SHORT COMMUNICATION

XDR Tuberculosis: A Report from the New Delhi Tuberculosis Centre, India

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Extensively drug-resistant tuberculosis or XDR-TB is relatively a new term coined initially by CDC and WHO in 2005, which described XDR-TB as cases having Mycobacterium tuberculosis (M. tuberculosis) isolates resistant to isoniazid and rifampicin and at least three of the six main classes of second line drugs namely aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and para-aminosalicylic acid.¹ The need of revision of definition was felt due to inadequacy of reliability and reproducibility for some of the second line drugs. Revised definition described XDR-TB cases as isolates resistant to isoniazid and rifampicin plus resistance to any fluoroquinolone and at least one of the three injectable second line drugs i.e. kanamycin, amikacin or capreomycin.²

XDR-TB is even more difficult to treat than MDR-TB. Treatment is often destined to fail with few categories of drugs left, to which the patients would still respond. 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).³

XDR-TB has been reported from almost all regions of the world. In the latest WHO report released in February 2008, the situation was even worse than earlier reported; by that date XDR-TB had been detected in 45 countries.⁴ This global epidemic of XDR tuberculosis has serious implications for the TB control programmes worldwide and demands urgent intervention. A report regarding XDR-TB is being presented from Delhi based on retrospective analysis of the data from New Delhi Tuberculosis Centre.

New Delhi Tuberculosis Centre, designated as Intermediate Reference Laboratory for the state of Delhi has been carrying out drug susceptibility testing since last many years with an excellent concordance with TRC Chennai—a supranational reference laboratory of WHO in external quality assessment. This centre being a referral centre, majority of samples received here are for drug susceptibility testing from retreatment cases or treatment failures suggesting that nearly all cases had history of prior treatment of tuberculosis. Samples were processed by Nassau’s method of decontamination. Oxalic acid was used as decontaminating agent. All mycobacterial isolates were identified by the standard biochemical tests, viz. growth rate, growth on LJ medium containing p-nitrobenzoic acid, growth temperature 35⁰C-37⁰C, pigmentation, Niacin test and heat sensitive catalase test.

Drug sensitivity of all M. tuberculosis isolates to first line antitubercular drugs viz. isoniazid, rifampicin, ethambutol and streptomycin and second line drugs such as kanamycin, ciprofloxacin, ofloxacin, ethionamide, cycloserine and Para-aminosalicylic Acid (PAS) was done by the standard Resistance Ratio method.⁵ M. tuberculosis H37 Rv served as susceptible control and laboratory resistant controls.

During the 6 years from 2001 to 2006, a total of 18,443 M. tuberculosis isolates were processed for drug sensitivity testing. Of those, 9614 (52.12%) were found to be multi-drug resistant. A total of 86 (0.89%) cases met the criteria of XDR among the MDR-TB cases. Year-wise detection of these XDR cases is given in Table I. A consistent decline was observed in the incidence of reported cases of XDR over the years right from the year 2001. These 86 cases were reported from 7 states with the largest number from Delhi (49) followed by neighbouring Rajasthan (10), Haryana (9), Uttar Pradesh (8), Uttarakhand (5), Punjab (4) and Madhya Pradesh (1). Of those 86 cases, only 5 patients were females and rest were males. A total of 53 out of 86 (61.6%) of the isolated resistant strains were resistant to more than 4 classes of drugs indicating severity of resistance (Table II).

Recently, there have been a number of reports on XDR-TB, (a) 19% of all MDR strains between 2000-2003 from Latvia, (b)15% of all MDR strains from Korea, (c) 12% of all MDR strains from Hong Kong (9 of 75 MDR strains), (d) 10.9% of all MDR strains from Iran (12 out of 113 MDR strains).¹,⁶,⁷ In USA, 4% of all MDR strains were XDR-TB between 1993-2006 and only 49 strains till date have been discovered to have XDR-TB as per definition.¹ In the present study, total of 86 isolates between the period 2001-2006 in the laboratory confirmed to the definition of XDR-TB as per latest definition amounting to 0.89% of the total MDR cases.

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Recently, a few other authors from India have also documented the presence of XDR-TB. In an abstract presented at American Thoracic Sociery 2007 Conference, from a private hospital, Mumbai, authors claimed that a total of 1,274 positive *M. tuberculosis* cultures, 32% were found to be MDR-TB, out of which, 9% were XDR. In another study from Lucknow, Uttar Pradesh, out of 68 MDR *M. tuberculosis* isolates obtained from sputum samples from December 2000 through December 2002, 5 (7.4%) isolates were XDR.9 Recently, in a study from National Reference Laboratory, TRC Chennai on the management of MDR patients, of 66 MDR isolates, 1 (1.5%) met the criteria of XDR.10 Thus, the different reports from India; reports show wide disparity in the magnitude of XDR resistance. While the detailed data regarding the methodology and quality control for DST testing in the Mumbai study is not known, the sample size in the latter two studies from Lucknow and Chennai is too small to draw any meaningful conclusion so as to make any comparison. The present study reports on data of a very large number of *M. tuberculosis* isolates tested for a period of 6 years and is comprehensive.

In relation to percentages and proportions, these cases may seem a small minority. However, this is a report of one tertiary level laboratory i.e. Delhi State TB Intermediate Reference Laboratory. Exaggerated to whole of the country, and given the gross inadequacy of the laboratory set-up for mycobacterial culture and sensitivity testing, especially of the second line drugs in the country, the number of such cases could be much more. Sixty one percent of XDR strains in this study were resistant to more than 4 classes of drugs, which is a grim reminder of the severity of the disease.

XDR-TB with HIV infection may have the deadliest combination as reported from Kwa Zulu Natal province in South Africa where 52 out of 53 cases died with a median survival of 16 days after sputum sample collection; 44 of them had been HIV positive. Data about HIV infection in this study is lacking since it is a retrospective analysis of laboratory data.

XDR-TB is a laboratory diagnosis and the existing tests for second line drugs lack standardization and are less reproducible. Moreover, the precise methods and the critical drug concentrations are yet to be defined for all second line drugs. The policy document on second line testing from WHO is likely to be available by this year. This study has also the limitation that drug susceptibility tests for second line drugs have not been validated by TRC, Chennai – a supranational laboratory. However, the susceptibility tests for first line drugs are routinely assessed by external quality assessment and are validated by TRC, Chennai with excellent concordance since 1995. Therefore, the results of the second line drug susceptibility tests at New Delhi TB Centre Laboratory for state of Delhi are reliable with reasonable certainty.

Besides documenting the existence of XDR-TB in India, this study also observed a steady decline in the isolation of MDR-TB as also XDR-TB strains over the years i.e. 2001-2006. This unexpected observation is difficult to explain. However, given the reliability of the quality of the laboratory testing, probable reasons could be a chance finding or a definite decline in drug resistance due to better implementation of RNTCP policies over these years resulting in successful completion of treatment and lesser creation of MDR and lesser inadvertent use of second line drugs. However, this trend needs to be corroborated by further studies.

Population-based surveillance data is needed to determine the magnitude and trend of XDR-TB especially in heavy HIV burden geographical areas. For this, high capacity quality assured laboratory infrastructure needs to be established, which can reliably and rapidly detect drug resistant TB. Prevention of creation of drug resistance by appropriate application of DOTS strategy is the best way to stop XDR/MDR.

The second strategy is strict control and appropriate use of second line drugs under supervision to treat MDR-TB and XDR-TB in accordance with standard guidelines.

**REFERENCES**


