INT J TUBERC LUNG DIS 11(2):189–194

Results of a national survey on drug resistance among pulmonary tuberculosis patients in Rwanda

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SUMMARY

BACKGROUND: One of the principal objectives of tuberculosis (TB) control is to minimise the emergence of drug resistance. The first national survey was conducted in Rwanda to determine the prevalence of *M. tuberculosis* drug resistance.

METHODS: Sputum samples were collected from all new and retreatment cases in the health districts from November 2004 to February 2005. Drug susceptibility testing of isolates against first-line drugs was performed by the proportion method.

RESULTS: Of 616 strains from new cases, 6.2% were resistant to isoniazid, 3.9% to rifampicin and 3.9% were multidrug-resistant TB. Among 85 strains from previously treated cases, the prevalence of resistance was respectively 10.6%, 10.6% and 9.4% (MDR-TB strains). Eight MDR cases showed additional resistance to ethambutol and streptomycin.

CONCLUSION: The level of MDR-TB among TB patients in Rwanda is high. The main reasons of this emergence of MDR-TB can be attributed to the disorganisation of the health system, migration of the population during the 1994 civil war and poor success rates, with a high number of patients transferred out and lost to follow-up. On the other hand, the use of treatment regimens administered twice weekly during the continuation phase could be another important factor and merit further investigations.

KEY WORDS: national survey; primary resistance; acquired resistance; tuberculosis; Rwanda

IN RWANDA, tuberculosis (TB) is one of the leading causes of mortality and morbidity.[1,2] In 2003, the annual incidence of new sputum smear-positive cases was estimated to be 161 per 100 000 population and the prevalence of all types was 664/100 000.[2]

The TB incidence in Rwanda, all forms notified, doubled from 40/100 000 in 1991 to 89/100 000 in 2005, mainly due to the impact of the human immunodeficiency virus (HIV) epidemic.[1]

One of the main strategies in TB control is adequate treatment of all detected cases. However, resistance to the available drugs is jeopardising the treatment of TB in some settings.[3] The problem is spreading at a faster rate in areas where an effective TB control programme is not in place.[4,5]

The present study is the first national drug resistance survey performed in Rwanda according to the protocol recommended by the World Health Organization (WHO)/International Union Against Tuberculosis and Lung Disease (The Union).[6] The aim of the study was to report on the prevalence and patterns of first-line anti-tuberculosis drug resistance among *Mycobacterium tuberculosis* isolates from new (primary resistance) and previously treated cases (acquired resistance).

MATERIALS AND METHODS

Study area and population

The National Tuberculosis Control Programme (NTP) of Rwanda was created in 1990 and has applied the DOTS strategy since the beginning. However, the national technical manual has been revised regularly.[7] After the 1994 civil war, which disorganised the health system completely, the NTP expanded progressively to reach full DOTS coverage in 2000. The current treatment regimen is $2RHZE/4R_3H_3$* for new smear-

* R, RMP = rifampicin; H, INH = isoniazid; Z, PZA = pyrazinamide; E, EMB = ethambutol; S, SM = streptomycin. Numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the number of times the drug is taken each week.

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Article submitted 3 August 2006. Final version accepted 28 September 2006.

positive cases and 2RHZES/1RHZE/5$R_3H_3E_3$ for retreatment cases.[7]

The required sample size was determined at 633 based on the number of new sputum smear-positive TB cases notified in 2002 through the NTP (n = 3956), on a 95% confidence interval and 1% precision, and on an expected multidrug resistance (MDR) prevalence of 2%. Adding 20% for loss, breakage and contamination of cultures, the final size was 760 new smear-positive cases.

Sputum smear-positive pulmonary TB cases registered during the period of the study (November 2004–February 2005) were eligible for inclusion. A detailed questionnaire comprising demographic and clinical information was developed to assist health care workers to accurately classify patients as new or retreatment cases. Before the start of the survey, brief training was given to all the personnel involved. A national coordinating team was set up, including amongst others the NTP coordinator, the Director of the National Reference Laboratory (NRL) and an epidemiologist from the School of Public Health at the National University of Butare.

Isolation of M. tuberculosis

All sputum samples were mixed with 1% cetylpyridinium chloride (CPC) as transportation medium, stored at ambient temperature, collected on a weekly basis from the health districts and transported to the NRL. Every sputum sample was accompanied by a shipment form that contained information on the date of sputum collection, the sample identification number, the type of case and the quantified result of microscopy examinations. At the NRL, each sample was cultured on Löwenstein-Jensen (LJ) medium after decontamination using the Petroff method.[8] Cultures were incubated at 37°C and read weekly for growth for a maximal duration of 10 weeks. Primary *M. tuberculosis* isolates were sent to the Mycobacteriology Unit at the Institute of Tropical Medicine (ITM, Antwerp, Belgium) for species identification and drug susceptibility testing (DST).

Identification and DST

The isolates were identified by microscopy, growth rate and temperature, colony morphology and niacin production.[9–11] DST was performed on all *M. tuberculosis* isolates against INH (0.2 μg/ml), RMP (40 μg/ml), SM (4 μg/ml) and EMB (2 μg/ml) using the proportion method on LJ medium.[11]

Definition of drug resistance

Classification of patients in new or previously treated cases followed WHO/Union definitions based on history taking.[6] Primary resistance is defined as the presence of resistance to one or more anti-tuberculosis drugs in strains obtained from patients who have never received treatment or who have been treated for less than 1 month (new cases). Acquired resistance is defined as resistance to one or more anti-tuberculosis drugs in patients who have previously received anti-tuberculosis treatment for at least 1 month. MDR-TB was defined as resistance to at least INH and RMP, the two most potent drugs and the mainstay of anti-tuberculosis treatment.[6]

Records of new patients harbouring strains resistant to any drug tested were checked again upon receipt of the results, with reclassification whenever indicated.

Statistical analysis

During the inclusion period, data were double entered on a weekly basis using SPSS 11.5 (SPSS, Inc, Chicago, IL, USA) by two different people to ensure accuracy. These data were later linked to the DST results from Antwerp. Both data sets were compared using Epi Info (version 6.04d, Centers for Disease Control and Prevention, Atlanta, GA, USA), and cleaned by verifying the paper-based questionnaires, sample transportation forms and DST results.

RESULTS

Patient demography

During the 4-month study period, 892 samples were transferred to the NRL. Of those enrolled, 132 (14.8%) remained culture-negative or were contaminated.

A total of 760 isolates were sent to the ITM. Upon receipt and subsequent culturing, 56 could not be used for DST: 31 (4.1%) were contaminated and 25 (3.3%) failed to grow. Another three isolates were identified as non-tuberculous mycobacteria (two *M. avium* and one *M. sp*). DST results were thus available for 701 *M. tuberculosis* isolates recovered from the same number of patients, of which 616 (87.9%) were new cases and 85 (12.1%) retreatment cases. A total of 452 (65.9%) patients were males and 234 (34.1%) females, giving a sex ratio of 1.9:1. The mean age of the patients was 34.2 years (range 3–82) (Table 1). The number of patients from urban (424, 60.6%) and rural (276, 39.4%) areas reflects the number of declared cases regularly registered with the NTP (data not shown). The provincial distribution of investigated cases is shown in Figure 1. Combined results for the 701 strains showed 88% pan-susceptible, 12% with any resistance and 4.6% MDR (Table 2).

Drug resistance among new cases

Of the 616 new cases, 65 (10.6%) showed any resistance to the four drugs tested (Table 2). Monoresistance was observed in 34 cases (5.5%), non-MDR polyresistance in seven cases (1.1%) and 24 (3.9%) new patients were MDR. Most (21/24) of these MDR-TB cases were resistant to all four drugs tested. Any resistance among new cases to each of the drugs was 7.5% for SM, 6.3% for INH, 5.2% for EMB and 3.9% for RMP.

Table 1 Characteristics of patients enrolled in the study

Patient characteristics	*n* (%)
Sex	
Male	452 (64.5)
Female	234 (33.4)
Unknown	15 (2.1)
Age group, years	
0–14	12 (1.7)
15–24	159 (22.7)
25–34	221 (31.5)
35–44	144 (20.5)
45–54	93 (13.3)
55–64	14 (6.1)
⩾65	43 (2.0)
Unknown	15 (2.1)
Origin of patient	
Urban	424 (60.5)
Rural	276 (39.4)
Unknown	1 (0.1)
Treatment history	
New cases	616 (87.9)
Retreatment	85 (12.1)

Drug resistance among previously treated cases

The patterns of acquired resistance to *M. tuberculosis* are shown in Tables 2 and 3. In total, 66 (77.7%) of the 85 previously treated cases were susceptible to all drugs and 19 (22.4%) were resistant to one or more drugs. Ten patients (11.8%) excreted bacilli resistant to a single drug, one (1.2%) was polyresistant (H+S) and 8 (9.4%) were found to be MDR-TB and resistant to all four drugs.

Among the 85 retreated cases, two of the five defaulters were pan-susceptible, whereas all (5/5) failure cases were MDR-TB (Table 3). The pattern among the relapse strains resembled that of the new cases: 64 (85.3%) remained fully susceptible, and only two (2.7%) were MDR-TB.

In general, the proportion of MDR-TB among the previously treated cases (9.4%) was significantly higher ($P = 0.002$) than among the new cases (3. 9%).

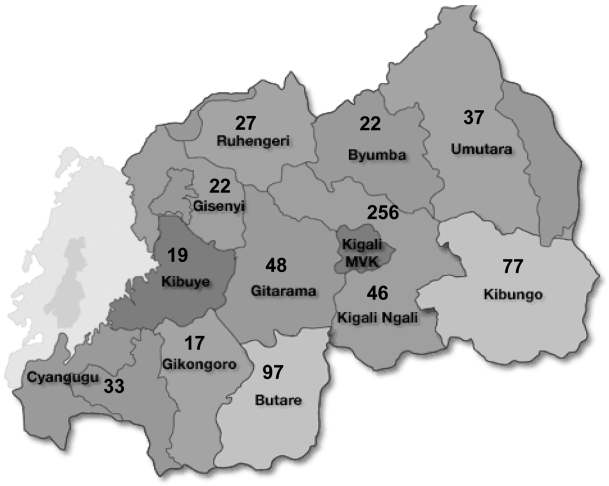


Figure 1 Map of Rwanda with number of included patients per province (total = 701). MVK = mairie de la ville de Kigali (city of Kigali).

Table 2 Patterns of resistance in *M. tuberculosis* strains isolated from new and previously treated cases

Resistance pattern	New cases *n* (%)	Previously treated cases *n* (%)	Combined resistance *n* (%)
Total	616	85	701
Susceptible to all drugs	551 (89.4)	66 (77.7)	617 (88.0)
Any resistance	65 (10.6)	19 (22.4)	84 (12.0)
Monoresistance	34 (5.3)	10 (11.8)	44 (6.3)
H	7 (1.1)	0	8 (1.1)
R	0	1*	1*
E	10 (1.6)	2*	12 (1.7)
S	16 (2.6)	7 (8.2)	23 (3.3)
MDR	24 (3.9)	8 (9.4)	32 (4.6)
H+R	1 (0.2)	0	1*
H+R+E	0	0	0
H+R+S	2 (0.3)	0	2*
H+R+E+S	21 (3.4)	8 (9.4)	29 (4.1)
Other resistance	7 (1.1)	1*	8 (1.1)
H+E	0	0	0
H+S	6 (1.0)	1*	7 (1.0)
H+E+S	1 (0.2)	0	1*
R+E	0	0	0
R+S	0	0	0
R+E+S	0	0	0
E+S	0	0	0

* Value too small to calculate a valid percentage.
H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug resistance.

DISCUSSION

Our study has some limitations: first a small number of samples that were either contaminated cultures or that did not grow on subculture were excluded. It is also possible that some of the samples were misclassified. Second, HIV testing was not performed due to operational complications, and it is therefore not possible to describe exactly how HIV seropositivity was linked to the resistance patterns observed.

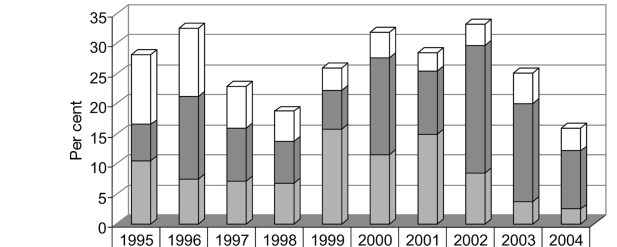
In general, our survey showed a high prevalence of primary and secondary resistance among pulmonary TB cases, with MDR-TB rates reaching 3.9% and 9.4% between new and retreated cases, respectively. These rates are higher than the data of 1993, with 1.3% MDR-TB among new cases and 6.5% among retreated patients,[12] but considerably lower than the 2002 study (7.0% and 25.5% among new and retreated cases respectively, article submitted). These observed differences may reflect the variations in the studied population: first, the previous studies included mainly patients from larger sentinel centres, whereas in the present study subjects were recruited from all TB detection centres.

Second, the two surveys did not use the standard WHO/Union methodology, and the NRL had not completed the accreditation process by a supranational laboratory (SRL) administered by the WHO/Union.

Table 3 Patterns of resistance in *M. tuberculosis* strains isolated from previously treated cases, by patient classification after first-line treatment

Resistance pattern	Return after default *n* (%)	Treatment failure *n* (%)	Relapse *n* (%)
Total cases	5	5	75
Susceptible to all drugs	2*	0	64 (85.3)
Any resistance	3*	5*	11 (14.7)
Monoresistance	2	0	12
H	0	0	8 (10.7)
R	0	0	0
E	1*	0	1*
S	1*	0	1*
MDR	1*	5	6 (8.0)
H+R	0	0	2
H+R +E	0	0	0
H+R+S	0	0	0
H+R+E+S	1	5	0
Other resistance	0	0	2*
H+E	0	0	1*
H+S	0	0	0
H+E+S	0	0	1
R+E	0	0	0
R+S	0	0	0
R+E+S	0	0	0
E+S	0	0	0

* Value too small to calculate a valid percentage.
H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug resistance.



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Defaulters	11.7	11.5	6.8	4.9	3.7	4.2	3.1	3.6	5.0	3.9
Transferred	6.0	13.6	8.8	6.9	6.4	16.1	10.5	21.1	16.3	9.6
Not evaluated	10.5	7.5	7.2	6.8	15.7	11.5	14.8	8.5	3.7	2.5

Figure 2 Defaulter, transfer and non-evaluated rate of smear-positive pulmonary TB cohorts, 1995–2004, Rwanda.

However, the observed increase in treatment failures and the overall trend of increasing MDR-TB rates in the 2002 study and the present study compared to the 1993 study could also reflect a real increase in MDR-TB rates.

During the civil war in Rwanda from 1990 to 1994, the NTP worked under extremely difficult conditions, with a disorganised health system.[13,14] After 1994, the NTP gradually became re-organised and re-supplied with the assistance of the Damien Foundation Belgium, but it did not perform well due to high transfers between treatment centres and hospitals and defaulter rates until 2002 (Figure 2). Nevertheless, TB treatment is not available in the private sector in Rwanda, and TB drugs cannot be found in private pharmacies or on the black market.

On the other hand, the standard regimen for treatment of smear-positive pulmonary TB has changed over time. In 1990, when the DOTS strategy was implemented, the regimen used was $2RHZE/4R_2H_2$ with only twice weekly drug administration during the continuation phase. In 2002, a new regimen, $2RHZE/4R_3H_3$, was introduced into all health centres and hospitals of the Ministry of Health network. However, often only one of the three weekly doses was administered under direct supervision. It is only recently, in May 2006, that the treatment regimen has been changed to daily dosages during the continuation phase. The above might be an indicator for the acquisition of resistance to RMP as a result of intermittent treatment.

Another factor relevant for the acquisition of RMP resistance is malabsorption of INH in HIV-positive patients.[15,16] Our study is limited by the lack of records on HIV-TB co-infection, but data on HIV prevalence among patients treated for MDR-TB in Kabutare Reference Treatment Centre show HIV co-infection rates similar to those in non-resistant TB cases.[1]

The MDR-TB rate found among new patients in Rwanda (3.9%) is higher than those reported in other African countries (median rate 1.4%, range 0.5% in Gambia to 2.6% in South Africa-Mpumalanga Province,[5] 1.4% in Bujumbura province and 3.4% in Mozambique).[17,18] The MDR-TB rate among previously treated patients in Rwanda (9.4%) is lower than in Benin (10.5%), Bujumbura province (12%) and Mpumalanga province (13.7%), but is higher than the median value for Africa (5.9%).[5,17,19]

Nevertheless, the results of this study fall within a range comparable to those of other countries, as indicated in the WHO's last report on drug resistance in the world.[5]

Since 2003, the NTP has spent considerable efforts on reducing the transfer rate by quarterly evaluation meetings at district level to exchange treatment results of transferred patients, intensive supervision and training. Home visits are carried out for patients lost to follow-up. Although the WHO target of 85% established in 1991 for 2000 [20] has not yet been met, the success rate steadily increased from 58% in 2002 to 76% in 2004, and to 81% for the first quarter of 2005. The treatment failure rate for new smear-positive cases was 1.1% in 2002, 1.4% in 2003 and 1.5% in 2004, whereas for re-treatment cases it was 4%, 7% and 6% respectively.

Rwanda is in a reasonable position to prevent the spread of drug-resistant TB and even lower the present figure, as some other countries have done, with daily treatment regimen and the implementation of programmatic management of drug-resistant tuberculosis. To achieve this, the NTP needs better organisation, with the following functions that should be strengthened and/or established without delay: 1) use of a standard MDR-TB treatment protocol with bacteriological follow-up, including culture and DST; 2) controlled use of second-line anti-tuberculosis drugs; 3) upgrading of

the NRL to perform DST in Rwanda; 4) establishment of a care and treatment programme for MDR-TB cases; and 5) establishment of a regular, nationwide drug resistance surveillance system.

In conclusion, our results demonstrate that resistance to the first-line drugs, especially MDR-TB, is widely prevalent in Rwanda. It is true and obvious that, as pointed out by Barr and Menzies,[21,22] the entire population of a country in a state of war has to live in very harsh conditions indeed, with the likely result of an increase in morbidity and mortality due to TB, the consequences of which will be felt for many years to come. In a war-ravaged country such as Rwanda, it is therefore imperative that the NTP provide adequate human and financial resources to prevent MDR by strengthening DOTS and particularly by conducting actions to reduce the number of transfers and by introducing programmatic management of drug-resistant tuberculosis.

Acknowledgements

This study was financially supported by the World Health Organization, the Global Fund against AIDS, Tuberculosis and Malaria, the Damien Foundation (Belgium) and GTZ (Deutsche Gesellschaft für Technische Zusammenarbeit). Material and technical support were also obtained from the National Tuberculosis Control Programme, the National Reference Laboratory, the Belgian Technical Cooperation in Kigali and the Mycobacteriology Unit at the Institute of Tropical Medicine in Antwerp, Belgium. We thank A Van Deun and Gladys Anyo for critical appraisal of the manuscript. Special thanks are also due to all the health workers who assisted in data collection.

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RÉSUMÉ

CONTEXTE : Un des principaux objectifs de la lutte contre la tuberculose (TB) est de réduire l'émergence de la resistance aux antituberculeux. Une première enquête nationale a été conduite au Rwanda pour déterminer la prévalence de la résistance de *Mycobacterium tuberculosis*.

MÉTHODES : Les expectorations de tous les cas nouveaux ou en retraitement provenant de tous les districts ont été collectées entre novembre 2004 et février 2005. Le test de sensibilité aux antituberculeux de première ligne des souches isolées a été pratiqué par la méthode des proportions.

RÉSULTATS : Parmi 616 souches provenant de nouveaux cas, 6,2% étaient résistantes à l'isoniazide, 3,9% à la

rifampicine et 3,9% étaient multirésistantes. Parmi 85 souches provenant de cas de retraitement, la prévalence de la résistance a été respectivement de 10,6%, 10,6% et 9,4%. Dans huit cas MDR, il y a eu en plus une résistance à l'éthambutol et à la streptomycine.

CONCLUSION : Le taux de TB-MDR est élevé chez les patients tuberculeux au Rwanda. Les principales causes de cette émergence de TB-MDR peuvent être la désorganisation du système de santé, les migrations de population pendant la guerre civile de 1994 ainsi qu'au faible taux de succès de traitement avec un nombre élevé de transferts et de perdus de vue. D'autre part, l'utilisation des régimes de traitement réduits à deux prises par semaine pendant la phase de continuation peut être un autre facteur important et mérite d'autres investigations.

RESUMEN

MARCO DE REFERENCIA : Uno de los principales objetivos de la lucha contra la tuberculosis (TB) es reducir al mínimo la aparición de farmacorresistencia. Se llevó a cabo en Ruanda la primera encuesta nacional, con el fin de determinar la prevalencia de farmacorresistencia de *Mycobacterium tuberculosis*.

MÉTODOS : Se recogieron muestras de esputo de todos los casos nuevos y en retratamiento por TB en los distritos sanitarios entre noviembre de 2004 y febrero de 2005 y se realizaron pruebas de farmacorresistencia de los aislados clínicos a los antituberculosos de primera línea mediante el método proporcional.

RESULTADOS : De las 616 cepas provenientes de los casos nuevos, el 6,2% demostró resistencia a isoniacida, el 3,9% a rifampicina y el 3,9% fue multidrogorresistente (MDR). En las 85 cepas de casos previamente tratados, la prevalencia de resistencia fue del 10,6%, 10,6% y 9,4% (cepas MDR) respectivamente. Ocho casos de TB-MDR presentaron además resistencia a etambutol y a estreptomicina.

CONCLUSIÓN : La proporción de TB-MDR en Ruanda es alta. Las principales razones de la aparición de MDR pueden atribuirse a la desorganización del sistema de salud, a la migración de la población durante la guerra civil de 1994 y a las bajas tasas de éxito terapéutico con gran cantidad de pacientes transferidos y perdidos durante el seguimiento. Otro factor importante, que merecería mayor estudio, es el uso de protocolos terapéuticos administrados dos veces por semana durante la fase de continuación.