Next-generation Xpert® MTB/RIF Ultra assay, new hope for diagnosis of tuberculosis

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TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs, but can also affect other organs. The disease is spread when people who are sick with pulmonary TB expel bacteria into the air.

Worldwide, tuberculosis (TB) is one of the top 10 causes of death, and the leading cause from a single infectious agent (above HIV/AIDS); millions of people continue to fall sick with the disease each year.

In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people, and there were an additional 300 000 deaths from TB (range, 266 000–335 000) among HIV-positive people.

There were an estimated 10.0 million new cases of TB (range, 9.0–11.1 million), equivalent to 133 cases (range, 120–148) per 100 000 population.

The development of the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA) was a major step forward for improving the diagnosis of tuberculosis (TB) and rifampicin resistance detection globally. That globally, use of rapid molecular tests is increasing, and many countries are phasing out the use of smear microscopy for diagnostic purposes.

The Xpert® MTB/RIF test cartridge can simultaneously identify Mycobacterium tuberculosis complex bacteria (MTB) and resistance to rifampicin in less than two hours, using the automated GeneXpert® platform. Despite substantial increased sensitivity for MTB detection compared with smear microscopy, Xpert MTB/RIF test sensitivity is nevertheless suboptimal, particularly with smear-negative and HIV-associated TB, and in pediatric populations (in patients with paucibacillary disease).

The Xpert® MTB/RIF Ultra test cartridge (Ultra) was developed as a next-generation test, with higher sensitivity for MTB detection especially among smear-negative TB patients as well as more accurate determination of rifampicin resistance. Ultra runs on the same GeneXpert platform as Xpert MTB/RIF, using software version 4.7b or later.

For the detection of MTB, Ultra incorporates two new multi-copy amplification targets (IS6110 and IS1081) and a larger DNA amplification reaction chamber than Xpert MTB/RIF that contributes to the increase in sensitivity, having improved the ability of the assay to detect low numbers of bacilli (16 bacilli per ml sputum compared to 131 per ml for Xpert® MTB/RIF).

WHO Technical Expert Group made the following statements regarding use of Ultra:

- Ultra is non-inferior to the Xpert MTB/RIF assay for the detection of MTB and rifampicin resistance and can be used as an alternative to the latter in all settings.
- The current WHO recommendations for the use of Xpert MTB/RIF also apply to the use of Ultra as the initial diagnostic test for all adults and children with signs and symptoms of TB and in the testing of selected extrapulmonary specimens (cerebrospinal fluid, lymph nodes

and tissue specimens).

- The interpretation of Ultra results for MTB detection are the same as for Xpert MTB/RIF with the exception of "trace calls"(new semi-quantitative category that corresponds to the lowest bacillary burden for MTB detection. The "MTB Detected, trace", henceforth referred to as "trace call" indicates that only the multi-copy targets were detected, and not the TB specific regions in the rpoB gene).
- Interpret "trace calls" as follows: Among persons with HIV, children and extrapulmonary specimens "trace calls" should be considered to be true positive results for use in clinical decisions and patient follow-up; Among persons not at risk for HIV, with an initial "trace call" positive result, a fresh specimen from the patient should undergo repeat testing and the result of the second Ultra test be used for clinical decisions and patient follow-up.
- Ultra can be used on all GeneXpert instrument platforms and is suitable for use at central or national reference laboratory level, regional and district levels. GeneXpert has the potential to be used at the peripheral level, provided uninterrupted electricity supply and temperature conditions can be ensured.

REFERENCES

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