2.4 Summary of WHO's 2013 policy recommendations

2.4.1 Using Xpert MTB/RIF to diagnose pulmonary TB and rifampicin resistance in adults and children

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (**strong recommendation**, high-quality evidence).
- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (**strong recommendation**, very low-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in **all adults** suspected of having TB (**conditional recommendation** acknowledging resource implications, high-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in **all children** suspected of having TB (**conditional recommendation** acknowledging resource implications, very low-quality evidence).
- Xpert MTB/RIF may be used as a follow-on test to microscopy in adults suspected of having TB who are not at risk of MDR-TB or HIV-associated TB, especially when further testing of smear-negative specimens is necessary (**conditional recommendation** acknowledging resource implications, high-quality evidence).

Remarks

These recommendations apply to the use of Xpert MTB/RIF for specimens of processed and unprocessed sputum.

These recommendations also apply to specimens of gastric lavage and aspirate from adults and children, the recommendation for adults is based on the generalization of data from children.

These recommendations support the use of a single sputum specimen for diagnostic testing, acknowledging that processing multiple specimens increases the sensitivity of Xpert MTB/RIF but also has resource implications.

Children suspected of having pulmonary TB but who have had a single negative result by Xpert MTB/RIF should undergo further diagnostic testing, and a child for whom there is a high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

Conventional microscopy and culture remain essential for monitoring therapy and for performing DST for anti-TB agents other than rifampicin (including for isoniazid and second-line anti-TB agents).

Expanding the scope of the use of Xpert MTB/RIF and its placement in diagnostic algorithms will have significant implications for operational implementation, and its use should be phased in within the context of national strategic plans for TB.

Emerging data have shown that Xpert MTB/RIF detects some rifampicin-resistant strains that are identified as susceptible by phenotypic DST. Sequencing these discordant results usually resolves in favour of Xpert MTB/RIF, and patients missed by phenotypic DST have poor treatment outcomes on first-line treatment.

2.4.2 Using Xpert MTB/RIF to diagnose extrapulmonary TB and rifampicin resistance in adults and children

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid (CSF) specimens from patients suspected of having TB meningitis (**strong recommendation** given the urgency of rapid diagnosis, very low-quality evidence).
- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific nonrespiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (**conditional recommendation**, very low-quality evidence).

Remarks

Individuals suspected of having extrapulmonary TB but who have had a single negative result from Xpert MTB/RIF should undergo further diagnostic testing, and those for whom there is a high clinical suspicion for TB (especially children) should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

For CSF specimens, Xpert MTB/RIF should be preferentially used instead of culture if the sample volume is low or if additional specimens cannot be obtained in order to make a quick diagnosis. If sufficient volume of material is available, concentration methods should be used to increase the yield.

Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB regardless of the method used. A pleural biopsy is the preferred sample. The sensitivity of Xpert MTB/RIF in testing samples of pleural fluid is very low. Nevertheless, any individual with a positive result from pleural fluid tested by Xpert MTB/RIF should be treated for pleural TB; those with a negative result from Xpert MTB/RIF should have other tests.

Conventional microscopy and culture are essential for monitoring therapy and for performing DST for anti-TB agents other than rifampicin (including for isoniazid and second-line anti-TB agents).

Emerging data have shown that Xpert MTB/RIF detects some rifampicin-resistant strains that are found to be susceptible by phenotypic DST. Sequencing these discordant results usually resolves in favour of Xpert MTB/RIF, and patients missed by phenotypic DST have poor treatment outcomes on first-line treatment.

These recommendations do not apply to samples of stool, urine or blood, given the lack of data on the utility of Xpert MTB/RIF for these specimens.

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3 *GRADE Working Group* (http://www.gradeworkinggroup.org, accessed 10.12.2013)

4 *WHO handbook for guideline development*. Geneva, World Health Organization, 2012 (available at http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf)

5 Vassall A et al. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. PLoS Medicine, 2011, 8:e1001120 (doi: 10.1371/journal.pmed.1001120).

6 *Strategic and Technical Advisory Group for Tuberculosis (STAG-TB): report of the tenth meeting*. Geneva, World Health Organization, 2010 (available at http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf?ua=1).

7 *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement*. Geneva, World Health Organization, 2011 (available at http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf)

8 *Prerequisites to country implementation of Xpert MTB/RIF and key action points at county level*. Geneva, World Health Organization, 2011 (available at http://whqlibdoc.who.int/hq/2011/WHO_HTM_TB_2011.12_eng.pdf)

9 *Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational „How-to"; practical considerations*. Geneva, World Health Organization, 2011 (available at http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf)

10 http://www.stoptb.org/wg/gli/meetings.asp

11 *Strategic and Technical Advisory Group for Tuberculosis (STAG-TB): report of the thirteenth meeting*. Geneva, World Health Organization, 2013 (available at http://www.who.int/tb/advisory_bodies/STAG_report2013.pdf?ua=1).

12 *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update*. Geneva, World Health Organization, 2013 (available at http://www.who.int/tb/laboratory/policy_statements/en/).

of MDR-TB, testing *previously treated* TB cases with Xpert MTB/RIF will result in a high PPV for the detection of rifampicin resistance.

5.3 Interpreting results from Xpert MTB/RIF

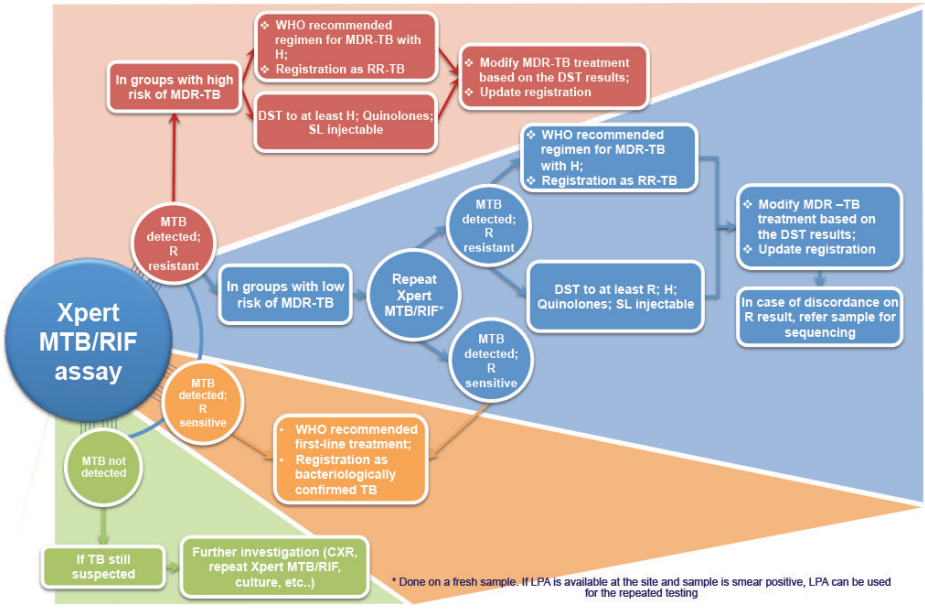
To complete any diagnostic algorithm, the test results need to be interpreted appropriately. Accurately interpreting results allows health-care workers and clinicians to make correct decisions about the interventions needed in relation to **patient management** and **registration**, and to any **additional laboratory work-up** that may be required. It is therefore important to train health-care staff how to interpret and follow-up any new test being introduced.

The interpretation of Xpert MTB/RIF results and follow-on steps will depend on both the result and the risk group from which the patient originated, based on the risk assessment as described in section 5.1. All patients identified as having TB by Xpert MTB/RIF should be initiated on the appropriate WHO-recommended treatment regimen as soon as possible. The prompt treatment initiation will have a positive effect on patients' outcomes, and a treatment regimen can be refined later if additional results become available.

As shown in Figure 1, an Xpert MTB/RIF result can indicate that *M. tuberculosis* (MTB) was not detected, MTB was detected and was not resistant to rifampicin (that is, it is rifampicin susceptible), or that MTB was detected and it was resistant to rifampicin. A small proportion of tests may result in an error or invalid result; these tests need to be repeated.

When Xpert MTB/RIF does not detect *M. tuberculosis*, the disease can be ruled out in most cases unless there is still a strong suspicion of TB

Figure 1. Interpreting results from Xpert MTB/RIF tests



CXR [chest X-ray], DST [drug-susceptibility testing], H [isoniazid], LPA [line probe assay], MDR-TB [multidrug-resistant TB], MTB [Mycobacterium tuberculosis], R [rifampicin], RR-TB [rifampicin-resistant TB]