the growth-based DST process at CRL requires several weeks before results are reported[10]. Because this study used the date of completion of the first test indicating drug resistance and GeneXpert is routinely

used in KEMRI/CDC, specimen processing to recording of DST results was faster at the regional laboratory. These findings corroborate the WHO recommendation of using rapid DST such as GeneXpert when available to identify drug resistance[3].

Though hospitals referring to the regional laboratory had a higher proportion of retreatment cases tested, the proportion of retreatment cases that underwent DST was far lower than the reported national estimate of greater than 80% in 2011 and 2012[6]. The finding that hospitals referring to the central reference laboratory with the most retreatment cases had lower proportions of cases tested suggests these hospitals may not have sufficient resources for management of retreatment cases or recordkeeping of DST results.

The facility TB registers captured demographic, clinical, and outcome data for each case registered. However, there was no standard field or register to record dates when specimens were sent for testing and when DST results were received. Given these limitations in the reporting and recording of testing for retreatment cases, the results from this study suggest that study in a wider geographic area may be warranted to better evaluate the proportion of retreatment cases tested for drug resistance in Kenya. Efforts are needed to create standardized tools for recording and reporting of DST results and to link systems at hospitals and laboratories to track specimens throughout the DST process.

Among all 326 retreatment cases tested for drug resistance, only 10 (3.1%) were found to be MDR-TB. In contrast, the WHO estimate for MDR-TB among retreatment cases in Kenya is 10% (range 3.5%–17%). The low prevalence of MDR-TB among retreatment cases in this assessment may be explained by the low number of cases that were tested for drug resistance, or may be due to a low prevalence of MDR-TB in western Kenya. A review of MDR-TB among retreatment cases reported nationally would be needed to better characterize detection of MDR-TB in Kenya.

Since the proportions of retreatment cases receiving DST was based on linking registered cases to laboratory reports, it is possible that this study underestimated this proportion if DST was performed but reports were unavailable. Missing data and incomplete records might also affect the estimates of overall time for DST. Additionally, this study describes differences in proportions tested at referring hospitals and time required for events of the testing sequence by location of reference laboratory. The study did not assess whether establishing a regional laboratory has improved these measurements in counties of Nyanza province over time. It is possible that the higher proportion of cases tested and shorter time in the hospitals referring to the regional laboratory was present before the laboratory was established. Hospitals selected for this study were the most active in referring cases for testing or had high TB caseloads. These hospitals may be more accessible to patients or may have staff with more experience managing retreatment cases. Therefore, the results presented in this study may not be generalizable to all hospitals registering retreatment cases.

This study suggests that the proportion of retreatment cases tested for drug resistance was higher and the time required for testing was shorter for hospitals referring to the regional laboratory compared to the central laboratory. These differences were likely due to distance

from hospitals to testing laboratories and the availability of GeneXpert for rapid diagnosis of drug resistance. The shorter time for identifying drug resistance at hospitals referring to the regional laboratory suggests that efforts should be made to establish additional laboratories with GeneXpert throughout Kenya to bring rapid testing for drug resistance closer to patients who need it.

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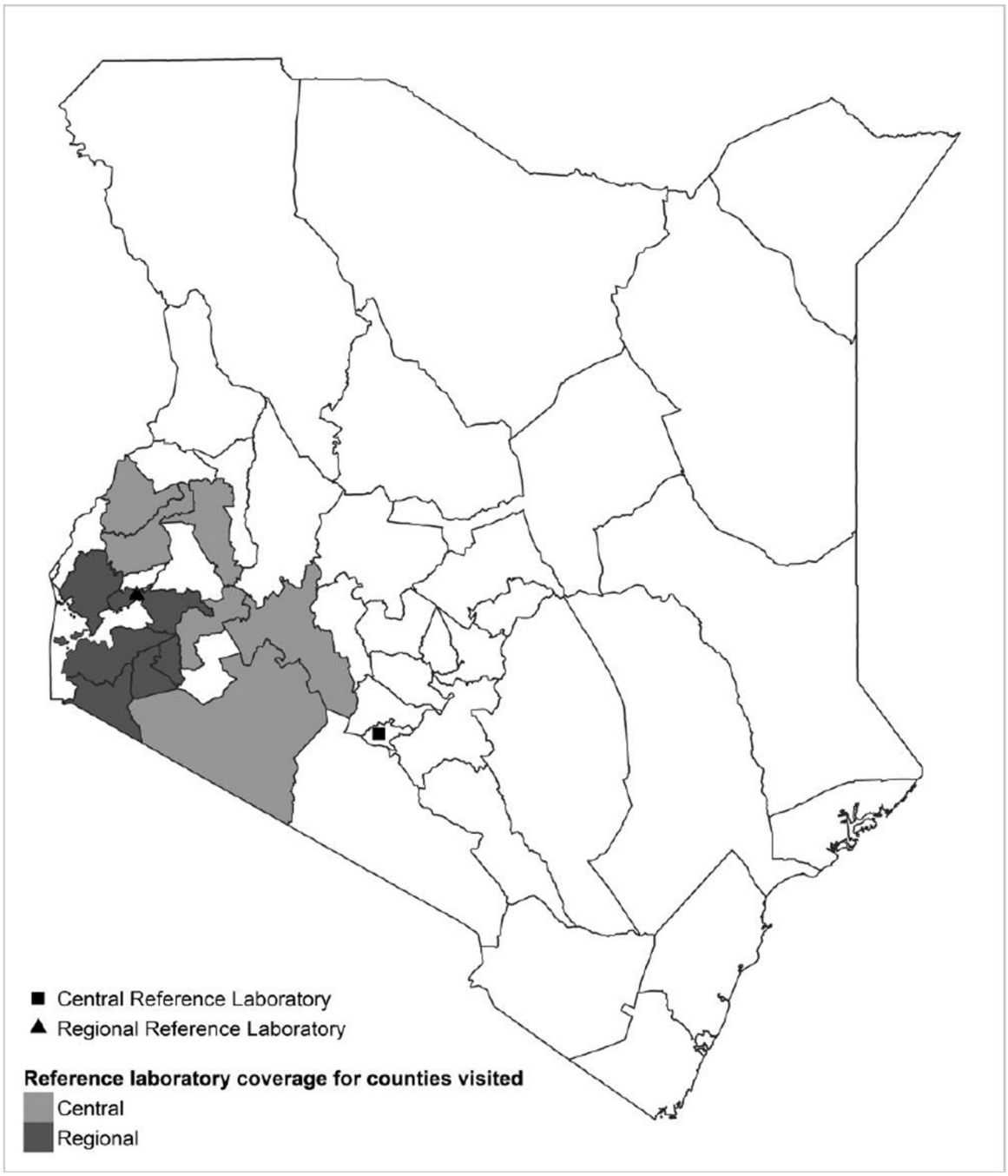

Figure 1.
Locations of reference laboratories and counties of hospitals visited by reference laboratory coverage.

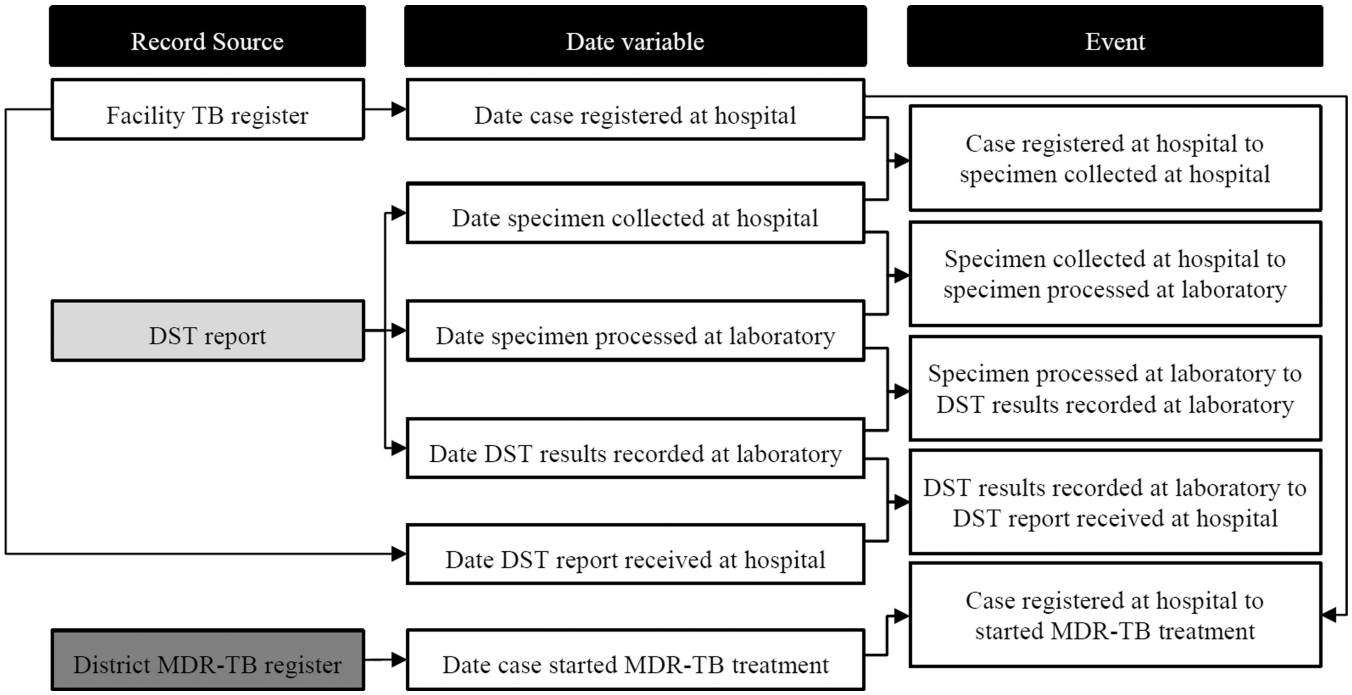

Figure 2.
Relationships among record sources, date variables, and events.

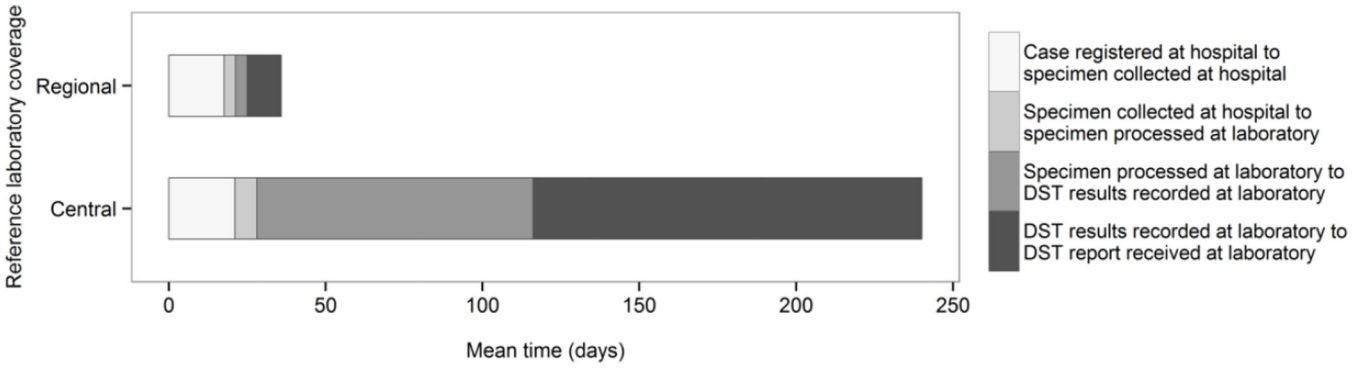

Figure 3.

Mean time in four events for testing retreatment cases for drug resistance by reference laboratory coverage.

Table 1

Number and proportion of retreatment cases tested by hospital and reference laboratory

Hospitals referring to regional laboratory	**No. cases**	**No. tested**	**(%)**
Hospital A	34	9	(26)
Hospital B	9	3	(33)
Hospital C	43	12	(28)
Hospital D	75	48	(64)
Hospital E	65	43	(66)
Hospital F	17	13	(76)
Hospital G	58	42	(72)
Hospital H	7	4	(57)
Hospital I	31	20	(65)
Hospital J	24	12	(50)
Hospital K	69	32	(46)
Total	*432*	*238*	*(55)*
Hospitals referring to central laboratory	**No. cases**	**No. tested**	**(%)**
Hospital L	66	1	(2)
Hospital M	129	24	(19)
Hospital N	12	10	(83)
Hospital O	34	19	(56)
Hospital P	71	10	(14)
Hospital Q	20	11	(55)
Hospital R	23	13	(57)
Total	*355*	*88*	*(25)*

Table 2

50th and 90th centile times in each event of testing retreatment cases for drug resistance by reference laboratory coverage

	Central			Regional			
		Time (days)			Time (days)		
Events	No. of records	50th	90th	No. of records	50th	90th	p-value*
Case registered at hospital to specimen collected at hospital	75	5	52	167	4	46	0.77
Specimen collected at hospital to specimen processed at laboratory	53	6	13	192	3	6	<0.05
Specimen processed at laboratory to DST results recorded at laboratory	51	75	111	199	0	2	<0.05
DST results recorded at laboratory to DST report received at hospital	5	88	283	53	1	7	<0.05

*Calculated using the Wilcoxon rank-sum test