REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

National Guidelines for Tuberculosis Prevention, Care and Elimination in LEBANON

National TB Program – 2017

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ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
BCG	Bacille Calmette Guérin
CPT	Co-trimoxazole Preventive Therapy
X-ray	Chest X-ray
DOT	Directly Observed Treatment
DOTS	Internationally recommended strategy for TB Control until 2005
DST	Drug Susceptibility Testing/Test
E	Ethambutol
EPTB	Extra pulmonary Tuberculosis
FBO	Faith-Based Organization
FDC	Fixed-Dose Combination
GF	Global Fund
H	Isoniazid
HIV	Human Immunodeficiency Virus
IGRA	Interferon-Gamma Release Assays
IPT	Isoniazid Preventive Therapy
IOM	International Organization of Migration
LED	Light Emitting Diode
LTBI	Latent Tuberculosis Infection
MCH	Maternal and Child Health
MDR-TB	Multi-Drug Resistant Tuberculosis
NACP	National HIV and AIDS Control Programme
NGO	Non-Governmental Organization
NRL	National Reference Laboratory

NSP	National Strategic Plan
NTP	National Tuberculosis Program
NTWG	National Technical Working Group
PHC	Primary Health Care
PLHIV	People Living with HIV
PMDT	Programmatic Management of Drug-resistant Tuberculosis
PTB	Pulmonary Tuberculosis
R	Rifampicin
S	Streptomycin
SOP	Standard Operating Procedure
TB	Tuberculosis
TST	Tuberculin Skin Test
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
Z	Pyrazinamide

Preface

Lebanon is a low TB burden country with estimated incidence of 16/100000, prevalence of 20/100000 and TB mortality rate of 1/100000.

The National Tuberculosis Program (NTP) in Lebanon operates through the PHC network and nine TB control centers across the country and implements all WHO recommended TB strategies: DOTS, stop TB, and End TB strategy. The NTP has a high treatment success rate of 90% among Lebanese nationals. However, the treatment success rate remains below the desired among the non-Lebanese patients where almost 50% in these groups leave the country before the completion of their treatment. Noting that currently over half of the persons referred to the program for investigation and treatment are non-Lebanese among whom one third are of Syrian nationality.

In Lebanon and during 2013, around 100 Syrian refugees have been TB diagnosed; including three cases of multi drug resistant (MDR). There has been Syrian and Lebanese returnees TB patients who were forced to interrupt their treatment because of the worsening security situation inside Syria. Treatment interruption leads to weaker identification of TB in the communities, low cure rate and potential increase in multidrug-resistant (MDR) TB.

During the last 15 years, 7548 TB cases were identified and evaluated at the National TB Program. After the marked decreasing of reported TB cases from 663 in 1999 to 375 cases in 2006, the number of reported cases started to increase again gradually reaching 689 in 2013 including 341 Lebanese, and 348 non Lebanese among which 106 Syrians were reported.

Dramatic increase of TB patients among non-nationals and the influx of Syrian refugees continued to affect the overall number of reported cases in 2014, 2015 and 2016, where 681, 664 and 679 cases were reported respectively.

In 2014, 345 non-Lebanese patients including 109 Syrian were reported, while 2015 figures, registered 354 non-Lebanese including 139 Syrian. These numbers continued to increase in 2016 to reach a number of 358 among non-Lebanese TB patients, including 147 Syrian.

These guidelines aim to help healthcare workers deal with TB patients and are part of our national prevention strategy. Adopting these guidelines and measures will certainly help in decreasing the overall incidence of the disease at the national level.

The ongoing collaboration between the public and private sector, the improvement of the surveillance system and TB control are important factors for the successful elimination of TB in our country. In this context, the MOPH would like to thank the National ID committee with all its members including Dr Abdul Rahman Bizri, Dr Jacques Mokhbat, Dr Pierre Abi Hanna, Dr Nadine Yared, Dr Nada Melhem, Dr Joseph Rachkidi and Dr Georges Salem for their valuable and much appreciated contribution to the recommendations and advices while writing these guidelines. I would like also to commend the Lebanese Infection Disease society, the Lebanese pulmonary society and the Lebanese society of Pediatricians for their comments.

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1 INTRODUCTION

Population of Lebanon is 4.6 million inhabitants. There are also 1.1 million UNHCR-registered Syrian refugees and nearly 500,000 Palestinian refugees; in addition, it is believed that there are 500,000 other Syrian refugees who are not registered. The national territory of Lebanon is administratively divided into seven governorates which, all together, include 26 districts.
Approximately 25% of the population is aged less than 15 years, the life expectancy is 82 years in females and 78 in males (2015 estimates).
Lebanon is in epidemiological transition. Communicable diseases have been decreasing for the last 20 years but still remain relatively frequent in socially disadvantaged groups of population, migrants and refugees.

Lebanon is an upper-middle income country with low incidence of tuberculosis. Yet, it is at amplified risk of increasing burden of tuberculosis due to the recent massive influx of Syrian refugees and imported workforce. The components for a national response to contain and prevent tuberculosis are already present and functioning. There is need to improve the diagnostic, therapeutic, case management, contact screening, and prevention performance and capabilities. Treatment success rates are high in Lebanese population (around 90%) but can be better and can improve among other population groups. Contact screening has to improve since around only 40% of contacts are screened. Treatment is provided freely for all residing in the country and affected by the disease. Non Lebanese constitute a little more than 50% of total cases since 2013. Main groups are the Ethiopian migrant workers and the Syrian refugees. Multi-drug resistant tuberculosis cases are few but may increase among Syrian refugees that could not have regular treatment. The Lebanese health authorities have issued ministerial decrees and decisions targeting treatment of latent tuberculosis. There is need to improve and broaden the list of those who deserve to be treated. Basic first-line anti-tuberculosis medications are available and dispensed free of charge. Second-line treatment options are also available and free of charge at the national tuberculosis program. There is need to shift to shorter second line treatment for multi-drug resistant tuberculosis and introduce newer pediatric formulations. There is demand by the medical community to expand treatment indications and options for latent tuberculosis.

Diagnostic capabilities for active disease are present in the country but very often based on smear microscopy that have low sensitivity in detecting *M. tuberculosis*. Very simple to use nucleic acid amplification techniques such as Xpert MTB/RIF is making a revolution in tuberculosis diagnosis. Both *M. tuberculosis* and resistance to Rifampicin can be diagnosed by a simple laboratory in about 2 hours. Culture and drug sensitivity testing is not routinely performed. Drug sensitivity for second line drugs are currently available in the country.

For the diagnosis of latent tuberculosis infection, there is still some confusion and lack of expertise about how to interpret tuberculin skin testing. Interferon-Gamma Release Assays (IGRAs) have potential benefit in very selected group of persons.

The number of special patient groups and those at higher risk of contracting the illness is increasing. Immuno-compromised individuals from any cause are at higher risk of sever and atypical disease. Meanwhile those incarcerated or live in over-crowded conditions are at higher possibility of getting infected. Infection control programs and practices will protect health care workers. However there is need for more and better equipment to be available at governmental and smaller hospitals.

These guidelines will provide the platform for unifying and improving the management of those affected by tuberculosis. They cover the issues of diagnosis, treatment, case management, and prevention.

The objectives of the guidelines are to establish a complete and comprehensive response to the threat of TB in the country given the newly acquired challenges posed by the conflict in the region and the emergence of MDR-TB and XDR-TB. The guidelines are also introducing tools and strategies that aim at Ending TB along the lines of the WHO End TB strategy:

- Achieve universal access to high-quality diagnosis and patient-centered treatment
- Reduce the human suffering and socioeconomic burden associated with TB
- Protect poor and vulnerable populations from TB, TB/HIV, and MDR-TB
- Support development of new tools and enable their timely and effective use
- Protect and promote human rights in TB prevention, care and control

In order for Lebanon to achieve these goals the health authorities with the help of the WHO need to collaborate with other local stakeholders such as national experts from universities, medical centers, scientific committees, and non-governmental organizations to implement a national strategic plan to end tuberculosis in the country. Ministerial decrees and decisions regarding all aspects relevant to TB ought to be reviewed.

Resources in Lebanon are limited and appropriate utilization of these resources is essential. Priorities must be determined. The application of evidence based protocols, learning from experiences and accumulating local data are integral to the success of end TB policy in Lebanon.

2 Definitions

2.1 Why are definitions needed?

Utilization of uniform criteria to define TB cases and treatment outcomes are essential for:

- Standardization of data collection for TB control;
- Proper patient registration and case notification;
- Selection and utilization of appropriate standard treatment regimens;
- Description of the distribution of TB cases according to site, bacteriology, treatment history and other variables such as demographic variables (M/F, children etc..);
- Cohort analysis to evaluate treatment outcomes;
- Monitoring of TB notification trends and evaluation of the effectiveness of TB control strategy at Governorate and National levels.

2.2 TB case definitions

2.2.1 Active TB and LTBI

- **Active TB** refers to disease that occurs in someone infected with *Mycobacterium Tuberculosis* (Mtb). Active TB whether pulmonary or extra-pulmonary is characterized by signs or symptoms of active disease
- **Latent TB Infection** (LTBI) refers to a person infected with *Mycobacterium Tuberculosis* (Mtb) without signs or symptoms of active disease.

2.2.2 Confirmed or not confirmed TB

- **Bacteriologically confirmed TB case**

  TB case from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid test, such as Xpert MTB/RIF assays or other molecular tests.

- **Clinically diagnosed TB case**

  It is a case who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a medical practitioner who has decided to give the patient a full course of TB treatment

2.2.3 Classification according to anatomical site affected with TB

- **Pulmonary tuberculosis case**

  Refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as pulmonary TB because there are lesions in the lungs

- **Extrapulmonary tuberculosis case**

  refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs or tissues other than the lung parenchyma, e.g. pleura, intra-thoracic lymphadenopathy (without radiographic abnormality in the lung), lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges etc.

2.2.4 Classification according to history of previous treatment

Classifications based on history of previous TB treatment now focus only on previous treatment and are independent of bacteriological confirmation or site of disease.

- **New patients**

  Patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

- **Previously treated patients**

  These are patients who have received more than 1 month of anti-TB drugs in the past:

  a. **Relapse patients** are those who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
  b. **Treatment after failure patients** are those who have previously been treated for TB and whose treatment failed at the 5^{th} month or the end of their most recent course of treatment.
  c. **Treatment after loss to follow-up patients** are those who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment.
  d. **Other previously treated patients** are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

- **Patients with unknown previous TB treatment history**

  These refer to the patients whose TB treatment history status does not fit into any of the categories listed above.

2.2.5 Classification according to HIV infection status

Persons who are infected with HIV, irrespective of their age, have much higher risk of developing TB than those who are not. This risk is estimated at 20 to 37 times higher. As a result, TB infection is more common among PLHIV than in the general population.

- **HIV-positive TB patient:** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in pre-ART register or in ART register once ART has been started.
- **HIV-negative TB patient:** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of diagnosis. Any HIV-negative TB patient subsequently found HIV-positive should be reclassified accordingly
- **HIV status unknown TB patient:** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's status is subsequently determined, he or she should be reclassified accordingly.

2.2.6 Classification according to TB drug resistance status

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*

- **Monoresistance** refers to a resistance to one first-line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Multidrug resistance (MDR-TB):** resistance to at least both isoniazid and rifampicin
- **Extensive drug resistance (XDR-TB): MDR-TB** with in addition resistance to any fluoroquinolone and to at least one of the following second-line injectable drugs: capreomycin, kanamycin, amikacin.
- **Rifampicin resistance (RR):** any resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. (monoresistance, polydrugresistance, MDR, XDR)

2.3 Treatment outcome definitions

These definitions refer to patients who do not have evidence of TB drug resistance (i.e.: rifampicin resistance and MDR) and are treated with first-line anti-TB medicines.

Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcome of treatment.

- **Cured:** refers to a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear-negative in the last month of treatment and on at least one previous occasion.
- **Treatment completed:** refers to a TB patient who completed treatment without evidence of failure but with no record to show that sputum smear results in the last month of treatment and on at least one previous occasion were negative, either because sputum smear examination was not done or because the result was not available.
- **Treatment success:** the sum of cured and treatment completed.
- **Treatment failed:** refers to a TB patient whose sputum smear is positive at month 5or later during treatment.
- **Died:** refers to a TB patient who dies for any reason before starting or during the course of treatment.
- **Transferred out:** refers to a patient who started treatment in one health facility in a country and is transferred with all information regarding diagnosis and treatment to a health facility in another country to be able to continue TB treatment after moving to the other country.
- **Lost to follow-up:** refers to a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- **Not evaluated:** refers to a TB patient for whom no treatment outcome is assigned (treatment outcome is unknown to the reporting unit).

3 Diagnosis of tuberculosis

3.1 Presumptive TB

It refers to patient who presents with symptoms or signs suggestive of TB.

The most important symptom that should lead to a sputum examination is a productive cough of a duration of 2 weeks or more with any **one** of the followings:

- Significant weight loss
- Persistent evening fever
- Night sweats

- Haemoptysis
- Chest pain
- Tiredness
- Loss of appetite

Other symptoms suggestive of Extra-pulmonary TB

If TB disease is in other parts of the body symptoms will depend on the area affected

- Enlarged non painful cervical lymph nodes with or without discharge
- Pleural effusion;
- Distended abdomen with ascites, typically in female adolescent or young woman
- Others

Positive TST or IGRA should be investigated for active TB

3.2 Tools to establish TB diagnosis

3.2.1 X-ray screening

The diagnosis of TB cannot be established on X-ray alone. Radiological lesions may suggest but cannot confirm TB.

Patients in whom chest X-ray (CXR) shows any radiological abnormality must be evaluated for TB through bacteriological and clinical examinations.

X-ray is useful for the identification of the site of TB. It can provide a significant and additional argument for the establishment of the diagnosis of TB in patients with symptoms and clinical signs compatible with TB and in whom bacteriological examinations are negative (sputum smear, Xpert MTB/RIF or culture).

X-ray film should be read by qualified

doctors. Chest imaging:

- Posterior-anterior radiograph of the chest is the standard
- Lateral views may be helpful in children
- In some instances CT scan may be needed
- Radiographic abnormalities are often seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe
- Lesions may appear anywhere and differ in size and shape mainly in HIV and immunocompromised persons
- Radiographic abnormalities in children tend to be minimal with a greater likelihood of lymphadenopathy, more easily diagnosed on the lateral film

3.2.2 Smear microscopy

The methods used for smear microscopy examination are the Ziehl-Neelsen stain with light microscopy and the fluorochrome stain with fluorescence microscopy (using light emitting

diodes (LED) illumination). A smear microscopy positive TB case is defined as patient with at least one positive smear (i.e. at least 1 acid-fast bacillus in 100 microscopic fields) in two samples examined.

This method is easy to perform and gives result in few hours.

The sensitivity of sputum-smear microscopy is relatively low since at least 5000 bacilli per ml of sputum are required for a positive result (in contrast 10 to 100 bacilli are needed for a positive culture). The sensitivity is further reduced in patients with extra pulmonary TB (EP TB), children and PLHIV.

- The results of sputum smear examination must be reported in a **standard laboratory register for TB** to be able to distinguish examinations done for diagnosis purpose (new) and follow-up examination.
- All persons with **presumptive TB should be prescribed smear microscopy as part of the diagnosis process**. Smear microscopy will be used as a test for follow-up during treatment.

3.2.3 Molecular tests, NAA (conventional PCR), Xpert MTB/RIF

Several techniques are used for **Nucleic Acid Amplification (NAA, PCR)**. Some require well- equipped laboratory, some can be used in a simple laboratory (Xpert MTB/RIF). The advantages are sensitivity and specificity as compared with smear microscopy and quick results for *M. tuberculosis* and Rifampicin resistance as compared with culture.

Xpert MTB/RIF bacteriological test can detect *M. tuberculosis* and rifampicin resistance in about 2 hours. When compared to liquid culture, Xpert MTB/RIF testing has approximately 90% sensitivity and 99% specificity. For the detection of rifampicin resistance, the sensitivity is 95% and the specificity 98%. In smear-negative culture-positive TB, Xpert testing has nearly 70% sensitivity.

- NAA tests (particularly Xpert MTB/RIF) must be carried out in sputum sample of people with presumptive pulmonary TB and/or chest X-ray abnormality regardless of smear examination result and being new or retreatment cases.

NAA tests are particularly important for the diagnosis of TB meningitis or disseminated TB because they provide quick results and indication on Rifampicin (and INH) resistance.

- NAA tests (particularly Xpert MTB/RIF) should be used for the diagnosis of

- Pulmonary TB in adult regardless of sputum smear result
- TB in children (ex.: using gastric fluid);

- EPTB, using non respiratory specimens (ex.: lymph node discharge fluid or tissue biopsy specimens etc…).

The results of the test must be reported in a standard laboratory register for TB

3.2.4 Culture (liquid or solid)

Commercially available broth culture systems (e.g., BACTEC, MGIT, Versa TREK, and MBBACT) allow detection of most mycobacterial growth in 4 to 14 days compared to 3 to 6 weeks for solid media

- Culture examinations should be done to confirm diagnosis (positive culture) if both smear and NAA tests are negative
- In case of negative culture the diagnosis can still be made based on clinical, X-ray and other findings
- Culture examinations should be done to test for resistance to second line drugs (quinolones and injectables)

The results of the culture must be reported in a standard laboratory register for TB

3.2.5 Serological tests

WHO conducted a systematic review of all existing serological tests and issued a negative recommendation:

"It is strongly recommended that commercial serodiagnostic tests not be used for the diagnosis of pulmonary and extra-pulmonary TB. Currently available commercial serodiagnostic tests (also referred to as serological tests) provide inconsistent and imprecise findings. There is no evidence that existing commercial serological assays improve patient outcomes, and high proportions of false-positive and false-negative results may have an adverse impact on the health of patients"

3.2.6 Histopathology

Histopathology cannot provide evidence to confirm the diagnosis of TB. The elementary histopathological lesion is characterized by follicular granulomas.
Bacteriological examination is necessary to confirm TB.

Follicular granulomas can be observed in a wide variety of diseases, both infectious and non-infectious, such as tuberculosis, leprosy, cryptococcosis, coccidioidomycosis, blastomycosissarcoidosis, Crohn's disease and others.

Histopathological evidence can be used as an adjunct to establish the diagnosis of TB in a patient who has symptoms, signs and other clinical features compatible with TB. Histopathology is helpful in setting the diagnosis of EPTB when bacteriological examinations are negative.

3.2.7 Skin test & IGRA

Both tests indicate that the person's body was likely infected with TB bacteria and should not be used as a confirmation of active TB disease

TST (PPD): also called the Mantoux tuberculin skin test or PPD (Purified Protein Derivative) is performed by injecting 0.1 ml of tuberculin 5 units into the skin in the volar aspect of the forearm. A person given the tuberculin skin test must return within 48 to 72 hours to have a trained health care worker look for a reaction on the arm. The health care worker will look for a raised, hard area or swelling (induration), and if present, measure its size using a ball-point pen placed about 2 cm away from the site of the infection, moved slowly towards the area of the test until resistance is faced where a mark should be placed. The procedure should be repeated from four directions (a cross shape) until the area of induration is determined from the four directions. The diameters of this area should be measured with a ruler. Redness by itself is not considered part of the reaction. The skin test result depends on the size of the raised, hard area or swelling.

TST is not specific to *M. tuberculosis*, it can be positive in children who had BCG vaccination as well as in those who are infected by environmental mycobacteria other than tuberculosis

Advantage of TST: - Simple to perform and relatively cheap-
Possible to perform without lab

Although not specific, there is **no major discordance with IGRAs** in a person with no reduced immunity or not recently vaccinated with BCG.

- **Positive skin test:** means the person's body was likely infected with TB bacteria. Positivity depends on the immunological status of the person (see algorithm in LTBI section). **Additional tests are needed to determine if the person has active TB disease**. Infection does not always lead to disease

IGRAs: Interferon-Gama Release Assays are a whole-blood test. IGRAs measure the person's reactivity to *M. tuberculosis*.

Advantage of IGRAs: - Requires a single patient visit to conduct the test.
- Results can be available within 24 hours.
- Does not boost responses measured by subsequent tests.
- Prior BCG (Bacille Calmette-Guérin) vaccination does not cause a false-positive IGRA test result.

Recommendation for IGRA: non conclusive PPD and evidence of contact with TB infectious patient

IGRAs tests are very expensive and are not useful in children under 5 years of age. Their use in children 5-18 years is not substantiated by sufficient data.

- **Positive IGRA:** means the person's body was likely infected with TB bacteria. Additional tests are needed to determine if the person has active TB disease.

3.3 Diagnosis of different forms of tuberculosis

There are many ways for categorizing the various forms of TB. For practical purpose, these guidelines highlight three forms of TB and the diagnosis pathway to identify multidrug resistant TB (MDR-TB).

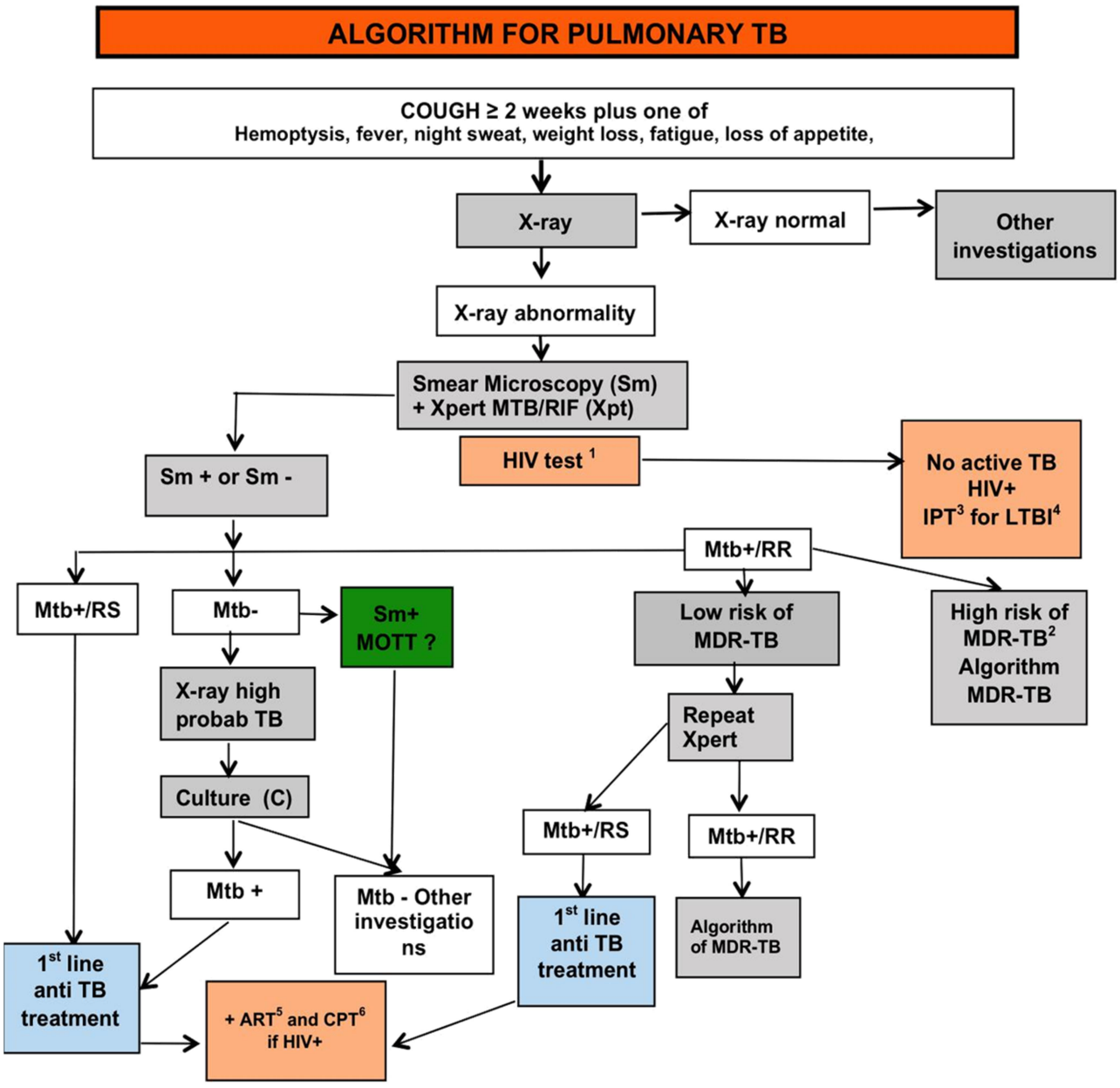
3.3.1 Pulmonary TB: algorithm

Pulmonary TB is the most frequent form of TB. Its clinical feature is characterized by a persistent cough with expectoration. The patient may present other symptoms such as chest pain, hemoptysis, fever, night sweats or loss of weight. If chest X-ray is performed, it shows radiological lesions in one or both lungs; the lesion is typically located in the upper right lobe with cavity formation. However, the observation of any lesion at the chest X-ray cannot at all confirm the diagnosis of pulmonary TB.

A pulmonary TB can be confirmed only by bacteriological tests: sputum smear microscopy, Xpert MTB/RIF test or culture.

A pulmonary TB may not be confirmed even though many attempts have been made using the bacteriological tests.

Figure 1: Algorithm for the Diagnosis of Pulmonary TB



1 HIV counseling and testing to be offered to all patients with TB.
2 High risk MDR-TB: relapse, failure of 1st line treatment, treatment after interruption (more than 2 months), contact with a person with MDR-TB, exposure in institutions or areas with high prevalence of MDR-TB prisoners, PLHIV.
3 IPT: INH Preventive Therapy
4 LTBI: Latent TB Infection
5 ART: Anti Retroviral Treatment
6 CPT: Cotrimoxazol Preventive Therapy

3.3.2 Extra pulmonary TB[i]

EPTB is a TB which involves organs or tissues other than lung parenchyma. The extra pulmonary organs and tissues that are most commonly affected with TB are pleura and lymph nodes. **Diagnosis should be based on at least one specimen with confirmed *M.tuberculosis* (eg: Xpert-testing or culture: Annex I)**.

Histopathology and strong clinical evidence consistent with active EPTB is sometime the only possibility to diagnose TB. Careful consideration should be made by a medical doctor to treat with full course of TB chemotherapy. After having eliminated other causes.

All EPTB cases who are coughing should have at least two sputum smear examinations; if one of them is positive, the TB should be categorized as bacteriologically confirmed pulmonary TB.

If TB is affecting several extra pulmonary organs/tissues, the disease will be categorized according to the most severely affected site.

All sample taken from an organ or a tissue suspected to be infected by Mtb should undergo

- **bacteriological examination**: smear, NAA Xpert MTB/RIF and/or culture (one partof the sample in one container without formaldehyde)[ii]
- **histopathology and other investigations** (other part of the sample in a second container with formaldehyde)

3.3.3 Childhood TB

The diagnosis of TB in children relies on thorough assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations such as tuberculin skin test, X-ray, sputum smear microscopy and Xpert MTB/RIF testing or culture.

Most children with TB have pulmonary TB. Bacteriological confirmation of TB is most often difficult to obtain in children; however, it should be sought whenever possible by microscopy, NAA Xpert testing or culture. It is important to highlight that a trial of treatment with anti-TB drugs must not be undertaken as method of diagnosing TB.

- Careful assessment of the **history of contact**

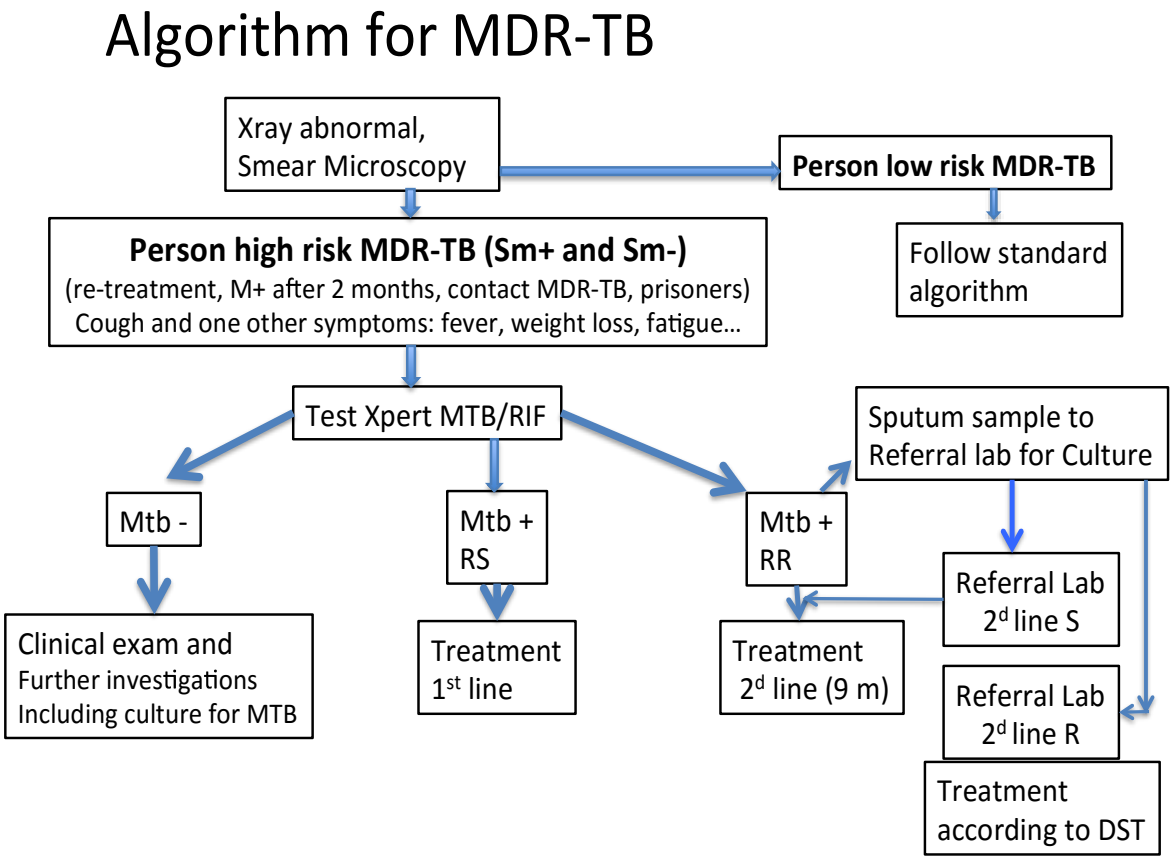
A child living in the same household or in frequent contact with a patient with smear-positive pulmonary TB (index TB case) is exposed to a significant source of TB infection.

- Identification of symptoms compatible with TB
    - Cough
    - Fever
    - Not eating well (anorexia)
    - Weight loss or failure to thrive
    - Fatigue, decreased activity
- Clinical examination (including growth assessment)
- HIV testing
- Tuberculin skin testing (TST)
  A TST should be regarded as positive as follows:
    - In high-risk children (including HIV-infected children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor): ≥5 mm diameter of induration;
    - In all other children (whether they have received a BCG vaccination or not); ≥10 mm diameter of induration.
    - A negative TST doesn't rule out TB in children
- Chest radiography.
  Chest X-ray significantly helps in establishing the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have radiological lesions suggestive of TB (persistent opacification in the lung together with enlarged hilar or subcarinal lymph nodes)
- **Bacteriological confirmation** should always be sought with smear microscopy **and** NAA or culture, and DST performed if drug-resistant TB is suspected
- Histopathology

  Appropriate specimen for bacteriology and/or histopathology from the suspected site:
  1) Sputum
  2) Gastric aspirate
  3) Lymph Node biopsy or FNA
  4) Lumbar Puncture (meningitis , disseminated TB to confirm or exclude meningitis)
  5) Taps and biopsies : pleural, pericardial , ascites , joint

3.3.4 MDR-TB: algorithm

Figure 2: Algorithm for the Diagnosis of MDR-TB



4 Treatment of TB

Treatment of TB is a fundamental intervention in TB control. TB treatment should use standardized regimens that have proven their efficacy and use efficient-quality-assured anti-TB medicines. They should be adequately administered to patients.

4.1 Treatment of new TB cases

4.1.1 Aim of TB treatment

The aims of the treatment of TB are to:

- Cure the patient and restore his/her quality of life and productivity
- Prevent death from TB or its late effects
- Prevent relapse of TB
- Reduce transmission of TB in community
- Prevent the development and transmission of drug resistance.

4.1.2 Rules to respect in TB treatment provision for drug susceptible TB

When TB treatment is provided to patients, some rules must be respected:

- **The full course of treatment should be given without interruption**.
- Direct supervision of TB treatment during the intensive phase as well as during the continuation phase through the involvement of health facilities' staff, community treatment supporters or mobile phone reminder;
- Utilization of TB drugs in fixed-dose combination (FDC);
- Adequate doses of anti-TB medicines;
- Regular and steady anti-TB drugs intake by patient;
- Single intake of all anti-TB medicines prescribed (not fragmented during the day);
- Monitoring by health workers of anti-TB drugs side effects.

Before initiating treatment:

- Clinical examination
- Weight
- Liver enzymes can be measured before treatment or during the first week of treatment and monitored monthly during treatment
- No need for other tests to be performed unless indicated by patient history or clinical examination

4.1.3 Essential anti-TB medicines

The dosages of the essential first-line anti-drugs for adults are presented in Table 1.

Table 1: Doses of first line anti TB in adults

Anti-TB drug	**Daily dose**	
	Dose (mg/kg body weight) and range	Maximum (mg)
Isoniazid	5 (4-6)	300
Rifampicin	10 (8-12)	600
Pyrazinamide	25 (20-30)	--
Ethambutol	15 (15-20)	--
Streptomycin*	15 (12-18)	1,000

*Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily; in that case the dose needs to be reduced to 10 mg/kg per day.

4.1.4 Standardized regimen

The use of FDCs has several advantages over individual drugs. First, the prescription errors are likely to be less frequent as dosages that should be used are more straightforward and the adjustment of doses according to patient weight is easier. Secondly, the number of tablets to be ingested is fewer and thus may encourage patient adherence. Thirdly, if treatment is not observed, patients cannot be selective in the choice of anti-TB drugs to ingest.

Standardized treatment means that all patients in a defined group receive the same treatment regimen. Standard regimens have proved to be effective in clinical control trials, advantages over individualized regimen prescription of drugs that are not evidence based

The regimen to be used to treat new TB patients includes:

- Initial (intensive) phase with 4 first-line anti-TB drugs: isoniazid, rifampicin, pyrazinamide and ethambutol in 4FDCs, are administered daily to patients for 2 months.
- Continuation phase with 2 first-line anti-TB drugs: isoniazid and rifampicin in 2FDCs, are administered daily to patient for 4 months.

2HRZE/4RH

In the two phases, the daily treatment should be administrated in single intake.

Table 2: Treatment administration in new patients (adults)

Pre-treatment Weight	2 month initial phase Number of HRZE* tablets in FDCs	4 month continuation phase Number of RH** tablets in FDCs
<33 kg	2	2
33-50 kg	3	3
51 kg+	4	4

*: H75mg/ R150mg/Z400mg/E275mg
**: R150mg/H75mg

All new TB cases should be treated with this regimen whether they are bacteriologically confirmed or clinically diagnosed and regardless of the anatomical site of the disease and their HIV infection status.

4.1.5 Daily versus intermittent treatment

Several intermittent regimen have been

proposed,

1. 3 times weekly throughout (intensive and continuation phases)
2. Daily in intensive phase and 3 times a week in continuation phase
3. Daily intensive phase and twice a week in continuation phase
4. Other….

All have their advantage and weaknesses. All intermittent regimens have also a risk of low dosage. There is no FDC for intermittent regimen, as a result they require ingestion of many tablets. Regimen using twice weekly intake have proved to be inferior to daily.

In all circumstances, it is more important to study carefully with the patient a treatment program using daily regimen provided by a near-by health facility or by a third party at home (community worker, social worker, health staff, relative) or to use mobile phone reminder etc… to reduce the time spent and the cost born by the patient to reach TB center. With this in place and an appropriate patient education, a weekly meeting with TB health worker is acceptable in the intensive phase and at least twice monthly meeting in continuation phase.

4.2 Treatment of previously treated TB patients without R resistance

If Xpert MTB/RIF testing is positive and does not identify any rifampicin resistance, then the patient should be treated with the regimen used for new cases:

2HRZE/4RH

If NAA Xpert MTB/RIF and/or culture are negative and the patient has been treated before and has clinical and radiological symptoms strongly in favor of TB

- In the initial phase containing streptomycin, isoniazid, rifampicin, pyrazinamide and ethambutol is provided to the patient for 2 months followed by isoniazid, rifampicin, pyrazinamide and ethambutol for 1 month (without streptomycin). All the drugs should be administered daily in 4FDCs (plus streptomycin the first 2 months)
- In the continuation phase, isoniazid, rifampicin and ethambutol are administered daily, for 5 months.

The administration of the retreatment regimen must be daily and monitored by the treating health workers.

2SHRZE/1HRZE/5RHE

Table 3: Administration of TB treatment in adults

Pre-treatment weight	3 month initial phase with 2 month SHRZE + 1month HRZE		5 month continuation phase
	Streptomycin	Number of HRZE* tablets in FDCs	Number of RHE** tablets in FDCs
<33 Kg	500mg	2	2
33-50 Kg	750mg	3	3
51 Kg+	1g	4	4

*: H75mg/ R150mg/Z400mg/E275mg

**: R150mg/H75mg/E275mg.

4.3 Treatment of TB in children

The principles of treatment of TB in children are the same as for the treatment of TB in adults. Higher dosages are needed in children

Table 4: Daily doses of first-line anti-TB drugs for children

Anti-TB drug	Dose (mg/kg body weight) and range	Maximum (mg)
Isoniazid	10 (7-15)	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	--
Ethambutol	20 (15-25)	--

Children, should be treated with 4 drugs in the intensive phase

2HRZE/4RH

Children with clinically diagnosed or confirmed limited pulmonary TB who are HIV negative and likely INH susceptible have the option to be treated with 3 drugs during intensive phase using FDCs:

2HRZ/4RH

Table 5: Administration of TB treatment in children (<25kg body weight)

Number of tablets			
Pre-treatment weight	**Initial phase**		**Continuation phase**
	RHZ*	**Ethambutol (100mg)**	**RH****
4-6 kg	1	1	1
7-10 kg	2	2	2
11-14 kg	3	2	3
15-19 kg	4	3	4
20-24 kg	5	4	5

*: R75mg/H50mg/Z150mg
**: R75mg/H50mg.

Streptomycin should not be used as part of first line treatment regimens for children with pulmonary TB or peripheral lymphadenitis (ototoxicity)

4.4 Treatment of extra pulmonary TB cases

EPTB should be treated with the same regimens (and same dosage) as those used in the treatment of pulmonary TB

2HRZE/4RH

Children with clinically diagnosed or confirmed **tuberculosis meningitis, disseminated or osteoarticular** TB should be treated with a 12 months regimen. For meningitis an aminoglycoside can be added but they do not cross well meninges and are toxic especially in children.

2HRZE/10RH

In TB meningitis and pericarditis adjuvant corticosteroid treatment can be used. Although sometimes required for diagnosis, surgery plays little role in the treatment of EPTB. Most of the time it is reserved for the management of late complications of the disease.

4.5 Treatment of MDR-TB and XDR-TB cases

Lebanon is adopting the WHO recommended standardized short course regimen for management of pulmonary MDR-TB in patients that have no resistance to second line drugs. The regimen should not be provided to extrapulmonary cases, pregnant women and children. Any treatment of a person with diagnosed MDR-TB plus a resistance to a second line drug or XDR-TB should be discussed with a TB clinical committee comprised of the NTP manager, the treating physician and three experts in infectious disease or pulmonology and laboratory.

Intensive phase: duration of 4-6 months and consisting of 4 second-line drugs

Continuation phase: duration of 5 months consisting of 2 second-line drugs, s*upported by selected first-line TB drugs.*

The recommended regimen for MDR-TB with no resistance to 2d line drugs is as follow:

4-6 Km-Mfx-Pto-Cfz-Z-H high-dose-E / 5 Mfx-Cfz-Z-E

Key:
Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide; Cfz=Clofazimin; Z=Pyrazinamide; H high-dose= high-dose Isoniazid; E=Ethambutol

The administration of treatment must be fully supervised by health workers.

The occurrence of adverse effects of second-line anti-TB drugs during the treatment of rifampicin-resistant TB/MDR-TB is relatively common. Treatment should be fully supervised, close monitoring of patients is necessary to ensure that adverse effects of drugs are identified quickly by health care personnel. The ability to monitor patients for adverse effects daily is essential during intensive phase.

Patient should be isolated and all infection control measures for MDR-TB should be implemented.

Protocol for the initiation and follow-up of short regimen for MDR-TB and treatment evaluation are described in annex II.

If the patient has also resistance to second line drug(s) including XDR-TB individualized treatment should be tailored to DST results by the TB clinical committee. The principle is to ensure that 5 drugs are documented to be (DST results) or believed to be (no DST but based on treatment history) active. Use of new drugs (delamanid and bedaquilin) will be discussed case by case following WHO recommendations on the introduction of these drugs in a treatment regimen.

NTP will also convene the clinical TB committee to provide guidance on case by case basis in the treatment of MDR-TB during pregnancy, breast feeding, in children and in patients with renal failure or liver diseases**.**

4.6 Treatment in special situations

4.6.1 HIV infected patient

Persons who are infected with HIV, irrespective of their age, have much higher risk of developing TB than those who are not. This risk is estimated at 20 to 37 times higher. TB is one of the leading causes of death in PLHIV and is associated with an excess in mortality in TB patients who are HIV-infected in comparison to those who are not. PLHIV are more likely to develop smear-negative pulmonary TB and EPTB than HIV-negative persons.

PLHIV with TB should receive same treatment like the HIV negative but should be given ART and CPT in addition. ART regimen may need to be adapted to be compatible with Rifampicin.

PLHIV constitute a high-risk population for TB. Systematic screening for TB should be performed in PLHIV using TB high risk population algorithm

PLHIV with no sign of TB should receive 6 months IPT

All patients diagnosed with TB should be offered HIV counselling and testing

Close collaboration between the NTP and National AIDS Program is essential.

4.6.2 Pregnancy

At the time of diagnosis women in childbearing age should be asked whether they are pregnant before the treatment is initiated. A pregnant woman with TB must be informed that successful treatment with standard regimen is important for successful outcome of pregnancy. First line anti-TB drugs included in standard treatment are safe in pregnancy. **Streptomycin must not** be given because of its ototoxicity for the fetus.

All pregnant women with TB should receive pyridoxine supplementation

4.6.3 Breastfeeding

The breastfeeding mother with TB should receive full course of TB treatment. It is the best way to prevent transmission of TB bacilli from mother to baby. Mother and baby should stay together and the baby should continue to be breastfed.

After having ruled out active TB in the baby, the baby should be given IPT (10mg/kg/day) for 6 months. The BCG vaccination should be considered after completion of IPT in children going in a high burden country.

Breastfeeding mothers need to receive pyridoxine

supplementation.

4.6.4 Oral contraception

Rifampicin interacts with oral contraceptive pill, with a risk of decreased protective efficacy against pregnancy. Therefore, any woman receiving or considering using contraceptive medications should be advised either to receive contraceptive pills containing higher doses of oestrogen (50ug) or use another form of contraception.

4.6.5 Liver disease

A patient with hepatitis virus carriage, positive past history of acute hepatitis and excessive alcohol consumption can receive anti-TB treatment provided he/she has no clinical evidence of chronic liver disease. However, patients with these conditions may develop reactions to anti-TB drugs.

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. The more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used.

Pyrazinamide should not be given to patients with chronic liver disease.

Full drug susceptibility test for first line drugs and quinolones should be undertaken and the patient transferred to TB referral department for the selection of appropriate regimen.

4.6.6 Renal failure

TB patients with renal failure or severe renal insufficiency will receive 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. Isoniazid and rifampicin are eliminated by biliary excretion, therefore, there will be no change in dosing of these anti-TB medicines. As there is a significant renal excretion of ethambutol and metabolites of pyrazinamide, these two drugs need to be given three times per week at the following doses: 25 mg/kg/day for pyrazinamide and 15 mg/kg/day for ethambutol. While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy.

Because of an increased risk of nephrotoxicity, streptomycin should be avoided in patients with renal failure

4.6.7 Adjuvant steroid therapy

Steroid therapy is beneficial to patients who have TB meningitis, pleural TB with large effusion and TB pericarditis. In this group of patients, 40-60 mg of prednisolone can be given for 4 weeks and then the dose is gradually decreased over several weeks. Other patients that may benefit from steroid therapy are those having:

1. TB laryngitis with airway obstruction;
2. Massive TB lymphadenopathy with signs of airway obstruction;
3. TB of renal tract to prevent ureteric scarring;
4. TB of the adrenal glands that may cause hypo-adrenalism;
5. Severe hypersensitivity reaction to anti-TB drugs.

5 Organizing treatment

5.1 Treatment supervision and adherence

TB is curable if patients are given a complete and uninterrupted adequate treatment in line with the NTP policy. However, poor adherence to TB treatment may occur and therefore can result in significant consequences such as:

1. Prolonged illness and disability for the patient;
2. Infectiousness of the patient causing continued transmission of TB in community;
3. Development of drug-resistant TB;
4. Death of patient.

TB is a complex disease that has biological, social, economic and cultural factors for the patient. Health care providers should be mindful of the strong impact that this disease can have on all aspects of the patient's life and the need for a comprehensive approach to the management of the patient.

Patients and health care workers share responsibility for treatment outcomes, therefore, the provider must do everything possible to educate, support, influence and persuade the patient to take their medication as prescribed and to complete treatment.

There is no “one standard approach” for treatment supervision. It is however required that the following be in place:

- A treatment supporter: someone in the community (community health workers) or in the PHC center or in TB center ensure treatment prescribed has been taken every day either by everyday direct supervision of treatment (DOT) or by weekly/twice a week, counting drug intake with the patient and asking for side effects.
- There is no need for hospitalization during intensive phase of treatment except if patient’s medical or social condition requires it.

5.2 Interruption of TB treatment

5.2.1 Prevention of interruption of treatment

Several measures must be taken to prevent the interruption of TB treatment, such as:

- The management of anti-TB drugs must be appropriately ensured at all levels to avoid any drug shortage;
- All patients who are identified as TB cases must be registered in the TB register and referred to the appropriate health facilities for TB treatment
- The treating health facility must establish for each TB patient a TB treatment card and TB identity card and collect all relevant information on the exact physical address and mobile phone number (personal or of a family member, neighbor or friend) to facilitate the location of the patient in case he/she is absent to treatment
- Before initiating TB treatment, the health staff responsible for treatment must explain to the patient and family members:
    - Who will be in charge of his/her treatment (identification of the health worker and/or community treatment supporter)
    - The duration of each phase of TB treatment

- Possible side effects of treatment and what to do if they occur
- The steps needed to monitor the treatment course
- The absolute necessity to follow strictly the instructions of the health staff or community treatment supporter regarding TB treatment
- The consequences if the treatment is abandoned
- The absolute necessity to inform, ahead of time, health staff or treatment supporter in case:
  - of planned absence or moving to other county or region
  - of physical address change

In order to make the arrangements needed for the continuation of TB treatment;

- Health staff in charge of treatment needs to identify any potential problems that may create obstacle for treatment adherence, such as the incompatibility of the time of treatment provision and working hours;
- Patient must have regular follow up in the TB diagnosis and treatment center or PHC center at least every other week during intensive phase and every month during the continuation phase;
- Any patient who did not take his/her treatment for 3 consecutive days during the intensive phase or for 1 week during the continuation phase must be considered as potential defaulter and immediately traced through treatment supporter or TB center
- Any patient who did not come to his/her monthly follow up session in the TB diagnosis and treatment center must be considered as potential lost to follow-up and immediately traced through the actors identified above;
- Tracing of absent to follow-up patient should be part of the weekly activity of any facility providing TB treatment services. The TB register and TB treatment cards should be checked on a fixed day of the week to find out patients who have not attended follow up session that week; these patients are potential lost to follow-up who should be immediately traced.

5.2.2 Action to be taken when a patient is absent to treatment

It is crucial to trace as soon as possible a patient who does not come back for treatment. For any patient who was lost to follow-up and found or who returned by him/herself, actions must be taken. These actions are identified in the Tables below and depend on the type of treatment, the duration of treatment interruption and the bacteriological evaluation.

Table 6: Management of new patients who interrupt treatment

Length of treatment	Length of interruption	Sputum result at return	Treatment outcome	Classification at return	Treatment action and registration
<1 month	<2 weeks	Not needed	-	-	Continue treatment at the point it was stopped
	≥ 2 weeks	Not needed	-	-	Restart treatment
1-2 months	<2weeks	Not needed	-	-	Continue treatment at the point it was stopped
	2-7 weeks	Smear +	-	-	Restart treatment
		Smear -	-	-	Continue treatment at the point it was stopped
	≥8 weeks	Smear +/-	Lost to follow up	Treatment after loss to follow up	Start retreatment, perform Xpert/DST and give new number
≥2 months	<2 weeks	Not needed	-	-	Continue treatment at the point it was Stopped
	2-7 weeks	Smear +	Give new number	Other	Start retreatment Perform Xpert/DST
		Smear -	-	-	Continue treatment at the point it was stopped

	≥8 weeks	Smear -/+	Lost to follow up	Treatment after loss to follow up	Start retreatment, perform Xpert/DST, give new number

Table 7: Management of re-treatment patients who interrupt treatment

Length of treatment	Length of interrupt On	Sputum result at return	Treatment outcome	Classification at return	Treatment action and registration
<1 month	<1 month	Not needed	-	-	Continue retreatment at the point it stopped
>1 month	4-7 weeks	Smear +	-	-	Re-start treatment, perform Xpert/DST
		Smear -	-	-	Continue retreatment at the point it stopped, perform Xpert/DST
	≥8 weeks	Smear +/-	Lost to follow up	Treatment after loss to follow-up	Perform Xpert/DST; Restart a treatment according to DST, give new number

5.2.3 Strategies to improve treatment adherence

5.2.3.1 Quality interaction with the patient

- Create a partnership with the patient
- Ask patient whether they do take the anti-TB drugs and do not assume that they do
- Give each patient adequate time at each visit
- Behave with respect with patient. Be positive and do not intimidate or frighten the patient
- Treat the person and not the disease
- Understand and address different cultural beliefs and values
- Adapt treatment to lifestyle
- Link patient with NGOs and any entity which can provide psycho-social support whenever needed.

5.2.3.2 Patient education

- Give the vital information during the first interview with patient
- Be cautious and clear with instructions as the patient might be anxious after having been informed on the nature of the disease
- Provide all the information needed on TB treatment to the patient, such as its duration, the critical need to adhere to daily treatment and to the whole duration
- Use educational materials that the NTP has made available
- Assess patient's beliefs about TB and adapt the education messages to the beliefs
- Review instructions, question patient to ensure his/her understanding

5.2.3.3 Treatment

- Tailor treatment plan to patient's suitability, and offer options
- Give clear instructions about the side effects of TB medication
- Ensure proper record keeping for each patient on treatment
- Follow up quickly on missed appointments
- Fast track patients coming for treatment and follow up
- Ensure that staff is supportive to patients
- Ensure confidentiality

5.3 Monitoring during TB treatment

The health workers ensuring TB treatment provision should monitor the evolution of the signs and symptoms. They should ask patients on their tolerance to anti-TB drugs and instruct them to report the occurrence of any symptom (that might be associated with an adverse effect of anti-TB drugs).

Liver enzymes should be measured before treatment and monitored monthly throughout the treatment,

Health care workers should record and report any treatment interruption.

Patient weight should be monitored each month, and dosages may need to be adjusted if weight changes.

A written record of all medications given, bacteriological response and adverse reactions should be maintained for all patients on the TB treatment card and TB identity card.

5.3.1 Monitoring TB patients

Monitoring treatment response should be done using Smear microscopy and, in special cases, culture.

New pulmonary cases

Sputum Smear examination and Xpert MTB/RIF should be done in all persons with presumptive TB and abnormality in X-ray according to the algorithm for the diagnosis of pulmonary TB

M 0*: time of diagnosis.

If the patient is smear positive or have Mtb confirmed in Xpert MTB/RIF and no Rifampicin resistance

M 2: at the end of the initial phase - sputum smear

M 4: at the end of month 4 of treatment – sputum smear

M 6: towards the end of month 6 of treatment – sputum smear

**(M 0: month 0, M 2: month 2 etc….)*

If M4 and M6 smear microscopy are negatives, patient is cured.

If any M2, M4 or M6 smear microscopy is positive, further investigations, including Xpert and culture, need to be carried out

Retreatment cases

M 0*: time of diagnosis. Smear microscopy together with Xpert or other NAA (if RR, patient directed to MDR-TB case management)
M 3: at the end of the initial phase - sputum smear
M 5: at the end of month 5 of treatment - sputum smear
M 9: towards the end of month 9 of treatment - sputum smear

**(M 0: month 0, M 2: month 2 etc….)*

If M5 and M9 smear microscopy are negatives, patient is cured.

If any M3, M5 or M9 smear microscopy is positive, further investigations, including culture and DST need to be carried out

Monitoring treatment with chest X-ray is indicated only in complex cases with severe form of TB. No improvement in chest X-ray during first line TB treatment in a bacteriology confirm case calls for an investigation for Drug resistance and/or associated disease. Complete resolution of lesions in the chest X-ray after a standard regimen is not necessarily obtained after 6 months regimen but it does not require prolonged treatment. Healing is slower than elimination of bacteria with adequate treatment regimen.

Patient with EPTB

The treatment assessment response in EPTB patient should be mainly clinical and sometime radiological. The weight of the patient must be monitored at each assessment visit.

Child with TB

Each child with TB should be assessed at least at the following intervals: 2 weeks after the start of treatment, at the end of the intensive phase, and every months until completion of treatment.

The assessment should include, as a minimum:

1. Symptom assessment;
2. Assessment of treatment adherence;
3. Enquiry about any adverse events;
4. Weight measurement
5. Monitor liver enzymes monthly.

5.3.2 Recording treatment outcomes

Monitoring TB patients must result in establishing the outcomes of TB treatment, using the standardized definitions of NTP. **The treatment outcomes need to be specified for all registered and notified TB patients in the TB treatment card, TB identity card and TB register of TB center**. Registering treatment outcome is as important as declaring new case of TB.

5.3.3 Cohort analysis

The cohort analysis must be carried in each TB center on a quarterly basis. The cohort analysis reports established in these centers should be, after verification, compiled and consolidated at national level. The evaluation of outcomes will help identify TB centers that are performing well and those that are facing difficulties. Successful practices initiated in a place can be replicated elsewhere.

5.3.4 Adverse effects of anti-TB drugs and their management

5.3.4.1 Adverse effects of anti-TB first line drugs and their management

The majority of TB patients who receive first-line anti-TB drugs complete their treatment without any significant adverse effects. However, adverse reactions may occur during TB treatment. Most of them are minor but there are major reactions that need specific and urgent measures. The health workers providing TB treatment should know how to prevent, monitor and manage the adverse reactions that may appear during the treatment.

Table 8 in Annex III describes side effects of first line anti-tuberculosis drugs and their management. Health personnel can prevent some drug-induced side-effects, for example isoniazid-induced peripheral neuropathy. This usually presents as numbness or a tingling or burning sensation of the hands or feet and occurs more commonly in pregnant women and in people with alcohol dependency, malnutrition, diabetes, chronic liver disease, renal failure. These patients should receive preventive treatment with pyridoxine, 10 mg/day along with their anti-TB drugs.

Health personnel can monitor adverse drug effects by teaching patients how to recognize the symptoms of common effects and urging them to report if they develop such symptoms as well as by asking about symptoms when patients come to collect drugs. Adverse reactions to drugs should be recorded on the TB treatment card and TB identity card.

If a patient develops a major side-effect, the treatment or the responsible drug must be stopped and the patient urgently referred to a clinician for appropriate management in TB referral center or hospital.

Management of cutaneous reactions

If a patient develops itching without a rash and there is no other obvious cause, the recommended approach is to try symptomatic treatment with antihistamines and skin moisturizing, and continue TB treatment while observing the patient closely.
If a skin rash develops, however, all anti-TB drugs must be stopped.

Once the reaction has resolved, anti-TB drugs are reintroduced one by one, starting with the drug least likely to be responsible for the reaction (rifampicin or isoniazid) at a small challenge dose, such as 50 mg of isoniazid. The idea of starting with a small challenging dose is that if a reaction occurs with a small dose, it will not be a major one as with a full dose. Therefore, the dose needs to be gradually increased over 3 days. This procedure is repeated, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the skin reaction. The alternative regimens listed in the following paragraph are also applicable when a particular drug cannot be used because it was the cause of a cutaneous reaction.

Management of drug-induced hepatitis

Of the first-line anti-TB drugs, isoniazid, pyrazinamide and rifampicin are the most commonly responsible for drug-induced hepatitis; in contrast, ethambutol is rarely involved in liver damage. Rifampicin can cause asymptomatic jaundice without evidence of hepatitis. It is important to try to rule out other possible causes (eg. viral hepatitis) before deciding that the hepatitis is induced by the TB regimen.

If the liver disorder is likely to be caused by anti-TB drugs, all drugs should be stopped. However, if the patient is severely ill with TB and it is considered unsafe to stop TB treatment, he/she should be hospitalized and a non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started.

If TB treatment has been stopped, it is necessary to wait for liver enzymes to revert to normal and clinical symptoms (nausea, abdominal pain) to resolve before reintroducing anti-TB drugs. If the signs and symptoms do not resolve and the liver disease is severe, the patient must be hospitalized and the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started.

Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms start again or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Rifampicin should be reintroduced first because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent. After 3–7 days, isoniazid may be also reintroduced. In patients who

have experienced jaundice but tolerate the reintroduction of rifampicin and isoniazid. It is preferable not to re-administer pyrazinamide to these patients.

Alternative regimens depend on which drug is the likely cause of the hepatitis:

- If rifampicin is the likely cause, the suggested regimen is 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol.
- If isoniazid cannot be used, 9 months of rifampicin, pyrazinamide and ethambutol can be considered.
- If pyrazinamide is discontinued before the patient has completed the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months.
- If neither isoniazid nor rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be continued for a total of 18–24 months.

FDCs are used in the treatment of TB in Lebanon. In order to cope with anti-TB drug-induced hepatitis that may occur in TB patients, the NTP should make available small quantities of anti-TB medicines in loose tablets. These loose tablets will be used in the process of reintroducing one TB drug at a time.

5.3.4.2 Adverse effects of anti-TB second line drugs and their management

Unlike first line drugs which are relatively well tolerated, second line drugs are usually more toxic and need specific follow-up.
Only staff involved in the management of drug resistant TB will need to consult reference for the identification and management of side effects of second line anti TB drugs during treatment of a patient with drug resistance tuberculosis: refer to pages 152-166 of the document “Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis” (WHO/HTM/TB/2014.11).

5.4 Transfer out agenda

WHO SOPS for the region are being finalized and will be available.

5.4.1 Standard dossier (to be prepared by NTP) for the transfer out:

Country, treatment center, address, e-mail address, telephone number
Diagnosis (results of lab tests, X-ray, clinical findings), date registration Treatment given so far, date of treatment started, adverse event if any

Referred to: treatment center/country, if possible contact details of recipient treatment center.

Provide to patient X-ray film if any and any other document relevant for the continuation of treatment in recipient treatment center/country.

5.4.2 Procedure:

Staff from TB center should make everything possible to keep the patient in country until completion of treatment or at least until completion of intensive phase.

Upon decision of transfer, the staff should spend time to obtain from the patient the followings

- Information about residence address (home country), likely lag time between consultation and arrival at residence etc…
- Attempt to contact via e-mail the health facility indicated by the patient close to patient's residence. Request help of International Organizations to ensure patient continue treatment in home country when Transfer is made to another country
- Dossier to be given to the patient + provision of drugs to cover lag time between consultation and arrival at residence

6 Intensified case finding, preventive therapy and TB prevention

6.1 Intensified case finding

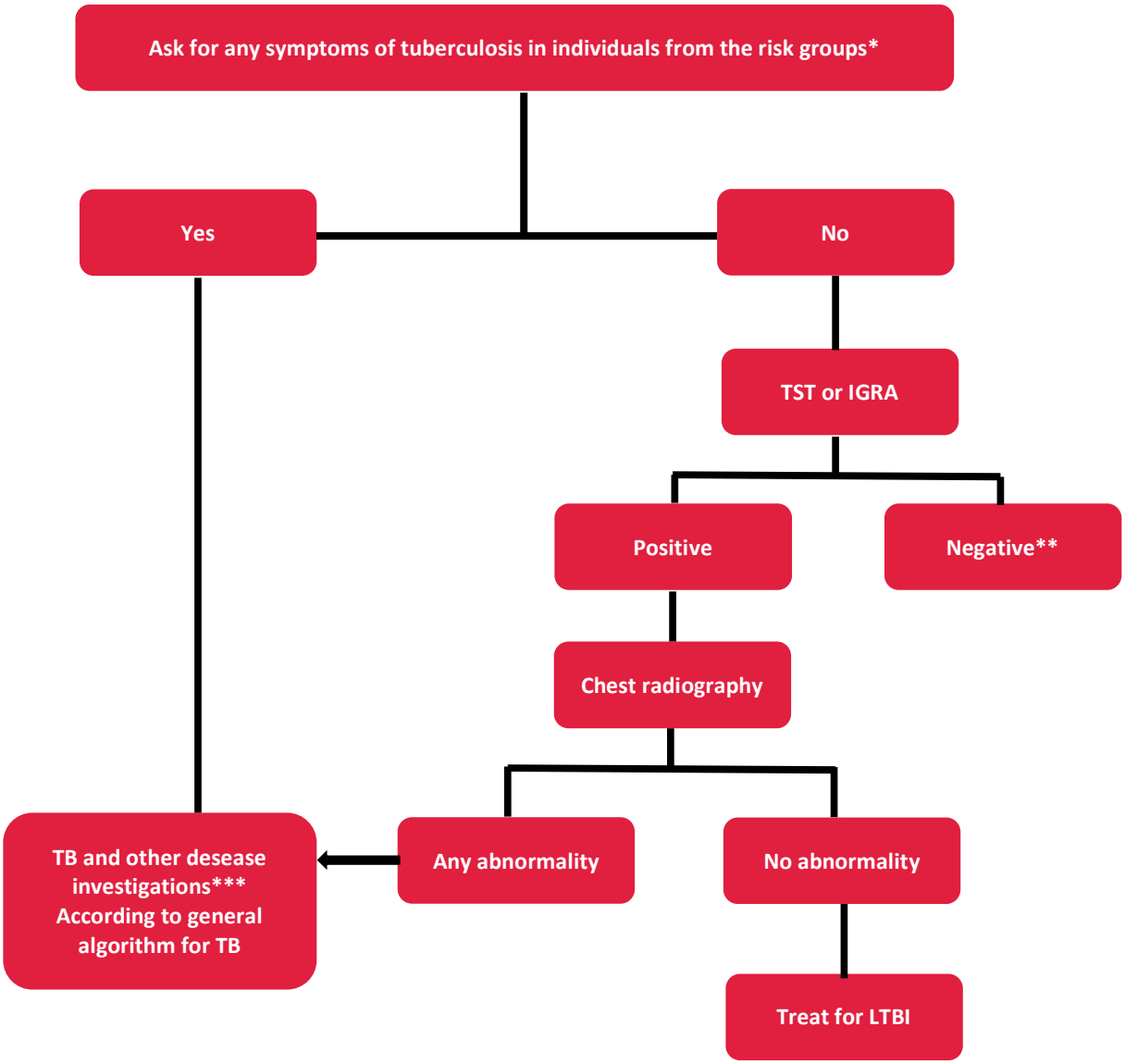
6.1.1 Definition of risk groups for systematic screening for TB

The NTP has identified the following risk groups for systematic screening for TB

1. People living with HIV
2. Adult and child contacts of patient with pulmonary TB
3. Prisoners
4. Refugees in crowded settings
5. On treatment with anti-TNF medication/or planning to
6. Organ or bone marrow recipient
7. On chemotherapy for cancer
8. Hemodialysis patient
9. Health care worker (nurse, medical or lab student, lab technician, physician, …)
10. Coming from high-endemic country or area

6.1.2 Algorithm to be used for screening risk groups for TB

Figure 3: Algorithm for Targeted Diagnosis and Treatment of LTBI in Individuals from Risk Groups

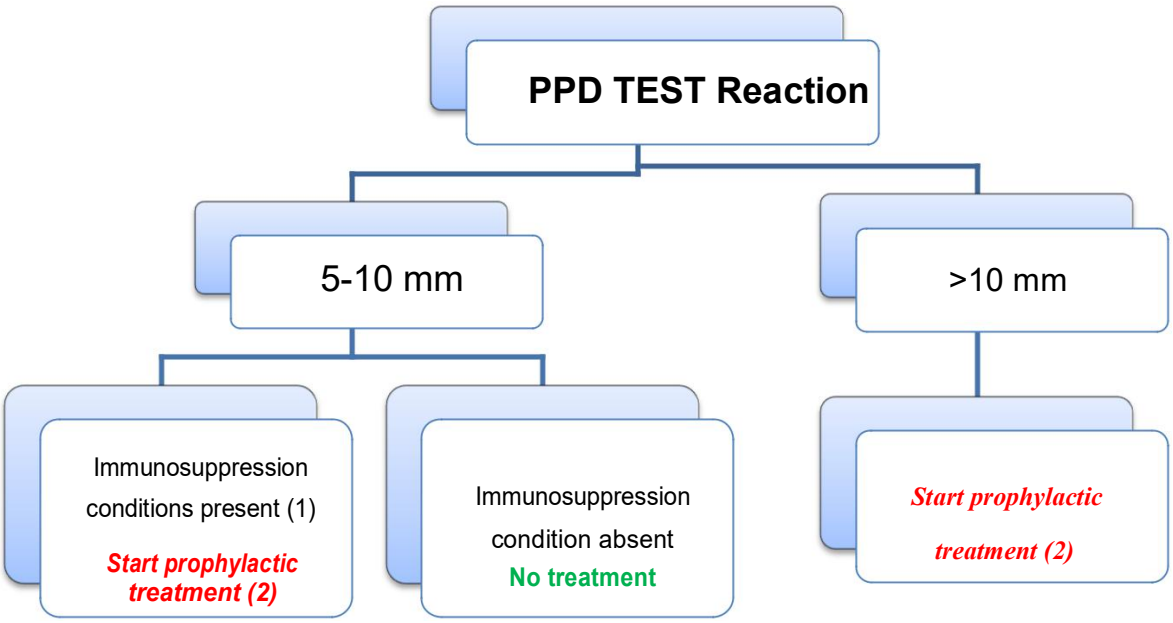


*Any symptoms of TB include any one of cough, hemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue. HIV test could be offered based on medical or local guidelines or clinical judgment. Similarly chest radiographs can be done if efforts are intended also for active TB case finding.

**Clients for whom LTBI treatment is not indicated should be provided information about TB including on the importance of seeking care if symptoms of TB developed.

***National TB guidelines should be followed when investigating for TB. In addition, those individuals in whom TB is excluded after investigations (including individuals with fibrotic radiologic lesions), can be considered for LTBI treatment.

Figure 4: Treatment of Latent TB infection according to the tuberculin skin test reaction classifications



(1) Immunosuppression conditions:

1. HIV-infected persons.
2. Persons with fibrotic changes on chest radiograph consistent with old TB.
3. Organ transplant recipients.
4. persons who are immunosuppressed for other reasons (including taking the equivalent >15mg/day of prednisone for 1 month or longer taking TNF- **a** antagonists)

(2) INH 300mg daily 6 months in adult and 6-9 months in the child (5mg/kg in adult, 10mg/kg in children)

6.1.3 Organizing contact investigation and reporting

TB contact investigation contributes to early detection and treatment of active TB cases. The index TB cases around whom contact investigation must be undertaken are:

- patients with bacteriologically confirmed pulmonary TB
- children with active TB
- co-infected HIV/TB patients and
- rifampicin-resistant/MDR/XDR-TB cases.

The contacts that must be systematically and actively screened in priority for TB are household members. The screening and the evaluation of contacts should involve community health workers and health staff of PHC center and TB centers.

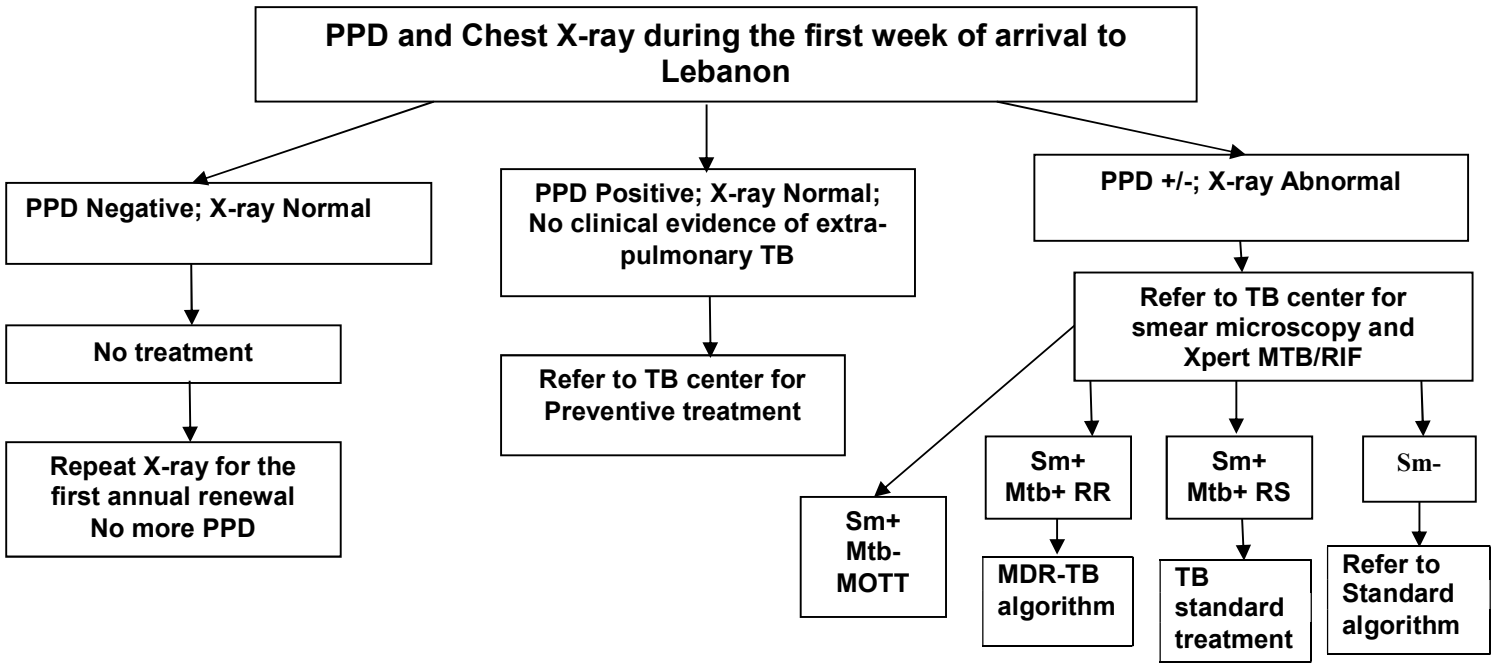
Contact screening should follow the algorithm for risk group (see above section 6.1.2)

A special register should be opened for contacts, indicating the name of index case, list of household contacts, whether screened or not, the one on IPT and active TB cases identified.

Children and PLHIV who are contacts but do not have any active TB must be treated with IPT. Babies under 1 year of age exposed to active TB in the household should receive 6 to 9 months of IPT irrespective of the result of the TST. (INH 100mg is available in dispersible tablet)

6.1.4 Organizing screening of migrants

Figure 5: TB Strategy for Work and Stay Permit



1."TB standard Treatment": 6 months treatment of which first 2 weeks or more are in-hospital treatment
2."Preventive Treatment": 6 months INH preventive treatment
3.All opacity/calcification should undergo bacteriological tests of sputum and other investigations as needed to rule out active TB
4.Extra pulmonary TB is NOT contagious. Follow algorithm for EPTB
5.No TB – No Treatment
6.Sm+ = smear positive, Mtb+ = Mycobacterium tuberculosis positive, RR = Rifampicin Resistance, RS = Rifampicin Sensitive
7.MOTT = Mycobacteria Other than Tuberculosis

6.2 Preventive therapy in LTBI:

Regimen to be used and monitoring

INH 6 months for Adults and 6 to 9 months for Children

1. Children: 10 mg/kg
2. Adult: 5 mg/kg, maximum 300mg

Monitoring: INH preventive therapy should be closely monitored for regular intake and full course (6months adults/6-9 months children) completed. A special register and treatment card should be opened for all persons on preventive therapy. Adherence to treatment should be ensured either through treatment supporter (DOT health worker or community health worker) or through mobile phone reminder. Monthly follow-up clinical assessment should be organized.
Rifampin 4 months is a possible alternate for INH 6 months if there is intolerance to INH in adults

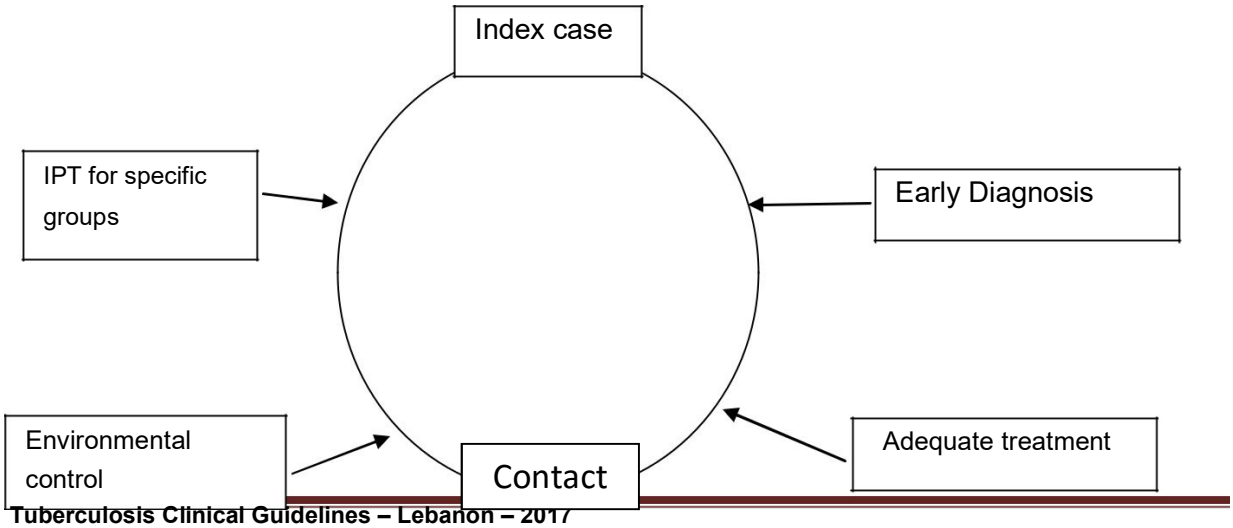
6.3 Prevention of tuberculosis:

TB is a preventable communicable disease if appropriate measures are taken. Its transmission chain revolves around the index case and exposed contacts. The following approaches are used to prevent:

- the contact from being infected which implies early diagnosis and adequate treatment of TB as well as environmental measures
- The infected contact from developing active TB through IPT.

6.3.1 Chain of transmission

Figure 6: Chain of Transmission of TB



6.3.2 TB contact investigation

TB contact investigation contributes to early detection and treatment of active TB cases and therefore reduces the duration of transmission of TB bacilli in community.

The index TB cases around whom contact investigation must be undertaken are:

- patients with bacteriologically confirmed pulmonary TB
- children with active TB
- co-infected HIV/TB patients and
- Rifampicin-resistant/MDR/XDR-TB cases.

The contacts that must be systematically and actively screened in priority for TB are household members. The screening and the evaluation of contacts should involve community health workers and health staff of PHC centers and TB centers.

Children and PLHIV who are contacts but do not have any active TB must be treated with IPT.

6.3.3 Prevention of TB transmission in laboratory

Laboratory workers are responsible for their own safety and that of their co-workers. Transmission of TB is common in laboratory setting if no precautions are taken. This essentially results from micro-aerosols, 1 to 5 microns in diameter, which carry TB bacilli. If there are no safety measures, these bacilli can be transmitted to laboratory workers.

The prevention of TB infection in laboratory must aim at reducing the production of aerosols. This can be achieved by provision of the following:

- Laboratories with good ventilation. This is through locating windows and doors in such a way that airborne particles are blown away
- Health staff must wash their hands each time they enter and leave laboratory
- Wearing of protective clothing such as laboratory coats while doing work and leaving them in the lockers when going home
- Access to laboratory must be allowed to the required staff only
- Wearing of disposable gloves while preparing and staining smears
- Eating, drinking and smoking should be totally prohibited in laboratory
- Sputum specimen should be collected outside on open air area but not in laboratory. Sputum preparation and smearing when done according to SOPs does not increase the risk of transmission of TB. Laboratory technicians must always be vigilant.

6.3.4 Preventing TB infection in health care settings

Although it is difficult to prevent TB infection in congregate setting the following measures need to be taken whenever possible:

- Administrative: This include early recognition, diagnosis and treatment of suspected cases of pulmonary TB, separation of presumptive and proven cases of pulmonary TB from others
- Patients should cover their mouths while coughing
- Environmental: this includes maximizing natural ventilation and using ultraviolet radiation where possible
- Personal protection: protection of PLHIV from possible exposure to any TB source and offering IPT.

6.3.5 Prevention of infection at home

The community should be instructed to isolate the patient with pulmonary TB in one room during night and request the patient stay either in the room or outside the house during the day and refrain to visit friends and relatives. **These requirements should be only for the first 15 days of treatment**. After this period, the patient can live in and outside the house without special precaution except covering his/her mouth when coughing. These simple methods can contribute to reducing the transmission of TB in indoor environment and subsequently in community.

6.3.6 Consumption of raw milk

Consumption of raw milk can lead to transmission of bovine TB. The community members must therefore be instructed to boil milk before consumption.

7 Tuberculosis in emergency and conflict situation

According to the WHO Communicable Diseases Control in Emergencies – Field Manual by M. A. Connolly, in the acute phase of an emergency, when mortality rates are high owing to acute respiratory infections, malnutrition, diarrheal diseases and malaria (where prevalent), TB control is not a priority. However this is not true for Lebanon where Syrian refugees suffer mainly from housing and economic issues and are not at an immediate risk of dying from acute infections. Moreover the distribution of Syrian refugees all over the country and not in campus as the case in Turkey or Jordan raises the possibility of transmitting the disease to the Lebanese population including MDR-TB.

Recommendations:

1. Close cooperation and coordination between NTP, UNHCR, IOM and other stakeholders mainly international and regional organizations**.**
2. Active involvement of relevant NGOs under the supervision of NTP.
3. Ensure availability of adequate human, technical, and financial resources to provide treatment for all refugees and good case management of active TB.
4. High-risk refugees (HIV, immunosuppression …) should be given priority and adequate treatment for TB and their underlying conditions.
5. Tracing and management of contacts as recommended.
6. Improvement of sanitary conditions and living circumstances of refugees.
7. Better access to health care for refugees.
8. Comprehensive preventive and immunization approach.
9. Good and healthy nutritional support mainly for the children and elderly.
10. Close follow up of the TB situation and pre-determining of needs and required assets.

8 References

1. *World Health Organization. Definition and reporting framework for tuberculosis – 2013 revision. WHO/HTM/TB/2013.2*
2. *World Health Organization. Global Tuberculosis Report 2016. WHO/HTM/TB/2016.13*
3. *World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adult and children: policy update. WHO/HTM/TB/2013.16*
4. *European framework for tuberculosis control and elimination in countries with a low incidence. J.F. Broekmans, G.B. Migliori, H.L. Rieder, J. Lees, P. Ruutu, R. Loddenkemper, and M.C. Raviglione. Eur Respir J 2002; 19: 765–775.*
5. *World Health Organization. Guidance on ethics of tuberculosis prevention, care and control; WHO/HTM/TB/2010.16*
6. *World Health Organization. Use of interferon-gamma release assays (IGRA) in low and middle-income countries: policy statement. WHO/HTM/TB/2011.18*
7. *World Health Organization. Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement. World Health Organization, 2011. WHO/HTM/TB/2011.15*
8. *World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. WHO/HTB/TB/2012.09*
9. *World Health Organization. Systematic screening for active tuberculosis; Principles and recommendations. WHO/HTB/TB/2013.04*
10. *Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Center for Disease Control and Prevention 2013.*
11. *World Health Organization. Treatment of tuberculosis Guidelines Fourth edition. WHO/HTB/TB/2009.420*
12. *Latent Mycobacterium tuberculosis Infection. Haileyesus Getahun, M.D., Ph.D., M.P.H., Alberto Matteelli, M.D Richard E. Chaisson, M.D., and Mario Raviglione, M.D. N Engl J Med 2015;372:2127-35.*
13. *Diagnosis and Treatment of Latent Tuberculosis Infection. Seung Heon Lee, M.D., Ph.D. Tuberc Respir Dis 2015; 78:56-63.*
14. *Latent tuberculosis infection - Revisiting and revising concepts. Padmini Salgame, Carolina Geadas, Lauren Collins, Edward Jones-Lopez, Jerrold J. Ellner. Tuberculosis 95 (2015) 373-384.*
15. *World Health Organization. Guidelines on the management of latent tuberculosis infection. The END TB Strategy. WHO/HTM/TB/2015.01*
16. *World Health Organization. Xpert MTB/RIF implementation manual- technical and operational "how to": practical considerations. WHO/HTM/TB/2014.1*

17. *World Health Organization. Definitions and reporting framework for tuberculosis, 2013 revision. WHO/HTM/TB/2013.2*
18. *World Health Organization. Guidance for national tuberculosis programs on the management of tuberculosis in children. Second edition WHO/HTM/TB/2014.03*
19. *American Thoracic Society, CDC, Infectious disease Society of America. Treatment of tuberculosis. Morbidity and Mortality Weekly Report: Recommendations and Reports, 2003, 52(RR-11):1-77.*
20. *World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis: WHO/HTM/TB/2014.11*
21. *World Health Organization. Introduction of bedaquilin for the treatment of multidrug-resistant tuberculosis at country level : WHO/HTM/TB/2015.10*
22. *World Health Organization. The use of delamanid in the treatment of MDR-TB: WHO/HTM/TB/2014.23*
23. *World Health Organization. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva, World Health Organization. WHO/HTB/TB/2009.419.*

9 Annexes

Annex I

Table 1. Meta-analysis of the sensitivity and specificity of Xpert MTB/RIF in diagnosing extrapulmonary TB and rifampicin resistance in adults and children compared against culture as a reference standard as well as against a composite reference standard, by type of extrapulmonary specimen

Specimen type	Comparison (No. of studies, No. of samples)	Median (%) pooled sensitivity (pooled 95% CrI)	Median (%) pooled specificity (pooled 95% CrI)
Lymph node tissue and aspirate	Xpert MTB/RIF compared against culture (14 studies, 849 samples)	84.9 (72–92)	92.5 (80–97)
	Xpert MTB/RIF compared against a composite reference standard (5 studies, 1 unpublished)	83.7 (74–90)	99.2 (88–100)
Cerebrospinal fluid	Xpert MTB/RIF compared against culture (16 studies, 709 samples)	79.5 (62–90)	98.6 (96–100)
	Xpert MTB/RIF compared against a composite reference standard (6 studies, 512 samples)	55.5 (51–81)	98.8 (95–100)
Pleural fluid	Xpert MTB/RIF compared against culture (17 studies, 1385 samples)	43.7 (25–65)	98.1 (95–99)
	Xpert MTB/RIF compared against a composite reference standard (7 studies, 698 samples)	17 (8–34)	99.9 (94–100)
Gastric lavage and aspirate	Xpert MTB/RIF compared against culture (12 studies, 1258 samples)	83.8 (66–93)	98.1 (92–100)
Other tissue samples	Xpert MTB/RIF compared against culture (12 studies, 699 samples)	81.2 (68–90)	98.1 (87–100)

Annex II

Shorter MDR-TB regimen

- Standardized shorter MDR-TB regimen with seven drugs and treatment duration of 9-12 months
- MDR TB or rifampicin-resistant-TB, regardless of patient age or HIV status
- Monitoring for effectiveness, harms and relapse will be needed, with patient-centered care and social support to enable adherence
- Reduced patient loss expected

Duration: 9 -12 months

Intensive phase: 4-6 months (Amikacin, Moxifloxacin, Prothionamide, Clofazimin, Pyrazinamide, Ethambutol, high dose Isoniazid)

Continuation phase: 5-6 months (Moxifloxacin, Clofazimin, Pyrazinamide, Ethambutol)

4-6 Am-Mfx-Pto-Cfz-Z-E-high dose H/ 5 Mfx-Cfz-Z-E

Exclusion criteria

- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance).
- Exposure to a second-line medicine in the shorter MDR-TB regimen for >1 month.
- Intolerance to one or more medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug- drug interactions, cardiotoxicity).
- Pregnancy.
- Extra pulmonary TB disease.
- If a medicine in the shorter MDR-TB regimen is not available to the Program.

Switch to the conventional MDR TB regimen in the following situations:

- Failing regimen.
- Drug intolerance.
- Return after interruption for more than 2 months
- Emergence of any exclusion criteria.

Annex III

Table 8: symptom-based approach to managing side effects of first line anti TB drugs

Side-effects	Drug(s) probably responsible	Management
Major		***Stop responsible drug(s) and refer to clinician urgently***
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
Minor		***Continue anti-TB drugs, check drug Doses***
Anorexia, nausea,	Pyrazinamide,	Give drugs with small meals or just

abdominal pain	rifampicin, isoniazid	before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration

Annex IV

List of Recording and Reporting Tools

1: Request for examination of biological specimen for TB

2: TB Laboratory Register for Smear Microscopy and X-pert MTB/RIF

3: TB Treatment Register

4: Tuberculosis Treatment Card

5: Quarterly report on TB case registration in TB diagnosis and treatment center

6: Quarterly report on TB and TB/HIV Treatment outcomes

7: TB Treatment Transfer

8: TB Treatment ID card

9: TB Contact Register

10: IPT treatment register