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Simultaneous, integrated diagnostic testing approach to detect COVID-19 and TB in high TB burden countries

Introduction

Globally, there have been more than 126 million COVID-19 confirmed cases including 2.7 million deaths¹ with the vast majority being recorded in the Americas and European regions. While cases and deaths are increasing in other regions of the world, the disparity in access to testing makes it difficult to fully understand the magnitude of COVID-19 cases and deaths in developing countries in Africa, Southeast Asia and Western Pacific regions.

Before COVID-19, tuberculosis (TB) was the leading cause of death from an infectious disease globally. Although great improvements have been made over the past several years to find and treat TB in the highest burden countries, there was a drastic decline in diagnosis and treatment of TB in 2020 due to the COVID-19 pandemic. Recent data in 9 countries representing 60% of the global TB burden show a decline in TB detection ranging from 16-41%². This drop has brought the overall number of people diagnosed and treated for TB in these countries to 2008 levels, a setback of 12 years.

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, informs contact tracing, and helps countries allocate resources and staff. 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-

¹ <https://covid19.who.int/>

² http://stoptb.org/news/stories/2021/ns21_011.html



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CoV-2 co-infection is associated with rapid and severe symptom development and disease progression with poor outcomes for both diseases^{3,4,5}.

- 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 diseases⁶.
- Multiplex 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.

This guide describes an approach to simultaneous, integrated testing for COVID-19 and TB disease for high burden countries. It should be adapted for use in line with the policies and guidelines of the national TB program and COVID-19 response.

Diagnostic Testing Approaches

Simultaneous, integrated testing for COVID-19 and TB (Figure 1)

When a person presents to a healthcare facility or provider with respiratory symptoms including cough and difficulty breathing, diagnostic tests for both COVID-19 and TB should be done at the same time (simultaneous testing) on a multiplex testing platform (integrated testing). If multiplex testing is not available, specimens should be referred for testing for both diseases according to national diagnostic algorithms. Where available, chest X-ray may be used for screening for TB; people with lesions suggestive of TB should provide a specimen for confirmatory TB testing.

Simultaneous, integrated testing is especially important for people who are at elevated risk of having one or both diseases or are vulnerable to unfavorable outcomes, including older populations and people with comorbidities like diabetes mellitus and chronic obstructive pulmonary disease. Countries may expand the symptoms to also include people who meet the definition of having Severe Acute Respiratory Infection (SARI) or Influenza-like Illness (ILI).

Situational testing

While countries should prioritize simultaneous, integrated testing for COVID-19 and TB, there

³ 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](https://doi.org/10.1080/23744235.2020.1806353)

⁴ 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>

⁵ 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](https://doi.org/10.1002/jmv.26311)

⁶ 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/hq-tuberculosis/covid-19-tb-clinical-management-info-note-dec-update-2020.pdf>



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are situations where testing for one disease or the other should occur. Examples include:

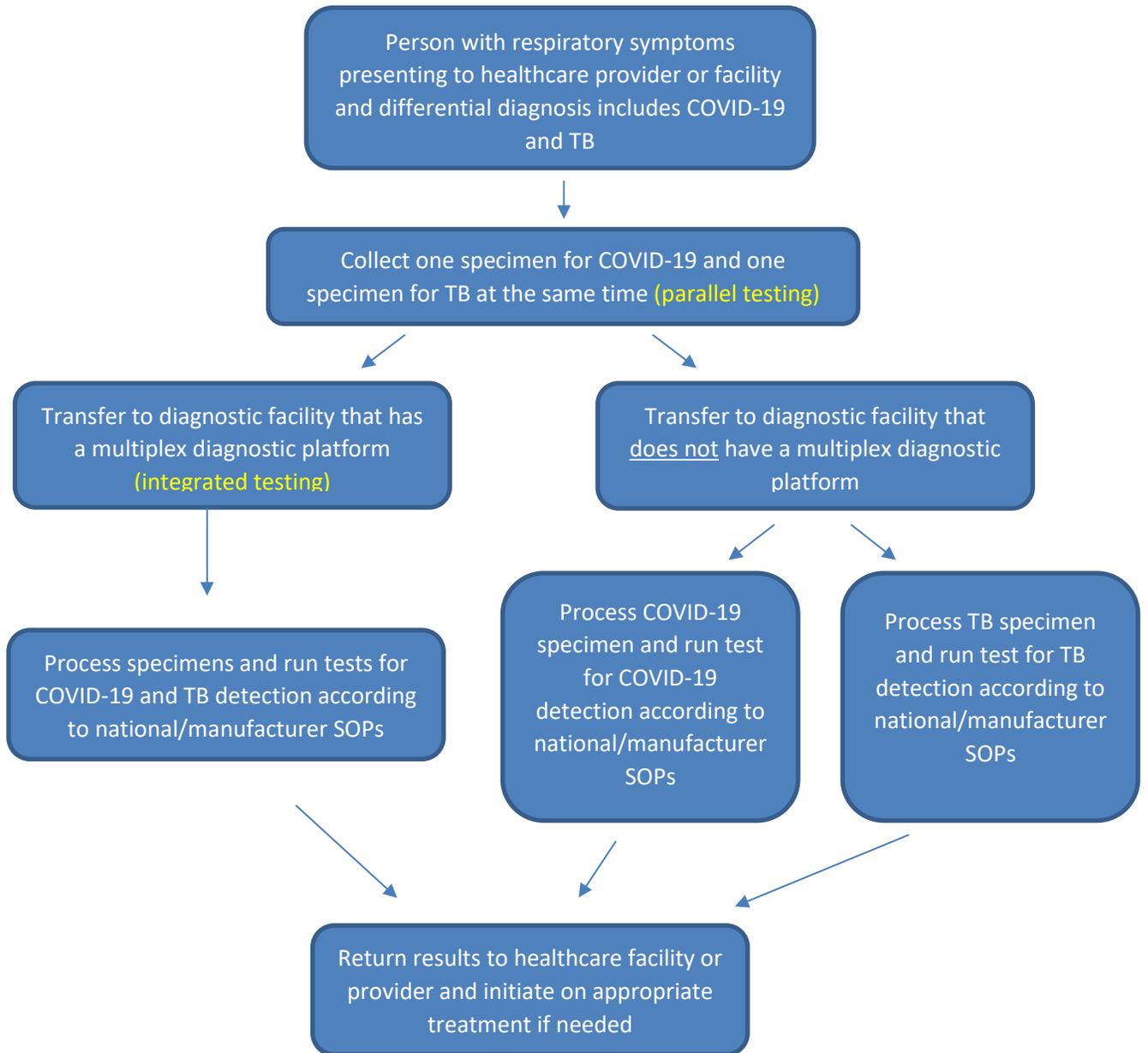
Testing for COVID-19 or TB co-morbidity in people diagnosed with the other disease:

Most countries are not currently carrying out simultaneous testing for both diseases, usually resulting in testing (and diagnosis) of either COVID-19 or TB. Given poor prognosis of people with TB and COVID-19 co-infection, countries should strive to test people diagnosed with COVID-19 for TB, and to test people diagnosed with TB for COVID-19. Treatment of TB should continue uninterrupted even if the person is also diagnosed with COVID-19.

Testing for COVID-19 or TB in people testing negative for the other disease:

Persons with respiratory symptoms that previously tested negative for COVID-19 and not diagnosed as having COVID-19 should be tested for TB. Persons with respiratory symptoms that previously tested negative for TB and not diagnosed as having TB should be tested for COVID-19.

Figure 1. Simultaneous, integrated testing for COVID-19 and TB in high TB burden countries





Nucleic acid amplification tests (NAATs) to use for simultaneous, integrated testing

The available NAATs for TB and COVID-19 require use of different specimen types: detection of pulmonary TB typically requires sputum, while detection of COVID-19 typically requires nasopharyngeal or oropharyngeal swabs or washes.

Countries may gain efficiencies in testing by multiplexing NAAT platforms that are able to test for both diseases. Following the [Global Fund's Interim Quality Assurance Requirements for the Procurement of COVID-19 Diagnostic Products](#), NAATs for detection of COVID-19 must meet **at least one of the following two criteria** in order to be eligible for procurement using Global Fund resources:

- Products approved pursuant to the WHO Emergency Use Listing (EUL) procedures
- Products approved pursuant to any other emergency procedure set up by one of the Regulatory Authorities as defined under the QA Policy (i.e., regulatory authorities of the founding members of the GHTF).

Table 1 summarizes NAAT platforms that can run WHO-recommended TB tests as well as SARS-CoV-2 tests that meet the quality assurance requirements of the Global Fund⁷:

Table 1. Diagnostic equipment able to detect TB and COVID-19 on the same NAAT platform

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 GF QA Policy ⁸
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

⁷ Table is up-to-date as of 18 March 2021. For updates to the list of SARS-CoV-2 NAATs approved by GF, see: https://www.theglobalfund.org/media/9629/covid19_diagnosticproducts_list_en.pdf

⁸ Regulatory authorities of the founding members of the Global Harmonization Task Force



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BD MAX	√		√ US FDA EUA, Health Canada/Interim Order
Molbio Truenat	√	Review in process	*

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

Diagnostic network mapping and expansion

Of the available NAAT platforms able to detect TB and COVID-19 using Global Fund resources, the GeneXpert system can be placed at peripheral sites, improving access to care and reducing diagnostic delay. 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 the GeneXpert assay, and therefore a Biosafety Level 2 laboratory with biosafety cabinet is not needed when specific conditions are met. For more information see the [WHO Laboratory biosafety guidance related to coronavirus disease⁹](#).

Options and considerations for testing

- a) Multiplexing with existing testing platforms: For countries planning to use existing GeneXperts or other equipment for multiplexing, the free capacity on instruments should be carefully measured on an instrument-by-instrument basis, being mindful that average national utilization rates may mask significant differences in utilization between sites. To meet the required testing capacity, countries should always consider procuring additional machines and expanding working hours of staff with commensurate payment (see point c)
 - i) Advantages: Leverages unused local testing capacity as well minimal implementation start-up costs (e.g., specimen transport, infrastructure requirements, etc.)
 - ii) Disadvantages: Requires site-level data on available testing capacity and potential need to prioritize specimens due to exceeded testing capacity onsite.

- b) Re-location of testing instruments: Patient access to timely TB testing should be a key factor when considering instrument re-location. Spatial analysis of existing footprint and referral linkages should be revised to minimize potential impact on testing turnaround times and result reporting due to relocating instruments.
 - i) Advantages: Relocated machines would increase instrument usage rates due to additional specimens being tested
 - ii) Disadvantages: Disrupts patient population accessing timely testing services and/or specimen referral linkages as originally designed

⁹ <https://www.who.int/publications/i/item/WHO-WPE-GIH-2021.1>



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- c) Procurement of additional instruments and/or expanding work hours: May be a preferred solution to ensure continued access to rapid testing for TB and minimize impact on existing services.
 - i) Advantages: Increases access to testing for all diseases without impact on existing testing services
 - ii) Disadvantages: Requires additional budget and human resources

Supply chain management of testing resources should be ensured to prevent lapses in testing capacity due to increased volumes. Mapping of existing instruments that can be used to test for TB and COVID-19 should include private sector sites that meet national quality assurance standards. Provision of free reagents to such sites may be considered, with the agreement that patients are not charged for the cost of the test reagents.

Collection and referral of specimens and reporting of results

Wherever possible sample collection at a symptomatic person's home should be provided. Health workers must provide specific instructions to the person on how to properly collect and pack sputum specimens. When home collection is not possible, sample collection should be made available from peripheral health centers where people first make contact with a healthcare provider, including both public and private sector facilities.

Electronic data reporting systems and diagnostic platforms with connectivity solutions should improve timeliness of results reporting across both TB and COVID-19 to patients 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, including private sector, 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.

The design of the specimen referral system must consider the national testing algorithms, existing testing infrastructure and current specimen referral mechanisms. Other considerations should include the mechanism for returning results electronically for priority results, biosafety and packing for transport, and coordination across disease programs through designated working groups.

Catch-up planning and demand generation

Catch-up campaigns to increase TB notification and treatment coverage are needed to find the back-log of TB cases that were missed during the first year of the COVID-19 pandemic and to plan for future efforts that may be needed as the pandemic matures. Campaigns can take



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different forms depending on the COVID-19 situation. For example, one-off or periodic, facility-based or community-based campaigns to promote and increase TB testing and patient support services may be useful for mobilizing community volunteers, civil society organizations and the public at large. Additionally, a campaign could be integrated with ongoing activities such as COVID-19 screening, testing and contact tracing; and reproductive, maternal, newborn and child health and immunization campaigns undertaken at community or household levels. These initiatives should be accompanied by media campaigns to inform and mobilize communities to demand TB services, address stigma, and to supplement efforts of healthcare workers. It should be planned with attention for logistics, to ensure tests, medicines, patient support, and personal protection materials are available to meet the demand generated by the campaign. Where outreach campaigns may not be feasible due to COVID-19 restrictions or a stretched healthcare system, consider use of community radio, television, SMS, social media, as suitable to the target populations.

Coordinated program management and policy enactment

A coordinated approach to program management, policy development and timely updates to both will be required to implement simultaneous, integrated testing. This will entail multi-stakeholder, coordinated development of diagnostic algorithms, planning and strengthening laboratory capacity to address the burden of both diseases, and observance of necessary infection prevention and control measures during specimen collection, packaging, transport and testing. Coordination is also required to rebalance and strengthen staffing and ensure capacity is built and staff are cross-trained for all activities required to implement bi-directional screening and testing.

References

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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>