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RESEARCH ARTICLE

The second national anti-tuberculosis drug resistance survey in Tanzania, 2017–2018

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Abstract

Objective: To determine the levels and patterns of resistance to first- and second-line anti-tuberculosis (TB) drugs among new and previously treated sputum smear positive pulmonary TB (PTB) patients.

Methods: We conducted a nationally representative cross-sectional facility-based survey in June 2017–July 2018 involving 45 clusters selected based on probability proportional to size. The survey aimed to determine the prevalence of anti-TB drug resistance and associated risk factors among smear positive PTB patients in Tanzania. Sputum samples were examined using smear microscopy, Xpert MTB/RIF, culture and drug susceptibility testing (DST). Logistic regression was used to account for missing data and sampling design effects on the estimates and their standard errors.

Results: We enrolled 1557 TB patients, including 1408 (90.4%) newly diagnosed and 149 (9.6%) previously treated patients. The prevalence of multidrug-resistant TB (MDR-TB) was 0.85% [95% confidence interval (CI): 0.4–1.3] among new cases and 4.6% (95% CI: 1.1–8.2) among previously treated cases. The prevalence of *Mycobacterium tuberculosis* strains resistant to any of the four first-line anti-TB drugs (isoniazid, rifampicin, streptomycin and ethambutol) was 1.7% among new TB patients and 6.5% among those previously treated. Drug resistance to all first-line drugs was similar (0.1%) in new and previously treated patients. None of the isolates displayed poly-resistance or extensively drug-resistant TB (XDR-TB). The only risk factor for MDR-TB was history of previous TB treatment (odds ratio = 5.7, 95% CI: 1.9–17.2).

Conclusion: The burden of MDR-TB in the country was relatively low with no evidence of XDR-TB. Given the overall small number of MDR-TB cases in this survey, it will be beneficial focusing efforts on intensified case detection including universal DST.

KEYWORDS
drug resistance, MDR-TB, survey, Tanzania, tuberculosis

Sustainable Development Goal: Good Health and Wellbeing

INTRODUCTION

Tuberculosis (TB) was the leading cause of death due to a single microorganism worldwide in the pre-COVID era [1–4]. According to the WHO Global TB Report 2020, almost half a million people developed rifampicin-resistant TB (RR-TB) in 2019, of which 78% had multidrug-resistant TB (MDR-TB) [1]. Most people with TB are cured using a 6-month drug regimen which is provided to patients with close monitoring and supervision. *Mycobacterium tuberculosis* (M. tb), the bacterium that causes TB, can develop resistance to the antimicrobial drugs during the long course of treatment [5]. The development of resistance could be due to inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs, poor quality medicines or bad storage conditions and treatment interruption [5–7]. Pharmacokinetic variability due to genetic polymorphisms [8, 9] and spontaneous mutation of M. tb [10, 11] may also contribute to the development of drug-resistant TB. However, the ongoing transmission of drug-resistant TB strains, including MDR-TB and extensively drug-resistant (XDR) is the dominant mode of spread in many endemic countries [12, 13]. MDR-TB is the resistance to the two most powerful anti-TB drugs, isoniazid and rifampicin [12]. Treatment of MDR-TB is difficult as treatment options are limited and expensive, recommended medicines are not always available, and patients experience many adverse effects from the drugs [5]. Patients with MDR-TB require treatment with second-line treatment regimens which are more complex than those used to treat patients without drug-resistant TB. In some cases, even more severe drug-resistant TB may develop. Extensively drug-resistant TB (XDR-TB) is defined as TB caused by M. tb strains that fulfil the definition of MDR-TB/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug [14].

The trends in incidence, prevalence and death of MDR-TB decreased globally from 2000 to 2017 with estimated annual percentage changes of −1.4%, −1.3% and −3.3%, respectively [13]. However, in 2019 more cases of MDR-TB/RR-TB were detected and notified globally than in the previous year, presenting a 10% increase from 186,883 to 206,030 cases [1].

According to WHO guidelines, detection of MDR-TB/RR-TB requires bacteriological confirmation of TB and testing for drug resistance [drug susceptibility testing (DST)] using rapid molecular tests, culture methods or sequencing technologies [1]. WHO estimated that only 44% of the estimated 465,000 MDR-TB/RR-TB incident cases in 2019 were notified [1]. The factors influencing detection of MDR-TB include suboptimal referral for DST, inadequate coverage of diagnostic DST, limited laboratory capacity and insufficient uptake of WHO-recommended rapid diagnostic tests. Furthermore, the global MDR-TB burden is underestimated by limiting the pool of patients considered to have MDR-TB to those with notified or incident TB [15–17].

The United Republic of Tanzania is among the 30 high TB and TB/HIV burden countries and had an estimated annual TB incidence rate of 237 per 100,000 population in 2019 [1]. Understanding the burden of TB drug resistance is critical to inform the development of appropriate treatment regimens, guiding resources for diagnosis and treatment and control of the disease. In settings without capacity for continuous surveillance of anti-TB drug resistance based on routine DST, WHO recommends surveys on new TB cases to be conducted at least every 5 years. The surveys can provide critical information for the TB program on the burden of drug resistance and common patient resistance profiles [18]. Surveys can also strengthen laboratory capacity, transportation and referral systems, as well as evaluate the accuracy of classification of patients by treatment history and risk factors for drug resistance [18]. The first anti-TB drug resistance survey (DRS) in Tanzania was conducted in 2006 [19]. The prevalence of MDR-TB among new patients and previously treated TB cases reported in that survey was 1.1% and 3.1%, respectively [19, 20]. We conducted the second nationwide anti-TB DRS in 2017–2018 to determine the levels and patterns of resistance to first and second-line anti-TB drugs among new and previously treated sputum smear positive pulmonary TB (PTB) patients.

METHODS

Survey design

We conducted a nationally representative cross-sectional health facility-based survey during June 2017–July 2018. The study was designed to conform to WHO guidelines for periodic DRSs [18].

Survey population

The survey population included newly diagnosed and previously treated smear positive PTB patients of all ages including children. All enrolled patients signed an informed consent form. Parents/guardians signed informed consent form for children younger than 18 years old. Children 15–18 years also signed an Assent Form. Patients whose previous and subsequent MDR-TB treatment course(s) have failed based on WHO guidelines (multiple episodes of TB treatment failures or more than one previously known episode of MDR-TB) were not eligible for the survey [18].

Sample size determination

The sample size was calculated according to the WHO Guidelines for Surveillance of Drug Resistance in Tuberculosis [18]. Taking into account correlation between individuals within a cluster with design effect of 2, the desired absolute precision of the estimate of 0.8%, and 15% of expected loses due to culture contaminations and other issues, the sample size of 1495 new smear positive PTB patients was required for the survey. All smear positive previously treated patients who met eligibility criteria were enrolled during the survey intake period.

Sampling strategy and selection of clusters

The unit of sampling was represented by a diagnostic facility that notified at least eight smear positive TB cases in 2015; whereas facilities with less than eight smear positive TB cases were excluded from the selection as they represented only 5% of all diagnosed smear positive cases in 2015. A cluster could include one or several diagnostic facilities depending on the number of notified cases in the selected health facility in 2015. Clusters were selected by probability proportional to size; 45 clusters were selected. In each cluster, a total of 34 new smear positive PTB patients and all previously treated smear positive PTB cases diagnosed during the intake period for the survey were enrolled into the study (Appendix A).

Training of survey staff

A 2-day training was conducted by zones before the start of the survey using the developed standardised training materials. The training was done on enrolment of study clients, sputum collection and transportation. At peripheral laboratory level, laboratory personnel were trained on use of light-emitting diode (LED) microscopy, specimen preparation, mixing of sputum with OmniGene-sputum transport solution, storage and transport of specimen. At the Central TB Reference Laboratory (CTRL) 1-day training was conducted for CTRL personnel and data management.

Data collection

Enrollment of patients

The study was conducted for a period of 12 months and/or until the required sample size of new smear positive cases was reached at each cluster. For persons suspected of having TB, two sputum samples (at the time of diagnostic workup and early morning the following day) were collected and tested at the cluster level using immunofluorescence LED smear microscopy in accordance with the national guidelines. All patients with smear positive results were eligible for enrollment after providing informed consent. Demographic information and previous TB treatment history was obtained from enrolled individuals during interview using a standardised questionnaire. HIV status was obtained from patient records available at the treatment facilities. Two additional sputum samples were collected from the enrolled individuals: one sputum sample at the time of enrollment and second one on the next morning.

Laboratory procedures

The sputum samples were transported to the CTRL in Dar es Salaam for Xpert MTB/RIF testing, smear examination with fluorescent microscopy, culture on Lowenstein Jensen solid media, and phenotypic DST to first- and second-line drugs following standard NTLP procedures. All culture positive isolates were identified by Capilia MPT64 test, an immunochromatographic test for the rapid identification of M. tb from solid cultures, before processed for DST [21]. Isolates that were positive on MPT64 test were subjected for DST. MPT64 negative results indicated the presence of non-tuberculous mycobacteria (NTM); such isolates were not tested for DST. The following critical concentrations for the first-line DST were used: 0.2 μg/ml for isoniazid, 40 μg/ml for rifampicin, 4 μg/ml for streptomycin and 2 μg/ml for ethambutol. For the second-line DST the concentration for kanamycin was 30 μg/ml, for ofloxacin 2.0 μg/ml and for capreomycin 40 μg/ml.

Survey monitoring

To ensure the quality of enrolment of patients and specimen collection regular supervision and monitoring of the field sites were conducted. A checklist was used to assess compliance to the survey procedures in line with the protocol. Observations and recommendations made during supervisory visits were immediately relayed to the clusters for action. A mid-term review was done in September 2017 came up with pertinent recommendations that were also implemented to improve the survey.

Quality assurance

All laboratory procedures adhered to the internal quality control procedures in accordance with international standards [18]. Handling of specimens for culture and DST was carried out in a high-risk TB (P3) laboratory, as defined in WHO's Tuberculosis Laboratory Biosafety Manual [22]. To ensure reliability and comparability of the Tanzania survey results, internal and external quality control of susceptibility testing was performed during the survey. All RIF-resistant specimens and 10% of randomly selected susceptible specimens identified were shipped to Antwerp Supra-national Laboratory (SRL) for EQA testing. Re-checking of strains at the SRL was conducted to validate the survey results. No changes in patient care were implemented based on the SRL results.

Data management and analysis

Completed questionnaires were entered into an electronic Epi Info database by trained data entry personnel. Entered data were stored in Access format, and data were double-entered and cleaned before analysis. The analysis was fully accounted for the cluster survey design. Missing laboratory results for 101 cases were imputed based on a probability model of the complete data for age, gender, treatment history, rifampicin, isoniazid and multidrug resistance. To address over/under-enrolment by facility, weights against calculated cluster size were included in the regression model. Different approaches (with imputation, without imputation,

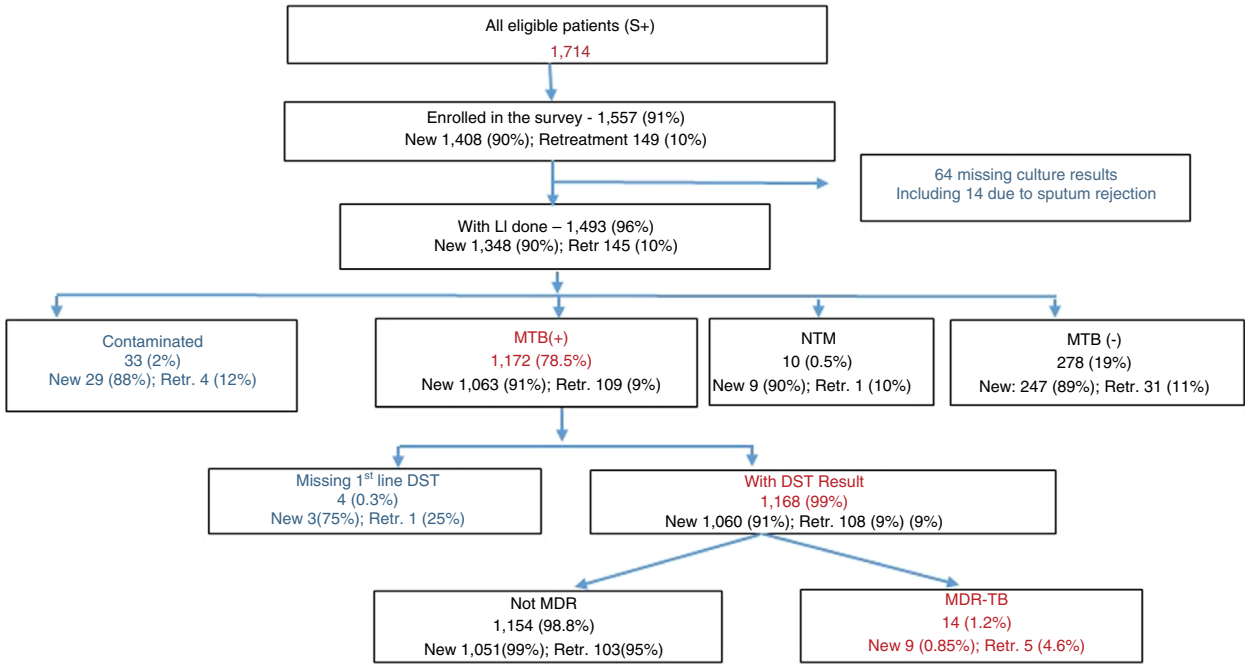

FIGURE 1 Culture/drug susceptibility testing flowchart for drug resistance survey in Tanzania

with weight and without weight) were used to estimate the prevalence of MDR-TB. As no significant differences were observed between the results from different methods, the results received without imputation of missing values were accepted as official DRS results in Tanzania.

Logistic regression was used to analyse association between possible risk factors and MDR-TB in Tanzania. Analysis was carried out using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Ethical considerations

The study was approved by the National Health Research Ethics Committee of Tanzania and the Center for Global Health at the U.S. Centers for Disease Control and Prevention (CDC). The study was reviewed in accordance with the U.S. CDC human research protection procedures and determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes. Written informed consent was obtained from all participants or their legal guardian; assent was also obtained from children 15–17 years old.

RESULTS

Demographic characteristics of the survey participants

A total of 1714 smear positive PTB cases were notified in the selected facilities during the survey period, thus were eligible for the survey. All 1714 were treated according to routine NTLP guidelines, and 1557 were enrolled for the survey; 1493 (96%) of them sent samples for investigation. Out of all samples received 1172 (78%) grew MTB and 10 (0.6%) grew NTM. There was no growth in 278 samples (Figure 1). Among MTB cases, 1063 (91%) were new and 109 (9%) were previously treated.

Among the 1172 enrolled patients with confirmed TB, the majority [825 (70.4%)] were males (Table 1). The proportion of males was higher among previously treated (80.7%) than new cases (69.3%). The mean age of the participants was 37 years (36.7 years for new and 40.5 years for previously treated patients); most of the patients [665 (56.7%)] were aged 25–44 years. Among MTB positive patients, 286 (24.4%) were infected with HIV. Almost one third (82/286) of all HIV-positive MTB individuals were diagnosed in Dar es Salaam. The proportion of HIV-positive individuals was higher among previously treated patients 39 (35.8%) than new patients [247 (23.2%)].

Resistance to first-line anti-TB drugs

Among 1172 MTB isolates, 1168 (99%) had DST results for all drugs (Figure 1). Results for resistance to first-line anti-TB drugs are summarised in Table 2. Of the 1168 TB patients with DST results 25 (2.1%) patients (including 18 new and 7 previously treated) had any resistance to the first- and second-line anti-TB drugs. Seventeen (1.5%) M. tb isolates were resistant to rifampicin (R), the same number of isolates (17 or 1.5%) were resistant to isoniazid (H). Fourteen (1.2%) MTB isolates were resistant to both R and H, meaning they were MDR-TB, including nine (0.8%) among new cases and five (4.6%) among previously treated cases.

TABLE 1 Profile of participants in the national anti-tuberculosis drug resistance survey, 2017–2018

Characteristic	New *n* (%)	Previously treated *n* (%)	Total *n* (%)
Total	1063 (91%)	109 (9%)	1172
Sex			
Male	737 (69.3)	88 (80.7)	825 (70.4)
Female	326 (30.7)	21 (19.3)	347 (29.6)
Age group (years)			
0–14	16 (1.5)	0	16 (1.4)
15–24	189 (17.8)	9 (8.2)	198 (16.9)
25–34	301 (28.3)	17 (15.6)	318 (27.1)
35–44	299 (28.1)	48 (44.0)	347 (29.6)
45–54	153 (14.4)	21 (19.3)	174 (14.9)
55–64	57 (5.4)	10 (9.2)	67 (5.7)
65+	48 (4.5)	4 (3.7)	52 (4.4)
Mean age	36.7	40.5	37
Median age (IQR)	36 (19)	40 (14)	37 (19)
Contact with MDR-TB case			
Yes	55 (5.2)	2 (1.8)	57 (4.9)
No	833 (78.4)	90 (82.6)	923 (78.7)
Missing	175 (16.4)	17 (15.6)	192 (16.4)
HIV status			
Positive	247 (23.2)	39 (35.8)	286 (24.4)
Negative	816 (76.8)	70 (64.2)	886 (75.6)
Smoking			
Yes	175 (16.5)	27 (24.8)	202 (17.4)
No	811 (76.3)	72 (66.0)	883 (75.3)
Missing	77 (7.2)	10 (9.2)	87 (7.4)
Alcohol use			
Yes	220 (20.7)	31 (28.4)	251 (21.4)
No	774 (72.8)	69 (63.3)	843 (71.9)
Missing	69 (6.5)	9 (8.3)	78 (6.7)
Diabetes			
Yes	15 (1.4)	1 (0.9)	16 (1.4)
No	975 (91.7)	98 (89.9)	1073 (91.5)
Missing	73 (6.9)	10 (9.2)	83 (7.1)

Note: Numbers rounded to make percentages sum to 100%.
Abbreviations: IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis.

TABLE 2 Results from the national drug resistance survey in Tanzania, 2017–2018

Drug resistance ($n = 1168$)	New *n* (%)	Previously treated *n* (%)	All TB patients *n* (%)
Total	1060 (100)	108 (100)	1168 (100)
Any resistance			
H	12 (1.1)	5 (4.6)	17 (1.5)
R	10 (0.9)	7 (6.5)	17 (1.5)
E	2 (0.2)	1 (0.9)	3 (0.3)
S	5 (0.5)	1 (0.9)	6 (0.5)
Total any resistance	18 (1.7)	7 (6.5)	25 (2.1)
Mono-resistance			
H only	3 (0.3)	0	3 (0.3)
R only	1 (0.1)	2 (1.9)	3 (0.3)
E only	1 (0.1)	0	1 (0.1)
S only	4 (0.4)	0	4 (0.3)
Total mono-resistance	9 (0.8)	2 (1.9)	11 (1.0)
Multidrug resistance			
Any H + R (MDR)	9 (0.8)	5 (4.6)	14 (1.2)
H + R only	8 (0.7)	4 (3.7)	12 (1.0)
H + R + E only	0	0	0
H + R + S only	0	0	0
H + R + E + S	1 (0.1)	1 (0.9)	2 (0.2)

Abbreviation: TB, tuberculosis.

The resistance pattern to individual first-line drugs (FLD) shows highest resistance to H [any 17 (1.5%), mono 3 (0.3%)] and to R [any 17 (1.5%), mono 3 (0.3%)] followed by resistance to streptomycin (S) [any 6 (0.5%), mono 4 (0.3%)] and ethambutol (E) [any 3 (0.3%), mono 1 (0.1%)]. Eleven (1.0%) cases, including nine (0.8%) new and two (1.9%) previously treated had mono-resistance to at least one FLD. Mono-resistance to FLD among new TB patients was highest to S [4 (0.4%)] followed by H [3 (0.3%)]. In contrast, mono-resistance among the previously treated patients was only observed for R [2 (1.9%)]. Drug resistance to all FLDs was seen in one new and one previously treated patient. None of the isolates displayed poly-resistance (other than MDR) or XDR-TB (Table 2).

The socio-demographic characteristics of the 14 identified MDR-TB patients are shown in Table 3. Of the 14 MDR-TB patients, 9 (64.3%) were new and 5 (35.7%) were previously treated. Eight (57.1%) MDR-TB patients were males and six (42.9%) were females. The age of the MDR-TB patients ranged from 25 to 54 years. The proportion of HIV-positive cases among patients with MDR-TB was 14.3%.

The distribution of MDR-TB cases by region is shown in Table 4. Only 6 (29%) of all the 21 regions participated in the study had MDR-TB cases. Of the 14 MDR-TB cases, majority [8, (57.1%)] were from Dar es Salaam. Kilimanjaro had 4 (28.6%) cases, while Mbeya, Mtwara, Songwe and Unguja regions each had 1 (1.7%) case.

Estimated prevalence of MDR-TB in Tanzania

Logistic regression was used to account for missing data and sampling design effects on the estimates the prevalence of

TABLE 3 Characteristics of patients with multidrug resistance in the national drug resistance survey in Tanzania, 2017–2018

Characteristics	New *n* (%)	Previously treated *n* (%)	Total *n* (%)
Total # MDR-TB patients	9 (64.3)	5 (35.7)	14 (100)
Sex			
Male	4 (44.4)	4 (80.0)	8 (57.1)
Female	5 (55.6)	1 (20.0)	6 (42.9)
HIV			
Negative	8 (88.9)	4 (80.0)	12 (85.7)
Positive	1 (11.1)	1 (20.0)	2 (14.3)
Age group (years)			
0–14	0	0	0
15–24	0	0	0
25–34	6 (66.7)	2 (40.0)	8 (57.1)
35–44	2 (22.2)	0	2 (14.3)
45–54	0	3 (60.0)	3 (21.4)
55–64	0	0	0
65+	1 (11.1)	0	1 (7)
Contact with MDR-TB case			
No	7 (77.8)	2 (40.0)	9 (64.3)
Yes	0	0	0
Unknown	2 (22.2)	3 (60.0)	5 (35.7)
Alcohol			
No	6 (66.7)	1 (20.0)	7 (50.0)
Yes	2 (22.2)	2 (40.0)	4 (28.6)
Unknown	1 (11.1)	2 (40.0)	3 (21.4)
Smoking			
No	7 (77.8)	2 (40.0)	9 (64.3)
Yes	1 (11.1)	1 (20.0)	2 (14.3)
Unknown	1 (11.1)	2 (40.0)	3 (21.4)
Diabetes			
No	8 (88.9)	3 (60.0)	11 (78.6)
Yes	0	0	0
Unknown	1 (11.1)	2 (40.0)	3 (21.4)

Note: Numbers rounded to make the percentages sum to 100.0%.
Abbreviation: MDR-TB, multidrug-resistant tuberculosis.

MDR-TB and their standard errors. Missing laboratory results for 101 cases were imputed based on probability model of the complete data for age, gender, treatment history, rifampicin, isoniazid and MDR-TB. To address over/under-enrolment by facility, weights against notification data (total number of patients with positive smear per cluster compared with the enrolled patients) were included in the regression model. Different approaches (with imputation, without imputation, with weight and without weight) were used to estimate the prevalence of MDR-TB (Table 5).

After comparing the results from different methods, the results received without imputation of missing values were accepted as official DRS results in Tanzania, namely estimated prevalence of MDR-TB among new cases is 0.85% [95% confidence interval (CI): 0.4–1.3], among previously treated cases is 4.6% [95% CI: 1.1–8.2] and overall is 1.2% [95% CI: 0.6–1.8].

Factors associated with MDR-TB

The proportion of MDR-TB cases was higher among females (6, or 1.7%) than males (8, or 1.0%), but this association was not statistically significant ($p = 0.3$). In this study, the only risk factor found to be significantly associated with MDR-TB was history of previous TB treatment (odds ratio = 5.7, 95% CI: 1.9–17.2; $p = 0.002$) (Table 6). Due to the small number of MDR-TB cases, using multivariate logistic regression model to adjust for other factors was not possible.

DISCUSSION

The findings of the second nationwide anti-TB DRS in Tanzania demonstrate the presence of M. tb strains that are resistant to the commonly used first-line anti-TB drugs. The overall prevalence of MDR-TB was 1.2%, being higher among previously treated TB patients (4.6%) than new cases (0.8%). The proportion of survey participants with MDR-TB was higher among male than female TB patients. History of previous TB treatment was the only risk factor for MDR-TB in this study. According to the old WHO definition for XDR-TB, none of the cases were identified in the survey. It is of interest to note that most of the MDR-TB cases were new rather than previously treated patients, suggesting that primary transmission of MDR-TB strains takes place among newly infected patients. This suggestion was also confirmed geographically: the majority of new MDR-TB cases were localised in Dar es Salaam (5/9, 56%).

The current findings shows that there was no increase in MDR-TB rates compared to the previous survey conducted in 2006 [15]. This finding is in line with the WHO conclusion that the burden of MDR-TB or RR-TB as a share of the number of TB cases remains stable globally during a few pre-COVID years [23].

The estimate of the prevalence of MDR-TB in Tanzania is still among the lowest in the recently reported DRS conducted in other African countries and globally (3.3% among new cases) [17, 18]. None of the patients in this survey had any resistance to fluoroquinolones or second-line injectable TB drugs.

In low- and middle-income countries TB prevalence is significantly higher among men than women, with strong evidence that men are less forthcoming in seeking and/or accessing TB care in many settings [24–26]. In the current survey we report a slightly higher proportion of MDR-TB among female TB patients than among male TB patients, but this difference was not statistically significant. Similar

TABLE 4 Multidrug resistance in the national tuberculosis drug resistance survey in Tanzania by regions, 2017–2018

Region	New *n*	MDR *n* (%)	Previously treated *n*	MDR *n* (%)	Total *n*	MDR *n* (%)
Dar es Salaam	377	5 (1.3)	45	3 (6.7)	422	8 (1.9)
Kilimanjaro	65	1 (1.5)	9	3 (33.3)	74	2 (2.7)
Mbeya	29	1 (3.4)	0	0 (0)	29	1 (3.4)
Mtwara	59	0 (0)	3	1 (33.3)	62	1 (1.6)
Songwe	61	1 (1.6)	6	0 (0)	67	1 (1.5)
Unguja	38	1 (2.6)	4	0 (0)	42	1 (2.4)

Note: Only regions with at least one MDR-TB case were included.
Abbreviation: MDR-TB, multidrug-resistant tuberculosis.

TABLE 5 Estimated prevalence of MDR-TB in Tanzania

Method	New	Previously treated	All
Individual level no imputation			
Simple random sampling	0.85 [0.4–1.6]	4.6 [1.5–10.5]	1.2 [0.7–2.0]
Cluster design, no weights	0.85 [0.5–1.5]	4.6 [2.1–10.0]	1.2 [0.7–2.1]
LR: no weights, no clustering	0.85 [0.3–1.4]	4.6 [0.7–8.6]	1.2 [0.6–1.8]
LR: weights, no clustering	0.74 [0.2–1.2]		
Robust standard errors no weights	0.85 [0.4–1.3]	4.6 [1.1–8.2]	1.2 [0.6–1.8]
Robust standard errors and weights	0.74 [0.3–1.2]		
Individual level with imputation			
Robust standard errors no weights	1.1 [0.4–1.8]	5.0 [1.0–8.9]	1.4 [0.7–2.2]
Robust standard errors and weights	0.97 [0.2–1.7]		

Abbreviations: LR, likelihood ratio; MDR-TB, multidrug-resistant tuberculosis.

findings were observed from the first national drug-resistant survey conducted in Ukraine, where the proportion of MDR-TB was higher among female TB patients than among male TB patients and this difference was statistically significant [27].

Different factors, such as HIV, have been reported elsewhere [28–30] to be associated with MDR-TB. We also investigated possible risk factors such as alcohol, smoking, diabetes and HIV but none of these was found to be statistically significant. However, our findings of not identifying an association between HIV and MDR-TB were in line with those reported by Lukoye and others in Uganda [31] and elsewhere [32–34]. It is also important to note that in this survey the lack of statistically significant association between MDR-TB and HIV may be due to the small number of MDR patients. History of previous TB treatment was the only factor significantly associated with MDR-TB in Tanzania. While transmission of MDR-TB strains seems to be the most common mechanism of getting MDR-TB, none of the 57 survey participants who reported to be household contacts of an MDR-TB case had MDR-TB [13, 35]. On the other hand, household contact studies by Fox et al. [34] in Vietnam showed that under 2% of household contacts of a TB case developed TB disease. This corresponds with the findings reported by earlier studies that previous exposure to anti-TB treatment was the most common risk factor for MDR-TB [37]. We also speculate that if MDR-TB was missed at the first diagnosis, especially when diagnoses were done only via smear microscopy, patients were likely to fail on the first-line TB treatment.

Assessment of risk factors of MDR-TB should be conducted regionally to develop the most effective strategy for MDR-TB control in each country. Across all regions, previous TB disease and treatment are essential factors associated with MDR-TB, indicating necessity of timely diagnosis, appropriate treatment and thorough monitoring [38, 39].

Survey limitations

Several limitations during the study were encountered starting from prolonged specimen collection over the planned period of time due to different reasons such as lack of reagents along the way which meant losing some eligible clients. Some clusters repeated enrollment due to inconsistent enrolling and missing eligible patients. As such, 9% of all eligible individuals were not enrolled in the survey. However, despite this limitation, the survey results were consistent with the results from the previous survey in Tanzania [20] as well as with the results that have been reported in neighbouring countries [26, 27]. Due to the high prevalence of HIV in Tanzania, and the fact that individuals living with HIV/AIDS were more likely to have smear negative TB than those without HIV, inclusion of smear negative specimens

TABLE 6 Factors associated with MDR-TB

Risk factors	MDR *n* (%)	Non-MDR *n* (%)	OR	95% CI	*p* Value
Patient classification					
New	9 (0.8)	1051 (99.2)	Reference		
Previously treated	5 (4.6)	103 (95.4)	5.7	1.9–17.2	0.002
Sex					
Male	8 (1.0)	815 (99)	Reference		
Female	6 (1.7)	339 (98.3)	1.8	0.6–5.2	0.3
Age groups					
0–14	0 (0)	16 (100)	N/A		
15–24	0 (0)	198 (100)	N/A		
25–34	8 (2.5)	308 (97.5)	4.5	0.9–21.2	0.06
35–44	2 (0.6)	344 (99.4)	Reference		
45–54	3 (1.7)	171 (98.3)	3.0	0.5–18.2	0.2
55–64	0 (0)	67 (100)	N/A		
65+	1 (2.0)	50 (98)	3.4	0.3–38.6	0.3
Age groups					
0–34	8 (1.5)	522 (98.5)	Reference		
35+	6 (0.9)	632 (99.1)	0.6	0.2–1.8	0.4
Age groups					
0–44	10 (1.1)	866 (98.9)	Reference		
45+	4 (1.4)	288 (98.6)	1.2	0.4–3.9	0.8
HIV status					
Yes	2 (0.7)	282 (99.3)	0.5	0.1–3.2	0.4
No	12 (1.4)	872 (98.6)	Reference		
Alcohol use					
Yes	4 (1.6)	245 (98.4)	1.9	0.6–6.7	0.3
No	7 (0.8)	834 (99.2)	Reference		
Missing	3 (3.8)	75 (96.2)			
Ever smoked					
Yes	2 (1.0)	200 (99)	0.97	0.2–4.5	0.9
No	9 (1.0)	870 (99)	Reference		
Missing	3 (3.4)	84 (96.6)			
Diabetes mellitus					
Yes	0 (0)	16 (100)	N/A		
No	11 (1.0)	1058 (99)			
Missing	3 (3.6)	80 (96.4)			
Contact with MDR-TB case					
Yes	0 (0)	57 (100)	N/A		
No	9 (1.0)	910 (99)			
Missing	5 (2.6)	187 (97.4)			

Note: Tanzania national anti-tuberculosis drug resistance survey, 2017–2018.
Abbreviations: CI, confidence interval; MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio.

and the use of molecular techniques could be considered for future survey [36, 37]. There may have been misclassification bias due to reporting/transcription errors of previous TB history of enrolled patients. Nevertheless, efforts to minimise this bias were undertaken by including additional questions regarding previous TB history and checking the history of previous TB treatment in hospital TB registers.

In addition, there were some laboratory challenges including storage of specimens and delays in shipping of specimens from the facilities to CTRL leading to loss of viability of possible drug-resistant strains in the specimens [24]. Despite these challenges, external quality assessment of DST of the isolates demonstrated consistency with the survey results.

CONCLUSION

The second TB DRS in Tanzania confirmed that the burden of MDR-TB in the country was relatively low. The findings show no evidence of XDR. Given the overall small number of MDR-TB cases in this survey, efforts should be aimed at improving case detection by including universal DST ensuring that all patients with presumptive DR-TB have access to DST for all anti-TB medicines, timely initiation of treatment and enhancing measures to prevent transmission of the disease to assure that levels of TB drug resistance remain low.

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APPENDIX A: LIST OF CLUSTERS FOR ANTI-TB DRUG RESISTANCE SURVEY; 2016–2017

Region	District	Name of diagnostic Centre	Cluster #
Arusha	Karatu District Council	Karatu Health Centre	11
Arusha	Arusha City East	Mount Meru Hospital	26
Arusha	Arusha City West	Levolosi Health Centre	16
Dar es Salaam	Dar Ilala I	Chanika Dispensary	5
Dar es Salaam	Dar Ilala I	Buguruni Health Centre	3
Dar es Salaam	Dar Ilala I	Kiwalani Dispensary	15
Dar es Salaam	Dar Kinondoni	Kimara Dispensary	14
Dar es Salaam	Dar Ilala I	Ukonga Dispensary	44
Dar es Salaam	Dar Ilala II	Infectious Disease Clinic (IDC)	8
Dar es Salaam	Dar Kinondoni	Gati Dispensary	7
Dar es Salaam	Temeke TB/LP Region	Kigamboni Health Centre	13
Dar es Salaam	Dar Ilala I	Amana Hospital	1
Dar es Salaam	Dar Kinondoni	Sinza Hospital	38
Dar es Salaam	Dar Kinondoni	Magomeni Health Centre	18
Dar es Salaam	Temeke TB/LP Region	Rangitatu Hospital	35
Dar es Salaam	Dar Kinondoni	Mwananyamala Hospital	29
Dodoma	Dodoma Municipal Council	DDRRH	6
Geita	Geita District Council	Nyarugusu Dispensary	34
Iringa	Kilolo District Council	Ilula Hospital	9
Kagera	Bukoba Municipal Council	Buyekela Dispensary	4
		Kashai[a] Dispensary	4
Kagera	Missenyi District Council	Mugana District Designated Hospital (DDH)	27
Kagera	Kyerwa District Council	Nkwenda Health Centre	32
Kilimanjaro	Same District Council	Same Designated Hospital	36
Kilimanjaro	Moshi Municipal Council	Mawenzi Referral Hospital	21
Manyara	Simanjiro District Council	Mererani Health Centre	23

(Continues)

Region	District	Name of diagnostic Centre	Cluster #
Mara	Rorya District Council	Barak Health Centre	2
		Shirati Hospital[a]	2
Mara	Tarime Town Council	Tarime Hospital	42
Mbeya	Mbozi District Council	Mbozi Mission Hospital	22
Mbeya	Rungwe District Council	Tukuyu District Hospital	43
Mbeya	Mbozi District Council	Vwawa District Hospital	45
		Mlowo Dispensary[a]	45
Morogoro	Ulanga District Council	Lugala Hospital	17
Mtwara	Mtwara District Council	Nanguruwe Health Centre	30
Mtwara	Newala District Council	Newala Hospital	31
Mtwara	Tandahimba Dist. Council	Tandahimba Hospital	41
Mwanza	Kwimba District Council	Mwamashimba Hospital	28
Mwanza	Mwanza Urban North	S'Toure Hospital	40
Njombe	Makambako Town Council	Makambako Hospital	19
Pemba	South Pemba	Abdalla Mzee Hospital	34
	North Pemba	Wete Hospital[a]	34
Pwani	Kibiti District Council	Kibiti Hospital	12
Pwani	Mkuranga District Council	Mkuranga Hospital	24
Ruvuma	Songea Municipal Council	Songea Regional Hospital	39
Shinyanga	Shinyanga Municipal Council	Shinyanga Regional Hospital	37
Shinyanga	Kahama Town Council	Kahama Hospital (Government)	10
Tanga	Mkinga District Council	Maramba Health Centre	20
Unguja	Town and West	Mnazi Mmoja Hospital	25

[a] Complementary health facility.