Operational research for Xpert MTB/RIF: Priorities and opportunities

Implementation and roll-out of Xpert MTB/RIF for rapid diagnosis of tuberculosis and multi-drug resistance

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Geneva

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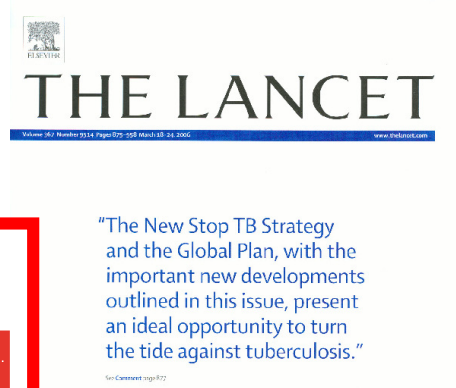
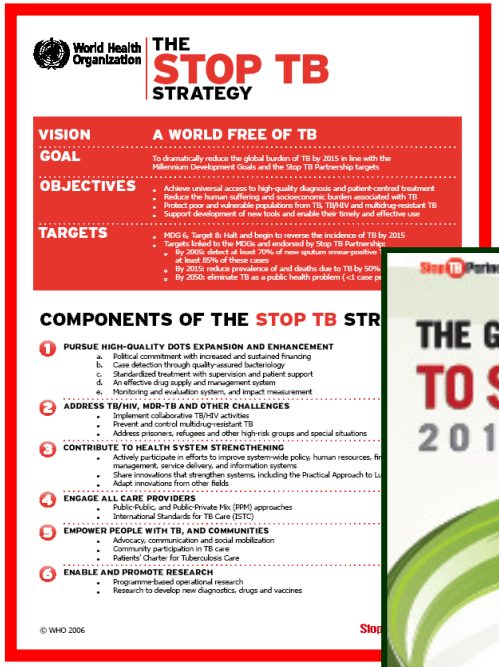
The Stop TB Strategy & the Global Plan to Stop TB

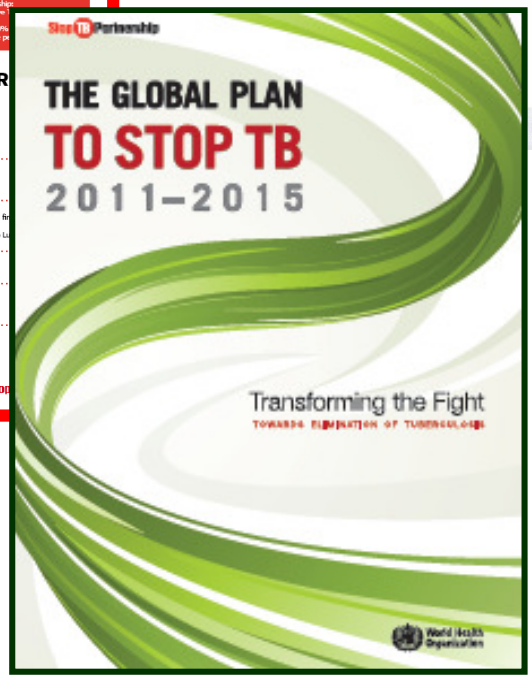
WHO THE STOP TB DEPARTMENT

1. Pursue high-quality DOTS expansion and enhancement
2. Address TB-HIV, MDR-TB, and needs of the poor and vulnerable
3. Contribute to health system strengthening
4. Engage all care providers
5. Empower people with TB and communities
6. Enable and promote research



"The New Stop TB Strategy and the Global Plan, with the important new developments outlined in this issue, present an ideal opportunity to turn the tide against tuberculosis."





- programme-based operational research
- research on introducing new tools into practice

Operational research: some definitions

- "Operations research helps policy-makers and program managers to review, redirect and restructure programs (…using) social science and other research methods to provide decision-makers with empirically-based and scientifically-valid answers to service delivery problems."

  Population Council, 2000

- "The use of systematic research techniques for program decision-making to achieve a specific outcome. OR provides policymakers and managers with evidence that they can use to improve program operations."

  WHO, 2003

- "The search for knowledge on interventions, strategies, or tools that can enhance the quality, effectiveness, or coverage of programmes in which the research is being done."

  Zachariah et al. LID 2009

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What does OR include ?

- **Diagnostic studies**: to assess the nature and extent of a health or service delivery problem.
- **Evaluative studies**: to evaluate ongoing innovative health interventions.
- **Intervention studies**: to test (…) the effectiveness of service delivery interventions explicitly designed to address a specific service delivery problem.

Population Council, 2000

- **Descriptive** (cross-sectional), **case–control**, and retrospective or prospective **cohort analysis**.

Zachariah et al. TLID 2009

Implementation research

Stop TB Partnership

- "(Research) to improve access to efficacious interventions against (…) diseases by developing practical solutions to common, critical problems in the implementation of these interventions"

  TDR, 2005

- "IR is that subset of health services research that focuses on how to promote the uptake and successful implementation of evidence-based interventions and policies that have been identified through systematic reviews. (IR…) often encompasses "impact research", which includes both research aimed at understanding what is happening during the processes of implementing changes in policy or practice and intervention studies that are designed to compare different approaches to implementing change."

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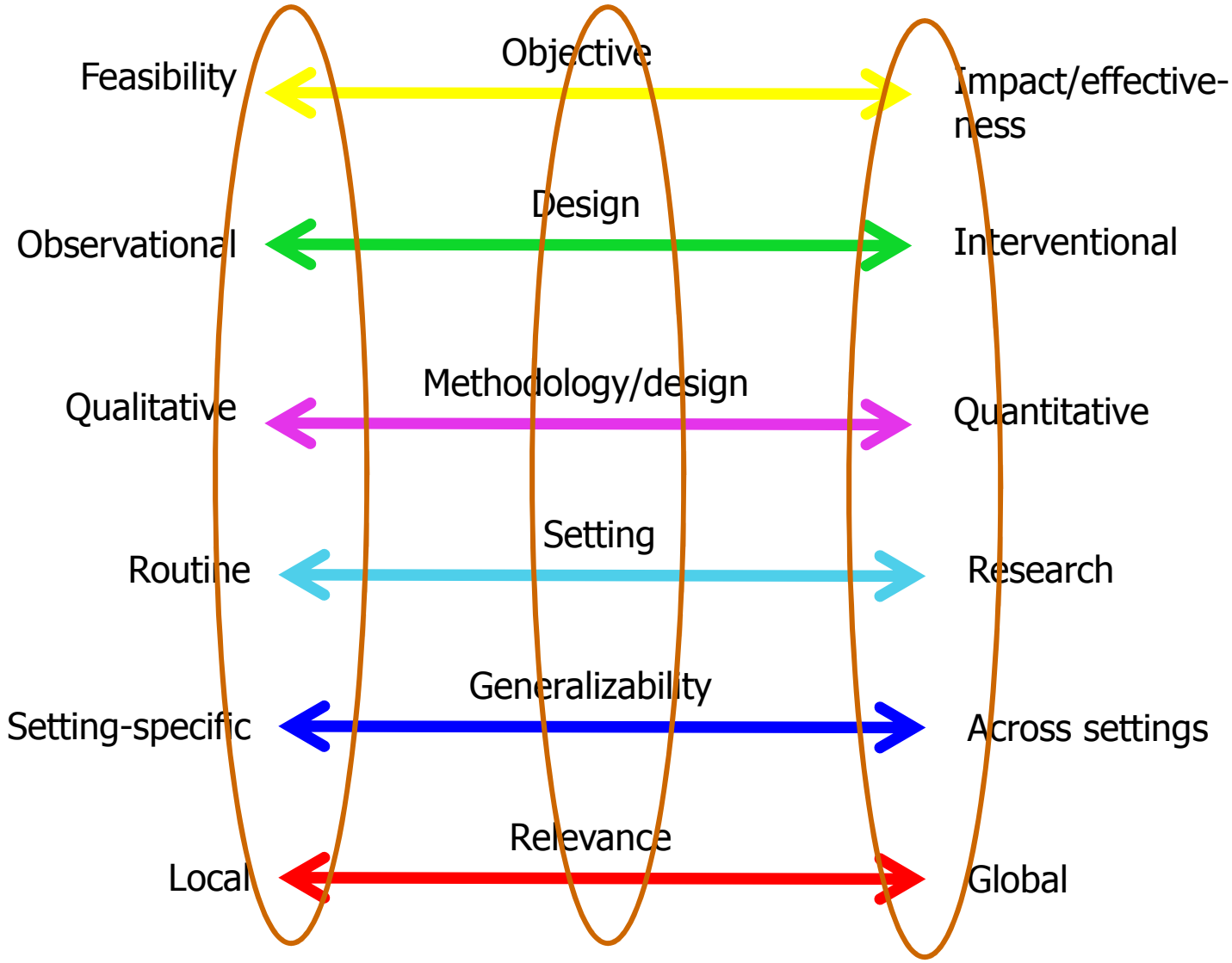
OR to improve Global TB control:
what are the needs ?

Stop TB Partnership

1. Better functioning TB programmes:
   - assess deficiencies and identify causes that are amenable to improvement by technical or managerial intervention
2. Evaluate new interventions to improve TB control:
   - effective and efficient use of new tools
   - determination of the conditions/requirements under which they can be effectively implemented
3. Inform Policy recommendations
   - impact research providing evidence on what can be expected from new interventions in real-life settings
     - Increasingly important for international policy decisions and funding
     - E.g. GRADE process for policy recommendation

Continua in Operational/Implementation Research



Role of OR/IR in evaluating TB control interventions

Stop TB Partnership

- **Systematic review of 3 WHO endorsed interventions:**
  (AIGHD, Amsterdam University)
  - IPT in HIV infected individuals & household contacts
  - Clinical algorithms for diagnosing smear-negative TB ("rule in") and screening for smear-negative TB ("rule-out") in HIV-infected individuals
  - Provision and delivery of second-line drugs to MDRTB patients

- **Lessons learnt** :
  - 114 studies reviewed
  - few *operational* studies are published in peer-reviewed literature
  - *effectiveness studies rare* for majority of interventions studied
  - *few* effectiveness studies use *comparative* designs
  - *limited number* of effectiveness studies done in *programmatic settings*
  - *geographically patchy*
    - very few studies from South-East Asia
    - very few studies from former SU or China
    - high disparity within regions (only few countries)
  - field dominated by limited number of research groups

So, what do we need?

Stop TB Partnership

Effectiveness studies of new tools/interventions for TB control:

→ look at conditions for *optimization of effect* and *access*

→ take place in *routine/programmatic* settings

→ using *standard* methods and definitions of outcomes

→ *comparative* design

→ various geographic/epidemiological settings: *multicenter* studies an advantage (eg. FIND studies on GeneXpert)

→ provide *setting-specific* as well as *generalizable* data

→ analysis of combined datasets (eg. individual-patient meta-analyses)

Potential designs

A. Before- and After

Cluster	Pre-innovation study Period →	Post-innovation study Period →
1	Control	Innovation
2	Control	Innovation

B. Parallel Groups Trials

Cluster	Study Period →
1	Innovation
2	Innovation
3	Control
4	Control

Key differences between *Explanatory* and *Pragmatic* trials

	Explanatory	**Pragmatic**
Question	Efficacy *does the intervention work?*	Effectiveness *does the intervention work when used in normal practice?*
Setting	Well resourced, rigorously controlled conditions	Normal clinical or public health practice
Participants	Selected. Participants who are poorly adherent are either considered as having a negative outcome or are not assessed	Little or no selection.
Intervention	Strictly enforced and adherence is closely monitored	Applied flexibly within the requirements of normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to participants, funders, communities and healthcare practitioners
Relevance to practice	Indirect: little effort made to match trial to decision-making needs of those in the usual setting in which the intervention will be applied	Direct: designed to meet the needs of those making decisions about intervention options in the setting in which the intervention will be implemented.

Potential designs

C. Stepped-Wedge

Cluster	Study period: →				
	1	2	3	4	5
1	control	innovation	innovation	innovation	innovation
2	control	control	innovation	innovation	innovation
3	control	control	control	Innovation	innovation
4	control	control	control	control	innovation

Opportunities

- Effectiveness studies can be embedded in TB programs
- Use routinely collected data for study outcomes: eg. notifications, treatment outcomes
- Increasing availability/use of individual patient-based recording systems
- Recent methodological developments (comparative designs, analysis of multi-site data)
- Increasing awareness and interest with funding bodies
- M&E component of GF applications

Xpert MTB/RIF implementation: *research questions*

Stop TB Partnership

- What is the effectiveness of the *risk assessment* and *patient management process* for the three groups recommended for Xpert MTB/RIF testing?
- What is the *impact* of Xpert MTB/RIF on *case-detection* of TB (HIV associated or not) and MDR-TB?
- What is the *impact* of Xpert MTB/RIF *on access to care ?*
  - does Xpert MTB/RIF *shorten diagnostic delay* and *time to treatment* ?
  - what is the *impact on access to care* by different socio-economic groups ?
  - what proportion of newly-detected cases has access to treatment services
  - what is the *impact* of the Xpert MTB/RIF on *treatment* and *treatment outcomes*?
- How *cost-effective* is the approach in routine settings ?

Xpert MTB/RIF implementation: *key research questions*

- Effectiveness and cost-effectiveness analyses of Xpert implementation (interlinked approach)
- What is the *role of chest X-ray* in the diagnostic pathway in situations where MDR-TB and HIV associated TB is of lesser concern?
- What is the role of the *private sector/non-programme providers* in Xpert scale-up?

Cost and cost-effectiveness analysis

Background:

- Cost and cost-effectiveness analysis conducted in FIND evaluation sites (India, S. Africa, Uganda)
- *but* limited data on costs of current diagnostic methods and non-existent data on costs of Xpert under routine conditions;
- *and* data on effectiveness of using chest X-ray as a screening tool prior to use of Xpert are lacking.
- As part of evidence for scale-up, more data on costs and cost-effectiveness of Xpert MTB/RIF (compared with conventional diagnostics) are needed, from representative settings

Objective:

- To assess costs and cost-effectiveness of implementing and rolling-out Xpert MTB/RIF compared with existing diagnostic methods, such as sputum smear microscopy, culture or DST in *representative settings*

Cost and cost-effectiveness analysis

Suggested approach and methods to generate evidence during Xpert scale-up:

1. Collect evidence *from representative settings* through collaboration among multiple implementers and partners with relevant experience and expertise
   - WHO, University of Amsterdam, LSHTM have held initial discussions about collaboration to support such efforts at global level
2. Representative settings in terms of costs, epidemiology, available resources, e.g.
   - low-income, high TB/HIV burden
   - low income, high MDR-TB burden
   - low-income, high TB/HIV and MDR-TB burden
   - middle-income, high MDR burden
   - middle-income, high MDR and TB/HIV burden

Cost and cost-effectiveness analysis

Suggested approach and methods to generate evidence during Xpert scale-up

3. Standard protocols: for representative sites based on a standard protocol developed for study in S. Africa**

4. Standard costing templates: to be developed based on revised tools used for FIND evaluation

5. Other data required to estimate *effectiveness*, based on a list of parameters - input required for model developed for FIND evaluation

6. Cost-effectiveness analysis: feed cost and other input data into the CE model developed for the FIND evaluation.

***provided funding for S. Africa study is mobilized*

Cost and cost-effectiveness analysis

Next steps

1. Costing tools: make them more user-friendly (timeline: around 1-2 months)
2. Cost-effectiveness model:
   - add transmission
   - improve data on treatment outcome and costs for MDR-TB
3. Expression of interest by early implementers
4. Mobilize funding, including for global coordination

Coordination

Proposition:

- Initial expression of interest to conduct OR/IR, cost or cost-effectiveness projects to produce evidence for scale-up of Xpert

  → *please let us know during this meeting*

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- Following this, brief communication on:
  - suggested research topic/question
  - study setting and target population
  - provisory timeline
  - expected funding source
  - potential partners

Coordination

Proposition:

- Development of standart protocols (TREAT-TB, WHO, AIGHD, LSHTM, LSTM, others)
- Identify funders: e.g. BMGF, USAID, TB CARE, PEPFAR, GFATM
- TREAT TB online mapping tool

Conclusions

- Need for OR/IR to enhance roll-out of Xpert MTB/RIF and gain evidence on effectiveness and cost-effectiveness in programme settings
- Outcomes will inform policy making
- Need for OR/IR at various levels, from country to regional, multi-country level
- Opportunities: increased involvement of various funding institutions in OR
- GFATM round 11 an important target
- Need to establish coordination: WHO as initial step – then identify suitable partners to take on coordination
- STP/WHO/GFATM document to assist for development of OR applications for funding

Thank you for your attention !