KNCV TUBERCULOSISFOUNDATION

Working Group on MDR-TB
Diagnostic research agenda

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Background

- "DOTS-Plus" pilot projects: management of MDR-TB in resource limited settings effective and feasible
- Only 2% of MDR cases currently on effective treatment
- MDR/XDR crisis calls for massive scale-up, and integration into DOTS programs, of programmatic management of DR-TB (PMDT)
- Goals (by 2015) *Global Plan to Stop TB 2006-15* and *Global MDR/XDR Response Plan 2007-8*:
  - universal access to sound MDR/XDR-TB management
  - 1.6 million MDR/XDR-TB patients on treatment

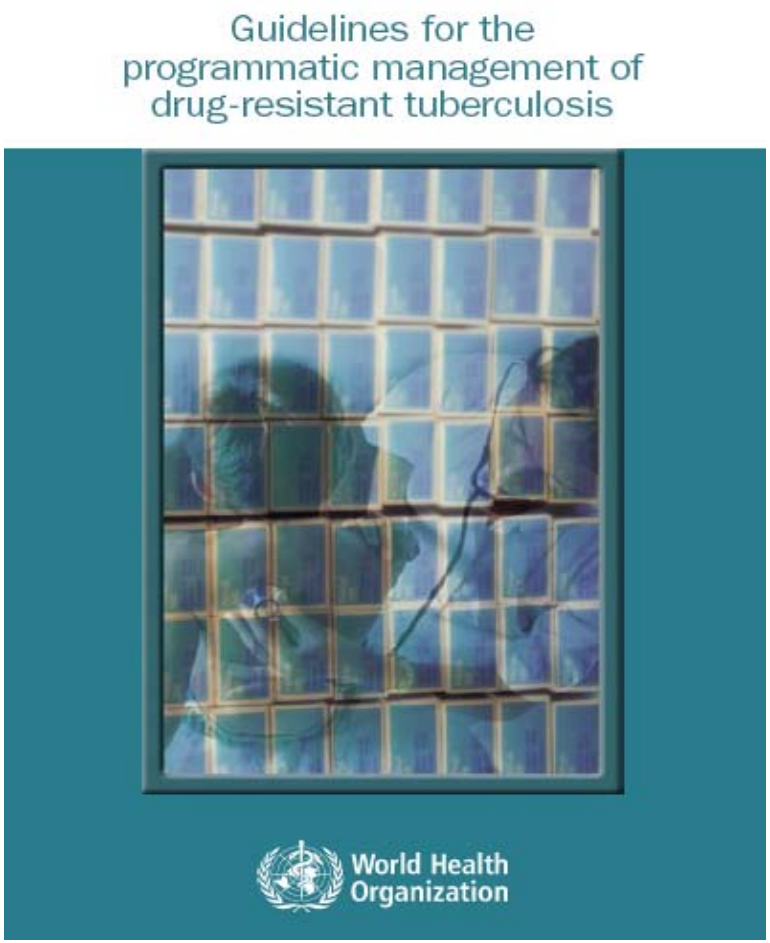
Guidelines for the programmatic management of drug resistant TB

Issued 2006, update in preparation

Based on the DOTS framework

Drawing on the evidence from DOTS-Plus pilots

Knowledge gaps remaining



World Health Organization

Updated research agenda: Objectives

- to identify the key questions to be answered in order to scale-up PMDT in resource-limited settings, according to the Global Plan
- focus on any resistant tuberculosis with clinical relevance (MDR, polydrug-resistance, XDR)
- indicate priorities guided by the explicit goal of rapidly scaling-up effective DR-TB management programs

Updated research agenda: Process

- Prepared by Research Subgroup
- Identified barriers to scale-up for each of the 5 tenets of the DOTS strategy
- Identified research questions needed to be answered to overcome these barriers
- Identified the top-5 priority areas and “must do’s” within these
- Comments by WG members and other stakeholders
- Endorsed at 6th annual WG meeting (Sept 2007)

Priority areas

- Laboratory issues
- Treatment strategies
- Programmatic aspects
- Epidemiological issues
- Management of contacts of DR-TB patients

Laboratory: problems

- Drug susceptibility testing (DST) for 2nd line drugs (SLD) poorly standardized
- Clinical value of resistance not always clear
  - SLD other than injectables & quinolones
  - mono-resistance (H, R)
  - cross-resistance
- DST takes too long
  - rapid DST tests are becoming available but limited evaluation under program conditions

=> Patients are treated with ineffective (but often toxic) drugs or are withheld effective drugs

Programmatic issues: problems

- Critical issues
  - How to identify of MDR patients in an efficient and equitable way
  - How to make sure patients get treatment
  - How to prevent transmission to other patients, staff and community

- Identifying MDR patients
  - At what stage in diagnostic/treatment process
  - How to bring MDR screening close to the patient

    => lab & specimen requirements
  - How to build/strenthen lab capacity for this?

Treatment: problems

- Regimens used in pilots complex, long and prone to side effects -> feasible and sustainable in scale up?
- Treatment monitoring complex and lab intesnive (culture)
- Evidence base is weak: urgent need for randomized-controlled trials of exisiting and new drugs for DR-TB
- Trials take long time (follow-up for relapse)

“Must do’s” related to new diagnostics

- Development and validation of tools for rapid detection of drug resistance, including XDR
- Define and evaluate (feasibility, cost-effectiveness) algorithms for selecting patients eligible for DST and second-line treatment in different settings, including:
  - special strategies for high-risk groups
  - use of rapid resistance testing methods
    - Culture-based, liquid compared to solid media
    - Molecular testing for rifampicin resistance
    - Molecular testing for isoniazid resistance
    - Molecular testing for resistance to other drugs

Other research topics related to new diagnostics

- Molecular basis of drug resistance
  - Mutations conferring resistance to 2nd line drugs
  - Role of molecular sequencing in improving/replacing conventional DST
- Host markers
  - Biomarkers for purposes of diagnosis and monitoring
  - Laboratory correlates of treatment outcome

Acknowledgement

- Peter Cegielski
- Einar Heldal
- Michael Kimerling
- Carole Mitnick
- Laura Podewils
- Rajeswari Ramachandran
- Hans Rieder
- Karin Weyer
- Matteo Zignol