



EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR-TB)

Multi-drug resistant tuberculosis (MDR-TB) is a form of tuberculosis resistant to *at least* the two principal first-line drugs rifampicin and isoniazid. The Global XDR-TB Taskforce convened by the World Health Organization in October 2006 defined extensively drug-resistant tuberculosis (XDR-TB) as a form of tuberculosis resistant not only to rifampicin and isoniazid, but also to certain second-line drugs (at least one, fluoroquinolone, and one of the three injectable drugs kanamycin, amikacin or capreomycin).

XDR-TB in itself is not a new problem. The existence of XDR-TB strains has been known to practitioners working in Eastern European and Central Asian countries. What is alarming about the recent outbreak is that it is occurring in a country with a very high HIV prevalence (South Africa), and risks spreading extremely rapidly amongst HIV positive people.

Doctors Without Borders/Médecins Sans Frontières (MSF) and XDR-TB

MSF is seeing an increasing number of cases of multi-drug resistant TB (MDR-TB) among the 17,000 patients it treats in over 94 projects in 44 countries. In a drug resistance survey MSF undertook among 326 TB in its TB project in Abkhazia (Georgia), 68 patients (20%) were found to have MDR-TB, among whom 15 patients (22%) were resistant to two or more second-line drugs and 2 patients (3% of the MDR patients) were resistant to three or more of the second-line drugs, and thus have XDR-TB.

Patients undergoing treatment for MDR-TB face long and arduous treatment lasting up to two years, much of which is often spent hospitalised in isolated wards. The drugs are very toxic, cause a wide range of side effects and are very expensive, costing up to \$15,000 per treatment course.

XDR-TB in KwaZulu Natal, South Africa – the spread of a new strain

A survey among suspected TB patients in the rural district of KwaZulu Natal between January 2005 and March 2006 revealed that 221 (41%) of 544 patients that tested culture positive for *M.tuberculosis* were infected by multi-drug resistant strains.

53 patients out of 221 (24% of MDR or 10% of all culture positive patients) were infected with XDR strains. 51% of the XDR patients had no prior TB treatment, suggesting that they had been newly infected by XDR-TB strains, and that resistance did not develop during treatment. 52 of the 53 XDR-TB patients died. The combination of XDR-TB and HIV infection leads patients to develop a highly aggressive form of tuberculosis that causes death in a very short time.

The emergence and rapid spread of XDR-TB in high HIV prevalence settings represent a major threat to global health. The phenomenon is a demonstration of the limitations of TB control programs, which have been relying on outdated tools for TB diagnosis and treatment.

XDR's implications for the TB drug and diagnostics R&D pipelines

The immediate responses of the public health community must not focus solely on strengthening control programs. It is also urgent to mobilise all necessary resources for the rapid delivery of new drugs and diagnostic tools.

Concerning drugs, it is crucial that the pipeline be filled with compounds that act through novel mechanisms that are able to target novel molecular targets, in order to avoid cross-resistance with drugs currently in use. Currently, there are a few new promising candidate drugs in the clinical phase of development. These candidate drugs have been shown to be active against MDR-TB

strains in vitro and in animal models, and therefore have the potential to be effective against MDR-TB in human patients. There is an urgent need for innovative thinking in the field of clinical trials for new TB drugs, in order to speed up the development of these new drugs and accelerate their delivery to patients.

A major limitation currently is the difficulty of diagnosing patients with TB. This problem is even more acute in the case of XDR-TB because the disease is so rapidly fatal that most patients will die before the results of their diagnosis are available. Rapid, reliable and field adapted diagnostic tools for TB and drug resistant forms of TB are an integral part of treatment strategies and urgently need to be developed.