

RESEARCH AGENDA ON DRUG RESISTANT TUBERCULOSIS

With A Focus On Scaling-up Programmes

Background

The Working Group on MDR-TB is an inter-institutional working group involving institutions/agencies and experts active in the management of multidrug-resistant tuberculosis (MDR-TB). The Working Group was established to perform the following functions: 1) assist in producing policy recommendations for World Health Organization (WHO) Member States on the management of MDR-TB, based on the assessment of the feasibility, effectiveness and cost-effectiveness data generated by pilot projects implemented by the agencies/institutions participating in the Working Group, or by the WHO; 2) coordinate and monitor the implementation of internationally comparable pilot projects for the management of MDR-TB; 3) establish a system that allows WHO Member States to have access to high-quality second-line drugs at reduced prices and, at the same time, prevents misuse of such drugs; 4) review progress achieved in countries managing MDR-TB through the Green Light Committee (GLC); and 5) identify resources to fund and implement MDR-TB control and to assist with global coordination of the initiative.

The MDR-TB Working Group indicated in its fifth meeting in Atlanta the need to revitalize its scientific component. Many research questions remain to be answered in order to scale-up the management of drug resistant tuberculosis (DR-TB) in resource-constrained countries, according to the Global Plan to Stop TB 2006-2015. Further research evidence on MDR-TB management will enable WHO to update the recently published "Guidelines for the programmatic management of drug-resistant tuberculosis". In August 2006, a Research Subgroup was installed; its initial terms of reference were the development of a research agenda in the field of DR-TB. This report summarizes its recommendations with regard to this agenda.

Objective

The objective of this document is to identify the key questions to be answered in order to scale-up the management of DR-TB in resource-constrained countries, according to the Global Plan to Stop TB 2006-2015. For this purpose, drug resistance was defined as any resistant tuberculosis with clinical relevance, including multidrug-resistant, polydrug-resistant (PDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).

Apart from providing a broad list of research topics, it was felt necessary to indicate priority areas within that list. The subgroup agreed that prioritization of this research agenda should be guided by the explicit goal of rapidly scaling-up effective DR-TB management programs.

Members of the Research Subgroup

The Subgroup consisted of: Peter Cegielski (US CDC, Atlanta, USA), Frank Cobelens (chair; KNCV Tuberculosis Foundation, The Hague, Netherlands), Einar Heldal (Norwegian Association of Heart and Lung Patients - LHL, Norway), Michael Kimerling (University of Alabama at Birmingham, USA), Carole Mitnick (Partners in Health/Harvard Medical School, Boston, USA), Laura Podewils (replacing Peter Cegielski; US CDC, Atlanta, USA), Rajeswari Ramachandran (Tuberculosis Research Centre, Chennai, India), Hans Rieder (The Union, Paris, France), Karin Weyer (Medical Research Council, Pretoria, South Africa) and Matteo Zignol (secretariat; WHO Stop TB, Geneva, Switzerland).

Process

The research agenda was constructed by first identifying areas of relevance for the scaling up of DR-TB management. In order to consider all potential areas of relevance, an initial listing was based on the chapters of *World Health Organization Guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2006.361)*. For each chapter, research topics and questions were identified and further specified. These topics and questions were then regrouped into larger and logically focused research areas. From this list, the subgroup selected a limited number of areas having highest priority. These priority areas were further detailed, with descriptions of the context and rationale. The resulting draft was circulated among members of the full MDR-TB Working Group to review, provide guidance on the priorities, recommend other stakeholders for review of the document, and advise on the processes for execution of the final research strategy.

Some general remarks

Research versus evaluation

Several types of research are needed to address the listed priority areas in this agenda: fundamental (basic), clinical, epidemiological, qualitative and operational. The common denominator of these approaches is that they aim to produce results that are generalizable beyond the setting in which the data were collected. Some topics, however, may be addressed by the systematic evaluation of existing projects or programs. Evaluation differs from research in that the results may be setting-specific and the applied methodology is not aimed at generalizability of the results. Evaluation, nevertheless, does provide useful information, in particular if the evaluation processes can be replicated in other settings. Once established, rigorous recording and reporting systems of DR-TB programs can be a rich source of evaluation data, and additionally, provide a platform for epidemiological or operational research.

Collaboration with the GLC

Natural sites for the implementation of research activities are the GLC-approved projects. In those settings, the management of drug resistant TB is performed according to international recommendations and using quality-assured drugs. In addition, the projects are continuously monitored by the GLC, assuring that all the conditions needed to successfully diagnose and manage patients with drug resistant TB are implemented. For these reasons, and to rapidly address multiple research topics, strong collaboration with the GLC is needed.

Abbreviations used

ARV	Antiretroviral drug
DOTS	Directly-observed treatment, short-course
DR	Drug resistant
DST	Drug susceptibility testing
GLC	Green Light Committee
MDR	Multi-drug resistant, i.e. resistance to at least isoniazid and rifampicin
PDR	Resistant to two or more first-line anti-tuberculosis drugs in the absence of multi-drug resistance
PMDT	Programmatic management of drug-resistant tuberculosis
SLD	2 nd -line antituberculosis drug
TB	Tuberculosis
XDR	Extensively drug resistant, i.e. multi-drug resistant in combination with resistance to at least a fluoroquinolone and one or more of the following injectable drugs: kanamycin, amikacin, capreomycin

Research priorities

While it is recognized that there is already much information to demonstrate successful models of DR-TB management, these experiences 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 the scale up of the programmatic management of drug-resistant tuberculosis (PMDT) and maximize its public health impact over the next 5 to 10 years.

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

- How can regimens be selected (either at the program or an 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, outcome & monitoring of adverse events), 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 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 and ongoing transmission to the drug resistance problem?
- How should contacts infected with DR-TB be managed?

The subgroup therefore focused on the following five areas for defining its research priorities:

- Laboratory aspects
- Treatment strategies
- Programmatic aspects
- Epidemiology of drug-resistant tuberculosis
- Management of contacts of drug-resistant TB patients

Each of these areas is further detailed in separate sections below, with its identified research priorities as well as some additional, but less urgent, research topics.

In a final section, a number of areas are listed in which research is also needed.

Priority area 1: Laboratory aspects

Context and rationale

Together with second-line drugs, appropriate laboratory support for MDR-TB management is crucial and non-negotiable. Nevertheless, affordable, appropriate and sustainable laboratory services remain the weak link in TB control worldwide, now being brought into stark relief by the need for rapid and extensive scale-up of MDR-TB treatment. Although most of the challenges around laboratory capacity strengthening center on the programmatic issues of infrastructure development, acquisition and maintenance of equipment, and external quality assurance, several fundamental questions remain. Reliable and reproducible second-line drug susceptibility testing methods are urgently needed. The lack of standardized methodologies currently compromises the clinical management of patients.

This part of the research agenda therefore focuses on the most burning laboratory research necessary to rectify this problem.

Research priorities

Improve laboratory methods for selection of drug regimens and of patients eligible for 2nd-line treatment:

- Standardization of DST for 2nd-line drugs
- Prognostic value of *in vitro* mono-resistance and cross-resistance between 2nd-line drugs (including newer generation fluoroquinolones)
- Development and validation of tools for rapid detection of drug resistance, including XDR

Other relevant research topics in this area

- Standardization of DST (solid and liquid media):
 - Standardization of DST for pyrazinamide
 - New methods for drugs for which conventional DST is unreliable
- *In vivo* correlation of *in vitro* DST results:
 - 1st-line drugs, eg. low and high dose isoniazid, borderline rifampin-resistance
 - *In vitro* synergy of different drug combinations
 - Post-antibiotic effect of 2nd-line drugs
- Molecular basis of drug resistance:
 - Mutations conferring resistance to 2nd-line drugs
 - Role of molecular sequencing in improving/replacing conventional DST

Priority area 2: Treatment strategies of drug-resistant tuberculosis

Context and rationale

The feasibility and cost-effectiveness of treating patients with DR-TB in resource-constrained countries is well established. Standard-of-care treatment, however, is long, toxic, and frequently unsuccessful. Randomized clinical trials, which contributed to improving and shortening therapy for drug-susceptible TB, have almost never been undertaken for DR-TB. This was due to a lack of perceived epidemiologic 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.

Recent progress, including new epidemiologic evidence, policy changes, and advances in TB drug development, have improved the environment for embarking on trials of DR-TB treatment. Documentation of the burden of MDR/XDR-TB, and sub-optimal treatment outcomes, demonstrate the need for research. The expansion of MDR-TB treatment programs provides the setting in which trials could be implemented. An innovative randomized, controlled trial design using optimized background therapy - used and honed for regulatory approval of new anti-retroviral agents - presents one tool for evaluating new agents in the context of heterogeneity. Other designs will also be useful. For the first time in 30 years, several new drug classes that hold promise for DR-TB treatment are under development. Lastly, clinical trials for DR-TB may allow accelerated regulatory approval for new anti-tuberculosis agents.

Such trials—and observational studies designed and analyzed to minimize bias in results—would address questions related to the optimization and scale up of treatment. Issues to be addressed include the efficacy of new agents, duration of treatment, dosing frequency, effect of individual agents or combinations (existing agents and new compounds), the importance of drug-susceptibility testing and previous treatment history in regimen selection, and role of adjunctive therapies (i.e., surgery) and support (i.e., nutritional). The challenge of studying these questions is compounded by enormous variability in host and bacillary populations. Producing valid results, which are generalizable across human populations and strain types, 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). This will require investment in capacity building for conducting such studies.

Over the long term, studies of treatment of DR-TB in special populations (e.g., children, pregnant/breastfeeding women, HIV co-infected patients, diabetics, etc.) will also be essential.

The long-term nature of treatment for drug-resistant TB also necessitates studies to identify surrogate markers for failure or relapse and interim endpoints (e.g., bacteriologic, antigen, etc), which may be used to shorten the duration of trials and other experimental interventions. The identification and use of such endpoints present further challenges for programs in resource-poor settings as they will necessitate substantial investment in infrastructure and quality assurance/control in laboratories in resource-poor settings.

Research priorities

Identify optimal treatment protocols for drug-resistant TB through (multi-center) clinical trials and cohort studies, focusing 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 2nd-line drugs needed according to DST results and treatment history; optimal duration of intensive (i.e.

with injectable) phase, shorter regimens; role of intermittent therapy; and dosing interval.

- Efficacy of candidate drugs (including compassionate use and pipeline).

Other relevant research topics in this area

- Effectiveness in adults and children of standardized and individualized regimens
- (Multi-center) clinical trials to clarify the role of 3rd-line drugs
- Validation of surrogate markers/interim endpoints for clinical efficacy
- Reliability and reproducibility of treatment history for prediction of drug resistance patterns
- Cost-effectiveness of various treatment approaches:
 - Surgical intervention as an adjunct to chemotherapy
 - Empirical treatment for XDR suspects
 - First-line retreatment (Category 2) regimen
 - Treatment of patients failing the Category IV regimen

Priority area 3: Programmatically relevant research

Context and rationale

As noted for priority area 1, the feasibility and cost-effectiveness of treating DR-TB in resource-constrained settings is well-established. The magnitude of the burden of MDR-TB alone—an estimated 500,000 new cases and 1-1.5 million prevalent cases in 2004—and the call for treatment of nearly 800,000 cases by 2015, demand concerted action to expand beyond the demonstration phase. Data from existing programs can be used to inform the implementation of new programs and scale up existing ones. Ongoing operational research can refine these answers.

To date, 54 sites have received GLC approval to treat patients with MDR-TB. Although the research recommended in other sections of this document will, over the longer term, provide crucial information on *optimal* approaches to prevent, diagnose, and treat MDR-TB, much can be learned from the operational experiences of existing programs. This section delineates important uses of existing program data, for example: documentation of screening strategies, human-resource allocation, and development of laboratory systems. Results of this work will complement the recently published treatment guidelines, providing operational guidance for implementation and scale up of MDR-TB treatment.

Research priorities

Define and evaluate strategies for integration/scale-up of drug-resistant TB management into larger DOTS programs:

- Algorithms for selecting patients eligible for DST and 2nd-line treatment in different settings, including special strategies for high-risk groups and use of rapid resistance testing methods
- Strategies for provision of 2nd-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)

Other relevant research topics in this area

- Minimum requirements for integration/scale-up of drug-resistant TB management into larger DOTS programs, for different approaches: standardized or individualized; hospital- or community-based
- Human resource needs in the context of increased DR-TB treatment at all levels (specific to ambulatory or hospital settings), including training and continuing education
- Laboratory requirements:
 - Evaluate existing laboratory capacity and strategies for rapid capacity building
 - Develop optimal strategies for appropriate levels of laboratory services in different settings (centralized vs decentralized)
 - Determine human resource needs (number and type of laboratory staff needed, staff development and retention strategies)
 - Identify strategies for improving coordination with other laboratory sectors (ie. a systems approach) and TB-HIV control programs
- Political commitment and coordination:
 - Elaborate strategies to ensure coordination between laboratories and TB programs
 - Elaborate strategies to ensure coordination between TB and HIV programs
 - Elaborate strategies to increase participation of private sector

- Elaborate strategies to increase participation of communities and patients
- Case finding strategies and diagnostic algorithms:
 - Evaluation of rapid resistance testing methods under field conditions to assess their feasibility, cost-effectiveness and cost-benefit under different settings, and to define their role in programmatic screening and diagnostic algorithms:
 - a) Based on culture on liquid media (compared to solid media)
 - b) Molecular testing for rifampicin resistance
 - c) Molecular testing for isoniazid resistance
 - d) Molecular testing for other drugs if available
 - Integration and operationalization of other new rapid DST tools: when, how and which tools
- Program evaluations, using surveillance and other routine data:
 - Evaluation of trends in drug resistance prevalence after scale up of MDR-TB treatment
 - Evaluation of strategies for implementing treatment for drug-resistant TB. For example, modeling the impact of various strategies in a given setting. Parameters should include type of treatment (drugs, setting, degree of standardization), timing of treatment introduction, infection control, resistance patterns at initiation, etc.
 - Evaluation of how program data are used to monitor patients and programs, as well as to adjust training and strategies
- Use of 2nd-line drugs outside GLC-approved projects and outside National Tuberculosis Programs
- Develop approaches for ensuring and evaluating treatment according to WHO guidelines

Priority area 4: Epidemiology of drug-resistant tuberculosis

Context and rationale

The scale-up of diagnosis and treatment of drug-resistant tuberculosis will have limited impact on incidence, prevalence and mortality unless parallel efforts are taken to prevent drug resistance. The scale-up of DOTS and treatment of drug resistant TB is taking place in many settings with very weak TB control programs. Drug-resistant tuberculosis has developed, to a large extent, because of weaknesses in these programs. The introduction of 2nd- and 3rd-line drugs, in the context of these operational problems, will likely lead to rapid resistance also to these drugs.

Although much is known about what creates drug resistance in TB, part of the variation in its occurrence is unexplained. The prevalence of drug resistant TB is very low with no increase in some areas, whereas in other areas the prevalence is high and/or increasing. Major obstacles to understanding the epidemiology of drug-resistant TB include the long generation time of the TB epidemic (it may take several years for weaknesses in TB programs to result in a level of drug resistance that is visible in program statistics); the coexistence and interaction of several risk factors; limited availability or quality of drug resistance data; and limited quality of routine TB statistics. This makes it necessary to complement monitoring and evaluation of routine activities with targeted research activities to get reliable data.

More epidemiological studies (expanding the coverage of the WHO/IUATLD DST project) are needed to identify areas of high and increasing levels of drug resistance, and to identify risk factors that promote 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 rifampin in the continuation phase of the Category 1 regimen; composition of and referral to retreatment regimens; drug quality; *M. tuberculosis* genotype; HIV prevalence; and level of use of antiretroviral treatment. Such analyses should help elucidate the factors with the greatest 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.

Research priorities

Identify and assess the relative importance of risk factors for drug-resistant TB, in particular to explain variation in MDR and XDR prevalence between settings

Other relevant research topics in this field

- Assess time trends and differences in drug resistance levels in different areas, complementing and expanding the global WHO/IUATLD drug resistance project
- Assess incidence, prevalence and mortality of drug resistant TB, with special focus on assessing the impact of interventions, in particular scaling up MDR-TB treatment

Priority area 5: Management of contacts of drug-resistant TB patients

Context and rationale

The management of contacts of drug-resistant TB patients is a complicated issue with a significant ethical dimension. Where possible, household infection control measures should be implemented to reduce the risk of transmission of resistant disease. The diagnosis of latent tuberculosis infection is challenging with the tuberculin skin test, which often returns false positive results. Newer diagnostics, which measure IFN- γ in response to specific TB antigens, could be used as an adjunct to increase the specificity of testing for latent infection. Once infection is determined, however, 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.

Optimal treatment combinations and duration for chemoprophylaxis of latent TB infection with resistant organisms are unknown. Standard isoniazid preventive therapy is unlikely to be efficacious for either MDR-TB or other isoniazid-resistant forms of TB. Yet no large-scale controlled trials have been conducted to evaluate preventive therapy among contacts of patients with resistant forms of TB. The use of pyrazinamide in combination with other drugs as preventive therapy has been associated with high frequencies of liver toxicity and death. Prophylaxis with second line drugs (SLDs) has not been widely used among contacts of patients with resistant disease. 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 insight 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.

In addition to examining appropriate chemoprophylaxis regimens, other possibilities for the management of contacts of drug-resistant TB patients should be explored. BCG vaccination has been recommended in some settings for high-risk contacts but may not protect against infection or subsequent disease later in life, and caution is warranted in use of BCG in adults and children with HIV infection. Links should also be made with vaccine-development researchers to allow the possibility of involving contacts of DR-TB patients in vaccine trials. Another approach is 'watchful waiting', whereby the contact is monitored closely for disease over the high-risk post-infection period (two years) and treated if disease occurs. Such watchful waiting, however, poses increasing ethical concerns where rates of MDR-TB are rising, or where MDR-TB is not confined to sporadic, time-limited outbreaks.

Research priorities

Clinical trials of the efficacy of several individual drugs and drug combinations for preventive treatment of persons presumably infected with drug-resistant TB

Other relevant research topics in this area

- Clinical series of infected contacts of MDR-TB patients treated with various drug combinations (drug tolerability, acceptance, adherence)
- Inclusion of DR-TB contacts in new vaccine-development trials

Other areas of research

1. Basic and clinical science on drug-resistant tuberculosis

- a) Mechanisms of resistance
- b) Molecular basis of resistance: genetic markers for drug resistance
- c) Host markers
 - i) Biomarkers for purposes of diagnosis and monitoring
 - ii) Laboratory correlates of treatment outcome
- d) Role of genotype/strain family in acquisition and spread of drug resistance
 - i) Relative fitness in relation to drug resistance
- e) Pharmacology
 - i) Drug-drug interactions among antituberculosis drugs
 - ii) In-vitro interaction between 2nd-line drugs and antiretroviral drug treatment
 - iii) Pharmacodynamics and pharmacokinetics of 2nd-line drugs
 - iv) Deterioration/shelf life of 2nd-line drugs under tropical conditions

2) Recording and reporting definitions

- a) Usefulness of the definitions adopted for case registration and treatment outcomes for monitoring and evaluation
- b) Operationalization and testing of cohort definitions and core data set
- c) Identification of indicators for early response, cure, etc; definition of cure, relapse
- d) Usefulness of the recording and reporting system for monitoring performance

3) Management of drug-resistant TB in special conditions and situations

- a) Children (safety & efficacy)
- b) HIV-coinfected patients
- c) Substance abusers
- d) Pregnant women
- e) Prisoners
- f) Elderly patients
- g) Patients with low body mass index

4) HIV infection and drug-resistant TB

- a) Interaction with HIV in transmission of (M)DR strains
- b) Interaction with HIV in acquisition of resistance
- c) Interaction between 2nd-line drugs and antiretroviral drug treatment
- d) Timing of antiretroviral drug treatment in drug-resistant TB patients
- e) Immune Reconstitution Inflammatory Syndrome in drug-resistant TB patients

5) Initial evaluation, monitoring of treatment and management of adverse effects (in pilot projects and clinical trials)

- a) Initial evaluation
- b) Monitoring of treatment
 - i) Minimal and ideal time points for smear microscopy, culture and DST
- c) Adverse effects
 - i) Prevalence of adverse effects
 - ii) Most (cost-)effective protocols for management of adverse effects

6) Treatment delivery and adherence

- a) Factors promoting adherence
- b) Identification of level (%) and nature (relative importance of intensive phase vs continuation phase; relative importance of continuous non-adherence vs. intermittent) of non-adherence that leads to poor outcomes

- 7) Ethical issues
 - a) Management of patients after drug-resistant TB treatment failure
 - b) Ethics of patient selection and exclusion

- 8) Drug resistance and infection control
 - a) (Cost-)effectiveness and relative contribution of infection control measures in resource-poor settings
 - i) For prevention of transmission to health care workers
 - ii) For prevention of patient-to-patient transmission
 - iii) For prevention of transmission to laboratory workers
 - iv) For prevention of transmission in the community

- 9) Management of 2nd-line antituberculosis drugs
 - a) Planning for drug supply in light of limited number of pre-qualified manufacturers
 - b) Strategies to accelerate quality testing, resulting in greater availability of low-cost, quality-assured 2nd-line drugs
 - c) Drug logistics considering deterioration of 2nd-line drugs under tropical conditions