Tuberculosis: TDR and XDR war of terminologies

Tuberculosis, MTB or TB (Tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*[1], which attacks the lungs but can also affect other parts of the body. It spreads through the air when people with active MTB infection cough, sneeze or transmit their saliva[2]. Roughly one-third of the world's population has been infected with *M. tuberculosis*, and new infections occur at a rate of one per second. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries is found to be positive in tuberculin tests, whereas only 5–10% of the US population tests positive. TB is the world's greatest infectious killer of women in their reproductive age and the leading cause of death among people with HIV/AIDS (www.prnewswire.co.uk/cgi/news). India has the largest total incidence, with an estimated 2.0 million new cases[3].

TB is broadly divided into three categories: Multi-drug-resistant tuberculosis (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB) and totally drug-resistant tuberculosis (TDR-TB). MDR-TB is resistant to the two most powerful first-line anti-TB drugs, isoniazidand rifampicin. XDR-TB is a form of TB caused by bacteria that are resistant to the most effective anti-TB drugs, or strains that have emerged from the mismanagement of MDR-TB. TDR-TB is a form of TB which is resistant to all currently used drugs. It was first discovered in 2007 in Italy and later in 2009 among a small percentage of patients in MDR-TB outbreak in Iran. However, it was widely reported in 2012, when TDR-TB was discovered in India. The first cases of TDR-TB in India were reported by the team of Zarir F. Udwadia from the P. D. Hinduja National Hospital and Medical Research Centre, Mumbai[4], where the physicians grappled with patients of TDR-TB. Consequently, a team of experts from the World Health Organization (WHO) and a central team of medical experts reached Mumbai to analyse the situation. This team involving experts submitted its report to the government, which indicated that there were no cases of TDR-TB in the country and the cases reported by the Mumbai hospital fell in the category of XDR-TB. On the basis of submitted report, the Health Ministry published a statement declaring that the laboratory at the Hinduja Hospital was not accredited for some of the tests that Udwadia's team had carried out and questioned the term 'totally drug-resistant TB'. TDR is neither recognized by WHO nor by the Revised National Tuberculosis Control Programme. 'The reported cases by Hinduja Hospital fall only within the category of XDR-TB based on standard WHO definitions and not at all as TDR-TB. Out of the 12 reported patients, nine are traced and found to be stable on the current treatment while three had died.'

Udwadia is a consultant chest physician at Hinduja Hospital and the only Indian doctor to be invited by WHO, Geneva to be part of a core task force to formulate new TB treatment guidelines for 2009 at a meeting held in Paris in October 2008. According to Udwadia, Mumbai would seem to be a prime breeding ground for drug-resistant infections. The city, home to more than 12 million people, is beset by poverty, overcrowding and harsh living conditions. He says that although the DOTS (Directly Observed Therapy, Short Course) programme has generally been successful for people with normal TB who do have access to it, for those with drug-resistant tuberculosis, it causes more than 8 months of delay as people are forced to go through standard treatments before they are diagnosed. During this time, they are generating further resistance.

Velayati *et al.*[5] carried out susceptibility testing against first- and second-line drugs on isolated *M. tuberculosis* strains. The strains identified as XDR or TDR *M. tuberculosis* were subjected to spoligotyping and variable number of tandem repeats (VNTR). Among the 146 MDR-TB strains, eight XDR isolates (5.4%) and 15 TDR isolates (10.3%) were identified. The remaining strains were either susceptible (67%) or had other resistant patterns (20%). Overall, the median of treatments and drugs previously received by MDR-TB patients was two courses of therapy of 15 months duration with five drugs (isoniazid [INH], rifampicin [RF], streptomycin, ethambutol and pyrazinamide). The median of *in vitro* drug resistance for all studied cases was INH and RF. The XDR or TDR strains were collected from both immigrant (Afghan, 30.4%; Azerbaijani, 8.6%; Iraqi, 4.3%) and Iranian (56.5%) MDR-TB cases. The smear and cultures remained positive after 18 months of medium treatment with second-line drugs (ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin and ciprofloxacin). Spoligotyping revealed Haarlem (39.1%), Beijing (21.7%), EAI (21.7%) and CAS (17.3%) superfamilies of *M. tuberculosis*. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB cases. This study shows that the isolation of TDR strains from MDR-TB patients from different regional countries is alarming and underlines the possible dissemination of such strains in Asian countries.

Currently there is a war of terminologies among the TB research team of Hinduja Hospital, the Indian Government and WHO. In this scenario one should not forget the fact that 400,000 deaths in India are caused by TB each year, and it is the leading cause of death in the 15–45 age group. If XDR-TB shows resistance to the all available drugs and transforms to the next level, then the question would arise as to how one should control and treat such cases.

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