Automated liquid culture for detection of mycobacteria and susceptibility testing to antimicrobials used in the treatment of tuberculosis

Brasília – DF
2020

Technology: Automated liquid culture for detection of mycobacteria and susceptibility testing to antimicrobials used in the treatment of tuberculosis.

Indication: Tuberculosis.

Applicant: Secretariat of Health Surveillance of the Ministry of Health of Brazil (SVS/MS).

Background: Tuberculosis is an infectious disease with a chronic course, caused by *Mycobacterium tuberculosis*. Diagnosis is a key strategy for timely treatment. Culture is considered the gold standard method for bacteriological certainty in tuberculosis diagnosis, drug susceptibility testing, and treatment monitoring. It can increase the diagnosis in up to 30% in patients with negative bacilloscopy. Although culture methods commonly use solid media, automated liquid culture system has advantages in reducing the time to availability of results of both bacterial culture and susceptibility testing to antimicrobials used in the treatment of tuberculosis. This Technical Report provides an evaluation of the automated liquid culture for detection of mycobacteria and susceptibility testing, in order to address the demand of SVS/MS, by the Technical Note No. 5/2019-CGPNCT/DEVIT/SVS/MS (General Coordination of the National Tuberculosis Control Programme/Department of Communicable Disease Surveillance/Secretariat of Health Surveillance/Ministry of Health of Brazil).

Research questions: Two research questions were structured. Firstly, 'Does automated liquid culture perform better for the diagnosis of tuberculosis, in terms of detection ratio and time to detection of mycobacteria from clinical specimens, compared with the Löwenstein-Jensen (LJ) solid culture medium?'. Secondly, 'Does susceptibility testing performed in automated liquid culture system detect resistance to first-line anti-tuberculosis drugs compared with susceptibility testing in solid culture medium (method of proportions)?'.

Scientific evidence: Culture, performed in both solid and liquid media, is considered a reference standard test for the diagnosis of tuberculosis. The studies selected for analysis showed no difference in accuracy between automated liquid culture and solid culture. The outcomes selected to assess the performance of automated liquid culture were detection ratio and time to detection of mycobacteria from clinical specimens; and in relation to susceptibility testing, detection of *M. tuberculosis* resistance to first-line anti-tuberculosis drugs. The average detection ratio was 82% (95% CI = 71-90%) for automated liquid culture system, and 65% (95% CI = 51-77%) for LJ solid culture medium; and the average time to detection in the automated liquid culture (14.07 days) was lower than in the solid culture (27.68 days), with a statistically significant difference ($p < 0.001$). Regarding the susceptibility testing performed in automated liquid culture system, in general, there was a high level of agreement with the method of proportions in solid culture (>90%), and time ranged from 3 to 14 days in MGIT method, and 7 to 42 days in the method of proportions in LJ.

Economic evaluation: The cost-minimization analysis showed that the replacement of solid culture with automated liquid culture for detection of mycobacteria would result in an additional cost of BRL 40.37, and for the susceptibility testing an additional cost of BRL 323.67 per test, based on values in the SIGTAP (Management System of the Table of Procedures, Medicines, Orthotics, Prosthetics and Special Materials). These additional costs could be reduced to BRL 29.08 and BRL 92.01 respectively, considering the costs of tests in solid culture obtained from the literature.

Budget impact analysis: A budget impact analysis over a five-year time horizon from the perspective of the Brazilian Public Health System (SUS) was conducted. In the reference scenario, considering that approximately 45% of mycobacterial culture and 70% of susceptibility testing would be performed in automated liquid culture system by the Central Public Health Laboratory (LACEN in Portuguese) of the States of Brazil, the total cost was estimated to be BRL 7,335,668.27. In the alternative scenario, considering 60% of mycobacterial culture and 100% of susceptibility testing performed in automated liquid culture system in the first year, the cost would be BRL 9,371,002.04, and 100% for both of them in the fifth year, it would be BRL 16,408,179.94. Therefore, the incremental budget impact with the use of automated liquid culture system for detection of mycobacteria and susceptibility testing for all tests performed by the LACENs was estimated to be BRL 2,035,333.77 in the first

year of incorporation, and BRL 9,072,511.67 after five years. The incremental budget impact is reduced when considering the costs of tests in solid culture obtained from the literature.

International recommendations: Automated liquid culture system for detection of mycobacteria and susceptibility testing has been widely recommended by the World Health Organization since 2007, including for low- and middle-income countries.

Conclusions: The main advantage of the automated liquid culture system is a shorter time to detection of mycobacteria with a better recovery rate than solid culture medium, and also to be suitable for an antibiotic susceptibility testing of *M. tuberculosis*. Its incorporation for the diagnosis and detection of antimicrobial resistance in the scope of SUS could increase the coverage of testing throughout the country, in a standardised manner, constituting an important strategy for the timely diagnosis and control of tuberculosis at the national level.

Initial Recommendation: CONITEC, at its 87th Ordinary Meeting, on June 3rd, 2020, decided that the subject matter should be made available in a public consultation with a preliminary recommendation in favour of the incorporation of automated liquid culture for detection of mycobacteria and susceptibility testing to antimicrobials used in the treatment of tuberculosis, in the scope of SUS. It was considered that this technology has advantages over solid culture medium for detection of mycobacteria and susceptibility testing, especially in terms of significant reduction in time to obtain results. As automated tests need to be performed in laboratories with adequate infrastructure and biosafety level 3, they should be purchased centrally by the Ministry of Health and provided to the LACENs. The subject matter was made available in a public consultation.

Public consultation: The Public Consultation No. 18/2020 was held from June 16th to July 6th, 2020. A total of 42 contributions were received, of which 15 were technical-scientific contributions, and 27 were experience or opinion contributions of patients, relatives, friends or caregivers of patients, health professionals or people interested in the subject. All contributions agreed with the preliminary recommendation and reinforced the main evidence in the report, highlighting the superiority of automated liquid culture for detection of mycobacteria and antimicrobial susceptibility test compared with solid culture medium, especially in terms of significant reduction in time to obtain results.

Final Recommendation: The CONITEC's members present at the 89th Ordinary Meeting, on August 5th, 2020, unanimously decided to recommend the incorporation of automated liquid culture for detection of mycobacteria and susceptibility testing to antimicrobials used in the treatment of tuberculosis, in the scope of SUS, as recommended by the Ministry of Health of Brazil. As agreed with its General Coordination of Public Health Laboratories (CGLAB in Portuguese), the purchase of the test kits should be centralized by the Ministry of Health and provided to the LACENs, which have the adequate infrastructure and biosafety level to carry out the tests within the scope of epidemiological control programs for diseases caused by mycobacteria. The Deliberation Record No. 540/2020 was signed.

Decision: To incorporate automated liquid culture for detection of mycobacteria and susceptibility testing to antimicrobials used in the treatment of tuberculosis, in the scope of SUS, according to Ordinance No. 33, published in the Official Gazette of the Federal Executive No. 164, Section 1, page 133, on August 26th, 2020.