World Health Organization

Diagnosis of tuberculosis and detection of drug-resistance

Rapid communication

Background

The World Health Organization (WHO) End TB Strategy calls for early diagnosis of tuberculosis (TB) and universal access to drug-susceptibility testing (DST) [1] but the diagnostic gaps remain significant in many countries worldwide. In 2022, 10.6 million people were estimated to have fallen ill with TB worldwide, approximately 7.5 million people were newly diagnosed with TB and notified, and, of them, only 4.0 million were bacteriologically confirmed with TB.[2] Among those who were bacteriologically confirmed with TB, 73% received DST for rifampicin, the most powerful first-line anti-TB drug.
The detection of TB remains particularly challenging in people with HIV and in children. The use of concurrent testing offers an important new approach to closing the diagnostic gaps in these populations.
The objectives of the current update are the following:

- Evaluate concurrent[3] use of WHO-recommended rapid diagnostic tests for diagnosis of pulmonary TB in children and TB in people with HIV;
- Consolidate individual product-specific recommendations into class-based recommendations and update the recommendations for technologies falling into the low-complexity nucleic acid amplification test (NAAT) classes.

Methods

In 2023, WHO commissioned a series of systematic reviews of published and unpublished data on the low complexity automated NAATs (LC-aNAATs) and low complexity manual NAATs (LC-mNAATs) and on concurrent testing approaches for TB diagnosis in children and people with HIV. The systematic reviews included data on diagnostic accuracy, impact on patient important outcomes, economic and implementation considerations, and qualitative evidence on feasibility, acceptability, equity, end-user values and preferences. WHO convened a Guideline Development Group (GDG) on 6-10 May 2024 to discuss the findings of the systematic reviews and make recommendations on the use of these technology classes.

The evidence was assessed and synthesized following the GRADE method. Evidence summaries in standard GRADE format were prepared in GRADEpro. The outcomes in the tables were those relevant to the PICO questions.
Standard methods were used to describe and analyze the aggregated and individual data. Estimates of effect were expressed as risk ratios, odds ratios, or hazard ratios with their 95% confidence limits. The absolute risk was also calculated where possible. During the discussion, the GDG members formulated successive drafts of the recommendations based on their assessment of the evidence. The GRADEpro "evidence to decision" template guided this process. Several factors determined the direction and strength of the recommendations (e.g., strong or conditional), including the certainty in the estimates of effect ("quality of the evidence"), values and preferences, how substantial the anticipated desirable and

[1] Global strategy and targets for tuberculosis prevention, care and control after 2015 (Resolution WHA67.1, Agenda item 12.1). Geneva: World Health Assembly; 2014 (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R1-en.pdf).

[2] Global tuberculosis report 2023. Geneva: World Health Organization; 2023.

[3] Concurrent use of tests: samples are taken simultaneously and testing is conducted for both tests. A positive result on either test is a positive result for the combination.

undesirable effects were, certainty on the balance of the benefits and harms, resource implications, health equity, acceptability, and feasibility.
The GDG made recommendations about which populations required a particular diagnostic approach, outlining considerations for implementation when possible. All GDG decisions were reached by discussion and consensus on the recommendations, including their strength and, where appropriate, the conditions to be attached to them.

This rapid communication aims to inform national TB programmes, clinicians and other stakeholders about the key findings and considerations on the use of concurrent testing approaches and low complexity NAATs for the detection of TB and drug-resistant TB. The concurrent use of tests for the diagnosis of TB in people with HIV and children is expected to result in a significant shift in the way these vulnerable populations are to be managed in health programs, and rapid preparation for this change is critical. Furthermore, implementation of these recommendations will result in an earlier and more timely diagnosis of TB in these important populations.

Key updates

Concurrent use of tests for diagnosis of TB disease

In adults and adolescents with HIV

Among adults and adolescents with HIV and with signs or symptoms of TB, or with a positive screening result for pulmonary TB (e.g., chest x-ray [CXR], C-reactive protein [CRP] or molecular WHO-recommended rapid diagnostics [mWRD]), serious illness, or advanced HIV disease (AHD), the concurrent use of LC-aNAATs on a respiratory sample and lateral flow urine lipoarabinomannan assay (LF-LAM) on urine was assessed. The available evidence on test accuracy included a total of 27 studies and 12,651 participants. Mathematical modelling was used to evaluate the cost-effectiveness of a concurrent use of LC-aNAAT and LF-LAM in this population. The qualitative evidence on end-user perspectives from systematic review and interview studies were also assessed.

The GDG concluded that concurrent use of LC-aNAATs on respiratory samples[4] and LF-LAM on urine for diagnosis of TB in adults and adolescents with HIV has improved accuracy with moderate cost requirements compared with a single LC-aNAAT. The intervention was considered cost-effective in most scenarios. From an end-user perspective the concurrent testing approach was considered acceptable and feasible in most settings with the potential to improve access to care by minimizing repeat visits and loss to follow up.

The following recommendation was agreed upon:

In adults and adolescents with HIV who have signs or symptoms or screened positive for TB, or seriously ill, or have advanced HIV disease, concurrent testing using low-complexity automated NAATs on respiratory samples and LF-LAM on urine should be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory samples alone (strong recommendation, moderate certainty of evidence).
Remarks:

- Seriously ill individuals include those requiring hospitalization

[4] For adults respiratory samples include: sputum, broncho-alveolar lavage, induced sputum

- Advanced HIV disease defined in people with HIV with a CD4 cell count of <200cells/mm3 or presenting with a WHO Stage 3/4 AIDS-defining illness
- This concurrent use recommendation supersedes prior LF-LAM guidance for people with HIV and the use of a single molecular test for diagnosis of TB in this group

In children

Among children who have signs or symptoms of TB, or with a positive screening result for pulmonary TB (e.g., CXR), the concurrent use of LC-aNAATs on respiratory specimens[5] and stool was assessed. The available evidence on test accuracy included a total of 20 studies and 5,724 participants. Mathematical modelling was used to evaluate cost-effectiveness of concurrent LC-aNAAT testing on a respiratory specimen and stool in children. The qualitative evidence on end-user perspectives from systematic review and interview studies were also assessed.

The GDG concluded that concurrent use of LC-aNAATs on respiratory specimens and or diagnosis of TB in children has improved accuracy with moderate cost requirements compared to single testing. The intervention was considered cost-effective in most scenarios. From an end-user perspective, the concurrent testing approach was considered acceptable and feasible in most settings, potentially improving access to care by minimizing repeat visits and loss to follow-up.

The following recommendation was agreed upon:

In children who have signs or symptoms or screened positive for pulmonary TB, concurrent testing using low-complexity automated NAATs on respiratory samples and stool should be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory or stool samples alone (strong recommendation, low certainty of evidence for test accuracy).

Remarks:

- The strong recommendation despite the low certainty of evidence is because the findings indicate large desirable effects, i.e. rapid and accurate diagnosis of TB in a highly vulnerable population—children—in whom diagnosing TB is often challenging, over trivial undesirable effects, i.e. negative consequences of this testing strategy.
- This recommendation prioritizes concurrent testing over the use of a single molecular test for diagnosis of TB in children.
- Use of LC-aNAATs on isolated specimens was also evaluated. The findings supported the use of LC-aNAATs in children with signs or symptoms or who screen positive for pulmonary TB on sputum, gastric aspirate, stool, or nasopharyngeal aspirate for initial diagnostic testing for TB rather than smear and/or culture.

In children with HIV

Among children with HIV who have signs and symptoms of TB, or with a positive screening result (e.g., CXR) for pulmonary TB, concurrent testing using LC-aNAATs on respiratory samples, stool, and LF-LAM on urine was assessed. The available evidence included 6 studies and 653 participants. Modelling was used to evaluate cost-effectiveness of concurrent LC-aNAAT use in this group. The qualitative evidence on end-user perspectives from systematic review and interview studies were also assessed.

[5] Respiratory specimen is defined as sputum, bronchoalveolar lavage, induced sputum, nasopharyngeal aspirate, gastric aspirate.

The GDG concluded that concurrent testing using LC-aNAATs on respiratory samples, stool, and LF-LAM on urine in children with HIV has improved accuracy and moderate cost requirements compared with single testing. Based on modelling, the intervention was considered cost-effective in most scenarios. From an end-user perspective, the concurrent testing approach was considered acceptable and feasible in most settings with the potential to improve access to care by minimizing repeat visits and loss to follow-up.

The following recommendation was agreed upon:

In children with HIV who have signs or symptoms or screened positive for pulmonary TB, concurrent testing using low-complexity automated NAATs on respiratory samples, stool and LF-LAM on urine may be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory and/or stool samples (**conditional recommendation, low certainty of evidence for test accuracy).**

Remarks:

- This recommendation prioritizes concurrent testing over the use of molecular test and LF-LAM in isolation for diagnosis of TB in children with HIV.
- Use of LC-aNAATs on isolated specimens was also evaluated. The findings supported the use of LC-aNAATs in HIV-positive children with signs or symptoms or who screen positive for pulmonary TB on sputum, gastric aspirate, stool, or nasopharyngeal aspirate for initial diagnostic testing for TB rather than smear and/or culture.

Low-complexity nucleic acid amplification tests: automated (LC-aNAATs) and manual (LC-mNAATs)

The performance of LC-aNAATs on respiratory and non-respiratory samples for pulmonary TB and resistance to rifampicin and selected non-respiratory samples for extrapulmonary TB was assessed in people with signs and symptoms of TB or with a positive screening test for TB (e.g., CXR). The available evidence on diagnostic accuracy included 51 studies with more than 23,000 participants for pulmonary TB, 40 studies with more than 5,000 participants for extra-pulmonary TB and 11 studies (2517 participants) for resistance to rifampicin.

The performance of LC-mNAATs on respiratory samples in people with signs and symptoms of TB or with a positive screening test for TB (e.g., CXR) was assessed. The available evidence on diagnostic accuracy for pulmonary TB included 28 studies with 19,047 participants.

The economic evidence was based on findings from systematic review (29 studies). The qualitative evidence on end-user perspective was based on a systematic review and interviews study.

The GDG determined that the LC-aNAAT class was accurate for detecting pulmonary TB and extrapulmonary TB in adults, children and in people with HIV. The accuracy and outcomes were similar to existing product-specific recommendations. Likewise, the LC-mNAAT class was found to be accurate in detecting pulmonary TB on respiratory samples in adults, children, and in people with HIV. The available information on resources required for the implementation of LC-aNAATs and LC-mNAATs varied. Overall, the evidence suggested the use of technologies belonging to the above-mentioned classes were cost-effective, and end-user perspectives indicated that their use was acceptable and feasible in most settings.

The following recommendations were agreed upon:

In adults and adolescents with signs or symptoms of tuberculosis or who screened positive for pulmonary tuberculosis, low-complexity automated NAATs should be used on respiratory samples as initial diagnostic tests for TB rather than smear microscopy or culture (strong recommendation, high certainty of evidence).

Remarks:

- Respiratory samples refer to sputum (expectorated or induced), tracheal aspirate or bronchoalveolar lavage
- Person screened positive: person in whom screening test has yielded a positive result
- For children refer to the section on concurrent use of TB diagnostic tests in children
- For people with HIV refer to the section on concurrent use of TB diagnostic tests in people with HIV
- For children with HIV refer to the section on concurrent use of TB diagnostic tests in children

In people with bacteriologically confirmed TB, low-complexity automated NAATs should be used on respiratory samples as an initial test for the detection of resistance to rifampicin rather than culture-based DST (strong recommendation, high certainty of evidence).

Remarks:

- This recommendation applies to all people with HIV
- The recommendation was extrapolated to children based on the generalization of data from adults and very limited data from children
- The recommendation was extrapolated to extrapulmonary TB based on the generalization of data from adults

In people with signs and symptoms of TB meningitis, low-complexity automated NAATs on cerebral spinal fluid should be used for the initial diagnosis of TB meningitis rather than smear microscopy or culture (strong recommendation, high certainty of evidence).

Remarks:

- This recommendation applies to all patients with signs and symptoms of TB meningitis including people with HIV and children

In people with signs and symptoms of extrapulmonary TB, low-complexity automated NAATs on lymph node tissue aspirate, pleural tissue, pleural fluid, synovial fluid, peritoneal fluid or pericardial fluid *should* be used for the initial diagnosis of TB rather than smear microscopy or culture (strong recommendation, high certainty of evidence).

Remarks

- This recommendation applies to all patients with signs and symptoms of the respective form of extrapulmonary TB including people with HIV and children
- Data on LC-aNAATs performance on pericardial fluid, urine, blood were limited or inconsistent

In adults and adolescents with signs or symptoms or who screen positive for pulmonary TB, low-complexity manual NAATs should be used on respiratory samples as an initial diagnostic test for TB rather than smear microscopy/culture (strong recommendation, high certainty of evidence).

Remarks:

- Recommendations apply to all people with HIV with the caveat of low/moderate certainty of evidence. Concurrent testing with a LC-aNAAT and LF-LAM is preferred approach when available for people with HIV
- Recommendation on LC-mNAAT is extrapolated to use in children on respiratory samples (including induced sputum, gastric aspirate) based on the generalization of data from adults and very limited data in children, acknowledging the difficulties of collecting sputum specimens from children
- The use of the test on pediatric stool samples was very limited and there was no data for nasopharyngeal aspirate. The recommendation was therefore not extrapolated to these sample types. If LC-mNAATs are the only tests available for pediatric testing, they should be accompanied by culture testing on appropriate sample types or upward referred for further investigation
- No recommendation was made on test use for extra-pulmonary TB due to insufficient data
- No rifampicin resistance result – positive diagnostic test results require follow up testing for drug susceptibility

The products for which eligible data met the class-based performance criteria for LC-aNAATs were:

- Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, USA) – for pulmonary TB and extrapulmonary TB and resistance to rifampicin
- Truenat MTB Plus and Truenat MTB-RIF (Molbio, Goa, India) – for pulmonary TB and resistance to rifampicin

Data on Truenat MTB Plus and MTB-RIF were more limited than those on Xpert MTB/RIF Ultra.

The product for which eligible data met the class-based performance criteria for LC-mNAATs is:

- TB-LAMP (Eiken Chemicals, Tokyo, Japan) – for pulmonary TB

Regulatory approval from national regulatory authorities or other relevant bodies is required before implementation of these diagnostic tests.

Extrapolation to other brand-specific tests cannot be made, and any new in-class technologies or new indications for technologies currently included in the class will need to be evaluated by WHO Prequalification (WHO/PQ) (https://extranet.who.int/prequal/) and Global Tuberculosis Programme (WHO/GTB) respectively.

Next steps

- The updated policy guidelines on newly established classes of diagnostic technologies for TB and drug-resistant TB will be released in the fourth edition of the *WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis*. 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 GTB website. Prior to the release of the guidelines the evidence and methods can be requested from the WHO Global Tuberculosis Programme at gtbpci@who.int

- The updated guidelines will be accompanied by the *WHO operational handbook on tuberculosis. Module 3: Diagnosis.* The handbook will provide guidance on the technologies currently recommended, steps to introducing the new class of tests into a health programme and the model algorithms.

- The release of the new guidance will be followed by a series of WHO webinars for different regions to disseminate the new guidelines. The updates will also be included on the online WHO TB Knowledge Sharing Platform[6] providing easy access to the guidelines, implementation aids and eLearning tools, all in one place. The webinars and the platform will support countries in updating their national guidelines, training staff, informing programme budgets and facilitating the transition to the use of the new interventions. National TB programmes and other stakeholders are encouraged to seek advice from WHO before introducing the latest technologies recommended in the revised guidelines.

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[6] https://extranet.who.int/tbknowledge