

Research subgroup

Progress reports from the MDRTB WG Subgroups

Tbilisi, 21 September 2007

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- “The history of the response to AIDS in Africa can be divided into two phases:
 1. fiddling while Rome burns, and then
 2. trying to use the fiddle to put out the fire”

William Easterly
How, and how not, to stop AIDS in Africa
NY Review of Books 2007

history

- 5th WG meeting Atlanta: revitalize research subgroup
 - Research agenda developed in 2001
 - Much has been learned from DOTS-Plus pilot
 - Many questions remain unanswered
 - Installed in its current form Aug 2006
 - Immediate goal: develop updated research agenda

 - Met once (Paris Nov 2006)
 - Regular telephone conferences
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members

- Peter Cegielski
 - Frank Cobelens
 - Einar Haldal
 - Michael Kimerling
 - Carole Mitnick
 - Laura Podewils
 - Rajeswari Ramachandran
 - Hans Rieder
 - Karin Weyer
 - Matteo Zignol
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updated research agenda

Pre-final document in your folder

- Objectives
 - Consensus process
 - Prioritization
 - Research priorities
 - Dissemination
 - Implementation
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objective

- 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
 - 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
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process

- ❑ 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 & grouped in research areas
 - ❑ Identified the top-5 priority areas
 - ❑ Circulated to WG members and other stakeholders for comments
 - ❑ Incorporated comments
 - ❑ Identified the “must do’s” within the top-5
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prioritization

- Priority should be with those research questions that are seen as the most important to facilitate and accelerate the scale up, and to maximize the public health impact, of the programmatic management of DR-TB over the next 5 to 10 years
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priority areas

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

- DST for 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
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laboratory: priorities

- Standardization of DST for 2nd line drugs
 - Prognostic value of *in vitro* resistance
 - Second-line drugs
 - Mono-resistance
 - Cross-resistance (newer generation fluoroquinolones)
 - Development and validation of tools for rapid detection of drug resistance, including XDR
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treatment: problems

- Regimens used in pilots complex, long and prone to side effects -> feasible and sustainable in scale up?

 - Evidence base is weak: no randomized-controlled trial data for DR-TB
 - lack of perceived epidemiologic significance
 - lack of suitable trial sites
 - heterogeneity of the patient population
 - absence of new anti-tuberculosis agents
 - limited political will
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treatment: priorities

- RCTs to study optimal use of existing drugs across multiple settings and against various drug resistance patterns
 - clinical efficacy of different standard and individual MDR-TB regimens
 - optimal duration of “intensive” phase
 - shorter regimens
 - role of intermittent therapy; dosing interval

 - RCTs to study the efficacy of candidate drugs
 - including compassionate use and pipeline
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programmatic issues: problems

- How can PMDT be integrated into TB control programs in a feasible and sustainable way?
 - Level of support/infrastructure attainable in pilots may not be feasible under program conditions

 - 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
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programmatic issues: priorities

- Define and evaluate:
 - 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
 - Strategies for provision of 2nd-line treatment in different settings, including:
 - adherence
 - use of incentives and enablers
 - strategies for selecting and implementing infection control measures for communities, households, and health-care settings
 - effectiveness of existing infection control measures
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epidemiology: problems

“Not just mop the floor, also close the tap”

- Huge differences in magnitude of DR-TB problem across the world
- Poor knowledge of relative contribution of causative factors in specific settings
 - Poor 1st-line DOTS?
 - Private sector?
 - Nosocomial transmission?
 - Amplification?
 - Genotype?

=> Several taps may be dripping and we need to know which ones to close

epidemiology: 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
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contacts: problem

- Little to offer to people infected with MDR *M. tuberculosis*
 - INH (probably) not efficacious
 - PZA combinations too toxic
 - No data on other drugs/combinations
 - Dilemmas
 - Infected contact of MDR-TB patients may be infected with *another* strain
 - Only small minority of infected contacts will progress to disease
 - “Watchful waiting” poses ethical concerns
 - Not offering preventive treatment may affect staff retention for PMDT
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contacts: priorities

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

- ❑ Endorsement by WG
 - ❑ Make document available on websites (WHO, partners)
 - ❑ Publish in peer-reviewed journal
 - ❑ Advocate the agenda among researchers and donors
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implementation

How make all this happen?

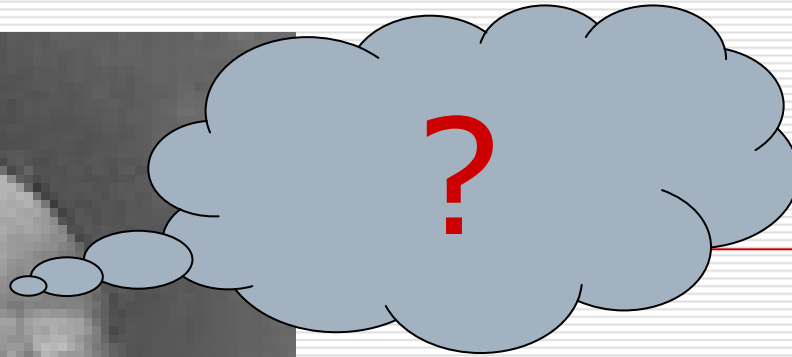
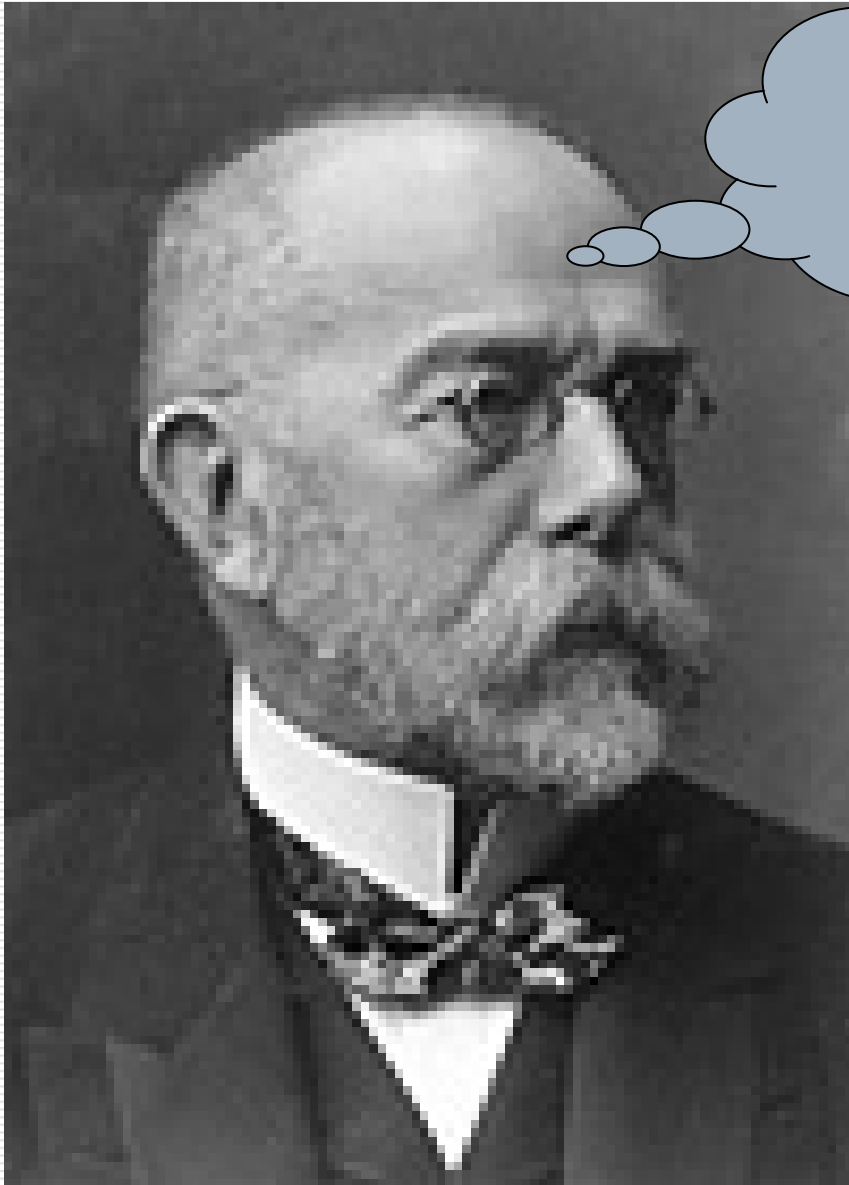
- ? Approach research funders to include elements of this agenda in their calls for research proposals
 - ? Prepare standard/template protocols for operational studies (e.g. GFATM funded)
 - ? Partnerships/funding mechanisms for clinical trials of existing drugs
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remaining terms of reference (1)

- promote resource mobilization for research activities on MDR-TB
 - assist GLC-approved projects in developing and implementing operational research plans
 - promote research collaborations between the agencies/institutions participating in the WG and between the GLC-approved projects
 - strengthen working relationships with the scientific community, particularly with the WGs on new diagnostics, new drugs and new vaccines
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remaining terms of reference (2)

- keep update a system to track research conducted by WG members and create a forum for exchanging data, experiences, and information on the epidemiology, diagnosis and management of DR-TB
 - assist the GLC in the scientific analysis of the evidence that supports the advice to WHO on policy for the programmatic management of DR-TB
 - steer the research on MDR-TB by reviewing and commenting on major publications on MDR-TB in peer reviewed journals
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Thank you!

laboratory: other topics

- Standardization of DST (solid versus 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
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treatment: other topics

- ❑ Effectiveness in adults and children of standardized and individualized regimens
 - ❑ RCTs to clarify the role of 3rd line drugs
 - ❑ Validation of surrogate markers/interim endpoints
 - ❑ Reliability and reproducibility of treatment history for prediction of drug resistance patterns
 - ❑ Indications for surgical intervention in particular settings and its effectiveness as an adjunct to chemotherapy
 - ❑ Empirical treatment approaches for XDR suspects
 - Patients with history of contact to XDR-TB patients
 - Patients not cured by the Cat4 regimen
 - ❑ Utility of the first-line retreatment (cat2) regimen
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2001 research agenda

□ Primary topics

- Identify optimal standardised protocols to treat MDR-TB
- Identify optimal protocols for diagnostic testing
- Identify minimum requirements for constructing and implementing DOTS-Plus

□ Secondary

- Identify threshold indicators for implementing DOTS
 - Other operational issues
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