XDR TB in South Africa - What lies ahead?

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Abstract

The emergence of XDR TB coupled with the high prevalence of HIV/AIDS has intensified the need to identify new treatment strategies and accelerate research into antibiotics against XDR TB before the world is faced with a global public health crisis. This article gives a short overview on the important health implications of XDR-TB in South Africa.

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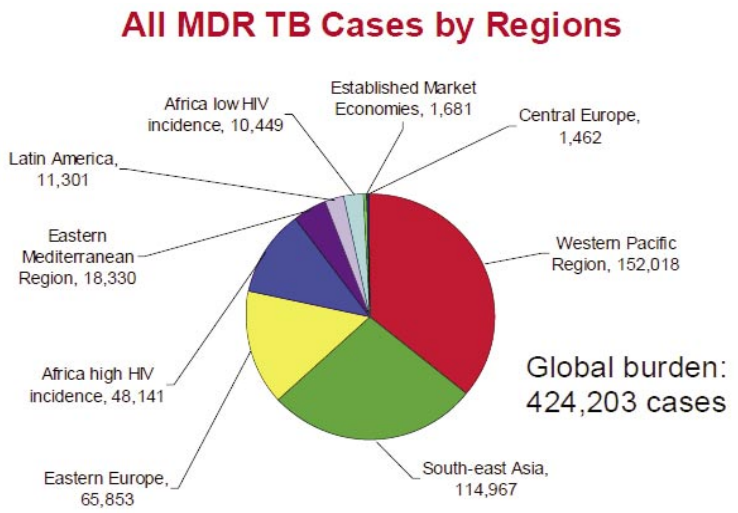
Introduction

The developing world awaits a catastrophe as tuberculosis (TB) places a burden on the public health system and is increasingly becoming the leading infectious cause of escalating morbidity globally. Years of extensive research into effective therapeutic strategies to combat this disease, have not succeeded in eradicating the causative agent - *Mycobacterium tuberculosis.* Poor drug compliance, poverty and HIV co-infection have contributed to the emergence of multidrug resistant strains of TB (MDR TB). Figure 1 shows the global burden of MDR TB with the highest prevalence in south-east Asia. While combinations of first and second line antibiotics have been effective in treating MDR TB, the world was alarmed when a new strain of extensively drug resistant TB (XDR TB) emerged in the early nineties. In 2006, South Africa became one the countries hardest hit by XDR TB when 52 out of 53 patients infected with this strain of TB died within a short period of time (98% case fatality rate). The emergence of XDR TB coupled with the high prevalence of HIV/AIDS has intensified the need to identify new treatment strategies and accelerate research into antibiotics against XDR TB before the world is faced with a global public health crisis.

Figure 1: MDR TB by Geographical Regions



Source: National Department of Health, South Africa. The Emerging Global Threat of XDR-Tb. TB Workshop 17-18 Oct, 2006 www.doh.gov.za/docs/thexdr-tb-f.html (accessed 22 November 2006)

Current management of TB

Globally, TB is a world wide threat, causing three million deaths annually, with 8 million new active cases per year.[1] Reports from the World Health Organization (WHO), estimates that an alarming 2.4 million people were infected with TB in 2001, making TB the most infectious agent in the world.[2] Currently the first line anti-TB drugs used are isoniazid, rifampin ethambutol, and pyrazinamide. These drugs are reasonably effective in treating individuals suffering from TB but are ineffective in totally eliminating the bacilli.[3] A setback of this regimen is that the course of treatment which lasts a minimum of six months is perceived to be lengthy and involves 2 to 4 drugs, resulting in poor compliance.[4] Poor compliance with the prescribed drug regimen coupled with their improper use, gives rise to multidrug resistant TB (MDR TB).

Multidrug Resistant Tuberculosis (MDR TB) is defined as an in vitro resistance of mycobacterium bacillus to at least rifampin and isoniazid.[5] The development of drug resistance and subsequent MDR TB is caused by chromosomal mutations in the different genes of the bacteria. MDR TB develops when a sequence of these mutations allows bacteria to become resistant to one drug or a group of drugs e.g. (rifamycins) at a time.[6] Currently MDR TB strains resistant to up to nine different agents have been reported.[7] Usually drug susceptible TB can be cured within 6 months but MDR TB requires intense chemotherapy for up to 2 years and this is very detrimental to a patient's health, due to high levels of drug toxicity.[8]

Cost of TB treatment

The cost of anti-TB medication for a patient on the six-month regimen is approximately three hundred and seventy-seven rand (R377), while for MDR TB, it is about thirty-one thousand rand (R31000) for the same period of time. The drug cost for XDR TB is not yet known but it is expected to be more expensive than that for MDR TB . The only drugs available to treat XDR TB in South Africa are ethionamide and cycloserine, which are currently being administered at King George V Hospital, Durban.

In countries where the rate of primary multidrug-resistant TB is low, standard treatment regimens include rifampin and isoniazid throughout the duration of therapy in addition to pyrazinamide (with or without ethambutol) for the first 2 months.[9] MDR TB treatment requires the use of second-line drugs, such as quinolones (ciprofloxacin, ofloxacin, sparfloxacin) that are less effective, more toxic, and costlier than first-line isoniazid- and rifampin-based regimens.[10] Aminoglycosides such as capremycin, viomycin, kanamycin and amikacin are also used in drug resistant situations.[11] It is worrying that no new first line antibiotics have been identified for the treatment of TB in the last 20 years.[6] Furthermore poor patient co-operation, poor quality of medicine as well as logistical problems have contributed to the increase in MDR TB cases.[6] MDR TB is largely a consequence of human activity as it did not exist before the introduction of chemotherapeutic drugs.[12]

Epidemiology of XDR TB

Extensively drug resistant tuberculosis (XDR TB) was originally defined as the presence of Mycobacterium tuberculosis isolates resistant to at least isoniazid and rifampin (MDR TB), plus additional resistance to at least three of the six classes of second-line drugs used to treat persons with MDR TB.[13] These forms of tuberculosis are both more difficult and expensive to treat. XDR TB is of particular concern among persons with HIV infection or other conditions that weaken the host's immunity. These persons are more likely to develop TB disease once they become infected with Mycobacterium tuberculosis, have been associated with a higher risk of death and the greatest concern is that XDR TB leaves some patients virtually untreatable with currently available drugs.[13]

In 2000, the Centers for Disease Control and Prevention (CDC), United States reported that 64% of patients affected by X-DR-TB died.[12] Between 2000 and 2004, the CDC and WHO surveyed an international network of TB laboratories to assess the number of cases of MDR and XDR TB. Of the 17,690 TB isolates, 20% were MDR and 2% were XDR.[10] Countries with records of XDR TB include United States (1993-2004), Latvia (2000-2002) and South Korea (2004) where 4%, 19% and 15% of their MDR TB cases, were XDR TB respectively.[10] In addition, a study conducted by the National Research Institute of TB and Lung diseases in Tehran, Iran between 2003 and 2005, showed that 10.9% of MDR TB strains tested were resistant to all eight second line drugs and these strains were identified as belonging to the MTB super family Harlem 1 and East African Indian.[14] The recent situation at Tugela Ferry in Kwa-Zulu Natal, South Africa is considered to be the tip of the ice berg in which 52 of the 53 patients co-infected with HIV/AIDS died.

Current global strategies for XDR TB

In an effort to curb the spread of XDR TB, the South African Medical Research Council, WHO and the US Center for Disease Control and Prevention in TB propose the following seven point plan: [15]

a. Rapid surveys to assess the current prevalence of XDR TB globally
b. Enhanced local laboratory capacity to carry out culture and drug resistance testing
c. Increased training of public health staff to identify, investigate and treat XDR TB outbreaks
d. Implementation of infection control precautions
e. Increased research support for drugs to treat XDR TB
f. Development of rapid diagnostic tests for TB
g. Access to antiretroviral drugs

For the family practitioner, there are a number of important issues to consider in implementing these strategies namely:

a. the need for forced hospitalization and compulsory treatment of these patients to reduce community exposure
b. Maintenance of confidentiality with the diagnosis
c. Possible stigmatization of these patients by other patients and the community

Other issues include the difficulty of making a diagnosis in such patients without running the risk of exposure to the infection by health care workers, accessibility to the drugs needed for their treatment and availability of isolation facilities e.g. XDR TB isolation wards or hospitals. The diagnosis of XDR TB will most probably be made by elimination after a patient on MDR TB treatment fails to respond to both first and second line regimens. The dilemma lies with the non-specific symptoms or signs for these patients beyond the non-response to treatment and laboratory isolation of extensively resistant strains of TB.

Conclusions

According to the South African National Health Act 61 of 2003, section 20, subsection 3 (b), "subject to any applicable law, every health establishment must implement measures to minimize disease transmission".[16] This implies that XDR TB should be a notifiable disease and the attending doctor has a legal obligation to supply all relevant information on the patient to the provincial health department who in turn has an obligation to transfer sufficient information to the national Department of Health (NDOH), in order to protect the larger population at risk. The emergence of XDR TB poses a threat in becoming a future epidemic that will complicate the HIV pandemic and plague mankind. It highlights the need for more aggressive focus on new anti-TB regimens, better diagnostic tests and stricter policy with regard to control and detection strategies. The national and provincial departments of health must as a matter of urgency identify well designed isolation units in all provinces to cope with the unknown number of possible or probable XDR TB patients that are already in the community.

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