Extensively drug-resistant tuberculosis (XDR-TB) among health care workers in South Africa

Julie Jarand[1,2], Karen Shean[2], Max O'Donnell[3], Marian Loveday[4], Charlotte Kvasnovsky[5,6], Martie Van der Walt[6], Shahieda Adams[1], Paul Willcox[2], Justin O'Grady[7], Alimuddin Zumla[7] and Keertan Dheda[1,7]

1 Lung Infection and Immunity Unit, Department of Medicine, University of Cape Town, South Africa
2 University of Calgary, Calgary, Canada
3 Boston University School of Medicine, Boston, MA, USA
4 South African Medical Research Council, Tygerberg, South Africa
5 Emory University School of Medicine & Rollins School of Public Health, Atlanta, GA, USA
6 South African Medical Research Council, Pretoria, South Africa
7 Centre for Infectious Diseases and International Health, University College London Medical School, UK

Summary

OBJECTIVE To determine the clinical profile and outcomes of health care workers (HCWs) with extensively drug resistant tuberculosis (XDR-TB) in the Eastern and Western Cape Provinces of South Africa.

METHOD Retrospective case record review of 334 patients with XDR-TB reported during the period 1996–2008 from Western and Eastern Cape Province, Cape Town, South Africa. Case records of HCWs with XDR-TB were analysed for clinical and microbiological features, and treatment outcomes.

RESULTS From 334 case records of patients with XDR-TB, 10 HCWs were identified. Eight of ten were HIV-uninfected, and four of 10 had died of XDR-TB despite treatment. All 10 HCWs had received an average of 2.4 courses of TB treatment before being diagnosed as XDR-TB.

CONCLUSIONS In the Eastern and Western Cape provinces of South Africa XDR-TB affects HCWs, is diagnosed rather late, does not appear to be related to HIV status and carries a high mortality. There is an urgent need for the South African government to implement WHO infection control recommendations and make available rapid drug susceptibility testing for HCWs with suspected multidrug-resistant (MDR)/XDR-TB. Further studies to establish the actual risk and sources of infection (nosocomial or community) are required.

keywords extensively drug-resistant, tuberculosis, health worker

Introduction

Multidrug (MDR)- and extensively drug (XDR)-resistant tuberculosis (TB) carry a high mortality rate and are a growing problem that threatens to destabilize tuberculosis control globally (WHO Report. World Health Organization, 2010; WHO, 2010; Centers for Disease Control and Prevention, 2006; Sotgiu et al. 2009; Gandhi et al. 2006). South Africa has a very high annual TB incidence of 948 per 100 000 population/year with approximately 8000–9000 patients per annum with multidrug-resistant TB (MDR-TB) passively detected per annum. The most recent report of 5% of the patients with MDR-TB being extensively drug-resistant TB (XDR-TB) in South Africa is likely an underestimate (WHO Report. World Health Organization, 2010; WHO, 2010). TB in all its forms is having a devastating effect on the world's population and poses a

great risk to the health and work outputs of health care workers (HCWs) (Menzies et al. 2007; Naidoo & Jinabhai 2006; Jo et al. 2008; Pillay & Malhati 2008; Galgalo et al. 2008; Joshi et al. 2006).

Health care workers in South Africa are at the forefront of the battle against the TB and HIV/AIDS epidemics (Naidoo & Jinabhai 2006; Joshi et al. 2006; Shisana et al. 2004). The shortage of HCWs has reached alarming levels in sub-Saharan Africa, which is home to 11% of the world's population and 24% of the global burden of disease, but only 3% of the world's HCWs (Wilkinson & Gilks 1998). Multiple factors contribute to this problem, such as high workload, poor remuneration, limited training opportunities and lack of resources (Pillay & Malhati 2008). Other significant contributing factors are fatalities and incapacitating disability related to HIV/AIDS and other infectious diseases of poverty. In 2002, an estimated

16% of HCWs in South Africa were infected with HIV (Shisana *et al.* 2004). South Africa has one of the highest rates of TB and HIV/AIDS in the world, and the occurrence of TB in HCWs has been reported to be substantial (Naidoo & Jinabhai 2006; Shisana *et al.* 2004; Wilkinson & Gilks 1998). However, the occurrence and importance of XDR-TB in HCWs in South Africa are not yet documented.

Health care workers with active tuberculosis (TB) need to be identified and treated. HCWs with active TB risk infecting their patients, their fellow staff, families and communities with *Mycobacterium tuberculosis (Mtb)*. Conversely, HCWs are also at risk of acquiring TB from their patients, fellow staff and family and community members. Over the past 15 years, the risk of TB in HCWs in southern Africa has been increased because of the resurgence of TB caused by the HIV epidemic and the emergence of MDR-/XDR-TB, which has added significant strain to already overwhelmed TB control programmes (Gandhi *et al.* 2006; Naidoo & Jinabhai 2006; Shisana *et al.* 2004). The prevalence of extensively drug-resistant tuberculosis (XDR-TB) is now being increasingly reported from South Africa (Gandhi *et al.* 2006; Dheda *et al.* 2010) and poses a major threat to HCWs and other patients in the wards and outpatient clinics, and those in congregate settings. XDR-TB is difficult to treat and has poor treatment outcomes, and together with HIV co-infection, may exacerbate the shortage and poor performance of HCWs in South Africa. The frequency, clinical profile and outcomes of HCWs with XDR-TB in South Africa remain unknown (Sotgiu *et al.* 2009). To ascertain whether XDR-TB is an emerging problem in HCWs in South Africa, we undertook a retrospective case record review of 334 patients with XDR-TB reported during the period 1996–2008 from the Eastern and Western Cape Provinces of South Africa.

Methods and patients

Using a validated data capture tool, we performed a retrospective study of case records of 334 patients with XDR-TB, diagnosed between January 1996 and February 2008, from the Western Cape and Eastern Cape provinces of South Africa. For the HCWs identified with XDR-TB, patient data, including demographics, microbiologic and treatment records, were collected. The diagnosis of XDR-TB was based on sputum culture positivity for *Mtb* bacilli, and was defined, based on drug susceptibility testing (DST), as resistant to isoniazid, rifampicin, any one fluoroquinolone and at least one-second-line injectable anti-TB drug. Case definitions for diagnosis and conversion are outlined in Table 1.

Results

Ten HCWs with XDR-TB were identified. Table 1 outlines patient characteristics, including gender, HIV status, occupation, place of work, number of previous TB episodes, chest X-ray abnormalities, number of resistant drugs, treatment accorded and treatment outcomes. Patients were predominantly female (9 of 10) with a median age of 40 years (range 26–50). The majority of patients (6 of 10) worked as nursing staff and one each in the following professions: doctor, radiographer, laundry staff and ward cleaner. Of the 10 patients, eight were HIV-uninfected. One HIV-positive patient had been treated with anti-retrovirals (ARVs) for 4 years prior to diagnosis of XDR-TB, and the other HIV-uninfected patient was started on ARVs at the time of XDR-TB diagnosis. All 10 patients had been treated for TB previously with an average of 2.4 previous TB episodes. The median duration of follow-up was 10 months (range 1–22 months) from the time of XDR-TB diagnosis.

Table 2 shows the individual patient characteristics (age, gender, year of diagnosis, occupation, HIV status, drug-resistant patterns and treatment accorded and treatment outcome) of the 10 HCWs with XDR-TB that were studied. Three patients underwent surgical resection because of failure to improve clinically, and they had unilateral disease. A high mortality was observed (4 of 10 patients died). Para-amino-salicylic acid (PAS) and capreomycin became available again in South African government-run hospitals in late 2006. Seven patients were treated with regimens containing these drugs, two patients were diagnosed and died before these drugs were available and one patient responded to a modified MDR-TB regimen which did not include capreomycin or PAS. Four patients died and six were still being maintained on treatment for XDR-TB at the end of the study.

Discussion

This case series study adequately answers our primary study aim, confirming that XDR-TB in HCWs is an important clinical problem, and should be of major concern to TB programme managers in South Africa. It affects a spectrum of HCWs, particularly nurses in the Western and Eastern Cape Provinces of South Africa. Whilst in MDR-TB sputum culture conversion is usually achieved in most patients within 3–4 months (WHO, 2010) of initiation of MDR-TB therapy, six of the 10 HCWs with XDR-TB in this study did not achieve culture conversion within this time frame. Moreover, two of the four converters reverted back to culture positivity prior to the end of follow-up, and the overall mortality was high

Table 1 Summary characteristics of health care workers with XDR-TB

	N = 10 (%)
Gender	
Male	1
Female	9
Median age in years (range)	41 (26–50)
Year of XDR diagnosis*	
1996	1†
2002	1†
2006	2
2007	4
2008	2
HIV	
Positive	2
Negative	8
Previous TB	10 (100%)
Mean no. of previous TB episodes	2.4
Median duration of follow-up (months)	10 (range 1–22)
Surgical resection performed	3 (30%)
Chest X-ray abnormalities	
Bilateral, non-cavitary	2
Bilateral, cavitary	4
Unilateral, noncavitary	1
Unilateral, cavitary	2
Not recorded	1
Occupation	
Nurse	5
Nursing student (3rd year)	1
Physician	1
Cleaner	1
Laundry staff	1
Radiographer	1
Facilities where patient worked	
District hospital	3
Specialised TB hospital	1
Prison	1
Variable (nursing student)	1
Physiotherapist office	1
Not recorded	3
Mean no. of resistant drugs	5
Median Time from MDR to XDR (months)	19 (range 0–74)
No. of pts who converted cultures to negative‡	4
Median time to culture conversion (months)§	1.7 (range 1.2–6.9)
Mean no. of drugs in treatment regimen	7
Outcomes	7
Died	4
Still on treatment	6

XDR-TB, extensively drug-resistant tuberculosis; MDR, multidrug-resistant.

*Date of diagnosis is the date the first sputum, culture positive for XDR-TB.

†Patients were diagnosed with XD-RTB retrospectively with the 2006 definition of XDR-TB[7].

‡Culture conversion is defined by having at least two consecutive negative sputum cultures, at least 1 month apart, and culture positivity at treatment initiation.

§Time to culture conversion is duration from treatment start date to date of first negative culture.

(40%). Thus, treatment-related outcomes seen in this limited case series of 10 patients were poor. This is concordant with other observations on treatment success (cured and completed) ranging from 34% to 67% and mortality of 7–36% in non-HCW populations (Sotgiu *et al.* 2009).

Health care workers acquiring XDR-TB adds to the growing burden of drug-resistant disease. It also concurrently exacerbates the shortage of HCWs as they can no longer work while undergoing prolonged inpatient treatment and during convalescence (Pillay & Malhati 2008; Wilkinson & Gilks 1998; Dheda *et al.* 2010; World Health Organization, 2006). This emphasises the need for intensified HCW screening, the widespread use of newer tools now available for the rapid diagnosis of MDR-/XDR-TB and instituting appropriate effective treatment. Importantly, the delay in diagnosis of XDR-TB in these HCWs indicates that undiagnosed and untreated, they are a risk to inpatients they manage, other fellow staff, and their families and communities.

Because of the limitations of our study design and the data obtained, it is unclear where and from whom the HCWs acquired the infection: in hospital as a nosocomial infection from inpatients with XDR-TB they cared for or from the community where XDR-TB is becoming more prevalent. Nosocomial transmission of drug-resistant *Mtb* strains has been well documented and therefore HCWs are clearly at risk (Gandhi *et al.* 2006; Menzies *et al.* 2007). Given that HCWs in our study were previously treated for TB, (including on at least two previous TB episodes in eight patients), community acquired, rather than nosocomial, XDR-TB may be a possibility. However, given the high prevalence of previous TB in patients with drug resistance in the Western Cape (Dheda *et al.* 2010) and studies demonstrating re-infection as an important modality of transmission (Verver *et al.* 2005), it is imperative that the transmission dynamics of these infections be ascertained. However, without identification of the *Mtb* strains and their molecular typing data from the HCWs studied, and from the index case, and from prior TB episodes, it was not possible to determine the transmission dynamics in the cases that we describe. The transmission patterns of drug-resistant *Mtb* strains and whether XDR-TB may harbor different *Mtb* isolates and strains are unknown. Recent observations that *Mtb* strains have a rapid rate of molecular evolution at the hypervariable and immunogenic *Mtb* PPE38 gene region, which may lead to evasion by the immune system, may be important. It may also be that *Mtb* strains may be more diverse than previously thought (McEvoy *et al.* 2009). Prospective studies are now required to address these important issues for proper interventions to be developed.

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Table 2 Individual characteristics of health care workers with XDR-TB

Patient no.	Sex/age	Year of XDR diagnosis*	Surgical resection	Occupation	Facility where patient worked	HIV status (Positive/Negative)	CXR abnormalities	No. of TB episodes prior to XDRTB	MDR resistance pattern	MDR treatment	XDR resistance pattern	XDR treatment	Culture conversion during XDR episode‡ (?Relapse)	Outcome
1	F/37	2006	Yes (left upper lobectomy)	Nurse	District hospital	Neg	Unilateral cavitary	2	H, R, S, E	Z, K, O, Y, T	H, R, A, O, Y, E	Cap, PAS, T, Z, O, Azithomycin, Augmentin, Dapsone	Yes (Yes)	Still on Rx
2	F/26	2008	Yes (right upper lobectomy)	Physician	District hospital	Neg	Unilateral non-cavitary	2	H, R, E	Z, A, O, Y, T	H, R, A, O, E	H, R, E, Z, S, Y, T, O	Yes (Yes)	Still on Rx
3	F/40	2002†	No	Nurse	TB hospital	Neg	Bilateral cavitary	3	H, R	Z, K, O, Y, T	H, R, S, K, O, E	E, Z, Ethio, Cyclo	No	Died
4	F/27	1996†	No	Nursing student (3rd year)	Nursing student	Neg	Bilateral cavitary	2	H, R, S	E, Z, K, O, X	H, R, S, A, O, K, Thiacetazone	Z, E, K, E, Thiacetazone	No	Died
5	F/42	2007	No	Nurse	Prison	Neg	Bilateral non-cavitary	1	H, R	E, Z, A, O, Y	H, R, A, O, Y	Z, E, T, Y, K, O, Cap, PAS, Dapsone	Yes (No)	Still on Rx
6	F/50	2007	No	Radiographer	District hospital	Pos	Bilateral cavitary	4	H, R	E, Z, A, O, Y	H, R, A, O	E, Z, Cap, PAS, Y, T, Dapsone	No	Still on Rx
7	F/44	2006	No	Nurse	NR	Neg	Bilateral non-cavitary	2	H, R	E, Z, A, O, Y	H, R, A, O, Y	H, R, E, Z, O, Cap, PAS, T, Dapsone	No	Died
8	M/50	2008	No	Laundry staff	NR	Neg	Bilateral cavitary	4	H, R	E, Z, A, O, Y	H, R, A, O	E, Z, Cap, PAS, Y	Yes (No)	Still on Rx
9	F/43	2007	No	Nurse	NR	Pos	Not done	1	H, R	E, Z, A, O, Y	H, R, A, O	E, Z, Cap, PAS, Y, Dapsone	No	Died
10	F/37	2007	Yes (left pneumonectomy)	Cleaner	Physiotherapist office	Neg	Unilateral cavitary	3	H, R	E, Z, K, O, Y, INAT	H, R, A, O, Y	E, Z, T, Cap, PAS, Augmentin, Amoxil	No	Still on Rx

H, isoniazid; R, rifampin; E, ethambutol; Z, pyrazinamide; S, streptomycin; K, kanamycin; A, amikacin; O, ofloxacin; C, ciprofloxacin; T, terizidone; X, cycloserine; Y, ethionamide; NR, not recorded; PAS, para-amino-salicylic acid; XDR-TB, extensively drug-resistant tuberculosis; MDR, multidrug-resistant.
*Patients were diagnosed with XDR-TB retrospectively with the 2006 definition of XDR-TB[7].
†Date of diagnosis is the date the first sputum, culture positive for XDR-TB, was collected.
‡Culture conversion is defined by having at least two consecutive negative sputum cultures, at least 1 month apart, and culture posistivity at treatment initiation.

Although XDR-TB in South Africa was initially thought to be almost exclusively associated with HIV coinfection (Gandhi *et al.* 2006), this study shows that HIV-uninfected HCWs are also at risk of acquiring XDR-TB. Therefore, MDR-/XDR-TB should be considered in any HCW suspected of TB, irrespective of HIV status, and all HCW should be screened with the newer rapid first- and second-line drug susceptibility tests if they are found to be smear or culture positive (Pai *et al.* 2006). All HCWs in South Africa should also be encouraged to be tested for HIV, and if HIV-infected, they should receive appropriate treatment for TB and HIV/AIDS. Upon recovery, they should also be relocated to work in areas with lowest risk of TB and in health settings where appropriate WHO-recommended infection control measures are being implemented.

The obvious limitations of our study, given its retrospective design and ascertainment bias, are the inability to calculate prevalence estimates, or to precisely delineate whether the XDR-TB in HCWs was acquired nosocomially or from the community. The physical, social and economic consequences of HCWs acquiring XDR-TB can be very severe and affect their daily lives.

Thus, it becomes important for the South African government to take immediate measures to provide the resources required to enable all hospitals and clinics providing TB care to follow and to implement the recommended WHO infection control procedures (WHO Report, 2009). This will go a long way in protecting HCWs and other inpatients from acquiring MDR-/XDR-TB from those patients and HCWs who have active disease. Furthermore, it is important that all health facility laboratories be equipped with the newer rapid diagnostic testing platforms now available, so that all patients and HCWs suspected of having TB need can be identified early, and appropriately isolated, to minimize the risk of transmission within hospitals and in the community.

Conclusions

In the Western and Eastern Cape provinces of South Africa XDR-TB is diagnosed rather late, does not appear to be related to HIV status and carries a high mortality. This underscores the need for the government to implement current WHO policy on TB infection control in all health care facilities in South Africa. There is also the need for making available rapid molecular biological DST for all HCWs and inpatients to rapidly detect, isolate, and treat all patients with MDR-/XDR-TB. Now that we have shown that HCWs succumb to XDR-TB, further studies to establish the source and mode of infection in HCWs, and the risk to their patients and families, are urgently required.

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Corresponding Author Keertan Dheda, Department of Medicine, H floor (Old Main Building), Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa. Tel.: +27 21 4066509; Fax: +27 21 4486815; E-mail: keertan.dheda@uct.ac.za