POLICY BRIEF

FINDING THE MISSING CASES – IMPROVING SCREENING AND DIAGNOSIS TO COMBAT DRUG RESISTANCE AND END TUBERCULOSIS

Task Force 6
Global Health Security and COVID-19
FINDING THE MISSING CASES – IMPROVING SCREENING AND DIAGNOSIS TO COMBAT DRUG RESISTANCE AND END TUBERCULOSIS

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ABSTRACT

Tuberculosis is the world’s top infectious killer. Ending the TB epidemic is one of the United Nations Sustainable Development Goals, to be achieved by 2030. While global TB incidence is slowly declining, drug-resistant TB remains a public health crisis and a health security threat (World Health Organization, 2020). A large number of TB and drug-resistant TB cases are not diagnosed and notified, especially in developing countries. In this context, improving TB screening and diagnosis, strengthening laboratory capacity, and improving surveillance will be critical to combatting drug-resistant strains of TB and ending TB.

Keyword: Tuberculosis, drug-resistant TB, screening and diagnosis, surveillance.
CHALLENGES

Tuberculosis (TB) and multi-drug resistant (MDR)-TB remain a public health crisis and a health security threat globally. In 2020, globally, an estimated 1.5 million people died from TB (World Health Organization, 2021a). The largest number of new TB cases occurred in the WHO South-East Asian Region (43% of new cases), followed by the WHO Africa Region (25%), and the WHO Western Pacific (18%). Ending the TB epidemic is one of the health targets of the United Nations Sustainable Development Goals (SDGs).

Timely screening, diagnosis, and treatment are critical to ending TB. A United Nations declaration on TB in 2018 included commitments to increase and improve diagnosis and treatment of TB, with a target of reaching 40 million people in the 5-year period 2018–2022 (World Health Organization, 2022). Yet, a significant proportion of TB and MDR-TB cases continue not to be diagnosed and notified. In 2020, an estimated 10 million people contracted TB, of which 30% were reported not to have been diagnosed and notified. The gap is proportionately wider for drug-resistant TB (DR-TB) – for example, only 44% of rifampicin-resistant TB (MDR/RR-TB) were reported and notified (World Health Organization, 2021b). Weaknesses in the detection and treatment of TB has contributed to an increase in MDR-TB, with the number of deaths estimated to have reached 182,000 in 2019 (The Global Fund, 2020).

There are significant challenges in increasing and improving TB screening, diagnosis, and treatment, especially in low- and middle-income countries (LMICs). These include gaps in national policies, limited investment in MDR-TB screening and diagnostic technology, skills shortages, and inadequate collection and use of data to improve case detection and drug resistance surveillance. Stagnation in TB control, especially in LMICs, has led to global acknowledgment of the importance of appropriate policies to advance TB screening and diagnosis.

This policy brief proposes strategies to strengthen screening and diagnosis of TB and MDR-TB, and outlines enabling policies and reforms to enable robust implementation (including adequate and sustainable financing, improving laboratory capacity, and improving surveillance).
i. Revise national TB policy and evaluate TB algorithms for screening and diagnosis, in line with WHO-endorsed diagnostic technologies.

A key challenge with national TB screening and diagnosis programs, especially in LMICs, is the timeliness and accuracy of diagnosis and reporting. Currently, most screening and diagnosis programs detect Mycobacterium tuberculosis with rifampicin resistant (RR)-TB. Current rapid diagnosis methods do not detect isoniazid mono-resistant TB (Hr-TB) upfront. The World Health Organization (WHO) has acknowledged the challenge of Hr-TB. In 2019, there were 1.4 million incident cases of isoniazid-resistant TB, of which 1.1 million were susceptible to rifampicin (World Health Organization, 2021b). Most of these cases were not diagnosed with DR-TB and did not receive appropriate treatment. The absence of Hr-TB detection leads to incomplete resistance profiles, resulting in misdiagnosis.

In turn, incomplete or inaccurate diagnosis leads to inappropriate treatment regimens. There are two possible scenarios. First, RR-TB cases are often misdiagnosed as multi-drug-resistant TB and are put on MDR-TB regimens. These regimens are unnecessarily toxic for the resistance profile and lead to poor patient outcomes. Alternatively, if a patient is mono-resistant to isoniazid but susceptible to rifampicin, in the absence of isoniazid testing upfront, they are assumed to have drug susceptible TB. They would be prescribed the standard TB drugs and be put on a sub-optimal treatment regimen for over 6 months, leading to poor outcomes, with the TB infection remaining. Evidence has shown that treatment of Hr-TB with standard first-line drug regimens for new patients resulted in higher treatment failure, relapse, and acquired multidrug resistance (Gegia, et al, 2017).

Current screening and diagnosis methods also impose a high burden on patients. Additional visits and multiple sample collections from the same patient will be required for additional drug susceptibility testing (DST). As many patients do not return for additional DST, there is a high risk of loss to follow up. Delays in obtaining the proper drug-resistance profiles at the first sample collection and initial diagnosis mean that the prescribed treatment regimens will be ineffective and encourage development of drug-resistant TB. There is also a high risk of further spread of TB, as undiagnosed or misdiagnosed individuals return to their communities.
The above situation is true in Indonesia. Although Indonesia has adopted universal testing of all TB patients for both rifampicin and isoniazid resistance, key gaps remain in the current diagnostic network for drug resistance such as the lack for universal DST using rapid molecular tests for all presumptive TB patients. This results in only 41% of the estimated 24,000 MDR-TB patients identified in 2019. The current testing of both drug resistance requires two assays rather than a single assay, which may lead to delay in completion of diagnostic workup.

Current TB screening and diagnosis methods also lead to higher treatment costs and higher government expenditure on TB. In Indonesia, the cost of treatment of a regular TB case is between Rp. 400 thousand and Rp. 1.2 million. The treatment cost can be more than 100 times if a patient develops MDR TB: the cost of one MDR TB case is Rp. 100 million - 120 million (REPUBLIKA.co.id, 2017). Timely and accurate diagnosis is thus the first and most important step to managing costs and getting value-for-money from the government’s expenditure on TB. This will also improve patient treatment outcomes, reduce TB infection rates, and improve population health outcomes in the long run.

Recently developed technologies for TB diagnosis offer the possibility to significantly improve screening and diagnosis. WHO Consolidated Guidelines on Tuberculosis (2021 update, Module 3: Rapid diagnostics for tuberculosis detection) evaluated and recommended three new classes of technology – one of which is moderate complexity automated nucleic acid amplification tests (NAATs) - for the detection of resistant strains of TB. Specifically:

"Moderate complexity automated NAATs, recommended for the initial detection of TB and resistance to rifampicin and isoniazid, [provide] more options for early diagnosis of TB and rifampicin-resistant TB but also [address] an important gap in the rapid diagnosis of isoniazid-resistant and rifampicin-susceptible TB" (World Health Organization, 2021b).

Adopting these new classes of technology requires revisions to national TB policies and evaluations of national TB algorithms for screening and diagnosis. To increase and improve the diagnosis of TB and the identification of both strains of drug-resistant TB, this paper calls for relevant authorities (e.g. MOH, national TB programs, international organizations supporting TB control programs) to accelerate their review and revision of national TB policy and algorithms to include WHO-endorsed diagnostic technologies for the detection of drug-resistant TB.
Specifically, TB diagnostic algorithms should be transformed to diagnose TB and detect true MDR TB cases with just one test. The current gap in diagnosis (i.e. upfront detection of Hr-TB) can be closed by utilizing first-line screening of Mycobacterium tuberculosis, rifampicin resistance, and isoniazid resistance in one step. The figure below provides illustrative algorithms that would substantially improve rapid and accurate diagnosis of TB and MDR-TB:

![Current algorithm and Potential algorithm diagrams](image)

Source: Authors

DST = drug susceptibility testing; FL-LPA = first line – line probe assay; SL-LPA = second line – line probe assay

Earlier and faster identification of true MDR-TB cases (resistant to both rifampicin and isoniazid) will enable clinicians to prescribe appropriate treatment at the beginning of the treatment regimen. For patients, this means better responsiveness to treatment and improved outcomes. From the health system perspective, this reduces “missing cases” and infection rates in the medium to long run. Indeed, improving screening and diagnosis is the first step towards achieving national and global targets of eliminating TB.

ii. Ensuring sustainable financing for TB control programs and adoption of cost-effective diagnostic technologies.

The adoption of diagnostic technologies also depends on financing sources available for such technologies. As Development Assistance for Health (external financing) declines (including in many LMICs) and domestic financing forms an
increasingly large share of financing for health, it is also critical that financing sources are sustainable, to ensure continuity of programs in the long run. Evidence-based decision making can also inform the adoption of cost-effective technologies, which will simultaneously ensure value-for-money while advancing health outcomes. Such cost-effective technologies will allow more efficient and rapid diagnosis of TB and MDR-TB, leading to timely, appropriate treatment regimens and preventing further transmission, thus reducing healthcare burden and poor treatment outcomes.

To this end, this paper calls for commitment to financing cost-effective diagnostic technologies for TB and MDR-TB. Evidence generation on the burden of disease (e.g. prevalence and incidence of drug resistance in each catchment/planning area) will help to inform decision making on which diagnostic platforms (to address different types of resistance) need to be adopted in different locales. To ensure long term sustainability, payment for these technologies should be included in domestic financing schemes (e.g. government budgets, national health insurance systems). Public Private Partnerships can be explored to develop holistic end-to-end solutions and to raise funding.

iii. Strengthening laboratory capacity to diagnose drug-resistant TB and support drug resistance surveillance.

Laboratories play a central role in patient care and surveillance. Unfortunately, the capacity of labs to deliver quality diagnostic services needed for effective control of TB – and particularly the growing threat of drug-resistant TB – is severely limited. Strengthening of quality lab infrastructure is essential to ensure that the most appropriate diagnostics, including liquid culture and rapid diagnostics as outlined in treatment algorithms, can be implemented into TB treatment and control programs. This is a prudent investment because the strengthening of quality laboratory capacity could have benefits well beyond improved TB diagnosis. With strong planning and careful integration, these investments could be made in a way that bolsters overall lab capacity for many infectious and chronic diseases in resource-poor settings. Alongside investments in laboratory capacity, collaboration between public and private sectors (e.g., capacity building) can help to improve domestic capabilities in the long run.
iv. Improving the collection and use of data to improve case detection, drug resistance surveillance.

Access to timely and accurate surveillance data on TB case notification and drug resistance patterns can help the policy makers in developing targeted policies to augment their response in the fight against TB. Artificial intelligence based chest X-ray interpretation products can reduce the time to detection from days to few minutes. Geographical hotspot mapping of testing/treatment facilities and TB case detections can help in optimizing the limited public health resources. Adherence monitoring apps can ensure increased medication adherence and thereby reduce chances of developing resistance. Connectivity between medical devices and laboratory information management system can reduce duplicate data entry efforts and time taken to share information with clinicians and patients. Using machine learning on the TB program data, the policy makers can identify pockets of patients with high probability of loss to follow-up and implement customized retention strategies to retain them in the system. The possibilities to optimize healthcare delivery, realize cost efficiencies and provide better care are immense with the adoption of digital technologies in managing TB care.

In conclusion, this paper calls for rapid action by national governments, TB programs, and key stakeholders to accelerate the adoption and implementation of updated WHO recommendations and endorsed technology for TB screening and diagnosis. This will enable timely and accurate diagnosis of TB and MDR-TB, facilitate appropriate treatment regimens, and reduce drug resistance. Enabling policies and reforms including adequate and sustainable financing, improving laboratory capacity, and improving surveillance will be required to support implementation. These are critical steps to achieving national and global targets of ending the TB epidemic by 2030.
References


