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Guidelines and Guidance

Scaling Up Programmatic Management of Drug-Resistant Tuberculosis: A Prioritized Research Agenda

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Background

Tuberculosis (TB) remains a significant global health problem, responsible for an estimated 1.7 million deaths per year worldwide [1]. Resistance to anti-tuberculosis drugs is an important threat to tuberculosis control. The risk of treatment failure and death with standard short-course chemotherapy is highest with resistance to both isoniazid and rifampicin (multidrug-resistant tuberculosis, or MDR-TB; see Glossary) [2]. Drug-resistant tuberculosis is "human-made": it results from treatment with inadequate drugs or drug regimens, improper case management, and preventable transmission. Its presence generally reflects weak tuberculosis control in the past or present. Between 1994–2007, resistance to any first-line drugs among new tuberculosis cases was reported from 127 settings included in the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, with a median prevalence of 17% [3]. The total number of MDR-TB cases estimated to have occurred worldwide in 2006 was 489,139, or 4.8% of all TB cases. [3].

MDR-TB treatment using currently available second-line drugs may cure only 65%–75% of patients [4]. These drugs are more expensive, less potent, and less well tolerated than first-line drugs [4]. Inadequate treatment with second-line drugs may result in extensively drug-resistant tuberculosis (XDR-TB; see Glossary) [5,6]. XDR-TB is associated with high fatality, especially in patients who are co-infected with HIV [5,7]. In affluent countries, treatment with second-line drugs is generally limited to centers with specialized services. Such services are unavailable in many countries, and a programmatic approach is needed to provide treatment to large numbers of MDR-TB patients.

In 1999, the World Health Organization (WHO) and partner agencies launched DOTS-Plus, a complementary DOTS-based strategy with provisions for treating MDR-TB based on the five tenets of the DOTS (directly observed treatment, short-course) strategy: sustained political commitment; a rational case-finding strategy; use of second-line drugs under appropriate case management conditions; an uninterrupted supply of quality-assured drugs; and standardized recording and reporting [8]. DOTS-plus pilot projects were started to obtain an evidence base for this strategy.

The Guidelines and Guidance section contains advice on conducting and reporting medical research.

Summary Points

- The World Health Organization calls for massive scale-up of programmatic management of drug-resistant tuberculosis in resource-limited settings.
- Several technical and operational barriers impede the achievement of this scale-up.
- A research agenda, developed by the Stop TB Partnership, identifies the most important barriers and prioritizes the research questions to be addressed in order to overcome these barriers.
- Research priorities include: new and improved tools for drug resistance testing; clinical trials of simplified and shorter second-line treatment regimens; new and improved strategies for diagnosis of drug-resistant tuberculosis, treatment adherence, and infection control; understanding of the geographic variations in occurrence of drug resistance; and clinical trials of prophylactic treatment of contacts of patients with drug-resistant tuberculosis.

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Abbreviations: DOTS, directly observed treatment, short-course; DR-TB, drug-resistant tuberculosis; DST, drug susceptibility testing; GLC, Green Light Committee; MDR-TB, multidrug-resistant tuberculosis; PMDT, programmatic management of drug-resistant tuberculosis; TB, tuberculosis; WHO, World Health Organization; XDR-TB, extensively resistant tuberculosis

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Glossary

Drug-resistant tuberculosis (DR-TB): Disease caused by a strain of *M. tuberculosis* that is resistant to any anti-tuberculosis drug.

Multidrug-resistant tuberculosis (MDR-TB): Disease caused by a strain of *M. tuberculosis* that is resistant to at least isoniazid and rifampicin [3,4].

Extensively drug-resistant tuberculosis (XDR-TB): Disease caused by a strain of *M. tuberculosis* that is resistant to isoniazid and rifampicin plus any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin, capreomycin) [6,7].

Concurrently, the Green Light Committee (GLC) was established by the Stop TB Partnership to facilitate access to concessionally priced, quality-assured second-line anti-tuberculosis drugs for MDR-TB management projects that meet the criteria for rational use [9,10]. Evaluation of the first GLC-endorsed pilot projects of MDR-TB management in five resource-limited countries showed treatment success rates of 59%–83% [11]. Based on the experiences from the DOTS-Plus pilot projects, the WHO recently issued guidelines for what is now called programmatic management of drug-resistant TB (PMDT). Funding for MDR-TB treatment has dramatically increased in the past few years, and is available through governments and donors, including the Global Fund to Fight AIDS, Tuberculosis and Malaria, and UNITAID. Now that the effectiveness and feasibility of MDR-TB management in resource-limited settings has been demonstrated, the emerging global MDR-TB epidemic requires moving beyond the pilot project stage in order to mainstream MDR-TB management into national tuberculosis control programs. Currently, fewer than 2% of all estimated MDR-TB patients receive appropriate treatment [1]. The Global Plan to Stop TB 2006–2015 urges a dramatic scale-up of MDR-TB treatment as a routine component of TB control; a 2007 addendum calls for the treatment of 1.6 million MDR-TB patients by 2015 [12,13].

Although much has been learned from the DOTS-Plus pilot projects, important knowledge gaps remain to be filled before MDR-TB management can be mainstreamed and fully integrated into TB control programs in resource-limited settings. An earlier research agenda that addresses these gaps was proposed in 2001, focusing on operational questions surrounding these pilots [14]. Although a number of these questions have been answered, providing part of the evidence base for the WHO's Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis [11,15–25], many have not. Biological and clinical issues underlying these operational questions needed to be addressed first, and the initial agenda focused largely on research to be done as part of the DOT-Plus pilot projects. To facilitate and inform rapid scale-up, additional questions have become urgent.

The Working Group on MDR-TB involves most stakeholder institutions, academics, agencies, and experts active in management of drug-resistant tuberculosis. It has called for a revised and extended research agenda that identifies the key research questions to be answered in order to scale up the management of drug-resistant tuberculosis programs. Its scope is expanded to cover all forms of drug-resistant tuberculosis (DR-TB), including XDR-TB.

Process

The research agenda was prepared by the Research Subgroup of the Working Group, which comprises various areas of expertise (clinical, laboratory, epidemiology, health systems, program management). The Subgroup first identified the barriers to scaling up DR-TB management within each of the five tenets of DOTS: political commitment, case finding, treatment, drug supply, and recording and reporting. This process was guided by the WHO PMDT guidelines, which are based on a critical appraisal of the existing evidence and had been recently issued [16]. For each component,

Table 1. Research Priorities

Priority Area	Research Priorities
Laboratory support	Improve laboratory methods for selection of drug regimens and of patients eligible for second-line treatment: • Standardization of DST for second-line drugs • Establishment of prognostic value of in vitro mono-resistance and cross-resistance between second-line drugs • Development and validation of tools for rapid detection of drug resistance, including for XDR-TB
Treatment strategies of DR-TB	Identify optimal treatment protocols for DR-TB through (multicenter) clinical trials and well-designed cohort studies, with a focus on: • Optimal use of existing drugs: clinical efficacy of different standard and individual MDR-TB regimens across multiple settings and against various drug resistance patterns with regard to the number and combination of second-line drugs needed according to DST • Efficacy of candidate drugs (including compassionate use and pipeline)
Programmatically relevant research	Define and evaluate strategies for integration/scale-up of management of DR-TB into larger DOTS programs: • Algorithms for selecting patients eligible for drug susceptibility testing and second-line treatment in different settings, including special strategies for high-risk groups and use of rapid resistance testing methods • Strategies for provision of second-line treatment in different settings, including adherence and use of incentives and enablers • Effectiveness of existing infection control measures and strategies for selecting and implementing infection control measures (for communities, households, and health care settings)
Epidemiology of DR-TB	Identify and assess the relative importance of risk factors for DR-TB, in particular to explain variation in MDR-TB and XDR-TB prevalence between settings
Management of contacts of patients with DR-TB	Clinical trials or well-designed cohort studies of the efficacy of several individual drugs and drug combinations in preventive treatment of persons presumably infected with DR-TB

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knowledge gaps were listed and translated into research topics that were further specified, grouped into logically focused research areas, and ranked by their priority. A draft was widely circulated among experts in the fields of DR-TB and programmatic management of tuberculosis, and their comments were considered and incorporated. Finally, the resulting agenda was discussed and endorsed during the annual meeting of the Working Group in Tbilisi, Georgia, September 2007.

Prioritization

There is already extensive information to demonstrate successful models of management of DR-TB [4,11,15,16]. These experiences, however, need to be expanded and optimized to maximize their public health impact. Therefore, the priorities were defined as those research questions considered the most important to facilitate and accelerate scale-up of PMDT, and to maximize its public health impact, in line with the Global Plan to Stop TB 2006–2015 [12,13].

In order to rapidly scale up effective programmatic management of DR-TB, evidence is needed to answer the following questions [14]:

- How can regimens be selected (either at the program or at the individual patient level) based on standardized and reproducible drug susceptibility testing (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 programmatic infrastructure needed for such scale-up, in terms of laboratory and treatment provision, and of efficient and equitable patient selection and prevention of transmission to other patients and health care workers?

Scale-up of DR-TB would have limited epidemiological impact if not combined with strategies to reduce development and transmission of DR-TB. Therefore, the subgroup identified two other questions of importance:

- What are, in various settings, the relative contributions of poor treatment, resistance amplification during treatment, and ongoing transmission to the drug resistance problem?
- How should infected contacts of DR-TB patients be managed?

Research Priorities

The research agenda, therefore, focuses on the following five priority areas: laboratory support, treatment strategies, programmatic aspects, epidemiology of DR-TB, and management of contacts of DR-TB patients. The most urgent research questions within these five areas are presented (Table 1) and discussed. The complete agenda identifies several additional research topics within these five priority areas, as well as other areas of research (see http://www.who.int/tb/).

Laboratory. Laboratory support, in particular for DST, is crucial for DR-TB management. Although DST for isoniazid and rifampicin generally gives reliable and reproducible results [26], susceptibility testing for second-line drugs does not [27]. The lack of standardized methodologies for second-line DST currently compromises the clinical management of patients. In addition, the clinical significance of in vitro mono-resistance is often unclear, as is that of cross-resistance within classes of drugs, such as between newer and older generation fluoroquinolones [28,29]. These doubts about in vivo–in vitro correlation of drug resistance result in withholding effective drugs from patients, or exposing patients to ineffective drugs. Another major impediment to effective management of DR-TB is the long turnaround time of DST: two to four weeks for methods using liquid culture media, and four to 12 weeks for methods using solid media. Several methods for rapid detection of drug resistance have been, or are being, developed [30,31]. Most are for rifampicin and isoniazid only, and data from validation studies in the context of TB control programs are limited. Rapid methods for detection of resistance to second-line and other first-line drugs would improve individual patient treatment by allowing use of effective drug regimens from the start of treatment. Molecular assays would simplify decentralization of (second-line) DST, and are therefore most promising in the context of PMDT, but must be adapted to the field setting.

Treatment strategies. Treatment strategies for DR-TB lack a solid evidence base. Recommendations on drug regimens, specifically the number of drugs and the duration of treatment, as well as treatment monitoring criteria, are based on clinical experience in small-scale pilot projects [11,17,18,20,21]. Designed to provide proof of principle, these pilots aimed at maximum efficacy. They applied treatment strategies based on complex drug regimens tailored to the individual patient's drug resistance profile (individualized regimens), long duration of treatment, and intensive monitoring of adverse events and treatment outcomes, and had rigorous approaches to ensuring treatment adherence [17]. For scale-up, feasibility, adherence, and effectiveness are all of paramount importance; simpler, effective strategies are needed. Possibilities for simplification that should be examined include the following: shorter treatment duration, fewer drugs (likely yielding fewer adverse events), more standardized approaches to treatment, and less intensive monitoring. In addition, new drugs need to be tested for efficacy and safety for treatment of DR-TB. Thus, there is a clear need for randomized controlled clinical trials and carefully designed cohort studies.

Randomized controlled trials, which contributed to improving and shortening therapy for drug-susceptible TB [32,33], have almost never been undertaken for DR-TB. This was due to a lack of perceived epidemiological significance of DR-TB; lack of suitable trial sites; the heterogeneity of the patient population; absence of new anti-tuberculosis agents; and limited political will [14]. Recent progress, including new epidemiological evidence [3], policy changes [12], and advances in TB drug development [34], have improved the environment for embarking on trials of DR-TB treatment. The expansion of MDR-TB treatment programs provides the setting in which trials could be implemented [11]. As proposed recently by Mitnick et al. [35], an innovative randomized controlled trial design using optimized background therapy—used for regulatory approval of new antiretroviral agents—presents one tool for evaluating new agents in the context of heterogeneity [36–39]. Other designs will also be useful [40]. And, for the first time in 30 years, several new drug classes that hold promise for DR-TB

treatment are under development [34]. Lastly, clinical trials for DR-TB may allow accelerated regulatory approval for new anti-tuberculosis agents.

The challenge of clinical trials among DR-TB patients is compounded by enormous variability in host and bacillary populations as well as social and environmental conditions. Producing valid results that are generalizable across human and mycobacterial populations will best be achieved through multi-site studies, preferably carried out in sites with a high burden of disease in heterogeneous populations (e.g., HIV-infected/uninfected; chronic/ "new" DR-TB cases; high-grade/low-grade resistance). Investment in capacity building will be required to conduct such trials.

Programmatic aspects. There is a further need to evaluate strategies specific to the various components required for integration of PMDT into existing TB control programs.

Selection of patients for DST can take place at various stages of the diagnosis and treatment process, e.g., when a patient starts treatment for a first TB episode, when a patient is still bacteriologically positive at the end of treatment, or when a patient is not cured by a subsequent treatment course [16]. Selection strategies should target those patients most at risk of having MDR-TB, including patients who may live far from DST facilities. This prospect is more promising in light of the advent of rapid resistance testing methods, in particular molecular assays, which have no rigorous requirements with regard to transport conditions of specimens and are becoming available for large-scale use [30].

Adherence to treatment for DR-TB is highly important for its success, but is complicated by its long duration and sometimes high frequency of adverse events [22–24]. Some of the DOTS-Plus pilot projects have reported high completion of treatment courses [22,23], but whether these results can be sustained if implemented at a large scale is unknown. Strategies therefore need to be developed that maximize treatment adherence in a sustainable way, and factors that affect adherence need to be studied, including the role of adverse events and levels of patient support.

Another concern when moving from rigorously controlled pilots to routine program conditions is infection control. Nosocomial transmission of MDR-TB is well documented, in particular in the context of high HIV prevalence [41]. Guidelines for control of tuberculosis infection in health care settings have recently been revised to include settings with high MDR-TB and HIV prevalence [42]. However, the high cost of engineering controls and some personal respiratory protection measures generally limits their application in resource-limited settings, and little is known about the effectiveness of less costly alternatives proposed in these guidelines [43,44]. Even less is known about infection control outside health care settings, such as in households and in the community [45]. Thus strategies are needed for infection control in a variety of settings.

Epidemiology. Preventing development and transmission of DR-TB is essential to effective PMDT. Although conditions leading to drug resistance in tuberculosis are well described, part of the variation in its occurrence is unexplained. In some areas the prevalence of DR-TB is very low with no increase, whereas in other areas the prevalence is high and/or increasing [3]. Major obstacles to understanding the epidemiology of DR-TB include the long generation time of the epidemic (it may take several decades before weaknesses or changes in tuberculosis control result in measurable changes in prevalence of drug resistance) [46]; the coexistence and interaction of several risk factors [47]; limited availability or quality of drug resistance data [3]; and limited quality of routine statistics. This makes it necessary to complement the monitoring and evaluation of routine activities with targeted research activities.

More epidemiological studies are needed to identify areas of high and increasing levels of drug resistance, and to identify risk factors that lead to increasing occurrence of drug resistance. Risk factors to be evaluated include type and quality of first-line treatment supervision; access to TB drugs outside TB programs; infection control practices; use of rifampicin in the continuation phase of the treatment regimen of new tuberculosis patients; composition of and transfer to retreatment regimens; drug quality; *Mycobacterium tuberculosis* genotype; HIV prevalence; and level of use of antiretroviral treatment. Such analyses should help define the factors with the largest impact on the drug resistance situation, and thereby the most effective interventions. In addition, any intervention should be monitored for its impact on the drug resistance situation.

Contacts of drug-resistant TB patients. The management of contacts of drug-resistant TB patients is a complex issue with a significant ethical dimension. Household infection control measures should be implemented to reduce the risk of transmission of resistant disease. Among household contacts found to be infected, the susceptibility pattern of the infecting strain remains unknown. In fact, data from observational cohorts suggest that strains isolated from contacts often *do not* have the same resistance pattern as those isolated from index cases [48,49]. Further, optimal treatment combinations and duration for preventive treatment of latent TB infection with resistant organisms are unknown. Standard isoniazid preventive therapy is considered unlikely to be efficacious for either MDR-TB or other isoniazid-resistant forms of tuberculosis [50,51]. Yet no large-scale controlled trials have been conducted of a preventive therapy regimen that could be used for contacts of patients with these resistant forms. The use of pyrazinamide in combination with other drugs as preventive therapy has been associated with high frequencies of liver toxicity and death [52]. Prophylaxis with second-line drugs has only been reported among small case series of contacts of patients with resistant disease [53]. Although toxicity is an accepted risk with treatment for active tuberculosis, since the alternative is death in a high proportion, the extent of accepted toxicity with preventive therapy is fundamentally different. Clinical series of infected contacts treated using various drug combinations, or a standard preventive therapy regimen based on representative population susceptibility profiles, may provide insights into drug tolerability, acceptance, and adherence. Well-designed preventive therapy trials should be considered in certain settings where MDR-TB therapy and a strong national program infrastructure are already in place.

Implementation

How to stimulate the implementation of this research agenda? Lessons can be drawn from experiences with the previous research agenda on DR-TB prepared in 2001 [14]. For several reasons, many research priorities remain unaddressed.

Most importantly, MDR-TB treatment was a marginalized intervention in 2001, perceived as necessary and possible in only a handful of settings. Consequently, research on MDR-TB was a priority of neither funding nor implementing agencies. Now, the magnitude and breadth of the epidemic, as well as illustrations of disparity in research resources [54], are fueling high-level interest and financial commitment [6,13,55]. Implementation of the research agenda was further hampered by the small scale of the pilots in which studies were to be conducted; since 2000, when the first cohort of 1,000 patients in two settings was approved to receive treatment through the GLC, more than 30,000 patients in 60 settings have been approved for treatment by the end of 2007 [1]. The landscape for research is also more promising. For example, research capacity of the pilot sites have been enhanced through increased funding, and the pharmaceutical industry is investing in the capacity of at least a dozen sites globally to participate in clinical trials of MDR-TB.

Further advocacy for funding will require development of study designs with budgets and timelines. Also, additional collaborations must be forged between treatment sites of drug-resistant tuberculosis and researchers. Research activities require coordination among these sites. Finally, evaluations of the various components of strategies for scaling-up of PMDT, such as infection control and treatment adherence, could be included in grants for tuberculosis program support.

Conclusion

With increasing recognition of MDR/XDR-TB worldwide, the time has come to move PMDT in resource-limited settings beyond the limited, pilot project phase. Successful scale-up of PMDT and integration into existing tuberculosis control programs require the following: 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; and finally, clinical trials to test the efficacy and effectiveness of new regimens for prophylactic treatment of contacts of patients with DR-TB. ■

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