World Health Organization

Update on the use of nucleic acid amplification tests to detect TB and drug-resistant TB: rapid communication

January 2021

Update on the use of nucleic acid amplification tests to detect TB and drug-resistant TB: rapid communication

ISBN 978-92-4-002026-9 (electronic version)
ISBN 978-92-4-002027-6 (print version)

© World Health Organization 2021

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (http://www.wipo.int/amc/en/mediation/rules/).

Suggested citation. Update on the use of nucleic acid amplification tests to detect TB and drug-resistant TB: rapid communication. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Background

In 2019, an estimated 10 million individuals fell ill with tuberculosis (TB) and 3 million of them were not reported to have been diagnosed and notified.[1] The gap is proportionately even wider for drug-resistant TB. Of the estimated 465 000 patients with rifampicin-resistant and multi-drug resistant TB (RR/MDR-TB), only 206 030 (44%) were diagnosed and notified. For the first time, the World Health Organization (WHO) has provided global estimates of the incidence of isoniazid resistance: in 2019, there were 1.4 million incident cases of isoniazid-resistant TB, of which 1.1 million were susceptible to rifampicin.[1] Most of these people were not diagnosed with drug-resistant TB and did not receive appropriate treatment.

To end the global TB epidemic by 2030, there is an ongoing need to scale-up capacity to test larger numbers of specimens. Molecular platforms that allow high throughput and can accommodate multiple disease-specific tests to diagnose a variety of health conditions represent an important development. Such platforms can significantly improve system efficiency, reduce costs, increase patient access, and ultimately improve quality of care.[2]

Among people with TB and rifampicin-resistant TB, additional testing for resistance to at least isoniazid and fluoroquinolones respectively, should be performed promptly to guide treatment decisions. WHO currently recommends using commercially available molecular line probe assays as the initial test to detect resistance to fluoroquinolones for people with rifampicin resistant TB.[3] Nevertheless, more automated, accessible, accurate diagnostics for the detection of resistance to first- and second-line anti-TB drugs are urgently needed. Monitoring of resistance to pyrazinamide, another important antibiotic for the treatment of both drug-susceptible and drug-resistant TB, remains very limited. [4, 5]

In 2020, WHO commissioned a systematic review of published and unpublished data on three classes of nucleic acid amplification tests (NAATs) not previously reviewed by WHO. The systematic review included data on diagnostic accuracy, economic information, and qualitative evidence on feasibility, acceptability, equity, end-user values and preferences. A Guideline Development Group (GDG) was convened by WHO on 7-18 December 2020 to discuss the findings of the systematic reviews and to make recommendations on these three classes of technologies.

The three classes of technologies that were evaluated include:

- Moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid;
- Low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents;
- High complexity hybridization-based NAATs for detection of resistance to pyrazinamide.

[1] World Health Organisation 2020. Global Tuberculosis Report 2020 WHO/HTM/TB/2020.22

[2] Information note. Global TB Programme and Department of HIV/AIDS. Considerations for adoption and use of multidisease testing devices in integrated laboratory networks.
https://www.who.int/tb/publications/2017/considerations_multidisease_testing_devices_2017/en/

[3] WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection. Geneva: World Health Organization; 2020

[4] Whitfield MG, Soeters HM, Warren RM et al. A Global Perspective on Pyrazinamide Resistance: Systematic Review and Meta-Analysis. PLoS One 2015; 10: e0133869.

[5] Chang KC, Yew WW, Zhang Y. Pyrazinamide Susceptibility Testing in Mycobacterium tuberculosis: a Systematic Review with Meta-Analyses. Antimicrob Agents Chemother 2011; 55: 4499-505.

The WHO assessment process for TB diagnostics has evolved into a mechanism which focuses on the evaluation of classes of TB diagnostic technologies rather than of specific products. The above-mentioned classes of technologies were defined for the purpose of this guidelines update. The classes are defined by the type of technology (e.g. automated/hybridization-based NAATs), the complexity of the test for implementation (e.g. low, moderate and high - considering the requirements of infrastructure, equipment and technical skills), and the target conditions (TB, resistance to first-line and/ or second-line drugs). The level of complexity is only one of the elements that should be considered to guide implementation. Other important elements include, but are not limited to, diagnostic accuracy, the epidemiological and geographical setting, operational aspects (turnaround times, throughput, existing infrastructure and specimen referral networks), economic aspects, and, finally, qualitative aspects on acceptability, equity, end-user values and preferences.

Table 1. Classes of technologies and associated products evaluated

Technology Class	**Products included in evaluation**
Moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid	Abbott RealTi*m*e MTB and Abbott RealTi*m*e MTB RIF/INH (Abbott) FluoroType MTBDR and FluoroType MTB (Hain Lifescience) BD MAX™ MDR-TB (Becton Dickinson) cobas MTB and cobas MTB-RIF/INH (Roche)
Low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents	Xpert MTB/XDR (Cepheid)
High complexity hybridization-based NAATs for detection of resistance to pyrazinamide	Genoscholar PZA-TB II (Nipro)

The objectives of the meeting were to:

- assess the available data on diagnostic accuracy (sensitivity and specificity) of three classes of technologies for diagnosis of active pulmonary TB and detection of drug resistance in adults and children with signs and symptoms of TB
- assess the available data related to the impact of these three classes of technologies on patient important outcomes, including cure, mortality, time to diagnosis and time to treatment initiation.
- assess the available qualitative data on feasibility, acceptability, equity and end-user values related to implementation of these three classes of technologies
- assess the available economic data on affordability, cost, and cost-effectiveness on implementation of these three classes of technologies to assist in the diagnosis of TB and detection of resistance to anti-TB drugs
- determine questions for future research and issues to be addressed by WHO in future policy recommendations.

This Rapid Communication aims to inform national TB programmes and other stakeholders about the key findings and considerations on the use of specific molecular assays as diagnostic tests for detection of TB and drug-resistant TB, following the assessment of new evidence.

Detailed recommendations will be presented in the 2021 update of the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection*.

Key findings

Moderate complexity automated NAATs for the detection of TB, rifampicin and isoniazid resistance on respiratory samples were found to be highly accurate

Intervention: Moderate complexity automated NAATs performed on respiratory samples from people with signs and symptoms of pulmonary TB for detection of TB and resistance to isoniazid and rifampicin, compared with culture and phenotypic drug susceptibility testing (DST).

Data assessed: 32 studies involving 16,726 samples.

Results: High diagnostic accuracy of moderate complexity automated NAATs was confirmed in people with signs and symptoms of pulmonary TB. Overall pooled sensitivity (95% CI) for TB detection was 93.0% (90.9 to 94.7) and specificity was 97.7% (95.6 to 98.8). Overall pooled sensitivity (95% CI) for rifampicin resistance detection was 96.7% (93.1 to 98.4) and specificity was 98.9% (97.5 to 99.5). Overall pooled sensitivity (95% CI) for isoniazid resistance detection was 86.4% (82.8 to 89.3) and specificity was 99.2% (98.1 to 99.7). Culture and phenotypic DST were used as the reference standard.

Low complexity automated NAATs for the detection of resistance to isoniazid, fluoroquinolones, ethionamide and amikacin in sputum were found to be highly accurate

Intervention: Low complexity automated NAATs performed on sputum from people with microbiologically diagnosed pulmonary TB, for detection of resistance to isoniazid, fluoroquinolones, ethionamide and amikacin, compared with phenotypic DST (for detection of resistance to isoniazid, fluoroquinolones and amikacin) or compared with gene sequencing of *inh*A promoter region (for detection of resistance to ethionamide).

Data assessed: 3 studies involving 1,605 participants.

Results: High diagnostic accuracy of low complexity automated NAATs was confirmed in people with microbiologically diagnosed pulmonary TB, Overall pooled sensitivity (95% CI) for isoniazid resistance detection was 94.2% (89.3 to 97.0) and specificity was 98.0% (95.2 to 99.2). Overall pooled sensitivity (95% CI) for fluoroquinolone resistance detection was 93.1% (88.0 to 96.1) and specificity was 98.3% (94.5 to 99.5). Overall pooled sensitivity (95% CI) for amikacin resistance detection was 89.1% (80.9 to 94.1) and specificity was 99.5% (96.9 to 99.9). Phenotypic DST was used as the reference standard for the three above-mentioned estimates. Overall sensitivity (95% CI) for ethionamide resistance detection was 96.4% (92.2 to 98.3) and specificity was 100.0% (82.5 to 100.0). Gene sequencing of *inh*A promoter region was used as the reference standard for ethionamide resistance detection.

High complexity hybridization-based NAATs for the detection of pyrazinamide resistance in *M. tuberculosis* isolates were found to be highly accurate

Intervention: Hybridization-based NAATs performed in isolates retrieved from patients with bacteriologically confirmed pulmonary TB, for detection of resistance to pyrazinamide compared with phenotypic DST.

Data assessed: 7 studies involving 964 participants.

Results: High diagnostic accuracy of high complexity hybridization-based NAATs was confirmed on isolates retrieved from patients with bacteriologically confirmed PTB. Overall pooled sensitivity (95% CI) for pyrazinamide resistance detection was 81.2% (75.4 to 85.8) and specificity was 97.8% (96.5 to 98.6). Phenotypic DST was used as the reference standard.

Overall conclusions

Available evidence supports the use of: (i) moderate complexity automated NAATs for the detection of TB and resistance to rifampicin and isoniazid; (ii) low complexity automated NAATs for the detection of resistance to isoniazid and second-line anti-TB agents; and (iii) high complexity hybridization-based NAATs for the detection of resistance to pyrazinamide. These findings were based on evaluation of data for the assays that met the class definition (Table 1). Extrapolation to other brand-specific tests cannot be made and any new in-class technologies will need to be specifically evaluated by WHO.

Next steps

- The updated policy guidelines on NAATs to detect TB and drug-resistant TB will be released later in 2021, as part of the 2021 update of the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection*. The summary of findings and the evidence to decision tables will be produced in conformity with the GRADE method and made available on the WHO Global TB Programme website.

- The release of the updated guidelines will be accompanied by updated operational guidance in the 2021 update of the *WHO operational handbook on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection*.

- The release of the new guidance will be followed by a series of WHO webinars for different regions to disseminate the new guidelines. The new diagnostics policies will also be included in an online knowledge sharing platform that the Global TB Programme will launch in early 2021. This will provide easy access to the guidelines, implementation aids and eLearning tools, all in one place. The webinars and the platform will support countries to update their national guidelines, train staff, inform programme budgets and facilitate rapid transition to more effective interventions. National TB programmes and other stakeholders are encouraged to seek advice from WHO before introducing the

预览已结束，完整报告链接和二维码如下：
https://www.yunbaogao.cn/report/index/report?reportId=5_24088