Multidrug resistant to extensively drug resistant tuberculosis: What is next?

Amita Jain* and Pratima Dixit

Post Graduate Department of Microbiology, CSM Medical University, Lucknow 226 003, India

**Corresponding author (Fax, +91-522 2287400; Email, amita602002@yahoo.com)*

Drug resistant tuberculosis is a man made problem. While tuberculosis is hundred percent curable, multidrug resistant tuberculosis (MDR-TB) is difficult to treat. Inadequate and incomplete treatment and poor treatment adherence has led to a newer form of drug resistance known as extensively drug resistant tuberculosis (XDR-TB). XDR-TB is defined as tuberculosis caused by *Mycobacterium tuberculosis* strain, which is resistant to at least rifampicin and isoniazid among the first line anti tubercular drugs (MDR-TB) in addition to resistance to any fluroquinolones and at least one of three injectable second line anti tubercular drugs i.e. amikacin, kanamycin and/or capreomycin. Mismanagement of tuberculosis paves the way to drug resistant tuberculosis. Emergence of XDR-TB is reported world wide. Reported prevalence rates of XDR-TB of total MDR cases are; 6.6% overall worldwide, 6.5% in industrialized countries, 13.6% in Russia and Eastern Europe, 1.5% in Asia, 0.6% in Africa and Middle East and 15.4% in Republic of Korea. Better management and control of tuberculosis specially drug resistant TB by experienced and qualified doctors, access to standard microbiology laboratory, co-morbitidy of HIV and tuberculosis, new anti-TB drug regimens, better diagnostic tests, international standards for second line drugs (SLD)-susceptibility testing, invention of newer anti-tubercular molecules and vaccines and knowing the real magnitude of XDR-TB are some of the important issues to be addressed for effective prevention and management of XDR-TB.

[Jain A and Dixit P 2008 Multidrug resistant to extensively drug resistant tuberculosis: What is next?; *J. Biosci.* **33** 605–616]

1. Introduction

Mycobacterium tuberculosis is infecting one third of the global population. Currently, tuberculosis management and control is potentially devastating threat worldwide due to emergence of drug resistant strains. The modern, standard short-course therapy for TB recommended by the World Health Organization is based on a four-drug regimen that relies on direct observation of patient compliance to ensure effective treatment. The rapid spread of drug resistance especially multi-drug resistant tuberculosis (MDR-TB) and currently extensively drug resistant tuberculosis (XDR-TB), both in new and previously treated cases, adds urgency to the need for decisive action for control measures (WHO 2006). Resistant to at least two major anti tuberculosis drugs; Isoniazid and Rifampicin with or without resistance to other anti-TB drugs has been termed MDR-TB. MDR-TB is more difficult to treat than drug-susceptible TB, requiring the use of less effective second line anti tubercular drugs (SLDs) which are often associated with major side effects.

2. Development of MDR-TB

A brief mechanism of development of drug resistance is summarized in figure 1. Drug resistance in *M. tuberculosis* occurs due to genetic factor, factors related to previous anti tuberculosis treatment and other factors.

Keywords. Drug resistant tuberculosis; extensively drug resistant tuberculosis (XDR-TB); multidrug resistant tuberculosis (MDR-TB)

Abbreviations used: DOTS, direct observation therapy strategy; INH, isonicotinic acid hydrazide; MDR-TB, multi drug resistant tuberculosis; SLD, second line anti tubercular drug; SRLs, supranational reference laboratories; XDR-TB, extremely drug resistant tuberculosis

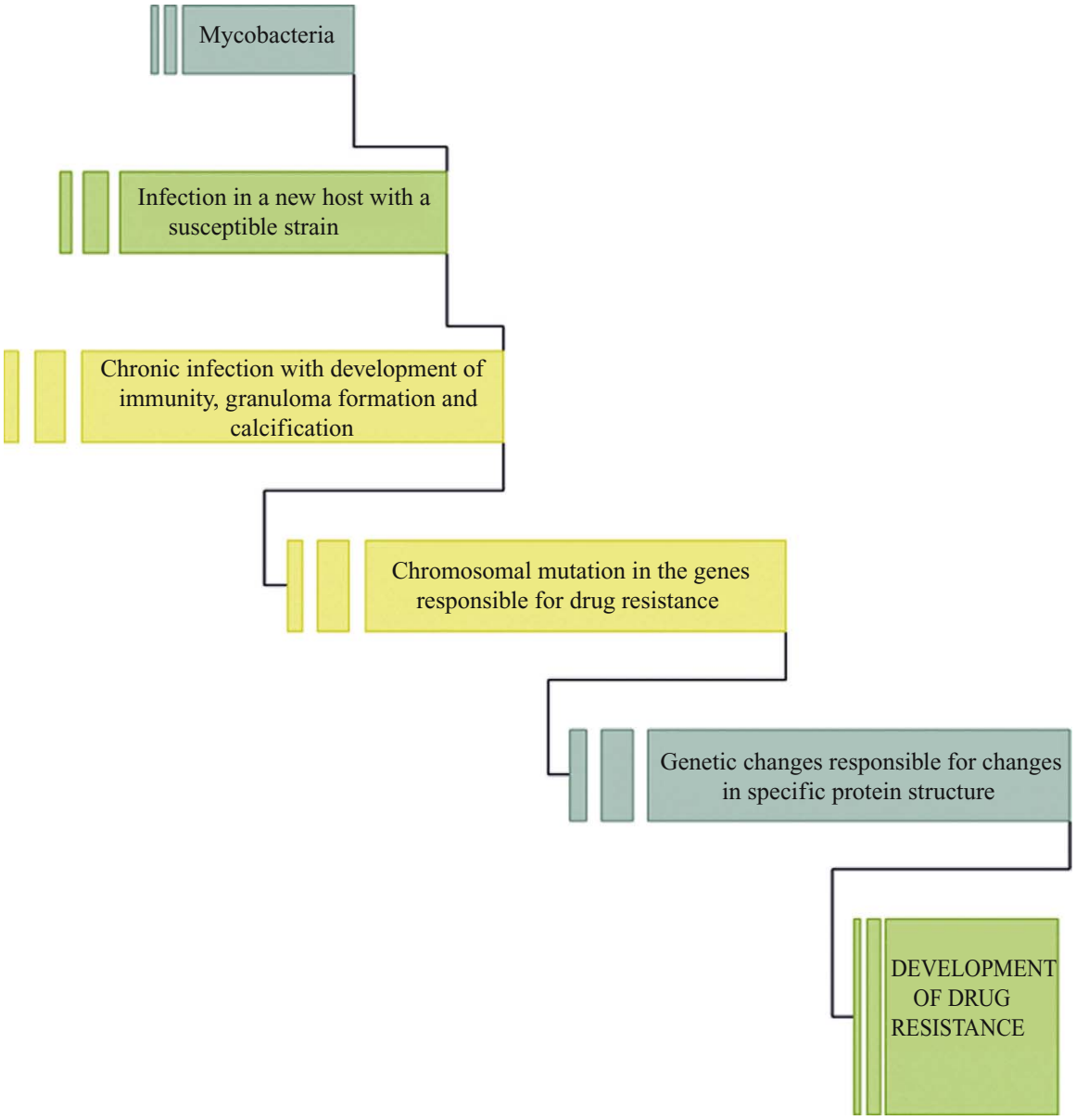

Figure 1. Mechanism of development of drug resistance in mycobacteria.

2. 1 *Genetic factors*

Though there is some evidence to postulate host genetic predisposition as the basis for the development of MDR-TB (Carpenter *et al* 1983; Weyer and Kleeberg 1992; Park *et al* 2002; Sharma *et al* 2003), the accumulation of changes in the genomic content, occurring through gene acquisition and loss is the major underlying event in the emergence of fit and successful strain variants in the *M. tuberculosis* complex (Kato-Maeda *et al* 2001a, b). Spontaneous chromosomally borne mutations occurring in *M. tuberculosis* at a predictable rate are thought to confer resistance to anti-TB drugs (Ramaswamy and Musser 1998; Sharma and Mohan 2004).

2.2 *Factors related to previous anti tuberculosis treatment*

2.2.1 *Incomplete and Inadequate treatment*: A review of the published literature (Sharma and Mohan 2006) strongly suggests that the most powerful predictor of the presence of MDR-TB is a history of treatment of TB, though some individuals who did not have previous TB treatment can be infected by MDR-TB. Many new cases of MDR-TB

are created each year by physician's errors (drugs, dosing intervals, duration). Professor Michael Iseman, the US "guru" of MDR-TB, has shown that two to four errors are needed to turn a fully susceptible organism in to a case of MDR-TB (Iseman 1993). MDR-TB develops due to error in TB management such as the use of single drug to treat TB, the addition of a single drug to a failing regimen, the failure to identify preexisting resistance, the initiation of an inadequate regimen using first line anti tubercular drugs and variations in bioavailability of anti-TB drugs predispose the patient to the development of MDR-TB (Sharma and Mohan 2003). Shortage of drugs has been one of the most common reasons for the inadequacy of the initial anti-TB regimen, especially in resource poor settings (Mwinga 2001). Other major issues significantly contributing to the higher complexity of the treatment of MDR-TB is the increased cost of treatment (Chan and Iseman 2002).

2.2.2 *Inadequate treatment adherence:* Non- adherence to prescribed treatment is often underestimated by the physician and is difficult to predict. Certain factors such as psychiatric illness, alcoholism, drug addiction, and homelessness do predict non-adherence to treatment (Sharma and Mohan 2004). Poor compliance with treatment is also an important factor in the development of acquired drug resistance (Goble *et al* 1993; Jacaban 1994). A study conducted in South India (Datta *et al* 1993), observed that only 43% of the patients receiving short course treatment (n=2306) and 35% of those receiving standard chemotherapy (n=1051) completed 80% or more of their treatment. The various reasons for default included travel to different places, symptom relief, adverse drug reactions and inability to afford treatment (Johnson *et al,* 2003). MDR-TB requires a two- to four-fold longer period of treatment compared with the drug susceptible TB (Chan and Iseman 2002). Shortest treatment course so far validated for drug susceptible TB is six months long (Chan and Iseman 2002). Most of the problems from which drug resistance originates are related to length of treatment (especially considering tolerability). The longer time that is required to treat MDR-TB clearly implies an additional risk of poor treatment adherence and consequently of treatment failure (Drobniewski and Balabanova 2002).

2.3 *Other factors*

Some other factors also play important role in the development of MDR-TB such as poor administrative control on purchase and distribution of the drugs with no proper mechanism on quality control and bioavailability tests (Prasad 2005). Tuberculosis control program implemented in past has also partially contributed to the development of drug resistance due to poor follow up and infrastructure.

3. Management of MDR-TB

There are three major issues to be considered for proper management of MDR-TB i.e. diagnostic techniques, drugs and adherence (Giovanni and Stefano 2004). The introduction of MDR-TB treatment as part of routine program activities will succeed only if the planned Sub national reference laboratories will function properly and also if a reliable supply of high quality of second line drugs is available to the patients (WHO 2008). When MDR is suspected on the basis of history of epidemiological information, the patient's sputum must be subjected to culture and anti- tuberculosis drug sensitivity testing and the WHO retreatment regimen or the empirical regimens employing second line reserve drugs suggested by the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDS) and Infectious Diseases Society of America (IDSA) (Blumberg *et al* 2003) must be initiated pending sputum culture report. Further therapy is guided by the culture and sensitivity report. These guidelines clearly mention that a single drug should never be added to a failing regimen. Furthermore, when initiating, at least three previously unused drugs must be employed to which there is *in vitro* susceptibility (Blumberg *et al* 2003).

Recognition of Prognostic markers may help clinicians to monitor the patients more closely and to correct factors such as malnutrition (Park *et al* 1996; Flament-Saillour *et al* 1999; Tahaoglu *et al* 2001; Drobniewski *et al* 2002; Mitnick *et al* 2003; Sharma and Mohan A 2004; Leimane *et al* 2005). Newer anti-TB drugs, immunotherapy, nutritional enhancement, surgery, mycobacterium vaccae vaccination and cytokine therapy are also helpful for the management of MDR-TB (Sharma and Mohan 2006). The judicious use of drugs, supervised standardized treatment, focused, clinical, radiological and bacteriologic follow-up and surgery at the appropriate juncture are the key factors in the successful management of MDR-TB (Sharma and Mohan 2006).

Direct observation therapy strategy (DOTS) is key ingredient in the TB control strategy. Based on an awareness of the multiple difficulties faced by any large scale intervention aimed at fighting MDR-TB, a special initiative has been launched within the frame work of the global TB strategy worldwide called DOTS-Plus (Espinal *et al* 1999). This newly conceived program consists of a comprehensive approach including the major DOTS principles but technically devoted to the intensive diagnostic and therapeutic management of MDR-TB (Farmer and Kim 1998; Espinal *et al* 1999). The World Health Organization (WHO) has also established a unique partnership known as the Green Light Committee to lower the prices of and to increase control over second line anti-TB drugs and to date 35 DOTS-Plus projects are underway across the globe (Gupta

Table 1. Factors associated with development of MDR-TB

S.No.	Factors	Description	References
1.	Genetic factors	• Accumulation of changes in genomic content • Gene acquisition and loss	(Kato-Maeda *et al* 2001).
		• Spontaneous mutation	(Sharma and Mohan 2004; Ramaswamy *et al* 1998)
2.	Incomplete and Inadequate treatment	• History of treatment of TB	
		• Shortage of drugs	(Mwinga 2001)
		• Increased cost of drugs	(Chan and Iseman 2002)
		• Physician error (drugs, dosing interval and duration)	(Iseman 1993)
		• Use of single drug to treat TB	(Sharma and Mohan 2003)
		• Addition of a single drug to a failing regimen	
		• Failure to identify preexisting resistance	
		• Initiation of an inadequate primary regimen	
		• Variations in bioavailability of anti-TB drugs	
3.	Inadequate treatment adherence	• Poor compliance	(Jacaban 1994; Malian and Adarm 1995; Goble *et al* 1993) (Sharma and Mohan 2004)
		• Psychiatric illness	
		• Alcoholism	
		• Drug addiction	
		• Homelessness	(Johnson *et al* 2003)
		• Travel to different places	
		• Symptom relief	
		• Adverse drug reactions	
		• Inability to afford treatment	
		• Length of treatment	
		• Adverse drug reactions	
4.	Other factors	• Poor infrastructure of NTCP	(Prasad 2005)
		• Poor administrative control on purchase and distribution of the drugs	
		• No proper mechanism on quality control	
		• No proper mechanism of bioavailability tests	
		• No appropriate laboratory support leading to over diagnosis of TB	(Floyd *et al* 2006)
		• Unnecessary treatment	
		• Side effects without benefit	
		• Service inefficiencies	
		• No specific therapy for MDR-TB DOTS strategy	(Sharma and Mohan 2006)

et al 2002; Gupta and Espinal 2003; Baltussen *et al* 2005; Kim *et al* 2007). The DOTS-Plus strategy of identifying and treating patients with MDR-TB appears to have the potential to be effectively implemented on a nationwide scale even in a setting with limited resources (Centre for Disease Control and Prevention 2006).

4. Challenges in management of MDR-TB

While tuberculosis is curable, MDR-TB may be fatal and the cure rates are frustratingly low. Management of MDR-TB is most difficult, complicated, challenging, and costlier and needs experienced and highly skilled persons (Rai and Panda 2004). Tuberculosis is easy to diagnose but diagnosis of MDR-TB depends on reliable and expensive culture and sensitivity test that are not available in most parts of the world. The second line drugs used in cases of MDR-TB are often less effective, more likely to cause side effects and are expensive (Sharma and Mohan 2006). Isoniazid and Rifampicin are the key stone drugs in the management of TB. While resistance to either isonicotinic acid hydrazide (INH) or rifampicin may be managed with other first line drugs, MDR-TB demands treatment with second line drugs that have limited sterilizing capacity and are more toxic (Sharma and Mohan 2004; Ormerod 2005).

Table 2. Management of MDR-TB

S.No.	Steps towards management	References
1.	Availability of specialized expertise, reliable diagnostic techniques and good quality anti-TB drugs and treatment adherence	(Giovanni and Stefano 2004)
2.	Availability of high quality second line drugs	(WHO 2008)
3.	Proper functioning of Planned sub national reference laboratories	(WHO 2008)
4.	Judicious use of anti-TB drugs	(Sharma and Mohan 2006)
5.	Focused, clinical, radiological and bacteriologic follow-up	(Sharma and Mohan 2006)
6.	Recognition of Prognostic markers	(Sharma and Mohan 2004; Mitnick *et al* 2003; Leimane *et al* 2005; Drobniewski *et al* 2002; Flament-Saillour *et al* 1999; Tahaoglu *et al* 2001)
7.	Use of newer anti-TB drugs, nutritional enhancement, immunotherapy, surgery, mycobacterium vaccae vaccination, cytokine therapy	(Sharma and Mohan 2006)
8.	Implementation of DOTS- plus for intensive diagnostic and therapeutic management of MDR-TB	(Espinal *et al* 1999; Farmer and Kim 1998)

Table 3. Challenges associated with management of MDR-TB

S.No.	Issues	Related factors	References
1.	Treatment	• Difficult to treat • Complicated treatment • Costlier treatment • Challenging treatment • Needs experienced and highly skilled physicians	(Rai and Panda 2004)
2.	Diagnosis	• Unreliable • Expensive	(Sharma and Mohan 2006)
3.	Second line drugs	• Less effective • Side effects common • Costly • More toxic • Limited sterilizing capacity	(Sharma and Mohan 2006) (Ormerod 2005; Sharma and Mohan 2004)
4.	Research	• Expensive • Slow • Difficult • Require specialized facilities for handling MTB • Few animal models • No new drug except rifabutin and rifapentine • Difficulties in the drug design	(Tomioka and Namba 2006) (Tomioka and Namba 2006) (Tomioka 2002)
5.	Other issues	• Tuberculosis associated with HIV infection	(Tomioka 2002)

Unfortunately, no new drug except rifabutin and rifapentine has been marketed for TB during the 40 years after release of Rifampicin. There are a number of constraints that have companies from investing in new anti-TB drugs. The research is expensive, slow and difficult and requires specialized facilities for handling MTB. There are few animal models that closely mimic the human TB disease. Development time of any anti-TB drug will be long. In fact minimum six month therapy will require with a follow up period of one year or more (Tomioka and Namba 2006). There are also large number of difficulties in the drug design for the development of new drug formulations with increased potential for antimycobacterial effects, excellent pharmacokinetics and tolerability.

5. XDR-TB- result of failing MDR management

In 2000, the Stop TB Partnership's Green Light Committee was created to increase access to SLDs worldwide while ensuring their proper use to prevent increased drug resistance. While assisting MDR TB treatment programs worldwide, and ensuring the proper use of SLDs in resource limited countries the committee encountered reports of multiple cases of TB with resistance to virtually all SLDs

(Gupta *et al* 2002). This led to the emergence of a new terminology in relation to the drug resistant tuberculosis, known as extensively drug resistant tuberculosis (XDR-TB). The worldwide emergence of XDR-TB and a provisional definition for this form of TB were first reported in November 2005 (Holtz *et al* 2005; Shah *et al* 2005) and the term XDR-TB for the first time was used in March 2006, in a report jointly published by US CDC and World Health Organization (WHO) (CDC 2006). According to this report, XDR-TB was defined as tuberculosis caused by *M. tuberculosis* that was resistant not only to isoniazid and rifampicin (MDR-TB) but also to at least three of the six classes of second-line anti-TB drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and para-aminosalycilic acid). This definition was dependent on difficult-to-perform drug susceptibility testing and some forms of drug resistance are less treatable than others. Hence this definition was difficult to accept. Eventually this definition was modified at a meeting of WHO- XDR-TB Task Force, held at Geneva (Switzerland) on 10–11 October 2006. Committee gave a much-accepted definition of XDR-TB which defines it as "resistance to at least Rifampicin and INH among the first line-anti tubercular drugs (MDR-TB) in addition to resistance to any fluroquinolones i.e. ofloxacin, ciprofloxacin and levofloxacin, and at least one of three injectable second line anti tubercular drugs i.e. amikacin, kanamycin and capreomycin (CDC 2006)."

6. Prevalence of XDR-TB

During November 2004--November 2005, CDC and WHO surveyed the WHO/International Union Against Tuberculosis and Lung Disease Global Supranational TB Reference Laboratory (SRL) Network to estimate world wide XDR-TB prevalence during 2000-2004. The report of this survey is based on data from 25 supranational reference laboratories (SRLs) on six continents that collaborate with National Reference Laboratories (NRLs) to increase culture and DST capacity and provide quality control for global surveys to assess anti-TB drug resistance. They used a standardized reporting form, requested anonymous, individual-level data from all reference labs on all isolates tested for susceptibility to at least three SLD classes, during 2000—2004. SRLs receive varying proportions of isolates from countries for surveillance, diagnosis, and quality assurance. Hence, to complement the SRL survey, additional population-based data were analyzed from the US national TB surveillance system, which contains data on all reported TB cases during 1993--2004, and Latvia's national MDR TB registry from the 2000--2002 cohort of MDR TB patients. Limitations in this surveillance were: (i) all SRLs did not test for susceptibility to SLDs, (ii) certain labs test for only one or two SLDs, (iii) labs used different (but generally accepted) media and methods to test for SLD susceptibility and (iv) SLD-susceptibility data from SRLs are based on a convenience sample and are not population-based, with one

Table 4. Prevalence of XDR-TB

Year of study	Prevalence of XDR-TB among all MDR-TB patients	Remark	Reference
2000-2004	6.6% overall worldwide,6.5% in industrialized countries, 13.6% in Russia and Eastern Europe, 1.5% in Asia, 0.6% in Africa and Middle East, 15.4% in Republic of Korea	Limitations of data: 1) all labs did not test for susceptibility to SLDs, 2) certain labs test for only one or two SLDs, 3) labs used different (but generally accepted) media and methods to test for SLD susceptibility and 4) SLD-susceptibility data based on a convenience sample size	(Shah *et al* 2007)
1993--2004	Germany: 10.3% Italy: 14.3%	Patients had a 5-fold higher risk for death and longer hospitalization with longer treatment durations	(Migliori *et al* 2007a, b)
2006	4% in France	-	(Bouvet 2007)
2006	Iran -10.9%	From 113 multi-drug resistant tuberculosis strains	(Masjedi *et al* 2006)
2004	Hong Kong: 12%	9/ 75 MDR-Tb strains, simultaneous resistance to ethionamide, amikacin, ofloxacin and cycloserine	(Kam and Yip 2004)
2006	India: 7.3%	5/ 68 MDR-TB strains	(Mondal and Jain 2007)
2006	Kwazulu Natal, South Africa (KZN) province	XDR-TB with HIV	(Gandhi *et al* 2006)
2008	India: 4/12; 33.3	AIDS patients, suspected of having HIV-TB, all died within 2.6 months of diagnosis	(Singh *et al* 2008)

Table 5. Issues associated with management of XDR-TB

Issues	Factors associated with management failure	Reference
Mismanagement of TB	• Faulty treatment habits of doctors • Erratic use of second line drugs • Lack of experience and skill • Paucity of reliable laboratories • Use of poor quality second line drugs • Unmonitored private sectors	(Nathanson *et al* 2006; Prasad *et al* 2002) (Prasad and Garg 2007)
Treatment associated factors	• Difficult to treat • Complicated treatment • Much costlier drugs • Lack of experienced skilled practioners • Lack of standard microbiology laboratory • Lack of proper management of patient care with standardized, empirical and individual approaches • Lack of good quality of all-frontline and six classes of second line drugs	(Gupta *et al* 2001; Iseman 1993) (Uplekar 2003)
Control program and infection control measures	• Poor strengthening of tuberculosis control program • No improvement of second-line drug management • Promotion of research • No focus on development of new diagnostics, vaccines and drugs • Infection in health care workers • Co morbidity with HIV	(Mukherjee *et al* 2004) (Hopewell *et al* 2006; Matteelli *et al* 2007) (Kim *et al* 2007; Migliori *et al* 2007)

exception: South Korea. Based on this surveillance data worldwide occurrence of XDR-TB was reported. Reported overall prevalence of XDR-TB among all multi-drug resistant tuberculosis isolates was 6.6% overall worldwide, 6.5% in industrialized countries (e.g. United States, United Kingdom, Ireland, Germany, France, Belgium, Spain, Japan and Australia) and 13.6% in Russia and Eastern Europe (e.g. Republic of Georgia, Czech Republic, Armenia and Azerbaijan). Prevalence of XDR-TB from Asiatic region (e.g. Bangladesh, Indonesia, Thailand Papua New Guinea and East Timor), Africa and Middle East was not well defined in this report due to a small number of TB cases taken in the study in comparison to other studied nations. However, reported XDR prevalence is around 1.5% in Asia (Bangla Desh, Indonesia, Papua New Guinea, Thailand and East Timor) and only 0.6% in Africa and Middle East. Republic of Korea represents maximum numbers of XDR-TB cases and represents 15.4% XDR-TB cases among all multi-drug resistant tuberculosis patients (Shah *et al* 2007). These data indicate that XDR TB is geographically widespread. The population-based data from South Korea, the United States, and Latvia provide a more representative picture of XDR TB on a population level in three disparate regions of the world and confirm that XDR TB has emerged in multiple settings, including the United States where TB control has been effective for many years.

A detailed description of XDR-TB findings and preliminary data from U S National TB Surveillance System was published in 2006 (CDC 2006). The US data indicated that 74 tuberculosis cases reported during 1993--2004 met the case definition for XDR- TB. A recent report from Germany and Italy reported 10.3% and 14.3% XDR-TB isolates respectively among 83 and 43 multi-drug resistant tuberculosis strains. These patients had a 5-fold higher risk for death and longer hospitalization with longer treatment durations, showing highly significant association between XDR-TB status and risk for death (Migliori *et al* 2007a, b). A recent study described that prevalence of XDR-TB in France was 4% of tested multidrug resistant strains (Bouvet 2007). A recent study done in Iran reported 12 (10.9%) XDR strains from 113 multi-drug resistant tuberculosis strains (Masjedi *et al* 2006). In Hong Kong, nine out of the 75 multi-drug resistant tuberculosis strains (12%) had extensive drug resistance with simultaneous resistance to ethionamide, amikacin, ofloxacin and cycloserine (Kam and Yip 2004). From India, 5 XDR-TB cases were recognized from 68 multi-drug resistant tuberculosis strains during a preliminary study done by us recently (Mondal and Jain 2007). Though this figure was based upon a small number of multi-drug resistant tuberculosis patients from a North Indian settings but this clearly indicates that the problem of XDR-TB is existing and true extent may be much higher than the

reported figure, because the annual risk of tuberculosis and prevalence of acquired multi-drug resistant tuberculosis and tuberculosis with HIV is increasing in India (Narain and Lo 2004). One case of XDR- TB is recently reported from Tuberculosis Research Center, Chennai (Thomas *et al* 2007).

7. XDR-TB with HIV/AIDS

Co-morbidity with tuberculosis and HIV/AIDS affects around 11 million people and killed nearly 200,000 in the year 2005. Yet, less than 0.5% of HIV-positive people were screened for tuberculosis that year (Editorial 2007). First report of XDR-TB with HIV came from Kwazulu Natal, South Africa (KZN) province (Gandhi *et al* 2006). Of 536 TB patients at Church of Scotland Hospital of KZN, which serves a rural area with high HIV rates, 221 were found to have MDR, of these, 53 were diagnosed with XDR-TB. Fifty-two of these patients died, most within 25 days. Of 53 patients, 44 were tested for HIV and all 44 were HIV-positive. In KZN two health care workers died from XDR-TB with HIV. Spoligotyping results of 46 XDR-TB isolates demonstrated that 85% strains belong to the KZN family and 15% were from Beijing family. A number of cases in KZN resulted from in-hospital infection. Acquisition of extensive drug resistance appears to be the primary mechanism for XDR-TB epidemic in South Africa and estimated that 63% - 75% of cases developed XDR-TB through acquisition. (Mlambo *et al* 2008). Also, a large number of XDR-TB patients in KwaZulu-Natal were infected with the same strain of *M. tuberculosis* (F15/LAM4/KZN) (Pillay and Sturn 2007). Dr Mario Raviglione, WHO Stop TB Department Director responded to this outbreak "This was a wake-up call that there were problems in the management of TB in southern Africa It is vital that we now go back to gather information about what went wrong so that we can learn any lessons from this. The incidence of TB is decreasing or stable in all regions of the world except for Africa, where it is on the increase, with HIV fuelling TB. Our big concern is that if we start seeing more XDR-TB cases in Africa we could see a major epidemic because of the high rates of HIV. HIV fuels XDR-TB. Once someone is infected with TB there is a 5-10% lifetime risk of developing the disease, but in a person with HIV the risk is 5-15% a year." The Global Task Force has said that control of XDR-TB will not be possible without close coordination of TB and HIV programmes and interventions. Dr Karin Weyer, TB Research Director at the South African Medical Research Council, warns: "We are afraid that this outbreak of XDR-TB might be the tip of the iceberg, as we haven't really looked properly elsewhere. There are higher prevalence rates in pockets of eastern Europe and South-East Asia but we are particularly worried in South Africa given our HIV problem, because of the rapid spread of XDR-TB amongst HIV patients and their rapid death." (Jacqui 2006).

A recent study from India was done by Singh *et al,* (2008) with 54 full-blown AIDS patients, suspected of having HIV-TB co-infection reported high mortality rate among HIV patients with XDR-TB. Out of the studied 54 patients, 12 (22.2%) were MDR-TB cases and among them, 4 (33.3%) were XDR-TB cases. All 4 patients, in whom XDR–TB was isolated, died within 2.6 months of diagnosis.

8. XDR-TB: Challenges, threats and solutions in management

Mismanagement of tuberculosis cases plays a major role in emergence of drug resistant tuberculosis and reasons for this mainly appears to be (i) faulty treatment habits of doctors (Uplekar *et al* 1991; Prasad *et al* 2002; Nathanson *et al* 2006), (ii) erratic use of second line drugs moreover poor quality drugs, (Prasad and Garg 2007), (iii) lack of experience and skill to manage drug resistant tuberculosis, (iv) use of poor quality second line drugs, (v) little or no access to reliable laboratory for drug susceptibility testing against first and second line drugs, and (vi) factors linked to poor control practices e. g. lack of measures to ensure adherence to treatment and treatment of tuberculosis in unmonitored private sectors played a major role in originating XDR-TB cases in developing countries. Treatment of multi-drug resistant tuberculosis cases is difficult, complicated, much costlier, challenging and needs experience skills with good quality of second line antituberculosis drugs, standard microbiology laboratory as well as proper management of patient care with standardized, empirical and individual approaches (Iseman 1993; Gupta *et al* 2001). Treating multi-drug resistant tuberculosis with second line drugs may cure >65% of patients and stop ongoing transmission (Mukherjee *et al* 2004; Van Deum *et al* 2004; Leimane *et al* 2005). However, most of the evidence of successful multi-drug resistant tuberculosis management is generated from high-income countries where treatment is provided in referral hospitals (Espinal and Dye 2005). It is vital that clinicians caring for tuberculosis patients are aware of the possibility of drug resistance and have access to laboratories that can provide early and accurate diagnosis so that effective treatment is provided as soon as possible. Effective treatment of multi-drug resistant tuberculosis cases requires good quality of all-frontline and all six classes of second line drugs available to the clinicians who have expertise in treating drug resistant cases especially multi-drug resistant tuberculosis. According to a report, poor quality of tuberculosis management in the private sector is seen in some parts of world (Uplekar 2003). A report from South Korea revealed that XDR- TB was significantly associated with the cumulative duration of previous treatment received

with second-line TB among patients in a tertiary care TB hospital (Jeon *et al* 2008). The inexorable rise of drug resistant strains (one in ten new infections is resistant to at least one antituberculosis drug), and the worrying spread of XDR-TB threaten to undermine tuberculosis control efforts.

Strengthening basic tuberculosis control programs and infection control measures is crucial for preventing the selective pressure and environments in which resistant strains are transmitted from person to person. Additionally, multi-drug resistant tuberculosis programmes that rely on quality assured and internationally recommended treatment regimen according to World Health Organization guidelines must be scaled up and strengthened to stop further SLDs resistance and spread of XDR-TB. The Green Light Committee of Stop tuberculosis partner provides a global mechanism to help affected countries to achieve these steps. The main priority interventions that will be needed for XDR management is the strengthening of tuberculosis control (through sound implementation of the Stop tuberculosis strategy and systematic application of treatment in both the public and private sector with focus on laboratory capacities and infection control), improvement of SLD management based on the new World Health Organization guidelines (Mukherjee *et al* 2004) and promotion of research and development of new diagnostics, vaccines and drugs against tuberculosis (Hopewell *et al* 2006; Matteelli *et al* 2007). It is vital that infection control procedures are improved in hospitals to stop XDR-TB from spreading. Health workers in hospitals should be trained in infection control procedures. Efforts should be made to improve tracing of contacts to be able to find patients in an early stage of the disease before they start spreading it to other people. A key priority identified is to strengthen basic TB control and so prevent drug resistance from occurring in the first place. If DOTS, the WHO-recommended treatment strategy for detection and cure of TB, is implemented properly it can prevent the development of drug resistance. It makes economic sense to treat TB properly in the first place. It costs US$ 52 to treat each patient with ordinary TB. If a patient develops MDR-TB, the cost of treatment dramatically increases to US$ 3168, which includes hospitalization and more expensive drugs. (Rajbhandari *et al* 2004). A study done by Huong *et al* (2005) from Vietnam suggested that, from a public health perspective, treatment of patients with multi-drug resistant tuberculosis with second-line drugs might not be necessary to prevent its spread and that directly observed therapy short course (DOTS), the internationally recommended standardized management strategy for tuberculosis, alone may suffice in some settings (DeRiemer *et al* 2005). In the absence of a specific public health treatment program, there was no apparent increase in the prevalence of multi-drug resistant tuberculosis among untreated patients between surveys conducted in 1996 and 2001 in Vietnam. Although a good DOTS program should reduce acquired drug resistance generated by erratic, unsupervised therapy and by an unreliable drug regimen. There is substantial evidence that treatment based on isoniazid and rifampicin will not cure or substantially improve tuberculosis in patients whose infecting organisms are already resistant to those drugs (Espinal *et al* 2000). Moreover, there is no evidence that ineffective treatment can reduce the transmission of multi-drug resistant tuberculosis strains. However, most patients who are promptly and properly treated for multi-drug resistant tuberculosis with second-line drugs can be cured even in poor settings (Gupta *et al* 2001; Nathanson *et al* 2006).

The appearance of XDR-TB among HIV-infected individuals is very concerning, as rapid progression of infection towards disease and the high potential of spread among immunosuppressed individuals greatly accelerate the consequences of bad control practices and management of drug resistant tuberculosis. However, presence of XDR-TB is independent poor prognostic factors in non-HIV-infected patients with MDR-TB (Kim *et al* 2007). Controlling community and hospital-acquired infections among patients (e.g. tuberculosis and tuberculosis - HIV) and health care workers is of importance (Migliori *et al* 2007).

Determination of the magnitude of the problem of XDR-TB in every region is essential. The emergence of XDR TB, coupled with increased use of SLDs, suggests that urgent measures are needed to establish population-based surveillance for SLD resistance and to plan public health responses. However, existing tests for susceptibility to SLDs are less reproducible than tests for susceptibility to isoniazid and rifampin, and better methods are needed (Heifets and Cangelosi 1999). Quick surveys are needed to determine where XDR-TB is and then longer-term surveillance needs to be put in place. Investment is urgently needed to strengthen the region's laboratory capacity.

No new TB drugs have been developed for four decades. There are several promising new candidates, but none will be available for at least five years. More investment in TB drug development is needed to guarantee future drugs supplies. A further complication is the interaction of antiretroviral drugs with TB medication, while little is known about the interaction between second-line TB drugs and antiretrovirals. Second-line TB drugs are less effective and more toxic than the first-line options.

"The world urgently needs new, safe and affordable diagnostics to simplify case detection," says Raviglione. "Despite scientific progress that is rapidly changing other fields, most of the world's TB patients have access only to conventional microscopy. This method at times requires repeated testing, may miss cases, and is not adequate for many HIV coinfected patients who may have TB that is not detectable with sputum examination only." Activities to

detect drug-resistant TB accurately and rapidly and treat it effectively should be expanded, including development of international standards for SLD-susceptibility testing, new anti-TB drug regimens, and better diagnostic tests. Such measures are crucial if future generations are to be protected from XDR TB. Plans have just been announced for the WHO Stop TB Department to collaborate with the Foundation for Innovative New Diagnostics (FIND) to start demonstration projects and introduce rapid-culture technology and new rapid drug-resistance tests in the southern African countries most affected. This will reduce the time needed to confirm a diagnosis of TB drug resistance from as long as 3 months to just 2 weeks, thus speeding up treatment.

9. Conclusion

Resistance to antituberculosis drugs has been noted since the drugs were first introduced, and occasionally outbreaks of drug-resistant tuberculosis have been reported worldwide. But recent outbreaks of XDR-TB have differed considerably from the previous outbreaks of drug-resistant tuberculosis and even multi-drug resistant tuberculosis outbreaks. WHO emphasizes that good TB control prevents the emergence of drug resistance in the first place and that the proper treatment of multi-drug resistant tuberculosis prevents the emergence of XDR-TB.

References

Baltussen R, Floyd K and Dye C 2005 Cost effectiveness analysis of strategies for tuberculosis control in developing countries; *Br. Med. J.* **331** 1364

Blumberg H M, Burman W J, Chaisson R E, Daley C L, Etkind S C, Friedman L N, Fujiwara P, Grzemska M, *et al* 2003 American Thoracic Society/Centers for Disease Control and Prevention/ Infectious Diseases Society of America: treatment of tuberculosis; *Am. J. Respir. Crit. Care Med*. **167** 603–662

Bouvet E 2007 Multidrug resistant tuberculosis: What is the risk in France?; *Rev. Prat*. **15** 1405-1408

Carpenter J L, Obnibene A J, Gorby E W, Neimes R E, Koch J and Perkins W L 1983 Antituberculosis drug resistance in south Texas; *Am. Rev. Respir. Dis.* **128** 1055–1058

Centers for Disease Control and Prevention 2006 Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs-worldwide; *MMWR* **55** 301–305

Chan E D and Iseman M D 2002 Current medical treatment for tuberculosis; *Br. Med. J.* **325** 1282–1286

Datta M, Radhamani M P, Selvaraj R, Paramasivan C N, Gopalan B N, Sudeendra C R and prabhakar R, *et al* 1993 Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme; *Tuber. Lung Dis*. **74** 180–186

DeRiemer K, Garcia-Garcia L and Bobadilla-del-Valle M 2005 Does DOTS work in populations with drug-resistant tuberculosis?; *Lancet* **365** 1239–1245

Drobniewski F A and Balabanova Y M 2002 The diagnosis and management of multiple-drug- resistant tuberculosis at the beginning of the new millennium; *Int. J. Infect. Dis*. **6** S21–S31

Drobniewski F, Eltringham I, Graham C, Magee J G, Smith E G and Watt B 2002 A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK; *Thorax* **57** 23 810–816

Editorial 2007 Stopping tuberculosis proves hard to do; *Lancet* **369** 965

Espinal M A and Dye C 2005 Can DOTS control multidrug-resistant tuberculosis?; *Lancet* **365** 1206–1209

Espinal M A, Dye C, Raviglione M, *et al* 1999 Rational 'DOT plus' for the control of MDR-TB; *Int. Tuberc. Lung Dis*. **3** 561–563

Espinal M A, Kim S J, Suarez P G, *et al* 2000 Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries**.** *JAMA* **283** 2537–2545

Farmer P and Kim J Y 1998 Community based approaches to the control of multidrug resistant tuberculosis: introducing "DOTS-plus"; *Br. Med. J*. **317** 671–674

Flament-Saillour M, Robert J, Jarlier V, *et al* 1999 Outcome of multi-drug-resistant tuberculosis in France: a nationwide case-control study; *Am. J. Respir. Crit. Care Med*. **160** 587–593

Floyd K, Hutubessy R, Samyshkin E, *et al* 2006 Health-systems efficiency in the Russian Federation: tuberculosis control. *Bull.WHO* **84** 43–51

Gandhi N R, Moll A and Sturm A W 2006 Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa; *Lancet* **368** 1575–1580

Giovanni Di Perri and Stefano Bonora 2004 Which agents should we use for the treatment of multidrug- resistant *Mycobacterium tuberculosis*?; *J. Antimicrob. Chemother*. **54** 593–602

Goble M, Iseman M D, Madsen L A, *et al* 1993 Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampicin; *N. Engl. J. Med*. **328** 527–532

Gupta R, Cegielski J P, Espinal M A, *et al* 2002 Increasing transparency for health: introducing the Green Light Committee; *Trop. Med. Int. Health* **7** 970–976

Gupta R and Espinal M and Stop TB Working Group on DOTS-Plus for MDR-TB 2003 A prioritised research agenda for DOTS-Plus for multidrug-resistant tuberculosis (MDR-TB); *Int. J. Tuberc. Lung Dis*. **7** 410–414

Gupta R, Raviglione and Espinal M A 2001 Should tuberculosis programmes invest in second line treatments for multidrug-resistant tuberculosis (MDR-TB)?; *Int. J. Tuberc*. *Lung Dis*. **5** 1078–1079

Heifets L B and Cangelosi G A 1999 Drug susceptibility testing of *Mycobacterium tuberculosis*: a neglected problem at the turn of the century; *Int. J. Tuberc. Lung Dis*. **3** 564–581

Holtz T H, Riekstina V, Zarovska E, *et al* 2005 XDR-TB: extreme drug-resistance and treatment outcome under DOTS-Plus, Latvia, 2000—2002; *Int. J. Tuberc. Lung Dis*. *(Suppl. 1)* **9** S258

Hopewell P C, Pai M, Maher D, *et al* 2006 International standards for Tuberculosis care; *Lancet Infect. Dis*. **6** 710–725

Huong N T, Lan N T, Cobelens F G, *et al* 2006 Antituberculosis drug resistance in the south of Vietnam: prevalence and trends; *J. Infect. Dis*. **194** 1226–1232

Iseman M D 1993 Treatment of multidrug-resistant tuberculosis. *N. Engl. J. Med.* **329** 784–791

Jacqui W 2006 Southern Africa is moving swiftly to combat the threat of XDR-TB; *Bull. WHO* **84** 924–925

Jacaban R F 1994 Multiple drug Resstant Tuberculosis; *Clin. Infect. Dis*. **19** 1–10

Jeon C Y, Hwang S H, Min J H, *et al* 2008 Extensively drug-resistant tuberculosis in South Korea: risk factors and treatment outcomes among patients at a tertiary referral hospital; *Clin. Infect. Dis*. **46** 42–49

Johnson J, Kagal A and Bharadwaj R 2003 Factors associated with drug resistance in pulmonary tuberculosis; *Indian J. Chest Dis. Allied Sci*. **45** 105–109

Kam K M and Yip C W 2004 Surveillance of *Mycobacterium tuberculosis* susceptibility to second-line drugs in Hong Kong, 1995–2002, after the implementation of DOTS-plus; *Int. J. Tuberc. Lung Dis*. **8** 760–766

Kato-Maeda M, Bifani P J, Krieswirth B N, *et al* 2001 The nature and consequence of genetic variability in *Mycobacterium tuberculosis*; *J. Clin. Invest*. **107** 533–537

Kato-Maeda, M, Rhee J T, Gingeras T R, *et al* 2001 Comparing genomes within the species *Mycobacterium tuberculosis*; *Genome Res*. **11** 547–555

Kim H R, Hwang S S, Kim H J, *et al* 2007 Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis; *Clin. Infect. Dis*. **45** 1290–1295

Leimane V, Rickstina V, Holtz T H, *et al* 2005 Clinical outcome of individualized treatment of multidrug resistant tuberculosis in Latvia: A retrospective cohort study; *Lancet* **365** 318–326

Masjedi M R, Farnia P, Sorooch S, *et al* 2006 Extensively drug-resistant tuberculosis: 2 years of surveillance in Iran; *Clin. Infect. Dis*. **43** 841–847

Matteelli A, Migliori G B, Cirillo D, *et al* 2007 Multidrug- resistant and extensively drug-resistant Mycobacterium tuberculosis: epidemiology and control; *Exp. Rev. Anti Infect. Ther*. **5** 857–871

Migliori G B, Loddenkemper R, Blasi F, *et al* 2007a 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.* **29** 423–427

Migliori G**,** Ortman J, Giardi E, *et al* 2007b Extensively drug-resistant tuberculosis, Italy and Germany; *Emerg. Infect. Dis*. **13** 1–4

Mitnick C, Bayona J, Palacios E, *et al* 2003 Community-based therapy for multidrug- resistant tuberculosis in Lima, Peru; *N. Engl. J. Med*. **348** 119–128

Mlambo C K, Warren R M, Poswa X, *et al* 2008 Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa; *Int. J. Tuberc. Lung Dis*. **12** 99–104

Mondal R and Jain A 2007 Extensively Drug-Resistant *Mycobacterium tuberculosis*, India; *Emerg. Infect. Dis*. **13** 1429–1431

Mukherjee J S, Rich M L, Socci AR, *et al* 2004 Programmes and principles in treatment of multidrug- resistant tuberculosis; *Lancet* **363** 474–481

Mwinga A 2001 Drug resistant tuberculosis in Africa; *Ann. N. Y. Acad. Sci*. **953** 106–112

Narain J P and Lo Y R 2004 Epidemiology of HIV-TB in Asia; *Indian J. Med. Res*. **120** 277–289

Nathanson E, Lambregts-van Wezenbeek C, Rich M L, *et al* 2006 Multidrug-resistant tuberculosis management in resource-limited settings; *Emerg. Infect. Dis*. **12** 1389–1397

Ormerod L P 2005 Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment; *Br. Med. Bull*. **73**–**74** 17–24

Park M H, Song E Y, Park H J, *et al* 2002 HLA-DRB1 and DQB1 gene polymorphism is associated with multidrug-resistant tuberculosis in Korean patients; *Hum. Immunol*. **63** S33

Park M M, Davis A L, Schluger N W, *et al* 1996 Outcome of MDR-TB patients, 1983–1993. Prolonged survival with appropriate therapy; *Am. J. Respir. Crit. Care Med*. **153** 317–324

Pillay M and Sturm A W 2007 Evolution of the extensively drug-resistant F15/LAM4/KZN strain of *Mycobacterium tuberculosis* in KwaZulu-Natal, South Africa; *Clin. Infect. Dis*. **45** 1409–1414

Prasad R 2005 MDR TB: Current Status; *Indian J. Tuberc*. **52** 121–131

Prasad R and Garg R 2007 XDR-TB: An emerging threat; *Chest India* **8** 3–4

Prasad R, Nautiyal R G, Mukherji P K, *et al* 2002 Treatment of new pulmonary tuberculosis patients: what do allopathic doctors do in India?; *Int. J. Tuberc. Lung Dis*. **6** 895–902

Rajbhandary S S, Marks S M and Bock N N 2004 Cost of patients hospitalized for multidrug resistant tuberculosis; *Int. J. Tuberc. Lung Dis*. **8** 1012–1016

Rai S P and Panda B N 2004 Outcome in Multidrug Resistant Tuberculosis patients with ambulatory treatment; *Indian J. Tuberc*. **51** 33–36

Ramaswamy S and Musser J M 1998 Molecular genetic basis of anti- microbial agent resistance in *Mycobacterium tuberculosis*: 1998 update; *Tuber. Lung Dis*. **79** 3–29

Shah S N, Wright A and Drobniewski F 2005 Extreme drug resistance in tuberculosis ("XDR-TB"): global survey of supranational reference laboratories for *Mycobacterium tuberculosis* with resistance to second-line drugs; *Int. J. Tuberc. Lung Dis. (Suppl 1)* **9** S77

Shah S N, Wright, A, Bai H G, *et al* 2007 Worldwide emergence of extensively drug-resistant tuberculosis; *Emer. Infect. Dis*. **13** 380–387

Sharma S K and Mohan A 2006 Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control; *Chest* **130** 261–272

Sharma S K and Mohan A 2004 Multidrug-resistant tuberculosis; *Indian J. Med. Res*. **120** 354–376

Sharma S K and Mohan A 2003 Scientific basis of directly observed treatment, short course (DOTS); *J. Indian Med. Assoc*. **101** 157–158,166

Sharma S K, Turaga K K, Balamurugan A, *et al* 2003 Clinical and genetic risk factors for the development of multidrug-resistant tuberculosis in non-HIV infected patients at a tertiary care center in India: a case-control study; *Infect. Genet. Evol*. **3** 183–188

Singh S, Sankar M M and Gopinath K 2008 High rate of extensively drug-resistant tuberculosis in Indian AIDS patients; *AIDS* **21** 2345–2347

Stop T B Partnership 2006 *The STOP TB strategy: building on and enhancing DOTS to meet the TB-related millennium development goals* (Geneva: World Health Organization)

Tahaoglu K, Torun T, Sevim T, *et al* 2001 The treatment of multidrug-resistant tuberculosis in Turkey; *N. Engl. J. Med*. **345** 170–174

Thomas A, Ramachandran R, Rehaman F, *et al* 2007 Management of multidrug resistance tuberculosis in the field: Tuberculosis Research Centre experience; *Indian J. Tuberc.* **54** 117–124

Tomioka H 2002 Prospects for development of new antituberculous drug; *Kekkaku* **77** 573–584

Tomioka H and Namba K 2006 Development of antituberculous drugs: current status and future prospects; *Kekkaku* **81** 753–774

Uplekar M 2003 Involving private health care providers in delivery of TB care: Global Strategy; *Tuberculosis* **83** 156–164

Uplekar M W and Shepard D S 1991 Treatment of tuberculosis by private general practiceners in India; *Tubercle* **72** 284–290

Van Deum A, Salim M A, Das A P, Bastian I and Potales F 2004 Results of a standardized regimen for multidrug resistant tuberculosis in Bangladesh; *Int. J. Tuberc. Lung Dis*. **8** 560–567

Weyer K and Kleeberg H H 1992 Primary and acquired drug resistance in adult black patients with tuberculosis in South Africa: results of a continuous national drug resistance surveillance programme involvement; *Tuber. Lung Dis*. **73** 106–112

World Health Organization Report 2008 *Global Tuberculosis Control* pp 109–112

World Health Organization 2006 Extensively drug-resistant tuberculosis (XDR.TB): recommendations for prevention and control; *Weekly Epidemiol. Rec*. **81** 430–432

*e*Publication: 15 October 2008