A frightening new abbreviation entered the medical lexicon for the first time in March 2006. XDR stands for extensively drug resistant TB though some experts have it as extreme drug resistant TB. It was a report from the Center for Disease Control (CDC) and World Health Organization (WHO) in the March 24th issue of Mortality and Morbidity Weekly Report (MMWR) that first drew global attention to XDR TB.¹ The original MMWR definition of XDR-TB was: resistance to INH and Rifampicin (i.e.) MDR-TB with further resistance to at least 3 of the 6 classes of 2nd line drugs (aminoglycosides, polypeptides, fluoroquinolones, thiocarboxylates, cycloserine and PAS.) At a WHO meeting in Geneva in October the same year a new and more practical definition was adopted. XDR-TB is now defined as resistance to INH and Rifampicin along with further resistance to any fluoroquinolone and at least one injectable 2nd line drug (amikacin, kanamycin, capreomycin).

The original MMWR report was a retrospective survey of 17,690 TB isolates from 49 countries worldwide. These isolates were tested for 2nd line drug susceptibility in the 14 supranational reference laboratories from the WHO network. 20% of all the isolates were MDR and 10% of all MDR isolates were XDR. XDR-TB was present in 17 countries from all continents with the highest XDR prevalence being 19% from Latvia.

In the latest WHO report released on Feb 26th 2008 the situation was even worse than earlier reported; by this date XDR-TB had been detected in 45 countries globally.²

The original survey was let down by having no data from India and Africa. Indeed, this is the sad paradox of MDR and XDR-TB; the diagnosis of XDR-TB is a microbiological one and the countries with the greatest XDR-TB burden lack the laboratory facilities to document that burden. Thus there is hardly any Indian data available, purely due to laboratory limitations, despite it being certain that we have vast number of XDR cases. A study from the Hinduja Hospital and Research Center in Mumbai revealed that of 1354 samples reaching the laboratory (a reference lab by default for the city of Mumbai) 724 were culture positive and 45% of these were MDR. 9% and 11% of the MDR samples were XDR by the old and new definitions respectively.³ These figures do not of course represent data from the community as only non-responders have samples sent for culture in the first place but are an eye-opener to the fact that XDR-TB has long existed in India. Clinicians treating these patients have long struggled with this form of virtually untreatable tuberculosis for many years, but have not given it a name and as a consequence not given it any attention. Even before these patients had a catchy name for their form of tuberculosis, doctors here recognized it as a form that was nearly impossible to treat and whose spread was frightening to contemplate.⁴

XDR-TB is even more difficult to treat than MDR-TB. Treatment is often destined to fail because, by definition, there are very few categories of drugs left to which these patients will still respond. The first study on the outcome of XDR-TB patients from KwaZulu Natal, South Africa, revealed staggeringly high mortality in these patients. This may have been partly due to the fact that almost all of these 53 patients were also HIV co-infected. 52 of the 53 XDR-TB patients died, the majority before sputum culture reports could even be received, with a median survival of just 16 days.⁵

Whilst the combination of XDR-TB and HIV is almost uniformly lethal, the survival in our Hinduja Hospital XDR series where most patients were not HIV positive was better. Of our 33 XDR-TB patients, 12 were alive and 8 of these had been declared cured after 2 years of extensive and complicated medical and surgical therapy. Data from larger XDR-TB cohorts treated under optimal conditions in Italy and Germany has only just become available.⁶ XDR-TB carries a five fold increase in the risk of death compared to patients with MDR-TB (relative risk 5.45; 95% CI, 1.95-15.27; P < 0.01)

As physicians we are all to blame, for the recipe for XDR tuberculosis is inappropriate use of second-line drugs in a patient in whom first line drugs are failing. Quinolones are used in a particularly cavalier fashion in this country. In a nationwide audit of antibiotic prescriptions for viral infections in 2004, of the 20 million antibiotics prescribed, ciprofloxacin and ofloxacin were by far the 2 commonest drugs prescribed.⁷ This pivotal group of 2nd line drugs should be not squandered away as general antibiotics. A 6 day course of levofloxacin is...
enough to lead to emergence of high grade resistance to M. Tuberculosis later. Thus it is not surprising that quinolone resistance in TB is a global phenomenon and a pivotal group of 2nd line drugs is being rendered worthless.

Our policy makers also indirectly contribute to XDR-TB. Existing cases are treated badly, converting sensitive to resistant strains. Then, patients who have failed to respond or relapse, and who in all probability have MDR-TB, are then subjected to Category 2 treatment (2HREZS/1HREZ/5HRE). This is a regimen destined to fail; a poor way to treat MDR-TB, and a colossal waste of resources which serves only to amplify resistance. Failures at the end of this 6 + 8 month period are finally labeled MDR (the majority without microbiological proof), and left to their own devices. There are no government provisions for their treatment and these unfortunate patients are treated without science or compassion converting MDR to XDR cases. XDR-TB has thus always existed in India; we now just have a catchy label to hang on these unfortunate patients who are truly the “no-hopers” of the Indian TB hierarchy.

What is really needed is good and responsible prescribing practice, ideally under supervision. Treatment of MDR and XDR TB is lab and labor intensive and should only be undertaken by a specialist, ideally in a few designated centers of excellence.

A strong laboratory network with surveillance systems in place is also urgently needed. Sadly, there are no more than a handful of laboratories reliably and accurately performing sensitivities to first, let alone second line drugs. TB drug sensitivity testing is one of the most neglected aspects of TB control. Promising new and rapid genotypic and phenotypic methods relevant to the developing world are needed. A quick diagnosis of MDR and XDR-TB translates into greater likelihood of patient cure and less spread of this potentially lethal strain thus benefiting individual and society.

Finally, new classes of drugs are needed urgently. There are some promising new candidates at clinical trial stage (Diarylquinoline TMC207, Nitroimidazole PA-824, Diamine SQ-109 to name the three most promising), and it is heartening that after decades of neglect we have global funds and attention again focused on tuberculosis.

The gravity of the XDR-TB has not escaped the keen attention of the WHO. The director of the Stop TB department Mario Raviglione said: “Either we intervene rapidly to stop the spread of this strain or you can foresee in the future that this strain will replace the other one. That would make it practically uncontrollable.” We in India need to take these prophetic words seriously.

REFERENCES