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National anti-tuberculosis drug resistance study in Tanzania

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SUMMARY

OBJECTIVE: To assess the prevalence of anti-tuberculosis drug resistance in a national representative sample of tuberculosis (TB) patients in Tanzania according to recommended methodology.

DESIGN: Cluster survey, with 40 clusters sampled proportional to size, of notified TB patients from all diagnostic centres in the country.

RESULTS: The survey enrolled 1019 new and 148 retreatment patients. The adjusted prevalence of *Mycobacterium tuberculosis* strains resistant to any of the four first-line drugs in new patients was 8.3%, while the prevalence of multidrug-resistant TB (MDR-TB) was 1.1%. In retreatment patients, the crude prevalence for any resistance and for MDR-TB was respectively 20.6% and 3.9%. The prevalence of drug resistance did not differ in relapse patients compared to failure patients. These estimates are among the lowest in those African countries with an estimated level of drug resistance in the last 5 years.

CONCLUSION: The low levels of drug resistance in Tanzania are likely due to a well performing TB control programme and the absence of noticeable involvement of the private sector in TB treatment.

KEY WORDS: tuberculosis; drug resistance; survey; MDR; 8-month regimen

MULTIDRUG-RESISTANT tuberculosis (MDR-TB) is defined as tuberculosis (TB) resistant to at least isoniazid (INH) and rifampicin (RMP). In 2006, nearly 500 000 new MDR-TB patients were estimated worldwide.[1] Treatment of these patients is feasible but substantially more costly than treating patients with fully susceptible *Mycobacterium tuberculosis* strains.[2] The Working Group on MDR-TB of the Stop TB Partnership developed a response plan to address the growing prevalence of MDR-TB,[3] in which countries are advised to perform drug resistance surveys to be able to provide insight in the magnitude of the resistance problem.

Information on anti-tuberculosis drug resistance levels is an essential management tool for evaluating the performance of national TB control programmes (NTPs).[4] Resistance in previously treated patients is an indicator of current treatment practices in the community. Drug resistance in previously untreated (new) patients reflects transmission of disease with resistant bacilli, and indicates the difficulties that NTPs will encounter when administering chemotherapy.

Tanzania is among the 22 high TB burden countries, with an estimated incidence (all forms) in 2007 of 297 per 100 000 population.[5] Information on anti-tuberculosis drug resistance comes from selected settings and studies.[6–9] These studies, together with data from routine testing by the Central Tuberculosis Reference Laboratory (CTRL), showed low levels of drug resistance and an estimated prevalence of MDR-TB of 1% among new TB patients.[10]

In 2006, a 6-month regimen with RMP throughout was introduced in Tanzania. Before then, RMP was never used for more than the initial 2 months in treatment regimens for new TB cases. The conventional short duration of RMP use was seen as one of the reasons for the low rates of acquired drug resistance in Tanzania.[11] In contrast, recent meta-analyses have attributed the development of drug resistance to the use of RMP for less than 4 months.[12,13]

Previous estimates of drug resistance in Tanzania have limited validity, as samples were not from a representative sample of TB patients and the surveys were not in accordance with current recommended methodology.[14] The only national surveys on drug resistance were carried out before or just after the introduction of the current TB control strategies and cannot serve as a basis for current treatment policies.[15–17] For this reason, the National TB & Leprosy Programme (NTLP) of Tanzania implemented a drug resistance survey (DRS) in a national representative sample of TB patients,

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with the objective of obtaining valid and representative data on anti-tuberculosis drug resistance.[18] Given its timing, it also provides much needed information on the prevalence of drug resistance in a treatment regimen with only 2 months of RMP.

STUDY POPULATION AND METHODS

The DRS was implemented in 40 diagnostic centres sampled proportional to size of the number of new smear-positive cases in 2004 from all diagnostic centres in the country. Each cluster was required to enrol 30 new smear-positive TB patients. During the enrolment period, the centres were required to include all retreatment patients. The enrolment period closed after 14 months.

All new sputum-positive patients diagnosed during the enrolment period were eligible to enter the study. Smear positivity was defined as at least two of three sputum samples showing acid-fast bacilli on Ziehl-Neelsen microscopy. A new patient was defined as a patient who had not received TB treatment for >1 month in the past. There were no restrictions on inclusion regarding age or clinical symptoms.

All enrolled patients provided a new morning specimen, which was sent to CTRL. If the expected transit time was >4 days (denoted a 'far cluster'), an additional morning specimen was collected with cetylpyridinium-chloride (CPC) for preservation.[19,20] This specimen was only used in the analyses if the specimen without CPC did not yield a positive culture or interpretable resistance results. Specimens with CPC were kept at ambient temperature to avoid crystallisation, while the others were refrigerated until transport.

At CTRL, the samples were decontaminated by modified Petroff's method unless pre-treated with CPC. The concentrated deposits were cultured onto slopes of Löwenstein-Jensen medium and incubated at 37°C for up to 8 weeks. Identified contamination was removed by sub-culturing the specimen. All positive culture slopes were assessed for *M. tuberculosis* by growth rate, acid fastness, colony morphology, pigment production, growth on 500 μg/ml ρ-nitrobenzoic acid, and sensitivity or resistance to thiophen 2-carboxylic acid hydrazide (TCH 2 mg/ml).

The drug concentrations used for drug susceptibility testing (DST) were 0.2 μg/ml and 1.0 μg/ml for INH, 40 μg/ml for RMP, 5 μg/ml for dihydrostreptomycin sulphate and 2 μg/ml for ethambutol (EMB). The slopes were read after incubation at 37°C for 6 weeks. The results were considered to be resistant if 1% or more of the colonies were growing compared to the drug-free controls.[21]

Before the survey, laboratory staff adequately completed proficiency testing for culture and sensitivity procedures through the Supranational Reference Laboratory (SRL) in Antwerp, Belgium. All retreatment patient strains were sent to the SRL for external quality assessment (EQA), together with all strains from new patients showing any resistance and the next registered fully susceptible strain. In case of discordance the original CTRL result was replaced by the SRL result, and only the latter was considered for this report.

Ten per cent of the data collection forms were checked manually for data entry mistakes in primary variables. Based on these findings, we programmed internal consistency checks. Errors were checked against the forms.

The primary outcome was the proportion of patients with drug resistance stratified by treatment history. To account for differential inclusion between the clusters, probability weights were calculated for the new patients in an adjusted analysis. As there was no projected sample size for retreatment patients, all weights for these patients were set to 1.

Statistical analyses were performed in Stata version 10.0 (Stata Corp, College Station, TX, USA). *P* values were derived from χ^2 tests or Kruskal-Wallis tests, where appropriate.

The sample size was based on the need to detect a statistically significant difference of 1% with the previous estimate of 1% MDR-TB among newly diagnosed smear-positive patients. For this, 374 new smear-positive patients were needed. This increased to 900 to accommodate a design effect of 2 and an anticipated loss of 20% of the samples. The final sample size was increased to 1200 to obtain smaller confidence intervals (CIs) around the prevalence estimate for specific areas and subgroups.

The study was approved by the Ethical Review Board of the National Institute for Medical Research, Tanzania. All patients gave verbal informed consent to participate in the study.

RESULTS

Enrolment took place from July 2006 to August 2007. A total of 1167 patients were included, of whom 1019 were new (Figure).

All but one of the 1019 new patients had a specimen cultured; of these, 73 (7.2%) were negative and 15 (1.5%) were contaminated. All specimens from retreatment patients were cultured, of which 20 (13.5%) were negative and none were contaminated. The overall culture contamination rate was 1.3%.

Of the 930 positive cultures from new patients, 21 (2.3%) had no DST result due to no growth in the control slope ($n = 4$), or an irreversibly contaminated primary slope (PSIC; $n = 17$). For retreatment patients, all but one of the 128 cultures provided information on susceptibility. There were no statistically significant differences between patients who had a DST result and those who did not with respect to sex (62.4% male vs. 64.9%), age (median 34.0 vs. 34.5 years) and the proportion of new patients (87.7% vs. 84.0%).

In new patients, the prevalence of resistance to at least one drug was 8.3% (95%CI 6.5–10.2; Table 1). The prevalence of monoresistance to INH was 3.7% (95%CI 2.6–5.2), and to RMP it was 0.1% (95%CI 0.003–0.6). MDR-TB was found in 1.2% (95%CI

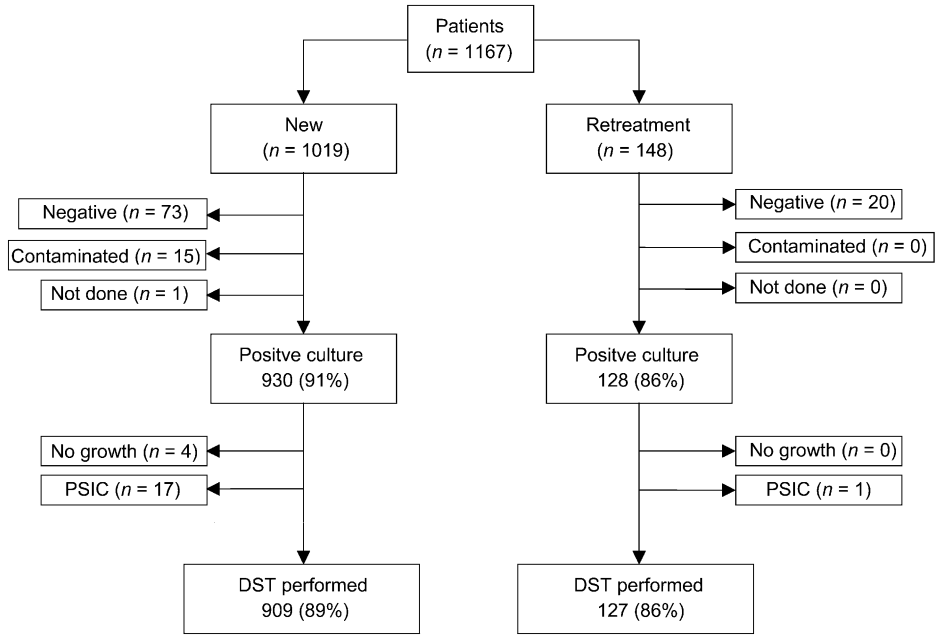

Figure Patient disposition. PSIC = irreversibly contaminated primary slope.

0.6–2.2) of the new patients. Applying the weights for non-inclusion did not substantially change the prevalence estimates for any resistance (8.3%, 95%CI 6.2–11.0) or MDR-TB (1.1%, 95%CI 0.6–2.0).

Of the 148 retreatment patients, 94 (64%) were relapse and 28 (19%) were failure patients. Of the remaining 26 (17%) retreatment patients, the previous outcome was not known.

In retreatment patients, the prevalence of resistance to at least one drug was 20.6% (95%CI 13.8–28.5). The prevalence of monoresistance to INH was 8.7% (95%CI 4.4–15.0), and to RMP it was 0.8% (95%CI 0.2–4.4). MDR-TB was found in 3.9% (95%CI 1.3–8.9) of the retreatment patients. The prevalence of any drug resistance did not differ in relapse (20.3%) or failure patients (20.8%). Of the five MDR-TB cases among retreatment patients, four were relapse patients (5.1%) and one (4.2%) a failure patient.

Table 1 Sensitivity results (unadjusted for study design)

	New patients *n* (%)	Retreatment patients			
		Relapse *n* (%)	Failures *n* (%)	Unknown *n* (%)	Total *n* (%)
Patients	1019	94	28	26	148
Positive cultures	930 (91.3)	79 (84.0)	25 (89.3)	25 (96.2)	128 (86.5)
DST result	909 (89.2)	79 (84.0)	24 (85.7)	24 (92.3)	127 (85.8)
Any resistance	75 (8.3)	16 (20.3)	5 (20.8)	5 (20.8)	26 (20.6)
H	58 (6.3)	15 (19.0)	5 (20.8)	3 (13.0)	23 (18.1)
R	12 (1.3)	4 (5.1)	1 (4.2)	1 (4.2)	6 (4.7)
S	35 (3.9)	6 (7.6)	1 (4.2)	2 (8.3)	9 (7.1)
E	15 (1.7)	7 (8.9)	2 (8.3)	0	9 (7.1)
Monoresistance	50 (5.5)	7 (8.9)	3 (13.0)	4 (16.7)	14 (11.0)
H	34 (3.7)	6 (7.6)	3 (13.0)	2 (8.3)	11 (8.7)
R	1 (0.1)	0	0	1 (4.2)	1 (0.8)
S	13 (1.4)	1 (1.3)	0	1 (4.2)	2 (1.6)
E	2 (0.2)	0	0	0	0
Polyresistance not MDR-TB	14 (1.5)	5 (6.2)	1 (4.2)	1 (4.2)	7 (5.5)
HS	10 (1.1)	1 (1.3)	0	1 (4.2)	2 (1.6)
HE	2 (0.2)	4 (5.1)	1 (4.2)	0	5 (3.9)
SE	1 (0.1)	0	0	0	0
HSE	1 (0.1)	0	0	0	0
Multidrug resistance	11 (1.2)	4 (5.1)	1 (4.2)	0	5 (3.9)
HR	1 (0.1)	0	0	0	0
HRS	1 (0.1)	1 (1.3)	0	0	1 (0.8)
HRE	0	0	0	0	0
HRSE	9 (0.9)	3 (3.8)	1 (4.2)	0	4 (3.1)

DST = drug susceptibility testing; H = isoniazid; R = rifampicin; S = streptomycin; E = ethambutol; MDR-TB = multidrug-resistant tuberculosis.

Table 2 Characteristics of the MDR-TB patients

	Sex	Age, years	History	Previous outcome	Times treated	Resistance
1	Female	40	Retreatment	Cure	Unknown	HRSE
2	Male	42	Retreatment	Failure	Unknown	HRSE
3	Male	35	Retreatment	Cure	Once	HRSE
4	Male	52	Retreatment	Cure	Once	HRSE
5	Male	56	Retreatment	Cure	Once	HRS
6	Unknown	Unknown	New	—	—	HRSE
7	Female	18	New	—	—	HRSE
8	Female	18	New	—	—	HRSE
9	Female	26	New	—	—	HRSE
10	Female	19	New	—	—	HRS
11	Male	30	New	—	—	HRSE
12	Male	30	New	—	—	HRSE
13	Male	34	New	—	—	HRSE
14	Male	36	New	—	—	HRSE
15	Male	40	New	—	—	HRSE
16	Male	45	New	—	—	HR

MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; S = streptomycin; E = ethambutol.

The 16 MDR-TB patients (Table 2) identified in the survey did not differ from those patients with a fully susceptible *M. tuberculosis* strain with respect to sex (31.3% vs. 38.1% females) and age (median 35 vs. 34 years). All MDR-TB patients were from an urban setting.

EQA at the SRL was performed on 271 of 362 strains sent to the SRL; the 91 other strains were lost to contamination ($n = 56$), remained negative in subculture ($n = 20$) or represented other mycobacteria or mixtures thereof with *M. tuberculosis* ($n = 15$). Accuracy (the proportion of strains with an adequate result at CTRL) reached over 95% for INH, RMP and EMB, and 90% for streptomycin (SM; Table 3). The sensitivity in detecting resistance to RMP or EMB reached only 50%, and was 70% for SM.

The RMP resistance missed by the CTRL comprised mainly retreatment strains, all of which were included in the rechecking sample. Non-identified missed RMP resistance was therefore only possible for strains from new patients, as only a limited number of initial susceptible strains were selected for EQA in this group. Among the 190 CTRL RMP-susceptible strains from new cases, only two were false-susceptible for RMP, of which one was also INH-resistant.

DISCUSSION

The adjusted prevalence of *M. tuberculosis* strains resistant to any of the four first-line drugs in new patients was 8.3%, while the prevalence of MDR-TB was 1.1%. In retreatment patients, the crude prevalence for any resistance was 20.6%, and for MDR-TB it was 3.9%. Taking both sensitivity and specificity for detecting RMP resistance into account shows that the prevalence of MDR-TB in new cases might be 1.4%. Settings with an MDR-TB prevalence among new patients below 3% are generally assumed to have a low MDR-TB burden.

Table 3 Test characteristics of DST at CTRL

	Isoniazid	Rifampicin	Streptomycin	Ethambutol
Accuracy, %	95.6	98.3	90.0	97.2
Sensitivity, %	89.8	50.0	69.0	50.0
Specificity, %	97.1	99.6	92.3	98.6

DST = drug susceptibility testing; CTRL = Central Tuberculosis Reference Laboratory.

Given the timing of the survey in relation to the introduction of the 6-month treatment regimen, the results can be interpreted as being obtained with regimens containing RMP for 2 months only. The low level of acquired drug resistance is contrary to the results of meta-analyses that indicate an increased risk for drug resistance with shorter duration of RMP use.[12,13] If the shorter use of RMP leads to more drug resistance, and consequently to a higher failure rate, this should be reflected in the level of drug resistance in failure patients. In the current survey, there are no obvious differences in the prevalence of drug resistance between relapse and failure patients. This either means that there are settings where the findings of the meta-analyses do not apply (there was a high heterogeneity level), or that findings in Tanzania should be attributed to other factors, such as widespread non-adherence in failure patients.

In addition to Tanzania, only five other African countries have reported drug resistance estimates in the last 5 years.[1] Prevalence of any resistance in new patients ranged from 6.3% to 26.9%; MDR-TB estimates in new patients ranged from 0.5% to 3.9%. In retreatment patients, the prevalence of any resistance ranged from 11.8% to 48.7%; MDR-TB estimates in retreatment patients ranged from 3.9% to 16.7%. Estimates for Tanzania ranked next to lowest for any of these comparisons. Direct comparisons between countries should be made with caution because of the different settings and methods and differences in human immunodeficiency virus (HIV) prevalence. Accumulating evidence shows a positive relationship between HIV and drug resistance.[1]

Several limitations of the survey should be

acknowledged. First, it took a long time to perform all DSTs.[18] This made rechecking at the SRL difficult, with high failure rates due to contamination or non-viable strains. Second, 131/1167 (11.2%) enrolled patients did not have a DST result. The main reason for this was a negative culture at CTRL which could have occurred due to the long transport time, use of CPC or harsh decontamination. The overall median transport time was 5 days and did not differ markedly between the clusters defined as far and close. The culture yield was high and similar for specimens with and without CPC. The contamination rate of 5% was not too low. Another possibility could be inadequate peripheral microscopy performance. Studies in Tanzania showed that peripheral smear microscopy has problems more frequently in false-negative slides than false-positive slides, making false-positive specimens and consequently negative cultures unlikely. To the extent that the aforementioned factors did lead to selection bias, we controlled this by applying sampling weights in the analysis. However, a combination of these factors could have caused bias in identifying resistant strains, leading to an underreporting of drug resistance with an unknown magnitude.

Third, there is no information on the HIV status of the patients enrolled. At the time of the study, HIV testing of TB patients was not rolled out to an adequate scale; inclusion of this procedure was therefore deemed not feasible at the time. Future drug resistance surveys should have a design that enables stratified analysis by HIV status.

The implementation of the survey showed that laboratory capacity for culture and DST in Tanzania is limited. The survey overburdened the CTRL, which may have been the reason why the accuracy, and particularly the sensitivity, of DST at the CTRL was far lower than that obtained in proficiency testing before the survey. The NTLP has designated a hospital with ample laboratory facilities for monitoring the treatment of MDR-TB patients, which requires strong emphasis on capacity building within the laboratory setup, including the performance of DST for second-line drugs.

Rapid molecular diagnostic testing for identification of possible MDR-TB patients are currently available.[22,23] The sensitivity and specificity of these tests are consistently high, especially for detecting RMP resistance.[24] A new generation of the test includes a less common mutation associated with INH resistance, which increases the sensitivity of the test.[25,26] Rapid diagnosis of (at least) RMP resistance avoids prolonged, unnecessary treatment with standard first-line regimens that are not effective given the resistance pattern at the start of treatment. The NTLP is embarking on the implementation of these tests in routine testing of sputum samples from retreatment patients. There is a need to scale up routine testing and the implementation of molecular techniques now that the NTLP has changed its first-line regimen to include RMP for the full 6 months of treatment; at the same time the possibility of treatment observation outside the health facility needs to be introduced.[27]

CONCLUSION

The DRS identified a low level of anti-tuberculosis drug resistance in Tanzania, in keeping with a well-functioning TB control programme and the absence of significant involvement of the private sector in TB treatment. These estimates can serve as a baseline for improved routine testing of retreatment patients. Introduction of molecular techniques would greatly enhance the feasibility and effectiveness of routine testing.

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RÉSUMÉ

OBJECTIF : Evaluer la prévalence de la résistance aux médicaments antituberculeux dans un échantillon national représentatif de patients tuberculeux (TB) en Tanzanie en respectant la méthodologie recommandée.
SCHÉMA : Enquête par grappes où 40 grappes ont été échantillonnées en proportion du nombre de patients déclarés comme TB provenant de tous les centres de diagnostic du pays.
RÉSULTATS : Dans l'enquête, 1019 nouveaux cas et 138 cas de retraitement ont été enrôlés. La prévalence ajustée des souches de *Mycobacterium tuberculosis* résistantes à l'égard de n'importe lequel des quatre médicaments de première ligne est de 8,3% dans les nouveaux cas et la prévalence de TB-MDR de 1,1%. Dans les cas de retraitement, la prévalence brute de n'importe quelle résistance est de 20,6% et celle de la TB-MDR de 3,9%. La prévalence de la résistance aux médicaments n'est pas différente dans les cas de rechute par rapport aux cas d'échec. Les estimations sont parmi les plus faibles des pays africains où l'on dispose d'une estimation de la résistance aux médicaments au cours des 5 dernières années.
CONCLUSION : En Tanzanie, les faibles niveaux de résistance aux médicaments sont probablement dus à la bonne performance du programme de lutte contre la tuberculose et à l'absence d'implication du secteur privé dans le traitement de la TB.

RESUMEN

OBJETIVO: Evaluar la prevalencia de resistencia a los medicamentos antituberculosos en una muestra nacional representativa de pacientes tuberculosos en Tanzania, mediante un estudio realizado en conformidad con los métodos recomendados actualmente.
MÉTODO: Se llevó a cabo un estudio de 40 conglomerados de pacientes tuberculosos provenientes de todos los centros diagnósticos del país, con un muestreo proporcional al tamaño de la población.
RESULTADOS: Se incorporaron al estudio 1019 pacientes nuevos y 148 pacientes en retratamiento. La prevalencia ajustada de cepas de *Mycobacterium tuberculosis* resistentes a alguno de los medicamentos de primera línea en los pacientes nuevos fue 8,3%, comparada con una prevalencia de 1,1% de TB multidrogorresistente (TB-MDR). En los pacientes en retratamiento, la prevalencia bruta de alguna resistencia fue 20,6% y la prevalencia de TB-MDR fue 3,9%. No se observó diferencia en la prevalencia de farmacorresistencia entre los pacientes en recaída o en fracaso terapéutico. Estas cifras se encuentran entre las más bajas de los países africanos que cuentan con un cálculo de resistencia en los últimos 5 años.
CONCLUSIÓN: La baja tasa de farmacorresistencia en Tanzania se debe muy probablemente al buen desempeño del programa de control de la TB y a la escasa influencia del sector privado en el tratamiento de la TB.