Rapid Diagnosis Of Multidrug-Resistant Tuberculosis Impacts Expenditures Prior To Appropriate Treatment: A Performance And Diagnostic Cost Analysis

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Background: In this study, we aimed to describe the impact of the Genotype® MTBDRplus line probe assay (LPA) for multidrug-resistant tuberculosis (MDR-TB) on total costs in a high-burden setting in China. The second objective was to evaluate the performance of HAIN on smear-positive sputum and clinical isolates.

Methods: All definitive TB inpatients at the Shandong Provincial Chest Hospital between May 2012 and May 2017 were included in the study. Two sputum specimens were collected from each patient to conduct smear microscopy, conventional drug susceptibility testing (DST), and the HAIN test. Laboratory and cost data were collected from the electronic medical record system.

Results: A total of 1670 definitive TB patients were included in this study. Of these patients, 1307 (78.3%) had smear-positive/culture-positive tuberculosis, and the remaining 363 (21.7%) had smear-negative/culture-positive tuberculosis. The sensitivity and specificity of the HAIN test for RIF resistance was 94.8% (95% confidence interval [CI]: 91.9–97.6%) and 98.8% (95% CI: 98.3–99.4%), respectively. For INH resistance, the sensitivity and specificity was 89.5% (95% CI: 85.7–93.2%) and 95.6% (95% CI: 94.5–96.7%), respectively. The mean time for detection of MDR-TB in smear-negative cases was determined to be 32 days by the HAIN test, which was significantly shorter than that by conventional DST (56 days). Similarly, the mean time for detection of MDR-TB by the HAIN test was significantly shorter than that by conventional DST in smear-positive cases (3 versus 53 days). In addition, by utilizing the HAIN test, the total health care cost decreased by 71.0% for smear-positive cases and 25.9% for smear-negative cases.

Conclusion: In conclusion, our data demonstrate that the HAIN test is an accurate rapid test for detecting both RIF and INH resistance in TB patients. The use of the HAIN test can decrease health care costs and reduce the detection time for MDR-TB patients in China, despite the increased costs for laboratory testing.

Keywords: tuberculosis, HAIN, multidrug-resistance, performance, cost

Introduction

Tuberculosis (TB), caused by the Mycobacterium tuberculosis (MTB) complex, remains a serious global threat to public health.1,2 In 2017, there were an estimated 10 million new cases worldwide, and 1.5 million people died of TB.1 Most drug-susceptible TB patients can be cured with current drug regimens, however, only half of patients with multidrug-resistant TB (MDR-TB), defined as having...
resistance to at least isoniazid (INH) and rifampin (RIF), achieve culture conversion by the end of treatment. The poor outcomes of MDR-TB accelerate the transmission of this severe form of TB in the community. The extent and burden of MDR-TB varies significantly across countries and regions. More than half of the global burden of MDR-TB occurs in India, China, and the Russian Federation.

Although China more than halved its tuberculosis prevalence in past decades, the MDR-TB epidemic has become the most threatening obstacle for TB control and prevention. According to a recent nationwide drug-resistance survey, 5.7% of new cases and 26.7% of previously treated cases were affected by MDR-TB in this country. Of the 58,000 estimated MDR-TB cases in China, only a fraction of these patients are diagnosed due to a Please verify this addition is accurate, as this is the first time DST appears in the manuscript apart from the abstract. limited laboratory capacity to diagnose MDR-TB. To address this concern, great effort has been made to accelerate the improvement of the capability of drug susceptibility testing (DST) in prefecture-level laboratories.

The phenotypic DST is considered the gold standard for drug-resistant TB; however, it has limitations, which are inherently linked to the slow growth rate of tubercle bacilli and the underlying biosafety hazard. Recent progress in elucidating the molecular mechanism conferring drug resistance of MTB enables the use of molecular diagnostics for a faster diagnosis of MDR-TB. Despite having a promising sensitivity and specificity, the high cost of molecular diagnostics constitutes a major barrier to its clinical application. There is no doubt that the diagnostic delay of MDR-TB results in initial ineffective therapeutic regimens. Naturally, this questions the cost differences between improved molecular diagnostics and ineffective therapeutic regimens. Importantly, it would provide new insights to areas where molecular tools are not routinely used so as to advocate for the implementation of these diagnostics to accelerate progress towards TB elimination. While a large number of studies have reported on the accuracy of TB diagnostic tests, there are few studies that have focused on this issue. Therefore, the primary objective of the present study was to describe the impact of the Genotype® MTBDRplus line probe assay (LPA) of MDR-TB on the costs of a high-burden setting in China. We also aimed to evaluate the performance of HAIN on smear-positive sputum and clinical isolates.

**Methods**

**Ethics Statement**

This study was approved by the Ethics Committee of Shandong Provincial Chest Hospital. All patients signed a consent form prior to being included in this study.

**Setting**

All definitive TB inpatients at the Shandong Provincial Chest Hospital between May 2012 and May 2017 were included in this study. Shandong Provincial Chest Hospital is the provincial TB hospital in Shandong, also called Shandong Provincial Center for Tuberculosis Control and Prevention. This hospital is a tertiary hospital with 400 beds designated for tuberculosis. Hospitalization criteria included severe and complicated TB cases, and TB patients requested to be hospitalized. Smear microscopy, mycobacterial culture, phenotypic DST, and HAIN tests were performed routinely on specimens collected from inpatients. Definitive TB patients were those with clinical TB symptoms plus at least one sputum sample that was culture-positive for MTB. The following data were collected from the electronic medical record system: 1) date of sputum collection, 2) reporting dates of laboratory examinations, 3) results of laboratory examinations, 4) costs of laboratory examinations, and 5) costs of anti-TB regimens.

**Laboratory Method**

Two sputum specimens were collected from each patient. Direct smears from each sputum specimen were examined using auramine O staining for acid-fast bacilli following the national guidelines for TB laboratories in China. After smear examination, one specimen from each patient was digested with N-acetyl-L-cysteine and sodium hydroxide (NALC-NaOH) for 15 mins. Then, phosphate-buffered saline (PBS) solution was added to a total volume of 45 mL. After centrifugation for 15 mins at 3000 × g, the supernatant was discarded and the sediment was resuspended in 1.5 mL of PBS solution. Next, 0.2 mL of suspension was inoculated onto Löwenstein-Jensen (L-J) medium. The growth of bacteria colonies was recorded weekly. For smear-positive sputum specimen, the sputum was directly used to performed the MTBDRplus test according to the manufacturer’s instructions. For smear-negative sputum specimens, the corresponding positive culture was used as an alternative for the MTBDRplus test.
Positive cultures from specimens were firstly identified as the *M. tuberculosis* complex with the MPT64 antigen kit. Indirect drug-susceptibility testing with L-J medium was performed to determine the susceptibility of MTB isolates to RIF and INH, with tested drug concentrations of 40.0 mg/L for RIF and 0.2 mg/L for INH.\(^\text{15}\)

**Data Analysis**

The sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated to evaluate the performance of the Hain test compared to conventional phenotypic DST. Cohen’s kappa statistic was used to assess the strength of agreement between the HAIN test and the conventional method. Kappa coefficient values higher than 0.75 indicated excellent agreement. The Student’s \(t\)-test was used to compare the median length of time until MDR-TB detection between the two diagnostic algorithms. The first diagnostic algorithm only used conventional DST to diagnose MDR-TB, while the combination of conventional DST and the HAIN test was performed to diagnose MDR-TB in the second algorithm (Figure 1).

The interval was calculated as the number of days between the receipt date of the specimen samples and the reporting date of the results. Costs of conventional and molecular diagnostic procedures for the identification of pulmonary MDR-TB were analyzed using costs paid for different laboratory techniques as well as therapeutic anti-TB drug regimens. To obtain the cost of the empirical treatment, the estimated cost per day of the standard first-line anti-TB regimen was multiplied by the mean number of days required to diagnose MDR-TB. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). \(P\) values less than 0.05 were considered statistically significant.

**Results**

**Rifampin Resistance Detection By HAIN**

A total of 1670 definitive TB patients were included in this study between May 2012 and May 2017. Of these patients, 1307 (78.3%) had smear-positive/culture-positive tuberculosis, and the remaining 363 (21.7%) had smear-negative/culture-positive tuberculosis. The sensitivities and specificities of the HAIN test for RIF resistance are shown in Table 1. Overall, of the 229 patients with RIF-resistant TB diagnosed by DST, HAIN correctly identified 217 patients, indicating a sensitivity of 94.8% (95% confidence interval [CI]: 91.9–97.6%). In addition, of the 1441 patients with RIF-susceptible TB diagnosed by DST, 1424 were confirmed by HAIN, demonstrating a specificity of 98.8% (95% CI: 98.3–99.4%). The sensitivity and specificity for diagnosing RIF resistance for the smear-positive patients was 94.1% (95% CI: 90.6–97.5%) and 98.8% (95% CI: 98.1–99.4%), respectively. For smear-negative patients, their positive cultures were used for the HAIN test, and the sensitivity of the HAIN test was 97.7% (95% CI: 93.3–100.0%) for this population. Statistical analysis revealed that the results of two methods showed high consistency regardless of specimen types.

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**Figure 1** Diagnostic algorithms of MDR-TB. (A) The first diagnostic algorithm of MDR-TB with phenotypic DST. (B) The second diagnostic algorithm of MDR-TB with HAIN test and phenotypic DST.
Isoniazid Resistance Detection By HAIN
INH resistance results analyzed by conventional DST and HAIN had a coincidence rate of 94.7% (1581/1670, 95% CI: 93.6–95.7%). Out of the 257 patients with INH-resistant TB diagnosed by DST, 230 were confirmed by HAIN, indicating a sensitivity of 89.5% (95% CI: 85.7–93.2%). The overall specificity of the HAIN test for detecting INH susceptibility was 95.6% (95% CI: 94.5–96.7%). In addition, 179 smear-positive and 51 smear-negative cases were identified by the HAIN test, demonstrating sensitivities of 88.6% (95% CI: 84.2–93.0%) and 92.7% (95% CI: 85.9–99.6%), respectively (Table 2).

Multidrug Resistance Detection By HAIN
In comparison with conventional DST, the HAIN test demonstrated a sensitivity of 90.5% (95% CI: 86.2–94.8%) for MDR-TB. In addition, the sensitivity ranged from 89.5% (95% CI: 84.5–94.5%) for smear-positive patients to 94.4% (95% CI: 87.0–100.0%) for smear-negative patients. Kappa values for the various specimens were all more than 0.75, indicating that the results of two methods showed high consistency (Table 3).

Length Of Time Until Detection Of Multidrug-Resistant Tuberculosis
In total, 195 MDR-TB patients identified by conventional DST, the HAIN test, or both were included in our analysis. As summarized in Table 4, the mean length of time until detection of MTB with mycobacterial culture was 26 and 23 days in smear-negative and smear-positive specimens, respectively. For the detection of MDR-TB, the mean length of time elapsed in smear-negative cases was 32 days for the HAIN test, with an interquartile range (IQR) of 25–38 days, which was significantly shorter than that of conventional DST (56 days). Similarly, the mean length of time until detection of MDR-TB by the HAIN test was

Table 1 Performance Of HAIN Test For Detecting Rifampin Resistance

| Classification | HAIN | DST | Total | Sensitivity (%), 95% CI | Specificity (%), 95% CI | PPV (%), 95% CI | NPV (%), 95% CI | Kappa value |
|----------------|------|-----|-------|-------------------------|------------------------|----------------|----------------|-------------|
| Smear-positive | R    | 174 | 1188  | 94.1(90.6–97.5)          | 98.8(98.1–99.4)         | 92.6(88.8–96.3) | 99.0(98.4–99.6) | 0.92        |
|                | S    | 14  | 1199  |                         |                        |                |                |             |
|                | Total| 188 | 1307  |                         |                        |                |                |             |
| Smear-negative | R    | 43  | 46    | 97.7(93.3–100.0)         | 99.1(98.0–100.0)        | 93.5(86.3–100.0)| 99.7(99.1–100.0)| 0.95        |
|                | S    | 3   | 317   |                         |                        |                |                |             |
|                | Total| 46  | 363   |                         |                        |                |                |             |
| Total          | R    | 217 | 234   | 94.8(91.9–97.6)          | 98.8(98.3–99.4)         | 92.7(89.4–96.1) | 99.2(98.8–99.7) | 0.93        |
|                | S    | 12  | 1436  |                         |                        |                |                |             |
|                | Total| 229 | 1670  |                         |                        |                |                |             |

Abbreviations: DST, drug susceptibility test; R, resistant; S, sensitive; PPV, positive predictive value; NPV, negative predictive value.

Table 2 Performance Of HAIN Test For Detecting Isoniazid Resistance

| Classification | HAIN | DST | Total | Sensitivity (%), 95% CI | Specificity (%), 95% CI | PPV (%), 95% CI | NPV (%), 95% CI | Kappa value |
|----------------|------|-----|-------|-------------------------|------------------------|----------------|----------------|-------------|
| Smear-positive | R    | 179 | 225   | 88.6(84.2–93.0)          | 95.8(94.7–97.0)         | 79.6(74.3–84.8)| 97.9(97.0–98.7)| 0.81        |
|                | S    | 46  | 1082  |                         |                        |                |                |             |
|                | Total| 225 | 1307  |                         |                        |                |                |             |
| Smear-negative | R    | 51  | 67    | 92.7(85.9–99.6)          | 94.8(92.3–97.3)         | 76.1(65.9–86.3)| 98.6(97.3–100.0)| 0.98        |
|                | S    | 16  | 296   |                         |                        |                |                |             |
|                | Total| 67  | 363   |                         |                        |                |                |             |
| Total          | R    | 230 | 292   | 89.5(85.7–93.2)          | 95.6(94.5–96.7)         | 78.8(74.1–83.5)| 98.0(97.3–98.8)| 0.81        |
|                | S    | 62  | 1378  |                         |                        |                |                |             |
|                | Total| 292 | 1670  |                         |                        |                |                |             |

Abbreviations: DST, drug susceptibility test; R, resistant; S, sensitive; PPV, positive predictive value; NPV, negative predictive value.
significantly shorter than that of conventional DST for smear-positive cases (3 versus 53 days).

### Cost Analysis Of Diagnosis And Treatment Of MDR-TB

We further analyzed the costs of procedures for the diagnosis and treatment of MDR-TB patients through medical payments for these procedures in China. For the first analysis, only conventional DST was used to diagnose MDR-TB, and the cost for identifying MDR-TB was 50.72 USD. Considering the daily cost of empirical treatment, the total costs of empirical treatment prior to the final diagnosis were 419.03 USD and 396.58 USD for smear-negative and smear-positive cases, respectively. For the second analysis, the combination of conventional DST and the HAIN test was used for the diagnosis of MDR-TB. The unit cost was 108.70 USD, which was higher than that of the first algorithm. Due to the shorter turnaround time of molecular diagnostics, the costs of empirical treatment were 239.44 USD for smear-negative cases and 22.45 USD for smear-positive cases. As a consequence, the total cost was decreased by 71.0% for smear-positive cases and 25.9% for smear-negative cases (Table 5).

### Discussion

The MDR-TB epidemic remains the main challenge to TB elimination in China. Delayed diagnosis is associated with disease progression at the individual level and accelerates its transmission within the community. Molecular tools provide an alternative to diagnose drug-resistant TB.

### Table 3 Performance Of HAIN Test For Detecting Multidrug Resistance

| Classification | HAIN | DST | Total |
|----------------|------|-----|-------|
|                | R    | S   |       |
|                |      |     |       |
| Smear-positive | 128  | 12  | 140   |
|                | 15   | 112 | 1167  |
|                | 143  | 1164| 1307  |
| Smear-negative | 34   | 4   | 38    |
|                | 2    | 323 | 325   |
|                | 36   | 327 | 363   |
| Total          | 162  | 16  | 178   |
|                | 17   | 1475| 1492  |
|                | 179  | 1491| 1670  |

#### Abbreviations:
- DST, drug susceptibility test; R, resistant; S, sensitive; PPV, positive predictive value; NPV, negative predictive value.

### Table 4 Comparison Of Turnaround Time To Identify MDR-TB Cases With Conventional DST And HAIN Test

| Classification | No. Of Cases | Mycobacterial Culture Mean (IQR, Day) | Conventional DST Mean (IQR, Day) | HAIN Mean (IQR, Day) |
|----------------|--------------|---------------------------------------|---------------------------------|---------------------|
|                |              | Conventional DST                       |                                 |                     |
| Smear-negative case | 40 | 26(21–33) 23(19–30) | 56(51–63) 53(49–60) | 32(25–38) 3(2–4) |
| Smear-positive case | 155 |                                        |                                 |                     |

#### Notes:
P<0.01(Conventional DST vs. HAIN for smear-negative case); P<0.01(Conventional DST vs. HAIN for smear-positive case).

#### Abbreviation:
- IQR, inter-quartile range.

### Table 5 Costs Of Algorithms For The Diagnosis And Treatment Of MDR-TB Patients Enrolled In This Study

| Algorithm | Classification             | Cost Of Diagnosis (USD) | Cost Of Empirical Treatment (USD) | Total (USD) |
|-----------|---------------------------|-------------------------|----------------------------------|-------------|
| Conventional DST | Smear-negative case | 50.72 | 419.03 | 469.75 |
|           | Smear-positive case | 50.72 | 396.58 | 447.30 |
| Conventional DST+HAIN | Smear-negative case | 108.70 | 239.44 | 348.14 |
|           | Smear-positive case | 108.70 | 22.45  | 131.14 |

#### Abbreviation:
- DST, drug susceptibility test.
In this study, our data demonstrate that the HAIN test shows excellent ability to detect RIF- and INH-resistant TB in China. The sensitivities observed in the present study (94.8% for RIF resistance and 89.5% for INH resistance) correspond with results reported in several recent studies. 

Remarkably, the mean length of time for detection of MTB from smear-positive and smear-negative specimens (23 versus 26 days). By comparison with MGIT results from different regions, evaluation for its diagnostic accuracy is essential for regional retooling and upscaling.

Another interesting finding of our study is that the mean length of time until detection of MTB from smear-positive specimens was slightly shorter than that from smear-negative specimens (23 versus 26 days). Similar findings were reported by Pfyffer and colleagues (20 versus 27 days for smear-positive and smear-negative specimens, respectively). 

Remarkably, the mean length of time for detection of MTB from smear-positive specimens by BACTECTM MGIT™ 960 was 10 days, which was half of that observed from smear-negative specimens (20 days). By comparison with MGIT™ results from previous studies, we speculate that the continuous monitoring of mycobacteria growth in the MGIT tube is the major contributor to the significant decrease in the length of time for detection of MTB for smear-positive specimens.

The speed in which drug-resistant tubercle bacilli are detected is the most obvious advantage of the HAIN test, allowing for the subsequent effective treatment of drug-resistant TB. 

In conclusion, our data demonstrate that the HAIN test is an accurate rapid test for detecting both RIF and INH resistance in TB patients. The use of the HAIN test can decrease health care costs and reduce the detection time for MDR-TB patients in China, despite the increased costs for laboratory testing. Further study will be carried out to determine the most optimal cost-effective diagnostic method in high-burden settings.
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Disclosure
The authors report no conflicts of interest in this work.

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