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Multidrug-resistant TB in Zambia: review of national data from 2000 to 2011

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Abstract

BACKGROUND Multidrug-resistant tuberculosis (MDR-TB) is posing a great threat to global TB control. The burden in Zambia is not well defined because routine surveillance data are scarce. We reviewed national MDR-TB data for the last decade to inform future public health policy with respect to MDR-TB in Zambia.

METHOD Retrospective review of national surveillance of MDR-TB data, TB programme and laboratory reports between 2000 and 2011.

RESULTS The total number of DSTs performed during this 11-year period was 2 038 and accounted for 2.6% (2 038/78 639) of all the retreatment cases notified. The total number of diagnosed MDR-TB cases for this period was 446, of which 56.3% (251/446) were male and 41.7% (186/446) female. Only one child was found to have MDR-TB. Poly-drug resistance accounted for 18.9% (172/911) of the DR-TB cases and 8.4% of the total DSTs. 8.8% (80/911) of the DR-TB cases showed either rifampicin mono- or poly-resistance other than MDR-TB. No XDR-TB was reported. There were no data available on DR-TB and HIV co-infection. Only 65 MDR-TB patients were notified and put on second-line treatment according to WHO guidelines.

CONCLUSIONS Multidrug-resistant tuberculosis may be an emerging challenge in Zambia. There is a need to invest in improving the capacity of the TB programme to detect and manage MDR-TB.

keywords tuberculosis, multidrug-resistant tuberculosis, surveillance, retreatments, diagnosis, Zambia

Introduction

Tuberculosis (TB) has remained a huge challenge to global health almost 20 years after WHO declared it a global emergency (Zumla *et al.* 2012) .The availability of cost-effective anti-TB drugs facilitated the recommendation and implementation of the directly observed treatment short-course (DOTS) strategy, as a TB control strategy especially for low- and middle-income countries (Raviglione & Pio 2002). Although notable progress has been made globally towards TB control with incident rates showing a downward trend over the past few years, the emergence of resistant strains, especially multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to both isoniazid and rifampicin, poses a great challenge to achieving targets which will translate into actual impact in terms of TB control and eventual elimination (WHO 2010; Zumla *et al.* 2012). The global burden of MDR-TB in 2010 was estimated to be 650 000 cases, of which the majority was reported from Eastern Europe and Asia, with sub-Saharan Africa accounting for a very small and undefined proportion (WHO 2010; Zignol *et al.* 2012a). In 2008, MDR-TB killed more than 150 000 people globally (WHO 2012a).

Global surveillance has mainly been based on reports from surveys conducted previously while routine surveillance data are limited (Zignol *et al.* 2012a; Zumla *et al.* 2012). The emergence of extensively drug-resistant TB (XDR-TB) is causing even greater concern for future TB control strategies (Gandhi *et al.* 2010), especially in highly HIV-prevalent countries, where the prognosis of these patients varies significantly from very poor with

100% mortality (Cooke *et al.* 2011) to relatively better outcomes in other cases (Orenstein *et al.* 2009).

In sub-Saharan Africa, MDR-TB surveillance data have been scarce in the past years and few countries have conducted drug resistance surveys (Wright *et al.* 2009; WHO 2010; Zignol *et al.* 2012a).The limitation is mainly due to inadequate diagnostic capacity and drug susceptibility testing (DST) in most sub-Sahara African countries (Wright *et al.* 2009). Zambia has made good progress in tuberculosis (TB) control with the estimated prevalence rates showing a downward trend and having very good treatment outcomes in new cases and retreatment cases regardless of the HIV status of the patients (Kapata *et al.* 2012; WHO 2012b).

In Zambia, TB is mainly diagnosed by microscopy, using Ziehl–Neelsen (ZN) stains (Kapata *et al.* 2011); culture and DST have been performed in Zambia since the late 1990s, although there are currently no reliable records and reports on this before the year 2000. Initially, routine culture and DST were only performed at the National Reference Laboratory (NRL), which catered for the whole country. The capacity to perform culture and DST gradually increased from one referral centre (NRL) to three by the year 2008, which included the University Teaching Hospital (UTH) and the Tropical Diseases Research Centre (TDRC). These laboratories cater for a population of approximately 13.4 million across a land surface area of about 752 000 square kilometres.

We conducted a retrospective review to understand the MDR-TB situation in Zambia, to ascertain the magnitude of the problem and to discuss possible mitigation issues to improve MDR-TB control efforts and patient management.

Methods

Review period and documents

We retrospectively reviewed reports from 2000 to 2011. Records reviewed included laboratory registers from the University Teaching Hospital, Tropical Disease Research Centre and the Chest Diseases Laboratory (National TB Reference Laboratory), National TB programme review reports, annual TB returns and notifications, Ministry of Health assessment reports and TB laboratory reports including external quality assurance reports. Cases reported from operational research studies were not included in the review.

Treatment regimens

The treatment regimens for Zambia were designed following WHO guidelines as follows: (i) Category I for all new TB cases, (ii) Category II for all retreatment TB cases and (iii) Category IV for all MDR-TB patients. The Category I treatment regimen was changed in 2007, from the 8-month regimen of rifampicin, isoniazid, pyrazinamide and ethambutol (RHEZ) in fixed dose combination in the intensive phase for 2 months followed by 6 months of isoniazid and ethambutol (EH) in fixed dose combination in the continuation phase, to the 6-month regimen of RHEZ for 2 months initial phase followed by 4 months of RH in the continuation phase.

Diagnosis

The mainstay of diagnosis in Zambia is smear microscopy; culture and DST is recommended to be performed only on samples from all patients enrolled on treatment as retreatment cases; those who fail to respond to treatment and all those who had interrupted treatment. The drugs routinely tested for are rifampicin, isoniazid, ethambutol and streptomycin. TB diagnosis is free in the public sector.

Definitions

The definition for a retreatment case was a case of TB diagnosed in a patient who had been treated before with first-line TB drugs for more than 1 month. Mono-resistant TB is defined as drug resistance to any one first-line TB drug. MDR-TB was defined as TB resistant to both isoniazid and rifampicin, while poly-resistant TB was defined as drug resistance to two or more first-line TB drugs excluding MDR-TB. XDR-TB was defined as MDR-TB that is resistant to at least one injectable second-line TB drug (kanamycin, amikacin, capreomycin) and any of the fluoroquinolones.

Multidrug-resistant tuberculosis diagnosis strategy

The diagnosis of drug-resistant TB (DR-TB) and MDR-TB is made by collecting sputum samples from the suspected patients and subjecting the specimen to culture on either solid media using Löwenstein–Jensen (LJ) or on liquid media using Mycobacteria Growth Indicator Tube (MGIT) and then performing DST on the positive samples. The suspected MDR-TB patients are usually the patients who fail first-line treatment and have sputum smear-positive results at three to 5 months of treatment and at the end of treatment; all retreatment cases are also considered to be MDR-TB suspects. The results of the DST are thereafter sent back to the referring facility where the patients are then given the results and notified into the treatment register and started on second-line

Table 1 Number and percentage of retreatment cases from the notifications of all forms of TB (2000–2011)

Year	Notification all forms (rate per 100 000 population)	Number of smear-positive retreatments (%)	Number of other retreatments (%)	Number of all retreatments (%)	Number of DSTs
2000	49 806 (504)	1 455 (2.9)	–	1 455 (2.9)	69
2001	52 757 (523)	1 522 (2.9)	6 498 (12.3)	8 020 (15.2)	63
2002	45 836 (440)	2 193 (4.8)	92 (0.2)	2 285 (5.0)	90
2003	55 275 (514)	2 538 (4.6)	3 412 (6.2)	5 950 (10.8)	96
2004	58 070 (524)	2 485 (4.3)	6 021 (10.4)	8 506 (14.6)	176
2005	53 569 (468)	2 039 (3.8)	5 524 (10.3)	7 563 (14.1)	439
2006	51 179 (434)	2 464 (4.8)	5 614 (11.0)	8 078 (15.8)	345
2007	50 415 (415)	2 442 (4.8)	5 833 (11.6)	8 275 (16.4)	79
2008	47 333 (378)	2 278 (4.8)	5 236 (11.1)	7 514 (15.9)	175
2009	48 510 (376)	2 485 (5.1)	5 444 (11.2)	7 929 (16.3)	171
2010	48 408 (365)	2 595 (5.3)	6 310 (13.0)	8 905 (18.4)	128
2011	48 566 (356)	2 474 (5.1)	1 685 (3.5)	4 159 (8.6)	207
Total no.	609 724	26 970	51 669	78 639	2 038

treatment. External quality assurance for the three laboratories is conducted by the supranational laboratories annually through proficiency testing. The notification reports and patients record cards are kept at the treatment facilities and regular monitoring, and supervision is conducted at these facilities by TB programme staff on a quarterly basis to ensure good quality data are collected. These reports are mainly based on the public sector, which provides for more than 90% of TB diagnosis and treatment facilities (Kapata *et al.* 2011).

Results

Retreatment cases

The total number of all types of retreatment cases for the 11-year period was 78 639 accounting for 12.9% (78 639/609 724) of the total number of all forms of TB cases notified (Table 1). Smear-positive retreatment cases and other retreatment cases accounted for 4.4% (26 970/609 724) and 8% (51 669/609 724) of all cases, respectively.

The total number of DSTs performed during the 11-year period was 2 038 which accounted for 2.6% (2 038/78 639) of all the retreatment cases notified. Only 0.3% of patients notified with any form of TB were subjected to the DST. The number of DSTs performed increased from 69 in 2000 to 207 in 2011, whereas the notification rate for the same period declined from 504/100 000 population in 2000 to 356/100 000 in 2011.

Children accounted for 6% (4 718/78 639) of the total number of retreatment cases notified. The number of male retreatment cases notified for the same period was 47 970, accounting for 61% of the total retreatment cases.

Table 2 Number and percentage of different resistance patterns out of the total drug-resistant TB cases

Type of resistance	Number	Percentage (%)	CI
Isoniazid mono-resistance	115	12.6	10.46–14.78
Rifampicin mono-resistance	44	4.8	3.43–6.22
Ethambutol mono-resistance	37	4.1	2.78–5.34
Streptomycin mono-resistance	97	10.7	8.64–12.65
Poly-resistance	172	18.8	16.83–20.84
MDR-TB	446	49	45.70–52.20
TOTAL DR-TB	911	100	

Resistance to pyrazinamide not routinely determined in all three reference laboratories.

Drug-resistant (DR) TB cases

The total number of MDR-TB cases diagnosed in the 11 years under review was 446; this accounted for 49% (446/911) of the total cases that were diagnosed as DR-TB from all the reference laboratories, and 22% (446/2 038) of the total DSTs (Table 2). Of the 911 DR-TB cases, 12.6% (115) were mono-resistant to isoniazid, 4.8% (44) to rifampicin, 4.1% (37) to ethambutol and 10.7% (97) to streptomycin. Poly-resistance accounted for 18.8% (172/911) of the DR-TB cases and 8.4% of the total DSTs, of which poly-resistance including rifampicin resistance, excluding MDR-TB, accounted for 8.8% (80/911) of DR-TB cases. The average age of patients with DR-TB was 39.4 years CI (38.1, 40.6); 44% (CI 40.9, 47.8) were females and 56% (CI 52.1, 59.1) were males. No XDR-TB cases were reported, and

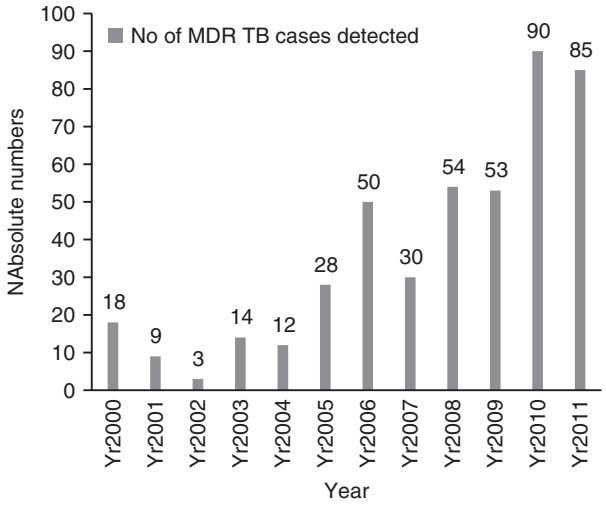

Figure 1 Number of MDR-TB cases diagnosed by year from 2000 to 2011.

only three cases of DR-TB were children younger than 15 years. No data were available on DR-TB and HIV co-infection for the review period.

Notification of MDR-TB cases

Data on initiation of second-line treatment were only available from 2010. For the 2-year period from 2010–2011, there were a total of 175 MDR-TB cases, of which just 65 (37%) were initiated on second-line treatment. There was a fourfold increase in the number of cases notified by year from 18 in 2000 to 85 in 2011 as shown in Figure 1.

Discussion

In Zambia, a national drug resistance survey was conducted in 2001, reporting the prevalence of MDR-TB to be low at 1.8% and 2.3% in new and retreatment cases, respectively (Mulenga *et al.* 2010). The number of cases diagnosed in the past 11 years with drug susceptibility testing performed on just 3% of the expected cases raises concerns with regard to selection bias and an overall underestimate as the sample cannot be considered representative. Nearly half of all the DR-TB cases diagnosed during the review period were MDR-TB. The number of MDR-TB cases detected through the routine surveillance system appears to have been increasing. This increase could be attributed to the improvement and expansion of the reference laboratory network and capacity to perform DSTs, including the introduction of newer methods of diagnosis such the Mycobacterium Growth Indicator Tube (MGIT). The MGIT services improved the turnaround time of performing culture and DST thus led to more tests being performed (Muyoyeta *et al.* 2009). Our study has highlighted that DST among the eligible samples is inadequate. National TB control guidelines state that all retreatment cases should be subjected to culture and DST upon notification, but adherence to this guideline is low. The restriction of DST services to a limited number of centralised laboratories is clearly a major obstacle to improving DST coverage. It needs to be investigated whether it would be more cost-effective to install DST services in more laboratories, or to invest in logistics for the transporting sputum samples to the existing reference laboratories for culture and DST, from high-risk patient groups and other cases where DR-TB is suspected.

The numbers of retreatment patients in the first 3 years (Table 1) of the review show some inconsistencies, mainly because during this period, the NTP was just being re-organised after disruption in the late 1990s (Mwaba *et al.* 2003). However, the small number the retreatment cases in 2011 needs to be explored. The majority of the MDR-TB cases (39%) were diagnosed in the latter 2 years. Considering that the cure rates for retreatment cases range from 50 to 70% (Kapata *et al.* 2011; WHO 2012b), it is likely that the cases that were selected to be sent for DST were at very high risk of being MDR-TB, such as treatment failures in the previously treated cohorts. Further reviews are required to understand this; especially that the prevalence of MDR-TB is low based on the drug resistance survey of 2001 (WHO 2010). However, other studies have shown rates of 9.5% MDR-TB in high-risk places, such as prisons (Habeenzu *et al.* 2007) and in tertiary referral hospitals such as the UTH, where the prevalence of MDR-TB in hospitalised patients was 16.2% (O'Grady *et al.* 2012). These findings underscore the need for improved routine surveillance and screening of patients, through culture and DST or indeed through the use of better and quicker diagnostics such as the Xpert MTB/RIF assay; proactive screening of cases such as routine screening on admission of patients into medical wards of the hospital should be advocated for to ensure that cases are not missed especially in high-risk groups such as patients who failed Category 1 treatment (Bates *et al.* 2012; O'Grady *et al.* 2012).

There was only one case of MDR-TB cases in children under the age of 15 years; this may not be representative of the true situation as only three childhood cases had DST performed. In a study conducted at the UTH, 2 childhood cases of MDR-TB were diagnosed when active case finding was applied using the Xpert MTB/RIF on gastric lavage aspirates in a study conducted within a

1-year period (Bates *et al.* 2013). This underscores the importance of MDR-TB surveillance in children through the routine programme and active case finding in risk groups such as contacts of known or suspected infectious MDR-TB patients, especially using the Xpert MT/RIF assay, as there is also evidence in the subregion of a childhood MDR-TB emerging problem (Zignol *et al.* 2012b).

Due to inadequate reporting and recording, no data were available on MDR-TB / HIV co-infections. Co-treatment of MDR-TB and HIV is extremely debilitating, with both medical and social impediments to adherence (Isaakidis *et al.* 2013). More investments should be made in improving data capturing to include data on HIV co-infection in MDR-TB (Klinkenberg *et al.* 2012).

The presence of other types of resistance patterns (Table 2), including rifampicin mono-resistance, indicates that DR-TB must be fully addressed and managed in terms of more investment into better diagnostics and availability of drugs as this may eventually complicate further TB control programmes if left unchecked. DR-TB other than MDR-TB accounted for 465 cases during the period under study when DST was only performed in 3% of the suspected cases. Almost all the DSTs were actually performed on pulmonary cases from which sputum samples could be collected and not from cases with extrapulmonary TB. MDR-TB that presents as EPTB was not documented and yet MDR-TB in EPTB does occur, although diagnosis is usually problematic (Maurya *et al.* 2012). Considering the high number of EPTB in retreatment patients, ways to improve diagnosis in this group of patients should be explored. There were no data on extensively drug-resistant TB as no routine DST to second-line drugs is currently performed in Zambia.

Conclusion

Multidrug-resistant tuberculosis in Zambia may increasingly pose a challenge and reverse the achievements made so far if not well managed. At global level, only 16% of patients requiring second-line treatment actually receive it (WHO 2012a), and so our proportion of 37% for 2010–2011 is encouraging, but more investments are needed to improve reporting systems, and for the development of better diagnostics and drugs to detect and treat MDR-TB. The NTP should be strengthened to improve the management of MDR-TB in Zambia while also realising that the best method to control MDR-TB is to ensure a good TB treatment programme for drug susceptible TB.

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