Rapid indication of multidrug-resistant tuberculosis from liquid cultures using \textit{FASTPlaqueTB-RIF}™, a manual phage-based test

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\textbf{SUMMARY}

\textbf{SETTING:} A Mycobacteriology Reference Laboratory in Johannesburg, South Africa.

\textbf{OBJECTIVE:} To determine the ability of \textit{FASTPlaqueTB-RIF}™, a rapid bacteriophage-based test, to correctly identify rifampicin susceptibility in clinical strains of \textit{Mycobacterium tuberculosis} after growth in the Bactec 460 semi-automated liquid culture system.

\textbf{DESIGN:} A comparative study of \textit{FASTPlaqueTB-RIF}™ and conventional drug susceptibility methods, with selection bias to include sufficient rifampicin-resistant strains.

\textbf{RESULTS:} Rifampicin susceptibility results were available for 133 strains of \textit{M. tuberculosis}. Using the Bactec 460 method, 42 of these strains were rifampicin-resistant and 91 strains were rifampicin-susceptible. A further one strain was found to have a mutation in the \textit{rpoB} gene which was strongly indicative of rifampicin resistance. Sensitivity, specificity and overall accuracy for the \textit{FASTPlaqueTB-RIF}™ were respectively 100%, 98.8% and 99.2% for detection of rifampicin resistance; 95.3% (41/43) of the rifampicin-resistant strains were also resistant to isoniazid (multidrug-resistant).

\textbf{CONCLUSION:} \textit{FASTPlaqueTB-RIF}™ offers performance comparable to the Bactec 460 method, with results available within 2 days and without the need for specialised equipment. This makes \textit{FASTPlaqueTB-RIF}™ a rapid test for rifampicin resistance suitable for widespread application. A combination of the \textit{FASTPlaqueTB-RIF}™ test with semi-automated liquid culture reduces the time required to report susceptibility results, enabling rapid and appropriate management of patients with MDR-TB. Rifampicin resistance was a good predictor of multidrug resistance in this population.

\textbf{KEY WORDS:} rifampicin; mycobacteriophage; drug susceptibility test; tuberculosis; multidrug resistance

\textbf{SUSCEPTIBILITY to rifampicin is of great importance in predicting the successful response of patients to standardised short-course chemotherapy for tuberculosis. Standard rifampicin-containing regimens will be effective even in patients infected with \textit{Mycobacterium tuberculosis} resistant to isoniazid and streptomycin. However, when resistance to rifampicin is present, the likelihood of successful treatment outcome is greatly reduced.1,2}

Rifampicin resistance has been identified as a good predictor of multidrug-resistant tuberculosis (MDR-TB) in many parts of the world.3,4 A worldwide problem,3 MDR-TB is commonly used to refer to resistance to at least the two most effective anti-tuberculosis drugs, isoniazid and rifampicin. Patients who are unsuccessfully treated due to drug resistance but who remain alive and infectious are a serious public health concern. Drug-resistant strains of \textit{M. tuberculosis} can be transmitted at approximately the same rate as drug-susceptible strains; such infections can lead to cases of primary MDR-TB.5

Strains of TB who do not receive appropriate (second-line) drugs are likely to remain infectious for longer periods and may therefore infect more contacts than patients with drug-susceptible disease.5

Reported outbreaks of MDR-TB have demonstrated high case fatality rates and rapid disease progression. In most cases these outbreaks have involved patients who were also infected with the human immunodeficiency virus (HIV). Patients with the acquired immune-deficiency syndrome (AIDS) and MDR-TB have a markedly poorer prognosis than HIV-negative patients with MDR-TB, with survivals of respectively 1.5 and 14.8 months.6

Semi-automated and automated culture systems, such as Bactec 460 (Becton Dickinson), MGIT (Becton Dickinson), and MB Bac/T (Organon Teknika Corporation) have been introduced. They are widely used in industrialised countries, and in reference laboratories in some developing countries. Their use has significantly reduced the time required to culture \textit{M. tuberculosis} compared with conventional manual
culture methods. Early detection of MDR-TB can improve treatment outcome for the individual patient and reduce the opportunity for spread of infection. As conventional susceptibility testing takes 3–4 weeks from a positive culture, there can be a significant delay in patients receiving appropriate treatment. Automated or semi-automated liquid culture-based systems take approximately 1 week to report susceptibility results from a positive culture.8

The FASTPlaque™ Rifampicin Susceptibility Test (Biotec Laboratories Ltd., Ipswich, UK) is a manual test for the rapid determination of rifampicin susceptibility of M. tuberculosis cultures within 48 hours.9 This test utilises specific mycobacteriophage (Actiphage™) to reflect the presence of viable M. tuberculosis.10–15 Mycobacteriophage are added to a clinical specimen and allowed to incubate for one hour to allow phage infection of target TB bacilli. After the incubation period, a virucidal solution (Virusol™) is added which destroys all phage that have not infected the tubercle bacilli. The remaining phage replicate in the infected bacilli until new progeny phage are released as the cells lyse. The progeny phage are amplified by the addition of a non-pathogenic rapid-growing mycobacterial host, M. smegmatis (Sensor™ cells), which is also able to support phage replication. Phage can be visualised as clear areas (plaques) in a lawn of Sensor™ cell growth. The number of plaques produced from a sample incubated in the presence of rifampicin-free control is compared with the number of plaques produced from a random rifampicin-containing sample. The absence of plaques in the rifampicin-containing sample indicates that the strain is sensitive to rifampicin (i.e., the tubercle bacilli are no longer viable and cannot support phage replication). The presence of plaques in the rifampicin-containing sample indicates that viable tubercle bacilli have survived (and can support phage replication) and that the strain is resistant to rifampicin.

This study compares the ability of the FASTPlaque™ test to correctly identify rifampicin susceptibility of strains of M. tuberculosis cultured in the Bactec 460 semi-automated system. Comparisons were performed using the Bactec 460 radiometric susceptibility test method.

MATERIALS AND METHODS

Cultures
Bactec 460 cultures were prepared from 140 clinical specimens received for routine diagnosis of tuberculosis and drug susceptibility testing by the Tuberculosis Laboratory, South African Institute for Medical Research, Johannesburg, South Africa.

Primary isolation of M. tuberculosis from clinical specimens was performed using a modified Petroff’s method (4% sodium hydroxide), and Bactec 460 semi-automated liquid culture. Positive cultures were confirmed as M. tuberculosis using an in-house polymerase chain reaction (PCR) method (MPB64) and Ziehl-Neelsen staining. Conventional rifampicin and isoniazid susceptibility testing was performed on positive Bactec 12B cultures using the Bactec drug susceptibility test (non-weekend method).16 The final concentrations of rifampicin and isoniazid were respectively 2.0 µg/ml and 1.0 µg/ml.

Positive M. tuberculosis cultures were mostly randomly selected for FASTPlaque™ testing. In addition, some known rifampicin-resistant strains were selected based on Bactec 460 susceptibility results to allow testing of a sufficient number of rifampicin-resistant isolates by the FASTPlaque™ test. However, the FASTPlaque™ testing was performed without knowledge of the Bactec 460 susceptibility result.

The clinical performance of FASTPlaque™ was evaluated by comparing the results with those of Bactec 460. The time taken for culture and susceptibility testing using the FASTPlaque™ test in combination with the Bactec 460 culture method was determined.

Preparation of M. tuberculosis test suspensions for FASTPlaque™ testing
The components of the FASTPlaque™ test were reconstituted according to the manufacturer’s instructions and used on the day of reconstitution. Fresh cultures (up to 1 week old) were used to prepare the inocula for the FASTPlaque™ testing. Test suspensions were prepared by adding 0.2 ml of the Bactec 460 culture (growth index [GI] >800) to 2 ml of FASTPlaque™ (FPTB) Medium Plus (supplemented Middlebrook 7H9-based medium).

FASTPlaque™ test procedure
The FASTPlaque™ test procedure was performed in a Class 2 bio-safety cabinet. Positive and negative assay controls were prepared and tested according to the manufacturer’s instructions.17

One rifampicin tablet (200 µg) was dissolved in 20 ml FPTB Medium Plus, and thoroughly mixed to ensure dissolution; 0.5 ml of the rifampicin solution was dispensed into a reaction vessel (RIF+), 0.5 ml of FPTB Medium Plus was dispensed into another reaction vessel (RIF−), and 0.5 ml of the M. tuberculosis test suspension was added to both the RIF− and RIF+ reaction vessels. The final concentration of rifampicin was 5 µg/ml. The vessels were gently shaken to mix and incubated for 24 hours in a static incubator at 37°C.

The vessels were removed from the incubator, 100 µl of Actiphage™ was added and the contents were mixed. The samples were incubated at 37°C for 90 minutes without further mixing. One hundred micro-
litres of Virusol™ solution was added to the sample. The contents of the tube were mixed well by inverting and rolling the reaction vessel to ensure that the Virusol™ came into contact with all the interior surfaces of the vessel, to allow efficient inactivation of all exogenous phage. The samples were allowed to stand at room temperature for 5 minutes. Five millilitres of FPTB Medium Plus were added to the vessel and mixed by inverting the reaction vessel once, and then 1 ml of Sensor™ cells were added to each reaction vessel. Five millilitres of molten FPTB Agar (Middlebrook 7H9-based agar blend) [at 50–55°C] was added to an empty sterile disposable plastic Petri dish (90 mm), then the entire contents of the reaction vessel were added. The lid of the Petri dish was closed and the contents were mixed well by swirling in both directions, ensuring that the entire bottom surface of the plate was covered. Care was taken to avoid agar splashing the lid of the Petri dish. The plates were allowed to set at room temperature. Once set, the plates were inverted and incubated at 37°C. After overnight (approximately 18–24 hours) incubation, the plates were removed and examined. The number of plaques on each plate was recorded.

Results were deemed to be valid if 100 plaques or more were observed on the RIF™ plates, the positive control had 20–300 plaques and the negative control had 10 plaques or fewer.

A strain was considered to be susceptible to rifampicin if 10 plaques or fewer resulted from the rifampicin-containing sample (RIF+). This equated with the negative control cut-off value of 10 plaques, and demonstrated that no or very few viable mycobacteria were present.

A strain was considered to be rifampicin-resistant if 50 plaques or more resulted from the rifampicin-containing sample (RIF+). This was indicative of viable TB bacilli surviving the rifampicin treatment.

An intermediate result was recorded when any strain produced between 11 and 49 plaques on the RIF+ plate. Intermediate results may indicate emerging rifampicin resistance, and a sample giving consistent intermediate results should therefore be submitted for conventional susceptibility testing to confirm low-grade resistance.

Discrepant results

FASTPlaqueTB-RIF™ and Bactec 460 susceptibility testing was repeated on isolates giving discrepant results between the two methods. Mutation analysis of the rpoB gene was performed on an isolate in which a discrepancy between the Bactec 460 rifampicin susceptibility test and the FASTPlaqueTB-RIF™ result was still observed after repeat testing.

**RESULTS**

One hundred and forty strains of *M. tuberculosi*s isolated from clinical specimens (133 sputum specimens, two cerebrospinal fluid, two gastric washes, one pus, one lymph node, one Bactec 13A culture) were used to compare the performance of the FASTPlaqueTB-RIF™ test with the Bactec 460 method for determination of rifampicin resistance.

The results of seven specimens were not available for comparison for the following reasons: one susceptible strain gave no plaques on FASTPlaqueTB-RIF™ plates after initial testing. This strain was shown to be FASTPlaqueTB-RIF™ susceptible after repeat testing. Four other specimens were mixed *M. tuberculosis* and non-tuberculous mycobacterial cultures, and hence Bactec 460 susceptibility results were unavailable. Two other specimens were contaminated on either Bactec culture and/or FASTPlaqueTB-RIF™ plates. The results of 133 specimens are summarised in Table 1.

One isolate consistently gave discrepant results between the FASTPlaqueTB-RIF™ test and the Bactec 460 method after repeated testing by both methods. Mutation analysis of this isolate revealed a mutation at codon 533, proposed to be associated with low-grade rifampicin resistance. A subsequent specimen from this patient was considered possibly to be an emerging rifampicin-resistant strain due to a slowly declining GI reading in the drug-containing vial of the Bactec 460 system. This isolate was therefore considered to be rifampicin-resistant. Repeat testing of the second discrepant isolate led to concordance of the FASTPlaqueTB-RIF™ result with the Bactec 460 method. This result was, however, considered to be discordant based on the initial result of the FASTPlaqueTB-RIF™ test for the purposes of the analysis. Resolved data are shown in Table 2.

| Table 1 Comparison of FASTPlaqueTB-RIF™ with Bactec 460 rifampicin susceptibility test results |
|-----------------------------------------------|----------------|----------------|
| FASTPlaqueTB-RIF                              | Susceptible | Resistant | Total |
| Susceptible                                  | 89          | 0         | 89    |
| Resistant                                    | 2*          | 42        | 44    |
| Intermediate                                 | 0           | 0         | 0     |
| Total                                        | 91          | 42        | 133   |

* One of these isolates was found to be FASTPlaqueTB-RIF™-susceptible on repeat testing. The second isolate contained an rpoB mutation at codon 533, suggesting low-grade resistance. Clinical history and Bactec growth index readings for this isolate also indicate emerging rifampicin resistance.

| Table 2 Comparison of FASTPlaqueTB-RIF™ with rifampicin susceptibility test results (Bactec 460 method and resolution of discrepant result) |
|-----------------------------------------------|----------------|----------------|
| FASTPlaqueTB-RIF                              | Rifampicin susceptibility result |
| SUSCEPTIBLE                                  | 89             | 0              | 89 |
| RESISTANT                                    | 1              | 43             | 44 |
| INTERMEDIATE                                 | 0              | 0              | 0  |
| TOTAL                                        | 90             | 43             | 133|
The sensitivity, specificity and overall accuracy of FASTPlaque™ TB-RIF™ in determining rifampicin susceptibility are shown in Table 3. Out of the 43 (95.3%) rifampicin-resistant strains, 41 were multidrug-resistant (resistant to at least rifampicin and isoniazid).

Specimens took 13.6 ± 5.3 days (mean ± standard deviation) to become positive on the Bactec 460 culture system. A Bactec GI of 20 or more was considered positive. Identification of the presence of M. tuberculosis complex in the Bactec 460 cultures was performed once the GI of the cultures had reached 300 or more (3.5 ± 2.0 days). Susceptibility testing by the Bactec method was performed at a GI of 500 or more. This was performed on a weekly basis (an additional 1–7 days following confirmation of M. tuberculosis). All the cultures had a GI of 800 or more at the time of testing and did not require further incubation to perform the FASTPlaque™ TB-RIF™ test.

Results of the Bactec 460 susceptibility test were available in 6.0 ± 1.3 days using the non-weekend schedule. FASTPlaque™ TB-RIF™ results were available within 2 days.

**DISCUSSION**

The FASTPlaque™ TB-RIF™ test showed excellent correlation with the Bactec 460 method in determination of rifampicin susceptibility. In addition, FASTPlaque™ TB-RIF™ identified a rifampicin-resistant strain that was determined to be susceptible by the Bactec 460 method. This strain was found to have a mutation at rpoB 533. Although the most common site of mutation leading to rifampicin resistance is at rpoB331, mutation at rpoB533 was found in 2% (1/41) strains in a recent study. Although there was no phenotypic evidence of resistance, the authors proposed that this mutation may confer low-grade rifampicin resistance. In this study the clinical history of the patient and subsequent Bactec 460 susceptibility data suggested rifampicin resistance in the isolate with rpoB533 mutation.

The performance parameters of the FASTPlaque™ TB-RIF™ test were 100%, 98.8% and 99.2% for sensitivity, specificity and overall accuracy, respectively (resolved data). Results of the FASTPlaque™ TB-RIF™ test were available within 2 days. Cultures used in this study had obtained a GI of more than 800 prior to testing by the Bactec 460 method, due to the processing schedule employed by the laboratory, and therefore no additional incubation was required prior to testing by the FASTPlaque™ TB-RIF™ test. Subsequent work has shown that cultures with a GI of 500 or more are suitable for FASTPlaque™ TB-RIF™ testing (0.5 ml of culture is diluted into 2 ml of FPTB Medium Plus), allowing earlier testing (unpublished data). It may be possible to test Bactec cultures with a GI of less than 500 by the FASTPlaque™ TB-RIF™ test, but this has not yet been evaluated.

This study demonstrates that the performance of FASTPlaque™ TB-RIF™ correlates well with the Bactec 460 susceptibility test, a well-established method. Results of the FASTPlaque™ TB-RIF™ test are available within 48 hours from M. tuberculosis cultures. Results from this study are very similar to those of a previous study in which FASTPlaque™ TB-RIF™ testing was performed from solid cultures (Löwenstein-Jensen or Middlebrook 7H11 media). Results of the FASTPlaque™ TB-RIF™ test were available approximately 4–6 days earlier than Bactec 460 results. This benefit may not be as significant in terms of patient management as when a laboratory utilises a conventional culture-based system that takes 3–4 weeks for susceptibility results. However, in some cases a more rapid result may positively impact on patient care and/or infection control procedures.

This test offers the potential for rapid indication of M. tuberculosis strains likely to be multidrug-resistant, thus aiding patient treatment and reducing spread of multidrug-resistant disease. In this study, 95.3% (41/43) of the rifampicin-resistant strains were multidrug-resistant. This is in agreement with other data reported in the literature showing that rifampicin resistance is often a good marker for multidrug resistance. Overall approximately 15% of strains tested in this laboratory were resistant to rifampicin, although this is unlikely to be representative of resistance in the general population since the laboratory is a reference centre for drug susceptibility testing. A review of all rifampicin-resistant strains tested in this laboratory over a 6-month period from October 2000 to March 2001 reported that 91.9% (487/530) of rifampicin-resistant strains were multidrug-resistant, 7.5% (40/530) were rifampicin mono-resistant and 0.6% (3/530) had other resistance profiles. Whilst a rapid indication of multidrug resistance can be a valuable aid in patient management, selection of individualised treatment regimens for patients with multidrug-resistant disease would require further susceptibility testing with a range of drugs.

No specialised equipment is required to perform the FASTPlaque™ TB-RIF™ test, giving the opportunity for its widespread application for rapid susceptibility testing in laboratories using either solid or liquid culture systems. The lack of a requirement for any dedicated equipment is of particular benefit for laboratories that use conventional manual culturing

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<th>Table 3</th>
<th>Sensitivity, specificity and overall accuracy of FASTPlaque™ TB-RIF™ in determining rifampicin susceptibility</th>
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<td>Sensitivity*</td>
<td>Specificity†</td>
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<td>100% (43/43)</td>
<td>98.8% (89/90)</td>
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* Sensitivity is the ability to detect true resistance. † Specificity is the ability to detect true susceptibility. ‡ Overall accuracy is the number of correct results over the total number of results expressed as a percentage.
methods. Labour time to perform the test is relatively short and requires only simple pipetting steps using standardised reagents, which are provided as part of the kit. Only basic consumable items, such as Petri dishes and pipettes, are needed to perform the test. The test is manual and results are simple to interpret, whereas the Bactec 460 susceptibility test method is semi-automated and requires repeated readings over several days to calculate susceptibility results. Whilst the semi-automated nature of the Bactec 460 method may be advantageous in high volume laboratories, the FASTPlaque™ method may be more applicable to low to medium volume laboratories and may require less hands-on time. The cost of reagents for Bactec 460 is usually linked to equipment leasing arrangements, depending on the number of tests performed. This may make the Bactec system less cost-effective than the FASTPlaque™ test for low to medium volume laboratories.

The cost of the Bactec 460 susceptibility test depends on the number of drugs tested simultaneously. In South Africa, as in other developing countries, initial susceptibility to two drugs only (rifampicin and isoniazid) may be performed for economic reasons. Testing of additional drugs, such as streptomycin and ethambutol, may be carried out depending on the initial susceptibility results. This can lead to a higher cost per drug tested and reagent wastage, since the drugs provided for the Bactec method are not available individually. The cost of radioactive disposal for the Bactec 460 method can also be a significant cost for many laboratories. In this situation, FASTPlaque™ may be a cost-effective test to rapidly indicate those patients likely to be multidrug-resistant, and have a positive impact on their treatment and on reduction of transmission of the disease to health care workers and the community.

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The FASTPlaque™ kits used in this study were supplied free of charge by Biotec Laboratories Ltd., Ipswich, UK.

References

**CADRE :** Laboratoire de référence en mycobactériologie à Johannesburg, Afrique du Sud.

**OBJECTIF :** Déterminer la capacité d’un test rapide basé sur les bactériophages, le FASTPlaqueTB-RIF™, pour l’identification correcte de la sensibilité à la rifampicine sur des souches cliniques de Mycobacterium tuberculosis après développement dans le milieu de culture liquide du système semi-automatique Bactec 460.

**SCHEMA :** Etude comparative du test FASTPlaqueTB-RIF™ et des méthodes conventionnelles de détermination de la sensibilité aux médicaments avec un biais de sélection visant à introduire un nombre suffisant de souches résistantes à la rifampicine.

**RÉSULTATS :** Les résultats de sensibilité à la rifampicine ont été disponibles pour 133 souches de *M. tuberculosis*. Avec la méthode Bactec 460, on trouve 42 souches résistantes à la rifampicine et 91 souches sensibles. Une autre souche s’avère avoir subi une mutation du gène *rpoB* qui était puissamment suggestive d’une résistance à la rifampicine. La sensibilité, la spécificité et la précision globale du test FASTPlaqueTB-RIF™ ont été respectivement de 100%, 98,8% et 99,2% pour la détection de la résistance à la rifampicine. On a trouvé aussi une résistance à l’isoniazide chez 95,3 % (41/43) des souches résistantes à la rifampicine (multirésistance).

**CONCLUSION :** Le test FASTPlaqueTB-RIF™ montre des performances comparables à la méthode Bactec 460 mais en fournissant des résultats dans les 2 jours sans nécessiter un équipement spécialisé. De ce fait, le test FASTPlaqueTB-RIF™ est à considérer comme un test rapide de résistance à la rifampicine adéquat pour une application très étendue. Une combinaison du test FASTPlaqueTB-RIF™ avec des cultures semi-automatiques en milieu liquide réduit le temps nécessaire à l’obtention de résultats de sensibilité, ce qui permet une prise en charge rapide et appropriée des patients atteints de tuberculose multirésistante. Dans cette population, la résistance à la rifampicine s’est avérée dans cette population un bon prédicteur de la multirésistance.

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**MARCO DE REFERENCIA :** Un Laboratorio de Referencia de Micobacteriología en Johannesburg, Sudáfrica.

**OBJETIVO :** Determinar la capacidad de un test rápido basado en los bacteriófagos FASTPlaqueTB-RIF™ para la identificación correcta de la sensibilidad a la rifampicina en cepas clínicas de Mycobacterium tuberculosis después de crecimiento en el medio de cultivo líquido del sistema semiautomático Bactec 460.

**MÉTODO :** Estudio que compara el test FASTPlaqueTB-RIF™ y los métodos convencionales de determinación de la sensibilidad a los medicamentos, con un sesgo de selección para incluir suficientes cepas resistentes a la rifampicina.

**RESULTADOS :** Se pudo disponer de resultados de sensibilidad a la rifampicina para 133 cepas de *M. tuberculosis*. Utilizando el método Bactec 460, 42 de estas cepas eran resistentes a la rifampicina y 91 eran sensibles a este medicamento. Otra cepa reveló una mutación del gen *rpoB*, el que es fuertemente indicativo de una resistencia a la rifampicina. La sensibilidad, especificidad y precisión global para el test FASTPlaqueTB-RIF™ fueron de 100%, 98,8% y 99,2% para la detección de la resistencia a la rifampicina. El 95,3% (41/43) de las cepas resistentes la rifampicina lo eran también a la isoniazida (multirresistencia).

**CONCLUSIÓN :** El test FASTPlaqueTB-RIF™ ofrece un rendimiento comparable al del método Bactec460, con disponibilidad de resultados en dos días, sin necesidad de equipo especializado. Esto hace considerar a FASTPlaqueTB-RIF™ como un test rápido de la resistencia a la rifampicina, aplicable ampliamente. Una combinación del test FASTPlaqueTB-RIF™ con los cultivos semiautomáticos en medio líquido reduce el tiempo requerido para el informe de los resultados de sensibilidad, permitiendo un manejo rápido y adecuado de los pacientes con tuberculosis multirresistente. La resistencia a la rifampicina se mostró como un buen predictor de la multirresistencia, en esta población.