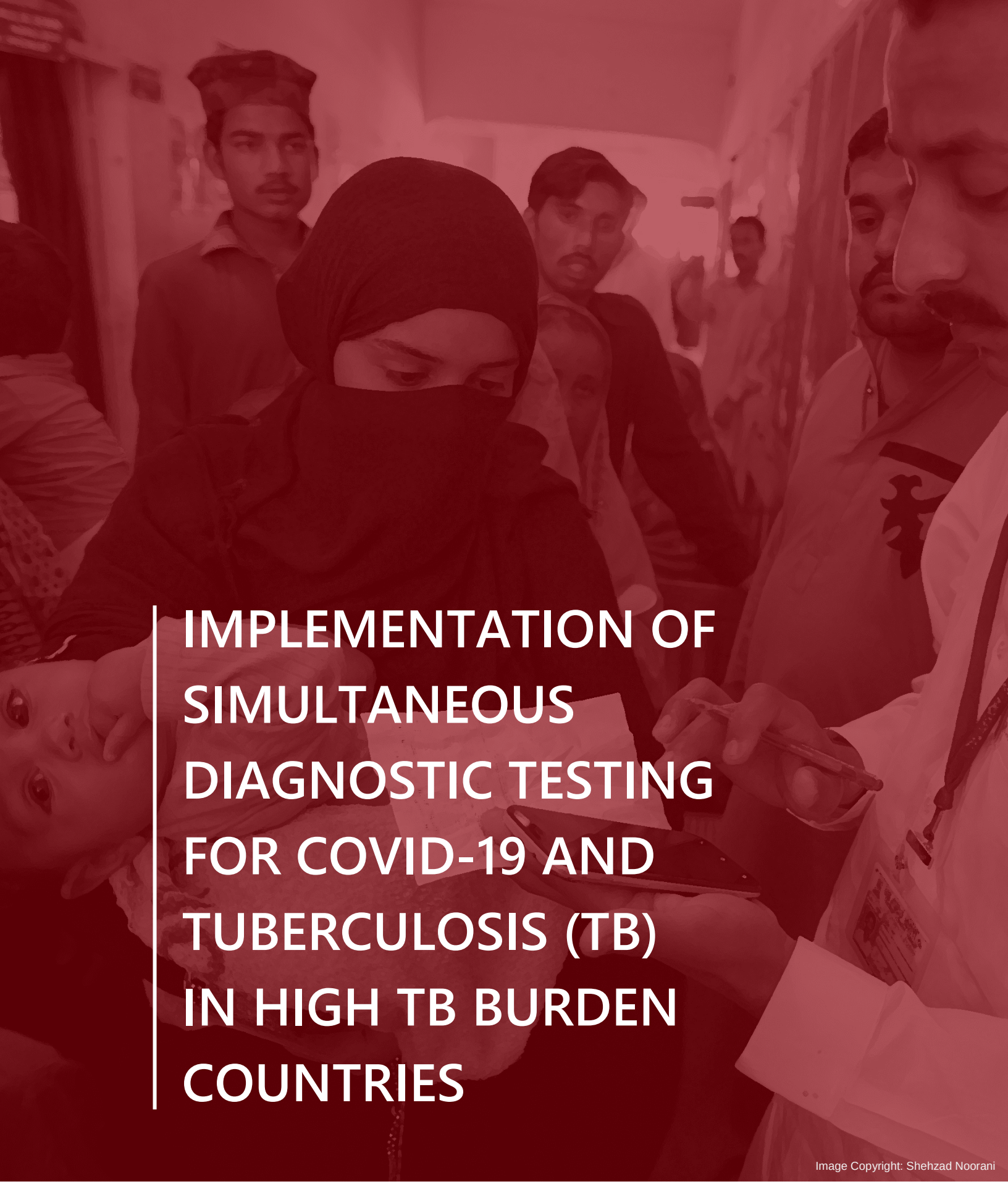

IMPLEMENTATION OF SIMULTANEOUS DIAGNOSTIC TESTING FOR COVID-19 AND TUBERCULOSIS (TB) IN HIGH TB BURDEN COUNTRIES

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USAID FROM THE AMERICAN PEOPLE

Stop TB Partnership

Implementation of simultaneous diagnostic testing for COVID-19 and TB in high TB burden countries

November 2021

This briefing note updates and expands upon guidance presented in the March 2021 USAID and Stop TB Partnership briefing note *Simultaneous, integrated diagnostic testing approach to detect COVID-19 and TB in high TB burden countries*.[1]

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Development of this document was made possible with financial support from the United States Agency for International Development. The views expressed herein are those of the authors and do not necessarily reflect those of the U.S. Agency for International Development or the U.S. Government.

[1] http://www.stoptb.org/assets/documents/covid/COVID-TB%20Testing%20Simultaneous_March%202021.pdf

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Introduction

Diagnostic testing is a critical and necessary step for the detection and control of pathogens of public health importance, including COVID-19 and TB. Testing identifies pathogens responsible for disease, guides appropriate treatment and informs contact tracing. Access to diagnostic testing for both COVID-19 and TB must urgently increase in countries most vulnerable to the devastating impact of both diseases.

A simultaneous, integrated approach to testing for COVID-19 and TB should be implemented in countries with a high burden of TB. While there are other pathogens that have similar respiratory symptoms, this approach is focused on COVID-19 and TB for the following reasons:

- COVID-19 and TB are respiratory diseases that manifest themselves with similar symptoms of cough, fever and difficulty breathing.
- Studies suggest that presence or history of TB increases the risk of SARS-CoV-2 infection, TB co-infection increases the risk of severe COVID-19 disease, and TB/SARS-CoV-2 co-infection is associated with rapid and severe symptom development and disease progression with poor outcomes for both diseases[2,3,4].
- Both TB and COVID-19 have co-morbidities or behaviors (malnutrition, diabetes, smoking, chronic obstructive pulmonary disease, HIV, etc.) that increase their risk for both diseases[5].
- Multi-disease diagnostic testing platforms exist that can test for both *Mycobacterium tuberculosis* and SARS-CoV-2.
- Both diseases require early detection and treatment to improve patient outcomes and reduce transmission among contacts and within communities.

For TB,[6] WHO recommends the use of a rapid nucleic acid amplification test (NAAT) as the initial diagnostic test for persons with signs and symptoms of TB. As such, implementation of additional testing capacity for TB should focus on establishing or expanding the availability of rapid molecular tests for TB.

For COVID-19[7], WHO considers NAATs to be the reference standard for diagnosis of acute SARS-CoV-2 infections. Because of their high sensitivity and specificity, NAATs are the preferred testing method in settings with a low prevalence of COVID-19 or in individuals with a low pre-test probability of having COVID-19.

WHO also recommends the use of rapid immunoassays to detect viral antigens (antigen-based rapid diagnostic tests or Ag-RDTs). Ag-RDTs are substantially less sensitive than NAATs, but offer the possibility of rapid, inexpensive and early detection of the most infectious COVID-19 cases in appropriate settings, such as in areas that are experiencing widespread community transmission, where the health system may be over-burdened and where it may not be possible to test all or any people with symptoms by NAAT.[8] Ag-RDTs perform

[2] Karla Therese L. Sy, Nel Jason L. Haw & Jhanna Uy (2020) Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. Infectious Diseases, 52:12, 902-907, DOI: 10.1080/23744235.2020.1806353
[3] M.S. Kumar et al. (9 January 2021) Mortality of TB-COVID-19 coinfection in India. International Journal of Tuberculosis and Lung Disease: https://theunion.org/news/mortality-of-tb-covid-19-coinfection-in-india
[4] Za Gao et al. (28 July 2020) Association between tuberculosis and COVID-19 severity and mortality: A rapid systematic review and meta-analysis. J Med Virol., 93:1, DOI: 10.1002/jmv.26311
[5] World Health Organization (15 December 2020) WHO Information Note: Tuberculosis and COVID-19: COVID-19: Considerations for tuberculosis (TB) care. https://www.who.int/docs/default-source/hqtuberculosis/covid-19-tb-clinical-management-info-note-dec-update-2020.pdf
[6] WHO consolidated guidelines on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021. https://www.who.int/publications/i/item/9789240029415
[7] WHO Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities Interim guidance (25 June 2021). https://www.who.int/publications/i/item/WHO-2019-nCoV-lab-testing-2021.1-eng
[8] Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays: interim guidance, 11 September 2020. World Health Organization. https://apps.who.int/iris/handle/10665/334253 and SARS-CoV-2 antigen-detecting rapid diagnostic tests: An implementation guide. 2020. World Health Organization. https://www.who.int/publications/i/item/9789240017740

well when the viral burden is high, i.e., in the days just before the onset of symptoms and the first 5−7 days after symptom onset. However, because of their lower sensitivity, Ag-RDTs are not recommended for use when the pre-test probability of the person having COVID-19 is low, such as in individuals without symptoms unless the person is a contact of a confirmed case.

Because the COVID-19 testing strategy will vary according to the epidemiological and geographic setting, available resources and the country specific context, it is likely that both NAATs and Ag-RDTs will play a role.

Simultaneous testing strategies

Simultaneous testing relies on collecting a specimen (usually a nasopharyngeal swab) for COVID-19 testing and a specimen (usually a sputum specimen) for TB testing during the same healthcare visit and transporting the specimens to the site(s) that conduct the laboratory testing.

Although the COVID-19 testing and TB testing could be done in different facilities, establishing the COVID-19 test and TB test at a common site could result in cost savings related to using a shared specimen transport and results reporting system as well as shared personnel, instruments and facility costs. The potential cost savings of a shared transportation system to a single site would need to be weighed against potentially longer turnaround times for getting test results, especially if Ag-RDTs could be implemented at or near the specimen collection site.

At a shared testing site, simultaneous testing may be done in a parallel manner (the COVID-19 test and TB test done on different testing platforms) or an integrated manner (the COVID-19 and TB test done on the same testing platform). Potential cost savings from integrated testing on a multi-disease testing platform may be generated relative to purchase, installation and maintenance costs; supply chain efficiencies; training and technical competencies of staff; shared quality assurance activities and streamlined workflow as well as flexibility for testing for other diseases or adapting to changes in testing demand.

See Annex 3 for more information on multi-disease testing platforms for TB and COVID-19.

The simultaneous testing strategy will vary according to the epidemiological situation, existing diagnostic networks and available resources. Different strategies may be required for different epidemiologic or geographic settings within a country. Country-specific considerations may include:

- existing molecular testing platforms and capacity for TB, COVID-19 and other diseases
- existing specimen referral systems
- financial aspects (available budget, cost of instruments and commodities, implementation costs, annual operating costs)
- procurement issues (supply chain, importation formalities)
- need for upgrading facilities to meet infrastructure requirements and operating conditions
- availability of a sufficient number of appropriately skilled human resources

WHO recommends that countries leverage and build upon existing diagnostic capacities to create a network of SARS-CoV-2 testing facilities. One opportunity is the network of laboratories that conduct TB NAATs, in part,

because the testing platforms used for TB NAATs can also be used for COVID-19 NAATs. Similarly, TB laboratories that conduct the urine lateral flow-lipoarabinomannan assay should be able to conduct Ag-RDTs for COVID-19. Furthermore, TB testing laboratories are often connected to health facilities that collect respiratory specimens with a reliable specimen transport system.

Successful implementation of any simultaneous testing strategy will require a strong training component to ensure that health care professionals that evaluate persons for possible COVID-19 or TB are aware of the requirements for simultaneous testing, the testing algorithm, which persons are eligible for simultaneous testing, how to order the tests, specimen requirements, specimen referral procedures and how to interpret, use and communicate the test results.

Scenarios for implementing simultaneous testing for COVID-19 and TB

The scenarios illustrate potential strategies to provide access to simultaneous testing for COVID-19 and TB.

Scenario 1: A country has a well-functioning network of laboratories that conduct Xpert MTB/RIF testing for TB. The testing sites are connected to specimen collection sites by a specimen referral system with short turnaround times.

In this situation, implementing Xpert SARS-CoV-2 testing at the Xpert MTB/RIF testing site would be a cost-effective approach to achieving simultaneous integrated testing. Xpert testing capacity should be increased as needed either through adding another or larger GeneXpert instrument or increasing working hours, e.g., add a second shift.

In this scenario, the prevalence of COVID-19 will likely vary considerably in the areas of the various testing laboratories of the network. Because of this uncertainty in prevalence (and hence uncertainty in positive and negative predicted values), NAATs are the preferred testing method.

The country may consider conducting a geospatial analysis of the testing network to assess coverage and identify potential areas in which to establish new simultaneous testing sites or expand the specimen transport network. The analysis may also identify areas in which the use of Ag-RDTs would be appropriate.

Scenario 2: Testing capacity for COVID-19 has been implemented in number of facilities, but those facilities do not have the capability to test for TB.

If an Ag-RDT is used or if the existing instrument for the COVID-19 NAAT is not compatible with WHO-approved rapid molecular tests for TB, implement a molecular test for TB that uses a multi-disease platform capable of testing for TB and COVID-19 at the existing COVID-19 testing facility. The biosafety requirements and technical complexity of the selected molecular test for TB should be compatible with the existing facility. The capacity of the testing platform should at a minimum be sufficient for the projected TB testing volume, and preferably, include extra capacity to accommodate surges in testing demand for either COVID-19 or TB.

If the current NAAT testing for COVID-19 is conducted on a multi-disease platform that can accommodate a WHO-approved rapid

molecular test for TB, implement the corresponding test for TB. Ensure that testing capacity matches the anticipated demand for COVID-19 tests and TB tests.

If molecular testing for TB cannot be implemented at a COVID-19 testing site, ensure that a sputum specimen is collected from each person being evaluate for COVID-19 and refer to a site that conducts molecular testing for TB. If necessary, establish a specimen referral system with a short turnaround time.

Scenario 3: In the capital city, a high-volume testing laboratory has been established to conduct HIV testing using the Roche cobas 8800 system (this same scenario could apply with an Abbott m2000 system or other centralized platform). Currently, the instrument is being used at 50% capacity. A specimen referral system connects the laboratory with collection sites throughout the country, but the specimen collection schedule (e.g., twice weekly) and transportation method (e.g., postal service) are key factors in the turnaround time that often exceeds 1 week.

The availability of unused capacity of the Roche cobas 8800 instrument suggests that implementation of the Roche cobas SARS-CoV-2 test and cobas MTB test could be a cost-effective approach to achieving simultaneous testing, assuming that the HIV program agrees and that care is taken to ensure that the COVID-19 and TB testing does not interfere with the HIV testing. Implementation of the testing should be accompanied by efforts 1) to integrate the referral of specimens for TB and COVID-19 into the referral of specimens for HIV while ensuring that the needs of all programs are met and 2) to improve the specimen referral system to decrease the turnaround time to an acceptable time for the simultaneous testing algorithm. Finally, the performance of the shared testing platform should be monitored to determine if the needs of the HIV, TB and COVID-10 programs are being met and whether establishing additional testing capacity may be warranted.

Scenario 4: A regional referral hospital serves a catchment area that is predicted to generating a demand for 20 COVID-19 tests and 20 TB tests per day, but neither TB nor COVID-19 testing is available at the hospital.

In this setting, the hospital should establish a specimen referral system connecting the specimen collection sites with the hospital while procuring and implementing a multi-disease testing platform that can perform TB and COVID-19 testing. Several TB/COVID-19 multi-disease platforms can be configured to accommodate the anticipated workload of 40 tests per day, e.g., BD MAX or GeneXpert 16-module instruments, or alternatively multiple platforms may be procured, e.g., Truenat or GeneXpert 4-module instruments, in order to match the anticipated workload.

Scenario 5: In a remote region of the country, the supply of electricity is unreliable and it is not feasible to establish a specimen referral system with a short turnaround time.

In this setting, battery-powered multi-disease platforms (e.g., Truenat or GeneXpert Edge systems) are one solution. Lessons learned from the rollout of Xpert MTB/RIF suggest that creative use of solar power and generators should enable implementation of GeneXpert or Truenat systems. Each of these systems has options that should allow one to match testing demand with instrument capacity.

Scenario 6: A large, urban hospital in an area

experiencing widespread community transmission of SARS-Cov-2 is implementing a service to screen persons for COVID-19. The hospital has a laboratory on-site that conducts immunoassays for HIV or other diseases.

In this setting, it should be possible to implement Ag-RDTs in the hospital laboratory by leveraging their expertise in conducting immunoassays. In so, a specimen should be collected and tested for COVID-19 using the Ag-RDT in the on-site laboratory and a specimen should be collected and transported to a facility that conducts TB testing. Programs may also consider implementing NAATs for COVID-19 at the TB laboratory to provide follow-up COVID-19 molecular testing if needed and to provide surge capacity.

Alternatively, the hospital laboratory could implement a TB NAAT and COVID-19 NAAT on a multi-disease testing platform.

Scenario 7: In a network of peripheral laboratories, AFB-sputum smear microscopy is the primary test used to aid in the diagnosis of TB.

Because WHO recommends replacing AFB-smear microscopy with a rapid molecular test as the initial diagnostic test for TB, countries should consider establishing the capacity to conduct TB NAATs and COVID-19 NAATs in the peripheral laboratories by installing a suitable multi-disease testing platform such as the GeneXpert system or Truenat system. This would not only provide the needed COVID-19 testing capability but also align the peripheral laboratory with WHO recommendations for TB testing.

As described in scenario 1, the prevalence of COVID-19 will likely vary considerably in the various peripheral laboratories, and hence, NAATs would be the preferred testing method.

Valerie and Tania Jean-Baptiste hold Kerby, their 6-month-old baby boy, who is being treated for TB.
Copyright: Maggie Steber 2019

Considerations for implementing the simultaneous testing algorithm and associated tests

Implementing a simultaneous testing algorithm and associated tests involves three interrelated processes: 1) design and implementation of a screening and diagnostic testing algorithm, 2) development of a laboratory network that provides the diagnostic services needed to support the use of the algorithm, and 3) building the laboratory capacity and human resources to conduct the needed tests.

Critical early steps include identifying the population to be tested, defining the screening and diagnostic testing algorithm, strengthening the laboratory network and selecting the testing platforms and tests to be used. The following sections organize the key steps around 1) policies and planning, 2) regulatory issues, 3) equipment, 4) supply chain, 5) procedures, 6) digital data, 7) quality assurance, 8) recording and reporting, 9) training and competency assessment and 10) monitoring and evaluation. The steps are only briefly summarized in this document. The reader is referred to *the WHO Operational Handbook for tuberculosis, Module 3*[9] for an in-depth discussion of the process. The process should be adapted for use in line with the policies and guidelines of the national TB program and COVID-19 response.

In general, a phased approach which builds upon existing diagnostic capacities and laboratory networks should be used to establishing simultaneous testing for TB and COVID-19. For example, countries could start by implementing COVID-19 testing at facilities that conduct molecular tests for TB (each WHO-approved rapid test for TB is conducted on a platform that can also accommodate a molecular test for COVID-19) and implementing molecular tests for TB at facilities that are conducting COVID-19 testing on a multi-disease platform compatible with an approved molecular test for TB. In both cases, it is essential that testing capacity is adequate to meet anticipated testing demand for each disease. A critical component of a testing strategy will be a specimen referral system with a short turnaround time that connects specimen collection sites with the testing sites, if testing is not conducted at the specimen collection site.

Key steps:

- ✓ Establish a technical working group to lead the process
- ✓ Define the screening and diagnostic algorithm
- ✓ Perform a situational analysis of the laboratory network and facilities
- ✓ Develop a realistic costed implementation plan and budget for on-going costs
- ✓ Select, procure and install equipment in safe, functional testing sites
- ✓ Ensure a reliable supply of quality-assured reagents and consumables
- ✓ Develop standard-operating procedures and clinical protocols
- ✓ Utilize diagnostic connectivity solutions
- ✓ Implement a comprehensive quality assurance programme
- ✓ Implement training, mentoring and competency assessment programs
- ✓ Monitor and evaluate the implementation and impact of the new test

[9] WHO operational handbook on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021. https://www.who.int/publications/i/item/9789240030589

1. Policies and planning

1.1 Establish a Technical Working Group (TWG) and define roles and responsibilities

A technical working group (TWG) comprised of representatives from all key stakeholders should be established to guide the implementation process for the simultaneous testing algorithm and associated diagnostic tests. The TWG should be mandated to 1) advise the MOH on implementation, 2) develop action plans, 3) oversee the implementation of the algorithm and associated tests and 4) assess the impact and success of introduction of the algorithm and tests.

1.2 Review WHO policies and available technical and implementation guides

The TWG should familiarize themselves with contents of the relevant WHO policies and guidance as well as any available guidance from USAID, Stop TB Partnership, Global Fund and implementing partners.

1.3 Define the purpose of the simultaneous testing system and the populations to be tested

Programs must clearly define the purpose, scope, and intended use of the simultaneous testing algorithm and associated tests as that will impact many aspects of the implementation plan. Programs must clearly define the criteria for selecting persons to be tested.

1.4 Develop or update national diagnostic algorithm and diagnostic and clinical guidelines

A new or revised diagnostic algorithm must be put in place only after a formal evaluation, review and approval. The following points should be considered when designing or reviewing algorithms:

- characteristics (risk groups) of the population being served
- the capacity of clinical services to offer diagnosis and treatment
- availability of X-ray systems with or without CAD software to be used as screening tools
- the current and planned capacity of the country's laboratories
- the adequacy of systems for specimen collection and transport
- the specific diagnostic tests and testing platforms in use or being considered for use

Annex 1 contains a model algorithm for testing for COVID-19 and TB in high TB burden countries. The model[10] relies on three screening and testing pathways:

1) Testing individuals for both TB and SARS-CoV2 should be considered when both TB and SARS-CoV-2 are prevalent in the patient's community and:

- clinical signs and symptoms meet the case definitions for both TB and COVID-19;
- there are risk factors for both diseases (e.g., exposures to known contacts); or
- there are risk factors for poorer outcomes from both diseases (e.g., diabetes, advanced age).

2) Testing people with confirmed TB for SARS-CoV-2 infection when:

- they meet the COVID-19 case definition,
- there is persistence or worsening of their condition despite appropriate treatment for the specific form of TB (e.g., drug-resistant TB); or
- they are contacts of confirmed or probable cases of COVID-19

[10] Global Fund Briefing Note: Testing for both Tuberculosis and SARS-CoV-2. 2021. https://www.theglobalfund.org/media/11438/covid19_tb-testing_briefingnote_en.pdf

3) Testing people diagnosed with COVID-19 for TB disease when:

- respiratory symptoms don't abate, e.g., prolonged cough (2 weeks or more), progression to haemoptysis, night sweats or weight loss;
- there is a previous history of TB in the same person or if they are a close contact with another person with confirmed TB; or
- chest radiography or imagery suggests TB

The TWG should develop or review of guidelines for the use of the simultaneous testing results in patient care decisions. Clinical guidelines should provide clear guidance to clinicians, nurses and health care professionals on the intended use of the simultaneous testing algorithm; target patient populations; how to order the tests; and how to interpret, use and communicate the results.

1.5 Perform a situational analysis

a. Specimen referral systems

Well-designed specimen referral systems underpin a strong diagnostics network and can help to optimize access to services, prevent the need and associated costs for patients to travel, lead to equity in access to health care, improve promptness of testing, and facilitate linkages to care. The model algorithm (Annex 1), relies on an integrated specimen transport and referral system for TB and COVID-19. As such, it is important to monitor and evaluate routinely to ensure the system is meeting the needs of both TB and COVID-19 programs. A checklist for evaluation a specimen referral system may be found in *GLI guide to TB Specimen Referral Systems and Integrated Networks.*[11]

b. Identify testing sites and capacities

Ideally, specimens should be referred to a laboratory that can conduct tests for both diseases. As such, the testing laboratory will need either a multi-disease testing platform or separate instruments to conduct the COVID-19 and TB tests.

A review of the country's lists of existing COVID-19 testing sites and TB testing sites and inventory of instruments and tests (in some countries it may be necessary to conduct a survey to generate the lists) should identify sites that have multi-disease testing platforms or could be upgraded to conduct both tests. Countries may also consider implementing COVID-19 and TB testing on a high-throughput multi-disease testing platform that is currently being used for another disease (e.g., HIV testing) provided the other disease program concurs and safeguards are in place to ensure that the use of the shared platform meets the needs of all programs, particularly that of the original disease program.

The testing capacity at a simultaneous testing site must match the anticipated demand for COVID-19 and TB testing. The existing workload and potentially available testing capacity at a site should be available from quarterly or annual reports from the laboratory. The epidemiology of TB and COVID-19 in the catchment area (i.e., area served by the specimen collection sites that refer samples to the testing laboratory) should provide an estimation of the number of persons needing simultaneous testing. Matching demand and capacity may require procurement and installation of testing equipment and hiring

[11] *GLI Guide to TB Specimen Referral Systems and Integrated Networks*. 2017. http://www.stoptb.org/wg/gli/assets/documents/GLI_Guide_specimens_web_ready.pdf

During an awareness setting, a health worker speaks to clients waiting at a clinic about TB symptoms. Copyright: Shehzad Noorani 2018.

additional laboratory staff.

Much of the information needed for identifying potential simultaneous testing sites and their capacities should be available from the Ministry of Health or disease programs. Some countries may decide to conduct a more comprehensive diagnostic network analysis[12] to address these issues. However, this comprehensive approach requires considerable human resources and time (3 to 6 months) as well as external expert technical assistance. This may not be appropriate or necessary for the urgent response to the needs for COVID-19 and TB testing. It may be sufficient to compile and analyze information in a spreadsheet to identify opportunities for simultaneous testing. Key information includes the population needing testing (what is the potential demand for testing?); number and locations of health facilities where people seek care for TB and for COVID-19 (where are specimens collected for testing?); number, locations, capabilities and capacities of testing sites for TB and COVID-19 (where is testing done?); and referral linkages (how do specimens get from collection sites to testing sites?).

b. Situational analysis of the prospective testing laboratories

A situational analysis of the testing laboratories and capacities should be conducted to inform the plans for implementing the new algorithms and associated tests. For most tests, key elements to be assessed include staff skills, expertise, and experience; IT capabilities; diagnostics connectivity; availability and adequacy of SOPs; supply chain; financial resources and quality assurance systems. The

[12] Nichols, K.; Girdwood, S.J.; Inglis, A.; Ondoa, P.; Sy, K.T.L.; Benade, M.; Tusiime, A.B.; Kao, K.; Carmona, S.; Albert, H.; et al. Bringing Data Analytics to the Design of Optimized Diagnostic Networks in Low- and Middle-Income Countries: Process, Terms and Definitions. Diagnostics 2021, 11, 22. https://doi.org/10.3390/diagnostics11010022

assessment should also determine needs for revision to training, recording and reporting forms and monitoring and evaluation (M&E) tools. For the prospective testing site, important considerations are the reliability of the electricity supply, temperature and humidity control, reagent storage requirements, waste disposal, biosafety requirements, physical facilities, number and technical skill of laboratory staff (e.g., precision pipetting, computer skills) and availability of internet and diagnostics connectivity.

1.6 Develop a costed operational plan for implementation in a phased manner

A detailed, costed, prioritized action plan for phased implementation with targets and timeline should be developed. Implementation of a diagnostic algorithm and associated tests often must overcome potential obstacles such as cost of instruments, ancillary equipment and consumables; requirements for improving or establishing the necessary laboratory and network infrastructure (e.g., a specimen transport system); the need for specialized, skilled and well-trained staff; the need for expert technical assistance; maintenance of confidentiality of patient information; and establishment of a quality assurance system.

Successful implementation of the plan will require financial and human resource commitments from MOH, with possible support of implementing partners. A budget should be developed to address activities in collaboration with key partners. Budget considerations are summarized in Annex 2.

2. Regulatory requirements for diagnostic tests

2.1 Determine importation requirements

For the COVID-19 test and the TB test, national authorities should be consulted to determine relevant processes to be followed for importation. Countries should work closely with the manufacturers and authorized service providers of equipment and consumables to determine importation and registration requirements and to enable initiation of country verifications, if required.

2.2 Conduct country verification study as required

Laboratories that are implementing a new test should conduct small-scale verification studies to demonstrate that 1) the laboratory can achieve the same performance characteristics as claimed by the manufacturer and 2) the method is suitable for its intended use in the population of patients being tested. Countries must make their own determination on the needs for verification based on national guidelines and accreditation requirements.

3. Equipment

3.1 Select, procure, Install and set-up equipment

The use of multi-disease instruments that can test for both COVID-19 and TB is recommended. See Annex 3 for a list of suitable testing platforms. It is anticipated that some sites will have already procured and installed a suitable multi-disease testing platform as part of testing for one of the diseases. Other sites will need to select, procure and install a suitable instrument. The most suitable instrument for a laboratory will depend on epidemiological and geographical settings; projected testing volumes; facility and biosafety requirements; human resources capacity and capabilities; and specimen referral systems. Note that different instruments may be best suited for different laboratories in different settings.

Whichever instrument is selected, most instruments will require expert set-up with all installation activities performed by the manufacturer's engineers. Potential set-up complexities include power supply and backup options, electrical connections, environmental conditions for the laboratory, biosafety and ventilation requirements, computing hardware and software, a maintenance, equipment warranty and necessary training.

Nurse with Victor, who is currently receiving treatment for TB. Copyright: Ashley Gilbertson 2018

3.2 Instrument verification and maintenance

All instruments must be documented to be "fit for purpose" through verification with known positive and/or negative material prior to commencing testing of clinical specimens. Instrument verification is conducted at installation, after service or calibration, or after moving instruments.

Many tests rely on precision instruments that require regular preventive maintenance and adhoc servicing and maintenance. Preventive maintenance should be performed on regular basis by the end-user to ensure good performance of the instrument.

3.3 Assess site readiness and ensure a safe and functional testing site

Each testing site should be evaluated for readiness using a standardized checklist prior to the testing of clinical specimens. In addition, existing testing sites should be regularly assessed for safety and operational functionality.

4. Supply chain

4.1 Review forecasting, ordering and distribution procedures

Uninterrupted availability of reagents and disposables at the testing site is essential to ensure consistent service during routine use. Purchasing and distribution strategies should be reassessed at regular intervals to ensure they are responsive to the needs and current situation.

4.2 Develop procedures to monitor reagent quality and shelf-life

The shelf-life of reagents and their required storage conditions must be taken into consideration in the design of a procurement and distribution system. The laboratory must establish standard operating procedures for handling the reagents and chemicals used to ensure both quality and safety. New lot testing, also known as lot-to-lot verification, should be performed on new batches of reagents or test kits to ensure quality.

5. Procedures

5.1 Develop standard operating procedures

Procedures must be defined, selected, developed or customized for:

- Identifying patients for whom the test should be performed
- Collecting, processing, storing and transporting specimens to the testing laboratory
- Laboratory testing
- Data analysis, security and confidentiality (See Section 6)
- Process controls (internal quality controls) and external quality assessment (See Section 7)
- Recording and reporting results (See Section 8)

A well-defined, comprehensive set of standard-operating procedures (SOPs) that addresses all aspects of the laboratory testing processes from sample collection to results reporting will be essential, in part, because errors at any step can have significant impact on the quality of the testing.

5.2 Update clinical procedures and strengthen the clinical-laboratory interface

In addition to laboratory-related SOPs, clear clinical protocols and guidance will be needed for the selection of patients to be tested, ordering tests, interpreting test results, and making patient care decisions. All clinical staff involved in the diagnosis and management of patients must be sensitized on updated procedures prior to use of the new testing algorithm and associated tests.

6. Digital data

6.1 Digital data and diagnostics connectivity

Laboratory information management systems (LIMS), electronic data reporting systems and diagnostic platforms with connectivity solutions should improve timeliness of results reporting to patients, healthcare providers and surveillance systems. The COVID-19 pandemic highlights the need to capture and report test results in real-time through integrated dashboards and mobile applications to facilitate access for clinical and programmatic decision-making across diseases. Programs should ensure that facilities testing for TB and COVID-19 have diagnostic data connectivity solutions available and functioning to report testing data. In settings where diagnostic connectivity is not yet available, reliable digital mobile solutions should be considered for quicker result reporting. Tracking the status of care and follow-up of people tested and treated for both TB and COVID-19 will require integrated data systems.

Many of the latest testing platforms offer the opportunity for the use of digital data. Diagnostics connectivity[13] refers to the ability to connect diagnostic test devices that produce results in a digital format in such a way as to transmit data reliably to a variety of users. For example, data can also be transmitted automatically to 1) clinicians and patients which allows for faster patient follow-up, 2) LIMS or electronic registers, reducing staff time and the chance of transcription errors, and greatly facilitating monitoring and evaluation processes, and 3) the MOH to assist with surveillance of disease trends.

6.2 Develop procedures for data backup, security and confidentiality

An SOP for regular backing up of data (e.g., to an external drive) is essential as well as an SOP for data retrieval. There also must be policies and procedures to ensure the security of laboratory data and confidentiality of patient data in line with national and international regulations.

7. Quality assurance, control, and assessment

7.1 Implement a comprehensive quality assurance programme

A comprehensive quality assurance or quality management programme is needed to ensure the accuracy, reliability and reproducibility of test results. A comprehensive discussion of the essential elements of a quality assurance system may be found in the *GLI Practical Guide to TB Laboratory Strengthening*.[14] In this section, quality control, external quality assessment (EQA) and quality indicator monitoring are described.

7.2 Establish and monitor quality controls

Quality control (QC) monitors activities related to the analytical phase of testing with the goal of detecting errors due to test failure, environmental conditions, or operator performance before results are reported. Internal quality controls typically involve examination of known substances at the same time and in the same manner as patient specimens to monitor the accuracy and precision of the analytical process.

7.3 Develop an external quality assessment (EQA) program

An EQA program includes proficiency testing, re-checking or inter-laboratory comparisons, regular on-site supportive supervision and timely feedback, corrective actions and follow-up.

7.4 Monitor and analyze quality indicators

Routine monitoring of quality indicators, also known as performance indicators, is a critical element of assuring the quality of any diagnostic test. Quality indicators specific to the TB test and COVID-19 test should be adapted from international guidelines or developed and analysed on a monthly or quarterly basis.

8. Recording and reporting

8.1 Review and revise request for examination and reporting forms

Depending on the current format of the country's requisition (specimen examination request) form, it may be necessary to make revisions to accommodate simultaneous testing. Countries should determine if an update of the examination forms is necessary, considering the cost and time taken for such a revision.

[13] *GLI Quick Guide to TB Diagnostics Connectivity Solutions*. 2016. http://www.stoptb.org/wg/gli/assets/documents/gli_connectivity_guide.pdf
[14] *GLI Practical Guide to TB Laboratory Strengthening*. 2017. http://stoptb.org/wg/gli/gat.asp.

The forms used for reporting test results must balance the need to convey the information provided by the test and the information essential to allow a clinician to interpret the results and to act promptly on the results.

8.2 Review and revise laboratory and clinical registers

Current laboratory and clinical registers may need to be modified to record the results of the diagnostic tests being implemented. Forms for laboratory records may also need to be modified. Countries should implement a standardized approach to record test results in laboratory and clinical registers and use it consistently across all testing and clinical sites.

9. Training and competency assessment

9.1 Develop and implement a training curriculum and strategy

Implementation of a testing algorithm and associated tests requires training beyond the steps required to carry out the test. Test users must be trained in the operation and maintenance of the test instrument, correct performance of the tests and carrying out the associated QA activities.

Clinician training or sensitization must be done in parallel with training of laboratory staff to ensure all clinicians involved in screening and care of patients understand benefits and limitations of the new test, are sensitized to the new testing algorithm, test requisition process, specimen requirements, specimen referral procedures and interpretation of results.

9.2 Assess and document the competency of staff

Competency assessments should be performed using a standardized template after training and periodically (e.g., annually) thereafter and should include assessment of the knowledge and skills for performing each of the tasks involved in diagnostic testing. The results of competency testing should be recorded in personnel files.

10. Monitoring and evaluation

10.1. Monitor implementation of the diagnostic test

During the initial planning phase, countries should establish a set of key indicators and milestones to monitor the implementation process. Once launched, utilization of the testing services should be tracked.

10.2. Monitor and evaluate impact of the diagnostic tests

A framework for monitoring and evaluation of the impact of a testing algorithm and associated tests is essential to inform decision-making. For each objective of a test, indicators to assess its impact should be developed. For each indicator, programs should define its purpose, target, data elements, data sources, how to calculate, process indicators and corresponding data elements. As part of demonstrating the impact of a testing algorithm and associated test and to assist with planning and policy making, programs should consider evaluating the cost-effectiveness and end-user perspective one year after implementation.

Suggested reading

Global Fund. COVID-19 Response Mechanism Information Note, 25 June 2021. https://www.theglobalfund.org/media/10749/covid19_c19rm-technical_informationnote_en.pdf

USAID and Stop TB Partnership. 2021. Simultaneous, integrated diagnostic testing approach to detect COVID-19 and TB in high TB burden countries. http://www.stoptb.org/assets/documents/covid/COVID-TB%20Testing%20Simultaneous_March%202021.pdf

Guidance note on Bi-directional TB-COVID screening and screening of TB among ILI/SARI cases: MoHFW, Govt of India: https://www.mohfw.gov.in/pdf/1TBCOVIDscreeningguidancenote.pdf

SARS-CoV-2 antigen-detecting rapid diagnostic tests: An implementation guide. 2020. World Health Organization. https://www.who.int/publications/i/item/9789240017740

Global Fund Briefing Note: Testing for both Tuberculosis and SARS-CoV-2. October 2021. https://www.theglobalfund.org/media/11438/covid19_tb-testing_briefingnote_en.pdf

ANNEXES

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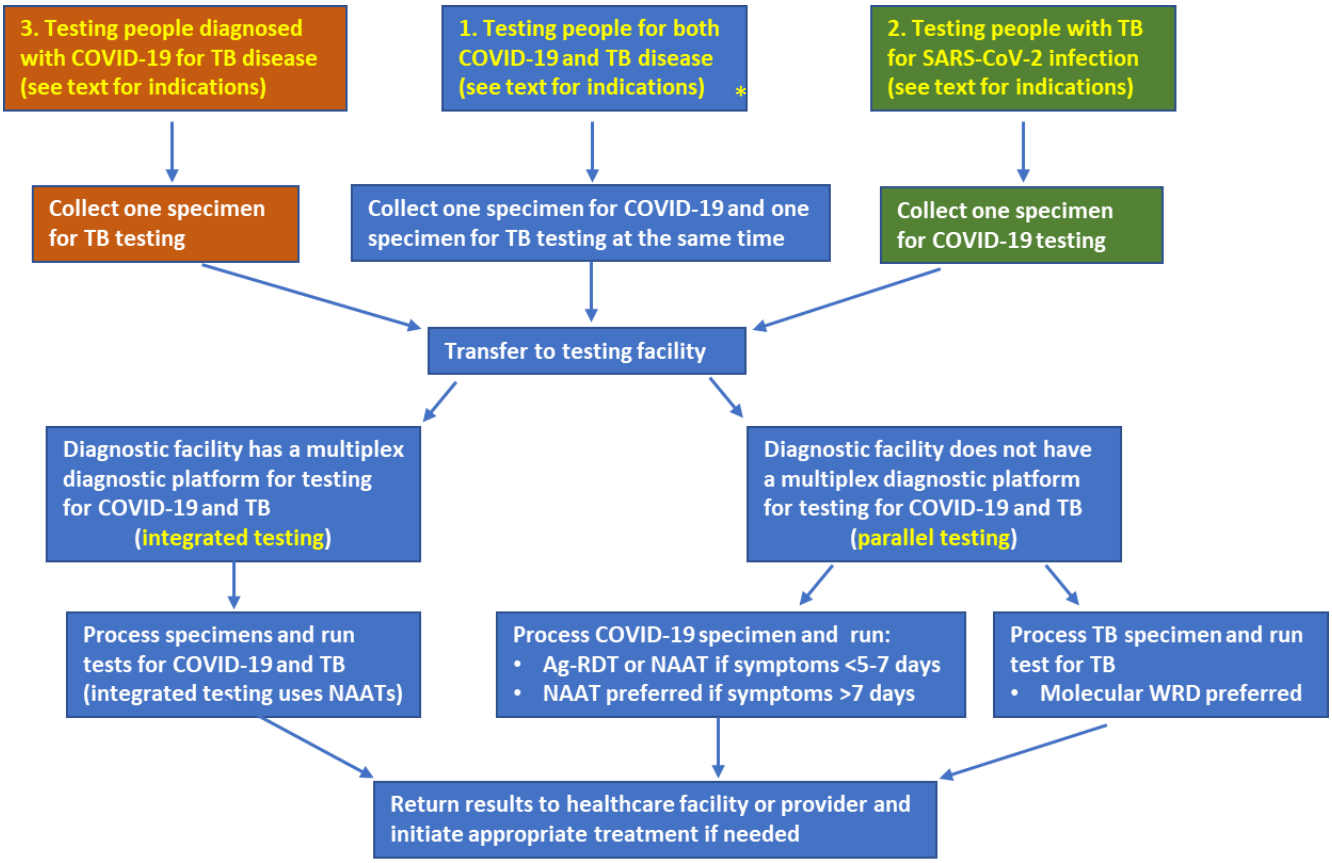
Annex 1. Model algorithm for testing for COVID-19 and TB in high TB burden countries

(Adapted from Global Fund Briefing Note[15] and USAID and Stop TB Partnership briefing note[16])



* Simplified algorithm showing main decision points. Other tests may be considered (e.g., chest X-ray with or without computer aided detection software).

Workflow 1. Testing people for both TB and SARS-CoV2 should be considered when both TB and SARS-CoV-2 are prevalent in the patient's community and:

- clinical signs and symptoms meet the case definitions for both TB and COVID-19;
- there are risk factors for both diseases (e.g., exposures to known contacts); or
- there are risk factors for poorer outcomes from both diseases (e.g., diabetes, advanced age)

Workflow 2. Testing people with confirmed TB for SARS-CoV-2 infection should be considered when:

- they meet the COVID-19 case definition,
- there is persistence or worsening of their condition despite appropriate treatment for the specific form of TB (e.g., drug-resistant TB); or
- they are contacts of confirmed or probable cases of COVID-19

[15] Global Fund Briefing Note: Testing for both Tuberculosis and SARS-CoV-2. October 2021. https://www.theglobalfund.org/media/11438/covid19_tb-testing_briefingnote_en.pdf

[16] USAID and Stop TB Partnership. 2021. Simultaneous, integrated diagnostic testing approach to detect COVID-19 and TB in high TB burden countries. http://www.stoptb.org/assets/documents/covid/COVID-TB%20Testing%20Simultaneous_March%202021.pdf

Workflow 3. Testing people diagnosed with COVID-19 for TB disease should be considered when:

- respiratory symptoms don't abate e.g., prolonged cough (2 weeks or more), progression to haemoptysis, night sweats or weight loss;
- there is a previous history of TB in the same person or if they are a close contact with another person with confirmed TB; or
- chest radiography or imagery suggests TB

Annex 2. Budgetary considerations for implementing a new testing algorithm and associated tests

Successful implementation of the plan will require financial and human resource commitments from MOH, with possible support of implementing partners. A budget should be developed to address activities in collaboration with key partners. Technical assistance may be needed.

Budgetary consideration
Policies and planning
• Workshop for stakeholder engagement and planning • Cost of TWG meetings • Technical workshop for guideline and algorithm update • Situational analysis cost – human resources (HR), travel and report writing • Printing and distribution costs for revised guidelines and algorithms • Development of a costed operational plan • Cost of external technical assistance, if needed
Regulatory
• Regulatory submission costs for a new test, if applicable • Importation processes and costs • Verification study, if required – samples, reagents, HR
Equipment

• Costs of assessing site readiness – travel, HR
• Costs of upgrading laboratory facilities and infrastructure (e.g., electricity, air conditioning, etc.) to ensure a safe and functional testing site
• Costs to adhere to biosafety precautions and biological and chemical waste disposal requirements
• Select, procure and install equipment
  • Purchase (or lease) of instrument and needed ancillary equipment
  • Delivery and importation costs
  • Installation by manufacturer or authorized service provider (e.g., per diems, travel)
  • Training
  • Instrument verification
  • Extended warranty or service contract
• Costs of routine preventive maintenance
• Costs of annual maintenance or calibration

Supplies
• Workshop for stakeholders involved in procurement to strengthen the supply chain • Cost of maintaining centralized stores and costs of distribution • Material cost per test, including but not limited to test reagents, consumables, sample collection items, printing paper, etc. Additional equipment costs that include additional equipment requirements (printer, computer, printer cartridges), shipping and courier costs • Costs of new lot testing
Procedures
• Workshop and HR for the development of SOPs • Printing and dissemination of revised standard operating procedures • Development, printing and dissemination of revised clinical protocols and guidance for the selection of patients to be tested, ordering tests, interpreting test results, and making patient care decisions
Digital data
• Purchase and implementation of a laboratory information management system, if applicable

• Purchase and installation of a diagnostics connectivity solution, if applicable • HR and training • Costs of data transmission (e.g., high speed internet service) • Costs associated with providing and maintaining a remote monitoring system in-country
Quality assurance, control and assessment
• Preparation and regular review of all testing and quality assurance documents (SOPs, checklists, *etc*.) based on national requirements • Cost of conducting quality controls (e.g., testing known positives or negatives) • Costs of HR for routinely collecting and analysing quality indicators • Costs of conducting on-site visits – travel, HR, preparation of checklists and reports • Costs associated with hosting an on-site visit and preparation of documents • Costs associated with providing PT panels and overseeing PT, reporting results and corrective actions and costs associated with testing PT panels at each site • Costs associated with re-testing of samples at a higher-level laboratory (e.g., shipment of samples, testing, reporting, etc.), if applicable
Recording and reporting
• Workshop and HR to update recording and reporting forms, registers, etc. • Preparation, printing and distribution of standardized test request and results reporting forms • Preparation, printing and distribution of standardized logbooks
Training and competency assessment
• Workshop and HR to update training packages for laboratory and clinical staff • Training-of-trainers workshop, participant and instructor travel, on-site trainings and sensitization meetings • Printing and distribution of updated training manuals and sensitization materials • Costs associated with facility and classroom-based training including travel, accommodation, printing materials, venue hire & catering. • Costs associated with annual competency testing of staff
Monitoring and evaluation
• Meetings to update monitoring and evaluation system and regular meetings to review impact of transition and re-plan • Monitoring and evaluation refresher training • Operational research study to measure clinical impact
Annual on-going costs
• Consumables and reagents for diagnostic testing • Costs associated with repeat testing and proficiency testing • Specimen referral and results reporting • Human resources • Equipment calibration and servicing • Diagnostics connectivity • Quality assurance

Annex 3: Multi-disease testing platforms for simultaneous testing for COVID-19 and TB

For simultaneous testing, multi-disease testing platforms are recommended because of potential cost savings related to purchase, installation and maintenance costs; supply chain efficiencies; training and technical competencies of staff; and streamlined workflow as well as flexibility for testing for other diseases or adapting to changes in testing demand.

Although there are a large number of nucleic acid amplification tests (NAAT) to detect SARS-CoV-2, the Table below only includes multi-disease testing platforms for which there is an approved SARS-CoV-2 NAAT and a WHO-recommended TB NAAT.

Nucleic acid amplification testing (NAAT) platform	TB NAAT is WHO-recommended	SARS-CoV-2 NAAT is on WHO Emergency Use Listing	SARS-CoV-2 NAAT is approved pursuant to emergency procedures of one of the Regulatory Authorities as defined under the Global Fund's Quality Assurance Policy
Cepheid GeneXpert	✓	✓	✓: US FDA EUA, Health Canada/ Interim Order, Australia TGA
Abbott Realtime	✓	✓	✓: US FDA EUA, Health Canada/Interim Order
Roche cobas 6800/8800	✓	✓	✓: US FDA EUA, Health Canada/Interim Order, Japan PMDA
BD MAX	✓		✓: US FDA EUA, Health Canada/Interim Order
Molbio Truenat	✓		*

*SARS-CoV-2 Truenat test is widely used in India following national regulatory approval

Of the above NAAT platforms able to detect TB and COVID-19, the GeneXpert and Truenat systems can be placed at peripheral sites, improving access to care and reducing diagnostic delay.

The Abbott system, BD MAX system, and Roche system are suitable for use in the intermediate or central tiers of the TB laboratory network considering the requirements of infrastructure, equipment and technical skills of laboratory staff. Because of size, cost and throughput, the BD MAX may be more suitable than the Abbott or Roche systems for use at the intermediate or regional level, whereas all three systems are suitable for use at the central level.

Current laboratory biosafety guidelines from WHO indicates that aerosol generation is minimal for sample manipulation procedures required for both COVID-19 and TB sample preparation for near point of care assays including the GeneXpert assay, and therefore a Biosafety Level 2 laboratory with biosafety cabinet is not needed when specific conditions are met.