STOP TB FIELD GUIDE 7

THE ROLE OF LABORATORY SYSTEMS IN TB CASE DETECTION

Stop TB Partnership

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StopTB Field guide 7: The role of laboratory systems in TB case detection

Global Health Campus
Chemin du Pommier 40
1218 Le Grand-Saconnex
Geneva, Switzerland

Design: Miguel Bernal and Diana Schwalb
Photo credits: Miguel Bernal, Shehzad Noorani, Sam Nuttall and Stella Rajagukguk

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STOP TB

FIELD GUIDE

THE ROLE OF LABORATORY SYSTEMS IN TB CASE DETECTION

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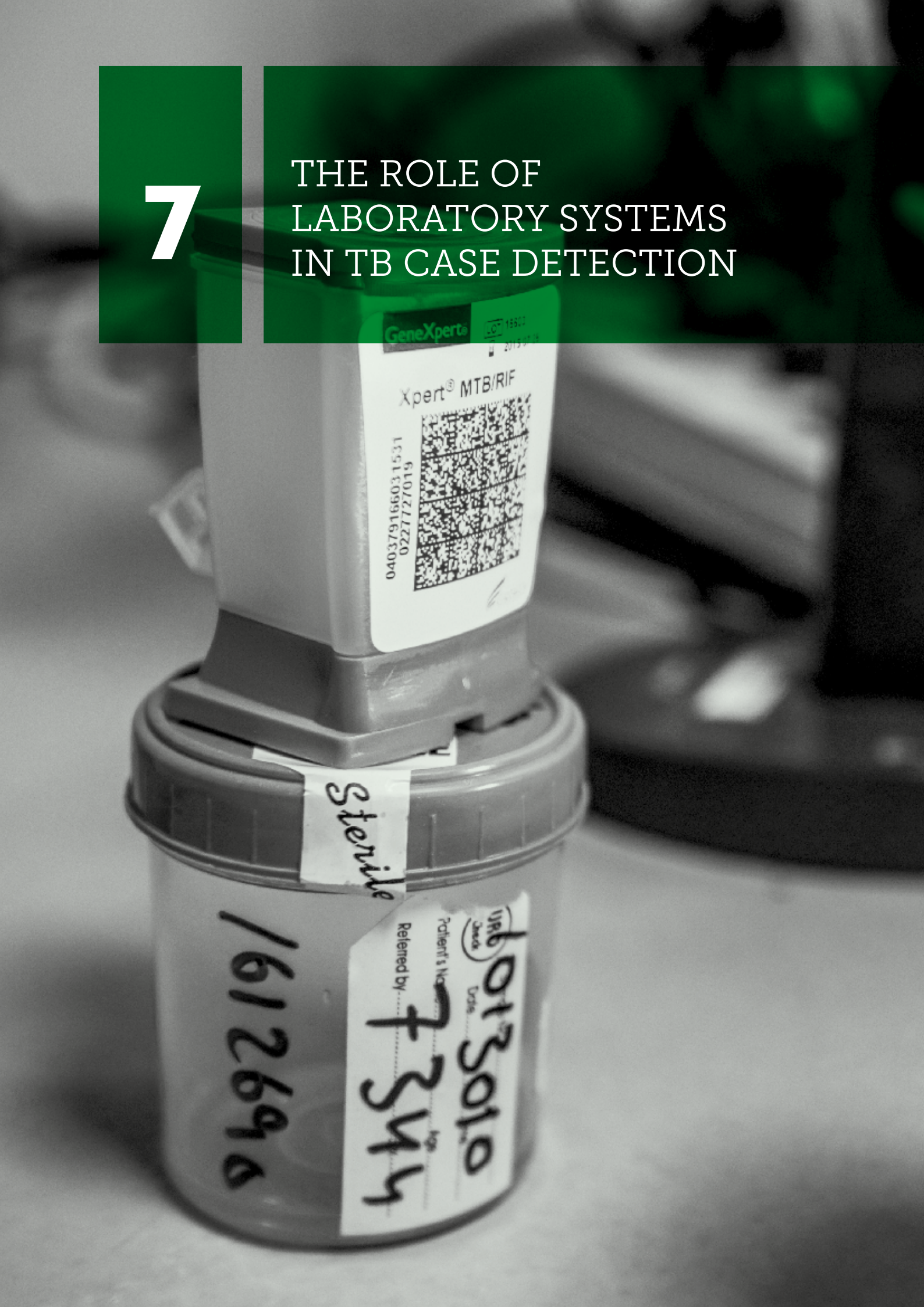

PURPOSE OF THIS DOCUMENT

This document is one in a series of 11 field guides produced by Stop TB Partnership in collaboration with the Global Fund to Fight AIDS, Tuberculosis and Malaria, Interactive Research and Development Global (IRD), KIT Royal Tropical Institute, and multiple global experts and implementation partners. The field guides rely on practical experiences and expertise of implementers and are meant to help national TB programmes and other TB programme managers to identify the best strategies for finding people with TB who are missed by routine health services.

This document is not to be treated as guidance, but rather as a collection of considerations, tools, experiences and examples that highlight the successes and challenges in implementing effective TB case-finding interventions and may assist in their planning. It aims to support TB programme implementers in making informed decisions around the expansion of laboratory services within the framework of interventions aimed at finding missing people with TB.

This field guide underwent extensive peer review by the agencies and individuals acknowledged below. It presents a range of examples from peer-reviewed literature and implementation practice. Where not cited, examples are provided by TB REACH.

Acknowledgements

The production of these field guides represents a significant effort, bringing together more than 60 experts from over 30 different institutions globally in the spirit of partnership to help address a major barrier in the TB response: the fact that millions of people with TB are still missed by the current routine health systems.

The development of the guides was generously supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria as part of the Strategic Initiative on TB: Address specific barriers to finding missing tuberculosis cases, develop innovative approaches to accelerate case finding, and scale up tools and approaches. The Strategic Initiative is implemented by the Stop TB Partnership together with International Research and Development Global, Pakistan, and KIT Royal Tropical Institute, Netherlands

The writing of these field guides was coordinated by Marina Smelyanskaya, under the guidance of Jacob Creswell. The core writing team consisted of (in alphabetical order) Mirjam I Bakker, Lucie Blok Andrew J Codlin, Jacob Creswell, Lisanne Gerstel, Ali Habib, Manjot Kaur, Liesl PageShipp, and Marina Smelyanskaya. Many others contributed to writing sections of different guides as well as reviewing them. A list of the writers and reviewers is presented below.

Many of the contributors attended a consultation in Amsterdam, Netherlands, in June 2018, to review and refine the draft of this guide. We thank the team at KIT Royal Tropical Institute for their support in organizing the consultation and review meeting and all participants for their time, ideas, and insights.

- Ramya Ananthakrishnan, REACH (Resource Group for Education and Advocacy for Community Health) India
- Sandra Alba, KIT Royal Tropical Institute, Netherlands
- Uliane Appolinario, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
- Mirjam I. Bakker, KIT Royal Tropical Institute, Netherlands
- Mercedes Becerra, Harvard Medical School, USA
- Stela Bivol, Center for Health Policies and Studies, Moldova
- Lucie Blok, KIT Royal Tropical Institute, Netherlands
- Frank Bonsu, National Tuberculoses Control Programme , Ghana
- E. Jane Carter, Warren Alpert Medical School, Brown University, USA
- Andre J Codlin, Friends for International TB Relief, Vietnam
- Jacob Creswell, Stop TB Partnership, Switzerland
- Luis Cuevas, Liverpool School of Tropical Medicine, UK
- Salah Edine-Ottmani, Morocco
- Carlton Evans, Innovación Por la Salud Y Desarrollo (IPSYD), Asociación Benéfica PRISMA, Perú
- Elizabeth Fair, Curry International Tuberculosis Center, University of California, San Francisco, USA
- Lisanne Gerstel, KIT Royal Tropical Institute, Netherlands
- Elmira Gurbanova, WHO, Azerbaijan
- Dr. Stephen John, Janna Health Foundation, Nigeria
- Peter Hansen, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
- Kyung Hyun Oh, Head, Korean Institute of Tuberculosis, Korea

- Kekeletso Kao, FIND, Switzerland
- Manjot Kaur, Interactive Research and Development, India
- Aamir Khan Executive Director, International Research and Development Global, Pakistan
- Amera Khan, Technical Officer, Stop TB Partnership, Switzerland
- Daniele Chaves Kuhleis, Brazil
- Daisy Lekharu, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
- Lynette Mabote, AIDS and Rights Alliance for Southern Africa (ARASA), South Africa
- Farihah Malik, Pakistan
- Anna Mandalakas, Baylor College of Medicine and Texas Children's Hospital, USA
- Enos Masini, WHO, Kenya
- Thulani Mbatha, Interactive Research and Development, South Africa
- Christina Mergenthaler, KIT Royal Tropical Institute, Netherlands
- Peter Mok, Independent Consultant, Malaysia
- Monde Muyoyeta, Centre for Infectious Disease Research in Zambia
- Sreenivas Nair, Stop TB Partnership, Switzerland
- Sode Novatus Matiku, New Dimension Consulting (NEDICO), Tanzania
- Drusilla Nyaboke, Republic of Kenya National Tuberculosis, Leprosy and Lung Disease Program, Kenya
- Chidubem Ogbudebe, KNCV Tuberculosis Foundation, Nigeria
- Madhukar Pai, McGill Global Health Programs, McGill International TB Centre, Canada
- Liesl PageShipp, Interactive Research and Development, South Africa
- Zhi Zhen Qin, Stop TB Partnership, Switzerland
- Oriol Ramis, Spain
- M. D'Arcy Richardson, USA
- Ataulhaq Sanaie, UK
- Melissa Sander, Tuberculosis Reference Laboratory Bamenda, Cameroon
- Anna Scardigli, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
- Simon Schaff, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, South Africa
- Bogdana Shcherbak-Verlan, PATH, Ukraine
- Marina Smelyanskaya, Stop TB Partnership, Switzerland
- Robert Stevens, UK
- Pedro Suarez, Management Sciences for Health, USA
- Guy Stallworthy, USA
- Ajaykumar Thirumala, Independent Public health laboratory consultant, India
- Stephanie M. Topp, James Cook University, Australia
- Pillar Ustero, Switzerland
- Brittney van de Water, Harvard Medical School, USA
- Frank van Doren, CheckTB! Netherlands
- Wayne van Gemert, Stop TB Partnership, Switzerland
- Kristian van Kalmthout, KNCV Tuberculosis Foundation, Netherlands
- Shibu Vijayan, PATH, India
- Luan Vo Nguyen Quang, Friends for International TB Relief/Interactive Research and Development, Vietnam
- Ashvini Vyas, Asha Kalp, India
- Eliud Wandwalo, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
- William Wells, USAID, USA
- Mohammed Yassin, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
- Ingrid Zuleta, KIT Royal Tropical Institute

The field guides were edited by Fiona Stewart and Marina Smelyanskaya.

Design was done by Miguel Bernal in coordination with Nina Saouter.

Photography for the guides was contributed by Miguel Bernal and Shehzad Noorani.

The time and expertise of all the contributors listed are gratefully acknowledged by the Stop TB Partnership.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
AFB	Acid-fast bacilli
CD4	A glycoprotein found on the surface of immune cells
CHW	Community health worker
CXR	Chest X-ray
DR-TB	Drug-resistant tuberculosis
DST	Drug-susceptibility testing
DS-TB	Drug-susceptible tuberculosis
EQA	External Quality Assessment
GDF	Global Drug Facility
GLI	Global Laboratory Initiative
HEW	Health extension worker
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
LAM	Lipoarabinomannan
LAMP	Loop-mediated isothermal amplification
LED	Light-emitting diode
LPA	Line probe assay
MDR-TB	Multidrug-resistant tuberculosis, defined as resistance to rifampicin and isoniazid
M&E	Monitoring and evaluation
MOTT	Mycobacterium other than tuberculosis
NATT	Nucleic acid amplification test
NTM	Nontuberculous mycobacteria
NTP	National tuberculosis programme
POC	Point of care
SOP	Standard operating procedure
SMS	Short message service (text message)
SPC	Sample processing control
TB	Tuberculosis
TST	Tuberculin skin test
UPS	Uninterrupted power supply
WHO	World Health Organization
Xpert	Xpert MTB/RIF assay, a cartridge-based nucleic acid amplification test (NAAT) for rapid tuberculosis diagnosis
ZN	Ziehl-Neelsen


GeneXpert
Xpert® MTB/RIF

1. INTRODUCTION

Programmes aimed at finding people with TB who are missed by routine health services usually focus their efforts on screening and engagement activities that occur before laboratory testing. These are entirely new services that indeed deserve additional attention; however, implementers often assume that the existing laboratory infrastructure can simply accommodate any increase in testing. In many settings, this is not the case and the multiple interventions described in this series must go hand-in-hand with strengthening laboratory networks and services.

In practice, it is very difficult to improve case detection without greatly increasing the numbers of people tested in laboratories (1), unless there are large-scale gains in clinical diagnoses. Thus, case-finding programmes should not deprioritize the strengthening of laboratory networks and systems. The World Health Organization (WHO) (2) and Global Laboratory Initiative (GLI) (3) have recently released case studies and guides on laboratory strengthening under the End TB Strategy. This field guide supplements these publications by focusing on the implementation experiences of rolling out new TB diagnostic tests, and expanding access to and increasing coverage of laboratory services. It also provides an overview of the available diagnostic tests for TB and discusses their relative strengths and weaknesses from an implementation and cost perspective. The field guide also provides a monitoring and evaluation (M&E) framework focused on the quality of TB diagnostic testing and measuring the performance of interventions aimed at expanding access to TB testing services.

2. PREPARING LABORATORY SERVICES FOR INCREASED DEMAND

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2.1 Increasing the number of people tested

Laboratories' limited capacity for TB testing is an issue most often encountered when projects aimed at finding the missing people with TB start to gain momentum. At the start of the intervention, programme teams commonly focus on the outreach and/or screening strategies to reach new populations because these services are often entirely new. It is often assumed that the existing laboratory infrastructure will be able to absorb the increased demands in testing volume. However, laboratories usually have a finite number of technicians and equipment to process clinical specimens. When those limits are reached, there may be an increase in the turnaround time between receiving the sputum and providing the result; a decline in the quality of testing; and/or sputum samples may be labelled as being of 'poor quality' and discarded before testing.

Instaling new testing equipment

The first logical step in planning laboratory support for intensive TB case-finding interventions is to map out which services already exist. This will involve obtaining information on existing laboratories, their testing capacities (both human and equipment) and supply chains. Open source tools, such as Laboratory Efficiency and Quality Improvement Planning (LabEQIP) can help to guide such mapping exercises.

Once existing laboratory networks have been mapped, implementers will need to estimate the number of samples to be tested and the approximate timelines for screening and testing. These considerations will inform the extent to which existing laboratory networks may be overburdened and the timeframe for when additional testing activities will take place.

TB programmes could consider the following questions:

- Will enhanced TB screening activities lead to a persistent increase in the number of laboratory tests over a year?
- Will campaign-like events result in spikes in the number of samples to be tested on select days of the week/month?

Establishing a systematic TB screening and active referral programme at a health facility or in the community will likely result in sustained increases in laboratory workloads, whereas mobile chest X-ray (CXR) camps will result in temporary increases in testing volumes. When considering this increased testing capacity, programmes may choose to install new testing equipment suitable to the context or work on improving the throughput of existing resources.

Unless a programme can guarantee very high numbers of samples at a testing site throughout the year, it is often advisable to purchase multiple 2-module or 4-module GeneXpert systems instead of a larger 16-module system. Small systems can be easily networked together to increase testing capacity when needed, but can then be redistributed to meet testing demands elsewhere if sputum submission patterns change. By contrast, the testing capacity of a 16-module system cannot be redistributed if a site's testing volume declines. Furthermore, the testing capacity of the entire system may be compromised if the platform experiences technical problems. Sputum transportation networks and the use of other non-TB cartridges (e.g. HIV viral load) are often needed to ensure high-enough testing numbers to justify this type of equipment. It is important for programmes to continuously monitor and forecast utilization rates for GeneXpert systems, so that they can rationally deploy testing capacity to meet the demand generated by routine TB screening services as well as new case-finding interventions.

Many TB programmes have introduced GeneXpert as a part of their active or enhanced TB case-finding efforts. However, TB programmes often underestimate how many microscopy laboratories require significant infrastructure upgrades to be able to house a GeneXpert system. GeneXpert systems have frequently been placed in laboratories with inadequate infrastructure, resulting in damaged hardware and wastage of cartridges (4). Here, considerations from WHO's Xpert MTB/RIF implementation "How-to" manual (5) are presented for implementers considering installing new GeneXpert machines or strengthening existing laboratory infrastructure.

Power supply

The power supply at microscopy centres in many high TB burden countries may be unreliable or may even be non-existent. In settings where power outages are common, one solution is to connect GeneXpert systems to an uninterrupted power supply (UPS) device. The ideal strength of a UPS device will depend on the duration of the power outages.

- If outages are short (less than 2 hours), a UPS device with low capacity will be sufficient to ensure that tests already running are not interrupted.
- If outages are prolonged (more than 2 hours), batteries and an inverter system may be a better option to allow for multiple test runs.

UPS devices must be recharged, so if power outages tend to last for a full day or longer, TB programmes should consider investing in a generator for the laboratory. In addition, if the electricity voltage is not stable, GeneXpert systems should be connected to a UPS device with voltage stabilization (and voltage boosting) capability. Another solution may be to utilize solar panels to power GeneXpert systems. This approach has been employed by several TB REACH projects and is recommended in rural areas. More ideas on powering GeneXpert machines in environments with unreliable power supply are provided in FIND's practical guide on this topic (6). In Nigeria, a project working with riverine communities of the Niger delta revived two laboratory sites already in possession of GeneXpert machines by installing solar power. The project also installed solar-powered GeneXpert machines in two additional laboratories. This expanded laboratory capacity coupled with effective case finding resulted in a 156% increase in the number of cases found through three quarters of project implementation.

Laboratory Space

GeneXpert systems are sensitive to extreme ambient temperatures. Air-conditioners are needed in settings where temperatures go above 30°C, and heaters are needed in cold settings (below 15°C) to avoid interference with the testing process. Adequate climate-controlled (between 2°C and 28°C) space must be available to store GeneXpert cartridges. GeneXpert systems are also sensitive to ambient dust, so laboratories may need to consider physical modifications and/or buying additional attachments for the machines to filter out dust; such filters can be procured directly from the manufacturer (Cepheid) or via Stop TB Partnership's Global Drug Facility (GDF).

Resource allocation

For many TB programmes, the choice of where to locate new GeneXpert systems is based on political reasons and not on the TB burden. For example, a TB programme may decide to give one GeneXpert system to every district or province in a country before providing a second or third system to high-volume testing sites. Although the aim is equal distribution of machines, it can result in underutilization of systems in low-burden sites and capacity constraints in high-burden sites. Careful mapping of the demand for laboratory services can make a strong investment argument for placing new equipment in sites where they can have the biggest impact.

Requirements for installing a new GeneXpert system	
Reagent storage	• Storage needs to have security • Climate control (between 2°C and 28°C) • Cartridges are bulky and the size of a storage facility will depend on the number of cartridges procured and how quickly they are consumed.
Laboratory space	• Climate controlled (between 15°C and 30°C) • Limited amounts of ambient dust • Secure premises to prevent theft (particularly of the connected computer)
Power supply	• Continuous power supply with stable voltage
Personnel	• Must be computer literate and may need to be comfortable interacting with software that is not in their native language
Biosafety	• Same biosafety requirements as for smear microscopy
Waste disposal	• Biohazardous waste disposal (for example, incineration)

Increasing testing capacity

Testing capacity is often a factor limiting interventions aimed at improving TB case detection. While WHO recommends direct Xpert testing (7), smear microscopy is still widely used for diagnosis in many under-resourced settings. As countries attempt to effectively utilize Xpert, microscopy users can also benefit from some of the practical recommendations listed in this field guide.

If using GeneXpert: Due to its modular design and the time to process each cartridge, a GeneXpert system can only process a certain number of samples per day. For example, a 4-module machine that is operational for an 8-hour working day can run a maximum of 16 tests per day. However, maximum throughput may be reduced to 12 tests per day in some settings if samples must be checked in each morning and the equipment cleaned and booted before use. Furthermore, GeneXpert systems are rarely operational for 8 hours a day; therefore, optimizing the number of hours for which the system operates is key to increasing throughput.

To optimize use:

- Prepare samples for testing at the start of the day;
- Allocate staff to re-load new cartridges without significant time gaps;
- Designate staff to focus on processing samples.

Number of functional GeneXpert modules	4 modules
Run-time of Xpert assay	114 minutes (aprox. 2 hours)
Hours/day the laboratory is staffed	8 hours
Maximum number of tests that can be performed in a day	8hrs ÷ 2hrs = 4 tests/day/module x 4 modules = 16

Replacing GeneXpert modules: Modules are not always fully functional and laboratories commonly need to replace modules that report high test failure rates. It takes time to export the malfunctioning modules and then import replacements. Once replacement modules are in country, people trained to make this swap may need to travel to remote field sites, adding to the cost and sometimes contributing to further delays. This process reduces testing capacity in many settings. If testing capacity is perpetually reduced for this reason, TB programmes should reach out directly to Cepheid (the manufacturer of GeneXpert technology).

One possible solution may be for TB programmes to procure a limited stock of replacement modules to keep in country for rapid installation at testing sites. It may also be easier to export malfunctioning modules in batches to avoid having to undergo repeated customs clearances. However, it should be noted that the warranty of replacement modules starts at the date of shipment, not the date of installation in the GeneXpert system. Therefore, there is a risk that warranties will expire before the replacement modules are installed.

If using smear microscopy: Smear microscopy is primarily dependent on the availability of lab technicians to read slides. Technicians should not read more than 20–25 slides per day (8), as higher workloads can result in lower quality readings and missed opportunities for diagnosis. Thus, hiring additional laboratory technicians or rotating staff through this activity will be a key way to increase laboratory throughput.

Testing pooled sputum

In pooled sputum testing, individual samples are mixed together and tested as a group. If the pooled test is negative, all individual samples can be declared negative without having to be individually re-tested. If the pooled test result is positive, at least one of the individual samples is positive, and all of the individual samples should be tested to identify the positive sample(s). The efficiency of this testing approach is highest when the disease prevalence is low (9). Pooled testing for other diseases is now commonplace at blood banks and in surveillance programmes. Several studies have examined the feasibility, efficiency gains and cost-effectiveness of pooling sputum samples from multiple people for TB testing (10,11,12). These studies indicate that a pooled testing approach could reduce the number of tests by over 30%, depending on the prevalence of TB in the population being tested.

Despite these potential gains, pooling samples is not a common strategy for TB testing because it requires laboratory technicians to keep more detailed records, may not fit with standard TB laboratory reporting forms, creates an opportunity for contamination of samples and has the potential to provide false-negative results if individual samples are diluted too much. Further research is still needed to determine the programmatic feasibility of this testing approach. However, multiple samples from the same patient (e.g. two front-loaded spot samples or a combination of a spot and a morning sample) could also be pooled together for testing with a molecular assay. This may not result in large savings in terms of the number of molecular assays used, as people are unlikely to be given two or three of these expensive tests in the first place; nevertheless, this approach may help to maximize test positivity and yield.

2.2 Human resources

Hiring new staff

If using smear microscopy: Programmes planning to increase the laboratory smear microscopy workload should budget for the recruitment of additional human resources. This will require coordination between the laboratory and the screening management teams to estimate the expected number of additional samples that will be tested. In laboratories performing a diverse array of tests, personnel may be rotated around the different tests throughout the day in order to address some of the test-based workload limitations.

If using GeneXpert: As discussed above, GeneXpert potentially warrants staff and resource optimization over additional hiring.

Note: Positive test results should never be incentivized, as laboratory technicians could begin to report false-positive results in order to obtain additional incentives.

Other staffing solutions

TB programmes may consider other staffing solutions to cope with the increased demand, such as weekend opening hours and paying existing staff overtime. This may be simpler and faster than recruiting additional personnel. Extending operating hours to include a Saturday could increase testing capacity by up to 20%. When personnel numbers are sufficiently high, staff could be structured into shifts so that the laboratory hours could be extended to times of the day more acceptable to patients (e.g. 7–9am and 6–9pm). Some high-volume testing sites that serve as the central node of a hub-and-spoke sputum transportation network operate in 24-hour shifts in order to ensure continuous testing and fast turnaround times for results. Extending the number of working hours in a week, rather than increasing the number of people working in the laboratory, is a primary way to increase testing capacity for diagnostics with a fixed throughput, such as GeneXpert systems. Performance-based incentives can be provided on top of salaries to make extra workloads more acceptable (for a more in-depth discussion around incentives, see the introductory field guide in this series).

Training

As new diagnostic tests are introduced, technicians will have to be trained to perform the new assays and manage the new equipment. In addition, doctors, nurses and other health workers will need to be made aware of the new tests.

Training on new tests for health workers may include, among other topics:

- The diagnostic algorithm (for example, 'who is eligible' for testing);
- How to fill out referral forms; and
- Interpretation of results.

If awareness among health care providers is low, they may not request the new diagnostics or identify those who are eligible. Training health care providers on how to interpret the results of new diagnostic tests is also vital. During the early roll-out of Xpert testing, many settings recorded declines in clinically diagnosed TB (13,14,15). Even though the Xpert assay is not 100% sensitive, it appeared that health care providers were ruling out a TB diagnosis based on a single negative Xpert result. It is important for TB programmes to train health care providers on how to interpret Xpert test results and when clinical TB diagnoses should be considered. Introduction of Xpert testing should not cause missed opportunities for diagnosis.

Who is eligible?

Ensuring that health care workers understand the diagnostic algorithm is key. Operationally, it is simple to say that the Xpert assay will replace smear microscopy as the first-line diagnostic test for all people with TB symptoms. However, in resource-depleted settings, Xpert eligibility might be limited to certain key risk groups (e.g. children, people with suspected multidrug-resistant [MDR-] TB, people living with HIV, and people with an abnormal CXR result) and it is much harder for providers to consistently refer eligible populations for testing. In some settings, TB programmes have decided that health care professionals should simply refer patients for a sputum test. The laboratory technicians are then responsible for deciding who is eligible for which test when patients arrive the laboratory to provide a sputum sample. This ensures that the new tests are being employed correctly. This simple activity only requires a re-design of the test referral form as long as laboratory technicians are well aware of the testing criteria.

In many settings, programmes have decided to train a cadre of GeneXpert "super users" to perform basic machine troubleshooting, repair (e.g. module replacement), calibration, software updates, and/or collection of information to send to the national TB programme (NTP) and Cepheid. These individuals can easily provide support to several GeneXpert systems (4–10 depending on their geography and distribution). Super users can be easily networked via no-cost forums such as WhatsApp groups in order to assist with troubleshooting (e.g. by sending screenshots of errors) and capacity-building of laboratory personnel.[1]

1. Country experiences shared in the Amsterdam consultation meeting.

Task-shifting

Ideally, TB diagnostic tests should be performed by highly trained laboratory technicians. Shortages of qualified personnel, however, can limit the expansion of TB diagnostic testing services. In such instances, programmes can consider task-shifting to less specialized health workers.

This approach reduces human resources costs, allowing programmes to employ more personnel within their existing budget and to expand either the services that are offered or the coverage of the services.

In Ethiopia, the principle of task-shifting laboratory services was applied to smear microscopy testing with great success (16,17). All-female health extension workers (HEWs) employed by the government collected sputum samples in rural communities suffering from acute physical access barriers. The HEWs were trained on biosafety procedures and how to correctly smear sputum onto clean slides at a local health post. Slides that were mounted in the community were stored in slide boxes and transported in batches to designated laboratories for staining and reading by laboratory technicians. Over a period of 4.5 years, 216,165 people with TB symptoms were tested using this approach, resulting in a sustained 98% increase in smear-positive TB case notification rates (16). Since HEWs were already employed for general health services, there was initial fear that this kind of task-shifting would crowd out their other tasks. However, these fears were unfounded, as the HEWs were eager to learn new skills and make a visible impact on their communities (18). A study from Afghanistan also showed that there was no significant difference between laboratory technicians certified after a 3-year training programme and technicians who were recent high-school graduates in terms of performance (19).

The same laboratory task-shifting principles can be applied to Xpert testing. The Xpert MTB/RIF assay is very simple to perform – simpler than smear microscopy – and excellent test results have been obtained even with lay health workers preparing samples and performing the test (4). In Botswana, nurses collected samples and performed tests so that the Xpert assay could be offered as a point-of-care (POC) test (20). As new POC technologies, such as the GeneXpert Omni system, are deployed, task-shifting will play a larger role in TB diagnosis.

2.3 Sample collection

Most TB tests are performed using sputum samples. Active TB case-finding programmes often suffer from low sputum collection rates and/or collection of poor-quality sputum. However, TB prevalence surveys have shown that it is possible to achieve very high sputum collection rates from people who have non-traditional TB symptoms, even those who do not report any symptoms at all (21). Using expensive molecular assays on low-quality sputum or saliva samples can translate into poor detection rates and higher costs (22).

Improving sputum collection rates and quality

Several simple activities can be implemented to improve the proportion of people who are able to provide a sputum sample.

Adjusting the environment to suit patients' needs

The environment in which people are asked to provide a sample can have an important link to sputum quality. In many settings, it is considered improper for females to cough up sputum, let alone to do so in public. A designated sputum collection area away from clinic waiting rooms and bathrooms that provides some modicum of privacy could make it more acceptable for people to submit spot samples. Some health facilities designate small "cough houses", which not only provide a semi-private space for sputum collection, but also protect health care workers and other patients from infectious droplet nuclei.

Preparing patients for submitting the perfect sample

Taking time to counsel patients and to encourage them to cough up a good sample is essential. Research has shown that simple verbal instructions on how to cough up a sample can improve the number of samples being submitted, the quality of samples (fewer rejections by laboratories), and TB detection among women (23,24). In light of these findings, a series of animated instructional aids has been produced and adapted to different settings in poster and video format, with support from the Stop TB Partnership's TB REACH initiative.

Figure 1. Posters and visual aids with sputum submission instructions

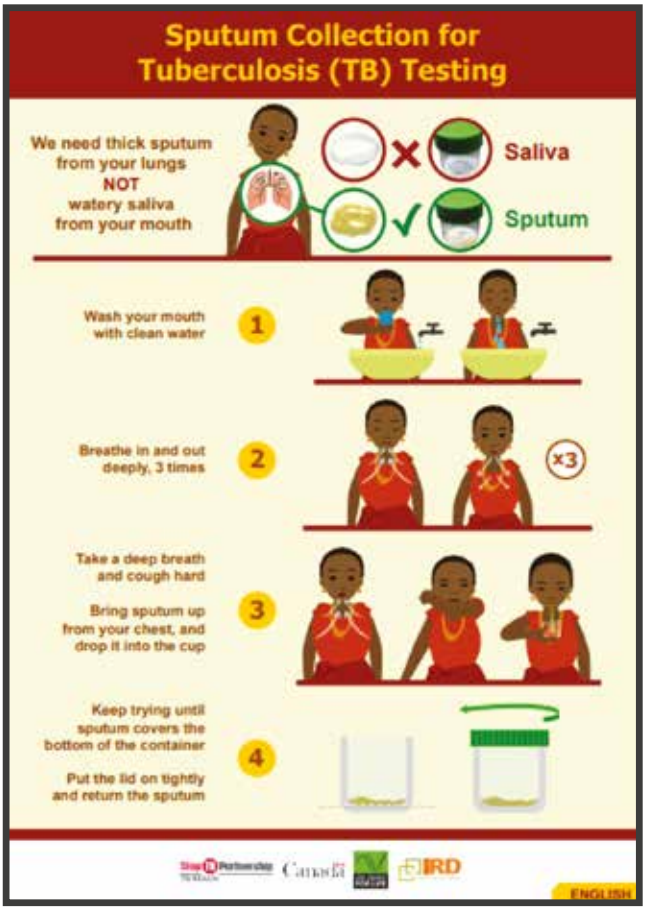

Figure 1. Posters and visual aids with sputum submission instructions

A small-scale evaluation of these instructional aids in Tanzania showed that they were highly acceptable in the community, led to better quality sputum being submitted, and resulted in significantly higher TB detection rates (25). Programmes may also consider the use of nebulizers or mucolator sachets to induce sputum if, after instruction, people still cannot cough up a sample of sufficient quality and size. The tools to induce sputum can be especially helpful for TB testing in children (see more in the field guide on case finding among children in this series).

Ensuring quality control

Laboratories act as the final quality control check for sputum samples. While it could be useful to have criteria for rejecting samples, research has shown that the visual inspection of samples for colour/consistency and volumes above 1mL is not able to accurately discern which samples contain TB during active case finding (26); therefore, rejecting samples based on these criteria may result in missed opportunities for diagnosis. Technicians should be trained to identify and reject samples that are of insufficient volume (<1mL) and those that contain diagnostic assay-interfering particles (e.g. food, chewing tobacco, etc.).

Spot vs morning samples

In passive, facility-based TB programmes, people seeking care are usually asked to give two to three sputum samples for diagnostic testing. These may include two samples coughed up on the spot and one produced first thing the next morning. Although studies have shown that front-loading (i.e. testing two spot samples) is as good as testing one spot and one early morning sample (24,27,28), people with TB detected via active case finding may be more likely to be paucibacillary than those detected during passive case finding; therefore, they may benefit more from testing a morning sample. However, it is not clear whether any potential incremental yield is worth the risk of losing people through the diagnostic algorithm and the added cost to patients. Thus, programmes operating in the field should strive to collect quality samples from patients right away.

2.4 Sputum transportation networks

An estimated 76% of people with TB in selected high-burden countries first access health services at facilities with no laboratory testing capacity (29).

It is well known that simply referring symptomatic individuals to another health facility for testing often results in large loss to follow-up, owing to the many barriers people face in accessing care. Consequently, transportation networks should be a key strategy for improving access to laboratory services and modern TB diagnostic tests for both people screened in the community and people already accessing health services (30). Programmes can choose to transport people, samples or both. This section focuses on the transport of samples, as it results in less loss to follow-up and fewer costs for people being tested. Table 1 summarizes some key questions programmes should ask when designing a sample transportation network and the sections below provide some considerations and answers to these questions.

Table 1. Key questions when designing a sample transportation network

Consideration	Questions
Area of coverage	• Will the sample transportation network connect collection sites in communities, health facilities or both? • How many collection sites will be connected to one testing site?
Frequency	• How frequently will samples be transported from a collection site to a testing site? • Will samples be collected via a regular, scheduled service or an ad hoc request a sample is collected?
Sample integrity	• Will the samples need to be preserved before they are transported to a laboratory for testing? • How will samples be packaged during transport to limit sample contamination and exposure to droplet nuclei?
Transportation method	• What kind of transportation methods are available and best suited for the route? • Will the programme procure its own vehicles or will it pay a fee per trip or per sample transported to individuals who already own a vehicle? • Is it possible to integrate TB sample transport with other sample transport services?
Reporting	• How will testing IDs be set up to facilitate disaggregated reporting of test results? • How will test results be returned to the collection site and how will patients be linked to treatment?

Area of coverage and transportation frequency

There is no single template or standard design for establishing a sputum sample transportation network. The area covered by the transportation network will depend on the availability and quality of diagnostic testing services in the country, and the capacity of the laboratories to accommodate increased testing numbers. It may be ideal to collect samples and temporarily store them at a collection site before transporting a larger number of samples together. In general, samples should be transported and tested as soon as possible; however, the number of samples being collected will likely dictate the frequency with which they are transported. In some urban settings, it may make sense to transport batches of samples a few times a day, while in remote rural settings, samples may be transported once a week. Programmes should consider ways to integrate TB sample transport with the transport of other biological specimens or other transportation networks in order to facilitate more frequent transport and faster turnaround times (as described in more detail below).

Engaging community health workers

Community health workers (CHW) can collect sputum samples and transport them to the nearest laboratory (see also the transportation method section below). Test results can then be relayed from the laboratory back to the CHW who submitted the samples so he/she can initiate treatment. Ideally, treatment should be initiated close to where the sputum was collected, as the same barriers to accessing diagnostics will likely apply to accessing treatment. The Stop TB Partnership's TB REACH initiative has supported numerous TB programmes to establish sputum transportation networks across various key populations (16,17,31–39). In general, the transport of sputum from the community works best when a (lay) health worker belongs to the community that is being screened. This person can easily visit homes and follow up with people to collect additional samples. For example, in Nigeria, a screening programme in nomadic pastoralists saw health workers collect sputum samples from people with a cough at market days and transport them to the nearest laboratory (38). Results were returned to the communities by the local TB supervisors.

Establishing collection sites at existing health facilities and private provider sites

Sputum transportation networks can expand access to diagnostic services for people attending routine health services. Often, these individuals are referred to another site for testing, resulting in delayed or missed opportunities for diagnosis and added costs for patients. Establishing a sputum collection site that regularly transports samples between health facilities is a fast, simple and inexpensive way to expand access to diagnostic services. TB programmes could consider including other potential collection points, such as private GP clinics and pharmacies, in their sputum collection network. Private providers are a common first point of access for people with TB symptoms in many settings, yet these facilities have the lowest availability of TB diagnostic services.

Maximizing staff and making testing capacity more efficient

Sample transportation networks can also be established to address the fact that the testing capacity and services at many existing laboratories are underutilized. When laboratory technicians consistently have low smear microscopy workloads (less than 10–15 slides per week), it can be difficult to maintain testing proficiency (8). If health facilities are connected to higher volume facilities via a regular sputum transportation link, a larger number of laboratory technicians can be stationed at the higher volume facility. This could guarantee the minimum workloads needed to maintain testing proficiency, and could simplify the process of managing staff (e.g. recruitment, training, redundancy, etc.) and ensuring testing quality. Similarly, many GeneXpert systems are not operating at or even near their maximum testing capacity because they are installed in health facilities with low testing volumes. Therefore, connecting health facilities via a regular sputum transportation link is an ideal way to increase Xpert testing volumes and to expand Xpert testing coverage without installing new machine capacity.

Transportation method

Innovative approaches

TB programmes can be innovative when it comes to building transportation networks, but the modes of transportation should be suited to the local transportation infrastructure. In Lesotho, a TB/HIV programme used horses to transport samples because mountainous roads were of such poor quality. In the Democratic Republic of the Congo, the use of canoes was key to accessing remote forest communities. In Madagascar, semi-autonomous drones have been used to reach remote mountainous communities that lack road access.

Motorcycles and bikes

More traditionally, programmes have used motorbikes or bicycles for sample transport. In some settings, health workers may already have access to a motorbike for transporting samples. Programmes can provide these health workers with transport stipends – based on the length of the journey – to cover fuel and motorbike depreciation costs. Riders can then visit several peripheral sites where sputum samples are collected or temporarily stored before transporting them to laboratories. In certain countries, there are organizations like Riders for Health International (https://www.ridersintl.org/) that are solely dedicated to this work. The Centre for Infectious Disease Research in Zambia (CIDRZ) bought bicycles for community volunteers who were then tasked with picking up and transporting samples at specific times of the day. They were allowed to keep the bicycles at their homes for personal use as a form of non-monetary incentive.

TB programmes should look to other health services for support in building a sputum sample transportation network. Although sputum sample transport can be done relatively cheaply, building a programme exclusively for TB testing is an inefficient approach and not in line with the Sustainable Development Goal (SDG) of integrating health services.

Integrated services

Sputum sample transport can be integrated into the sample transportation networks available for other diseases. This is particularly true when samples are being transported between health facilities. The costs of a specimen transportation network could easily be shared with HIV programmes and other primary health services in a way that aligns with the SDG of integrating health services. When samples have to be transported from the community, integration with other disease services may be more difficult, since such services may be lacking entirely. However, given that many other disease programmes are also trying to move service delivery to the community, it is worth exploring how sample transportation services could be shared.

Looking beyond health services

Many non-health programmes have been successful at supplying products to remote areas. TB programmes may find that there are well-established distribution networks into which sputum transport can be integrated. These could be the supply chains of for-profit companies, but more realistically these could be existing courier services. There may also be a natural flow of people using public transportation networks that can be tapped into when designing a sputum transportation network. If individuals travel regularly between sites where sputum samples are collected and sites where they are tested, those individuals could be approached and given a small stipend to transport samples with them on their existing journey. For example, many health centres are responsible for supervising CHWs in a defined catchment area, and health facility staff could pick up sputum when making supervision visits.

Delays with transport and sample preservation

Transporting sputum samples to a laboratory may take several days. During this period, exposure to heat, sunlight, humidity and a host of other factors can degrade the quality of the sputum samples.

- Samples that are being sent for only smear microscopy may be kept at ambient temperatures (20–30°C) for up to 2 days and up to 1 week if they are stored in a refrigerator (2–8°C) without affecting test positivity rates (30).
- Because bacteria viability is not required for Xpert testing, samples may be inactivated (thus preserving their DNA) by adding 70% ethanol or other commercial products before transport at ambient temperatures.
- Samples destined for culture testing can be maintained for up to 1 week in a refrigerator, but if storage and transport exceeds 3 days at ambient temperatures, cetyl pyridinium chloride (CPC) should be added to the samples to inhibit growth of the contaminating flora.

Several products, including DNA Genotek's OMNIgene•Sputum, Longhorn's PrimeStore MTM, Whatman's FTA card, and Hain's GENO•CARD, have emerged with the aim of preserving sputum samples during transport without the need for refrigeration. Of these, OMNIgene•Sputum is the only one that is compatible with culture testing. The body of literature evaluating these products is still in the nascent stage, and a recent WHO review concluded that further research was needed before recommendations on their use could be provided (40).

Packaging samples

It is important to properly package sputum samples so as to minimize leakage during transport. Leakage of a single sample could easily lead to cross-contamination of the other samples being transported and create a risk of infection. In many high TB burden countries, sputum containers do not have sufficiently tight lids to prevent leakage.

Programmes may consider wrapping the container lids with Parafilm, depositing containers into individually sealed plastic bags, or procuring good-quality sputum mugs, such as the ones available through GDF. It is better to transport samples in a box or cooler rather than in a bag, so as to minimize movement of the containers. Staff responsible for sputum collection and transport can very easily cut a piece of cardboard to fit snugly inside a cooler or box and then drill or cut wells in the piece of cardboard for the sputum containers. This solution allows for neat packing and layering of samples, and can greatly reduce the movement of samples and the potential for leakage.

Results and reporting

Returning diagnostic test results back to their site of origin is a common challenge faced by TB programmes. The GLI guide to TB specimen referral systems and integrated networks provides many examples of paper forms for tracking the referral of specimens and the return of results (30).

Testing IDs

Programmes should consider devising a testing ID scheme that makes it easy to identify and disaggregate test results in a laboratory register. For example, samples transported from Health Facility A can be labelled with the health facility moniker before a sequential number; alternatively, samples can be labelled with patient initials and a sequential number to minimize transcription errors. Analysis of routine laboratory data by collection site and date of testing can help to optimize the operation of sputum transportation networks, for example, by reducing or increasing the number of days on which samples are collected.

Electronic referral systems

Programmes can establish electronic referral systems that use the internet, mobile networks or even SMS messages to track when samples are collected, transported and received, and to return results back to the sending site (41). The complexity of these systems can vary greatly. Results tracking systems can be very simple, just replicating the steps of a paper-based system. Results could be relayed to a health worker at the sending site via Skype (very low cost) or by SMS (providers often have low-cost unlimited texting packages). In many settings, programme personnel prefer SMS messages to phone conversations for returning results, as these avoid transcription errors and loss of information; SMS messages can also be used to confirm receipt. More robust electronic results referral systems can integrate directly into screening, lab and treatment databases via web portals and mHealth apps. Laboratories could even send notifications to patients directly, alerting them that their results are available. For more details on information systems, please see the relevant field guide in this series.

Privacy

Patient privacy is a concern, particularly when looking to send notifications directly to patients. In certain settings, such notifications may be universally acceptable, but this is not always the case. TB is still stigmatized in many settings, and cell phones may be shared or family and friends may have access to a person's phone. If people with TB have not told their family and friends about their health seeking and a TB programme accidentally discloses their TB status, this violation of privacy can have serious consequences.

Even if violence and discrimination around a TB diagnosis are not common in a setting, it is best to provide a person with a notification that test results are available, instead of sending the TB results themselves. In light of these concerns, people being evaluated for TB should be given the choice to opt in to a results sharing method. Informing patients of a positive test result should ideally occur in conjunction with some form of counselling or empowerment activities so that they do not feel isolated and are instead motivated to start treatment promptly and encourage their family and friends who may have been exposed to get tested.

3. AVAILABLE DIAGNOSTIC TESTS

3. AVAILABLE DIAGNOSTIC TESTS

Improving TB diagnosis is a complex endeavour. Many diagnostic tests are available, but each has its own set of strengths and weaknesses that must be carefully considered, along with its costs, when rolling out active or enhanced TB case-finding services.

3.1 Smear microscopy

While Xpert MTB/RIF testing is the recommended first-line diagnostic for TB, smear microscopy is the most common test for TB in many settings. The vast majority of smear tests are performed using the acid-fast bacilli (AFB) Ziehl-Neelsen (ZN) staining technique and conventional light microscopy. This process is very cheap (less than US$ 1 [42]) and fast, and relies on an interdisciplinary skill (light microscopy). The stains are stable for a long time and locally available. Furthermore, the test requires little infrastructure and is highly specific (few false-positive results). It can even be performed in settings with no power, using microscopes with mirrors.

After decades of use by TB programmes, a robust External Quality Assessment (EQA) scheme and standardized reporting forms are common for smear microscopy testing (8,43). However, ZN smear microscopy testing is highly dependent on the skill of the individual performing the test and the time taken (or available) to read slides. Consequently, while ZN smear microscopy can achieve reasonably high sensitivity rates in controlled research settings, under programmatic conditions, it is often poorly sensitive, meaning that many people with smear-negative results actually have TB (44).

In 2011, WHO recommended the use of light-emitting diode (LED) fluorescence microscopy as an alternative to ZN staining (45). This procedure is slightly more sensitive than ZN staining, but has a slightly lower specificity (46,47). In addition, it takes less time to examine fluorescently stained slides than it does to examine ZN stained slides. Large-scale implementation in high TB burden countries like India have shown that when LED fluorescence microscopy replaces ZN staining, more people with smear-positive TB are detected among those already seeking testing services (48,49). However, the switch to LED fluorescence microscopy has been limited due to the need for specialized equipment, the higher cost and the shorter shelf life of reagents.

Although smear microscopy is highly specific, it is not an ideal test for active TB case-finding programmes that will conduct a large number of diagnostic tests for people in a low TB prevalence setting (i.e. with low pre-test probability). In these circumstances, the proportion of false-positives can be as high as half of all positive test results. It is very important for active TB screening programmes that will encounter low prevalence rates to use a TB diagnostic test with higher specificity than smear microscopy. The primers in molecular tests only amplify Mycobacterium tuberculosis DNA and all positive cultures can be tested to differentiate M. tuberculosis complex from mycobacteria other than tuberculosis (MOTT; or nontuberculous mycobacteria [NTM]).

Box 1. Understanding the issue of false-positive results by smear microscopy

ZN smear microscopy test performance			
Sensitivity	40%	Specificity	98%

Smears performed	TB prevalence among those tested	True positives	False negatives	True negatives	False positives	False positivity rate
5,000	20%	400	600	3,920	80	16.7%
	4%	80	120	4,704	96	54.5%

In this fictitious example, the ZN smear microscopy test performance and number of smears performed are the same for each population, but one population has a TB prevalence that is 5x higher than the other. In the higher prevalence population, 80 false-positive results are recorded among a total of 480 positive test results (400 TP + 80 FP), giving a false-positivity rate of just 16.7%. While this rate is not ideal, historically it has been acceptable in the absence of affordable and scalable diagnostic tests with better performance. By contrast, in the lower prevalence population, 96 false-positive results are recorded among a total of 176 positive test results (80 TP + 96 FP), giving a false-positivity rate of 54.5%.

3.2 Molecular assays

At present, only a few molecular assays are commercially available for TB testing. Although several molecular diagnostic tests and platforms are under development, none of them have been sufficiently evaluated to warrant a WHO recommendation on their use (50).

Xpert MTB/RIF assay (Xpert)

The Xpert MTB/RIF assay is a nucleic acid amplification test (NAAT) that is able to simultaneously detect TB and resistance to rifampicin in just 2 hours. The assay is substantially more sensitive than smear microscopy (51); however, it still has a suboptimal sensitivity of 68% among smear-negative, culture-positive samples. The rapid identification of rifampicin resistance enables TB patients to be started on effective treatment much quicker than with culture-based drug-susceptibility testing (DST). The Xpert MTB/RIF assay became commercially available in late 2009, and shortly thereafter WHO released a narrow set of recommendations on its use (52). Over time, WHO has updated its policy to recommend the Xpert MTB/RIF assay as the initial test for adults and children with signs and symptoms of TB (7). Besides South Africa, very few countries have entirely replaced smear microscopy with direct Xpert testing because of costs (US$ 9.98 per cartridge plus significant up-front investments in equipment and recurring maintenance costs). Nevertheless, utilization of the assay has been increasing every year.

Xpert MTB/RIF Ultra (Ultra)

The next-generation Xpert MTB/RIF Ultra assay was specifically designed to address the shortcomings of the current Xpert MTB/RIF assay. Early demonstration studies have indicated a 19–37% increase in sensitivity among smear-negative, culture-positive samples compared to the current Xpert assay (53,54). This makes the Ultra assay ideal for people with paucibacillary disease, such as people living with HIV/AIDS and children. However, these gains in sensitivity have resulted in a slightly lower specificity of the Ultra assay compared to the current Xpert assay. In 2017, WHO released a policy recommendation stating that TB programmes could replace the Xpert assay with the Ultra assay (55). It also gave specific recommendations on how to interpret positive test results with extremely low bacteria burdens ("trace call" positive) in light of a patient's TB treatment history in order to preserve the assay's specificity. The Ultra assay can be procured for the same price as the current Xpert assay (US$ 9.98). Programmes that choose to switch to the new Ultra assay should consider developing indicators to monitor the switch, in particular the levels of "trace call" positive patients and how care for these individuals is managed.

The run time for the current Xpert assay is estimated to be 114 minutes per sample. With the Ultra assay, negative samples run for just 65 minutes, while positives run for 77 minutes (56). Therefore, by simply switching to the new Ultra assay, programmes can increase their already installed GeneXpert system capacity by up to 50% (depending on the test positivity rate).

Loop-mediated isothermal amplification (LAMP)

Eiken's loopamp MTBC Detection Kit (TB-LAMP) assay is the only molecular test other than the GeneXpert platform that is currently commercially available and WHO-recommended for TB case finding. TB-LAMP is a rapid, manual assay that can be read with the naked eye under ultraviolet light. It does not require sophisticated instruments and has biosafety requirements similar to those of smear microscopy. In 2016, WHO recommended its use as an initial test for adults with signs and symptoms of TB (57). However, the uptake of TB-LAMP by TB programmes has been very slow, primarily due to the inferior sensitivity of the assay compared to Xpert, particularly among smear-negative, culture-positive specimens (42% for TB-LAMP vs. 68% for Xpert). In addition, the TB-LAMP assay does not provide information about drug resistance and has unit costs similar to those of Xpert (US$ 9.30 per test; EUR 650.70 for the Loopamp PURE DNA Extraction and MTBC Detection kits for 84 samples, EUR 1 = US$ 1.20).

Line probe assays (LPAs)

WHO recommends LPAs for rapid DST of people with suspected MDR-TB (58). Given the focus of this field guide on improving TB case detection via active and enhanced TB case-finding activities, the use of LPAs will not be discussed in detail. However, these assays could play a role in TB case-finding programmes by confirming and detailing the drug resistance profiles of people with suspected MDR-TB and facilitating more rapid linkage to appropriate TB treatment.

3.3 Urine lipoarabinomannan (LAM) assays

The LAM antigen is present in the cell walls of TB bacteria and is shed into urine during active TB. Different urine-based assays have been able to detect LAM in TB/HIV coinfected patients, but not in HIV-negative TB patients (59,60). In addition, studies have shown that the LAM assay is able to accurately predict TB mortality (61) and that POC testing and LAM-guided treatment initiation reduced TB mortality for HIV-positive hospital in-patients (62). Based on these findings, in 2015, WHO issued a recommendation on the use of LAM assays (63): Alere's Determine TB LAM Ag assay may be used to aid in the diagnosis of TB in people living with HIV who have low CD4 counts or are seriously ill regardless of their CD4 count. Due to this narrow recommendation and issues with the sensitivity of the LAM assay, uptake by TB programmes has been fairly limited.

3.4 Culture

Automated liquid culture is the current reference test for TB diagnosis. People with extremely low numbers of TB bacteria in their sputum who are missed by all other diagnostic tests can still be detected on culture. Although culture is extremely sensitive, it is expensive and very reliant on specimen quality and technician proficiency. Furthermore, it can take up to 8 weeks to produce a result due to the slow speed of TB bacteria growth, and culture facilities are available at only a handful of laboratories in most countries. Therefore, because of limited access to this test, it is rarely used for TB case detection. In most settings, culture is still the primary method used to diagnose and manage MDR-TB, even though molecular tests can now identify people with drug-resistant (DR-) TB and determine their resistance profiles.

Molecular assays identify the DNA mutations that confer resistance (genotypic DST), whereas culture-based DST looks at how live bacteria respond to antibiotics (phenotypic DST). Since molecular assays are not able to cover every single mutation that confers drug resistance, phenotypic DST will still play a role in MDR-TB diagnosis for the foreseeable future. For example, in the Kingdom of Eswatini, an estimated 30% of MDR-TB has a mutation that cannot detected by the Xpert assay and can only be diagnosed with culture-based DST (64).

Recent TB prevalence survey results from Kenya, Bangladesh, the Philippines and Viet Nam have highlighted the challenges in using culture as the reference standard in large-scale surveys. These were the first countries to incorporate Xpert testing into the prevalence survey diagnostic algorithm. In each country, people with Xpert-negative, culture-positive results were detected in large numbers, as expected. However, large numbers of people were also identified with Xpert-positive, culture-negative results. Initially, the Xpert results were questioned, but as more and more people with Xpert-positive, culture-negative TB were identified, survey managers began to question the quality of culture practices. Inadequate sputum storage facilities in the field (no refrigeration), long transportation times from field sites, too strong of a decontamination wash in the laboratory, and culture contamination rates have all been suspected as the reason for such low culture positivity rates.

Given these issues, people with Xpert-positive, culture-negative TB and abnormal CXRs were included in the final TB prevalence rate calculations, resulting in increased TB burden estimates for each country. These surveys highlight the challenges programmes may face when inoculating large volumes of cultures with samples collected through a transportation network.


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4. MONITORING & EVALUATION

4. MONITORING & EVALUATION

WHO has released multiple documents outlining the policies, procedures and targets for laboratory strengthening under the End TB Strategy (65,66). The following sections contain additional considerations for the M&E of active and enhanced case-finding initiatives.

4.1 External Quality Assessment (EQA) schemes

Assessing the quality of laboratory systems must be an essential component of any active or enhanced TB case-finding programme. Poor-quality diagnostic testing can result in missed or incorrect diagnoses and can compromise the impact and cost-effectiveness of TB case-finding activities. There is a standard EQA framework for smear microscopy and culture/DST services that is implemented by NTPs in almost all high TB burden settings (8). Despite its establishment, this framework may not be functioning optimally and/or it may not cover all of the laboratories that are diagnosing TB, particularly those in the private sector. In some settings, this framework may be functioning well, but its outputs are not being used to make data-driven decisions on which laboratories should be targeted for retraining of technicians and additional oversight to improve services.

Blinded re-reading of slides and proficiency panel testing are key components of the EQA strategy for smear microscopy. However, the use of patient actors/mystery clients and sputum samples that have been spiked with TB bacteria may be another way to evaluate the quality of laboratory services under routine conditions (67).

An assessment of private laboratory smear microscopy services in Pakistan showed that quality was extremely poor and was not correlated with either the cost of the smear test or whether the laboratory held any ISO certifications. A quality check of this scale takes more effort than the standard EQA scheme, but can provide valuable information about laboratory services and can be used to extend EQA schemes to laboratories, particularly those in the private sector, that refuse to participate in the standard smear microscopy EQA scheme.

Xpert-specific

Each Xpert assay contains multiple internal controls that ensure testing quality (68). For example, when TB DNA fails to amplify, a sample processing control (SPC) must amplify in order for a negative test result to be assigned. If both the TB DNA and the SPC fail to amplify, the test result is declared invalid. The use of an internal control in this fashion helps to avoid false-negative results due to sample processing errors or Xpert cartridge defects. Monitoring test failure rates and investigating and addressing the reasons for test failure are important quality assurance activities, and connectivity solutions can facilitate these efforts (see next section).

Proficiency testing panels for Xpert have been developed and rolled out in some high TB burden settings (69,70). However, because of their costs and the presence of internal controls in each Xpert cartridge, their uptake has been limited. The Stop TB Partnership's TB REACH initiative funded the development of a standard operating procedure (SOP) for regional and national reference laboratories to develop their own proficiency testing panels that can be distributed to Xpert testing sites throughout the country.

Culture-specific

Although culture is not widely used for detecting people with TB, it may have a role to play in certain active case-finding projects and it continues to play an important role in diagnosing DR-TB. Almost all TB culture facilities are part of an existing EQA scheme with a regional, national and/or supranational reference laboratory.

4.2 Connectivity solutions & remote monitoring

As TB laboratories begin to install diagnostic equipment that has built-in connectivity or is connected to computers, there is an opportunity to send test results to a server and to remotely monitor TB testing activities in real-time from a central location. Real-time, remote monitoring of testing data is a powerful tool for TB case-finding programmes and even for the routine services provided by NTPs. Monitoring testing data can help programmes to rationally deploy equipment/modules based on utilization and even manage laboratory staff. For example, if no test results are received from a laboratory by noon on a given day, a member of a central monitoring team can call the laboratory to understand why no tests have been performed. Solutions to any problems can be identified and deployed to restart testing long before a more passive, paper-based system would have identified the interruption or downturn in testing. Remotely monitoring failure rates can help to identify which laboratory technicians are in need of targeted retraining and which equipment/modules are in need of maintenance. Integrating testing data with inventory data systems can help to manage the supply chain of reagents/consumables without the need for central monitoring or for supply chain team members to make field visits.

Digital data can also make it easier to track people with TB and link them to appropriate treatment, particularly those with DR-TB. If laboratories already have WiFi connections, establishing network connections will be very straightforward. If no WiFi connection exists, then 2G/3G/4G-enabled dongle USB modems or WiFi hotspots can be procured and set up to allow for transmission of data with minimal up-front and recurring costs. Often, there are existing servers in country to which test data can be sent.

In addition, space could be rented from secure cloud services without the need to invest in hardware. In many instances, cloud services offer more robust storage solutions (e.g. continuously operational, systematized back up, stronger firewalls and security, etc.). However, programmes must understand their local data protection and sharing laws before deciding to store data on a cloud server. Some countries prohibit medical data of their citizens from being transmitted outside the country, regardless of whether or not security standards are met. Please refer to the field guide on strengthening information systems and linkages to care in this series or the GLI quick guide on TB diagnostics connectivity solutions (41) for additional details on this topic.

Xpert-specific

System One's GxAlert software is the most widely deployed connectivity platform for GeneXpert.[2] Experiences from high TB burden settings have shown that the software is robust, easy to set up in laboratories, and a powerful tool for strengthening laboratory systems once it is fully functional (71,72). The GxAlert software is developed by a third party and the network can be easily customized to direct testing data to a dedicated in-country server or to a remote cloud server.

Cepheid has its own monitoring software platform called C360 that integrates seamlessly with its existing Dx software and can be used not only for transmitting test results to a central server, but also for receiving Dx software updates.[3] Users must sign a data-sharing agreement with Cepheid, as test results are stored on servers based in North America or Europe and are visible to the manufacturer to help it further develop its products. Individual projects or case-finding programmes should consult with their NTPs before signing such an agreement.

[2] *System One GxAlert:* http://www.systemone.id/gxalert/
[3] *Cepheid C360 Disease Surveillance and System Monitoring Software:* http://www.cepheidc360.com/

4.3 Indicators and impact

A standard system for monitoring and reporting smear microscopy testing activities already exists (43). This system involves counting the number of tests performed and those tested positive (for diagnosis and follow-up care). It also counts the number people tested and detected with TB (for diagnosis and follow-up care). Since people are asked to provide two to three samples for smear testing in most high TB burden settings, a simple count of tests performed and positive results would over-estimate the total number of people diagnosed with TB. While reporting via this monitoring system may not be perfect at the laboratory level, it provides a robust picture of TB diagnostic testing activity in the overall health system. Aggregate testing data are often publicly available going back several years.

Setting up pre/post evaluation for new projects

For active and enhanced TB case-finding projects, it is of great importance to understand the number of people undergoing diagnostic evaluation by any TB diagnostic test and the number of people receiving a positive result across all tests. Without increasing the total number of people evaluated for TB by any test, it will be hard to achieve increases in TB treatment rates. Projects are encouraged to establish a baseline for TB testing and detection rates from passive and active TB screening services against which increases because of screening activities can be measured. A simple pre/post calculation can be used to determine the number of additional people detected with TB and the percent change from baseline. These data can then be compared to the number of people with TB detected through screening activities and treatment notification rates in order to demonstrate that screening activities have led to more people being tested, detected and ultimately treated.

Finding people earlier

Smear grades can be analysed to assess whether active or enhanced TB case-finding activities have found people earlier in their disease course. Programmes can develop a baseline cohort of smear-positive patients stratified by their individual smear grade or by grade groupings (e.g. scanty and 1+ vs 2+ and 3+). These baseline data can be compared with the same data from the period when active case-finding activities were implemented to see whether a higher proportion of smear-positive patients are being detected in the lower smear grades (35,73). This measurement is not precise because smear grade does not always correlate with duration of disease and there can be mistakes in the grading of smear results. However, along with symptom duration, such an analysis could be a useful measure to build a fuller picture of the impact of TB case-finding activities. This type of analysis would also be possible with the semi-quantitative Xpert results, but it may be difficult to find a suitable baseline against which to compare intervention period results, since molecular assays are far from universal.

Avoiding pre-treatment loss to follow-up

It is important to continuously compare laboratory results with TB treatment initiation rates. Pre-treatment loss to follow-up (i.e. people who are registered in laboratories as having positive test results but not found in treatment registers) is not routinely monitored or reported in most high TB burden countries. When this figure is captured, however, it is usually substantial. A systematic review of pre-treatment loss to follow-up in low- and middle-income countries showed that this figure ranges from 6% to 38% of people detected with TB in laboratories (74). Losses could be higher in active TB case-finding programmes that do not consider support for patients who face barriers in accessing care and may be especially challenged in accessing treatment. Such substantial losses reduce the impact and cost-effectiveness of case-finding activities and all efforts should be made to link people with TB to treatment.

As a health system begins to introduce new diagnostic tests, it is important to evaluate their impact on treatment initiation rates and patient outcomes. Many hypothesized that the higher sensitivity of the Xpert assay would increase the number of people treated for drug-susceptible (DS-) and DR-TB. While expanded access to molecular DST testing has resulted in gains in DR-TB detection, these gains have not always translated into better DR-TB patient outcomes (75). Many high TB burden sites have high rates of clinical diagnosis and treatment after the provision of a smear-negative result, and the introduction of Xpert testing has merely increased the proportion of people treated for DS-TB who have bacteriologically-positive results, without changing the total number of people treated (13,14,15). In other words, people who were formerly diagnosed and treated clinically are now being treated and notified as having bacteriologically-confirmed TB (shift between notification categories). In some sites, the total number of people treated for DS-TB has even fallen after the introduction of Xpert, with doctors unwilling to make clinical diagnoses following an Xpert-negative result, despite its low sensitivity among smear-negative samples (68%). While this evidence is strong, it does not reflect the reality of every TB programme. In certain parts of the world, including West Africa and Latin America, treatment of smear-negative TB is extremely low (76), and any gains in bacteriologically-positive TB detection and treatment would increase overall notification rates.


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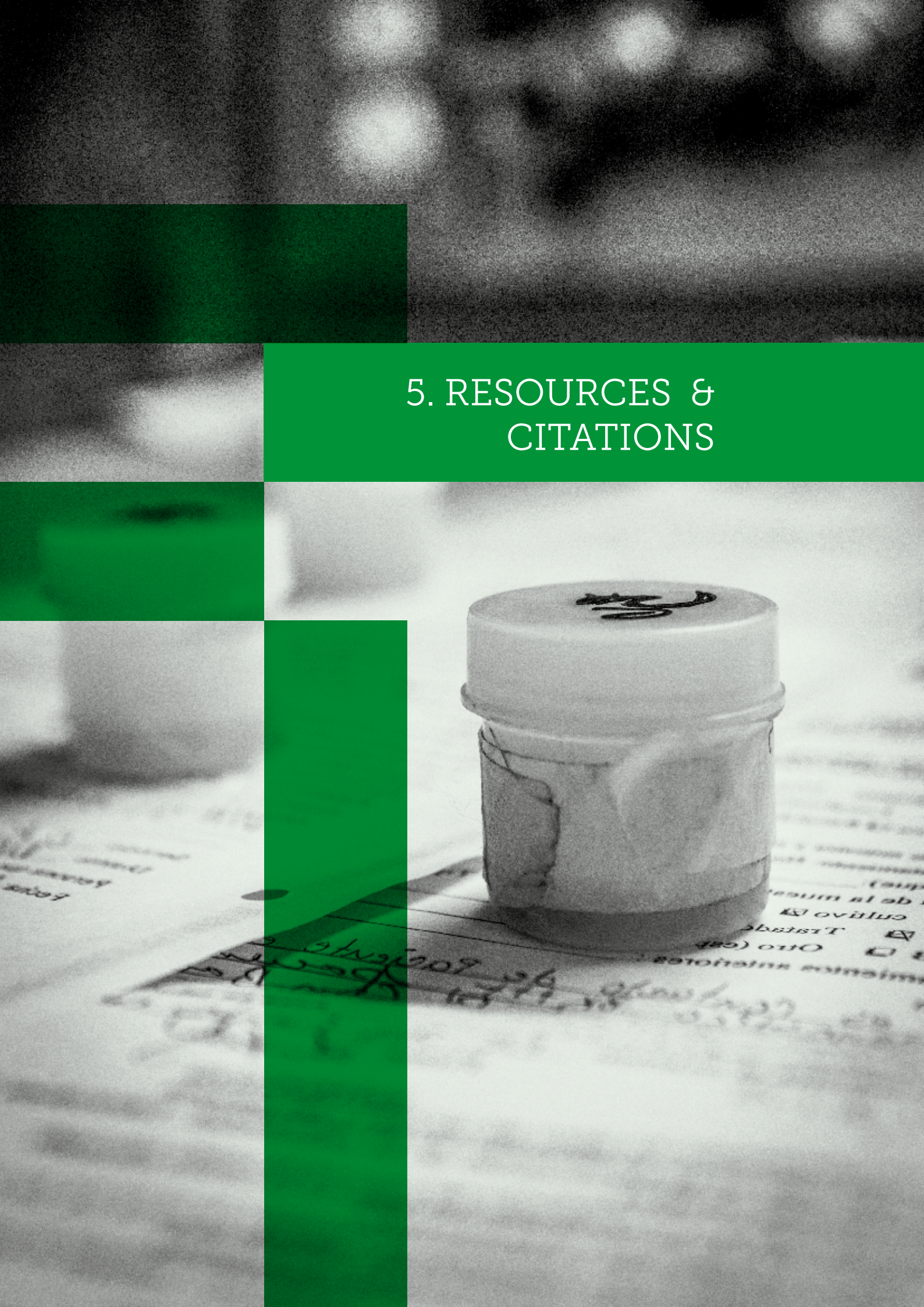
5. RESOURCES & CITATIONS



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This document is one in a series of 11 field guides produced by Stop TB Partnership in collaboration with the Global Fund to Fight AIDS, Tuberculosis and Malaria, Interactive Research and Development Global (IRD), KIT Royal Tropical Institute, and multiple global experts and implementation partners. The field guides rely on practical experiences and expertise of implementers and are meant to help national TB programmes and other TB programme managers to identify the best strategies for finding people with TB who are missed by routine health services.

Stop TB Partnership

Global Health Campus
Chemin du Pommier 40
1218 Le Grand-Saconnex
Geneva, Switzerland