

Extensively drug-resistant (XDR) tuberculosis: a new threat to global public health

Pratt RJ

Professor of Nursing, Director, Richard Wells Research Centre, Thames Valley University, London W5 2BS

Accepted for publication: 12 March 2007

Key words: Tuberculosis, *Mycobacterium tuberculosis*, human immunodeficiency virus (HIV), multidrug-resistant (MDR) tuberculosis, extensively drug-resistant (XDR) tuberculosis, antituberculosis drugs

Abstract

Throughout the world, eight million people develop active tuberculosis (TB) each year and 5,000 of them will die from this disease every day. Although treatable and curable, globally about 3% of all newly-diagnosed patients have multi-drug-resistant TB (MDR TB) making their treatment complicated, expensive and uncertain. In September 2006 the World Health Organization announced a further worsening of the MDR TB pandemic with multiple reports in all regions of the world of the emergence of extensively resistant (XDR) strains of TB resistant to virtually all anti-tuberculosis drugs. XDR TB may become the primary health scourge of the 21st century and in this brief report, the current status of our understanding of this new peril is discussed.

Introduction

The emergence and transmission of extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* that are virtually untreatable with currently available antituberculosis drugs has now been identified in all regions of the world, including the UK and other countries in the European Union.

Persons infected with the human immunodeficiency virus (HIV) are especially vulnerable to tuberculosis (TB) and XDR TB in these patients is often rapidly fatal.

Since first reported, the incidence of XDR TB has shown a trend to increase, especially in regions of the world where there is a high prevalence of HIV infection eg Africa. The World Health Organization (WHO) has estimated that US\$650million is needed annually to diagnose and treat over 1.5 million patients with drug-resistant TB by 2015.

XDR TB is a new and frightening manifestation of the disease that is certain to increase in importance everywhere. Infection prevention and control practitioners are the main source of reliable information and advice to healthcare colleagues and patients and the following are questions that are frequently asked.

What is XDR TB?

XDR TB is a type of MDR TB, which is also resistant to the second-line antituberculosis drugs (SLDs) used to treat MDR-TB (see Table 1). The description was first used in 2006 (Centers for

Disease Control and Prevention, 2006a) following a joint survey by the WHO and the Centers for Disease Control and Prevention (CDC) in the US and the case definition was revised later that year (Centers for Disease Control and Prevention, 2006b).

Persons with MDR TB are treated with SLDs. These are 'second line', because they are less effective, more toxic, and more expensive than first-line isoniazid- and rifampicin-based regimens.

How common is XDR TB?

In 2000 multiple cases of MDR TB, which were resistant to virtually all SLDs, were reported. To assess the frequency and distribution of XDR TB, the WHO/CDC surveyed an international network of TB laboratories.

The survey determined that of 17 690 isolates from 49 countries during 2000 to 2004, 20% were MDR and 2% were XDR.

In addition, population-based data on drug susceptibility of TB isolates were obtained from the US (for 1993 to 2004), Latvia (for 2000 to 2002) and South Korea (for 2004) where 4%, 19% and 15% of MDR TB cases, respectively were XDR (Centers for Disease Control and Prevention, 2006a).

In 2005 physicians at the Church of Scotland Hospital in KwaZulu-Natal Province in South Africa noted that there was a high rate of rapid death among HIV-infected patients who also had TB.

They conducted a study that revealed that 53 of 544 HIV-infected patients were found to have XDR TB and 52 of them died on average within 25 days, including those on antiretroviral therapy (Raviglione et al, 2007).

Fortunately, TB services in the UK are among the best in the world and drug resistance is uncommon in this country. In the UK in 2005, just 1.1% of all TB isolates were classed as MDR, only a very small proportion of which may now be classed as XDR TB using the new case definition (Health Protection Agency, 2007).

There is no evidence to suggest that XDR TB is increasing in the UK – at least not yet.

XDR TB is a new and frightening manifestation of the disease that is certain to increase everywhere

Table 1. MDR and XDR TB

Multidrug-resistant (MDR) TB	Extensively drug resistant (XDR) TB
Resistant to at least isoniazid and rifampicin, the two most powerful first-line antituberculosis drugs	MDR TB plus resistance to any fluoroquinolone and at least one of three injectable second-line antituberculosis drugs (capreomycin, kanamycin, amikacin) (Centers for Disease Control and Prevention, 2006b)

How do people become infected with or develop XDR TB?

There are two means by which people either become infected with or develop XDR TB – primary infection with a XDR strain of *M. tuberculosis* or the development of extensive drug resistance in a person with initial drug-sensitive TB due to a variety of secondary causes, eg non-adherence to antituberculosis drug regimens.

Initial infection with *M. tuberculosis* is common and it is estimated that one-third of the world's population is infected with this bacteria. Following primary infection, latent infection persists and only 10% of infected persons develop active TB during their lifetime. People with active (open) pulmonary or laryngeal TB expel small respiratory droplets in their breath, which contain the even smaller tubercle bacilli.

These small drops of moisture quickly evaporate and the remaining dried residue containing tubercle bacilli (known as 'droplet nuclei') are very buoyant and are then carried along by normal air currents.

Susceptible persons become infected by inhaling droplet nuclei deep into their alveoli. If the person they became infected from has MDR or XDR TB, then they will have acquired primary MDR or XDR TB infection.

However, this will only become a problem for them if they are one of the unlucky 10% who develop active TB following infection. Unfortunately, persons who are co-infected with HIV and *M. tuberculosis* have 10% annual risk of developing active TB and, consequently, are at an increased risk of MDR/XDR TB if they have been previously exposed to this strain of *M. tuberculosis*.

Of the 53 patients found to have XDR TB in the KwaZulu-Natal outbreak in 2005 (described above), 55% claimed they had never been treated for TB (implying that they had primary infection with an XDR strain of *M. tuberculosis*) and two-thirds of these patients had recently been hospitalised (suggesting they may have been exposed and infected while in hospital).

Persons being treated for active TB, which is fully sensitive to the first-line antituberculosis drugs, ie rifampicin- and isoniazid-based regimens, may subsequently develop MDR TB which would necessitate the use of SLDs. If they are then prescribed SLDs – which in many parts of the world are either not available or too expensive to use – the same reasons why they developed MDR TB may drive the development of XDR TB.

These reasons are principally problems that occur as a result of poorly managed clinical care, eg incorrect drug prescribing by

physicians, poor quality drugs or an erratic supply of drugs. Patient non-adherence to their antituberculosis drug regimen for whatever reason is another important reason why drug-resistance develops.

Is MDR and XDR TB highly infectious?

Drug-resistant strains of *M. tuberculosis* are neither more infectious nor less infectious than drug-sensitive strains. The problem is that people with active MDR and XDR TB are infectious for longer periods of time than persons with drug-sensitive TB (who can usually be rendered non-infectious quickly by the use of isoniazid and rifampicin therapy).

The extended period of infectiousness presents a real risk of further transmission of MDR/XDR strains of *M. tuberculosis* to susceptible persons (including healthcare workers).

Is XDR TB treatable?

Yes, in some countries with good TB control programmes. However, successful outcomes depend a great deal on the extent of drug resistance, the severity of the disease and especially whether the patient's immune system is compromised.

Treatment success is absolutely dependant on expert clinicians who have experience in treating patients who have XDR TB and having access to all six classes of SLDs.

However, in most parts of the developing world (and is some parts of the industrially developed world), successful treatment of XDR TB is not possible, especially in patients who are co-infected with HIV.

Will previous BCG vaccination prevent XDR TB?

The BCG vaccine mainly protects against severe forms of TB in children, such as TB meningitis. It is less effective in preventing the more commonly occurring pulmonary TB in adults.

Any protection afforded by BCG would apply to drug-sensitive as well as drug-resistant strains of *M. tuberculosis*. However, the effect of BCG vaccination against XDR TB is likely to be very limited.

Why are HIV-infected persons especially vulnerable to XDR TB?

TB is the most common opportunistic infection in HIV-infected persons. Active TB stimulates HIV replication, which further suppresses immune function, which in turn then exacerbates TB (Pratt, 2003).

Consequently it is easy to understand why ongoing active XDR TB that cannot be halted by antituberculosis drug treatment will quickly worsen both conditions. The future would seem grim in those countries with a high prevalence of HIV infection and TB.

What infection control measures are used when caring for patients with XDR TB?

A variety of administrative and engineering measures to prevent the nosocomial transmission of *M. tuberculosis* in hospital are comprehensively described in previous papers in this journal (Curran et al, 2006; Pratt and Curran, 2006) and elsewhere (Pratt et al, 2005).

Patients with MDR/XDR TB are cared for in a fully monitored negative pressure respiratory isolation room and personal respiratory protection is used to further minimise the risk of exposure and infection to healthcare workers and visitors.

In England, a particulate filter respirator (filtering half-mask) approved for use in protecting against airborne transmitted diseases and meeting the European standard EN 149 is recommended in national guidelines (National Institute for Health and Clinical Excellence, 2006) when caring for patients with MDR (and XDR) TB.

The grade of respirator recommended is the FFP3, which is the highest grade in this category.

The extended period of infectiousness presents a real risk of further transmission

Box 1. Priorities for the immediate strengthening of TB control

- Accelerate access to rapid tests for rifampicin resistance
- Ensure adherence to World Health Organization (WHO) drug-resistance guidelines, improve programme management, access to MDR TB drugs under proper conditions including direct observation. Ensure all HIV-infected patients are adequately treated for TB and started on antiretroviral therapy
- Accelerate implementation of infection control measures to reduce transmission, especially among HIV-infected persons
- Strengthen laboratory capacity to diagnose, manage and survey drug resistance. Start rapid survey so that the size of the XDR TB epidemic can be determined
- Initiate information-sharing strategies that promote prevention, treatment and control of XDR TB.

(WHO Global Task Force on XDR Tuberculosis Control, 2006)

What are the risks of healthcare workers, especially HIV-infected colleagues, of becoming occupationally exposed and infected with XDR TB?

The risk is dependant on a variety of factors, such as the competence of and adherence to evidence-based TB infection prevention and control measures in the hospital or clinic in which they practise.

References

- Centers for Disease Control and Prevention. (2006a) Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs – worldwide: 2000 to 2004. *MMWR* **55(11)**: 301-5.
- Centers for Disease Control and Prevention. (2006b) Notice to readers: revised definition of extensively drug-resistant tuberculosis. *MMWR* **55(43)**: 1176.
- Curran ET, Hoffman PN, Pratt RJ. (2006) Tuberculosis and infection control: a review of the evidence. *British Journal of Infection Control* **7(2)**: 18-23.
- Health Protection Agency. (2007) Frequently asked questions – tuberculosis. See: www.hpa.org.uk/infections/topics_az/tb/faq.htm#xdr (accessed 12 March 2007).
- National Institute for Health and Clinical Excellence. (2006) *Tuberculosis: clinical diagnosis and management of tuberculosis and*

The future would seem grim in those countries with a high prevalence of HIV infection and TB

Clearly the risk is greater in hospitals in resource-poor regions of the world as opposed to a metropolitan teaching hospital in the UK. Healthcare staff should be encouraged to be aware of their HIV status and if infected, they should not care for patients with active MDR/XDR pulmonary TB.

Is it safe to travel to countries where XDR TB has been identified?

XDR TB has been found in every region in the world, although it is uncommon. HIV-infected travellers or other immunosuppressed persons are most at risk if they do come into contact with a person suffering from XDR TB. Air travel carries only a minimal risk of TB infection of any kind.

How will the potential for a global pandemic of XDR TB be avoided?

The WHO Global Task Force on XDR TB has developed a plan for the immediate strengthening of TB control in all countries (see Box 1).

However, the WHO notes that XDR TB poses a grave public health threat, especially in populations with high rates of HIV infection and where there are few healthcare resources.

TB is spread by the very air we breathe and it is too soon to know if XDR TB will increase in incidence step-by-step and become the next 21st century plague. If so, the consequences to humankind are unthinkable.

measures for its prevention and control. Developed by the National Collaborating Centre for Chronic Conditions, Royal College of Physicians: London. See: www.nice.org.uk (accessed 12 March 2007).

Pratt RJ, Grange JM, Williams VG. (2005) *Tuberculosis: a foundation for nursing and healthcare practice.* Hodder (Arnold) Publishers: London.

Pratt RJ, Curran ET. (2006) Personal respiratory protection and tuberculosis: national evidence-based guidelines in England and Wales. *British Journal of Infection Control* **7(3)**: 15-7.

Pratt RJ. (2003) *HIV and AIDS: a foundation for nursing and healthcare practice (fifth edition).* Hodder (Arnold) Publishers: London.

Raviglione MC, Smith IM. (2007) XDR tuberculosis – implications for global public health. *New England Journal of Medicine* **356(7)**: 656-9.

The British Journal of Infection Control Call for papers

The editors are continuously seeking papers suitable for publication in the *British Journal of Infection Control*.

If you have recently undertaken any research or studies on aspects of care related to infection control then we would be pleased to consider it for publication.

Manuscripts of up to 4,000 words, short papers up to 1,000 words or communication/letters up to 500 words in length should be forwarded to Tracey Cooper via email to: editor@icna.co.uk

Please note that all papers are subject to a double-blind peer review process.