



What is MDR-TB and XDR-TB? How widespread is drug resistant TB? Was it predicted? Can it be treated?

The bacterium that causes tuberculosis (TB), *Mycobacterium tuberculosis*, is naturally sensitive to the antibiotic drugs used to treat the disease. Most cases of TB, and the majority of TB-related deaths each year, are the result of drug-sensitive TB.

Widespread use, or misuse, of anti-TB drugs can, however, lead to loss of drug sensitivity, giving rise to various forms of drug resistant TB:

- ◆ Multidrug-resistant TB (**MDR-TB**) is a specific form of TB that is resistant to the two most powerful anti-TB antibiotic drugs, isoniazid and rifampicin;
- ◆ Extensively drug-resistant tuberculosis (**XDR-TB**) is resistant to these two so-called 'first-line' anti-TB drugs, rifampicin and isoniazid, in addition to any antibiotic from the fluoroquinolone group, and at least one of the three injectable anti-TB drugs (capriomycin, kanomycin or amikacin).

As the reach of TB control programmes has increased throughout the world, so the widespread use of anti-TB drugs has also expanded. A seemingly unavoidable consequence has been the parallel development of drug resistance. Available data confirms that both MDR-TB and XDR-TB are already geographically widespread, including in places where TB control has been effective for many years.

Treatment of drug resistant TB is possible, but requires the use of 'second-line' drugs that are less effective, more toxic and costlier than first-line isoniazid- and rifampicin-based regimens. Cure rates for MDR-TB are reported to range from 6% to 59%. Diagnosis and treatment of drug resistant TB are not available in some of the countries most affected by TB, including in

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many parts of Africa. As a result, the vast majority of the drug resistant TB that occurs goes undetected and untreated.

A Global Project on Anti-tuberculosis Drug Resistance Surveillance was started in 1994 by the World Health Organization (WHO) and the International Union Against TB and Lung Disease (IUATLD). The project has now collected data from over 100 countries. The highest reported levels of drug resistant TB are seen in China (Henan and Liaoning provinces), Estonia, Israel, Kazakhstan, Lithuania, Latvia, Russia (Tomsk Oblast) and Uzbekistan (Karakalpakstan), where MDR-TB comprises over 6.5% of new TB cases. The project's latest overall estimate is that MDR-TB represents about 4% of all new and previously-treated TB globally.

In places where the overall numbers of TB cases are high, however, even a seemingly low percentage estimate of drug resistance can mask very high absolute numbers of drug resistant TB cases. In China, India and South Africa, for example, the general TB burden is so high that even relatively low *percentages* of drug resistant TB translate into extremely large numbers of affected individuals.

Drug resistant TB is likely to be far more widespread than is currently estimated, because of serious weaknesses in the current knowledge base. Despite over a decade of research by the Global

Surveillance Project, information about the extent of TB drug resistance is seriously lacking from many of the most important locations today, including: Countries with the highest burden of TB; settings outside of capital cities; areas where the HIV epidemic is fuelling the TB epidemic; and countries where prevalence of drug resistance is expected to be high because of historically poor TB control.

Detailed population-based epidemiological studies of TB drug resistance are urgently required.

In Africa, for example, surveys of drug resistance have previously been conducted in Lesotho and Swaziland, although the studies were conducted up to ten years ago. More recent TB drug resistance surveillance includes studies from

Botswana, South Africa, The Gambia and Zambia, but samples are relatively small and only include patients registered with the health systems.

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In March 2006, the US Centers for Disease Control (CDC) and WHO co-published new survey results from 49 countries indicating that MDR-TB was detected in 20% of samples tested, and that XDR-TB was found in 2% of cases. Although the survey sample was significantly dominated by large sample from Korea, and some variations in methods of drug sensitivity testing and XDR-TB definitions were also a factor, this was nevertheless the first data regarding the occurrence of XDR-TB worldwide. It was much worse news than anticipated.

At the time, the *Morbidity and Mortality Weekly Report*, which published the CDC/WHO survey, warned: "A growing number and proportion of XDR-TB cases could seriously hamper TB control globally."

Then later in 2006, a report of high levels of MDR-TB and XDR-TB emerged from a rural area of KwaZulu Natal (KZN) province in South Africa. The study looked at consecutive patients who presented with signs and symptoms of TB, including cough, fever and weight loss, over the course of about a year. Among confirmed cases of TB, the prevalence of MDR-TB was 39%, and of XDR-TB was 6%. Most worrying was that of the people diagnosed with XDR-TB, 70% had died within 30 days from admission.

In this part of KZN about 80% of patients presenting with active TB are also co-infected with HIV, and people living with HIV (PLHIV) are far more

likely to develop active TB in their lifetime than HIV negative people. Furthermore, over half of the XDR-TB patients (55%) had not been previously treated for TB, and an additional 30% had documented cure or completion of previous TB treatment course. This suggested that many of the cases were newly infected with an XDR strain of TB, a supposition supported by bacterial genotyping results.

Unease grew further when contact tracing revealed that patients with XDR-TB were from a dispersed geographic region, and had no known contact with each other apart from receiving health care from the same district hospital.

In South Africa – and much of the rest of Africa – effective TB infection control facilities and practices are extremely limited. As a result, it is highly probable that in KwaZulu Natal cluster of cases, transmission of XDR-TB strains occurred among PLHIV and *inside* of health care centres (also known as 'nosocomial' transmission).

Speaking at the IUATLD conference in late 2006, Dr Kevin de Cock, head of the WHO AIDS programme commented: "What brought XDR-TB to our attention in South Africa was the link with HIV, and the fact that many of the people with high mortality XDR-TB were also HIV-infected."

Compared to the rest of the region, South Africa has the capacity for TB drug resistance testing. "If this had happened somewhere else," added Dr de Cock, "we might never have known."

The cluster of XDR-TB cases reported in South Africa may not be so much an 'outbreak', but the visible emergence of a longer-term shift in the nature of TB and its interaction with HIV. What is different now is

that we have a new window through which we can witness the spread of drug resistant TB.

The management of MDR- and XDR-TB – both from a case and programme management perspective – clearly needs to be strengthened. The Global Fund (GFATM) has since agreed to 'retrofit' second-line TB drugs (SLD) into existing grants, and has let it be known it welcomes Round 7 proposals that include provision for SLDs.



On-line campaign on drug resistant TB

Drug-resistant TB poses a grave global public health threat, especially in populations with high rates of HIV, and requires an immediate and urgent global response.

In the 50 days leading up to World TB Day (Saturday 24th March, 2007), Health and Development Networks and the AIDSCareWatch Campaign are focusing on drug resistant TB.

The campaign aims to increase awareness, bring front-line perspectives to current MDR- and XDR-TB discussions, and advocate for TB patients to receive the best possible care.

If you are already a member of the **Stop-TB eForum**, do nothing. To join, go to the campaign website.

For a campaign update or further information, or to give your suggestions how the Campaign can be improved, please get in touch with us.

10% of new TB infections are resistant to at least one anti-TB drug

<http://www.healthdev.org/stop-tb>