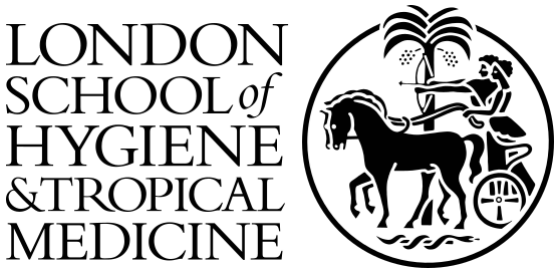

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Access to second-line drug susceptibility testing results among patients with Rifampicin resistant tuberculosis after introduction of the Hain® Line Probe Assay in Southern provinces, Zimbabwe

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ABSTRACT

Objectives: To determine the proportion of rifampicin-resistant tuberculosis (RR-TB) patients who accessed second-line drug susceptibility testing (SL-DST) results following introduction of the Hain technology in southern provinces, Zimbabwe.
Design: Cohort study using secondary data.
Results: Xpert MTB/RIF results were used to identify 133 RR-TB patients for this study. Their mean age (SD) was 37.9 (11.1) years, 83 (62%) were males and 106 (80%) were HIV-infected. There were 6 (5%) participants who had pre-treatment attrition. Of the 133 pulmonary TB (PTB) patients, 117 (80%) had additional sputum specimens collected; 96 (72%) specimens reached the National TB Reference Laboratory (NTBRL); 95 (71%) were processed; 68 (51%) had SL-DST results. Only 53 (40%) SL-DST results reached the peripheral facilities. Median time from specimen reception at the NTBRL to SL-DSTs was 40 days, interquartile range (IQR: 28–67). Median time from presumptive diagn7osis of RR-TB by health care worker to SL-DST results was 50 days (IQR: 39–80), and increased to 79 days (IQR: 39–101) in facilities >250 km from the NTBRL. The proportion with any fluoroquinolone resistance was 9 (13.2%).
Conclusion: Although RR-TB patients with PTB were initiated timely on treatment, access to SL-DSTs by facilities needs improvement. Health inequities exist as remote areas are less likely to get SL-DST results in time.

Introduction

Zimbabwe introduced new tuberculosis (TB) management guidelines in December 2016. The thrust of the guidelines is to detect TB cases early and to improve access to drug susceptibility testing (DST) (Ministry of Health and Child Care, 2016). Early detection of TB patients has been enhanced by increasing both speed and sensitivity of TB screening and diagnostic methods. This was not possible with previous methods (mycobacterial culture and smear microscopy). The former is slow while the latter is less sensitive for diagnosing TB, especially in pauci-bacillary disease such as found in children and people living with HIV (PLHIV). The rate of HIV/TB co-infection in Zimbabwe was around 68% in 2016 (World Health Organisation, 2016).

The new guidelines ushered in a new TB diagnostic algorithm – a giant leap towards universal access to DST. First, Xpert MTB/RIF® technology (Cepheid, Sunnyvale, CA, USA) replaced smear microscopy as the initial diagnostic test for TB. Second, in case of rifampicin resistant TB (RR-TB) detected on Xpert MTB/RIF, the Hain® line-probe assay (LPA) (Nehren, LifeSciences, Germany) took precedence as a confirmatory test in addition to culture and DST (CDST) and furthermore assesses resistance to isoniazid and second-line drugs (SLD).

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The recommended laboratory turnaround time for Xpert MTB/RIF is 48 h while that for the Hain LPA is three weeks, which accounts for culture growth, when required. However, Hain LPA may be carried out on acid fast-bacilli sputum positive deposits, thus offsetting the need for preliminary culture, and this expedites the time to diagnosis. Moreover, molecular tests are specific for *Mycobacterium tuberculosis* (MTB), even in cultures contaminated by commensals. Thus, notwithstanding contamination, patients may not be asked to submit new sputum samples.

Faster diagnostic tests may not be the *sine qua non* for favourable treatment outcomes, which are dependent on patients having started treatment. Studies have shown that faster diagnosis associated with molecular testing as compared to phenotypic methods may not translate to favourable treatment outcomes if patients are not initiated on appropriate treatment early (Nair et al., 2016). High rates of pre-treatment attrition have been observed in India and Zimbabwe when molecular and phenotypic tests were used (Charambira et al., 2016; Nair et al., 2016; Shewade et al., 2015; Singla et al., 2014). Prior to the introduction of Hain LPA in Zimbabwe, 44% of RR-TB patients had pre-treatment attrition while 67% of those started on treatment were initiated on treatment within two weeks of diagnosis (Charambira et al., 2016). Pre-treatment attrition may result in community transmission of RR-TB and poor health outcomes, and this is exacerbated by the low proportion of RR-TB patients who accessed DST results for isoniazid and SLD. Without SL-DST results, it is impossible to know whether there is resistance to fluoroquinolones (FQ) and/or second-line injectable (SLI) agents and thus to be able to switch patients to individualised treatment.

Zimbabwe subscribes to the World Health Organization's (WHO) End TB strategy of reducing TB incidence by 90% by 2035. A key component of the first pillar of the End TB Strategy is early diagnosis of TB, including universal access to DST (STOP TB Partnership, 2015). Thus, timely and accurate SL-DST results are crucial to inform clinical decision making on individualised treatment among RR-TB patients. Early initiation of RR-TB patients on appropriate TB medicines reduces mortality and community transmission of TB (Lönnroth et al., 2013).

The TB diagnostic algorithm has changed since the last study when DSTs were done using phenotypic methods. The introduction of Hain LPA could be a game changer in improving diagnosis and treatment of RR-TB in Zimbabwe as patients with this type of TB may have multidrug-resistant TB (MDR-TB–defined as resistance to at least isoniazid and rifampicin) (World Health Organisation, 2017) or extensively drug-resistant TB (XDR-TB, defined as MDR-TB with added resistance to FQs and SLIs). MDR-TB and XDR-TB are more expensive and difficult to treat than drug sensitive TB. The burden of FQ resistance was 10.4% according to the last drug resistant survey (Ministry of Health and Child Care, 2017). In neighbouring South Africa, the prevalence of FQ and ethionamide resistance was 13% (95% CI: 5.0–21.0) and 44.7% (95% CI: 25.8–63.9), respectively (National Institute for Communicable Diseases, 2014). There is no information in Zimbabwe about access to SL-DST results after introduction of the Hain LPA.

The aim of this study was to determine among patients diagnosed with RR-TB on Xpert MTB/RIF assays in the southern region of Zimbabwe, the number, proportion and associated clinical and temporal characteristics of those who had SL-DSTs.

Methods

Study design

A cohort study using secondary data.

General setting

Zimbabwe is among the 14 countries globally with a triple-burden of TB, TB/HIV and MDR-TB (World Health Organisation, 2017). The country is divided into northern and southern regions. Each region comprises five provinces and is served by a National Reference Laboratory. The southern provinces have the highest burden of human immunodeficiency virus (HIV) and TB and they share borders with South Africa and Botswana (Columbia University, 2016). Xpert MTB/RIF technology was introduced to Zimbabwe in 2011 while Hain-LPA (both first-line and second-line) was introduced at the NTBRL in December 2015, exactly a year before the introduction of the new TB guidelines.

Specific setting

We focused our study on the southern provinces since there were no interruptions in Hain-LPA testing at the National Tuberculosis Reference Laboratory (NTBRL), the laboratory which services the five southern provinces. Xpert MTB/RIF testing was decentralised to district and rural health facilities to improve access to DST, and all presumptive TB patients are required to produce a sputum specimen for Xpert testing. If RR-TB is detected, a second specimen is collected and sent to the NTBRL for Hain SL-LPA and CDST.

Specimen referral to the NTBRL

About 5 mL sputum is collected in screw-capped containers which are triple-packaged in zip-lock bags and cold-chain maintained using dry-ice packs before transportation to district laboratories by motorbikes from Medecins Sans Frontieres; TB CARE1; Ministry of Health's and SWIFT, a private courier. From district laboratories, specimens are sent to the NTBRL using public transportation systems. In Bulawayo Metropolitan province where the NTBRL is located, specimens are transported by TB CARE1 directly to the NTBRL.

NTBRL processes

Details of specimens that reach the NTBRL are logged into the Laboratory Information Management System (LIMS) which assigns a unique number, the date and time of receipt and the tests that are ordered. All specimens are decontaminated using sodium hydroxide to kill commensal bacteria. The resultant sputum pellet is inoculated onto both Lowenstein-Jensen (LJ) agar and MGIT-960 liquid media before they are incubated for growth. All pure growths of MTB are sub-cultured and DSTs are carried out on LJ and MGIT 960 media using the proportion method (Salman and Rusch-Gerdes, 2006; Stop TB Partnership, 2014). The performance of the NTBRL as measured by the results from external quality assurance programmes has hitherto been excellent.

Hain second-line LPA testing at the NTBRL

Hain SL-LPA is done using the Genotype *MTBDRsl v2.0* (Hain LifeSciences, GmbH), a WHO-approved test for the detection of MTB complex and mutations that confer resistance to FQ and SLIs. The recommended specimens are smear-positive sputum deposits and solid or liquid culture growths. The paper-based results are printed and sent to requesting facilities using various transport systems such as motorbikes and facility ambulances. Since Hain does not give resistance patterns to individual FQ or SLIs, phenotypic CDST provides complementary results (Figure 1).

Zimbabwe has a decentralised model of care for MDR-TB treatment. All RR-TB patients are initiated on standard treatment regimens comprising 6–8 months-long intensive phase on kanamycin, levofloxacin, cycloserine, ethionamide and Pyrazinamide, followed by

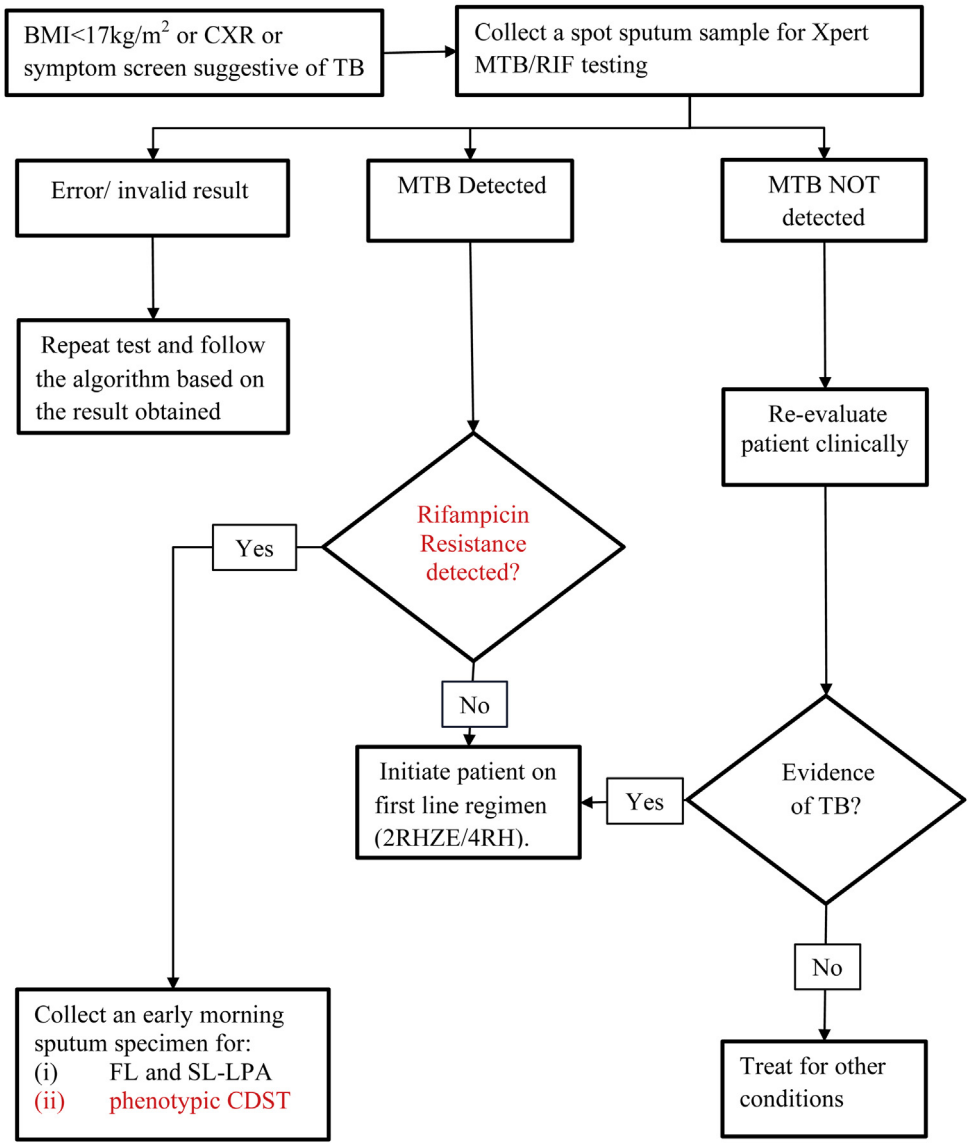

Figure 1. The simplified new TB testing algorithm for Zimbabwe, 2016–18.
BMI = Body mass index; CXR = Chest X-ray; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; MTB = *Mycobacteria Tuberculosis*; CDST = Culture and drug susceptibility testing; FL = First line; SL-LPA = second line Line probe assay.

14 months-long continuation phase on levofloxacin, cycloserine, ethionamide and Pyrazinamide. Pyridoxine is given to prevent neurological adverse events due to cycloserine. The intensive phase is administered either in hospital or at home and is directly observed, while the continuation phase is administered from home. Once SL-DST results are received from the NTBRL, patients with resistance to any of the drugs are switched to individualised treatment.

Study population

All pulmonary TB patients diagnosed with RR-TB on the Xpert MTB/RIF between April 2017 and August 2018 in the southern provinces, Zimbabwe.

Sampling strategy and study procedure

Cluster sampling was used to select the study health facilities based on the TB notifications for the year 2016 for each health facility. First, a list of health facilities (clusters) and their corresponding notifications was compiled in MS Excel. Second, health facilities that notified <10 patients in 2016 were removed from the list and cumulative notifications were compiled from the remaining clusters. Third, probability proportional to size sampling was done to select 30 clusters using a defined starting point and sampling interval. All RR-TB patients in each cluster were included in the study

Data variables, sources of data and data collection

The following variables were collected: patient name; site name; district; province; age, sex; HIV status; distance to NTBRL; ART status; history of TB; date presumed of RR-TB by HCWs; treatment initiation status; resistance to FQs (genotypic or phenotypic); dates of (specimen collection; specimen receipt by NTBRL; Xpert testing; initiation on MDR-TB treatment); SL-DST results; FL-DST results). Google maps were used to calculate distance to the NTBRL. Data were collected by data collectors and the principal investigator using a structured proforma from August–October 2018. Data were obtained from facility laboratory registers. Patient names and age were documented to ease tracking of patients in presumptive TB registers, TB treatment registers and LIMS at the NTBRL

Analyses and statistics

Data were double-entered in EpiData (v4.0.1.44) and were analysed using EpiData v2.2.2.186 (EpiData Association, Odense, Denmark). Medians were calculated if data were not normally distributed, otherwise means were calculated. Frequencies were run to calculate the proportion of patients that accessed SL-DST results or were never initiated on treatment. The chi-square test was used to measure the association between demographic and clinical factors and having a SL-DST done at NTBRL. Levels of significance were set at 5%.

Ethics

Ethics approval was obtained from the Ethics Advisory Group, International Union Against Tuberculosis and Lung Disease (The Union), (EAG-15/18) and the Medical Research Council of Zimbabwe (MRCZ/E/201).

Results

The socio-demographic and clinical characteristics of the 133 RR-TB participants are shown in Table 1**.** Males comprised 83(62%) of the study population. The mean age (SD) was 37.9 (11.1) years. The numbers of PLHIV were 106 (80%), and of these, 91% were on antiretroviral therapy. There were 47(35%) participants with previous histories of TB. Matebeleland South and Bulawayo metropolitan provinces had the highest proportions of participants at 26% and 33% respectively.

Time to treatment initiation is shown in Table 2. The median time from RR-TB diagnosis to treatment initiation was one day (IQR: 0–3). A total of 127 (95%) (95% CI: 90.5–97.9) RR-TB patients were initiated on the standard MDR-TB regimen, of whom 116 (91%) were initiated within one week of diagnosis. There were six 6 (5%) (95% CI: 2.1–9.5) who had pre-treatment attrition, and death accounted for five of these patients.

Table 3 shows the characteristics of participants who had SL-DST results at the NTBRL. Of the 133 participants, 68(51%) had a SL-DST done at the NTBRL. At univariate analysis, neither sex nor age nor HIV status were associated with having a SL-DST done. Patients with a previous history of TB were 77% more likely to have a SL-DST done compared with those newly diagnosed, $P = 0.02$; while facilities located <50 km away from the NTBRL were 61% more likely to have SL-DSTs done at the NTBRL than those >250 km away, $P = 0.03$.

The cascade of care shows that of the 133 participants, 117 (88%) (95% CI: 81.4–92.5) had sputum collected; 96 (72%) of the specimens reached the NTBRL; 95 (71%) specimens were processed and 68 (51%) of the specimens had SL-DST results. Only 53 (40%) results reached the peripheral facilities (Figure 2).

Table 4 shows the drug-resistance patterns of the specimens. Of the 68 SL-DST results produced by the NTBRL, 59 (87%) were sensitive to both FQ and SLIs. The proportion with any FQ resistance was 9 (13%) (95% CI: 7.1–23.3).

The median time taken from presumption of RR-TB to SL-DST results at the NTBRL was 50 days (IQR: 39–79.8). The time taken increased to 79 days (IQR: 39–101) in facilities that were >250 km away from the NTBRL (Table 5).

There were 71 RR-TB patients with FL-DST results. Of these, 35 (49%) had rifampicin mono-resistance, and RR-TB was not confirmed by in 4(6%) patients. There were 32 MDR-TB patients, and 11 of them had low-level isoniazid resistance.

Table 1
Socio-demographic and clinical characteristics of patients diagnosed with rifampicin resistant tuberculosis on Xpert MTB/RIF in southern provinces of Zimbabwe, April 2017–August 2018.

Variable	Number	(%)
Total	133	
Sex:		
Male	83	(62)
Female	50	(38)
Age category in years:		
<25	13	(10)
25–34	39	(29)
35–44	54	(41)
45–54	14	(11)
55–64	8	(6)
65+	3	(2)
Missing age	2	(1)
Type of TB patient:		
New	83	(63)
Retreatment	47	(35)
Not recorded	2	(2)
Treatment status:		
Initiated	127	(95)
Not initiated	6	(5)
• Died	5	(83)
• LFU	1	(17)
HIV status:		
Negative	26	(20)
Positive	106	(80)
Not recorded	1	(<1)
Province:		
Matebeleland South	35	(26)
Matebeleland North	16	(12)
Bulawayo Metropolitan	44	(33)
Midlands	21	(16)
Masvingo	17	(13)
Distance from NTBRL (km):		
<50	43	(32)
50–250	53	(40)
>250	37	(28)
Median (IQR)	155 (12–274)	

SD = Standard deviation; NTBRL = National Tuberculosis Reference Laboratory; IQR = Inter-quartile range; km = Kilometers; LFU = loss to follow-up (attrition).

Discussion

This is the first study to determine access to SL-DST among RR-TB patients following introduction of the Hain LPA in southern Zimbabwe. The study has some interesting findings.

First, the intervals from presumption of RR-TB to diagnosis and treatment initiation were short, and within targeted timelines. Only 10(9%) patients experienced treatment delays of >7 days. Most importantly, 95% of the RR-TB participants were initiated on standard MDR-TB treatment which is a higher proportion of treatment initiation compared with previous studies in northern Zimbabwe and India (Charambira et al., 2016; Kant et al., 2017) but was consistent with the findings from some parts of India (Shewade et al., 2018). This could be attributed to decentralisation of both Xpert MTB/RIF testing and MDR-TB treatment in Zimbabwe. Pre-treatment attrition in this study was consistent with other findings from Africa and India (MacPherson et al., 2014; Shewade et al., 2018), and was mainly due to deaths. It was,

Table 2
Time to treatment initiation among patients diagnosed with rifampicin resistant TB on Xpert MTB/RIF in the southern provinces of Zimbabwe, April 2017–August 2018.

Time interval (days)	Number initiated on treatment	(%)
Total	127	
≤7	116	(91)
8–14	7	(5)
15–21	2	(2)
21–28	1	(1)
Missing data	1	(1)

Table 3
Socio-demographic and clinical characteristics associated with having second line drug susceptibility testing among patients diagnosed with rifampicin resistance on Xpert MTB/RIF in the southern provinces of Zimbabwe, April 2017–August 2018.

Variable	Total	Number who had SL-DST results (%)†		RR 95% CI	*P*-value
Total	133	68	(51)		
Sex					
Male	83	44	(53)	1.08 (0.83–1.41)	0.57
Female	50	24	(48)	1.00	
Age in years					
<25	13	6	(46)	1.00	
25–34	39	20	(51)	1.05 (0.77–1.44)	0.75
35–44	54	33	(61)	1.13 (0.88–1.45)	0.33
45–54	14	5	(36)	0.81 (0.37–1.76)	0.58
55–64	8	3	(38)	0.80 (0.26–2.50)	0.70
65+	3	1	(33)	0.64 (0.10–5.13)	0.69
Missing age	3	0	(0)	–	–
Type of TB patient					
New	83	37	(45)	1.00	
Retreatment	47	31	(66)	1.77 (1.08–2.90)	**0.02**
Not recorded	3	0	(0)	–	–
HIV status					
Negative	26	15	(58)	1.00	
Positive	106	52	(49)	0.93 (0.79–1.11)	0.43
Not recorded	1	1	(100)	–	
Province					
Matebeleland South	35	19	(54)	0.85 (0.52–1.39	0.53
Matebeleland North	16	8	(50)	0.71 (0.31–1.64)	0.43
Bulawayo Metropolitan	44	27	(61)	1.00	
Midlands	21	9	(43)	0.60 (0.30–1.23)	0.16
Masvingo	17	5	(29)	0.38 (0.15–0.94)	**0.03**
Distance to NTBRL (km)					
<50	43	27	(63)	1.61 (1.04–2.48)	**0.03**
50–250	53	27	(51)	1.24 (0.90–1.75)	0.22
250	37	14	(38)	1.00	–

RR = Relative risk; SL-DST = Second line drug susceptibility test; NTBRL = National Tuberculosis Reference Laboratory; CI = Confidence interval; TB = Tuberculosis;† = row percentages.

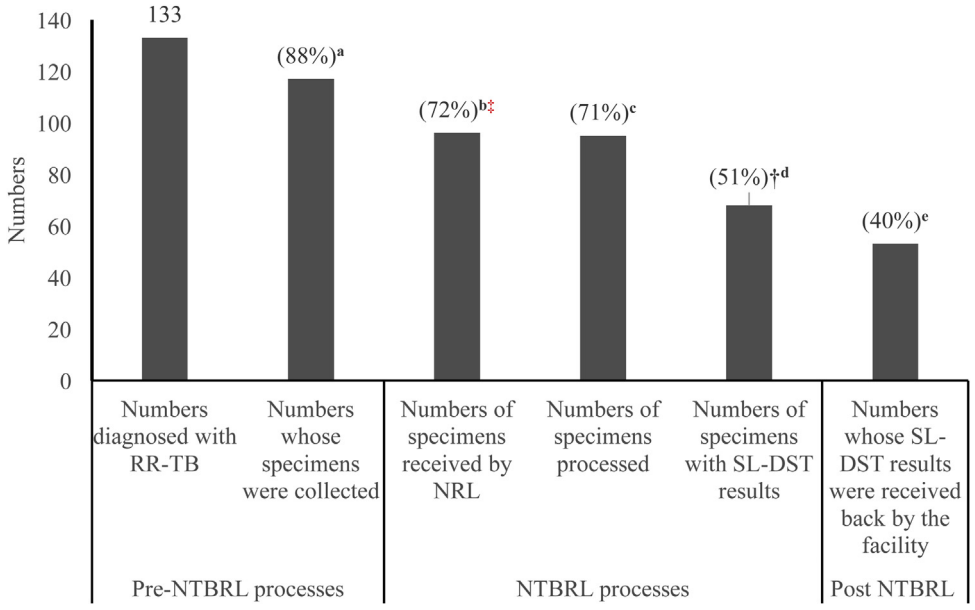

Figure 2. Cascade of care from diagnosis of RR-TB to reception of second line DST results at peripheral facilities among patients diagnosed with rifampicin resistant TB on Xpert MTB/RIF in the southern provinces of Zimbabwe, April 2017–August 2018.
[a,b,c,d,e] = denominator for calculations is 133 RR-TB patients diagnosed with RR-TB on Xpert MTB/RIF assay
‡ = only one specimen was received per patient; † = Losses were due to no growth on culture; poor documentation on laboratory request forms regarding tests to be done (diagnosis/follow −up). Follow up tests are for disease prognosis, and only need culture. NBTRL = National Tuberculosis Reference Laboratory; RR-TB = rifampicin resistant TB; SL-DST = Second-line drug susceptibility testing.

Table 4
Drug-resistance patterns among patents diagnoses with rifampicin resistant tuberculosis, by treatment history and demographic factors, April 2017–August 2018, Zimbabwe.

Variables		Sensitive to all the SLD n (%)	Any FQ‡ resistance n (%)
Total	68	59 (87)	9 (13)
Sex			
Male	44	40 (91)	4 (9)
Female	24	19 (79)	5 (21)
Age category			
<25	6	5 (83)	1 (17)
25–34	20	18 (90)	2 (10)
35–44	33	27 (82)	6 (18)
45–54	5	5 (100)	0 (0)
55–64	3	3 (100)	0 (0)
>65	1	1 (100)	0 (0)
Type of TB patient			
New	37	32 (86)	5 (14)
Retreatment	31	27 (87)	4 (13)
Treatment status			
Initiated	65	58 (89)	7 (11)
Not initiated	3	1 (33)	2 (67)
HIV status			
Positive	52	43 (83)	9 (17)
Negative	15	15 (100)	0 (0)
Not recorded	1	1 (100)	0 (0)
Province			
Matebeleland South	19	15 (79)	4 (21)
Matebeleland North	8	7 (88)	1 (12)
Bulawayo Metropolitan	27	25 (93)	2 (7)
Midlands	9	8 (89)	1 (11)
Masvingo	5	4 (80)	1 (20)

SLD = second-line drugs; FQ = Fluoroquinolone; XDR-TB = extensively drug-resistant tuberculosis; R = Rifampicin; H = Isoniazid. ‡ = Only 5(7%) had FQ mono-resistance while 4(6%) had extensively drug-resistant TB (XDR-TB).

however, lower than the 10.3% reported among drug-susceptible TB patients in Bulawayo Metropolitan province (Mugauri et al., 2018).

Second, there were huge leakages in SL-DST results produced at the NTBRL compared with those received by peripheral facilities. This finding is consistent with findings from South Africa (Jacobson et al., 2017). Reasons for leakages could be attributed to challenges in transporting the paper-based laboratory results to health facilities. Leakages in pre-NTBRL processes may be due to failure to collect sputum specimens for SL-DST as reported elsewhere (Murongazvombo et al., 2018). Even when sputum specimens are collected, some do not reach the NTBRL owing to specimen transportation challenges. Within the NTBRL, specimen leakages may stem from culture no growths and culture contaminations as described in a previous study (Timire et al., 2018a,b). No growths are likely to be common among specimens that have long transit times to the NTBRL since MTB may lose viability. Lack of sufficient clinical data on request forms on the type of test to be done (diagnostic or treatment monitoring tests) may result in some specimens getting culture results and not SL-DSTs. Culture is done routinely to monitor MDR-TB treatment.

Third, the cascade of care of RR-TB patients may be a tracer for quality of care they receive. The proportion of patients with SL-DST done at the NTBRL was inversely proportional to distance from the NTBRL. Facilities >250 km away from the NTBRL are mostly in remote areas with poor road networks leading to logistical challenges in getting specimens to the NTBRL. Even if the specimens finally reach the NTBRL, the MTB may have lost viability. Challenges with processes of sputum specimen transportation to NRLs have been reported in other countries (Kilale et al., 2013; Qi et al., 2011).

Increased access to SL-DST among previously treated patients could be attributed to adherence to guidelines on sputum specimen collection for SL-DST by HCWs for this group of patients. Previously treated TB is a known risk factor for RR-TB, and even before the introduction of new guidelines CDST was prioritised for this group.

The high proportion of RR-TB patients initiated on treatment in this study means that most patients were enrolled into care, and had high chances of providing a sputum specimen for SL-DST. The converse is true for a high pre-treatment attrition. However, the consequences of starting the standard MDR-TB regimen (with FQ and SLIs as backbone agents) early meant that about 13% of patients with undetected FQ resistance were potentially exposed to sub-optimal treatments. This figure is comparable to the proportion of FQ resistance (10%) among RR-TB patients in Zimbabwe (Ministry of Health and Child Care, 2017), but was remarkably lower than the proportion of patients who were started on suboptimal therapies in South Africa and China (Jacobson et al., 2017; Chen et al., 2016). Suboptimal therapies are a wastage of drugs; lead to poor treatment outcomes; expose patients to toxicities and increase risk of acquisition of further drug resistance, and ongoing community transmission of DR-TB strains (Chen et al., 2016; Kendall et al., 2017). The proportion of participants who were started on a suboptimal therapy may be higher if low-level isoniazid resistance is taken into account: at least 11 of the 32 participants diagnosed with MDR-TB had low-

Table 5
Time taken in days among patients diagnosed with RR-TB on Xpert MTB/RIF (April 2017–August 2018), Zimbabwe.

	Presumption to RR-TB diagnosis		Specimen collection to receipt by NTBRL		Specimen receipt by NTBRL to SL-DST result		Overall delay in SL-DST result‡	
Variable	Median	IQR	Median	IQR	Median	IQR	Median	IQR
All patients	1	0–1	8	4–19.3	40	28–67	50	39–79.8
Type of TB patient								
New	1	0–1	8.5	5–27.3	38.5	27.3–67.8	50	38.3–78
Retreatment	1	0–1	6.5	3.3–19.0	41.5	28.5–66.3	58	39.3–83.8
Not recorded	1.5	0–1.5	–	–	–	–	–	–
Distance to NTBRL								
<50 km	1	1–3	5	2–11	41	27–67	49	36–73.5
50–250 km	0	0–1	7	4–19	38	24–53	50	40.8–73.5
250 km	1	0–1	18	8–30.8	46	28–76	79	39–101

RR-TB = Rifampicin resistant tuberculosis; SL-DST = second line drug susceptibility test; IQR = Interquartile range; NTBRL = National Tuberculosis Reference Laboratory; FQ = Fluoroquinolone; XDR-TB = extensively drug resistant tuberculosis. ‡ defined here as time from presumption of RR-TB to the date when a SL-DST was produced by the NTBRL.

level isoniazid resistance. Cross resistance between low-level isoniazid resistance and ethionamide resistance, one of the drugs in the standard MDR-TB regimen has been reported (Bollela et al., 2016; Qamar et al., 2017).

The median time to SL-DSTs was comparable to results obtained in South Africa but was much shorter than in China (Jacobson et al., 2017; Chen et al., 2016). Delayed access to SL-DST implies that some patients on the standard MDR-TB regimen, especially those in facilities >250 km from the NTBRL may receive suboptimal therapies for longer periods. These patients, if they get SL-DST results at all, may get switched to effective, individualised regimens after 79 days – the overall delay in SL-DST results! Rapid diagnosis, early and regulated treatment on effective MDR-TB drugs is key for RR-TB control efforts (Chen et al., 2016). Early access to SL-DSTs is indispensable, as it informs better clinical decisions regarding the number and choice of effective drugs in the regimen, usually a mix of ≥4 drugs during the intensive phase and ≥3 drugs during the continuation phase (Ahuja et al., 2012; Kendall et al., 2017).

Several programmatic implications arise from this study. The NTP should ensure both increased speed and access to SL-DSTs through strengthening sputum transportation; relay of results back to requesting facilities and ensuring adherence to national guidelines on sputum collection and referral. Post-NTBRL leakages in SL-DST results may be reduced if the NTP introduces electronic reporting to increase both speed and access to SL-DST results by health facilities. Short message services (SMSs) have improved result turn-around times in early infant diagnosis as compared to courier-based reporting (Vojnov et al., 2017). The NTP may also consider investing in point-of-care diagnostics that offer sensitivity patterns to FQ and SLIs even in peripheral areas to ensure equity of access to SL-DSTs (Xie et al., 2017). Electronic tracking of specimens referred for SL-LPA is also recommended, a lack of which was a barrier to accessing SL-DSTs in India (Shewade et al., 2015).

Low-level isoniazid resistance may predict ethionamide resistance. In Pakistan, 26.6% of low-level isoniazid resistant MTB strains were confirmed to have ethionamide resistance (Qamar et al., 2017). Zimbabwe's current guidelines are silent on this, and FL-DST reporting templates may need to be updated in order to capture low-level isoniazid resistance.

The high proportion of PLHIV among RR-TB patients poses a diagnostic dilemma; PLHIV produce pauci-bacillary specimens, and without preliminary culture, weak bands are produced which cannot be interpreted. The full benefits of LPA, like shortened SL-DST result turn-around time may not be realised in HIV-burdened settings since LPA can only be carried out on smear-positive sputum deposits.

Pre-treatment attrition mainly due to death implies delayed health seeking behaviour. Delayed health seeking behaviour may result in amplification of drug resistance and in community transmission of TB. There is a need to intensify health promotion messaging on benefits of early health seeking and to increase active case finding strategies (contact tracing and targeted active screening for TB) as per national guidelines.

The strengths of this study were: the study was done in a routine programme setting, and the results may be generalisable to this population. Quality of data was improved by use of different data sources as we tracked patients from facility registers and registers at NTBRL as we checked for accuracy (consistency and completeness) of data. We assessed the overall access to SL-DSTs regardless of the method used (phenotypic or genotypic). In most cases the results from the two methods were available with an excellent concordance. Data collection allowed for laboratory processes to be completed or at least for the specimens to reach the NTBRL, especially for those specimens that were collected close to the end of the collection period. To cater for any anticipated teething challenges, we collected data for RR-TB which was diagnosed at least four months after the introduction of Hain technology. All data were double-entered to minimise data entry errors.

Our limitations were that we do not know if the patients who had FQ resistance were switched to individualised regimes as we did not collect this data. In addition, the overall delay in getting SL-DSTs was underreported in this study. This is because the delay was based on a proxy date when SL-DST results were produced by the NTBRL, instead of the date when results were received by facilities. The latter dates were poorly documented, with most results yet to be transcribed from NTBRL forms onto TB registers or patient treatment booklets.

We could not assess pre-diagnosis attrition as this was not within the scope of our study. However, studies in Zimbabwe and India have shown higher proportions of pre-diagnosis attrition than those of pre-treatment attrition (Shewade et al., 2017; Murongazvombo et al., 2018). We anticipated that our pre-treatment attrition was much lower than pre-diagnosis attrition. Stigma related to TB may result in higher pre-diagnosis attrition since a positive TB result is viewed as a proxy for HIV positive status (Craig et al., 2017).

In conclusion, access to SL-DST in Zimbabwe needs improvement. Health inequities exist as patients in peripheral areas are less likely to get SL-DST results in time. Strengthening specimen referral and result feedback mechanisms may increase access to SL-DST results.

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Author contributions

CT, KCT, AMVK and ADH conceived and designed the study and all authors read and approved the study protocol; CT and BM collected the data. CT and KCT analysed the data. CT drafted the manuscript and all authors critically reviewed the manuscript. All authors read and approved the final manuscript.

Disclosure policy

The authors declare that there is no conflict of interest regarding the publication of this paper.

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