9. **Maximizing research opportunities to address M/XDR-TB**

Although much has been learned on MDR-TB management in recent years, important knowledge gaps are contributing to the current high costs and complexity of case finding and treatment. For this reason, the Working Group on MDR-TB developed a research agenda that identifies the key research questions to be answered in order to strengthen the evidence-base of current guidelines, accelerate the scale-up, and simplify the management of drug-resistant TB programmes. Other groups have arrived at similar conclusions.

Governments, development agencies, research funding agencies, and technical agencies have a critical role to facilitate the implementation of research to improve the programmatic management of drug-resistant TB and make diagnosis and effective treatment available to all those in need.

The most urgent research questions are discussed in this document.

9.1 **Diagnostic test development**

**The problems**

DST of isoniazid and rifampicin gives reliable and reproducible results, conversely to susceptibility testing for second-line medicines, which currently compromises case finding of XDR-TB and clinical management of MDR-TB. More evidence is needed to illustrate the clinical relevance of second-line drug resistance, and also of cross-resistance, such as between newer and older generation fluoroquinolones. The turnaround time of DST is several weeks depending on the culture method used, causing delays in identifying patients in need of second-line treatment as well as in selecting effective medicines.

**The solutions**

Several methods for rapid detection of drug resistance have been, or are being, developed. Line-probe assays for molecular resistance testing have been recently endorsed by WHO.

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and are expected to accelerate dramatically case finding and treatment of MDR-TB, thus reducing the period of infectiousness. Molecular assays also simplify decentralization of DST. They are however currently only available in commercial form for rifampicin (and to some extent isoniazid), and must be adapted to the programme setting. Development of rapid methods which can detect second-line drug resistance in the remote areas would accelerate the process of identifying a suitable treatment regimen in patients with XDR-TB.

**Urgent actions needed**

Governments, development agencies, and technical agencies should facilitate field-testing of available molecular resistance assays in order to adapt their utilization for screening and diagnostic purposes at local level. Researchers and research funding agencies should work towards the development of rapid methods for detection of resistance to first and second-line in the remote areas.

**9.2 Treatment (including preventive therapy)**

**The problems**

The currently recommended second-line treatment regimens are complex, of long duration, and require intensive monitoring of adverse events and treatment outcomes. Treatment efficacy is poor unless stringent approaches are taken to ensure treatment adherence. There is justifiable concern about the feasibility and success of these regimens when second-line treatment is scaled-up beyond the pilot project stage. Regimens are needed with shorter duration, fewer medicines, fewer adverse events, and which offer standardized approaches to treatment, with less intensive monitoring, yet without compromising effectiveness. However, well designed comparative studies, including randomized-controlled clinical trials of possible drug combinations have never been conducted; current guidelines are based on clinical experience only.

Highly promising new compounds, however, are being evaluated for safety and efficacy against TB in humans. Some of these medicines have the potential to significantly improve treatment efficacy for MDR-TB when used in relatively simple and short regimens.

However, current funding is almost exclusively targeted on research and development of new medicines up until licensure, and no financial or technical mechanism covers the essential “Phase IV” step in which the optimum treatment duration and combination of currently available and new medicines are put to rigorous testing.
Similar problems exist with preventive treatment of infection with MDR-TB organisms. Standard isoniazid preventive therapy is ineffective, and pyrazinamide in combination with other medicines as preventive therapy has been associated with unacceptably high frequencies of liver toxicity and death. No large-scale controlled trials have been conducted of a preventive therapy regimen that could be used for contacts of patients with MDR-TB, and funding for such studies is very limited.

The solutions

Since large-scale use requires solid evidence, it is essential that these study questions be addressed in randomized-controlled clinical trials. These trials will need to be done in a coordinated fashion in several settings in order to take into account the enormous variability in host and bacillary populations as well as social and environmental conditions.

Urgent actions needed

Research funding agencies should consider investing in (i) clinical trials aiming at shortening, simplifying and improving efficacy of treatment regimens for drug-resistant TB using available medicines and also new compounds, and (ii) preventive therapy trials to define optimal treatment combinations and duration for preventive treatment of infected persons exposed to patients with drug-resistant TB.

9.3 Programmatic aspects

The problems

The pilot projects on management of drug-resistant TB have yielded best practices on a variety of operational issues that need to be translated into cost-effective strategies adapted to much larger, countrywide scale. This is particularly urgent with regard to identification of MDR-TB patients, treatment adherence, and infection control. Selection strategies of patients eligible for second-line treatment should target those most at risk of having MDR-TB, and include patients who live far from DST facilities and those treated in the private sector.

Adherence to treatment for MDR-TB is highly important for its success but complicated by its long duration and sometimes high frequency of adverse events. Strategies need to be developed that maximize treatment adherence in a sustainable way, and factors that affect adherence need to be studied.
Nosocomial transmission of MDR-TB is well documented, in particular in settings with high HIV infection prevalence. The high cost of some of the infection control measures limits their application in resource-limited settings, and little is known about the effectiveness of less costly alternatives proposed in the current guidelines. The Global Fund and other donor agencies encourage the inclusion of operations research (OR) in programs they support. In the case of the Global Fund the proportion of proposals including OR and the proportional budgets for OR increased from Rounds 1–5 to Round 6. Of note, over the total Global Fund portfolio, the budget allocated to OR increased from 0.4% to 3% but funding opportunities are not fully utilized yet.

The solutions

For each of these three areas, strategies that optimize integration of management of drug-resistant TB into existing TB control programs need to be developed and evaluated for cost-effectiveness. This is possible through OR, which should be part of all TB programs in order to improve policy, programme implementation, and ultimately access to care. The challenges related to designing, planning, implementing and taking full advantage of OR in countries are well known. Instruments to support programs willing to take on OR activities are now available although more will need to be developed. At the moment technical assistance for OR is insufficient and needs to be strengthened.

Urgent actions needed

Governments, development agencies, and technical agencies should work in partnership to incorporate OR on drug-resistant TB into the activities of TB control programs. Governments and technical agencies should make full use of existing funding opportunities for OR.

9.4 Prevention of drug resistance

The problems

Preventing development and transmission of drug-resistant TB requires knowledge about its causal factors. The conditions leading to drug resistance in TB are well described, yet...
the substantial variation in its worldwide distribution suggests that their relative importance may vary between settings. Examples of such potential causal factors include type and quality of first-line treatment supervision; access to anti-TB medicines outside TB programs; use of fixed-dose combinations; the quality of medicines used, infection control practices, M. tuberculosis genotype; HIV prevalence; and level of use of antiretroviral treatment. Without knowledge of the most important contributing factors, a targeted, cost-effective control response to the problem of MDR-TB is not possible. This is still the case for many settings, partly due to the limited availability or quality of drug resistance data, as well as of the limited quality of routine statistics. In addition, investigation of the causes of drug resistance is an area of work that has been largely undervalued and neglected by the research community and donors. The Global Fund and other donors are encouraging countries to include operations research and monitoring and evaluation components in their grant applications, and yet these opportunities are frequently ignored.

The solutions

Understanding the role of risk factors to the development and transmission of drug resistance that are amenable to control interventions is the recipe for “turning off the tap”. Drug resistance surveillance of adequate quality is within reach for many countries now that molecular resistance testing is possible on a large scale. Combining this with targeted research activities that build on and complement routine monitoring and evaluation would provide a strong framework for identifying these risk factors.

Urgent actions to be taken

Governments, technical agencies and research funding agencies should consider investing in research aimed at understanding the causal factors for the development of drug resistance. Governments and technical agencies should make full use of existing funding opportunities for OR.

Conclusions

Data from 2007 show that overall investments for TB research and development appear to be decelerating rather than accelerating. At this pace, less than half of the US$ 9 billion recommended by the Global Plan to Stop TB, 2006–2015 will be spent on TB research and development by 2015.9


Governments, in particular those of the BRICS economies (Brazil, Russia, India, China and South Africa), development agencies, research funding agencies and technical agencies have a critical role to play in facilitating research on drug-resistant TB, particularly in the areas of field-testing of diagnostic tests, clinical trials to shorten treatment regimens and to develop efficacious preventive regimens, operations research, and exploring the role of risk factors in the development of drug-resistant TB.