The Union
International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

MANAGEMENT OF TUBERCULOSIS

A Guide to Essential Practice

Seventh Edition
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Riitta A. Dlodlo, Grania Brigden and Einar Heldal

with

Brian Allwood
Chen-Yuan Chiang
Paula I. Fujiwara
Stephen M. Graham
Nathalie Guillerm
Anthony D. Harries
Kobto G. Koura
Ajay M. V. Kumar
Yan Lin
Jamilah Meghji
Kevin Mortimer
Alberto Piubello
Barbara Roth
Srinath Satyanarayana
Moorine Sekadde
Ivan Solovič
Jamhoih Tonsing
Armand Van Deun

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Editor International Union Against Tuberculosis and Lung Disease (The Union)
68, Boulevard Saint Michel, 75006 Paris, France

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Available on The Union's website (theunion.org)

Preface

The world is moving towards universal health coverage. But the question we need to ask ourselves is 'Do people with presumptive and diagnosed tuberculosis, children, adolescents and adults, have equal access to good quality diagnosis, treatment and support?'

It has been estimated that almost half of the people with tuberculosis are 'missed' by health services. Several studies suggest that the half that are detected frequently receive unsatisfactory treatment and delayed care, and face various challenges caused by health service-related and other issues. Attention given to the management of tuberculous infection has also been limited.

Despite significant gains in providing tuberculosis services in recent decades, a lot remains to be done. We need multisectoral action and meaningful engagement with private health sector providers, civil society organisations, communities and other relevant stakeholders under committed national tuberculosis programme leadership.

This Guide was first published in 1986. The current, 7th edition contains a basic description of the tuberculosis disease, its diagnosis, prevention and treatment, as well as the co-management of tuberculosis and comorbidities that persons with tuberculosis are susceptible to. How to organise tuberculosis services and to monitor the tuberculosis situation, and the results of various interventions are also discussed.

The Union hopes this Guide will help those caring for individuals with tuberculosis in low- and middle-income countries, including remote locations and settings with severely limited resources, so that the vision of universal health coverage becomes a reality.

Authorship

International Union Against Tuberculosis and Lung Disease (The Union), Paris, France *(Riitta A. Dlodlo, Grania Brigden, Einar Heldal, Chen-Yuan Chiang, Paula I. Fujiwara, Stephen M. Graham, Nathalie Guillerm, Anthony D. Harries, Kobto G. Koura, Ajay M. V. Kumar, Yan Lin, Kevin Mortimer, Alberto Piubello, Srinath Satyanarayana, Moorine Sekadde, Jamhoih Tonsing, Armand Van Deun)*; Catholic University Ruzomberok, Slovakia *(Ivan Solovič)*; Centre for International Child Health, University of Melbourne, Melbourne, Australia *(Stephen M. Graham)*; Liverpool School of Tropical Medicine, Liverpool, UK *(Jamilah Meghji, Kevin Mortimer)*; London School of Hygiene & Tropical Medicine, London, UK *(Anthony D. Harries)*; National Tuberculosis and Leprosy Programme, Uganda *(Moorine Sekadde)*; Stellenbosch University and Tygerberg Hospital, South Africa *(Brian Allwood)*; Yenepoya Medical College, Yenepoya (deemed University), Mangaluru, India *(Ajay M. V. Kumar)*; independent consultants *(Einar Heldal, Oslo, Norway and Barbara Roth, Melbourne, Australia)*.

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The Union also gratefully acknowledges the contribution of Ms Irène Roy to the production of this Guide.

Abbreviations and acronyms

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ARV	antiretroviral
BCG	bacillus Calmette-Guérin
BMU	basic management unit
CAD	computer aided detection
CPT	cotrimoxazole preventive therapy
DNA PCR	DNA polymerase chain reaction
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
DTG	dolutegravir
FEFO	first expire, first out (approach in stock management)
HIV	human immunodeficiency virus
HLM	(United Nations) high level meeting on tuberculosis
IGRA	interferon-gamma release assay
LF-LAM	lateral flow lipoarabinomannan (antigen test)
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
NTP	national tuberculosis programme
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
TB-LAMP	loop-mediated isothermal amplification assay
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1 Introduction

Tuberculosis (TB) is the world's deadliest infectious disease, with over 95% of deaths occurring in low- and middle-income countries. Tuberculosis mostly affects young adults in their most productive years, but all age groups are at risk.

Tuberculosis care has gained considerable political attention since the last edition of this Guide published in 2010, with a number of high-level political events held on tuberculosis. Tuberculosis was included in the 2017 G20 Leaders' Declaration as part of the G20 fight against antimicrobial resistance, the BRICS nations agreed to promote research and development of innovative medical products, including tuberculosis drugs at the 2017 Health Ministers Meeting, and 2017 ended with the first Global Ministerial Conference on 'Ending TB in the Sustainable Development Era: A Multi-Sectoral Response' held in Moscow. In 2018, the first-ever United Nations High-Level Meeting (HLM) on Ending Tuberculosis was held in New York, which led to a historic Political Declaration listing specific, measurable milestones to achieve by 2022. Tuberculosis-related targets included:

- Successfully diagnose and treat 40 million people with tuberculosis by 2022.
- Successfully diagnose and treat 3.5 million children with tuberculosis by 2022.
- Successfully diagnose and treat 1.5 million people with drug-resistant tuberculosis, including 115,000 children with drug-resistant tuberculosis, by 2022.
- Provide preventive treatment to at least 30 million people, including 4 million children under five years of age, 20 million other household contacts of persons affected by tuberculosis and 6 million people living with HIV by 2022.

The International Union Against Tuberculosis and Lung Disease (The Union) is the oldest international non-governmental organisation to address public health issues. At their first post-war conference held in Paris in 1920, 31 national lung associations came together to found the International Union Against Tuberculosis (IUAT). In the hundred years since its foundation, The Union has gained immense experience in collaborating with partners in providing care for millions of people with tuberculosis in some of the poorest countries in the world through National Tuberculosis Programmes (NTPs).

This edition of the Guide is based on this experience and outlines the essentials of tuberculosis practice and the best standards of care currently available to help achieve the high-level targets of the UN HLM. This Guide recommends a person-centred approach to ensure that the individual's care and needs, and not just programme priorities, are taken into account. It is important to fight against the stigma and injustices that people with tuberculosis face: tuberculosis is curable and there is no justification for discrimination against them. Community participation and engagement play a crucial role in addressing stigma, as well as in finding persons with or at risk of tuberculosis, and should therefore be encouraged.

Whilst anyone can acquire tuberculosis, this is especially a problem among 'high-risk' groups. These groups (for example, persons incarcerated in detention centres; those with insecure housing; undocumented migrants; people who work closely with cattle, the source of *Mycobacterium bovis*; and other marginalised groups) are often hard to reach with the usual public health services. Services for these groups may need to be adapted to address the broader context of their lives and circumstances, but it is important to ensure that at-risk populations have access to quality tuberculosis care. A quality tuberculosis service should also screen for individuals with comorbidities, such as HIV, diabetes mellitus, smoking and mental health disorders, which increase the risk of developing tuberculosis and are associated with poorer outcomes.

In many countries, non-governmental organisations (NGOs) often collaborate with government-run tuberculosis services, working in difficult conditions in remote areas, where they provide the only medical care available. NGO activities should nevertheless always be undertaken in coordination with the government programme. This especially applies to people with multidrug-resistant tuberculosis, for whom services should be provided under the direction of the NTP, and not as projects run by NGOs or private specialists working in isolation.

This edition of the Guide has been extensively updated, and includes new information on the management of persons with tuberculous infection, bacteriological diagnosis of tuberculosis, co-management of individuals with tuberculosis and certain comorbidities, treatment of drug-resistant tuberculosis, active use of NTP data by service providers at all levels of the health services and the use of operational research to strengthen the quality of tuberculosis care. Recording and reporting forms have been included for country adaptation. For the first time, Supplementary Materials, including samples of data analysis and support supervision checklists with summary tuberculosis data tables, are available on The Union's website (theunion.org). The question-answer format of the previous Guide has been retained and attention has been paid to writing in plain language.

In countries with a high burden of tuberculosis, any practitioner who provides health care should be aware of this disease and tuberculosis services should be an integral part of all health care services, particularly as universal health care is further developed. This Guide is to help all health care practitioners, including nurses and paramedical staff, and persons responsible for tuberculosis care in health facilities, basic management units and provincial and other referral centres. It can also be used by others interested in finding out more about the disease. A well-functioning NTP is key to a country's response to tuberculosis. This Guide will provide NTPs, and all those who work alongside them, with basic information about tuberculosis management and services. It is hoped that the information and recommendations in this Guide can be adapted to local requirements and provided in the local language to ensure that the essentials of tuberculosis care are practised. NTPs need to support and supervise practitioners and coordinators to ensure that they and their teams have accurate information and skills to implement quality tuberculosis care measures, as these are key to curing millions of people of ill-health, reducing the impact of tuberculosis in the community, and thereby, contributing to the reduction of poverty among those affected.

Although new techniques will play a vital role in eliminating tuberculosis, much can be done with the tools and knowledge that we already possess. We hope that this Guide will provide guidance to all those involved in tuberculosis care and prevention, including communities, by offering quality comprehensive care to all those who need it so that tuberculosis can cease to be the world's leading infectious killer disease.

2 Tuberculosis

2.1 What do we know about tuberculosis?

Persons with tuberculosis can present themselves at any health facility. In settings with a high tuberculosis burden, it is important that all health care workers, including community health workers, are informed about the basics of tuberculosis. They must be able to recognise symptoms and signs suggestive of tuberculosis, identify persons with presumptive tuberculosis, understand how tuberculosis is diagnosed and start appropriate treatment promptly.

2.1.1 What is tuberculosis?

Tuberculosis is an infectious disease, caused in most cases by a micro-organism called *Mycobacterium tuberculosis*.* The micro-organisms usually enter the body by inhalation through the lungs. They spread from their initial location in the lungs to other parts of the body via the blood stream, the lymphatic system, the airways or by direct extension to other organs.

- *Pulmonary tuberculosis*, i.e., tuberculosis of the lungs, is the most frequent form of the disease, and over 80% of cases belong to this type. This form of tuberculosis can be infectious.
- *Extra-pulmonary tuberculosis*, i.e., tuberculosis affecting organs other than the lungs, most frequently the pleura, lymph nodes, spine and other bones and joints, the genitourinary tract, the nervous system and abdomen. Tuberculosis may affect any organ and may even become disseminated. This type of tuberculosis is usually not infectious.

* The bacterium that causes tuberculosis, referred to as micro-organism in this Guide.

2.1.2 How does tuberculosis develop?

Tuberculosis affects the human body in two main stages. The first stage occurs when an individual is exposed to micro-organisms from a person with an infectious type of tuberculosis and becomes infected *(tuberculous infection)*.† In the second stage, the person with tuberculous infection falls ill and manifests various symptoms and signs that indicates that s/he has developed the disease *(tuberculosis disease)*.

How do tuberculosis micro-organisms spread?

The likelihood that a person with tuberculosis will infect another person is determined by the number of micro-organisms present in the lungs and their ability to spread into the surrounding air. Persons with pulmonary tuberculosis in whom the micro-organisms are so numerous as to be detectable under a microscope when sputum specimens are examined *(smear-positive tuberculosis)* are the most infectious cases. Those with micro-organisms that cannot be detected directly under the microscope *(smear-negative tuberculosis)* are less infectious, and the severity of their disease is usually milder than that of persons with smear-positive disease. With the increasing use of rapid molecular testing, it is not as easy to gauge the person's infectiousness. It should be assumed that all individuals with pulmonary tuberculosis have the potential to spread micro-organisms; treatment should therefore be started promptly and appropriate contact investigations should be initiated. Persons with *extra-pulmonary tuberculosis* are not usually infectious, unless they have pulmonary tuberculosis as well.

Persons with infectious tuberculosis expel micro-organisms into the air in tiny droplets when talking, coughing, laughing or sneezing. These small droplets dry rapidly, and become 'droplet nuclei' carrying the micro-organisms that may remain suspended in the air in an enclosed space for several hours. Any person entering the room may inhale these micro-organisms. If the micro-organisms establish colonies in the lungs of the person who inhales them and begin to multiply, the person is said to have acquired *tuberculous infection*. Exposure to the micro-organisms is greatest among those in close and prolonged contact with an infectious case (that is, those living in the same household with a smear-positive patient).

† Also referred to as latent tuberculous infection (LTBI).

Tuberculosis micro-organisms are rapidly destroyed when exposed to sunlight and their concentration in the air is reduced by good ventilation. Except in the event of close and prolonged contact with an infectious case of tuberculosis, the chance of getting infected from a single contact with a person who has infectious tuberculosis is very small.

Individuals who have tuberculous infection are well, and do not have any symptoms or evidence of illness due to the infection. The infection can be detected using a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) only if there is an immune system response to the micro-organisms (it is this response that is detected by the test; see discussion on TST and IGRAs in Chapter 4). Text Box 2.1 gives a comparison of the major characteristics of individuals with tuberculous infection and those with tuberculosis disease.

Text Box 2.1: Characteristics of individuals with tuberculous infection and those with tuberculosis disease*

Characteristic	*Tuberculous infection*	*Tuberculosis disease*
Symptoms	None	Most present with cough, weight loss, fever, night sweats
Tuberculin skin test	Positive	Usually positive
Interferon-gamma release assay	Positive	Usually positive
Sputum bacteriology	Negative	Usually positive
Chest radiograph	Normal	Usually abnormal
Infectiousness	No	Often infectious (before treatment)
Tuberculosis case	No	Yes
Preferred treatment	Preventive treatment	Tuberculosis treatment

* Adapted from reference[1]

What happens after infection?

The majority of persons (estimated at 90%) with tuberculous infection will not become ill with tuberculosis disease. Of those who do develop tuberculosis disease, most fall ill within the first 2 years of the infection, especially if their immune defence mechanisms are compromised. Having had tuberculosis before does not protect against future tuberculous infection, and patients who have been cured may be re-infected.

Text Box 2.2: Risk factors for transition from tuberculous infection to tuberculosis disease

- Being a child contact less than 5 years of age
- HIV infection
- Diabetes mellitus
- Excessive alcohol and substance use, including tobacco use
- Low body weight or malnutrition
- Silicosis or other occupational lung diseases
- Cancer and immune-modulation treatment
- Migration from regions with high rates of tuberculosis

What factors and other comorbidities increase the risk of tuberculosis?

Several factors and other diseases increase the risk of developing tuberculosis disease. Anything that affects the immune defence mechanism of the body will increase the risk of developing tuberculosis (Text Box 2.2). Tuberculosis comorbidities, such as HIV infection, diabetes mellitus, tobacco smoking, alcohol and drug use, and mental health disorders that significantly increase the risk of developing tuberculosis are described in Chapter 5. Other conditions that affect the immune defence mechanisms, such as malnutrition, cancers and immune-modulation treatment also increase the risk of developing tuberculosis.

2.1.3 What is drug-resistant tuberculosis and how does it develop?

Large populations of tuberculosis micro-organisms always contain some micro-organisms that have spontaneously mutated to become resistant to a drug. Thus, if a person is treated with a single drug when they have a large population of micro-organisms, the drug kills those micro-organisms that are susceptible to the drug but allows those that are spontaneously resistant to the drug to multiply. If the micro-organisms in a person are resistant to all but one of the drugs s/he receives, the treatment has the same effect as a single-drug treatment regimen. Drug resistance is of clinical importance when the person has a disease caused by micro-organisms that are resistant to the drugs essential for treatment.

For practical purposes, drug resistance is divided into two categories: resistance in individuals who have *not been previously treated for tuberculosis or who received treatment for less than one month (new patients)* and resistance in people who have *previously been treated for tuberculosis for one or more months (previously treated patients)*. Although the risk of acquiring drug-resistant tuberculosis is higher in people who have received treatment before, it can also occur in those who have never been treated for tuberculosis but have been exposed to a person with a drug-resistant strain of tuberculosis.

Resistance to at least the two most important drugs, isoniazid and rifampicin, is termed *multidrug-resistant tuberculosis* (MDR-TB). *Extensively drug-resistant tuberculosis* (XDR-TB), defined as MDR-TB plus resistance to any fluoroquinolone and any of the second-line injectable drugs (amikacin, kanamycin or capreomycin), has emerged and is more difficult to treat. Management of persons with drug-resistant tuberculosis is discussed in section 3.2.5. More detailed discussion of both definitions and treatment is available in the *Field Guide for the Management of Drug-Resistant Tuberculosis*.[2]

2.1.4 What is the significance of drug resistance for a tuberculosis programme?

The steady increase in the different types of drug-resistant tuberculosis in many parts of the world is a matter of great concern, particularly as treatment outcomes are frequently unfavourable. The cost of treatment and of treatment support, including the provision of direct observation of second-line drug intake and of support for periods of up to 24 months, is high, and adverse drug events are frequent. The first priority should therefore always be to ensure an effective tuberculosis programme so that resistance is prevented.

NTPs should set up an effective system for identifying persons with multidrug-resistant tuberculosis, or at least rifampicin-resistant tuberculosis, and provide these persons with appropriate treatment and patient-centred care to ensure cure. This is essential to reduce further spread of resistant strains.

2.2 How is tuberculosis diagnosed?

Diagnosis is defined as 'the process of determining health status and the factors responsible for producing it'.[3] In this instance, it refers to the process by which a health care worker decides whether a person has tuberculosis.

2.2.1 When should a person be evaluated for tuberculosis?

The most frequent symptoms of pulmonary tuberculosis are as follows:

- Cough for 2 weeks or more: every person presenting with this symptom should be designated a *person with presumptive tuberculosis;*
- Sputum production, which may be blood-stained (haemoptysis), shortness of breath and chest pain;
- Loss of appetite and loss of weight, a general feeling of illness (malaise) and tiredness (fatigue), night sweats and fever.

Any person presenting with any of these symptoms should be presumed to have tuberculosis. If s/he is, or was, in contact with a person with infectious tuberculosis, such a person is even more likely to have tuberculosis.

In case of extra-pulmonary tuberculosis, symptoms will depend on the organ involved. Chest pain from tuberculous pleurisy, enlarged lymph nodes and sharp angular deformity of the spine are some of the presenting symptoms or signs of extra-pulmonary tuberculosis.

2.2.2 Among whom is tuberculosis most likely to be found?

Tuberculosis is most frequently found in the following populations:

- Persons who present themselves on their own initiative at a health facility with symptoms and/or signs suggesting tuberculosis;
- Those (especially children and young adults) living in the same household as people with infectious forms of tuberculosis, that is, pulmonary tuberculosis, and especially, smear-positive pulmonary tuberculosis;
- Those with risk factors for tuberculosis, such as malnutrition, HIV infection, diabetes mellitus, silicosis and tobacco smoking;
- Those with abnormalities on chest radiograph.

Tuberculosis is likely to be detected most efficiently where health care workers, community health workers and community members are *highly aware* of the symptoms and/or signs suggestive of tuberculosis. Currently, about 40% of people with tuberculosis are not diagnosed or notified to NTPs. The numbers of these 'missing' persons need to be rapidly reduced if we are to end tuberculosis by 2030. Some of these people can be found among the so called 'key populations' that include vulnerable and 'at-risk' populations. It is essential that tuberculosis services are extended to prison inmates, slum dwellers, ethnic minorities, refugees and people living in remote or marginalised communities, among others.

2.2.3 How is a diagnosis of tuberculosis confirmed?

A diagnosis may be proposed by the health care worker after a review of the symptoms and signs of tuberculosis disease based on a clinical history and physical examination of the person. A variety of tests are conducted to confirm the diagnosis.

What is the value of bacteriology?

Each individual being evaluated for tuberculosis needs to undergo rapid molecular testing and/or microscopy of a sputum specimen before starting treatment.

Some rapid molecular tests (for example, Xpert® MTB/RIF; Cepheid, Sunnyvale, CA, USA) can detect considerably more bacteriologically positive cases. Even greater numbers of tuberculosis-positive individuals can be detected using culture. Rapid molecular tests have also the great advantage of being reliable diagnostic tools for rifampicin-resistant tuberculosis. Of all the diagnostic tools, culture is the most accurate. However, it is not practical for diagnosis or treatment monitoring because of the long turnaround time and expertise required. Culture helps establish a firm diagnosis of *recurrent tuberculosis*, as it does not yield false-positive results due to the late excretion of dead TB bacilli, which may constitute a substantial part of positive follow-up results on microscopy and on Xpert, which can produce positive results even 5–6 years later and is thus less suitable for diagnosing relapse.

For smear microscopy, the sputum is spread on a slide and then stained using Ziehl-Neelsen or Auramine fluorescence acid-fast staining techniques. If acid-fast bacilli (AFB) are detected, the person is said to have AFB smear-positive tuberculosis. Smear microscopy can only be used to detect persons with relatively many bacilli in their sputum, who are therefore also the most infectious and have the worst prognosis. In high tuberculosis prevalence settings, AFB microscopy is also highly specific for the presence of TB bacteria, both alive and dead.

The loop-mediated isothermal amplification assay (TB-LAMP®; Eiken, Tokyo, Japan), another point-of-care test, can be performed in approximately 1 hour and read with the naked eye under ultraviolet light. Its use is recommended for the diagnosis of tuberculosis in adults instead of or as a follow-on test to smear

microscopy. It is able to detect *Mycobacterium tuberculosis* complex but does not indicate resistance to any tuberculosis drug. Its sensitivity is similar to that of Xpert. There is limited evidence of its use among people living with HIV.

The lateral flow lipoarabinomannan (LF-LAM; Alere Determine™ TB LAM Ag, Abbott Diagnostics, Lake Forest, Illinois, USA) assay, an inexpensive, urine-based test, is recommended for people living with HIV who are severely immunocompromised (CD4 cell count ≤100 cells/mm^3) and are hospitalised. The use of this test has been shown to reduce deaths among these individuals.

Line-probe assays (LPA; for example, the Hain GenoType MTBDR*plus* V1 and V2; Hain LifeScience, Nehren, Germany; and Nipro NTM+MDRTB Detection Kit 2; Nipro Corporation, Osaka, Japan) are less rapid molecular tests that also require considerably more laboratory infrastructure and competence. They are used to detect drug-resistant tuberculosis.

Whenever tuberculosis is suspected, the test of choice is any rapid molecular test, and at least one sample should be collected for the purpose. When rapid molecular tests are not available, at least two sputum specimens should be collected for microscopy.

First specimen. A sputum specimen is collected on the spot at the time of the person's first visit; this specimen is obtained in a well-ventilated area, preferably in the open. After clear instructions by a health care worker, the individual is asked to clear his/her throat, take 2–3 deep breaths and expectorate into a sputum container. The sputum specimen is then brought to the health care worker who checks that the volume (about 5 ml) and quality (thick mucopurulent secretions and not saliva) are satisfactory. The health care worker should ensure that the lid of the sputum container is tightly closed, and a sputum request form is correctly and completely filled out. The specimen should then be sent to the laboratory or its transportation arranged. The health care worker should also explain how and when the person will be informed of the test result.

Second specimen. A morning sputum specimen is preferred for this due to its better quality and the higher number of AFB present. The person is given a sputum container for collection of the first sputum upon waking the following day. However, this requires the person to visit the clinic the following day to return the container. If this is not feasible, the morning specimen may be replaced by a second spot sputum produced 1–2 hours after the first.

A single, positive rapid molecular test or AFB microscopy (or culture) result is sufficient to diagnose the person as bacteriologically positive and start treatment. If a specimen is positive and the person fails to return, s/he should be followed up by telephone (many patients or their family members have cellular phones) or visited at home and started on treatment to prevent deterioration of the person's condition and further transmission of tuberculosis micro-organisms.

Persons whose sputum remains negative on all tests but who are thought to have tuberculosis by the treating clinician should be reviewed by a Medical Officer prior to commencing treatment. The person should undergo chest radiography if this is available. If the chest radiograph indicates shadows in the lung fields consistent with pulmonary disease, a course of broad-spectrum antibiotics (without anti-tuberculosis activity) may be prescribed. If the person remains ill after completion of the course of antibiotics, they may be asked to undergo repeat rapid molecular testing or two sputum smear examinations. If test results remain negative, the Medical Officer may choose to treat the person for tuberculosis and record the person as a patient with bacteriologically negative (clinically diagnosed) pulmonary tuberculosis. Other conditions (lung malignancy, bronchiectasis, congestive cardiac failure, etc.) that could explain the person's continued symptoms should be eliminated first.

Specimens other than sputum (for example, bronchoalveolar lavage, cerebrospinal fluid, lymph node aspirate, etc.) may also be subjected to rapid molecular testing for the diagnosis of extra-pulmonary tuberculosis. Results are likely to be highly variable, particularly as regards test sensitivity. High sensitivity is often reported from testing of adenopathy, tissues and fluid from bones and joints. For cerebrospinal fluid, sensitivity is approximately 50% (better than many other tests, and much faster than culture, thus the test may be life-saving for these patients). Fluids such as pleural and peritoneal effusions have a very low yield on molecular tests.

2.2.4 How do we know if a person has drug-resistant tuberculosis?

Resistance to one or more of the core drugs on which the tuberculosis treatment regimen is based will most often lead to treatment failure or relapse if the person survives. Resistance should be suspected whenever treatment response is unsatisfactory: non-conversion of sputum AFB after 2–3 months or reversion to positive towards the end of treatment or after successful treatment, usually accompanied by clinical deterioration or lack of improvement.

The core drug in drug-susceptible regimens is *rifampicin*, and resistance to rifampicin is often found with resistance to isoniazid (that is, multidrug-resistant tuberculosis). In persons with multidrug-resistant tuberculosis, first-line treatment outcome is no different from the natural course of tuberculosis without treatment. This means that it is important that rifampicin resistance is detected as early as possible and ideally, at the time the person is tested for presumptive tuberculosis. This is now possible, and rifampicin resistance can be diagnosed rapidly and accurately using molecular methods, such as Xpert and LPAs, which are now recommended by the World Health Organization for routine use by NTPs. LPAs can also be used for detecting resistance to isoniazid, fluoroquinolone and second-line injectables. Culture-based techniques, such as the proportion method on Löwenstein-Jensen medium or automated liquid systems, can be used to test for a greater number of drugs, but in practice they are less suitable because of the delayed turnaround and very high demands on infrastructure and biosafety. Overall, the specificity of all these tests in skilled hands is almost 100%, meaning that there are virtually no false-positive results. In case of molecular tests, this is true even when the bacilli are dead. However, all techniques miss some resistance. For example, the rapid diagnosis of rifampicin resistance using molecular techniques is not entirely reliable. It is thus highly recommended to rely on any positive result in case of discordance between tests. To exclude clerical errors and incorrectly identified specimens, an unexpected rifampicin-resistant result should be confirmed by repeating the test using a second specimen.

Isoniazid resistance occurs along a spectrum, and LPAs can help detect 'high-level' resistance that is associated with mutations in the *kat*G or in the *inh*A promoter areas. Those without these mutations may continue to respond to isoniazid at higher doses. People who are receiving treatment for isoniazid-resistant tuberculosis should be retested for rifampicin after the initial months of treatment to ensure that they have not progressed to multidrug-resistant tuberculosis (see section 3.2.5).

2.2.5 Is X-ray useful?

Diagnosis using chest radiography in persons with suspected tuberculosis presents a challenge. Abnormalities identified on chest radiography may be due to tuberculosis or to a variety of other conditions, and radiographic patterns are not specific for tuberculosis. Some individuals who have previously had tuberculosis that is now cured (and who therefore do not require treatment) may have radiography results that resemble tuberculosis requiring treatment. Chest radiographs may be helpful in persons who are not bacteriologically confirmed, but these can only be read reliably by an experienced Medical Officer.

With increasing access to and decreasing cost, digital X-rays are a potentially important diagnostic tool for tuberculosis. Computer-aided detection (CAD) software capable of analysing digital images and scoring persons with presumptive tuberculosis for likelihood of disease is available. Individuals scored as having probable tuberculosis could then be asked to undergo sputum examinations.

2.2.6 What about the tuberculin skin test and interferon-gamma release assays?

The tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) should be used in the diagnosis of *tuberculous infection* rather than tuberculosis disease, as these do not distinguish between infection and disease.

2.2.7 How is tuberculosis diagnosed in children?

Most children with tuberculosis, particularly those under 5 years of age, are not able to provide sputum specimens and may be bacteriologically negative. Tuberculosis is diagnosed based on a careful assessment of clinical and contact history. Diagnosis is most challenging in those at greatest risk of poor outcomes: infants and young children with severe disease, children living with HIV or those with multidrug-resistant tuberculosis. Prompt diagnosis and treatment of serious forms of tuberculosis, such as disseminated tuberculosis, tuberculous meningitis and spinal tuberculosis, and high coverage of BCG vaccination are required if death and disability are to be avoided. More information on this is available in *The Union's Desk Guide for Diagnosis and Management of TB in Children*.[4]

Children tend to have mild forms of tuberculosis and do well on treatment. They can be managed as outpatients.

Text Box 2.3: Steps to be followed when assessing children with presumptive tuberculosis

- Ask about cough that has not been improving, especially if persistent (for longer than 2 weeks).
- Check and record weight: is there any loss or poor weight gain or malnutrition? It is important for the health care worker to review the weight-for-age recordings in the child's health card.
- Ask about fever, reduced appetite and playfulness.
- Ask about a history of close and recent contact with a known or presumptive case of tuberculosis. It is important to find out whether the index case was smear- or Xpert-positive and whether they had drug-susceptible or drug-resistant tuberculosis.
- Collect a sputum specimen for bacteriological confirmation, especially in older children and adolescents. Consider gastric aspiration or sputum induction for those unable to provide a sample.
- Collect other specimens, depending on the suspected location of tuberculosis: chest radiograph for possible pulmonary or pleural tuberculosis (see *Diagnostic Atlas of Intrathoracic Tuberculosis in Children*[5] for more information), fine-needle aspiration from lymph nodes or lumbar puncture for cerebrospinal fluid, unless there are signs of raised intracranial pressure.
- Determine HIV status.

All close (household) contacts, particularly children, of especially smear-positive index cases, should be carefully evaluated in order to decide if tuberculosis disease is present, and then treated if diagnosed. Contacts without evidence of tuberculosis (disease) should be offered preventive treatment for tuberculous infection (see Chapter 4).

2.2.8 Who should be considered to be a tuberculosis case?

Any person diagnosed with tuberculosis should be recorded as a case. Those who have tuberculosis micro-organisms or DNA detected by laboratory testing should be recorded as *bacteriologically confirmed*. All others should be recorded as *clinically diagnosed* cases. Both categories can be subdivided into *pulmonary* and *extra-pulmonary* cases according to disease site. Once diagnosed, all cases should be *recorded* in the tuberculosis register and *evaluated* with all other cases, irrespective of whether or not they receive tuberculosis treatment. This includes all persons with tuberculosis who do not return after sputum specimen collection and who cannot be traced, and those who die before the start of treatment.

3 Tuberculosis treatment

Provided the diagnosis of tuberculosis is made at an early stage of the disease and the person is not seriously ill (either from tuberculosis or any other disease), they can be cured. To achieve cure, the person with tuberculosis needs to be treated with the drugs that they are susceptible to and for the right duration. People with drug-resistant tuberculosis may be more difficult to cure because current second-line drugs are less effective than isoniazid and rifampicin.

3.1 What are the principles of tuberculosis treatment?

What is the basis of treatment?

Tuberculosis drugs are the most important component of tuberculosis treatment. Adequate treatment is one of the most efficient means of preventing the spread of tuberculosis micro-organisms. The current requirements for adequate treatment are an appropriate *combination* of at least three effective tuberculosis drugs, to not only kill the micro-organism but also protect against the development of resistance. These should be prescribed in the correct *dosage*, taken *regularly* by the person with tuberculosis for a *sufficient period* of time to prevent relapse of the disease after completion of treatment.

Treatment must be offered *free of charge* to every person with a diagnosis of tuberculosis.

What is the role of person-centred care in tuberculosis treatment?

Person-centred (or patient-centred) care is the shared management of an illness by the person and health care workers. Studies have shown that this results in increased adherence to treatment of chronic conditions and reduced ill-health. It is based on *communication* and *partnership* between the person who is ill and service providers. Tuberculosis treatment is prolonged and persons with tuberculosis can benefit greatly from a person-centred approach to care. They need support and information about the nature of the disease and its treatment, as well as encouragement to complete treatment and achieve cure.

The person with tuberculosis and, if possible, at least one member of their close social network in whom they have confidence, should be provided with answers to the questions listed in Text Box 3.1.

Text Box 3.1: Basic information to be provided to all persons with tuberculosis

- What is tuberculosis?
- What are tuberculosis risk factors?
- What tests are available to find out their presence?
- How does a person get tuberculosis?
- How is tuberculosis treated?
- Can tuberculosis be cured?
- Is treatment free of charge?
- What drugs are used and for how long?
- The treatment is long – what support is available?
- How is response to treatment followed up?
- What are the possible adverse effects of tuberculosis drugs?
- What should be done if adverse effects occur?
- When should the patient contact the treatment provider?
- What happens when tuberculosis treatment has been completed?

If people with tuberculosis understand the disease and its treatment, information is likely to be passed on to the community and, as a result, the community learns more about the disease. Other individuals with tuberculosis may be encouraged to come forward to seek diagnosis and treatment.

Besides helping the person with tuberculosis to understand key aspects of the disease, it is important that the health care worker has a clear understanding of the problems the person may face in taking the treatment and attending the clinic regularly. These problems may be psychosocial and linked to how the person and the community view tuberculosis. They may also be linked to difficulties in accessing care, for example, the cost of transport, the distance to be walked or inconvenient clinic opening hours. All problems should be examined, and solutions to overcome these should be found together by the person with tuberculosis, the designated treatment supporter and the health care worker.

What is directly observed treatment in tuberculosis care?

The regimens proposed in this Guide will cure most persons with tuberculosis without promoting drug resistance. However, to achieve this, it is vital that the person takes the *total quantity of drugs* prescribed without missing a dose. This requires a person-centred approach to care, as explained above, and continuous support. It is important that there is consensus between the patient and the supporter/observer as to the most convenient way to provide this support during treatment. Direct observation of medication intake, preferably in fixed-dose combinations, can be done by health care workers or trained community health care workers. New technologies, such as video-observed therapy or other recommended digital adherence tools, can also be considered. In general, family members are not recommended as treatment observers, except in case of children with tuberculosis. Treatment should be provided to people as outpatients, unless hospital admission is clinically indicated.

When the person has completed the treatment for the duration prescribed, the drugs should be discontinued. Additional treatment is unnecessary if all the drugs prescribed have been taken and the person is well. Although it is distinctly unusual for a person to relapse after adequate treatment, they should be encouraged to come in for re-examination if symptoms suggestive of tuberculosis recur.

When should tuberculosis treatment be started?

Treatment should be started as soon as possible after bacteriological confirmation of the disease is received. Persons with negative bacteriological results need to be referred to an experienced Medical Officer for further assessment as explained in section 2.2.3.

What are the phases of treatment?

Treatment of drug-susceptible tuberculosis comprises two phases. An *initial 2-month intensive* phase of treatment consisting of the combination of drugs recommended in this Guide is effective in eliminating most of the micro-organisms and in minimising the effect of the small number of micro-organisms that become resistant to the drugs due to spontaneous mutations. The role of the intensive phase is to reduce the risk of treatment failure.

The *continuation* phase is important to ensure that the person is permanently cured and does not relapse after completion of treatment. The continuation phase does not require as many drugs as does the intensive phase, but the continuation phase should cover a sufficient period of time, usually 4 months, to ensure that the person is permanently cured.

In order to treat drug-resistant tuberculosis, some regimens require an intensive phase and a continuation phase, but these are of different durations (see section 3.2.5).

What if the person has been treated previously?

Before treatment initiation, it is essential to obtain a comprehensive clinical history of the person with tuberculosis to determine whether or not they have been previously treated for tuberculosis and the duration of the treatment received. If the person possesses a *Tuberculosis Patient Identification Card* for their previous treatment, it should contain the previous registration number, type of tuberculosis and date of starting tuberculosis treatment.

Any person who has previously been treated for *one month or longer* is at risk of having micro-organisms resistant to one or more drugs. Investigations should be carried out to assess whether they have resistance to rifampicin. The results of these tests should guide the choice of the suitable treatment regimen for these persons.

3.2 How is tuberculosis treated?

Tuberculosis is treated with antibiotics. The most important drugs for the treatment of drug-susceptible tuberculosis are isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). These are available in fixed-dose combinations that may contain two, three or four tuberculosis drugs, as follows:

- Rifampicin with isoniazid (RH);
- Rifampicin with isoniazid and pyrazinamide (RHZ);
- Rifampicin with isoniazid and ethambutol (RHE);
- Rifampicin with isoniazid, pyrazinamide and ethambutol (RHZE).

Fixed-dose combinations are preferred because they reduce the number of pills to be taken each day. It is very important to check the recorded expiry date for the drugs and to manage the drugs according to the first expire-first out (FEFO) approach (see section 6.5.4). The use of rifampicin for conditions other than mycobacterial diseases should be restricted to appropriate indications to prevent the development of resistance in the community. To prevent the emergence of tuberculosis drug resistance, tuberculosis drugs should be made available only through NTP mechanisms.

3.2.1 What formulations do tuberculosis drugs come in?

The recommended dosage for each tuberculosis drug, which is calculated per kilogram of body weight, has been internationally agreed (Table 3.1).

This Guide recommends that only a limited variety of formulations for each drug be made available. This simplifies the supply management of the drugs, enhances safety in prescription and allows the correct dosage to be administered in the following formulations usually recommended for treatment of adults: {RH} 150 mg/75 mg; {RHZE} 150 mg/75 mg/400 mg/275 mg; Z 400 mg; E 400 mg.

Table 3.1: Tuberculosis drug doses for daily administration in children (<25 kg) and adults

Drug	*Daily dose in children in mg/kg (range)*	*Daily dose in adults in mg/kg (range)*
Isoniazid	10 (7–15)	5 (4–6)
Rifampicin	15 (10–20)	10 (8–12)
Pyrazinamide	35 (30–40)	25 (20–30)
Ethambutol	20 (15–25)	20 (15–25)

3.2.2 How to choose a tuberculosis treatment regimen?

Tuberculosis treatment has to be based on a combination of drugs (regimen) that cures most people with tuberculosis and reduces the risk of creating difficult to treat or incurable (drug-resistant) disease. People with drug-resistant tuberculosis are at risk of death and of inadvertently transmitting resistant micro-organisms to close contacts and the community at large. Resistance to one drug may lead to the development of resistance to any other drug when the latter is administered as the sole companion drug to a drug to which the micro-organism is already resistant.

The choice of an appropriate treatment regimen should ideally be determined based on the person's drug resistance profile. As explained earlier in this Guide, at the time of treatment initiation, all persons with tuberculosis should undergo drug susceptibility testing to exclude at least rifampicin resistance. If this is not possible, rapid molecular testing should be offered to individuals who have been previously treated to rapidly identify rifampicin resistance. Where rapid molecular testing is not available, history of previous treatment or contact with persons with known drug-resistant tuberculosis should be used to inform the choice of the regimen. If there is no history of contact with persons with drug-resistant tuberculosis or of previous treatment, the standard regimen for drug-susceptible tuberculosis can be used.

Treatment follows a sequence or cascade of regimens: at every stage, the regimen selected offers the greatest chance of cure in a person with an unsuccessful outcome on a previous regimen. Drug composition should also be chosen in such a way that the simplest, easiest and most tolerated regimen is used first, followed by a more complicated regimen if this is unsuccessful.

3.2.3 What treatment regimen should be used in people with no history of previous treatment?

The treatment regimen of choice comprises *daily* rifampicin and isoniazid for a total of 6 months. During the initial 2-month intensive phase, the regimen is strengthened by pyrazinamide and ethambutol (2RHZE/4RH).* This is the (first) treatment offered to 'new patients', that is, people with tuberculosis who have *not been previously treated for tuberculosis or who received treatment for less than one month*. If possible, new patients should undergo testing to check for rifampicin resistance. The recommended drug dosages are shown in Table 3.2.

The risk of selecting drug-resistant mutants is highest when bacterial load is greatest, that is, at an early stage of treatment when the person is sputum smear-positive. Directly observed treatment (see above) during the intensive phase has proved effective in reducing the risk of resistance development among persons receiving tuberculosis treatment. During the intensive phase, arrangements should be made to ensure that each dose of drug intake is observed. The safest approach is to directly observe and support adherence for the whole course of treatment wherever possible.

Table 3.2: Number of tuberculosis drug tablets by treatment phase, tablet content and weight band for people on first-line treatment

Month of treatment	*Drug*	*Weight, kg*		
		<37	*37–55*	*>55*
1–2 (daily) Intensive phase	RHZE (R 150 mg, H 75 mg, Z 400 mg, E 275 mg) combined tablets	2	3	4
3–6 (daily) Continuation phase	RH (R 150 mg, H 75 mg) combined tablets	2	3	4

* H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol.
Numbers before the letters indicate the duration in months of the phase of treatment.

3.2.4 How to treat people who have had tuberculosis treatment before?

People who have had tuberculosis treatment before include those undergoing treatment for relapse, treatment after failure or treatment after loss to follow-up (see section 7.2). Persons with bacteriologically confirmed tuberculosis who have taken tuberculosis drugs for one or more months in the past should undergo drug susceptibility testing to determine the appropriate regimen.

This Guide recommends that rapid molecular testing be performed first to determine the presence of rifampicin resistance. In the *absence of rifampicin resistance* and where LPAs are not available, this Guide recommends a regimen consisting of 6 months of rifampicin, isoniazid, pyrazinamide and ethambutol (6HRZE). Isoniazid should be retained despite possible isoniazid resistance, as it often has a beneficial effect. Drug dosages according to body weight are the same as in the intensive phase of first-line treatment (see Table 3.2). This regimen is recommended based on expert opinion. A repeat test for rifampicin resistance is recommended at 2 months or if treatment fails according to the usual criteria, whichever comes first.

Some countries prescribe first-line treatment (2RHZE/4RH) for previously treated people if rifampicin resistance has been ruled out using rapid molecular testing. We believe that this is not desirable, as it increases the risk of developing rifampicin resistance in case of *undetected* isoniazid resistance.

If rapid molecular testing *reveals rifampicin resistance*, the person has multidrug-resistant tuberculosis, and a LPA for second-line drugs is required to determine the appropriate treatment regimen. This is discussed briefly below.

3.2.5 What are the treatment choices for drug-resistant tuberculosis?

Since the detection of rifampicin resistance has become easier due to the increasing use of rapid molecular diagnostic testing, the term 'drug-resistant tuberculosis' in this Guide refers to persons resistant to rifampicin alone, as well as those who are resistant to both rifampicin and isoniazid. Recommendations for the treatment of rifampicin-resistant tuberculosis are rapidly changing as new trial results and new drugs become available. The current WHO guidelines (May 2019) recommend two different approaches to treatment:[6] 1) a customised, all-oral prolonged regimen that relies on the most effective drugs, some of which have potentially toxic side effects or 2) a shorter 9–12-month standardised treatment regimen containing an injectable agent. This Guide recommends the shorter regimen because it is the first complete treatment regimen containing second-line drugs to be supported by the findings of a randomised controlled trial.[7] In addition, the results of this trial closely match the programmatic experience of using this regimen. The Union's experience in this area suggests high treatment success and low loss to follow-up rates among those treated with the shorter regimen. The shorter regimen is also less burdensome for patients, their families and health services, facilitates the provision of direct observation support and is protective against the development of resistance to new drugs.[8]

The current shorter standardised regimen can be offered to persons with drug-resistant tuberculosis with no history of previous treatment with second-line drugs and/or those who are susceptible to fluoroquinolones and second-line injectables (LPA for second-line drugs is recommended). The shorter regimen contains moxifloxacin, pyrazinamide, ethambutol and clofazimine throughout the entire duration of treatment. As shown in Table 3.3, this drug combination is supplemented by amikacin, isoniazid and prothionamide during the 4-month intensive phase, which may be extended if the sputum smear at 4 months is positive until the monthly sputum smear examinations are negative (maximum duration: 6 months). The continuation phase is fixed at 5 months, regardless of the final duration of the intensive phase.

If there is no bacteriological response and the patient's clinical status does not improve by month 6, treatment failure is likely. A repeat LPA for second-line drugs should then be performed; if no LPA for second-line drugs was done at treatment initiation it should be done now to identify resistance to fluoroquinolones and/or second-line injectables.

Because this regimen contains an injectable agent that can cause hearing loss, audiometry should be performed at baseline and on a monthly basis while the injectable is used. If hearing loss or renal failure is detected, the injectable should be changed to any one of the following drugs: bedaquiline, delamanid or linezolid. More details are available in The Union's *Field Guide for the Management of Drug-Resistant Tuberculosis*.[2]

The future of drug-resistant tuberculosis treatment lies in all-oral regimens, and several clinical trials and programmatic operational research for more effective and shorter, all-oral regimens, containing bedaquiline, delamanid, pretomanid and repurposed drugs, such as linezolid, clofazimine and fluoroquinolones, are ongoing.

Table 3.3: Tuberculosis drugs and number of tablets by tablet content and weight band for patients on the shorter treatment regimen for drug-resistant tuberculosis

Month of treatment	*Drug*	*Weight, kg*			
		30–39	*40–54*	*55–70*	*>70*
1–4 (daily) (may be prolonged)	Amikacin (g)[§]	0.5	0.75	1	1
	H (300 mg)[†]	1	1.5	2	2
	Prothionamide (250 mg)	2	2	3	3
	Moxifloxacin (400 mg)[⋆]	1	1.5	2	2
	Clofazimine (50 mg)	1			
	Clofazimine (100 mg)		1	1	1
	E (400 mg)	1.5	2	3	3.5
	Z (400 mg)	2	3	4	5
5–9 (to 11) (daily) (5 months fixed)	Moxifloxacin (400 mg)	1	1.5	2	2
	Clofazimine (50 mg)	1			
	Clofazimine (100 mg)		1	1	1
	E (400 mg)	1.5	2	3	3.5
	Z (400 mg)	2	3	4	5

[§] Patients aged ≥60 years should receive a maximum of 0.75 g; amikacin should be given intermittently if the intensive phase is extended; amikacin should ***not*** be given to pregnant women.

[†] Isoniazid dosage is higher for MDR-TB treatment than for first-line treatment; thus 300 mg tablets are used.

⋆ An electrocardiogram should be periodically performed when moxifloxacin is used.

H = isoniazid; E = ethambutol; Z = pyrazinamide; MDR-TB = multidrug-resistant tuberculosis.

3.2.6 How is tuberculosis treated in children and adolescents?

First-line treatment regimen in children and adolescents is the same as the one recommended for adults (2HRZE/4HR). Children with severe forms of tuberculosis, such as meningitis and osteo-articular tuberculosis, should have a prolonged continuation phase comprising 10HR. Children tolerate tuberculosis drugs well and ethambutol can be given safely in children of all ages at the recommended dosages.

It is important that NTPs provide young children (<25 kg) with tuberculosis treatment using child-friendly formulations as per weight-based dosage guidelines below. These formulations provide treatment at the recommended dosages (in mg/kg), are dispersible in water and fruit-flavoured, and therefore easier to administer to young children and less prone to dosage errors than tablets (or portions of tablets). They are also cheap and readily available through the Global Drug Facility. Table 3.4 shows the number of tuberculosis drug tablets by phase of treatment, tablet content and weight band to be given for children.

Children should be weighed at each follow-up visit, the weights recorded in the child health cards and *Tuberculosis Treatment Card* (Appendix, Form 5) and drug dosages should be adjusted if necessary. The best treatment supporters are their caregivers who should be provided with information on tuberculosis, as discussed in section 3.1 above. Family members and other caregivers should also be evaluated for tuberculosis because they could be the source of the disease of their child. Adolescents can use adult formulations and may need additional adherence support. Those breast-feeding infants and children are encouraged to continue to breastfeed during the infant/child's tuberculosis treatment.

Hospital admission should be considered when clinically indicated, particularly in new-borns and young infants with other comorbidities or those who fail to respond to treatment.

Table 3.4: Number of tuberculosis drug tablets by treatment phase, tablet content and weight band in children weighing <25 kg

	Intensive phase (number of tablets per day)		*Continuation phase (number of tablets per day)*
Weight bands, kg	*RHZ (75/50/150 mg)*	*E (100 mg)*	*RH (75/50 mg)*
4–7	1	1	1
8–11	2	2	2
12–15	3	3	3
16–24	4	4	4
≥25	Use adult dosages and formulations		

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol.

3.2.7 How are pregnant or breast-feeding women treated for tuberculosis?

Pregnant and breast-feeding women with tuberculosis should start or continue their treatment in the same way as other people. Breast-feeding mothers can continue to breast feed during treatment. This is important for both their own health, as well as the health of the unborn or new-born babies.

3.3 What adverse effects can tuberculosis drugs have?

Adequate treatment of each person with tuberculosis for the full duration of the prescribed regimen is very important if treatment success is to be achieved. Adverse events can occur, and where possible, should be managed without discontinuing or changing the regimen. Frequent side effects include skin rashes and abdominal complaints that are mild and can often be managed symptomatically. Careful history taking can often help establish whether the complaints presented by a person on treatment are adverse drug reactions.

When should tuberculosis drugs be permanently discontinued?

Very infrequently, severe drug reactions occur that require the drugs to be discontinued permanently and the patient needs to be hospitalised for management. These reactions include the following:

- Severe reactions, such as shock, purpura and fever. These are very rare but may be caused by rifampicin or pyrazinamide. The drug thought to be responsible for the reaction should never be given again.
- Impairment of vision in a person with tuberculosis on ethambutol (rarely, isoniazid can also be responsible). People on tuberculosis treatment should be informed of this risk and told to report immediately any occurrence of impaired vision (including reduced colour discrimination, blurring or spots). If ethambutol is thought to be responsible, it should never be given again.

What adverse reactions indicate that the drugs should be discontinued while the cause is investigated?

- Jaundice or severe abdominal discomfort may be caused by drug-induced hepatitis. Pyrazinamide, isoniazid and rifampicin can cause drug-induced hepatitis. Any person with these symptoms should stop taking their tuberculosis medications, undergo liver function tests and be referred urgently to the Medical Officer for further consideration.

- Skin rash is most frequently due to pyrazinamide or isoniazid. If the rash is severe but the person is clinically well (that is, does not suffer from advanced tuberculosis or serious forms of the disease such as meningitis or disseminated disease), the best course of action is to discontinue all drugs and recommence them after the reaction has subsided. If symptoms recur, the person should be referred to the Medical Officer.

What reactions do not require treatment interruption?

- Numbness or tingling may be caused by isoniazid. When it occurs, it can be treated by administering vitamin B6 (also known as pyridoxine) supplements at a dose of at least 50 mg daily. Pregnant and breastfeeding women, people living with HIV, people with diabetes and people with excessive alcohol use are at increased risk of peripheral neuropathy and could benefit from vitamin B6 supplements when tuberculosis treatment is commenced.
- Joint symptoms may be caused by pyrazinamide. It is important to check dosage by weight, as these symptoms are usually caused by over-dosage. They may be easily alleviated with acetylsalicylic acid.
- Patients on rifampicin should be advised to expect a red/orange tinge to body fluids (tears, saliva, sputum, sweat and urine) and reassured, as this is not dangerous.
- Rifampicin has many interactions with other drugs. It is important to ascertain whether the patient is taking oral contraceptives, anti-epileptic drugs, corticosteroids, oral treatment for diabetes, oral anticoagulants or certain types of antiretroviral drugs, in which case dose adjustments, changes to medications or the use of alternative family planning methods may be required.

3.4 How is treatment progress monitored?

Treatment monitoring is based mostly on AFB microscopy because of the difficulty and delays involved in culture testing. Since molecular techniques yield positive results longer than microscopy even after tuberculosis micro-organisms have been effectively killed, these techniques cannot be used. Even so, follow-up microscopy is only a convenient screening tool, and unexpected positive results need to be complemented by clinical and resistance testing evidence. Due to the possible confusion with dead micro-organisms, failure results based on careful microscopy will most often be false in settings with low baseline resistance to rifampicin and extensive drug-susceptible tuberculosis disease at diagnosis. Only culture can be used to reliably confirm true failure, and to a lesser extent, relapse. For this reason, culture confirmation with drug susceptibility testing is always recommended. Culture is also recommended, if possible, for the routine monitoring of the treatment of all types of tuberculosis other than drug-susceptible tuberculosis.

The results of bacteriological investigations should be recorded (see Chapter 7) for all patients before starting treatment. After the initial 2-month intensive phase, a single sputum specimen, preferably an early morning specimen, should be examined using microscopy. If the patient is AFB-positive, s/he should undergo rapid molecular testing for rifampicin resistance, followed by a switch to the treatment regimen for rifampicin-resistant tuberculosis, if necessary. Otherwise, patients should be started on the continuation phase. In all persons with bacteriologically confirmed disease, a single microscopy examination is done at 5 months. If the result is negative, treatment should be continued and a single sputum microscopy examination repeated at 6 months. If negative, the person is declared cured. If AFB are detected at month 5 or 6, the person is declared a treatment failure.

Persons who occasionally miss an appointment during the continuation phase should have the total time missed added to the treatment duration that had been originally planned.

3.4.1 Can a person on tuberculosis treatment infect others?

Treatment is effective in rapidly reducing the infectiousness of any person with susceptible micro-organisms. This is because the drugs rapidly decrease the number of micro-organisms and the person's cough soon subsides, resulting in fewer micro-organisms being expelled into the air. In most settings, no special precautions for preventing the spread of micro-organisms need be taken once the person is on treatment; the best prevention is to ensure that people with tuberculosis are diagnosed and promptly started on appropriate treatment, and that drugs are taken regularly. If the person has drug-resistant tuberculosis, the same principle applies as long as they are prescribed the drug combination that is most appropriate for their resistance pattern.

3.5 What about lung health after tuberculosis?

Pulmonary tuberculosis may result in damage to the lungs. In some people, particularly those with a late diagnosis, the damage can be severe enough to leave them with long-term respiratory symptoms and impairment. This is called post-tuberculosis lung disease. There is conflicting evidence about risk factors, and smoking and HIV infection may play a role. The severity of post-tuberculosis lung disease differs, and can range from mild to severe. People may have major lung destruction, cavities, fibrosis (scarring), bronchiectasis, chronic airflow obstruction or pleural fibrosis, among others.

It follows that people who have completed tuberculosis treatment should be assessed for residual respiratory symptoms, such as shortness of breath, cough, sputum production or wheeze. Where possible, people with symptoms should be referred to a Medical Officer for investigations that include chest radiography and lung function tests.

What symptoms do persons with post-tuberculosis lung disease have?

Symptoms vary depending on the nature and degree of lung damage. People may complain of shortness of breath, especially on exercise. They may have a chronic cough that can be productive. Some people are prone to recurrent infections caused by organisms other than tuberculosis micro-organisms. It should be noted that people who have had tuberculosis may develop it again.

What should be done when a person who has had tuberculosis before presents with respiratory symptoms?

If the person presents with symptoms after cure or treatment completion, it is important to ascertain whether the symptoms are new and worsening (days-weeks) or old (months-years).

New symptoms

These may be caused by an acute chest infection, recurrent tuberculosis or another cause entirely. It can be difficult to differentiate between the causes. Useful investigations include:

- History and clinical examination to explore the cause(s) of the new symptoms.
- Chest radiographs that should be compared to old X-rays (if available) to identify new changes. Note: Since many persons will have old changes on chest X-ray after a first episode of tuberculosis, it is important to look for *new* changes.
- Submission of sputum for smear and culture. Note: rapid molecular tests may remain positive for months or even years after successful treatment completion. A positive smear microscopy result with a positive culture is suggestive of tuberculosis (disease).

If recurrent tuberculosis is not suspected and no other cause is found, a short course of antibiotics can be given for lower respiratory tract infection. Cases should be reviewed to ensure that symptoms improve, failing which further investigations are warranted. Needless courses of empiric tuberculosis treatment should be avoided.

Longstanding symptoms

These may be related to the lung damage caused by tuberculosis. Although evidence in support or these approaches is limited, patients may benefit from the following (if available):

- History, clinical examination, chest radiography and lung function tests to determine the baseline level of function and disease.
- Advice to stop smoking or cannabis use.
- Advice to remain active and follow a pulmonary rehabilitation/exercise programme.
- Education about airway clearance exercises.
- Submission of sputum for culture, where possible, if symptoms worsen.
- Yearly immunisation against influenza and pneumococcus every 5 years.
- If the lung function tests show airflow obstruction (or if the person has prominent wheeze), inhaled bronchodilators (salbutamol), but preferably long-acting bronchodilators may be prescribed.
- Care should be exercised in prescribing inhaled corticosteroids, as it is not known whether these are good for this group of patients.

4 Tuberculosis prevention

Early detection and prompt initiation of correct treatment in people with tuberculosis is key to reducing transmission. Other prevention measures include i) reducing exposure to tuberculosis micro-organisms through airborne infection control measures; ii) identifying persons with tuberculous infection and preventing the development of tuberculosis disease through preventive treatment; and iii) BCG vaccination. Management of various comorbidities, such as the provision of antiretroviral treatment for people living with HIV, maintaining glycaemic control in persons with diabetes mellitus, smoking cessation among tobacco users etc., also contribute to the prevention of tuberculosis (see Chapter 5).

4.1 What measures should be taken for tuberculosis infection prevention and control?

Airborne infection control comprises measures aimed at minimising the risk of transmitting micro-organisms through the air.[9] Prevention of transmission in health facilities and other high-risk congregate settings is based on a series of priorities:

- *Administrative* systems need to be put in place when there is a high degree of clinical suspicion of tuberculosis: persons with cough should be rapidly separated from others, promptly investigated and started on treatment if tuberculosis is diagnosed. All settings where tuberculosis is diagnosed should have an airborne infection control and prevention plan, staff training and support programmes and a focal person or a committee to oversee the implementation of various infection control measures.
- *Environmental* control measures, such as the maximisation of natural ventilation, control of air flow, filtration and use of ultraviolet germicidal irradiation, should be implemented.

- *Personal respiratory protection* is the lowest priority. No matter how effective, personal respiratory protection cannot compensate for deficiencies in administrative and environmental controls. The most appropriate personal protective equipment for preventing exposure to micro-organisms is a respirator. Surgical masks should be used by persons with cough before treatment is initiated to prevent respiratory secretions from becoming airborne, that is, to ensure cough hygiene. More information on these measures is available in The Union's *Programmatic Guide on Implementing Collaborative TB-HIV Activities*.[10]

4.2 How to identify persons with tuberculous infection?

People who are or who have been in close contact with a person with infectious pulmonary tuberculosis are at an increased risk of tuberculous infection and tuberculosis disease. To ensure that exposed persons are identified as early as possible and offered appropriate treatment, a systematic process of identifying them and facilitating diagnostic investigations and treatment should be implemented. This is called *contact investigation*. It allows for early diagnosis of tuberculosis and an opportunity to treat tuberculous infection, thereby preventing future tuberculosis disease.

4.1.2 Contact investigations: definitions

The *index case* is a person with bacteriologically confirmed pulmonary tuberculosis around whom a contact investigation is centred. A *contact* is a person who has been exposed to an index case. A *household contact* is defined as a person who has shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during 3 months before the start of the current course of treatment. A *close contact* is a person who is not in the household but who has shared an enclosed space, such as a place of social gathering, workplace or facility for extended periods during the day with the index case during 3 months before the start of the current course of treatment.[11]

4.1.3 How is contact investigation implemented?

Although contact investigation is recommended in many national tuberculosis guidelines, its implementation is frequently weak. The Union has conducted operational research on contact investigations in several sub-Saharan African countries.[12,13] These projects have shown that contact investigation is feasible in field conditions in resource-limited settings. The main steps in the management of child contacts that were followed by The Union included:

1 Line listing the household and close contacts, especially children less than 5 years of age and people living with HIV, of people with bacteriologically confirmed tuberculosis;

2 Clinical evaluation of contacts during a home visit and referral to a health facility or basic management unit (BMU) if they have symptoms or signs suggestive of tuberculosis or are likely to benefit from tuberculosis preventive treatment (TPT) (see Text Box 2.2);

3 Clinical evaluation in a health facility or at a BMU. Sputum is tested and/or chest X-ray performed for individuals with symptoms;

4 Appropriate management of contacts: those with tuberculosis disease (see Chapter 3) should be offered tuberculosis treatment; those with tuberculous infection (see 4.3.2 below) should undergo preventive treatment;

5 Prompt treatment initiation and support for treatment completion; and

6 Accurate recording, reporting and use of all collected data for decision-making.

The main results and lessons learnt in the project in selected African countries are summarised in Text Box 4.1.

Text Box 4.1: Main results of and lessons learnt from the Transmission Investiguée Tuberculoses Infantiles (TITI) project: tuberculosis prevention in children[12]

Main results	*Lessons learnt: enablers for contact investigation*	*Lessons learnt: barriers to contact investigation and their solutions*
Ratio of 0.8 contacts per index case was established 46% of index cases had at least 1 child under 5 years of age at home 2.8% of contacts were found with tuberculosis and 88% were successfully treated 92% of eligible children were started on TPT 94% completed TPT	Standardised recording and reporting tools are required: • Stamp to indicate number of children in index patient's card • Preventive treatment register • Child contact's card • Chest X-ray request form • Home visit note book Simple and clear referral procedures are required Home visits are well accepted 3RH (75 mg/50 mg) is well tolerated and is as effective as 6H in preventing tuberculosis in children	Health care workers perceive tuberculosis diagnosis in children difficult: offer training and mentorship to create confidence Reading of chest X-rays is weak: offer on-the-job, refresher and other training

R = rifampicin; H = isoniazid. Numbers before the letters indicate the duration in months of the phase of treatment. TPT = tuberculosis preventive treatment.

4.3 What is tuberculous infection and how is it treated?

As described in section 2.1.2, exposure to tuberculosis micro-organisms may result in tuberculous infection. The risk of getting infected depends on several factors and include proximity of contact, duration of contact and infectiousness of the index case, as well as host factors, such as adequacy of immune defence mechanisms of the exposed persons (infants, children and elderly, people living with HIV). Approximately 10% of people with tuberculous infection develop tuberculosis disease. This occurs within 2 years of being infected for 5% of cases; the remaining 5% develop tuberculosis disease later. There are certain groups of people who are at high risk of developing tuberculosis disease. These groups are listed in Text Box 2.2. The most at-risk populations to develop disease once infected are people living with HIV and children under five years of age.

4.3.1 How is tuberculous infection diagnosed?

Currently, there are two tests that can be used to diagnose tuberculous infection. The *tuberculin skin test* (TST) measures a person's immune response to tuberculosis micro-organisms. It is administered by a health care worker who injects a certain amount of tuberculin solution intradermally on the anterior surface of a person's forearm. The reaction (an induration or swelling) is read 48–72 hours later, requiring the person to revisit the clinic. An induration that is of a certain minimum diameter is suggestive of exposure to tuberculosis micro-organisms. The interpretation of the TST result is often difficult, and there are no clear cut-off values for a positive result. A positive reaction may also be caused by conditions other than tuberculosis, and a negative result does not always rule out tuberculous infection. A positive TST reaction may result from BCG vaccination and exposure to other mycobacterium species. A negative reaction may be caused by severe immune depression, such as advanced HIV infection or malnutrition. A large induration suggests the presence of tuberculous infection but cannot indicate whether or not the person has progressed or will progress to tuberculosis disease. Furthermore, standardised and quality-assured tuberculin is not routinely available in many peripheral health facilities.

Interferon-gamma release assays (IGRAs) are more specific than TST, as they do not react to BCG and most other mycobacterium species. However, like the

TST, they cannot distinguish between infection and disease. IGRAs are costly and require specific laboratory equipment. Also, a venous blood sample has to be drawn for the test.

For people living with HIV and children under the age of 5, the risk of developing tuberculosis disease is so high that tuberculous infection treatment, known as TPT, is recommended if they have been in contact with a person with bacteriologically confirmed pulmonary tuberculosis and have a negative symptom screen (see Chapter 2). If resources are available, a TST or IGRA and chest-X-ray may be carried out; however, the lack of these tests should not delay the start of TPT. Better, and ideally, point-of-care tests should become available to facilitate diagnosis of tuberculous infection.

4.3.2. How is tuberculous infection treated?

TPT is the treatment of those with tuberculous infection who do not have tuberculosis disease. TPT can prevent the infection from progressing to tuberculosis disease. This protective effect may last several years, depending on the degree of ongoing transmission of tuberculosis micro-organisms in a given community. Adherence to and completion of the preventive treatment course by people who are not sick have posed serious challenges when a 6-9 month isoniazid regimen has been used. Recent advances have led to the recommendation of newer and shorter regimens (see Text Box 4.2). These shorter regimens should be recommended in the national guidelines and implemented.

TPT should be offered at least to people living with HIV (who should also be on antiretroviral treatment),[14] and children under five years of age. Children five years of age and older, adolescent and adult contacts and other at-risk populations (Text Box 2.2) can also be considered after presence of tuberculosis disease has been carefully ruled out.

It is important that information regarding the benefits and risks of TPT are shared with eligible persons so they can make an informed decision before starting treatment. Treatment support should be provided for individuals on TPT to ensure treatment adherence and completion. However, those on TPT do not need to have directly observed treatment. It is also important to monitor the appearance of any drug side effects and symptoms suggestive of tuberculosis disease that necessitate discontinuation of TPT.

Text Box 4.2: Treatment regimens for tuberculous infection

Drug regimen	*Notes*
Daily isoniazid for 6–9 months (6H/9H)	Frequently used before 'newer' regimens
Daily isoniazid for 36 months (36H)	Can be used in people living with HIV in settings with high tuberculosis burden
Daily rifampicin for 4 months (4R)	Rifampicin has many drug-drug interactions, caution should be exercised when prescribing, particularly to those on antiretroviral therapy
Daily isoniazid and rifampicin for 3 months (3RH)	Particularly suitable for children as fixed-dose combination preparation is available
Isoniazid and rifapentine weekly for 3 months (3HP)	No paediatric formulation currently available (2019)
Isoniazid and rifapentine daily for one month (1HP)	Only been studied in people living with HIV

HIV = human immunodeficiency virus.

4.4 How does the bacillus Calmette-Guérin vaccine work?

The bacillus Calmette-Guérin (BCG) vaccine contains a live but weakened form of *Mycobacterium bovis* which is administered to stimulate a response by the body's immune defence mechanisms to the tuberculosis micro-organisms. The vaccine provides high level of protection in children against serious forms of tuberculosis, such as meningitis and disseminated tuberculosis. It provides much less protection against pulmonary tuberculosis in adolescents and young adults and therefore contributes little in controlling the spread of tuberculosis micro-organisms in the community. It has a protective effect against leprosy and buruli ulcer.

In most countries, BCG vaccination is included in the Expanded Programme on Immunisation (EPI). It is recommended that the vaccine be given at birth or as early in life as possible. It should not be given to children who are known to be HIV-infected. The vaccine is injected intradermally into the upper portion of the left arm at a dose of 0.05 ml for those up to 1 year of age (and at a dose of 0.1 ml for those more than 1 year of age). There is no scientific justification for revaccination with BCG. The development of a more effective vaccine is a high priority in the global strategy to End TB.

5 Tuberculosis and comorbidities

There are several factors and other medical conditions that could increase the risk of people becoming infected with tuberculosis micro-organisms when exposed and then developing tuberculosis disease. These are called comorbidities. Comorbidities may affect the clinical presentation of tuberculosis, and can adversely affect tuberculosis treatment outcomes; tuberculosis could also lead to the aggravation of comorbidities. Comorbidities should be rapidly detected to ensure earlier diagnosis and satisfactory treatment outcomes. Relevant national programmes and departments need to collaborate and take joint decisions on organising *bidirectional screening and concomitant management* of people with more than one condition. Good management of comorbidities will also contribute to the *prevention* of tuberculosis.

5.1 Tuberculosis in people living with human immunodeficiency virus

HIV infection is the strongest known risk factor for the development of tuberculosis disease in persons with tuberculous infection. This risk is reduced when a person living with HIV is on efficacious antiretroviral treatment (ART), although the risk remains higher than among HIV-negative people. Tuberculosis is also the leading cause of death in people living with HIV. Due to the strong association between these two conditions, persons with tuberculosis should be offered counselling and testing for HIV and those with HIV infection should be screened for tuberculosis.

5.1.1 How does human immunodeficiency virus infection affect tuberculosis?

HIV infection progressively leads to extensive destruction of the body's immune defence mechanisms, particularly of CD4 T-cell lymphocytes, making those affected more prone to infections. Tuberculosis is the most important opportunistic infection in settings with a high burden of both tuberculosis and HIV. Even in this era of 'Treat All',[15] tuberculosis remains a frequent entry point to the detection of HIV infection and initiation of HIV care, including ART.

5.1.2 How does HIV infection influence the diagnosis of tuberculosis?

When a person has both HIV infection and tuberculosis, each disease speeds up the progress of the other. People living with HIV progress faster from tuberculous infection to tuberculosis disease. Tuberculosis accelerates the progress of HIV infection. All people living with HIV, including those who have been newly diagnosed with HIV, should be systematically investigated for tuberculosis.

Tuberculosis can occur at any stage during the course of HIV infection. In early HIV infection, when the immune defence mechanisms of the body are almost normal, tuberculosis presents with symptoms and signs that are similar to those in an HIV-negative person with tuberculosis, and a high proportion of such adults are bacteriologically confirmed, especially if they undergo rapid molecular testing. As HIV infection progresses, the presentation of tuberculosis is likely to become more unusual, and extra-pulmonary and disseminated forms of tuberculosis become more frequent. In such persons, the clinical presentation of tuberculosis disease may be different from the expected. It should be noted that individuals with advanced HIV disease may be symptom-free and have no chronic cough. They may present with non-specific symptoms, such as loss of weight and chronic fever, and chest radiographs may have abnormal shadows in the lung fields or intra-thoracic lymphadenopathy or they may be normal. Tuberculosis may be disseminated with circulating micro-organisms that can be detected on blood culture. A lateral flow lipoarabinomannan (LF-LAM) urine antigen test is an easy point-of-care tuberculosis diagnostic test that can be offered to persons with advanced HIV disease.

5.1.3 How should people living with HIV be screened for tuberculosis?

People in HIV care should be screened for symptoms of tuberculosis at every contact with the health services, unless they are already on tuberculosis treatment. If they have any one of the following symptoms, they may have the disease and a sputum sample should be collected for bacteriological testing, preferably for rapid molecular testing:

- Current (any) cough
- Weight loss
- Fever
- Night sweats

If the result is positive, tuberculosis treatment should be started promptly. Persons who are well, gain weight and have none of the above symptoms should be considered for initiation of TPT according to the national guidelines. This is discussed in Chapter 4 of this Guide.

5.1.4 When should HIV counselling and testing be offered in tuberculosis care?

The current HIV status of all people with presumptive or diagnosed tuberculosis should be ascertained. HIV counselling and testing should be provider-initiated and offered to everybody who does not know their current HIV status or has had a HIV-negative result more than 3 months earlier. HIV can be diagnosed easily and quickly as results of point-of-care tests are available in less than an hour. In infants and children, a DNA polymerase chain reaction test is generally used because of persisting maternal anti-HIV antibodies that could lead to a false-positive rapid HIV test result. Rapid HIV test results can be confirmed using other tests, such as enzyme immunoassays. Testing algorithms recommended nationally should be followed.

If the person is negative, post-test counselling should explain how they could remain HIV-negative. In case of a positive result, the person should have an early referral to the HIV care services. For those known to be living with HIV, details of their current ART should be recorded in the relevant sections of the tuberculosis recording and reporting tools. Ideally, all persons diagnosed with tuberculosis should know their HIV status by the time their tuberculosis treatment is started. HIV status of all people should remain confidential.

5.1.5 How is tuberculosis treated in people living with HIV?

The treatment of drug-susceptible tuberculosis in people living with HIV is the same as in non-HIV-infected people: treatment is with the standard 6-month regimen (see Table 3.2), which should be given daily. Patients may need additional support to adhere to both tuberculosis treatment and ART. The rifamycin group of tuberculosis drugs has considerable interactions with antiretroviral (ARV) drugs, as they are metabolised faster, which results in less ARV drug being available to the body. An efavirenz-based treatment (usually with two non-reverse transcriptase inhibitors) is thus currently the preferred option for initial ART for those on tuberculosis treatment. People already on ART may need to be switched to efavirenz-based regimens for the duration of tuberculosis treatment. Those on dolutegravir regimens receiving rifampicin for tuberculosis should receive an additional 50 mg dolutegravir 12 hours after their ARV drug regimen.

NTPs should ensure co-location of facilities offering treatment for tuberculosis and HIV or any another approach that facilitates access for people who need both treatments: in many settings, tuberculosis treatment is given by HIV care providers to reduce the burden on people with both tuberculosis and HIV. Tuberculous infection prevention and control measures should be implemented to make health facilities as safe as possible.

5.1.6 When to start antiretroviral treatment in persons with both HIV and tuberculosis

The first priority is to start tuberculosis treatment regardless of the person's CD4 cell count. If they are newly diagnosed with HIV and are not on ARV drugs, ART initiation should follow as soon as possible and ideally, within 8 weeks of starting tuberculosis treatment. People who are severely immunosuppressed, that is, have CD4 cell counts less than 50 cells/mm^3, should start ARV drugs within 2 weeks of starting tuberculosis treatment.

Some people living with HIV, who may not be on ARV drugs when they are diagnosed with tuberculosis, should also be started on ARV drugs. As explained above, the ARV regimen of people already taking ARV drugs should be reviewed for drug-drug interactions. Furthermore, cotrimoxazole preventive therapy should be given to all people living with HIV who have tuberculosis.

5.2 Tuberculosis in people with diabetes mellitus

Diabetes mellitus has reached pandemic proportions, with several hundreds of millions of people worldwide with the disease. Diabetes increases the risk of tuberculosis two- to three-fold. People with diabetes have worse tuberculosis treatment outcomes than people who do not have diabetes. Tuberculosis may impair glycaemic control in people with diabetes.

5.2.1 How does diabetes mellitus influence the diagnosis of tuberculosis?

Tuberculosis may present atypically, with more severe symptoms and signs, in those with diabetes. Among persons with diabetes, tuberculosis may progress faster, present with more systemic and chest symptoms, and be associated with a higher grade smear and culture positivity. There is evidence to show that persons with uncontrolled hyperglycaemia are more likely to have more severe forms of tuberculosis. Chest radiographic findings in people with both diabetes and tuberculosis are inconsistent. Some persons have isolated lower lung lesions and an increase in consolidation and cavitation.

5.2.2 When should testing for diabetes be offered in tuberculosis care? Should diabetes clinics offer tuberculosis screening?

Bidirectional screening is the recommended strategy for early detection of both tuberculosis and diabetes. All adults with tuberculosis should be screened for diabetes. A fasting blood glucose or, if available, glycosylated haemoglobin test should be performed. If these are not available, a random blood glucose test can be considered as a screening test, and all persons with ≥6.1 mmol/l (≥110 mg/dl) should be referred for a second test.

Tuberculosis screening among people with diabetes should be considered in settings with a tuberculosis prevalence of more than 100/100,000, and should be provider-initiated for newly diagnosed persons with diabetes. People with a positive symptom screen should be investigated further using sputum testing, ideally rapid molecular testing. In persons with known diabetes, there should be a heightened index of suspicion of tuberculosis.

5.2.3 How is tuberculosis treated in people with diabetes?

The 6-month standard tuberculosis treatment regimen (Table 3.2) is recommended for people with diabetes and drug-susceptible tuberculosis. Comprehensive treatment includes careful support for and counselling about increased physical activity, diet, the need to quit smoking if the person is a current smoker, and the administration of a glucose-lowering drug.

5.2.4 What glucose-lowering drugs should be used in persons with both tuberculosis and diabetes?

Metformin is the first-line drug of choice for people with both tuberculosis and diabetes. It has many advantages: low risk of hypoglycaemia, effectiveness, beneficial effects on cardiovascular disease, absence of clinically relevant interaction with rifampicin and low cost. It also augments host immune responses to tuberculosis treatment. The starting dose for metformin is 500 mg once or twice a day; this can be increased to 1,000 mg twice a day.

5.2.5 Where are people with both tuberculosis and diabetes treated?

Because persons with diabetes are at an increased risk of tuberculosis, those with both conditions should be managed in the tuberculosis clinic for at least the first 2 weeks of tuberculosis treatment, and if possible, until the end of the initial 2-month intensive phase, to reduce the likelihood of transmission of tuberculosis micro-organisms within the diabetes services. During this time, diabetes care should be administered by health care workers in the tuberculosis clinic in consultation with a diabetes expert if necessary.

More information on diabetes and tuberculosis can be found in The Union publication on *Management of Diabetes Mellitus-Tuberculosis: a Guide to the Essential Practice*.[16]

5.3 Tuberculosis in people who smoke

Smoking is associated with an increased risk of tuberculous infection and of progression from tuberculous infection to tuberculosis disease, increased disease severity, delayed sputum smear conversion and increased risk of unfavourable treatment outcomes. In addition, smoking is also associated with increased risk of recurrence after successful completion of tuberculosis treatment. Health care workers should therefore advise smokers to quit. Counselling to stop smoking should be part of tuberculosis care.

There is no difference in the diagnosis and treatment of tuberculosis in smokers and non-smokers.

5.3.1 What are the key principles of protecting people with tuberculosis from tobacco smoke?

National programmes and health care workers should follow two key principles:

- Ensure a smoke-free environment in tuberculosis services, if not the entire health facility, by introducing a smoke-free policy and ensuring that the policy is properly implemented.
- Actively provide brief advice to current smokers with tuberculosis to quit smoking. This should be done at every contact the smoker has with the health services.

5.3.2 How to assess a person's smoking status?

Smoking status should be determined and recorded in the tuberculosis recording and reporting tools. In order to determine smoking status among people with tuberculosis, the following questions should be asked:

- Did you ever smoke?
- Do you smoke now?
- Do you smoke daily?

A person's smoking status can be classified based on the responses to these questions and recorded. More information on smoking and tuberculosis is available in The Union Guide on *Smoking Cessation and Smoke-Free Environments for Tuberculosis Patients*.[17]

5.3.3 How to provide help with smoking cessation

Health care workers in tuberculosis services should be trained on the adverse health effects of smoking and second-hand smoking on tuberculosis and of the importance of a smoke-free environment. At each visit, the health care worker should actively give any current smoker brief advice on how to quit smoking, consisting of a standard message on tobacco harm and a tuberculosis-specific message (see Text Box 5.1). It is recommended that the brief advice be of at least 30 seconds to 1 minute duration.

Text Box 5.1: General and tuberculosis-specific advice for smokers

General advice for smokers	*Tuberculosis-specific advice for smokers*
• Smoking is very harmful • It is extremely important for you to quit smoking now • One of the best things that you can do to improve your health is to quit smoking • Occasional or light smoking is still dangerous • We can help you quit smoking	• You need to stop smoking now in order to recover completely from tuberculosis • Quitting will reduce your risk of getting tuberculosis again • By smoking in your home you are putting your children and family at greater risk of getting tuberculosis

5.4 Tuberculosis and mental health

Tuberculosis and mental health disorders are related. Undergoing tuberculosis treatment and managing the stigma, and long-term health and other (for example, socio-economic) effects of tuberculosis can affect the mental health and wellbeing of individuals. Depression is frequent in people with tuberculosis. Existing mental health disorders can put people at a higher risk of tuberculosis. As our understanding of the association between tuberculosis and mental health grows, it is important to consider measures to support the mental wellbeing of people with tuberculosis and to ensure that these are incorporated into national programmes.

5.4.1 What is the link between tuberculosis and mental health disorders?

Depression can affect as many as half of those on tuberculosis treatment, and is associated with delays in diagnosis and treatment, poor treatment outcomes, disability, poor quality of life, treatment failure and death. Text Box 5.2 outlines the various ways that mental health disorders can present in people with tuberculosis. Furthermore, some tuberculosis drugs are associated with psychiatric side effects, particularly cycloserine, isoniazid, ethionamide, ethambutol and rifampicin.

Text Box 5.2: Mental health disorders that may occur during tuberculosis treatment

1. As a result of the diagnosis – linked to stigma
2. As a result of the tuberculosis medications
3. Exacerbation of current diagnosed mental health concerns
4. New presentation of undiagnosed mental health concerns

5.4.2 How to screen for mental health disorders and substance use and provide support during treatment

It is important to be aware of mental health disorders and substance use in people with tuberculosis and screen for these risk factors at the start and during tuberculosis treatment. For people with tuberculosis as well as evidence of mental health disorders, it is important to offer increased support, including counselling and adherence support throughout treatment and refer for specialist mental health services where appropriate. For people who use substances (illicit and prescription drugs, alcohol, etc.) replacement therapies, as well as counselling services during tuberculosis treatment and for stopping substance use, should be offered where available.

5.5 Collaborative services between tuberculosis, HIV and other programmes

Collaborative and person-centred services facilitate the concept of *"one patient – one health care worker – one health system – two (or more) diseases"*. National tuberculosis and HIV programmes have pioneered collaborative services since the early 2000s. Similar collaboration is now required between tuberculosis programmes and programmes for non-communicable diseases, harm reduction among people who use alcohol or drugs and tobacco control. Setting up of a joint coordinating body responsible for the development of a national plan, its implementation and monitoring at the national level is a key step. This plan should include development of national guidelines and tools, resource mobilisation, monitoring and evaluation, as well as operational research, pre-service and in-service training and advocacy, communication and social mobilisation. The coordination bodies at provincial, regional, district and/or local levels need to ensure that the national plan and national guidelines are disseminated to relevant implementers, who need to play an essential role in the implementation, supervision and monitoring of collaborative activities on the ground.

5.5.1 Why are collaborative services necessary?

As a result of effective collaboration between tuberculosis and HIV programmes, the management and outcomes for people living with HIV and tuberculosis have significantly improved in many countries, and unnecessary duplication of service delivery structures has been avoided. The vision for additional collaborative services is based on this experience.

5.5.2 What are the objectives of collaborative services?

The overall goal of collaborative services is to reduce the burden of tuberculosis among persons at risk, as well as the burden of a particular comorbidity among persons with tuberculosis. Specific objectives include early diagnosis through, for example, bidirectional screening, improved treatment outcomes among people with the health conditions in question and the reinforcement of health systems through training, mentorship, supervision, data use and operational research.

More information on The Union's experience in collaborative services can be found in *Programmatic Guide on Implementing Collaborative TB-HIV Activities* and *Management of Diabetes Mellitus-Tuberculosis: a Guide to the Essential Practice*.[10,16]

6 Programmatic planning for tuberculosis care

Ending the tuberculosis epidemic requires stopping transmission of tuberculosis micro-organisms by early detection and the effective treatment of people with tuberculosis without creating drug resistance. Urgent efforts and public health actions are required.

6.1. What is the role of the national tuberculosis programmes in ending the tuberculosis epidemic?

NTPs are responsible for bringing together all relevant stakeholders that are required for eliminating tuberculosis. The aims of *public health* differ from those of clinical medicine in that efforts are focused on communities instead of individuals. Public health actions go beyond clinical care and are necessary to prevent and successfully treat conditions of public health importance. These require coordinated efforts to be undertaken by teams of health care workers. In case of tuberculosis, NTPs aim to reduce the number of new cases of tuberculosis annually to the point where the disease is eliminated in a country. This requires partnership with people with tuberculosis, their families and the communities at large. Engaging all health sector players, civil society organisations and other key stakeholders also help to reinforce public health aims. In this effort, the following key components are equally important:

- Political commitment and coordination of disease control activities, including the prevention of tuberculosis;
- Diagnosis and provision of laboratory services;
- Provision of treatment, person-centred care and adherence support, including the management of other conditions (comorbidities) that individuals with tuberculosis may have;
- Provision of quality-assured drugs and supply management; and
- Recording, reporting and active use of locally available data for decision-making.

Delayed diagnosis and poor quality treatment of persons with tuberculosis have been clearly shown to have a harmful impact on the tuberculosis situation. When they are not cured of the disease, such individuals continue to interact with other members of the community, thereby increasing the risk of the transmission of tuberculosis micro-organisms to others, and increasing the burden of disease in the community. Without appropriate treatment, these individuals will continue to deteriorate with very poor outcomes. They are also at high risk of developing *drug-resistant* tuberculosis. It follows that inadequate and incomplete treatment of people with tuberculosis fuels the epidemic.

To end the tuberculosis epidemic, NTPs must pay careful attention to strengthening tuberculosis services. This can be done, for example, through an analysis of the existing *care cascades* for presumptive tuberculosis and tuberculosis disease, and utilising the vast amounts of routinely collected data by NTPs (see section 7.7.1). In cascade analysis, services to be provided, for example, to individuals with presumptive tuberculosis are 'broken down' into 'steps' through which they need to pass in order to get to the desired 'end' (in this case, from presentation with symptoms and signs suggestive of tuberculosis to a diagnosis and then to starting treatment and eventually, successfully completing treatment). The number and proportions of persons who have thus transitioned through the 'steps' are then assessed, which will then indicate the number and proportions of persons who did not. The latter reflects gaps and missed opportunities that NTPs should address.

6.2 What are the main functions of a national tuberculosis programme?

The first necessary action of NTPs is to mobilise political commitment and ensure that it translates into adequately funded and ambitious national strategic plans developed under the NTP leadership. Participation of all partners is vital to ensure coordination and a common understanding of the plan. With the dynamic landscape, NTPs need to be able to rapidly adopt better and newer diagnostics, treatments and vaccines as they become available. It is also necessary to provide better quality services through the existing health infrastructure. Multisectoral collaboration and community participation are necessary to address the drivers that fuel the tuberculosis epidemic – comorbid conditions and socio-economic and other barriers that inhibit people from seeking appropriate care.

Most countries, and especially countries with a high tuberculosis burden, need to have a NTP embedded within the ministry of health. The main functions of NTPs are to ensure the following:

- Tuberculosis services should be guided by the national tuberculosis strategic plan, which should be fully costed. Costs should be borne by the national governments, and no catastrophic costs should be borne by individuals with tuberculosis. Plans need to be reviewed and revised periodically;
- Tuberculosis services should be provided in accordance with national policies and guidelines that are reviewed regularly to ensure their technical soundness. These services should be integrated into the general health care services and offered in a standardised manner in all parts of the country;
- A laboratory network for early tuberculosis diagnosis and treatment monitoring should be in place, including facilities capable of testing for drug resistance;
- Complete treatment regimens for tuberculous infection and tuberculosis disease with medications that are quality-assured in line with international recommendations should be made available in an uninterrupted manner;
- Where regular drug supplies cannot be assured, drugs required a full treatment regimen should be set aside for each patient enrolled for treatment at the outset. This will ensure that every patient who commences treatment is able to complete it;
- Person-centred care and support, including the direct observation of treatment by an agreed person, or the use of new adherence tools, should be provided to all persons with tuberculosis; and
- Accurate recording and reporting should be ensured so that good quality data are available for decision-making to strengthen the quality of both clinical and programmatic management of tuberculosis at all levels of the health services.

6.3 How should the tuberculosis service be organised?

The tuberculosis service should be structured in four levels:

1. Facility-level: responsible for the identification of persons with presumptive tuberculosis and treatment of those with tuberculosis;
2. District-level or basic management units (BMUs):* under the stewardship of Tuberculosis Coordinators, these form the cornerstone of the tuberculosis service;
3. Intermediate (provincial, regional or county) level: provides support to facilities and BMUs; and
4. Country-level: NTP, responsible for coordinating the overall management of the tuberculosis service.

6.3.1 Facility-level tuberculosis services

In many settings, tasks earlier centralised at the district-level BMU hospitals are increasingly being implemented in *primary health care facilities* closer to the homes of people with tuberculosis. Facilities vary from small rural health posts or health centres to busy urban clinics, mission hospitals, private-for-profit clinics and hospitals and district hospitals that also serve as BMUs.

Most services are provided by tuberculosis focal nurses who also support community health care workers serving the facility catchment population. Focal staff, in turn, are supported by BMU Tuberculosis Coordinators and visiting clinical and Medical Officers. The services offered by facilities are listed in Text Box 6.1.

* In this Guide, the basic management unit is understood to provide secondary-level TB services, while intermediate TB services are provided at the provincial level.

Text Box 6.1: Major tuberculosis services offered at primary health care facilities

Services to identify and evaluate people with presumptive tuberculosis:

- Identifying and evaluating people with presumptive tuberculosis, transporting sputum specimens to laboratories and receiving and interpreting laboratory test results;
- Screening household and other close contacts of index cases (people with infectious types of tuberculosis);
- Evaluating household contacts of children with tuberculosis to identify sources of disease;
- Screening people living with HIV in care for tuberculosis

Services to treat, follow up and support people with tuberculous infection and tuberculosis disease:

- Starting people with bacteriologically confirmed tuberculosis on treatment and referring those with negative sputum results for further investigation to BMU/district hospital;
- Ensuring person-centred care and adherence support, and preventing treatment interruption and loss to follow-up;
- Assigning a preferred treatment supporter to every person starting tuberculosis treatment to facilitate directly observed treatment;
- Following up people with multidrug-resistant tuberculosis;
- Counselling and testing people with presumptive and diagnosed tuberculosis for HIV infection, diabetes and other comorbidities;
- Initiating HIV and other care, if available;
- Starting TPT in eligible contacts, especially children aged less than 5 years and people living with HIV;
- Assigning a treatment outcome to every person who has completed treatment for tuberculous infection or tuberculosis disease

Management of tuberculosis services, supplies, and recording and reporting:

- Maintaining facility-level stocks of essential consumables, including sputum specimen containers, drugs, and recording and reporting forms;
- Maintaining TB records and preparing quarterly reports;
- Validating, tabulating, analysing and using facility tuberculosis data for decision-making;
- Providing support and mentorship to community health workers and treatment supporters working in the facility catchment area;
- Attending BMU tuberculosis performance review meetings

Facilities use *Presumptive Tuberculosis Registers* (Appendix, Form 1), *Request and Reporting Forms for Sputum Smear Microscopy and/or Rapid Molecular Test* (Appendix, Form 2), *Tuberculosis Treatment Cards* (Appendix, Form 5) and *Facility Tuberculosis Registers* (Appendix, Form 6). Facilities should submit *Quarterly Facility Tuberculosis Reports* (Appendix, Form 7).

BMUs should have a specimen transport system, as this is more efficient and patient-friendly than requesting people to transport their own specimens, which should be used only as a last resort in the absence of an alternative transport arrangement. In such cases, travel support should be provided to people who take their own specimens to laboratories to avoid catastrophic patient costs and/or the person abandoning the tuberculosis case finding (or care) cascade due to unaffordability.

6.3.2 Basic management unit

The *basic management unit* (BMU) is defined as a functional area serving an average population of 50,000 to 150,000 (up to 300,000 in large cities). The BMU/district-level facility is part of the general health services and comprises of:

- A BMU/district hospital with a laboratory (diagnostic centre; large BMUs may have more than one diagnostic centre); and
- A network of health facilities.

A BMU laboratory usually provides diagnostic and treatment follow-up services, and performs sputum smear microscopy and frequently also rapid molecular testing. Experience from many countries has shown that one such facility per BMU offers an adequate balance between access to, and quality of, diagnostic services.

In an increasing number of countries, rapid molecular testing is recommended as the initial diagnostic test for tuberculosis. Access to this test is frequently more centralised than microscopy. This is due to the cost and complexity of the infrastructure required, such as uninterrupted electricity supply. The erratic availability of cartridges and time required for the maintenance of modules may create periods when rapid molecular testing is not fully functional. Adequate investments are required to improve and maintain diagnostic services (rapid molecular testing and microscopy), and to ensure a reliable specimen transport system and prompt communication of test results to clinicians.

As explained above, tuberculosis treatment can be started at the local facility if sputum specimens can be collected at the facility, transported to the nearest laboratory and results communicated back to the tuberculosis focal person. A positive result confirms the diagnosis. If the result is negative and the person continues to be ill, they may need to be referred to the BMU hospital for further investigation, diagnosis and initiation of treatment, although the treatment may be continued at their nearest health facility.

In most settings, the BMU hospital has a double function. It serves as a primary health care facility for people living nearby who do not have access to any other (primary-level) health facility. Registers for presumptive tuberculosis and tuberculosis disease may be in use for persons evaluated and followed up at the BMU hospital. These people do not then appear in tuberculosis registers in other facilities. At the same time, the BMU health administration is located in the BMU hospital, and includes the Tuberculosis Coordinator who maintains the *BMU Tuberculosis Register* (Appendix, Form 6) and *Tuberculosis Laboratory Register for Sputum Smear Microscopy* (henceforth, *Tuberculosis Laboratory Register*; Appendix, Form 3) that covers the *entire* BMU (unless there is more than one diagnostic centre). The BMU hospital may also house the BMU tuberculosis drug stocks, and supply these and other consumables to facilities.

Some non-governmental organisations and private facilities may refer persons with presumptive tuberculosis to BMU facilities, but then follow them up with treatment in the community. BMU Tuberculosis Coordinators should ensure that these organisations are supported, receive supervision and supplies, and report regularly on their tuberculosis activities, and that their staff are properly trained.

Each BMU should have a Tuberculosis Coordinator. This person, usually a paramedical professional, is responsible for ensuring that tuberculosis care and prevention services are implemented according to the national guidelines. Ideally, s/he should have demonstrated capacity in organising similar services at a facility level. S/he is usually a member of the BMU health management team and has a *supervisory* role. This post may be a full-time or a part-time position, depending on the workload. The main tasks are given in Text Box 6.2.

Text Box 6.2: Key tasks and responsibilities of a Basic Management Unit (district) Tuberculosis Coordinator

Overall management of tuberculosis services:

- Ensuring that all requirements for good quality tuberculosis services are met, including the availability of well-trained human resources;
- Ensuring a well-functioning specimen transport system, with a loop for communicating results from laboratories back to clinicians;
- Ensuring uninterrupted availability of tuberculosis drugs, laboratory materials, NTP forms and other supplies. This includes monitoring of lead times and action taken in case of delays;
- Conducting BMU-level data-driven performance review meetings and participating in provincial-level meetings;
- Participating in operational research to find answers to challenges in the implementation of tuberculosis services, and then applying research findings to address the issues identified

Overseeing tuberculosis recording and reporting:

- Ensuring that all NTP recording and reporting tools in BMU facilities are well-maintained and contain good quality data;
- Ensuring that active use is made of available tuberculosis data for decision-making and strengthening of services in both facilities and the BMU. This includes:
  - Revising the *Tuberculosis Treatment Cards* regularly. This card is usually filled in by the clinician or nurse deciding to start treatment with details regarding the regimen to be used;
  - Keeping the *BMU Tuberculosis Register* up to date;
  - Compiling the data reported in *Quarterly Tuberculosis Facility Reports* from the facilities into BMU reports;
  - Preparing, reviewing and submitting the *Quarterly Reports on Case Finding in BMU* and on *Tuberculosis Treatment Results* to the provincial level

Supportive supervision of tuberculosis services:

- Regular data-driven supervision of health facilities that are involved in the tuberculosis services at BMUs. This includes provision of feedback;
- Supporting facility staff to follow up on agreed action points summarised in the abovementioned feedback to improve the quality of the services provided

Support person-centred care:

- Supporting the evaluation and management of persons referred to BMU hospitals, including the management of persons with drug-resistant tuberculosis;
- Ensuring good-quality clinical services for people with presumptive and diagnosed tuberculosis in health facilities at the BMU, for example, by
  - Regularly checking the *BMU Tuberculosis Register* against the *Tuberculosis Laboratory Register* to make sure that all persons with a positive diagnostic sputum result are enrolled for treatment or, if they cannot be traced, that they are declared in the tuberculosis register as lost to follow-up;
  - Ensuring that all adults commenced on treatment undergo diagnostic sputum testing;
  - Making sure that all persons are started on appropriate treatment regimens based on a history of previous treatment and drug resistance results;

- Arranging support and directly observed administration of drug intake daily by a trained designated treatment supporter for all persons on tuberculosis treatment ;
- Providing counselling and testing for comorbid conditions, such as HIV infection, diabetes mellitus, smoking, etc. to all persons with tuberculosis and ensuring that those found to have other conditions receive or are referred for appropriate care;
- Organising contact investigation among all household and other close contacts of persons with infectious forms of pulmonary tuberculosis, providing appropriate treatment to such persons;
- Monitoring treatment response in accordance with the national guidelines;
- Ensuring that all persons are assigned a treatment result at completion of treatment

Coordination and collaboration with staff of other programmes in the BMU, such as laboratory and pharmaceutical services, HIV/AIDS, maternal and child health and other relevant services

6.3.3 Intermediate or provincial-level tuberculosis services

In order to maintain good-quality tuberculosis services, a system of support, mentorship and data-driven supervision should be in place to support BMU Coordinators. This is usually provided by a Tuberculosis Coordinator working at the *intermediate* or *provincial level*. This person is frequently a medical or paramedical officer with post-graduate training in public health. In addition to tuberculosis services, they may oversee the management of other conditions, such as lung diseases or other communicable diseases. Coordinators are usually members of the provincial health team. Their role is largely *supervisory* and *managerial*. Text Box 6.3 lists the main tasks of Provincial Tuberculosis Coordinators. They resemble the tasks of a BMU Coordinator, except that these apply to tuberculosis services and activities at the provincial level: the 'unit of management' is the BMU, whereas for BMU Coordinators this is the health facility.

Text Box 6.3: Key tasks and responsibilities of a Provincial Tuberculosis Coordinator

Resource mobilisation for tuberculosis services:

- Coordinating with relevant authorities to obtain adequate resources for new and existing services in BMUs in the province;
- In particular, resources may be required to guarantee adequate access to services among vulnerable populations, such as those living in remote areas, those belonging to displaced communities and prison inmates. This may involve advocating the establishment of new treatment facilities, mobile clinics or community-based schemes

Collaborating and coordinating services:

- For example, with provincial focal staff of HIV and non-communicable disease programmes, laboratory and pharmaceutical staff;
- With central tuberculosis unit staff

Human resource management:

- Participate in the recruitment of BMU Tuberculosis Coordinators;
- Provide tuberculosis training, both on-the-job and in the classroom, and mentoring of new and existing health care workers

Overall management of tuberculosis services:

- Ensuring that all the requirements for good-quality tuberculosis services are available, including the availability of well-trained human resources in all provincial BMUs;
- Overseeing specimen transport, with a loop for communicating results from laboratories back to clinicians;
- Ensuring uninterrupted availability of tuberculosis drugs, laboratory materials, NTP forms and other supplies. This includes consumables required for infection control;
- Conducting provincial data-driven performance review meetings and participating in national review meetings;
- Leading and participating in operational research

Supportive supervision of tuberculosis services:

- Regular data-driven supervision of BMUs. This includes providing regular feedback;
- Supporting BMU Coordinators and teams in following up the action points agreed upon in the abovementioned feedback to improve service quality;
- Reviewing quarterly BMU reports, compiling the provincial *Quarterly Reports on Case Finding in BMU* and on *Treatment Results* for submission to the central level

Overall management of tuberculosis laboratory and pharmaceutical services:

- Maintaining a quality control system for tuberculosis laboratory services;
- Overseeing stock levels of tuberculosis drugs and materials and ensuring their rational use in order to prevent stock-outs and overstocking

Participating in tuberculosis surveys and campaigns (such as prevalence and drug susceptibility surveys and active case finding campaigns)

6.3.4 Central-level/national-level tuberculosis services

The Central Unit of a NTP needs to be staffed by a full-time director and a team of well-trained officers to carry out the functions described below. Their duty is to lead and manage all tuberculosis-related collaborative activities and ensure good-quality services nationwide. The NTP should work closely with the departments responsible for primary health care, hospital care, laboratory services, pharmaceuticals, planning, human resource development, and training and finances.

The NTP Director is responsible for all tuberculosis-related activities in the country. The functions of the Central Unit are listed in Text Box 6.4.

Text Box 6.4: Key functions of a Central Tuberculosis Unit

Political commitment:

- Advocating for political commitment by providing key information and data to policy makers on tuberculosis and the cost of not eliminating tuberculosis;
- Facilitating translation of this commitment into meaningful national resource allocation to support tuberculosis services in the country

Resource mobilisation:

- Advocating for both human and financial resources;
- Advocating for both internal (national) and external funding

Making national policies, guidelines, standard operating procedures and strategic plans:

- Ensuring all-round participation in the preparation, review and costing of these documents and annual plans;
- Implementing, monitoring and evaluating annual plans
  - Monitoring frequently takes place through annual data-driven support supervision visits to provinces in the country, review of the provincial *Quarterly Reports* on *Case Finding in BMU* and on *Treatment Results* and data-driven national performance review meetings;
  - Evaluation frequently takes place through periodic external NTP reviews, national surveys, operational research, etc.

Ensuring a facilitating 'environment' and framework for tuberculosis care and prevention; monitoring the management of drug-resistant tuberculosis and recording and reporting:

- Ensuring diagnosis and treatment of persons with drug-resistant tuberculosis, and the decentralisation of services safeguarding service quality at all times;
- Ensuring through training, post-basic education, mentorship and supervision that national tuberculosis policies and guidelines are adhered to by health care workers at all levels of services;
- Ensuring good-quality provincial reports and promoting the use of data in decision-making to improve the quality of clinical and programmatic tuberculosis activities;
- Providing feedback on the abovementioned reports to the provinces and other departments that the NTP works with;
- Providing regular data-driven support supervision for provinces and provincial coordinators

Collaboration with key departments, such as the laboratory, pharmaceutical and radiology services, primary health care and hospital services:

- Coordinating with the laboratory department to ensure that a network of tuberculosis laboratory services is properly set up and supervised;
- Overseeing quality assurance activities and ensuring that these are supported by training;
- Ensuring, in collaboration with pharmaceutical and logistics/supply chain management systems, the quantification of required supplies, including reserve stocks, their timely procurement, and proper storage and regular delivery of diagnostic and treatment supplies throughout the country

Collaboration ancoordination with other relevant programmes:

- Collaborating with, for example, national programmes for HIV/AIDS, non-communicable diseases, mental health, tobacco control, etc. to ensure
  - Integrated management and support, including bidirectional screening, for example, for HIV infection and diabetes among persons with tuberculosis and for tuberculosis among people living with HIV, and provision of or referral for treatment of comorbidities;
  - Programmatic collaboration in planning, implementation, monitoring and evaluation of integrated and person-centred care for people with tuberculosis and comorbidities

Collaboration with communities, partners, civil society organisations, non-governmental organisations and other relevant stakeholders:

- Coordinating, monitoring and evaluating the implementation of national tuberculosis strategies by the different partners;
- Ensuring that all institutions with tuberculosis activities that are not directly related to the ministries of health are recognised and supported by the NTP and agree to follow the national tuberculosis guidelines. These institutions could include university teaching hospitals, city hospitals, other government departments with their own health facilities and different types of both formal and informal private health facilities
  - Facilitating and supervising the provision of tuberculosis supplies and ensuring staff training. In return, these institutions should report to NTPs on their tuberculosis activities

Facilitating operational research:

- Facilitating operational research into solutions to local challenges; translating research findings into revised strategies, policies and practices to address and resolve issues

6.4 How should the tuberculosis laboratory service be organised?

A well-functioning laboratory network is the first requirement for the successful management of tuberculosis. If the diagnosis is not made reliably and if follow-up examination to measure response to treatment is not trustworthy, all other activities will be affected. The network should be managed by one or more dedicated national or sub-national reference laboratories that also provide more advanced testing services. Laboratories at the provincial and peripheral levels should be integrated into the general health service and ensure the proper functioning of daily routine testing services, at least of AFB microscopy, and as far as feasible, also the WHO-recommended molecular techniques, Xpert® MTB/RIF or line-probe assays (LPAs). In low-income countries, mycobacterial culture is rarely feasible at these levels. In all but the smallest programmes, provincial-level facilities are crucial in providing supervision and quality assurance to peripheral-level facilities.

6.4.1 What are the tasks of the laboratory service?

The tasks of the tuberculosis laboratory service are to:

- Confirm the bacteriological diagnosis of tuberculosis;
- Ensure that persons with rifampicin-resistant tuberculosis are correctly diagnosed and determine whether there is resistance to the main second-line drugs;
- Monitor treatment response in persons with pulmonary tuberculosis; and
- Monitor resistance to tuberculosis drugs.

6.4.2 What is the basic laboratory diagnostic strategy?

Because unlike other techniques, AFB microscopy can assure complete coverage of the population at all times with minimal infrastructure requirements, it remains an essential test in all diagnostic centres. Where possible, it should be used in conjunction with rapid molecular diagnostics, which can help detect considerably more bacteriologically positive cases and can be partially decentralised. However, the infrastructure requirements for molecular testing – continuous supply of electricity, storage of cartridges, room acclimatisation and instrument maintenance and calibration – are complicated.

Mycobacterial culture has the highest diagnostic yield, but it is too slow and sample transportation, infrastructure and safety requirements are too cumbersome for it to be practical for routine diagnosis and monitoring under programme conditions.

Rapid molecular testing can substitute for AFB microscopy as a primary test in all cases with presumptive tuberculosis if resources and access can be guaranteed. If rapid molecular testing requires specimen transfer, an efficient specimen referral/transport system should be in place to reduce diagnostic delays and associated deaths and/or loss to follow-up. A robust system of communicating results back to the care provider is of vital importance. Modern communication technologies can help this, but alternative arrangements need to be in place in case these fail.

If adequate resources for accessible diagnosis using rapid molecular testing are not available, it should be used as a second test instead for AFB-negative people who do not respond to, for example, a course of antibiotics, particularly where chest X-ray is not available. In addition to a tuberculosis diagnosis, Xpert also provides information on rifampicin susceptibility, which can be used to guide the choice of an appropriate treatment regimen. This may be an important consideration for prioritising Xpert use for all diagnostic specimens in settings with a high prevalence of rifampicin resistance. In settings with a low prevalence of rifampicin resistance, the diagnostic network should be developed to allow early detection of rifampicin resistance among people who convert late, fail or relapse. This sort of a network needs a system of referring sputum specimens to laboratories with rapid molecular testing. Samples from persons who are rifampicin-resistant on rapid molecular testing should additionally be sent to the nearest LPA laboratory for rapid testing of susceptibility to fluoroquinolones and second-line injectables.

Samples for rapid molecular testing can be transported safely and conveniently by adding about 10 drops of liquefied sputum to about 1 ml of denatured alcohol in a 2 ml cryovial at room temperature and left to stand overnight. Ideally, samples should also be referred to the national or sub-national culture reference laboratory for full drug susceptibility testing. This requires rapid cold chain transportation or the use of preservatives to ensure the survival of the tuberculosis bacilli. Given the excessive delay in obtaining culture-based susceptibility test results and the excellent results that the standardised treatment regimen generally yields, even in case of rifampicin-resistant tuberculosis, treatment should be started without waiting for culture-based results.

Decentralised, rapid and reliable diagnosis of drug resistances other than resistance to the main drugs – isoniazid, rifampicin, fluoroquinolones and second-line injectables – is not feasible yet. Programmatic attempts to provide comprehensive drug susceptibility profiles based on the referral of specimens have generally failed. Furthermore, a comprehensive drug susceptibility profile, while desirable, is not essential for the standard treatment regimens presented in this Guide, since the comprehensive drug susceptibility profile impacts on treatment outcome only if there is existing resistance to the core drugs and/or most other drugs. In this Guide, we recommend the cascade approach to tuberculosis treatment regimens; we therefore expect only a small number of people to fail or relapse. As long as no incurable drug resistance has been created, patients remain readily curable by the next regimen in the cascade. Susceptibility testing for drugs other than the more important ones in order to determine appropriate treatment regimens should thus be reserved for persons who have acquired resistance to all the core drugs (i.e., those with extensively drug-resistant tuberculosis) and may need salvage treatment regimens.

6.4.3 How is the laboratory network managed?

To be able to function properly, peripheral laboratories need to be supported, usually by the national reference laboratory, and assisted by the intermediary (provincial or regional) laboratories. This support should cover equipment, supplies, training, supervision and quality assurance. AFB microscopy requires a good-quality binocular microscope, with 100x oil immersion objective for Ziehl-Neelsen staining. For Auramine fluorescence microscopy, a power peak-protected, blue light-emitting diode illumination instrument with 20x and 40-50x dry no coverslip objectives, and a battery pack should be provided. Fluorescence microscopes should be provided when more than 15–20 smears need to be examined per day. Good-quality reagents are crucial and stock solutions should be prepared and prequalified at the intermediate level. These should be supplied regularly, since even if kept in the dark, Auramine shelf life is particularly limited. Practical training is required to perform fluorescence AFB microscopy. Quality assurance of microscopy laboratories relies on reviewing laboratory performance by analysing routine performance reports and limiting rechecking to negative smears, followed by targeted problem-solving supervision visits. Special attention should be paid to total workload, proportion of positives among diagnostic versus follow-up smears and the proportion of scanty and 1+ smears.

Quality assurance and supervision are easily compromised by excessive decentralisation of microscopy laboratories. To ensure quality is maintained, sending slide panels with known results (panel testing) instead of rechecking routine smears may be a better option for quality assurance. Detailed information on establishing and carrying out these activities is given in *Priorities for Tuberculosis Bacteriology Services in Low-Income Countries* published by The Union.[18]

Running an Xpert network is less demanding once the initial installation of the equipment, often in an air conditioned space with stand-by battery power, has been completed. Cartridge stock-outs and frequent breakdown of machines or modules have been the main problems, requiring intensive logistical support. Such occurrences have regularly resulted in total breakdown of Xpert testing, forcing a return to microscopy only. With good training the recommended molecular techniques require little human intervention; quality control is then limited to the analysis of system errors recorded by the machine and occasional panel testing of a few samples provided by the manufacturer, or using panels of well-characterised strains from the WHO supranational tuberculosis reference laboratory network.

6.5 What supplies are needed in tuberculosis care and how are these managed?

In order to have the best outcomes in the management of tuberculous infection and tuberculosis disease, health facilities need:

- Adequate supply of laboratory items to diagnose people with tuberculosis and monitor treatment response. This is discussed in section 6.6 below;
- Sufficient and regular supply of medicines so that patients on treatment can be provided uninterrupted treatment. These include:
  - Tuberculosis drugs;
  - Ancillary medicines for the management of drug side effects (anti-emetics, antacids, pyridoxine, potassium replacement, thyroxine, medicines for psychiatric conditions, etc.);
  - Medicines for the management of possible comorbidities (cotrimoxazole, antiretroviral drugs, metformin, etc.); and
- Forms and stationery for recording and reporting.

The supply of medicines for the management of comorbidities and drug side effects may be supervised by another department. Close coordination with pharmacy and other relevant staff is key to the prevention of treatment interruption due to stock-outs.

6.5.1 How are tuberculosis supplies managed?

Tuberculosis commodities are part of the country's general pharmaceutical supplies. The supply management process comprises the following four steps:

1. Selection of laboratory supplies and tuberculosis drugs: based on the diagnostic algorithms and treatment regimens recommended by the national guidelines, the NTP selects the formulations and packaging by promoting whenever possible *fixed-dose combinations* (FDC), *child-friendly formulations* and the use of blister packs over loose tablets (better conservation and hygiene).
2. Procurement:
   - Quantifying needs: this is usually done once a year for a country based on morbidity figures, consumption figures, current and future planned activities, etc. It should be reviewed every 6 months to ensure that it continues to reflect the country's needs.
   - Qualifying the suppliers: depending on the country, this activity is facilitated by the national central medical store or supported by the Global Drug Facility to guarantee access to quality-assured tuberculosis commodities. This activity is meant to prevent substandard items, which could jeopardise diagnosis and tuberculosis treatment outcomes, from entering the supply chain.
3. Storage and distribution: this is the joint responsibility of the NTP and the national central medical store, the peripheral stores and health facilities. Ensuring good storage and distribution practices along the supply chain maintains the integrity of tuberculosis drugs and laboratory supplies until they reach the patient. Inventory management at each storage level forms the basis for reordering.
4. Use of supplies: this step requires the monitoring and supervision of the implementation of the NTP-approved protocols and regimens, but also the regular reporting of diagnostic activities, morbidity and consumption data to help the NTP adjust needs and improve the quality of the tuberculosis service, including patient care.

The NTP oversees the entire process. Good collaboration with other relevant departments and programmes, such as the national AIDS and non-communicable disease programmes, is required. For the efficient functioning of the drug supply chain, the roles and responsibilities of each stakeholder need to be clear, with documented procedures in place for every step.

6.5.2 What are the main tasks of the BMU Tuberculosis Coordinator in supply management?

For good-quality tuberculosis diagnosis and care, tuberculosis laboratory consumables and drugs must be available at all times. This is the main supply chain management-related task of a BMU Coordinator. S/he must also safeguard against overstocking, which could result in expired supplies and wastage. Other tasks pertain to

- Preparing consolidated stock level reports and orders for the BMU based on *Quarterly Tuberculosis Case-Finding Reports* and their submission to the provincial level. This facilitates the quantification exercise for the entire country;
- Overseeing the storage, order placement and distribution of tuberculosis supplies to health facilities in the BMU;
- Supervising, monitoring and training in the use of tuberculosis commodities.

To ensure long-term sustainability, tuberculosis supplies should ideally be managed through the national (general) supply chain mechanism. This mechanism needs to be monitored by the NTPs, provincial and BMU Tuberculosis Coordinators. When the general mechanism does not work well (for example, due to procurement delays because of a lack of funding or lack of transport from the central stores to provinces and BMUs), Tuberculosis Coordinators at all levels need to find emergency solutions to redistribute available drugs to ensure that these reach patients on treatment. If tuberculosis case reporting is unreliable, tuberculosis drugs may have to be distributed based on consumption until accurate reporting has been re-established.

6.5.3 How are tuberculosis drugs ordered to maintain an uninterrupted supply?

In many countries, the transfer of information (post and telecommunications) is difficult and transportation of goods is unreliable, so delays can occur. Supplies may not always reach BMUs and health facilities on time, especially if these are far from where the supplies are stored. It is very important to make allowances for delays that may be caused by these problems. This is accomplished by

- Placing orders at regular intervals and always according to the agreed timetable. In a BMU, orders are ideally placed once every quarter based on case finding reports. For remote facilities with a significant number of patients on treatment, orders can also be placed every quarter. For facilities situated closer to the stores, a system of monthly orders may be adopted.
- Calculating and adding a 'reserve' stock of supplies to every order.

Reserve stocks are necessary at all levels of the supply chain; the quantity varies according to the ordering frequency, the reliability of the delivery system and storage capacity. The goal is to avoid stock-outs without creating overstock, which could lead to expiry and diversion of resources. It is commonly accepted that the reserve stock should be equivalent to the requirements of the lead time. The *lead time* is defined as the time between sending the order and receiving the goods from the supplying store. As the number of diagnosed people with tuberculosis may vary and delivery of drugs can be delayed, it is common to increase the reserve stock. In Union-supported programmes, experience has shown that a reserve stock equivalent to the total consumption in one quarter can be added to quarterly BMU drug orders. It is, however, recommended that facilities with fewer patients place orders only on demand, so drugs are delivered only after individual patients have been identified to avoid having expired medicines in stock. Much larger reserve stocks are required at the provincial levels and their quantities should be determined based on the frequency of in-country drug distributions, availability of transport, etc.

Tuberculosis drug orders are placed once the *Quarterly Report on Tuberculosis Case Finding in BMU* has been consolidated. These morbidity data are compiled in the *Quarterly Facility Tuberculosis Report* and the *Quarterly Report on Tuberculosis Case Finding in BMU* (Appendix, Form 7 and Form 8) and then transferred to the *Quarterly Order Form for Drug Supplies at BMU Level* (Appendix, Form 10). The quantity of supplies required for tuberculosis treatment in each quarter is determined as follows:

The number of patients to be treated is determined based on the *Quarterly Report on Tuberculosis Case Finding in BMU* that has been completed for the preceding quarter.

- The number of patients is entered under the column headed 'Cases'. The total number of adult new cases (bacteriologically confirmed, clinically diagnosed and extra-pulmonary cases) is given in the first column under 'A' (2RHZE/4RH), the number of previously treated cases without rifampicin resistance is entered in the line below (6RHZE) and the number of paediatric cases in the third line (2RHZ(+E)/4RH).
- The quantity of each drug that is required in a quarter (column B) is estimated by multiplying the number of cases by a "factor", F, which is the average number of tablets to be taken by a patient during the entire course of treatment, and by totalling all the numbers in the two columns (A x F).
- The reserve stock is equal to the amount required for the specified interval, usually a quarter. This figure (column C) is entered into the second section of the form.
- The quantity of drugs in the store (pharmacy inventory) at the end of the quarter should be counted and entered under column D.
- The total quantity to be ordered is calculated by adding the quantity of drugs required for the patients registered during the quarter (column B) and the quantity of reserve stock needed (column C), and then subtracting the quantity of drugs in the store (column D), i.e., B + C – D.

This approach works well for orders of first-line drugs and has the advantage of facilitating close monitoring of whether the amount of drugs dispensed actually correspond to the number of patients reported (see section 6.6.5). This helps prevent irregularities in ordering (for example, non-existing patients) causing losses with possible risk of incorrect treatment and development of drug resistance.

In some settings, reliable case finding reports may not be available or are delayed. In these situations, the quantities of the drugs to be ordered can, as an emergency solution, be determined based on the consumption figures from the dispensary records. In hospitals where most people with tuberculosis only receive part of their treatment, ordering is also usually based on consumption. The quantities to order (Qo) are determined as follows:

- The total consumption of medicines during the previous quarter (M);
- The reserve stock (based on The Union's experience with projects, this is generally thought to be equivalent to the total consumption of BMUs and health facilities in one quarter). This means that the reserve stock is equivalent to M;
- The quantity of drugs in the store (pharmacy inventory) (D);
- The total quantity to be ordered is calculated by adding the quarterly consumption, multiplying it by 2 to include a reserve stock and subtracting the quantity of drugs in stock, that is, Qo = 2M-D

A small stock of single tuberculosis drugs could be kept at BMUs for persons with severe adverse drug reactions. In such situations, regimens using fixed-dose combinations should be discontinued. Because it is impossible to predict the type of single drugs required by these patients, it is recommended that the bulk stock be kept at BMU stores and orders be delivered based on real needs. This can be requested under 'other' on *Quarterly Order Form for Drug Supplies* (Appendix, Form 10).

6.5.4 How are supplies stored?

The basic rules of stock management are the same at each level of the supply chain.

Drug stocks should be kept in secure conditions, and controlled for temperature and humidity as per the manufacturer's instructions. This is especially important in case of tuberculosis drugs, as some of them are particularly sensitive to humidity, which can affect their potency and shelf life expectancy. Stores should be neat and shelves and pallets should be used. Access to the store should also be limited to authorised staff to prevent theft.

Stock management requires strict controls. For each individual drug or laboratory item, a stock card should be maintained for record keeping. All items received (in) or delivered (out) to health facilities or for destruction should be recorded. Every month, a physical stock count (inventory) of current stock quantities and expiry dates should be carried out to ensure that this tallies with the balance indicated on the stock card. Before re-ordering new supplies, it is good practice to make this inventory to avoid any over- or under-supply.

Tuberculosis commodities should be distributed according to the date of expiry of each individual item. Items that expire first should always come out of the stock first (i.e., follow the FEFO, first expire first out, rule). Managing stocks properly at all levels of the supply chain will ensure that expired drugs are not delivered to patients. Items with expiry shorter than the time between two deliveries should not be distributed to peripheral health facilities, as this could lead to a waste of resources.

Damaged or expired drugs should be quarantined as they may be less effective and their use may contribute to the development of drug resistance. These quarantined items should be disposed of and physically destroyed according to the national guidelines.

Sufficient stocks of single-use injection materials (syringes, needles and water for injection) should always be maintained so that injectables can be administered safely.

6.5.5 How is the use of supplies monitored?

Monitoring the use of tuberculosis commodities facilitates stock availability, ensures quality patient care and prevents irrational use of drugs. Monitoring of storage, stock availability, distribution, use and reordering are an essential part of the regular supervision carried out by Provincial Tuberculosis Coordinators of BMUs and by BMU Tuberculosis Coordinators of facilities. Supervision also facilitates the redistribution of drugs among facilities when necessary. Supply chain management issues should be an integral part of supervision checklists.

It is recommended that the quantity of tuberculosis drugs dispensed annually be verified against the number of registered patients with tuberculosis to see if these correspond. This can be done using the NTP reports, as explained in Text Box 6.5.

Text Box 6.5: How to compare quantity of tuberculosis drugs dispensed yearly with the number of patients registered with tuberculosis

This comparison can be done using the following NTP reports; the order of use should be in the reverse order to that used to calculate drug requirements.

- From *Quarterly Order Form for Drug Supplies*, calculate the quantity of each drug used in the year (four quarters): stock at the beginning of the year plus drugs received during the year minus stock at the end of the year
- For each drug, calculate the corresponding number of people who could have been treated by dividing with the corresponding 'factor' on the form
- Compare with the number of people who actually received drugs according to the *Quarterly Report on Tuberculosis Case Finding in BMU*. This comparison can be done both by facility and for the whole BMU.

Please note: the purpose of this comparison is not to find an exact correspondence, but to detect major differences and then examine the reasons for the difference.

Significant differences in facilities may be explained by

- Patients transferring in (adding to consumption) or transferring out, being lost to follow-up or dying (reducing the consumption)
- Drugs dispensed to patients during admission to a BMU hospital before referral for continued treatment in a facility may also be taken into consideration
- Errors in numbers (poor quality of data), but consumption higher than originally estimated based on the number of reported patients may also be due to loss of drugs; this should be further investigated.

6.6 How are laboratory supplies managed?

As the quantity of materials required in a peripheral laboratory is small, it can be supplied every 6 months (every other quarter) rather than every quarter. The minimum requirement for reserve stocks should at least be the equivalent of materials required in one quarter. More reserve stocks may be supplied to remote laboratories. Most laboratory consumables do not expire rapidly, but are difficult to procure and/or transport, and supplies tend to be erratic. If shelf life allows, stocks of these items should be sufficient to cover at least 6 months at the intermediary/provincial level and 1 year at the national level.

Given that the shelf life of rapid molecular diagnostic reagents is 12–24 months, procurement and distribution needs to be more frequent and preferably staggered, with proportionally smaller stocks. The most accurate method of calculating requirements of laboratory supplies should be based on the reported number of tests performed and the amount of supplies left in stock. When there is an expansion or a change in strategy, the best estimate of the expected increase of laboratory materials should be based on past experience. To avoid interruptions at the implementing level, a push system for supplies from the national and/or provincial level, without waiting for requests, will be most effective. Laboratory performance reports, such as the *Quarterly Report for Peripheral Tuberculosis Laboratory Performance and Stock Situation* (Appendix, Form 11), are the basis for distributed stocks. The amounts of different reagents and other consumables required per test are calculated using a computer spreadsheet provided by the supplying authority, assuming, for example, for each AFB microscopy smear test 3–5 ml of the various staining solutions, 1 slide and 1 sputum container, 0.1 ml immersion oil (for Ziehl-Neelsen microscopy, not for fluorescence) and 1 ml burning spirit, etc. After adding the reserve stocks allowed and subtracting the balance in stock, the calculated requirements are rounded off to the nearest packing unit. The reserve stocks allowed depend partly on the shelf life of the items, but mainly on the expected delay between the order and delivery (lead time). This can be very long for international procurements, so that for a country, large reserves spanning even 1 year may be justified. This type of quantification can be used for any of the consumables needed for the various laboratory tests in routine use in the programme.

In recent years, the logistics of laboratory supplies have been simplified by the procurement of kits, as for examples, consumables, basic microscopy equipment, etc. for Ziehl-Neelsen or for fluorescence microscopy. Consumable kits for microscopy typically contain all items required to perform 1,000 smears. These are supposed to be distributed as one kit (unit) per end user. For small laboratories performing few tests, the number of consumables in a kit may exceed consumption by the expiry date of the reagents. More importantly, the quality of the primary staining solutions provided in these kits is not always the best, necessitating a more robust technique; sometimes this is also done by reducing the expiry date. The shelf life of ready-to-use primary staining reagents, crucial for optimal microscopy results, is a maximum of 5 years for carbolfuchsin (Ziehl-Neelsen) and only a few months for Auramine (fluorescence microscopy) working solutions. For a concentrated Auramine stock solution, this is about 2 years. Furthermore, in light of the procurement and distribution delays, the risk of kit reagents expiring is thus very real. Local reagent production at the provincial level, where satisfactory control of all elements of the preparation, quality control and distribution can be assured, should remain a valid option.

7 Monitoring tuberculosis care

Good quality detection and care of persons with tuberculosis requires the maintenance of accurate records on each person, with periodic reporting of case finding results and treatment outcomes. This is also important for ensuring adequate supplies of drugs and essential materials. In addition, the information that is routinely collected and validated needs to be analysed and used so that challenges with both clinical and programmatic management are identified and acted upon. The NTP central unit should provide regular feedback to the provincial and BMU health teams.

Recording and reporting tools should be simple and concise, and should be safely filed and stored. Data to be collected should be in line with international definitions and recommendations, with country adaptation where necessary. The amount of data is best kept to the *absolute minimum* because the more information is collected, the more difficult it is to ensure its accuracy. Operational research (see section 7.9) can be conducted to answer questions that cannot be answered through analysis of the routinely available data.

To facilitate breakdown and review of the data entered into registers, it is a good practice to:

- Separate the quarters clearly by adding an empty row below a line drawn after the last registered patient in a given quarter, OR start entries for each quarter on a new page of the register;
- Write positive sputum results in red ink; and
- Avoid the use of white-outs (correction fluid) so that all changes in the registers remain visible.

This Chapter describes recording and reporting forms, registers and reports for patients with presumptive and diagnosed tuberculosis and explains how staff can use local data to strengthen tuberculosis care and prevention, and how these data can also be used for supervision and performance review.

7.1 Records of diagnostic examinations ('presumptive tuberculosis')

Health staff should enter details of all individuals who present themselves to a health facility with symptoms and signs suggestive of tuberculosis in the *Presumptive Tuberculosis Register* (Appendix, Form 1). The following information should be registered: name, address and phone number (in case the person does not return for test results), whether they have a known contact and if they belong to a risk group. If a person with presumptive tuberculosis participated in an active case finding intervention or campaign, this could be indicated under a specified risk group. The *Presumptive Tuberculosis Register* is used to monitor the number of people with presumptive tuberculosis, and losses and delays at each step of the *case finding cascade*, from identifying persons with presumptive tuberculosis to the collection of sputum specimen, sending it to the laboratory and receiving test results. A tuberculosis registration number should be assigned and noted down in the 'Remarks' column if tuberculosis is diagnosed. This information can be used to assess the *quality* of the case finding services, and measures required to strengthen the services to ensure *universal health coverage*. The *Tuberculosis Laboratory Register* (see below) has a more restricted scope, as it contains information only on those samples that have reached the laboratory.

The *Presumptive Tuberculosis Register* is used to monitor

- How many people with presumptive tuberculosis are identified and registered by comparing rates of presumptive tuberculosis per 100,000 population in the catchment area;*
- How many of those registered undergo complete evaluation;
- How many of those who were evaluated are sputum-positive ('positivity rate'). This can be used to assess whether case finding and testing are well targeted.

In small facilities, one register for presumptive tuberculosis, usually kept in the outpatient department, may be sufficient. In large facilities with a large number of people with presumptive tuberculosis, each entry point into the tuberculosis services may need to have this register. The number of people identified at each entry point can also be recorded in one register by including a variable 'Unit/ Department in which detected'.

* Numbers are transformed into rates per 100,000 population (the absolute number is divided by the catchment population multiplied by 100,000) in order to compare between areas and over time.

When laboratory results are returned to facilities or units, the type of test and the result should be recorded in the *Presumptive Tuberculosis Register*.

Health staff should collect a sputum specimen for smear microscopy and/or rapid molecular testing from every (adolescent and adult) person with presumptive tuberculosis at the first visit. The *Request and Reporting Form For Sputum Smear Examination/Rapid Molecular Test* (Appendix, Form 2) should then be filled in. In addition to the address and telephone number of the person with presumptive tuberculosis, the following information regarding the type of test and the reason for testing should be recorded: i) microscopy 'Diagnosis' or the month of treatment under 'Month of follow-up' in case of treatment monitoring; and ii) rapid molecular test, if the aim is to detect tuberculosis or rifampicin resistance in a new or previously treated person.

The laboratory fills in the lower part of the request form with the results of each sputum examination and sends it back to the requesting facility, ideally also informing them by telephone in case of a positive test result. Settings using LPA or TB-LAMP may include additional boxes for these tests.

When sputum samples are received in the laboratory, the information on the request form is entered in the *Tuberculosis Laboratory Register for Sputum Smear Microscopy* (Appendix, Form 3) or a *register covering both smear microscopy and rapid molecular testing* (depending on the test to be carried out), with key explanations and elaborations in the corresponding questions and answers, available from: http://www.who.int/tb/publications/definitions_faq/en/#.[19] Each person examined for diagnosis will have two sputum examinations if sputum microscopy is used and one examination if rapid molecular testing is used. In the case of microscopy, the results of the two samples are entered *in a single line* in the *Tuberculosis Laboratory Register* to facilitate tabulation and analysis of data.

7.2 Records of cases of tuberculosis

When the doctor, clinical officer or nurse decides that the person has tuberculosis, a health care worker completes a *Patient Identity Card* (Appendix, Form 4) that is kept by the person. This card contains their name, age, sex, address and phone number, as well as the name, address and phone number of the treatment supporter. It also includes the *BMU Tuberculosis Register* number and the name of the BMU and facility. The site of disease, result(s) of bacteriological examination at diagnosis, the date of treatment start and the regimen prescribed are recorded. Space is provided for the dates of follow-up appointments and the results of follow-up sputum examinations. This card is a confidential document, as it contains medical information. All persons with tuberculosis should be informed of this and advised to present the card only to health care workers who may need to know their condition before other treatments are prescribed. This card is especially useful if the persons on tuberculosis treatment move to another facility to continue treatment.

At the time of diagnosis, the health care worker fills in a *Tuberculosis Treatment Card* (Appendix, Form 5), which is kept at the facility where the person receives treatment. Sputum test results should be recorded immediately on this card.

If treatment is supervised by a treatment supporter, they should tick off each date to indicate the daily intake of medicines in a copy of the *Tuberculosis Treatment Card* or the *Patient Identity Card* or a specially designed *Treatment Supporter Card*. When the treatment supporter collects drug supplies with or without the patient (weekly, every 2 weeks or monthly), the information on the card is copied into the *Tuberculosis Treatment Card* kept in the facility.

At treatment completion, the treatment supporter's card is filed at the facility. Treatment cards are crucial to assess and verify adherence and treatment outcomes. Details about HIV status, cotrimoxazole preventive therapy and antiretroviral treatment, if HIV-positive, diabetes and tobacco smoking status can also be included in the card. Some NTPs may consider including a list of contacts, with names, ages, if screened, if found to have tuberculosis and those started on TPT (that is, not found to have tuberculosis).

In facilities with more than a handful of persons with tuberculosis, it may be practical to have a *Facility Tuberculosis Register* (Appendix, Form 6), which contains selected key information from the *Tuberculosis Treatment Card* to facilitate supervision. The BMU Tuberculosis Coordinator should then regularly copy the information from the *Facility Tuberculosis Registers* into the *BMU Tuberculosis Register*, which usually has the same format.

In BMUs with more than one laboratory offering tuberculosis tests ('diagnostic centres'), the BMU Coordinator may decide to have *'Sub-BMU Tuberculosis Registers'* covering the facilities in the catchment area of each diagnostic centre.

At the end of each working day, the health care worker responsible, frequently a tuberculosis nurse, should collect all the *Tuberculosis Treatment Cards* of the people who were seen during the day and transcribe the relevant information into the *Facility Tuberculosis Register*, particularly the results of follow-up smear examinations.

The health care worker responsible should meet with laboratory staff once a week to ensure that all people recorded in the *Tuberculosis Laboratory Register* as bacteriologically confirmed have been enrolled on treatment or referred to another BMU for treatment initiation. Those found positive in the *Tuberculosis Laboratory Register* and for whom no record has been made in any other *BMU Tuberculosis Registers* should be entered into the *BMU Tuberculosis Register*, traced, started on treatment and evaluated with all other patients. If this person is not found, the treatment result should be recorded as *lost to follow-up*.

People diagnosed with tuberculosis should be recorded in numerical order by the date when they become known to the health care worker responsible for the tuberculosis register *('date of registration')*. Numbering commences with number 1 (one) at the beginning of each calendar year, regardless of when the person was diagnosed or when they commenced treatment.

All people with tuberculosis detected and/or enrolled on treatment at the BMU should be registered in the *BMU Tuberculosis Register*, which is the main source document for the quarterly reports required by the NTP. This register *includes* those people who may have *died* or were *lost to follow-up before* starting treatment. It also includes those who had been hospitalised prior to being *referred* (in a situation where the hospital does not report patients, who are then only reported by the BMU) or transferred (in a situation where the hospital reports patients while the BMU registers them as 'transfers in', and does not include them in the case finding report). It should also include people with rifampicin-resistant

tuberculosis independently of whether they started first-line and/or multidrug-resistant tuberculosis treatment. These people are also entered in the MDR-TB register (see *Field Guide for the Management of Drug-Resistant Tuberculosis*).[2] Persons enrolled on treatment and registered at another BMU, and who transferred to this BMU to continue treatment should be recorded in the *BMU Tuberculosis Register* as *transferred in*.

Accurate recording is important. This includes classification according to the i) correct 'disease site' and ii) history of previous tuberculosis treatment, as shown in Text Box 7.1.

Text Box 7.1: Classification of tuberculosis cases

Classification according to disease site	
	Definition
Pulmonary tuberculosis	Those with tuberculosis of the lungs, including those who are bacteriologically confirmed (using sputum smear and/or rapid molecular testing) and those who are clinically diagnosed (without bacteriological confirmation)
Extra-pulmonary tuberculosis	All other individuals, including those with tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion (the specific site should be recorded)
Miliary and disseminated tuberculosis	These are classified as *pulmonary* because the lungs are also generally affected. People with both pulmonary and extra-pulmonary tuberculosis will be categorised as pulmonary tuberculosis
Classification according to history of previous tuberculosis treatment	
New case	Person who has never been treated previously or was treated for less than 1 month
Relapse case	Person who, having been previously treated, was declared cured or treatment completed prior to being reported with tuberculosis again
Treatment after failure	Person who, while on treatment, is smear-positive at 5 months or later during the course of treatment and who then starts a 'new' treatment
Treatment after loss to follow-up	Person who had been on treatment for 1 month or longer and who returns to the health service after having interrupted treatment for 2 or more months, when s/he starts a 'new' treatment
Transfer in	Person who was originally registered in another *BMU Tuberculosis Register* but transferred to the current BMU to continue care; s/he retains the previous registration number from the referring BMU and outcomes are reported as part of the original BMU cohort; or a person who was hospitalised prior to being *referred* (in contrast to *transfer*, see below) to the BMU (and therefore was not included in a *Quarterly Report on Tuberculosis Case Finding in BMU* from the hospital)
Other	All other registered patients, for example, 'chronic patients' who could not be cured by the most powerful regimen used in a given programme (treatment for multidrug-resistant tuberculosis) and are being followed up without adequate treatment

As discussed in Chapter 3, it is critical that health staff determine whether all persons with bacteriologically confirmed tuberculosis have *previously* been treated for as much as 1 month. Incorrect designation may result in inappropriate diagnostic investigations and incorrect treatment since people who have been treated before are at higher risk of resistant strains. The correct assignment of previously treated people to one of the three groups – *relapse, treatment after failure* and *treatment after loss to follow-up* – allows precise evaluation of epidemiological trends and drug resistance patterns. People who are registered as relapses, failures and treatment after loss to follow-up are given a new registration number when a new treatment regimen is initiated.

7.3 Records of treatment outcome

The result (outcome) of treatment for every individual with tuberculosis should be recorded as soon as it becomes available. It is important that the outcome definitions presented in Text Box 7.2 are adhered to so that comparisons can be made across BMUs, provinces and countries over time. The *first of these events* to occur is recorded as the treatment outcome.

When analysing the results for all individuals registered for tuberculosis treatment, individuals moved to multidrug-resistant treatment are given a result according to the modified definitions presented in the *Field Guide for the Management of Drug-Resistant Tuberculosis*.[2] This is followed by a separate sub-analysis for (1) new patients, (2) previously treated patients not found to have rifampicin-resistant/multidrug-resistant tuberculosis, and (3) patients with rifampicin-resistant/multidrug-resistant tuberculosis.

Text Box 7.2: Definitions of treatment outcomes of all individuals registered for tuberculosis treatment

Treatment result	*Definition*	*Comment*
Cured	Person with bacteriologically confirmed tuberculosis who was smear-negative (or culture-negative) in the last month of treatment and on at least one previous occasion	
Treatment completed	Person who completed treatment but whose smear (or culture) results are not complete enough to classify them as cured	
Treatment success	Sum of the number of people who were cured and those who completed treatment	
Treatment failure	Person with bacteriologically confirmed tuberculosis who was smear-positive (or culture-positive) at 5 months or later of treatment (confirmed by a second specimen)	Could be due to the presence of dead bacilli, non-adherence to treatment or drug resistance
Died	Person who died for any reason *before* or *during* treatment	May be an indicator of diagnostic delay, the effect of the HIV epidemic in the community, the proportion of multidrug-resistant tuberculosis or of elderly tuberculosis patients in the community
Loss to follow-up	Person who did not start treatment or whose treatment was interrupted for ≥2 consecutive months	This proportion reflects service quality and its ability to 'hold cases'
Moved to MDR-TB treatment	*Preliminary* outcome for person with detected rifampicin resistance who is started on MDR-TB treatment before the end of first-line treatment. When MDR-TB treatment outcome becomes available and is recorded in the MDR-TB register, the result should be entered here instead of in "Moved to MDR-TB treatment", which should be crossed out.	With shorter MDR-TB regimens, most of these people will have a treatment outcome at the time of submission of the quarterly report
Transferred out	Person who is known to have been transferred out to another BMU to continue treatment but for whom no information about treatment outcome is available	Health staff should find out the outcome and decide how results can be communicated between BMUs. It may also be important to ascertain the reasons why people on treatment move
Not evaluated	Person whose outcome is unknown	Unacceptable outcome that should be as low as possible

7.4 What reports should be prepared?

Reporting case finding results and treatment outcomes have been found to be most useful every 3 months (quarterly) when tuberculosis activities are assessed during supervisory visits and at performance review meetings. This assessment is intended to detect challenges faced by the health services in providing tuberculosis care, leading to agreed actions and the estimation of supply requirements.

Quarterly Facility Tuberculosis Report (Appendix, Form 7)

This new report, which provides a quick overview of selected key data, is used by facility staff and BMU Tuberculosis Coordinators to monitor how tuberculosis services are implemented in each facility. It is filled in with the help of the information in the *Presumptive Tuberculosis Register* and the *Facility Tuberculosis Register*, and also includes information about stock levels of tuberculosis drugs. It may be filled in by the staff in the facility or by the BMU Coordinator during visits or at performance review meetings.

First, information in the *Presumptive Tuberculosis Register* and the *Facility Tuberculosis Register* for the quarter that had just ended is *validated* by comparing entries against each other, the treatment cards and the *BMU Tuberculosis Register*. All individuals registered during the quarter are then entered line by line: the first row is for presumptive cases (tuberculosis case finding) and HIV status among them. Where several registers for presumptive tuberculosis are in use in one facility, the information contained in them should be combined for presentation in the facility report. People with presumptive tuberculosis may also be reported by risk group (household/close contact, people living with HIV, person diagnosed with diabetes, etc.), especially if active case finding is taking place. The following five rows are dedicated to the following data from the *Facility Tuberculosis Register*: number of people registered, HIV indicators, those on directly observed treatment (DOT), treatment outcomes (for all categories of people registered 1 year before) and the number of previously treated people tested for rifampicin resistance. NTPs may consider modifying groups tested for rifampicin resistance according to their algorithms. The last row should present stock levels of tuberculosis drugs with months of stock available (calculated from stocks cards, see section 6.6) and expiry dates.

Quarterly Report on Tuberculosis Case Finding in BMU (Appendix, Form 8)

Descriptions of cases recorded during the quarter in the *Quarterly Facility Tuberculosis Report* are presented in greater detail in the *BMU Tuberculosis Register*. Any case classified as 'Transfer in' is not reported but any case classified as 'Other' should be reported. A person is classified as having bacteriologically confirmed tuberculosis if any diagnostic sputum test (by type of test: microscopy, rapid molecular test or both) result is positive. People with pulmonary tuberculosis with no bacteriological confirmation may be reported separately; these fall into two categories: i) those who have a negative sputum test result (and are clinically diagnosed), and ii) those who do not have any diagnostic test result at all even though they have been started on treatment. This is especially important in settings where many people are not tested, which is frequently the case in facilities lacking a specimen transport system. Recording and reporting the proportion of people on tuberculosis treatment without a diagnostic test facilitates monitoring of interventions to correct the situation.

The next step in preparing the report is to determine the number of registered people with tuberculosis in the quarter under three main groups: i) pulmonary tuberculosis, bacteriologically confirmed, ii) pulmonary tuberculosis, clinically diagnosed, and iii) extra-pulmonary tuberculosis. Each group is then divided into new cases, relapses and others (treatment after loss to follow-up, failure, other previously treated). The example below shows how to collect data systematically from a paper-based register; this is also important when validating information in electronic registers.

- Note where the quarter starts and ends; draw a line below the last patient registered in the quarter.
- Tick the box against each patient when working down the register line by line in section 1 of the report form or on a separate sheet of paper copying block 1.
- Check if the patient has a positive sputum test result before treatment (on smear microscopy or on rapid molecular test) and then check the "Category of case". If they have a positive test and the category is 'new', add a '|' in the first box as shown in Table 7.1.
- If the next patient has extra-pulmonary tuberculosis and is a relapse, add a '|' in the first box under 'Extra-pulmonary' and 'Relapses'.
- Use the same method for all patients when tallying.
- The total number of cases here should correspond with the total number of cases entered in the tuberculosis register, with the exception of 'Transferred in' patients.

Table 7.1: Determining the distribution of tuberculosis cases by category

Pulmonary tuberculosis: bacteriologically confirmed			*Pulmonary tuberculosis: clinically diagnosed*			*Extra-pulmonary tuberculosis*			*Total*
New cases	Relapses	Other*	New cases	Relapses	Other*	New cases	Relapses	Other*	
𝍸 |			||||			||	|		**13**

* Other includes treatment after failure, treatment after loss to follow-up and people classified as 'other' in Text Box 7.1.

Conditions determined by the NTP to be comorbidities are each accorded a section in the register which is then filled in. A section for contact management cascade can also be included to capture the number of contacts (by age group) of people with bacteriologically confirmed tuberculosis, the number screened and found eligible and started on preventive treatment and those found with tuberculosis (not shown in the form).

In this revision of the *Quarterly Report*, it is proposed to include information on the type of diagnostic sputum test (sections 4 and 5). Whether a rapid molecular test or smear microscopy or both were used for individuals with presumptive tuberculosis and tuberculosis disease should be indicated. This information is available in the laboratory and *Presumptive Tuberculosis Registers* and *Quarterly Facility Tuberculosis Reports*. Also, the number (and proportion) of persons with a positive test result is recorded to assess whether case finding activities are able to target the 'right' people.

Optional information could include:

i) Risk groups among people with presumptive tuberculosis, especially if active case finding is carried out, and
ii) Information on the type of test used and those with positive test results to assess implementation and yield of different case-finding algorithms.

A copy of the *Quarterly Report on Tuberculosis Case Finding in BMU* should be kept on file at the centre because it will be used 12 months later when reporting on treatment outcomes.

Quarterly Report on Tuberculosis Treatment Results (Appendix, Form 9)

The *Quarterly Report on Tuberculosis Treatment Results* (Appendix, Form 9) is completed for the same quarter as the report on case finding, but for a cohort registered 12 months earlier. For example, when this report is prepared for the second quarter during the first and second weeks of the third quarter, the form should include details of the treatment outcomes of persons registered in the second quarter of the previous year. The treatment result for every person should have been recorded by this point in time. All registered persons with tuberculosis (the full 'cohort') should be included in this first outcome analysis, including persons who have been moved to multidrug-resistant treatment. Persons registered with tuberculosis are assessed under four separate groups:

i) New bacteriologically confirmed cases;
ii) Previously treated bacteriologically confirmed cases;
iii) All other new cases;
iv) All other previously treated cases.

As they have different levels of drug resistance and have been treated with different treatment regimens (see section 3.2.4), this Guide recommends that new and previously treated cases be assessed separately. It should be noted that WHO reports assess new and relapse cases together.[20]

This Guide also differs from the WHO reports in the following respect: it proposes that people found to have drug-resistant tuberculosis and started on treatment for drug-resistant tuberculosis and marked with the (preliminary) outcome 'Moved to MDR-TB treatment' be *included* in the cohort. Such individuals are excluded from the WHO report under this heading. The rationale for this approach is as follows. With increasing use of the shorter treatment regimens for drug-resistant tuberculosis, most people will have finished their treatment by the time the *Quarterly Report on Tuberculosis Treatment Results* is prepared. It follows that the 'final' outcome can be copied from the *MDR-TB Register* into the *BMU Tuberculosis Register* instead of "Moved to MDR-TB treatment", which should be crossed out. *MDR-TB Registers* frequently include only those people who are started on drug-resistant tuberculosis treatment, while people who may have been lost to follow-up or who died before starting this treatment are not accounted for. If this approach is adopted, it will be possible for NTPs to account for all people detected with tuberculosis in a quarter.

The *Quarterly Report on Tuberculosis Treatment Results* also includes a separate section on results of all people with confirmed rifampicin/drug-resistant tuberculosis who were entered in the tuberculosis register during the quarter. In addition, a separate treatment outcome report is generated for people started on drug-resistant tuberculosis treatment during the quarter, as described in the *Field Guide for the Management of Drug-Resistant Tuberculosis*,[2] in line with the WHO recommendations.

Treatment results of people recorded as *transferred in* should *not* be included in the report, but sent to the BMU that transferred them and then reported by that unit.

When preparing the *Quarterly Report on Tuberculosis Treatment Results*, the BMU Tuberculosis Coordinator should consult the *filed* copy of the *Quarterly Report on Tuberculosis Case Finding in BMU* for the same quarter 12 months earlier. The number of cases to be reported is taken from this case finding report and entered in the first column of the *Quarterly Report on Tuberculosis Treatment Results*. The total number of cases evaluated in each category (according to the type of case) should tally with the numbers reported in the *Quarterly Report on Tuberculosis Case Finding in BMU* for that quarter (previously completed). Where the numbers differ, an explanation should be provided.

If no treatment result is recorded in the register at the time of preparing the report, the outcome should be 'not evaluated'. If a person is transferred to another BMU to continue treatment, the outcome at that BMU should be obtained and entered in the register. If a transferred person has no other ('real') outcome, the outcome should be 'transferred out'. People with unknown results should be classified with a 'not evaluated' outcome, and there should be as few such results as possible (note that reports to WHO include 'transferred out' patients under 'not evaluated').

Another part of the *Quarterly Report on Tuberculosis Treatment Results* concerns persons with tuberculosis and comorbidities, such as HIV infection and diabetes mellitus. In settings with a high HIV prevalence among people with tuberculosis, NTPs may decide to analyse and report tuberculosis treatment results by HIV status.

When completed, the report is forwarded to the next level of the health service (and eventually to the Central Level), and a copy kept on file for future reference.

Quarterly "Sub-BMU/District" Reports

In BMUs with *'Sub-BMU' Tuberculosis Registers* for the catchment area of a diagnosing centre, the BMU Tuberculosis Coordinator fills in *Quarterly 'Sub-BMU' Tuberculosis Reports* based on each *Sub-BMU Tuberculosis Register*, and compiles these into an overall *Quarterly Report on Case Finding in BMU*. Details of persons in *Facility Tuberculosis Registers* are copied into the *Sub-BMU Tuberculosis Register*, but not into the *BMU Register*, which should include only the people in the catchment area of the BMU/district hospital laboratory. Work practices should involve a minimum of copying to avoid errors. Coordinators should know which tuberculosis register is the most up-to-date and correct.

Quarterly Order Form for Drug Supplies at BMU Level (Appendix, Form 10)

This form is discussed in section 6.5.3.

7.5 What is the timetable for the submission of quarterly reports?

Facility and BMU quarterly reports should be prepared in the second week following the end of each quarter for the quarter being evaluated. The BMU reports should then be submitted to the Provincial Tuberculosis Coordinator no later than the end of the month in which they were completed. Once they have been verified for accuracy and validated by the person responsible of the appropriate supervisory level, they should be forwarded to the central level, where they are compiled and tabulated, no later than the end of the quarter in which they are prepared. Data contained in these reports should inform ways to strengthen both clinical and programmatic management of tuberculosis services (see section 7.7).

7.6 Electronic data systems and quality of tuberculosis data

It is possible to manage a NTP recording and reporting system without electronic data systems, although they are helpful in generating quarterly reports for submission to higher levels of the health system. NTP data are increasingly being included into the general health management information systems, such as the District Health Information System 2 (DHIS2).

In many settings, there are electronic case-based *BMU Tuberculosis Registers* where data are re-entered from the paper-based BMU registers. Electronic registers may be used to generate routine quarterly reports and facilitate flexible tabulation and data analysis; however, paper-based facilities and *BMU Tuberculosis Registers* are still required for back-up, documentation of changes and verification/quality control of all information. Hand-held devices are being increasingly used. They facilitate, for example, the recording of information about patient follow-up visits and sending out of reminders for appointments and taking medicines. The expansion of case-based electronic systems beyond pilot systems has been hindered by unreliable internet access, intermittent power supplies, lack of basic computer skills among staff, lack of technical support and numerous incompatible systems. Data quality remains a major challenge in many settings, as it depends largely on the quality of the data in the source documents and accuracy of data entry in electronic systems. Electronic data systems alone cannot improve data quality. That is why this Guide advocates the use of data by local staff during supervision and performance review, which would help ensure that data quality of basic data sources is maintained.

7.7 How are tuberculosis situation and services assessed?

The tuberculosis situation is assessed by following both the epidemiological situation and the interventions using quarterly reports. It is important for health care workers and Tuberculosis Coordinators to take an active interest in tabulating and analysing their routinely available tuberculosis data at the facility, BMU and provincial levels. Active data use at all levels of services is likely to improve data quality. Good quality data in turn facilitate operational research and surveys in specific areas when necessary. External programme reviews by a group of experts can also be performed periodically.

7.7.1 How local staff can use routine data to assess the tuberculosis situation and improve case detection and management

A large amount of data are generally recorded and reported in tuberculosis programmes and then simply submitted to the next level. These data are rarely used fully by facility, BMU or provincial staff. This Guide recommends that facility, BMU and provincial staff collect, validate, tabulate, analyse and use their own quarterly tuberculosis data. They can use key indicators to identify values that lie outside the expected range, find challenges and agree on action points to address these. Summary data tables can be combined with supervision checklists and performance review meeting agenda to make these more "data-driven".

Eighteen core indicators (Table 7.2) can be used to assess whether the two main goals of tuberculosis prevention and care have been achieved: the interruption of transmission by early detection and the effective treatment of (infectious) patients without creating drug resistance. These indicators are grouped into seven key areas: presumptive tuberculosis and multidrug-resistant tuberculosis, tuberculosis case finding, TB-HIV, DOT, treatment outcomes and drug management. Data for each indicator are collected from quarterly reports, which in turn are based on *Presumptive Tuberculosis Registers* (indicators 1–2), *Facility and BMU Registers* (indicators 3–16, 18) and stock cards (indicator 17).[21,22] NTPs should modify the indicators according to their situation. In settings with a large number of drug-resistant tuberculosis cases, more relevant indicators may be added, such as the proportion of new and previously treated patients with rifampicin resistance, persons started on drug-resistant tuberculosis treatment and patients with treatment success.

Table 7.2: Core indicators for assessing whether tuberculosis care and prevention goals have been achieved[21,22]

Main goals in tuberculosis care and prevention	#	*Indicator*
I: Detect all presumptive TB patients	1	Presumptive TB patients identified per 100,000 population
	2	Proportion of sputum-positive patients among presumptive TB patients tested
II: Detect TB (all forms)/new bacteriologically confirmed TB patients	3	All TB patients registered per 100,000 population
	4	Number of new pulmonary bacteriologically confirmed TB patients per 100,000 population
	5	Proportion of new pulmonary TB patients aged ≥5 years with no smear microscopy or rapid molecular test result
III: Test all TB patients for HIV and if positive, start CPT and ART	6	Proportion of TB patients with recorded HIV test results
	7	Proportion of TB patients who are HIV-positive among those with a recorded HIV test result
	8	Proportion of HIV-positive TB patients on CPT during TB treatment
	9	Proportion of HIV-positive TB patients on ART during TB treatment
IV: Provide all TB patients with daily treatment support and observation by a health worker, trained community volunteer or trained family member	10	Proportion of all TB patients who are administered DOT by health worker or trained community volunteer, including trained family member (proportion with any kind of DOT according to NTP)
V: Treat all TB patients successfully	11	Proportion cured (only relevant in new pulmonary bacteriologically confirmed patients, from district level upwards)
	12A	Proportion with treatment completion
	12B	Proportion successfully treated (cured and treatment completed)
	13	Proportion who failed treatment
	14	Proportion lost to follow-up
	15	Proportion who died
	16A	Proportion who transferred out
	16B	Proportion with 'not evaluated' treatment outcome
VI: Provide adequate stock of TB drugs	17	Levels of stock (months of consumption for each drug)
VII: Sputum test all previously treated TB patients for rifampicin resistance (with rapid molecular test)	18	Proportion of previously treated TB patients with rapid molecular test result

TB = tuberculosis; HIV = human immunodefiency virus; CPT = cotrimoxazole preventive therapy; ART = antiretroviral treatment; DOT = directly observed treatment; NTP = National Tuberculosis Programme

An expected value is defined for each indicator, the rates of presumptive tuberculosis and active tuberculosis disease in facilities are compared with the BMU average, and the indicator value for the BMU is compared with the provincial average. Certain indicator values are expected to be 100% (proportion of persons with a known HIV result, proportion who started CPT, proportion who started ART, those with treatment success) or 0% (unsuccessful outcomes). A list of frequent reasons for values lower and higher than expected has been prepared to assist health staff in analysing their data, so health staff can 'see' to what extent they are able to interrupt transmission, close gaps in tuberculosis care cascades and agree on necessary action. Expected values of indicators are presented in Supplementary Materials* (Table 2). Table 7.3 gives expected values of indicators pertaining to presumptive tuberculosis.

Table 7.3: Presumptive tuberculosis: expected indicator values and suggested explanations for variations[21,22]

#	*Indicator*	*Expected value*	*Possible explanations for deviations (poor data quality is relevant for both indicators)*	
			Below expected	*Above expected*
1	Presumptive people with TB per 100,000 population	Compare with health service level immediately above	• Limited access to facilities • People seek care elsewhere • Staff use (excessively) strict criteria for presumptive TB • Estimated catchment population is too high	• Staff use (excessively) wide criteria for presumptive TB • People from other catchment areas seek care • Estimated catchment population is too low • Active case finding campaign
2	Proportion of people with presumptive TB screened using smear microscopy or rapid molecular test who had positive result	5–15%	• Staff use (too) wide criteria for presumptive TB • Poor quality sputum specimens • Laboratory staff miss positive slides (false-negative)	• Staff use (excessively) strict criteria for presumptive TB • Persons with presumptive TB present late • Laboratory staff read negative slides as positive (false-positive)

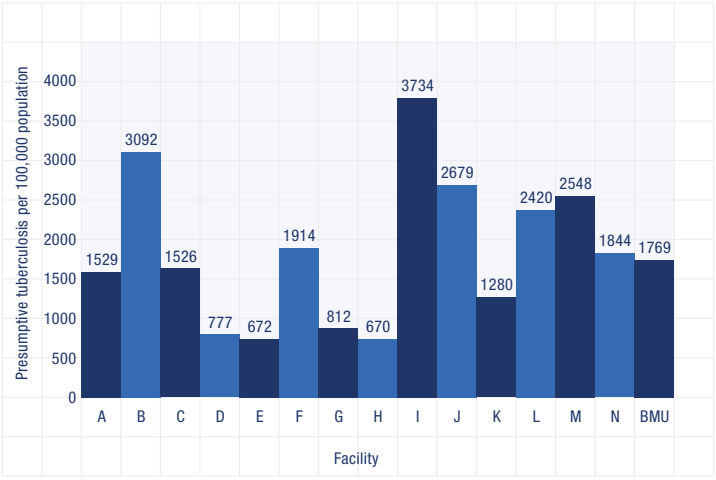
TB = tuberculosis

* Supplementary Materials are available on The Union's website (theunion.org).

Rate of presumptive tuberculosis cases per 100,000 population

This is an indicator of the quality of the general health services, that is, how well people with presumptive tuberculosis are identified and diagnosed. It marks the start of the case finding cascade. The numerator used to estimate the rate is the number of presumptive tuberculosis cases identified in a given area, for example, the BMU during a period of time. The denominator is the population of that area during the period. Figure 7.1 presents the presumptive tuberculosis rate per 100,000 population for all 14 facilities in a BMU, where the BMU rate was 1,769/100,000 and the provincial rate 1,662/100,000 population.[21] The rates ranged widely from 670 to 3,734/100,000 population. This should be discussed, for example, in performance review meetings to examine possible causes for the divergence in rates, identify 'best practices' to find more persons with presumptive tuberculosis that could be applied in facilities with low rates and create an action plan to assist facilities with low rates to find 'missing' persons with presumptive tuberculosis.

Figure 7.1: Presumptive tuberculosis rate per 100,000 population by facility during a programme pilot year in a Zimbabwean BMU



Rate of new bacteriologically confirmed tuberculosis cases reported per 100,000 population

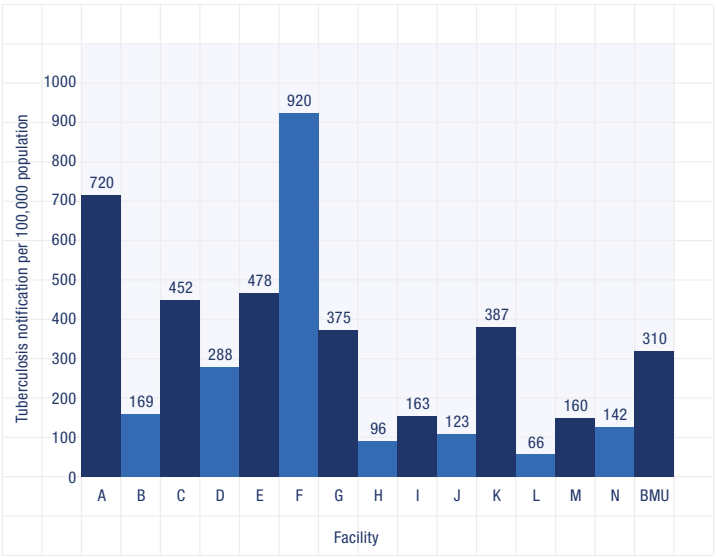
To calculate the rate of new bacteriologically confirmed tuberculosis cases reported per 100,000, the numerator used is the number of new cases of bacteriologically confirmed tuberculosis registered in a given area during a specific time period; the denominator is the population of that area during the same period.

This is the most practical and inexpensive method of tuberculosis *surveillance* in most countries. Its accuracy and completeness should have the highest priority among NTP surveillance activities. These surveillance activities should be coordinated by NTPs so that private sector service providers and other types of service providers also submit case reports. In areas with relatively complete registration of cases (good quality data), this rate provides a 'real' measure of the burden of disease rather than an estimate.

Population estimates may pose a challenge: are they sufficiently reliable to permit the calculation of rates, comparisons with rates in other areas and the determination of trends? When the denominator is not reliable, it may be meaningful only to follow trends in the numerator and not the rate.

Figure 7.2 shows the tuberculosis notification rates by facility at the BMU, for which the presumptive tuberculosis rates were presented above.[21] The notification rate in this BMU was 310/100,000 population, while the provincial rate was 521/100,000 population. Disaggregated data facilitates the examination of the reasons for the wide variation and helps provide targeted interventions to facilities that are likely to most benefit from support and supervision.

Figure 7.2: Tuberculosis notification rate per 100,000 population by facility during a programme pilot year in a Zimbabwean BMU



Practical steps that may be taken by facility, BMU and provincial teams to assess local data are outlined in Text Box 7.3. The same steps can also be followed during supportive supervision visits and review meetings.

Text Box 7.3: Steps to be taken by local staff in analysing their own tuberculosis data, and approach to be followed in quarterly data-driven supervision[21]

1. *Validate data* in facility and BMU reports by comparing these with the source documents (registers). Poor data quality is a frequent reason for indicator values falling outside the expected range.

2. At *facility level*: done quarterly by the visiting supervisor *with* the facility team or by the facility team itself
   - Fill in the data for the last quarter from the facility report by copying these into the last row of the *summary tables*. These tables already contain the data from previous quarters, including the last full year, which facilitates analysis of time trends. An example is presented in Table 3 of the Supplementary Materials.*
   - If not done already, calculate percentages and rates per 100,000 population for the last full year ('baseline') using data in the summary tables.
   - If not done already, classify all indicators for the last full year as either within or outside the expected range of values (see Table 2 of the Supplementary Materials).*
   - Now look at each indicator value for the most recent quarter and decide if they still seem to be within the expected range by assessing absolute numbers and percentages in the quarters in the current year (while rates are usually only calculated for full years) with main focus on the last quarter. Do the values seem to be different from the previous year?
   - Enter all indicator values into the feedback summary and group them into strengths and weaknesses based on the above assessment. Also, observations made during the supervision visit should be noted (see Table 4 of the Supplementary Materials).*
   - Then discuss *as a team* the identified indicators with divergent values, their background/ reasons and agree if they require any *action points*.
   - For each action point, indicate the person responsible and timeline.
   - Present the data in tables as figures and wall charts to facilitate analysis.

3. *BMUs*: usually done by BMU Tuberculosis Coordinator
   - First, analyse summary tables showing tuberculosis data for the *whole BMU* for time trends and classify indicator values as *within* or *outside* the expected range, as described above for facilities (Table 5 in the Supplementary Materials* gives an example of BMU data for presumptive TB for the whole district).
   - Then, tabulate the data for the last quarter for each facility and for each indicator. In these tables, each facility should be assigned a separate row.
   - Analyse the data in these tables and identify facilities with absolute numbers, percentages and rates that clearly differ from the district (average) indicator values ('outliers'). Include them under 'outside the expected range' in the feedback section of the checklist, find out background information/reasons for unsatisfactory performance and develop *action points* to be discussed with relevant facility teams.
   - Present the data in the tables as figures to facilitate analysis.

4. *Provinces*: a similar analysis can be done by provincial Tuberculosis Coordinator for the entire province as an entity, and then separately by BMU

5. The same process is then repeated for each quarter, starting with a review of the progress made on action points at the end of the previous quarter based on the trends revealed by the data of the most recent quarter.

* Supplementary Materials are available on The Union's website (theunion.org).

7.7.2 How to conduct 'data-driven' support supervision and performance review meetings

Regular supervision of the provincial tuberculosis services by the central unit, of the BMU by the province and of the facility by the BMU is necessary to assess the tuberculosis situation, organise follow-up training and provide support. The local staff's assessment of their own data should also be supported in order to ensure 'data-driven' supervision. Checklists are frequently used to guide supervision, and summary data tables are included in the checklists (examples of checklists used by provincial services to supervise BMUs and by BMUs to supervise facilities are given in the Supplementary Materials, Tables 8 and 9).*

All supervision visits should take place according to a schedule that is shared in advance. Before a visit the supervising team should i) review the report of the previous visit, and ii) prepare the summary data tables. This helps to determine the focus of each visit.

On arrival at the facility, the team meets the persons responsible for the facility, goes through the recommendations from the previous visit and agrees on the focus of the current visit. The team then meets with the Tuberculosis Focal Person to verify and update the data in the summary tables and assess whether the main challenges correspond to those discerned on the basis of the data reviewed before the visit. Outcomes of more recent cohorts than those routinely reported can be assessed if necessary to evaluate any improvement or identify a problem. The tuberculosis situation at the facility involving routine case detection and management, staff training, infection control, HIV care services and pharmacy-related activities are assessed by visiting the relevant units. At the end of the visit, the supervision team meets with the facility team. Challenges found based on the data and observations made during the visit are reviewed and discussed, following which action points are agreed upon, the timeline decided and persons in charge selected to implement the action points. The supervision team leaves a handwritten copy of their feedback, including these action points, and retains a copy for its own use. During subsequent visits, progress in carrying out the agreed action is reviewed and the process repeated.

* Supplementary Materials are available on The Union's website (theunion.org).

The same approach is followed when provincial teams visit BMUs using a checklist with summary tables for the *entire BMU as an entity* and *by facility*. The team assesses BMU-level functions, reviews and updates the data and visits the laboratory and provincial pharmacy. The BMU hospital, where the office of the BMU Tuberculosis Coordinator, the laboratory and the pharmacy are frequently located, is usually visited. Selected facilities may also be visited, and during these visits a facility supervision checklist is used.

NTPs need to ensure that supervisors are well trained, and checklists are updated and kept simple. The frequency of supervision of the facility by the BMU is usually quarterly; however, this can be increased if there are key challenges.

How to conduct 'data-driven' performance review meetings

BMU teams convene quarterly performance review meetings with the BMU Tuberculosis Coordinator that are attended by Tuberculosis Focal Persons from the facilities. At these meetings, the BMU team presents summary data tables with data for *the entire BMU as an entity* and *by facility*, identifying divergent BMU indicator values that require improvement, and facilities with divergent indicator values so that these can receive additional support. Each facility then presents their summary tables, focusing on challenges and proposed action points. Coordinators and teams are encouraged to agree on recommendations for the entire BMU and each facility. Performance review meetings are also an opportunity to update and validate information recorded in *Facility* and *BMU Tuberculosis Registers*.

What benefits have been reported by teams that have strengthened the use of their routine tuberculosis data?[21]

Data-driven supervision brings several benefits:

- Use of data facilitates precise identification of the facilities (in the BMU) and BMUs (in the province) and components of tuberculosis services which require reinforcement. Also, priorities can be set.
- Supervision is a *key NTP activity,* but it is frequently general in nature, involving the use of long checklists. It is not always accompanied by a clear feedback summary. Including data tabulation and analysis into preparing for and implementing supervision can give this activity a *focus* and an *agenda for strengthening* the services.
- The use of data analysis facilitates the detection of *'cold spots'*, that is, facilities and BMUs with low presumptive and diagnosed tuberculosis rates that are not usually identified by 'conventional' supervision. If we assume that every year similar numbers of persons develop tuberculosis in the catchment area of the facilities in a BMU (and BMUs in a province), the existence of these 'cold spots' can raise several questions. Do symptomatic persons avoid certain facilities because of difficult access, poor quality services or stigma? Do they prefer non-NTP providers? Do staff fail to identify people with symptoms suggestive of tuberculosis, to collect sputum samples, send these to the laboratory and receive results? Are catchment populations used to calculate the rates inaccurate? In settings where many people with presumptive tuberculosis attend facilities other than the one nearest to them, analysis of the entire BMU may be more useful. Universal access to health services is key to ending tuberculosis, and the identification of 'cold spots' may be as important as that of 'hot spots', which currently receive considerable attention.
- Active use of routinely available tuberculosis data by health facilities, BMUs and provinces *enhances* the *quality* of these data. This inexpensive and sustainable approach promoted in this Guide can improve data quality by making data relevant to facility and BMU staff. This may prevent 'creative' reporting, where unreasonably high success rates are generated by an excessive focus on targets, especially when funding is linked to outcomes. Accurate recording of the number of persons with tuberculosis and drug stock levels are *vital* for *supply management* and prevention of stock-outs. Availability of quality data may reduce the need for surveys and result in more resources directed towards strengthening the services. This will also facilitate operational research, which is required to revise NTP practices.

7.8 How is drug resistance monitored?

Surveillance of tuberculosis drug resistance is useful at the population level as a means of monitoring the *adequacy* of a tuberculosis programme. At the start of an epidemic, clinically significant resistance is a man-made problem due to individual or programmatic malpractice (the prescription or provision of inappropriate or inadequate treatment regimens and/or partial or irregular treatment), leading to resistance acquired during treatment. Once resistance to the drug is no longer rare, it starts to be transmitted, which leads to the appearance of primary resistance.

In a well-run programme, almost all resistance is primary, even in persons with treatment failure and relapse, as this type of resistance already existed at treatment start, although it may not have been detected. When programme performance is inadequate, additional resistance is acquired. When no further resistance is created and programmatic conditions are favourable, the number of resistant cases will decrease very slowly because of the potentially very long latency of the disease. Thus, an excellent programme is characterised by a fairly steady prevalence of resistance that shows a clearly declining trend, but only after a longer observation period.

Surveillance should thus mainly focus on detecting increasing trends; this is normally first visible in previously treated cases and, after transmission, also in new cases. Classical drug resistance surveys have focused on determining the point prevalence among new cases. Surveys are operationally demanding, not helpful for the management of most of the individuals tested and have to be repeated every 5 years or so using exactly the same methodology to provide an estimate of the trends. It is more efficient to monitor resistance continuously among failure and relapse cases to spot any trends after establishing tuberculosis prevalence among new cases through a single survey. This strategy has also several advantages: it helps i) avoid the selection of the worst cases, ii) provides adequate coverage, iii) leads to an accurate database and meticulous data analysis, and iv) fixed, standardised laboratory methods and techniques. Whatever the strategy used, the focus should be on resistance to core drugs. Also, for this reason, restricting this effort to molecular testing for the detection of rifampicin resistance may be a good start.

With the increasing use of rapid molecular testing also among new cases, it is important to ensure that test results are entered in *Facility* and *BMU Tuberculosis Registers* and included in *Quarterly Facility* and *Quarterly Reports* on *Case Finding in BMU* so that data for routine monitoring of drug resistance is readily available.

7.9 What is operational research and why is it important for national tuberculosis programmes?

Operational research can be defined as 'research into strategies, interventions, tools or knowledge that can enhance the quality, coverage, effectiveness or performance of the health system or programmes in which the research is being conducted'.[22] Operational research helps to generate *context-specific knowledge* on:

- The importance of implementing certain policies in order to improve the quality of tuberculosis care and prevention;
- The gap between policies and practices under field conditions;
- Problems in implementing measures; and
- Ways to improve the effectiveness of existing policies and/or practices.

7.9.1 What topics are appropriate for operational research in tuberculosis care?

Identifying topics for operational research is guided by two principles: i) an understanding of the goals and objectives of NTP policies, and ii) the constraints that preclude reaching these objectives. Research questions should address these constraints. For example, are these due to a gap in knowledge or are the tools and strategies to reach the objectives being poorly utilised?

NTPs should identify and publish priority operational research issues to evaluate programme operations with the aim of improving them. Operational research studies may be descriptive, case control or cohort analyses. Data for studies can be obtained using *routine* NTP *recording* and *reporting tools*.

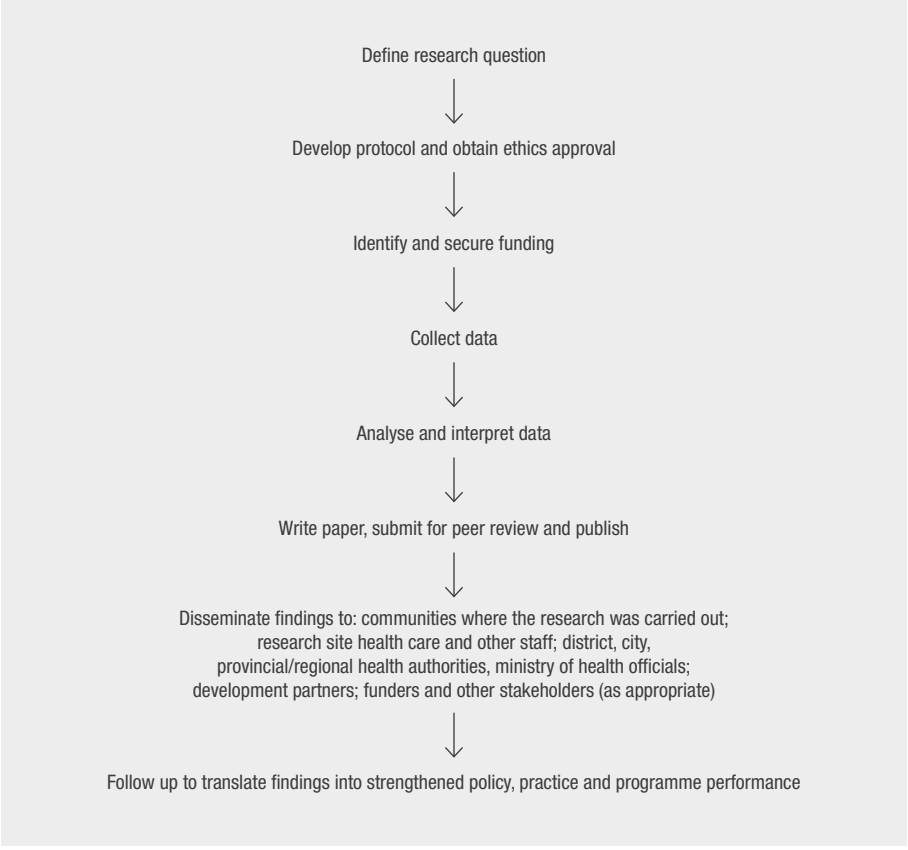
7.9.2 Who should engage in operational research in tuberculosis care?

NTPs can form partnerships with researchers from academic and other institutions in or outside of the country to support operational research. Researchers should be encouraged to train and mentor the officers in, for example, NTPs, national AIDS programmes, and programmes for non-communicable diseases and tobacco control to design and implement operational research. NTPs and researchers need and strengthen each other's capacities: NTPs help identify the most relevant research questions, while researchers provide guidance as to the methodology to be used.

7.9.3 How should operational research results be used and disseminated?

Ideally, operational research results should be used to improve the design and operation of the health system so as to improve the quality and efficiency of service delivery for tuberculosis management. These results can be disseminated through in-country stakeholder meetings, publications in journals and in local print and electronic media, and presentations in national and international forums. Figure 7.3 shows the steps from research question to dissemination and translation of findings into policy, practice and better performance.

Figure 7.3: Steps from research question to translation of findings into strengthened policy and practice[23]



7.9.4 What is Structured Operational Research Training Initiative or SORT IT and why national tuberculosis programmes should adopt this model?

The recording and reporting systems of many public health programmes in low- and middle-income countries generate a lot of data. However, the full potential of these data to inform improvements in public health is rarely achieved. This is mainly due to the limited human resources available for conducting and publishing programme-relevant operational research.

In order to address this gap, The Union and its partners have developed a model called the Structured Operational Research and Training IniTiative (SORT IT).[24] This year-long training and mentorship course aims to teach the practical skills for conducting and publishing operational research that are required to influence policy and practice.* Adopting the SORT IT model helps NTPs to

- Conduct operational research according to their own priorities;
- Build sustainable operational research capacity;
- Make evidence-informed decisions for improving programme performance.

* https://www.who.int/tdr/capacity/strengthening/sort/en/

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Appendices

Form 1	Presumptive Tuberculosis Register
Form 2	Request and Reporting Form for Sputum Smear Microscopy and/or Rapid Molecular Test
Form 3	Tuberculosis Laboratory Register for Sputum Smear Microscopy
Form 4	Patient Identity Card
Form 5	Tuberculosis Treatment Card
Form 6	Facility/BMU Tuberculosis Register
Form 7	Quarterly Facility Tuberculosis Report
Form 8	Quarterly Report on Tuberculosis Case Finding in BMU
Form 9	Quarterly Report on Tuberculosis Treatment Results
Form 10	Quarterly Order Form for Drug Supplies at BMU Level
Form 11	Quarterly Report on Peripheral Tuberculosis Laboratory Performance and Stock Situation

FORM 1: PRESUMPTIVE TUBERCULOSIS REGISTER (1/2)

Date of registration	Presumptive TB patient number	Name	Surname	Sex M/F	Age	Address and phone number	Known contact (yes/no)	TB risk group 1 = health care worker, 2 = miner, 3 = prison inmate, 4 = other, specify	DR-TB risk group 1 = previous TB treatment, 2 = RR-TB contact, 3 = other, specify

DR-TB = drug-resistant tuberculosis; RR-TB = rifampicin-resistant tuberculosis.

FORM 1: PRESUMPTIVE TUBERCULOSIS REGISTER (2/2)

Sputum smear microscopy (two samples)									Rapid molecular test					HIV test result***	Remarks (including TB registration number if TB is detected)
Date sputum collected		Date sputum sent to laboratory		Date smear result received		Smear microscopy result		Laboratory serial number	Date sputum collected	Date sputum sent to laboratory	Date result received	MTB result* and laboratory serial number	RIF resistance result** and laboratory serial number		
1	2	1	2	1	2	1	2								

* MTB result: **D** (Detected), **ND** (Not detected), **E** (Error), **Iv** (Invalid). ** RIF resistance result: **S** (Susceptible), **R** (Resistant), **Id** (Indeterminate).

*** HIV test result: **N** (Negative), **P** (Positive), **Id** (Indeterminate), **ND** (Not done). MTB = *M. tuberculosis;* RIF = rifampicin; HIV = human immunodeficiency virus; TB = tuberculosis.

FORM 2: REQUEST AND REPORTING FORM FOR SPUTUM SMEAR MICROSCOPY AND/OR RAPID MOLECULAR TEST

Facility referring the patient: _____

BMU: _____ Date of collection: ____ / ____ / ____

Full name of patient: _____

Telephone: _____ Age: _____ Sex: ☐ Male ☐ Female

Address: _____

_____

TB number: _____ MDR-TB Unit number: _____

Nature of the sample: ☐ Sputum ☐ Other (specify): _____

HIV: ☐ Negative ☐ Positive ☐ Unknown

Request for: ☐ Sputum smear microscopy ☐ Rapid molecular test

Reason for testing (tick one of the following boxes):

Microscopy: ☐ Diagnosis ☐ Monitoring If monitoring, which month _____

Rapid molecular test:

☐ Diagnosis of tuberculosis in presumptive cases

☐ Detection of rifampicin resistance in diagnosed tuberculosis cases

◯ New case ◯ Previously treated ◯ Late converter

☐ Contact of RR-TB case

Full name of the health worker requesting the test: _____

Telephone: _____

Signature of the health worker requesting the test: _____

RESULTS (to be completed in the laboratory)

Sputum smear microscopy

Serial number of laboratory test: _____ Date of receipt: _____

☐ Ziehl-Neelsen ☐ Auramine staining

Collection date	Sample	Visual appearance*	Result				
			Negative	Scanty Number AFB**	+	++	+++
	1						
	2						

* Mucopurulent, traces of blood, saliva

** Scanty AFB: Indicate the exact number (1–9) for 100 fields

Examination carried out by (full name): _____

Date: _____ Signature: _____

Rapid molecular test

Date	Test no	Result	
		MTB*	RIF resistance**

If error, specify error code: _____

* MTB result: **D** (Detected), **ND** (Not detected), **E** (Error), **Iv** (Invalid)

** Rifampicin resistance result: **S** (Susceptible), **R** (Resistant), **Id** (Indeterminate)

Examination carried out by (full name): _____

Date: ____ / ____ / ____ Signature: _____

This form should be duly completed and sent to the Treatment Unit.

FORM 3: TUBERCULOSIS LABORATORY REGISTER FOR SPUTUM SMEAR MICROSCOPY

Name of laboratory _____

Laboratory serial number	Date specimen received	Full name of patient	Sex M/F	Age	Name of requesting facility	Address of patient	Phone number	Reason for examination		Result of examination*		HIV test result**	TB number or referring BMU	Remarks
								Diagnosis	Follow-up (months of treatment)	1	2			
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														

* Negative, scanty (number AFB), +, ++, +++.

** HIV test result: **N** (Negative), **P** (Positive), **Id** (Indeterminate), **ND** (Not done).

FORM 4: PATIENT IDENTITY CARD (TO BE PRESENTED TO ANY HEALTH WORKER CONSULTED)

Name: _____

Address: _____

_____ Phone: _____

Sex: ☐ Male ☐ Female Age: _____

Treatment supporter, name: _____

Treatment supporter, address/phone: _____

_____

Date treatment started: ____ / ____ / ____ TB number: _____

Name of BMU: _____ Result of rapid molecular test: MTB: _____ RR-TB: _____

Month	Date	Sputum examinations				Weight	Date of appointment
		Microscopy		Rapid molecular test			
		Laboratory number	Result	Laboratory number	Result MTB / RR-TB		
0							
2							
5							
End							

MTB = *M. tuberculosis;* RR-TB = rifampicin-resistant tuberculosis.

Disease site: (tick one)

☐ Pulmonary ☐ Extra-pulmonary, specify: _____

Category of patient: (tick one)

☐ New ☐ Treatment after failure ☐ Relapse ☐ Treatment after loss to follow-up

☐ Transfer in ☐ Other, specify:_____

I. INITIAL INTENSIVE PHASE

Start date: ____ / ____ / ____

Write the number of tablets below in the appropriate box

RHZE	RHZ paediatric	E 100 mg	RR/MDR-TB (specify drugs)

R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol.

II. CONTINUATION PHASE

Start date: ____ / ____ / ____

Write the number of tablets below in the appropriate box

RH adult	RHZE	RH paediatric	RR/MDR-TB (specify drugs)

RR/MDR-TB = rifampicin-resistant/multidrug-resistant tuberculosis.

Appointment dates

Appointment date	Attended (yes or no)

Notes: _____

_____

_____

_____

FORM 5: TUBERCULOSIS TREATMENT CARD (1/2)

TB number: _____

Name: _____

Sex: ☐ Male ☐ Female Age: _____ Date of registration: ____ / ____ / ____

Address: _____

_____ Phone: _____

Treatment supporter: Name: _____

Address: _____

_____ Phone: _____

Basic Management Unit: _____ Treatment Unit: _____

Disease site: (tick one)

☐ Pulmonary ☐ Extra-pulmonary Site (specify): _____

Category of patient: (tick one)

☐ New ☐ Treatment after failure ☐ Relapse ☐ Treatment after loss to follow-up

☐ Transfer in ☐ Other, specify: _____

I. INITIAL INTENSIVE PHASE

For patients previously treated former TB number*: _____

Regimen and number of tablets:

New and retreatment		Children	
RZHE		RHZ paediatric	E 100 mg
	2 months		

Month	Date	Sputum examinations				Weight	Date of appointment
		Microscopy		Rapid molecular test			
		Laboratory number	Result	Laboratory number	Result MTB / RR-TB		
0							
2							
5							
End							

MTB = *M. tuberculosis;* RR-TB = rifampicin-resistant tuberculosis.

TB-HIV		
	Date	Result†
HIV test		
CPT start		
ART start		

Patient uses tobacco? No ☐ Yes ☐ If yes, willing to quit within the next 30 days? No ☐ Yes ☐

Day / Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Enter X on day when drugs were swallowed under direct observation, and Ø on day when the patient does not come for treatment. * Attach the previous card

† HIV test result: **P** (Positive), **N** (Negative), **Id** (Indeterminate), **ND** (Not done), HIV-positive patients should be referred to HIV clinic. CPT = cotrimoxazole preventive therapy; ART = antiretroviral treatment.

Please turn over

FORM 5: TUBERCULOSIS TREATMENT CARD (2/2)

II. CONTINUATION PHASE

Regimen and number of tablets:

New cases (daily)	RH
4 months	

Retreatment (daily)	RHZE
4 months	

Children (daily)	RH paediatric
4 months	

Day / Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Enter X on day of observed administration or when drugs are collected. Draw a horizontal line ——————• through the number of days supplied. Ø = drugs not taken

Remarks: _____

_____

_____

_____

_____

Treatment outcome

Date of outcome: ____ / ____ / ____

☐ Cured ☐ Treatment completed ☐ Treatment failure ☐ Changed to MDR-TB treatment ☐ Died ☐ Lost to follow-up

☐ Transfer out; BMU name _____

FORM 6: FACILITY/BMU TUBERCULOSIS REGISTER (1/2)

Date registered __/__/__	TB number	Full name	Sex M/F	Age	Address and telephone number	Treatment unit	Treatment start date	Regimen*	Disease site: pulmonary/ extra-pulmonary	Type of case†					
										New	Relapse	Treatment after failure	Treatment after loss to follow-up	Transfer in	Other

* **New**: 2RHZE/4RH; **Retreatment**: 6RHZE; **Children**: 2RHZE/4RH.

† **New**: never treated or treated previously for <1 month; **Relapse**: previously treated, declared cured, returns smear-positive; **Treatment after failure**: smear positive ≥5 months after starting treatment, commenced on retreatment; **Treatment after loss to follow-up**: returns smear-positive after loss to follow-up, commenced on retreatment; **Transfer in**: registered and started treatment in another BMU; **Other**: previously treated with unknown outcome, so-called "chronic patients", etc.

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment.

FORM 6: FACILITY/BMU TUBERCULOSIS REGISTER (2/2)

Result of rapid molecular test / laboratory serial number **MTB result:** **D** (Detected), **ND** (Not detected), **E** (Error), **Iv** (Invalid) **Rifampicin resistance result:** **S** (Susceptible), **R** (Resistant), **Id** (Indeterminate)	Results of smear examination								Result of treatment (tick)‡									TB-HIV			Remarks (Specify BMU if transferred, ART clinic, etc)
	Before treatment		2 months		5 months		End treatment														
	Result	Laboratory number and date	Result	Laboratory number and date	Result	Laboratory number and date	Result	Laboratory number and date	Date of result	Cured	Completed	Failure	Moved to MDR-TB treatment	Died	Lost to follow-up	Transfer out	Not evaluated	HIV test result (P, N, Id, ND)§	CPT (Date)	ART (Date)	

‡ **Cured**: smear (culture) negative at end of treatment and on one previous occasion; **Completed**: completed treatment, no smear examination results to classify as cured; **Failure**: smear (culture) positive ≥5 months after starting treatment, confirmed by a second positive smear; **Moved to MDR-TB treatment** (preliminary outcome): rifampicin resistance detected and MDR-TB treatment started before end of first-line treatment; **Died**: died from any cause before or during treatment; **Loss to follow-up**: did not start treatment or treatment interrupted for ≥2 consecutive months; **Transfer out**: left to another BMU for continuation of treatment; treatment result unknown; **Not evaluated**: outcome is unknown.

§ HIV test result: **P** (Positive), **N** (Negative), **Id** (Indeterminate), **ND** (Not done).

FORM 7: QUARTERLY FACILITY TUBERCULOSIS REPORT (1/2)[1]

Name of facility: _____ Name of BMU:_____ Quarter: _____ Year: _____

1. PRESUMPTIVE TUBERCULOSIS CASES REGISTERED DURING THE QUARTER (from Presumptive Tuberculosis Register)

Number identified	Number with sputum sent to laboratory	Number with diagnostic laboratory test result*	Number with positive sputum test result	Number with HIV test result	Number with HIV+ result

* Sputum smear microscopy or rapid molecular test.

2. TB CASES REGISTERED DURING THE QUARTER (from Facility Tuberculosis Register)

Pulmonary TB: bacteriologically confirmed		Pulmonary TB: clinically diagnosed		Extra-pulmonary TB: bacteriologically confirmed or clinically diagnosed		Total	Pulmonary TB cases aged ≥5 years	Pulmonary TB cases aged ≥5 years without diagnostic test result
New	All previously treated	New	All previously treated	New	All previously treated			

3. TB-HIV CASES REGISTERED DURING THE QUARTER (from Facility Tuberculosis Register)

Number of TB patients registered	Number of TB patients with HIV test result	Number of TB patients with HIV+ result	Number of TB patients with HIV+ result on CPT*	Number of TB patients with HIV+ result on ART*

* CPT = cotrimoxazole preventive therapy; ART = antiretroviral treatment.

4. DIRECTLY OBSERVED TREATMENT (DOT, from Facility Tuberculosis Register)

Number of TB patients registered	Number on health facility-based DOT	Number on community-based DOT/DOT by trained family member	Number not on DOT

[1] Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union from Heldal E, Dlodlo RA, Mlilo N, Nyathi BB, Zishiri C, Ncube RT, Siziba N, Sandy C. Local staff making sense of their tuberculosis data: key to quality care and ending tuberculosis. Int J Tuberc Lung Dis 2019; 23(5): 612–618.

FORM 7: QUARTERLY FACILITY TUBERCULOSIS REPORT (2/2)

5. TREATMENT OUTCOMES REGISTERED DURING THE QUARTER ENDING 12 MONTHS BEFORE (from Facility Tuberculosis Register)

Number registered (all TB cases)	Cured + treatment completed (treatment success)	Failure	Moved to MDR-TB treatment	Died	Lost to follow-up	Transferred out	Not evaluated

6. PATIENTS REGISTERED DURING THE QUARTER TESTED FOR RIFAMPICIN RESISTANCE (from Facility Tuberculosis Register)

Number of previously treated TB cases registered	Number of previously treated TB cases with specimen sent to laboratory for rifampicin resistance test	Number of previously treated TB cases with specimen sent to laboratory with result	Number of previously treated TB cases with rifampicin resistance among those with resistance result

7. SUMMARY OF DRUG STOCK STATUS (from stock cards)

Drug	Quantity (tablets)	Months of stock	Expiry date	Comment
RHZE adult*				
RH adult				
RHZ paediatric				
RH paediatric				
E 100 mg				
H 100 mg				
H 300 mg				
Other, specify				

* R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol.

FORM 8: QUARTERLY REPORT ON TUBERCULOSIS CASE FINDING IN BMU

Name of the Basic Management Unit (BMU): _____ BMU Tuberculosis Coordinator: _____

Patients registered in quarter _____ of (year) _____ Signature: _____ Date: ____ / ____ / ____

1. All tuberculosis patients registered in the quarter*

Pulmonary TB: bacteriologically confirmed			Pulmonary TB: clinically diagnosed			Extra-pulmonary TB			Total
New cases	Relapses	Other previously treated**	New cases	Relapses	Other previously treated**	New cases	Relapses	Other previously treated**	

* Except transfer in. ** Includes treatment after lost to follow-up, treatment after failure, other previously treated.

2. All new and relapse tuberculosis patients registered in the quarter (confirmed and clinically diagnosed, pulmonary and extra-pulmonary)

Age group (years)																TOTAL		
0–4		5–14		15–24		25–34		35–44		45–54		55–64		65+				
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	Male	Female	Total

3. TB-HIV

Number of patients with known HIV status	Number of HIV-infected	Number on ART	Number on CPT

4. People with presumptive tuberculosis registered by type of diagnostic sputum test

Type of sputum test	Laboratory register			Presumptive register			
	Tested	MTB detected*	RR detected**	Identified	Tested	MTB detected*	RR detected**
Both smear microscopy AND rapid molecular test							
Smear microscopy only			Not applicable				Not applicable
Rapid molecular test only							

* MTB detected = any positive sputum test for *M. tuberculosis.* ** RR detected = rifampicin-resistant tuberculosis.

5. People with pulmonary tuberculosis by history of previous treatment and type of diagnostic sputum test

Type of sputum test	New TB patient			Previously treated TB patient		
	Tested	MTB detected*	RR detected**	Tested	MTB detected*	RR detected**
Both smear microscopy AND rapid molecular test						
Smear microscopy only			Not applicable			Not applicable
Rapid molecular test only						

* MTB detected = any positive sputum test for *M. tuberculosis.* ** RR detected = rifampicin-resistant tuberculosis.

FORM 9: QUARTERLY REPORT ON TUBERCULOSIS TREATMENT RESULTS

Patients registered in the quarter ending 12 months prior to reporting date

Name of the Basic Management Unit (BMU): _____ BMU Tuberculosis Coordinator: _____

Patients registered in quarter _____ of (year) _____ Signature: _____ Date: ____ / ____ / ____

1. Treatment results*

Type of case	Number registered**	Cured	Treatment completed	Failure	Died	Lost to follow-up	Moved to MDR-TB treatment	Transferred out	Not evaluated	Total
New: Positive on smear microscopy and/or rapid molecular test										
Previously treated: Positive on smear microscopy and/or rapid molecular test										
All other new†										
All other previously treated†										

* All registered patients, including patients with RR/MDR-TB and moved to MDR-TB treatment. If result of MDR-TB treatment is available in MDR-TB register, this result should be entered here in place of "Moved to MDR-TB treatment".

** From *Quarterly Report on Tuberculosis Case Finding* for that quarter.

† Not positive on sputum smear or rapid molecular test, extra-pulmonary TB, other.

2. RR/MDR-TB: All patients with RR/MDR-TB registered in the quarter, including patients who did *not* start MDR-TB treatment

Number registered**	Cured	Treatment completed	Failure	Died	Lost to follow-up	Moved to MDR-TB treatment (and still on treatment)	Transferred out	Not evaluated	Total

FORM 10: QUARTERLY ORDER FORM FOR DRUG SUPPLIES AT BASIC MANAGEMENT UNIT

Name of the Basic Management Unit (BMU): _____ BMU Tuberculosis Coordinator: _____

Patients registered in quarter _____ of (year) _____ Signature: _____ Date: ____ / ____ / ____

Enter the number of patients enrolled during the previous 3 months (from the *Quarterly Report on Tuberculosis Case Finding*)

Regimens	Tablets	Cases A	Factor F	Total quantity needed per quarter B=AxF	Quantity needed per month B/3	Reserve stock C=B	Stock on hand D	Expiry date(s)	Months of stock D/(B/3)*	Total ordered Qo=B+C-D	Quantity delivered
2RHZE/4RH (new adult cases)	RH 150/75 tablet		420								
	RHZE 150/75/400/275 tablet		210								
6RHZE (previously treated cases, rifampicin-susceptible or not tested)	RHZE 150/75/400/275 tablet		630								
2RHZ(+E)/4RH (children)	RHZ 75/50/150 dispersible tablet		210								
	RH 75/50 dispersible tablet		420								
	Ethambutol 100 mg tablet		210								
Prophylaxis (adult)	Isoniazid 300 mg tablet										
Prophylaxis (children)	Isoniazid 100 mg tablet										
Other											

* RHZE is used both in new adult cases and previously treated cases. To calculate months of RHZE stock, divide the total RHZE stock with the quantity needed per month for both new adult cases and previously treated cases.

FORM 11: QUARTERLY REPORT ON PERIPHERAL TUBERCULOSIS LABORATORY PERFORMANCE AND STOCK SITUATION

Name of the Basic Management Unit (BMU): _____ Name of laboratory: _____ Patients registered in quarter _____ of (year) _____

1. Patients

Number of presumptive TB patients			Number of patients with follow-up microscopy		Total number tested
Microscopy +	Molecular test +	Total tested	Positive	Total	

2. Microscopy (indicate the method in use by ticking below)

☐ Ziehl-Neelsen (ZN) ☐ Fluorescence microscopy (FM)	Positive	Scanty	Negative	Total
Number of smears examined for diagnosis				
Number of smears examined for follow-up				
Total smears examined				

3. Rapid molecular tests

Type	Tests for presumed TB		Tests for presumed RR-TB		Test result: failure or indeterminate	Grand total of tests performed
	TB+	Total	RIF-resistant	Total		
Xpert MTB/RIF						
Xpert ULTRA						
LPA first-line	Not applicable					
LPA second-line						

4. Stocks in hand at the end of the quarter (the quantitites delivered will be filled in by the supplier)

For kits, use estimates to quarters of a box; estimate solutions to +/– one quarter of a litre

Microscopy	Stock	Delivered	Unit
Microscopy kits for 1,000 ZN smears	_____	_____	kits
Microscopy kits for 1,000 FM smears	_____	_____	kits
Carbol fuchsin solution	_____	_____	Quarter l
Auramine stock solution	_____	_____	Quarter l
Phenol solution	_____	_____	Quarter l
Destaining solution	_____	_____	Quarter l
Counterstaining solution	_____	_____	Quarter l
Immersion oil	_____	_____	Quarter l
Microscopy slides	_____	_____	pcs

Molecular test supplies	Stock	Delivered	Unit
Cartridges Xpert MTB/RIF	_____	_____	pcs
Cartridges Xpert ULTRA	_____	_____	pcs
LPA first-line kit	_____	_____	pcs
LPA second-line kit	_____	_____	pcs

Sputum containers	Stock	Delivered	Unit
	_____	_____	pcs

ABOUT THE INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE (THE UNION)

The Union is a global scientific organisation with the mission to improve health among people living in poverty. We do that by conducting scientific research, working with governments and other agencies to translate research into better health for people around the world, and delivering projects directly in the field. The Union is made up of a global membership body of people who help advance our mission, and a scientific institute that implements public health projects within countries. For close to 100 years, we have been leaders in the fight against some of the world's biggest killers, including tuberculosis, lung diseases and tobacco use.

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