# Evaluation of Xpert® MTB/RIF for the Detection of Mycobacterium Tuberculosis in Sputum-Smear Negative Patients Using Bronchoalveolar Lavage Fluid

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**Research Article**

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## Abstract

Background

An estimated three million cases of tuberculosis (TB) are missed annually and much time elapse for the diagnosis of suspected sputum-smear negative cases, hence, the need for rapid and accurate diagnostic test. This retrospective study was conducted to evaluate the use of the Xpert®MTB/RIF assay on BALF specimens in TB diagnosis in terms of time to treatment initiation and its effect on empirical treatment.

Methods

Bronchoscopy was offered to sputum smear-negative patients with suspected pulmonary tuberculosis (PTB). Collected BALF was tested by fluorescent microscopy, MGIT960, and Xpert®MTB/RIF assay. First-line drug sensitivity tests were performed on positive samples. Similar tests were done using sputum.

Results

Between November 2017 and November 2019, a total of 395 suspected TB patients underwent bronchoscopy in our hospital. BALF samples were collected and analysed using different methods. Using BALF culture as the standard reference test, the sensitivity and specificity of Xpert®MTB/RIF for TB diagnosis using BALF specimens were 79.2% and 95.8%, respectively. The positive and negative predictive values were 87.5% and 93.0%, respectively. Rifampin resistance was highly predictive of multidrug resistant tuberculosis (MDR-TB) using Xpert®MTB/RIF, with a value of 72.7%.

The median time to treatment initiation using BALF was 5 days (IQR=4-7 days) for fluorescent staining, 6 days (IQR=3-8 days) with Xpert®MTB/RIF and 31 days (IQR=29-35 days) for culture.

Further, 179(45.3%) out of the 395 sputum smear-negative patients suspected of PTB were already started on empirical treatment before bronchoscopy. After bronchoscopy, 96(24.3%) tested positive for TB whilst 83(21%) tested negative with Xpert®MTB/RIF using BALF.

Conclusion

Xpert®MTB/RIF done using BALF for sputum smear-negative patients suspected of PTB increases the diagnostic accuracy of TB and decreases the time to treatment initiation of PTB as well as the rate of empirical treatment use.


## Background

Tuberculosis (TB) is a chronic and deadly infectious disease that affects one-third of the world's population. In 2019, the World Health Organization (WHO) estimated the global incidence of TB to be 10.0 million[1]. An estimated three million cases of TB are missed annually; 1.4 million of these missed cases are from the South-East Asia region alone, the region with the highest estimated number of missed cases[2]. China is one country with a high TB burden, with deaths in both immunocompetent and HIV positive individuals [3]. Thus, there is a critical need for more reliable and timely diagnosis of suspicious cases to enable effective treatment to be initiated.

The WHO's proposed diagnostic protocols for pulmonary TB include clinical history and examination findings, as well as radiological and laboratory investigations. For clinical diagnosis, symptoms such as cough for more than two weeks duration, fever, night sweats, and haemoptysis have been recommended as diagnostic criteria. The spectrum of radiological findings associated with pulmonary TB includes apical lesions, consolidations, tree in buds, cavitations, pleural effusion, miliary shadows, and ground glass appearance, among others. Together, these findings form the basis of clinical diagnosis, with a sensitivity and specificity of 24% and 94%, respectively. There are also various laboratory investigations for TB diagnosis. For instance, culture, either liquid or solid medium, remains the "gold standard" for diagnosis; although culture gives the highest sensitivity (100%) and specificity (100%), it takes a long time to obtain the required results (2-6 weeks), which may not be favourable in all cases[4]. The Xpert®MTB/RIF assay (Cepheid, USA) was endorsed by the WHO for use in TB diagnostics[5] and can detect *Mycobacterium tuberculosis* (MTB) and rifampin(RIF) resistance within 2 hours, with high sensitivity and specificity, as evidenced in results from several countries[6-8].

Currently, most Xpert® MTB/RIF research for TB diagnosis has been performed using sputum samples with a known valid accuracy of results[9]; however, sputum quality has a significant impact on the final outcome of assay results[10]. In situations where patients are not able to produce sputum or for sputum smear-negative results, BALF can be used to accurately diagnose the disease[11]. Further, fiberoptic bronchoscopy not only assists in visualisation of various lung segments but also has the added advantage to obtain a biopsy for histopathology, where necessary, thereby, increasing the diagnostic yield of the test[12]. Also, sputum smear-negative patients are treated empirically before final diagnosis are concluded which often leads to over treatment [13] and drug side effects. Thus, the aim of this study was

to evaluate the use of the Xpert® MTB/RIF assay on BALF specimens for TB diagnosis in terms of time to treatment initiation and its effect on empirical treatment.

## Methods

This was a retrospective study performed at the Affiliated Hospital of Shaoxing University between November 2017 and November 2019.

*Study population*

The medical records of all patients with suspected pulmonary TB who had the Xpert® MTB/RIF performed on bronchial washing or BALF at the Affiliate Hospital of Shaoxing University, between November 2017 and November 2019, were reviewed. These records investigated included clinical, radiological and laboratory data. Concurrently, Xpert® MTB/RIF assays performed on sputum samples during the same period were also reviewed.

*Patient Selection Criteria*

*Inclusion criteria*

Both previously treated TB and new patients with clinical suspicion of pulmonary TB(PTB), exhibiting any two of the following symptoms: dry or productive cough for more than 3 weeks together with loss of appetite, fatigue, intermittent fever > 3 weeks, drenching night sweat> 2weeks, weight loss>4kg,haemoptysis. Additionally, the patients must have any one of the following radiological features: cavitations, consolidation, ground-glass opacity and pleural effusion. Also, HIV status of patients should be known.

*Exclusion criteria*

Patients without full clinical history or all three laboratory investigations requested, or with a previous clinical history of lung cancer or fungal infections.

*Bronchoscopy procedure*

Under aseptic conditions, a flexible bronchoscope (Fujinon Fujifilm Light Source XL-4450) was used to inspect all segments of the bronchial tree. A biopsy was performed in areas that showed abnormality, as depicted by the computer tomography (CT) scan or as per the clinician's discretion. Then, 50-100 mL of normal saline was instilled in that segment of the lung and was aspirated into 2 sterile specimen tubes. The BAL fluids collected were sent for fluorescent microscopy and culture, and an Xpert® MTB/RIF assay.

*Fluorescent microscopy and liquid culture*

The BALF was divided into two parts; one was sent for fluorescent microscopy and the other for culture. Smears were prepared from direct inoculation of BALF after centrifugation and were stained using auramine-rhodamine staining for 15 minutes. Next, the slides were rinsed with water and flooded with 0.5% acid alcohol for 2 minutes. Then, they were rinsed in water. The smears were counter-stained with potassium permanganate and left for 2 minutes. Slides were then rinsed in water, air-dried, and viewed using an LED fluorescent microscope Olympus BX41TT (Olympus Corporation, Tokyo, Japan). The same process was repeated for sputum samples.

For culture, BAL fluid sediments were first decontaminated by adding 4% NaOH at a ratio of 1 part BALF to 2 parts 4% NaOH. The mixture was then shaken vigorously for 15 minutes using a Vortex Mixer V5 (EssenScien, USA). Then, sterile normal saline was added up to 45 mL and the mixture was centrifuged at 4000xg for another 15 minutes at 4℃. The supernatant was discarded and 1 mL of sterile normal saline was added to the sediments. Then, 0.5 mL aliquots of the sample were inoculated into the BACTEC-MGIT 960 (M960) culture system (Becton-Dickinson, Sparks, Maryland, USA) and were cultured for 6 weeks. The same protocol was repeated using patient sputum samples [14].

*Drug sensitivity test (DST)*

BALF was inoculated with a BACTEC MGIT 960 Mycobacterium liquid culture system. The Mycobacterium was isolated and cultured, and the positive samples were identified. Sensitivity tests for 4 anti-tuberculosis drugs were carried out using a modified version of the Roche absolute concentration indirect method. The specific steps were follows: isoniazid (1, 10 ug/ ml), rifampin (50, 250 ug/m1), streptomycin (0, 100 ug/ml), ethambutol (5, 50 ug/ml)[14].

*Xpert® MTB/RIF*

According to the manufacturer's instructions, one part (mL) reagent was added to one part (mL) BALF. The mixture was shaken vigorously using a Vortex Mixer V5 (EssenScien, USA) for 1 minute and was then left for 15 minutes at room temperature. Then, 2 mL of the mixture was

inoculated into the cartridge containing washing buffer, reagents for lyophilized DNA extraction and PCR amplification, and fluorescent detection probes. The results of the MTB/RIF assay were ready after 2 hours, indicating whether the sample was MTB positive or negative and whether it was rifampin resistance. Tests were performed on sputum samples using the same procedure [15].

*Diagnosis of TB*

In our preliminary analysis, *Mycobacterium tuberculosis* positive culture was used as the gold standard for diagnosis of pulmonary TB. Subsequent analysis was based on the presence of histological or cytological evidence of caseous granuloma containing acid-fast bacilli.

*Data analysis*

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of active pulmonary TB were calculated using the website http://vassarstats.net/clin1.html. Further, 95% confidence intervals (CIs) were estimated according to an exact binomial distribution. Sensitivity and specificity values were compared using McNemar's test. Statistical analyses were performed using GraphPad Prism 7. P<0 .05 indicated a statistically significant difference.

## Results

*Patient characteristics*

Between November 2017 and November 2019, a total of 395 patients with suspected TB underwent bronchoscopy at our hospital, with BALF samples collected and analysed by different methods. In total, 119 of these patients were diagnosed with TB according to the diagnosis standard for tuberculosis (ws288-2008). Figure 1 provides a flow chart describing each investigational step. Table 1 shows the Characteristics of 395 patients who underwent bronchoscopy in the study.

*Performance comparison of three methods*

We utilised three different methods to analyse 395 BALF samples. The results are shown in Figure 2A. The positive rate of liquid culture was 31.1% (MTB-106 cases, NTM-17 cases). The positive rate of fluorescent microscopy was 11.9% (MTB-42 cases, NTM-5 cases) and that of Xpert was 24.3% (MTB-96 cases, NTM-0 cases).

Further, we excluded the NTM cases and compared the MTB cases between the two groups (Figure2B). Figure 2C shows the flow of patients and samples from study intake to outcome, as guided by the results from different test modalities. The sensitivity, specificity, PPV, and NPV of the three methods are shown in Table 2.

*Xpert® MTB/RIF in predicting MDR-TB*

Figure3 depicts the drug sensitivity and resistant test information of MTB samples. In total, 78.2% of samples were sensitive, 12.6% were single drug-resistant, and 9.2% were multidrug-resistant (Figure 3A).Figure3B provides more detail on the drug resistance results, showing that in our research, isoniazid resistance was most common, followed by streptomycin resistance, and then rifampin and ethambutol resistance.

*Time to treatment initiation: BALF verses Sputum*

To address our hypothesis that BALF may have better diagnostic value than sputum, we collected data from another group of TB patients with natural sputum retention. This sputum group comprised of 120 patients, and there were no statistical significant differences in age and gender between this group and the BALF group. We compared the sensitivities of the detection methods and time to treatment initiation of both groups, as shown in Figure 4.

## Discussion

At present, sputum smear microscopy for acid-fast bacilli (AFB) remains an important initial step for TB diagnosis. However, this method has limited sensitivity due to problems with sputum quality [16] and this poses much challenge to the search for a rapid and more accurate test to diagnose missed TB cases.

Of the 395 patients, 8(2%) tested positive for HIV. Consolidation was the most common radiological presentation (28.4%), with the most common symptom being cough (71.9%). Majority of the patients were males-219(55.4%) and the average age was 56 years.

Using bronchoscopy, the pathological location is usually in full view, large pathological samples can be obtained, and a large amount of bacteria can be recovered with minimal contamination of samples by oral and pharyngeal bacteria [17]. In a retrospective study of

bronchoscopic samples in Hong Kong, which used the culture method as the reference standard, the sensitivity of AFB smears was 21% (95% CI: 9.6–37.3%)[18]. In our study, the sensitivity of fluorescent microscopy, using auramine-rhodamine staining instead of acid-fast staining, was 39.6% (95% CI: 30.4–49.6%).The drawback was its inability to distinguish between MTB and NTM. There were 5 NTM cases classified as false positive, so the specificity of fluorescent microscopy was 98.3% (95% CI: 95.8–99.4%).

With culture as the reference standard, the sensitivity of the Xpert® MTB/RIF assay was 79.2% (95% CI: 70.1–86.3%) and the specificity was 95.8% (95% CI: 92.7-97.7%). When pathologically and clinically diagnosed PTB in addition to culture-confirmed TB were used as a combined reference standard, the sensitivity and specificity of the Xpert® MTB/RIF assay were 79.80% (95% CI: 71.3-86.4%) and 99.6% (95% CI: 97.7-99.9%), respectively. Thus, whatever the standard, the sensitivity of Xpert® MTB/RIF assay is significantly higher than that of fluorescent microscopy. Furthermore, the Xpert® MTB/RIF assay simultaneously identifies MTB and detects rifampicin resistance by detecting mutations in the region of the rpoB gene[19-20].Our study suggests that rifampicin resistance is highly predictive of MDR-TB with a value of 72.7%.The results of Xpert® MTB/RIF indicated that 9 samples were rifampin-resistant, 8 of which were finally proven to be multidrug-resistant by DST.

In addition to comparing the merits of different methods, we also compared the advantages of using bronchoalveolar lavage fluid (BALF) and sputum specimen. When the final diagnosis included clinical or radiological evaluation as the reference standard, the sensitivities of the three different methods with BALF was 89.1%, 79.8%, and 35.3%, respectively, while that of sputum was 72.9%, 69.5%, and 24.5%, respectively. Our study indicates that, compared to sputum, BALF has significantly higher detection sensitivity ($p<0.05$), which means that using BALF instead of sputum may help reduce the missed diagnosis rate of TB.

In TB, the time to diagnosis and treatment initiation is essential [21], especially in situations as this, where much time has elapsed in determining the actual diagnosis of suspected pulmonary TB patient presenting with sputum smear-negative result. Our study observed a median time to treatment initiation in the BALF group as 6 days (interquartile range [IQR] 3-8 days) for Xpert®MTB/RIF assay, whilst culture results took 31 days(IQR=29-35 days). Fluorescent positive stain results had the shortest median time to treatment of 5 days (IQR=4-7 days).Therefore, it may be useful to combine BALF fluorescent microscopy and *Xpert® MTB/RIF* for the rapid diagnosis of TB, especially MDR-TB.

Although, it is less infectious than sputum smear-positive, sputum smear-negative PTB accounts for transmissions in communities due to delay in diagnosis and also initiation of appropriate treatment, and this leads to extensive lung damage [22] and by the time a diagnosis has to be made, more invasive diagnostic procedures may be required. In this study, 179(45.3%) out of the 395 sputum smear-negative patients suspected of PTB were already started on empirical treatment whilst awaiting bronchoscopy. After bronchoscopy and using BALF specimen, 96 (24.3%) tested positive for TB on *Xpert® MTB/RIF* whilst 83(21.0%) tested negative, and were continued on empirical treatment based on clinical and radiological findings at presentation. This significant reduction further confirms the usefulness of *Xpert® MTB/RIF* and BALF in definitive diagnosis of PTB [11] and helps reduce the rate of empirical treatment use, especially with concern of several drug side effects and drug resistance.

## Conclusion

In conclusion, *Xpert® MTB/RIF* done using BALF *for* sputum smear-negative suspected PTB increases its diagnostic accuracy and, decreases the time to treatment initiation of PTB and rate of empirical treatment use. Therefore, where tolerable and appropriate, BALF should be the recommended choice of specimen collected for accurate and early diagnosis of pulmonary tuberculosis.

### Limitations of the study

1. This study was performed at a single site; hence, the results may not be a true representation of the general population.
2. The retrospective nature of the study makes it prone to biases.
3. The outcome of treatment was not done.

## Declarations

### Ethical approval and consent to participate

This study was approved by the "People's Republic of China Health Industry Standards. Diagnostic Standards for Legal Infectious Diseases (WS288-2008)". A waiver of consent was given due to the retrospective nature of the study.

### Availability of supporting data

All relevant data are within the paper.

### Funding

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### Authors' contributions

1.Ernest Oyeh( first author) and Zhenghao Zhang( contributed equally)

were the principal investigators who designed the research , supervised data and sample collection, conducted the analyses and drafted the manuscript.

2.Faxiang Jin,Yanan Wang and Peng Xu collected BALF samples and supervised the performance of fluorescent microscopy, MGIT960, and Xpert® MTB/RIF.

3.Wenfang Xu( corresponding author) coordinated the study and revised the manuscript.

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### Competing interests

All authors: not applicable.

### Consent for publication

Authors approve the publication of this manuscript.

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## Tables

**Table 1. Characteristics of 395 patients who underwent bronchoscopy in the study**

| | N (%) |
|---|---|
| Age(years) | 56.0 (46.0–67.0) |
| Gender | |
| Male | 219(55.4%) |
| Female | 176(44.6%) |
| | |
| Presenting Symptoms | |
| Cough | 284(71.9%) |
| Haemoptysis | 116(29.4%) |
| Fever | 86(21.8%) |
| Fatigue | 45(11.4%) |
| Comorbidity | |
| Diabetes | 68(17.2%) |
| Hypertension | 59(14.9%) |
| Chronic obstructive lung disease | 43(10.9%) |
| Old TB | 41(10.4%) |
| Carcinoma | 29(7.3%) |
| Imaging features | |
| Consolidation | 112(28.4%) |
| Ground-glass opacity | 104(26.3%) |
| Cavitations | 62(15.7%) |
| Pleural effusion | 12(3.0%) |
| HIV status | |
| Positive | 8(2.0%) |
| Negative | 387(98.0%) |
| Patients on empirical treatment | |
| Before bronchoscopy | 179/395(45.3%) |
| After bronchoscopy | 83/395(21.0%) |

**Table 2. Performance of fluorescent microscopy, Xpert, and MGIT960 using BALF culture or final diagnosis as standard.**

| Performances relative to culture | | | | |
|---|---|---|---|---|
| | Sensitivity% 95%CI | Specificity% 95%CI | Positivepredictive value%(95%CI) | Negativepredictive value%(95%CI) |
| | | | | |
| Xpert®MTB/RIF assay | 79.20% (70.1%-86.3%) | 95.80% (92.7%-97.7%) | 87.50% (78.8%-93.1%) | 92.60% (88.9%-95.2%) |
| | 84/106 | 277/289 | 84/96 | 277/299 |
| Fluorescent microscopy | 39.60% (30.4%-49.6%) | 98.30% (95.8%-99.4%) | 89.40% (76.1%-96.0%) | 81.60% (77.0%-85.4%) |
| | 42/106 | 284/289 | 42/47 | 284/384 |
| | | | | |
| MGIT960 | - | - | - | - |
| | Performances relative to final diagnosis | | | |
| | Sensitivity% 95%CI | Specificity% 95%CI | Positive predictive value%(95%CI) | Negative predictive value%(95%CI) |
| | | | | |
| Xpert®MTB/RIF assay | 79.80% (71.3%-86.4%) | 99.60% (97.7%-99.9%) | 98.90% (93.5%-99.9%) | 92.00% (88.1%-94.7%) |
| | 85/119 | 275/276 | 95/96 | 275/299 |
| Fluorescent microscopy | 35.30% (26.9%-44.7%) | 98.20% (95.6%-99.3%) | 89.40% (76.1%-96.0%) | 77.90% (73.1%-82.0%) |
| | 42/119 | 271/276 | 42/47 | 271/384 |
| MGIT960 | 89.10% | 100.00% | 100.00% | 95.50% |
| | (81.7%-93.8%) | (98.3%-100%) | (95.6%-100%) | (92.2%-97.5%) |
| | 106/119 | 276/276 | 106/106 | 276/289 |

## Figures

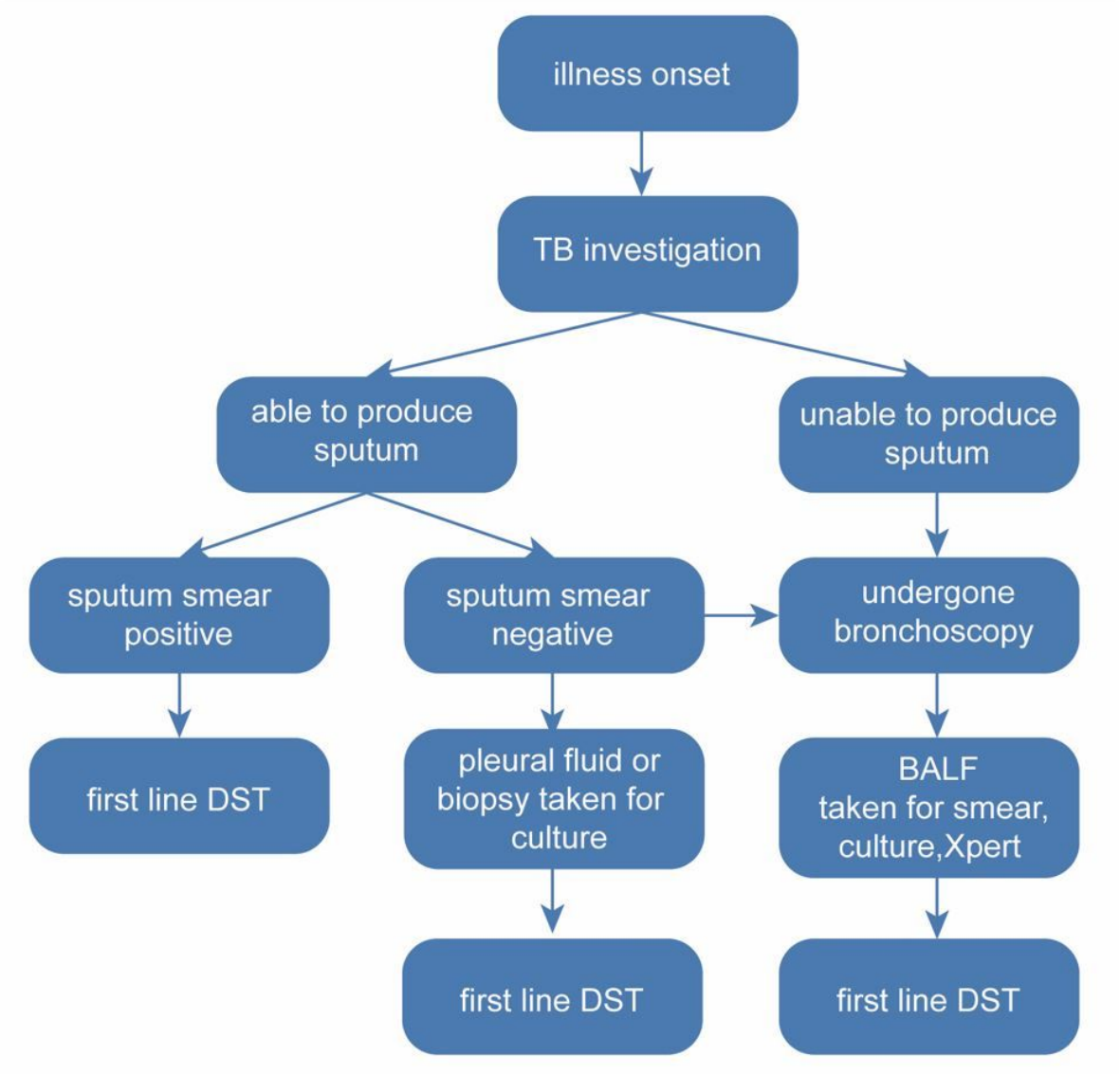
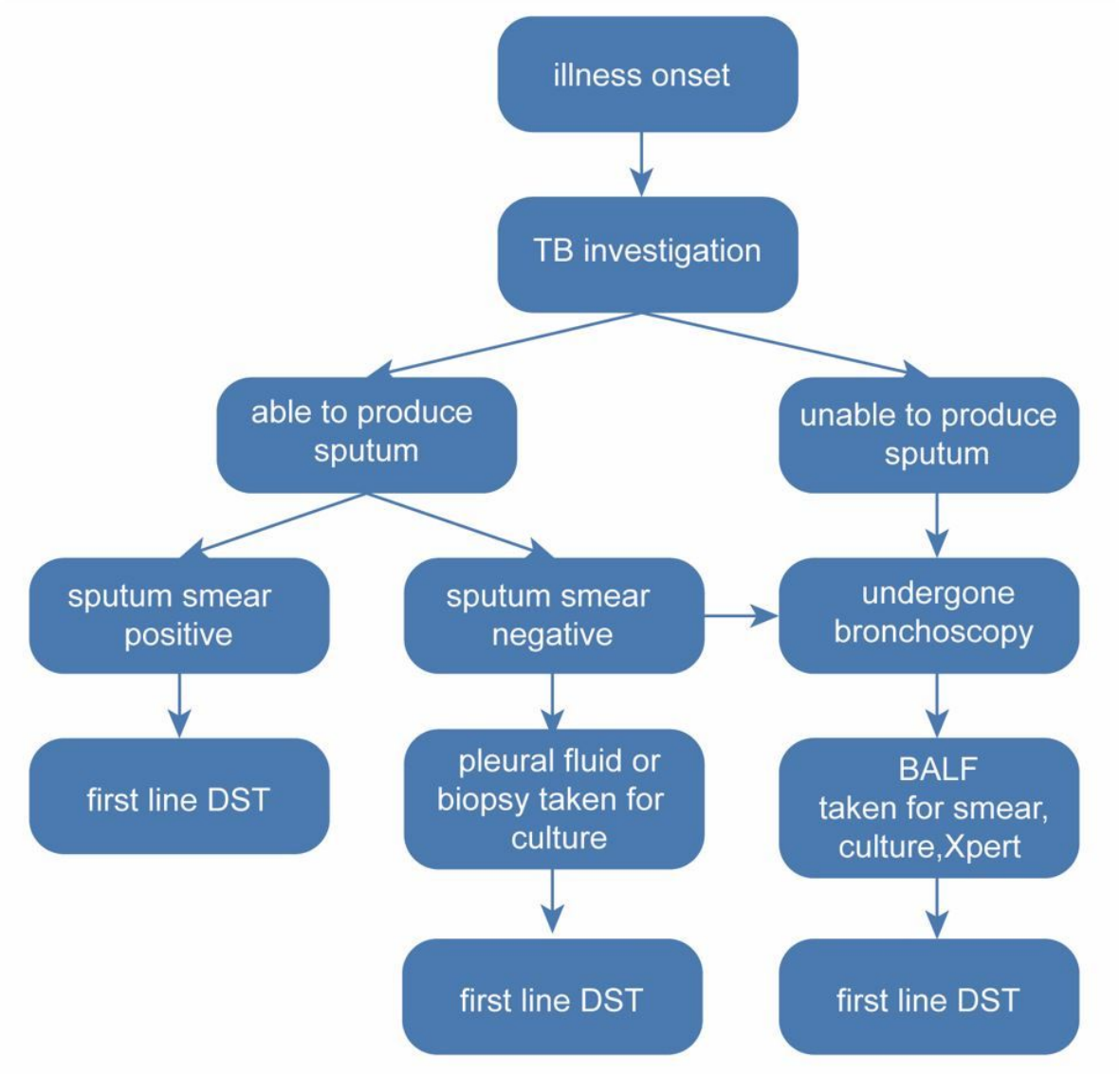



**Figure 1**

Flow chart of each investigational step.

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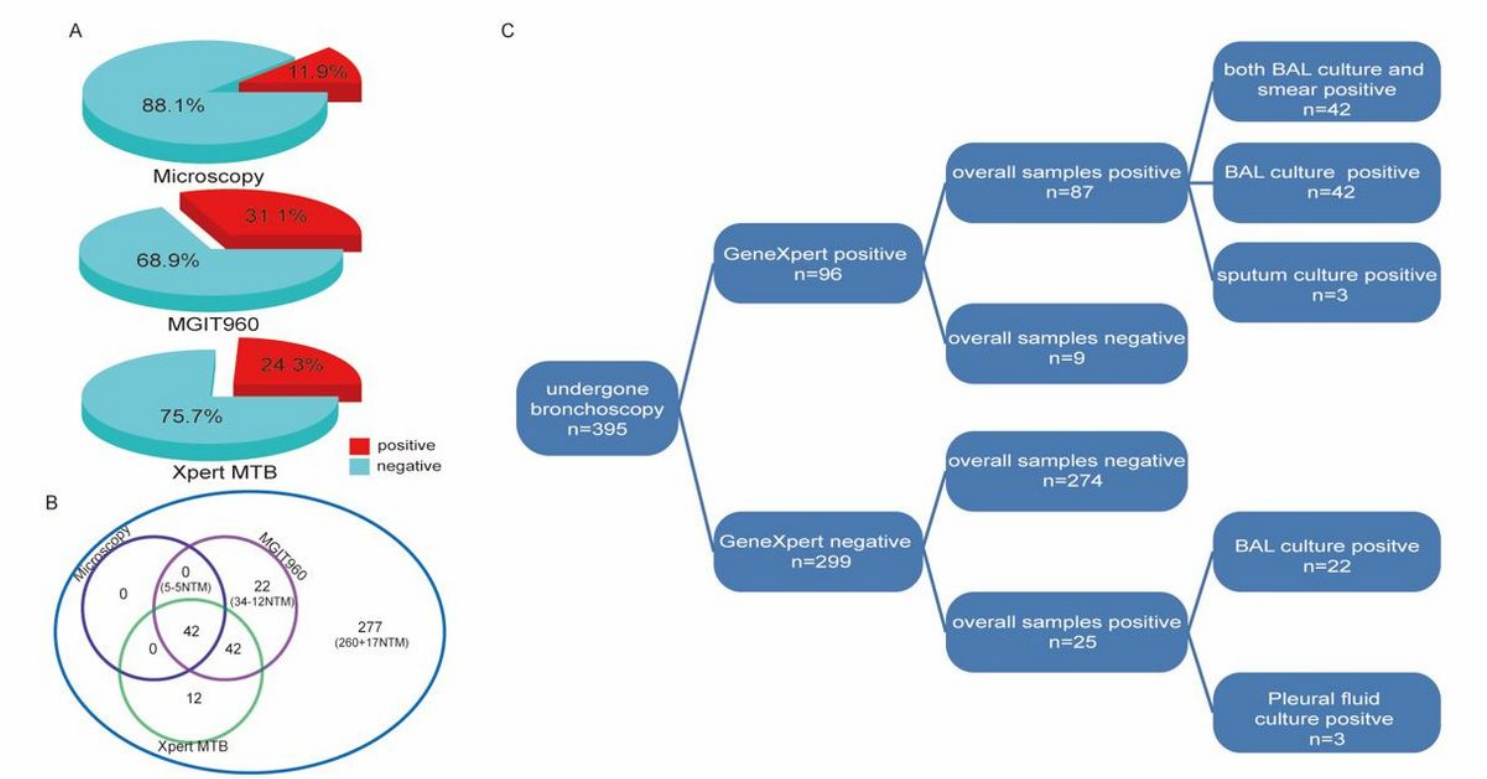
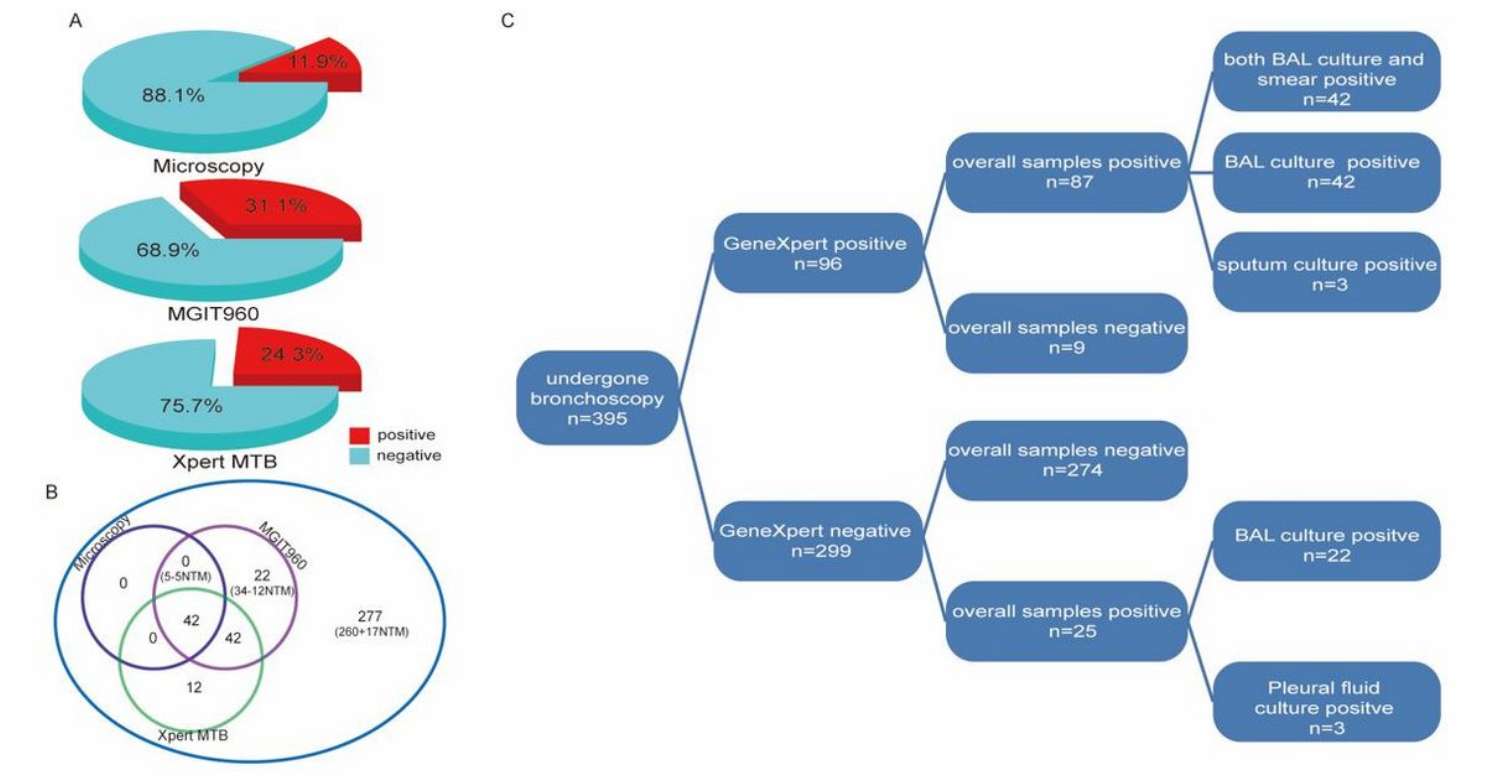



Figure 2

Performance of fluorescent microscopy, Xpert® MTB/RIF, and MGIT960. A) Positive rate of the three different methods; B) intersection of positive specimens; C) the number of patients at each investigational step between recruitment and final outcome, with results derived from different diagnostic modalities.

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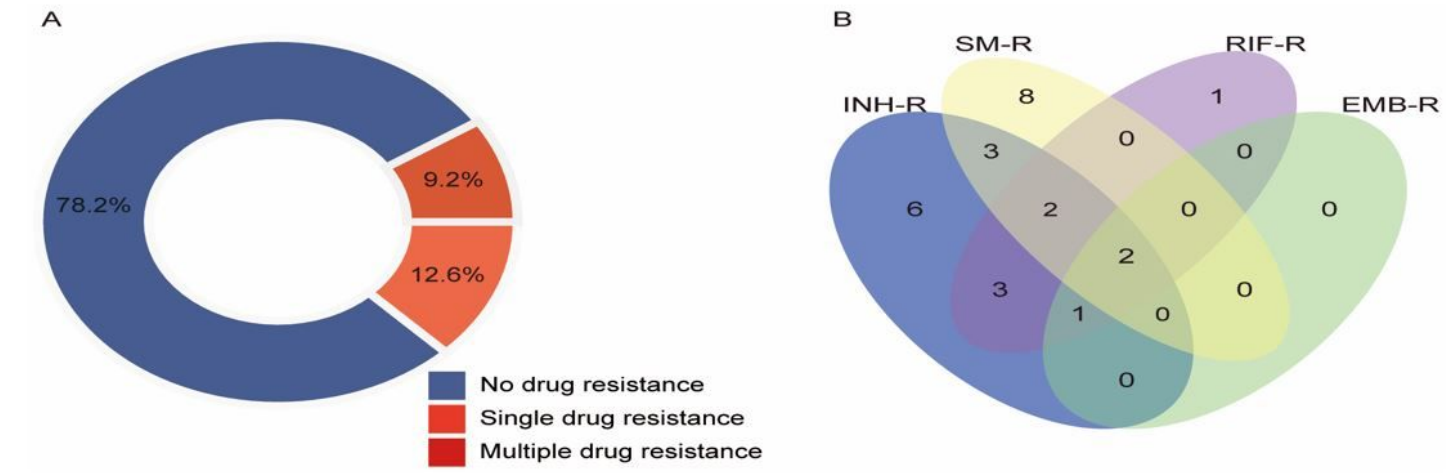



Figure 3

Drug sensitivity information for tuberculosis patients. A) Proportion with drug resistance; B) Venn diagram of drug resistance information. INH-R: isoniazid resistance; SM-R: streptomycin resistance; RIF-R: rifampin resistance; EMB-R: ethambutol resistance.

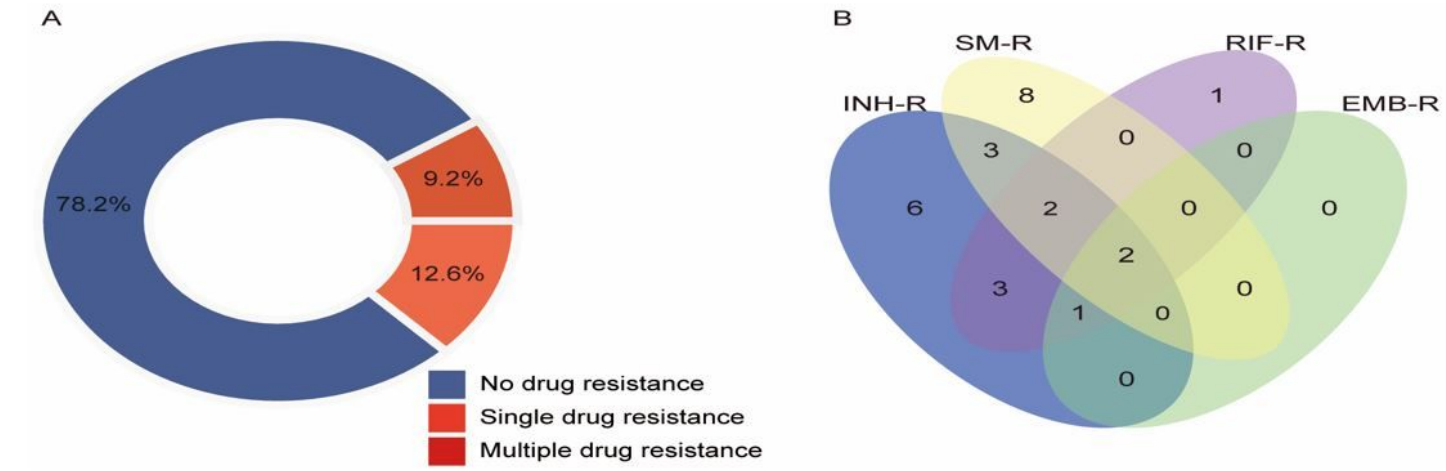



Figure 3

Drug sensitivity information for tuberculosis patients. A) Proportion with drug resistance; B) Venn diagram of drug resistance information. INH-R: isoniazid resistance; SM-R: streptomycin resistance; RIF-R: rifampin resistance; EMB-R: ethambutol resistance.

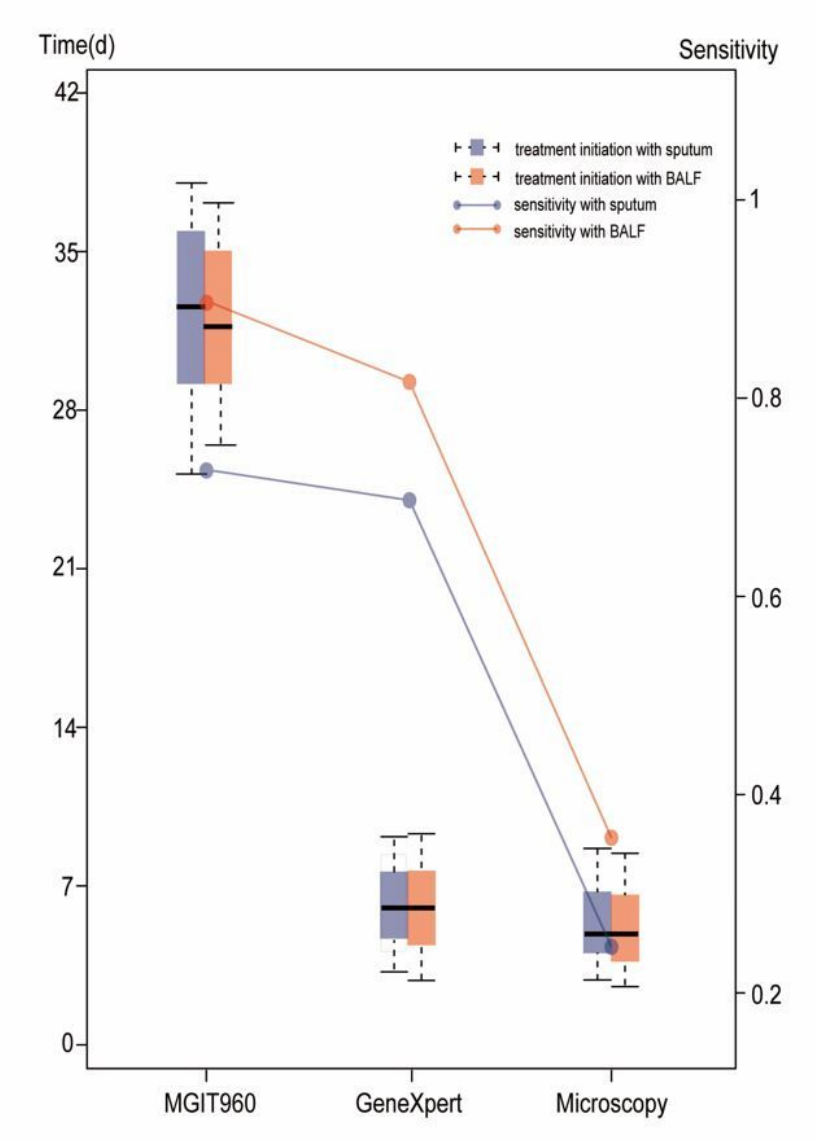
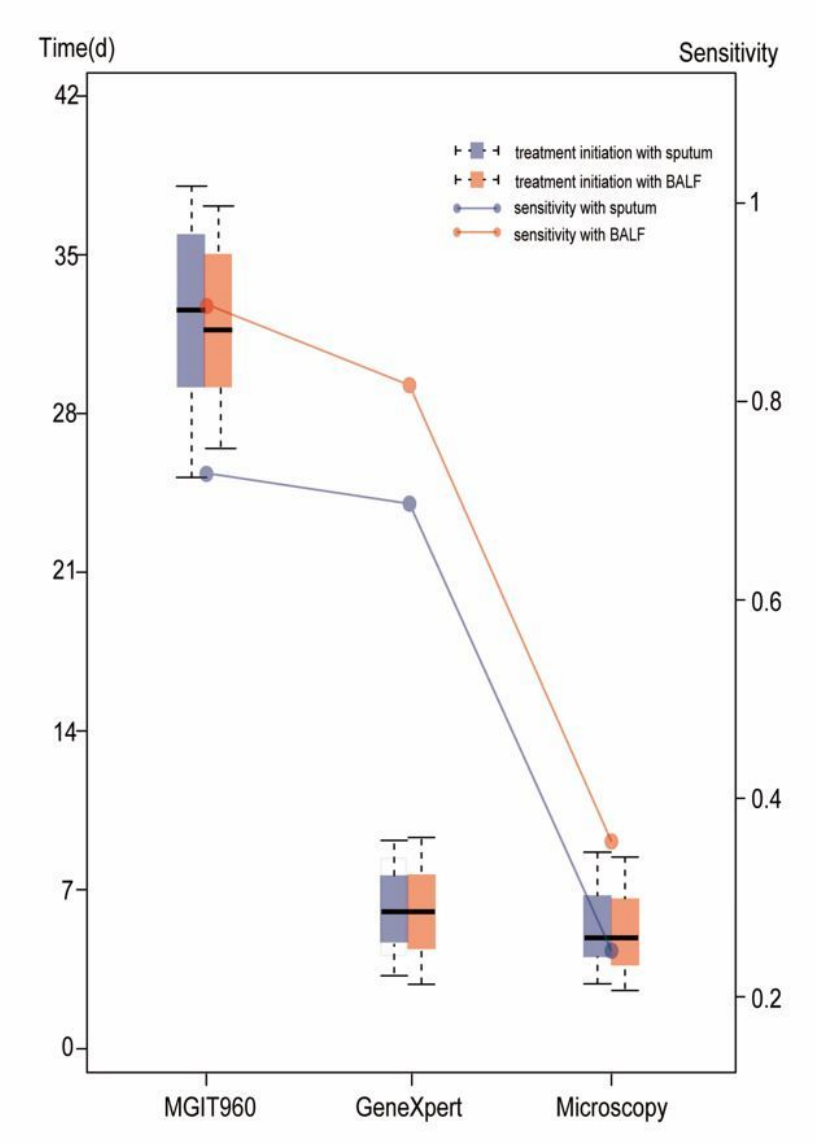



**Figure 4**

Treatment initiation of positive samples and sensitivities of the three methods with sputum or BALF.

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