

WHO INTERIM GUIDANCE ON XPert MTB/ RIF

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OVERVIEW

- Background
- Evidence base
- Policy development
- WHO interim policy recommendations
- Implementation considerations
- Patient management
- WHO plan of supporting roll-out
- Conclusion

BACKGROUND (1)

- Sputum smear microscopy
 - >125 years old
 - Poor sensitivity (~60%), reduces further in HIV Pos.
 - Can not diagnose resistance, species identification
- Conventional Culture & Drug susceptibility test
 - Slow and cumbersome
- Molecular Line Probe Assays
 - Complex and costly
 - Requires sophisticated infrastructure



BACKGROUND (2)

- 2006: FIND with the support from NIH, partners with Cepheid and the Uni. of New Jersey to develop an automated NAAT for TB based on GeneXpert multi-disease platform
- 2009: the Xpert MTB/RIF assay completed
 - Demonstration studies started
- 2010: WHO global consultation
- December 2010: WHO endorses Xpert MTB/RIF

Xpert MTB/RIF is an automated, cartridge based, Nucleic Acid Amplification Test which detects TB as well as Rifampicin resistance in 2 hours



EVIDENCE BASE (1)

○ Analytical studies:

- Analytical sensitivity of 5 genome copies of DNA and 131 cfu/ml of M.Tb spikes in sputum
- No cross reactivity with non-TB isolates
- Rifampicin resistance correctly detected
- Procedure does not generate detectable aerosols

EVIDENCE BASE (2)

Indicators	Validation studies	Demonstration studies	Single centre studies
Individuals/ Sites	1730/ 4	6673/ 6	4575/ 12
Detection of Tuberculosis			
Sensitivity in single test	92.2% of C+ (72.5% in Sm-)	91% of C+ (99% in Sm+ 80% in Sm-)	92.5% (~60% in Sm-)
Specificity	99%		98%
Detection of rifampicin resistance			
Sensitivity	99.1%	95.1%	98%
Specificity	100%	98.4%	99%

WHO POLICY DEVELOPMENT

- Expert group meeting in Sept 2010
 - Reviewed available data
 - Evidence synthesis process
 - Recommendations for wide spread use of Xpert
- Strategic Advisory Group- TB
 - Endorsed the recommendations
- Global consultation in Dec 2010
 - Agreement on interim algorithms
 - Positioning in risk groups at different levels
 - Implementation considerations
- Development of policy statement

RECOMMENDATIONS

Solid evidence base to support widespread use of Xpert for detection of TB and Rif resistance

- Xpert MTB/RIF should be used as an initial test in individual suspected of having MDR-TB or HIV associated TB (**Strong recommendation**)
- Xpert MTB/RIF may be considered as follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear neg specimens (**Conditional recommendations** acknowledging major resource implications)

Testing all suspects can be strongly dependent on country situation and programme

REMARKS

- These recommendations apply to use of Xpert
 - In sputum specimens (lack of data on EP)
 - One sputum specimen for diagnosis (resource implications)
 - Also for children (generalization of data)
- Conventional microscopy, culture and DST are still needed for
 - Monitoring
 - Prevalence surveys
 - DST for other 1st line and 2nd line anti-TB drugs

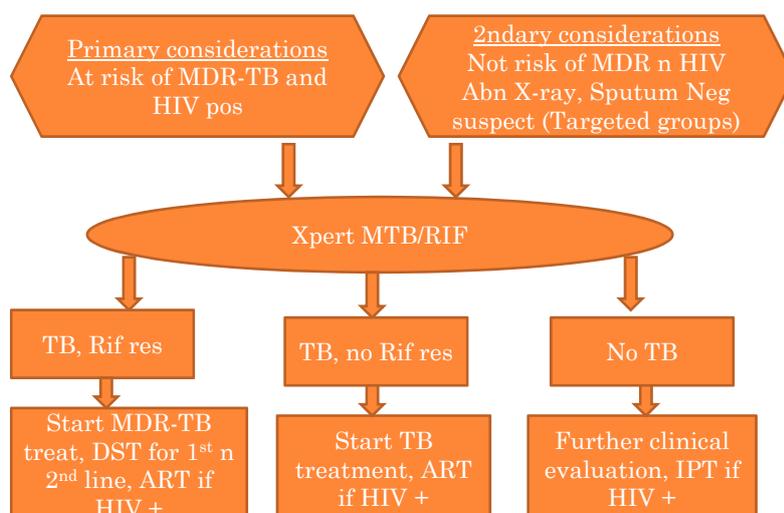
IMPLEMENTATION CONSIDERATIONS (1)

- Positioning
 - At district/ sub-district level
 - Stable electric supply, security, storage space, dedicated staff and similar bio-safety as microscopy
- Should not be used for monitoring
- Country specific algorithms based on epidemiology, resources and cost effectiveness
 - Negative Predictive Value for Rif resistance is high (99%) and thus no need for confirmation of negative
 - Positive Predictive Value for Rif resistance increases with the prevalence of Rif resistance
 - ❖ careful risk assessment and targeted testing reduces chance of false positives

IMPLEMENTATION CONSIDERATIONS (2)

- Integrated into National TB control programme and laboratory strengthening
 - Access to TB and MDR-TB treatment
- Recommended temperature for cartridge storage is 2-28 degrees
- Annual calibration is required
- Cost implications
 - Expensive than microscopy but same as culture
 - Increase of case detection
 - Other indirect savings due to early diagnosis

SUGGESTED ALGORITHM



INTERIM CASE DEFINITIONS

- TB case
 - Atleast one sputum smear positive for TB
 - Positive on conventional culture, LPA or Xpert
 - Smear neg, EP- diagnosed by health practitioner
- Case of MDR-TB
 - Resistant to H and R by conventional DST or LPA
 - Resistance to R (proxy to MDR) by conventional DST, LPA or Xpert MTB/RIF (under consideration)

REGISTERING TB CASES

- Xpert MTB/RIF positive:
 - for all TB cases diagnosed with Xpert and R sensitive
- Xpert MTB/RIF positive with rif resistance:
 - for all TB cases diagnosed by Xpert and R resistant
- All diagnosed patients should be monitored by sputum smear and culture as per current guidelines
- All current treatment outcome definitions should be applied including “Cured” to patients diagnosed by Xpert

WHO PLAN OF SUPPORTING ROLL-OUT

- Support in implementation
 - Establishment of dedicated website to map the uptake, communicate operational problems etc.
 - Revision of case definitions and algorithms based on the experiences
 - Operational research
 - Impact evaluation
 - Cost effectiveness etc.
 - Periodic meeting of implementers to share and review findings
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CONCLUSION

- Xpert MTB/RIF represents a major milestone for global TB diagnosis and care
 - Implementation should be guided by epidemiology, available resources and feasibility
 - The programme should strengthen laboratory capacity and prepare to provide access to TB and MDR-TB treatment
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THANKS

