A historical review of XDR tuberculosis in the Western Cape province of South Africa

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There are limited data on the temporal relationship between the regional introduction of multidrug-resistant tuberculosis (MDR-TB) treatment and the subsequent development of extensively drug-resistant TB (XDR-TB). The first XDR-TB case in the Western Cape province of South Africa was recorded in 1992, approximately 5 - 7 years after the regional introduction of MDR-TB-like treatment. Between 1990 and 2002 we identified 48 patients with XDR-TB in the Cape Metropole region of the Western Cape province. Patients were predominantly HIV-uninfected and median survival was 10.8 months. XDR-TB has therefore been present in the Western Cape at least since 1992. These data inform public health policy relevant to the introduction of new anti-TB drug regimens.

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To the Editor: Tuberculosis (TB) is out of control in Africa. More ominous is the increasing resurgence of multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), reported in 2006 after the outbreak in KwaZulu-Natal, South Africa.[1] Studies have confirmed the prior existence of XDR-TB in several countries.[2,3] The prevalence of XDR-TB since 2002 and its associated poor treatment-related outcomes were also documented in several provinces of South Africa.[4] These data indicate that the overall culture conversion rates, independent of HIV status, were less than 20%.[4,5] Many of these patients subsequently reverted their culture status. XDR-TB in South Africa is therefore difficult to treat and many patients are therapeutically destitute.

Some hope is in sight with the impending arrival of new anti-TB drugs such as TMC 207 and OPC67683.[6,7] However, there is increasing concern that these drugs will lose their efficacy with time because of increasing drug-specific resistance emerging. Cogent public health strategies must be put in place to prevent emerging drug resistance. Better planning of such a strategy requires a clearer understanding about the temporal genesis of drug resistance relative to the introduction of a drug within a specific public health context. For further insight into this question we sought to establish the earliest record of XDR-TB (based on the current World Health Organization (WHO) definition) in the Western Cape province, relative to the introduction of MDR-TB treatment in 1985. Such data also inform on the evolution of XDR-TB as a specific disease entity, and the environmental and host factors driving drug resistance.

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Methods

Subjects were retrospectively identified from the MDR-TB records of all patients attending the Brooklyn Chest Hospital before December 2002 after approval from the University of Cape Town Health Sciences Faculty Research Ethics Committee. Brooklyn Chest Hospital was then the central management centre for all drug-resistant TB cases in the Cape Metropole.[8] Patient outcomes and prevalence of XDR-TB from 2003 to 2007 in the Western Cape region of South Africa have been reported elsewhere.[4] Sputum culture and sensitivity data were extracted from reference laboratory reports. Patients were defined as having XDR-TB if they were resistant to rifampicin and isoniazid in addition to having resistance to a fluoroquinolone and at least one aminoglycoside.

Results

There were ~2 919 MDR-TB cases treated in the Cape Metropole region of the Western Cape province from 1990 to 2002 (inclusive) where data were available. Patient data before 1990 were not available. A total of 48 patients met the criteria for XDR-TB (32 HIV-uninfected, 2 HIV-infected, and 14 who refused testing or whose HIV result was unavailable). After the introduction of MDR-TB treatment in the Western Cape in 1985 - 1987, the first documented case that we found was recorded in June 1992. As a group the patients were young (median age 34.3 years, range 15 - 59 years); the average weight at diagnosis was 46.7 kg (standard deviation 10.6 kg); 54.2% (26/48) were female; and 77.1% (37/48) were of mixed ancestry.

Table I shows drug sensitivity testing profiles. Patients were not tested for sensitivity to para-aminosalicylic acid (PAS) or capreomycin and so none received appropriate XDR-TB-specific treatment (capreomycin or PAS) at the time.

Most subjects had their MDR-TB treatment continued but with the addition of clofazamine in 19 patients and thiacetazone in 7. Two patients had their MDR treatment withdrawn after the diagnosis of XDR-TB. Outcome data were incomplete, as 28 patients were lost to follow-up. Of the remaining 20 patients, 18 died within a mean of 10.8 months (range 1 - 32 months) from the time of diagnosis.

Discussion

We show that XDR-TB (using the 2006 revised definition) was prevalent in the Cape Metropole area of the Western Cape as early as 1992, ~5 - 7 years after the introduction of MDR-TB treatment in this region in 1985 and following the diagnosis of the first MDR-TB cases.[9,10] There was therefore a lag period of ~5 - 7 years, as far as we can tell, before the first passively detected XDR-TB cases were diagnosed. Similarly, MDR-TB was recognised in the mid-1980s in

Table I. Resistance patterns for MDR-TB patients meeting current WHO XDR-TB definitions

	Drug sensitivity testing*	
Drug	No. tested	No. resistant (%)
Rifampicin	48	48 (100)
Isoniazid	48	48 (100)
Ofloxacin	48	48 (100)
Kanamycin	50	35 (70.0)
Streptomycin	48	41 (85.4)
Amikacin	32	8 (25.0)
Ethionamide	46	13 (28.3)
Thiacetazone	46	33 (71.7)
Ethambutol	46	25 (54.3)
Cycloserine	37	13 (35.1)
Pyrazinamide	2	2 (100)

*No patients were tested for sensitivity to PAS or capreomycin. Capreomycin and drug sensitivity testing to capreomycin were not available in South Africa before 2006/2007.

the Western Cape ~9 years after the widespread use of rifampicin in this area. Resistance in almost all cases was probably acquired, as all the patients had prior MDR-TB treatment. Given these findings increased public health awareness and vigilance will be required, with appropriate targeting of treatment and withdrawal in those at high risk of amplifying resistance, when newer drugs such as TMC 207 are introduced into clinical practice.[11] Several strategies, including the use of fixed-dose combination tablets, should be considered to minimise erratic use of individual drugs.[12,13] If such strategies are not strictly enforced, our data indicate that within ~7 years widespread resistance is likely to emerge.

XDR-TB was invariably fatal despite almost all tested patients being HIV-uninfected. This is in keeping with recent reports in South Africa[4,14] indicating the prevalence of highly virulent strains, and dispels the notion that XDR-TB in Africa is almost exclusively associated with HIV-related attenuated host immunity.

Survival in some patients, despite lack of appropriate treatment, was as long as 32 months. These data therefore reaffirm the urgent need to build community stay and palliative care facilities in high-burden settings to prevent ongoing disease transmission in therapeutically destitute patients.

Our study has several limitations including biases inherent in the retrospective study design, including missing data; selection and treatment bias; and patients lost to follow-up. As data were only available from 1990, the presence of XDR-TB before this date could not be ascertained. Furthermore, drug susceptibility testing in the Western Cape in the early 1990s was not standardised and many cases may have been missed, or patients may have died before reaching health services. Patients could also have been misdiagnosed and treated elsewhere in the province despite Brooklyn Chest Hospital being the designated treatment facility. It is therefore likely that we have underestimated the prevalence of XDR-TB before 2002. It is also not clear whether these cases were acquired or due to primary transmission of disease. However, our main objective was to establish temporality rather than document incidence, outcomes or transmission dynamics.

In summary, without strengthening the full spectrum of the health care system from access to rapid diagnostics through to improved laboratory capacity, and appropriate protection of new drugs through strict control policies, we are likely to face the emergence of even more extensively drug-resistant TB within several years as each new agent is brought to the market.

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