Summary of outcomes from WHO Expert Group Meeting on Drug Susceptibility Testing - PRELIMINARY -

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EGM on DST: Objectives

1. To review critical concentrations for phenotypic DST methods;

2. To review the evidence base and evaluate data from a systematic review on the accuracy and reproducibility of WHO-endorsed DST methods

3. To evaluate data assessing the relationship between DST results and treatment outcomes with use of that drug;

4. To review available data from laboratory validation and field evaluation studies on the performance characteristics of Hain MTBDRsl molecular line probe assays for the diagnosis of second-line drug resistance

5. To outline issues to be addressed by WHO in subsequent policy recommendations.

Data sources used for decisions in EGM

- Systematic review and meta-analysis of the accuracy and reproducibility of WHO-endorsed phenotypic DST methods for first- and second-line anti-TB drugs;
- Delphi survey among SRLs;
- Individual Patient Data (IPD) meta-analysis of patients with MDR-TB on association of DST results with patient outcomes;
- Laboratory validation and field evaluation studies on the performance characteristics of Hain MTBDRsl molecular line probe assay for the diagnosis of second-line drug resistance.

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1. Methods and concentrations

Summary of updates in recommended methods & concentrations

- Established for Levofloxacin, Moxifloxacin (2 levels)
- Removal of Ciprofloxacin
- Changed for quinolones, aminoglycosides and cycloserine

	MGIT 960	LJ	7H10	7H11
Ciprofloxacin	removed	removed	removed	removed
Ofloxacin		revised to 4 µg/ml		
Levofloxacin	Revised to 1.5 µg/ml		revised to 1µg/ml	
Moxifloxacin	established at 0.5 and 2.0 µg/ml		established at 0.5 and 2.0 µg/ml	
Amikacin		established at 30 µg/ml	established at 4 µg/ml	
Capreomycin			revised to 4 µg/ml	removed
Kanamycin	established at 2.5 µg/ml			
Cycloserine		revised to 30 µg/ml		

Critical concentrations for first- and second-line DST

2008 guidance updated Table

Drug group[a]	Drug	DST method available	DST critical concentrations (µg/ml)			
			Löwenstein-Jensen[b]	Middlebrook 7H10[b]	Middlebrook 7H11[b]	MGIT960
Group 1 **First-line oral anti-TB agents**	Isoniazid Rifampicin[c] Ethambutol[d] Pyrazinamide	Solid, liquid Solid, liquid Solid, liquid Liquid	**0.2** **40.0** **2.0** -	**0.2** **1.0** **5.0** -	**0.2** **1.0** **7.5** -	**0.1** **1.0** **5.0** **100.0**
Group 2 **Injectable anti-TB agents**	Streptomycin[e] Kanamycin Amikacin Capreomycin	Solid, liquid Solid, liquid Solid, liquid Solid, liquid	**4.0** **30.0** **30.0** **40.0**	**2.0** **5.0** **4.0** **4.0**	**2.0** **6.0** - -	**1.0** **2.5** **1.0** **2.5**
Group 3 **Fluoroquinolones**	Ofloxacin[f] Levofloxacin Moxifloxacin[g] Gatifloxacin[h]	Solid, liquid Solid, liquid Solid,liquid Solid	**4.0** - - -	**2.0** **1.0** **0.5/2.0** **1.0**	**2.0** - - -	**2.0** **1.5** **0.5/2.0** -
Group 4[i] **Oral bacteriostatic second-line anti-TB agents**	Ethionamide Prothionamide Cycloserine P-aminosalicylic acid	Solid, liquid Solid, liquid Solid Solid, liquid	**40.0** **40.0** **30.0** **1.0**	**5.0** - - **2.0**	**10.0** - - **8.0**	**5.0** **2.5** - **4.0**
Group 5[i] **Anti-TB agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)**	**Clofazimine** **Amoxicillin/clavulanate** **Clarithromycin** **Linezolid**	**Liquid** **None** **None** **Liquid**	- - - -	- - - -	- - - -	- - - **1.0**

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2. DST method accuracy and reproducibility

- Expert Group agreed that DST for **Isoniazid**, **Rifampicin**, **SL injectables** and **fluoroquinolones** are accurate and reproducible across various settings.

It was therefore concluded that testing for these drugs be recommended. All FQs should be tested to guide the choice of the most appropriate agent.

- Expert Group agreed that reaching accuracy and reproducibility for most of Group 4 and 5 drugs remain technically challenging or problematic.

It was therefore concluded that country investment in developing such capacity cannot be recommended until more research has been done.

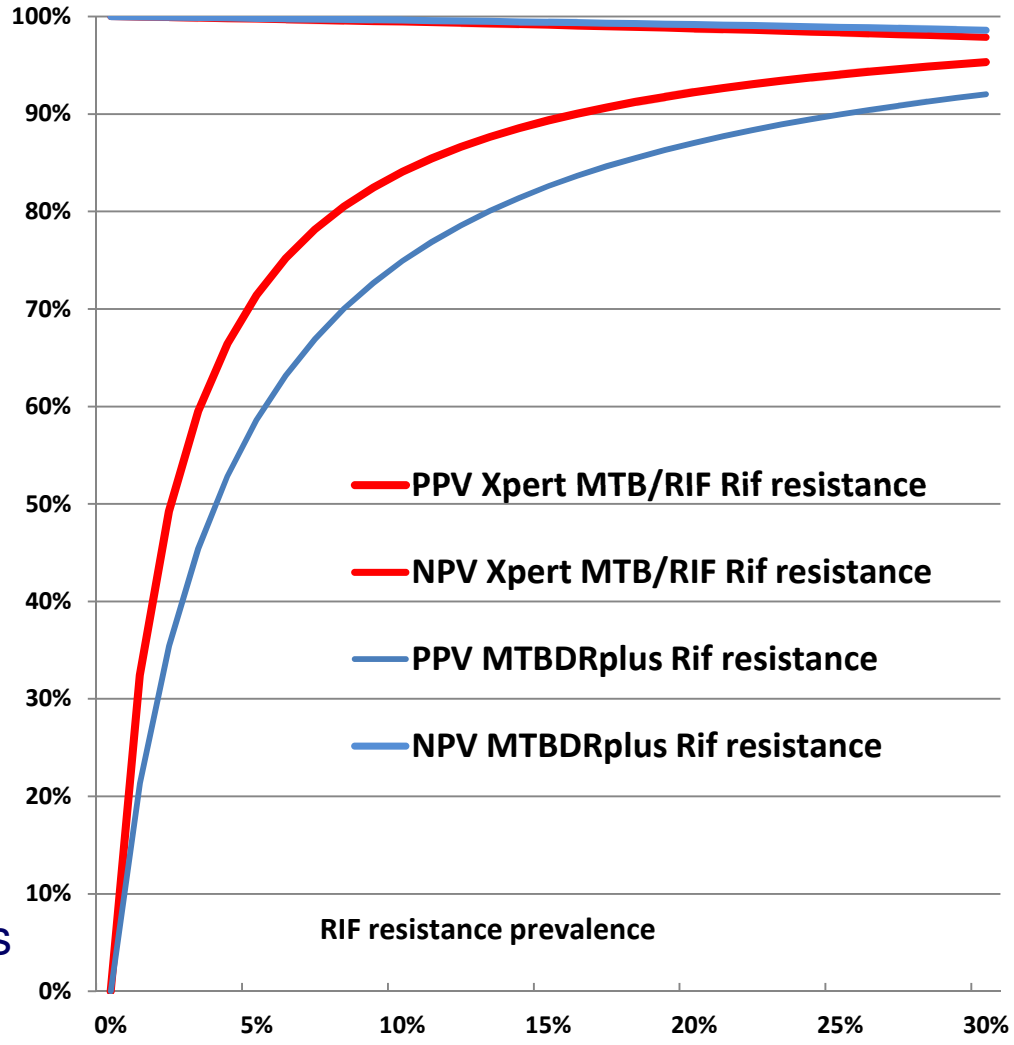
2. DST methods comparison

MDR-TB risk groups = high prevalence of Rif-resistance

- Either LPA or Xpert MTB/RIF can be used as primary diagnostic test for **Rif-resistance**, once country proficiency has been documented using phenotypic DST as reference standard

Groups not at risk of MDR-TB = low prevalence of Rif-resistance

- Second independent test is required to confirm **Rif-resistance**, e.g. XP and LPA, Xpert MTB/RIF and phenotypic DST, LPA and phenotypic DST etc. once country proficiency has been documented using phenotypic DST as reference standard



World Health Organization

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3. DST results relationship with treatment outcomes

Expert Group acknowledged number of limitations of the IPD data used for review: dataset with only MDR patients; regimens highly variable; DST methods and drug concentrations variable; 'effect' of individual drugs only assessed; confounding, etc..

Expert Group concluded that:

- The relationship of DST with treatment outcomes was clear for DST results to identify MDR- and XDR-TB.
- The relationship of DST with treatment outcomes was less pronounced and much more variable for other drugs. Although DST to some of the 2nd-line drugs showed minimal/modest effect in treatment outcome, more research and data are required.

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4. MTBDRsl molecular line probe assays

MTBDRsl LPA:

- Not a replacement for phenotypic DST (strong)
- May be used as a triage test to guide further treatment decisions (conditional; treatment approach to be outlined)
- Test cannot be used to define XDR-TB for surveillance purposes (conditional)

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5. Research priorities

- Studies that systematically evaluate head-to-head test comparisons using appropriate design and linked to patient outcomes;
- Borderline Rifampicin resistance (prevalence, geographic spread);
- Studies to describe molecular mutations for second-line drugs to advance development of molecular/genotypic tests;
- DST to some Group 5 drugs and new/under development drugs

Next steps

- Additional analyses from the IPD data set to answer questions forthcoming from the Expert Group
- Preparation of draft EGM report
- Presentation of preliminary recommendations at STAG
- Updated WHO policy guidance by Q3, 2012