MDR/XDR-TB Colour Test for drug susceptibility testing of *Mycobacterium tuberculosis*, Northwest Ethiopia

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Highlight review
- Colour test was rapid and simple, and used for DST.
- Colour test had high sensitivity and specificity for RIF, MDR-TB and CFX resistance detection.
- Colour test had low sensitivity and high specificity for INH resistance detection.

Abstract

Background: Appropriate-technology tests are needed for *Mycobacterium tuberculosis* drug-susceptibility testing (DST) in resource-constrained settings. We evaluated the MDR/XDR-TB colour plate thin-layer agar test (TB-CX) for *M. tuberculosis* DST by directly testing sputum at University of Gondar Hospital.

Methods: Sputum samples were each divided into 2 aliquots. One aliquot was mixed with disinfectant and applied directly to the TB-CX quadrant petri-plate containing culture medium with and without isoniazid, rifampicin or ciprofloxacin. Concurrently, the other aliquot was decontaminated with sodium hydroxide, centrifuged and cultured on Lowenstein-Jensen media, then the stored *M. tuberculosis* isolates were sub-cultured in BACTEC™ Mycobacteria Growth Indicator Tube™ (MGIT) 960 for reference DST.

Results: TB-CX test yielded DST results for 94% (123/131) of positive samples. For paired DST results, median days from sputum processing to DST was 12 for TB-CX versus 35 for LJ-MGIT (P<0.001). Compared with LJ-MGIT for isoniazid, rifampicin and MDR-TB, TB-CX test had: 59%, 96% and 95% sensitivity; 96%, 94% and 98% specificity; and 85%, 94% and 98% agreement, respectively. All ciprofloxacin DST results were susceptible by both methods.

Conclusion: The TB-CX was simple and rapid for *M. tuberculosis* DST. Discordant DST results may have resulted from sub-optimal storage and different isoniazid concentrations used in TB-CX versus the reference standard test.

Keywords: Colour test, drug susceptibility testing, drug resistant, thin layer agar, tuberculosis

Background
The emergency of multidrug-resistant tuberculosis (MDR-TB), and pre-extensive (Pre-XDR TB) and extensively drug-resistant tuberculosis (XDR-TB), together with TB and HIV co-infection, necessitate appropriate-technology, affordable techniques for rapid detection and DST for *Mycobacterium tuberculosis* (World health organization, 2018), which may reduce morbidity, mortality, transmission and drug resistance amplification (Raviglione M, 2006, Minion J et al., 2010, Jeon D, 2015). Ethiopia is one of the triple burden countries with frequent TB, MDR TB and TB-HIV co-infected patients (World health organization, 2018).

The World Health Organization (WHO) approves the GeneXpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) to detect rifampicin (RIF) resistance directly from specimens, and line-probe assays (LPA) such as GenoType® MTBDRplus (Hain LifeSciences, Nehren, Germany) to improve MDR-TB detection (World Health Organization, 2008, World Health Organization, 2012). In addition, GenoType® MTBDRsl assay (Hain LifeSciences) is available for the rapid detection of second-line TB drug resistance but is not routinely performed for patients in Ethiopia (World Health Organization, 2008, World Health Organization, 2013).

Conventional *M. tuberculosis* DST using solid medium such as Löwenstein-Jensen (LJ) is slow, whereas liquid medium based methods such as Mycobacteria Growth Indicator Tube™ 960 system (BD Diagnostics, Sparks, USA) (MGIT) can provide first and second-line DST results approximately 10 days after *M. tuberculosis* is isolated in sufficient concentrations for indirect DST but prohibitively expensive in resource-constrained settings (Martin A et al., 2009).

Thin-layer agar (TLA) has been in use for *M. tuberculosis* colony and micro-colony detection for many years (Welch DF et al., 1993, Mejia GI et al., 1999, Satti L et al., 2010, Shibabawa A et al., 2019). The MDR/XDR-TB Colour Test (TB-CX) is a non-commercial, in-house thin-layer agar technique in which sputum mixed with disinfectant without centrifugation or other processing (or sub-cultured *M. tuberculosis* isolates) are inoculated onto selective TLA containing STC redox indicator (2, 3 diphenyl-5-(2-thienyl) tetrazolium chloride) that causes a colour change in the media when bacteria grow, making positive results apparent by naked-eye examination (Lee S et al., 2006, Shibabawa A et al., 2019). Four TB-CX petri-plate quadrants are inoculated concurrently to test for TB and also provide concurrent DST (Robledo J et al., 2008, Tovar MA et al., 2010, IFHAD, 2011, Toit K et al., 2012, Zhang A et al., 2018, Mekonnen B et al., 2019, Shibabawa A et al., 2019).
The colour test assessed drug resistance of isoniazid (INH), RIF, ciprofloxacin (CFX), and MDR-TB with excellent sensitivity, specificity and agreement with the MGIT reference standard method (Toit K et al., 2012). The present study evaluates the performance of TB-CX test when used to directly test patient sputum, against the reference standard, MGIT phenotypic DST results. The TB-CX test provides susceptibility to CFX as proxy for detection of fluoroquinolones (FQs) due to a high degree of cross resistance between the FQs, although CFX is not currently recommended for treatment of MDR-TB patients (Devasia RA et al., 2009, Von Groll A et al., 2009).

There is a need to describe the comparative merits of these tests to inform their use in high burden TB settings with limited resources. The purpose of the present study was to assess the yield, speed and accuracy of performing DST for INH, RIF and CFX using the TB-CX directly on sputum samples compared with reference standard indirect DST using MGIT.

Methods

Study design and period
A comparative cross sectional study was conducted between March 2016 and August 2017 at the University of Gondar Hospital, Ethiopia. A total of 200 study participants > 15 years who had bacteriologically confirmed or clinically diagnosed pulmonary TB were enrolled. The study enrollment method, TB-CX and LJ results were described previously (Shibabawa A et al., 2019).

Specimen processing
One sputum sample was collected from each patient and divided into 2 aliquots. One aliquot was mixed with disinfectant and applied directly to the TB-CX plate, as described (Shibabawa A et al., 2019). Concurrently, the other aliquot was decontaminated with sodium hydroxide, centrifuged and cultured on LJ media, then *M. tuberculosis* colonies were sub-cultured for MGIT DST.

TB-CX DST
The TB-CX was prepared as previously described (Toit K et al., 2012). The first quadrant is control and contains no drugs (to detect any *M. tuberculosis*, whether drug resistant or susceptible), the second quadrant contains green colouring with 0.2 µg/ml of INH, the third quadrant contains yellow colouring with 1 µg/ml of RIF, and the fourth quadrant contains blue colouring with 2 µg/ml of CFX. Two drops of sputum-disinfectant mixture (Toit K et al., 2012) were added to each quadrant using a disposable plastic pipette; one drop to each quadrant before adding the second
drop to each quadrant to improve mixing and balance the inoculum (Figure 1). After inoculation, the TB-CX test were permanently double sealed with parafilm and then a Ziploc bag and incubated at 37°C. Plates were read 3 times per week for 6 weeks until > 10 colonies appeared in the drug-free control quadrant. *M. tuberculosis* growth was detected because red colonies were seen by naked eye inspection due to a redox reaction with STC, cording colony morphology was then confirmed using a conventional light microscope (10x objectives) without opening the TB-CX plate or bag containing it. Once the control quadrant was positive, resistance was defined as any growth appearing concurrently in the quadrants with drugs as compared to the no drug control quadrant. A susceptible strain was defined as > 10 colonies first growing on the no drug control quadrant without any concurrent growth in the drug-containing quadrants. The TB-CX protocol recommends that after 11 or more colonies growth is observed in the no drug control quadrant then DST is immediately interpreted and no subsequent assessments are made (IFHAD, 2011). However, for exploratory purposes we additionally re-inspected each TB-CX plate until 6 weeks incubation were completed.

**MGIT DST**

MGIT SIRE kits were used following manufacturers instruction with critical concentration of 0.1 µg/ml, 1 µg/ml, 2 µg/ml for INH, RIF and CFX, respectively (Mycobacteriology laboratory Manual, 2014). CFX was obtained from Sigma-Aldrich, dissolved in sterile distilled water and filter sterilized through a 0.22 µm membrane. All stock solution were stored at -20°C for 6 months. Stored *M. tuberculosis* complex (MTBC) colonies were sub-cultured and incubated in MGIT instrument at 37°C until instrument indicated a tube was positive, then it was removed and checked for pure MTBC growth by Ziehl Neelsen positivity, blood agar plate negativity and MPT64 antigen (Capilia TB) test positivity. If the sample was positive for MTBC, then DST was performed using one 7 ml MGIT tube as a control, another tube for each of INH, RIF and CFX. When 1% or more of the test population grew in the presence of the critical concentration of the drug, an isolate was defined as resistant (Mycobacteriology laboratory Manual, 2014).

**HIV testing**

HIV counselling and testing were provided for all participants following the algorithm (KHB/STAT-PAK®/Unigold™) recommended by Federal Ministry of Health of Ethiopia.

**Quality control**
For each TB-CX batch, quality control using susceptible, MDR- and CFX-resistant *M. tuberculosis* strains were performed at The Ohio State University, USA. Because the TB-CX plates were then shipped at ambient temperature, upon arrival in Ethiopia, quality control was repeated for each batch using susceptible *M. tuberculosis* H37Rv on all quadrants. Two batches of TB-CX plates that passed quality control in Ohio but then failed quality control after shipping to Ethiopia were discarded. All TB-CX were read blind to the results of reference standard method. MGIT DST quality control used drug susceptible H37Rv and INH, RIF and/or CFX known drug-resistant *M. tuberculosis* strains.

**Statistical analysis**

Data were entered in EpiData v. 3.1 (EpiData Association, Odense, Denmark) and analysed using SPSS version 20 (Statistical Package for the Social Sciences, Chicago, IL, USA). Time for TB-CX DST was recorded from sputum processing until 11 or more colonies growth was observed in the drug free control quadrant, allowing DST interpretation according to the TB-CX protocol (IFHAD, 2011). Time for MGIT DST was recorded from sputum processing until sufficient LJ growth, plus sub-culturing time of LJ colonies in MGIT tubes, plus time taken for MGIT DST. The Wilcoxon rank test for paired samples compared time to resistance detection for TB-CX versus LJ-MGIT, excluding TB-CX with uninterpretable DST results. Key proportions were reported with their 95% confidence interval (95%CI) and *P* value <0.05 was considered statistically significant. Sensitivities, specificities and predictive values were calculated for the detection of drug resistance by TB-CX versus MGIT using MedCalc version 11.6.1 (MedCalc software, Mariakerke, Belgium).

**Results**

**Clinical characteristics**

Two hundred participants were enrolled. Median age was 30 years and 61% were 15-34 years old. Most participants were males (63%), urban dwellers (57%) and literate (57%). Of 200 participants, 26% had previous history of anti-TB treatment, 13% were HIV positive, 4% had history of contact with rifampicin mono-resistant/MDR-TB patients, 14% had a family history of TB and 58.5% were ZN smear negative (Shibabawa A et al., 2019).

**DST yield**
Of the 200 patients enrolled, 66% (131) had positive TB-CX test and 68% had positive LJ culture. One specimen with interpretable TB-CX DST had contaminated LJ culture so was excluded from analysis. Insufficient growth in the drug free quadrant (<11 colonies) for interpretable DST was occurred in 6% (95%CI: 2-10, 8/131) of positive TB-CX, which were excluded from analysis. All LJ positive samples had interpretable MGIT DST. Overall, 65% (130) had positive culture by both TB-CX and LJ culture (Shibabawa A et al., 2019). This study compares DST results by TB-CX versus LJ-MGIT for the 94% (122/130) with paired results by both tests.

**DST speed**

The time from sputum processing to TB-CX DST was median 12 days (inter-quartile range, IQR 9-16, range 6-26 days), which was significantly faster than LJ-MGIT DST, median 35 days (IQR 29-39, range 22-72 days) (P< 0.0001) (Figure 2).

**DST accuracy**

By MGIT, the prevalence of INH resistance was 30% (37/122) and RIF resistance was 19% (23/122). Figure 3 shows the colonies observed in the TB-CX test control and drug containing quadrants.

The TB-CX sensitivity was 59%, 96% and 95% for detecting resistance to INH, RIF and MDR-TB and specificity was 96%, 94%, and 98%, respectively. All isolates were susceptible to CFX in both methods. The agreement between the TB-CX and MGIT was 85%, 94%, 100% and 98% for INH, RIF, CFX and MDR-TB, respectively (p<0.001) (Table 1). No TB-CX had contamination preventing interpretation, although 1.5% (3/200) of culture-negative TB-CX were partially contaminated.

TB-CX plate re-reading > 1 week after completing per-protocol interpretations for susceptible isolates revealed later growth in 15 quadrants for INH, 14 for RIF and none for CFX up to 6 weeks.

**Discussion**

Appropriate-technology diagnostic methods are needed for low-income countries with a high incidence of TB and drug resistance. The present study evaluated the performance of the TB-CX
for direct detection of resistance from sputum specimens to INH, RIF and CFX, as an alternative method in a resource-limited country, Ethiopia.

The time for detection of resistance to INH, RIF and CFX by TB-CX was faster (median: 12 vs 35 days) compared to LJ-MGIT DST, avoiding the pre-isolation culture step before performing MGIT DST. MGIT DST was performed using stored *M. tuberculosis* colonies were sub-cultured using MGIT tubes that might have delayed time to MGIT DST. Our study was comparable to other studies that reported median time for TB-CX detection of drug resistance of 10 and 11 days (Robledo J et al., 2008, Martin A et al., 2009) and high accuracy of MDR-TB detection.

The addition of STC to the media made the red colonies visible to the naked eye in early stages of growth and made the interpretation of the TB-CX test DST easy. No contamination on the drug containing quadrants was noted on the 122 *M. tuberculosis* isolates throughout the study. But 1.5% (3/200) samples were contaminated from TB-CX test negative drug containing quadrants.

The TB-CX test showed excellent sensitivity for RIF and MDR-TB detection while the sensitivity for INH resistance detection was lower than expected. The specificity was excellent for all drugs and MDR-TB detection as in studies conducted in different areas (Robledo J et al., 2008, Martin A et al., 2009, Toit K et al., 2012, Ardizzoni E et al., 2015). The sensitivity of the TB-CX test for INH (59%) was comparable with one study by Hussain et al (71%) (Hussain A et al., 2012) but lower as compared to other reports (Robledo J et al., 2008, Martin A et al., 2009, Toit K et al., 2012, Mekonnen B et al., 2019). This could be explained by the fact that our study was performed through direct inoculation of sputum that may have reduced the sensitivity of the TB-CX test compared to indirect inoculation with isolates. Deviations from the recommended TB-CX protocol such as shipping the TB-CX at ambient temperature and using the TB-CX for up to 4 months after preparation instead of the recommended 66 days (IFHAD, 2011) may have contributed to sub-optimal sensitivity. However, discordant DST results were probably principally explained by our use of different isoniazid concentrations in TB-CX versus the reference standard test. Unlike rifampicin that usually clearly indicates dichotomous resistance or susceptibility, isoniazid resistance is a continuum with frequent intermediate results so our use of different isoniazid concentrations in the TB-CX test and MGIT test would be expected to cause some discrepant results. In an experiment that will be reported separately comparing TB-CX results with a reference standard assay that determines minimum inhibitory concentration to isoniazid, we found that TB-
CX sensitivity for detecting isoniazid resistance was 93% when compared with the same isoniazid concentration in the reference standard. However, when compared with the next dilution of isoniazid in the reference standard, the sensitivity of the TB-CX to detect isoniazid resistance fell to 70%. Thus, in the present research our use of different isoniazid concentrations in the TB-CX versus the MGIT reference standard may fully explain the low isoniazid sensitivity that we observed. This finding suggests that the concentration of isoniazid used in the TB-CX should be reconsidered (IFHAD, 2011).

Except for low isoniazid DST sensitivity, the agreement between TB-CX test and MGIT DST was excellent for individual drugs and MDR-TB detection, which was comparable with other studies (Martin A et al., 2009, Toit K et al., 2012, Ardizzoni E et al., 2015). This method might be a priority for TB prevention and care by providing earlier results directly from specimens compared to conventional methods and reducing the use of empirical treatment resulting from delay of conventional methods for TB DST. Moreover, it could be of added value in TB patient follow up and monitoring of treatment in smear positive cases and provide information on culture conversion in smear negative cases.

In addition to good specificity and short time to resistance detection, the TB-CX test has other merits. It does not require additional sophisticated laboratory, colonies are easy to visualize by naked eye due to an indicator in the medium and avoids bio-safety risks. A demerit of TB-CX test is laborious, requiring time for repeated observation of M. tuberculosis growth in order to report the accurate DST pattern based on the protocol, which may limit their use to only laboratories that process moderate to low numbers of specimens for DST.

Uninterpretable TB-CX DST results due to low bacillary load seen in smear negative specimens or after extended sample storage time before specimen processing may cause scanty culture growth, delaying or preventing DST interpretation. This is supported by Banda et al who stated that mycobacterial viability declined with prolonged storage (Banda et al., 2000). The TB-CX protocol recommends that after 11 or more colonies growth is observed in the drug free quadrant then DST is immediately interpreted and no subsequent assessments are made (IFHAD, 2011). We found that re-reading of the susceptible TB-CX after > 1 week sometimes
demonstrated delayed growth in drug-containing quadrants that did not indicate drug resistance, demonstrating the importance of following the protocol.

Conclusions
Our findings showed that the colour TB-CX test was simple and rapid for simultaneous detection of *M. tuberculosis* and INH, RIF and CFX DST. This method might be a priority for TB prevention and care by providing earlier results directly from specimens than conventional methods and reducing prolonged empirical treatment, facilitating early appropriate treatment of patients with MDR-TB in resource-constrained settings. Moreover, it could be of value in following up patients with TB and monitoring treatment, potentially providing information on culture conversion. The TB-CX test format favours its implementation in laboratories without additional mycobacterial diagnostic equipment. Further studies are necessary to assess INH DST reliability either using the same concentration of INH in the TB-CX versus the reference standard test, or a composite reference standard, or ideally using a reference standard test that determines the minimum inhibitory concentration for isoniazid.

Ethics
Ethical approval was obtained from University of Gondar Ethical Review Board (Ref. No: O/V/P/RCS/05/19/2016) and permission letter was obtained from the hospital director. All participants were volunteers and sputum samples were collected after obtaining written informed consent from adult participants and also from parents or guardians for those who were less than 18 years old. The TB-CX results were unvalidated so did not influence treatment that followed national protocols. Confidentiality was maintained for all data collected.

Author contributions
AS: Conceived and designed the study, participated in sample collection, performed laboratory experiments, analysed and interpreted the data, wrote the first draft and final write up of the manuscript; BG: Designed the study, analysed and interpret the data and, edit and approve the final manuscript, agreed with manuscript results and conclusions; HK: Made the colour plates, edit and approve the final manuscript; ET: Edit and approve the final manuscript; JMB: Critical review,
edit and approve the final manuscript; CE: Lead the team that developed TB-CX, wrote and shared the TB-CX protocol, critical review, edit and approve the final manuscript; JT: Made the colour plates, analysed and interpret the data and, edit and approve the final manuscript; SW: Designed the study, analysed and interpret the data and edit and approve the final manuscript, agreed with manuscript results and conclusions; BT: Designed the study, analysed and interpret the data and, edit and approve the final manuscript, agreed with manuscript results and conclusions.

*Conflict of interest:* We declare that we have no competing interests.

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Figure 1: Colour TB-CX test sputum processing, detection and final confirmation of dots with cording formation characteristics of *Mycobacterium tuberculosis* complex.
Figure 2: Comparison of turnaround time in days to DST between TB-CX test versus LJ-MGIT
Figure 3: Growth was observed as red dots indicating colonies either in growth control and/or drug containing quadrants. **A**). Growth only in control quadrant (white/clear) and susceptible to all drugs. **B**). Growth on control quadrant and resistant to RIF drug (yellow) and susceptible to INH and CFX. **C**). Growth on control quadrant and resistant to INH (green) and susceptible to RIF and CFX. **D**). Growth on control quadrant and MDR TB (resistant to both RIF and INH) with susceptible to CFX (Blue).
Table 1: Performance characteristics of TB-CX test (n = 122 isolates)

<table>
<thead>
<tr>
<th>TB-CX test</th>
<th>MGIT DST</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>Total agreement % (95% CI)*</th>
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<td>88 (68-98)</td>
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*p value < 0.001 and statistically significant agreement exists between the two tests

S-Susceptible; R-Resistant; MGIT-Mycobacteria Growth Indicator Tube; DST- Drug Susceptibility Testing; RIF- Rifampicin; INH- Isoniazid; CFX- Ciprofloxacin; MDR-TB- Multi-drug resistant tuberculosis; CI- Confidence interval; NPV-Negative predictive value; PPV-Positive predictive value