A retrospective evaluation study of diagnostic accuracy of Xpert® MTB/RIF assay, used for detection of *Mycobacterium tuberculosis* in Greece

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Abstract

Tuberculosis (TB) is a deadly disease that is caused by the bacterium Mycobacterium tuberculosis (MTB). TB is a global public health issue due to resistance strains. To prevent further spread of drug-resistant strains and to treat the patients correctly, it is important to rapidly and accurately detect drug resistant MTB.

The aim of this study was to analyze cumulative laboratory data from routine specimens from patients with suspected tuberculosis in order to determine diagnostic accuracy of the Xpert® MTB/RIF system (Cepheid, USA). The reference methods used was cultivation and drug susceptibility testing (DST) on Löwenstein- Jensen solid media and/or on semi-automated liquid culture system MGIT Bactec 960, BD, USA.

510 routine pulmonary and extrapulmonary specimens from patients with suspected tuberculosis were used in this study.

Overall, the combined sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values for detecting MTB-complex was 79.6 %, 97.1 %, 88 % and 94.6 %, respectively. For the detection of rifampicin resistance was the sensitivity 85.7 %, the specificity 97 %, the PPV 75 % and the NPV 98.5 %.

The results in this study indicate that GeneXpert MTB/RIF is an assay with a high overall sensitivity and specificity, accurate for detection of MTB-complex and rifampicin resistance.

Key words: Mycobacterium tuberculosis, tuberculosis, GeneXpert MTB/RIF
Background

Tuberculosis (TB) is a deadly disease that is caused by the bacterium *Mycobacterium tuberculosis* (MTB). The disease usually affects the lungs (pulmonary TB) (1). Extrapulmonary TB is defined as TB affecting other sites of the body (2). The bacteria are spreading by air transmission from people with pulmonary TB (1). Members of the mycobacterium genus have a unique cell wall structure that contains a high concentration, over 60%, of lipids. The cell wall is the major reason for the bacterium virulence, it is associated with impermeability to stains and dyes, antibiotic resistance and resistance to human defense mechanism (3). The bacilli are classified as acid fast bacteria (AFB) due to their resistance to decolourization by acids during staining procedures (4).

*Tuberculosis in the world*

TB is a global public health issue aggravated by the emergence of drug resistance strains (2). Worldwide is TB, only after human immunodeficiency virus (HIV) and AIDS, the greatest killer due to a single infectious agent. In 2013, there were 9.0 million new TB cases and 1.5 million TB deaths. Low- and middle income countries have the highest morbidity and mortality of TB (1). Asia accounted for 56% of the new TB cases and the African region for 29%. High-income countries, such as those in Western Europe, USA and Australia, have the lowest TB rates. The incidence rates of TB are decreasing worldwide and the mortality rate has decreased by 45% between 1990 and 2013. Compared to HIV-negative individuals, HIV infected individuals have a 29 times higher risk of developing TB (2). In low-incidence countries, many of the TB patients originate from countries with high incidence of TB. Budget cuts in low-incidence countries is also associated with the fact that TB incidence rates are decreasing slowly or even increasing in some countries. Greece is a low-incidence country (5).

*Treatment of tuberculosis*

Isoniazid and rifampicin are the most powerful anti-TB drugs. Recommended treatment for drug-susceptible TB is the combined use of the four so called first-line drugs; isoniazid, rifampicin, ethambutol and pyrazinamide for a period of six-months (2). If the bacteria do not respond to at least isoniazid and rifampicin, the patient has a form of TB called multidrug-resistant tuberculosis (MDR-TB) Treatment for MDR-TB is longer and includes second line-anti TB drugs as well (1). A marker for MDR-TB is rifampicin resistance. In 2013, 480 000 new cases of MDR-TB were reported. Between 2012 and 2013 had reported cases of MDR-
TB increased with 23%. It is estimated that 20.5% of recurrent previously treated TB patients have MDR- TB. To prevent further spread of drug-resistant strains and to treat the patients correctly, it is important to rapidly and accurately detect drug resistant MTB (2).

**Decontamination**

Before culturing specimens have to be decontaminated, in order to eliminate the normal flora. If the normal flora grows as well on the medium, it would rapidly overgrow and inhibit growth of the TB bacilli. A common decontaminating method is the modified Petroff. Some specimens should not be decontaminated, such as spinal- and synovial fluid, bone marrow, pus from abscesses, lymph nodes and biopsies. The decontamination process is a rough method and there is a risk of killing TB bacilli (4).

**Acid fast bacteria (AFB) smear microscopy and culture on Löwenstein-Jensen media**

AFB smear microscopy is a rapid and inexpensive method that is very useful to identify highly contagious patients. An acid fast stain that is common for mycobacterium detection is the Ziehl-Neelsen staining. The AFB stain procedure involves dropping the cells in suspension onto a slide, then air drying the liquid and heat fixing the cells. The slide is flooded with Carbol Fuchsin, which is then heated to dry and rinsed off in tap water. The slide is then flooded with a mild solution of hydrochloric acid in isopropyl alcohol to distain the Carbol Fuchsin, thus removing the stain from cells that are unprotected by a waxy lipid layer. Thereafter, the cells are stained in methylene blue and viewed on a microscope under oil immersion. Stained AFB will appear pink in light microscopy. However, microscopy is not a sensitive method (25-75% compared to culture) and gives no information about viability, resistance and identification of the bacilli. A high number of bacilli are required for a positive result, 5*10³ to 10⁴ bacilli per ml (4).

The “gold standard” for diagnosis of TB is culture on solid media, such as the Löwenstein-Jensen (LJ) medium. Culture is a more sensitive method and is useful for detecting low mycobacterial loads, for species identification, detect TB at an early stage of the disease and to perform drug susceptibility testing (DST) (2). Both AFB staining and culture are methods used for monitoring the effectiveness of treatment. Media for growth of mycobacterium are egg-enriched, containing glycerol and asparagine, and liquid media, with serum or bovine albumin, used. Glycerol favors MTB growth but the bacterium grows slowly with a generation time of 18-24 hours. LJ medium is the most commonly used media, it is an egg-based media that contain malachite green as an inhibitor of non-mycobacterial organism.
Egg-based media have a disadvantage, if a contamination occurs the culture is generally lost. Compared to solid media, liquid media gives a faster detection of MTB growth. In liquid media, detection may be noticeable after 7-14 days compared to 21-42 days in LJ media. After 8-12 weeks the result negative can be given. MTB grows with rough, crumbly, waxy and non-pigmented colonies (4).

DST on cultured specimens is an effective method to check for strains that are resistance to first- and second-line TB drugs (2). The most common method is the proportion method, there the growth of the bacteria is compared on drug-containing and drug-free control media (6).

**Xpert® MTB/RIF assay**

A molecular method, the Xpert® MTB/RIF (Cepheid, USA), was endorsed in 2010 by the World Health Organization (WHO) (7), for the rapid identification of MTB-complex (i.e., *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. canettii*, *M. microti*, *M. caprae*, *M. pinnipedi*, *M. mungi*, and *M. orygis*) (8) in clinical samples and the detection of mutations affecting resistance to rifampicin (7). The XpertMTB/RIF is a molecular test that fully automates sample processing, DNA amplification and detection. The method is based on a real-time-PCR reaction, performed inside a single closed cartridge, and requires very short hands-on time. The cartridges contain lyophilized reagents, buffers and washes. It targets the rifampin-resistance determining region of the *rpoB* gene. The XpertMTB/RIF have a high degree of specificity that is ensured by the utilization of three specific primers and five unique molecular probes (A-E) that are labeled with fluorophores emitting at different wavelengths of the spectrum. The DNA sequence for MTB-complex covers the *rpoB* core region which makes possible the detection of MTB-complex and of rifampicin resistance simultaneously. Each probe is designed to hybridize to a different sequence within the wild-type *rpoB* (rifampicin sensitive) gene, as presented in figure 1. When the probe hybridizes to its complementary sequence, the molecular beacon undergoes conformational changes, which results in fluorescence signal. If a mutation blocks the hybridization, the probe will stay in its non-fluorescing state (7).
Detection is based on a six-color laser, as shown in figure 2, and results are available in only 2 hours (7). MTB-complex is detected when at least two of the five probes give a positive signal. A sample processing control (SPC) is included in the test that verifies that the bacteria have been processed correctly. In a negative specimen gives the probes no or one positive signals (8). The cutoff value for XpertMTB/RIF is 131 cfu/ml of MTB-complex in sputum and sensitivity for five genome copies of purified DNA. This method can also detect rifampicin-resistant strains that got a sensitive result on DST. XpertMTB/RIF detect DNA from viable and non-viable bacilli, for this reason the method is not recommended to monitoring the treatment process of patients (9).
**Measurement of diagnostic accuracy**

Sensitivity measures the ability of the test to correctly give a positive result to patients with the disease. Specificity measures the ability to give a negative result to patients without the disease. Positive prediction value (PPV) calculates the probability of patients with a positive test actually has the disease. Negative prediction value (NPV) calculates the probability of patients with a negative test not to have the disease. The values for PPV and NPV are related to the prevalence of the disease in the population (10).

**Aim**

To analyze cumulative laboratory data from routine specimens from patients with suspected tuberculosis in order to determine diagnostic accuracy of the Xpert® MTB/RIF system (Cepheid, USA), compared to the results from cultivation and clinical data when available.
Materials and methods

Five hundred and ten (510) routine pulmonary and extrapulmonary specimens from patients with suspected tuberculosis were used in this study. The specimens were taken in hospitals all over Greece and analyzed in the microbiology department & national reference laboratory for mycobacteria at”Sotiria” chest diseases hospital in Athens. Only high- risk TB patients were selected out and analyzed with the XpertMTB/RIF.

Pulmonary specimens included sputum, brushing, bronchial secretions, alveolar washing, bronchoalveolar lavage and gastric fluid. Extrapulmonary specimens included ascetic fluid, cerebrospinal fluid (CSF), lymph node, fine needle aspirated biopsies, pericardial fluid, tissue, pus, synovial fluid, urine, pleural fluid and bone.

Processed by the modified Petroff method specimens were cultured on LJ media (and/or on the semi-automated liquid culture system MGit Bactec 960, BD, USA). In addition, real-time-PCR analysis with the GeneXpert instrument using Xpert® MTB/RIF cartridge has been applied, according to the manufacturer’s instructions. The specimens were also analyzed by light microscopy to investigate presence of acid fast bacilli. DST was performed on LJ culture media by using the proportion method.

Calculation and Statistics

Data were processed using the SPSS statistic data program. The analytical sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of the method for the diagnosis of tuberculosis were calculated, by using the follow formulas;

\[
\text{Sensitivity} = \frac{\text{true positive}}{\text{true positive} + \text{false negative}} \times 100
\]

\[
\text{Specificity} = \frac{\text{true negative}}{\text{true negative} + \text{false positive}} \times 100
\]

\[
\text{Positive predictive value (PPV)} = \frac{\text{true positive}}{\text{true positive} + \text{false positive}} \times 100
\]

\[
\text{Negative predictive value (NPV)} = \frac{\text{true negative}}{\text{true negative} + \text{false negative}} \times 100
\]
True positive and true negative include the specimens that are positive and negative in both XpertMTB/RIF and culture. False positive include the specimens that are positive in XpertMTB/RIF and culture negative and false negative include XpertMTB/RIF negative and culture positive specimens.

**Ethical consideration**
Patients were categorized as Greek or immigrants/foreigners. No ethical approval was required for this study.
Results

In this study were 439, out of the 510 specimens, included. The 71 excluded specimens included; one error and three invalid on XpertMTB/RIF, 20 cultures contaminated and two specimens for which culture was not performed. 45 specimens have results on XpertMTB/RIF but culture results were still pending when this study has been completed. Of the 439 specimens, 339 specimens were negative on both methods, ten were XpertMTB/RIF positive and culture negative, 74 positive on both methods and 19 were XpertMTB/RIF negative and culture positive, as presented in table 1.

Table 1. Comparison between results from GeneXpert MTB/RIF and culture on Löwenstein Jensen media and/or MGIT Bactec 960.

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Xpert results</th>
<th>Culture results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>All samples</td>
<td>336</td>
<td>19</td>
</tr>
<tr>
<td>(n=439)</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>Greek</td>
<td>250</td>
<td>7</td>
</tr>
<tr>
<td>(n=309)</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>Foreigner/ immigrant</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td>(n=130)</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>210</td>
<td>13</td>
</tr>
<tr>
<td>(n=292)</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>126</td>
<td>6</td>
</tr>
<tr>
<td>(n=147)</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Among the 439 specimens, 309 (70 %) were from Greeks and 130 (30 %) from immigrants/foreigner born patients. 250 specimens from the Greek patients were XpertMTB/RIF and culture negative, and 46 specimens were positive on both Xpert MTB/RIF and culture. Six specimens were XpertMTB/RIF positive and culture negative and seven specimens were XpertMTB/RIF negative and culture positive. Among the foreigners/immigrant, 86 were negative and 28 were positive on both methods. Four specimens were positive on XpertMTB/RIF but culture negative and twelve specimens were XpertMTB/RIF negative but culture positive.
147 of the 439 specimens (33 %) were extrapulmonary and 292 (67 %) specimens were pulmonary. Of the extrapulmonary specimens, 126 were negative and nine positive on both methods. Six specimens were XpertMTB/RIF positive but culture negative and six specimens were XpertMTB/RIF negative but culture positive. Among the pulmonary specimens, 210 specimens were negative and 65 specimens were positive on both methods. Four specimens were XpertMTB/RIF positive and culture negative and 13 specimens were negative on XpertMTB/RIF but culture positive.

The results from microscopy (presented in table 2) were that acid fast bacilli were found in 31 specimens. Among these 31 specimens, 26 specimens were positive on XpertMTB/RIF and culture, four specimens were negative on XpertMTB/RIF and culture, and one specimen was positive on XpertMTB/RIF but culture negative. Negative microscopy results were found in 406 specimens and among these were 331 specimens negative on XpertMTB/RIF and culture. 47 specimens were XpertMTB/RIF and culture positive, nine specimens were positive on XpertMTB/RIF and culture negative, and 19 specimens were negative on XpertMTB/RIF and culture positive. Two specimens were suspicious on microscopy, one of them was negative on both XpertMTB/RIF and culture and the other was positive on both XpertMTB/RIF and culture.

**Table 2.** Comparison between GeneXpert MTB/RIF, culture on Löwenstein Jensen media (and/or MGIT Bactec 960) and Ziehl-Neelsen stained smear microscopy results.

<table>
<thead>
<tr>
<th>Microscopy results</th>
<th>Xpert results</th>
<th>Culture results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative</strong> (n=406)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>331</td>
</tr>
<tr>
<td>Positive</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td><strong>Positive</strong> (n=31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td><strong>Suspicious</strong> (n=2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Overall, the combined sensitivity, specificity, PPV and NPV were 79,6 %, 97,1 %, 88 % and 94,6 %, respectively. For pulmonary specimens, the sensitivity was 83,3 %, the specificity 98,1 %, the PPV 94,2 % and the NPV 94,1 % and for extrapulmonary specimens the sensitivity was 60 %, the specificity 95,4 %, the PPV 60 % and the NPV 95,4 %. For Greek born patients the sensitivity was 86,7 %, the specificity 97,6 %, the PPV 88,5 % and the NPV 97,2 % and for foreigner born patients the sensitivity was 70 %, the specificity 95,5 %, the
PPV 87,5 % and the NPV 87,7 %. For AFB negative specimens was the sensitivity 71,27 %, the specificity 97,3 %, the PPV 83,92 % and the 94,6 % and for AFB positive specimens the sensitivity was 100 %, the specificity 80 %, the PPV 96,3 % and the NPV 100 %. The results are presented in table 3.

Table 3. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values of the GeneXpert MTB/RIF analyze with culture on Löwenstein Jensen media and/or MGIT Bactec 960 as reference.

<table>
<thead>
<tr>
<th>Specimen type,</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples (n=439)</td>
<td>79,6 %</td>
<td>97,1%</td>
<td>88 %</td>
<td>94,6 %</td>
</tr>
<tr>
<td>Pulmonary (n=292)</td>
<td>83,3 %</td>
<td>98,1%</td>
<td>94,2%</td>
<td>94,1%</td>
</tr>
<tr>
<td>Extrapulmonary (n= 147)</td>
<td>60 %</td>
<td>95,4 %</td>
<td>60 %</td>
<td>95,4 %</td>
</tr>
<tr>
<td>Greek born (n= 309)</td>
<td>86,7 %</td>
<td>97,6 %</td>
<td>88,5 %</td>
<td>97,2 %</td>
</tr>
<tr>
<td>Foreigner (n= 130)</td>
<td>70 %</td>
<td>95,5 %</td>
<td>87,5 %</td>
<td>87,7 %</td>
</tr>
<tr>
<td>Acid fast bacilli negative (n= 406)</td>
<td>71,27 %</td>
<td>97,3 %</td>
<td>83,92 %</td>
<td>94,6 %</td>
</tr>
<tr>
<td>Acid fast bacilli positive (n= 31)</td>
<td>100 %</td>
<td>80 %</td>
<td>96,3 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Of the Xpert MTB/RIF positive specimens, 75 specimens had also results from DST for rifampicin resistance, as presented in table 4. Of these specimens, one XpertMTB/RIF resistant specimen missing a signal for probe A was culture sensitive. Two specimens that were missing a signal for probe B were also resistance on culture. One specimen was missing a signal for probe C on the XpertMTB/RIF and was sensitive on culture. Four XpertMTB/RIF resistant specimens did not have a signal for probe E and were resistant on culture. In total, resistance was detected in six specimens by both methods whereas two specimens were resistant on XpertMTB/RIF but sensitive on DST. 64 specimens were wild type on XpertMTB/RIF and sensitive on DST. One specimen showed both resistant and sensitive strains and one specimen was sensitive in DST but undetermined on XpertMTB/RIF.
**Table 4.** Comparison between GeneXpert MTB/RIF and Drug susceptibility testing on Löwenstein- Jensen media on the search for rifampicin resistant strains among patients with suspected tuberculosis.

<table>
<thead>
<tr>
<th>Xpert MTB/RIF</th>
<th>Drug susceptibility testing (n= 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistant</td>
</tr>
<tr>
<td>Resistant</td>
<td>6</td>
</tr>
<tr>
<td>Wild type</td>
<td>1</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0</td>
</tr>
</tbody>
</table>

The sensitivity, specificity, PPV and NPV for the XpertMTB/RIF to detect rifampicin resistant was 85.7 %, 97 %, 75 % and 98.5 %, respectively, as presented in table 5.

**Table 5.** Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values of the GeneXpert MTB/RIF assay with drug susceptibility testing on Löwenstein- Jensen media as reference.

<table>
<thead>
<tr>
<th>Drug susceptibility testing (n= 75)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>85.7 %</td>
<td>97 %</td>
<td>75 %</td>
<td>98.5 %</td>
</tr>
</tbody>
</table>
Discussion

The purpose of this study was to evaluate the performance of the XpertMTB/RIF in the diagnosis of tuberculosis. The results on the performance of XpertMTB/RIF correlated well with previous studies (11-14). These studies have reported the sensitivity and specificity for pulmonary specimens to range from 67 % to 90, 6 % and 94 % to 100% respectively. In a meta- analysis by the World Health Organization, the sensitivity and specificity for extrapulmonary specimens ranged from 43,7 % to 84,9% % and 92,5 % to 98,6 % respectively, depending on specimens origin. In this study, the accuracy of the assay in the extrapulmonary specimens couldn't be analyzed by specimen's origin due to lack of adequate number of specimens. However, in extrapulmonary specimens taken as one entity, the assay exhibited reduced sensitivity (60%), compared to that on pulmonary (83,3%).

The results for Greeks and immigrants/foreigner were similar in this study, this is explained by that the XpertMTB/RIF were used to analyze high risk patients. The patients are selected out and that makes the results similar for the two categories, although some patients have originated from a high- incidence country.

410 specimens (93,4%) out of the 439 specimens analyzed in this study got the same result, negative or positive, on both XpertMTB/RIF and culture. The remaining 29 (6,6 %) specimens were either negative on XpertMTB/RIF and positive on culture or the opposite. Some of these differences may be explained by the clinical data. Nine specimens with a negative result on XpertMTB/RIF had a positive result on culture with < 10 colonies. Thus it is possible that the bacteria load may have been too low for the XpertMTB/RIF to detect the DNA from MTB- complex. The same problem may have been with two additional specimens, one CSF specimen and one from a patient with previous TB. These specimens were also negative on XpertMTB/RIF but positive on culture. This shows a problem in the sensitivity for the XpertMTB/RIF. Another specimen was positive on culture but negative on XpertMTB/RIF, two new specimens from this patient were collected and two new runs on the XpertMTB/RIF were done. The results were still negative on the XpertMTB/RIF so the culture from the initial specimen may have been contaminated, which gave a false positive result. One specimen got a negative result on XpertMTB/RIF but positive on culture, the specimen was confirmed positive with another molecular method. In this case, the XpertMTB/RIF may have given a false negative result. For nine specimens, the reason for discrepancies observed was unclear. Xpert MTB/RIF is a method with high specificity and false positive results may be explained by the detection of dead MTB that would not be
detected on culture. For reliable results a good quality of specimen collection is very important. A patient with a negative XpertMTB/RIF result can still have TB (2).

For the XpertMTB/RIF ability to detect rifampicin resistance, previous reports showed a sensitivity of 94,4 % to 99,1% and a specificity of 98,3 % to 100 % with DST as reference method (15,16). In this study, the value for sensitivity and specificity was 97 % and 85,7 % respectively. Among the 75 specimens that were positive in XpertMTB/RIF, 70 specimens (93, 3 %) had the same result on both XpertMTB/RIF and DST. Two specimens, one missing a signal from probe A and one for C were found resistant in XpertMTB/RIF but sensitive in DST. One specimens that was found to be wild type on XpertMTB/RIF and resistant on DST had a mixed population of sensitive and resistant bacilli, as revealed by another molecular assay (i.e. MTBDRplus).

A limitation in this study was that data regarding patient clinical evaluation were missing and thus it was not possible to resolve all discrepancies observed between the XpertMTB/RIF assay and culture.

**Conclusion**

For diagnosing tuberculosis and detecting rifampicin resistant strains the GeneXpert MTB/RIF is an assay with a high overall specificity and sensitivity. It is a rapid method that could complement the reference methods.

**Scientific output**

The high diagnostic accuracy of Xpert MTB/RIF has been considered a breakthrough in the fight against tuberculosis (9). The patients get the correct treatment and the spread of MDR-TB are prevented.
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