

Super TB: Another Manmade Disaster

Aditi Chaturvedi, Rangeel Singh Raina, Vijay Thawani, Harish Chaturvedi¹, Deepak Parihar

Departments of Pharmacology, and ¹Anatomy, Vir Chandra Singh Garhwali Government Institute of Medical Sciences and Research, Srikot, Pauri-Garhwal, Uttarakhand, India

ARTICLE INFO

Article history:

Received 15 December 2012

Accepted 15 December 2012

Available online ***

Keywords:

Drug sensitivity testing,

Totally drug resistant,

Tuberculosis,

XXDR

ABSTRACT


Resistant tuberculosis is a man made disaster due to negligence of patients, physicians, and policy makers. It has been fuelled by inadequate use of sputum smear microscopy, excessive dependence on chest radiography, illogical manufacture and irrational prescription of improper combinations of medicines, inadequate dose, duration and noncompliance to the prescribed treatment. The resultant gift is the dreaded Totally Drug Resistant Tuberculosis (TDR-TB). Culture and drug sensitivity testing (DST) should not blindly direct the management of TDR-TB, but has the importance in individualising the drug therapy in TDR-TB patients. The DST which is a crucial part of Directly Observed Treatment Short course (DOTS) plus has been introduced in a phased manner in India. However measuring resistance to second line anti-tubercular drugs (SLDs) with DST is complex and lacks standardization. The WHO has categorized the SLDs based on their efficacy. Most of the DST methods have a turnaround time of several months and empirical regimen should be switched to individual regimen depending on DST results. Newer assays like microscopic observation drug susceptibility assay, line-probe assay and bacteriophage assay can be used for rapid detection of drug resistance. Pharmacovigilance is urgently needed for resistant tuberculosis as SLDs are less efficacious and more toxic. Presently, the treatment of TDR-TB is not consolidated. Precaution in the treatment, prevention of spread of the infected cases and use of newer vaccines are some of the strategies which have to be used to contain the new mighty variant of microbe *Mycobacterium tuberculosis*.

Introduction

Tuberculosis (TB) has caused morbidity and mortality since centuries to terrorise the mankind as stubborn and die hard disease. The annals of TB are full of the accounts how it extensively swept across large regions of the globe in epidemics and it continues to tease the innovative capabilities of research scientists. In the recent past there has been an upsurge in TB with multi-drug resistance TB (MDR-TB), extensively drug resistant TB (XDR-TB) and now the

newer form Totally Drug Resistant TB (TDR-TB) has come up, which is perturbing and warrants focussed attention.

The TDR-TB was first reported in 2009 from Iran when the patients suffering from TB were found resistant to all the first line antitubercular drugs (FLDs) and second line antitubercular drugs (SLDs).^[1] The term extremely drug resistance tuberculosis (XXDR-TB) was earlier used in 2007 in Italy, for patients refractory to all FLDs and SLDs.^[2-4] In 2012 the print media first time reported about the patients of TDR-TB in India.^[5,6] Though XDR and TDR-TB have been reported from many other countries, the reports underrate the true extent of the problem, justifying widespread surveys to find its prevalence.^[7,8] The term TDR-TB is not recognised by WHO because absolute correlation of clinical response with drug sensitivity testing (DST) is not established. A patient may show clinical response to an anti-tubercular drug in spite of demonstrating resistance in DST. Currently there is no internationally acceptable standardized DST for SLDs, therefore WHO is against the use of these tests to blindly guide the treatment.^[9] The WHO expert group in 2012 decided on the possible definitions of TDR-TB and mentioned that the term 'totally' may create fear amongst the patients and community and distort the opinion of an average TB patient and the term 'TDR' is inadequate to address to this form of TB, so a new definition, apart from the one existing for XDR-TB, is not desirable.^[10] Hence WHO

Access this article online	
Website: www.sysrevpharm.org	Quick Response Code:
DOI: 10.4103/0975-8453.107140	

Correspondence:

Dr. Aditi Chaturvedi;

E-mail: aditichaturvedi150@yahoo.com

recommends treatment of TDR-TB to be the same as XDR-TB, though it accepts that the newer form being more severe than XDR. We hereby review in brief this super form of TB, known to many as TDR-TB.

Factors contributing to TDR-tuberculosis

Resistant TB is a manmade disaster with negligence on the part of patients, physicians and policy makers. Factors like less use of sputum smear microscopy, excessive dependence on chest radiography, improper combinations of medicines, errors in medicine dosage and duration of treatment, non or low patient compliance to the treatment has led to the world's most dreaded Totally drug resistant tuberculosis (TDR-TB) which has the potential to create havoc both for the patient and community.^[11] The surfacing of TDR-TB has challenged the STOP TB strategy, especially in countries with higher prevalence of HIV. Revised National Control TB Programme (RNCTP) and state health authorities are following a wellplanned strategy to face the challenges of drug resistant tuberculosis under supervision of Government of India. These include nationwide Directly observed treatment short course (DOTS) coverage, research in monitoring the pattern of drug resistance, rapid detection of drug resistance, and improving methods for prevention and management of drug resistance. The DST, crucial to DOTS plus programme, is being introduced in a phased manner in India.^[12]

Role of DST in TDR-tuberculosis

Though culture and drug sensitivity testing (DST) should not blindly be directing the management of TDR-TB, it is important in individualising the drug therapy for TDR-TB patients. The DST should be done in all the patients undergoing retreatment, with chronic TB and those with history of contact with patients with drug resistant TB.^[13] In 2010, 16 out of the 36 countries with high burden of tuberculosis did not have single laboratory capable of performing TB culture and DST per five million people.^[14] Greater part of the Africa and the Indian subcontinent still remain poorly

served in this respect.

Four DST methods viz. absolute concentration method, resistance ratio method, proportion method (with variants), and BACTEC-460 radiometric method have been standardized for FLDs and are used globally for measuring drug resistance [Table 1].^[15, 16] These methods give accurate results when standardized and quality controlled. Most of the DST methods have a turnaround time of several months and empirical regimen should be switched to individual regimen as soon as result is obtained. Newer assays like microscopic observation drug susceptibility assay, line probe assay, bacteriophage assay can be used for rapid detection of drug resistance [Table 1].^[20-22] Measuring the resistance to SLDs is complicated and lacks standardization for many medicines. The WHO has grouped the SLDs based on their efficacy into five classes [Table 2]. For MDR, XDR and TDR-TB, individualized treatment based on DST reports provides high cure rates provided that the patient adherence is intensively checked. The reliability of DST for SLDs is dependent on the peak serum concentration and minimum inhibitory concentration (MIC) of the anti-tubercular medicines. The SLDs like kanamycin, paraaminosalicylic acid and capreomycin have peak serum concentrations much higher than the MIC, therefore high concentrations can be maintained in the lesions throughout the treatment phase. Some SLDs like cycloserine, ofloxacin, ethonamide have peak serum concentrations closer to MIC values, signifying sub-inhibitory levels during most of the treatment and low reliability of DST for the SLDs.^[24] Therefore, it is essential to establish international quality assurance programme for SLD analysis. Other rapid and surrogate methods that can be used are early bactericidal activity (EBA) assay and nucleic acid amplification test (NAAT) for drug resistance which holds immediate promise for scaling up laboratory capabilities [Table 1].^[25, 26] The DST needs recruitment of qualified TB labworkers and DST results need expert interpretation as strains showing susceptibility may not be truly susceptible. Therefore rational use of DST results should exclude resistant SLDs rather than include susceptible SLDs in the treatment regimen. To ensure precision, laboratories with experience and competency in performing FLDs testing should test SLDs.^[24]

The RNTCP programme in India has collaborated with Foundation for Innovative New Diagnostics (FIND) in validation and demonstration

Table 1: Common drug sensitivity testing methods^[12, 17-19]

DST method	Principle	Preferably performed for medicines	Turnaround time
Proportion method (preferred method)	Measures ratio of colonies on medicine containing to the medicine free medium. > 1% = resistance.	For most of anti-tubercular medicines except pyrazinamide, fluoroquinolones	28-42 days
Minimum inhibitory concentration (MIC) or Absolute concentration method	Several concentrations of medicines tested and resistance expressed in terms of MIC.	First line drugs (FLDs) except pyrazinamide, kanamycin, ofloxacin	28-42 days
Resistance ratio (RR) method	Determines ratio between the MIC of test and reference strain (RR > 8 = resistance).	FLDs except pyrazinamide	28-42 days
BACTEC-460 radiometric method	Resistance determined by comparing volatile radioactive CO ₂ in control and medicine vial	FLDs, Second line drugs (SLDs), rifabutin	7-10 days
MODS (Microscopic-observation drug-susceptibility) assay).	Characteristic tangles of mycobacterium tuberculosis seen under inverted light microscope	FLDs,	7 days
Line probe assays	Genotypic molecular methods	FLDs including, pyrazinamide, ofloxacin, amikacin, capreomycin,	< 48 hrs
Bacteriophage assay	Use of mycobacteriophages as indicators of viability.	Rifampicin	48-72 hrs
Mycobacterial Growth Indicator Tube (MGIT 960 system)	Alternative to BACTEC 460. Is a fluorometric and detects oxygen consumption in the presence / absence of drug	FLDs and SLDs, rifabutin, linezolid, capreomycin	7-10 days
Nucleic Acid Amplification Test (NAAT)	Cannot replace conventional tests. Has high specificity and positive predictive value.	Rifampicin	2-4 hrs

Table 2: Antitubercular medicine groups based on WHO guidelines for the management of drug resistant tuberculosis, based on the efficacy^[23]

Group	Medicines
1	First line oral agents:Isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb) ^a
2	Injectable agents:Kanamycin (Km); amikacin (Am); capreomycin (Cm); viomycin (Vm); streptomycin (S)
3	Fluoroquinolones:Moxifloxacin (Mfx); levofloxacin(Lfx); ofloxacin (Ofx)
4	Oral bacteriostatic second line agents:Ethionamide (Eto); protonamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)
5	Agents with unclear role in resistant TB:Clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high dose isoniazid (highdose H); ^b clarithromycin (Clr)

^aRifabutin is not in the WHO List of Essential Medicines. It has been added here as it is used routinely in patients on protease inhibitors in many settings, ^bHigh-dose H is defined as 16–20 mg/kg/day

studies of the Xpert MTB/RIF assay which is a fully automated Nucleic Acid Amplification Test (NAAT) assay and takes just two hours in the diagnosis of *Mycobacterium tuberculosis*, MDR-TB and HIV with TB. In 2011-12, India was to introduce this WHO endorsed technology at 18 sites, expected to enable diagnostic service for about eight million people and improve the quality and accuracy of TB diagnosis for all TB suspects accessing healthcare services through the private or public health sectors. The FIND negotiated preferential pricing structure for the Xpert MTB/RIF assay is expected to favour public sector collaboration with the private health sector for TB diagnostic services. The laboratory expansion plan for India is extensive and provides a model for large scale implementation of culture and DST services in collaboration with the private sector.^[27]

New agents and pharmacovigilance in resistant TB

Medicine buyers have to be aware of the fact that efficacy of SLDs is lesser and side effects greater when compared to FLDs. Availability of some of these agents being limited, the cost of remedies is high. Medicine management still remains a major challenge, with 4/24 countries reporting stock outs of SLDs in 2009.^[27] Progress could be achieved by facilitating registration and importation of medicines, complying with quality assurance standards set by WHO, reinforcing national medicine management and increasing production capacity of the quality assured products.

Pharmacovigilance, for resistant TB is recommended because national TB control programmes usually do not measure Adverse Drug Reactions (ADRs) and the contribution of ADRs to mortality is not clear. The widespread recognition by health workers that anti-TB medicines often cause ADRs is inadequate in the published information. There is a dearth of literature about SLDs induced mortality, morbidity and loss in quality of life, particularly in low resource settings. With the increasing use of extensive regimens for drug-resistant TB, with the added use of ARV therapy in patients with HIV associated TB, and with the advent of new medicines to treat TB, there is strong need for improved pharmacovigilance.^[27]

Precautions for prevention of TDR

The currently available treatment of TDR-TB is not consolidated. Precaution in the treatment, prevention of spread of the infected cases and introduction of newer vaccines are some important tools. Any health care provider, public or private, undertaking to deliver the TB services must realize the responsibility to both the individual and the community to fulfil these duties.

The Government policies and the curriculum of lab technology needs to ensure that their graduates have the skills to do SLDs-DSTs. Considering the difficulty of providing high quality DST results, centralised, well equipped, well staffed and controlled DST services should be preferred over a dense network of low quality DST labs throughout the nation where not only standard DSTs but highly specialised drug susceptibility tests like NAAT are also available so that quality is not compromised.^[28]

WHO advises against simply adding a single new medicine to the failing regimens. The compassionate use of experimental medicines outside clinical trials has been addressed by the WHO for TDR tuberculosis.^[9]

The XDR and TDR-TB are disasters of human errors causing failing TB programs, where the remedy for the malady has become a tragic comedy. The TDR-TB threatens the gains made in the past in the treatment of both TB and HIV. Infection control encompasses administrative control to lessen the risks of exposure, infection and disease through policy and practice, environmental controls to reduce concentration of infectious bacilli in the air, in areas where contamination is likely, and personal respiratory protection with N95 masks which filter 95% of the airborne particulates to protect the personnel working in environment with contaminated air. Combination of these strategies can avert TDR-TB even in resource limited settings.^[29]

Future demands for TDR management

Future research and development in the fields of surveillance to determine the geographical distribution and extent of TDR-TB, its association with HIV, molecular testing to develop new diagnostic tools for TB diagnosis, drug resistance determination, should be explored to expand the scope of drug resistance surveillance, expansion of MODS to include SLDs needs to be explored. Interaction of SLDs and ARV treatment needs to be studied. Development of new anti-TB medicines and strict implementation of infection control strategies are required to control and prevent the spread of TDR-TB. International standards for TB care must be sincerely adopted and endorsed throughout the world, especially in high burden countries.

Though attention is being paid to improve treatment outcomes in resistant cases, thoughtfulness for palliative and end of life care of patients and families in TDR patients is lacking. It is recommended that existing problems such as dyspnea, cachexia, pain, hemoptysis can be taken care with palliative care for patients, especially at home to enhance the performance of control programmes.^[30]

Vaccines

Though *Bacillus calmette-guérin* (BCG) reduces the risk of severe paediatric TB, protection offered in adult TB is variable. Newer vaccines are in various phases of clinical trials such as DDA/TDB vaccine, BCG::RD1, rBCG-Hly.^[31] Dimethyldioctadecylammonium

(DDA) and trehalosedibehenate (DDA/TTB) liposomes, act as adjuvant and have shown to induce strong humeral responses to the associated antigen without increased reactogenicity and are currently in phase I clinical trials.^[32] rBCGΔureC::Hly has been equipped with membrane perforating listerolysin (Hly) from listeria monocytogens and provides better protection by increase in CD8+ cell response in aerosol challenge than the conventional BCG vaccine.^[33] BCG::RD1 vaccine has been prepared by reintroduction of RD1 gene locus and is said to provide better protection but also increased virulence.^[34] Mycobacterium vaccae is an inactivated whole cell non TB mycobacterium which has currently completed phase III trial in BCG-vaccinated HIV+ adults.^[35]

Conclusion

As the miniscule microbes continue to score over the so claimed most potent and powerful macrobes of planet earth, the treatment options for TDR-TB continue to remain limited. The patient support, regular follow up, treatment adherence to DST sensitive medicines and palliative support to the patient and families are still cherished but yet missing in the mainstay in management of TDR-TB.

The emergence of TDR-TB indicates the return of powerful TB bacilli with renewed zeal to challenge the researchers to develop new anti-TB medicines and effective vaccines. The health professionals need to realize the need to be more vigilant on the use-misuse of anti-TB medicines and lab workers to attain the skills required in DSTs. It is a reminder to the community at large that prevention still remains better than cure. May the better sense prevail.

References

- Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, Ziazarifi AH, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: Super extensively drug-resistant tuberculosis of totally drug-resistant strain in Iran. *Chest* 2009;136:420-5.
- Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: The new XDR-TB threat. Is "science" enough to tackle the epidemic? *Eur Respir J* 2007;29:423-7.
- Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM. First tuberculosis cases in Italy resistant to all tested drugs. *Euro Surveil* 2007;12:3194. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3194> [Last accessed on 2012 Jul 14].
- Migliori GB, Ortmann J, Girardi E, Besozzi G, Lange C, Cirillo DM, et al. Extensively drug-resistant tuberculosis, Italy and Germany. *Emerg Infect Dis* 2007;13:780-2.
- Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C. Correspondence: Totally drug-resistant Tuberculosis in India. *Clin Infect Dis*. published online 2011. Available from: <http://cid.oxfordjournals.org/content/early/2011/11/24/cid.cir889>. [Last accessed on 2012 Jul 14].
- Iyer M. Times of India. New deadlier form of TB hits India. 2012. Available from: http://articles.timesofindia.indiatimes.com/2012-01-07/india/30601741_1_multi-drug-resistant-tb-tb-patients-tb-germs. [Last accessed on 2012 Jul 14].
- Singh JA, Upshur R, Padayatchi N. XDR-TB in South Africa: No time for denial or complacency. *Plo S Med* 2007;4:50.
- Manissero D, Fernandez de la Hoz K. Surveillance methods and case definition for extensively drug resistant TB (XDR-TB) and relevance to Europe: Summary update. *Euro Surveil* 2006;11:E061103.1.
- WHO. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008. Available from: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf. [Last accessed on 2012 Jul 16].
- Totally Drug-Resistant TB: A WHO consultation on the diagnostic definition and treatment options Dates: 21-22 March 2012 WHO/HQ. Geneva, Switzerland. Available from: http://www.who.int/tb/challenges/xdr/Report_Meeting_totallydrugresistantTB_032012.pdf. [Last accessed on 2012 Jul 16].
- Davies PD. Drug-resistant tuberculosis. *J R Soc Med* 2001;94:261-3.
- Katoch VM. New generation methods for drug susceptibility testing for tuberculosis. *Indian J Tuberc* 2008;55:61-3.
- Schaaf HS, Reuter H. Practical approaches to ordering diagnostic tests. In: Schaaf HS, Zumla AI, editors. *Tuberculosis: A Comprehensive Clinical Reference*. 2nded. Gurgaon, India: Elsevier Publishers; 2009. p. 219.
- WHO Stop TB Department. Drug-resistant tuberculosis. Frequently Asked Questions. Available from: <http://www.who.int/tb/challenges/mdr/TDRFAQs160112final.pdf>. [Last accessed on 2012 Jan 24].
- Canetti G, Fox W, Khomenko A, Maheler HT, Menon NK, Mitchison DA, et al. Advances in techniques of testing mycobacterial drug sensitivity and the use of sensitivity tests in tuberculosis control programmes. *Bull World Health Organ* 1969;41:21-43.
- Siddiqui S. Bactec TB system. Product and procedure manual. Townson, MD: Beckton Dickinson; 1989.
- Rodrigues C. Drug susceptibility testing to 1st & 2nd line drugs in the diagnosis of MDR & XDR TB. Available from: <http://www.maptb.org.my/files/uatld2007/Drug%20susceptibility.pdf>. [Last accessed on 2012 Jul 17].
- Pfyffer GE, Bonato DA, Ebrahimzadeh A, Gross W, Hotaling J, Kornblum J, et al. Multicenter laboratory validation of susceptibility testing of *Mycobacterium tuberculosis* against classical second-line and newer antimicrobial drugs by using the Radiometric BACTEC 460 technique and the Proportion method with solid media. *J Clin Microbiol* 1999;37:3179-86.
- Springer B, Lucke J, Maibach RC, Ritter C, Bottger EC. Quantitative drug susceptibility testing of *Mycobacterium tuberculosis* by use of MGIT 960 and Epi Center instrumentation. *J Clin Microbiol* 2009;47:1773-80.
- Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis. Part II. Active tuberculosis and drug resistance. *Expert Rev Mol Diagn* 2006;6:423-32.
- Oberhelman RA, Soto-Castellares G, Caviedes L, Castillo ME, Kissinger P, Moore DA, et al. Improved recovery of *Mycobacterium tuberculosis* from children using the microscopic observation drug susceptibility method. *Pediatrics* 2006;118:100-6.
- Kalantri S, Pai M, Pascopella L, Riley L, Reingold A. Bacteriophagebased tests for detection of *Mycobacterium tuberculosis* in clinical specimens: A systematic review and meta-analysis. *BMC Infect Dis* 2005;5:59.
- Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. World Health Organization Geneva 2008. WHO the stop TB department. Available from: http://www.stoptb.org/assets/documents/about/cb/meetings/15/2.08-11%20Rolling%20out%20diagnostics%20in%20the%20field/2.08_11.3%20DST%20policy%20.pdf. [Last accessed on 2012 Jul 17].
- Kam KM, Sloutsky A, Yip CW, Bulled N, Seung KJ, Zignol M, et al. Determination of critical concentrations of second-line anti-tuberculosis drugs with clinical and microbiological relevance. *Int J Tuberc Lung Dis* 2010;14:282-8.
- Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of Tuberculosis. *Proc Am Thorac Soc* 2006;3:103-10.
- Sirgela FA, Donald PR, Guthic JO, Umaphathy, Paramasivand KC, Tame CM, et al. A multicentre study of the early bactericidal activity of anti-tuberculosis drugs. *J Antimicrob Chemother* 2000;45:859-70.
- Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015: WHO progress report 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501330_eng.pdf. [Last accessed on 2012 Jul 17].
- Revised National TB Control Programme training manual for *Mycobacterium tuberculosis* culture & drug susceptibility testing. Available from: <http://tbcindia.nic.in/pdfs/Training%20manual%20M%20tuberculosis%20C%20DST.pdf>. [Last accessed on 2012 Jul 19].
- Moll AP, Friedland G, Gandhi NR, Shah NS. Extensively drug-resistant tuberculosis (XDR-TB). In: Schaaf HS, Zumla AI, editors. *Tuberculosis: A comprehensive clinical reference*. 2nd ed. Gurgaon, India: Elsevier Publishers; 2009. p. 553.

30. Harding R, Foley KM, Connor KR, Jaramillo E. The Lancet Infectious Diseases, Early Online Publication, 11 June 2012. Available from:[http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(12\)70084-1/abstract](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(12)70084-1/abstract). [Last accessed on 2012 Jul 14].
31. Thole J. New vaccines for Tuberculosis. Current and future perspectives. Available from:http://www.molecular-tb.org/gb/pdf/ppt/07_JTholle.pdf. [Last accessed on 2012 Jul 19].
32. Milicic A, Kaur R, Sandoval AR, Tang CK, Honeycutt J, Perrie Y, *et al.* Small Cationic DDA: TDB liposomes as protein vaccine adjuvants obviate the need for TLR Agonists in inducing cellular and humoral responses. PLoS One 2012;7:e34255.
33. Grode L, Seiler P, Baumann S, Hess J, Brinkmann V, Eddine AN, *et al.* Increased vaccine efficacy against tuberculosis of recombinant *Mycobacterium bovis* bacille Calmette-Guérin mutants that secrete listeriolysin. J Clin Invest 2005;115:2472-9.
34. Skeiky YA, Sadoff JC. Advances in tuberculosis vaccine strategies. Nat Rev Microbiol 2006;4:469-76.
35. Stop TB Partnership Working Group on New TB Vaccines. Tuberculosis Vaccine Candidates-2011. Tuberculosis Vaccine Pipeline-2011. Available from: http://www.stoptb.org/wg/new_vaccines/assets/documents/TB%20Vaccine%20Pipeline%202011_FINAL.pdf. [Last accessed on 2012 Jul 27].

Cite this article as: Chaturvedi A, Raina RS, Thawani V, Chaturvedi H, Parihar D. Super Tb: Another manmade disaster. Syst Rev Pharm 2012;3:37-41.

Source of Support: Nil, **Conflict of Interest:** None declared.