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Management of Drug-Resistant TB

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1. Introduction

Although major progress has been made to reduce global incidence of drug-susceptible tuberculosis (TB), the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB over the past decade presents an unprecedented public health challenge to which countries of concern are responding far too slowly. Indeed, a recent WHO TB surveillance report indicates the highest global level of drug-resistance ever recorded, which affected disproportionately developing countries with an estimated 440,000 MDR-TB cases worldwide resulting in 150,000 deaths in 2009 [1]. Even more troubling is being the recent emergence of new strains of totally drug-resistant *M. tuberculosis* (Mtb), currently occurring in densely populated cities such as Teheran (Iran) [2] and Mumbai (India) [3]. Given that an untreated TB patient can infect up to 15 contacts in a year in overcrowded areas [4], it is highly likely that totally drug-resistant TB will continues spreading and one would worry that TB will again become an incurable disease.

While part of the increase in drug resistance can be attributed to difficulty in treating patients who are double infected with HIV, which represent about 13% of total TB cases [5], detailed field studies revealed that the emergence drug-resistant TB is clearly a direct consequence of misdiagnosis and mismanagement of drug susceptible TB, which result in only a fraction of TB patients getting correct diagnosis and appropriate therapy ([6,7] and Fig.1). In other words, "Resistance is man-made, caused by exposure to the wrong treatment, the wrong regimen, the wrong treatment duration" says TB expert Giovanni Miglio [8]. Therefore, a comprehensive approach to ensure rapid detection, proper treatment and public health measures needs to be applied globally to cure TB patients and prevent further transmission of the disease. This chapter discusses various challenges facing the management of drug resistant TB and presents the efforts of WHO and its partners for the development of strategies and guidelines for optimal TB control.
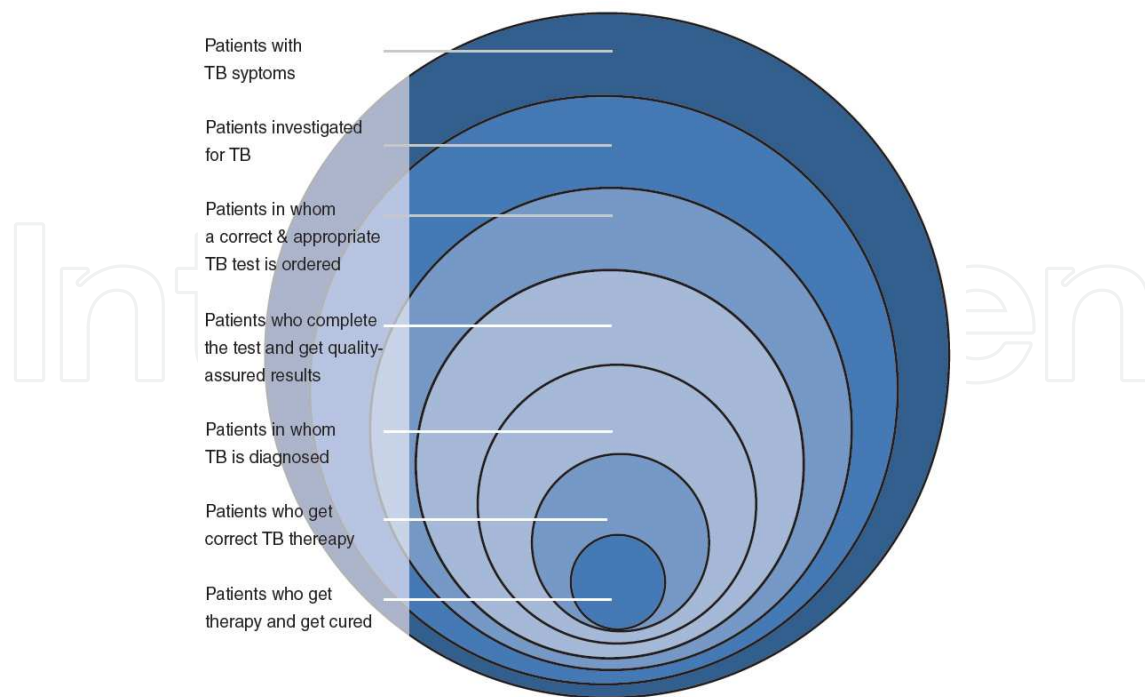
Figure 1. Misdiagnosis and mismanagement can result in only fraction of TB patients getting correct diagnosis, appropriate therapy, and positive outcomes. Reprinted from Ref. 9 with permission from Dr. Madhukar Pai.

2. Standard treatment for drug-susceptible TB

Symptoms associated with active TB are generally defined as loss of weight and energy, poor appetite, fever, a productive cough, and night sweats. Although highly suggestive of TB, such symptoms might easily be assigned to another disease. Therefore accurate diagnosis is important before initiating drug therapy. The current standard laboratory test consists on the analysis of 3 sputum specimens for acid-fast bacilli smears and culture, with nucleic acid amplification performed on at least 1 specimen [10].

In 1994, the WHO introduced the DOTS (Directly Observed Treatment, Short-course) as a major plan to control TB globally [11]. The DOTS strategy focuses on five main points of action: 1) government commitment to control TB, 2) diagnosis based on sputum-smear microscopy tests done on patients with TB symptoms, 3) direct observation short-course chemotherapy treatments, 4) a continuous supply of drugs, and 5) standardized reporting and recording of cases and treatment outcomes [11]. The standard short course (SSC) treatment recommended by WHO [12] consists of 2 months of intensive phase of daily oral administration of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB) followed by 4 months continuous phase of daily INH and RMP alone.

INH is only active against growing tubercle bacilli [13]. RMP is active against both growing and stationary phase bacilli with low metabolic activity and is associated with high sterilizing activity *in vivo* [14]. PZA plays a unique role in shortening TB treatment from the previous 12

months to 6 months because it kills the persistent Mtb population in the lung [15]. EMB is active against growing Mtb but has no effect on dormant bacilli. The combination of drugs acting at different stages of the Mtb life cycle during SSC therapy has been successful in TB treatment in most endemic countries when patients adhere to a fairly strict daily regimen. SSC therapy causes minor or no side effects and is affordable, costing less than $40 for a full course of treatment. Side effects, if they occur, are manageable and usually do not result in the interruption of the treatment.

Aproximately 90% of people infected with Mtb develop an efficient immune response that successfully contains the infection but unfortunately without killing all the bacteria. Surviving bacteria persist in the lung as non-replicative (i.e. dormant) organisms [16]. In this stage of latent TB infection (LTBI), people do not exhibit TB symptoms and cannot pass the infection on to other individuals. However, in weakened immune system conditions (old age, HIV infection or therapeutic immunosupression), dormant bacteria revert into dividing organisms leading to TB reactivation [16].

LTBI is highly suspected in individuals previously exposed to those with known active TB, which would include people in hospitals, homeless shelters and prisons, or people having recently traveled to countries where TB is highly endemic. The stage of clinical latency is of surpassing importance for TB control as most cases of active TB arise from the vast reservoir of the latently infected population [17]. In fact, it estimated that the infection reactivates and cause active TB in approximately 5 to 10% of latently infected persons [18].

Purified protein derivative (PPD) skin test (also known as the Mantoux test) is the major diagnostic tool used to identify LTBI patients. A positive skin reaction to the PPD test reflects a local cellular immune response, which is interpreted as recent or remote exposure to the TB bacterium. However, despite its usefulness and simplicity, the PPD test have a low predictive value since false-positive reactions can occur as a result of previous BCG vaccination or sensitization to environmental mycobacteria [19,20,21]. In fact, the skin test uses a crude mix of Mtb antigens shared among many mycobacterial species. As a replacement for the PPD test, new interferon-gamma release assays (IGRAs) have been recently developed and shown to be more accurate for LTB diagnosis [22]. IGRAs measure *ex-vivo* production of IFN-gamma by circulating T cells in whole blood in response to more specific Mtb antigens such as ESAT6, CFP10 and TB7.7.

Although LTBI is symptom-free and non contagious, many countries have adopted its treatment in order to reduce the risk of infection progression to active TB and the spread of the disease to the general population. Six to 9 month treatment with INH alone was proven to be effective and safe [10]. Unfortunately, if LTBI results from exposure to a person with MDR- or TB XDR-TB, preventive treatment options are very limited or may not be possible. In both active and latent TB cases, it is crucial that health care providers make every effort to ensure that infected persons complete the entire course of treatment. They must explain clearly the benefit of the treatment and also possible side effects (or drug interactions). Additionally, They should identify potential barriers to the course of treatment, which will help to establish an efficient plan to ensure adherence.

Understanding the mechanisms of TB latency is crucial to development of better control strategies. Infection with Mtb occurs initially in alveolar macrophage, in which the bacteria replicate and induce cytokines that initiate the inflammatory response in the lungs, leading ultimately to the formation of granuloma [23]. Granuloma is defined as an immune structure consisting of connective tissue, lymphocytes and activated macrophages, which has a central necrotic core containing extracellular bacteria. Within the granuloma the bacterium is exposed to multiple stresses that include, among others, hypoxic, nutrient limiting, oxidative, nitrosative and acidic conditions [24,25], which trigger a genetic program controlled by the transcription factor DosR [25]. The later regulates the development of a quiescent physiological state, which maintains viability of non-dividing bacteria for extended periods of time. The granuloma contains the infection and prevents its spread to other organs [26]. However, dormant bacteria are capable of reactivation controlled by Rpf (resuscitation promoting factor) genes, which is associated with reversal of the non-replicating state into a metabolically active growing and dividing bacteria [27]. Thus, life-long immunity is not gained by a first episode of active TB disease and the disease may develop again at a later stage, either through relapse with the same strain or reinfection with a new strain.

Deciphering the molecular basis of dormancy and reactivation is therefore necessary for developing more efficient TB therapies. Adjuncts of agents that would block transitions between active growth, dormancy, and resuscitation or kill effectively dormant bacteria can significantly enhance the efficacy of current treatments for latent infection. Such agents would also shorten the treatment duration of active TB.

3. Molecular basis of Mtb resistance to SSC drugs

The frequency of spontaneous mutations that confer resistance to an individual TB drugs *in vitro* are well known and vary from 1 in 10^5 (EMB) to 1 in 10^{10} (RMP) [28].

Resistance to INH: INH is a drug precursor that is activated by Mtb catalase-peroxidase enzyme (KatG) to generate a range of highly reactive species [29]. Active INH targets essentially enoyl-acyl carrier protein reductase (InhA enzyme), which is involved in mycolic acid synthesis [29]. Resistance to INH occurs more frequently than for most anti-TB drugs, at a frequency of 1 in 10^6 bacilli *in vitro* [13]. Clinical isolates of INH-resistant Mtb often lose catalase and peroxidase activities due to KatG S315T mutation [30]. Resistance to INH can also occur through mutations in the promoter region of *inhA*, causing overexpression of InhA, or by mutations at the InhA active site, lowering InhA affinity for INH [31]. *katG* mutation can be associated with *inhA* mutations, leading to higher levels of INH resistance [32].

Resistance to RMP: RMP interferes with RNA synthesis by binding to the β subunit of mycobacterial RNA polymerase, which is encoded by *rpo*B. Mtb resistance to RMP occurs at a frequency of 10^{-7} to 10^{-8} as a result of mutations in *rpo*B. Mutations at positions 531, 526 and 516 in *rpo*B are among the most frequent (96%) in RMP-resistant strains [33].

Resistance to PZA: PZA requires conversion to its active form, pyrazinoic acid (POA), by the pyrazinamidase/nicotinamidase enzyme encoded by Mtb *pncA*, which then permeates

through the membrane, disrupts bacterial membrane potential and affects membrane transport [34]. PZA resistance is linked to defective pyrazinamidase/nicotinamidase activity, which results from mutations that might occur at different regions (3-17, 61-85 and 132-142) of *pncA* [34]. While most PZA-resistant strains (72–97%) have *pncA* mutations, some do not have *pncA* mutations but rather express defective pyrazinamidase/nicotinamidase activity [13], which suggests possible mutations in a putative *pncA* regulatory gene, yet to be identified.

Resistance to EMB: Arabinosyl transferase, encoded by *embB*, an enzyme involved in the synthesis of cell wall arabinogalactan, has been proposed as the target of EMB in Mtb [35]. Mutation to EMB resistance occurs at a frequency of 10^{-5} [13]. The *embB* codon 306 mutation account for only 68% EMB resistant strains [36], suggesting that there may be other mechanisms of EMB resistance. Therefore, further studies are needed to identify potential new mechanisms of EMB resistance.

Because the mutations described above are unlinked, the probability of developing bacillary resistance to 4 drugs used simultaneously is unlikely. Clinical drug-resistant TB is definitely the result of genetic mutation amplification through mismanagement of the TB disease. This includes intermittent therapy due to irregular drug supply, inappropriate drug prescriptions and most importantly poor patient adherence to treatment [37]. Sequential accumulation of mutations in different genes involved in individual drug resistance results in the emergence of multiple drug resistance.

4. Diagnosis of multidrug resistant tuberculosis

Conventional culturing of the etiologic agent combined with drug susceptibility testing (DST) is the 'gold standard' for diagnosing drug resistant TB in order to initiate adequate treatment. However, this approach is rarely used because it requires 3 to 4 months to produce results. Indeed, only 7% of all MDR-TB cases are detected globally [1]. Hence, the deficiency in tools for rapid DST is associated with inadequate treatment regimens, which tragically increase transmission and spread of drug resistant TB, especially in HIV-infected individuals [38]. This alarming situation stimulated the development of a great number of rapid culture- and molecular-based methods that are currently being evaluated in TB diagnosis laboratories. The Nitrate Reductase Assay (NRA) is based on detection of nitrate reduction into nitrite by Mtb organisms capable of growth in the presence of the test antibiotic [39]. Whereas the Microscopic Observation of Drug Susceptibility (MODS) uses inverted microscope to detect the formation of cord-like structure by Mtb isolates resistant to the test drug [40]. The commercial Mycobacterium Growth Indicator Tube 960 (MGIT 960) is a drug-containing culture system based on the fluorescence detection of resistant bacteria [41]. The Genotype MTBDR*plus* is a molecular line-probe assay that detects simultaneously mutations in the rpoB gene that confers resistance to RMP as well as mutations in the katG gene and the inhA promoter, which are associated with resistance to INH [42]. The Alamar blue and resazurin assays are liquid-based colorimetric tests [43]; a color change in wells containing drug-exposed bacteria reflects resistance. The MTT assay relays on the ability of drug-resistant (viable) bacteria to cleave the tetrazolium

rings of MTT, which produces a violet-purple color [44]. Many of these assays gave excellent detection of MDR-TB, within a significantly shorter time frame when compared to conventional culturing methods (Table 1).

The effective implementation of these rapid diagnostic tests for TB and drug resistance will increase the proportion of patients promptly placed on appropriate therapy, and therefore will improve substantially management and control of TB disease globally. However a major limitation to the use of these rapid tests is their affordability and the availability of equipped laboratories in resource-constrained countries, which unfortunately tend to have the highest burden of MDR-TB cases. Thus, global initiatives are needed to make new diagnostics accessible to low-income countries.

	MTBDRplus	MODS	NRA	AB	Resazurin	MTT	MGIT 960	LJPM
Average time to results, days	2	7	7	8	8	8	9	30
Results within 8 days, %	100	90	77	87	87	74	42	-
Results within 10 days, %	100	100	100	100	97	87	81	-

MODS = microscopic observation drug susceptibility; NRA = nitrate reductase assay; AB =Alamar Bbue ; MTT = 3-[4,5-dimethyl- thiazol-2-yl)-2,5-diphenyltetrazolium bromide; MGIT = Mycobacterium Growth Indicator Tube; LJPM = Löwenstein-Jensen proportion method.

Table 1. Time to results and percentage of results obtained within 8 and 10 days. Reprinted from Ref. 45 with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.

5. Treatment of drug-resistant TB

The emergence of MDR- and XDR-TB has shattered the initial optimism that DOTS based programmes would progressively eliminate TB. MDR TB is defined as resistance to at least the two most potent first-line TB drugs—ie, INH and RMP [46,47]. XDR TB strains are resistant to INH or RMP, any fluoroquinolone, and at least one of three second-line injectable drugs—ie, capreomycin, kanamycin, and amikacin [46,47]. In order to control the spread of drug resistant TB, the WHO extended the DOTS programme in 1998 to include the treatment of MDR-TB (called "DOTS-Plus") [48]. Implementation of DOTS-Plus requires the capacity to perform drug-susceptibility testing and the availability of second-line agents, in addition to all the requirements for DOTS. Clinical pilot experiences from the past few years showed that high cure rates of drug resistant TB are achieved in settings where DOTS-Plus has been established [49-51].

Resistance to INH is the most common form of TB drug resistance reported, either in isolation or in combination with other drugs [13]. INH monoresistant TB is relatively easy to treat with SCC treatment. Up to 98% cure and less than 5% relapse can be achieved when all four drugs

INH, RMP, PZA and EMB are used during the 6-month treatment period [52]. RMP-resistant TB often carries a much more ominous prognosis, as the outcome of SCC treatment is poor in terms of both disease status at the end of the treatment and relapse [13]. Moreover, RMP monoresistance in Mtb is rare and usually reflects resistance to INH as well, i.e., MDR-TB [53]. In fact, SCC cures less than 60% of MDR-TB, with a recurrence rate of about 28% among patient with apparent success [38,54].

The current recommendation for individualized treatment regimens is a combination of at least four drugs to which the Mtb isolate is likely to be susceptible [55]. Drugs are chosen with a stepwise selection process through 5 groups of TB drugs (Table 2) on the basis of efficacy and safety [55]. More than 5 drugs can be used if the sensitivity to a given drug is unclear or if the regimen contains few bactericidal drugs. The duration of the intensive phase of treatment (when an injectable drug is given) should be at least 6 months (or 4 months after culture conversion). The continuation phase (without the injectable drug) should last until 18 months after culture conversion [55].

Although the effectiveness and feasibility of MDR-TB management in resource-limited settings have been demonstrated, less than 2% of all estimated MDR-TB patients currently receive appropriate treatment [5]. Thus, the growing MDR-TB epidemic globally requires moving beyond the pilot project stage in order to scale up DOTS-plus based TB management as a routine component of national TB control programmes. However, there are potential difficulties with implementing DOTS-Plus in low-income countries as it can absorb a large part of resources dedicated to existing DOTS programmes, and subsequently decrease the overall standard of care [56]. Note that the emergence of drug resistant TB in these countries is actually the result of limited resources to implement the simple DOTS programme.

A major barrier to the management of drug resistant TB in low-income countries is the prohibitive price of second-line drugs. Therefore in an attempt to address this issue, in 2000, the WHO and its partners established the Green Light Committee (GLC) initiative to facilitate access to quality-assured second-line TB drugs at reduced prices [57,58]. Evaluation of the first GLC-endorsed pilot projects of MDR-TB management in five resource-limited countries showed treatment success rates of 59%–83% [59]. During 2012, the number of patients with MDR-TB approved for treatment by the GLC Committee was only 42,033 with 13,000 actually starting treatment. It is clear that these numbers remain small compared to the estimated annual incidence (440,000 cases) of MDR-TB [1]. Therefore, substantial funding through public-private partnerships is desperately needed to scale up the availability of second line drugs.

Other than the price of second-line drugs, frequent adverse events and the long duration of the regimen further compromise adherence to TB treatment, even in the most advanced industrialized countries. These drawbacks have resulted in resurgence in research efforts during last decade to develop new TB drugs. In recent years, a number of new drug candidates with novel modes of action and excellent activity against Mtb have entered clinical trials [60]. OPC-67683 (nitro-dihydro-imidazooxazole) and diarylquinoline TMC207 are the most promising of these new drugs since both are highly active against drug-resistant and susceptible Mtb strains and possess excellent sterilizing activity [61]. These and other drugs under

TB drug group	Daily dose
Group one: first-line oral TB drugs (use all possible drugs)	
Isoniazid	5 mg/kg
Rifampicin	10 mg/kg
Ethambutol	15–25 mg/kg
Pyrazinamide	30 mg/kg
Group two: fluoroquinolones (use only one, because they share genetic targets)	
Ofloxacin	15 mg/kg
Levofloxacin	15 mg/kg
Moxifloxacin	7.5–10 mg/kg
Group three: injectable TB drugs (use only one, because they share very similar genetic targets)	
Streptomycin	15 mg/kg
Kanamycin	15 mg/kg
Amikacin	15 mg/kg
Capreomycin	15 mg/kg
Group four: less-effective second-line TB drugs (use all possible drugs if necessary)	
Ethionamide/Prothionamide	15 mg/kg
Cycloserine/Terizidone	15 mg/kg
P-aminosalicylic acid (acid salt)	150 mg/kg
Group five: less-effective drugs or drugs on which clinical data are sparse (use all necessary drugs if there are less ily than four from the other groups)	
Clofazimine	100 mg
Amoxicillin with clavulanate (every 12 h)	875/125 mg
Linezolid	600 mg
Imipenem (every 6 h)	500–1000 mg
Clarithromycin (every 12 h)	500 mg
High-dose isoniazid	10–15 mg/kg
Thioacetazone	150 mg

Table 2. Categories of TB drugs. Reprinted from Ref. 55 with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.

development give hope that a safe and effective TB regimen of shorter duration will be available within the next few years.

6. Adverse drug reactions to second line TB drugs

The treatment of MDR-TB is a challenging issue due to the adverse events associated with long-term exposure (18 to 24 months) to second line drugs, all in great contrast to the short treatment period of drug sensitive TB. Adverse events significantly influence treatment

outcome and patient compliance, leading to acquisition of more resistance and spread of drug-resistant strains. Initial evidence of the prevalence of adverse events associated with the use of second-line drugs was deducted from observation of patients enrolled in five DOTS-Plus sites: Estonia, Latvia, Peru, the Philippines and the Russian Federation. The data collected from these sites showed that among 818 patients enrolled on MDR-TB 30% required removal of suspected drugs from the regimen due to adverse events [62] and Table 3.

Adverse events can be distinguished as major or minor and may not be consistently found among all patients treated for MDR-TB [39]. The major adverse events associated with second line drugs include auditory toxicity (ototoxicity) and neurologic side effects [63].

Ototoxicity causes damage to the outer hair cells in the cochlea and vestibular labyrinth leading to permanent hearing loss. Ototoxic hearing loss is common in patients treated with amino-glycosides (Streptomycin, Kanamycin and Amikacin). A prospective cohort study of the incidence of ototoxicity in MDR-TB individuals (with normal hearing) showed that 57% of aminoglycoside-treated patients developed high-frequency of hearing loss [64]. The same study showed that HIV-positive patients (70%) were more likely to develop hearing loss than HIV-negative patients (42%). Susceptibility to hearing loss increases further in patients bearing mutations in mitochondrial genes [65]. Numerous mutations linked to susceptibility to ototoxicity have been identified in the mitochondrial MT-RNR1 gene that encodes the human 12S rRNA ribosomal subunit. In particular, the A1555G mutation causes increased binding of aminoglycosides to the 12S rRNA ribosomal subunit [66], which results in the disruption of mitochondrial protein synthesis and death of the cell. In this regard, a recent study in South Africa detected A1555G mutation in a significant proportion of the population (0.9% of Black and 1.1% of Afrikaner), indicative of high proportion of individuals genetically predisposed to developing aminoglycoside-induced hearing loss. It is unfortunate that the widespread and poorly controlled use of aminoglycosides will lead to many individuals suffering from permanent deafness. Auditory monitoring should be an integral part of the care programme of MDR-TB patients, particularly in countries where aminoglycosides are still commonly used. In addition, identification of patients who are genetically predisposed will significantly reduce the risk of developing ototoxicity.

Patients with neurologic side effects (depression, psychosis and suicidal tendencies) have less favorable outcome and increased risk of death. Cycloserine is the most significant TB drug associated with central nervous system (CNS) toxicity. Cycloserine is used as second line drug in TB treatment based of its structural analogy to D-alanine. Cycloserine competitively inhibits two necessary enzymes (alanine racemase and alanine ligase) that incorporate alanine into an alanyl-alanine dipeptide, an essential component of the mycobacterial cell wall [67]. Early studies revealed that neurological and psychiatric manifestations are present in as many as 33% of patients treated with cycloserine [68]. The principal side effects associated with cycloserine therapy are convulsions, exacerbations of bipolar states and multiple neurological symptoms including excitation, dizziness, headaches, insomnia and anxiety [69]. Cycloserine-mediated neurologic side effects are exacerbated even more when used in combination with isoniazid [70]. These variable psychotropic responses are related to cycloserine action as an

Adverse event*	Suspected agent(s)†	Affected n (%)
Nausea/vomiting	PAS, TM, FQ	268 (32.8)
Diarrhoea	PAS, TM	173 (21.1)
Arthralgia	FQ, TM, CS, AG	134 (16.4)
Dizziness/vertigo	CS, CM, AG, FQ	117 (14.3)
Hearing disturbances	CM, TM, AG	98 (12.0)
Headache	CS, FQ	96 (11.7)
Sleep disturbances	CS, FQ	95 (11.6)
Electrolyte disturbances	CM, TM	94 (11.5)
Abdominal pain	PAS, TM	88 (10.8)
Anorexia	PAS, TM	75 (9.2)
Gastritis	TM, PAS	70 (8.6)
Peripheral neuropathy	TM, AG, CS	65 (7.9)
Depression	CS	51 (6.2)
Tinnitus	CM, CS, AG	42 (5.1)
Allergic reaction	FQ	42 (5.1)
Rash	FQ, PAS	38 (4.6)
Visual disturbances	CS, TM	36 (4.4)
Seizures	CS	33 (4.0)
Hypothyroidism	TM, PAS	29 (3.5)
Psychosis	CS	28 (3.4)
Hepatitis	TM	18 (2.2)
Renal failure/nephrotoxicity	AG, CM	9 (1.2)

Table 3. Frequency of adverse events and suspected agents among 818 patients receiving MDR-TB treatment.PAS: para-aminosalicyclic acid; TM: thioamides; FQ: fluoroquinolones; CS: cycloserine; AG: aminoglycosides; CM: capreomycin.. Reprinted from Ref. 62 with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.

agonist of the neuronal NMDA (*N*-methyl-D-aspartate) receptor for glutamate [71], which is a major excitatory neurotransmitter in the mammalian CNS [72]. The most dramatic effect of cycloserine reported so far is the suicide of 2 patients during the postoperative antibiotic treatment course following pulmonary resection [73]. Because of its neurological toxicities, cycloserine was prevented very early from being part of first line TB drugs but was recently reintroduced as one of the cornerstones of treatment for MDR- and XDR-TB [46]. Although co-administration of pyridoxine (vitamin B6) with cycloserine can reduce partially the neurological side effects, the later should be prescribed after psychiatric evaluation for patients with apparent convulsions and agitation [55]. Some clinicians favor terizidone (two cycloserine molecules combined) as they found the side effects associated with it are less severe and more manageable [55]. However, given the little evidence demonstrating safety and efficacy of terizidone, it should be used with caution in TB patients intolerant to cycloserine.

Although adverse events associated with second-line drugs are a major obstacle in the management of MDR-TB, compared with first line treatment, DOTS-Plus programmes have achieved cure rates of greater than 70% even in resource-poor settings [74,75]. In general, the

main adverse effects of anti-TB drugs occur during the first two to three weeks of treatment. If they are recognized in time and managed properly, high rates of treatment completion and cure can be achieved. Proper monitoring should include patient education, clinical examination and appropriate laboratory tests. Special training for staff on the various adverse events associated with second line drugs is essential for successful management. In particular, staff should consider altering dosages when appropriate, supplementary drugs to treat adverse events and replacement of drugs when toxicity cannot be managed.

7. Management approaches for the contacts of MDR TB patients

MDR-TB and XDR-TB cases are currently on the increase and it is expected that the number of their contacts will also increase, especially in densely populated area. Therefore, identification and proper management of these contacts are major components of drug resistant TB containment. In this regard, WHO recommend the identification of all close contacts of MDR-TB cases through contact tracing and their evaluation for TB infection.

A contact is defined as an individual who has a risk of acquiring TB because it has been exposed to Mtb by sharing air space with a person with infectious TB (the source case). The index case (a person with suspected or confirmed TB disease) is defined as the initial case of TB for a contact investigation [76]. He is not necessarily identical with the source case [76]. Many guidance documents focus on the source case and not the index case, as it is the source case who will have exposed the contacts, not necessarily the index case. Close contacts are those people sharing common habitation rooms with the source case. This can also include individuals with evidence of prolonged and frequent exposure to a source case in the workplace, school, prison, hospital ward, or social settings [77]. Contact tracing is defined as the systematic finding of contacts of patients with infectious TB disease [77]. The tracing helps identifying individuals who are particularly at high risk, such as individuals with HIV infection, young children and elderly.

The management of contacts of drug-resistant TB patients, in term of preventive chemoprophylaxis, remains a complex issue with a significant ethical dimension. In case of drug-susceptible TB, the provision of preventive INH therapy to suspect LTBI individuals is effective at reducing the risk of developing disease among infected contacts [10]. In theory, such a preventive approach should also work for LTBI individuals exposed to MDR and XDR Mtb strains. Unfortunately, health care providers cannot predict with certainty the susceptibility pattern of a contact's isolate from the source case's isolate. Indeed, many divergent drug susceptibility test profiles in source-contact pairs have been reported [78,79], due either to infection of the contact by another source case or to infection before the source case acquires resistance. Such a scenario likely occurs in high-burden TB areas where different drug resistant strains may circulate in homes, schools, and work places. Therefore, the lack of effective drugs with acceptable adverse-event profile in an otherwise healthy individual is a prominent barrier to the treatment of drug resistant TB contacts. Indeed, if, to some extent, the occurrence of toxicity is accepted by MDR-TB patients (since the alternative is high risk of death), convincing healthy contacts to cope with adverse-events during preventive therapy in is fundamentally different.

Given the lack of clear evidence in support of preventive therapy, the WHO does not recommend universal use of second-line drugs for chemoprophylaxis in MDR-TB contacts. Current guidance for the management of drug resistant TB contacts are largely based on expert opinions, which do not reject nor support provision of preventive therapy with the currently available drugs. In this context a guidance document presenting the most up-to-date evidence and expert opinion regarding the management of contacts of MDR- and XDR-TB patients has been recently proposed (March 2012) by the European Centre for Disease Prevention and Control (ECDC) [76]. Box 1 summarizes key recommendations provided by ECDC document.

Which factors should be evaluated to decide whether to provide preventive therapy to MDR TB contacts considered to have LTBI?

When evaluating an MDR TB contact and deciding between the two options (to provide preventive therapy and/or careful clinical observation and information), an overall individual risk assessment should be conducted, taking into consideration the following: the MDR TB contact's risk for progression to TB disease; the drug susceptibility pattern of the source case of infection; and the contact's risk for adverse drug events if initiating preventive therapy.

Are there any specific risk groups to whom special attention should be paid?

Children below the age of five years and immunocompromised persons in close contact with MDR TB patients and considered to have LTBI are at particular risk of progressing to TB disease. These risk groups might benefit from preventive therapy. The preventive therapy may be interrupted if, based on further examination, infection is found to be unlikely.

Persons over five years of age in close contact with MDR TB patients and considered to have LTBI could also be considered for preventive therapy if the individual risk assessment indicates this course of action.

If the decision is made to put an individual on preventive therapy, the selection of the drugs should be based on:

the drug susceptibility pattern of the source case's likely infecting strain;

local patterns of drug resistance;

the potential adverse events in individual patients, taking into account age and other risk factors;

the selection of single or multiple drugs and the duration of treatment will depend on the availability of drugs with bactericidal activity for the particular infecting strain; alternatively, the decision can follow national guidelines.

Which arrangements should be in place if preventive therapy is considered?

If preventive therapy is considered by the expert physician or other healthcare provider, national legislation should ensure that the treatment costs for the patient are covered.

If preventive therapy is considered to be relevant for a particular individual, careful clinical monitoring and follow-up is essential for the detection of drug-adverse events and signs of TB disease if the preventive therapy is not effective.

Specific opinions for XDR TB contacts

As the currently available treatment options are very limited for XDR TB, it is likely that the risks of preventive therapy outweigh the benefits for contacts of XDR TB patients. Thus, the option to inform and observe the contacts will be preferable, given the currently available drugs and evidence.

How should health authorities conduct follow-ups for MDR TB and XDR TB contacts suspected to have LTBI?

All MDR TB and XDR TB contacts considered to have LTBI who, after a comprehensive individual risk assessment, are not given preventive therapy should be followed-up by careful clinical observation.

Follow-ups should be performed according to existing national guidelines.

All persons in contact with MDR TB or XDR TB (after exclusion of TB disease) should be informed about the risks and symptoms, carefully observed, and provided with easy access to a specialized TB clinic in case of symptoms between

assessments. No specific time period for follow-up or periodicity of clinical assessments is recommended, but regular systematic, clinical observation is essential for the early detection of TB disease.

Individuals repeatedly in contact with infectious MDR TB or XDR TB cases (e.g. healthcare workers) should be re-examined periodically.

Box 1. ECDC expert opinions regarding preventive therapy of MDR- and XDR-TB contacts.

Studies conducted so far on the benefits and adverse events of preventive therapy are not conclusive in term of optimal treatment and duration for preventive treatment of MDR-TB contacts [80]. Therefore, well-designed randomized clinical trials for preventive therapy are urgently needed in settings where MDR-TB therapy and a strong national programme infrastructure are already in place. Further research is also needed to define the most effective contact-tracing procedures for contacts and the most effective follow-up procedures in healthcare workers constantly exposed to drug resistant TB. In addition, specific management approaches need to be established for children below the age of five years, children with HIV infection, immunocompromised individuals, pregnant women, and the elderly. Finally, whether MDR Mtb strains are more or less infectious and/or transmissible than drug-susceptible strains need to be clarified.

8. Compliance issues from patients and health care providers

The treatment for MDR-TB is long and complex and relies on a handful of antibiotics with uncertain efficacy. The WHO has launched an 8-point plan to ensure optimal management of XDR-TB patients with currently available drugs (Box 2). However, guidelines do not always translate easily into real world practice. In addition to directly observed treatment, what support can be offered to convince a patient to continue painful treatment? And how should patients who have exhausted all treatment options with existing second-line drugs be cared for?

1. Strengthen quality of basic TB and HIV/AIDS control

2. Scale up programmatic management of MDR-TB and XDR-TB

3. Strengthen laboratory services

4. Expand MDR-TB and XDR-TB surveillance

5. Develop and implement infection control measures

6. Strengthen advocacy, communication and social mobilization

7. Pursue resource mobilization at all levels

8. Promote research and development of new tools

Box 2. WHO 8-point plan

In many cases, MDR-TB treatment results in poor compliance with subsequent development of further drug resistance (i.e. XDR-TB), which leaves infected patients, namely HIV positive individuals, virtually untreatable using currently available drugs. The WHO defines a

defaulter as being off drugs for more than 8 weeks after completing at least one month of treatment [81]. It is an operational definition to guide physicians in the decision of using a retreatment or second line regimen if the patient comes back to the health facility after defaulting. However it is imperative that health providers understand predictive factors for treatment default so that they can implement additional measures to target the population at risk. In this context, a recent review (2010) assessed TB treatment compliance and the factors predictive for poor adherence based on the analysis of 4 studies performed in Sub-Saharan Africa in the last 10 years [82]. The review revealed a high proportion of patients defaulting, which varied between 11.3% and 29.6%. Defaulting appears to be associated with many factors such as distance from the hospital, not being on the first course of TB medications, lack of repeated smears, drug-associated side effects, transportation difficulties, absence of family support and poor knowledge about TB disease and its treatment. Thus it is unfortunate that health care institutions continue to blame vulnerable and powerless patients who are unable, for this multitude of reasons, to comply with the treatment. Since distance from health care centers is a major factor, national programmes should at least consider making drugs more widely available, by either providing TB treatment in smaller health centers, or organizing mobile TB clinics, especially in rural areas.

It is time to admit that TB disease is not a 'patient problem' by default but rather a social and community responsibility that requires close cooperation and collaboration at all levels of the health care system. Forcing a patient to continue an ineffective, toxic regimen that results in uncertain outcome also raises an ethical issue yet to be resolved. Ereqat and colleagues reported a recent case of a MDR-TB patient who withdrew from treatment after 2 years while still sputum-positive [83]. Due to persistent efforts to force compliance, the patient disappeared carrying with him the potential to infect all people with whom he has contact. The authors suggest consulting with legal practitioners about the legality of enforced treatment and how patients who refuse or interrupt treatment can be managed to protect them and their potential contacts. It is obvious that in the absence of alternative treatment, this approach might end up with a response to TB without medication (i.e incarceration). For this type of recalcitrant patients, other TB specialists [84,85] propose directing efforts towards exploring possible regimens with better chances of cure and securing an appropriate living environment. Indeed, the threat of incarceration will just encourage patients to disappear and propagate the disease. Providing supportive accommodation with access to counseling and palliative care, when required, should reduce the risk of transmission to others [84]. Overall, until newer drugs become available, management that balances the risk of disease spread with individual human rights is likely to be more humane and less costly to health services compared with involuntary detention [85]. In this context, Upshur and Colleagues propose a list of additional considerations to the management of drug resistant TB as moral correlates to the current WHO 8-point plan (Box 3).

A paramount issue in TB management is that in many countries with limited resources most of the healthcare is provided by the private sector where the number of qualified medical personnel to prevent and treat drug resistant TB remains very limited. In this regard, the World Medical Association (WMA, http://www.wma.net) revealed that many doctors are no longer being taught to diagnose and treat TB. Thus, private physicians make frequent errors in dealing

1. Adherence research

2. Building the evidence-base for infection control practices

3. Supporting communities

4. Enhancing public health response while addressing the social determinants of health

5. Embracing palliative care

6. Advocacy for research

Box 3. Additional considerations to the WHO 8-point plan

with TB cases. They prescribe too few drugs or the wrong drugs, give inadequate doses of drugs, or prescribe an inadequate duration of treatment [86]. The standardized method of determining cure is based on bacteriologic laboratory testing for the growth of Mtb on culture media. However many health care providers rely on clinical observation to determine treatment outcome [87], either because of shortages in equipment and adequate infrastructure or because they trust their own observation above test results. Such mismanagement is a major cause of acquired drug resistance and treatment failure. On the other hand, on many occasions lung cancer was misdiagnosed and treated as sputum negative TB, a medical error due to high TB prevalence and radiological similarities [88].

It is therefore important that healthcare personnel at the forefront in the fight against TB acquire appropriate and state-of-the art training on TB management. In this regards, the WMA launched in its website a new online refresher course for care providers in many languages. The course provides basic clinical care information for TB including the latest diagnostics, treatment and information about multidrug-resistant TB. It also provides information on how to ensure patient adherence and infection control and includes many aspects of TB care and management. Dr. Julia Seyer, medical adviser at the WMA, said: 'When we started an online MDR-TB training course in 2006, we discovered that many physicians were missing the most basic knowledge about normal TB'.

In summary, both the lack of patient adherence to treatment and deficiencies in programme managements are compromising the effectiveness of MDR TB treatment and the interaction of these two issues raises further the barrier to achieving efficient TB control. From the various opinions on the issue of non-compliance it can be concluded that:

• Addressing therapy-related adverse events should contribute positively in improving patient's compliance. Therefore, potential adverse effects must be carefully evaluated when designing the therapy plan. Alternative plans should be discussed with the patients to minimize the possibility of therapeutic barriers.

• Healthcare system quality is significantly related to compliance. Long waiting times and unhappy experiences during clinic visits are frequent complains from TB patients. A healthcare system that considers patient satisfaction would enhance patient adherence to TB treatment.

• Compliance is also affected by the characteristics of TB disease. While non-adherence is not a major issue when treating short duration infections, this is not the case for TB, a chronic

disease by definition. Therefore, special effort should be made to explain the nature of the disease with a particular focus on the asymptomatic stage of TB.

• Healthcare expenditures are a very important factor that affects compliance. TB patients often feel that the cost of long-term treatment would be a financial burden, which definitely threatens therapy compliance. Therefore, health care personnel should discuss the patient's resources and help identifying sources that might provide financial assistance to low-income patients.

Overall providing care centered on patient needs and expectations is a key component for the success of TB control programmes.

9. Programmatic management of drug resistant TB

Policies, strategies, protocols and guidelines for TB management are well explained and articulated on the paper. However, their implementation in resource-limited sittings remains challenging due to weak case finding strategies, unclear patient tracing mechanisms (especially defaulters), a lack of MDR-TB rapid diagnostic tools, absence of childhood TB case finding approaches and inadequate patient support services. Furthermore, specialized drug resistant TB services are limited to locations that often exclude many patients living in remote areas from receiving adequate health care. Recording systems, mainly paper-based, are time consuming for health care providers, and therefore reduces time for quality care. Addressing these many challenges requires collaboration from different components of national TB control programmes. These components include case detection, treatment, prevention, surveillance, and adequate monitoring/evaluation of the programme's performance. Such objectives are the backbone of DOTS-Plus management programme introduced by the WHO in 1998 [48]. Many DOTS-plus pilot projects provided evidence base for this strategy in the management of drug resistant TB [59,89,90]. Based on the success of pilot projects, the WHO issued in 2006 guidelines for what is now called programmatic management of drug-resistant TB (PMDT), which were recently updated with extra focus on the detection and treatment of drug-resistant TB in resources limited settings [91]. Priority topics identified in the new WHO document are:

• Case-finding through use of rapid molecular tests; investigation of contacts and other high-risk groups;

• Regimens for MDR-TB and their duration in HIV-positive and HIV-negative patients;

• Monitoring during treatment;

• Models of care.

PMDT is currently highly supported by funding for MDR-TB treatment, which has dramatically increased in the past few years. Multi-billion dollar funds are now available through governments and donors, including the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID and the GLC committee [90]. Such fund was essential to demonstrate the feasibility and effectiveness of PMDT in many resource-limited settings, where it is needed most [92].

The current status of MDR-TB epidemic requires urgent moving of PMDT beyond this pilot project stage in order to respond to the call of Stop TB for the treatment of 1.6 million MDR-TB patients in the near future [93].

Although the last WHO document on TB control provides comprehensive guidelines for good PMDT, The WHO recognizes that many crucial management issues remain to be addressed. Thus, during the development of the recent PMDT document, a review published in 2008 [92] revealed some important gaps in knowledge that need to be addressed in order to optimize PMDT:

- Lack of high quality evidence from randomized controlled trials for optimizing treatment regimens in patients with MDR-TB, including the best combination of drugs and treatment duration;

- Very limited information about treatment and management of pediatric MDR-TB;

- Identification of the most effective chemoprophylaxis for contacts of MDR-TB cases;

- The therapy for symptomatic relief from adverse reactions linked to second-line TB drugs.

It is also important to note that social stigma and discrimination are still major obstacles for access to TB care services in many countries [94,95]. Similarly, financial issues and geographical accessibility is also a barrier for the continuation of treatment [96,97]. Misconceptions about TB are highly prevalent, which discourages seeking help in time or encourage those with TB to seek help from traditional healers [98]. Therefore national TB programmes must also include specific strategies to combat these issues in order to optimize the implementation of good PMDT.

Diversity in the epidemiology of MDR-TB poses a challenge for its management in various settings [99]. Ideally, TB management approaches need to be adapted to each particular setting. However it is possible to build a minimal package that could be adapted to specific countries wishing to implement proper TB management approaches. Accordingly, in 2003 a Stop TB Working Group on DOTS-Plus for MDR-TB identified key research questions to be answered in order to scale up the management of all forms of drug-resistant TB and to maximize its public health impact [99]. The working group felt that evidence is needed to address the following questions:

- How can regimens be selected (either at the programme or at the individual patient level) based on standardized and reproducible DST that adequately reflects *in vivo* responsiveness to treatment?

- How can setting specific treatment strategies be optimized with respect to effectiveness, complexity (dosing, eligibility, duration, and monitoring of outcome and side effects), safety, adherence, and affordability?

- What is the minimum infrastructure needed to scale-up PMDT, in terms of:

  ◦ laboratory and treatment provision

  ◦ efficient and equitable patient selection

  ◦ prevention of transmission to other patients and health care workers

• How should infected contacts of DR-TB patients be managed?

Ensuring that these research questions are addressed is the responsibility of all parties involved in the management of MDR-TB. If adequately addressed, they will generate a solid evidence-base to support existing WHO guidelines.

The integration of PMDT into existing TB control programmes beyond the limited pilot project phase has become a critical emergency in order to respond to the increasing spread of MDR/XDR-TB worldwide. However, analysis of current WHO strategies by many experts in the field of TB management [100] suggest that successful PMDT will still require:

• New and improved tools for drug resistance testing;

• Clinical trials to test the efficacy and effectiveness of simplified and shorter second-line treatment regimens as well as of candidate second-line drugs;

• New and improved strategies for identifying patients with drug-resistant disease, promoting treatment adherence, and improving infection control;

• Better epidemiological data to explain geographic variations in occurrence of drug resistance and to identify the greatest contributors to development of drug resistance in specific settings;

• Clinical trials to test the efficacy and effectiveness of new regimens for prophylactic treatment of contacts of patients with DR-TB.

10. Patient centered care approach

Acquiring adequate care for TB is becoming increasingly complex and costly when patients are infected with drug resistant Mtb. This problem is further amplified when patient access to health care centers is limited and adequate patient-clinician relationships are absent. To address this issue Stop TB included patient centered approach as one of its important under-lying principles. It insists on respect for patients right as individuals and as partners in TB care and control. Therefore what are usually characterized as 'patient problems' need to be reconfigured into solidarity with patients and programmatic challenges. Patient-centeredness can be traced back to the adoption of the right to health as part of the International Human right declaration in 1948 [101], but it is only in the 1990s, as result of the community reaction to the AIDS epidemic, that its importance has been perceived. Since then, the rise in prevalence of all forms of TB in HIV individuals has become one of the major stimulating factors for implementation of patient-centered approaches in TB care.

Promoting patient-centered case management involves assessing each TB patient's needs and identifying a treatment plan that ensures the completion of therapy. Policies and guidelines for patient-centered approaches are currently widely distributed. Unfortunately, their application in the field is progressing very slowly. Applying a patient-centered approach takes time and requires effort at many levels. It is a new way of thinking, teaching, providing care,

prevention and communication [102]. Therefore, many countries will continue to experience substantial difficulties in treating drug resistant TB patients at high risk of defaulting.

A systematic review of factors that contribute to non-adherence [103] indicate that many social and economic barriers prevent patients from successfully completing their treatment. A wide range of interacting factors impact on the patient behavior, which is subject to changes during the course of treatment. According to Doctor Without Borders [104], one of the major challenges faced by drug resistant TB patients is the long and arduous treatment period, which can involve large numbers of tablets each day, as well as injectables, both expensive and not always easily available or accessible. Low-income patients living in remote area often struggle to reach specialized TB clinics, in particular when the harsh winter weather affect severely the country's road network and compromises the transportation system. Therefore, in the absence of efficient patient-centered approaches, it is almost impossible to convince patients to continue this forceful effort every day for up to two years.

In the Russian Federation, the proportion of MDR-TB patients defaulting from treatment has increased from 12% in 2001 to almost 30% in 2004 [105], despite the expansion of the DOTS programme to include the treatment of drug resistant TB in 2000. This failure to control drug resistant TB was mainly attributed to the absence of patient-centered strategies adapted to many risk factors for non-adherence such as poverty, unemployment, homelessness, alcoholism, drug abuse and mental illness, to name a few [105]. In response to the alarming proportion of defaulters, a novel patient-centered TB treatment delivery programme (Sputnik) was introduced in Tomsk City [106]. Sputnik care providers accompanied patients through treatment by remaining responsible for patients from the time of enrollment in the programme until the end of treatment (Box 4). The programme paid a particular attention to care giving. In addition to clinical preparation, nurses received a comprehensive training on how to care for patients facing a myriad of biosocial challenges. Indeed, a review of the emotional support that nurses provide to patients living with MTR-TB [107] concluded that nursing of TB patients could be improved with an integrated approach where the nurses are responsible for treating not only the patient, but also ambient factors that affect health, such as family and community.

A high nurse-to patient ratio (2:15),

More staff time per patient to facilitate bonding and defaulter searching

Provision of portable phones to nurses, which increases flexibility

Easier access to specialists

Expanded social and psychological support, which included clothing and assistance with

procuring documentation required to access social services

Box 4. Sputnik programme package

The application of the Sputnik programme led to a mean adherence of 79.0% and a cure rate of 71.1%, indicating that adapted patient-centered approaches contributed significantly to improving TB patient adherence.

In 1998, the Centers for Disease Control and Prevention (CDC) and the Institute of Medicine of the National Academy of Sciences conducted a study to determine if TB eradication in the United State was feasible. The resulting report "*Ending Neglect: The Elimination of Tuberculosis in the United States*" concluded that TB elimination would require "aggressive and decisive action beyond what was in effect." One of the top objectives of the new CDC plan is to ensure that patient-centered case management and monitoring of treatment outcomes are the standard of care for all TB patients [108]. In particular, the CDC guidelines recommend all patients with active TB must be tested for HIV infection and that all patients double infected with Mtb and HIV infection must be appropriately and adequately treated. To ensure adherence to treatment, the CDC recommend the inclusion of multiple enablers (e.g., transportation vouchers and housing for the homeless) and incentives that will motivate the patient (e.g., food coupons), and other treatment enhancers such as alternative treatment delivery sites, and strategies to overcome social and cultural barriers.

Addressing social and economic barriers definitely increases patient access to adequate TB care. However, health education would also strengthen patient-centered approaches. Understanding an illness and how it affects ones life, as well as available treatment options, are necessary for a patient and community to take an active role in TB management. With input from community health professionals from several countries, a literacy tool kit "Within Our Reach: A TB Literacy Toolkit" was developed in 2009 for health educators, outreach workers, counselors, and supervisors who provide services to TB patients [109] and (Box 5).

Increasing knowledge about TB, the link between TB and HIV, TB treatment, and TB transmission

Raising awareness that TB is a serious but treatable disease

Giving patients confidence that they can complete TB treatment and be cured

Educating caregivers and families about how to support TB patients

Reducing stigma attached to TB and HIV

Box 5. Supporting objectives of the TB Literacy Toolkit

The tools are designed to educate TB and HIV patients, their caregivers, and their communities about TB and what it takes to complete a full course of TB treatment. The kit developers suggest that individual sessions should be conducted with flipcharts between the health provider and patient, and videos should be played in a waiting area or during community education events.

Patient-centeredness has become a central approach towards realizing universal access for all patients to efficient TB care. However scaling up this approach is progressing slowly in high TB-burden countries and is mainly challenged by the socio-economic determinants of knowledge and attitudes about TB among health care providers and the general population. Therefore optimal patient-centeredness approach requires collaborative efforts between all organizations serving TB patients to ensure that health care providers, policy makers, community leaders and the public are knowledgeable about TB disease.

11. Drug resistant TB infection (tansmission) in the community and hospitals

TB is a highly contagious disease, acquired mainly through inhalation of airborne aerosols. Infection can occur by inhaling as few as 5-10 living bacteria. People with active TB infection spread the bacterium not only by coughing and sneezing but also by spitting, speaking, singing or laughing. The infectiousness of a TB patient is directly related to the number of droplet nuclei carrying Mtb that are expelled into the air. These droplets rapidly evaporated to form tiny particle nuclei, which could remain airborne for several days [110]. Given this mode of propagation, a person with active TB can spread the germs to up to 15 people in a year, if left untreated [4]. Therefore the process of TB spread also needs to be controlled in order to successfully combat the TB epidemic. In this regards, Nardell recommend the term "transmission control of TB" instead of "infection control of TB", since a third of the world's population is already infected with TB, a situation that appear to be stationary [111].

Because MDR strains carry mutations in major metabolic activities, in particular INH resistant strains lacking catalase activity [112], some researchers have suggested that they may be less virulent and less transmissible [113]. Contrasting with this hypothesis, the epidemic that occurred in New York City in the 1990s [114,115], which affected mainly HIV-infected persons, proved that MDR strains are highly virulent and transmissible. Current data on MDR TB prevalence in Africa, Eastern Europe and Asia [116] provides further evidence of this phenomenon. Drug resistant TB can be transmitted in virtually any setting but healthcare settings, correctional institutions and homeless shelters have an increased risk of transmission. The level of drug resistance TB in hospital settings varies according to local TB prevalence. For instance an university hospitals in Paris (France), reported MDR rates of respectively 1.2% among TB cases [117], while in university hospitals in Manila (Philippine), this figure was an alarming 53.5% [118].

It is generally thought that the emergence of drug-resistant TB (usually termed acquired) occurs in settings where patients fail to adhere to proper treatment regimens or receive inadequate treatment. It is difficult to assign the current magnitude of the epidemic to acquired resistance alone. Another mechanism for the perpetuation of resistance, which has largely been neglected in the development of TB control programmes, is the direct transmission of drug-resistant strains (called primary or transmitted resistance) [119]. In the 2006 XDR-TB outbreak in KwaZulu-Natal (South Africa), 52 of 53 people who contracted the disease (all of them HIV infected) died within weeks [120]. This outbreak received international attention because 85 percent of infected patients had genetically similar XDR strain, indicating that resistance was likely transmitted rather than acquired. Consistent with these findings, a study conducted in Tomsk (Siberia) –a setting where HIV infection is not widespread and effective TB treatment is available– to identify factors leading to increases in MDR-TB cases [121], revealed that a patient was six times more likely to develop MDR-TB if hospitalized for drug-susceptible TB than if not hospitalized. These results strongly suggest that nosocomial transmission of TB rather than resistance (acquired predominantly by nonadherence) is increasingly responsible for the rising MDR TB case rates in Russia and probably in many other places.

Worthy of note is that nosocomial transmission of TB is a risk not only to inpatients but also health care workers (HCWs). In fact, early studies revealed transmission of MDR-TB from patient to patient and from patient to HCWs [122]. A systematic review by Joshi and colleagues [123] demonstrated that TB is a significant occupational problem among HCWs in many low- and middle-income countries and that most health care facilities in these sittings lack resources to prevent nosocomial transmission of TB. HIV-infected HCWs have a particularly high risk of TB, which may be fatal if the disease is caused by a drug-resistant strain [124]. Indeed, dramatic nosocomial outbreaks of MDR TB occurred the late 1980s, largely in HIV infected HCWs, and caused many deaths [110]. This situation increased the concern of HCWs about the safety of working in institutions with a large numbers of admissions for active TB. Indeed, it is estimated that 1% to 10% of HCWs are infected annually in hospitals with more than 200 admissions per year for TB [110]. The risk of TB transmission to HCWs is particularly high in certain areas of the hospital, such as emergency rooms and units that admit patients with active TB [125].

A review of several reports of TB outbreaks with transmission to HCWs in industrialized countries revealed that many factors contribute to nosocomial transmission, such as delayed diagnosis, poor ventilation with positive pressure in isolation rooms, aerosolization of bacilli through mechanical ventilation, bronchoscopy and dressing change [110]. There was also strong evidence that technicians involved in cough-inducing procedures, histologic preparations and autopsies are at high risk, even in institutions caring for few patients with TB [126]. These outbreaks revealed many deficiencies in the knowledge of TB and its transmission as well as strategies used to control the disease. Therefore, various health authorities have implemented effective control programmes based on the early detection of TB and the prompt isolation and treatment of persons with TB in addition to introducing strong measures to prevent nosocomial transmissions of TB. For instance, the US Centers for Disease Control (CDC) [127] recommended the following levels of controls: **1. Administrative controls,** which reduce risk of exposure. **2. Environmental controls,** which prevent spread and reduce concentration of droplet nuclei. **3. Respiratory-protection controls,** which further reduce risk of exposure in special areas and circumstances. (Box 6).

Implementation of a full hierarchy of these measures lead to a significant reduction in nosocomial transmission of TB in the United States [128]. Whereas the extent of the epidemics in low and middle income countries is still attributed, in large part, to ineffective transmission control strategies. In these countries, double infection with TB and HIV has further accelerated the transmission of drug resistant TB and increased the spread of HIV. Such a dramatic situation blocks the efforts of both the Stop TB Partnership and anti-retroviral therapy programmes. It is regrettable that many health care institutions continue to house HIV positive individuals with patients who have drug-resistant TB, thus leading to nosocomial transmission with subsequent community transmission. In this regards, health authorities in Haiti implemented an effective community-based transmission control programme with a baseline triage and separation strategy [111]. Patients are admitted to either the general medical ward, a TB pavilion, or very basic isolation rooms based on smear results and HIV status (Fig. 2).

Administrative Controls
• Assign responsibility for TB infection control • Conduct TB risk assessment • Develop and institute a written TB infection-control plan • Ensure the timely availability of recommended laboratory processing, testing, and reporting of results
• Implement effective work practices for the management of patients with suspected or confirmed TB disease • Ensure proper cleaning and sterilization or disinfection of potentially contaminated equipment • Train and educate health-care workers • Test and evaluate health-care workers for TB infection and disease • Apply epidemiology-based prevention principles • Use posters and signs demonstrating and advising respiratory hygiene and cough etiquette • Coordinate efforts with the local or state health department.

Environmental Controls
Reduce concentration of infectious droplet nuclei through the following technologies:
• Ventilation technologies (Natural ventilation and Mechanical ventilation) • High efficiency particulate air filtration • Ultraviolet germicidal irradiation

Respiratory Protection Controls
• Implement a respiratory-protection programme • Train health-care workers on respiratory protection • Educate patients on respiratory hygiene and the importance of covering their cough • Test HCWs for mask fit and functionality

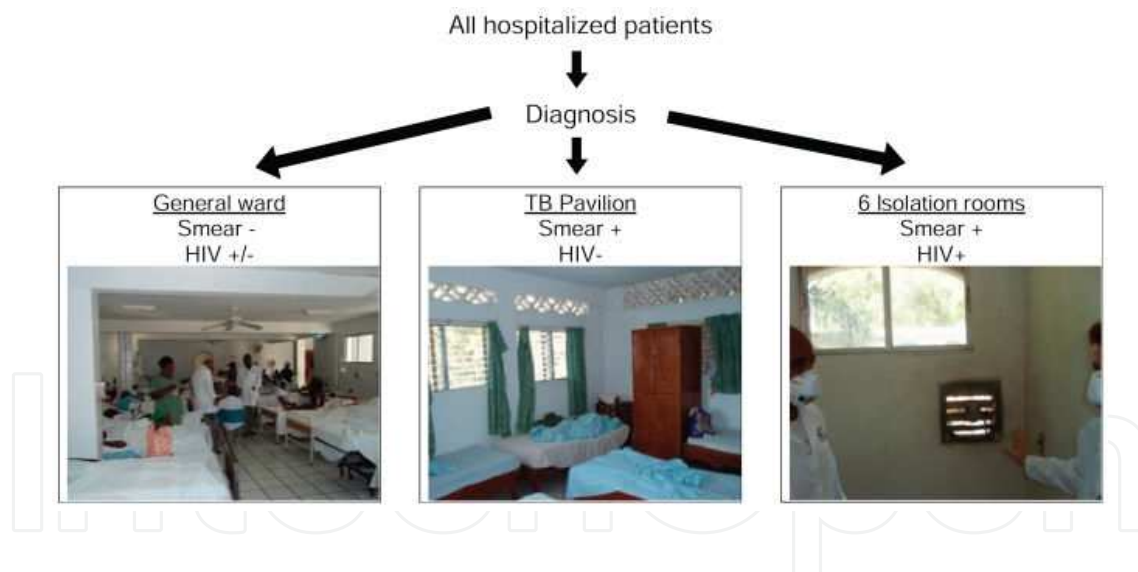**Box 6.** TB Infection-Control Programme: Level of Controls

Figure 2. Community-based TB treatment triage strategy in Haiti. The general medical ward has natural ventilation and UV air disinfection. The TB ward has natural ventilation with fenestrated brick and more UV fixtures to disinfect the air than the general ward has. The six isolation rooms are off a common corridor, and each has a large exhaust fan built into the wall that draws air into the room from the corridor, as well as a UV fixture. Reprinted from Ref. 111 with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union

Although this simple baseline strategy is not sufficient, Nardell considers that its implementing in other resource-poor settings would contribute significantly to reduce the burden of TB epidemic [111].

12. Conclusion

Founded in 2001, the goal of The Stop TB Partnership for 2015 was to reduce the global burden of TB disease (deaths and prevalence) by 50% relative to 1990 levels. The reality of the global incidence of all forms of TB in 2012 indicates that this timetable is unrealistic. Despite billions of dollars already spent on TB control programs, less than 2% of drug resistant TB cases currently receive appropriate treatment in high burden countries allowing the disease to spread faster than the implementation of adequate management programs. This dramatic situation severely attenuates global efforts to control TB.

One of the major challenges now is to develop innovative approaches to expand the detection and treatment of drug resistant cases globally. To achieve this goal, substantial funding and development of extensive human resources is needed. Among the response priorities, the following are of paramount importance: 1) developing tools for rapid detection of drug resistance; 2) clinical trials to test simplified, safe and shorter second-line treatment regimens; 3) developing approaches to enhance treatment adherence; 4) clinical trials to test the efficacy of new prophylactic treatment regimens for contacts of patients; and finally 5) developing safe and more efficient second-line drugs.

However, even with increased detection and treatment of drug resistant TB, focusing on the care of TB and neglecting living conditions in low-income countries has little chance of completely reversing the burden of TB. The severity of the TB epidemic in the Western world during the 19th century was largely due to the low living standards prevalent among the poor during the industrial revolution. As living standards improved, TB mortality began to decrease long before any vaccinations or specific therapy was introduced. Reminiscent of the 19th century situation is the persistence of TB in poor and marginalized populations in most modern cities of the world. As the British historian Thomas Mc-Keown said in 1976, "the overall health of the population is less related to medical advances than to standards of living and nutrition" [101]. Thus the control and eventual eradication of the TB epidemic will need support and cooperation from multiple levels within the medical and scientific community, as well as all levels of government worldwide in order to address living standards and develop better drugs and therapeutic tools for the clinic.

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