

GLI GUIDE

to TB Specimen Referral Systems and Integrated Networks



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Abbreviations

AFB	Acid-fast bacilli
BAL	Bronchoalveolar lavage
CPC	Cetyl pyridinium chloride
CSF	Cerebrospinal fluid
DST	Drug-susceptibility testing
EID	Early infant diagnosis of HIV
GIS	Geographic information system
GLI	Global Laboratory Initiative
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
LIMS	Laboratory information management system
M&E	Monitoring and evaluation
MDR-TB	Multidrug-resistant tuberculosis
MoH	Ministry of Health
MTB	<i>Mycobacterium tuberculosis</i> complex bacteria
NRL	National tuberculosis reference laboratory
NTM	Non-tuberculous mycobacteria
NTP	National tuberculosis programme
PLHIV	People living with HIV/AIDS
SOP	Standard operating procedure
TB	Tuberculosis
TWG	Thematic working group
UAV	Unmanned aerial vehicle
WHO	World Health Organization

Background

The WHO End TB Strategy calls for the early diagnosis of TB and universal drug-susceptibility testing (DST), with ambitious targets that can only be achieved when all patients have access to modern diagnostics at or near the point-of-care, as well as access to more advanced testing available at regional or central levels. Specimen referral systems play a critical role in ensuring access to laboratory services by allowing patients to receive care and treatment at one location, while their specimens are transferred to various levels of a tiered laboratory system for testing. Referral systems can efficiently increase access to diagnostics in areas where testing is not available, prevent the need and associated costs for patients to travel, and lead to equity in access to health care. Furthermore, for certain tests, centralized or regionalized testing and a robust specimen referral system may be more cost-effective than placing staff and procuring and maintaining equipment to conduct testing at lower levels.

While a common way to refer to specimen referral systems is specimen transport systems, this terminology minimizes the importance of all of the other essential components involved in referral. In order to refer specimens reliably, a comprehensive system is needed that not only includes the needed transport mechanisms and equipment to move specimens between locations safely, but also includes logistics, results reporting, trained personnel, data management, monitoring and evaluation, a policy framework, standard operating procedures, a comprehensive plan with sufficient financing, and proper governance. Ideally, individual specimen referral systems (e.g., referral systems for TB specimens, outbreak response specimens, HIV specimens, etc.) would be organized and connected into a comprehensive, coordinated public health specimen referral network for seamless referral of any type of specimen at any level of the health system.

Well-designed and well-managed specimen referral systems underpin a strong diagnostics network, but unfortunately, until recently they have received little attention in many resource-constrained countries where the challenges to creating and maintaining such systems are substantial. There is often a lack of understanding, expertise, and a system-wide approach in specimen referral, which can lead to fragmented design and implementation of disease- or specimen-specific systems. Planning and implementing an effective system are often ad-hoc and tools are not fully developed or disseminated and available to countries. During planning and implementation, there may not be a thorough understanding of the true costs of the

referral system, in part due to challenges with data collection. Certain countries also face a lack of engagement of the private sector for the provision of laboratory services or for specimen referral services (e.g., courier services) for the public sector. At a programmatic level, referral systems frequently lack proper biosafety and biosecurity measures and are weakly supervised, coordinated, monitored and evaluated. Continuous quality improvement processes are largely absent.

Recently, *Guidance for Developing a Specimen Transport and Referral System for Viral Load and Infant Virologic HIV Diagnosis Testing Networks*¹ was developed as a collaboration between the US Centres for Disease Control and Prevention (US CDC), the US Agency for International Development (USAID), the Clinton Health Access Initiative (CHAI), the African Society for Laboratory Medicine (ASLM) and the World Health Organization (WHO). The guidance highlights the importance of specimen referral systems, describes their components, and provides technical specifications for the handling and transport of specimens for HIV-specific testing purposes. This *GLI Guide to TB Specimen Referral Systems and Integrated Networks* provides analogous design and technical specifications for the handling and transport of specimens for TB testing and builds a case for integrated approaches to specimen referral across sample types and diseases. That is, while there are disease-specific considerations with respect to storage of specimens, packaging, shipment conditions, specimen collection sites, testing laboratories, etc., the underlying architecture of a well-designed specimen referral system can readily support the referral of many types of specimens for many types of tests. Furthermore, multiple referral systems can be connected to form an integrated network across a country that meets the needs of various disease programmes. An integrated network can leverage resources of various disease programmes to improve efficiencies and maximize cost-effectiveness of the network and individual referral systems.

This guide includes information relevant for TB programme and laboratory managers, as well as Ministry of Health (MoH) officials across disease programmes interested in establishing integrated solutions for specimen referral. An associated specimen referral toolkit with additional tools, documents and reading materials is currently under development by Kameko Nichols (The Nichols Group LLC) and will soon be publicly available on the GLI website.

¹ *Guidance for Developing a Specimen Transport and Referral System for Viral Load and Infant Virologic HIV Diagnosis Testing Networks*. CDC, USAID, WHO, CHAI, ASLM. 2016. A draft copy is available at <http://www.aslm.org/resource-centre/hiv-viral-load-testing/hiv-viral-load-scale-tools/>

Coordination of a Specimen Referral System

Within one country and even within the national TB programme (NTP) or other disease programmes, there may be more than one specimen referral mechanism depending on the specimen types, tests needed, laboratory tier, region, funding availability, donor priorities and transport options. Frequently, the national disease programmes and national reference laboratories (NRLs) are not aware of all of the specimen referral mechanisms being used in the country. This fragmentation is sometimes justified, but when it is not properly coordinated can lead to inefficiencies, duplications and unnecessary expenditures on specimen referral. Therefore, it is important to understand which programmes, donors and partners are supporting which specimen referral mechanisms and the respective coverage, costs, efficiency and effectiveness of service providers.

Coordination can be facilitated through the establishment of an integrated national specimen referral technical working group (TWG), which ideally should be a subcommittee or task force of the national laboratory TWG. In large countries, regional TWGs may also be needed. The group should meet regularly and be governed by written terms of reference. Strong commitment and leadership from the MoH are essential for ensuring success of the TWG. Broad stakeholder inclusion in the TWG is important and should include stakeholders representing the MoH, various disease programmes, NRLs, disease surveillance programmes, emergency outbreak response centres, technical experts, donors and implementing partners.

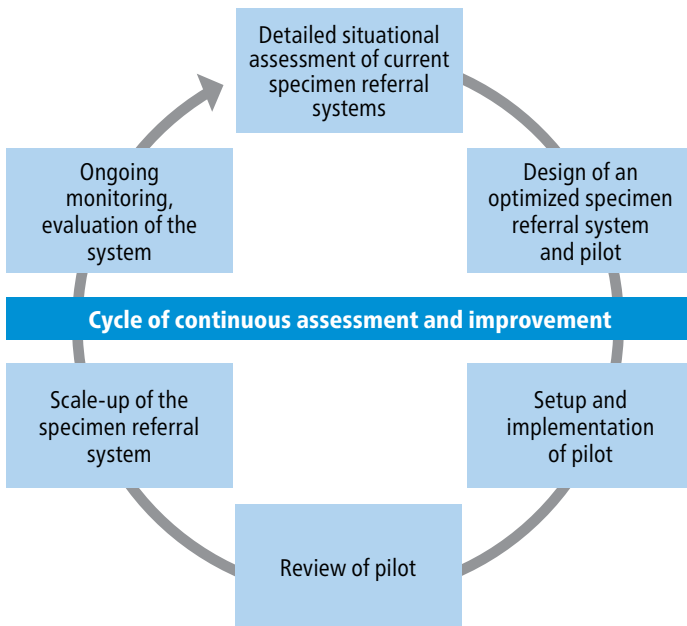
Existing specimen referral systems should be identified and mapped, and their operations, routing and schedules described. Any disease- or system-specific standard operating procedures (SOPs), guidelines and policies should also be collected such that the TWG can take them into consideration in setting the overarching SOPs, guidelines and policies for a specimen referral system suitable for use with any diagnostic specimen; these should all be made part of the national laboratory strategy and policy.

Members of the TWG should also discuss how to gain efficiencies and harmonise or integrate parts or all of the various referral systems, particularly if there are overlapping or competing fragmented systems. Any barriers to coordination between competing fragmented systems must be addressed. While integration may not occur immediately, processes should be established to ensure that resources are not being used inefficiently under multiple specimen referral systems.

Planning for a Specimen Referral System

The process of creating a specimen referral system may be broken into six phases (Figure 1). Timelines for these types of projects may be difficult to predict, but it is important to establish and monitor timelines to maintain momentum and track progress. Learning from experiences from other organizations or companies that have similar systems in-country, or in similar countries in the region, can help in planning for each of the phases.

Fig. 1. Planning and Evaluation Phases



Phase 1: Detailed situational assessment of current specimen referral systems

During this phase, data on the current specimen referral systems in the country should be collected from all available documentation. Any information available on costs and current bottlenecks should also be gathered and analysed. This phase of

data collection and assessment may be challenging where there are multiple financial or accounting systems, donors, funders, mechanisms and implementing agencies involved. However, it is encouraged to avoid performing a disease-specific assessment in isolation and instead examine the available systems used for diseases of public health importance. For example, in countries with a high burden of TB and HIV, at least both the TB- and HIV-specimen referral systems should be examined.

A landscape assessment (see Annex A) should be conducted to gain an understanding of existing specimen referral systems, laboratory networks and testing capacities. The assessment could be quite time- and resource-intensive depending on the number of referral systems to be assessed (e.g., just the TB system or systems for all diseases of public health importance) and scope (regional or national). Adequate time and resources must be budgeted for the assessment.

The landscape assessment should enable the TWG to map out each specimen referral system; identify potential gaps, overlaps, duplications and areas for integration or harmonisation of the current systems; and develop a strategy and plans for an integrated network of specimen referral systems. Throughout the process, the TWG must keep all stakeholders informed and engaged to ensure a strong commitment by all to the development and implementation of the system.

Phase 2: Design of a specimen referral system pilot

With the national strategy and plans as a guide, a specimen referral system should be designed to address the gaps, overlaps, duplications and opportunities for improvement identified by the landscape analysis, and a pilot project developed. A pilot project is usually conducted in one or more small geographic regions and may be designed to address issues in specimen referral at the local, regional or national level. If there are multiple issues to address, it may be useful to design a series of pilot projects that evaluate the potentially most impactful interventions in a phased manner. In areas where disease-specific specimen referral systems overlap, it may be beneficial to consider designing and piloting a specimen referral system that can carry specimens for the overlapping disease programmes.

The design of the pilot project should be led or managed by the TWG with input from all relevant local stakeholders including referring and referral sites, clinicians, disease programmes, implementing partners and transportation services. The detailed operational plan for the pilot project must include a robust monitoring and evaluation (M&E) framework using the quality indicators described later in this guide. Adequate funding and staffing for conducting and evaluating the pilot project must be available.

Phase 3: Setup and implementation of pilot

Depending on the design and existing infrastructure, there may be a significant amount of pre-implementation work. All relevant local stakeholders (e.g., referring

and referral sites, clinicians, transportation services) must be engaged and sensitized to the plan. Clear lines of communications between referring and referral sites must be established. Participants will need to be trained in the new system, processes, forms and procedures. Specimen referral forms and transportation logs may need to be revised or developed and implemented. Baseline (i.e., pre-implementation) data will need to be collected using the M&E framework for the pilot.

Phase 4: Review of pilot

During this phase, any information and feedback from the pilot phase is analysed. The analysis may lead to redesigning or modifying the specimen referral system and conducting additional pilot tests or to implementing the system regionally or nationally.

Phase 5: Scale-up of the specimen referral system

Scale-up of the referral system may be done at a regional or national level or by a phased approach, depending on the country's resources, support and needs. Critically, this is not the end of the process – the scale-up itself will have a process of consensus building, analysis, planning and implementation.

Phase 6: Ongoing monitoring and evaluation, and continuous improvement

After the specimen referral system is in place, it must be monitored and evaluated regularly as part of a continuous improvement cycle. A continuous improvement approach will ensure the system's responsiveness, effectiveness and efficiency. The monitoring and evaluating can be conducted by the TWG or led by a management team in the MoH.

Key System Design Components

Designing a specimen referral system requires a significant amount of planning and consensus building. Unfortunately, one solution does not fit all, so each aspect of system design needs to be considered for the specific setting and the level of integration of specimens carried. However, there are essential considerations and components that should be included in the design of any specimen referral system. A list of questions that are helpful to ask to assess and/or develop a national specimen referral system is provided in Annex A.

Management

It is important that there is strong country commitment at the highest levels and among funding partners, which is a crucial element that cannot be underestimated. Similarly, direct management of the system should be a formal role and not merely a task that is added to an existing manager.

Given the complexities of a specimen referral system, a team may be needed to manage and supervise the national specimen referral system. Expertise will be needed in specimen transport and storage procedures for each type of specimen for each disease, transportation and logistics, data management, electronic reporting, bio-safety, biosecurity and confidentiality issues. In complex systems, it may be necessary to create local or regional teams that can interact with focal persons in each facility, manage daily activities of the system, identify bottlenecks and address issues and challenges. Management and supervision of the national referral system should be led by the MoH, although some aspects could be outsourced to organizations with expertise in logistics.

Adequate laboratory testing capacity

Implementing an effective specimen referral system is likely to result in an increase in the workload for the receiving laboratory in terms of testing volumes, data entry and quality management. It is essential that the increase in workload is carefully estimated and that the laboratories receiving the additional work have the capacity (i.e., infrastructure, equipment, consumables, reagents, personnel, waste management capacity and budget) to conduct the additional work.

Confidentiality of patient information

The confidentiality of patient information must be maintained throughout the entire specimen referral process from specimen collection and transport to results return by all persons involved, including clinicians, nurses, laboratory personnel, data clerks and transport personnel. Important measures to maintain confidentiality include: 1) only authorized personnel should have access to patient information, 2) all persons should be trained in national standards and policies for maintaining confidentiality and held accountable for maintaining confidentiality, and 3) procedures should be in place to secure patient information (e.g., information on test requisition forms and results reports) in the clinic and laboratory and during transport, such as returning results in sealed envelopes or by secure digital means.

Transport options

The type or mode of transport to use is dependent upon resources, locations of the facilities, distances to be travelled, terrain and local settings. The transport can be owned by the facility, owned by another level of government, or provided to the facility through the MoH, partners or a commercial company. Examples of types of transport and considerations for developing a transport mechanism are described in Annex B. Commercial courier services, dedicated motorcycles, cars, boats, unmanned aerial vehicles (UAVs, also known as drones), public transport systems (e.g., buses, trains, aircraft) and national postal systems have been used to transport specimens.²

Logistics and scheduling

At its core, a specimen referral system is a logistics system. Specimens need to be moved physically from collection points to first-line diagnostic testing sites and then possibly to specialized testing sites. It must be decided if there will be a fixed schedule for pick-ups and results return, or if the system can be used on-demand. Consideration may also be needed for referrals from community-level facilities or from health posts. The current referral pathways should be mapped out for each specimen type and at each relevant level or tier of the health system, as there are often different mechanisms of transport available between different tiers. There should be clear delineations of which facilities refer to which laboratories, based on testing algorithms and capacity of equipment and staffing. The catchment area of a referral laboratory may start according to administrative boundaries, but then it is useful to plot all referring and referral facilities on a map to determine if there is a closer testing facility in a nearby region that could provide the testing and the optimal pick-up stops within a route. If samples are collected on scheduled days and

² *Guidance for Developing a Specimen Transport and Referral System for Viral Load and Infant Virologic HIV Diagnosis Testing Networks*. CDC, USAID, WHO, CHAI, ASLM. 2016. A draft copy is available at <http://www.aslm.org/resource-centre/hiv-viral-load-testing/hiv-viral-load-scale-tools/>

vehicles are shared across multiple programmes, the needed time should be built into the schedule of the vehicles so that other activities that require transport, such as patient outreach sessions, are not planned at the same time.

Results return

Return of paper results often uses the same system as specimen transport. However, where possible, electronic or mobile delivery of results is preferred (e.g., by email, SMS or SMS printers). Results can be sent automatically to clinicians upon result availability, allowing for faster patient follow-up. Results can also be automatically sent to laboratory information management systems (LIMS). See more in the *GLI Quick Guide to TB Diagnostics Connectivity Solutions*.³ Regardless, the return of results needs to be considered in the overall design, as getting the specimens to the referral laboratory is only one part of the overall cascade (see Annex C).

Documentation including SOPs

National testing algorithms and the organization of the laboratory network are essential to designing the logistics of a specimen referral system. There are also other national guidelines and policies that either may exist or should exist related to referrals. Further, SOPs, job aids and guidelines are needed for the specimen referral system, including policies and procedures for specimen collection, packaging, sample transport, temperature control or cold chain maintenance in transit, specimen and shipment tracking, biosafety, biosecurity, spill containment and clean-up, and results return. Other documents need to be available, such as referral forms and registers, tracking slips and chain of custody forms, transport logs and data collection tools for monitoring and evaluation purposes. Examples of these types of documents can be found on the GLI website⁴ as well as in Annex D. Links to these documents will also be found in the associated toolkit. For example, the GLI Training Package on Xpert MTB/RIF⁵ includes modules relevant to the collection, packaging and transport of specimens for Xpert testing; the GLI Practical Guide to TB Laboratory Strengthening⁶ has examples of test request forms, transport logs and registers; and an SOP⁷ for the collection and transport of specimens for TB culture is available (reproduced in Annex E). If any of the transport or logistics are outsourced, formal service agreements or contracts should be in place.

A specimen referral handbook and education materials should be developed to

³ Global Laboratory Initiative. *GLI Quick Guide to TB Diagnostics Connectivity Solutions [Internet]*. 2016. Available at: http://www.stoptb.org/wg/gli/assets/documents/gli_connectivity_guide.pdf

⁴ <http://www.stoptb.org/wg/gli>

⁵ Global Laboratory Initiative. *GLI Training Package on Xpert MTB/RIF [Internet]*. 2017. Available at: http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp

⁶ Global Laboratory Initiative. *GLI Practical Guide to TB Laboratory Strengthening [Internet]*. 2017. Available at: http://stoptb.org/wg/gli/assets/documents/GLI_practical_guide.pdf

⁷ *Standard operating procedure (SOP) for sample conditions and transport for culture procedure*.

Available at http://www.stoptb.org/wg/gli/assets/documents/29_specimen_condition_transport.doc

communicate the guidelines; this would be developed by the laboratory, but shared with and serve as a guide for clinicians, couriers, laboratory staff and anyone who collects, packages and transports specimens and results. This handbook should be incorporated into all national lab manuals, not just TB.

Training and sensitization

Implementation is smoother when all stakeholders are sensitized early in the process. Stakeholders extend beyond the central level MoH laboratory directorate or department, implementing partners and donors to include clinicians, nurses, staff of referring sites and referral laboratories and transporters. Clinicians need to be well-trained and sensitized on the specimen requirements for the available laboratory tests for diagnosing and monitoring patients and procedures for requesting laboratory tests and referring specimens. Clinical staff will need to know procedures for selecting and ordering tests and completing test requisition forms. Clinical and laboratory staff will need to know procedures for collecting and labelling specimens, storing specimens, packaging specimens, completing referral forms and arranging transport. Laboratory staff need to be sensitized on where to refer and where to accept specimens for testing. Proper biosafety, packaging and quality training need to be provided to laboratory and clinical staff and transporters.

For example, as part of efforts to improve TB specimen referrals in Uganda⁸, the National TB Reference Laboratory partnered with Becton-Dickenson to develop a 3-day training curriculum that included modules on the structure of the specimen referral system, specimen collection SOPs, safe packaging and transport of specimens, specimen tracking, occurrence management and continuous quality improvement (see Case Study 1). During the pilot phase of the project, over 600 health facility and laboratory staff and 75 postal staff were trained.

Communication

Communication systems need to be properly set up and implemented according to well-documented procedures. Each facility should designate a focal person to facilitate sharing of information such as a delay in the return of results, testing interruptions, notification of priority results (e.g., detection of rifampicin-resistant TB) or follow-up of missing or rejected specimens. A communication system is needed that notifies a receiving laboratory that a shipment (specimens or results) is being sent and notifies the referring site of the receipt of the shipment by the receiving laboratory. Similarly, there needs to be a dialogue between patients, clinicians and laboratories so that all parties understand if there is a reagent stock-out or testing backlog or if equipment is down.

⁸ Joloba, M., Mwangi, C., Alexander, A., Nadunga, D., Bwanga, F., Modi, N., Downing, R., Nabasirye, A., Adatu, F.E., Shrivastava, R., Gadde, T., Nkengasong, J.N. 2016. *Strengthening the tuberculosis specimen referral network in Uganda: the role of public-private partnerships*. J. Infect. Dis. 213(S2):S41–46, DOI: 10.1093/infdis/jiw035

Monitoring and evaluating quality and system performance

Monitoring and evaluation (M&E) for specimen referral systems should examine the performance of the system at a high level as well as its operations at a more detailed level. The national laboratory's quality assurance department should monitor the specimen referral system to ensure that good quality specimens reach the testing sites in a timely manner, results are returned rapidly, biosafety and biosecurity measures are followed properly, and packaging and transportation equipment meet applicable national and international standards.

It is crucial that the M&E framework for any specimen referral system is considered early in the design phase in order to collect the data needed for monitoring the selected indicators. This requires standardizing the registers and forms used across all current systems, as well as the quality control practices during specimen collection, packaging and transport. For example, the quality of the specimens would need to be logged at the referring site before they are sent to the testing laboratory, and transport logs (also referred to as chain of custody documents) would need to accompany the shipments to show how many specimens and results are transported per facility. These logs should be signed by both sending and receiving parties, including transporters, along every change of hands to create a tracking system.

Table 1 provides a suggested minimum list of performance indicators to be monitored. Additional indicators such as the completeness of documentation (e.g., use and completeness of registers, logs, forms) or adherence to SOPs and packaging standards may be assessed during supervisory visits. A detailed description of the indicators in Table 1, as well as their targets and data sources, is included in Annex F.

Indicators calculated using aggregate data (e.g., total number of referred specimens tested) are useful to monitor overall performance, but to facilitate detecting problems and initiating corrective actions it may be necessary to disaggregate the data by referring facility, referral laboratory, courier, courier route or district.

Table 1. Key performance indicators for a specimen referral system

Indicators that should be monitored monthly by the referring facility
Number of specimens referred for testing
Proportion of referred specimens for which a result was returned
Proportion of referred specimens for which a result was received within the target turnaround time
Proportion of specimens which were picked up by the transport service within the target turnaround time
Indicators that should be monitored monthly by the receiving (referral) laboratory
Number of referred specimens tested at the referral laboratory
Proportion of shipments that arrive at the referral laboratory within the specified transport time
Proportion of test results that were picked up by the transport service or transmitted electronically within the specified turnaround time after generation of the test result
Proportion of specimens that were rejected because of factors related to inadequate or improper transport, packaging or documentation (disaggregated by referring site)
Indicators that should be monitored monthly by the courier^a as part of their service agreement
Number of shipments and number of specimens transported
Proportion of shipments that are delivered within the specified transport time
Proportion of shipments that were lost or damaged (disaggregated by route or district)
Indicators that should be monitored annually at the regional or national level by the TWG or MoH
Number of specimen collection sites participating in the specimen referral system
Unit costs such as cost per specimen or result transported per facility or per month
Annual review of consolidated indicators for each region and for the country

^a The courier service may be operated by the MoH or outsourced to another government entity, implementing partner, non-governmental organization or private company.

Other Considerations for System Design

Other uses of the specimen referral system, including integration

This guide encourages integration of specimen referral systems such as those for diagnostic testing for other diseases (e.g., HIV, Ebola, malaria, HCV), testing needed for patient monitoring (e.g., blood chemistries), surveys (e.g., drug resistance or prevalence surveys), disease surveillance and outbreak investigations. An integrated national specimen referral system may be particularly useful for specimens destined for sophisticated or complex testing that can only take place at the national reference laboratory. Where possible, integration with other specimens and disease programmes should be considered; however, it must be done in situations where it is feasible and efficient and not solely for the sake of integration. Mapping the flow of various specimen types between facilities and referral laboratories can be helpful to search for overlaps in disease-specific referral systems and identify opportunities to coordinate activities.

It is crucial to assess the diagnostic network in its current state and to consider plans for introduction of new diagnostics. Multi-disease testing devices in particular, including GeneXpert® (Cepheid, Sunnyvale, USA) for TB and HIV testing purposes as well as point-of-care or reference level high-throughput platforms that may be available in the near future, should be considered to gain efficiencies in referral systems and other programmatic areas.

The logistics network used for specimen referrals can also be utilized for other purposes. This use can happen either at the same time as when the specimens are transported (e.g., bringing inventory or consumption reports on supplies and regular facility statistics from the referring facility to a higher tier) or in the reverse direction as the vehicle travels to the referring facility (i.e., transport of quality control or proficiency testing panels, transport of other laboratory or health supplies or drugs). The benefit of using the same system is based around efficiencies, including costs. However, this must be balanced with the risk that the system becomes overloaded with other priorities and specimen referral suffers in terms of biosafety, quality and turnaround times.

Use of network mapping optimization software

Mapping health facilities and the diagnostics network is critical during design of a specimen referral system as well as for introduction of new equipment. Mapping of

the specimen referral systems can be facilitated by the use of a geographic information system (GIS). Information on pick-up and drop off sites, referral routes and schedules from each disease-specific system can be used to create a map to help visualise this information. Software programs are available that can use these inputs to rationalise and optimize the systems.

The Laboratory Efficiency and Quality Improvement Planning tool (LabEQIP) is one example of a GIS-based referral network optimization software tool. LabEQIP is an open-source tool developed by LLamasoft Inc. (Ann Arbor, USA)⁹ in partnership with the United States Agency for International Development (USAID), the US Centers for Disease Control and Prevention (CDC) and the Supply Chain Management System (SCMS) project (previous USAID-funded project), and is now managed by USAID's Global Health Supply Chain Program – Procurement and Supply Management Project (GHSC-PSM).

LabEQIP is aimed at assisting Ministries of Health, donors and other key stakeholders involved in national laboratory health programs in developing more efficient laboratory networks and advancing high-quality service delivery through data-driven optimization and GIS-based visualization applications. LabEQIP can also provide insights and key analysis on referral network optimization, external quality assurance (EQA) performance and human resource allocation.

The Referral Network Optimization function of the LabEQIP tool allows the user to make evidence-based decisions about referral systems. It uses established algorithms to provide models of various referral assignments and opportunities for analysing different instrument placement strategies to enhance alignment of demand and instrument utilization. It provides solutions that allow for improved efficiency and increased patient access to necessary medical testing. This is especially useful as countries make changes to their laboratory networks, such as changing equipment availability, or introducing a new diagnostic service (e.g., scale-up of viral load testing). LabEQIP is able to simulate events such as adding new facilities, equipment or laboratory capacity to determine how that impacts the route network and the costs (assuming an estimated cost per kilometre for transport can be determined and then applied to the simulation) before such activities are actually carried out. In other words, 'what if' scenarios can be easily examined before any funds are spent.

Costs and sustainability

The costs of a specimen referral system will vary greatly depending on the type and method of transport used, distances travelled and components included. Even if the infrastructure and resources from another specimen referral system is built upon to save on costs, there will still be resources required to assess the current systems available, design an integrated system, implement it, and then monitor and evaluate

⁹ <http://www.llamasoft.com/>

it over time. There are also significant staffing and management needs in terms of personnel and time.

If a new system is created, it may be run by the MoH or the services could be outsourced to a private courier company. If the MoH operates its own referral network, there will be additional set-up costs such as procuring vehicles, specimen transport equipment and other gear as well as recruitment and training of drivers and other staff. There will also be ongoing running costs, such as fuel, replacement parts, refresher training, staffing, offices, insurance, programme management, oversight and M&E.

Specimen referral systems should be optimized for cost-effectiveness and long-term sustainability. It is usually more cost-effective to build up from existing specimen referral systems, instead of creating and maintaining an entirely new system for one specimen type or disease programme. The definition of sustainability should not be limited to the eventual transfer of operations to the MoH; outsourcing services can be more sustainable in terms of operations and costs, as long as the MoH is able to pay for the service over time, reducing reliance on outside donors. Long-term financing and innovative financing mechanisms should be considered, especially ones that already exist in-country.

However, outsourcing does not need to happen at every level of the health system; segmentation may be possible, based on the health tier. For example, at lower levels, services could be provided by mobilized health worker cadres such as outreach teams while a private courier company is contracted to provide services at higher levels.

TB-Specific Considerations for Collection, Storage, Packaging and Transport

Although this guide encourages integrated specimen referral systems, there are disease- or specimen-specific considerations for collection, packaging and transportation as well as potential differences in collection sites and testing sites. TB-specific considerations are described in detail in Annex G. An overview of transport regulations, guidelines, and practical guidance for TB specimens is presented in Annex H.

Primary TB specimens (e.g., sputum specimens) are classified as Category B infectious agents and should be packaged according to the requirements for Category B substances.¹⁰ Important considerations for the transport of specimens for TB testing include packaging (use of a triple packaging system), storage (most TB specimens should be stored at 2–8 °C), and transportation conditions (use of a cool box, avoiding exposure to high or freezing temperatures).

The most common diagnostic specimen for TB is the sputum specimen, and the two most important considerations for transporting sputum specimens for culture tests, in addition to biosafety, are 1) preserving the viability of the mycobacteria, and 2) inhibiting the growth of contaminating flora. Viability of tubercle bacilli can be maintained for up to 7 days by keeping the specimens at 2–8 °C; however, contaminating flora may grow under these conditions and result in increased contamination rates for the culture tests. If the delay (storage and transport) exceeds 3 days and storage at 2–8 °C is not possible, cetyl pyridinium chloride (CPC)¹¹ may be added to the sputum specimen to inhibit growth of the contaminating flora. Sputum specimens containing CPC must be stored at ambient temperature (20–30 °C) and be delivered to the testing laboratory within 7 days. Products that can be used instead of CPC to preserve specimens for culture are commercially available (e.g., OMNIgene•SPUTUM from DNA Genotek Ottawa, Canada); however, a recent WHO Technical Expert Group meeting concluded that there is limited evidence that use of commercial transport products improves test performance compared to untreated specimens transported under ambient conditions for culture. The evidence from a FIND-conducted study suggested that OMNIgene•SPUTUM-treated specimens likely improves culture positivity and contamination rates for solid culture (using

¹⁰ Guidance on regulations for the Transport of Infectious Substances 2015–2016. Geneva, World Health Organization. 2015. (WHO/HSE/GCR/2015.2). http://www.who.int/ihr/publications/who_hse_ihr_2015.2/

¹¹ CPC is not recommended for commercially available liquid media.

LJ), but the effect of OMNIgene•SPUTUM on positivity and contamination rates using automated liquid systems (MGIT) was much smaller and was inconsistent, making interpretation for MGIT difficult.¹²

For sputum samples being sent only for Acid-fast bacilli (AFB) AFB-smear microscopy, viability is not an issue and storage and transport at ambient temperature (20–30 °C) for a total of 1 to 2 days or storage and transport at 2–8 °C for a total of up to a week does not significantly affect the positivity rate of smear microscopy.

For sputum samples being transported for rapid molecular tests only such as the Xpert MTB/RIF test or line probe assays, viability is also not an issue, but stability of nucleic acids is a consideration. Tubercle bacilli (and their DNA) remain intact in sputum specimens stored at 2–8 °C. Because viability is not required, the bacteria in the sputum specimens can be inactivated and DNA stabilized by adding 70% ethanol and then stored and transported at ambient temperature or at 2–8 °C. Commercial products (e.g., PrimeStore MTM from Longhorn Vaccines and Diagnostics, San Antonio, USA; or Sputum DNA Collection, Preservation and Isolation Kit from Norgen Biotek, Thorold, Canada) that inactivate the bacteria and stabilize DNA and allow storage and transport at ambient temperatures are available; however, the aforementioned WHO Technical Expert Group meeting concluded that there is no evidence that use of commercial transport products improve performance of molecular tests.¹¹

Little information is available on the stability of tubercle bacilli in specimens other than sputum. Bronchoalveolar lavage fluid, neutralized gastric aspirates, tissue specimens and cerebrospinal fluid (CSF) should be transported to the testing laboratory immediately, preferably on the same day as collection. Great care (i.e., storage and transport at the proper temperature, immediate transport to the laboratory, and immediate testing at the laboratory) must be taken to ensure the quality and utility of invasively obtained specimens such as tissue biopsies and CSF.

¹² Technical Expert Group Meeting Report: Commercial products for preserving clinical specimens for the diagnosis of tuberculosis. Geneva, World Health Organization. 2017. (WHO/HTM/TB/2017.19). http://www.who.int/tb/areas-of-work/laboratory/policy_statements/

Case Studies

Case study 1: Integrated network for referral of TB and HIV specimens in Uganda

TB specimen transport

In Uganda, there are 900 basic management units of the National Tuberculosis and Leprosy Program (NTLP) that collect specimens from persons being evaluated for TB and one laboratory (the National TB Reference Laboratory or NRL) that performs culture and drug-susceptibility testing (DST). Prior to 2008, there was no formal specimen referral system, and only 50 of the 900 sites referred any specimens for *M. tuberculosis* culture and DST. A total of 655 specimens were sent to the NRL in 2008. To address this weakness, the Uganda Ministry of Health partnered with Becton Dickinson (BD), the US CDC, the NTLP, the NRL and the Uganda postal service (Posta Uganda) to develop a formal TB specimen referral system that focused on timely and efficient referral of specimens for culture and DST.

Initially, the NRL collected global positioning system (GPS) coordinates for sites referring specimens for culture and DST, post offices, and testing laboratories and data on district population densities; and the number of specimens referred per TB unit. By the end of 2011, 835 of 900 TB units were mapped and visualized. Using this information, a national specimen referral system was designed in which sputum specimens could be collected from persons being evaluated for TB or MDR-TB at any of the 900 NTLP units, packaged by trained personnel, delivered promptly (at least daily) to the nearest local or main post office within the national Posta Uganda system, and promptly transported by Posta Uganda to the NRL in Kampala for culture and DST.

This phased roll-out of the specimen referral system generated a large increase in the number of referring sites (from 50 to 400) and number of specimens received (from 655 to 5813) by the end of 2011. In addition, specimen transport times were greatly reduced; 94% of specimens reached the NRL within the 3-day target transport time in 2011 as opposed to only 9% in 2008.

HIV specimen transport

The Uganda Early Infant Diagnosis of HIV infection (EID) programme relies on the collection of dried blood spots (DBS) from infants at local health facilities and spec-

imen transport to centralized testing laboratories. Initially, the specimen transport relied on Posta Uganda, but many health facilities were outside the catchment areas of Posta Uganda collection centres, which led to batching of shipments and long delays in the testing process. To address such problems, the EID programme developed a specimen referral system to increase the numbers of health facilities that could reliably refer specimens to the testing centre and shorten turnaround times. The EID programme began by identifying health facilities that might serve as a coordination centre or ‘hub’ for specimen transport that would serve all health facilities in a catchment area with a 30 km to 40 km radius. The hub would be responsible for collecting specimens from each health facility in the catchment area and arranging transportation to the testing facility. Health facilities within the catchment area (20 to 40 facilities) were mapped using GIS and courier routes designed to allow each health facility to be visited at least once a week by the courier. The courier would also be responsible for returning the results to the referring health facility. The EID programme provided a motor bike and operator for the courier service.

The initial pilot implementation project (2011-2012) involved 19 hubs serving 616 health facilities. An analysis of the performance of the system at the end of 2012 revealed that the hub network system improved access to laboratory services as evidenced by increases in monthly EID testing volumes of 36% to 51% in the various districts; reduced specimen transport times from 12 days to 7 days and result return times from 12 days to 5 days; and reduced overall transportation costs by 62%.

Integrated specimen transport

Since 2012, the MoH has worked to expand the EID hub system to include about 100 specimen transport hubs which support more than 3,000 health facilities (about 90% coverage). The system has also expanded to include transportation of specimens for sophisticated tests (e.g., HIV viral load and TB culture) that are only available at national reference laboratories like the Central Public Health Laboratory or the TB NRL. Similar to what was observed with EID testing, the turnaround time for viral load testing decreased from 90 days to 21 days and the cost for specimen transport and results return was decreased to USD 1.58 per test.

By including health care facilities that collect specimens for TB testing into the EID couriers’ routes, the system has expanded access to sophisticated TB testing by enabling more facilities to more easily connect to the Posta Uganda system for the transport of the specimens to the NRL. This was especially important in areas where access to a local Posta Uganda post office was difficult.

To further improve the delivery of laboratory services, the testing capacities of the specimen transport hubs are being strengthened to allow them to conduct testing such as CD4 counts, complete blood counts (CBC), and blood chemistries and thereby shorten turnaround times even further by eliminating the need to ship samples to the centralized laboratories in Kampala. For example, to improve the capacity to detect

rifampicin-resistant TB, the NRL collaborated with the EID program to establish the capacity to perform Xpert MTB/RIF testing at the EID specimen referral and testing hubs and to integrate the transportation of sputum specimens into the EID specimen referral system. An electronic reporting system was also established that delivered real-time notification of test results to the treating clinician, regional MDR-TB focal person, and the National TB Program and NRL. Using the integrated system, detection of a case of rifampicin-resistant TB in a peripheral site and notification of the appropriate health care workers and National Programs usually happens within 48 hours of specimen collection - less than the time it would take to ship a specimen to the NRL.

Case study 2: Steps for modelling a national integrated sample transportation network in Ethiopia

This project, led by the Ethiopian Public Health Institute (EPHI) and the MoH and supported by CHAI, aimed to integrate and optimize the sample transportation network across TB and HIV and estimate a fair cost for the implementation of this framework. The steps included:

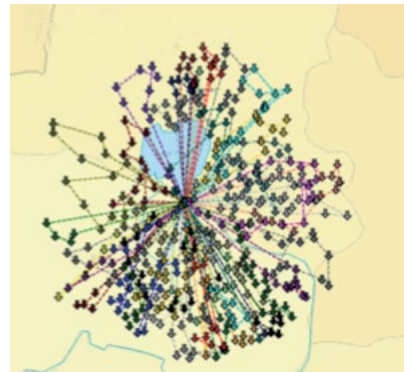
Map national sample transportation needs

1. Convene laboratory managers from disease areas of interest to sensitize them to the sample transportation quantification and network rationalization project.
2. Create a database listing all facilities to be served by the sample transportation network including their GPS coordinates, facility category and types of samples to be collected, as well as the laboratories per sample type. Samples included were for the following tests: viral load, EID, CD4, Xpert MTB/RIF, TB culture, 1st-line DST, and 2nd line DST.
3. Match each facility to an appropriate laboratory according to the sample testing needs and indicate the desired pick-up frequency per facility and sample type.

Route optimization

1. Validate the referral networks with a GIS software to ensure that the referral laboratory assigned to each facility is in fact the closest available, unless there are other reasons for it (Fig. 2).
2. Select a supply chain optimization provider. The Ethiopia MoH released a Request for Quotation for a provider defining the requirements for the route mapping exercise and selected Llamasoft to rationalize their sample transportation network.
3. The provider (Llamasoft) modelled the routes using the compiled database and the requirements defined by the MoH: all routes starting and ending at a testing site, the maximum number of stops each driver could make per day, the maximum number of kilometres a vehicle could drive per day, and the overnight fee if routes were longer than a day. The output from Llamasoft provided details for each route, including the start and ending laboratories as well as the facility stops within the route and the total number of kilometres to be travelled.

Fig. 2. Referral route mapping example



Outcome

The output from the route rationalization exercise combined with a bottom-up calculation of the sample transportation cost per km helped identify a number of opportunities to refine the scope of services to be provided by the integrated sample transport network. For example, the optimized routes highlighted a small number of facilities in remote areas that contributed disproportionately to the total cost, for which alternative transportation, testing models (point-of-care) or reduced sample collection frequency could be arranged. More importantly, with the national modelling of the integrated sample transportation network complete, EPHI could engage with service providers to agree on the total cost of service delivery needs and the appropriate scope for an implementation pilot before national roll-out.

Case study 3: Sample referral system in Indonesia

Indonesia is an archipelago with challenging geographic conditions, given it consists of approximately 17 000 islands spread out over 34 provinces and 500 districts and municipalities. Throughout the country, a network of TB microscopy centres is available at most primary-level health facilities at the sub-district level (12 000 TB microscopy centres). Despite this vast network, diagnosis of multidrug-resistant (MDR) TB remains a challenge because detection of drug resistance is limited to 62 GeneXpert laboratories and 8 laboratories that are qualified to perform culture and DST. As such, a sample referral system is needed to reach patients who are not able to access rapid and high-quality TB testing, as well as to ensure the quality of samples upon arrival at the laboratory.

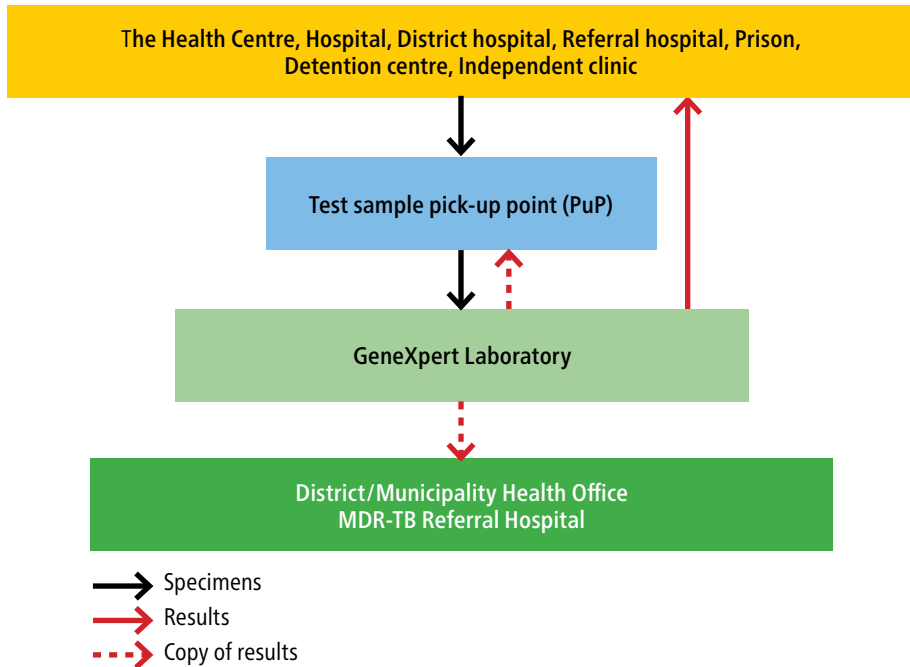
In this pilot project led by Challenge TB, a hub and spoke design was chosen in which a courier service would collect specimens from health facilities and transport them to a Test Sample Collection Station or Pick-up Point (PuP). A PuP is the laboratory of a health centre or hospital that receives specimens from health facilities in its vicinity (a maximum of 5 health facilities) and packages and ships the specimens to laboratories for Xpert MTB/RIF testing or for culture and DST (Fig. 3).

In this system, the health facility 1) collects the specimen, 2) packages the specimen and stores it in a special container at room temperature until shipment, and 3) ships the specimen and test requisition forms to the PuP. The PuP 1) receives the referred samples and confirms the completeness of forms, 2) packages the specimen for transport, and 3) arranges for the courier to pick up the TB specimens and forms and transport to the testing laboratory. The testing laboratory 1) receives the TB specimen and forms, 2) conducts the testing, and 3) reports results of the testing to the initial health facility by text messages, phone or email with copies sent to the District or Municipality Health Office and the PuP.

To develop the system, a step-wise planning process was used that included:

1. Establishing the roles and responsibilities of each party involved in the system and developing SOPs
2. Identifying the specimen referral need in each area
3. Selecting the district or city where the specimen transport system will be implemented
4. Developing a budget
5. Mapping all of the health centres, HIV clinics, prisons, detention centres, paediatric clinics, hospitals (public, private, military, police), PMDT sites that collect TB specimens
6. Selecting Test Sample PuPs
7. Selecting a courier and establishing a contract for specimen transport tailored to the need of each site

Fig. 3. Sample referral system in Indonesia



8. Providing training on packaging and transport of TB specimens for staff of the health facilities, PuPs, courier, and District/Municipality Health Office
9. Procuring and distributing the appropriate packing materials to the PuPs and health facilities
10. Developing procedures to ensure data protection, security and confidentiality
11. Monitoring and evaluation

Lessons learnt from the pilot project:

1. The PuP model can be expanded, but districts must be able to decide their options.
2. Provincial Health Offices should identify the PuPs strategically and link them properly to a testing laboratory.
3. Specimen referral should be available to all persons eligible for Xpert MTB/RIF testing as per NTP guidelines (i.e., people living with HIV, paediatric TB, TB with comorbidity, extrapulmonary TB, prisoners).
4. Clear mapping and networking between the health centres, PuPs, and testing laboratory are necessary.
5. The testing laboratory should be involved in the planning of the specimen referral system.
6. The transport system should be flexible in order to provide the services to the patients as needed.

7. The PuPs should contact directly the transport agency to fix the time of pick-up.
8. A contract is needed with a designated courier to fix the responsibility of each party; this should be managed by the province.
9. Different modalities may be tried for transportation, for example motorbike, travel, boat or whatever is suitable locally.
10. A record of the pick-up and delivery should be required before making a payment for the transportation.
11. Electronic reporting is necessary for quick reporting of the results (e.g., SMS, email).

Case study 4: Introduction of sample transport tracking in Lesotho

This project, led by the MoH in Lesotho and supported by Riders for Health and CHAI, aimed to improve the visibility of samples in transit and results delivered through a nationwide system utilizing mobile phones as barcode scanners for sample transporters.

The steps involved in development of a sample transport tracking (STT) system included:

1. Consolidation and barcoding of Ministry of Health test requisition forms

- Several test forms were consolidated into one form with different test types on one sheet increasing ease of use. Barcode stickers with unique number sequences were introduced on the forms in order to make sample follow-up easier. Barcode stickers could be affixed to samples, forms and registers to track the sample.

2. Development of mobile application and dashboard

- Following consultation with all concerned stakeholders in Lesotho, CHAI developed a mobile STT application on ODK Collect, an open source platform that could be interoperable with other MoH systems. The mobile application consisted of four data capturing applications, each documenting a stage in the sample or result delivery process: sample pick-up, sample delivery, results pick-up and results delivery.

The information from the mobile application was transmitted to the sample transport tracking dashboard which served as a comprehensive tool used to display data, including visualization of data across national, district and facility level. Partial integration with the MoH Lab Information System allowed for the viewing of various lab statuses of each sample within the laboratory.

The steps involved in implementation of the STT system included:

1. The system was implemented through sample transporters managed by Riders for Health in four Lesotho districts labs and a select number of health facilities. The app and a barcode scanner were installed on mobile phones used by Riders for Health sample transporters and they were trained on their use.
2. Barcodes on each sample were scanned on pick-up and the drop-off at the laboratory, and the information was transmitted to the STT app via 3G internet connection.
3. Laboratory front desk staff then entered the unique sample tracking barcode from the request form as well as the patient details into the Laboratory Information Server.
4. The sample barcode was linked with patient details electronically along with the bar code. Health facilities could then follow-up on the results via the STT dashboard.

5. Once testing of the samples was completed, the result was printed with the same bar code as the sample that had been brought in. The result was then picked up by the sample transporter and scanned into the mobile application.
6. When the sample transporter then delivered the result to the health facility, the bar code was scanned to confirm result delivery. The data were then transmitted back to the STT server, and the sample-to-result feedback loop was closed.

In terms of outcomes, the development and implementation of the STT pilot conducted over a 3 month period resulted in:

1. Deployment of the system in a real-world environment in order to identify operational requirements as well assessing the system's feasibility and functionality.
2. Visibility on the samples and results transit and accurate data on turnaround times throughout the entire process, from sample collection to results delivery.
3. Development of recommendations on how to scale-up the STT system nationwide.
4. Initiation of in-country transition of the system to the MoH IT and Labs Directorate team, in preparation of scale-up and roll-out of the system by MoH Lesotho.

Case study 5: Use of unmanned aerial vehicles (drones) for specimen transport in Madagascar and Papua New Guinea

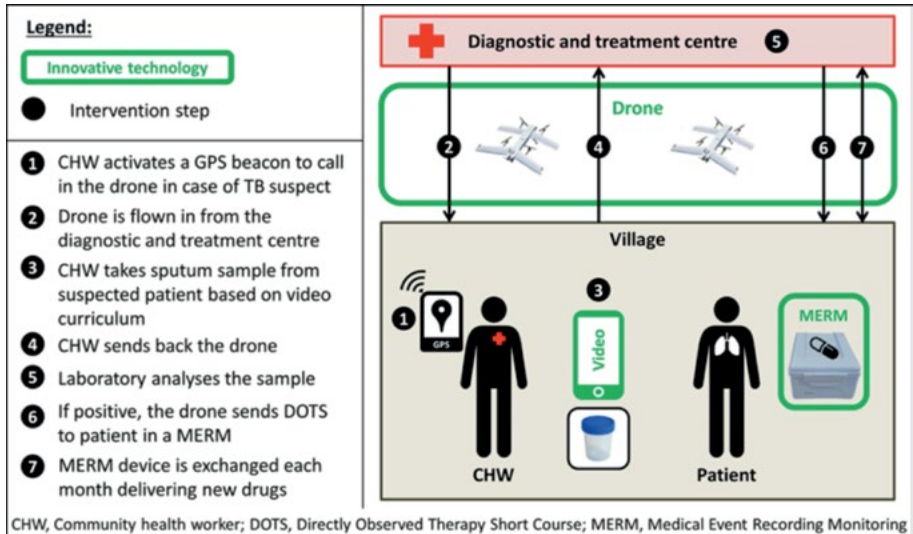
DrOTS: Drone Observed Therapy in remote Madagascar¹³

In the district of Ifanadiana in Madagascar, the bulk of the population lives in remote villages that are only accessible by footpaths that take many hours to traverse. To increase TB case finding and treatment completion in these villages, an innovative approach is being employed that relies on a specimen referral system that utilizes unmanned aerial vehicles (UAVs, also known as drones) to transport TB specimens to the testing laboratory (Figs. 4 & 5). The drones also deliver the results and medicines for DOTS (Directly Observed Therapy Short Course) to the village.

Fig. 4. DrOTS in Madagascar



Fig. 5. DrOTS system



¹³ Small, P., Andriansolo, R., Grandjean Lapierre, S., Knoblauch, A., Niaina Rakotosamimanana, N. (2017). DrOTS in Remote Madagascar [Powerpoint slides]. Retrieved from: http://www.villagereach.org/wp-content/uploads/2017/08/2017_06_28-UAV-Webinar-DrOTS-in-Madagascar1.pdf

The drones have vertical take-off and landing capabilities, a load capacity of two kilograms, and a range of 60 kilometres. The drones are autonomous and rely on GPS beacons to direct their flights.

This project (Drone Observed Therapy Short Course or DrOTS) is being gradually implemented across 36 randomly selected villages which are within the drone flight range of 30 km.

Drone-based specimen transport in Papua New Guinea¹⁴

Much of the population of Papua New Guinea lives in remote areas with little access to diagnostic and treatment services and very poor transportation infrastructure. To improve access to diagnostic testing, Médecins Sans Frontières (MSF) teamed with a company called Matternet to conduct a pilot project to determine the feasibility of using drones to transport TB specimens from a remote area of Papua New Guinea (a health clinic near Malalaua) to an MSF laboratory capable of conducting TB testing at Kerema hospital. The distance between these two points by air is 43 km. The pilot project test flights between the two sites carried dummy cargo over the 43 km of swamps and jungle in 55 minutes, including a stop to replace the drone's batteries. By car, the journey would have taken at least four hours.

Although the drones used in this pilot project have a limited range (~30 km), it should be possible to create a network of recharging hubs that would allow the transport of samples over long distances.

Considerable work remains to be done before a drone-based transport system could become a reality. An editorial by Lippi and Mattiuzzi¹⁵ describes some of the remaining issues such as reliability, safety, biosafety, biosecurity, maintaining a cold chain and regulatory approval.

¹⁴ Meier, P., Soesilo, D. 2016. Drones in Humanitarian Action. Case Study No. 2: Delivery – Using Drones for Medical Payload Delivery in Papua New Guinea. <http://drones.fsd.ch/en/using-drones-for-medical-payload-delivery-in-papua-new-guinea-case-study/>. MSF. 2014. Papua New Guinea: Innovating to reach remote TB patients and improve access to treatment. <http://www.msf.org/en/article/papua-new-guinea-innovating-reach-remote-tb-patients-and-improve-access-treatment>.

¹⁵ Lippi G, Mattiuzzi C. 2016. Biological samples transportation by drones: ready for prime time? *Ann. Transl. Med.* 4:92. doi: 10.21037/atm.2016.02.03.

Case study 6: Sputum sample transportation: Revolutionizing TB diagnosis in Zimbabwe

This project was led by Riders for Health¹⁶ and supported by the USAID-funded TB CARE I and Challenge TB projects.

Background

Despite significant investment in the infrastructure of TB laboratories in Zimbabwe in recent years, most rural communities remained out of reach of laboratories where TB microscopy was performed. This situation was compounded by the lack of a transportation system for TB specimens (sputum), resulting in most patients being referred to the nearest diagnostic centres at their own expense. This posed a significant barrier in access to care. In response, a specimen transportation system to improve access to laboratory services was developed, successfully piloted and scaled up in Zimbabwe.

Sputum Transportation

In 2010, in partnership with Riders for Health, TB CARE I launched a specimen transportation system in three cities: the capital city of Harare; Bulawayo, the second largest city; and Chitungwiza. Riders for Health was contracted to implement specimen transportation and were provided with motorcycles, which they maintain. Riders for Health recruited and trained riders to implement specimen transportation, with close supervision from local staff. Services rendered are invoiced monthly, and paid for through project funds. The system transports not only sputum samples, but also other specimens that require laboratory investigation to the nearest diagnostic centre on a daily or weekly basis, depending on the geographic location. The riders also deliver the results back to the referring health facility, with documentation of all specimens collected in customized paper-based registers. Following the successful completion of the three-city pilot project, the specimen transportation system was scaled up to 24 districts. It currently consists of a total of 42 motorcycles, which serve 649 health facilities, over 40% of the country's health establishments. The success of the system hinges on the dedicated cadre of specimen transporters as opposed to the traditional Ministry of Health system that relied on an Environmental Health Technician with other responsibilities besides specimen transportation.

The specimen transportation system has improved access to laboratory diagnostics. In 2010, 38 663 specimens were transported using the system. This increased to 225 592 specimens in 2016, representing a six-fold increase. The turnaround time from sputum collection to receipt of results declined dramatically. Prior to the

¹⁶ Riders for Health is a not-for-profit NGO that specializes in the management of vehicles for health care and other public services in conditions in which there is no widespread network of vehicle-maintenance facilities. Riders for Health has programmes in Liberia, The Gambia, Lesotho, Zimbabwe, Nigeria, Kenya and Malawi.

specimen transportation system, two to three weeks elapsed from sputum collection to diagnosis in remote rural districts; the turnaround time in these areas is now only seven days. In urban settings, only one or two days are needed. The cost of running the system in 2016 was \$US 784 773, translating to a unit cost of \$US 3.48 per specimen ferried.

The percentage of new pulmonary TB cases without initial sputum investigations plummeted from a high of 19% in 2010 to 9% in the first half year of 2014. As the transport system also carries follow-up sputum samples for treatment monitoring, the cure rate also improved from 71% in 2010 to 75% in the first half of 2013. An important outcome of the transport system has been renewed trust in the health care system by the communities that it serves. Trust is essential for positive health care seeking behaviour, a fact often recounted by patients and health care workers during TB CARE I site assessments:

- *“I had sputum positive TB in 2003 and I was successfully treated. But early this year, I had a chronic cough for 3 weeks, I thought that I had TB again so I submitted my sputum samples and within 24 hours, I had my results. Luckily, it was negative. Thanks to this service many TB patients are going to be diagnosed and treated on time before they become too sick.”* – Patient at Kuwadzana clinic, Harare city
- *“Before the Riders came, patients did not get tested because there was no specimen being collected due to lack of transport.”* – Mashame Rural Health Centre, Gokwe North district

The specimen transportation system is contributing to improved access to appropriate care by ensuring that specimen collection from health facilities is more reliable and is done in a timely manner, thereby reducing delays in diagnosis. With the end of TB CARE I support, the country has requested funding from the Global Fund to sustain a more integrated specimen transportation system.

Case study 7: Sputum sample transportation system for drug-resistant TB diagnosis and treatment follow-up: Bangladesh experience

This project was led by the National Tuberculosis Control Program of Bangladesh and supported by the USAID-Funded Challenge TB Project.

The National Tuberculosis Control Program and its partner NGOs manage the TB control programme across the 64 districts of Bangladesh. The National TB Reference Laboratory in Dhaka provides support to four TB reference laboratories in four divisional headquarters, 39 GeneXpert sites, and 1,109 microscopy centres across the country. Despite these resources, access to drug-resistant tuberculosis (DR-TB) diagnosis, treatment and follow-up remains a challenge in Bangladesh. Diagnostics are not available to many presumptive DR-TB patients and follow-up cultures for patients undergoing treatment are delayed or often missed because of socioeconomic factors and the long distance patients have to travel to most laboratories. Country experience shows that specimen transport is more efficient than the patient travelling to provide a specimen.

The Challenge TB Bangladesh project has been implementing a sample transportation system in three city corporations and 22 districts during the past two years. The project also involved partners such as BRAC and the Damien Foundation to measure the sputum transport system in their working areas. To date, the project has provided orientation to 200 field staff, mostly from peripheral TB microscopy centres, on sputum transportation methods and provided sputum transportation kits to the health facilities. The kits consist of a transport cool box that can accommodate three samples, three zip lock bags and three biohazard stickers (Fig. 6). The sputum specimens are taken in a falcon tube, placed inside a zip lock bag with a biohazard sticker and placed in the box. The box is then couriered to the GeneXpert site.

In BRAC-supported areas, their staff collects the specimen from the microscopy centres in the transportation box and transports it to the nearest GeneXpert sites. This approach is particularly adopted in areas where courier services are limited.

Lessons Learned

In 2016, the Challenge TB Bangladesh project presented an abstract at the 47th Union World Conference on Lung Health testing this transportation mechanism. In total, 2152 samples taken from 661 presumptive DR-TB patients and 476 DR-TB patients on treatment were transported by courier. Of these, 1482 samples from the 476 DR-TB patients on treatment were inoculated for culture at the Dhaka NRL and the

Fig. 6. Sample transportation boxes



Chittagong Regional TB Reference Laboratory and 121 (8%) were positive. Among 661 presumptive DR-TB patients, 269 (41%) TB and 28 (4%) DR-TB cases were detected. The estimated cost per sample transported is around \$1, compared with patient travel costs of \$25. The average time for sample transportation was 2.5 days. The findings are promising for the NTP to improve diagnoses of TB patients by Xpert MTB/RIF and ensuring timely treatment follow-up for DR-TB patients. Coverage gaps in the courier system originally were a challenge, but this was overcome by using partners' staff to transport specimens.

This sputum referral system is a cost efficient and replicable mechanism that can contribute to increased timely diagnosis and treatment monitoring for DR-TB patients. For the system to succeed, it is necessary to create synergy among partners, contract a courier company, and orient all field level staff on sputum sample transportation system countrywide scale-up. Once the system is in place, it increases patients' access to diagnostic and follow-up testing and decreases patients' inconvenience and out-of-pocket expenditure.

Case study 8: Sample transport and result retrieval: Nigeria experience

The USAID-funded Challenge TB project in Nigeria supported a sample transport and result retrieval system for TB diagnosis among PLHIVs using courier services (Fig. 7). The aim of the intervention was to increase utilization of GeneXpert testing among PLHIVs and improve the turnaround time (TAT) for test results.

Fig. 7. Sample transportation



Background

In Nigeria, TB remains a leading cause of morbidity and mortality, and the country is classified as a high TB, TB/HIV and MDR-TB burden country. An estimated 586 000 people developed TB in 2015. A recently conducted Joint International Tuberculosis Diagnostic Network Assessment recommended the establishment of an integrated sample referral mechanism to enable timely access to quality diagnostic testing at all levels.¹⁷

Intervention

Early 2016, the intervention started in 156 ART facilities without GeneXpert machines across 7 states in phases. Samples from these ART facilities are transported to 32 GeneXpert sites.

A local logistics company was contracted to transport samples for TB diagnosis from ART facilities (sample pick-up sites) to GeneXpert sites using motorbikes. A meeting to introduce the intervention, define roles and obtain the commitment of all stakeholders was held and included representatives from the NTP (national, state local government area, and facility levels), USAID, implementing partners, health workers and the courier company (Riders for Health Nigeria). A routing chart was developed and used to map the most efficient travel plan between pick-up sites and the GeneXpert locations. The chart also contains the coordinates of the facilities and details of the contact persons in all service delivery points. Every transport cluster of facilities was assigned to a specific rider.

DOTS providers at sample pick-up sites were trained on sputum collection, packaging and storage procedures, biosafety, and recording and reporting (R&R) tools. Health workers from different units of the hospital were also trained to create awareness and increase demand for GeneXpert. The riders were oriented on safe driving, motorbike maintenance and biosafety well as completion of relevant R&R tools. Relevant equipment including sputum cups, transportation boxes and R&R tools were also provided.

¹⁷ Joint International Tuberculosis Diagnostic Network Assessment of Nigeria Report – March 2016

Each presumptive TB case is entered in a register kept by the DOTS provider, and each sample is accompanied by a sputum request form. The riders pick up the samples and document the identification number of the sample as well as date and time of sample pick-up in the sample log sheet.

When the samples arrive at the laboratory they are logged in (date and time) and signed off by the laboratory scientist. The laboratory scientist carries out the assay and documents the date and time that the result was ready on the log sheet. When the test results are picked up by the rider (often after the delivery of another batch of samples), the laboratory scientist documents the date and time of the result pick-up, and the rider delivers the test results back to the sample pick-up site. When the results arrive, the date and time of delivery are documented by the DOTS provider.

Regular mentoring and supervision is provided by the TB supervisor, state coordinator of Riders for Health and the KNCV project officer to ensure adherence to SOPs and proper documentation. A monthly summary of all log-ins are made and discussed with stakeholders to identify challenges and proffer solutions. Periodic data quality assurance is also carried out to ensure high levels of data quality are maintained.

Results

The number of samples delivered to GeneXpert sites from May 2016 (when all facilities were engaged) to March 2017 increased significantly, from approximately 500 to over 2,500 specimens monthly. The majority (84%) of the test results were returned within 3 days after collection (21% even within 1 day). This represents an improvement of the average turnaround time from 6 days prior to the intervention to 3 days. During the intervention the unit cost of transporting sputum samples and retrieving the results has continued to decrease, from 5000 naira (~15 USD) to the current level of below 2000 (~6 USD).

Challenges

The intervention encountered challenges including:

- Downtime of GeneXpert machines, due to breakdowns, cartridge stock outs and power outages
- Inadequate storage facility necessary to preserve sputum samples that were not processed
- Long distances and hard to reach areas
- Resistance by some health workers who preferred the old order of moving the samples themselves

Conclusions

A robust sample transportation and result retrieval system with quality improvement tools leads to optimization of the Xpert MTB/RIF assay for diagnosis of TB. It also leads to a reduction in the turnaround time of results, enabling clinicians to make timely decisions on the management of TB patients. This is important in Nigeria, given that Xpert MTB/RIF assay, which is recommended for diagnosis of all forms of TB, is not widely available. With the capacity built on efficient sample transportation and results retrieval, there are opportunities for the integrated movement of all diagnostic samples from PLHIVs and all presumptive TB cases.

Case study 9: Specimen transportation system by community-based DOTS partners in Mozambique

Mozambique is a large country (786 380 sq km) with a population of nearly 28 million. Despite significant investments in the expansion of microscopy and the GeneXpert network, diagnostic services are still out of reach for most of the rural population. The situation is worsened by a weak specimen transportation system; there is no standardized system across different provinces and districts.

To strengthen the specimen transportation system in Mozambique, the USAID-funded Challenge TB project in coordination with the provincial health directorate selected two project-supported provinces in Central and Northern Mozambique to pilot a new system in six districts: Angoche, Ribaue and Mogovolas in Nampula province; and Ile, Derre and Molumbo in Zambézia province.

The implementation of the specimen transportation system was sub-contracted to Community-Based DOTS (CB-DOTS) partners:

1. CB-DOTS Implementing Agencies are well established in the community and are a link between the health facility and the community
2. They are responsible for identifying and referring presumptive TB patients to a health facility for screening
3. Volunteers support the transport of samples from the presumptive patient's home to the peripheral health facility, and the return of the results (Fig. 8)
4. They refer contacts of TB index cases for TB screening at the health facility
5. It is easier to manage the system at the district level to ensure that the motorbikes are regularly maintained, rider's salaries are paid on time, and a report is submitted to the district.

Prior to the rollout, crucial activities were undertaken, such as:

- Purchase of six motorbikes
- Development of guidelines, a log-book, and tools for data collection and monitoring
- Motorbike riders, selected district lab supervisors, and a representative of CB-DOTs implementing agency were trained
- Mapping each health facility within the district using GIS
- Mapping of optimal routes to allow each health facility to be visited at least once a week to collect samples and return results.

During the pilot phase, patients continued bringing their samples to the health facilities and community volunteers also collected samples from households and delivered them to the health facilities.

Fig. 8. Sample transportation through CB-DOTS



During a 6-month pilot phase, Challenge TB supported specimen transportation system implementation for a total of USD 42 940, comprising of investment costs of USD 31 920 and running costs of USD 11 020. The breakdown is shown in Table 2.

Table 2. Costs for six transporters for a 6 month period (October 2016 – March 2017)

Items	Unit Cost USD	Total Cost, USD Oct 2016 – March 2017
Investment costs		
Purchase of motorbikes	5 000	30 000
Sample transportation box installation on the motorbikes	320	1 920
Total investment costs		31 920
Running costs		
Insurance (annual cost)	40	120
Riders salaries (monthly cost)	140	5 040
Motor bike maintenance (monthly cost)	60	2 160
Fuel (per litre)	1	3 600
Total running costs		11 020
GRAND TOTAL		42 940

Results from October 2016 to March 2017

The specimen transportation system covered all 57 health facilities in the selected districts. The average turnaround time before implementation was 15 days (ranging from 2 to 30 days), and during the pilot it was reduced to an average of five days (maximum seven days). All the GeneXpert machines are linked together using GxAlert, where real-time test results for rifampicin-resistant TB are delivered by SMS to the referring health facility clinician, the district NTP supervisor, provincial MDR-TB focal person, and the National MDR-TB focal point person.

The number of specimens transported across the six sites increased by 79% (from 2750 during October 2015–March 2016 to 4909 during October 2016–March 2017), and as a result, the number of TB cases increased from 720 before the pilot phase to 1175 during the pilot phase.

The cost of transporting one sputum sample was USD 8.7 (42 940 USD / 4909 samples). Focusing on only running costs, the cost per sample was USD 2.2 (11 020 USD / 4909 samples).

The pilot was scheduled to end in September 2017 and the plan is to expand to more districts in the future.

References and Suggested Reading

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ANNEX A

Collecting information for planning and evaluating an integrated specimen referral system

The questions¹⁸ listed in this annex are designed to assist with the collection the information needed to develop or evaluate an integrated specimen referral system. As such, data for many of the questions will have to be collected for each disease programme and disease-specific specimen referral system that might be included in the integrated network. If the initial objective is to develop or evaluate a disease-specific specimen referral system (e.g., for TB specimens), the landscape analysis can focus on the TB programme, policies, guidelines, laboratory network and existing TB specimen referral processes. However, it is encouraged to avoid performing a disease-specific assessment in isolation and instead examine the available systems used for the diseases of public health importance to identify potential gaps, overlaps and duplications and to identify opportunities for coordination and improving efficiencies and cost-effectiveness.

1. Landscape Analysis

- a. Ministries, programs, partners, and donors (stratify by disease programme if appropriate)
 - Which ministries have programmes relevant for specimen referrals (e.g., Ministry of Health [MoH], military, police, and penitentiary system)?
 - Which disease-specific (i.e., vertical) programmes provide laboratory services that involve specimen referrals?
 - Who are the main partners that support laboratory services in-country?
 - Who are the main donors that support laboratory services in-country?
- b. Policies and guidelines
 - Is there a comprehensive national laboratory strategic plan (NLSP) that includes a specimen referral system?
 - Are there NLSPs for disease-specific programmes?
 - Are there national policies and procedures governing the security of laboratory data and confidentiality of patient data?
 - Are there national guidelines for the packaging or transport of biological specimens?

¹⁸ The questionnaire in this annex is a minor modification of an unpublished questionnaire created by Kameko Nichols under a consultancy with the African Society for Laboratory Medicine (ASLM) as part of the Global Health Security Agenda. The original questionnaire will be included in the specimen referral toolkit, which is under development.

- c. Roles, responsibilities, coordination, and communication
- Is there a department or focal person in the MoH that is responsible for laboratory issues?
 - Does the MoH have a dedicated organizational unit or person in charge of laboratory coordination?
 - Is there a national technical working group (TWG) that is responsible for MoH-related laboratory issues? If yes, which programmes participate in the TWG?
 - Is there a TWG that is responsible for issues related to specimen referral systems?
 - Is there a focal person at each disease-specific National Reference Laboratory (NRL) that is responsible for laboratory issues and interfacing with the MoH?
 - Is there a focal person at each NRL that is responsible for the specimen referral system?
 - Are there dedicated budgets for laboratory services available at all levels of the laboratory system (national, regional, peripheral)?
2. Laboratory Network and Infrastructure
- a. Laboratory network organization (answer for the general laboratory tiered network or for each disease-specific network; e.g., TB laboratory network, HIV laboratory network)
- Are there disease-specific laboratory networks? If yes, for which diseases?
 - Are all disease-specific laboratory services fully integrated into the general laboratory network?
 - Is there a designated NRL that oversees the general tiered laboratory network?
 - Are there designated disease-specific NRLs that oversee the disease-specific tiered laboratory networks?
 - How is each laboratory network structured? (e.g., NRL, regional laboratories, district laboratories, etc.?)
 - What are the numbers of laboratories at each tier or level?
 - Are there lists of tier-specific laboratory minimal testing packages?
 - For each laboratory at each tier, which tests are available?
 - For each laboratory at each tier, what are the laboratory's testing capacity and throughput (current and maximum) for each test?
 - For each laboratory at each tier, are there multi-disease testing devices (including GeneXpert for TB and HIV testing) or plans to introduce such devices?
 - Is there a formal system of supportive supervision within the laboratory networks?

- How many primary-level health facilities are there in the country?
 - Where are the specimens collected for each major test type (e.g. HIV viral load, EID, CD4, TB culture, Xpert MTB/RIF, TB microscopy, malaria smears, malaria RDTs, HCV, blood chemistries)?
- b. GIS mapping
- Are GPS road network maps available?
 - Is there a map or database that lists estimated driving times between most or all towns in the country?
 - Is there a current GIS map or database of laboratories in the laboratory network?
 - Is there a current GIS map or database of primary health facilities in the country?
- c. Private service offerings
- Do other types of laboratories (private, academic, military, animal health and environment) link into the national laboratory network for diagnostic testing?
 - Do public laboratories provide services for private health care facilities such as conducting testing on specimens from a private health centre?
 - Do private laboratories provide services for public health care facilities such as conducting testing on specimens from a public health centres?
 - Are there private laboratories that provide services? If so, what are the names of the providers and is there any official regulation or interaction with the public sector?
- d. Communications and information
- Is there a formalized system of communication within the networks?
 - Is there a laboratory information system (LIS) in country?
 - If there is an electronic LIS, what does it cover (e.g., disease, tiers of laboratory system, geographic coverage)?
 - Is there a national patient identification number or system?
 - What level of connectivity exists across health facilities at central levels (mobile networks, internet, wireless data, etc.)?
 - What level of connectivity exists across health facilities at regional levels?
 - What level of connectivity exists across health facilities at provincial levels?
 - Are the communications between each tier of the laboratory system (e.g., national, regional, and peripheral) reliable?
 - Is there a national standard for patient reports and do laboratories follow this standard for reporting?

3. Available Referral Systems

a. Structure of current specimen referral systems (stratify by disease programme if necessary)

- Are national sample referral and transportation systems in place?
- What are the sample transportation systems that currently exist in the country at national, regional and district levels?
- Who is currently responsible for providing specimen referral services at the different laboratory tiers?
- Who pays for sample transport at the different laboratory tiers?
- What types of transport are used for sample transportation? Stratify by area or laboratory tier.
- What diseases and samples are covered under the current sample transportation system(s)?
- What is the structure of the specimen referral system (hub and spoke, patient referral, sample referral etc.)?

b. Regional and facility level linkages

- For each laboratory that receives referred samples, list which laboratories refer which types of specimens to it for which tests.
- For each laboratory or primary health facility that refers samples, list which types of specimens are referred to which laboratories for which tests.

c. Documentation and communication

- Are there standard operating procedures (SOPs) for national and international sample transportation?
- Are clinical and laboratory staff trained in SOPs for sample collection, referral, packaging, transportation and reception?
- Are couriers trained in SOPs, biosafety, biosecurity, spill clean-up, etc.?
- Is there a laboratory handbook available with information on SOPs for packaging, transit, turnaround times, test menus, etc.?
- Are request forms standardized for all testing and being used at all levels?
- Are standardized transportation logs and chain of custody forms available and used by anyone transporting specimens?
- Is triple packaging used for all national and international sample transportation?
- Is there a system in place that allows for a sample to be tracked from the submitting laboratory to the testing laboratory?
- How are results of laboratory tests delivered? Paper, SMS printer, electronically, etc.?
- Is there a system in place that allows for the results or reports to be tracked to the referring laboratories? If a result isn't delivered, how do doctors, nurses, or patients follow-up?

- How do facilities and laboratories communicate about specimen quality, rejections, missing results, etc.?
 - d. Performance of the current system
 - What is the proportion of specimen collection sites participating in the current specimen referral system?
 - What is average turnaround time from collection to pick-up?
 - What is average turnaround time from pick-up to delivery to the testing laboratory?
 - What is average turnaround time from obtaining a result to delivery of the results to the referring laboratory or clinician?
 - e. General transportation infrastructure
 - What are the most common types of vehicles in different areas of the country? Is it common for rural areas to use motorcycles?
 - What is the fuelling situation – are there areas where fuel is difficult to obtain?
 - What type of public transport is available in urban and rural areas?
 - What is the road network like in country, including urban and rural areas?
 - Is road transportation subject to closure or delays during the wet season? If so, what proportion of the year is likely to be affected? Is there an alternative transportation strategy available?
 - 4. Cost Considerations
 - a. Costs of MoH-provided courier services
 - What are the estimated monthly maintenance and operation costs for the vehicles used?
 - What are the estimated monthly costs for drivers?
 - b. Private courier costs
 - What are the estimated unit costs for private courier transport? (e.g., cost per sample or per km)
 - Is there a surcharge for services for hard-to-reach regions?
 - c. Public transport costs
 - What are rates for public transportation (e.g., local bus or train service to transport patients)?
 - What are the costs of postal services for transporting specimens (e.g., cost/km, cost/weight)?
 - What are the costs for transporting specimens by train or by air?
 - d. Communication costs
 - What are the costs related to the reporting of results (e.g., mobile phone or data charges)?
 - What are the costs of maintaining communications between referring facilities and testing laboratories (e.g., a hot-line to track specimens)?
-

5. Multi-sector Engagement

a. Postal services

- What is the current coverage of the national postal services?
- How many postal facilities are there and does the postal service function in village, rural and district areas?
- Does the postal service offer courier services that can pick-up and deliver to individual buildings?
- What are the postal services capabilities (cold chain, frequency of delivery, cost bundling, etc.)?

b. Courier services

- What private sector courier companies are present in-country?
- What are the courier services' capabilities (coverage, cold chain, frequency of delivery, cost bundling, etc.)?

c. Mobile providers

- What are the top 3 mobile phone providers?
- Which phone provider has the greatest reach in the country? Specify % coverage where possible.

d. Other transportation systems

- Is there any distribution system that requires cold chain (e.g., frozen fish, supermarkets, flowers, etc.)?
- What are modes of transport used for cold chain delivery?

Mechanisms for the transport of specimens

The physical movement of specimens from one facility to another can occur by many possible mechanisms and modes of transport (e.g., cars, motorcycles, buses, airplanes, etc.). A national specimen referral system may include a combination of transport methods tailored to transporting specimens in urban or rural settings or from peripheral facilities to a distant central reference laboratory. For example, in Uganda, TB specimens may be transported from health facilities to a nearby transportation hub or local testing laboratory using a motorcycle courier service provided by the MoH, and from the transportation hub to the national reference laboratory by Posta Uganda.

Whatever mode of transport is used, the transport procedures must be well-documented and all personnel properly trained. In general, steps to follow in developing a mechanism to transport specimens include:

1. Identify the modes of transport that are available in the various regions and between the various tiers of the laboratory system.
2. Determine whether the transport services will be contracted out or developed within the MoH.
3. Develop a document that defines the specimen transport services that must be provided and the requirements that must be met including specifics on national and international guidelines for packaging and transport of infectious material; training of staff; staff certifications (e.g., licensed motorcycle operators) and qualifications for proper handling and safe transport of infectious specimens; documentation required for specimen tracking and transport of specimens and results; standard operating procedures; turnaround times; and implementation plans. This document may be used as the basis for tender specifications or contract negotiations.
4. If outsourcing, conduct a tender process as required by national regulations, select a vendor and enter into a contract. If not outsourcing, obtain the necessary vehicles and trained operators.
5. Obtain necessary permits and approvals from all relevant government departments such as permits for handling and transporting biohazardous material.
6. Train staff on appropriate and safe specimen handling techniques, patient confidentiality procedures and how to handle emergency situations such as biological spills.

7. Provide appropriate personal protective equipment, spill kits and proper packaging materials including safe and secure shipping containers.
8. Pilot the system in a small geographical area before expanding to regional or national coverage to identify potential operational challenges.
9. Monitor the system to make sure that adequate service is being provided and take corrective action as needed.

Types of transport

Courier services. Commercial courier companies specialize in collecting and delivering packages. Couriers range from large international corporations such as FedEx or DHL to small companies that provide a courier service in a limited geographical area. However, not all courier companies are able or willing to transport potentially infectious biological samples. Advantages of professional courier services may include logistics expertise, on-demand or regularly scheduled pick-ups, short transportation times, individualized pick-up and delivery, tracking of shipments, documentation of transportation, reliability, and security of samples during transport. Potential disadvantages of professional courier services include cost, limited geographical coverage and lack of experience in transporting biohazardous material. Also, commercial couriers may not be a cost-effective way to return results.

In some settings, courier services have been provided by the government such as the motorcycle courier service provided by the MoH in Uganda or by private transportation partners such as Riders for Health in Lesotho. Potential advantages include the ability to design a dedicated courier system to meet the needs of the collection sites and receiving laboratories, the opportunity to implement service in hard-to-reach or underserved areas, and cost. Potential disadvantages include the need to maintain a fleet of functioning vehicles, the availability of well-trained, competent vehicle operators and fuel shortages.

Shared government vehicles. Government-owned and operated vehicles are often used by programme officials to conduct supervisory visits and to deliver supplies and commodities. Some programmes have also used the vehicles to transport specimens and results. A limiting factor of this mode is that the government vehicles often do not visit the collection sites frequently enough for timely transport of specimens and results. Also, with shared priorities, specimens are not always transported within the appropriate cut-off times and in a quality-controlled manner.

Local or national public transportation systems. Public transportation systems (buses, trains, boats, planes) carry persons and packages from one location to another on a regular schedule. Such systems could be used to transport specimens, although considerable effort may be needed to ensure that all personnel are properly trained, standard operating procedures are followed, and that a system is in place to track specimens. Additional limitations may include limited coverage, pick-up and delivery sites may be limited by the carrier, and special permits maybe needed to

transport people and potentially infectious material in the same vehicle. Transport by air must comply with IATA regulations for packaging, labelling and transport.

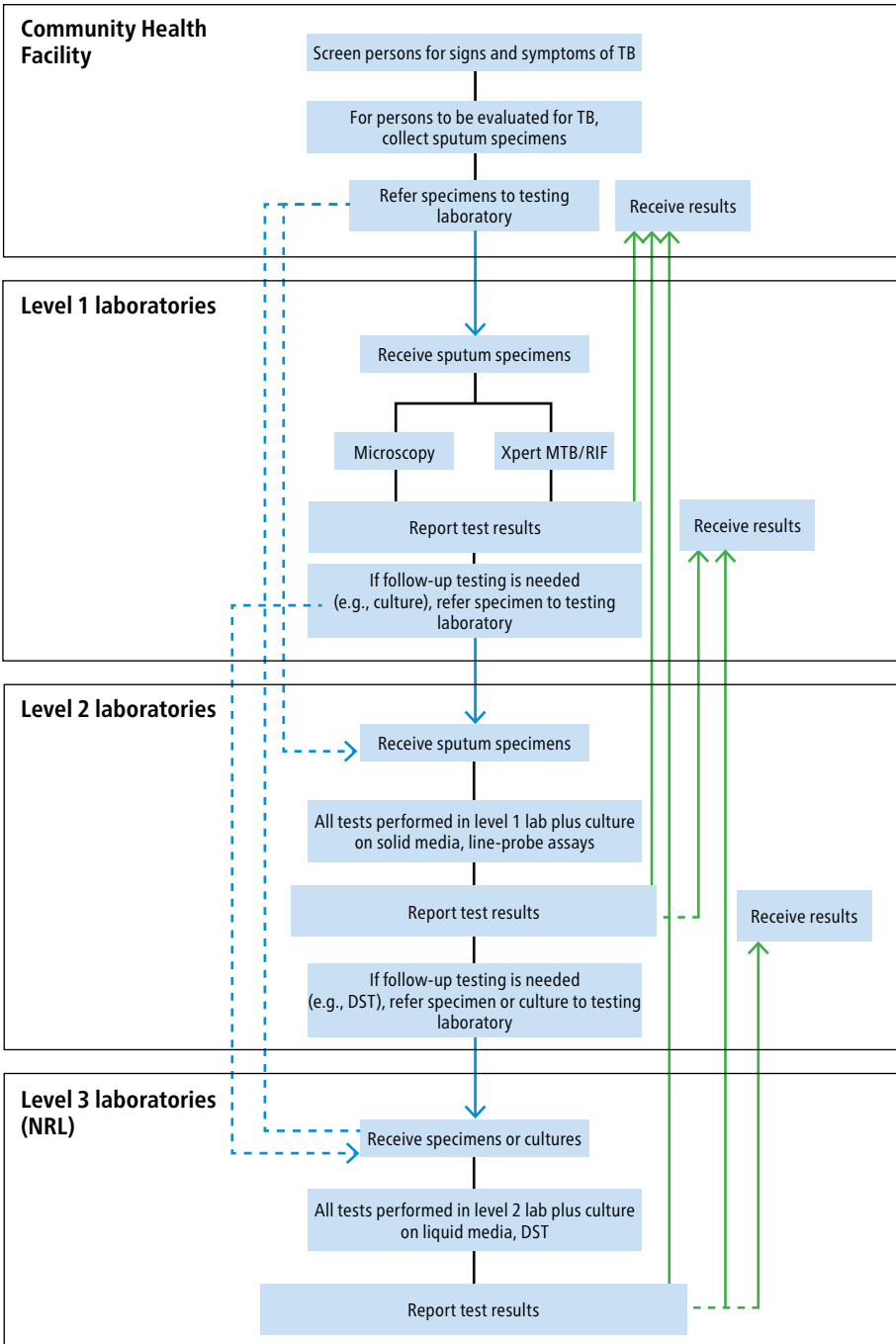
National postal service. National postal services have been used to transport specimens and return results. One benefit of using the national post is that it is usually a parastatal entity, which may be easier for the MoH to contract with than a private courier. The postal service also has a mandate to be present across an entire country, although actual coverage varies by country, and some health facilities in the periphery may not have easy access to local post offices. Transport times can vary significantly between different sites. Samples needing a short transit time or careful temperature control may not be suitable for shipment using the postal system. Specific regulations and permits may be needed to transport infectious material using the postal system.

Unmanned aerial vehicles (UAVs). The use of UAVs or drones to transport specimens and results has been piloted in several countries including the transporting of TB samples (See Case Study 5). Their use is promising as a solution for hard-to-reach areas, potentially bypassing the need to build traditional transportation infrastructure. However, in many countries, it is not yet legal to fly UAVs and few countries have suitable regulations for the use of UAVs.¹⁹ Further, much work needs to be done to develop guidance on the practical use of UAVs including licensing requirements for pilots, packaging and biosafety requirements, air traffic control protocols, emergency procedures, etc. More studies are needed to identify limitations and potential of UAVs and determine if a practical, sustainable transportation system could include the use of UAVs.

¹⁹ http://www.chemonics.com/OurWork/OurProjects/Documents/GHSC_PSM_UAV%20Analysis_final%20Updated.pdf

ANNEX C

Example of TB specimen and results flow



ANNEX D. Examples of forms for specimen referral and transport²⁰

Example of a TB specimen referral register²¹

S. No.	Name of patient	Age	Medical record No. (MRN)	Lab Serial No.	Type of sample	DD/MM/YY of sample collection	DD/MM/YY of sample picked up	Shipper's name	DD/MM/YY results received from Lab	Results	DD/MM/YY results given to the patient/HCW	Sample rejected	Turn-around time (TAT)	Name and signature of technician	Remark
	Address	Sex				Time	Time	Signature	Time	Time	Time				

²⁰ Additional examples can be found in the associated specimen referral toolkit.

²¹ Federal Democratic Republic of Ethiopia, Ministry of Health, Ethiopian Public Health Institute. 2014. Implementation Guideline for GeneXpert MTB/RIF Assay in Ethiopia. Available at: http://www.challengetb.org/publications/tools/country/GeneXpert_Implementation_Guideline_Ethiopia.pdf

Example of an integrated specimen shipment inventory log

Submitting Center

Center Name: _____
 No. specimens shipped: _____
 Date and time of pick-up: ____/____/____ : ____:____
 Signature: _____

Submitting Center: Complete the Patient Identifier and place an X in "f" box for each test requisition form submitted and in 's' box for each specimen submitted.

Receiving Laboratory

Laboratory Name: _____
 No. specimens received: _____
 Date and time of delivery: ____/____/____ : ____:____
 Signature: _____

Receiving Laboratory: In the bottom line, place X in "f" box for each test requisition form received and in 's' box for each specimen received. Use comments section to describe discrepancies.

Patient identifier or name	HIV Diagnosis		EID DNA PCR		DBS		Viral load		EDTA Tube, purple		TB - AFB Microscopy		Sputum		TB - Xpert MTB/RIF		Sputum or other specimen		TB - LPA		Sputu or culture		TB - Culture		Sputum or other specimen		TB - DST		Sputum or culture		Hepatitis		Red or yellow tube		Hematology		EDTA Tube, purple		Chemistry		Red or yellow tube		Comments							
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s				
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s				
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s		
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s		
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s		
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s		
	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s	f	s		

Example of a TB specimen shipment inventory log

TB Specimen Shipment Inventory Log	
Submitting Center Center Name: _____ No. specimens shipped: _____ Date and time of pick-up: ____/____/____ :____ Signature: _____	Receiving Laboratory Laboratory Name: _____ No. specimens received: _____ Date and time of delivery: ____/____/____ :____ Signature: _____
Submitting Center: Complete the Patient identifier and place an X in 'f' box for each test requisition form submitted and in 's' box for each specimen submitted.	
Receiving Laboratory: In the bottom line, place X in 'f' box for each test requisition form received and in 's' box for each specimen received. Use comments section to describe discrepancies.	

Shipment condition	Comments			
Packaged according to SOP	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr><td style="padding: 2px;">Y</td><td style="padding: 2px;">N</td></tr> </table>	Y	N	
Y	N			
Documentation complete	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr><td style="padding: 2px;">Y</td><td style="padding: 2px;">N</td></tr> </table>	Y	N	
Y	N			
Cold chain maintained	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr><td style="padding: 2px;">Y</td><td style="padding: 2px;">N</td><td style="padding: 2px;">N/A</td></tr> </table>	Y	N	N/A
Y	N	N/A		

Patient identifier or name	Test requested							Specimen				Comments	
	TB - AFB Microscopy	TB - Xpert MTB/RIF	TB - LPA	TB - Culture	TB - DST	TB - Other test	Test form complete (Y/N)	Sputum	other specimen culture	Properly packaged (Y/N)	Adequate volume (Y/N)		
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	
	f	f	f	f	f	f	Y/N	s	s	s	Y/N	Y/N	

Example of a transport (chain of custody) log

To be completed for samples or results being transported from site to site, kept by laboratory porter or in vehicle									
Date of pick-up (DD-MM-YYYY)	Time of pick-up (HH:MM)	Total number of items transported (samples or results)	Pick-up site	Shipper initials	Date of drop-off (DD-MM-YYYY)	Time of drop-off (HH:MM)	Drop-off site	Recipient initials	

Example of a TB specimen receipt and testing register²² – Part 1

S. No.	Lab No.	Name (in full) & Address	Sex (M/F) & Age	Name of referring site (DMC/DOTS-plus site) & District	Reason for Testing (mark one)		Date Specimen Collected from Patient	Date Specimen Received in culture lab	Specimen Condition (CPC or [MP, BLD, SAL, Contam]) †	Culture lab concentrate & smear result ‡
					Diagnosis	Follow-up				

* Using standard RNTCP definitions for TB type: NSP, NSN, NEP, Relapse, TAD, Failure, or Other
 † CPC=specimen contains CPC. If CPC present then no further description needed. For all other specimens with no CPC, describe condition. MP=unconcentrated specimen, BLD=gross blood in specimen, SAL=Subway specimen, Contam if gross bacterial overgrowth is suggested by visual examination.
 ‡ Sinear results for specimen deposit after concentration in culture laboratory, using standards definitions: 3+, 2+, 1+, Sc, Neg.

²² Central TB Division, Revised National TB Control Programme Training Manual for Mycobacterium tuberculosis Culture & Drug susceptibility testing. Available at: <http://tbcindia.nic.in/WriteReadData/1892s/6995271860Training%20manual%20M%20%20tuberculosis%20C%20DST.pdf>

Part 2

Culture Results				Standard DST Results						Date Sending Report to DOTS-Plus Site & DTO			
Date Inoculated	Type (Solid / Liquid)	Culture Results §	Date Result Reported	Date Inoculated	Type (Solid / Liquid)	RIF (R/S)	INH (R/S)	SM (R/S)	EMB (R/S)	Date Result Reported	Culture	DST	Remarks

‡ **R**=Resistant, **S**=Sensitive, **NA**=no result.
 § **Negative**=no growth, **Contam**=contaminated, **NTM**=Non-Tuberculosis Mycobacteria/rapid grower, **3+**=confluent growth, **2+**= >100 colonies, **1+**=10-100 colonies;
Sc(number)=Scanty<10 colonies (indicate number of colonies). Positive culture results should only be reported after identity for *M. tuberculosis* is confirmed with PNB, Niacin, Catalase, Rapid Immunoassay, or other methods.

Example of a TB specimen rejection log

TB Specimen Rejection Log															
Name of Laboratory: _____			Contact Person: _____												
For type of Specimen:		Enter S (sputum), GA (gastric aspirate), CSF (cerebrospinal fluid), BAL (Bronchioalveolar fluid), BAL (Bronchioalveolar fluid), C (culture), or write in other specimen types													
For test requested:		Enter M (microscopy), X (Xpert MTB/RIF), FL-LPA (first-line line probe assay), SL-LPA (second-line line probe assay), or write in other tests													
For Reason Rejected: Tick appropriate box or write in reason															
Referring facility	Patient name or ID	Type of specimen	Test requested	Date received	Reason Rejected							Date rejection notice sent	Rejected by (initials)		
					Inadequate volume	specimen leaked	Specimen contaminated	Specimen label missing or illegible	incomplete or missing examination form	Transport time exceeded maximum allowed time	cold chain not maintained			Other	

ANNEX E

Example of an SOP for TB sample conditions and transport for culture procedure^{23,24}

Institution Laboratory name Location Head/Responsible person	Standard Operating Procedure (SOP) Sample conditions and transport for culture procedure	Code: Version: no. Date: of release Page: 52 of ___78
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1. **Scope**
2. **Definitions and abbreviations**
3. **Personnel qualifications**
 - 3.1 Medical fitness
 - 3.2 Education and training
4. **Procedure**
 - 4.1 Principle
 - 4.2 Samples
 - 4.3 Equipment and materials
 - 4.4 Reagents and solutions
 - 4.5 Detailed instructions for the procedure
 - 4.6 Reading and reporting
 - 4.7 Quality control
5. **Related documents**

Annex E.1 Request and reporting form for TB culture and Drug Susceptibility Test (DST)

	Written by	Examined by	Released by	Replaced	New version
Name				Code:	Code:
Date					
Signature					
Laboratory area:	No of copies:	Reason for change:			

²³ Links to additional SOPs can be found in the associated specimen referral toolkit.

²⁴ The standard operating procedure (SOP) for sample conditions and transport for culture procedure is available at: http://www.stoptb.org/wg/gli/assets/documents/29_specimen_condition_transport.doc.

1. Scope

This SOP specifies the minimum requirements for the quality and quantity of biological specimens sent to a TB laboratory for culture and conditions for transportation of specimens to the laboratory.

2. Definitions and abbreviations

BAL: bronchoalveolar lavage

CPC: cetyl pyridinium chloride

NTM: non-tuberculous mycobacteria

NTP: national tuberculosis programme

3. Personnel qualifications

3.1 Medical fitness

In accordance with national laws and practices, arrangements should be made for appropriate health surveillance of TB laboratory workers before enrolment in the TB laboratory; at regular intervals thereafter, annually or bi-annually; after any biohazard incident; and at the onset of TB symptoms. All cases of disease or death identified in accordance with national laws and/or practice as resulting from occupational exposure to biological agents shall be notified to the competent authority.

Laboratory workers should be educated about the symptoms of TB and provided with ready access to free medical care if symptoms arise. Ideally, individual medical records shall be kept for up to 10 years following the end of occupational exposure.

Confidential HIV counselling and testing should be offered to laboratory workers. Options for reassignment of HIV-positive or immuno-suppressed individuals away from the high-risk areas of the TB laboratory should be considered.

3.2 Education and training

Basic education and training must be given on the following topics:

- potential risks to health (symptoms of TB disease and transmission);
- precautions to be taken to minimize aerosol formation and prevent exposure;
- hygiene requirements;
- wearing and use of protective equipment and clothing;
- handling of potentially infectious materials;
- laboratory design, including airflow conditions;
- prevention of incidents and steps to be taken by workers in the case of incidents;
- good laboratory practice and good microbiological techniques;
- organization of work flow and procedures;
- waste management;
- importance of laboratory results for patient management; and
- importance of laboratory results for the national TB programme.

The training shall be:

- given before a staff member takes up his/her post;
- strictly supervised;
- adapted to take account of new or changed conditions; and
- repeated periodically, preferably every year.

4. Procedure

4.1 Principle

Specimen quality –from the moment of collection to the arrival of specimens at the laboratory where they will be cultured – is the responsibility of the setting in which specimens are collected, that is, either the peripheral laboratory where patients were given sputum containers or the clinics where sampling/biopsy is performed.

Since the laboratory is usually the only place where there is quality control of specimens received, laboratories at all levels must monitor quality indicators (e.g. specimen volumes, proportion of saliva sputum specimens, and late arrival of specimens) and report problems so that corrective action may be taken wherever necessary.

Specimens sent to the laboratory should be of adequate volume, as specified below, accurately labelled for identification, and accompanied by a written laboratory request form according to WHO recommendations.

Specimens should be sent to the laboratory as soon as possible after collection, in leak-proof containers surrounded by absorbent material in a shock-resistant outer package that is properly labelled according to the national and/or international regulations for infectious material.

4.2 Samples NA

4.3 Equipment and materials

Wide-mouthed, unbreakable, leak-proof, screw-capped containers. Containers should have a volume capacity of 50 ml and made of translucent material in order to observe specimen volume and quality without opening the container.

4.4 Reagents and solutions NA

4.5 Detailed instructions for the procedure

4.5.1 Sample collection

Sputum

The large majority of specimens received for diagnosis are sputum samples.

- If good specimens are to be obtained, patients must be instructed in how to produce sputum. Specimens should be collected in a separate, ventilated room or preferably outdoors. Keeping both hands on hips, cough forcibly and collect sputum in the mouth; spit the sputum carefully into a wide-mouthed, unbreakable, leak-proof container and close the lid tightly.

- Ideally, a sputum specimen should be 3–5ml in volume, although smaller quantities are acceptable if the quality is satisfactory.
- If specimens are to be cultured using a centrifugation method (see SOP Specimen processing for culture), sputum specimens should preferably be collected directly into 50-ml centrifuge tubes to avoid the need for their transfer from one container to another.
- Label each specimen with the unique identification number from the laboratory request form.
- Collect two or three specimens from each patient according to NTP policy (INSERT NTP POLICY HERE)

Laryngeal swab

Laryngeal swabs may be useful in children and patients who cannot produce sputum or may swallow it.

- Collect laryngeal swabs in the early morning, before patients eat or drink anything.
- Use a sterile absorbent cotton swab for collection.
- Transport each specimen in a container with a few drops of sterile 0.9% saline solution in order to keep the swab wet.

Other respiratory specimens

- Bronchial secretion (2–5 ml) and BAL (20–40 ml)
- Pleural effusions (20–50 ml)
- Transbronchial and other biopsies taken under sterile conditions should be kept wet during transportation by adding few drops of sterile 0.9% saline to the tissue.

Note: *Specimens are sometimes sent in formalin or bleach! It may therefore be advisable to remind the physician of collection conditions, the day before surgery.*

Gastric lavage

Gastric lavages often contain NTM and are therefore rarely used for adults; they are indicated for children, however, who produce almost no sputum

- Make the collection early in the morning, when the patient has an empty stomach.
- Neutralize the specimen by adding 100 mg of sodium bicarbonate to the gastric aspirate and transport it immediately to the laboratory.

Extrapulmonary specimens

The laboratory may receive a variety of specimens for diagnosis of extrapulmonary TB – body fluids, tissues, urine, etc. These specimens may be broadly divided into two groups which are processed in different ways:

- Aseptically-collected specimens (spinal fluid, pericardial, synovial and ascitic fluid, blood, bone marrow, etc.), which are usually free from contaminating flora.
 - All liquid specimens should be collected in sterile containers without using any preservative.
 - Specimens can be inoculated directly into liquid vials and transported to the laboratory for culture.
 - Specimens must be transported to the laboratory immediately; they should be processed as soon as possible or kept at 2–8 °C.
 - The optimal volumes are at least 3 ml of cerebrospinal fluid and 5–10 ml of blood, collected in citrate blood tubes.
- Specimens with resident or contamination flora.
 - A urine specimen should consist of a single, early-morning, midstream sample of, collected in a wide-mouthed sterile vessel (of at least 200 ml capacity).
 - Semen and prostate secretions are sent without any additions.
 - Menstrual blood samples should be discouraged.
 - Stool samples should be discouraged; however, stool samples from immunocompromised patients may be used, mainly to detect NTM.

4.5.2 Transport conditions

Sputum specimens should be transported to the laboratory as soon as possible. If a delay of a few days cannot be avoided, keep specimens cool (refrigerated, but *not frozen*). Up to a week in at 2–8 °C will not significantly affect the positivity rate of smear microscopy; however, the additional growth of contaminants will result in an increased contamination rate on culture media. If the delay exceeds 3 days, an equal volume of cetyl pyridinium chloride (CPC; solution of 1% CPC in 2% sodium chloride) should be added to sputum (see SOP preparation of reagents for culture). Specimens containing CPC can be kept for up to 7 days but must be kept at room temperature (>20 °C because CPC crystallizes at lower temperatures). The addition of CPC must be indicated on the accompanying documents (see form below) because CPC has to be removed before culturing.

Transport packaging

Primary TB specimens (e.g., sputum specimens) are classified as Category B infectious agents and should be packaged according to the requirements for Category B substances.²⁵ The basic packaging system for local surface transport of all specimens consists of three layers:

²⁵ Guidance on regulations for the Transport of Infectious Substances 2015–2016. Geneva, World Health Organization. 2015. (WHO/HSE/GCR/2015.2). http://www.who.int/ihr/publications/who_hse_ihr_2015.2/

- Primary receptacle – the specimen container – packaged with enough absorbent material to absorb all fluid in case of breakage.
- Secondary packaging – a second durable, watertight, leak-proof packaging to enclose and protect the primary receptacle(s). Several cushioned primary receptacles may be placed in one secondary packaging, but sufficient additional absorbent material must be used to absorb all fluid in case of breakage. *For cold transportation conditions*, ice or dry ice shall be placed outside the secondary receptacle. Wet ice shall be placed in a leak-proof container;
- Outer packaging – secondary packagings are placed in outer shipping packagings with suitable cushioning material. Outer packagings protect their contents from external influences, such as physical damage, during transit.

For *surface transport* there is no maximum quantity per package.

For *air transport* of Category B infectious agents, no primary receptacle shall exceed 1 L for liquids or the outer packaging mass limit for solids. The volume shipped per package shall not exceed 4 L or 4 kg. Also, training in IATA transportation regulations for packaging, labelling, and transport is required.

4.6 Reading and reporting: Use form in Annex E.1.

4.7 Quality control

Before specimens can be accepted in the laboratory, the accompanying request forms must be checked carefully for identity (sample and request form labelled with the same number). Specimens that cannot be identified exactly will be not processed.

Specimens should be examined on receipt of the sample, to ensure that they correspond in type, quantity, quality and volume to the appropriate criteria. Any deviations must be documented and noted on the final report since they may affect the results.

The transport conditions and duration must be checked. Delays in transportation or exposure of specimens to extremes of temperature without protective measures must be documented and noted in the report.

5. Related documents

Collins C, Grange J, Yates M. *Organization and practice in tuberculosis bacteriology*. London, Butterworths, 1985.

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Kent PT, Kubica GP. *Public health mycobacteriology: a guide for the level III laboratory*. Atlanta, GA, United States Department of Health and Human Services, Centres for Disease Control, 1985.

Laboratory services in tuberculosis control. Part II: Microscopy. Geneva, World Health Organization, 1998 (WHO/TB/98.258).

Lumb R, Bastian I. *Laboratory diagnosis of tuberculosis by sputum microscopy.* Adelaide, Institute of Medical and Veterinary Science, 2005.

Definitions and reporting framework for tuberculosis: 2013 revision. Geneva, World Health Organization, 2013 (WHO/HTM/TB.2013.2), available at: <http://www.who.int/tb/publications/definitions/en/>

Smithwick RW. *Laboratory manual for acid-fast microscopy.* Atlanta, GA, Centre for Disease Control, 1976.

ANNEX E.1

Request and reporting form for TB culture and Drug Susceptibility Test (DST)

Patient identification (ID):
 TB register number: Previous TB register number: MDR register number:
 Surname and first name of patient: Age (yrs): Sex:
 Ward / Department: Address:
 *HIV-status: Pos / Neg / Unknown

TB Disease type and treatment history

Site: pulmonary History: new (never treated before for ≥ 1 month)
 extrapulmonary (specify): relapse
 failure
 Previous treatment: return after default
 Cat.1 chronic excretor
 Cat.2 MDR contact
 Cat.4 (second-line drugs) uncertain
 Other

Origin of request:

Region ID: District ID: Local laboratory ID:
 Date specimen was collected:/...../20..... Specimen ID number:
 Local laboratory: smear result: 1st 2nd 3rd specimen
 microscopy technique used: hot Ziehl-Neelsen direct smear
 old staining concentrated smear
 fluorescence

Request for testing at the reference laboratory:

Reason: diagnosis Specimen: sputum
 follow-up at months during treatment sputum in preservative, type
 follow-up at months after treatment
 other specify:
 Requested tests: microscopy (type) culture DST (first/second line)
 Person requesting examination: Name: Position:

Reference laboratory results:

Date received in the Reference Laboratory/...../.....
 Reference Laboratory specimen ID:

Microscopic examination: previously reported on date/...../.....

ID #	Neg	1-9	1+	2+	3+	
						<input type="checkbox"/> hot Ziehl-Neelsen <input type="checkbox"/> cold staining <input type="checkbox"/> fluorescence <input type="checkbox"/> direct smear <input type="checkbox"/> concentrated smear

* Information that can be disclosed optionally

ID = identification number or code

ANNEX E. EXAMPLE OF AN SOP FOR TB SAMPLE CONDITIONS AND TRANSPORT FOR CULTURE PROCEDURE

Culture result: previously reported on date/...../..... will follow

ID #	Contaminated	Neg	Non-TB mycobacteria (species)	<i>Mycobacterium tuberculosis</i> complex			
				1–9 colonies actual count	10 – 100 col 1+	>100 – 200 col 2+	>200 col 3+

Results of *M. tuberculosis* drug susceptibility testing: will follow

phenotypic method used

genetic method used

ID #	Legend: S = susceptible; R = resistant; C = contaminated; ND = not done												
	INH	Rifampicin		Ethambutol		Streptomycin		Pyrazinamide		Ofloxacin		Kanamycin	
µg/ml													
result													

Date:/...../..... Signature:

ANNEX F

Framework of indicators and targets for specimen referral systems

Monitoring and evaluation (M&E) for specimen referral systems should examine the performance of the overall system at a high level as well as its operations at a more detailed level to ensure that good quality specimens reach the testing sites in a timely manner, results are returned rapidly, actions are properly documented in registers and forms, biosafety and biosecurity measures are followed properly, and packaging and transportation equipment meet the country's standards. Standardized registers and forms must be used throughout the system and all required information properly entered in all forms. Quality control should be practiced and documented during specimen collection, packaging and transport. For example, the quality and volume of the specimens should be recorded in the specimen registers at the referring site before they are sent to the testing laboratory and in the specimen receipt logs at the receiving site upon receipt.

The main objectives of a specimen referral system are:

- Increase access to diagnostic testing;
- Improve the timeliness of diagnostic test results (i.e., shorten turnaround times between specimen collection and return of results);
- Improve the quality of diagnostic testing by improving the quality of the specimens being tested and reliability of the specimen referral system; and
- Reduce the cost of diagnostic testing by improving the cost-effectiveness of specimen referral.

The following tables describe indicators for monitoring a specimen referral network system. Data collection for monitoring the specimen referral system will be facilitated through the use of standardized registers and forms that have complete and accurate entries for all specimens. Key documents include:

- Specimen referral registers and shipment inventory logs and files with copies of test examination request forms and completed transport forms (referring site);
- Laboratory registers (referring and receiving sites);
- Specimen shipment inventory logs and transport logs and files with copies of completed transport forms (receiving site); and
- Specimen rejection logs (travels with the transporter and copies kept at the referring and receiving sites).

Specimen receipt registers should be specifically listed.

Examples of these documents are in Annex D as well as on the GLI website.²⁶ Links to these documents will also be provided in the accompanying specimen referral toolkit. The documents should be customized to the local situation.

During supervisory visits, the use of the registers, forms and logs should be assessed. A review of a sample of the registers, forms and logs should allow assessment of the proportion of shipments with correctly completed transport logs; proportion of specimens with correctly completed specimen referral and test requisition forms; and proportion of referred specimens with correctly completed entries in the specimen referral register, shipment registers and specimen receipt registers. Supervisory visits are also an opportunity to assess the application of quality control practices and adherence to SOPs, biosafety and biosecurity measures, and packaging and transportation standards.

Collection of data for monitoring turnaround times may be facilitated through the use of barcoded labels and a scanning system that records the date, time and name of the individual in possession of the specimen at every step during the referral process (see Case Study 4 on Lesotho).

There are many indicators that could be tracked. Key indicators should be monitored routinely (e.g., monthly) by the sites and courier, and reported to the district or regional quality officer. Other indicators may be more useful for monitoring trends or investigating specific issues or as quality checks during supervisory visits. Additional indicators may also be developed by the TWG or quality officer to address specific aspects of the local situation.

Indicators calculated using aggregate data (e.g., number of referred specimens tested) are useful to monitor overall performance, but to facilitate detecting problems and initiating corrective actions, it may be necessary to disaggregate the data by referring facility, referral laboratory, courier, courier route or district. For example, if specimens are referred to more than one laboratory (e.g., specimens sent to a local testing hub for Xpert MTB/RIF testing and specimens sent to the NRL for culture), the indicators should be monitored separately for each referral laboratory.

Several indicators measure performance against target times or specified times rather than against a defined time because of variability in the factors that determine the time such as frequency of sample pick up, mode and distance of transportation, testing method, etc. The target or specified times should be established by the Technical Working Group.

²⁶ <http://www.stoptb.org/wg/gli>

Indicators to be monitored at the referring facility

Indicator 1.1	Number of specimens referred for testing and number of shipments dispatched
Indicator 1.2	Proportion of referred specimens for which a result was returned
Indicator 1.3	Proportion of referred specimens for which a result was received within the specified target time
Indicator 1.4	Proportion of specimens which were picked up by the transport service within the target turnaround time

Detailed description of indicators, targets, indicator calculations and remarks

Indicator 1.1: Number of specimens referred for testing and number of shipments dispatched	
Purpose	Assess the utilization and uptake of referral services, identify gaps, and assist with planning
Target	Expected to increase initially
Numerator	Number of specimens referred; number of shipments dispatched
Denominator	Not applicable
Monitoring	Monitored monthly at each referring facility
Data Sources	Specimen referral register, shipment inventory logs, transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by laboratory to which the specimens are referred • Although the number is expected to increase over time, there may be temporary decreases as the system is implemented if there is a transition from one system to another or while confidence in the reliability of the new system is established

Indicator 1.2: Proportion of referred specimens for which a result was returned	
Purpose	Assess the overall performance of the specimen referral and testing system
Target	>95%
Numerator	Number of referred specimens for which a result was returned
Denominator	Total number of specimens referred
Monitoring	Monitored monthly at each referring facility
Data sources	Specimen referral register
Remarks	<ul style="list-style-type: none"> • 'Sample rejected' should be considered a valid returned result • If applicable, disaggregate by referral laboratory • The indicator should be calculated for specimens for which the target turnaround time for the requested test has passed <ul style="list-style-type: none"> — For microscopy and molecular tests and rejected samples, this indicator may be calculated using information from the prior month rather than the current month — Because of the long turnaround time for culture and DST, this indicator may be calculated using data for specimens that were referred 60 to 90 days earlier • The number of referred specimens for which a test result was returned may be monitored by as an additional output measure to assess the extent to which the system is improving access to diagnostic testing

Indicator 1.3: Proportion of referred specimens for which a result was received within the specified target time	
Purpose	Assess whether the referral system is meeting the target of improving the timeliness of diagnostic test results
Target	>95%
Numerator	Number of referred specimens for which a test result was received within the specified time
Denominator	Total number of specimens referred for which a result was returned
Monitoring	Monitored monthly at each referring facility
Data sources	Specimen referral registers
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by referral laboratory • Target time should be determined for each test required (e.g., Xpert MTB/RIF or culture) and the collection schedule used (e.g., on demand, daily, twice weekly, etc.) • For this calculation, an entry that the specimen was rejected should be counted as a result and a target time for rejected sample notification determined • The indicator should be calculated for specimens for which the target turnaround time for the requested test has passed <ul style="list-style-type: none"> — For microscopy and molecular tests and rejected samples, this indicator may be calculated using information from the prior month rather than the current month — Because of the long turnaround time for culture and DST, this indicator may be calculated using data for specimens that were referred 60 to 90 days earlier • During a quarterly or semi-annual supervisory visit, the average time between collection of the specimen and receipt of the result by the referring site may be calculated as an additional performance indicator

Indicator 1.4: Proportion of specimens which were picked up by the transport service within the target turnaround time	
Purpose	Assess the performance of the system with respect to the timeliness of specimen pick-up
Target	>95%
Numerator	Number of referred specimens which were picked up by the transportation service within the specified time after specimen collection
Denominator	Number of specimens picked up by the transportation service
Monitoring	Monitored monthly at each referring facility
Data sources	specimen referral registers or transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by courier • Target should be determined for each collection schedule (e.g., on demand, daily, twice weekly). For example, <24 hr for daily pick-up or <7 days for weekly pick-up • During a quarterly or semi-annual supervisory visit, the average time between collection of the specimen and pick-up by the transport service may be calculated as an additional performance indicator

Indicators to be monitored at the referral laboratory

Indicator 2.1	Number of referred specimens tested at the referral laboratory
Indicator 2.2	Proportion of shipments that arrive at the referral laboratory within the specified transport time
Indicator 2.3	Proportion of test results that were picked up by the transport service or transmitted electronically within the specified turnaround time after generation of the test result
Indicator 2.4	Proportion of specimens that were rejected

Detailed description of indicators, targets, indicator calculations and remarks

Indicator 2.1: Number of referred specimens tested at the referral laboratory	
Purpose	Assess the utilization and uptake of referral services, identify gaps, and assist with planning
Target	Expected to increase initially and as new collection sites are added
Numerator	Number of referred specimens that were tested in the referral laboratory
Denominator	Not applicable
Monitoring	Monitored monthly at each referral laboratory
Data sources	Specimen receipt and testing registers
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by referring facility • Although the number is expected to increase over time, there may be temporary decreases as the system is implemented if there is a transition from one system to another or while confidence in the reliability of the new system is established

Indicator 2.2: Proportion of shipments that arrive at the referral laboratory within the specified transport time	
Purpose	Assess the performance of the system with respect to the timeliness of specimen transport
Target	>95%
Numerator	Number of shipments that arrived at the referral laboratory within the specified transport time
Denominator	Total number of shipments received
Monitoring	Monitored monthly at each referral laboratory
Data sources	Transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by courier or route • Target transport time will depend on the mode of transportation and distance and should be specified in the courier's service agreement. Target may vary by referring facility and courier • During a quarterly or semi-annual supervisory visit, the average time between pick-up of a shipment to receipt by the receiving laboratory may be calculated as an additional performance indicator

Indicator 2.3: Proportion of test results that were picked up by the transportation service or transmitted electronically within the specified turnaround time after generation of the test result	
Purpose	Assess the timeliness of reporting results
Target	>95%
Numerator	Number of test results that were generated for referred specimens that were picked up by the transportation service or electronically transmitted within the specified turnaround time after generation of the test result
Denominator	Number of test results that were generated for referred specimens and returned to the referring sites
Monitoring	Monitored monthly at each referral laboratory
Data sources	Specimen receipt and testing registers and transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by courier or route • Target turnaround may depend on mode of transportation (e.g., courier service or postal system) and frequency of service. For electronic transmission, the target is <24 hours. • During a quarterly or semi-annual supervisory visit, the average time between generation of a test result and pick-up by the transportation service or electronic transmission may be calculated as an additional performance indicator • The number of test results that were generated for referred specimens and returned to the referring sites may be monitored by as an additional output measure to assess the extent to which the system is improving access to diagnostic testing

Indicator 2.4: Proportion of specimens that were rejected because of factors related to inadequate or improper transport, packaging, or documentation	
Purpose	Assess the performance of the system with respect to transport, packaging, and documentation
Target	<5%
Numerator	Number of specimens that were rejected because of factors related to inadequate or improper transportation or packaging or documentation
Denominator	Number of specimens received
Monitoring	Monitored monthly at each referral laboratory
Data sources	Specimen receipt and testing register and specimen rejection log
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by referring facility or courier • Reasons for rejecting specimens include: <ul style="list-style-type: none"> — Inadequate specimen volume or quality — Specimen leaked — Specimen contaminated or of insufficient quality — Specimen label is missing or illegible — Specimen not packaged according to SOP — Incomplete or illegible test requisition form — Transport time exceeded maximum allowed time — Cold chain not maintained (if applicable) • During a quarterly or semi-annual supervisory visit, the number of specimens received by the referral laboratory could be compared to the number of specimens sent to the referral laboratory (i.e., sum of indicator 1.1 for all referring facilities) as an additional indicator to assess potential issues with the transportation process

Indicators to be monitored by the courier²⁷ as part of their service agreement

Indicator 3.1	Number of shipments and number of specimens transported
Indicator 3.2	Proportion of shipments that were delivered within the specified transport time
Indicator 3.2	Proportion of shipments that were lost or damaged

Detailed description of indicators, targets, indicator calculations and remarks

Indicator 3.1: Number of shipments transported; number of specimens transported	
Purpose	Assess the utilization and uptake of referral services, identify gaps, and assist with planning
Target	Expected to increase initially and as new collection sites are added
Numerator	Number of shipments that were transported; number of specimens transported
Denominator	Not applicable
Monitoring	Monitored monthly by the courier
Data sources	Transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by route or district • Monitoring the indicator should be included in the courier's service agreement • Although the number is expected to increase over time, there may be temporary decreases as the system is implemented if there is a transition from one system to another or while confidence in the reliability of the new system is established

Indicator 3.2: Proportion of shipments that were delivered within the specified transport time	
Purpose	Assess the performance of the system with respect to the timeliness of specimen transport
Target	>95%
Numerator	Number of shipments that were delivered within the specified transport time
Denominator	Total number of shipments transported
Monitoring	Monitored monthly by each courier
Data sources	Transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by route or district • Monitoring the indicator should be included in the courier's service agreement • Target transport time will depend on the mode of transportation and distance and should be specified in the courier's service agreement. Target may also vary by referring facility, referral laboratory, and transport route • Indicator should be calculated for transport of specimens, and if applicable, for transport of results • Average time between pick-up of a shipment to delivery to the receiving laboratory may be calculated as an additional performance indicator

²⁷ The courier service may be operated by the MoH or outsourced to another government entity, implementing partner, non-governmental organization or private company

Indicator 3.3: Proportion of shipments that were lost or damaged in transit	
Purpose	Assess the reliability of transport
Target	<5%
Numerator	Number of shipments that were lost or damaged in transit
Denominator	Total number of shipments
Monitoring	Monitored monthly by each courier
Data sources	Transport logs
Remarks	<ul style="list-style-type: none"> • If applicable, disaggregate by route or district • Monitoring the indicator should be included in the courier's service agreement • The district or regional quality officer may also compare the number of shipments received by the referral laboratory (indicator 2.2) with the number of shipments dispatched from the referring facilities (sum of indicator 1.1 for all referring facilities) as an additional quality check.

Indicators to be monitored at the regional or national level by the TWG or MoH

Indicator 4.1	Number of specimen collection sites participating in the specimen referral system
Indicator 4.2	Cost per specimen or result transported

Detailed description of indicators, targets, indicator calculations and remarks

Indicator 4.1: Number of specimen collection sites participating in the specimen referral system	
Purpose	Assess the utilization and uptake of referral services, identify gaps and assist with planning
Target	Initially expected to increase and eventually include all specimen collection sites in a catchment area
Numerator	Number of collection sites participating in the specimen referral system
Denominator	Not applicable
Monitoring	Monitored annually by the TWG or a management team in the MoH
Data source	Survey or mapping of specimen collection sites
Remarks	<ul style="list-style-type: none"> • The indicator may be monitored nationally or by the catchment area of a testing laboratory • For planning and budgeting purposes, measurement of the proportion of eligible specimen collection sites that participate in the specimen referral system or the proportion of all specimen collection sites in the region or country that participate in the specimen referral system might be useful

Indicator 4.2: Cost per specimen or result transported	
Purpose	Provide information for planning and budgeting and assess cost effectiveness
Target	Cost analysis done annually
Numerator	Total cost of specimen transport system
Denominator	Number of specimens or results transported
Monitoring	Monitored annually by the TWG or a management team in the MoH
Data source	Survey or cost analysis
Remarks	<ul style="list-style-type: none"> • For contracted specimen transport services, the cost per specimen could be calculated as the total cost of the contracts divided by the number of specimens or results transported • For government provided services, a cost analysis similar to that done during the initial landscape analysis might be needed • Sub-analyses may be needed to assess costs in different settings (e.g., a hard-to-reach peripheral setting or an urban setting) or different routes (e.g., peripheral facility to a nearby testing hub or a peripheral facility to the national laboratory)

ANNEX G

Requirements for TB specimen collection, storage, packaging, transport and documentation

In general, the transport of TB specimens must be made as soon after collection as possible to facilitate the prompt diagnosis of TB and initiation of treatment and to maximize the likelihood of successful laboratory testing. The freshness of the specimen is especially important for culture examination. All specimens must be collected and labelled in accordance with SOPs.

Primary TB specimens (e.g., sputum specimens) are classified as Category B infectious agents and should be packaged, labelled and transported according to the requirements for Category B substances.²⁸

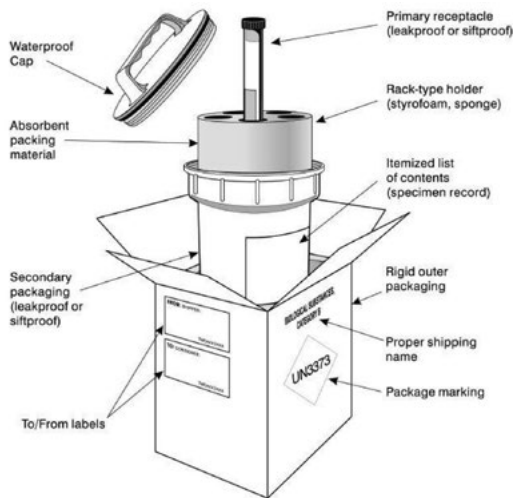
Packaging and documentation requirements

TB specimens must be shipped using a triple packaging system that is labelled according to national and international regulations for infectious material. The basic packaging system consists of three layers:

- A primary receptacle which contains the leak-proof specimen container and is packed with enough absorbent material to absorb all fluid in case of breakage.
- A secondary receptacle which includes durable, watertight, leak-proof packaging to enclose and protect the primary receptacle(s). Several cushioned primary receptacles may be placed in one secondary receptacle, but sufficient additional absorbent material must be used to absorb all fluid in case of breakage. For cold transportation conditions, ice (wet ice, ice packs) or dry ice shall be placed outside the secondary receptacle. Wet ice shall be placed in a leak-proof container. Temperature monitoring devices may be placed inside the transport box to monitor transport conditions.
- Outer packaging which surrounds the secondary receptacle to protect the contents from external influences, such as physical damage, during transit. Outer packaging should be shock-resistant and contain suitable cushioning material. The outer shipping packaging must be labelled in accordance with national and international regulations for infectious material.

²⁸ Guidance on regulations for the Transport of Infectious Substances 2015–2016. Geneva, World Health Organization. 2015. (WHO/HSE/GCR/2015.2). http://www.who.int/ihr/publications/who_hse_ihr_2015.2/

An example of packaging for local transport is shown below.



For transport of primary TB specimens by air or internationally, packaging for Category B infectious substances (UN3373, IATA) is required.

The documentation required for all referred samples and shipments includes a test requisition form for each specimen (e.g., Annex E.1), an inventory list of all specimens and forms included in a shipment (Annex D), and a transport log (Annex D).

Specimen referral for AFB smear microscopy

Sputum specimens are usually the only sample referred for testing by AFB microscopy alone. If other types of specimens are referred for AFB smear microscopy only, use the conditions described for referral for culture.

Sputum specimens	
Collection and storage	<ul style="list-style-type: none"> • Minimum volume: 1 ml for direct microscopy; 3–5 ml if samples are to be concentrated • Collect samples into a clean leak-proof wide-mouth container • If transport is delayed by more than 1 hour, specimens should be stored at 2–8 °C
Packaging and transport	<ul style="list-style-type: none"> • Freshly collected specimens may be transported at ambient temperature (20–30 °C) if delivered to the testing laboratory within one day Refrigerated specimens must be delivered to the testing laboratory within 7 days of collection • Transport in a cool box at 2–8 °C. Protect samples from extreme heat and cold
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<ul style="list-style-type: none"> • Purulent sputum specimens are optimal for direct smear microscopy

Specimen referral for Xpert MTB/RIF testing

For samples being referred for Xpert MTB/RIF testing, bacterial viability is not an issue, but stability of nucleic acids is a consideration. The bacteria in a sputum specimen may be inactivated prior to transport. Inactivated samples may not require transport in accordance with requirements for the transport of infectious material.

If specimens other than sputum specimens (e.g., bronchoalveolar lavage fluid, gastric aspirates, tissue specimens, and CSF) are referred for Xpert MTB/RIF testing, use the conditions described for referring samples for culture.

If samples are being referred for Xpert MTB/RIF and culture, use the conditions for referring samples for culture.

Sputum specimens	
Collection and storage	<ul style="list-style-type: none"> • Minimum volume: 1 ml, 2–4 ml samples are preferred • Collect samples into a clean leak-proof wide-mouth container • If transport is delayed by more than 1 hour, specimens should be stored at 2–8 °C. If necessary, specimens may be stored at ambient temperature (maximum 35 °C) for up to 3 days, then refrigerated at 2–8 °C
Packaging and transport	<ul style="list-style-type: none"> • Specimens must be delivered to the testing laboratory within 10 days of collection • Transport in a cool box at 2–8 °C
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<ul style="list-style-type: none"> • For Xpert MTB/RIF testing, bacteria in the sputum specimens can be inactivated and then stored and transported at ambient temperature or at 2–8 °C. Commercial products (e.g., Primestore from Longhorn Vaccines and Diagnostics or Sputum DNA Collection KIT from Norgen Biotek) and 70% ethanol have been used to inactivate bacteria for transport; however a recent WHO Technical Expert Group meeting concluded that there is no evidence that use of commercial transport products improves performance with molecular tests. The meeting also noted that the addition of the commercially available OMNIgene•SPUTUM (DNA Genotek) to sputum specimens requires centrifugation and the addition of GeneXpert sample reagent to the sediment prior to Xpert MTB/RIF testing.^a

^a Technical Expert Group Meeting Report: Commercial products for preserving clinical specimens for the diagnosis of tuberculosis. Geneva, World Health Organization. 2017. (WHO/HTM/TB/2017.19). http://www.who.int/tb/areas-of-work/laboratory/policy_statements/

Specimen referral for culture

In addition to biosafety, the two most important considerations for storing and transporting specimens for culture tests are 1) preserving the viability of the mycobacteria and 2) inhibiting the growth of contaminating flora. Considerable information is available for storing and transporting sputum specimens for culture. In contrast, little information is available on the viability of tubercle bacilli in specimens other than sputum. Bronchoalveolar lavage fluid, gastric aspirates, tissue specimens and cerebrospinal fluid should be transported to the testing laboratory immediately,

preferably on the same day as collection. Great care (i.e., storage and transport at the proper temperature, immediate transport to the laboratory and immediate testing at the laboratory) must be taken to ensure the quality and utility of invasively obtained specimens such as tissue biopsies and CSF.

Sputum specimens	
Collection and storage	<ul style="list-style-type: none"> • Minimum volume: 3–5 ml • Collect samples into a sterile leak-proof wide-mouth container • If transport is delayed by more than 1 hour, specimens should be stored at 2–8 °C • If specimens cannot be stored and transported at a 2–8 °C and if egg-based media are to be inoculated and if total of storage and transit time exceeds 3 days, cetyl pyridinium chloride (CPC) may be added according to SOP before or immediately after collection and specimens stored and transported at ambient temperature (20–30 °C). CPC recrystallizes at cool temperatures which removes its ability to protect the specimen from contamination
Packaging and transport	<ul style="list-style-type: none"> • Freshly collected specimens may be transported at ambient temperature (20–30 °C) if delivered to the testing laboratory within one hour • Refrigerated sputum specimens must be delivered to the referral laboratory within 7 days of collection, preferably within 3 days • CPC-treated specimens must be delivered to the referral laboratory within 7 days of collection • Transport in a cool box at 2–8 °C. Samples containing CPC must be transported at ambient temperature (20–30 °C)
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<p>Cetyl pyridinium bromide has been used as an alternative to CPC</p> <ul style="list-style-type: none"> • A centrifugation step is needed to remove CPC and sediments should be inoculated onto egg-based media only (as egg yolk neutralizes CPC to a certain extent) • CPC treated samples cannot be used with liquid culture systems such as MGIT and are not suitable for use in fluorescence microscopy • Products that can be used instead of CPC to preserve specimens for culture are also commercially available (e.g., OMNIgene•SPUTUM from DNA Genotek); however, a recent WHO Technical Expert Group meeting concluded that there is limited evidence that use of commercial transport products improves test performance compared to untreated specimens transported under ambient conditions for culture. The evidence from a FIND-conducted study suggested that OMNIgene•SPUTUM-treated specimens likely improves culture positivity and contamination rates for solid culture (using LJ), but the effect of OMNIgene•SPUTUM on positivity and contamination rates using automated liquid systems (MGIT) was much smaller and was inconsistent, making interpretation for MGIT difficult.^a

^a Technical Expert Group Meeting Report: Commercial products for preserving clinical specimens for the diagnosis of tuberculosis. Geneva, World Health Organization. 2017. (WHO/HTM/TB/2017.19). http://www.who.int/tb/areas-of-work/laboratory/policy_statements/

Bronchoalveolar lavage fluid	
Collection and storage	<ul style="list-style-type: none"> • Minimum volume: 3 ml for bronchial secretions and 20 ml for BAL • Collect samples into a sterile leak-proof container • If transport is delayed by more than 1 hour, specimens should be stored at 2–8 °C
Packaging and transport	<ul style="list-style-type: none"> • Samples should arrive in the testing laboratory within one day of collection, preferably on the day of collection • Transport in a cool box at 2–8 °C
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<ul style="list-style-type: none"> • Minimize time between specimen collection and testing

Gastric aspirate	
Collection and storage	<ul style="list-style-type: none"> • 5–10 ml is optimal; maximum volume is 15 ml • Collect samples into a sterile leak-proof container • If transport is delayed >1 hour, neutralize with 100 mg sodium carbonate, mix carefully and store at 2–8 °C
Packaging and transport	<ul style="list-style-type: none"> • Samples should arrive in the testing laboratory within one day of collection, preferably on the day of collection • Transport in a cool box at 2–8 °C
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<ul style="list-style-type: none"> • Even after neutralization, bacterial viability may decline rapidly • Minimize time between specimen collection and testing

Cerebrospinal fluid	
Collection and storage	<ul style="list-style-type: none"> • 10 ml is optimal; minimum volume is 2–3 ml. Smaller volumes (e.g., 1 ml) are acceptable for paediatric patients • Collect samples aseptically into a sterile leak-proof container • Store at ambient temperature (20–30 °C); do not refrigerate
Packaging and transport	<ul style="list-style-type: none"> • Samples should arrive in the testing laboratory within one day of collection, preferably on the day of collection • Transport in a cool box at 2–8 °C
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<ul style="list-style-type: none"> • Minimize time between specimen collection and testing

Tissue specimen	
Collection and storage	<ul style="list-style-type: none"> • As much as possible; add 2–3 ml sterile saline • Collect samples into a sterile leak-proof container • Preservatives and fixatives must not be used • Store at ambient temperature; do not refrigerate
Packaging and transport	<ul style="list-style-type: none"> • Samples should arrive in the testing laboratory within one day of collection, preferably on the day of collection • Transport in a cool box at 2–8 °C
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log
Remarks	<ul style="list-style-type: none"> • Minimize time between specimen collection and testing • The homogenization of tissue specimens may create infectious aerosols and requires the use of appropriate biosafety precautions

Specimen referral for drug-susceptibility testing

Phenotypic and molecular drug-susceptibility testing (DST) can be conducted directly from primary specimens (e.g., sputum specimens) or from isolates recovered by culture on solid or liquid media. Primary specimens being referred for phenotypic or molecular (except Xpert MTB/RIF, see above) DST should use the collection, storage, packaging and transportation conditions described for referring samples for culture.

Cultures (solid or liquid media)	
Collection and storage	<ul style="list-style-type: none"> • Actively growing cultures should be shipped as soon as growth is evident • If necessary, growth may be sub-cultured on fresh media or stored at 2–8 °C
Packaging and transport	<ul style="list-style-type: none"> • Samples should be promptly shipped to the testing laboratory. Viable mycobacteria are most reliably recovered from actively growing or fresh cultures • Cultures of <i>M. tuberculosis</i> bacteria should be shipped in unbreakable screw-capped tubes (preferably plastic) as primary watertight containers and packaged according to national and international regulations • Transport at ambient temperature, protect from extreme temperatures
Documentation	<ul style="list-style-type: none"> • Test requisition form for each specimen, shipment inventory log, transport log

<p>Remarks</p>	<ul style="list-style-type: none"> • Cultures of <i>M. tuberculosis</i> bacteria are considered Category A infectious substances (UN2814) and should be packaged according to the requirements for Category A substances (P620, IATA),^a particularly when transporting by air. However, for specimens being transported by ground transportation, according to the European Agreement Concerning the International Carriage of Dangerous Goods by Road (ADR),^b cultures may be classified as Category B infectious substances when the cultures are intended for diagnostic or clinical purposes • Mycobacteria remain viable on solid or liquid media at ambient temperature (20–30 °C) for weeks or months. • Petri-dish cultures and large volumes of liquid cultures must not be shipped • If glass tubes (e.g., LJ cultures) are shipped, they must be packaged to prevent breakage • For molecular DST (e.g., line-probe assays), bacteria in the specimens can be inactivated. Inactivated samples can be stored and transported at ambient temperature or at 2–8 °C. Inactivated samples may not require transport in accordance with requirements for the transport of infectious material. Commercial products (e.g., Primestore from Longhorn Vaccines and Diagnostics or Sputum DNA Collection KIT from Norgen Biotek) for inactivating bacteria for shipment for molecular DST are available; however, a recent WHO Technical Expert Group meeting concluded that there is no evidence that use of commercial transport products improves performance for molecular tests.^c
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^a Guidance on regulations for the Transport of Infectious Substances 2015–2016. Geneva, World Health Organization. 2015. (WHO/HSE/GCR/2015.2). http://www.who.int/ihr/publications/who_hse_ihr_2015.2/

^b European Agreement concerning the International Carriage of Dangerous Goods by Road. United Nations. 2017. <https://www.unece.org/trans/danger/publi/adr/adr2017/17contentse0.html>

^c Technical Expert Group Meeting Report: Commercial products for preserving clinical specimens for the diagnosis of tuberculosis. Geneva, World Health Organization. 2017. (WHO/HTM/TB/2017.19). http://www.who.int/tb/areas-of-work/laboratory/policy_statements/

Overview of specimen transport regulations, guidelines and practical guidance

Title	Language*	Year	Target audience
Transport Regulations and Guidelines			
UN Recommendations on the Transport of Dangerous Goods: Model Regulations Basis for international and national regulations addressing transport of infectious material by air, road, rail and sea http://www.unece.org/trans/danger/publi/unrec/rev19/19files_e.html	E/F/S PDF is in English only	2015	Governments and international organizations
European Agreement Concerning the International Carriage of Dangerous Goods by Road Legal framework for transportation of infectious materials by road. http://www.unece.org/fileadmin/DAM/trans/danger/publi/adr/adr2015/ADR2015e_WEB.pdf	E	2014	EU member states and partner states
WHO Guidance on Regulations for the Transport of Infectious Substances 2015–2016 Provides practical guidance for classifying, documenting, marking, labelling and packaging infectious substances to facilitate compliance with applicable international regulations for the transport of infectious substances by all modes of transport, nationally and internationally http://www.who.int/ihr/publications/who_hse_ihr_2015.2/en/ http://www.who.int/entity/ihr/e-Guide_2015_12_Mar_15.pptx	A/E/F/R/S	2015	Shippers of infectious substances
IATA dangerous goods regulations Rules and guidelines for shipping dangerous goods by air http://www.iata.org/publications/store/Pages/dgr-print-manuals.aspx	E/F/S/G/R	2017	Shippers, ground service providers and airlines
Biosafety			
WHO Laboratory Biosafety Manual – Third Edition Practical guidance on biosafety techniques for use in laboratories at all levels. Regulations for the transport of infectious substances are reflected (part IV.15) http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/	C/E/F/P/R/S	2004	Ministries of Health, laboratory managers, laboratory technicians

WHO Tuberculosis laboratory biosafety manual Describes the basic requirements for facilities and practices, which can be adapted to follow local or national regulations or as the result of a risk assessment http://www.who.int/tb/publications/2012/tb_biosafety/en	C/E/F/P/R/S	2012	TB programmes and laboratory managers, laboratory technicians
Laboratory Practical Guidance, Training, and Procedures			
GLI Mycobacteriology Laboratory Manual, 1st edition http://www.stoptb.org/wg/gli/assets/documents/gli_mycobacteriology_lab_manual_web.pdf	E	2014	TB laboratory technicians and managers
GLI Practical Guide to TB Laboratory Strengthening Section 2.2: Specimen collection, transport and registration includes specimen logs, registers and examination request forms http://www.stoptb.org/wg/gli/assets/documents/GLI_practical_guide.pdf	E	2017	TB laboratory and programme managers, MoH officials, partners
WHO Infectious Substances Shipping Training – a course for shippers classroom Modules addressing the classification, documentation, marking, labelling, packaging of infectious substances, and the preparation of shipments requiring the use of dry ice http://www.who.int/ihr/i_s_shipping_training/fr/	E/F/P/R/S/	2015	Shippers of infectious substances
GLI Training Package on Xpert MTB/RIF. Module 3: Collecting and transporting sputum specimens Modular Xpert MTB/RIF training package in PowerPoint format for country customization http://stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp	E/F/P/S	2014	TB laboratory technicians, managers, clinicians
GLI Training Package: Programme Modules for Diagnostic Network Strengthening Module 3: Plan and Establish a Sample Referral Network for TB Diagnosis http://stoptb.org/wg/gli/assets/documents/PM3%20Referral%20Network.zip	E	2017	TB programme and laboratory managers, implementation partners
GLI Standard Operating Procedure: Sample conditions and transport for culture procedure http://stoptb.org/wg/gli/assets/documents/29_specimen_condition_transport.doc	E		TB laboratory technicians and managers
FIND Specimen Collection Manual https://www.finddx.org/wp-content/uploads/2016/03/Specimen-Collection-Manual_TB-03-03_V1.0.doc	E		TB laboratory technicians, managers, clinicians

^a Language key: A (Arabic), C (Chinese), E (English), F (French), G (German), S (Spanish), P (Portuguese), R (Russian)



www.stoptb.org/wg/gli